ORGANIC SEMINAR ABSTRACTS
1990-91, SEMESTER I

University of Illinois

Department of Chemistry
Box 68, Roger Adams Laboratory
1209 West California Street
Urbana, Illinois 61801-3731

January, 1991
NOTICE: Return or renew all Library Materials! The Minimum Fee for each Lost Book is $50.00.

The person charging this material is responsible for its return to the library from which it was withdrawn on or before the Latest Date stamped below.

Theft, mutilation, and underlining of books are reasons for disciplinary action and may result in dismissal from the University.

To renew call Telephone Center, 333-8400

UNIVERSITY OF ILLINOIS LIBRARY AT URBANA-CHAMPAIGN
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape Selective Artificial Nucleases: Binding Interactions, Chiral Recognition and Cleavage Mechanism</td>
<td>1</td>
</tr>
<tr>
<td>Philip Kym</td>
<td></td>
</tr>
<tr>
<td>Nonpeptide $\beta$-Turn Mimics</td>
<td>11</td>
</tr>
<tr>
<td>Thomas Murray</td>
<td></td>
</tr>
<tr>
<td>Developments in the Asymmetric Osmylation of Olefins</td>
<td>21</td>
</tr>
<tr>
<td>Viji Anantharaman</td>
<td></td>
</tr>
<tr>
<td>Lewis Acid Mediated Asymmetric Ene Reaction: An Analysis of Internal, Relative and External Stereocontrol</td>
<td>29</td>
</tr>
<tr>
<td>David C. Forbes</td>
<td></td>
</tr>
<tr>
<td>Quantitation of the $\beta$-Silicon Effect on Carbenium Ions</td>
<td>40</td>
</tr>
<tr>
<td>Chao Liu</td>
<td></td>
</tr>
<tr>
<td>Asymmetric Grignard Additions in Chiral Ether Solvents</td>
<td>50</td>
</tr>
<tr>
<td>Patrick G. Murray</td>
<td></td>
</tr>
<tr>
<td>Asymmetric Conjugate Addition Reactions Mediated by Chiral Organometallics</td>
<td>60</td>
</tr>
<tr>
<td>Chien-Tien Chen</td>
<td></td>
</tr>
<tr>
<td>Mechanism of Proline Racemase</td>
<td>70</td>
</tr>
<tr>
<td>Jeff Burns</td>
<td></td>
</tr>
<tr>
<td>CC-1065 and Some Analogues: Synthesis, Biological Activity and Mechanism of Action</td>
<td>80</td>
</tr>
<tr>
<td>Khaled Saleh</td>
<td></td>
</tr>
<tr>
<td>Reduction of Quinones by NADH and NADH Model Compounds: One Step Hydride Transfer or Multistep Electron-Proton-Electron Transfer?</td>
<td>90</td>
</tr>
<tr>
<td>Mingbao Zhang</td>
<td></td>
</tr>
</tbody>
</table>
SHAPE SELECTIVE ARTIFICIAL NUCLEASES: BINDING INTERACTIONS, CHIRAL RECOGNITION AND CLEAVAGE MECHANISM

 Reported by Philip Kym
 September 27, 1990

INTRODUCTION
The development of reagents that site specifically bind to and subsequently cleave DNA has been one of the most actively pursued research areas of the past decade. Restriction endonucleases, natural enzymes which recognize and specifically cleave four to eight base-pair sequences of DNA, have become an invaluable tool for biochemically digesting DNA. Understanding the molecular basis on which these DNA cutters operate would be advantageous in the development of drugs designed to target specific genes for activation or cleavage. Sequence-specific synthetic probes that recognize sequences of between fifteen and twenty base-pairs have been developed, and are being utilized in the mapping of the human genome.\(^1\) An alternative approach to site-specific recognition of DNA has been to develop molecules that recognize differences in local conformation. Shape selective DNA recognition is particularly exciting in view of recent biochemical studies that indicate conformational heterogeneity to be important in the regulation of transcription and recombination of DNA.\(^2\) The following aspects of DNA chemistry will be discussed in this paper: conformational heterogeneity, binding interactions with chiral synthetic probes, molecular recognition of conformation and a metal-based light-induced cleavage mechanism.

DNA STRUCTURAL CHARACTERISTICS
DNA is a flexible biopolymer that exists in a variety of conformations. The different forms of DNA differ in helix geometry, base-pair orientation and groove size.\(^3\) The interactions that determine DNA structure are base-pair stacking and the orientation of the sugar-phosphate backbone to the helix axis. Figure 1 illustrates the three most important forms of DNA: B-DNA, A-DNA, and Z-DNA. Single crystal X-ray analyses have shown several differences in the shape of these helices. Thus, the conformational heterogeneity of DNA can be exploited in the development of artificial probes that recognize DNA conformation. The efficient design of conformation specific probes is dependant on an understanding of the molecular interactions that govern the differences in DNA shape.

The DNA described by Watson and Crick in the 1950s is now called B-DNA. X-ray crystal data show the helix in B-DNA to be aligned in a right-handed sense with an average of 10.0 base-pairs per turn.\(^4\) The nucleotides all have the \textit{anti} base-sugar conformation and a C\(_2\) endo pucker of the

Copyright © 1990 by Philip Kym
deoxyribose ring. The helix contains two distinctive grooves because the glycosidic bonds of a base-pair are not diametrically opposite each other. The major groove is 12 Å wide and 8.5 Å deep, while the minor groove is 6 Å wide and 7.5 Å deep. Figure 2 gives a two dimensional illustration of the grooves. Notice that the minor groove always contains the purine N-3 and the pyrimidine O-2 of the base-pair.

A-DNA is a wide and stubby right-handed double helix, with the base-pairs sharply tilted 10° to 19° toward the helix axis.4 The width of the cavernous major groove is only large enough for water
molecules and metal ions to enter. The minor groove is shallow and generally accessible to surface binding molecules. The principle difference between A- and B-DNA is the sugar orientation which is C3-endo for A-DNA as opposed to C2-endo for B-DNA.

Z-DNA is a topologically unique form of DNA.\textsuperscript{5} It exists as a left-handed double helix with an average of 12 base-pairs per turn. The repeating helical unit is two base-pairs which leads to the Z-pattern of the sugar-phosphate backbone. The fundamental difference between B- and Z-DNA is that the nucleotides in the left-handed double helix alternate in syn/anti -base conformation (Figure 3). Since the syn conformation is more stable for purines than pyrimidines, the sequence of Z-DNA is usually a purine/pyrimidine alternation. Additional Z-DNA structural peculiarities include the C3\textsuperscript{endo} sugar pucker, a crevice-like minor groove and a shallow, almost convex major groove.

**METAL COMPLEX CHARACTERISTICS**

Octahedral complexes with three bidentate ligands do not contain an inversion center and therefore exist in two enantiomeric forms. Barton utilized this concept in designing complexes of various low-spin d\textsuperscript{6} metals with the bidentate ligands shown in Figure 4. The metal-ligand complexes were synthesized by refluxing one equivalent of ruthenium(III)chloridetrihydrate with three equivalents of the bidentate ligand in the presence of a ten fold excess of lithium chloride.\textsuperscript{7} Alternatively, mixed ligand complexes have been prepared by isolating bis(polypyridyl)rutheniumdichloride and subsequently reacting it with an equivalent of a different ligand. Enantiomeric separation is achieved by diastereomeric precipitation with antimony D-tartrate.

Tris(1,10-phenanthroline)ruthenium(II) complexes were the probes selected to study DNA binding interactions. Ruthenium was selected as the metal center because of its inertness to racemization and its intense absorption in its metal to ligand charge-transfer (MLCT) band.\textsuperscript{7b,8} Additionally, the electronic structure of the ground and excited states of the related tris(bipyridine)-ruthenium(II) has been extensively studied.\textsuperscript{9} The 1,10 phenanthroline ligand is a proven intercalator with unique spectral characteristics that are easy to monitor. Spectral monitoring of the organometallic complex incubated with B-DNA indicates two weak, noncovalent binding modes: intercalation and
surface or groove binding. DNA-Binding Mode

Intercalative binding favors the $\Delta$-Ru(phen)$_3^{2+}$ isomer, while the surface-bound mode favors $\Lambda$-Ru(phen)$_3^{2+}$.

DNA BINDING MODE

Intercalation involves insertion of a planar, heteroaromatic chromophore between two adjacent base-pairs of the DNA double helix. Stabilization is achieved through noncovalent $\pi$-stacking interactions between the aromatic system of the intercalator and the DNA base-pairs. The intercalating molecule is held rigidly perpendicular to the helix axis. Intercalation can be followed spectroscopically by monitoring absorption changes in the intercalator upon binding to DNA. Evidence for intercalation as a binding mode of Ru(phen)$_3^{2+}$ includes helical unwinding of closed circular DNA, hypochromism of the Ru(phen)$_3^{2+}$ MLCT band, and intensity increases in the luminescence spectrum of Ru(phen)$_3^{2+}$. Intercalators typically unwind DNA by inducing changes in backbone torsion angles with accompanying distortions in base-pair orientation relative to the helical axis. The observed unwinding angle of Ru(phen)$_3^{2+}$ bound to supercoiled plasmid DNA was 19%. This is comparable to the unwinding angle of 26% observed with the known intercalator ethidium bromide. A decrease of 17% in the intensity of the MLCT band indicated a mode of binding that involves strong $\pi$-stacking interactions between the aromatic chromophore and a nucleotide base-pair. Increased luminescence indicated a decreased mobility of the complex once sandwiched into the DNA helix. Incubation of $\Delta$-Ru(phen)$_3^{2+}$ with B-DNA glucosylated in the major groove resulted in a dramatic decrease in binding affinity of the metal complex to the double helix. This suggested that the two non-intercalated phenanthroline ligands of $\Delta$-Ru(phen)$_3^{2+}$ lie in the major groove of B-DNA.

A systematic study of the various polypyridyl ligands performed to determine their ability to intercalate gave the following results: phi >> DIP $\geq$ phen $>$ bpy. These results correlate well with the relative size of the intercalating ligand surface. The intercalative preference of DIP over phen is surprising in that the phenyl rings are rotated out of the phenanthroline plane. Barton's most recent proposal of how DIP intercalates has one of the phenyl rings situated in the minor groove, the phenanthroline system partially $\pi$-stacked with the adjacent DNA base-pairs, and the other phenyl ring oriented in the major groove with the ancillary ligands. Precedence for positioning a phenyl ring in the minor groove has been shown in the X-ray structure of ethidium bromide intercalated into B-DNA.

Surface binding interactions are more difficult to characterize. This difficulty arises from the identical excited state lifetimes of the surface bound and free ruthenium complexes. Photophysical studies have shown that $\Lambda$-Ru(phen)$_3^{2+}$ is the preferred enantiomer for surface binding. The surface bound complex is held less tightly than the intercalated complex to the B-DNA helix. The fact that Ru(phen)$_3^{2+}$ binds to the groove at all is peculiar in that it lacks hydrogen bond donor/acceptor moieties. The typical noncovalent binding interaction of groove bound molecules has been shown to
be hydrogen bonding. The noncovalent forces that contribute to metal complex-DNA binding are electrostatic attraction between the positively charged complex and the negatively charged phosphate oxygens, local dispersion contacts, and entropically favored exclusion of several water molecules from the hydrated surface of the base-pairs.

Recent NMR studies have yielded results which provide further evidence for and more completely characterize the two distinct DNA binding modes. A synthetic oligonucleotide d(GTGCAC)$_2$ was incubated with the enantiomers of M(phen)$_3$ (M = Ru$^{2+}$, Co$^{3+}$, and Rh$^{3+}$). The ruthenium and rhodium complexes are substitutionally inert while the cobalt complex is racemic at 25° C. The oligonucleotide, acting as a chiral shift reagent, shifted the enantiomeric proton resonances to differing extents, indicating two different binding modes (Table 1). Binding of the Δ enantiomers to the oligonucleotide shifts the H5 and H6 proton resonances upfield. The magnitude of these shifts is similar to that observed for known intercalators when bound to DNA. Incubation of racemic Co(phen)$_3^{3+}$ with the oligonucleotide resulted in unequal populations of enantiomers. This provided support for the concept that enantiomeric discrimination is due to the interactions of the metal complex with the double stranded helix. At higher temperatures, the DNA double helix melts and there is no enantiomeric excess observed.

The chemical shift changes of certain oligonucleotide resonances upon metal complex binding give evidence as to the preferred grooves of the intercalative and surface binding interactions. For example, the adenine H2 proton which is situated in the minor groove of the double helix is shifted more upfield when the Δ enantiomer is bound than when the Δ enantiomer is bound. Likewise, the major groove thymine methyl protons are more sensitive, i.e. give a larger downfield shift, when the Δ enantiomer is bound. Barton suggests that the extent of the chemical shifts reflects proximity, and thus the groove location of the organometallic complex.

NMR studies using tris(phenanthroline) complexes of paramagnetic metals (Ni$^{3+}$, Cr$^{3+}$) give proton relaxation data which suggests that surface bound interactions of Δ-M(phen)$_3^{3+}$ with B-DNA occur from the minor groove. As the ratio of metal complex to DNA is increased, the adenine H2

<table>
<thead>
<tr>
<th>Metal</th>
<th>Isomer</th>
<th>H4,7</th>
<th>H5,6</th>
<th>H2,9</th>
<th>H3,8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ru</td>
<td>Δ</td>
<td>0.414</td>
<td>0.290</td>
<td>0.171</td>
<td>0.201</td>
</tr>
<tr>
<td></td>
<td>Δ</td>
<td>0.305</td>
<td>0.418</td>
<td>0.159</td>
<td>nr</td>
</tr>
<tr>
<td>Co</td>
<td>Δ(65%)</td>
<td>0.274</td>
<td>0.202</td>
<td>0.098</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td>Δ(35%)</td>
<td>0.138</td>
<td>0.194</td>
<td>0.064</td>
<td>nr</td>
</tr>
<tr>
<td>Rh</td>
<td>Δ</td>
<td>0.309</td>
<td>0.204</td>
<td>0.104</td>
<td>0.127</td>
</tr>
<tr>
<td></td>
<td>Δ</td>
<td>0.161</td>
<td>0.204</td>
<td>0.071</td>
<td>0.068</td>
</tr>
</tbody>
</table>

a. nr = not resolvable
proton signal is shifted upfield and significantly broadened. The metal-adenine H2 proton distances for the \(\Lambda\) enantiomer of the Ni(phen)$_3^{3+}$ and Cr(phen)$_3^{3+}$ complexes bound to d(GTGCAC)$_2$ were calculated to be 4.4 \(\pm\) 0.2 Å and 5.4 \(\pm\) 0.2 Å, respectively. Molecular modeling studies were performed in which the metal complex was oriented to achieve maximum correlation with NMR experimental data. From these studies, three molecular interactions were determined to be particularly important: (i) surface binding near the AT base-pair in the minor groove, (ii) major groove intercalation between the central GC base-pairs, (iii) and left-side intercalation between the TA and GC base-pairs. Modeling of the \(\Lambda\)-enantiomers revealed that a system of 93-94\% surface binding and 6-7\% intercalative binding best describes the experimental data.

Evidence that \(\Lambda\)-M(phen)$_3$ enantiomers bind in the minor groove close to AT base-pairs is interesting in that this location has also been identified as a binding site for polypyrroles and metalloporphyrins.\textsuperscript{16} In the case of the polypyrroles netropsin and distamycin, hydrogen bonding interactions with the adenine N-3 and the thymine O-2 are the dominate directing forces.\textsuperscript{13} The factors that govern binding of metalloporphyrins to DNA are steric effects and electrostatic attraction.\textsuperscript{16} These binding interactions parallel those observed with the chiral phenanthroline complexes. The common link between the phenanthroline-metal complexes and the metalloporphyrins is the cationic metal center. Therefore, it appears that electrostatic attraction is crucial in directing positively charged molecules to the AT base-pair in the minor groove.

**CHIRAL RECOGNITION: IN THEORY AND PRACTICE**

The enantioselectivity of the DNA binding interaction is determined by steric interactions of the ancillary ligands with the helical groove. The shape of \(\Delta\)-Ru(phen)$_3^{2+}$ and \(\Lambda\)-Ru(phen)$_3^{2+}$ can be described as right- and left-handed propellers, respectively (Figure 5). When a phenanthroline ligand

\[ \text{Figure 5} \]

\[ \Delta\text{-Ru(phen)}_3 \quad \Lambda\text{-Ru(phen)}_3 \]
of $\Lambda$-Ru(phen)$_3^{2+}$ intercalates into a B-DNA double helix, the orthogonal phenanthroline ligands fit snugly along the helical groove. In the case of $\Lambda$-Ru(phen)$_3^{2+}$, however, the two non-intercalated ligands have hydrogen atoms which sterically clash with the phosphate oxygen atoms of the helical backbone (Figure 6).

Complete stereoselectivity can be achieved when the bidentate ligand is changed to 4,7-diphenyl-1,10-phenanthroline (DIP). The additional steric bulk causes the $\Lambda$ isomer to be completely prevented from intercalating into B-DNA. The left-handed Z-DNA helix, however, has a wide and shallow major groove which cannot discriminate in the binding of the enantiomers. The major groove of left-handed DNA is wide and shallow because the C3' endo sugar conformation pushes the base-pairs away from the helical axis (vide supra). The result is that $\Lambda$-Ru(DIP)$_3^{2+}$ is a completely enantioselective probe for Z- or other non-right-handed DNA.

Changing the metal center from $\Lambda$-Ru(DIP)$_3^{2+}$ to $\Lambda$-Co(DIP)$_3^{3+}$ converts the metal complex to a molecular probe which can stereoselectively cleave a DNA strand at regions of non-B-form conformation. Effective cleavage at Z-form fragments has been accomplished in the simian virus 40 genome$^{17a}$ and plasmids pBR322 and pLP32.$^{17b}$ Of particular interest, is that the sites of cleavage, i.e. the sites of non-B-form DNA, correspond to the borders of gene coding regions. Thus, $\Lambda$-Co(DIP)$_3^{3+}$ is a molecular probe sensitive to DNA sequences involved in genetic regulation.

Figure 6. Schematic illustration of steric interactions of the $\Delta$ and $\Lambda$ enantiomers with B-DNA.
Groove binding interactions have also been used in the design of stereoselective molecular probes. A-Tris(3,4,7,8-tetramethylphenanthroline)ruthenium(II) [A-Ru(TMP)$_3^{2+}$] was found to bind to the shallow minor groove of A-DNA, while no binding was observed when it was incubated with B-DNA. Furthermore, circular dichroism measurements, after dialysis experiments, indicated a 92% enantiomeric preference for binding of the A isomer. The selectivity for A-DNA is due to an exact fit of the tetramethylated phenanthroline ligand into the shallow minor groove. Binding interactions with B-DNA are precluded by the extra bulk that the methyl groups bring to the ligand. Intercalation is sterically prohibited as the ligand width precludes it from even partially squeezing between the inner helix and surface binding is prevented because the extra length prevents the ligand from residing inside the groove. Understanding selective A-DNA binding interactions with molecular probes may lead to an understanding of how proteins selectively bind to DNA fragments of this conformation.

**DNA CLEAVAGE BY METAL COMPLEXES**

Once an organometallic complex is bound to a particular site along the DNA double helix, irradiation with visible or near-UV light can initiate single stranded cleavage. The mechanism of cleavage is dependant on the metal center used in the complex. Barton has used three different d$^6$ metal centers to induce photocleavage: ruthenium(II), cobalt(III), and rhodium(III). Each of these metal centers has unique excited state properties which affect their mechanism of cleavage. The photochemical differences of various d$^6$ metals are determined by the type of transition between the ground state and the lowest energy excited state of the metal complex. The three observed transitions are intraligand (IL, $\pi\rightarrow\pi^*$), ligand field (LF, d$\rightarrow$d), and charge-transfer (CT, d$\rightarrow\pi^*$).

Polypyridyl complexes of Ru(II) undergo a charge-transfer transition when photolized. An electron is excited from a ruthenium $t_2g$ orbital to a polypyridyl ligand $\pi^*$ orbital. The result is a new chemical species which can transfer its excitation energy to another molecule or follow redox active electron transfer pathways. With A–Ru(TMP)$_3^{2+}$ bound to DNA, a primary excited state pathway appears to be transfer of energy to molecular oxygen. This results in conversion of ground state $^3$O$_2$ to excited state $^1$O$_2$ which subsequently catalyzes single strand cleavage of DNA. The existence of $^1$O$_2$ was determined by running the photolysis in D$_2$O. The slower quenching of $^1$O$_2$ in D$_2$O compared to H$_2$O leads to a more efficient cleavage reaction. The cleavage reaction initiated upon the irradiation of A-Ru(TMP)$_3^{2+}$ bound to DNA was observed to have twofold site selectivity. The primary cleavage specificity was a result of A-Ru(TMP)$_3^{2+}$ binding selectively to regions of A conformation. A secondary cleavage specificity was observed at guanine residues. The guanine specific cleavage was not related to the binding of the metal complex, but instead has been shown to be a consequence of $^1$O$_2$ involvement.

Excited state cobalt(III) metal complexes have been shown to undergo either intraligand or ligand field transitions, depending on the wavelength of irradiation and the ligands attached to the metal center. Co(NH$_3$)$_6^{3+}$ and Co(bpy)$_3^{3+}$ complexes always undergo ligand field d$\rightarrow$d transitions, but for
Co(phen)$_3^{3+}$ the major photochemical transition shifts from ligand field at 442 nm to intraligand at 325 nm. The IL states of Co(phen)$_3^{3+}$ do not show cleavage enhancement in the presence of D$_2$O. The DNA cleavage reaction is expected to be similar to that of Co(III)-bleomycin mediated photooxidative single strand cleavage of DNA.\textsuperscript{22} Light induces reduction of Co(III) to Co(II) with concomitant oxidation of the ligand. The oxidized ligand could then mediate hydrogen atom abstraction from the DNA sugar moiety. Once formed, the sugar radical can follow a number of routes that result in single strand DNA cleavage (Scheme I).\textsuperscript{23} Diffusible hydroxyl radical (-OH), the catalyst in oxidative Fe(III) and Cu(II) mediated cleavage, does not appear to be involved in the reaction because the cleavage is isolated to single inter-base positions.

Scheme I

Photooxidative DNA cleavage via Rh(III) complexes is thought to occur through a mechanism similar to that seen with the Co(III) complexes.\textsuperscript{24} The cleavage reaction using Rh(III) is often more efficient than with Co(III). This can be explained by the greater stability of the Rh(II) complexes. The reduced rhodium species can be reoxidized to effect a second round of cleavage whereas the reduced cobalt species largely dissociates. An important observation is that for both Co(III) and Rh(III) complexes, the single strand cleavage is localized to the sites where the metal complexes were bound.
CONCLUSION

Chiral organometallic complexes have been designed to recognize DNA on the basis of local conformation. The noncovalent binding interactions do not involve hydrogen bonding. Instead, they involve electrostatic and van der Waals attractive forces. Most importantly, favorable binding interactions are governed by whether the asymmetric metal complex matches the shape and size of the DNA helical groove. Once bound, the metal complex can initiate site selective cleavage of the DNA double helix by activation with visible or near-UV light. The chemistry involved here has successfully identified regions of altered DNA conformation; these regions have proven to be important in genetic regulation. The results presented here represent a small step toward the ultimate goal of understanding the molecular interactions that govern site selective binding of small molecules to DNA.

REFERENCES
(4) Dickerson, R. E. Science 1982, 216, 475.
(9) (a) Sutin, N.; Creutz, C. Pure Appl. Chem. 1980, 52, 2717. (b) Balzani, V.;
(13) (a) Patel, D. J.; Shapiro, L. J. Biol. Chem. 1986, 261, 1230. (b) Klevit, R. E.;
(14) (a) Rehmman, J. P.; Barton, J. K. Biochemistry 1990, 29, 1710. (b) Rehmman, J. P.;
NONPEPTIDE \( \beta \)-TURN MIMICS

Reported by Thomas Murray

October 4, 1990

INTRODUCTION

The \( \beta \)-turn is a vital structural element in nearly all proteins. Roughly one third of globular protein structure consists of hairpin turns (\( \beta \)-turns). Recent reports\(^1\) also suggest that \( \beta \)-turns have a prominent role in receptor binding, antibody recognition, and posttranslational modification. Various methods\(^2\) have been used to enforce a \( \beta \)-turn structure in highly flexible peptides including D-amino acid substitution, cyclization of peptidic side-chains, and replacement of amino acid side-chains with bulkier groups, however, these approaches still allow much conformational freedom and therefore somewhat ambiguous results. By using conformationally constrained nonpeptidic \( \beta \)-turn mimics one can (1) verify active site conformations of a peptide at a specific receptor, (2) increase potency by stabilization of the biologically active conformer, (3) decrease degradation by eliminating metabolized conformations, and (4) study turn regions in the nucleation of protein folding.

Recently several groups have begun to design nonpeptidic mimetics.\(^4\) Factors that need to be considered in designing such molecules include the relative positions of side chains, the angle by which the peptide enters and leaves the \( \beta \)-turn, and the type of turn to be mimicked. The various approaches have been classified as di- or tetrapeptide mimics and their synthesis, conformation, and biological activity will be discussed.

BACKGROUND

The \( \beta \)-turn consists of a tetrapeptide sequence wherein a reversal in direction of the protein chain occurs as the carbonyl oxygen of the first residue hydrogen bonds to the NH of the fourth residue (Figure 1). The conformations of such a sequence are governed by the torsion angles \( \phi \) and \( \psi \) of residues i+1 and i+2. Venkatechalam\(^3\) first postulated \( \beta \)-turns using hard sphere calculations, and determined there were seven possible classes (I-VII) and some enantiomers (I'-III'). The two most common conformations observed in X-ray structures are classified as type I and II and they differ by a 180° rotation of the central peptide unit. The preference for the \( \beta \)-turn arises primarily from a steric interaction between the side chains of residues i+1 or i+2 and either the carbonyl of residue i+1 or the NH of residue i+2.\(^1\) Examination of protein X-rays and model peptides in solution have revealed that the hydrogen bond from i+3 to i is not of major importance to the stability of \( \beta \)-turns.\(^1\) Side chain-backbone interactions and unusual amino acids also

Copyright © 1990 by Thomas Murray
increase β-turn probability. For these reasons Pro, Gly, Asp, Arg, and Ser all have high tendencies to occur in β-turns.

![Figure 1](image)

**DIPEPTIDE MIMICS**

The simplest class of nonpeptidic β-turns involves mimics of the two internal amino acids. Work in this area has resulted in tremendous successes, but also includes serious limitations. Freidinger and co-workers first utilized nonpeptide mimics while investigating the active conformation of Luteinizing Hormone-Releasing Hormone$^5$ (LH-RH, Figure 2). Many studies have concluded that the active conformation of LH-RH is a type II β-turn consisting of residues 5-8.$^6$ By inserting molecule 1 in place of Gly-Leu one can enforce the β-turn by restricting rotation about $\psi_2$ and forcing the Glu-Leu bond to be trans. Compound 7 utilizes the lactam backbone to mimic the turn region of LH-RH. The synthesis of analogue 7 includes the novel

Glutamic Acid-Histidine-Trp-Ser-Tyr$^5$-Gly$^6$-Leu$^7$-Arg$^8$-Pro-Gly-NH$_2$

(LH-RH)

![Figure 2](image)

formation of a γ-lactam$^7$ as the crucial step (Scheme I). Treatment of 3 with sodium hydride effected an intramolecular N-alkylation of the methionine sulfonium salt. Previous studies had shown that cyclization would result in amide O-alkylation and this methodology has been frequently used in peptide degradation. Results of biological testing showed compound 7 to have 2.8-8.9 greater potency than LH-RH in inducing the release of LH both *in vitro* and *in vivo*. The
high activity *in vitro* suggests that the increased potency is from improved receptor binding due to conformational constraints and not from increased resistance to proteases.

**Scheme I**

![Scheme I diagram]

Compound 1 has also been used to mimic a type II β-turn in the tripeptide Pro-Leu-Gly-NH₂ (PLG). PLG has been shown to selectively enhance binding of dopamine agonists to dopamine receptors. To prove that the active conformation is a type II β-turn Johnson and co-workers synthesized a series of conformationally constrained PLG analogues (Figure 3) using the (R)- and (S)- isomers of compound 1. The (R)- and (S)- isomer mimic a type II and type II' β-turn, respectively. Biological studies were performed to test their ability to enhance the binding of

![Figure 3]

$[^{3}\text{H}]\text{ADTN}$ (2-amino-6,7-dihydroxy-1,2,3,4-tetrahydrophthalene) to dopamine receptors. Both enantiomers of 8 were tested either by direct incubation of 8, ADTN, and receptor or by using preincubation of 8 and receptor. The (R)- enantiomer of 8 was 10,000 times more active than PLG while (S)- isomer was inactive, however, only under preincubation conditions did they
observe increased activity. The results obtained indicate that the active conformation is a type II β-turn. The reason for the activity only under preincubation conditions is not yet known but the authors suggested that metabolism of 8 into an active species or possibly a partitioning phenomenon could be the explanation. It is interesting to note that the X-ray crystal structure of (R)-8 forms an elongated peptide while (S)-8 adopts a type II' turn.9 While the results using mimic 1 are encouraging, there are limitations. First, only type II or II' can be mimicked while 70% of all known β-turns are of type I. Second, the side chain for residue 2 has been completely neglected. It has been proposed that side chains 2 and 3 are very important in receptor recognition due to their exposed nature. Finally, the torsion angle ϕ3 is free to rotate thereby creating undesirable conformations. This last limitation has been circumvented by the development of a rigid bicyclic heterocycle.

Nagai and Sato10 synthesized compound 13 to serve as a type II β-turn. The merits of structure 13 as a nonpeptide β-turn mimic include the enforced turn and the angle at which the peptides enter and leave the turn which are similar to the actual peptide backbone. The constrained analogue also locks torsion angles ϕ3 and ψ2 into the β-turn conformation. It has been shown that the solution structure of cyclic decapeptide GS (Figure 4) contains a β-sheet with two type II' β-turns at the sequences D-Phe-L-Pro.11 Structure 13 was found to be superimposable with the D-Phe-L-Pro backbone upon inspection of molecular models. The synthesis of 13 is shown in Scheme II. N-phthaly-L-Glutamine anhydride was reacted with thiophenol in the presence of dicyclohexylamine (DCHA) to give the thioester quantitatively. Treatment with diazomethane gave the corresponding methyl ester 10. Reduction of the thioester to an alcohol with Rainey nickle followed by pyridinium chlorochromate oxidation afforded 11 in 34% yield from 9. Reaction of aldehyde 11 with L-cysteine-hydrochloride formed the thiazolidine 12 which was subsequently cyclized to diasteriomer 13 in 51% yield. The configuration at C-5 was determined to be cis by NOE measurement.
Compound 13 was next incorporated into an analogue of GS replacing residues Phe-Pro thereby enforcing the β-turn structure (Figure 4). 11 A circular dichroism spectra of both GS and analogue 14 indicates close similarity in solution state conformations. The antibiotic activity of compound 14 and GS are summarized in Table I. The antibiotic activities are nearly identical

![Figure 4]

<table>
<thead>
<tr>
<th>Strain</th>
<th>GS</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> MC1-1380</td>
<td>3.13</td>
<td>3.13</td>
</tr>
<tr>
<td><em>Bacillus subtilis marfung</em> 168</td>
<td>3.13</td>
<td>3.13</td>
</tr>
<tr>
<td><em>Escherichia coli</em> C-600</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

suggesting that the active site conformation of GS contains a β-turn. The bicyclic heterocycle 13 has also been used in other model peptides to simulate a β-turn. 12 Like Freidingers system, this constrained analogue has potential drawbacks. The side chains of amino acid residues i+1 and i+2 are left out and only a type II or II' β-turn can be mimicked. The constrained analogue is also bulky which may cause receptor recognition problems.

There are other dipeptide mimics of interest which will be briefly noted. Kemp 13 has designed a monocyclic lactam, LL-3-amino-2-piperidone-6-carboxylic acid, to mimic the backbone configuration of a rare cis peptide bond between residues i+1 and i+2. The cis peptide bond is found in some cyclic peptides. A bicyclic spiro lactam by Johnson has been used to replace Pro-
Tyr in an immunogenic peptide. By using molecular modelling and 2D $^1$H NMR it was postulated that the bicyclic lactam mimics a type II $\beta$-turn. Feigel has used the rigid tricycle 2,8-dimethyl-4-(carboxymethyl)-6-(aminomethyl)phenoxathinin S-dioxide to simulate a $\beta$-turn while Ernest employed 8-amino-5,6,7,8-tetrahydro-2-naphthoic acid as a simple model turn. Each of these systems have potential advantages and disadvantages in their ability to mimic $\beta$-turns. These problems are currently being addressed by using tetrapeptide analogues.

**TETRAPEPTIDE MIMICS**

The failure to mimic the amino acid side-chains in their proper orientation has led to tetrapeptide mimetics. This new class not only addresses the spatial relationship of side-chains $R^1$-$R^4$ but also maintains a type I or type II $\beta$-bend. The ease of incorporation of a mimetic unit into synthetic peptides and proteins was also taken into consideration in the design. Kahn has developed compounds 15 and 16 which mimic a type I and II $\beta$-turn, respectively (Figure 5). A model study towards the synthesis of 15 or 16 has been published in which the key step is a Diels-Alder reaction of an azodicarbonyl system (Scheme III). The intramolecular cycloaddition proceeded easily despite the strain of the tricyclic heterocycle produced. The synthesis of model compound 23 is shown in Scheme III. Cyclocondensation of N-chlorosulfonylisocyanate with 17 gives a trans $\beta$-lactam in 72% yield. After benzylating the lactam, 18 was treated with hydrazine generating diacylhydrazide 19 in 84% yield. The next step involved acylation of 19 with 3,5-hexadienoyl chloride. The deviation in the synthesis of a type I or II turn involves the use of (E,E) diene for 15 and (E,Z) diene for 16. This product is then oxidized with iodobenzenediacetate which undergoes exo-cycloaddition in 94% yield. The strained tricycle 21 undergoes facile amide cleavage upon reaction with glycine methyl ester. The final step involved reduction of the alkene and reductive cleavage of the hydrazide bond to form 23.

![Figure 5](image_url)

Molecular modelling explored the conformational space accessible to compounds 15 or 16 by using a molecular dynamics program at high temperatures. By implementing elevated temperatures various conformational barriers were overcome without extended computational time. The molecule simulated had all side-chains removed therefore the difference between 15 and 16
was negated. After minimization with MM2 module in the SYBYL modeling program, five classes (A-E) of structures were obtained. Class A was 3.5 kcal/mol lower in energy than class B while classes C-E are greater than 5 kcal/mol making their conformation highly unlikely to be present in any significant population. The root mean square (r.m.s.) deviation between ring conformation A and type I or II β-turn are approximately 0.6 and 0.5 Å, respectively. Conformation B and type I or II turns deviate by about 0.5 and 0.3 Å. Molecular modelling yielded a favorable correlation between the side-chain conformation of the synthetic analogue and the natural peptide backbone. Kahn and Bertenshaw have also reported the incorporation of model β-turn 22 into Merrifield solid phase peptide synthesis allowing easy incorporation into synthetic peptide and proteins. However, to date no analogue of a biologically active peptide using 15 or 16 has been published.

Scheme III

While system 15 or 16 is useful in mimicking a chain reversal and the proper side-chain positioning, a problem arises in that the mimic occupies volume outside of the β-turn. This excess volume could lead to steric problems between the receptor and the peptide mimic. A new model has subsequently been designed by Olson et. al. which contains many significant features. The backbone is comprised of a 9-membered ring similar to the 10-membered pseudocyclic ring of the β-turn (Figure 6). A 10-membered covalent ring occupied too much volume and was therefore unacceptable. The intramolecular hydrogen bond has been replaced by a methylene bridge and all amides have been replaced by methylenes except the central peptide unit. This central amide is considered important due to its exposed position in the β-turn and may be involved in hydrogen bonding with the receptor. The tetrapeptide mimic also allows for the introduction of side-chain
residues \(i+1\) and \(i+2\) in their proper conformation. The synthesis of model compound 24 has recently been reported and will not be discussed in this abstract.\(^{20}\)

![\(\beta\)-TURN to TETRAPEPTIDE MIMIC](image)

**Figure 6**

The \(^1\)H NMR of 24 showed that several conformational isomers were present at room temperature. This was not unexpected due to puckering and cis/trans isomerization about the amide bond (Figure 7). By warming the sample from 35°C to 55°C in 5°C increments the authors observed coalescence of several of the proton resonances thereby indicating that several conformations are present in solution. Molecular modeling of mimetic 24 used a conformational search option of SYBYL and the side chains were replaced by methyl groups and the methylenic hydrogens were removed. After minimization, reattachment of side-chains, and reminimization 27 independent conformations were obtained (13 trans, 14 cis). Each of the 27 conformations were then compared to the 6 standard \(\beta\)-turns (I-III and I'-III'). Of the 13 trans conformations of 24 four were within 2.5 kcal/mol of the lowest energy conformation. Each of the four conformations fits at least one of the classical turns (I, I', II, II') to within 0.5 Å r.m.s. deviation. For the cis-configuration there are only two low energy conformations within 2.5 kcal/mol. These conformations fit a type I' and II turn, but with a r.m.s. deviation between 0.53-0.60 Å. The molecular modelling plus NMR data provide evidence that mimetic 24 is a good model to study the \(\beta\)-turn. The flexibility allowed in 24 allows conversion between type I, II, and their enantiomers which can be a valuable tool in synthetic peptides. By using a versatile molecule such as 24 the exact type of \(\beta\)-turn in the natural peptide need not be known.

![24, Trans to 24, Cis](image)

**Figure 7**
There are other tetrapeptide mimics which merit discussion. The initial tetrapeptide mimic designed by Currie used 5H-6-oxo-2,3,4,4a,7,7a-hexahydropyran[2,3-b]pyrrole to mimic a type II' β-turn. The rigid bicycle enforces a 5- to 2-hydrogen bonded turn in a leucine enkephalin analogue. The mimetic peptide was one third as potent an analgesic as morphine. Belanger designed two pentapeptide mimics for methionine enkephalin. They tried to model the bioactive conformation of the side chains, however, biological tests showed poor activity. Kemp has designed a 10-membered cyclic dilactam extremely similar in structure to 23. This molecule was postulated to mimic a type II or II' β-turn and biological results are pending.

CONCLUSION

In summary, a β-turn mimic needs to consider the following variables: (1) the system designed should be for a type I or II β-turn or flexible enough to mimic both, (2) enforcing a turn through a semi-rigid molecule, (3) the positioning of the side-chains within the β-turn may be essential in the design of bioactive drugs, (4) side-chains i+1 and i+2 should be easily changed in the synthesis, (5) the central amide may also need to be retained for its ability to hydrogen bond to the receptor, and (6) the β-turn chimera should also lie predominantly within the volume occupied by the original peptide backbone. The dipeptide mimics satisfy the first two goals and have been useful in creating synthetic peptides of equal or greater potency than their natural analogues. The tetrapeptide mimics have the potential to satisfy all the requirements above and future investigations hold great promise as to the role of the β-turn.

REFERENCES


(3) Venkatechalam, C. M. Biopolymers 1968, 6, 1425.


INTRODUCTION

The vicinal dihydroxylation of olefins by osmium tetroxide is a synthetically valuable transformation for the construction of polyoxygenated molecules. The osmylation of olefins proceeds via an osmate ester intermediate resulting from addition of osmium tetroxide to the olefin, though it is still not clear whether this is a [3+2] or [2+2] cycloaddition. The ability to control the \( \pi \)-facial selectivity in the osmylation to construct optically active vicinal diols is the goal of current research as is the regeneration of the highly toxic and expensive osmium reagent. In recent years, several stoichiometric and catalytic approaches to the asymmetric osmylation have emerged using chiral ligands to effect asymmetric induction. The origin of enantioselectivity in these reactions has not been fully elucidated although several mechanistic explanations have been proposed. The synthetic methodology and mechanistic aspects of these asymmetric osmylations will be discussed.

STOICHIOMETRIC ASYMMETRIC OSMYLATION

It was observed in early work by Criegee\(^2\) that pyridine and certain tertiary amines accelerated the addition of OsO\(_4\) to olefins. This observation presented the possibility of using a chiral amine ligand with OsO\(_4\) to effect asymmetric induction, producing chiral vicinal diols. In 1980, Sharpless and co-workers\(^3\) used acetate derivatives of the diastereomeric cinchona alkaloids, dihydroquinidine and dihydroquinine in the osmylation of \((E)\)-substituted olefins to produce enantiomerically enriched vicinal diols. The two alkaloid derivatives gave opposite stereoselectivities, with dihydroquinine acetate affording the \((S,S)\)-diol and dihydroquini dine acetate affording the \((R,R)\) diol. The mechanism proposed to rationalize the diastereoselectivity involves initial addition of OsO\(_4\) to a prochiral olefin (Scheme I). This adduct would react at

Scheme I

\[
\begin{align*}
\text{OSO}_4 + \text{L} & \rightarrow \text{L-OsO}_4 \\
\text{L-OsO}_4 + \text{R-CHR} & \rightarrow \text{L-OsO}_4 \cdot \text{R-CHR} \\
\text{L-OsO}_4 \cdot \text{R-CHR} & \rightarrow \text{L-OsO}_4 \cdot \text{R-CHR} \\
\text{L-OsO}_4 \cdot \text{R-CHR} & \rightarrow \text{L-OsO}_4 \cdot \text{R-CHR} \\
\text{L-OsO}_4 \cdot \text{R-CHR} & \rightarrow \text{L-OsO}_4 \cdot \text{R-CHR} \\
\end{align*}
\]
different rates with the chiral amine ligand due to differential steric interactions in the diastereomeric transition states 1 and 2. Binding of the ligand would lead to insertion of the olefin into the Os=O bond to form the metallocycle 3. Upon addition of a second ligand, the metallocycle rearranges in a fast step to form the familiar osmate ester 4. Although the mechanism was consistent with the observed results, it was not clear how asymmetry was transferred from the chiral alkaloid to the final diol product.

In 1986, Narasaka and Yamada introduced chiral $C_2$ symmetric amines derived from L-tartaric acid as potential ligands for asymmetric dihydroxylation. Various chiral diamines were screened in the oxidation of (E)-trans-stilbene (Scheme II). It was found that the bulk of the $R^1$ group on the chiral ligand 5 significantly influenced the selectivity of the reaction with $R^1=$ naphthyl and $R^2=$ H giving the highest enantiomeric excess (90% e.e.). The stereochemistry of the resulting diols indicated that an initially formed OsO$_4$-amine complex approached the double bond from the pro-$R$ face of the olefin plane.

**Scheme II**

Tokles and Snyder reported a complementary method employing (−)-(1R,2R) bis(dimethylamino)cyclohexane as the chiral ligand. While affording 86% e.e. for 1-heptene, this ligand gave only a 34% e.e. for trans-stilbene. The enantioselectivity can be rationalized with either the Sharpless mechanism discussed earlier or the generally accepted [3+2] addition mechanism. According to the Sharpless mechanism, asymmetric induction results from differential steric interactions in the nucleophilic addition of the amine ligand to the OsO$_4$-olefin complex. Since the chiral 1,2-diamine chelates more effectively to osmium than the dihydroquinidine acetate, it generates large steric interactions despite its small steric size when compared to dihydroquinidine acetate. In the [3+2] addition, $\pi$-facial selectivity would arise from steric interactions between the $N$-methyl groups and the olefin substituents upon addition of the OsO$_4$-amine complex to the double bond. Both mechanisms predict the correct stereochemical outcome but in this reaction the Sharpless mechanism appears more plausible since the $N,N$-dimethyl group and the olefin substituents are quite distant in the proposed transition state.
In recent work by Tomioka and co-workers, use of a chiral diamine with $D_2$ symmetry derived from two trans-3,4-diphenylpyrrolidine units resulted in excellent asymmetric induction (83-99% e.e.) in the osmylation of trans-substituted olefins. Comparable enantioselectivities were obtained by Hirama using an $N'N'$-dineohexyl-2',2'-bipyrrrolidine ligand.

A mechanistic study by Tomioka is consistent with Sharpless' proposal of an organometallic intermediate resulting from oxygen attack at the osmium center analogous to nucleophilic attack of a carbonyl group exclusively at the carbon center. In Tomioka's study, (Scheme III), trans-stilbene was oxidized with OsO$_4$ and the chiral ligand at -110°C in THF to afford the cis-diol in high enantiomeric excess. The chiral monoamine in contrast, was very slow to react under these conditions. An X-ray crystal structure of the osmate ester-diamine complex of trans-stilbene was obtained which clearly indicated binding of both nitrogens of the diamine to the osmium center. Tomioka concluded from this data that the [3+2] cycloaddition pathway leading to structure could not predict the stereochemical outcome of the osmylation and that the observations were more consistent with the Sharpless mechanism. Initially the ligand adds to the OsO$_4$-olefin complex followed by intramolecular attack by the second pyrrolidine moiety via chelation to form intermediate. This intramolecular attack of the ligand triggers the insertion of the olefin into the Os=O bond, forming the organometallic intermediate.

Scheme III
In later studies, Tomioka\(^9\) found that a slight structural modification of the chiral diamine resulted in dramatic changes in both the degree and sense of enantioselectivity in the asymmetric osmylation. Replacement of the phenyl groups of the pyrrolidine moiety decreased enantioselectivity and in the case of \textit{trans}-stilbene and styrene, changed the sense of selectivity. This result can be attributed to the new steric interactions in this system between the methyl groups of the xyllyl moiety and the olefin substituents which make the transition structure \textbf{A} unfavored. The reaction likely proceeds via a transition state like \textbf{B} in which the olefin substituent is rotated away from the xyllyl group, accounting for the reversed selectivity. These studies support the mechanism originally proposed by Tomioka involving the organometallocycle intermediate.

Recently, Corey and co-workers\(^{10}\) reported the use of chiral diamine \textbf{11} derived from chiral 1,2-diphenyl-1,2-diaminoethane in asymmetric osmylations affording \textit{cis} diols in very high yield and optical purity. The method allows recovery of both the ligand and OsO\(_4\) making it a synthetically efficient process. Corey rationalized the stereochemical course of the osmylations by the generally accepted [3+2] cycloaddition pathway involving a bidentate octahedral complex of the amine ligand and OsO\(_4\) as the reactive species.

According to this mechanistic model, the OsO\(_4\)-ligand complex forms a nearly \(C_2\) symmetric structure (\textbf{12}) with the mesityl groups placed so as to avoid severe steric repulsions. In the cycloaddition, one equatorial electron-rich oxygen and one axial nucleophilic oxygen attach to the carbons of the double bond. With this restriction, only oxygens 1 and 2 or equivalently 3 and 4 are available for cycloaddition. The other equatorial-axial pairs are effectively shielded by the bulky mesityl groups. Attack at the \textit{si-si} face of the olefin is favored since it avoids steric
repulsions between the olefin substituents and mesityl groups. Although the model explains the observed stereochemistry, it does not explain the high selectivity observed for trans-stilbene or methylstyrene since these olefins would be expected to suffer steric interactions between the phenyl groups on the olefin and the phenyl groups on the amine ligand. In addition, the proposed reactive species has not been characterized by X-ray as has Tomioka's ligand, so the structure of the intermediate is speculative.

The stoichiometric asymmetric osmylations, notably those employing chiral diamines afford cis 1,2-diols with good to high enantiomeric excess. However, the substrates are limited to trans-substituted olefins and 1,2-disubstituted olefins. An additional drawback is that osmium tetroxide must be used stoichiometrically.

**CATALYTIC ASYMMETRIC OSMYLATION**

In view of the high cost and toxicity of osmium tetroxide, a catalytic asymmetric osmylation method is desirable particularly for large-scale preparations of optically active cis 1,2-diols. Catalysis usually involves oxidative alkaline hydrolysis of the osmate ester with a secondary oxidant such as N-methylmorpholine N-oxide (NMO) or tert-butyl hydroperoxide to release the diol and regenerate OsO₄ in the reaction mixture.

Sharpless and co-workers developed a novel catalytic asymmetric osmylation employing aryl ester derivatives of the previously discussed cinchona alkaloids and NMO as the secondary oxidant. The reaction gave moderate enantioselectivity but e.e.'s improved significantly by slow addition of the olefin and in later work, by the addition of K₃Fe(CN)₆ and changing from a 1:1 acetone-water solvent to a tert-butanol-water solvent. The reaction is highly efficient in that as little as 0.2-0.4% of OsO₄ is required for the transformation. From the experimental evidence, a mechanism was proposed involving two diol-producing catalytic cycles only one of which was responsible for high asymmetric induction (Scheme IV).

The rate-determining step in both stoichiometric and catalytic asymmetric osmylations is thought to be the formation of the osmate ester. In the catalytic procedure, the ligand is thought to bind to osmium tetroxide to form an OsO₄-alkaloid complex which is far more reactive than free osmium tetroxide. This asymmetric oxidant adds to the olefin; the resulting adduct is then oxidized by NMO to form the putative osmium(VIII)trioxoglycolate complex which can take two different courses. At low concentrations of olefin, (i.e. when the olefin is added slowly), the glycolate undergoes hydrolysis (path a) to release the diol in high optical purity and which can react with more olefin. Alternatively, in the presence of excess olefin, the glycolate can add to a second equivalent of olefin to form a bis-glycolate complex (path b). This too is oxidized by NMO to afford 5, then hydrolyzed to release diol but with low enantioselectivity. Use of K₃Fe(CN)₆ or K₂CO₃ in place of NMO in a tert-butanol-water solvent remarkably improves
enantioselectivity even without slow addition of the olefin presumably due to complete suppression of the second non-productive cycle in the asymmetric osmylation.

Scheme IV

The addition of amines such as pyridine or quinuclidine to the osmylation reaction mixture normally inhibits catalysis because these chelating amines not only bind to OsO₄ but also to the resulting osmate ester making them difficult to reoxidize and hydrolyze. The cinchona alkaloids are unique in that they bind strongly to OsO₄ to accelerate the addition step, but do not bind well to the resulting osmate ester species. Kinetic data further indicate that only one amine ligand is involved in the rate-limiting step. At high alkaloid concentrations, the OsO₄-alkaloid complex binds a second ligand to form a coordinatively saturated 18-electron complex. The inherent stability of the 18-electron bis-alkaloid adduct renders it unreactive toward a secondary oxidant such as NMO. Similarly in Tomioka's and Corey's stoichiometric procedures, the chiral diamines
form a coordinatively saturated bidentate amine complex with OsO₄ which precludes catalysis, due to inhibition of the reoxidation/hydrolysis leg of the catalytic cycle. Thus the chelating chiral diamines, while exhibiting high enantioselectivity in the asymmetric osmylation must necessarily be restricted to the stoichiometric procedure. The catalytic asymmetric osmylation process is applicable to simple olefins, allylic alcohols and esters, α, β-unsaturated esters and aldehydes and several other unsaturated systems.¹⁶

The origin of enantioselectivity in these catalytic osmylations is not clear although the structure of the OsO₄-alkaloid complexes have been studied extensively by NMR and X-ray crystallography¹⁷. The solid state and NMR studies indicate that the chiral center in the alkaloid is quite remote from the osmium center so it is difficult to interpret how this center effects asymmetric induction in the osmylation. In a recent study aimed at improving the amine ligand for asymmetric induction,¹⁸ it was found that aryl ethers of dihydroquinidine gave higher e.e. for simple alkyl olefins than the original p-chlorobenzoate derivative. The best ligand was found to be 9-o-(2'-methoxyphenyl)dihydroquinidine. It is clear that the enhanced selectivity arises from steric rather than electronic factors since the acetate derivatives and methoxy ethers gave very low e.e.'s. Moreover, variation of the para substituent from nitro to methoxy had no significant effect on the e.e. This improved ligand was found to give higher e.e.'s for alkyl substituted olefins and α,β-unsaturated systems while the p-chlorobenzoate derivative was preferred for aryl substituted olefins.

NMR studies show that the conformation of the alkaloid-OsO₄ complex is influenced by the benzylic substituent on the alkaloid. It is likely that the benzylic substituent governs the size and conformation of the cavity in which binding to the osmium center as well as addition to the olefin take place. At room temperature, this catalytic procedure gives comparable e.e.'s to the stoichiometric procedures conducted at low temperatures, making it a synthetically valuable method. The process has been further improved by adaptation to a polymer-bound OsO₄-alkaloid complex which allows repetitive use of both OsO₄ and the alkaloid.¹⁹

CONCLUSION

Methodology for stoichiometric and catalytic asymmetric osmylation of olefins has progressed significantly in recent years. The goal of current research efforts is to expand the methodology to incorporate cis-substituted and trisubstituted olefins and to investigate further the origin of enantioselectivity in the osmylation reaction.

REFERENCES

LEWIS ACID MEDIATED ASYMMETRIC ENE REACTION: 
AN ANALYSIS OF INTERNAL, RELATIVE AND EXTERNAL 
STEREOCONTROL

Reported by David C. Forbes

November 1, 1990

INTRODUCTION

First discovered by Alder in 1943,\(^1\) the ene reaction in the most general sense involves the reaction of an allyl unit containing an allylic hydrogen (ene) with a multiple bond (enophile), usually an aldehyde or electron deficient olefin. This reaction is observed both intra- and intermolecurarily, with the creation of a new carbon-carbon bond with migration of the ene double bond and transfer of the allylic hydrogen to the enophile (Scheme I).

Scheme I

\[ \begin{align*}
\text{[ene]} + \text{[enophile]} & \rightarrow \text{[product]} \\
\text{(endo) or (exo)} & \rightarrow 1a \\
\end{align*} \]

Mechanistically, the thermal ene reaction has been proposed\(^2,3\) to occur through either a concerted or a stepwise reaction. The actual mechanism is still a matter of controversy. Recent experimental data has shown that both types of mechanisms can occur, with the exact pathway dependent on the geometrical orientation and reaction conditions.\(^2,3\) The cyclic transition structure (1a), is related to the well known and well studied Diels-Alder [4+2] cycloaddition. It can also be regarded as an intermolecular variant of the symmetry allowed 1,5 hydrogen shift.\(^2\) If a synclinal arrangement is not possible than a stepwise mechanism will occur possibly through transition structure 1b. Reaction conditions of the thermal ene generally require higher temperatures than those associated with the Diels-Alder cycloaddition due to the high energy of activation involved with this system. This limits not only the mechanistic exploration of this interesting reaction but also its synthetic utility.

The reactivity of the dienophile in the Diels-Alder reaction is highest when electron deficient. Likewise, complexation of Lewis acids to enophiles containing basic groups in the ene
reaction have allowed lower reaction temperatures to be used.\textsuperscript{3,5} Only recently has the synthetic utility and versatility of the Lewis acid catalyzed ene reaction been explored. Not only have these reactions been shown to have a broad scope which complements the thermal ene reaction but with the incorporation of Lewis acids, a high degree of stereocontrol has been observed.\textsuperscript{4} This abstract will discuss the origin of the remarkable regio- and stereocontrol involved with various Lewis acid mediated asymmetric ene reactions.

**BACKGROUND**

Perhaps the most controversial aspect of the ene reaction involves a generalized explanation of the reaction mechanism. In 1978 Oppolzer reported\textsuperscript{2b} that the ene and enophile react in a supra-supra facial orientation (Scheme I). This is consistent with a concerted mechanism which has experimental support and is further consistent with orbital symmetry considerations. Other possible mechanisms that have been proposed include: 1) a free-radical mechanism involving an intermediate diradical\textsuperscript{6} (or a radical pair, if a promoting transfer of a hydrogen atom is involved\textsuperscript{7}), and 2) an ionic mechanism.\textsuperscript{2,8}

With regards to Lewis acid mediated ene reactions, the reaction can be viewed as occurring through zwitterionic intermediate 2 or as a concerted mechanism (3) involving a polar transition structure (Scheme II).\textsuperscript{3} Snider has also shown that the energies of the two mechanisms (i.e. concerted or stepwise) are similar and the outcome of the reaction varies as a function of ene, enophile, and catalyst.\textsuperscript{3} For example, different Lewis acids can produce vastly different stereo- and regiochemical outcomes.\textsuperscript{11}

**Scheme II**

![Scheme II](image_url)

The addition of a Lewis acid to the reaction mixture adds to the complexity of this reaction. In general, the choice of Lewis acid has depended upon the enophile. Enophiles of low reactivity such as acrylates or propiolates, have required strong Lewis acids\textsuperscript{3} for successful reaction. Conversely, reactive aldehydes such as bromal or chloral have required catalysis by mild Lewis acids.\textsuperscript{4,5}
Two problems that have been associated with Lewis acid mediated ene reactions are acid catalyzed olefin migration of the ene adduct\(^3\) (4→5) and acid catalyzed polymerization of the ene (Scheme III).\(^3,4\) To avoid these side reactions, Snider and coworkers have incorporated the use of proton-scavanging Lewis acids. With the use of alkylaluminum halides as Lewis acids, proton catalyzed side reactions are minimized by loss of the proton as methane (6→7). This occurs without altering the efficiency of the reaction.\(^3\)

**Scheme III**

\[
\begin{align*}
H &= H \\
H &= H \\
\text{Me}_2\text{AlCl} &\rightarrow \text{AlMeCl}_2
\end{align*}
\]

**ORIGIN OF STEREOCONTROL**

**Internal Stereocontrol**

Lewis acid mediated ene reactions employing di- or trisubstituted olefins and unsymmetrical carbonyl compounds react to afford ene adducts containing two new vicinal stereogenic centers of high selectivity.\(^3,5\) Because a high degree of stereocontrol is obtained, a cyclic transition structure is proposed as the favored pathway for this reaction (Scheme IV). Whether the mechanism is concerted or stepwise,\(^2\) a high degree of stereocontrol is often observed.

**Scheme IV**

Examination of the possible transition structures in Scheme IV reveals that the preferred transition structure (T1) has both alkyl substituents (R = alkyl) occupying the preferred pseudo
equatorial position as opposed to transition structure (T2) where the alkyl substituents of the aldehyde is occupying the less likely pseudo axial positions. With reference to the ene, selectivity is strictly based on geometrical orientation. If one of the methyl substituents of the ene was placed in a pseudo axial position (T3), the allylic hydrogen will not participate in the proposed cyclic transition structure. Even though face selectivity is not achieved on the enantioselective level, diastereoselectivity is achieved. Thus based on the possible cyclic transition states, T1 is seen to be the energetically favored one.4,5 For example, the thermal ene reaction employing trans-2-butene and methyl glyoxylate in the presence of SnCl₄, a diastereoselectivity of 82:18 anti/syn was observed.19

Lewis acid mediated reactions with employment of β-pinene and chloral have provided additional insight into the stereocontrol of the thermal ene reaction. Work performed by Gill and coworkers has experimentally shown the preference for the anti relationship between the trichloromethyl group of the aldehyde and the coordinated Lewis acid in the aldehyde-Lewis acid complex (Scheme V).5

**Scheme V**

Without Lewis acid mediation, the thermal ene reaction involving β-pinene and chloral affords the exo₁² adduct in high yield, as shown below. With the incorporation of a catalyst, formation of the endo adduct is observed exclusive. The transition states depicting the endo/exo orientations are believed to be primarily guided by steric biases.4,5 Since the catalyst is large relative to the trichloromethyl moiety, addition is observed endo implying selectivity based on steric. As shown in the Lewis acid complex transition structure of Scheme V, the trichloromethyl group is forced endo.

Schemes IV and V also depict the high degree of regiochemistry observed in the ene reaction in both the enophile and ene. Due to the inherent affinity between Lewis acids and
aldehydes, one can easily predict the carbon of the aldehyde existing as an electron deficient species. Thus, the new carbon-carbon bond is formed exclusively at this site. With respect to the ene, one must consider the preferred geometrical orientation associated with the allylic hydrogen and the double bond (Scheme IV). As shown in Scheme VI, the products formed are a function of tertiary, secondary, or primary hydrogen abstraction. Based on the distribution of the products below, it is clear both thermodynamic and kinetic factors must be considered.

Scheme VI

![Scheme VI Diagram]

Relative Stereocontrol

In the examples above either one or two new stereogenic centers were formed in the ene reaction. However, employment of this methodology does produce racemic ene adducts 8 and 9 as shown in Scheme VII. One may now logically look into an improved system where an ene adduct can be obtained enantioselectively. The goal being the development of reagents capable of controlling the absolute configuration of the product.

Scheme VII

![Scheme VII Diagram]

The incorporation of a chiral auxiliary to form new stereogenic center(s) in high enantiomeric excess has just recently been reported in the ene reaction. Initial work in this field developed by Achmatowicz and coworkers (Scheme VIII).
In Scheme VIII, the asymmetric ene reaction using 1-pentene and the chiral glyoxylate ester as the enophile mediated by various Lewis acids, afforded only low levels of enantioselectivity. Taking note of the chiral auxiliary used, asymmetric induction was not efficiently transcribed. Realizing this, both Corey\textsuperscript{16} and Oppolzer\textsuperscript{17,18} have shown that with the incorporation of 8-phenylmenthol, successful asymmetric induction is obtained. Whitesell and coworkers\textsuperscript{15} have also investigated the application of this system using glyoxylate esters. As an ester moiety, cleavage and recovery of the chiral auxiliary can be achieved quite readily. As seen in 10, one face of the carbonyl is effectively blocked while the other side is exposed, explaining the observed enantioselectivity.

10

Shown in Table 1 are a series of simple mono- and disubstituted alkenes which are reacted under Lewis acid conditions to afford the desired α-hydroxy esters.\textsuperscript{15} The products listed below, as reported by the author, all show a remarkable degree of enantioselective control.
TABLE 1 Reaction of mono- and disubstituted alkenes with phenmenthyl glyoxylate,\textsuperscript{a,b}\nLewis acid employed being SnCl$_4$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ENE</th>
<th>Product</th>
<th>YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>G'\textsuperscript{O}COH</td>
<td>99</td>
</tr>
</tbody>
</table>
| 2     |     | G'\textsuperscript{O}COH | 100 R = H
|       |     |       | 90 R = Bu
|       |     |       | 89 R = TBS |
| 3     |     | G'\textsuperscript{O}COH | 90    |
| 4     |     | G'\textsuperscript{O}COH | 94    |
| 5     |     | G'\textsuperscript{O}COH | Anti/Syn 15:1 85 |
| 6     |     | G'\textsuperscript{O}COH | Anti/Syn 8:1 85 |

\textsuperscript{a} Taken from reference 15 \textsuperscript{b} G* = 8-phenylmenthol

As seen in Table 1, entries 1-4 involve the formation of one stereogenic center relative to the preexisting facial preference of the glyoxylate ester 10. Assuming a cyclic transition structure, as depicted in Figure 1, one can explain the origin of selectivity.

\textbf{Figure 1}

However, a concerted mechanism invoked can not be observed in entries 5 and 6 since cis and trans olefins produce the same product. Whitesell reports\textsuperscript{15} that a cationic intermediate must be formed rapidly and reversibly (i.e. cis-trans isomerization as shown in Scheme IX). The reversal of this cationic species to starting material must be faster than the conversion to product.
Thus the loss of proton, product formation, is not only the rate limiting step but also the product determining step.

**Scheme IX**

![Diagram of Scheme IX](image)

**External Stereocontrol**

To date only four systems have exemplified the use of reagent-based control on the absolute stereochemistry for the ene adduct (Scheme X).\(^{19-21}\) Work in this field incorporates the use of chiral Lewis acids (Figure 2). Thus, chiral auxiliaries are not required to obtain stereocontrol (i.e. an achiral ene and enophile can be utilized). The transcription of information from an external source to the achiral species is what is referred to as external stereocontrol. This novel approach has been reported by Mikami,\(^{19}\) Yamamoto,\(^{20,24}\) Narasaka\(^{21}\) and others. Examples of both intra- and intermolecular asymmetric ene reactions are also discussed.\(^{19-21,24}\) Unfortunately, mechanistic information (i.e. origin of stereocontrol) has not yet been speculated for these systems.

**Scheme X**

![Diagram of Scheme X](image)

**Figure 2**
With regard to chiral Lewis acid mediated ene reactions, it has been reported that a higher degree of selectivity is obtained with the incorporation of 4Å molecular sieves. This has also been shown in catalytic Diels-Alder and catalytic asymmetric epoxidation reactions. With respect to the ene reaction, Mikami has proposed that the incorporation of molecular seives is essential for the in situ preparation of the chiral catalyst when working with the glyoxylate-ene chemistry. In contrast, Yamamoto has shown the ability to attain high enantioselectivity with and without the incorporation of molecular sieves (eq. 2). Again, the actual role of the molecular sieves are not yet known. Narasaka has suggested that the dehydrating ability may be partially responsible for the degree of high enantioselectivity. Shown below are three of the four reactions reported thus far involving the successful incorporation of a chiral external source. The fourth reaction of this series being a slight modification of the third example.

\[
\begin{align*}
\text{1)} & \quad \text{O} \rightarrow \text{I} \\
\text{2)} & \quad \text{O} \rightarrow \text{OH} \\
\text{3)} & \quad \text{O} \rightarrow \text{OH} \quad \text{O} \rightarrow \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{SUMMARY} \\
\end{align*}
\]

With all three types of stereocontrol, the Lewis acid mediated asymmetric ene reaction not only proceeds smoothly under mild reaction conditions but also creates adducts of high stereoselectivity. The selectivity of these reactions is dependent on the type of ene, enophile, and Lewis acid employed. Just the quantity of current examples of the Lewis acid mediated ene reaction depicts the synthetic utility. Much work is still required in the asymmetric ene reaction; both mechanistic studies and the elucidation of the external stereocontrol. In conclusion, the Lewis acid mediated ene reaction has gained considerable success as a powerful tool in synthetic organic chemistry.
REFERENCES

(14) Oppolzer, W.; Schneider, P. *Tetrahedron* 1984, 40, 1391.


INTRODUCTION
Silicon compounds have found widespread use in organic synthesis due to the unique activating and directing effects of organosilicon groups. Under appropriate conditions, silicon-containing substituents can stabilize either a positive or negative charge and when attached to an aromatic ring, can significantly perturb its \( \pi \)-system. One of the most profound substituent effects found in organosilicon chemistry is the \( \beta \)-silicon effect; this is defined as the stabilizing influence of silicon on a carbenium ion in the \( \beta \) position. Behavior of \( \beta \)-functional organosilicon compounds is both mechanistically interesting and synthetically important since silyl-substituted carbenium ions are believed to be intermediates in some synthetic transformations. Despite the tremendous growth in the use of organosilicon compounds in synthesis, information as to the relative consequences of the \( \beta \)-silicon effect was rather qualitative until quite recently.

The desire to interpret and predict the organosilicon substituent effects in relevant reactions has spawned experimental and theoretical studies concerning the quantitative description of the \( \beta \)-silicon effect. Investigations in recent years have mainly concentrated on three aspects: evaluation of the energetic effects contributed by different electronic interactions, measurement of the influence of substituents \( \alpha \) to the carbenium carbon, and determination of the role played by the ligands or groups on silicon in its stabilizing ability.

HYPERCONJUGATIVE AND INDUCTIVE FACTORS
Carbenium ion stabilization by \( \beta \)-silicon substituents is generally believed to be predominantly due to hyperconjugation, that is, by (\( \sigma \)-p)\( \pi \) conjugation between the \( \sigma \) orbital of the silicon-carbon bond and the vacant p orbital of the adjacent carbenium ion. Inductive contributions of the silicon atom have also been considered to account for the electronic effect.
In order to partition the modes of silicon involvement in β effect, Lambert and coworkers measured the solvolysis rate for β-silyl cyclic systems 1 and 2, using cyclohexyl trifluoroacetate 3 as the reference compound. Rates were measured in 90% trifluoroethanol and both 1 and 2 gave cyclohexene as the only product. Solvolysis rate enhancements of 3.3 × 10^4 times for cis-isomer 1 and 2.5 × 10^6 times for trans-isomer 2 were noted. This large rate acceleration of 4 orders in magnitude shown by cis-isomer 1, in which the C-Si bond and the developing empty p orbital are gauche to each other, was proposed as evidence for a major contribution by inductive stabilization.

Jorgensen felt that the relatively large inductive effects shown in this study were surprising. He assumed that a more rigid ring system would be a better test for inductive vs. hyperconjugative effects. To obtain a true estimation of the effects of induction and hyperconjugation, it was important to evaluate the energies of model systems by carefully choosing, with appropriate conformations, fully developed positive charged centers (possibly in the absence of any medium effects). Jorgensen and coworkers carried out ab initio molecular orbital calculations at the MP3/6-31G* level on β-silyl-substituted cations 5-7. The corresponding ethyl carbenium ions 4a-b and β-methyl-substituted analogues were used for comparison.

In order to resolve the relative importance of hyperconjugative and inductive stabilization, the model systems were chosen to investigate conformations in which the C-X bond (X = Si, C, H) was parallel or perpendicular to the p orbital of the cation. The calculations indicated that conformation 5a is 8.9 kcal/mol more stable than ethyl cation 4a; this result can be taken as a measure of the inductive effect due to the β-silyl group. Conformation 5b showed a stabilization
energy of 38.0 kcal/mol compared to ethyl cation 4b. The comparison of the two cases indicated that dramatic stabilization is obtained through hyperconjugation (29.1 kcal/mol), while relatively minor stabilization is obtained from inductive effects (8.9 kcal/mol). These results parallel the commonly accepted rationalizations concerning the β-silicon effect. The calculations of the vinyl cations also showed, compared to CH2=CH+, cation 6 and 7 are stabilized by 28.6 kcal/mol (at MP3/6-31G*) and 42.8 kcal/mol (at 6-31G*//3-21G*) respectively. The significance of hyperconjugative effects are reflected by geometrical changes in the calculated structures as well as by the orientation dependence of the stabilization effect.

Theoretical estimations of stabilization obtained in the models have been supported by subsequent solvolysis experiments. Lambert and coworkers reported the quantitative separation of the hyperconjugative and inductive contributions in solution by using conformationally biased systems including trifluoroacetates 10 and 11. In these two tert-butyl-substituted isomers, the trimethylsilyl group is frozen into the gauche or trans relationship with respect to the leaving group. Compound 10 reacts about $10^4$ times faster than cyclohexyl trifluoroacetate, while 11 reacts about $10^{12}$ times faster than the reference compound. The very large value for the biased trans compound 11 clearly showed that hyperconjugation vastly outweighs induction as a mechanistic model.

\[
\log(k_{si,θ}/k_H) = \cos^2θ[\log(k_{si,θ}/k_{Li,θ})] + \log(k_{Li,θ}/k_H)
\]

(1)

where $k_H$ is the observed rate for unsilylated model (cyclohexyl), and $k_{si,θ}$ is the observed rate for the silylated model with a Si-C-C-X dihedral angle of $θ$ (X is the leaving group). This expression is adapted from the mathematics for the dependence of β hydrogen-deuterium isotope effect in which there is a cosine-squared dependence of hyperconjugative contribution on the dihedral angle. By using equation 1, the total rate acceleration of $10^{12}$ for the trans system can be separated into a hyperconjugative factor of about $10^{10}$ and an inductive factor of about $10^2$. Since the inductive effect is orientation independent, for cis system, the same rate acceleration of $10^2$ is suggested for induction and an equal amount for hyperconjugation.
Compared to the theoretical results obtained by Jorgensen and coworkers, the solvolysis results show attenuated rate accelerations (for the trans system, hyperconjugation and induction have been attenuated by factors of $10^9$ and $10^4$ respectively). The different magnitudes of stabilizations can be rationalized by solvent effects on ion stability and the diminished $\beta$ effect for secondary versus primary carbenium ions.

Recently, Lambert and coworkers extended their work to five-membered ring systems in both experimental and theoretical approaches. While an optimal overlap between the $\beta$ C-Si bond and cation p orbital is possible in six-membered rings, it is prevented in five-membered rings due to angular constraints. Five-membered rings can adopt envelope, half-chair (twist), or even planar conformations, so that the dihedral angles are not known. Consequently, reduced $\beta$ silicon participation is expected in the stabilization of positive charge.

The solvolysis rate ratios for the five- and six-membered ring systems 12-15 are shown in Table I. Comparison of the solvolysis of the two ring systems is instructive. Cyclopentyl trifluoroacetate reacts 6.3 times faster than cyclohexyl trifluoroacetate; this may be rationalized by the higher ground state energy of the five-membered ring due to higher angle and eclipsing strain. It is necessary to correct the ground state differences for the comparison of the solvolysis data based on the hyperconjugation theory.

![Chemical Structures]

**Table I.** Rate Ratios of Trifluoroacetates in 97% Trifluoroethanol at 25°C

<table>
<thead>
<tr>
<th>system</th>
<th>$k$, $s^{-1}$</th>
<th>$k_{rel}$</th>
<th>$k_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexyl</td>
<td>$7.10 \times 10^{-10}$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10 (cis, tBu)$^a$</td>
<td>$2.80 \times 10^{-5}$</td>
<td>$4.00 \times 10^4$</td>
<td>1.2</td>
</tr>
<tr>
<td>11 (trans, tBu)$^b$</td>
<td>$1.70 \times 10^3$</td>
<td>$2.40 \times 10^{12}$</td>
<td>$7.30 \times 10^7$</td>
</tr>
<tr>
<td>12 (cis)</td>
<td>$2.40 \times 10^{-5}$</td>
<td>$3.30 \times 10^4$</td>
<td>1</td>
</tr>
<tr>
<td>13 (trans)$^b$</td>
<td>$4.00 \times 10^0$</td>
<td>$5.70 \times 10^9$</td>
<td>$1.70 \times 10^5$</td>
</tr>
<tr>
<td>cyclopentyl</td>
<td>$4.50 \times 10^{-9}$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>14 (cis)</td>
<td>$8.10 \times 10^{-4}$</td>
<td>$1.80 \times 10^5$</td>
<td>1</td>
</tr>
<tr>
<td>15 (trans)</td>
<td>$6.20 \times 10^{-2}$</td>
<td>$1.40 \times 10^7$</td>
<td>75.9</td>
</tr>
</tbody>
</table>

$^a$ Measured in 90% trifluoroethanol. $^b$ Measured as the 3,5-dinitrobenzoate and converted to the trifluoroacetate.
When corrected for ground state differences, the rate enhancement from silicon for the cis five-membered ring is about 5 orders of magnitude, which is a larger enhancement than that for the six-membered ring (both unbiased and biased versions showed rate enhancements of about 4 orders of magnitude). Based on the cosine-squared relationship between the hyperconjugation and the Si-C-C-X dihedral angle, the different rate accelerations indicate that average cis dihedral angle in five-membered ring must be smaller than 60 degrees (calculated value is about 50 degrees). For the trans systems, the five-membered ring shows a rate enhancement of about 7 orders of magnitude which is smaller than that in the six-membered ring. The rate accelerations for unbiased and biased six-membered rings are about 9 and 12 orders of magnitude, respectively. These data indicate that, on average, the trans five-membered ring must have reduced hyperconjugation because of its smaller and less favorable dihedral angle.

The quantitative application of the cosine-squared dependence of the rate enhancement provides an indication of the angular relationship in the five-membered rings, but it only gives a very approximate result.

Considering the difficulties in the experimental examination of five-membered ring conformations, Lambert and coworkers have performed ab initio calculations at the 3-21G*/STO-3G level on the cyclopentyl cation with a β-silyl substituent. This theoretical approach tested for dramatic stabilization when introducing a β-silyl group to the cyclopentyl cation. The stabilization energy is 15.8 kcal/mol when the cation is in the twist form with a pseudoaxial silyl group. A smaller effect (5.6 kcal/mol) is shown by a pseudoequatorial silyl group due to the less favorable dihedral angle for hyperconjugation. Partition of stabilization models by applying the Sunko-Hehre equation suggested the maximum stabilization (i.e., if C-Si bond and empty p orbital are in optimal parallel orientation) is 16.7 kcal/mol, of which 15.8 kcal/mol is from hyperconjugation and 0.9 kcal/mol is from inductive stabilization. Furthermore, the calculated geometries were consistent with hyperconjugation.

**SUBSTITUENTS α TO THE CARBENIUM CARBON**

As shown above, Jorgensen's ab initio study predicted a significant stabilization energy of 38 kcal/mol for β-silyl substituted ethyl cation 5b. While Lambert's solvolysis work measured a rate acceleration of $2.4 \times 10^{12}$ (this figure corresponds to a stabilization energy of about 17 kcal/mol due to the β-trimethylsilyl group) for the biased trans trifluoroacetate 11. In a gas phase experiment, Squires and coworkers estimated that the ethyl cation Me$_3$SiCH$_2$CH$_2^+$ (16) is stabilized by 39 kcal/mol due to β-trimethylsilyl substitution; this is in excellent agreement with Jorgensen's theoretical data (vide supra). The differences of stabilization effects between the sovolysis and the gas-phase systems are shown in Table II. It is believed that solvent effects and
Incomplete charge development in the sovolysis transition state are responsible for these differences, but the major contribution is from the $\alpha$-substituent effects on the carbenium center.

**Table II. Different Evaluations for Stabilization Effects**

<table>
<thead>
<tr>
<th>System</th>
<th>Method</th>
<th>$\Delta E$</th>
<th>Rate Accel.</th>
<th>$\Delta E$</th>
<th>Rate Accel.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_3$SiCH$_2$CH$_2^{+}$ (5)</td>
<td>MP3/6-31G* calc.</td>
<td>38</td>
<td>1.4x10$^{28}$</td>
<td>29</td>
<td>5.4x10$^{22}$</td>
<td>3d</td>
</tr>
<tr>
<td>11</td>
<td>solvolytic expt.</td>
<td>16.9</td>
<td>2.4x10$^{12}$</td>
<td>13.6</td>
<td>1x10$^{10}$</td>
<td>3c</td>
</tr>
<tr>
<td>Me$_3$SiCH$_2$CH$_2^{+}$ (16)</td>
<td>gas phase expt.</td>
<td>39</td>
<td>2.5x10$^{29}$</td>
<td>--</td>
<td>--</td>
<td>4c</td>
</tr>
</tbody>
</table>

Quantitative evaluation of the influence of $\alpha$-substituent effects on the stabilizing ability of $\beta$-silyl group were approached both by theoretical calculations and gas-phase experiments. The ab initio calculations on stabilization energies for primary, secondary and tertiary alkyl cations as well as secondary cyclopropyl cation reveal that the $\beta$-silicon effect is attenuated with increasing methyl substitution $\alpha$ to the carbenium carbon as shown in Table III.

**Table III. Stabilization Energies for Primary, Secondary and Tertiary Carbenium Ions from Ab Initio Calculations at MP2/6-31G* Level**

<table>
<thead>
<tr>
<th>XR$^{+}$</th>
<th>$\Delta E$, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$CH$_2$CH$_2^{+}$ (17)</td>
<td>14.6$^c$</td>
</tr>
<tr>
<td>H$_3$SiCH$_2$CH$_2^{+}$ (5)</td>
<td>33.2$^c$</td>
</tr>
<tr>
<td>CH$_3$CH$_2$C$^+$CH$_3$ (18)</td>
<td>6.6</td>
</tr>
<tr>
<td>H$_3$SiCH$_2$C$^+$CH$_3$ (19)</td>
<td>22.1</td>
</tr>
<tr>
<td>CH$_3$CH$_2$C$^+$(CH$_3$)$_2$ (20)</td>
<td>5.0</td>
</tr>
<tr>
<td>H$_3$SiCH$_2$C$^+$(CH$_3$)$_2$ (21)</td>
<td>15.9</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>8.6</td>
</tr>
<tr>
<td>H$_3$Si</td>
<td>17.5</td>
</tr>
</tbody>
</table>

$^a$ X = CH$_3$, SiH$_3$. $^b$ $\Delta E$ for the equation XR$^{+}$ + CH$_4$ $\rightarrow$ HR$^{+}$ + XCH$_3$. $^c$ Reference 3d.

Compared to the $\beta$-methyl group, the $\beta$-silyl group provides greater stabilization, which are reflected in calculated geometric structures of $\beta$-silyl substituted carbenium ions. This may be
related to less beneficial hyperconjugation of the β-methyl group compared to that of β-silyl system.

For cyclopropyl cations 22 and 23, the stabilizations due to β-methyl and β-silyl groups are greater and less than those for secondary cations 18 and 19, respectively. The β-silyl results can be rationalized by a diminished hyperconjugative component due to less than optimal orbital alignment in the cyclopropyl ring. While, for β-methyl, the larger stabilization (compared to that of 18) reflects the intrinsic stabilizing ability of alkyl groups to small rings.

For the tertiary carbenium ions, the β effect is further reduced because more methyl groups are α to the cationic carbon. The decline in the β effect for primary, secondary and tertiary cations is apparent in the calculated structural results.

The theoretical predictions for α-substituents reducing the β effect are also supported by gas-phase experiments. High-pressure mass spectrometry has been used to study the properties of the association complex of trimethylsilyl (Me₃Si⁺) with a variety of alkenes. From these experiments, the enthalpy of formation of Me₃Si-alkene⁺, and further, the extent of β-silicon effect can be obtained. The absolute values of β-silicon stabilization energies in β-trimethylsilyl carbenium ions (Me₃SiR⁺) are shown in Table IV.

Table IV. Stabilization Energies for Me₃SiR⁺ (R = alkene)

<table>
<thead>
<tr>
<th>Me₃SiR⁺</th>
<th>ΔEᵃ, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₃SiCH₂CH₂⁺ (24)</td>
<td>48.2ᵇ</td>
</tr>
<tr>
<td>Me₃SiCH₂C⁺HCH₃ (25)</td>
<td>38.4</td>
</tr>
<tr>
<td>Me₃SiCH(CH₃)C⁺HCH₃ (26)</td>
<td>38.2</td>
</tr>
<tr>
<td>Me₃SiCH₂C⁺(CH₃)₂ (27)</td>
<td>28.1</td>
</tr>
<tr>
<td>Me₃SiCH(CH₃)C⁺(CH₃)₂ (28)</td>
<td>28.8</td>
</tr>
<tr>
<td>Me₃SiC(CH₃)₂C⁺(CH₃)₂ (29)</td>
<td>25.8</td>
</tr>
<tr>
<td>Me₃SiCH₂C⁺HC₆H₅ (30)</td>
<td>21.8</td>
</tr>
</tbody>
</table>

ᵃ ΔE for the equation Me₃SiR⁺ + RH₂ → HR⁺ + Me₃SiRH. ᵇ Calculated to a bridged structure.

The data show both the magnitude of stabilization energies and the concomitant decline in ΔE caused by α-methyl or phenyl groups; this is consistent with the order of increase in stabilization afforded by the type and number of substitutions on the carbenium carbon. The
consistent decrease of about 10 kcal/mol in the \( \beta \) effect with the addition of each successive \( \alpha \)-methyl group might be the result of delocalization of positive charge away from the carbenium carbon caused by \( \alpha \)-methyl groups. The effect of \( \alpha \)-phenyl is significantly larger than that of two \( \alpha \)-methyl groups as shown in compounds 28 and 30. These values do present a consistent picture for the effect of \( \alpha \)-substituents, but the uncertainties call for further determinations. The uncertainties of \( \pm 10 \) kcal/mol for absolute values and about \( \pm 5 \) kcal/mol for relative values are caused by the uncertainties in the enthalpies of formation of \( \beta \)-silicon-containing cations and molecules.

The quantitative description of the effect of substituents \( \alpha \) to carbenium carbon in gas phase might be helpful to provide insight into solvolytic experiments, which usually involve compounds with \( \alpha \)-substituents.

**EFFECTS OF LIGANDS ON SILICON**

Since the \( \beta \)-silicon stabilization stems from the electropositive (i.e. metallic) character of silicon,\(^1c,2d,8\) the electronic nature of the silyl group should be an important factor in its stabilizing ability. Some experimental results have provided indirect evidence for the influence of ligands attached to silicon on the \( \beta \) effect.\(^2d,9,10\) However, until recently only a few studies have directly focused on the relationship of the ligands on silicon to the degree of \( \beta \)-carbocation stabilization.\(^5\)

Brook and coworkers have examined the stabilizing ability of silyl groups bearing a variety of different ligands in the addition of bromine to silylstyrenes (Scheme I).\(^5a,b\)

**Scheme I**

The fluoride-induced eliminations, performed in CDCl\(_3\) using Bu\(_4\)NF as the fluoride source, takes place in an *anti* fashion as is the usual case. The important feature of the reaction of this styrene system is the changes of *syn/anti* addition ratios; this is balanced by the relative stability of cations 32 and 33. For instance, methylstyrene (\( R = \text{Ph}, R' = \text{Me}, \) with only the phenyl group providing stabilization to cation 33) shows 95/5 of *anti*- and *syn*-additions; this indicates the primary addition route: *anti* attack on the bromonium ion 32. In contrast, with the extra stabilization afforded by \( \beta \) silyl group, (trimethylsilyl)styrene shows 100% *syn*-addition via
the stabilized carbenium ion 33. Therefore, the degree of syn-addition can be used as a measure of the stabilizing ability of nearby groups including silyl groups.

The ratios of syn/anti addition of bromine to a series of (halomethylsilyl)styrenes (31a-31g in Table V) show a good correlation between the electron-withdrawing ability of the ligands on silicon and the degree of syn-addition. The syn/anti addition ratios increase as the ligands on silicon become more electron donating. This electronegativity/syn-addition correlation provides a quantitative description for the argument based on the hyperconjugation mechanism: as electron-donating groups are placed on silicon, which lowers the electronegativity of silicon, the Cδ-Siδ+ bond becomes more polarized, and thus the β effect will be more significant.

**Table V. Degree of syn-Addition vs. Group Electronegativity**

<table>
<thead>
<tr>
<th>β-silylstyrene</th>
<th>SiXYZ</th>
<th>%syn-addition</th>
<th>group electroneg.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>(halomethylsilyl)styrene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31a</td>
<td>SiMe3</td>
<td>100</td>
<td>2.06</td>
</tr>
<tr>
<td>31b</td>
<td>SiMe2Cl</td>
<td>100</td>
<td>2.12</td>
</tr>
<tr>
<td>31c</td>
<td>SiMe2F</td>
<td>85</td>
<td>2.18</td>
</tr>
<tr>
<td>31d</td>
<td>SiMeCl2</td>
<td>75</td>
<td>2.19</td>
</tr>
<tr>
<td>31e</td>
<td>SiCl3</td>
<td>55</td>
<td>2.26</td>
</tr>
<tr>
<td>31f</td>
<td>SiMeF2</td>
<td>40</td>
<td>2.32</td>
</tr>
<tr>
<td>31g</td>
<td>SiF3</td>
<td>15</td>
<td>2.47</td>
</tr>
<tr>
<td>(alkoxy/phenoxysilyl)styrene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31h</td>
<td>Si(OMe)3</td>
<td>80</td>
<td>2.46</td>
</tr>
<tr>
<td>31i</td>
<td>Si(OPh)3</td>
<td>85</td>
<td>2.48</td>
</tr>
<tr>
<td>31j</td>
<td>Si(OC6H4OMe-p)3</td>
<td>85</td>
<td>2.48</td>
</tr>
<tr>
<td>31k</td>
<td>Si(OC6H4Cl-p)3</td>
<td>80</td>
<td>2.48</td>
</tr>
</tbody>
</table>

However, in the case of (alkoxy/phenoxysilyl)styrenes 31h-31k (as shown in Table V), a quite different relationship exists. The silyl groups bearing alkoxy or phenoxy ligands show an enhanced β effect compared to halomethylsilyl groups. The deviations from the electronegativity correlation could be just an artifact of an insufficiently sophisticated electronegativity model, the steric bulk of the silyl group or the through-space interaction of oxygen lone pairs with the empty p orbital of carbenium ion. To determine the reasons for the deviation, further examination is required.

**CONCLUSION**

The influences of structural changes on the extent of the β-silicon effect have been approached quantitatively both in experimental and theoretical studies. It has been shown that hyperconjugation from β-organosilicon functional groups provide the major contribution to their
stabilization of carbenium ions. The electronic structural changes at the position $\alpha$ to a cationic center and on the silyl groups both have significant effect on the apparent silyl stabilizing ability. To increase mechanistic understanding and synthetic utility, further quantitative investigations on solvent effects, steric bulk of the $\beta$-silyl groups and $\alpha$-substituents might be interesting.

REFERENCES


ASYMMETRIC GRIGNARD ADDITIONS IN CHIRAL ETHER SOLVENTS

Reported by Patrick G. Murray  
November 12, 1990

INTRODUCTION

Among the many carbon-carbon bond forming reactions known, perhaps the most studied and most useful involve the addition of reactive organometallic nucleophiles to carbonyl compounds. The original reaction, pioneered by Victor Grignard in the early 1900's, utilized organozinc and organomagnesium reagents as carbon nucleophiles. Later, organolithium reagents extended the scope of this reaction, and it has since become a mainstay in modern synthetic methodology. Advances in asymmetric synthesis in recent years have further increased the usefulness of this fundamental organic reaction.

Given the widespread use of Grignard type reactions, surprisingly little is known about the structure of the organometallic in ether solution\(^1\) or the reaction mechanism.\(^2\) The polar-covalent carbon-metal bond results in a rather negatively charged carbon species, typically represented as \(\delta^\cdot\text{RMgX}\delta^+\). The actual species present in ether solution, though, is best described by the Schlenk equilibrium,\(^3\) (Scheme I) where the position of equilibrium depends on R, X, solvent, concentration, and temperature, but usually lies to the left.

Scheme I

\[
2 \text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2 \rightleftharpoons \text{R}_2\text{Mg} : \text{MgX}_2
\]

In a chiral environment, achiral reagents and prochiral substrates may react to afford optically enriched products. Grignard reagents, for example, can add asymmetrically to carbonyl compounds in the presence of a chiral solvent. Such chiral solvents induce diastereomeric transition states, and this transition state non-equivalence results in the preferential formation of one enantiomer of product. Presented herein is a survey of asymmetric additions to carbonyl compounds involving Grignard reagents, where optical activity is induced through the agency of chiral ethereal solvents.

EARLY DIMETHOXYBUTANE AND CARBOHYDRATE ETHERS

Cohen and Wright reported\(^4\) in 1952 the preparation of optically pure 1,2-dimethoxyethane and 2,3-dimethoxybutane (I) and subsequent utilization of these chiral...
ethers to induce optical activity in Grignard additions. The ethers were prepared as shown in Scheme II.

Scheme II

![Chemical structure](image)

Cohen and Wright used the $(R,R)$-$(+)$-2,3-dimethoxybutane (1) ether in benzene to achieve product enriched approximately 5% in $(R)$-alcohol (2) from the reaction between ethylmagnesium chloride and ethyl benzoyleformate (Scheme III). The Grignard reagent was added slowly to a solution of the ketoester (inverse addition) to afford product in 30% yield. The same reaction with ethylmagnesium bromide gave only slight (ca. 2%) asymmetric induction.

Scheme III

![Chemical structure](image)

From these and similar studies, it was suggested that because a single equivalent of the chiral ether was as effective as a large excess, a 1:1:1 coordination complex was forming between the organometallic species, the solvent, and the benzoyleformate (Figure 1). Although such a model is not useful for ascribing the origin of asymmetric induction in the system, it may have been intended only to describe the nature of the complex. In any event, it mandated a better understanding of the reaction transition state and the structure of the Grignard reagent.

While the investigators suggested that the ether must contain at least two coordination sites in order for asymmetric induction to occur, no attempts were made to correlate the stereochemistry of the chiral ether to the rotations observed in the product.
Cohen and Allentoff\textsuperscript{5} in 1957 further explored asymmetric Grignard additions in optically active ether solvents. It was postulated by these authors that perhaps the carboethoxy group in the benzoylformate system (vide supra) might also be participating in coordination of the metal, thus obscuring interpretation of the role of ether solvent in complexation. To eliminate this possibility, the synthesis of 2-phenyl-2-butanol in the same chiral 2,3-dimethoxybutane solvent was chosen for study. This product was selected because it had been previously resolved (and thus the rotation was known) and because it was accessible by two paths: reaction of ethylmagnesium bromide with acetophenone, or reaction of phenylmagnesium bromide with 2-butanone. Results from these experiments are presented in Table I.

Table I. Grignard addition in (R,R)-2,3-dimethoxybutane

<table>
<thead>
<tr>
<th>Grignard</th>
<th>ketone</th>
<th>ether</th>
<th>% yield</th>
<th>% e.e.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ethylbromide</td>
<td>acetophenone</td>
<td>Et\textsubscript{2}O</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethylbromide</td>
<td>acetophenone</td>
<td>2,3-DMB</td>
<td>45</td>
<td>3.60 (R)</td>
<td></td>
</tr>
<tr>
<td>bromobenzene</td>
<td>2-butanone</td>
<td>2,3-DMB</td>
<td>54</td>
<td>17.4 (R)</td>
<td></td>
</tr>
</tbody>
</table>

While the overall yields for the reactions are significantly lower in the chiral bis-ether solvent (attributed to precipitation of the magnesium halide), modest enantioselectivity is achieved in the bromobenzene / 2-butanone system. The authors suggest that if a 1:1:1 Grignard:ketone:ether complex is operating, steric preferences widen the energy gap between the two diastereomeric transition states in the case where phenyl is transferred. Thus, the reversible formation of the diastereomeric complex in the transitions state leads to optically enriched product to a greater extent for the bromobenzene / 2-butanone system.

While the explanation does not rationalize enantioselectivity, the authors thus explain the trend that optical activity in the product increases as the size of the organic group on the Grignard reagent becomes larger. One explanation is that as the ketone approaches the
ether-coordinated magnesium atom of the Grignard reagent and begins to complex with it, one of the already coordinated ether oxygens is displaced. In the optimum situation, this displaced arm of the chiral ether could conceivably permit steric discrimination between the re and si faces of the carbonyl compound during the transition state. A number of similar but stereochemically non-productive displacements are also possible, and perhaps serve to dilute enantioselectivity.

Inch\textsuperscript{6} in 1969 recognized the potential for suitable substituted carbohydrates to promote asymmetric induction, and conducted a series of Grignard reactions in benzene using the glucofuranose derived polyether (3) as a cosolvent. Table II reports the overall yield and enantioselectivity for these additions.

![Image](image.png)

\textbf{Table II. Grignard additions in carbohydrate-benzene solvent}

<table>
<thead>
<tr>
<th>Grignard</th>
<th>substrate</th>
<th>% yield</th>
<th>% e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{3}MgBr</td>
<td>C\textsubscript{6}H\textsubscript{5}COC\textsubscript{6}H\textsubscript{11}</td>
<td>95</td>
<td>70 (R)</td>
</tr>
<tr>
<td>CH\textsubscript{3}MgI</td>
<td>C\textsubscript{6}H\textsubscript{5}COC\textsubscript{6}H\textsubscript{11}</td>
<td>88</td>
<td>65 (R)</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{11}MgBr</td>
<td>C\textsubscript{6}H\textsubscript{5}COCH\textsubscript{3}</td>
<td>50</td>
<td>28 (S)</td>
</tr>
<tr>
<td>EtMgBr</td>
<td>C\textsubscript{6}H\textsubscript{5}COCH\textsubscript{3}</td>
<td>45</td>
<td>27 (S)</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}MgBr</td>
<td>C\textsubscript{6}H\textsubscript{11}COCH\textsubscript{3}</td>
<td>60</td>
<td>26 (S)</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}MgBr</td>
<td>C\textsubscript{6}H\textsubscript{5}CHO</td>
<td>81</td>
<td>24 (R)</td>
</tr>
<tr>
<td>CH\textsubscript{3}MgBr</td>
<td>C\textsubscript{6}H\textsubscript{5}COEt</td>
<td>70</td>
<td>24 (R)</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}MgBr</td>
<td>CH\textsubscript{3}COEt</td>
<td>70</td>
<td>10 (S)</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}MgBr</td>
<td>C\textsubscript{2}H\textsubscript{5}CHO</td>
<td>60</td>
<td>9 (R)</td>
</tr>
</tbody>
</table>

The 1,2:5,6-di-O-isopropylidene-\textalpha-D-glucofuranose solvent modifier was first allowed to react with 1 equivalent of Grignard reagent (to presumably form the 3-OMg derivative). The chiral Grignard-carbohydrate complex is then formed upon addition of a second equivalent of RMgX. Earlier rotation studies\textsuperscript{7} of chiral ethers support the formation
of a chiral Grignard-sugar complex, which probably coordinates with the carbonyl oxygen of the substrate during reaction. This chiral coordination complex then allows addition to occur with facial selectivity. Although structurally complex, the polyether 3 may operate simply as a bulky but chiral tetrahydrofuran (vide infra).

**TARTRATE AND TETRAHYDOFURAN DERIVED CHIRAL ETHERS**

Bruer and Haller\(^8\) reported enantioselective Grignard type additions with organocadmium reagents in the presence of \((2R, 3R)-(+)\)-diisopropyl-\(O,O\)-dimethyltartrate (4).

![Image of compound 4]

In the best case, addition of diphenylcadmium to propanal produced \((R)\)-1-phenyl-1-propanol in 2.5% optical purity. The chirality transfer may be muted in this system because of competing complexation of the Grignard reagent with the ester oxygens, resulting in low asymmetric induction.

Based on reports of Grignard reagents associating more strongly with tetrahydrofuran than with non-cyclic ethers,\(^9\) Iffland and Davis\(^10\) prepared optically active 2-methyltetrahydrofuran (5) by the route illustrated in Scheme IV for use as a chiral solvent in a number of Grignard reactions.

**Scheme IV**

![Scheme IV diagram]

Enantioselectivities were again rather modest; in the best case, the reaction of phenylmagnesium bromide with pivaldehyde in \((S)\)-5 afforded \((R)\)-2,2-dimethyl-1-phenyl-1-propanol in 11% optical purity. Interesting as well is that when the Grignard reagent was prepared initially in diethyl ether, and the chiral 2-methyltetrahydrofuran added before the
reaction was allowed to take place, lower optical purity in the product resulted. The authors suggested that perhaps the THF solvents are not as effective solvators of Grignard reagents as presumed, and suggested thermodynamic studies of the relative basicities of 2-methyltetrahydrofuran and tetrahydrofuran.

The enantioselectivity observed using 5 as a chiral solvent might be rationalized with a mechanism analogous to that proposed for the early dimethoxybutane solvents.\textsuperscript{4,5} For example, upon displacement of one coordinating THF molecule from the Grignard reagent by the approaching aldehyde, a steric bias induced by the relative position of the other THF molecule (still coordinated) could permit preferential approach of the \textit{re} face of the aldehyde. Thus, one might expect a bis-THF molecule (6) or a more conformationally rigid solvator like the bi-\textbeta–naphthol derived ether (7) to enhance enantioselectivity even further.

\begin{center}
\begin{tikzpicture}
\node (image) at (0,0) {\includegraphics[width=0.5\textwidth]{image.png}};
\end{tikzpicture}
\end{center}

\textbf{CHIRAL AMINO ETHERS}

In 1969, Seebach\textsuperscript{11} synthesized the diethyltartrate derived \((S,S)-(+)\)-2,3-dimethoxy-\(N,N,N',N'\)-tetramethyl-1,4-diaminobutane (8).

\begin{center}
\begin{tikzpicture}
\node (image) at (0,0) {\includegraphics[width=0.2\textwidth]{image.png}};
\end{tikzpicture}
\end{center}

The investigations with this solvent were unique in that nitrogen atoms had been incorporated into the chiral ether to aid complexation and coordination. Also, additions were performed with organolithium reagents, which differ in coordination, aggregation behavior and reactivity from the corresponding magnesium compounds in ether solution.\textsuperscript{12,13} Results of butyllithium addition to various carbonyl compounds in the presence of 8 are reproduced in Table III.
Table III. Butyllithium additions to aldehydes with (S,S)-8 in pentane

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>eq 8/BuLi</th>
<th>Temp (°C)</th>
<th>% e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅CHO</td>
<td>8</td>
<td>-78</td>
<td>20.2 (R)</td>
</tr>
<tr>
<td>C₆H₅CHO</td>
<td>15</td>
<td>-78</td>
<td>20.6 (R)</td>
</tr>
<tr>
<td>C₆H₅CHO</td>
<td>2</td>
<td>-120</td>
<td>22.3 (R)</td>
</tr>
<tr>
<td>C₆H₅CHO</td>
<td>4</td>
<td>-120</td>
<td>25.0 (R)</td>
</tr>
<tr>
<td>C₆H₅CHO</td>
<td>9</td>
<td>-130</td>
<td>33.0 (R)</td>
</tr>
<tr>
<td>CH₃CHO</td>
<td>2</td>
<td>-120</td>
<td>14.0 (S)</td>
</tr>
<tr>
<td>C₂H₅CHO</td>
<td>2</td>
<td>-120</td>
<td>19.0 (S)</td>
</tr>
<tr>
<td>(CH₃)₂CHCHO</td>
<td>2</td>
<td>-120</td>
<td>22.0 (R)</td>
</tr>
</tbody>
</table>

As shown, optical activity resulted in all cases, but optical yields varied. The highest selectivity was obtained at -130 °C with benzaldehyde using a chiral ether to butyllithium ratio of 9:1. While Seebach deemed mechanistic conclusions unjustified in this preliminary study, describing the origin of enantioselectivity in these systems in general may not be straightforward, since the concentration of 8 effects optical purity in the product, especially at low temperatures. In any event, the additional amino coordination sites do not appear to improve enantioselectivity drastically; the highly congested environment about the asymmetrically solvated lithium species may be detrimental to increased enantioselectivity.

Seebach¹⁴ later found that (-)-1,2,3,4-tetramethoxybutane (9) gave yet higher enantioselectivity in some cases than even 8. For example, this solvent afforded (R)-1-phenyl-1-pentanol in 29% e.e. upon addition of butyllithium to benzaldehyde, and 45% e.e. when butyllithium was added to o-tolyl aldehyde.

In 1979, Seebach¹⁵ expanded the number of approaches to developing chiral ether solvents designed for enantioselective Grignard. Three new chiral ethers were developed, the structures of which are shown in Figure 2.
The $C_2$ axis of symmetry associated with 8 was removed (10), the nitrogen atom was converted to a center of chirality upon complexation with a metal atom (11), and the number of heteroatoms was increased, in an attempt to produce more stable complexes (12). Results of the reaction of butyllithium with benzaldehyde at -78 °C in each of the new chiral amino ethers are given in Table IV. Reactions were on a 10 mmol scale, and the ratio of aldehyde and the total reaction volume (dilution with pentane) were varied.

**Table IV. Effect on enantioselectivity of amino ether, concentration of aldehyde, and reaction volume for butyllithium addition to benzaldehyde**

<table>
<thead>
<tr>
<th>amino ether</th>
<th>equiv. aldehyde</th>
<th>total vol. (mL)</th>
<th>% e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10</td>
<td>40</td>
<td>34 (R)</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>400</td>
<td>29 (R)</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>40</td>
<td>30 (R)</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>400</td>
<td>30 (R)</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>100</td>
<td>38 (S)</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>400</td>
<td>52 (S)</td>
</tr>
</tbody>
</table>

As indicated, moderately high enantioselectivity is obtained when 12 is utilized in a 2:1 molar ratio to aldehyde in somewhat more dilute pentane solution. Interestingly, 12 promoted preferential $si$-face attack with all aldehydes and organolithium compounds
studied. Seebach has proposed a model to account for the observed facial selectivity (Figure 3).

Thus, to the extent that the less hindered face of the aldehyde can more easily approach the organolithium species, asymmetric induction will occur. This model does not invoke coordination of the substrate carbonyl oxygen to lithium, and so differs from the model proposed for the magnesium Grignard additions. If complexation occurs in a fashion similar to that represented in Figure 3, it seems that the chiral amino ethers contain much superfluous functionality. However, the additional steric bulk associated with the stereocenters may serve to direct approach of the incoming carbonyl compound.

In 1983, Jalander and Strandburg\textsuperscript{16} successfully used (-)-1-isopropyl-2-methoxy-4-methylcyclohexane to induce a 19.4 % e.e. in the addition of phenylmagnesium bromide to 2,2-dimethylpropanal. This chiral ether solvent was prepared by methylation of (-)-menthol. No attempts were made to rationalize either the observed stereoselectivity or the absolute configuration of the preferentially formed enantiomer.

\textbf{CONCLUSION}

Although early attempts to promote asymmetric induction in Grignard additions to prochiral carbonyl compounds using chiral ether solvents met with marginal success, the experiments did demonstrate the potential viability of the technique. More dramatic increases in facial selectivity became possible with the incorporation of amino functionality into the chiral ethers and the use of organolithium nucleophiles. Also, the effect of factors such as concentration of the chiral ether, temperature, and the structure of both the Grignard reagent and the substrate were shown to bear upon observed enantioselectivity. Although the chiral ether solvents have been utilized in a few synthetic applications,\textsuperscript{17,18}
Further enantioselectivity is necessary before chiral ether solvents will be used routinely to
effect asymmetric additions to carbonyl compounds in Grignard reactions.

REFERENCES

(3) Schlenk and Schlenk, Ber. 1929, 62B, 920.
(17) ibid., 15-19.
ASYMMETRIC CONJUGATE ADDITION REACTIONS MEDIATED BY CHIRAL ORGANOMETALLICS

Reported by Chien-Tien Chen November 15, 1990

INTRODUCTION

The organometallic reagent mediated addition to a carbon-carbon double bond of an \( \alpha, \beta \)-unsaturated carbonyl compound, a process known as 1,4-conjugate addition, is a versatile synthetic method. It provides a general and reliable method for constructing new carbon-carbon bonds \( \beta \) to a carbonyl functional group, with the type and variety of ligands that can be transferred to the \( \alpha, \beta \)-unsaturated carbonyl compound complementing the stabilized carbanions used in the Michael reaction. The versatility of this reaction has prompted numerous investigators to search for methods to effect the conjugate addition process with asymmetric induction.\(^1\) These efforts have focused on four strategies utilizing (1) chiral coordinating ligands, (2) homocuprates and heterocuprates with a chiral nontransferable ligand (RL\(^*\)CuM), (3) cuprates containing a chiral transferable ligand (R\(^*\)LCuM), and (4) chiral substrates. This abstract will discuss the mechanistic aspects of strategies (1) - (3) as well as the catalytic asymmetric conjugate addition of organometallic reagents to \( \alpha, \beta \)-unsaturated carbonyl compounds.

MECHANISTIC VIEWPOINTS

Reversible d, \( \pi^* \) - Complexation, \( \beta \)-Cupration Sequence Pathway

Despite the fact that copper-mediated conjugate additions of carbon nucleophiles to \( \alpha, \beta \)-enones has been widely used in synthesis, the mechanistic details of the reaction are unclear. The intermediacy of a copper (III)-\( \beta \)-adduct, which can undergo C-C bond formation by reductive elimination is generally accepted, even though it lacks direct experimental support.

Recently, Corey and co-workers reported\(^2\) that treatment of 1 with dimethylcuprate in THF gave a mixture of two adducts, 2 and 3 in a ratio of 92:8 (Scheme I). This result was surprising, since a predominance of 3 was expected based on a stereoelectronic effect,\(^3\) in which the oxygen atom removes electron density hyperconjugatively from the d (Cu), \( \pi_3^* \) - complex or the Cu (III) \( \beta \)-adduct. This result has been explained by reversible formation of syn and anti copper-enone complexes, with a faster rate of product formation from the syn d, \( \pi^* \) - complex. It was observed that in the presence of 5 equivalents of TMSCl the reaction rate increased and only the anti product was obtained (ratio 3:2 > 99:1). In addition, in toluene-THF 20:1 the reaction of 1 with lithium dimethylcuprate was not stereoselective (2:3 = 1:1), but became specific for 3 in the presence of TMSCl. Without TMSCl in THF the syn d, \( \pi^* \)-complex goes on to syn copper (III) \( \beta \)-adduct and

Copyright © 1990 by Chien-Tien Chen
hence to product more rapidly than the predominant anti d, π*-complex, probably due to steric reasons. In the presence of TMSCl the predominant anti complex is rapidly trapped and converted to 3.

Further studies demonstrating the reversible formation of a copper (III)-β-adduct have been conducted in the same group. By treating Z-enone 4 with 2 equivalents of lithium dimethylcuprate no significant amount of 1,4-adduct was detected, however, an equilibrium mixture of 98 : 2 E : Z-enone was obtained (Scheme II). In the presence of TMSCl 41% of the enone was recovered in a ratio 5 : 95 E : Z together with 59% of 1,4-adduct. This result clearly indicates a common intermediate for both processes, which is the copper (III) β-adduct reversibly formed in the absence of TMSCl.

Scheme II

Stereochemical Difference Between One And Two-Electron Processes

The stereochemistry of nucleophilic and electrophilic reactions has been widely investigated, and theoretical studies have recently been carried out. Yamamoto and co-workers have reported a stereochemical difference between a nucleophilic process and an electron-transfer process in an acyclic system. Two Michael acceptors (6 and 7) bearing a stereogenic center at the γ-position were employed in nucleophilic and free radical additions with organometallic reagents. The diastereoselectivities of 6 and 7 with various organometallic reagents are shown in Table I.

It was reasoned that the reversal of diastereoselectivity in the addition of organocoppers and other organometallic reagents (entries 3 and 4; anti selective) to 6 was an indication of an electron transfer process. A similar explanation can account for the reversal of diastereoselectivity in entries
5 and 6. Both MeCu and R_2CuLi can produce the radical anion of 6, however, only R_2CuLi, the stronger reductant, can produce the radical anion of 7 due to its more negative E_{red}. On the other hand, the diastereoselectivity observed in the methylcopper addition to 7, as well as the stereoselectivity in entries 3 and 4, can be predicted from nucleophilic addition (vide infra).

Table I

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>RM</th>
<th>Temp. (°C)</th>
<th>pDNB (equiv)</th>
<th>Products</th>
<th>syn/anti</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>MeCu</td>
<td>-78→20</td>
<td>0</td>
<td>77/23</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Me_2CuLi</td>
<td>-78→20</td>
<td>0</td>
<td>87/13</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Me_3AlLi</td>
<td>-78→0</td>
<td>0</td>
<td>37/63</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>AllylSnBu_3 + TiCl_4</td>
<td>-78→20</td>
<td>0</td>
<td>29/71</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>MeCu</td>
<td>-78→20</td>
<td>0</td>
<td>38/62</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Me_2CuLi</td>
<td>-78→20</td>
<td>0</td>
<td>62/38</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>MeCu</td>
<td>-78</td>
<td>3</td>
<td>33/67</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>Me_2CuLi</td>
<td>-78</td>
<td>3</td>
<td>33/67</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>Me_2CuLi</td>
<td>-78</td>
<td>1</td>
<td>39/61</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>Bu_2CuLi</td>
<td>-78</td>
<td>1</td>
<td>39/61</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

A change from syn to anti selectivity was observed by conducting the cuprate reactions in the presence of p-dinitrobenzene (pDNB) (entries 7-10). Due to its electron-accepting ability, pDNB was proposed to accept an electron from MeCu and the cuprates thus preventing the formation of the radical anions of 6 and 7. Predominance of the anti isomer in the nucleophilic additions of organometallic reagents (entries 3-5 and 7-10) can be explained via 8 (a modified Felkin model). In the radical anion intermediate 9, the interaction between HOMO of substrate and R* group dictates the stereoselectivity (electrophilic-like attack)\(^5\) (Scheme III).

Scheme III

CHIRAL COORDINATING LIGANDS

In the early 1970's, Kretchmer reported\(^7\) the first attempt to effect asymmetric induction in organocopper conjugate addition reactions with limited success (3-6% e.e.). Seebach and co-
workers observed higher asymmetric induction (up to 58% e.e.) for various organometallics employing chiral amino ethers.

The use of 4-(alkylthio)methoxyproline derivatives as tridentate coordinating ligands afforded conjugate addition products with e.e.'s as high as 94%. The simultaneous chelation of copper and lithium in the reacting species accounted for the high enantioselectivity. Similarly, Koga applied chiral (tridentate) ligand 11, derived from 2-phenylalanine, to the enantioselective conjugate addition reaction of the dithioacetal derivatives 10 with α, β-unsaturated esters, providing 12 with up to 67% e.e. (Scheme IV).

**Scheme IV**

![Scheme IV](image)

Tomioka has reported a $C_2$ symmetric chiral diether as the chelating ligand in the conjugate addition of organolithium reagents to α,β-unsaturated aldimines (Scheme V). High asymmetric induction was observed with both cyclic and acyclic α, β-unsaturated aldimines, thus demonstrating for the first time the potential generality of this method.

**Scheme V**

![Scheme V](image)

The stereochemical outcome of this reaction was rationalized on the basis of intermediate complex 15. In this complex, the organolithium forms a five-membered chelated complex with 13, in which four substituents take an all-trans arrangement due to steric factors. The lone pair of nitrogen coordinates to the fourth coordination site of lithium, leading to favorable complex 15 and unfavorable complex 16 (Scheme VI). In complex 15, the N-cyclohexyl bond would be syn to the Li-O1 bond so that the R group of the organolithium attacking the sp$^2$ carbon of the aldimine from the bottom face is favored. The alternative complex 16, with the N-cyclohexyl bond syn to the Li-O2 bond, is not favored due to steric hindrance.
CUPRATES CONTAINING A CHIRAL NONTRANSFERABLE LIGAND

An early study of heterocuprates R(Het) CuLi by Crabbe\textsuperscript{13} used the alcoholates of (-)-N-methylephedrine and 1,2:5,6-di-O-isopropylidine-\alpha-D-glucofuranose as chiral ligands (Het), however, very low enantiomeric excesses of conjugate addition products were observed. Better results with heterocuprates coordinated by oxygen were reported by Huche\textsuperscript{14} who observed a 34\% e.e. for the methylated product from chalcone. Mixed cuprates RR*CuLi have been studied by Gustafsson and Nilsson\textsuperscript{15} with disappointing results.

The sensitivity of the optical yields to substrate structure, chiral ligand, cuprate composition, solvent, and external ligands noted in the previous studies makes it difficult to determine the exact parameters responsible for the high stereoselectivity. For instance, Bertz and co-workers performed\textsuperscript{16} a series of studies with chiral amidocuprates, however only (R)-or (S)-\alpha-methylbenzylamine and (4S, 5S)-(+) 5-amino-2, 2-dimethyl-4-phenyl-1, 3-dioxane derived chiral organocuprates afforded conjugate addition products with moderate enantioselectivities (50\% e.e.).

In certain situations, much higher optical yields have been recorded. Based on the results that chiral pyrrolidine derivatives were effective in inducing highly enantioselective additions of organometallic reagents to carbonyl compounds,\textsuperscript{17} the use of (S)-1-methyl-2-hydroxymethylpyrrolidine and cuprous salt in the addition of methyl Grignard to chalcone was investigated by Mukaiyama.\textsuperscript{18} An interesting result of the investigation was that both (E)- and (Z)-isomers of chalcone afforded product with the same absolute configuration (S). These results suggest that both reactions involve the same radical anion intermediate generated by one-electron transfer from the cuprate to the enone.

Leyendecker and co-workers reinvestigated\textsuperscript{19} this reaction and obtained products with 88\% e.e. under more dilute condition. Higher optical yields achieved upon dilution suggested the importance of an internally chelated species.

Corey et al. have demonstrated\textsuperscript{20} that a well devised chiral controlling ligand 17 can accomplish conjugate addition reactions with high enantioselectivity (75-95\% e.e.). The results have been rationalized in terms of complexes\textsuperscript{18} (Scheme VII). In these models lithium is chelated by the conjugate base of 17 as a tridentate ligand and associated with an alkylcopper fragment. Selective approach to the re face of C(3) in 2-cyclohexenone is proposed to occur such
that nucleophilic copper forms a $d, \pi^*$-complex as the carbonyl oxygen coordinates either with the lithium ion in the complex 18b or with a second lithium ion in the complex 18a, held in place by the alkoxy group in 17. The alternative pathway involving attack by Cu on the $si$ face of C(3) in 2-cyclohexenone is clearly less favorable for steric reasons.

**Scheme VII**

![Scheme VII](image)

An elegant approach reported by Dieter21 employed organo (hetero) cuprates with $L$-proline derived chiral ligands as the enantioselective control element (Table II). The stereochemical outcome of this reaction can be rationalized by a model with three basic assumptions and postulates

**Table II**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>X</th>
<th>temp., °C</th>
<th>solvent</th>
<th>e.e. (%)</th>
<th>config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>OCH$_3$</td>
<td>-78</td>
<td>Et$_2$O</td>
<td>83</td>
<td>$S$</td>
</tr>
<tr>
<td>2</td>
<td>$n$-Bu</td>
<td>OCH$_3$</td>
<td>-78</td>
<td>Et$_2$O</td>
<td>56</td>
<td>$S$</td>
</tr>
<tr>
<td>3</td>
<td>tert-Bu</td>
<td>OCH$_3$</td>
<td>-78</td>
<td>Et$_2$O</td>
<td>67</td>
<td>$S$</td>
</tr>
</tbody>
</table>

(Scheme VIII). First, the cuprate reagent is assumed to be a dimer with a planar array of the metal atoms and the chiral ligands located at the diagonal corners to minimize unfavorable electronic and steric interactions. Second, bidentate coordination of the chiral ligand to the metal cluster through the heteroatom of the side chain is assumed to be necessary for high asymmetric induction. Third, the inversion of configuration about the N-atom can form two diastereomeric chiral ligands which coordinate to the planer cluster in a different chiral sense and lead to enantiomeric products. Based on these assumptions, the alkyl group transfer from the face-to-face arrangement affords the $S$ enantiomer for the cuprate with the N-Cu bond trans to the side chain (-CH$_2$OCH$_3$) and the $R$ enantiomer for the cis relationship. The selectivity towards the $S$ enantiomer can be accounted for by the energy difference between the diastereomers 19a and 19b. The stereoisomer 19a with N-Cu bond trans to the side chain is assumed to be favored, and comparison can be made with the hydrindane system.
Incorporation of the chiral center in the transferable ligand has resulted in highly diastereoselective conjugate addition reactions. Yamamoto reported\textsuperscript{22} the conjugate addition of a copper azaenolate to 2-cyclopentenone giving, after hydrolysis, 3-acetonylcyclopentanone with 75\% enantiomeric excess. Malmberg demonstrated\textsuperscript{23} that incorporation of a chiral group R* in the addition to prochiral enones resulted in highly diastereoselective conjugate addition (as high as 98 \% e.e.).

Although this approach does provide a solution to the problem of asymmetric induction in organocopper conjugate addition reactions they are limited in terms of ease, efficiency, and generality.

**CATALYTIC ASYMMETRIC CONJUGATE ADDITION REACTIONS.**

Some of the approaches mentioned earlier lead to high enantioselectivities in the conjugate addition reactions, however all require stoichiometric amounts of chiral auxiliaries. Recently, the catalytic asymmetric conjugate addition of organometallic reagents to prochiral enones has been carried out by several groups. Lippard and co-workers reported\textsuperscript{24} the first catalytic asymmetric conjugate addition of Grignard reagents to cyclohexenone with very high regioselectivity (1,4/1,2 addition > 100) by using N,\textsuperscript{N}’-disubstituted aminotroponeimine derived chiral complexes (Scheme IX). Although the enantioselectivities were not promising, the efficiency of the catalysts was remarkable (only 0.6 ~ 4 mol \% was needed). This work does open the way to the potential applicability of catalytic asymmetric conjugate additions.

Recently, Feringa et al. reported\textsuperscript{25a} the zinc-mediated 1,4-addition of Grignard reagents
with alkoxides as nontransferable ligands and afforded products with moderate enantioselectivities (14\% e.e.) using chiral TMEDA analogue 22 (Figure 1). Further work demonstrated\(^{25b}\) that these kind of complexes can be efficient catalysts for the conjugate additions of Grignard reagents to various \(\alpha,\beta\)-unsaturated ketones. Further investigation on a whole series of chiral ligands showed that conjugate addition reactions using chiral diamino alcohol derived Zn(II) complexes (23 and 24) proceed with higher enantioselectivities (up to 33\% e.e.)\(^{25c}\) (Scheme X).

### Scheme X

\[
\text{Scheme X}
\]

The enantioselective additions with a diamino alcohol derived catalyst can be explained by a model shown in Scheme XI. ZnCl\(_2\) reacts with the alkoxide derived from Corey’s diamino alcohol and subsequently with \(i\)-PrMgBr to give complex 25 containing a tetracoordinate Zn (II) monoalkyl species. A similar Li analogue of 25 had been proposed as the key complex in the enantioselective cuprate additions by Corey.\(^{21}\) Binding of the Grignard reagent via coordination of the oxygen to the Mg exo to the bicyclic Zn complex forms the active catalyst complex 26. Activation of the enone via coordination to Zn involves a pentacoordinated Zn (II) intermediate 27. Selective transfer of the Mg-bound alkyl group to the \(re\) face of the enone results in the formation of \((R)\)-28.

### Scheme XI

\[
\text{Scheme XI}
\]

A highly enantioselective catalytic conjugate addition was disclosed recently by Soai.\(^{26}\) An in situ prepared catalyst with a Ni(II)-bipyridyl-chiral ligand for the addition of dialkylzinc reagents
to aryl substituted enones was utilized to afford β-substituted ketones with high e.e. (up to 90%) (Scheme XII). The major drawback of the system was that only aryl substituted enone systems work and the enantioselectivities were very sensitive to the carbonyl substituent (R). A similar approach by Bolm\textsuperscript{27} employed a chiral bipyridine as the chiral ligand binding to Ni(II) to obtain β-substituted ketones with enantiomeric excesses as high as 74%. Again, this approach was limited to certain substrates. Today, it is still a challenging problem to find a catalytic enantioselective conjugate addition reaction both with high e.e. and general applicability.

Scheme XII

\[
\text{Ph}-\text{C}R + \text{Bu}_2\text{Zn} \xrightarrow{\text{catalyst}} \text{Ph}-\text{C}R \quad \text{90\% e.e. (R)}
\]

catalyst = Ni(II)-chiral ligand-achiral ligand in MeCN/toluene

CONCLUSION

As shown, four strategies were equally effective in inducing asymmetric conjugate additions with greater than 90\% e.e., however those approaches are not applicable to all enone systems. Mechanistic studies of these reactions should be pursued further. Spectroscopic investigations of the organometallic-enone complex as well as direct isolation of these unstable complexes for X-ray studies (if possible) to gain further insight into the nature of organometallic-enone interactions may be helpful in devising appropriate chiral reagents. Efforts to effect chiral organometallic mediated conjugate addition reactions in organic synthesis have received success in some cases. Continuing investigations to develop more powerful and versatile chiral organometallic reagents (or catalysts) are necessary to accomplish this task.

REFERENCES

MECHANISM OF PROLINE RACEMASE

Reported by Jeff Burns

November 19, 1990

INTRODUCTION

As its name implies, proline racemase is an enzyme which catalyzes the racemization of proline. The enzyme possesses many interesting characteristics that have prompted much investigation. The investigations into the properties and mechanism of proline racemase have identified several transition state analogs, led to the modification and refinement of labeling studies, and resulted in the discovery that interconversion of active forms of an enzyme can become rate limiting.

Proline racemase was isolated along with proline reductase from the bacteria *Clostridium sticklandii* by Stadtman and Elliot in 1956. *Clostridium sticklandii* was known to have the capability of reducing DL-proline to δ-aminovaleric acid as shown in equation 1. Purification of crude extracts from *Clostridium sticklandii* afforded an enzyme which reduced D-proline but had no effect on L-proline. This fact prompted Stadtman and Elliot to investigate whether two reductases (one for D-proline and another for L-proline) or a single enantiospecific reductase and a racemase were present.

A second enzyme was isolated which was unable to reduce D-proline to δ-aminovaleric acid, but was able to convert either enantiomer of proline into a racemic mixture. From these initial observations it was concluded that the reduction of DL-proline relies on D-proline reductase and proline racemase. In 1968, Cardinale and Abeles initiated investigations into the nature of the active site, the reaction mechanism, the inhibitory power of transition state analogs, and the possible presence of cofactors.

\[
\begin{align*}
\text{L-proline} & \quad \xrightarrow{\text{proline racemase}} \quad \text{proline reductase} \\
& \quad \xrightarrow{\text{D-proline}} \quad \delta\text{-aminovaleric acid}
\end{align*}
\]

PROLINE RACEMASE

A Dimer Of 38.5 kD

From an initial binding study using pyrrole-2-carboxylate, Rudnick and Abeles determined that the enzyme exists as a dimer of two identical subunits. The electrophoretic mobility indicated that the subunit possessed a molecular weight of 38.5 kD. It was further found
that only one active site was present in each dimer.

A Sulfhydryl Enzyme

The original characterization of proline racemase was carried out by Stadtman and Elliot.1 The first evidence offered for the sulfhydryl nature of proline racemase was the dependence of enzyme activity on a reducing reagent (e.g. mercaptans and NaBH₄).1 Cardinale and Abeles2 suggested that the observed dependence on a reducing reagent resulted from the necessary reduction of a disulfide linkage (eq 2).

\[
\begin{array}{c}
\text{S-S} \\
\text{HS-CH₂OH} \\
\text{H-S-S} \\
\text{I-CO₂⁻} \quad \text{With proline or} \\
\text{pyrrole-2-carboxylate} \\
\end{array}
\]

Additional evidence for the sulfhydryl nature of proline racemase was the observed deactivation of the active (reduced) form by treatment with iodoacetate (eq 2).2,3 In the absence of β-mercaptoethanol, the incorporation of iodoacetate was 4% of that observed when β-mercaptoethanol was present.2 The high reactivity of the thiols was clearly indicated by the observed 93% reduction in enzyme activity upon the addition of iodoacetate in the presence of a large excess of β-mercaptoethanol. In addition, alkylation with [1-14C]iodoacetate followed by tryptic digestion of the labeled enzyme resulted in only one polypeptide which was radioactive. Sequencing of this polypeptide showed that the alkylated residue was cysteine.3

Both proline and pyrrole-2-carboxylate, a potent inhibitor, were shown to protect the active form of the enzyme from iodoacetate deactivation (eq 2).2,3 In one case, the enzyme was inhibited 53% by treatment with iodoacetate, but this inhibition was reduced to only 3.5% when the active site was "protected" by proline or pyrrole-2-carboxylate.2

Involvement Of Metals

The effects of metals on the catalytic activity of proline racemase was originally investigated by Stadtman and Elliot.1 A 25% decrease in catalytic activity was observed upon addition of Mg²⁺, and both iron and cobalt were found to "markedly" inhibit proline racemase. Such deactivation provides additional support for the presence of thiols in the active form of the enzyme.

The only other investigation concerning the presence of metals was carried out by Cardinale and Abeles.2 Enzyme inhibition in the presence of several bidentate ligands, especially 1,10-phenanthroline (67%), was observed. It was proposed that a metal ion was present at the enzyme
active site and that this metal ion activated the $\alpha$-hydrogen by strong complexation with the proline carboxylate group. However, "no direct evidence for the involvement of a metal ion in the reaction of proline racemase" was observed. The need to investigate the presence of a catalytically active metal was recognized, but the issue remains unresolved.

**No Required Cofactor**

Most amino acid racemases require the cofactor pyridoxal phosphate for activation of the $\alpha$-hydrogen. Given this observation, the effects of pyridoxal phosphate and hydroxylamine on enzyme activity were investigated. Addition of pyridoxal phosphate had no effect on racemization, and addition of hydroxylamine, which usually inhibits pyridoxal phosphate dependent enzymes, actually enhanced the racemization. These observations are not surprising given that pyridoxal phosphate is needed for racemases specific for amino acids, whereas proline is an imino acid.

Both Stadtman and Elliot and Cardinale and Abeles investigated the effect of adding oxidation-reduction cofactors (e.g. FAD and DPN) which are required by other enzymes to catalyze inversions similar to proline racemization. These cofactors were found to have no effect on enzyme activity, and it was concluded that racemization does not occur via an oxidation-reduction reaction. Instead it was proposed that the racemization proceeds through a carbanion intermediate.

Furthermore the absorption spectrum of the enzyme displayed no evidence for the presence of any cofactor, and techniques typically used to remove enzyme cofactors such as treatment with charcoal, elution through Sephadex G-200, and extensive dialysis had no effect on the activity of proline racemase. The possibility of activation of the $\alpha$-hydrogen by a carbonyl group in the enzyme was rejected because "carbonyl reagents" (NaBH$_4$, NaCN, and H$_2$NOH) did not inhibit enzyme activity. Finally, it was suggested that the enzyme operates by general acid-general base catalysis, which is consistent with the presence of two catalytic thiols (one protonated and one deprotonated) originally proposed by Rudnick and Abeles.

**MECHANISM**

**One-Base Mechanism**

The initial mechanisms proposed by Cardinale and Abeles are a one-base mechanism and a two-base mechanism. The one-base mechanism shown in Scheme I involves a single basic group at the enzyme active site which abstracts the $\alpha$-hydrogen of proline and then returns it with equal facial selectivity. This one-base mechanism requires a flexible basic group (B-) that is capable of interaction with both faces of the planar intermediate species, rotation of the planar species, or a combination of both. The one-base mechanism was rejected based on results of
Scheme I

racemization in D₂O (vide infra). In order for deuterium incorporation to occur in the one-base mechanism, the α-hydrogen removed from proline by the base (step 1) must undergo exchange with D₂O (step 2) followed by protonation of the proline carbanion species by the protonated base DB (step 3).

To determine the rates of deuterium incorporation and product formation, L-proline (or D-proline) was allowed to racemize in 95% D₂O. The results from four separate experiments are collected in Table I. In experiment one, L-proline was allowed to racemize 5% before the reaction

<table>
<thead>
<tr>
<th>Expt</th>
<th>Starting Substrate</th>
<th>Aliquot</th>
<th>% Racemization</th>
<th>% D-proline Remaining After D-amino acid oxidase</th>
<th>% Proline Deuterated at C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-proline</td>
<td>1</td>
<td>5.0</td>
<td>---</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>5.0</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>L-proline</td>
<td>1</td>
<td>9.8</td>
<td>---</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>9.6</td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>3</td>
<td>D-proline</td>
<td>1</td>
<td>7.2</td>
<td>---</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>6.6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>D-proline</td>
<td>1</td>
<td>12.2</td>
<td>---</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>13.5</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

(a) Data taken from reference 2. (b) For aliquot 1, the determination was made by measuring the optical rotation following derivatization with Sanger's reagent (2,4-dinitrofluorobenzene). For aliquot 2, the determination was made prior to derivatization with Sanger's reagent. (c) It has been noted that treatment with D-amino acid oxidase removes essentially all of the D-proline, regardless of isotopic incorporation.

was quenched and the reaction mixture divided into two aliquots. The optical rotation of the reaction mixture indicated that 5% D-proline was present. Aliquot one was derivatized with
Sanger's reagent. The optical rotation of the derivatized proline mixture indicated that D-proline was still present as 5% of the total proline. Deuterium analysis of the derivatized proline showed that 5.2% of the total proline contained deuterium (column four). Aliquot two was treated with D-amino acid oxidase, which selectively converts D-proline to Δ1-pyrroline-2-carboxylate, and the remaining D-proline was determined manometrically. Column three indicates that essentially all of the D-proline is removed by reaction with D-amino acid oxidase. The L-proline remaining in aliquot two was derivatized with Sanger's reagent and analyzed for deuterium content, which was 0.6% for experiment one (column four). Racemization was carried out twice for each proline enantiomer (experiments 1-4). These results are inconsistent with a one-base mechanism because it requires significant deuterium incorporation into L-proline.

Two-Base Mechanism

The two-base mechanism (Scheme II) proposed by Cardinale and Abeles is consistent with experimental results. The foundation of the two-base mechanism is the presence of two equivalent basic groups at the enzyme active site. One basic group is deprotonated, and the other basic group is protonated. The deprotonated base abstracts a proton from the α-carbon of proline to form a planar proline species, which is then capable of abstracting a proton from either of the protonated basic groups of the enzyme. This mechanism does not rely on basic group flexibility nor rotation of the anionic intermediate. Observed deuterium incorporation is in agreement with the two-base mechanism.

Two Enzyme Forms

As a result of possessing two basic groups in the active site, two free forms of the enzyme exist (E_L and E_D) differing in states of protonation. Basic group S_A may be protonated and basic group S_B deprotonated or vice versa. Perhaps this is the only difference between the two enzyme forms. Scheme II shows the specificity of E_L and E_D and the two pathways available for their interconversion.

Rudnick and Abeles were able to obtain early evidence for the existence of two different forms of proline racemase by two separate experiments. In the first experiment, it was observed that an increase in concentration of DL-[2-3H]proline resulted in a decreased rate of tritium loss from proline. This was explained as follows: as the DL-proline concentration is increased, the enzyme exists predominantly as the bound enzyme-substrate complex and is unable to undergo solvent-mediated interconversion with loss of tritium to the solvent (lower pathway of Scheme II). Thus, the major pathway for enzyme interconversion is via racemization of a substrate molecule. These results showed D-proline to be a noncompetitive inhibitor that binds tritiated E_D preventing loss of tritium. In the second experiment, it was observed that the initial tritium loss from L-[2-
3H]proline was unaffected by increasing the L-[2-3H]proline concentration. It was proposed that ED is able to undergo a solvent-mediated interconversion to the EL form. The tritium loss from L-[2-3H]proline follows saturation kinetics because the enzyme is able to interconvert via the solvent-mediated pathway.

**Scheme II**

Knowles and co-workers have investigated4,7,8 enzyme oversaturation and stress that information obtained from irreversible enzyme studies may be misleading. As the D-proline concentration increases, the rate limiting step for racemization of L-proline will become interconversion of ED to EL4,7,8. It is usually assumed that enzyme interconversion is much faster than the actual catalytic steps. The investigations into proline racemase prove that this is not always the case. Cleland recognized9 this possibility in 1963. Knowles and co-workers concluded4,8 that because most enzymes operate under reversible conditions, the kinetic behavior of enzymes studied under irreversible conditions (e.g. in determining initial rate constants) may be very misleading.8 Under reversible conditions, Vmax may depend on enzyme interconversion and not on conversion of substrate to product.
Recent Investigations

The more recent investigations of proline racemase have been carried out by Knowles and co-workers.\textsuperscript{4,6,7,8,10,11} The results from these investigations rely heavily on mathematical derivations developed earlier,\textsuperscript{12} and on fractionation factors ($\phi$) of reactants, intermediates, and transition states. Fractionation factors\textsuperscript{13} express the preference a solute has for deuterium relative to the preference the solvent has for deuterium. Fractionation factors can be determined directly by mass spectrometry and indirectly by changes in optical rotation, equilibrium constants, and kinetic isotope effects. The fractionation factor for the equilibrium below can be arrived at by rearrangement of the expression for the equilibrium constant. Fractionation factors for exchangeable protons bound to N, O, and S are typically 1, 1, and 0.5 respectively.\textsuperscript{13,14}

\[ \text{SH} + \text{DOD} \rightleftharpoons \text{SD} + \text{HOD} \]

\[ K_{eq} = \frac{ ([SD][HOD]) }{ ([SH][DOD]) } = \frac{ ([SD]/[SH]) }{ ([DOD]/[HOD]) } = \phi \]

It was initially shown\textsuperscript{4} that the observed rate constant of racemization is different when proline racemase is unsaturated, saturated, and oversaturated. Figure one shows the dependence of the observed rate constant $k_{obs}$ on the substrate concentration, $c$. Starting in the unsaturated region, increasing substrate concentration increases the observed rate constant. Values near the top of the curve correspond to saturation of the enzyme. The observed rate constant is greatest in this range of concentration. Additional substrate oversaturates the enzyme, and the observed rate constant falls. The decline in the observed rate constant results from the reduced rate of interconversion of $E_D$ and $E_L$ as discussed earlier.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1}
\caption{Figure I}
\end{figure}
Following the discovery that enzyme interconversion can limit the rate of racemization, the rate of enzyme interconversion was investigated. The addition of unlabeled L-proline to an equilibrated pool of [\textsuperscript{14}C]proline was followed. As unlabeled L-proline was converted to D-proline, there was an increase in the amount of \( E_D \). The result was a shift in radioactivity to the L-proline (i.e. more L-proline contains \( {\textsuperscript{14}}C \)). By measuring the distribution of the \( \textsuperscript{14}C \) label as a function of the optical rotation, which indicates the extent of racemization of the added unlabeled L-proline, the concentration \( c_p \) was determined. \( c_p \) is the concentration at which the kinetic behavior changes form saturated to oversaturated. The value for \( c_p \) and the value for the rate constant in the unsaturated region were used to calculate the interconversion rate between \( E_D \) and \( E_L \). This value is approximately \( 10^5 \) s\(^{-1} \), which is about 100 times greater than \( k_{\text{cat}} \).

The estimation of the interconversion rate led Knowles and co-workers\(^{10} \) to investigate catalysis of the interconversion, especially interconversion mediated by water. The water-mediated interconversion of \( E_D \) and \( E_L \) was proposed to proceed in a manner identical to racemization of proline (Scheme II). A proton is removed from \( \text{H}_2\text{O} \) to form \( \text{HO}^- \) bound in the fully protonated active site. The hydroxide is then able to abstract either proton to form \( E_D \) or \( E_L \).

Next, Knowles and co-workers\(^{6} \) obtained information regarding the degree of bonding to the two protons which are transferred in the catalytic step(s). Four different experiments were carried out to obtain three sets of values and a ratio of values for the bonding at the two proton sites \( S_A \) and \( S_B \) during proton transfer. The values obtained for the fractionation factors are 0.44 and 0.38 for \( S_A \) and \( S_B \), respectively. The greater value for \( S_A \) indicates that during proton transfer the hydrogen associated with \( S_A \) is more likely to be deuterium than the hydrogen associated with \( S_B \). This difference means that \( S_A \) will abstract a deuterium from D-proline faster than \( S_B \) will abstract a deuterium from L-proline. The important implication is that the racemization of deuterated D-proline will be more rapid than racemization of deuterated L-proline. This difference in racemization of deuterated proline enantiomers was observed.\(^{6} \)

After determining the difference between the two hydrogens associated with \( S_A \) and \( S_B \) during proton transfer, the concertedness of the proton abstractions was investigated.\(^{11,15} \) A "double fractionation" experiment was carried out by allowing unlabeled D-proline to racemize in a mixture of \( \text{H}_2\text{O} \) and \( \text{D}_2\text{O} \). Then deuterated D-proline was allowed to racemize in a \( \text{H}_2\text{O}-\text{D}_2\text{O} \) mixture of the same composition. If the deuterium content of the product L-proline is different for the racemization of nondeuterated and deuterated D-proline, then the reaction is stepwise. Knowles and co-workers observed that the deuterium content in the product L-proline was the same for both nondeuterated and deuterated D-proline. This implies that the mechanism is concerted, but it is also possible that the two basic groups have equal preference for deuterium which would result in no difference in the deuterium content of L-proline upon changing from
nondeuterated to deuterated D-proline. Therefore, the concertedness of the mechanism can not be known with certainty.

Based on the potential energy surface presented in Figure II, Knowles and Albery\textsuperscript{8} make a reasonable argument for the preference of a two step process. Three possible routes exist for the water-mediated interconversion of $E_D$ and $E_L$. The first is the concerted proton transfer that is represented by the diagonal line across the potential energy surface. The second route is the protonation of the water molecule to form the fully deprotonated enzyme and $H_3O^+$ (upper left corner). This route is from the lower left corner to the upper left corner of the potential energy surface. Protonation of the dianionic enzyme leads to $E_D$ in the upper right corner. The third possibility suggested by Knowles and Albery is the abstraction of a proton from water by the deprotonated enzyme site (from the lower left to the lower right). This is followed by protonation of the hydroxide ion, again leading to $E_D$. The proposal relies on similarity between the water-mediated interconversion and the racemization of proline. Assuming proline were able to follow the same three routes for water, the upper left corner represents the formation of a pentavalent carbocation. Therefore, the upper left corner is of very high energy and causes the potential energy surface to slope steeply from the upper left corner down to the lower right corner. The
contribution from the concerted process may be important, but the slope of the potential energy surface tends to shift a concerted reaction pathway towards a stepwise reaction pathway.

SUMMARY

The enzyme proline racemase has been shown to be a sulfhydryl enzyme in which two thiols are catalytically involved. The racemization utilizing the two thiols occurs via a two-base mechanism in which one thiol is deprotonated and the other thiol is protonated. The catalytic involvement of the two thiols was determined by the more quantitative method employing fractionation factors. An estimate of the concertedness of the reaction has also been made. Because of the equivalency of the two catalytic groups, Knowles and co-workers were not able to assert that racemization is a concerted process. But a reaction coordinate that lies between extremes is favored based on a potential energy surface.

REFERENCES

(1) Stadtman, T. C.; Elliot, P. J. Biol. Chem. 1957, 228, 983-997.
(2) Cardinale, G. J.; Abeles, R. H. Biochemistry 1968, 7, 3970-3978.
(3) Rudnick, G.; Abeles, R. H. Biochemistry 1975, 14, 4515-4522.
CC-1065 AND SOME ANALOGUES: SYNTHESIS, BIOLOGICAL ACTIVITY AND MECHANISM OF ACTION

Reported by Khaled Saleh

November 26, 1990

INTRODUCTION

CC-1065 (1) is an antitumor antibiotic isolated from Streptomyces zelensis by Martin's group at the Upjohn Company in 1978. The compound possesses exceptional in vitro cytotoxic activity. It causes 90% inhibition of mouse leukemia L1210 cells at 40 pg/mL. It also showed a broad spectrum of antimicrobial activity and in vivo antitumor activity. The compound was found to cause delayed toxic death in mice, therefore efforts have been directed toward the synthesis of analogues that could have equal antitumor activity without exhibiting delayed toxicity. These analogues were also useful in determining the mechanism of action of CC-1065 at the molecular level. This paper presents the synthesis of CC-1065 and some of its analogues, their resultant biological activity, and their proposed mechanism of action.

SYNTHESIS OF CC-1065 AND ANALOGUES

CC-1065, four analogues having the same cyclopropylpyrroloindole (CPI) left-hand subunit but bearing different central- and right-hand subunits, and their corresponding enantiomers were synthesized by Warpehoski's group at the Upjohn Company (Chart I). Compounds containing the reactive cyclopropylpyrroloindole (CPI) subunits alone and linked to one or two indole subunits have been designated as (+)-A, (+)-AB and (+)-ABC, respectively. A compound with identical structure to CC-1065 but lacking the hydroxyl and methoxyl group has been designated as (+)-AB'C. The corresponding enantiomers containing the (-)-CPI subunit have been designated as (-)-A, (-)-AB, (-)-ABC and (-)-AB'C'. This report describes the latest synthesis of the left-hand subunit that was carried out by Boger's group at Purdue University,

Copyright © 1990 by Khaled Saleh
and discusses the method adopted by the Upjohn Company for obtaining the analogues of the central- and right-hand subunits.

Chart I

The retrosynthetic analysis of the CPI subunit is illustrated in Scheme I. The synthetic approach is based on regioselective nucleophilic addition of \textit{trans}-1-piperidino-1-propene to a \textit{p}-quinone diimide thereby introducing the 3-methylpyrrole ring. Implementation of a 5-\textit{exo-dig}-aryl

Scheme I
alkyne-radical cyclization introduces the 3-hydroxypyrroline ring. Selective deprotection and coupling to chiral acetylmandelic acid allows the chromatographic resolution of the two enantiomers. Deprotection and conversion of the primary alcohols to chlorides provide a reactive molecule that can be condensed with the carboxylic acid of the different right-hand subunits. Cyclopropane ring closure provides the desired compounds.

The 3-methylpyrrole ring in the left-hand segment of CC-1065 was introduced by treatment of p-quinone diimde 2 with trans-1-piperdino-1-propene (3) in CH₂Cl₂ which proceeded with selective C-6 nucleophilic addition to give compound 4. Acid catalyzed elimination of piperidine afforded the desired compound 5 (Scheme II).

Scheme II

Selective bromination of the indole was effected using N-bromosuccinimide at low temperature, with acid catalysis (Scheme III). Alkylation with 3-bromopropyne using sodium hydride in DMF provided the alkyne substrate 6 in 67% yield from 5. 5-Exo-dig aryl radical-alkyne cyclization of 6 was carried out using tri-n-butyltinhydride with catalytic AIBN to give the unstable methylideneindole 7. This compound was immediately subjected to hydroboration followed by treatment with basic hydrogen peroxide to give 3-hydroxymethyl indoline 8 in 40% yield.

Scheme III

After removal of the benzoyl protecting group, the phenylsulphonyl group was replaced by the tert-butoxycarbonyl group by treatment with sodium bis-(2-methoxyethoxy) aluminium hydride, followed by reaction with di-tert-butyldecarbonate to give 9 in 60% from 8 (Scheme IV). Resolution of the alcohol was achieved by chromatographic separation of the corresponding
diastereomeric (R)-O-acetylmandelate esters. The separated diastereomers (1S, 2'R)-10 and (1R, 2'R)-10 were treated independently with lithium hydroxide to provide the two enantiomeric alcohols. The resultant primary alcohols were then converted to primary chlorides (S)-11 and (R)-11 (Ph3P, CCl4) in 87% yield. The benzyl ether was removed by phase transfer catalytic hydrogenolysis (25% of HCO2NH4 THF, 10% Pd/C) and the tert-butoxycarbonyl protecting group was removed by treatment with anhydrous hydrochloric acid, thus affording the unstable indoline chlorides (S)-12 and (R)-12. Each of the enantiomers was then coupled separately with the different central- and right-hand subunits to afford the desired compounds described above.

Scheme IV

The BC subunits were synthesized by condensation of indole-2-carboxylic acid and ethyl-5-amino-indole-2-carboxylate with dimethylaminopropylcarbodiimide (EDC, DMF), followed by ester saponification (50% overall yield).3c

Synthesis of the B'C' subunit was carried out starting from ethyl 5-amino-indole-2-carboxylate (13) prepared using Gassman's modified oxindole synthesis (Scheme V).5 Treatment of 13 with ethylmercaptomethyl acetate in presence of sulfuryl chloride and Proton Sponge followed by triethylamine catalyzed Sommlett-Hauser rearrangement, and acid induced cyclization gave 14. Conversion of the amide to the thioamide using Lawsson's reagent was followed by Raney nickel reduction to give the pyrroloindole carboxylate 15. Reduction of the pyrrole double bond was carried out using borane dimethylsulfide in TFA to give 16. The indoline 16 was treated with potassium isocyanate in acetic acid to introduce the carbamoyl group and the ester group was then hydrolyzed using lithium hydroxide to give compound 17. Compounds 16 and 17 were then coupled to give the B'C' subunit.3b The CC-1065 dihydropyrroloindole dimer (central- and right-hand subunits) was obtained from mild alkaline hydrolysis of natural CC-1065, conditions that specifically cleave the more susceptible vinylogous amide.6
Coupling of the reactive indole chloride (S)-12 with carboxylic acids of the different subunits (EDCI, NaHCO₃) was followed by ring closure using 1:1:1 NH₃/H₂O/CH₃CN to give the desired (+)-analogues in 20-30% yield (Scheme VI). Reactions with the opposite enantiomer (R)-12 provided the corresponding (-)-analogues.

**BIOLOGICAL ACTIVITY**

These compounds were tested for in vitro cytotoxic activity against L1210 tumor cells and antitumor efficiency against P388 leukemia in mice. Their ability to cause delayed death in mice was also evaluated. The results indicated that only (+)-CC-1065 and (+)-AB'C' caused delayed death in mice. (+)- and (-)-CC-1065, (+)- and (-)-AB'C', and (+)-ABC showed comparable high potency both in vitro and in vivo, and high efficacy against P388 leukemia in mice. Compounds (+)-AB, (+)-A showed decreased biological activity consistent with the decrease in chain length. (-)-ABC and (-)-AB were active only at very high concentration and their reactivity was attributed to enantiomeric contamination by their corresponding enantiomers. However, (+)- and (-)-A were comparable in their biological activity.

**MECHANISM OF ACTION**

CC-1065 was studied at the molecular level to determine the origin of its biological potency. The compound was found to bind at the A-T rich regions of DNA in a nonintercalative manner and to subsequently form an irreversible covalent adduct to adenine at specific sequences.
The ability to bind to DNA is derived from its structure that is characterized by a banana shape and a twist along its length that mimics the pitch in B DNA. The structure is also characterized by a hydrophobic concave face and a hydrophilic convex one. The methylene carbons on the concave face allow favorable hydrophobic interaction with the nucleic acid carbons of DNA. The hydroxyl and the methoxyl groups on the convex face could play a role in bridging the water molecules to the phosphate backbone of the DNA. CPK models indicate a snug fit of the compound in the deep and narrow yet still sterically accessible minor groove of B DNA.

The mechanism by which CC-1065 reacts with DNA and its sequence specificity was determined using singly labelled 5'-32P, 117 base pair, SV40 DNA. The compound after incubation with DNA at 37 °C was found to be attached to five different adenines in distinct sequences (five alkylation sites). The sites of alkylation were determined using the thermally induced strand cleavage assay. Heat treatment of CC-1065-DNA covalent complex at 100 °C for 30 min leads to the liberation of the adenine-CC-1065 adduct and to strand breaks to the 3'-side of the modified adenines. The site of the cleavage is determined by polyacrylamide gel electrophoresis in which the cleaved fragments migrate according to their molecular weight. The mechanism of covalent alkylation is outlined in Scheme VII. Adenine in specific sequences attacks the cyclopropyl carbon nucleophilically with acid catalysis to give the DNA-CC-1065 complex. Treatment of this complex with heat induces breakage of the glycosidic bond to liberate the

Scheme VII
adenine-CC-1065 adduct with concomittant cleavage of the DNA strand to the 3'-side of the modified adenine

These results stimulated the search for the origin of CC-1065 sequence specificity. The analogues were useful in determining which structural and functional features of CC-1065 were responsible for its sequence specificity and resultant biological activity. These studies were carried out using the same 117 bp DNA fragments. (-)-CC-1065 was found to be attached to four adenines in distinct sequences that were different from the (+)-CC-1065 alkylation sites. The different analogues were compared in their ability to alkylate any of the five (+)-CC-1065 and any of the four (-)-CC-1065 alkylation sites on the same piece of DNA. The ability to alkylate was judged from the concentration required to obtain the earliest detectable cleavage at these sites using the thermally induced strand cleavage assay.

All the (+)-enantiomers were able to alkylate the (+)-CC-1065 alkylation sites. However, as the size of the chain decreases, higher concentrations were required. This indicated that the (+)-A subunit has enough structural information to recognize the specific sequence. The right-hand subunit increases the apparent rate of the reaction through noncovalent binding interactions that could drive the covalent bonding reaction. These results could be correlated to the biological activity in which the more elaborated analogues showed higher cytotoxic activity than the aborted ones. Since (-)AB'C' (-)-ABC and (-)-AB were able to recognize the (+)-CC-1065 DNA alkylation site only at very high concentrations, the activity could be attributed to enantiomeric contamination. However, (-) A was able to recognize the specific sequence since it requires only 10 fold higher concentration than its enantiomer.

The compounds were also compared in their reactivity to alkylate the (-)-CC-1065 alkylation sites on DNA. (-)-AB'C' was able to alkylate these sites, however (-)-ABC, (-)-AB, and (-)-A were not. This result could explain the lack of biological activity of (-)-ABC and (-)-AB since they were unable to recognize either the (+)- and (-)-CC1065 alkylation sites. (+)- and (-)-A, which can both recognize the (+)-CC-1065 alkylation sites, have comparable biological activity.

These results also indicate that the (-)-CC-1065 mechanism of sequence recognition is different from that of (+)-CC-1065. (-)-CC1065 requires (-)-AB'C' as a minimum structure to be able to recognize its alkylation sequences, indicating the B'C subunit to be the main determinant of the reactivity of this compound. Consequently, higher binding affinity is required for alkylation to occur. The differences in the mechanism of sequence recognition of (+)- and (-)-CC-1065 resulted in different consensus sequence for the two compounds. The thermally induced strand cleavage assay using several different DNA fragments indicated that (+)-CC1065 strongly prefers an adenine or thymine two base pairs in the 5'-direction of the covalently modified adenine. Since, (-)-CC1065 prefers adenine or thymine flanking both sides of the modified adenine. Also MPE:Fe(II) footprinting of the CC-1065-DNA covalent complexes indicates that (+)-CC-1065 is
oriented in the 5'-direction of its covalently modified adenine. This is also confirmed by an NOE experiment of (+)-CC-1065-octamer complex. (-)-CC1065 is oriented in the opposite 3'-direction. These differences could indicate different biochemical mechanisms for the cytotoxicity of the two compounds and the differences in the ability to cause delayed death in mice.

**MOLECULAR MODELING**

To explain the experimental observations described above, qualitative modeling studies were performed on (+)-CPI and (-)-CPI adducts with the duplex oligomer 5'CGTTA*ACG3'. Using the MOSAIC modeling program and the AMBER set of force field parameters, energy minimization was performed starting from the idealized DNA helices to which a ring-opened CPI moiety is attached. The covalently modified adenine, A*, is in a good consensus bonding sequence for both (+)-CC-1065 (5'TTA*) and (-)-CC-1065 (5'TA*A). One model confirms the 5'-orientation of (+)-CPI when bonded to a (+)-CC-1065 site and indicates that a favorable van der Waals interaction places the phenolic hydroxyl group within hydrogen-bonding distance of a phosphate oxygen. This interaction suggests a mechanism for acid catalyzed activation of the (+)-CPI moiety toward nucleophilic attack.

Another model explains the reactivity of the (-)-A subunit with adenine in the (+)-CC-1065 site (5'TTA*). The energy minimized structure places the acyl appendage in the 3'-direction of the adduct site, a result which is in agreement with the orientation of the (-)-CC-1065 when bound to DNA. However, in order to maintain the phenol-phosphate interaction, the molecule is skewed in a manner that pulls the appendage out of the groove. This orientation could explain the 10 fold decrease in reactivity of the (-)-A subunit. The lack of reactivity of (-)-CPI compounds with larger acyl appendages than methyl indicate that leaving such large hydrophobic appendages protruding out of the groove is not favorable.

A third model explains the lack of reactivity of (-)-A with adenine in the (-)-CC-1065 alkylation site. This model indicates that in order to maintain a favorable van der Waals interaction, the phenol hydroxyl group interaction with the phosphate would be sacrificed. This causes a severe loss in reactivity. These results show that the sequence specificity of the (+)-CC-1065 compounds is primarily determined not by sequence-dependent noncovalent binding, but by the sequence requirement inherent in the covalent bonding step. These sequences are characterized by conformational flexibility that allows a susceptible adenine to get close enough for bond formation or allows electrophilic activation of the (+)-CPI that may occur simultaneously with the N-3-adenine nucleophilic attack, a mechanism similar to the bifunctional catalysis that occurs in some enzymatic reactions.
CONCLUSION

CC-1065 has gained considerable attention because of its potent antitumor activity. Synthetic analogues were useful in determining the origin of sequence specificity and the resultant biological activity. These studies have shown that the left-hand subunit has enough structural information to recognize reactive sequences and covalently bond to adenines where the acid catalysis is provided by the DNA itself. However, the noncovalent binding provided by the right-hand subunit is required for the high biological activity. Some of the analogues show promise as chemotherapeutic agents since they do not cause delayed death in mice. This research is still in its beginning stages since several questions still need to be answered. The minimum structural information required for sequence specificity and biological activity could be determined by the synthesis and biological testing of analogues with structural modification in the left-hand subunit.

REFERENCES


REDUCTION OF QUINONES BY NADH AND NADH MODEL COMPOUNDS: ONE-STEP HYDRIDE TRANSFER OR MULTISTEP ELECTRON-PROTON-ELECTRON TRANSFER?

Reported by Mingbao Zhang December 6, 1990

INTRODUCTION

The dihydropyridine nucleotide coenzyme NADH 1 (reduced nicotinamide adenine dinucleotide) is one of the most important coenzymes in nature. Research shows that about 250 known enzymatic reactions depend on this coenzyme. The general process is a reversible interconversion of 1 and NAD+ 2 via a formal exchange of a hydride with a substrate in the presence of an appropriate enzyme (Scheme I).

Scheme I

\[
\begin{align*}
S + & \quad \text{H}^+ \quad \text{Enz} \\
\text{NADH} & \quad \text{S} + \quad \text{H}^+ \quad \text{Enz} \\
1 & \quad \text{NAD}^+ \\
& \quad \text{CONH}_2 \\
& \quad \text{Ad} \\
\end{align*}
\]

In order to understand the mechanism of the enzymatic process, the nonenzymatic reduction of substrates by NADH and NADH model compounds (denoted as PyH2, Figure 1) have been extensively studied. But there is still no concensus on whether the process occurs by a one-step hydride transfer or by a multistep mechanism involving electron transfer or charge-transfer complexes. Among the substrates that have been reduced nonenzymatically by NADH and NADH model compounds, quinones have been extensively studied, and their reduction has been the focus of a great deal of controversy. With quinones, the reductions could proceed by a hydride transfer, or by a combination of electron and hydrogen atom transfers or by an electron-proton-electron transfer (e-p-e) mechanism (Scheme II). Moreover, since phenoxides, phenoxy radicals, and semiquinones are all energetically accessible, all of these mechanisms are possible, which undoubtedly increases the complexity of this reaction system. In this abstract, a mechanistic analysis of the NADH-quinone reactions will be presented based on recent publications.

Copyright © 1990 by Mingbao Zhang
Figure 1. NADH model compounds (PyH2), and p-benzoquinone derivatives (Q)

**ONE-STEP HYDRIDE TRANSFER MECHANISM**

In 1974, MacFarland and coworkers first studied the oxidation of NADH by several p-quinone derivatives in aqueous solution. The kinetics of this reaction was studied at a single concentration of NADH and quinones. Based on the large kinetic isotope effect found using NADH-d1, it was concluded that the reaction was probably proceeding by a one-step hydride transfer mechanism.

Scheme II
Miller and coworkers extended this study in 1985 using o- and p-quinone derivatives in aqueous buffered solution. It was shown that the reaction of NADH with quinones was first order in each reactant, and that neither pH nor oxygen affected the reaction. Furthermore, when using NADH-4,4'-d2, no incorporation of deuterium onto the hydroquinone carbon skeleton was detected, although a primary kinetic isotope effect was observed. Based on these experimental results, it was concluded again that the reaction proceeded by a one-step hydride transfer mechanism (Scheme III).

Scheme III

More information was obtained from kinetic/thermodynamic correlations. Thermodynamically, a one-step hydride transfer (eq 1) is equivalent to a two-electron, one proton process (eq 2). If a one-step hydride transfer is involved in the activation process, it might be reasonable to expect a linear correlation between log $k_{obs}$ and $E^\circ_{Q/Q^-}$. Indeed, a fairly good linear correlation was obtained with a slope of 16.9 V$^{-1}$ for p-quinones ($r = 0.99$) and 16.4 V$^{-1}$ for o-quinones ($r = 0.98$). Interestingly, the slopes of the two correlation lines do not differ by very much, but the o-quinones oxidize NADH with rate constants approximately 2 orders of magnitude greater than those for the corresponding p-quinones at the same $E^\circ_{Q/Q^-}$ (pH = 7). This intrinsic difference in reactivity has been related to the formation of an internally hydrogen bonded o-QH$^-$ (Figure 2) by Miller and coworkers. 

Figure 2. Internally hydrogen bonded o-QH$^-$
Miller used an energetic analysis to show that the multistep e-p-e mechanism might not be favored in this case. By using electrochemical data for p-benzoquinone and NADH, it was shown that the formation of NADH$^+$ and Q$^-$ is endothermic by 0.83 eV, while hydride transfer is exothermic by 0.5 eV (eqs 3 and 4).

$$\begin{align*}
Q + \text{NADH} &\rightarrow Q^- + \text{NADH}^+ & \Delta G = 0.83 \text{ eV} \quad (3) \\
Q + \text{NADH} &\rightarrow QH^- + \text{NAD}^+ & \Delta G = -0.50 \text{ eV} \quad (4)
\end{align*}$$

With Rehm-Weller eq 5 and eq 6, where the work term $w_p$ is the energy required to bring the products A$^-$ (acceptor) and D$^+$ (donor) to the mean separation in the activation complex, the activation free energy change $\Delta G^\ddagger$ can be estimated, and thus the rate constants for electron transfer can be theoretically predicted according to eq 7, where $k_B$ is the Boltzmann constant, and $Z$ is the preexponential term. By assuming that the work term $w_p$ in eq 6 is negligible and the intrinsic barrier (the activation Gibbs energy when the Gibbs energy change is zero) $\Delta G_0^\ddagger = 5.0 \text{ kcal/mol}$, the calculations showed that the predicted electron transfer rate constants for several p-quinones were about $10^4$ times slower than the corresponding $k_{obs}$ values determined experimentally. This raises the impossible situation where the one-electron transfer rate is slower than the overall rate. Therefore, the multistep electron-proton-electron transfer mechanism could be ruled out.

$$\begin{align*}
\Delta G^\ddagger &= (\Delta G/2) + [(\Delta G/2)^2 + (\Delta G_0^\ddagger)^2]^{1/2} \quad (5) \\
\Delta G &= \Delta G^\circ + w_p \quad (6) \\
k &= Z \exp(-\Delta G^\ddagger/k_BT) \quad (7)
\end{align*}$$

Thus, the one step hydride transfer mechanism for NADH-quinone reactions seems to be generally accepted. However, this mechanism has been firmly rejected by Fukuzumi and coworkers in 1987. They discredited the linear correlations between $\log k_{obs}$ and $E^\circ (Q/QH^-$ at pH 7) used by Miller and coworkers to support the one-step hydride transfer mechanism by pointing out that when the intrinsic barrier of the reaction $\Delta G_0^\ddagger$ is sufficiently large, any homologous series of reactants will give a linear Gibbs energy relationship between $\log k_{obs}$ and $\Delta G^\circ$ with $\alpha = 0.5$, without providing any definitive information about the transition state. This can be expressed by the Rehm-Weller eq 5. When the intrinsic free energy barrier $\Delta G_0^\ddagger$ is far greater than the driving force $\Delta G$, then eq 5 can be rewritten as eq 8. For any homologous series of reactants, the intrinsic barrier $\Delta G_0^\ddagger$
remains constant, so that a linear Gibbs energy relationship will be obtained. Fukuzumi further pointed out that the work term $w_p$ that was ignored in Miller's calculation is actually fairly large.\textsuperscript{3}

Facing these "flaws" in one-step hydride transfer mechanism, one might be curious about what the multistep e-p-e mechanism can do.

**ELECTRON-PROTON-ELECTRON TRANSFER MECHANISM**

As mentioned earlier, the mechanism of the interconversion of NADH and NAD\textsuperscript{+} in the presence of oxidizing agents has been subjected to a great deal of controversy, although it seems clear that with one-electron oxidants (e.g., ferrocenium cations), multistep e-p-e mechanism may be more likely than the one-step hydride transfer mechanism.\textsuperscript{3,8} However, for other substrates (e.g., NAD\textsuperscript{+} model compounds), a one-step hydride transfer may be more favored.\textsuperscript{6,9-10} There are two important variants for multistep e-p-e mechanism. With one-electron oxidants, one variant is shown in Scheme IV.\textsuperscript{11} The other one is the so-called inner-sphere electron-proton-electron transfer mechanism, as shown in Scheme V. The first variant will not be discussed here, since quinones are usually regarded as two-electron oxidants.

**Scheme IV**

\[
\begin{align*}
\text{NADH} + \text{OX}^+ & \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} \text{NADH}^\cdot + \text{OX}^+ \\
\text{NADH}^\cdot + \text{B} & \overset{k_2}{\underset{k_{-2}}{\rightarrow}} \text{NAD}^+ + \text{BH}^+ \\
\text{NAD}^+ + \text{OX}^+ & \overset{k_3}{\underset{k_{-3}}{\rightarrow}} \text{NAD}^\cdot + \text{OX}^+ \\
\text{Net Reaction: NADH} + 2\text{OX}^+ + \text{B} & = \text{NAD}^\cdot + 2\text{OX} + \text{BH}^+ 
\end{align*}
\]

**Scheme V**

\[
\begin{align*}
\text{PyH}_2 + \text{Q} & \overset{K_{CT}}{\underset{K_{CT}}{\rightleftharpoons}} [\text{PyH}_2 \text{Q}] \\
[\text{PyH}_2 \text{Q}] & \overset{k_{et}}{\underset{k_{et}^{-1}}{\rightarrow}} [\text{PyH}_2^\cdot \text{Q}^-] \\
[\text{PyH}_2^\cdot \text{Q}^-] & \overset{k_{H^+}}{\rightarrow} [\text{PyH}^+ \text{Q}^-] \\
[\text{PyH}^+ \text{Q}^-] & \overset{k_{et}^{-1}}{\rightarrow} [\text{PyH}^+ \text{Q}^-] \overset{\text{fast}}{\rightarrow} \text{PyH}^+ + \text{Q}^- 
\end{align*}
\]
In 1987 Fukuzumi and coworkers suggested\(^3\) that the distinction between one-step hydride transfer and multistep e-p-e mechanism might not be clear without considering the energetic profile of the reaction. Energetic considerations showed that for \(p\)-quinone oxidations, the e-p-e mechanism seemed to provide more quantitative information about the transition state than the one-step hydride transfer mechanism.\(^3,4\) Thus, Fukuzumi reported that \(\log k_{\text{obs}}\) for the formal hydride transfer reactions from both X-BNAH and AcrH\(_2\) (both are NADH models, Figure 1) to \(Q\) in MeCN can be expressed as a single linear function of \(\Delta G^\circ_H\) (eq 13). In contrast, two different linear functions were obtained (eqs 14 and 15) when \(\Delta G^\circ_H\) was used, where \(F\) is the Faraday constant (Scheme VI).

\[
\log k_{\text{obs}} = 14.6 - 15.3 \left(\frac{\Delta G^\circ_H}{F}\right) \quad \text{(for both X-BNAH and AcrH\(_2\))}
\]

\[
\log k_{\text{obs}} = -3.5 - 7.9 \left(\frac{\Delta G^\circ_{\text{H}^-}}{F}\right) \quad \text{(for X-BNAH)}
\]

\[
\log k_{\text{obs}} = 0.82 - 8.5 \left(\frac{\Delta G^\circ_{\text{H}^-}}{F}\right) \quad \text{(for AcrH\(_2\))}
\]

By comparing with the Brønsted catalysis law (eq 16), the slopes in eqs 13-15 can be related to the Brønsted term \(\alpha\). Since \(\log K_{\text{eq}} = -\Delta G^\circ/2.3RT = -\left(\Delta G^\circ/F\right)(F/2.3RT)\), where \(R\) is the gas constant, and \(T\) is temperature, the Brønsted catalysis law can be rewritten as eq 17. From eq 17 one would see immediately that the slopes in eqs 13-15 correspond to \(-\alpha F/2.3RT\). Obviously, eq 13 results in an \(\alpha\) of unity, while eqs 14 and 15 lead to the calculation of \(\alpha = 0.5\).

\[
\log k_{\text{obs}} = \alpha \log K_{\text{eq}} + C
\]

\[
\log k_{\text{obs}} = -\left(\frac{\alpha F}{2.3RT}\right)(\Delta G^\circ/F) + C
\]

These relationships reveal that the change in \(\Delta G^\circ_H\) is directly reflected in the activation barrier of the hydride-transfer reactions (\(\alpha = 1\)), while only about one half of the change in \(\Delta G^\circ_{\text{H}^-}\) is reflected in this process (\(\alpha = 0.5\)). This might suggest that the activation barrier of hydride-transfer reactions from NADH model compounds to quinones depends only on \(\Delta G^\circ_H\) (\(\alpha = 1\)) and is therefore independent of \(\Delta G^\circ_{\text{et}}\). Since \(\Delta G^\circ_H = \Delta G^\circ_{\text{et}} + \Delta G^\circ_{\text{H}^+}\) (Scheme VI), it is reasonable to conclude that the activation process might involve either an electron-transfer followed by a proton-transfer process or a direct transfer of a hydrogen atom from PyH\(_2\) to Q followed by an exothermic electron transfer from PyH\(^-\) to QH\(^-\) (Scheme VI). The correlation of \(\log k_H/k_D\) with \((\Delta G^\circ_{\text{H}^+}/F)^2\) (in MeCN) gives a single linear relationship that is consistent with the theoretical prediction based on the assumption that proton transfer is involved in the activation process. The involvement of hydrogen atom transfer
in the activation process was ruled out by the absence of corresponding linear correlation between \( \log k_H/k_D \) and \( (\Delta G°_H/F)^2 \).

Scheme VI

\[
\begin{align*}
\text{PyH}^+ + Q^- & \xrightarrow{\Delta G°_{H+}^{\text{et}}/k_{H+}} \text{PyH}^- + QH^- \\
\Delta G°_{\text{et}} & \quad \left\{ \begin{array}{c}
\Delta G°_{H^-}^{\text{et}}/k_{H^-} \quad \text{PyH}_2 + Q \xrightarrow{\Delta G°_{H^-}^{\text{et}}/k_{H^-}} \text{PyH}^+ + QH^-
\end{array} \right. \\
\end{align*}
\]

Previous studies carried out by Fukuzumi\cite{12-14} and other research groups\cite{8} support the inner-sphere e-p-e mechanism. One of the key features of this mechanism is the presence of a charge-transfer complex (CT) formed between NADH model compounds and quinones prior to the first electron transfer step. Fukuzumi reported\cite{3,13} that several charge-transfer complexes of quinones and NADH models [PyH\(_2\)-Q] have been isolated from benzene and characterized by IR (KBr pellet) and UV/visible spectroscopy. Such charge-transfer complexes have been proposed to be the basis of inner-sphere electron transfer rather than outersphere electron transfer.\cite{3} It has also been pointed out that the work term \( w_p \) in eq 6 is of great importance in those electron transfer processes via charge-transfer complexes formed between neutral donors and neutral acceptors.\cite{15}

The effects of metal ions such as Mg\(^{2+}\) and Zn\(^{2+}\) on hydride transfer reactions from NADH and NADH models to substrates have also attracted considerable interest in relation to the role of metal ions in the redox reactions of nicotinamide coenzymes.\cite{12,16-17} The metal ion effects have also been used as probes to test the nature of hydride transfer.\cite{12,16} It has been shown that Mg\(^{2+}\) ion could accelerate or retard the hydride transfer reactions depending on the substrates and the concentration of Mg\(^{2+}\).\cite{16,17} Metal ions have also been reported to affect the magnitude of the primary kinetic isotope effect (Table I). Fukuzumi has suggested\cite{3} that these metal ion effects can be quantitatively evaluated by using the proposed multistep e-p-e mechanism and by considering the changes in the redox potentials of NADH models and quinones in the presence of metal ions. On the other hand, the one-step hydride transfer mechanism cannot give a satisfactory explanation.

As stated earlier, a charge-transfer complex between NADH model compounds and quinones as a reaction intermediate prior to the first electron transfer step has been proposed and characterized for the non-metal ion mediated hydride transfer reactions. Similarly, a ternary complex [BNAH-Mg\(^{2+}\)-Q] was also observed by UV/visible spectroscopy for e-p-e type of reactions.\cite{12}
Table I. Effects of Mg$^{2+}$ on the Rate Constants and Primary Kinetic Isotope Effects for reactions of Various Quinones(Q) with a NADH Model Compound BNAH.

<table>
<thead>
<tr>
<th>Q</th>
<th>$k_{\text{obsd}}^H$</th>
<th>$k_H / k_0$</th>
<th>$k_{\text{obsd}}^H$</th>
<th>$k_H / k_0$</th>
<th>$k_{\text{obsd}}^H$</th>
<th>$k_H / k_0$</th>
<th>$k_{\text{obsd}}^H$</th>
<th>$k_H / k_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>7.6</td>
<td>6.1</td>
<td>0.59</td>
<td>5.4</td>
<td>1.0</td>
<td>3.5</td>
<td>53</td>
<td>1.9</td>
</tr>
<tr>
<td>3b</td>
<td>50</td>
<td>5.5</td>
<td>2.9</td>
<td>6.3</td>
<td>3.0</td>
<td>4.6</td>
<td>96</td>
<td>2.5</td>
</tr>
<tr>
<td>3c</td>
<td>730</td>
<td>5.2</td>
<td>60</td>
<td>5.8</td>
<td>24</td>
<td>6.1</td>
<td>61</td>
<td>2.1</td>
</tr>
<tr>
<td>3d</td>
<td>75</td>
<td>5.6</td>
<td>4.5</td>
<td>5.8</td>
<td>5.1</td>
<td>4.3</td>
<td>13</td>
<td>2.1</td>
</tr>
</tbody>
</table>

| a. | Reference 13,14   | b. Reference 16 |

The success that the e-p-e mechanism has had in providing explanations of metal ion effects and primary kinetic isotope effects has been taken as strong evidence for this mechanism. Very recently, Fukuzumi proposed\textsuperscript{18-21} a new approach to probe the mechanism of the reduction by NADH and NADH model compounds. The idea was to utilize the differences in the pH dependences of the one-electron and two-electron redox properties of the substrates. By comparing the pH dependences of the rate constants with the pH dependences of corresponding redox potentials, it was possible to distinguish mechanisms. They investigated the reduction of p-benzoquinone derivatives by an acid-stable NADH model compound 9,10-dihydro-10-methylacridine (AcrH\textsubscript{2} Figure 1). The study showed that the pH dependences of log $k_{\text{obs}}$ and primary kinetic isotope effects were consistent with that of one-electron reduction potentials ($E_{\text{red}}^1$) of p-benzoquinone. Furthermore, a single linear relationship (eq 18) between log $k_{\text{obs}}$ and $E_{\text{red}}^1$ was obtained for several p-quinones, while no such single linear relationship was found between log $k_{\text{obs}}$ and the two-electron reduction potentials ($E_{\text{red}}^2$). All of these results strongly suggest that the activation barrier of the reduction of quinones by AcrH\textsubscript{2} is correlated with the energetics of the one-electron pathway rather than the two-electron pathway.\textsuperscript{20}

$$\log k_{\text{obs}} = 14.4E_{\text{red}}^1 - 1.3$$

(18)

Theoretical work has been reported by Kreevoy and coworkers.\textsuperscript{9-10} They find that no high-energy intermediates intervene between reactants and products in hydride transfer reactions between NAD$^+$ analogues, thus they believe that both outersphere and inner-sphere e-p-e mechanisms must
be rejected. However, recent electrochemical study of 10-methylacridine/acridinium redox couple showed that acridinium (a NAD$^+$ model used by Kreevoy and coworkers$^{9-10}$) is a rather strong oxidant. With such strong oxidant, electron transfer process is not necessarily impossible.$^{11}$

CONCLUSION

In summary, one-step hydride transfer and multistep electron-proton-electron transfer mechanisms have been proposed for the reduction of quinones by NADH and NADH model compounds. Evidence has been offered to support both mechanisms, although multistep electron-proton-electron transfer mechanism seems to provide more quantitative information about the transition state. However, it should be pointed out that the mechanistic controversy over the reduction by NADH and NADH model compounds is probably going to continue unless evidence appears that unequivocally discriminates between these possible pathways. It has been suggested by Miller and coworkers$^4$ that an accurate description of the process should include solvent motion and tunnelling, and the stepwise mechanism and classical transition state theory may be not sufficient for an accurate description of such a process.

REFERENCES

and references cited therein.
ORGANIC SEMINAR ABSTRACTS
1990-91, SEMESTER II
University of Illinois

Department of Chemistry
Box 68, Roger Adams Laboratory
1209 West California Street
Urbana, Illinois 61801-3731

June, 1991

Copyright © by The Board of Trustees of the University of Illinois
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Reagent Structure and Stereochemical Aspects of the Reformatskii Reaction</td>
<td>1</td>
</tr>
<tr>
<td>Mark E. Schnute</td>
<td></td>
</tr>
<tr>
<td>Chiral Recognition Between the Enantiomers of a Molecule</td>
<td>10</td>
</tr>
<tr>
<td>Paul Pospisil</td>
<td></td>
</tr>
<tr>
<td>Toward the Development of Asymmetric Simmons-Smith Reagents</td>
<td>21</td>
</tr>
<tr>
<td>Wonjae Lee</td>
<td></td>
</tr>
<tr>
<td>Current Progress in the Mechanism of DNA Degradation by Bleomycin</td>
<td>31</td>
</tr>
<tr>
<td>Jason Rockhill</td>
<td></td>
</tr>
<tr>
<td>Computer Generation of Novel Dopamine Agonists</td>
<td>41</td>
</tr>
<tr>
<td>J. Kreps</td>
<td></td>
</tr>
</tbody>
</table>

*Due to an oversight, this abstract is not included.*
REAGENT STRUCTURE AND STEREOCHEMICAL ASPECTS OF THE REFORMATSKII REACTION

Reported by Mark E. Schnute

INTRODUCTION

One of the first tools synthetic organic chemists were able to include to their now vast repertoire of organometallic carbon-carbon bond forming reactions were those involving zinc. The development of magnesium organometallic reagents by Grignard in the early 1900’s may have overshadowed the importance of zinc; however, one method which has endured and adapted to the changes in organic chemistry is the Reformatskii reaction, originally discovered by Sergei Nikalayevich Reformatskii in 1887. The classical Reformatskii reaction (Scheme I) involves the formation of β-hydroxyesters by the reaction of metallic zinc with an α-haloester and a ketone or aldehyde. The resulting β-hydroxyester can be subsequently hydrolyzed to the corresponding β-hydroxyacid or dehydrated to an unsaturated ester with an overall extension of the carbon chain by two atoms. Over time, however, its applications have vastly expanded, and a more general definition of the Reformatskii reaction would be any reaction of a carbonyl or carbonyl equivalent with the organometallic species derived from the insertion of zinc into a carbon-halogen bond activated by a carbonyl. If a properly substituted bromoester and carbonyl compound are employed where \( R^1 \neq R^2 \) and \( R^3 \neq R^4 \), the Reformatskii reaction becomes a method to potentially construct two adjacent carbon centers stereoselectively. This review will discuss recent work toward the partial control of the diastereoselectivity as well as enantioselectivity in the reaction by modifications to the α-bromocarbonyl and the introduction of chelating groups or chiral elements into the electrophile.

Scheme I

In order to explain and subsequently design systems to control the stereochemical outcome of the Reformatskii reaction, it is first necessary to understand the reagent structure in solution; however, it is only recently that advances in this area have been achieved. The question of whether the Reformatskii reagent is a C-metallated or an O-metallated species in solution has been probed by \(^1\text{H}\) and \(^{13}\text{C}\) NMR as well as by IR spectroscopy. The \(^{13}\text{C}\) NMR spectra of the reagents

Copyright © 1990 by Mark E. Schnute
from tert-butyl bromoacetate, -propionate, and -isobutyrate (Table I) in a variety of solvents all lack the vinylic resonance expected for C-1 of an enolate structure. In addition, the coupling constant ($J_{C_1-H}$) of 128-132 Hz is consistent with an sp$^3$ hybridized carbon. The carbonyl carbon C-2, however, does show a noticeable downfield shift when compared to the parent t-butylester (1a-c) which varies depending on the polarity of the solvent. Infrared spectroscopy performed on 2a has shown a shift in the carbonyl absorption from 1660 cm$^{-1}$ in DMSO to 1580 cm$^{-1}$ in THF indicating a weaker C-O bond in the latter solvent. This has been interpreted as a C-metallated species with zinc coordination to the carbonyl oxygen. An X-ray

Table I. $^{13}$C NMR of Reformatskii Reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Solvent</th>
<th>C$_1$$^a$</th>
<th>$J_{C_1-H}$</th>
<th>$\Delta \delta^{b}$</th>
<th>C$_2$</th>
<th>$\Delta \delta$</th>
<th>C$_3$</th>
<th>$\Delta \delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>DMSO</td>
<td>20.8</td>
<td>128.6</td>
<td>-1.4</td>
<td>177.4</td>
<td>7.9</td>
<td>75.5</td>
<td>-3.9</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>Pyridine</td>
<td>20.4</td>
<td>130.0</td>
<td>-1.8</td>
<td>179.5</td>
<td>10.0</td>
<td>76.7</td>
<td>-2.8</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>THF</td>
<td>22.7</td>
<td>132.0</td>
<td>1.4</td>
<td>186.2</td>
<td>17.4</td>
<td>80.4</td>
<td>0.8</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>H</td>
<td>CH$_3$</td>
<td>THF</td>
<td>33.3</td>
<td>128.0</td>
<td>4.1</td>
<td>187.4</td>
<td>13.3</td>
<td>81.8</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>THF</td>
<td>38.2</td>
<td>2.9</td>
<td>9.9</td>
<td>185.8</td>
<td>9.9</td>
<td>80.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

$^a$ ppm $^b$ Difference in $\delta$ reported C$_1$(2a-c) - C$_1$(1a-c)

crystal structure of 2a (Figure 1) obtained from THF by Dekker and coworkers indicates that the reagent is dimeric forming a nonplanar eight membered ring with zinc tetrahedrally coordinated to carbon, bromine, and the carbonyl oxygen as well as a solvent molecule. This observation is in agreement with the NMR evidence indicating carbonyl participation. Based on ebulliometric and cryoscopic molecular weight determinations in various solvents, the dimeric nature of the Reformatskii reagent (2a) in solution was also confirmed except in extremely polar solvents such as DMSO were it exists as a C-metallated monomer. The steric bulk of the ester group has been shown to have little effect on the reagent structure, whereas, substitution at the $\alpha$-carbon could destabilize the dimer as exemplified by the decreased $\Delta \delta$ values of the carbonyl carbon (C-2) in the $^{13}$C NMR spectra (Table I, entries 3-5) which approaches that of the monomeric species found in DMSO (entry 1).
Parameterization

Figure 1: X-ray crystal structure of (BrZnCH₂COO-tert-Butyl·THF)₂²⁻a.

REACTION PATHWAY

Extensive theoretical studies of the mechanism of the Reformatskii reaction have been conducted by Dewar and Merz⁷ employing the MNDO method (Modified Neglect of Diatomic Overlap). In this study the dimer was found to be the most stable form of the reagent; however, the lowest energy pathway leading to products was calculated to proceed through an oxygen metallated enolate complex with the aldehyde or ketone. As shown by the reaction pathway proposed by Dewar (Scheme II), reaction of 3 to form the zinc chelated product (5) would proceed through an antiaromatic transition state and consequently a high energy barrier would be involved. On the other hand, if interconversion to the enolate structure (4) occurred, the desired product could be formed via an aromatic six center transition state similar to a [3,3]-sigmatropic shift. Considering the dimeric species, the reaction could proceed through a six centered transition state forming a carbon-carbon bond between C-1' and C-5 or a four centered transition state involving C-1' and C-1 (Scheme III). While the latter was calculated to involve a high activation energy, Dewar was unable to deduce a pathway leading through a six membered ring that did not break up the dimeric structure.

Scheme II
Assuming coordination of the aldehyde or ketone to zinc displaces a solvent molecule, it is clear that the exo position of the carbonyl limits the approach to C-5 to no less than 6 Å. However, if in solution the ring is fluxional, a ring flip would place the electrophilic carbonyl over the dimer ring and in close contact with C-5 (Scheme III). Likewise if complexation occurred by an S_N2 displacement of the solvent molecule, a similar structure could be proposed. Therefore, based on the limited mechanistic understanding of the reaction it is difficult to rule out any of the possible pathways.

Scheme III

TRANSITION STATE STRUCTURES
One explanation of the stereochemical potential of the Reformatskii reaction was originally proposed by Zimmerman and Traxler and invokes a six membered cyclic transition state which minimizes steric interactions. The diastereoselectivity of the reaction of simple bromoesters with ketones and aldehydes has been studied for various solvents, temperatures, and substitution patterns, and a strong dependence on whether kinetic or thermodynamic control is in effect has been observed. Based on work by Gaudemar (Table II) it is believed that kinetic control predominates in dimethoxymethane at -78 °C. It is noteworthy that changing the solvent from dimethoxymethane to DMSO, where it is known that the reagent is monomeric, drastically lowers the selectivity. This strongly indicates that the dimeric structure is important in explaining the stereochemical outcome of the reaction. A transition state picture must also consider the influence of the ester since under kinetic control, there is a correlation between its steric bulk and improved selectivity while an attenuated effect is observed under thermodynamic control. The use of an
aldehyde as opposed to a ketone can also strongly influence selectivity and in some cases even completely reverse it. An alternative transition structure to the Zimmerman-Traxler model that incorporates these observations could be proposed by invoking the dimer (6) where orientation of substituents about C-5 are governed by steric requirements of the dimer formation and at C-1' by steric interactions with one of the esters.

**Table II.** Diastereoselectivity in the Reformatskii reaction.

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Solvent</th>
<th>ratio 7 : 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>CH₂(OMe)₂</td>
<td>38 : 62</td>
</tr>
<tr>
<td>Et</td>
<td>Me</td>
<td>CH₂(OMe)₂</td>
<td>50 : 50</td>
</tr>
<tr>
<td>i-pr</td>
<td>Me</td>
<td>CH₂(OMe)₂</td>
<td>70 : 30</td>
</tr>
<tr>
<td>t-butyl</td>
<td>Me</td>
<td>CH₂(OMe)₂</td>
<td>85 : 15</td>
</tr>
<tr>
<td>t-butyl</td>
<td>Me</td>
<td>DMSO</td>
<td>60 : 40</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>CH₂(OMe)₂</td>
<td>50 : 50</td>
</tr>
<tr>
<td>t-butyl</td>
<td>H</td>
<td>CH₂(OMe)₂</td>
<td>53 : 47</td>
</tr>
</tbody>
</table>

**CHIRAL AUXILIARIES**

Numerous attempts to achieve an asymmetric Reformatskii reaction by using α-bromoesters derived from optically active alcohols (Figure 2) have been reported. Notable among these are terpene skeletons\(^\text{11,12}\) such as (-)-menthol (9) and (-)-borneol (10), a carbohydrate template 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose\(^\text{12}\) (11), and recently lactic acid derivatives\(^\text{13}\) such as (1-benzyloxyprop-2-yl) bromoacetate (12). However, none have shown great promise, exhibiting relatively low asymmetric induction and generally poor yields. The failure of chiral auxiliaries in the ester functionality can be explained by the distance of the chiral moiety from the reaction center as well as the limited role that the ester plays when the reaction is under thermodynamic control.

**Figure 2.** Optically active bromoesters used in the Reformatskii reaction.
OXAZOLIDINONES

More promising results have been achieved in controlling the stereochemical outcome of the Reformatskii reaction by using sterically crowded 3-(2-bromopropionyl)-2-oxazolidinones (13a-d). The resulting products can be cleaved to the methyl esters achieving diastereomeric ratios as high as 98:2 in high yield with predominantly syn-selectivity (Table III). By extending this method to an optically active oxazolidinone (13d), diastereofacial control in the reaction has been attempted. Contrary to results with (13b,c), diastereoselectivity was lost and low asymmetric induction was obtained in the syn product case (42% ee); however, 100% ee was observed in the anti-isomer. The observed stereochemistry has been explained by formation of a six membered cyclic transition state with the carbonyl of the oxazolidinone coordinated to zinc (Figure 3). Enantioselectivity is a result of 1,3 steric interactions between the oxazolidinone substituent lying over the ring (16) and either hydrogen (syn) or phenyl (anti) as opposed to carbonyl attack from the open face. A more complex oligomeric species, however, can not be ruled out.

Table III. N-(α-Bromoacyl)oxazolidinones in the Reformatskii reaction.

<table>
<thead>
<tr>
<th></th>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>R_4</th>
<th>yield (%)</th>
<th>ratio 14:15</th>
<th>% ee (14:15)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>81</td>
<td>38 : 62</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>99</td>
<td>96 : 4</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>n-Butyl</td>
<td>n-Butyl</td>
<td>(CH_2)_5^-</td>
<td>98</td>
<td>98 : 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>i-Pr</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>82</td>
<td>52 : 48</td>
<td>42% : 100%</td>
</tr>
</tbody>
</table>

a % ee based on optical rotation of methylesters.

Figure 3. Transition states leading to anti products.
NITROGEN CHELATION

Zinc can form strong coordinate bonds to nitrogen as well as oxygen, and this characteristic has been utilized in two methods to control stereochemistry by using α or β-amino ketones and external amine chelating agents. Early work by Guette and coworkers showed that (-)-sparteine, a naturally occurring diamine, could induce high asymmetric induction in Reformatskii reactions of ethyl bromoacetate with benzaldehyde. Although optical purities in excess of 90% were obtained, yields were generally low. Lucas and Guette have prepared γ or δ-amino-β-hydroxyester in predominantly the erythro configuration by a Reformatskii reaction with the corresponding α(β) tertiary amino ketones (18a-c). Diastereomeric ratios as high as 88:12 can be obtained even with bulky substituents in the α position of methyl bromoesters (Scheme IV).

The best stereocontrol is obtained with β-aminoketones using the more nucleophilic amino group (18a) as would be expected for stronger coordination to the zinc. The proposed bicyclic transition state involves coordination of the zinc to the enolate as well as to the nitrogen and carbonyl of the electrophile. In this case, the additional chelation by nitrogen might prevent dimer formation. This technology has been used to control the cis to trans ratio in the synthesis of (1S,2S)-1-hydroxy-2-[(S)-valylamino]-cyclobutane-1-acetic acid, a microbial inhibitor.

Scheme IV

CHIRAL ACETALS

Reformatskii reagents have shown reactivity towards numerous electrophiles other than carbonyls including nitriles, azomethines, oxiranes, imines, and acetals. The use of Reformatskii reagents in additions to imines for the stereoselective construction of β-lactams (Scheme V) has recently been reviewed and offers high yields as well as solely the cis isomer in many cases. Acetals provide the opportunity to build a chiral moiety into the Reformatskii

Scheme V
acceptor thus allowing for a stereocontrolled synthesis of β-hydroxy esters. The reaction of chiral cyclic acetals (20a-d) with the Reformatskii reagent derived from ethyl bromoacetate in the presence if TiCl₄ produces the 3-alkoxyesters 21 and 21' (Scheme VI) in diastereomeric ratios as high as 92:8 (Table IV). Cleavage of the chiral auxiliary results in the optically active β-hydroxyesters. The proposed mechanism and reactivity of chiral acetals toward various nucleophiles has recently been reviewed. It is generally believed that the cyclic acetal is in a chair conformation such that 1,3-diaxial interactions are minimized, and the Lewis acid is coordinated to the oxygen adjacent to the axial methyl. As a result the Lewis acid weakens the carbon-oxygen bond and anti attack by the nucleophile can occur. Based on the configuration of the major product when a Reformatskii reagent is used, a simular mechanism might be in effect.

Table IV. Chiral Acetals in the Reformatskii Reaction.

<table>
<thead>
<tr>
<th>20</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>yield (%)</th>
<th>ratio 21:21'</th>
<th>% ee (22)</th>
<th>config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>80</td>
<td>75 : 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>80</td>
<td>86 : 14</td>
<td>71</td>
<td>(S)</td>
</tr>
<tr>
<td>c</td>
<td>n-C₇H₁₅</td>
<td>Me</td>
<td>Me</td>
<td>73</td>
<td>92 : 8</td>
<td>84</td>
<td>(R)</td>
</tr>
<tr>
<td>d</td>
<td>C₂H₅</td>
<td>Me</td>
<td>Me</td>
<td>73</td>
<td>87 : 13</td>
<td>73</td>
<td>(S)</td>
</tr>
</tbody>
</table>

**CONCLUSION**

After over 100 years, the potential of the Reformatskii reaction to construct carbon-carbon bonds stereoselectively is only now beginning to be utilized, and much is still to be learned about the reagent itself. In order to improve stereoselectivity, it will be necessary to use rational design to construct a reagent that exploits the dimeric nature of the reagent or strong chelating ability of the zinc atom. Also, the Reformatskii reagent should not be considered to be limited to reactions with prochiral ketones and aldehydes, but rather, many acceptor molecules should be considered as possible candidates. Although at present the scope of stereocontrolled Reformatskii reactions is
limited, the simplicity of the reagent and broad range of its reactivity, still largely undiscovered, offers inherent advantages that have yet to be fully exploited.

REFERENCES


CHIRAL RECOGNITION BETWEEN THE ENANTIOMERS OF A MOLECULE

Reported by Paul Pospisil  January 21, 1991

Chiral recognition describes a differential level of noncovalent interactions between two or more dissymmetric entities. Although the complexes formed between two different enantiomers are currently the focus of much attention because of their ubiquity and importance in nature (e.g., substrate-enzyme interactions), here the focus is given to intermolecular complexes of enantiomers of one molecule. The possibilities of complexation are between two like (d•d) or two antipodal (d•l) enantiomers, resulting in homo- and heterochiral complexes, respectively. The phenomenological manifestations arising from these interactions of tetrahedral, main group systems will be surveyed and attempts towards evaluating the energies of the complexes will be discussed.1

THEORETICAL BASIS

To determine which type of interaction, i.e. homo- vs. heterochiral, will be preferred, evaluation of the energy difference between the two noncovalent intermolecular interactions ($\Delta E$) is important. This energy difference can be expressed as:

$$\Delta E = \Delta E_{R\cdot R} - \Delta E_{R\cdot S} \quad \text{where} \quad R\cdot R = S\cdot S \quad \text{and} \quad R\cdot S = S\cdot R$$

The energetic differences are small in comparison to the energies of noncovalent interactions; in the solid state they are on the order of a few kilocalories (kcal/mol) whereas in solution they are in the calorie range (cal/mol). The distances at which chiral discriminations are thought to be effective are medium to short range ($r^{-6}$ to $r^{-12}$). Generally, noncovalent interactions are found to span from a long range, for electrostatic interactions (dipole-dipole, ion-dipole, H-bonding), through a medium range, for van der Waals interactions of neutral molecules, to a short range, for repulsions at interpenetration regions of paired electron shells.2

Chiral discrimination depends both on the nature of the forces as well as the extent of interaction between two enantiomers during complexation (Figure 1). The strength of interaction

Figure 1. The hetero- (R•S) and the homochiral (R•S) complexes of a model compound.

Copyright © 1990 by Paul J. Pospisil
of two molecules depends on the optimal geometric orientation possible between the enantiomers in the complex. Early modeling studies\textsuperscript{3a} showed that at long to medium intermolecular distances electrostatic interactions, such as Coulombic, dipole-dipole, ion-dipole, as well as interactions that are dominated by dispersion forces normally resulted in energetic differences too small to account for chiral discrimination. In experimental cases discrimination at these distances has been observed, and a higher stability of a homo- or heterochiral complex due to a stronger intermolecular interaction (e.g. stronger hydrogen bonding in one complex) has been invoked (e.g. reference 29).

At shorter intermolecular distances and restricted orientations larger energetic differences between homo- and heterochiral interactions have been demonstrated in models. A homochiral preference for the complexation of neutral enantiomers due to dispersion forces was predicted by Craig.\textsuperscript{3a} Another model system\textsuperscript{3b} that accounts for short range discriminations such as those observed in the solid phase (vide infra) is based on meso and $d,l$-2,3-dicyanobutane. This model uses an intramolecular interaction to predict an intermolecular interaction. \textit{Ab initio} calculations were executed as a function of the dihedral angle of the carbon-carbon bond connecting the two moieties that represent chiral methyls. It was found that between possible configurations the energy minimum was -3.0 kJ/mol lower than for the least favored conformation. Craig proposes that a favored interaction between a homochiral or a heterochiral complex will result for that system that is able to fill available space most efficiently. That is, the binding energy can increase by shortening inter-group distances. More recently Salem\textsuperscript{4} modeled two freely rotating chiral tetrahedral molecules and observed a discrimination due to "chirality forces" which required a simultaneous six center interaction between two triplets of atoms. This model attempted to examine the effect of chiral discrimination at short distances considering atom-atom interactions. Topiol\textsuperscript{5} extended this model to include a simultaneous eight center interaction. The fourth atom of both tetrahedra was incorporated into the model as these become involved in any array of extended interactions beyond the original two molecules.
THE SOLID STATE

In the solid state the differential energies of chiral nonbonding interactions are strongest. Historically, the chiral complexations in the solid state were also the first to be identified. In 1848 Pasteur\(^6\) crystallized hemihedral sodium ammonium tartrate as a conglomerate. Hemihedral crystals have half the faces of those required by full symmetry. By inspecting the morphology, opposite symmetries of the two types of crystals were detected. The two forms correspond to the two homochiral complexes (\(d\cdot d\) and \(l\cdot l\)). The special case in which the homochiral complexes are distinguishable by morphology has only been detected in nine other systems. Since Pasteur's time a large amount of data about the macroscopic properties of chiral molecular solids as well as about their crystal structures has been reported.\(^7\)

Chiral molecular solids crystallize as (1) racemates in which heterochiral complexes are formed, (2) conglomerates in which homochiral interactions are favored, or (3) solid solutions in which the extent of chiral discrimination is weak. The first two cases are the more interesting ones with regard to chiral recognition.

Racemates, which constitute the largest subset of these molecular solids, can be differentiated from conglomerates with phase diagrams (Figure 2). Conglomerates display a higher lattice stability when pure as reflected by their higher melting points (\(\Delta H_{\text{ fus}}\)). Racemates, display the opposite behavior, achieving the highest melting point and therefore the highest lattice stability with 1:1 mixtures.

Figure 2. Phase diagrams for (a) conglomerate and (b) racemate. T is the melting temperature of racemate (R) or pure enantiomer (A).

Conglomerates are of considerable interest with regard to industrial purifications. However, only about 250 systems have been reported to crystallize as conglomerates. A considerable effort in industry has been devoted to finding the propitious solvent, temperature and concentration conditions that will favor the crystallization of the conglomerate (e.g. D- and L-glutamic acid are separated industrially through conglomerates).\(^8\)
Measurements on heats of sublimation ($\Delta H_{\text{Sub}}$), heats of fusion ($\Delta H_{\text{Fus}}$), densities and vapor pressures$^{11}$ of the conglomerates and racemates have been performed. For chiral molecular solids the closest packed crystals are not necessarily the most stable ones. The stability depends on a large number of parameters including preferential intermolecular stabilizations.

The free energies ($\Delta G$) for the hypothetical transformation from pure enantiomers to their racemates generally range between 0 to -2 kcal/mol. For conglomerates to form, the difference in intrinsic crystal lattice stabilization energies between it and the racemate has to be large enough to offset an entropic factor. Only then will the free energy be negative and the spontaneous crystallization occur.$^{11,12}$

Thus far only a few studies have addressed the preference of a homo- vs. a heterochiral interaction at a molecular level. Cesario$^{13}$ has compared a series of phenylhydroxy acids, as these show an unusually high incidence of conglomerate formation (Table 1). The unit cells of the pure enantiomer vs. that of the racemate of each of these systems as well as their bulk thermodynamic properties were analyzed. Cesario concluded that due to intermolecular hydrogen bonding the structures of the intercrystalline complexes, favor crystal packing in space groups that are preferred by conglomerates. The racemates in this series almost invariably have space groups that are usually found in conglomerates but are statistically rare for racemates.

Table 1. Phenylhydroxy acids; a series of compounds with high incidence of conglomerate formation. (conglomerate or racemate/space group).

<table>
<thead>
<tr>
<th>X</th>
<th>Conformer</th>
<th>Space Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>cong./P2_1</td>
<td>cong./P2_12_12_1</td>
</tr>
<tr>
<td>F</td>
<td>rac./P2_1</td>
<td>threo cong./P2_1</td>
</tr>
<tr>
<td>Cl</td>
<td>cong./P2_1</td>
<td>erythro rac./P2_1</td>
</tr>
<tr>
<td>Br</td>
<td>cong./P2_1</td>
<td>m-F rac./C_2</td>
</tr>
<tr>
<td>o-Cl</td>
<td>cong./P2_1</td>
<td>p-F rac./C_2</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MONOLAYER STUDIES**

Although investigations of the degree of association between enantiomeric pairs are rare, a highly promising method is emerging. It involves the study of amphiphilic monolayers at the air/water interface.$^{14}$ These are based on surface studies made by Langmuir and Blodgett in the 1920's. There are several advantages to studying chiral intermolecular interactions with
monolayers. First, the 3-dimensional problem of interactions present in the solid or solution state is reduced to a simpler 2-dimensional one at an interface. Second, by adjusting the area of the monolayer the degree of association between the enantiomers can be changed continuously to resemble interactions from a gas to a crystal-like environment. Finally, the extent of homo- or heterochiral interactions can be quantified by changes in the bulk properties of the monolayer such as surface pressure and surface tension. Both of these measurable thermodynamic properties can be related to energy changes.

Monolayers are films of surfactants, one molecule thick, that are deposited onto an ultra-pure water surface. These surfactants are amphiphiles, possessing both a polar hydrophilic head, such as hydroxyl, carboxyl or amino group and a long, hydrophobic straight chain hydrocarbon tail. By making the side chain long enough (>C₁₀) micelle formation is minimized as the whole amphiphile becomes more hydrophobic. To study enantiomeric interactions, chiral polar groups are employed. It is the difference in homochiral vs. the heterochiral interactions between these centers that give rise to closer or looser packing of the monolayer. Strong interactions are manifested by a contraction in the surface area of the film. The changes in the surface area can be monitored by using a variety of methods, such as a Langmuir balance.

![Graph](image)

**Figure 3.** Idealized surface pressure (π) vs. area (A) isotherm representing the proposed molecular orientations and aggregations during a compression cycle.

The surface pressure (π) can be calculated from the change in the surface tension between the aqueous surface prior to (γ°) and after (γ) having been covered by the monolayer. By correlating the surface pressure (π) to the area (A) for a given monolayer at various temperatures,
the molar enthalpy (ΔH) is calculated using the two dimensional analog of the Clausius-Clapeyron equation (Equation 1).

\[ \Delta H = T \Delta A \frac{d\pi}{dT} \quad \text{where } \pi = \gamma - \gamma^0 \quad (1) \]

The phase changes of a monolayer that are obtained by contracting or expanding the surface area of the film can be followed by characteristic changes of a pressure/area isotherm as shown for an ideal case in Figure 3. As the area of the surface is decreased, the amphiphile head groups are pushed closer together and the hydrocarbon tails are found to stack. In this way the arrangement of the polar head groups can be controlled. Thus, the cross-sectional area in the "solid" monolayer phase is similar to that present in crystals (~ 20 Å).

The use of monolayers to evaluate the interactions between two stereogenic centers dates back to research performed in the 1950's. However, only in the last two years have the magnitudes of these interactions been determined. The first studies by Zeelen examined the force/area relationship of various N-stearoyl amino acid amphiphiles of the homochiral enantiomers and their racemic mixtures. A dependence on the extent of interaction between the chiral amphiphiles was established both as functions of the pH of the aqueous subphase and of structural features of the enantiomers.

Lundquist examined the temperature dependence of the π/A isotherms of (R,S) and (S)-2-tetracosanoyl acetate. At low temperatures a preference for interaction of homoenantiomeric amphiphiles in the solid monolayer phase was observed. In contrast at higher temperatures no chiral recognition was detected.

More recently, both Dupeyrat and Arnett have independently investigated systems which show preferential interactions with enantiomerically pure amphiphiles. Arnett has performed rigorous studies on D, L and L-stearoyl tyrosine as well as on D, L and L-stearoyl serine methyl ester monolayers (Figure 4). By measuring a set of physical properties of the monolayers, i.e. measuring force/area isotherms, hysteresis in compression/expansion cycles and surface shear viscosities, a temperature dependent chiral recognition process was established. Favorable interactions allow the formation of quasi crystalline domains for the enantiomerically pure systems. Therefore, the stabilities of the homoenantiomeric and racemic monolayers differ to a varying extent at each of the temperatures investigated (20 °C, 25 °C, 30 °C, 40 °C). The different stabilities are attributed to the inability of the homoenantiomeric microcrystalline domain to expand as easily as the racemic one. This solid domain is conceptually equivalent to the formation of a crystal from solution. The crystals of stearoyl serine methyl ester however, are racemates. This indicates that the results of the monolayer studies may not in all cases be generalized to crystal packing preferences. The "solidified" monolayers were visualized by
scanning tunneling microscopy and epifluorescence. No recognition was observed in the liquid monolayer phase.

Andelman \(^{24}\) has recently reported modeling studies for chiral discrimination in monolayers by considering possible interactions of systems such as those shown in Figure 4. A simple model makes the assumptions that the tetrahedra of the amphiphilic heads have three of the groups restricted to the water surface and that the interactions are between two points at short distances. By modifying the nature of the substituents this model predicts a preference for heterochiral complexes if van der Waals forces are involved. In contrast, electrostatic interactions are predicted to show a homochiral preference.

\[
\text{Figure 4. Enantiomeric and racemic surfactants in which chiral headgroups are oriented in the air/water interphase.}
\]

**SOLUTION PHASE**

Generally, chiral interactions in solution are too weak to be detected; this is especially true in dilute solutions where the solvent molecules compete effectively with the possible complexation sites of two enantiomers. However, in more concentrated solutions effects due to chiral recognition interactions can become detectable and when the interaction of a set of enantiomers in solution is strong enough a transition to the solid phase will occur.\(^1\) Various physical measurements of bulk properties have been performed on solutions of homochiral enantiomers and their racemates. These include measurements of differences in density, aggregation states, dipole moments, surface tension, viscosity, indices of refraction and UV studies. An important weakness with these studies is that the differences in the measured effects are so small that they
could be attributed to experimental error. Therefore it is not surprising to find contradictory reports on which chiral interactions are favored.25

Small yet marked deviations from ideal behavior that point towards the presence of diastereomeric complexes are detectable in calorimetric measurements as well as in polarimetric and NMR investigations.26,27,28 In microcalorimetric studies of both aqueous tartaric acid and threonine solutions Amaya27 detected a difference in heats of solvation in favor of the racemic solution by about 0.5 cal/mol, indicating non-ideal behavior.

Uskokovic29 was the first to detect a difference in the 1H NMR spectra of an enantiomerically pure compound and a racemic mixture in an achiral solvent. At specific concentrations and temperatures, enantiomers of dihydroquinine were found to dimerize via intermolecular hydrogen bonding to give rise to distinguishable homo- and heterochiral complexes. The nonequivalence of the S•S and R•S complexes is rationalized by invoking dimerization of the enantiomers. However, no preference of the homo- over the heterochiral complexes of the dihydroquinine enantiomers was observed. More recently, Hara28 reported a similar type of interaction in which nonequivalence in the 1H NMR spectra is observed for the association between D- and L-amino acid derivatives. A preferential homochiral interaction as shown in Figure 5 is observed at temperatures of -20 °C. This discrimination is found to be highly dependent on the presence of the tert-butyl ester substituent.

![Figure 5. Proposed structure for the homochiral dime (L•L) interlinked by two intermolecular hydrogen bonds.](image)

**ENANTIOSELECTIVE CRYSTALLIZATION**

Weissbuch has presented30 a model for the spontaneous generation and amplification of optical activity in α-amino acids that has demonstrated the importance of chiral recognition forces. This model relied on the ability of centrosymmetric crystals of glycine to serve as a nucleation site for selective crystallization of one enantiomer from a racemic amino acid solution. The resulting enantiomerically enriched medium might resemble the "primordial soup" from which nonracemic life could have evolved.
Glycine has been found to crystallize from water as a monoclinic, centrosymmetric, \( \alpha \)-form crystal.\(^{31}\) Further it has been shown that glycine crystals are enantiopolar, that is they comprise two enantiomeric sets of regularly intermeshed polar crystals that are related to each other by symmetry elements (i.e. center of inversion). The crystal will have different faces with different polarities. This implies that glycine is adsorbed differently on two of its crystal faces. On one face along the crystal’s polar axis the pro-\((R)\) and on the opposite face the pro-\((S)\) hydrogens are directed away from the crystal’s center. One crystal face was blocked selectively and placed into a racemic solution of a chiral amino acid. It was observed that only one enantiomer was occluded onto the free glycine surface.\(^{32}\)

Thin platelets of glycine have a tendency to float on the water surface at the air interface. By addition of a slight enantiomeric excess of amino acids with hydrophobic side chains, such as phenylalanine, one face of the glycine has been shown to orient exclusively towards air at the aqueous interface. The second face of glycine then serves as the nucleation site on which a selective crystallization of one enantiomer is found to take place. This system serves as a chiral amplification model that only requires a small initial enantiomeric excess. There are several theories that explain how a small excess could have been generated under prebiotic conditions.\(^{33}\)

CONCLUSION

In summary, chiral recognition between enantiomeric pairs is measurable with currently available techniques in the solid phase but is usually too weak to be detected in the liquid phase. The gap between the theoretical models that describe the interactions at a molecular level and the actual empirical systems that focus on measuring bulk properties is still large. Model studies involving monolayers, although having severe limitations, offer an approach towards studying these interactions. To date, no clear understanding of this subset of interactions at the frontier of supramolecular chemistry has yet emerged.

REFERENCES

(2) Craig, D. P.; Mellor, D. P. Topics Curr. Chem. 1976, 63, 1 and references therein.

TOWARD THE DEVELOPMENT OF ASYMMERIC SIMMONS-SMITH REAGENTS

Reported by Wonjae Lee

February 7, 1991

INTRODUCTION

The asymmetric cyclopropanation reaction has become an important subject of research in organic synthesis. Optically active cyclopropyl compounds are biologically active in certain natural products. Also, the cyclopropane moiety provides a potentially valuable building block in organic synthesis.

There are a number of the cyclopropanation reagents and catalysts known at this time. Free carbenes and metal carbenoids have been used for the addition to olefins. Transition metal carbene complexes can transfer carbene units to olefins to form cyclopropanes. Addition of diazocompounds to olefins, catalyzed with copper or rhodium complexes, produces cyclopropane products. The Simmons-Smith reagent, generated from methylene iodide with Zn-Cu couple in the presence of olefins forms cyclopropanes (Scheme I).

Scheme I

Several addition reactions to prochiral olefins to form new asymmetric centers are well known. They include the catalytic hydrogenation of prochiral olefins with rhodium or iridium complexes, Sharpless epoxidation of allylic alcohols and chiral manganese complexes in the oxidation of unfuctionalized olefins. All of these discriminate between the two enantiofaces of a prochiral olefin, allowing addition of some group (2H, O) preferentially to one side of the olefin.

Until now, only a few examples of the asymmetric Simmons-Smith cyclopropanation have been achieved. The Simmons-Smith reaction primarily gives asymmetric cyclopropanation products using chiral phenylsulfoximines as substrates. It has been modified by the addition of chiral auxiliaries, including acetals of diisopropyl tartrate or homo chiral ketal. In both cases, high diastereoselectivities have been achieved. However, the lack of isolated reactive species or intermediates has limited the further development of this reagent for asymmetric cyclopropanation. Research is still necessary to improve the generality of the reagent and to develop better chiral reagents or catalysts for asymmetric cyclopropanation.
In this review, the structure and mechanism, including proposed and calculated transition states, of the Simmons-Smith reagent and asymmetric modification of the reagent will be discussed.

**STRUCTURE OF THE SIMMONS-SMITH REAGENT**

The zinc carbenoid generated from methylene iodide with Zn-Cu couple was first introduced by Emschwiler in 1929 and it was suggested that the reactive species was iodomethylzinc iodide\(^1\) (Scheme II). Simmons and Smith carried out the reaction in the presence of olefins for a new synthetic route to cyclopropane derivatives\(^4\) (Scheme I). Furukawa developed the modified Simmons-Smith reaction using diethylzinc instead of the Zn-Cu couple. It was reported to be particularly useful for the synthesis of substituted cyclopropanes when methylene iodide carries an alkyl or aryl substituent, whereas the reactions of those with Zn-Cu generally give poor yields\(^12\) (Scheme III).

Scheme II

\[
\begin{aligned}
\text{CH}_2\text{I}_2 + \text{Zn} &\rightarrow \text{CH}_2\text{ZnI} + \text{Zn}^2
\end{aligned}
\]

Scheme III

According to the Schlenk equilibrium, bis(iodomethyl)zinc can be another possible species in solution (Scheme IV). However, the equilibrium in iodomethylzinc iodide is expected to lie to the left, if its behavior is similar to that of ethylzinc iodide (EtZnI). Ethylzinc iodide exists largely in the monomeric form in solvents such as diethyl ether and tetrahydrofuran as do other...
ethylzinc halides. The presence of α-iodine atom in the Simmons-Smith reagent, however, may disturb the Schlenk equilibrium. In fact, the formation of bromomethylzinc bromide in tetrahydrofuran at 35-40°C was mainly observed by NMR with two further species. The former was, on standing, completely converted to further species, probably, Zn(CH₂Br)₂. Recently, the structure of the species chelated by ethers in Furukawa reagent has been identified as (ICH₂)₂Zn by Denmark. The X-ray structure of bis(iodomethyl)zinc complex with (1S,2R,3S)-bornanediol-derived bis-ether demonstrates a monomer in the solid state (Figure 3). In solution, an NMR study shows the bis(iodomethyl)zinc species lies in rapid dynamic equilibrium with a dimethoxyethane complex.

The Simmons-Smith cyclopropanation proceeds with the mixture of methylene iodide and Zn-Cu couple in refluxing diethyl ether in the presence of olefins. It was reported that the copper plays no role other than activating the zinc surface for reaction. Recently, improved methods for zinc activation were reported, using a catalytic amount of TiCl₄ and acetyl chloride as efficient promoters in the presence of CuCl for cyclopropanations of alkenes with less reactive dihalomethanes. After the formation of zinc carbenoid from CH₂I₂ and Zn-Cu couple,
cyclopropanation by methylene transfer occurs. During the reaction no carbene-like insertion products or rearranged cyclopropanes are detected.\textsuperscript{4}

The reaction leads to cyclopropane derivatives in a stereospecific way. The cis- and trans olefins react to yield pure cis- and trans cyclopropanes, respectively. The reaction of the Simmons-Smith reagent with olefin follows second-order kinetics, first order each in olefin and in iodomethylzinc iodide. The possibility of a two-step (addition and elimination) mechanism was ruled out because the reaction of trans-1,6-dichloro-3-hexene with (ClCH\textsubscript{2})\textsubscript{2}Zn gives the only product of trans-cyclopropane without the isomeric cyclopropane, which could come from an intermediate\textsuperscript{18} (Scheme V).

\textbf{Scheme V}

\[
\text{\textacutenot} \quad \text{\textit{ClCH}^2Zn} \quad 95\% \\
\]

The reactivity of an olefin with the Simmons-Smith reagent increases with increased alkyl substitution on the double bond. Table I summarizes the results with the relative reactivity of the olefins in two zinc carbenoids and other carbene reactions using cyclohexene as the standard.\textsuperscript{12} Competition studies indicate a larger steric requirement with the Simmons-Smith reagent compared to the zinc carbenoid prepared from Et\textsubscript{2}Zn and CH\textsubscript{2}I\textsubscript{2} and other halocarbenes.\textsuperscript{4,19} In Furukawa reagent, the inductive effect might predominate over the steric effect in non polar solvents.

\textbf{TABLE I. Relative reactivity of olefins (k/kc for reactant)}

<table>
<thead>
<tr>
<th>Olefin</th>
<th>CH\textsubscript{2}I\textsubscript{2} + Et\textsubscript{2}Zn</th>
<th>CH\textsubscript{2}I\textsubscript{2} + Zn-Cu</th>
<th>CH\textsubscript{2}I\textsubscript{2} + Zn-Cu-Cl</th>
<th>CH\textsubscript{2}I\textsubscript{2} + Zn-Cu-Br</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Et\textsubscript{2}O</td>
<td>n-Pentane</td>
<td>Benzene</td>
<td>Et\textsubscript{2}O</td>
</tr>
<tr>
<td></td>
<td>8.82</td>
<td>16.2</td>
<td>12.5</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>9.65</td>
<td>2.18</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>0.15</td>
<td>0.27</td>
<td>0.15</td>
<td>0.36</td>
</tr>
</tbody>
</table>
solvents, as shown larger relative reactivities than the Simmons-Smith reagent. The Hammett ρ-value for p-substituted styrenes with zinc carbenoid generated from diethylzinc and CH₂I₂ in benzene was -1.61, suggesting the importance of the inductive effect of the substituent in determining rate of methylene transfer from diethylzinc and methylene iodide.¹²

Hydroxyl groups in proximity to the double bond of the substrate can direct cyclopropanation²⁰ (Scheme VI). In cyclopentenes and cyclohexenes, an allylic or a homoallylic hydroxyl group induces stereospecifically cis introduction of the methylene group with a large rate enhancement. However, when the hydroxyl group is three carbons removed from the double bond, cis control is largely lost. Thus remarkable stereospecificities in cyclic allylic and cis-acyclic allylic alcohols can be afforded by directing effect of hydroxyl groups.²¹

Scheme VI

PROPOSED AND CALCULATED TRANSITION STRUCTURE

It was originally suggested that the cyclopropane forming reaction occurs by a one step methylene transfer mechanism in which a nucleophilic displacement at carbon of iodomethylzinc iodide by the π electrons in double bond occurs such that both new carbon-carbon bonds are formed simultaneously. The transition state(1) with the linear HCH fragment was proposed, in which inversion of the methylene must occur during the reaction. In this transition state, I-C and Zn-C bond breaking have proceeded to a great extent than C-C bond forming.⁴

Other proposed and calculated transition states in carbenoid reactions are shown to compare to those of the Simmons-Smith reaction. For the reactions of aryl carbenoids with alkene, Closs has proposed the transition structure(2), where an attack by the π electrons of the olefins as a nucleophile is assumed to occur from the opposite side of the halogen atoms, analogous to a normal SN₂ reaction.²² Houk reported a computational result of the reactions of
CH2FLi, the prototype carbenoid with ethylene. The structure is theoretically calculated transition state.

Recently, the molecular orbital calculations were used to investigate the transition structure of the Simmons-Smith reagent with ethylene by Kahn's group. The computed structures of the zinc carbenoid-ethylene complex and the transition state are represented in Figure 4. It was calculated that bromomethylzinc bromide and ethylene form a complex (4) before they react to form cyclopropane. It is not expected that this complex can be present in the solution. Compared to open structure of bromomethylzinc bromide in ground state, in particular, the transition state shows trigonal bridged structure, where bromine atom is bridged between carbon and zinc, similar to the Houk's result. Apparently, the transition structure looks like the butterfly mechanism, but the CH2 group is in a plane nearly parallel to the ethylene plane, as proposed by Closs. Also, it shows that the ZnBr2 moiety is substantially decomplexed, freeing the carbene character of CH2 group which does not invert during the reaction. The calculated transition structure occurs with an advanced C-X bond breaking in an early transition structure, which indicates the loose coordination between the CH2 group and ethylene.

![Figure 4. RHF/3-21G* optimized geometries for structures of bromomethylzinc bromide-ethylene complex (4) and transition structure (5)](image)

**ASYMMETRIC SIMMONS-SMITH REACTIONS**

Through the hydroxy directing effect, Johnson utilized chiral phenylsulfoximines as the resolving reagent for asymmetric induction in Simmons-Smith reaction to obtain optically active cyclopropanes with high optical yields (>90%) (Scheme VII). Addition of the anions of optically active sulfoximines to the α,β-unsaturated ketones gave β-hydroxy sulfoximes as a mixture of two diastereomeric adducts. The diastereomers were separated by column chromatography and subjected to the Simmons-Smith reagent to give the cis-directed diastereomeric cyclopropyl
derivatives. Treatment with aluminium amalgam or mild thermolysis released optically pure cyclopropyl ketone and the starting sulfoximine.

The asymmetric Simmons-Smith cyclopropanation has been modified by the use of chiral auxiliaries. Yamamoto reported an asymmetric Simmons-Smith reaction using a chiral acetal with α,β-unsaturated aldehyde, excess methylene iodide and diethylzinc, affording the corresponding cyclopropanes in a reasonable yield with high diastereoselectivity (88-94% de)⁶ (Table II). He indicated that the observed selectivity can be ascribed to the high affinity of zinc reagent for the ethereal oxygen, totally controlled by the auxiliary tartrate ligand. Also, he indicated that at least O* in (6) should be a preferable coordination site of the zinc reagent. But the stereoselective results can be rationalized by bi-chelation of the zinc reagent with the oxygen atom and carbonyl group of substrate in the opposite face (6).

**Table II.** Asymmetric Simmons-Smith reaction of α,β-unsaturated acetals derived from (R,R)-diisopropyl tartrate

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>yield, %</th>
<th>% de</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>n-Pr</td>
<td>H</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>Et</td>
<td>Me</td>
<td>81</td>
<td>89</td>
</tr>
</tbody>
</table>

Similarly, the asymmetric cyclopropanation of 1-alkenylboric esters was reported by diastereofacial selective Simmons-Smith reaction of the esters modified by chiral tetramethyltartaramide. Subsequent oxidation of the resulting cyclopropylborates afforded 2-substituted cyclopropanols in 89-94% ee.⁷ Also with the use of diol as a chiral auxiliary, highly
diastereo-differentiating Simmons-Smith reactions of enol ether derivatives have been performed to prepare optically active cyclopropanols.\(^8\) Mash developed independently a procedure to achieve asymmetric cyclopropanation of unsaturated cyclic ketones with homochiral ketals.\(^9\) In his results, cyclic ketals exhibit a high diastereoselectivity (70-90%), whereas acyclic acetals exhibit little or no diastereoselectivity (Scheme VIII).

**Scheme VIII**

![Chemical structure](image)

Using mechanistic studies of diastereoselective cyclopropanation, diastereoselectivity was explained as the result from preferential chelation of the Simmons-Smith reagent at the least sterically hindered lone pair of electrons on the dioxolane oxygen proximal to the alkene (the pseudo-equatorial dioxolane oxygen)\(^7\). The regiochemical preference could either antagonize or reinforce diastereoselectivity due to steric hindrance of the dioxolane oxygen atoms. In fact, without dioxolane oxygen, cyclopropanation exhibits no diastereoselectivity. Mash mentioned the appendage oxygen was unnecessary for efficient diastereoselection and even reduced the diastereoseletivity observed (Table III). This reduction seems to be the result of competition between appendage and dioxolane oxygens for chelation controlled delivery of the Simmons-Smith reagent to the opposite faces of the alkene.\(^10\)

**Table III.** Simmons-Smith cyclopropanations of 2-cyclohexen-1-one ketals

<table>
<thead>
<tr>
<th>ene ketals</th>
<th>R</th>
<th>yield, %</th>
<th>diastereomer ratio (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)OCH(_2)Ph</td>
<td>98</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)OCH(_3)</td>
<td>86</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>C(CH(_3))(_2)OCH(_3)</td>
<td>91</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>COOCH(_3)</td>
<td>37</td>
<td>3:2</td>
</tr>
<tr>
<td>5</td>
<td>CH(_3)OH</td>
<td>50</td>
<td>1:2</td>
</tr>
<tr>
<td>6</td>
<td>CH(_3)</td>
<td>86</td>
<td>9:1</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)CH(_2)CH(_2)Ph</td>
<td>92</td>
<td>&gt;9:1</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>90</td>
<td>19:1</td>
</tr>
</tbody>
</table>
SUMMARY

For about 30 years the Simmons-Smith reagent has been effectively used for the synthesis of cyclopropanes owing to broad generality, olefin stereospecificity, highly stereoselectivity by hydroxy directing effect and no side reactions. However, limited knowledge of this reactive species has led to only a few asymmetric Simmons-Smith cyclopropanation reactions and much is still to be studied. Recently, variations of the Simmons-Smith reaction using AlR₃ and Sm(Hg) have been introduced to afford high regio- and diastereoselectivity. The new zinc and cupper multicoupling carbenoids from the Simmons-Smith reagent with cupper nucleophiles leading to methylene homologated organocupper has been investigated. The chiral Simmons-Smith reagent or asymmetric cyclopropanation with the use of chiral additives, like Sharpless epoxidation, or further variation of this reagent based on the knowledge of the structures of the reactives species in solution might be expected to yield optically active cyclopropane derivatives.

REFERENCES


(13) Kahn, S. D.; Lim, D., unpublished results.


CURRENT PROGRESS IN THE MECHANISM OF DNA DEGRADATION BY BLEOMYCIN

Reported by Jason Rockhill

INTRODUCTION

The bleomycin family, 1, of antitumor antibiotics are currently used in the treatment of carcinomas and lymphomas such as Hodgkin's disease. These glyco-peptide based drugs were isolated from *Streptomyces verticillus* in 1966 by Umezawa and co-workers. They were found to degrade DNA by single and double strand scission. Later, *in vivo* studies showed that some soft tissue tumors were reduced in size by treatment with bleomycin. However, in clinical use, the drug exhibited cardiotoxicity in a significant enough percentage (=10%) of those treated with bleomycin, that current use is limited. In an effort to enhance the effectiveness of bleomycin and reduce the toxicity, many investigators have tried to determine the mechanism by which bleomycin degrades DNA.

![Bleomycin Structure](image)

The structure of bleomycin can be divided into three metal binding domains, two sugar residues, and a bithiazole cap. Takita *et. al.* determined the primary structure of bleomycin 1 in 1972, which was later synthesized. The three binding domains are: the pyrimidine, the β-amino alanine, and the β-hydroxy histidine. Each of these domains is proposed to contribute to complexation of a metal ion which is usually iron (II). This complexation is through N1 of the
pyrimidine, the imidazole, a free amino group, an amide, and a secondary amine. The actual complex has never been crystalized, but the proposed structure, 2, is based on an X-ray crystal structure of a modified copper(II) complex.\(^7\) Between the pyrimidine and the imidazole, a polypeptide is attached that has a bithiazole cap on the end. At the end of the cap is a terminal amine which in clinical use is predominantly in the A\(_2\) or B\(_2\) form. This cap has been implicated in the binding of bleomycin to DNA. Proton NMR studies suggests that the bithiazole rings lie in the minor groove with the charged tails attracted to the phosphate backbone.\(^8\) However, intercalation by the bithiazole moiety is also possible due to the planar \(\pi\) system, but the results are inconclusive.\(^9\) Furthermore bleomycin has two sugar residues, a gulose and carbamoylated mannose. These residues have not been implicated in the selectivity or reactivity of bleomycin. They may help in drug uptake by the cell because of a preference to the sugar moieties by the cell although this has yet to be shown experimentally.

Bleomycin has shown selectivity for d(GT) and d(GC) sequences in single strand cleavage of natural DNA.\(^{10,11}\) Cleavage occurs at the deoxyribose ring to which the thymine or cytosine is attached. The drug seems to favor cleavage after a purine moiety since poly(dAdU) is cleaved after the deoxyadenosine. For double stranded cleavage, a self-complimentary sequences of pyrimidine-G-C-purine with cleavage between the deoxyguanosine and the cytosine moieties was preferred by bleomycin.\(^{12}\) This again shows the preference for cleavage after the purine nucleoside.

The mechanism by which bleomycin cleaves DNA is under debate. There are certain aspects that are generally agreed upon. First, bleomycin is "activated" by the presence of iron(II) and molecular oxygen. This activated species is then capable of radical abstraction of the hydrogen from the C-4 carbon of the deoxyribose ring. At this point the pathway diverges to give two different sets of products. With addition of another equivalent of molecular oxygen, the DNA will degrade into free nucleic base propenals, 5'-monophosphate oligomers, and 3'-phosphoglycolate oligomers. This is the useful pathway in cancer treatment because it leads directly to strand scission. Without additional molecular oxygen but with the addition of hydroxide ions, the DNA
will degrade to nucleic bases (guanine, cytosine, thymine, and adenine), a 5'-monophosphate oligomer, and an oligomer that contains a modified sugar on the 3' end which is currently termed the alkaline-labile product. Only free nucleic bases can be obtained when bleomycin was activated under anaerobic conditions with iron(III) and hydrogen peroxide.\textsuperscript{13}

This talk will address the debated intermediates in the proposed mechanism of DNA cleavage by bleomycin. The first area of intense debate is the nature of the activated complex. The hydrogen abstraction step seems to be generally accepted but the mechanism and intermediates involved in the formation of the products from this point is inconclusive. The kinetics of the degradation as well as proof for the 4' radical intermediate will also be discussed.

"ACTIVATED" BLEOMYCIN

The actual "activated" complex that removes the 4' hydrogen, has yet to be observed. Results vary greatly depending on the conditions in which the activated complex was examined. One EPR study showed distinct steps in the pathway to activation (Scheme I).\textsuperscript{14} The initial event is the formation of a 1:1 complex of bleomycin (BLM) and iron(II). This complex is EPR silent suggesting that the iron(II) might be in a low spin state. Molecular oxygen then joins the complex in a process that is first order in molecular oxygen concentration was well as in the iron(II)-bleomycin complex concentration and proceeds with a half-life of 0.2 seconds.\textsuperscript{14} The resulting iron(II)-bleomycin-oxygen complex is EPR silent. This soon reacts with another iron (II)-bleomycin complex to give a 1:1 mixture of "activated" bleomycin and iron(III)-bleomycin.\textsuperscript{15} The activated bleomycin has an EPR signal as does the iron(III)-bleomycin but each signal is distinct. The "activated" complex then decays to iron(III)-bleomycin at the same time as the attack on the DNA. It should be noted that the "activated" bleomycin decays in the presence or absence of DNA, thus the activated complex is not stable compared to the iron(III)-bleomycin complex.\textsuperscript{14}

Scheme I

\begin{center}
\begin{tikzpicture}

\node at (0,0) {Fe(II) + BLM \rightarrow Fe(II) \cdot BLM \rightarrow Fe(II) \cdot BLM \rightarrow \text{ACTIVATED BLM} \rightarrow Fe(III) \cdot BLM \rightarrow \text{Free bases and Base Propenals}};

\node at (0,0) {$O_2$ \rightarrow Fe(II) \cdot BLM \rightarrow O_2 \cdot Fe(II) \cdot BLM \rightarrow \text{ACTIVATED BLM} \rightarrow Fe(III) \cdot BLM \rightarrow \text{Free bases and Base Propenals}};

\node at (0,0) {$t_{1/2} = 0.2s$ \rightarrow $t_{1/2} = 6s$ \rightarrow $t_{1/2} = 2 min.$};

\end{tikzpicture}
\end{center}

A few physical properties of "activated" bleomycin have been determined.\textsuperscript{14,16} Mössbauer and EPR studies suggest a low spin ferric iron that has at least one oxygen atom obtained from molecular oxygen.\textsuperscript{16} The lone electron is localized around the iron nucleus. This suggest a superoxide type of structure such as iron(III)-bleomycin-$O_2^-$. However, it has been postulated that the activated complex could exist in the +5 oxidation state. It has been shown that 0.85 equivalents
of thio-NADH as well as 1.5 equivalents of potassium iodide were oxidized per mole of activated bleomycin. These compounds are two and one electron reducing agents respectively.

Many comparisons have been made between the activated bleomycin complex and other iron containing systems such as porphyrins in hemoglobin. Since bleomycin is not a planar ring system of ligands, the chemistry is quite different. First, molecular oxygen complexes a low spin iron(II) in bleomycin whereas in porphyrin complexes, the iron is usually high-spin state and changes to low-spin state upon complexation. Also the ligands act as a cage to inhibit other species from interacting with the iron once the complex binds to DNA. Compounds I of horseradish and chloro- peroxidases are perhaps the most similar in that they are proposed to have the iron(V) as the active species.

**EVIDENCE FOR THE COMMON INTERMEDIATE**

The activated bleomycin removes the 4' hydrogen at the same time that the activated bleomycin decays to iron(III)-bleomycin. This process is the rate determining step in the cleavage of DNA. To determine if the C-4' radical was a common intermediate for both pathways, Stubbe et al. developed conditions that allowed sufficient degradation of poly(dA -[4'-3H]dU) to compare the specific activity of the products to the unreacted deoxyuridine. Secondly, results from the degradation of poly(dA -[4'-3H]dU) under anaerobic conditions were similar to results under conditions that lead to the formation of both products suggesting that this was indeed a common intermediate in both pathways. The ratio of hydrogen rate abstraction to tritium was 7.2 for free nucleic base release only compared to 12.5 under conditions that favored release of both. The large isotope effects mean that the hydrogen abstraction is the rate-determining step for either pathway and the C-4' radical is a common intermediate.

**THE RELEASE OF BASE PROPENALS**

The mechanism for base propenal release was first proposed as a result of degradation studies that identified free nucleic bases and base propenals as the major products. Previous work had shown by 1H NMR, the presence of 3'-phosphoglycolate oligomers that were produced in amounts equivalent to the base propenals. However, from these studies a clear mechanism could not be determined since free nucleic bases were released at the same time. A study that labeled a hydrogen at each carbon of the deoxyribose ring helped to suggest which events were associated with each pathway. It was then possible to show that 2'(R) proton removal lead to base propenal formation. Furthermore, labeling the 2'(S) hydrogen suggested that the nucleic base propenal produced was in the trans conformation and that proton removal at the C-2' carbon was stereospecific. This supported the proposed mechanism shown in Scheme II.
The events at the C-4' carbon after the formation of the radical are still debatable. A possibility is seen in Scheme II, with the peroxide being reduced to the hydroperoxide. The reducing agent has yet to be determined but the iron-bleomycin complex is a possibility. This could then undergo a Criegee rearrangement to yield the opened ring which in the presence of base could result in the propenal. It has been proposed that the rearrangement might form a six membered ketal or a carbonyl at the C-4' position.

To determine the origin of oxygen at the C-4' position, a pulse-chase experiment with $^{18}$O labeled molecular oxygen was carried out. The results showed incorporation of a single oxygen atom at levels between 90 and 98% at what was the C-4 position. Given the proposed mechanism in Scheme II, the other labeled oxygen should be found on the base propenal. This was not observed, however, the aldehyde is capable of undergoing rapid hydration so the label could be washed out. A control was run by incubating $[^{18}$O]thymine propenal with activated bleomycin. The resulting propenal was analyzed by GC-MS and 90% of the label was retained in the product. If Scheme II is correct, then an exchange must have taken place.

There have been various proposals for the possible Criegee rearrangement (Scheme III). Saito et al. proposed that the 4'-hydroperoxy, when cis to the phosphate group, spontaneously rearranged to give a ketal which would then open to give trans base propenal and strand scission. For a model, 4'-hydroperoxy-3'-benzoyl nucleosides 11 were synthesized and the two C-4' isomers separated and their structures assigned. Each sample was then placed in a buffered aqueous solution at various pHs ranging from 6.0 to 8.9. The compound with the hydroperoxy and the benzoyl groups cis decomposed to yield the trans propenal. Kinetic studies showed that
half-life decreased drastically with increasing pH (3.0 hrs at 6.0 and seconds at 8.9) which fell in the observed kinetic parameters.

Scheme III

In contrast, the other isomer (hydroperoxy trans to the benzoyl group) did not yield a propenal. The only product isolated in any quantity was nucleic base. Based on these results Saito et al. proposed the formation of a ketal in the mechanism for the Criegee rearrangement (Scheme III). They predicted that a phosphate group should behave like a benzoyl group in DNA.

This has been disputed by Stubbe et al. The 18O labeled peroxide 11 decomposed into labeled acetate and benzoate, each containing one atom of oxygen. If a Criegee rearrangement had taken place then the thymine propenal or the malondialdehyde (MDA) would have been labeled. The products were always produced in 1:1:1 ratio of either thymine/MDA or thymine propenal to benzoate and acetate. They also showed that the ratio of thymine propenal to thymine/MDA was a function of pH and temperature. As the pH increases so does the overall rate and the production of thymine. The product of the study by Saito et al. was reinterpreted to be a benzoyl migration. The compound with the trans configuration of the deoxyribose would not be in the correct conformation for migration.

Stubbe et al. suggested the possibility of 12b being an intermediate, as earlier proposed. The compound [1-[(2-acetyloxy)acetyl]oxy]-3-oxopropyl] thymine was proposed, which did indeed decompose into thymine/MDA and thymine propenal. The ratio of products was dependant on pH as was compound 11. In this study, the rate of thymine propenal production was 0.03 min⁻¹, which is essentially the same as reported for base release from DNA. Given the ester aldehyde's sensitivity to conditions, this might be the intermediate that thymine propenal production goes through in the constraints of the DNA polymer.

FREE BASE RELEASE

Initial studies by Berger et al. showed that nucleic bases were exclusively released when natural DNA was treated with anaerobically activated bleomycin followed by hydrolysis with hydroxide ion. This was further elaborated by the tritiated labels on the deoxyribose ring in the previously mentioned study. As expected, under anaerobic conditions, the 4' and 2' labels were found as tritiated water. Interestingly, tritiated water was also found as a product of the 3'-labeled
sample. The 3' label would yield tritiated water only if a base removed the 3' hydrogen, causing ring opening and release of nucleic base as seen in Scheme IV. This is probably not the preferred pathway since it is more plausible that the base removes the proton off the C-4' hydroxyl group given the relative basicities of the two protons.

Scheme IV

Further evidence for the proton abstraction at the C-4' hydroxy group, leading to intermediate 15 was found by Stubbe et al. Since the 2'-deoxy-4'-pentulose moiety is not stable, previous work has shown that treatment of the reaction mixture with sodium borohydride results in a relatively stable product 20 (Scheme V). With this in mind, a hexamer, d(CGCGCG), was degraded followed by reductive treatment to give the C-4' hydroxyl group. The nucleosides that were not degraded were then cleaved off and the products analyzed by HPLC to reveal dC, dG, and 21 in a 2:2:1 ratio respectively. The existence of the 4' ketone was also confirmed by comparison of the 2-deoxy-pentitol 22 with synthetically made epimers. Given the proposed mechanism, 22 exists as a racemic mixture which coelutes by HPLC with both epimers. Co-migration with each epimer suggests that the stereochemical integrity was lost at the C-4' position. This suggested that indeed the intermediate contained a 4' ketone.
The 1',4'-keto-aldehyde intermediate 15 has not been universally accepted. Hecht. *et. al.* used a self-complimentary dodecanucleotide that was treated with Fe(II)-O₂·bleomycin to supposedly yield a 1',4'-dihydroxy-2'-deoxy nucleoside.²⁹ In the presences of base (0.2 N NaOH, 90° C, several minutes) this was cleaved to yield a 4'-hydroxy-2'-cyclopentenone nucleotide. This product comigrated with synthetically prepared samples by anion exchange and C₁₈ reverse-phase HPLC. However, the study failed to quantify the results in terms of nucleic base to cyclopentenone or show its effectiveness on a variety of DNA fragments. It seems mechanistically possible that the intermediate 15 that Stubbe²⁷ proposed could be hydrolyzed by strong base to the products observed by Hecht.²⁹

**CONCLUSION**

The mechanism of DNA degradation by bleomycin has progressed to the point where new intermediates are proved. Total understanding of the mechanism of degradation by bleomycin is still elusive. However, much of the work of Stubbe *et. al.* has advanced knowledge of the mechanism. It is now known that the C-4' radical is a common intermediate for both pathways. The formation of base propenals most likely goes through a 1,3-ester-aldehyde intermediate 12b whereas another 1,4-keto-aldehyde 15 could be an intermediate in the release of free nucleic bases. Further elucidation of the bleomycin mechanism could add insight to other agents that function as antitumor agents through a radical mechanism. Some examples are tallysomycin (a derivative of bleomycin that mainly cleaves both strands of DNA) and streptonigrin, as well as many metal complexes ((OP₂)₂·Cu¹ and methidium-propyl-EDTA·iron(II) which are potential antitumor agents. If they, along with bleomycin, can be understood mechanistically, the clinical applicability could be increased. However, in light of the proposed mechanism, the nature of bleomycin should always inflict damage on non-cancerous cells.
REFERENCES

(1) Friedman, M.A. Recent Results Cancer Res. 1978, 63, 152.


COMPUTER GENERATION OF NOVEL DOPAMINE AGONISTS

Reported by J. Kreps March 21, 1990

Random screening of large numbers of compounds from natural and synthetic sources has been a traditional and successful approach to the challenge of developing new pharmaceuticals. An advantage to this method is that it allows evaluation of complex and unusual structures (in the case of natural products) that would probably never have been suggested by the medicinal chemist. The mass screening approach is also of value when little is known about the disease of interest and active compounds have yet to be reported.

The disadvantage to the method is of course the huge amount of expense and effort involved. It is estimated that less than one compound in 10,000 synthesized ever reaches the market, and only after a development period of perhaps 10-15 years and an investment of well over $100 million.\textsuperscript{1,2} Computer-assisted drug design may hold the promise of increasing the efficiency and reducing costs associated with the search for active new lead compounds. Furthermore, sophisticated computer models may prove useful in optimizing the potencies and minimizing side effects of both new and existing therapeutic agents, making this an area of interest both to the pharmaceutical industry, and, in a broader sense, to society as a whole.

Computer models are routinely generated in studies of biological host molecules such as enzymes and receptor proteins. Enzymes, which are relatively small, hydrophilic, and more easily isolated than receptors, are being successfully examined by X-ray crystallography in ever-increasing numbers. The result is that the three-dimensional crystal structures of the active sites of hundreds of free enzymes and enzyme-inhibitor complexes are now available for computer-assisted study. Structure determination of membrane-bound biological receptor molecules, on the other hand, has proven to be more problematic. Beyond difficulties in isolation and purification, there is uncertainty as to the biologically-active conformations of these large, lipophilic proteins once they are removed from the hydrophobic environment of the cellular membrane. Nonetheless, computer models of the three-dimensional structures of receptor binding sites can be developed from analyses of structure-activity relationships (SAR) gleaned from ligand binding assays.

MODELS OF THE D\textsubscript{2} DOPAMINE RECEPTOR BINDING SITE

The Pharmacophore

The first step in mapping the binding site of a receptor is to identify the relevant pharmacophore. It is assumed that the binding interaction of substrate and receptor and subsequent activation of the latter is defined by a particular three-dimensional arrangement of the substrate's

Copyright © 1991 by J. Kreps
functional groups, designated as the pharmacophore. In a lock-and-key analogy of this relationship, both agonist and antagonist are keys which fit the lock; however, only the agonist is able to turn the tumblers. Model pharmacophores can be proposed by analysis of the binding affinities of a variety of compounds. Beyond identifying a particular pattern of binding sites, such an analysis can provide information regarding receptor volumes that are available or unavailable to potential ligands.

**Dopamine Receptors**

Dopamine (DA), a neurotransmitter of the peripheral and central nervous systems, has been linked to a number of mammalian physiological pathways affecting perception, voluntary and involuntary movement, behavior, and secretion of the hormone prolactin. Dopamine receptors are generally classified as either D₁, which stimulate adenylate cyclase, or D₂, which either inhibit this enzyme or are independent of it. Dopamine receptor antagonists are used to treat schizophrenia and other forms of psychosis, certain motor disorders, and to suppress nausea. Clinical use of agonists, all of which activate the D₂ receptor primarily, is involved in the treatment of neurological disorders such as Parkinsonism, endocrinological disorders, and treatment of shock, impotence, hypertension, and substance abuse. Their possible use as neuroleptics is under investigation. Agonists and antagonists alike usually exhibit some affinity for both D₁ and D₂ receptors, however, which may explain the frequently observed side effects that accompany their use. It is hoped that better models of these receptors will result in more selective therapeutic agents.

**The Wikstroem Model**

Dopamine was first identified as a neurotransmitter around thirty years ago. Since that time a number of investigators have produced a large body of SAR for a variety of dopaminergic compounds. Despite an abundance of data, a well-characterized pharmacophore for the dopamine receptor has proven to be an elusive target for several reasons.

First of all, although it is proposed that multiple subclasses of dopamine receptors exist, neither the exact number nor the individual physiological role of each has been agreed upon. It is currently held that there are two main types of DA receptors, D₁ and D₂; the issue, however, is clouded by the fact that the D₂ receptor can exist in either an agonist high- or low-affinity state, an effect apparently modulated by guanine nucleotides. A second difficulty is the well-documented affinities of many DA receptor ligands for other neuroreceptors such as those of serotonin or adrenergic synapses. Still other problems stem from the chiral nature of the receptor. Not only is it common for the enantiomers of a ligand to exhibit widely different binding affinities; sometimes one enantiomer is an agonist while the other an antagonist. Often in binding affinity experiments, characterization of an effector as agonist or antagonist depends on the use of animal behavior
studies. In such cases, quantitation is difficult and uncertainty regarding the possible effects of in vivo transport and metabolism is introduced. Furthermore, the D₂ presynaptic receptor (or autoreceptor) has recently been shown to exhibit significantly higher affinity than D₂ postsynaptic receptors for certain agonists, leading to selective stimulation of these autoreceptors.⁸,⁹ This result can lead to unexpected physiological and behavioral responses. SAR derived from binding assays are at the heart of every receptor model, whether ball and stick or computer-generated. Difficulties which cloud the interpretation of some work can hinder the development of an unambiguous pharmacophore.

Early attempts to establish the D₂ pharmacophore were based on the structure of dopamine (1), and some of the hydroxylated 2-aminotetralins (for example, 2) which show D₂ affinity. The catechol function was found to be nonessential but single hydroxyl groups at other positions on the aromatic ring, especially meta to the attached aminoalkyl side chain, were related to the binding affinity.¹⁰ In 1985, Wikstroem and co-workers proposed a model of the D₂ receptor based on simple manual overlay of active agonists 3-8 (Figure 1)¹¹. These conformationally-restrained structures were positioned by superimposing the basic nitrogens and the hydrogen bonding

heteroatom substituent located on the aromatic ring. Besides the ring itself, other essential features of this model are the basic nitrogen with indicated stereochemistry at the extended phenylethylamine distance from the ring. With model in hand, these workers were able to describe certain receptor regions as having greater or lesser tolerance to bulky substituents on the ligand, explain the observed behavior of other D2 agonists, and predict the activity of untested agonists. Such a model is useful for suggesting the nature of the binding interactions; however, it is likely too vague to be of significant value in suggesting widely different compounds for further study.

**Computer-assisted Agonist Design**

Computer-assisted methods, on the other hand, can be very useful in developing D2 agonists and suggesting new lead compounds. These methods offer all of the intrinsic advantages of the electronic medium. Models are easy to generate, to store, to retrieve, to scale up or down, to alter, and to copy for other people or other formats. A pharmacophore can be generated, as above, by superimposing known agonist compounds; the computer, however, can build the model in three dimensions. The user is able to decide which conformation(s) of a given molecule to use, including, but not limited to, low energy conformations. Bond angles and interatomic distances can be calculated and the geometric constraints of the pharmacophore determined. Three-dimensional mapping of the receptor site surrounding the pharmacophore is aided by calculation and display of the common volumes occupied by active and inactive compounds.\(^2\) Perhaps the most interesting feature of a computer-generated pharmacophore is that it enables the investigator to compare the structure of known compounds to the model and evaluate the fit. There is evidence that such techniques may suggest entirely new classes of potential ligands.\(^12\)

**The Tonani Model**

In a 1987 report, Tonani et al. proposed a D\(_2\) agonist pharmacophore based on analysis of 18 different compounds.\(^13\) The affinities of these ligands had been determined in vitro by competitive binding assays with \(^{3}\text{H}\) spiperone on porcine anterior pituitary tissue. The labelled ligand is presumed to bind solely to the D\(_2\) sites since no D\(_1\), serotonin, or adrenergic receptors are found in this region.\(^15\) The binding affinities had been separately determined for each enantiomer. The compounds used (Figure 2) are, with one exception (26), fused-ring compounds with varying degrees of conformational restraint. The lowest energy conformations for each compound were determined in the following manner: The rotatable bonds of compounds 9-15 and 26 were moved in increments of 30°, and the energy of each resulting conformer was calculated by molecular mechanics. The X-ray crystal structure of compound 16, apomorphine, was used as a basis for
constructing 16-19. Similarly, the X-ray structure of 20 was used to build 20-25. These latter sets of structures were subsequently minimized by molecular mechanics.

Figure 2. D2 agonists used to develop a pharmacophore. After Tonani et al.  

These low-energy conformations were superimposed on the structure of the conformationally rigid 24, pergolide, one of the most potent agonists known.\(^{16}\) The points that were lined up were the basic nitrogen, the heteroatom (oxygen in 10-19 and 26; nitrogen in 20-25), and the aromatic planes. Compound 9, lacking a heteroatom, was positioned by overlapping hydrogen 'R' on top of the pergolide nitrogen. Dummy atoms representing hydrogen bonding points on the receptor were placed 2.8 Å from the basic nitrogen and the heteroatom of each compound, in the same direction as the appropriate lone pair or attached hydrogen.
Tonani et al. proposed that the general pharmacophore for D₂ agonists includes an aromatic ring and two hydrogen bonding moieties, the heteroatom and the basic nitrogen, in the geometry of pergolide (24). They were not able to specify whether the sp³ oxygen heteroatoms act as donors or acceptors. These conclusions were drawn after analyzing the overall quality of the fit of these molecules to the pergolide structure, both in terms of energy costs and correlation between suggested hydrogen bond interactions and observed binding affinities.

If the proposed pergolide-receptor hydrogen bonds are indeed a legitimate part of the fit to the D₂ pharmacophore, then deviation from this fit should correlate to an increase of the agonist's dissociation constant Kᵋ, reflecting a drop in binding affinity. Deviations in fit were quantitated as the calculated distance between the receptor hydrogen bonding site of the agonist-receptor complex and the receptor hydrogen bonding site of the pergolide-receptor complex (Figure 3). A linear correlation (R=0.717, S=0.608, n=26) was observed only with respect to the proposed hydrogen bond from the heteroatom to the receptor. Although no correlation between Kᵋ and fit to the model was observed for the basic nitrogen hydrogen bond, the authors speculate that an optimum range for a distance between actual site and model site might be the observed 0-1.3 Å. They note as well that the energy costs of deforming a particular agonist from the lowest energy conformation to the geometry of the model cover a range of 0.1-4.9 kcal mol⁻¹, which they consider reasonable.

Figure 3. Tonani model: difference in geometry between reference compound and overlaid agonist. Het = superimposed heteroatoms on aromatic ring; D₁ = dummy atom which accepts hydrogen bond from reference compound; D₂ = dummy atom which accepts hydrogen bond from superimposed agonist.

These workers have approached the problem by selecting a particular optimal geometry and attempting to correlate the fit of low-energy conformations of other agonist species to observed activity. The lack of appreciable correlation may stem from having chosen an improper reference compound. It is possible to imagine compounds 20-25 binding in a slightly different orientation than the oxygen-containing heteroatom agonists. Lack of expected correlation in the hydrogen bonding directionality of the basic nitrogen could be explained by the ability of the receptor to conform somewhat to the agonist. Although this notion of flexible fit is, in fact, contrary to the idea of an unchanging pharmacophore target, flexibility in the receptor could allow a variable geometry of interactions with its hosts. Finally, the validity of superimposing sp³ hybridized
heteroatoms over the sp² hybridized nitrogen of pergolide is questionable when searching for three-dimensional geometric relationships.

**Computer Evaluation of Alternate Superpositions**

A different model for the D₂ receptor, based on manual overlay of two-dimensional structures, had been proposed in 1985 by Grol et al.¹⁷ It included two separate hydrogen bonding sites for the catechol moiety and two separate binding sites for the basic nitrogen. These workers realized that overlay of the basic nitrogen and a meta hydroxy group ignored the difference in distance between the equivalent 5-hydroxy oxygen and nitrogen in 27 (6.4 Å) and the 6-hydroxy oxygen and nitrogen in 28 (7.4 Å). Their model (Figure 4) alleviated this problem by describing two nitrogen binding sites, B₁ and B₂, on the receptor. They postulated that these sites were 2.4 Å apart and could be a phosphate group or similar species, assuming the nitrogen to be protonated.

![Diagram showing alternate D₂ pharmacophore](attachment:image)

**Figure 4.** Alternate D₂ pharmacophore after Grol et al. *J. Med. Chem.* 1985, 28, 679-683.

An evaluation of this model was recently described by Van Drie et al.¹⁸ After superimposing all compounds in the manner of Grol, these workers compared the volumes that would be occupied by several inactive compounds to the volumes occupied by active agonists 27 and 28. The volume occupied solely by inactive compounds was considered to be a forbidden region of the receptor, unavailable to active agonists. They next tested a series of 27 catecholamines of varying binding affinities to determine if inactive compounds did occupy the forbidden region. Their findings indicated that with some modification this model could
discriminate between active and inactive compounds on this basis, although some inconsistencies remain.

**COMPUTER-GENERATED D₂ AGONISTS**

Interesting developments have been reported recently concerning the design of novel agonists for the D₂ receptor. A group at Abbott Laboratories has incorporated SAR and modeling studies into a pharmacophore (Figure 5) containing a basic nitrogen hydrogen bond acceptor, a phenolic hydrogen bond donor, and the corresponding receptor binding sites.¹²,¹⁸ The information contained in this model was used to search large databases of three-dimensional structures for the purpose of finding novel D₂ agonists.

The experiment began by specifying two atoms, one aliphatic and one aromatic, with an allowed range of distance (5.5 -6.6 Å) between them. A portion of the search additionally stipulated the presence of a fused aliphatic-aromatic ring. These search criteria were then applied by the ALADDIN program to the two-dimensional structures contained in the databases; compounds which matched these constraints were hits. Each hit generated was redefined by the program to make the aliphatic atom a nitrogen atom and the aromatic atom an aromatic carbon with attached hydroxyl group. All other heavy atoms within a structure retained their hybridization state but were redefined as carbon atoms. Side chains and substituents were removed from these compounds. The net result was a series of two-dimensional structures that might be expected to match the bioactive geometry.

These structures were converted to low energy three-dimensional structures through the use of the program CONCORD; they were then evaluated by ALADDIN in terms of new

\[
\begin{align*}
N \text{ binding pt - Oxygen} &= 6.5-8.0 \, \text{Å} \\
N \text{ binding pt - OH binding pt} &= 8.4-10.0 \, \text{Å} \\
\text{Nitrogen - OH binding pt} &= 7.5-9.5 \, \text{Å} \\
\text{Oxygen - Nitrogen} &= 5.8-7.5 \, \text{Å} \\
\text{Indicated torsion angle} &= 85° - 135°
\end{align*}
\]

constraints, the four distances and one torsion angle specified in Figure 5. The resulting hits were expected to fit the pharmacophore, with 2.4 Å between the receptor binding sites and the agonist binding sites.

The databases used in this search were FCD (59,305 commercially available compounds; about 50% of it was searched in this experiment); POMONA89 (14,450 compounds; many biologically-active); and MODELED (Abbott's proprietary database of dopaminergic compounds; 3000 compounds, multiple conformations of each). They were chosen in part to determine what effect the nature of the database might have on such a search.

The search generated 499 distinct compounds, indicating the great potential of this method in the design of D2 agonists. Despite the fact that the proprietary database MODELED was enriched with dopaminergics, approximately half of the proposed compounds came from FCD and POMONA89. This suggests that specially prepared databases are not necessarily required in these searches. Moreover, the search turned up compounds from every one of the general classes of fused-ring structures known to be D2 agonists which was represented in the databases. Most importantly for the drug design process, the search suggested a number of novel structures from previously untested classes of dopaminergic fused-ring compounds, some of which are illustrated (Figure 6).


Random checks on 50 molecules indicated that a significant portion of hits (about half) were missed because the assigned three-dimensional structure is not the only low energy conformation available. The problem of generating additional conformations will need some attention. Another concern regards the sophistication of the pharmacophore: Were any known inactive compounds included as hits?
Additional techniques are available with which to evaluate the proposed agonists prior to synthesis and testing. The author suggests that they will perform steric tests, to see which compounds fit within the calculated available volume of the receptor. She indicates as well that their own CoMFA (Comparative Molecular Field Analysis) studies predict that some of the suggested compounds will be potent agonists.

SUMMARY

Three-dimensional computer models of receptor binding sites are a useful means of gaining insight into the interactions of guest and host molecules. This is essential both for developing drugs for new systems, for which no current therapy exists, and for optimizing the potencies of existing drugs. As models for receptor binding sites increase in sophistication, it will be possible to suggest modifications designed to increase specificity and reduce side effects. Currently available computer methods permit the facile generation and evaluation of receptor pharmacophores. Recent advances in this field indicate the possibility of doing rapid, large-scale computerized screening of molecules by comparing the structure of compounds within a database to a three-dimensional model of a proposed active agent. Such searches are liable to suggest entirely new classes of novel lead compounds for further investigation.

REFERENCES


NOTICE: Return or renew all Library Materials! The Minimum Fee for each Lost Book is $50.00.

The person charging this material is responsible for its return to the library from which it was withdrawn on or before the Latest Date stamped below.

Theft, mutilation, and underlining of books are reasons for disciplinary action and may result in dismissal from the University.

To renew call Telephone Center, 333-8400

UNIVERSITY OF ILLINOIS LIBRARY AT URBANA-CHAMPAIGN
<table>
<thead>
<tr>
<th>The Origin of Chirality</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sean Murphy</td>
<td></td>
</tr>
<tr>
<td>Diastereoselectivity in Intermolecular Free Radical Additions to Alkenes</td>
<td>9</td>
</tr>
<tr>
<td>Lawrence R. Marcin</td>
<td></td>
</tr>
<tr>
<td>Synthesis, Conformations, and Complexation Chemistry of Calix[n]arenes</td>
<td>17</td>
</tr>
<tr>
<td>Kathryn R. Conser</td>
<td></td>
</tr>
<tr>
<td>Elucidation of a Photochemical Mechanism: Photocycloaddition of Enones to Alkenes</td>
<td>25</td>
</tr>
<tr>
<td>Mauricio Suarez</td>
<td></td>
</tr>
<tr>
<td>Mechanism and Inhibition of Phospholipase A2</td>
<td>33</td>
</tr>
<tr>
<td>Mark A. Cole</td>
<td></td>
</tr>
<tr>
<td>Some Recent Advances in Organometallic Wittig Equivalents</td>
<td>41</td>
</tr>
<tr>
<td>Michael Palucki</td>
<td></td>
</tr>
<tr>
<td>Catalytic Enantioselective Borane Reduction of Carbonyl Compounds Mediated by Chiral Amino Alcohols</td>
<td>49</td>
</tr>
<tr>
<td>Yuelong Liu</td>
<td></td>
</tr>
<tr>
<td>Synthetic and Mechanistic Aspects of Asymmetric Allylboration</td>
<td>57</td>
</tr>
<tr>
<td>Sriram Shankar</td>
<td></td>
</tr>
<tr>
<td>Current Progress in the Preparation of Chiral Sulfoxides</td>
<td>65</td>
</tr>
<tr>
<td>Hua Du</td>
<td></td>
</tr>
<tr>
<td>Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids</td>
<td>74</td>
</tr>
<tr>
<td>Li Deng</td>
<td></td>
</tr>
</tbody>
</table>
THE ORIGIN OF CHIRALITY

Reported by Sean Murphy

October 28, 1991

WHY STUDY THE ORIGIN OF CHIRALITY?

Why does nature prefer to use L-amino acids, D-sugars and right-handed DNA? How did nature select one enantiomer over its seemingly equivalent mirror image? People have researched these questions since the time of Pasteur simply because they were curious. Besides curiosity, organic chemists are interested in the origin of chirality because it deals with asymmetric synthesis. But unlike most asymmetric synthesis done today, the optically active compounds are made from racemic starting materials. Perhaps nature has discovered an efficient way for generating chirality that we have not yet learned, and we can use this method in our own asymmetric syntheses.

In order to perform asymmetric synthesis from racemic starting materials, researchers have tried to employ a variety of chiral influences. These include circularly polarized light, the effects from an asymmetric weak nuclear force, the adsorption onto chiral surfaces and the combination of magnetic and gravitational fields. The experiments designed to test these influences for the possible origin of chirality will be discussed. One other theory, surprisingly, utilizes no chiral influence. This is known as spontaneous symmetry breaking.

SPONTANEOUS SYMMETRY BREAKING

A racemic mixture does not actually contain an exactly equal number of enantiomers due to statistical fluctuations. There is a 50% chance that if $10^7$ chiral molecules were generated, there would be a 0.021% excess of one enantiomer.\textsuperscript{1,2} As the number of molecules increases, the relative deviation decreases, but there still exists a slight excess which could be amplified to measurable levels. Local asymmetries could also be amplified and lead to global chirality.

Havinga and co-workers\textsuperscript{3} reported a clever way to create chirality based on a local asymmetry using N-methyl-N-ethyl-N-allylanilinium iodide, 1. This salt crystallizes only as all S or all R-crystals. If an S-crystal starts to form, it quickly depletes the solution of the S-anilinium cations, leaving an excess of the R-anilinium. Now, in chloroform, the cation can racemize as shown in Scheme I, and produce a racemic mixture, which again will be depleted of the S-enantiomer by further crystal growth. In their experiments, after allowing supersaturated solutions to stand for a few months, the mother liquor showed only a slight optical rotation, whereas the crystal had a large optical rotation of the opposite sign. Chirality was indeed generated. This experiment demonstrates spontaneous symmetry breaking but it is difficult to see how this particular event could have occurred on prebiotic earth. The primordial soup was a complex mixture of many compounds, and would not crystallize as pure substances. There are, however,
other models employing spontaneous symmetry breaking which are more important for the origin of chirality.

**Scheme I**

\[
\begin{align*}
&\text{(S) - 1} & & \text{(R) - 1} \\
&\text{CH}_3\text{N}-\text{CH}_2\text{CH}_3 & \text{I} & \text{CH}_3\text{N}-\text{CH}_2\text{CH}_3 & \text{I} \\
&\text{Ph} & & \text{Ph} \\
&\text{CH}_3\text{N}-\text{CH}_2\text{CH}_3 & \text{I} & \text{CH}_3\text{N}-\text{CH}_2\text{CH}_3 & \text{I} \\
&\text{Ph} & & \text{Ph} \\
\end{align*}
\]

Frank\textsuperscript{4} proposed a model where statistical fluctuations could be amplified to high levels of chirality. In his model, a chiral product is produced from achiral starting materials. The product then catalyzes its own production, and hinders the production of the other enantiomer. Once a slight excess of one enantiomer is formed, it breaks the symmetry and creates chirality.

Alberts and Wynberg\textsuperscript{4} have given an example of a reaction where the product catalyzes its own production. They studied the condensation of ethyllithium with benzaldehyde to form 1-phenyl-1-propanol, 2H, as shown in Scheme II. A solution of (+)-(R)-[1-\textsuperscript{2}H]-1-phenyl-1-propanol, 2D, was added to 2 equivalents of ethyllithium to form the lithium alkoxide. Presumably, the excess ethyl lithium was then complexed to the chiral alkoxide so when benzaldehyde was added, the condensation was stereoselective. From optical rotation and NMR data, the reaction formed a 17% enantiomeric excess (ee) of the (+)-enantiomer. The reaction was also performed with the titanate of 2D and diethylzinc, providing a 32% ee in favor of the (+)-isomer. This reaction shows that autocatalysis is possible. Although this particular example would be impossible in the aqueous solution of the primordial soup, it may provide clues to help researchers discover prebiotic autocatalytic reactions.

**Scheme II**

\[
\text{PhCHO} \xrightarrow{(+)-\text{PhC}^*\text{D(OLi)Et / EtLi}} \text{H}_3\text{O}^+ \quad \text{(S)-2D} \quad \text{(+)} \quad \text{(+)-2D}
\]

\[
\text{or: (+)-(PhCDEtO)}_4\text{Ti / ZnEt}_2 \quad \text{(+)-2D}
\]

**Biotic Theories**

The biotic theory is a special case of Frank's autocatalytic amplification model. In this theory, life forms are used instead of molecules. One variation states that the first life forms were achiral, and then evolved into the present chiral form. For the case on earth, the life with L-amino acids developed before the D-life and spread quickly so D-life never formed. Another variation has both D and L-life forming as the first life forms. By chance, the L-amino acid life evolved more
acids developed before the D-life and spread quickly so D-life never formed. Another variation has both D and L-life forming as the first life forms. By chance, the L-amino acid life evolved more quickly and was able to take over the earth. Although biotic theories are possible theoretically, they are difficult to prove experimentally. Most of the experimental evidence is for abiotic theories which assume chirality was generated before life began. The abiotic theories utilizing chiral influences will be discussed next.

CIRCULARLY POLARIZED LIGHT

Light can be chiral by spinning the electric and magnetic vectors clockwise or counterclockwise about the axis of motion. Chiral light is preferentially absorbed by one enantiomer of a molecule and can therefore induce chirality in a racemic mixture. Circularly polarized light (CPL) can be used for asymmetric synthesis, photoresolution, and photodecomposition. The theoretical ee produced in the first two processes is limited by g, the anisotropy factor, which is the difference in CPL absorbed for two enantiomers divided by the average extinction coefficient. Anisotropy values are typically small. Photodecomposition however, can theoretically produce a 100% ee, but the rate of change in the ee is limited by g.

Bonner et al. were able to induce an enantiomeric excess of 2.50% starting from a racemic solution of leucine. A dilute solution of leucine in 0.1 N HCl was irradiated with left circularly polarized light (LCPL) at 212.8 nm from a laser source. The GC analysis of the products showed that 75% of the sample had decomposed, but since the L-leucine absorbed more of the light, more of it decomposed, leaving an excess of D-leucine. Likewise, right circularly polarized light produced an excess of L-leucine. Shortly after this, Norden showed asymmetric photodecomposition of tartaric acid, alanine and glutamic acid. This experiment used wavelengths >200 nm from a Xe lamp to produce 0.06-0.22% ee. This light source is more appropriate for the origin of chirality because it produces a broad band of UV light similar to the sun's radiation.

These experiments show the possibility of implicating CPL in the production of optically active prebiotic compounds, but where does the CPL come from? Wolstencraft measured the polarity of light at 350 and 582.5 nm over the period of a day in Sutherland, South Africa. He found that the 350 nm light was polarized -0.5% in the morning and +0.5% in the evening, but the net polarization over the whole day was zero. The polarization comes from aerosol scattering in the atmosphere. He then hypothesized that if a lake sat on the western side of a hill or mountain, the primordial soup in the lake would be irradiated with RCPL in the evening but would receive no sunlight in the morning due to the shade from the hill. In this way, L-amino acids would be in excess and life could then begin. This theory assumes that life originated in only one lake and that by chance the hill blocked the morning light and not the evening light. The wavelength detected is
also of the wrong energy to photodecompose amino acids. Wolstencroft should have also measured the UV region in order to strengthen his argument.

Another, more distant source of CPL has been implicated in the origin of chirality. Neutron stars emit cones of RCPL and LCPL above and below their poles. Bonner and Rubenstein hypothesized that interstellar dust clouds left over from supernova explosions and composed of organic matter were irradiated by only one side of a neutron star and in this way became chiral. Later, the earth could have passed through this dust cloud and was able to accumulate $10^8$ to $10^{10}$ metric tons of matter, comparable to the mass of living matter today estimated at $10^{11}$ metric tons. Although these ideas are difficult to prove, they are none the less possible explanations.

There is yet another possible source of circularly polarized light, but unlike the others, this one only produces LCPL. The source of this unique light is $\beta$-decay.

**$\beta$-DEcay**

When some radioactive atoms decay, they give off electrons and this process is called $\beta$-decay. In 1956, Lee and Yang predicted that the electrons from $\beta$-decay should be left-handed, that is, spin counter-clockwise about their axis of motion. Then, in 1957, Wu et al. observed that the electrons given off in the decay of $^{60}$Co were in fact predominantly left-handed. This effect is said to violate parity because both enantiomers are not created equally. The cause of this effect is the electro-weak nuclear force which sees the right and left-handed electrons differently.

The chiral electrons from $\beta$-decay can produce CPL. High energy electrons can spontaneously emit a circularly polarized photon thereby slowing themselves down. These photons are called Bremsstrahlung, or brake radiation. Soon after the discovery of Bremsstrahlung, Ulbricht hypothesized that this light source could induce chirality through photochemical processes, an idea known today as the Vester-Ulbricht hypothesis.

Many researchers have tried to find experimental evidence for the Vester-Ulbricht hypothesis, but all experiments so far have either failed or been inconclusive. Bonner has proposed an explanation for why the experiments have failed to produce a measurable ee. The polarization of Bremsstrahlung is almost 100% at high energies and decreases to zero at low energies. The polarization in the relatively low energy UV region, which is useful for photodegradations, is negligible. At energies where the polarization is higher, the photon is of the wrong wavelength to be absorbed and therefore cannot induce photochemical reactions.

Researchers have also tried to induce chirality with the left-handed electrons given off in $\beta$-decay. As with Bremsstrahlung, all attempts have either failed or are unconfirmed. This is not surprising considering that the electrons are also not polarized except at speeds comparable to the
speed of light. Electrons this energetic have little chance of interacting with the chiral electric fields of organic molecules, and thus cannot degrade one enantiomer more than the other.

The use of β-decay to explain the origin of chirality has many faults and no solid experimental evidence to support it.¹ Yet, one more theory utilizes the parity violating weak nuclear force. This theory involves very small energy differences between enantiomers.

**THE PARITY VIOLATION ENERGY DIFFERENCE**

Due to the weak nuclear force, chiral molecules are expected to differ in energy in their ground state by a parity violation energy difference (ΔEpν). Tranter¹,¹⁸ calculated the energy difference for the zwitterion forms of alanine, valine, serine and for the aspartate anion. The energy for the L-amino acid was always lower than the D-isomer by 5 to 11x10⁻¹⁸ kcal/mol. This predicts one extra L-amino acid for every 10¹⁷ molecules.

Much of the literature discusses chirality amplification mechanisms and some claim that the ΔEpν is large enough to be amplified to levels high enough for life to begin. Despite all of the theoretical work done, no experiments have shown any ΔEpν or its amplification. One model, suggested by Yamagata,¹⁹ predicts that the energy difference will become apparent in polymerizations. Tranter²⁰ extended this model to quartz. Before looking at the details of the model, the use of quartz for the origin of chirality will be discussed.

**Asymmetric Adsorption onto Quartz**

Quartz crystals are chiral and have chiral surfaces on which molecules can adsorb. Morimoto and co-workers²¹ observed up to 37% ee of L-α-aminopropionitrile adsorbed onto D-quartz from an aqueous solution of the racemate. α-Aminonitriles can be hydrolyzed to amino acids or form polymers themselves which may be precursors of the present biopolymers. Amino acids have also shown differential adsorption on quartz,¹,²² but to lesser extents and only in non-aqueous solutions. The adsorption of prebiotic compounds onto quartz could lead to a greater concentration of amino acids on the surface compared to the solution, and this could accelerate the polymerization process. Other minerals and clays have been implicated in the origin of chirality, and may be more plausible, but at present the amount of research done on these is small.

**Models for the Amplification of ΔEpν**

In order for quartz to induce chirality in amino acids or their precursors, the quartz itself must be chiral. Tranter proposed a model²⁰ for the asymmetry of quartz based on the parity violating energy difference. First, he assumes the crystals are in equilibrium, with the energy difference for a crystal of n unit cells being ΔE. Then, by thermodynamics, the ratio of L over D crystals is given by:

\[ \frac{L}{D} = e^{-\frac{\Delta E}{kT}} \]
Assuming that the parity violating energy difference per unit cell ($\Delta E_{pv}$) is the same for each cell added, then $\Delta E = n^*\Delta E_{pv}$. He defines $\varepsilon = -\Delta E_{pv}/kT$, so the new expression is:

$$L / D = e^{\varepsilon \text{ne}} = 1+\text{ne}, \quad \text{for } |\text{ne}|<<1$$

For $\Delta E_{pv}$, he used a calculated value which predicts the L-unit cell to be more stable. Now he concludes that for a 1% ee of L-quartz, there must be $10^{15}$ unit cells which corresponds to a crystal 0.1 mm on each side. In order for this mechanism to work, relatively large crystals, $10^{15}$ units cells, must be in equilibrium, and be able to interconvert between the L and D crystals. The model hinges on this assumption, but he proposes no mechanism for $10^{15}$ unit cells to change easily from one enantiomer to the other.

Tranter also proposed a kinetic model. Here, $\Delta E_{pv}$ affects the transition state of the reaction when ions are added onto the growing crystal. Since the Si and O ions should be added on slightly faster in the L-configuration than in the D-configuration, the L-quartz should form faster and therefore be more abundant. Again, $10^{15}$ unit cells must be formed to get a 1% ee. This kinetic model is also flawed. Keszthelyi\textsuperscript{23} has pointed out that the crystal chirality is determined after a nucleation of only 1000-10,000 unit cells. After nucleation, the crystal growth is template directed and the crystal becomes almost all L or all D by the time it reaches $10^{15}$ unit cells.

The original model, proposed by Yamagata,\textsuperscript{21} was also kinetic and dealt with the formation of oligonucleotides. He calculated that one enantiomer of an oligonucleotide with $10^8$ units would be in great excess over the other enantiomer if the monomer addition rates were different by $\Delta E_{pv}$. Some 18 years later, Joyce et al.\textsuperscript{24} reported that oligomer formation from a racemic mixture is very inefficient and the largest oligomer they detected was a trimer. Larger oligomers should also form but in increasingly smaller yields, and one forming with $10^8$ units is unimaginable.

The weak nuclear force is the only true asymmetric influence known but it appears to be incapable of generating molecular chirality. The asymmetric adsorption onto quartz, however, is still a valid theory because local asymmetries in the abundance of quartz have been observed.\textsuperscript{25}

**MAGNETIC AND GRAVITATIONAL FIELDS**

Experimenters have tried to implicate the earth's gravitational and magnetic fields in the origin of chirality. Alone these forces are not chiral, but taken together they produce a chiral environment, which is equal but opposite for the northern and southern hemispheres. The strength of these combined forces are very small, and some believe they are too small to explain the origin of chirality. Regardless, many experiments have been performed to probe their effects.

In 1985, Takahashi et al.\textsuperscript{26} reported the highest ee ever obtained from a magnetic field. They performed the electrochemical reduction of phenylglyoxylic acid (PhCOCO$_2$H) to mandelic acid (PhC$^*$H(OH)CO$_2$H) in a magnetic field of 0.17 T. They reported optical yields, which are the
percent ee's measured by optical rotation. L-Mandelic acid was formed in 21.3% optical yield when the magnet had the north pole up and no ee was seen when the magnet was off or turned perpendicular to the earth's surface. However, the same enantiomer was also produced in excess when the magnet had the south pole up. If the magnetic field had caused the observed asymmetry, the D-isomer should have been formed in excess. Because of this anomaly and the high yield, Bonner has recently attempted to repeat the experiment, but without success. He also reports that a group in Munich tried also unsuccessfully to repeat the experiment. Bonner states that since only the calculated optical yields were given, and not the raw data, it is difficult to propose possible systematic errors in their experiment which would explain the observed anomaly.

All other experiments involving magnetic and gravitational fields show no or very slight induced chirality. All positive result have been unrepeatable. One striking example of the difficulty in reproducing this type of experiment is found in a report by Daugherty and co-workers. The sign and magnitude of the product mixture's optical rotation from three different types of reactions run in a magnetic field varied according to time of day and the date on the calendar.

**CONCLUSIONS**

The theories involving CPL, adsorption onto chiral surfaces and autocatalysis are plausible, but it takes some imagination to see how they can be implemented all the way from the formation of organic molecules to the chirality seen today. As for applications in synthetic chemistry, the adsorption onto chiral surfaces is presently used for resolutions and CPL could be useful when synthesizing molecules with high anisotropy values. Although not useful at present, the use of autocatalysis may open up a new field in organic asymmetric synthesis. As for the true origin of chirality, no one theory stands out as the best. It is difficult to rule out some of the plausible theories remaining because we do not yet know how life began. Once this is known, we can devise better experiments to try to explain the origin of chirality.

**REFERENCES**


DIASTEREOSELECTIVITY IN INTERMOLECULAR FREE RADICAL ADDITIONS TO ALKENES

Reported by Lawrence R. Marcin

October 31, 1991

INTRODUCTION

The addition of free radicals to alkenes has become a valuable synthetic method for the formation of C-C bonds. The effects that influence the chemo- and regioselectivities of radical additions have been widely investigated. These effects have been found to be largely steric and polar in origin, with some influence by radical stabilization. However, until recently, little has been known about the factors that control the stereochemistry in radical addition reactions. This review will discuss work reported in the past three years which utilizes chiral auxiliaries such as 2,5-dimethylpyrrolidine amides, 1, oxazolidines, 2, Oppolzer’s camphor sultam, 3, and the “Ballaster benzoxazole”, 4, to achieve high levels of diastereoselectivity in intermolecular free radical additions to alkenes.

Background

Research performed by Giese and co-workers in the 1980’s with cyclic systems demonstrated that achieving high diastereoselectivity in intermolecular radical addition reactions was possible. It was found that the addition of various alkenes to 2-substituted cyclopentyl and cyclohexyl radicals is largely determined by steric factors. In the cyclopentyl radical system 5 the ring substituent X acts to shield the syn face from addition of acrylonitrile (6) (Scheme 1). As the substituent X increases in size from ethoxy to t-butoxy, then methyl, a higher anti: syn ratio of products is observed, 77:23, 80:20, 92:8, respectively.

As one may suspect, the substitution of the alkene is also important in the stereoselectivity of the reaction. Alkenes substituted with electron withdrawing groups are more reactive towards nucleophilic alkyl radicals, which can be interpreted using Frontier Molecular Orbital theory as a decrease in the SOMO-LUMO energy difference. Table 1 illustrates that when terminal alkenes add to 2-ethoxycyclopentyl radical (5a) there is a direct relationship between decreasing reactivity
and increasing selectivity. This is in agreement with the Hammond postulate⁴ and the reactivity-selectivity principle.⁵

Table 1. Stereoselectivity-Reactivity Relationship for 2-Ethoxycyclopentyl Radical.

<table>
<thead>
<tr>
<th>Alkene</th>
<th>anti: syn Attack</th>
<th>k rel</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂C=CCICN</td>
<td>72:28</td>
<td>31.0</td>
</tr>
<tr>
<td>H₂C=CHCN</td>
<td>77:23</td>
<td>3.6</td>
</tr>
<tr>
<td>H₂C=CHCOMe</td>
<td>86:14</td>
<td>2.0</td>
</tr>
<tr>
<td>H₂C=CHCO₂Me</td>
<td>88:12</td>
<td>1.0</td>
</tr>
<tr>
<td>H₂C=CHPh</td>
<td>90:10</td>
<td>0.15</td>
</tr>
</tbody>
</table>

In order to fully understand the necessary constraints for asymmetric induction in radical reactions one must be familiar with the physical characteristics of radicals and the proposed transition state models for alkene addition. Carbon-centered radicals are nucleophilic or electrophilic species depending on their substitution at the radical center.¹ᵇ Electron donating groups like alkyl or alkoxy increase nucleophilicity. Electron withdrawing groups such as ester or nitrile increase electrophilicity. Most carbon-centered free radicals adopt a planar or near-planar structure with the unpaired electron occupying a p orbital.⁶ This geometry allows equal attack from either of the two faces. Thus, if a chiral auxiliary is used as a substituent on the radical it has to preferentially shield one prochiral face of the radical from addition of the alkene to induce asymmetry.

Theoretical studies and experimental evidence propose an early, reactant-like transition state for radical additions to alkenes.¹ᵃ,⁷ The evidence favors an unsymmetrical transition state in which only the attacked olefinic carbon atom deviates considerably from its ground state geometry with a pyramidalization of ~150°. Calculations by Houk have shown that radicals approach the olefinic carbon atom at angles between 103° and 109°, regardless of the electronic nature of the radical.⁷ᶜ Intermolecular transition state distances usually are very close to 2.2 Å. In consideration of the data that support an early transition state it is not unreasonable to analyze stereoselectivities based on ground-state conformation arguments. Therefore, to achieve selectivity in achiral radical
additions to alkenes substituted with chiral auxiliaries, the auxiliary must preferentially shield one diastereoface of the alkene from radical attack.

Radical addition reactions in the following work were carried out by either the "tin method"\textsuperscript{8} or the "mercury method".\textsuperscript{9} Scheme 2 illustrates both proposed radical chain mechanisms. Reactions carried out by the tin method are typically done photolytically at room temperature, or with radical initiators thermally. The advantage of the mercury method over tin lies in its very mild reaction conditions. High temperature initiators or photolytic conditions are not required. Hydrido mercurials, generated from treatment of mercurial chlorides with sodium borohydride, start the chain reaction by decomposition even at very low temperatures.

Scheme 2

<table>
<thead>
<tr>
<th>Tin Method:</th>
<th>R-I + Bu\textsubscript{3}Sn• → R• + Bu\textsubscript{3}Sn-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>R• + Z=Y</td>
<td>R• + R•</td>
</tr>
<tr>
<td>R• + Z-Y + Bu\textsubscript{3}Sn-H → R• + Bu\textsubscript{3}Sn•</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mercury Method:</th>
<th>R-HgX + NaBH\textsubscript{4} → R-HgH → R•</th>
</tr>
</thead>
<tbody>
<tr>
<td>R• + Z=Y</td>
<td>R• + R•</td>
</tr>
<tr>
<td>R• + Z-Y + R-HgH → R• + R•</td>
<td></td>
</tr>
</tbody>
</table>

**PYRROLIDINE AUXILIARIES**

In 1989, Porter and co-workers reported the first use of a 2,5-disubstituted pyrrolidine as a chiral auxiliary on the alkene in free radical macrocyclizations.\textsuperscript{10} As a result of the high selectivities achieved in these macrocyclizations, Porter and Giese in a joint study pursued the idea of using the same C\textsubscript{2} symmetric pyrrolidine in more challenging intermolecular asymmetric radical additions of which only one reported example existed.\textsuperscript{11} Porter and Giese studied the α, β-unsaturated amide 9 derived from (E)-4-oxo-2-pentenoic acid.\textsuperscript{12} Addition of n-hexyl radical (10) to 9 gave four isomeric products: two isomers from β addition (11a,b) and two isomers from α addition (12a,b) (Table 2). Virtually no regioselectivity was observed, providing 1:1 mixtures of α and β addition products. Isomers from β addition were formed with little diastereoselectivity, however isomers from α addition were formed in ratios as high as 16:1. With the (S,S)-pyrrolidine auxiliary, the newly formed stereogenic center had S configuration, and inverse results were obtained using the (R,R)-pyrrolidine. The stereochemistry of these compounds was proven by degradation and independent synthesis.
Table 2. \textit{n}-Hexyl Radical Addition to an \textit{\alpha}, \textit{\beta}-Unsaturated Amide.

\begin{center}
\begin{tabular}{cccc}
\hline
Temp. & Radical Method & Solvent & Product Ratio (11a:b:12a:12b) \\
\hline
100 °C & tin & C$_6$H$_5$CH$_3$ & 8.5 : 7.2 : 1.0 \\
80 °C & tin & C$_6$H$_6$ & 10.0 : 9.0 : 1.0 \\
0 °C & mercury & CH$_2$Cl$_2$ & 16.3 : 16.0 : 1.0 \\
\hline
\end{tabular}
\end{center}

The diastereoselectivity observed in the above examples can be explained by Figure 1. In the lowest energy conformation of the alkene, as predicted by MM2 calculations,$^{12b}$ addition to one face of the alkene at the \textit{\alpha} position, by approach over the pyrrolidine group, is sterically impeded by a methyl substituent. Attack on the other face is not nearly as hindered. This work achieved unprecedented diastereoselectivities in intermolecular acyclic free radical additions to acyclic alkenes and prompted further studies with the pyrrolidine system.

![Preferred Addition Geometry](image)

Figure 1. Preferred Addition Geometry.

Porter then pursued the idea of adding a chiral acyclic radical to alkenes using a pyrrolidine amide as a radical substituent.$^{13}$ Chiral radicals were generated from the bromoamide 13, which was used as a mixture of diastereomers (Scheme 3). Upon reaction with ethyl acrylate (14) at 80 °C products 15 and 16 were formed in 35-50\% yields and 15-25\% yields, respectively, as well as significant amounts of uncharacterized higher oligomers. Product 15 was formed as a 12:1 mixture of the two possible diastereoisomers. The major isomer had an \textit{S} configuration at the newly formed carbon center when the pyrrolidine auxiliary utilized was (\textit{R, R}). Product 16 was formed as a 1:1 mixture of two major stereoisomers, presumably with the \textit{S} configuration at C-2, but, with both \textit{R} and \textit{S} configurations at C-4.
Scheme 3

Porter and Giese have clearly demonstrated high diastereoselectivities in radical additions to the olefinic carbon directly adjacent to a chiral amide system, but several problems severely limit the general use of this methodology. First, the degree of regioselectivity in the addition to these systems is poor. Second, the dimethylpyrrolidine amide auxiliaries are not easily removed. Lastly, the preparation of 2,5-disubstituted pyrrolidines is cumbersome and tedious. For these reasons other auxiliaries have been actively pursued.

OXAZOLIDINE AUXILIARIES

In a recent preliminary communication Porter has reported that oxazolidines serve as excellent auxiliaries for control of \( \alpha \)-diastereoselectivity in radical additions to alkenes. Table 3 illustrates that in cyclohexyl radical addition to amide 18 high selectivity (\( >80:1 \)) is achieved when \( R \) is \( t \)-butyl. Hydrolysis of product 19 to the succinic acid derivative 20 revealed that, starting from the \( S \) oxazolidine, the new stereogenic center in the major diastereomer has \( R \) configuration. These auxiliaries are far more attractive than the previously discussed dimethylpyrrolidines because they are easily prepared in one step from commercially available materials and the products of addition are easily hydrolyzed.

Table 3. Cyclohexyl Radical Addition to Oxazolidine Substituted Alkenes.

<table>
<thead>
<tr>
<th>Substituent (R)</th>
<th>Phenyl</th>
<th>( i )-Propyl</th>
<th>( t )-Butyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>selectivity 19a:19b</td>
<td>1.1 : 1.0</td>
<td>10 : 1</td>
<td>( &gt;80 : 1 )</td>
</tr>
</tbody>
</table>

CHIRAL SULTAM AUXILIARIES

Curran and co-workers have exploited a totally different chiral auxiliary to achieve high levels of asymmetric induction in radical addition reactions. They have demonstrated that a chiral
radical derived from Oppolzer’s camphor sultam undergoes allylations with high diastereoselectivity. A series of asymmetric allylation reactions with allyltributyltin (22) is illustrated below (Table 5). Good selectivity (12:1) is achieved at 80 °C, and the selectivity increases as the temperature decreases. Although excellent selectivity is achieved at -78 °C, the reactions are not practical due to inefficient propagation of radicals. However, at -20 °C reactions go to completion in 6 hours, and the products are obtained in high yields (>95%) with excellent diastereoselectivities (Entry 4).

Table 5. Allylations Using Sultam Radical.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiation</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Ratio 24a:24b</th>
<th>ΔΔG‡ kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIBN</td>
<td>C₆H₆</td>
<td>80 °C</td>
<td>12:1</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>Et₃B</td>
<td>CH₂Cl₂</td>
<td>25 °C</td>
<td>14:1</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>Et₃B</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>22:1</td>
<td>1.7</td>
</tr>
<tr>
<td>4</td>
<td>Et₃B</td>
<td>CH₂Cl₂</td>
<td>-20 °C</td>
<td>25:1</td>
<td>1.6</td>
</tr>
<tr>
<td>5</td>
<td>Et₃B</td>
<td>CH₂Cl₂</td>
<td>-78 °C</td>
<td>&gt;30:1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Through related X-ray structures and MM2 calculations Curran has proposed a transition state model (23) to account for the high levels of asymmetric induction. Features of this model include: i) the amide radical has an s-cis geometry; ii) O₁ and the amide oxygen are opposed to minimize dipole repulsion; iii) the allylating reagent approaches from the top face of the radical because the bottom face is impeded by O₂. This model is highly similar to that developed by Porter for the asymmetric radical derived from dimethylpyrrolidine systems. Even though the two different chiral auxiliaries are not structurally related, they both work to block one face of the radical. Oppolzer’s sultam is commercially available and is easily removed by literature methods.¹⁸

**BALLESTER BENZOXAZOLE**

Recently Curran and Rebek have reported high regio- and stereoselection in the addition of achiral radicals to a mixed fumarimide substituted with a new chiral auxiliary derived from Kemp’s triacid referred to as the “Ballester benzoxazole”.¹⁹ Radical additions to the alkene unit in structure
25 affords a mixture of the four products 26, 27 and 28a,b (Table 5). Unlike the other systems discussed previously, remarkable regioselectivity for the β position is observed. Not a trace of α addition products was detected at temperatures below 0 °C (Entries 3-5). Also, the high β-diastereoselectivities are unprecedented in radical additions to chiral alkenes. This observed diastereoselectivity can be explained once again in terms of steric arguments. The large protruding benzoxazole ring effectively shields one diastereoface of the olefin from radical addition. Addition products 26 and 27 are readily hydrolyzed with lithium peroxide to afford the acid esters and the recovered auxiliary in good yields.

Table 5. Radical Additions to the “Ballester Benzoxazole”.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Radical</th>
<th>Method</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Ratio 26:27:28</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-Butyl</td>
<td>tin</td>
<td>C₆H₆</td>
<td>80 °C</td>
<td>78:19:3</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>t-Butyl</td>
<td>mercury</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>88:9:3</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>t-Butyl</td>
<td>mercury</td>
<td>CH₂Cl₂</td>
<td>-40 °C</td>
<td>97:3:0</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexyl</td>
<td>mercury</td>
<td>CH₂Cl₂</td>
<td>-20 °C</td>
<td>94:6:0</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>n-hexyl</td>
<td>mercury</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>82:18:0</td>
<td>42</td>
</tr>
</tbody>
</table>

CONCLUSION

Several approaches to achieve high levels of asymmetric induction in intermolecular free radical additions to alkenes have met with success. The chiral pyrrolidine auxiliary achieves high α-diastereoselectivity, but lacks any real practical application. However, it has provided insight into the rational design of other auxiliaries, such as the use of chiral oxazolidines. Oxazolidine auxiliaries are easily prepared, achieve even higher selectivities than their pyrrolidine relatives, and are easily hydrolyzed. Other approaches include the use of Oppolzer’s camphor sultam as an auxiliary on the radical. This approach achieves high asymmetric induction in allylation reactions and is attractive because both enantiomers of the chiral sultam are commercially available. A novel approach to control β-diastereoselectivity has been realized by addition of radicals to a mixed fumarimide substituted with a chiral auxiliary derived from Kemp’s triacid. This method achieves unprecedented levels of regioselectivity and very high levels of β-diastereoselectivity, but requires a multistep synthesis of the auxiliary.
It is obvious that improvement is still needed before intermolecular radical reactions are generally used to dictate acyclic stereochemistry. However, with the current interest in this area, it is certain that major advances will continue to be made in the future.

REFERENCES
SYNTHESIS, CONFORMATIONS, AND COMPLEXATION CHEMISTRY OF CALIX[n]ARENES

Reported by Kathryn R. Conser November 7, 1991

INTRODUCTION

Calix[n]arenes have received attention recently because of their potential to act as hosts, enzyme mimics, catalysts, or surfactants.\(^1\) Although these compounds have been known since the 1940's, their chemistry has been investigated extensively only since the late 1970's. Calix[n]arenes are cavity-bearing macrocycles composed of phenol rings linked by ortho methylene bridges, with ring sizes ranging from four to eight members. As a class of \([1_n]\)metacyclophanes, calix[n]arenes resemble cyclodextrins structurally, although they have considerably greater conformational flexibility in solution. Methods for regioselective derivatization of calix[n]arenes have been developed recently and have increased the types of compounds that can be tested for host-guest chemistry. This review will summarize the recent work with this class of compounds that has been aimed toward their application in host-guest chemistry. Their synthesis, conformational characteristics, and complexation chemistry will be the focus of this discussion.

SYNTHESIS

The standard method for synthesizing calix[n]arenes is a "one-pot" procedure involving the base-catalyzed condensation of \(p\)-tert-butyl phenol and formaldehyde\(^1,2\) (Scheme I). Calixarenes with ring sizes ranging from 4-8 are formed in this reaction, with the even-numbered ring species predominating. Conditions have been optimized for preferential formation of the tetramer (n=4),\(^2\)

Scheme I

Copyright © 1991 by Kathryn R. Conser
the hexamer \((n=6)\), and the octamer \((n=8)\). Occasionally it is desirable to synthesize calix[n]arenes linearly, i.e. by adding one phenol at a time followed by ring closure. Although this approach is comparatively inefficient, it permits the introduction of variously derivatized monomers in a specific order.

Calix[n]arene derivatives can be prepared that bear substituents on both the lower (phenolic) and upper rims. The most common lower rim derivatives include ethers and esters, usually formed as shown in Scheme II. Upper rim derivatives of calix[n]arenes differ at the para substituent on the phenol ring. A common method for their synthesis involves a Claisen rearrangement, since reactions involving direct substitution at the upper rim are rare (Scheme III). Methods for selective upper rim functionalization of \(p\text{-}\text{tert}\text{-}\text{buty}l\text{calix}[4]\text{arenes}\) utilizing the Claisen rearrangement were reported recently. Similar reactions involving the Fries rearrangement of O-acylated calix[6]arenes have also been reported. Another way to synthesize upper rim derivatives is via the \(p\)-quinonemethide (Scheme IV). These functionalized calixarenes, particularly the \(p\)-allyl derivatives, are important because they allow further manipulation of the para substituent to give various derivatives on the upper rim.

Chiral calix[4]arenes possessing four different para substituents or with a meta substituent on only one ring have been prepared. Compounds of this type can be synthesized by linear chain elongation, followed by ring closure under dilute conditions. Recently, Shinkai reported the synthesis and first successful optical resolution of an asymmetrically substituted calix[4]arene.
CONFORMATIONS

Calixarenes are conformationally mobile in solution. The smallest of these compounds is the cyclic tetramer for which 4 "up, down" conformations are specified, namely: cone, partial cone, 1,2-alternate, and 1,3-alternate\(^1\) (Fig. 1). Each conformation has a specific \(^1\)H NMR splitting pattern, hence it is possible to distinguish conformations in solution, when the molecule is fully substituted on the upper and lower rims. Additionally, NOE experiments have been performed to define conformations and to provide rigorous assignments of the proton signals.\(^{12}\) For compounds where substitution is not uniform, the \(^1\)H NMR spectrum becomes very complicated; however, \(^{13}\)C NMR signals can also be used to distinguish conformations in these cases.\(^{13}\)

\(^{1}\)H NMR studies of calix[4]arenes in CDCl\(_3\) and benzene-\(d_6\) show that the cone is the preferred conformation, presumably due to intramolecular hydrogen bonding, but that there is inversion on the NMR time scale at room temperature.\(^{14}\) Variable temperature studies have shown coalescence of the signals for the methylene protons connecting adjacent aryl rings. A standard technique involving the rate of inversion and the Eyring equation allows the free energy of activation for inversion to be calculated.\(^{14}\) Coalescence temperatures decreased when more polar solvents such as pyridine were used, indicating the disruption of intramolecular hydrogen

---

**Figure 1. Calix[4]arene conformations**
bonding.\textsuperscript{14} It is proposed that inversions occur by rotation of the aryl rings in an "O-substituent through the annulus route" because activation energies appear to be insensitive to the nature of the para substituents on the calix[4]arene.\textsuperscript{14} The O-methoxy derivatives of calix[4]arenes interconvert easily at room temperature, but with larger substituents conformational mobility becomes restricted.\textsuperscript{5}

The X-ray crystal structure of \textit{p-}(1, 1, 3, 3-tetramethylbutyl)calix[4]arene (\textit{p-}tert-octyl-calix[4]arene) showed that it crystallized in the cone conformation.\textsuperscript{15} This conformational preference was attributed to strong intramolecular hydrogen bonding. Therefore it seems that conformations of parent calix[4]arenes are determined by intramolecular hydrogen bonding in both the solid state and in solution, while the lower rim derivatives are more influenced by their O-substituents.

Calix[8]arenes have a larger cavity than calix[4]arenes, and hence they are expected to have more conformational freedom. Surprisingly, the variable temperature spectra of calix[8]arenes are almost identical to those of calix[4]arenes in nonpolar solvents. However, low temperature spectra of calix[4]arene in pyridine-\textit{d}_{5} showed separation of the methylene proton signals, while in calix[8]arene they remained a singlet.\textsuperscript{16} It was suggested that the calix[8]arene exists in a "pinched" conformation in solution, thereby creating a contiguous pair of cyclic tetramers which allow two circular arrays of hydrogen bonding (Figure 2). The pyridine served to break up the intramolecular hydrogen bonding and allow more conformational freedom. In contrast, an X-ray crystal structure of \textit{p-}tert-butylcalix[8]arene showed that the molecule exists in a flat, "pleated-loop" conformation in the solid state.\textsuperscript{14}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Calix[8]arene in a "pinched" conformation}
\end{figure}

Parent calix[6]arenes have been shown by \textsuperscript{1}H NMR to be more flexible in solution than the corresponding tetramers or octamers, existing preferentially in "winged" or "hinged" conformations.\textsuperscript{14} The "winged" conformation has two aryl groups pointing out from the average plane with the other four groups up or down, while in the "hinged" conformation, three adjacent aryl groups, all with the same relative orientation, form a group which is "anti" to the other group of three. Derivatives of calix[6]arenes are also conformationally mobile in solution, inverting via the "oxygen through the annulus" route, except in the case of very bulky O-substituents.\textsuperscript{17} Crystal structures for OH-calix[6]arenes indicate that they exist in a "hinged" conformation.\textsuperscript{18} In contrast,
crystal structures of ether derivatives show two aryl rings pointing out to create a "winged" conformation.\textsuperscript{14}

COMPLEXATION CHEMISTRY OF CALIXARENES

The ability of calix[n]arenes to complex small molecules is a requirement for their potential use as hosts or enzyme mimics. Structural proof of calixarene complexation was provided in the crystal structure of \textit{p-tert-}butylcalix[4]arene as a 1:1 toluene complex, with the aromatic guest situated inside the cone.\textsuperscript{19}

Studies of calix[4]arene complexation in solution have been performed.\textsuperscript{20} \textsuperscript{1}H NMR studies of various calix[4]arenes in toluene showed that the extent of complexation depended on the para substituent. It has been suggested that bulkier para substituents can bend over and block the cavity of the calixarene, as observed in solid state crystal structures.\textsuperscript{15,20} Studies of aliphatic amine complexation show that much stronger complexes are formed.\textsuperscript{20,21} Confirmation that amines deprotonate the calix[4]arene and that association occurs through ion pairing were shown by 2D NOE studies.\textsuperscript{21} Water soluble calix[n]arenes with amino and carboxyl substituents on the upper rim have been synthesized and found to weakly bind aromatic hydrocarbons.\textsuperscript{22} However, water-soluble calix[n]arene derivatives with sulfonate groups on the upper rim exhibited strong but unselective binding of aromatic hydrocarbons, while lower rim derivatives showed selective but weak binding.\textsuperscript{23}

Aside from studies with neutral guests, attention has been focused on the ability of calix[n]arenes to bind alkali metal cations. Izatt found that parent calix[n]arenes could function as cation carriers across an H\textsubscript{2}O-organic solvent-H\textsubscript{2}O membrane with a reverse flux of protons.\textsuperscript{24} The transport occurred only if the aqueous source phase was basic, which deprotonated the calix[n]arene and allowed it to form a neutral complex upon binding the cation. This system complements 18-crown-6, which transports alkali cations similarly when the source phase is neutral.

Ketone and ester functionalities have been shown to bind cations in natural systems,\textsuperscript{25} so these derivatives of calix[n]arenes were synthesized to test their binding ability with alkali cations.\textsuperscript{26} \textsuperscript{1}H NMR spectra confirmed that these derivatives adopt the cone conformation.\textsuperscript{26} The ionophoric activity of these compounds was determined by metal picrate extraction studies, transportation ability, and stability constant measurements.\textsuperscript{26} Extractions of metal picrate salts from aqueous solutions into CH\textsubscript{2}Cl\textsubscript{2} showed that the tetramer derivatives selectively bind Na\textsuperscript{+}, with ester derivatives being less efficient than ketone derivatives. The hexamer esters showed better selectivity for K\textsuperscript{+} than Na\textsuperscript{+}, but exhibited little selectivity for larger cations. The octamer derivatives were the poorest ionophores of the three calix[n]arene oligomers tested. Equilibrium constants determined in MeOH and CH\textsubscript{3}CN showed that most of the tetramers were selective for
Na\(^+\), while the hexamers were most selective for K\(^+\). In most cases, the selectivities were comparable to known neutral crown ethers and cryptands.

A recent study has evaluated the role of conformation in the complexation of alkali cations.\(^{27}\) Calix[4]arene derivatives with various polyether bridges connecting opposing phenolic oxygens (calixcrowns) were synthesized to lock the calixarene in either the cone, partial cone, or 1,3-alternate conformation. The differences in free energy between isomers is a way to measure Cram's view of preorganization quantitatively.\(^{28}\) When the calixcrowns were treated with alkali metal picrates, all were selective for K\(^+\), but the largest free energy of complexation was found for the partial cone isomer. This result indicated the partial cone as the preferred conformation for binding, even though the cone is most stable in solution.

Shinkai has shown that alkali metal and organic ammonium cations bind differentially to water-soluble calix[n]arenes in solution.\(^{29}\) Ammonium cations were shown to decrease ring inversion to a much larger extent than alkali cations. Shifts in \(^1\)H NMR signals of both the ammonium cation and the calixarene suggested a structure with the cation inside the calixarene cavity. The di- and tri-ammonium cations showed higher coalescence temperatures, which indicated that these cations bind on the cavity edge, effectively creating an electrostatic bridge which inhibits inversion.\(^{29}\)

Other cations have been shown to bind various calix[n]arene derivatives. For calix[4]arenes containing ligating amide groups at the phenolic oxygen, extraction efficiencies and stability constants were greater for alkaline earth cations than for alkali metal cations.\(^{30}\) Extending beyond the main group metals, reactions of \(p\)-tert-butylcalix[4]arene with transition metal amides have yielded some complexes of titanium, cobalt, and iron.\(^{31}\) In addition, metal picrate extraction studies with \(p\)-phenylazocalix[6]arene showed high selectivity for Ag\(^+\), Hg\(^+\), and Hg\(^{2+}\).\(^{32}\) Finally, a 2:1 complex of Eu(III):calix[8]arene has been synthesized which crystallized in the "pinched" conformation.\(^{33}\)

CONCLUSION

The study of calix[n]arenes has been facilitated by recent successful synthetic work, allowing easy access to these compounds. The ready availability of specific calix[n]arene derivative conformers will allow more definitive work to be done to study their potential application as hosts, catalysts, and enzyme mimics. There is a need for molecules that exhibit selective binding in host-guest chemistry, and calix[n]arenes are strong candidates for further development because of the ease with which their physical properties can be tuned by appropriate substitution, their conformational flexibility, and their selective binding upon derivatization.
REFERENCES AND NOTES


(25) In ref. (26), the authors mention that "ester groups participate in ion binding with the natural receptors such as valinomycin and nonactin," but they do not give any further references.


ELUCIDATION OF A PHOTOCHEMICAL MECHANISM: PHOTOCYCLOADDITION OF ENONES TO ALKENES.

Reported by Mauricio Suarez

November 11, 1991

INTRODUCTION

Photoannulation between alkenes and α,β-unsaturated ketones has been extensively studied. It was first reported by Ciamician in 1908 that if carvone was irradiated with Mediterranean sunlight a chemical transformation was accomplished. The structure of the product was unambiguously determined forty-two years later by Buchi, who showed that the reaction involved a cycloaddition between the two alkenes (Scheme I). During the late 60's, 70's and 80's with the work of Dauben, Hammond, de Mayo, Eaton, Corey and Chapman, among others, the reaction evolved into one of the most frequently utilized photochemical reactions in organic synthesis. Photoannulation of enones show two important synthetic characteristics: orientation specificity in which electron rich alkenes yield preferentially the regioisomer in which the polar group of the alkene is further from the carbonyl group of the enone (normally referred to as head-to-tail isomers), whilst electron deficient alkenes show the reverse orientation (head-to-head isomers); frequent formation of thermodynamically unfavorable trans-fused ring systems which are usually very hard to make by other means. The mechanism of this reaction is still a subject of considerable attention and debate.

![Scheme I](image)

COREY MECHANISM

In his 1964 pioneering paper Corey proposed the first mechanism for this reaction (Scheme II).

![Scheme II](image)

It is assumed that the triplet excited state of the enone is (n,π*). Calculations performed on
2,5-cyclohexadienone as a model by the Huckel method indicate that the β- carbon is quite negative relative to the α–carbon. With this in mind it is postulated that the factor responsible for both the "relative rate factors" (determined from yields) and the orientation specificity in the photoaddition process is the geometry of the intermediate π-complex (now called an exciplex). The π–complex would be of the donor-acceptor type, the excited ketone functioning as an acceptor and the olefin as donor (Scheme III).

Scheme III

There is no reason to believe that product yields in photocycloaddition of enones with alkenes are determined in a single step, as suggested by Corey's model. It has been demonstrated for the Norrish type II reaction of aromatic ketones that the photoproduct yields depend on the overall quantum efficiency of the process and not on the rate of a single specific step. However, the simplicity and attractiveness of Corey's proposal has made a modification of his mechanism (known as the Corey-de Mayo mechanism) extremely popular and has been used to explain the regiochemical outcome of the reaction for the last 25 years.

COREY-DE MAYO MECHANISM

By quenching experiments it was proven that the reactive excited state of the enone was a triplet having energies of around 70 kcal/mole. Kearns et al., based on the properties of phosphorescence emission (non overlap with S0–T1 absorption and polarization measurements) from steroidal enones at 77 °K and 4.2 °K concluded that the lower energy triplet was π,π* and that the lowest n,π* triplet lies only a few kcal/mol higher in energy.

Temperature dependence of the quantum yield and product distribution for photoannulation of cyclopentenone with several different olefins was studied by de Mayo. For some olefins the quantum yield would increase as the temperature was lowered (cyclohexene, cyclopentene, cis-dichloroethylene) while for others it would decrease (trans-3-hexene). For example, for the cyclopentenone-cyclohexene system the quantum yield increased from 0.46 at 27 °C to 0.72 at -102 °C. It was concluded that the large changes in the quantum efficiencies of adduct formation with temperature were a result of a temperature dependence of the partitioning rate constants of the biradical. De Mayo explicitly considered reversion of all possible reaction intermediates to ground state enone and alkene to explain the quantum inefficiency of the process. Scheme IV shows a potential energy surface that corresponds to the Corey-de Mayo mechanism.
**BONNEAU-SCHUSTER MECHANISM FOR FLEXIBLE ENONES**

Bonneau et al.\(^{10}\) studied the excited state of cyclohexenes and cyclohexenones via transient absorption spectroscopy (TAS). Irradiation of 1-acetylcyclohexene produced two transient intermediates, \(A\) (11 ns, \(\lambda_{\text{max}}\) 285nm) and \(B\) (45 ns, \(\lambda_{\text{max}}\) 345nm). The rate of decay of \(A\) was equal to the rate of growth of \(B\), since the lifetime of \(A\) decreased in the presence of oxygen, Bonneau concluded that \(A\) was a triplet state of acetylcyclohexene giving rise to \(B\), a ground state trans-enone. Cyclohexenone and cyclopentenone showed transients (\(\tau\) of 25 and 30 ns respectively, in cyclohexane) in the same region as transient \(A\) and were quenchable by oxygen. Bonneau concluded that these were also \(\pi,\pi^*\) states. Subsequently other cyclohexenones have been examined by Schuster, Bonneau, Sciano and Turro.\(^{1b,11,12,13}\) Some of their results are summarized in Table I.

**TABLE I.** Triplet lifetimes of enones (ns) and quenching rate constants measured by TAS

<table>
<thead>
<tr>
<th>ENONE</th>
<th>(\tau_{\text{air}})</th>
<th>(\tau_{\text{ext}})</th>
<th>(K_q, \text{NA mol}^{-1}\text{s}^{-1})</th>
<th>Quencher = Naphthalene (NA)</th>
<th>Solvent = acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-CYCLOHEXENONE (1)</td>
<td>23</td>
<td>24</td>
<td>(1.0 \times 10^9)</td>
<td>(\tau_{\text{air}}); lifetimes obtained from direct observation of triplet decay.</td>
<td></td>
</tr>
<tr>
<td>4,4-DIMETHYLCYCLOHEXENONE (2)</td>
<td>23</td>
<td>28</td>
<td>(1.0 \times 10^9)</td>
<td>(\tau_{\text{ext}}); lifetimes obtained from Stern-Volmer plots.</td>
<td></td>
</tr>
<tr>
<td>3-METHYLCYCLOHEXENONE (3)</td>
<td>72</td>
<td>69</td>
<td>(-)</td>
<td>(K_q); quenching rate constants obtained from Stern-Volmer plots.</td>
<td></td>
</tr>
<tr>
<td>CYCLOPENTENONE (4)</td>
<td>125</td>
<td>-</td>
<td>(4.1 \times 10^9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TESTOSTERONE ACETATE (5)</td>
<td>380</td>
<td>295</td>
<td>(5.0 \times 10^9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[4.3.0]BICYCLONON-1(6)-EN-2-ONE (6)</td>
<td>1700</td>
<td>-</td>
<td>(\geq 10^{10})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One observes in Table 1 that there is a clear correlation between the rigidity of the enone and the lifetime of the transient assigned as the triplet state. The lifetime become longer as the structural
constraint of twisting around the double bond increases. This was explained by assuming that the non-rigid enone triplets could attain a lower energy configuration via twisting of the double bond, making the T^1-S^0 gap smaller, increasing the rate of intersystem crossing back to ground state and therefore decreasing the lifetime. Determination of k_q values from the quenching by naphthalene are also consistent with the argument; the rigid enones having higher energy perpendicular π,π* triplets are quenched at diffusion control rates while the flexible enones with lower energy twisted π,π* triplets quenched slower. Thus, the rigid enones must have triplet excitation energies near 70 kcal/mol, while the energies of twisted triplets must be near 60 kcal/mol. This result was recently confirmed with time resolved photoacoustic calorimetry experiments (PAC).

In an interesting experiment performed by Schuster et al., it was shown that alkenes quench, with a Stern-Volmer behavior, the lumiketone rearrangement of enone 2, giving photoannulation products (Scheme V). From this result it was concluded that rearrangement and photoannulation have a common intermediate.

Scheme V

When the quenching was monitored with TAS, it was observed that concentrations of tetramethylene up to 3.8 M had little effect on the rate of decay of the twisted π,π* triplet (λ_{max}=280nm). It was also observed that the lifetime of 2 in isooctane is indistinguishable from its lifetime measured in neat cyclohexene. These facts are inconsistent with the common intermediate being the enone triplet.

Table II shows the results of quenching of enone 2 with a series of alkenes. The mismatch between values of kτ (based on product quenching studies) and values of kτ_T (determined from flash experiments) is clear. The inevitable conclusion is that, at least for these systems, the Corey-de Mayo mechanism does not apply. The mechanism in scheme VI was proposed by the authors.

<table>
<thead>
<tr>
<th>ALKENE</th>
<th>Kτ^i</th>
<th>Kτ_T^ii</th>
</tr>
</thead>
<tbody>
<tr>
<td>TME</td>
<td>0.48</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CP</td>
<td>0.43</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DME</td>
<td>1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CH</td>
<td>0.13</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

TABLE II. Results of quenching studies of enone 2 with various alkenes
There are no data on the identity of intermediate (I); the possibility of its being a ground state trans-3- cyclohexenone was suggested.\textsuperscript{13} This seems unlikely since Corey was unable to detect any trans -cyclohexenone by IR in a hydrocarbon matrix at -190 °C\textsuperscript{16} and in recent experiments Schuster was unable to detect it by photoacoustic calorimetry.\textsuperscript{14} Also, it is known that trans-cycloheptenone reacts thermally with DME giving the head to head isomer which is the opposite regiochemistry observed normally during photoannulation of electron rich alkenes.\textsuperscript{17}

**SCHUSTER-HOUK MECHANISM FOR RIGID ENONES**

It was shown\textsuperscript{18} that compounds 3,4,5 and 6, all of them showing longer lived triplet lifetimes consistent with a slightly twisted or even planar π,π* triplet, are quenched directly with alkenes. Quenching rate constants were directly obtainable from the variation in enone triplet lifetime with alkene concentration , according to (Eq 1), where $\tau_o$ is the intrinsic lifetime of the triplet and $\tau_T$ is the triplet lifetime observed at a certain concentration of quencher.

$$ (\tau_T)^{-1} = (\tau_o)^{-1} + k_q [\text{alkene}] $$  \hspace{1cm} \text{Eq. 1.}

The most striking observation was that the largest values of $k_q$ were those for electron deficient alkenes, i.e. acrylonitrile (AN), α-chloroacrylonitrile (CAN) and fumaronitrile (FN). As a representative example, data for the quenching of cyclopentenone are presented in Table III. It is known that the quantum efficiency for enone cycloaddition is higher for electron rich alkenes.\textsuperscript{1,4} It comes as a surprise to observe an inverse correlation between $k_q$ and the quantum efficiency for cycloaddition. These results are not consistent with formation of a donor-acceptor exciplex; an alternative explanation evokes the formation of a 1,4-biradical directly from the enone triplet and the alkene. This possibility has been explored through its theoretical implications by Houk et al.\textsuperscript{19}

**TABLE III. Rate constants for quenching of cyclopentenone triplets with alkenes.**

<table>
<thead>
<tr>
<th>ALKENE</th>
<th>$K_q \times 10^{-7} \text{M}^{-1} \text{s}^{-1} (\text{MeCN})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN</td>
<td>200</td>
</tr>
<tr>
<td>CH</td>
<td>33</td>
</tr>
<tr>
<td>DME</td>
<td>3</td>
</tr>
</tbody>
</table>

CAN = α-chloroacrylonitrile
CH = 2- cyclohexenone
DME = 1,1-dimethoxyethylene
who showed that with a Mulliken population analysis at the unrestricted Hartree-fock 16-31G* level, the β-carbon of 90° twisted π,π* triplet acrolein is positive relative to the α-carbon. This is the opposite polarization expected from Corey's model. He further suggests that this twisted triplet could behave as a biradical, the β carbon being mostly an alkyl radical (nucleophilic) and the α carbon an α-ketoalkyl radical (electrophilic).

To test the hypothesis, calculations on the transition states of the addition of triplet acrolein to various alkenes were undertaken (Scheme VI). Geometries were obtained using a 3-21 G basis set, energy evaluations being performed on these geometries at the PMP 3/6-31G* level. The results are shown in Table IV. Examination of the table reveals that electron-poor alkenes show a preference for head-to-head addition while electron-rich alkenes preferentially add to give head-to-tail adducts. This leads to the same regiochemical predictions as the original Corey model, but now the formation of the biradical is the product-determining step, rather than the formation of an oriented π complex.

Scheme VII

<table>
<thead>
<tr>
<th>Compound (R₁, R₂)</th>
<th>TS 1</th>
<th>TS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H,CN)</td>
<td>0.0</td>
<td>0.9</td>
</tr>
<tr>
<td>(=CH)</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>(Me,Me)</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>(H,OMe)</td>
<td>1.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Previous calculations at the PMP 2/6-31G* level showed that attack on the less substituted side of the alkene was invariably favored by 1 or 2 Kcal/mol.
Recent trapping experiments with hydrogen selenide performed by Weedon et al.\textsuperscript{21} contradict Houk's calculations. They found that the relative yields of trapped products from the photochemical reaction of cyclopentenone with ethyl vinyl ether indicate that the biradicals (assumed to be generated from transition states similar to TS1 and TS3) are formed in a 1.0:1.0 ratio. It seems that the regioselectivity is controlled by the fate of the biradical.

**THE BIRADICAL**

A PAC experiment\textsuperscript{22} using a high concentration (0.4 M) of cyclopentenone, conditions in which at least 98% of the triplet decays through self quenching, showed an acoustic wave that was deconvoluted giving a lifetime of 37 ns. This is in excellent agreement with the value of 37 ns for a 250 nm transient observed by flash photolysis under comparable conditions. This transient was assigned to a mixture of isomeric biradicals en route to cycloaddition. The good fit to a single exponential decay for both the TAS and PAC experiments may be interpreted to mean either that one of the two biradicals dominates or that the two have fairly similar lifetimes. The possibility of this transient being an excimer, not necessarily on the reaction pathway, is not discussed. It seems that its existence would explain the single exponential decay without further assumptions.

Rudolph and Weedon\textsuperscript{23} used a radical clock to determine the lifetime of the 1,4 biradical en route to photoannulation. In the system designed the biradical contains a cyclopropylmethyl radical that can either open up to form a homoallylic radical which undergoes internal hydrogen abstraction or form the photocycloaddition products (Scheme IX). Irradiation of cyclopentenone with vinylcyclopropane gave a mixture of adducts 7 and 8 along with comparable amounts of the products 9 and 10.

![Scheme VIII](image)

The sum of the rate constants for ring closure of the biradical to the cyclobutane products plus the rate constant for reversion to starting materials must be comparable to the rate constant for rearrangement of the secondary cyclopropylethyl radical. The cyclopropylethyl radical has been estimated to open with a rate constant of $2 \times 10^7$ s\textsuperscript{-1}\textsuperscript{24} Hence, the lifetime of the biradical must be of the order of 50 ns, very close to Schuster's assignment of 37 ns for a lifetime of a similar biradical (vide supra).
CONCLUSION

Recent studies on the mechanism of photoannulation give strong evidence of the absence of an exciplex on the reaction pathway. Two different mechanisms have been proposed depending on the flexibility of the enone double bond. Enones capable of forming twisted π,π* triplets require an intermediate (of unknown nature) before the biradical and rigid enones are quenched directly by the alkene.

Transient absorption spectroscopy, time resolved photoacoustic calorimetry and chemical tools such as radical clocks have been used to prove the energetics and lifetimes of ephemeral excited states and biradicals.

A lot of questions remain and a lot remains to be done before chemists are able to exchange the vast number of empirical rules (that exist for the prediction of the regio and stereochemical outcome of the reaction) for a single, detailed, mechanism. Having such a mechanism will obviously enhance the utility of this already important synthetic method.

REFERENCES

12) Schuster, D.I; Dunn, D.A; Bonneau, R. J. Photochem. 1985, 28, 413-418.
16) Corey, E.J; Tada, M; La Mahieu, R; Libit, L. J. Am. Chem. Soc. 1965, 87, 2051-2052.
19) Broeker, J.L; Houk, K.N. 1991, personal communication to M.S.
MECHANISM AND INHIBITION OF PHOSPHOLIPASE A₂

Reported by Mark A. Cole

November 14, 1991

INTRODUCTION

Enzymes are exceedingly intricate molecules which catalyze biochemical reactions with incredible ease. Not only are enzymes highly specific in their choice of substrate, but they are also able to catalyze reactions with more than a millionfold rate enhancement over the uncatalyzed reaction.¹ The ability to inhibit an enzyme comes only after the enzyme's ability to function is known. From knowing the mechanism of action and an enzyme's active site, intelligent choices for inhibitors can be made.

Phospholipase A₂ (PLA₂) is a ubiquitous enzyme in nature which occurs in virtually every mammalian tissue that has been examined. The enzyme occurs in a large variety of snake venoms and mammalian exocrine glands, where it serves a digestive role. Interest in the action of PLA₂ also comes from its implication in mediating the inflammatory response through the release of arachidonic acid. Arachidonate is the precursor of the eicosanoid mediators of inflammation including leukotrienes, thromboxanes, and prostaglandins. A buildup of these mediators can lead to asthma, toxic shock, psoriasis, burn trauma, cystic fibrosis, and rheumatoid arthritis. Another product from the catalyzed hydrolysis reaction is lysophosphatidylcholine, which is a platelet-activating factor. The ability to inhibit PLA₂ would have some very desirable pharmacological benefits and is a major goal of current pharmacological research. Hydrolysis-resistant phospholipids would also enable construction of drug-carrying liposomes that are better able to withstand metabolic degradation.

BACKGROUND

Phospholipases are a class of lipolytic enzymes that catalyze the hydrolysis of phospholipids, which are derivatives of glycerophosphates in which the two hydroxyls are esterified to long chain fatty acids and the phosphoryl group forms a phosphodiester bond with a polar unit (Scheme I). All four ester groups in a phospholipid are susceptible to enzymatic hydrolysis. A phospholipid that cleaves the acyl ester at the sn-1 position is designated phospholipase A₁, and one that cleaves at the sn-2 position is designated phospholipase A₂. An enzyme that cleaves the phosphodiester bond on the glycerol side is designated a phospholipase C, and on the polar side a phospholipase D (Scheme I). In general phospholipases have specificity for the position on the glycerophosphate backbone rather than for the particular fatty acid or polar group present.

©1991 by Mark A. Cole
PLA₂ was the first phospholipase to be recognized; its discovery was based on the observation that pancreatic juice or cobra venom would hydrolyze phosphatidylcholine. Secreted PLA₂'s are convenient for chemical studies as they are small water soluble proteins (usually 120 - 134 amino acids, ~14,000 kdaltons) that are unusually stable, due in part to their seven disulfide bonds. This family of PLA₂'s shows a great deal of homology and is referred to as the Class I/II family. PLA₂ is readily crystallized in well-ordered lattices and has been cloned in a variety of cDNA libraries, allowing for site-directed mutagenesis to probe the enzyme's structure and mechanism.

**SUBSTRATE BINDING**

PLA₂ is only slightly active against a monomeric substrate, but its rate accelerates dramatically when the substrate is aggregated. Phospholipids are able to form a variety of structures ranging from a simple monolayer to more complex aggregates such as micelles or vesicles. The binding region of PLA₂, also known as the i-face, is a region of the enzyme with a high concentration of cationic residues. This largely "positive" face is thought to be "attracted" to the interfacial surface of the aggregate which would be made up of the phosphate units and the carbonyls of the ester chains. Once bound to the enzyme, individual phospholipids could proceed up the hydrophobic channel to the active site of the enzyme.

**CATALYTIC MECHANISM**

Recently Scott *et al.* have been able to crystallize PLA₂ in a complex with a transition-state substrate analogue. From this work some proof can be given to Verheij *et al.*'s original proposal for the mechanism of PLA₂. The formation, stabilization, and collapse of the transition state is schematically outlined in Scheme II. N1 of the active site histidine (His48) abstracts a proton from a water molecule bound in the active site (A water molecule has been found at this position in all high resolution crystal structures of Class I/II
Scheme II

[Diagram of molecular interactions involving residues Asp49, Gly30, His48, Asp99, Tyr73, Tyr52, and HOH.]
PLA$_2$'s). The hydroxyl remaining attacks the $sn$-2 carbonyl forming a tetrahedral intermediate which is electrostatically stabilized by the bound Ca$^{2+}$ ion and a backbone amide N-H from a glycine (Gly30). The proton abstracted by His48 is ideally situated to protonate the bridging $sn$-2 oxygen in concert with the productive collapse of the tetrahedral intermediate. The positive charge acquired by the enzyme when it abstracts the proton from the attacking water molecule is presumably stabilized through an extended hydrogen-bond network that includes His48 and a carboxylate (Asp99).

Support for this mechanism can be seen in the results from site-directed mutagenesis studies of the enzyme. His48 is absolutely necessary for catalytic activity. Any alteration to another amino acid or chemical modification to the imidazole ring completely inhibits the enzyme.$^5$ On the other hand, the Asp99 is not completely necessary.$^7$ Replacing the aspartate with asparagine results in a decrease in activity, but the enzyme still maintains 65% of its enzymatic activity. The observed 25-fold reduction is low compared with the values of ~25,000 for an analogous substitution in some of the serine proteases, such as subtilisin and rat pancreatic trypsin. Whereas in trypsin the introduction of an asparagine disrupts hydrogen bonding in the active site (and therefore stabilization of the active site imidazole), the situation in PLA$_2$ is such that only minimal structural change is necessary to create hydrogen bonds. The Asn99 residue in the mutant is still able to stabilize the imidazole of His48 for general base catalysis.

Substitution of serine for glycine at position 30 significantly alters the properties of the enzyme.$^8$ Substitution of serine for Gly30 reduces activity 50-fold and lowers the affinity for calcium ions 20-fold. In the proposed mechanism calcium serves a dual purpose by both fixing the substrate phosphate, and stabilizing the negative charge on the carbonyl oxygen at the $sn$-2 position. The bulkier serine makes it likely that the backbone amide bond can no longer hydrogen bond the carbonyl oxygen, due to steric limitations. The removal of this key stabilizing hydrogen bond will undoubtably reduce the catalytic rate constants, thereby reducing the enzyme's activity.

This catalytic system is reminiscent of the serine proteases.$^9$ There are three main differences, however. First, in PLA$_2$ only water can serve as the source of the nucleophile. There has been no evidence of an acyl intermediate.$^{3,5}$ In the serine proteases the active site serine is deprotonated to create a nucleophile in the acylation step. In the deacylation step of the serine protease mechanism, virtually any dispersed potential nucleophile can attack the carbonyl of the acyl enzyme. Second, tyrosines are present in the catalytic network of PLA$_2$, two of which are absolutely conserved in all Class I/II enzymes (Tyr52 and Tyr73). Although these Tyr residues extend the catalytic network by forming hydrogen bonds with the carboxylate of Asp99, site directed mutational studies
show that the principal function of these tyrosines is to provide structural support.\textsuperscript{8} Third, the hydrogen-bonding patterns of the imidazole ring of histidine differ. Blow\textsuperscript{10} points out that the catalytic triad of serine proteases extracts a proton from serine at N3 of the active histidine, while the aspartate carboxylate interacts through N1. The direct opposite is true in the case of PLA\textsubscript{2}. Moreover the interaction between His\textsubscript{48} and Asp\textsubscript{99} involves a hydrogen-bond with the carboxylate in the anti rather than the syn conformation seen in serine proteases. This is noteworthy because the anti lone pair is a much weaker base (\(\sim 10^4\) fold) than the syn lone pair.\textsuperscript{11}

\textbf{RATE DETERMINING STEP}

To probe the rate determining step, Dennis \textit{et al.} employed \textsuperscript{13}C NMR to quantitate the degree of H\textsubscript{2}\textsuperscript{18}O exchange into a suitably \textsuperscript{13}C labeled substrate and product during reaction with PLA\textsubscript{2}.\textsuperscript{12} By using H\textsubscript{2}\textsuperscript{18}O they were hoping to take advantage of the general \textsuperscript{18}O isotope effect on the \textsuperscript{13}C chemical shifts that had been previously established by Van Etten and Risley.\textsuperscript{13} Since PLA\textsubscript{2} exhibited dramatically enhanced rates on aggregated substrates, such as micelles, over monomers, it was proposed that product release from the enzyme was the rate determining step.

Using isotope exchange to determine the rate determining step is based on two assumptions. The first is that hydrolysis occurs via O-acyl cleavage, which had been previously shown.\textsuperscript{12,14} The second is that since there is no evidence for the formation of an acyl-enzyme intermediate, the reaction presumably goes through a tetrahedral intermediate. As a result the enzyme is likely to be able to distinguish between the two non-bridging oxygens in a tetrahedral intermediate. Therefore, the collapse of such an intermediate back to the starting material would release the same oxygen that attacked the ester, resulting in no net incorporation of \textsuperscript{18}O in the substrate. Exchange of \textsuperscript{18}O during hydrolysis would occur only if the products remained bound sufficiently long for reformation of the substrate using either of the two equivalent oxygens on the bound free acid.

The theoretically expected incorporations of \textsuperscript{18}O into reactants and products of the enzymatic reaction when carried out in the presence of H\textsubscript{2}\textsuperscript{18}O are summarized in Scheme III. If the hydrolysis step is the rate limiting step, no exchange of \textsuperscript{18}O into the substrate would occur (Scheme III, top line). The \textsuperscript{13}C NMR spectrum would contain one peak for the substrate ester, and two peaks for the fatty acid. If the slow step is the product release, exchange of \textsuperscript{18}O into the substrate ester would be expected to occur. If exchange occurs (Scheme III, bottom line), two peaks would be expected for the substrate ester\textsuperscript{15} and three peaks for the fatty acid, with the third due to nuclear shielding.\textsuperscript{15,16}
Dennis used phospholipids that had been $^{13}$C labeled in the $sn$-2 ester position and hydrolyzed them with PLA$_2$ in a 50:50 (v/v) H$_2^{16}$O / H$_2^{18}$O mixture. The results from this experiment showed three peaks, one for the substrate ester and a peak for the free fatty acid which could be resolved into two peaks. The value of 176.51 ppm for the fatty acid agreed well with the previously known chemical shift, as well as the fact that the two resolved peaks were separated by 0.026 ppm, which is characteristic of a carboxylic acid containing a single $^{18}$O label.$^{17}$ These results led to the conclusion that the hydrolysis step was the rate determining step of the PLA$_2$ mechanism.

**INHIBITORS**

Inhibition of an enzyme can be accomplished in either a reversible or irreversible manner. Heat and chemical reagents are two examples of irreversible inhibitors. Enzymes can be inhibited reversibly by noncovalent binding of inhibitors. In competitive inhibition an inhibitor binds reversibly to the active site of an enzyme preventing a substrate from binding. In noncompetitive inhibition an inhibitor binds to an enzyme in a different site than the active site, while the substrate is simultaneously also bound, but no reaction is catalyzed by the enzyme. In choosing a competitive inhibitor, knowledge of the active site architecture is important. In the case of PLA$_2$, since the proposed mechanism has a tetrahedral intermediate at the rate determining step, a tetrahedral phospholipid analogue should make a good inhibitor.

Gelb et al.$^{18}$ chose first, fluorinated ketones (1) where the hydrated form of 1 (2) was proposed to be the inhibitory species. These inhibitors were shown to be very tight binders to the enzyme (300-fold over the analogous ester substrate), but they must be in
their hydrated form (2) for inhibition. They concluded that enforced tetrahedral groups would make for even better inhibitors. The next group of inhibitors (3-4) contained a phosphonate group in place of the ester at the sn-2 position of the glycerol backbone. These compounds proved to be extremely potent inhibitors (IC$_{50}$ = 5µM) that bound to the enzyme some 2000-fold tighter than the analogous ester substrate.

A second class of inhibitors was chosen not to mimic the tetrahedral intermediate state but rather to replace the susceptible ester bond with a more stable bond. Through the use of computer modeling, Campbell and Sainsbury\textsuperscript{20} designed a furanone (5) where the sn-2 unit is bonded through a ketone function rather than an ester group. Using models it appeared that the furanone and the analogous ester substrate were superimposable through the first three methylene groups adjoining the carbonyl function. Inhibition proved to be quite good, with IC$_{50}$ = 64µM. Among the first inhibitors developed were the amide analogues where the ester linkages have been replaced with amide bonds.\textsuperscript{21} The compounds did inhibit the enzyme, but their potency was not good and they have since been surpassed by the previously mentioned inhibitors.

**CONCLUSION**

By combining known crystal structures of enzymes with site directed mutagenesis, the mechanism of action of phospholipase A$_2$ has been determined. With this knowledge of the active site, inhibitors have been designed to further probe the mechanism and structure of the enzyme. With the design of new and improved inhibitors, hopefully therapeutic benefits will be obtained from the knowledge.
REFERENCES

(20) Campbell, M. H.; Fox, J. L.; Sainsbury, M.; Liu, Y. Tetrahedron 1989, 45(14), 4551-4556
SOME RECENT ADVANCES IN ORGANOMETALLIC WITTIG EQUIVALENTS
Reported by Michael Palucki
November 21, 1991

INTRODUCTION

A simple and general method for methylenation of carbonyl compounds was discovered nearly 40 years ago by Wittig and co-workers during the course of their studies on the reactivity of methylenetriphenylphosphorane. Since then, modifications of the original Wittig conditions have led to the generalization of olefination methodology and have also permitted substantial stereoselective control in these reactions. Limitations to Wittig-type reactions nonetheless still exist, however, particularly with regard to the sensitivity of the phosphorane ylides to the steric environment of the substrate and to their tendency to deprotonate carbonyl compounds. Another major drawback of the classical Wittig reaction is the inability of phosphorane ylides to olefine carboxylic acid derivatives. In order to circumvent these and other limitations of phosphorane reagents, organometallic olefination reagents have been developed and studied extensively, and this review will discuss the recent advances in such organometallic Wittig equivalents.

OLEFINATION VIA PROPOSED 1,1-DIMETALLIC INTERMEDIATES

One of the first effective organometallic Wittig reagent equivalents was discovered by Fried and co-workers in 1966 using a modified Simmons-Smith reagent (zinc-methylene iodide) for the methylenation of 17β-acetoxy-11β-hydroxyestr-5(10)-en-3-one. Fried et al. reported only a small amount of the expected cyclopropanation product, with the exocyclic olefin as the major product. Miyano et al. examined a variety of aldehydes under similar conditions in the presence of excess zinc with reported olefination yields of 18-61%. A gem-dimetallic species [IZnCH₂ZnI] was suggested as the reactive intermediate in these olefinations in contrast to the suggested reactive intermediate of the Simmons-Smith reaction [XCH₂ZnX].

Working with the same dimetallic reagent, Takai et al. reported increased olefinic yields for a variety of carbonyl compounds including aldehydes, enals and ketones in the presence of Lewis acids such as AlMe₃ (62 to 86% yields) and TiCl₄ (55 to 92% yields).
The gem-dimetallic species was proposed to add to the activated carbonyl group, followed by β-elimination to generate the olefin.\(^7\)

Support for the bimetallic nature of the reactive intermediate was provided by trapping experiments with Me₃SnCl in which the Oshima reagent gave exclusively 2 while the Simmons-Smith reagent gave predominantly 1.\(^8\)

Other Lewis acids such as VCl₄, WCl₄, AlCl₃, and ZrCl₄ were examined, although reactions carried out in the presence of TiCl₄ generally gave superior yields. Oshima expanded the scope of the reaction by transferring alkyl groups other than methylene in the synthesis of α,β-unsaturated esters, providing a mild alternative to the Horner-Emmons reaction. In the complete absence of a Lewis acid, the corresponding Reformatsky product predominated.

Takai et al. directly compared the reactivity of methylenetriphenylphosphorane and the Oshima reagent in the olefination of a β-acetoxy ketone.\(^9\)
The high basicity of the phosphorane is apparent from the competitive formation of elimination by-products. Taking advantage of the reduced basicity of the Oshima reagent, Lombardo's synthesis of C₂₀ gibberellins resulted in no epimerization of the stereogenic center adjacent to the ketone. Additionally Takai observed high stereoselectivity for the (Z)-enol product in the olefination of ester substrates by the introduction of N, N, N',N'-tetramethylene diamine (TMEDA) to the reaction mixture.

The hydrozirconation of an alkenylzinc halide has been proposed to afford a dimetallic zinc-zirconium intermediate. This species olefinates aldehydes and ketones efficiently as well as stereoselectively.

Functional group compatibility for the alkenylzinc reagents includes esters, nitriles and chlorides. The dimetallic zinc and zirconium intermediates react highly stereoselectively with aldehydes, yielding (E) olefins (>99% E) with high yields, while reaction with ketones affords an E/Z mixture of the product olefin. The dimetallic zinc and zirconium intermediates are unstable at room temperature and decompose after several minutes; however, in the presence of a ketone or aldehyde the olefin is generated in good yields. Similarly, the hydrozirconation of an alkynylzinc halide affords a 1,1-dimetalloalkene of zinc and zirconium, which upon reaction with aldehydes yields the allene products in satisfactory yields (55%-89%).

OLEFINATION VIA PROPOSED METAL-ALKYLIDENE INTERMEDIATES

The Tebbe reagent has enjoyed widespread use as a methylenating reagent because its synthetic accessibility and its ability to olefine carbonyl compounds in high yield. The ability of the Tebbe reagent to olefine carboxylic acid derivative provides a distinct advantage over methylenetriphenylphosphorane. Thus, vinyl ethers are prepared from esters and enamines from amides. The proposed mechanism involves the titanium methylidene as the reactive species, which undergoes metathesis with a carbonyl compound via an intermediate oxametallocycle to give the corresponding olefin and Cp₂Ti=O
Pine, et al. recently compared the reactivity of the Tebbe reagent to that of Ph₃P=CH₂ and showed that the Tebbe reagent was clearly superior (in respect to isolated yields) for the olefination of a variety of carbonyl compounds, especially hindered ketones.¹⁵

Grubbs et. al. utilized the Tebbe reagent with a variety of olefins to synthesize titanium cyclobutanes which can olefinate carbonyl compounds under aluminum-free conditions.¹⁶

It has been proposed that these methylenations proceed via the same titanium methylidene intermediate. Grubbs has shown that aldehydes react faster than ketones. Amides and esters also react to give the corresponding enamines and enol ethers, but acid chlorides and anhydrides β-eliminate to produce the corresponding titanium enolates.

Olefination yields obtained using the Grubbs metallacyclobutanes are generally comparable to or better than those obtained using the Tebbe reagent.

The principal drawback to the Tebbe reagent is that it is limited to carbonyl methylenation. Schwartz et al. have developed a related zirconium-based complex which can transfer higher olefins cleanly to a variety of carbonyl compounds. The complex is readily prepared in a one-pot procedure starting with zirconocene hydridochloride and an alkyne followed by slow addition of an organoaluminum hydride.¹⁷
Olefinations of carbonyl compounds using 6 gave poor yields, due to the low reactivity of 6. Initial attempts to isolate the more reactive alkylidene complex were unsuccessful. However, when the bridged alkylidene 6 was treated with HMPA in the presence of a strongly coordinating ligand, such as triphenylphosphine, a transition metal alkylidene complex 7 was isolated.

The olefination of ketones and esters using the isolated alkylidenes resulted in yields of 80-100%. Transferring higher substituted olefins raises the issue of stereochemical control. Assuming that the Zr-alkylidene based olefination reaction is analogous to the Ti-based system, in which the mechanism proceeds through an oxametallocycle, the stereochemical factors leading to the preferential formation of either of the possible oxametallocycle stereoisomers will determine product distribution. By replacing the carbonyl functionality with an N-alkyl imine group (=NR), exact stereocontrol could take place. Schwartz has correlated the E/Z selectivity of the olefin formed and the size of the substituent group on the imine nitrogen, where X=NR and found that there is a preference for the formation of the Z olefin over the E olefin.

The tedious synthesis of Zr carbene complexes limits their utility as practical reagents for carbonyl olefination, so Schwartz has developed alternative zirconium(IV) "metalloazines". The Zr(IV) metalloazines are readily prepared from Zr(IV) salts and hydrazone derivatives of aldehydes and ketones, or from Zr(II) phosphine complexes and diazoalkanes.
The zirconium metalloazine complexes are susceptible to electrophilic attack either at the carbon center or at the zirconium bound nitrogen. This represents an umpolung of carbonyl reactivity with regard to the hydrazone from which it is derived. Addition of aldehydes or ketones to a solution containing a zirconium metalloazine results in a mixture of condensation products from attack at carbon and nitrogen.\textsuperscript{20}

\[
\begin{align*}
\text{8} + \text{R}^3 \text{R}^4 & \rightarrow \text{R}^3 \text{R}^4 + \text{R}^1 \text{Ph} \\
\text{Ph} & \text{H} \\
\text{Ph} & \text{H}
\end{align*}
\]

Kauffman has developed a molybdenum analogue of the Tebbe reagent from molybdenum pentachloride and 2 equivalents of methyllithium.\textsuperscript{21b}

\[
\text{MoCl}_5 + 2\text{CH}_3\text{Li} \xrightarrow{-\text{CH}_4} \xrightarrow{-2\text{LiCl}} \text{CH}_2=\text{MoCl}_3 \longrightarrow \frac{1}{2} \text{Cl}_3\text{Mo} \biggm\langle \biggm\rangle \text{MoCl}_3
\]

The suggested mechanism is analogous to that of the titanium methylidene reagents in which an intermediate oxametallacycle is produced followed by elimination to afford the olefin and oxametal species. Kauffman examined only aldehydes as substrates and obtained yields in the range of 65-89%. An attractive feature of this method is the reasonable stability of the Mo complex.

Schrock has synthesized and isolated a wide variety of tantalum and niobium alkylidene complexes and employed them in the olefination of ketones, aldehydes, esters, and amides in yields ranging from 60 to 90%.\textsuperscript{22} The syntheses of these alkylidenes are tedious, however, and the method therefore has limited applicability in organic synthesis.

**OLEFINATION VIA OTHER METHODS**

Recently, Petasis and Bzowej introduced an alternative aluminum-free methylenating reagent.\textsuperscript{23} The method involves the use of dimethyltitanocene, which is readily prepared from 2 equivalents of methyllithium and titanocene dichloride. Olefination yields using the Petasis reagent are comparable to those using the Tebbe reagent. Preliminary experiments carried out by Petasis have suggested a non-carbene mechanism, in which initial coordination of the carbonyl oxygen to the titanium complex is followed by methyl transfer from the titanium to the carbonyl carbon. Loss of methane results in the olefin and titanocene oxide.
Luh et al. recently developed a NiCl$_2$(PPh$_3$)$_2$ catalyzed conversion of cyclic dithioacetals to olefins with a variety of Grignard reagents. The mechanism has been suggested to involve an oxidative addition and reductive elimination process. Olefination yields ranged from 58 to 94% using 5 mol% catalyst.$^{24}$

**CONCLUSION**

Recent advances in the development of transition metal organometallic Wittig equivalents have provided the organic chemist with a wide variety of tools to transform efficiently as well as selectively a variety of carbonyl compounds to olefins. Amides, esters and hindered ketones do not undergo olefination products under Wittig conditions but are smoothly transformed by a variety of organometallic reagents. The reduced basicity of the organometallic reagents compared to their Wittig counterparts results in fewer unwanted side reactions as well as no epimerization of stereogenic centers α to the carbonyl.

**REFERENCES**


(12) Knochel, P., Submitted for publication.


CATALYTIC ENANTIOSELECTIVE BORANE REDUCTION OF CARBONYL COMPOUNDS MEDIATED BY CHIRAL AMINO ALCOHOLS

Reported by Yuelong Liu

December 2, 1991

INTRODUCTION

One group of enantioselective reactions that has received special attention in recent years is that in which organometallic compounds, normally unreactive to ketones and aldehydes, can be activated by catalytic amounts of amino alcohols so that they undergo enantioselective carbonyl addition. Organometallic reagents of this type include dialkyl zinc and tetraalkyl lead compounds,\(^1\,\,2\) and chirally modified boranes and borates.\(^3\) This abstract will discuss the most recent advances in developing chiral borane reagents, especially those modified by chiral amino alcohols for asymmetric reduction of achiral ketones and some other carbonyl compounds.

BACKGROUND

Amino-borane complexes, extensively studied as reducing reagents,\(^4\) have practical advantages in organic synthesis because they are stable to air and water and soluble in a variety of solvents. A simple approach to creating an asymmetric reducing reagent would be to utilize an optically active amine. Early attempts with this approach were made in 1969 by Fiaud and Kagan, who prepared chiral amine-borane complexes using (S)-1-methyl-2-phenylethylamine and its derivatives, but these complexes gave only poor optical yields of 3.6-5% ee in the reduction of acetophenone.\(^5a\) Similarly, Borch and Levitan achieved only 3% ee using 1-phenylethylamine.\(^5b\) Later, several research groups tried along this line to improve enantioselectivity, but with little success.\(^6\) One of the guiding principles in developing asymmetric reducing reagent is that a more rigid system may lead to a more ordered transition state and thus to a higher enantioselectivity. Therefore, the incorporation of additional complexing ligands in the chiral amine can, in theory, lead to better reagents.

The first practical procedure for asymmetric reduction of ketones with a borane reagent chirally modified in this fashion appeared in the early 1980's when a series of work was carried out by Itsuno and coworkers,\(^3c\,\,7-12\) in which complexes of borane and a chiral amino alcohol (1 or 2) in THF were employed. Surprisingly, the slightly modified amino alcohol 2 is much more efficient than 1, indicating that the phenyl group in 2 plays an important role far more than sterically. In Itsuno's typical procedure, a 2:1 mixture of borane and the chiral amino alcohol in THF was allowed to react at 0 °C for several hours, giving a reducing reagent to which the ketone

Copyright © 1991 by Yuelong Liu
was added for reduction at 0-30 °C. Reduction of ketone with this reagent was faster than that with borane alone in THF at the same temperature. Using this procedure, Itsuno et al. reduced a number of aromatic ketones in good to excellent optical yield. As shown in Table I, the asymmetric reduction of the aromatic ketones with the reagent from (S)-amino alcohols always gave the products with R-configuration. The reversed stereoselectivity with the same degree of asymmetric induction was achieved by use of the enantiomer of the (S)-amino alcohol. Therefore, with predictability of absolute configuration, this method allows both enantiomers of secondary alcohols to be synthesized readily from aromatic ketones. It is equally interesting to note that enantioselectivity depends critically on the ratio of borane to the amino alcohol used in the asymmetric reduction, with the highest % ee at the ratios of 2.0-3.0 : 1.8-9.

Table I Asymmetric Reduction of Ketones with the Reagent Prepared from 2:1 Borane and the Chiral Amino Alcohol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Amino alcohol</th>
<th>% ee</th>
<th>Abs config</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCOME</td>
<td>(S)-1</td>
<td>49</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>PhCOME</td>
<td>(S)-2</td>
<td>94</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>PhCOn-Pr</td>
<td>(S)-2</td>
<td>94</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>PhCOn-Pr</td>
<td>(S)-2</td>
<td>96</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>PhCOn-Pr</td>
<td>(R)-2</td>
<td>6.6b</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>PhCOn-Bu</td>
<td>(S)-2</td>
<td>100</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>n-BuCOMe</td>
<td>(S)-2</td>
<td>55</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>n-C6H13COMe</td>
<td>(S)-2</td>
<td>58</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>i-BuCOMe</td>
<td>(S)-2</td>
<td>61</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>t-BuCOMe</td>
<td>(S)-2</td>
<td>73(79)d</td>
<td>R</td>
</tr>
</tbody>
</table>

a The yield was 100% in each case based on GC analysis. b The reagent was prepared from 1:1 borane and (S)-2. c ee corrected for the (R)-2 of optical purity of 94% ee. d The reaction was run at -78 °C.

At present, there have been several reagents reported to be effective in the asymmetric reduction of aromatic ketones,3a,13 but only limited success has been achieved for aliphatic ketones with these reagents. For example, the chiral binaphthyl-LiAlH4 and chiral diamino-LiAlH413 reagents, which are highly effective for aromatic ketones, reduced 2-octanone in only 24% ee and 26% ee, respectively. When Itsuno's reagent was applied to aliphatic ketones, it turned out to be fairly successful; a reasonably high degree of enantioselectivity was obtained with both straight and branched chain aliphatic ketones,10a as shown in the Table I. It is clear that the Itsuno reagent has the ability to differentiate small differences in the steric size of the alkyl groups attached to the carbonyl carbon of the ketones. The enantioselectivity of the reagent obviously reflects the order
of the steric bulkiness of the alkyl chain. Further improvement in the optical yields can be expected when the asymmetric reduction is performed at lower temperatures.

Itsuno and coworkers extended this method to ketones containing different functional groups, such as keto esters, hydroxy ketones, $\alpha$-halogeno ketones, and oxime ethers. Satisfactory results were obtained.$^{11a}$

**CARBONYL REDUCTION MEDIATED BY ENZYME-LIKE CATALYSTS (CBS)**

In 1987, Corey and coworkers developed an enzyme-like, catalytic enantioselective process for ketone reduction, which is dubbed CBS after the initials of the authors on this methodology—Corey, Bakshi, and Shibata.$^{14-15}$ The stoichiometric reagent in the reduction is borane, the catalyst is one of the chiral oxazaborolidines (Scheme I), among which 3 and 4 were used in the original CBS process. The results obtained with (S)-3 as catalyst for the reduction of ketones by borane in THF were quite satisfactory.$^{14}$ Under optimum conditions (usually 0.6 equiv of borane, 0.05 equiv of (S)-3 as catalyst, THF solution, 25 °C), excellent optical yields were achieved for a variety of ketones. The reaction proceeded to completion within 1 min after the mixing of reagents, and the chiral amino alcohol was easily recovered upon workup without racemization, making this method especially attractive for large scale synthesis. It should be noted that the enantioselectivity of these reductions often decreases somewhat with increasing the amount of BH$_3$ above 0.6 equiv or with decreasing temperature.$^{14}$ One possible explanation is that the non-catalytic reduction with BH$_3$ may compete and the catalyst tends to dimerize by self-association at lower temperature so that the effective concentration of the catalyst (monomer) decreases.

Compared to (S)-3, which is both air and moisture sensitive, the B-methylated oxazaborolidine (S)-4 is more stable, and in some cases more effective. Table II summarizes the excellent results obtained for 9 different ketones of widely varying structure with the use of 0.6 equiv of borane in THF for 2 min at the indicated temperature.$^{15}$ All of the reactions proceeded to completion and the secondary alcohol was the only detectable product by gas chromatography.
Table II Borane Reduction of Ketones Catalyzed by (S)-4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Equiv of BH$_3$</th>
<th>Equiv of (S)-4</th>
<th>Rxn temp, °C</th>
<th>Config of Prod (%) ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_5$COCH$_3$</td>
<td>0.6</td>
<td>0.1</td>
<td>2</td>
<td>R (96.5)</td>
</tr>
<tr>
<td>2</td>
<td>C$_6$H$_5$COC$_2$H$_5$</td>
<td>0.6</td>
<td>0.1</td>
<td>-10</td>
<td>R (96.7)</td>
</tr>
<tr>
<td>3</td>
<td>C$_6$H$_5$COC$_2$H$_5$</td>
<td>0.6</td>
<td>0.1</td>
<td>32</td>
<td>R (95.3)</td>
</tr>
<tr>
<td>4</td>
<td>t-BuCOCH$_3$</td>
<td>0.6</td>
<td>0.1</td>
<td>-10</td>
<td>R (97.3)</td>
</tr>
<tr>
<td>5</td>
<td>α-tetralone</td>
<td>0.6</td>
<td>0.1</td>
<td>-10</td>
<td>R (97.3)</td>
</tr>
<tr>
<td>6</td>
<td>α-tetralone</td>
<td>0.6</td>
<td>0.25</td>
<td>-10</td>
<td>R (83.3)</td>
</tr>
<tr>
<td>7</td>
<td>C$<em>6$H$</em>{11}$COCH$_3$</td>
<td>0.6</td>
<td>0.1</td>
<td>-10</td>
<td>R (86.0)</td>
</tr>
<tr>
<td>8</td>
<td>C$_6$H$_5$CO(CH$_2$)$_2$CO$_2$CH$_3$</td>
<td>0.6</td>
<td>0.1</td>
<td>23</td>
<td>R (84)</td>
</tr>
<tr>
<td>9</td>
<td>C$_6$H$_5$CO(CH$_2$)$_2$CO$_2$CH$_3$</td>
<td>0.6</td>
<td>0.1</td>
<td>23</td>
<td>R (91)</td>
</tr>
<tr>
<td>10</td>
<td>C$_6$H$_5$CO(CH$_2$)$_3$CO$_2$CH$_3$</td>
<td>0.6</td>
<td>0.1</td>
<td>0</td>
<td>R (94)</td>
</tr>
<tr>
<td>11</td>
<td>C$_6$H$_5$CO(CH$_2$)$_3$CO$_2$CH$_3$</td>
<td>0.6</td>
<td>0.1</td>
<td>0</td>
<td>R (96.7)</td>
</tr>
</tbody>
</table>

MECHANISM

Based on the results above and observations of $^{11}$B NMR spectrum data, Corey et al. proposed a mechanism for the CBS process,\textsuperscript{14} as shown in Scheme II. The mechanistic picture accords with all the facts available, including the experimental results obtained in Itsuno's group. It unambiguously explains the observed stereochemistry of the reduction. The authors believe that the complex B is ideally structured to serve as an effective reagent for carbonyl reduction. The bi- or tricyclic boron catalyst functions at the boron atom as a Lewis acid, which is capable of activating the ketone that is to be reduced. The neighboring bridged nitrogen atom in turn binds to borane, activating it for the hydride transfer. The two achiral reaction partners are thus brought from the surrounding solution into proximity by the catalyst to a chiral environment such that one
of the enantiotopic sides of the carbonyl group is preferentially directed toward the hydride-transferring boron atom, and the hydride transfers from the NBH$_3^-$ unit to the carbonyl carbon via a six-membered cyclic transition state. Nevertheless, it is equally important for the catalytic course of the asymmetric reduction that the product alcolholate group is transferred from the boron atom in the ring to another boron atom, thereby removing it from the catalyst to complete the catalytic cycle.

This mechanistic model for the enantioselective reduction of various ketones with different chiral catalysts has been proven so reliable in explaining all the observed experimental results that Corey allows himself to be seduced into inventing a word "chemzyme", short for chemical enzymes, for his CBS catalysts, which share natural enzymes' ability to tell left from right.\textsuperscript{16b}

**MODIFIED CBS PROCESS**

With the modified oxazaborolidines 5-9\textsuperscript{17} as enantioselective catalysts in the borane reduction of achiral ketones to chiral secondary alcohols, enhanced asymmetric induction has been achieved in some cases. The modified CBS process also follow the stereochemical course which is expected for the catalytic transition state assembly 10. It is worthwhile to note that the β-naphthyl catalysts are in several instances more effective than the phenyl analogs, especially in the case of aromatic ketones. This would seem to indicate that there is π-π interaction brought into play between the aromatic ring of the ketone and the aryl substituent of the catalyst at the position β to the bridged nitrogen atom in the transition state, which accounts for the enhanced enantioselectivity observed for the aromatic ketones. Furthermore, substitution of i-propyl, α-naphthyl, o-methoxyphenyl, or H for β-naphthyl or phenyl leads to catalysts which are much less effective and selective.\textsuperscript{17b}

**Reduction of Aldehydes**

Using $^2$H-catecholborane as stoichiometric reducing reagent, aldehydes have been reduced to chiral 1-deutério primary alcohols in the presence of 8 as catalyst in excellent optical yields.\textsuperscript{17b} This modified CBS process provides alcohols of either S or R absolute configuration through the use of 8 or its enantiomer and does not necessitate the synthesis of 1-deutério aldehydes. The S configuration of the products presented in Table III is consistent with the proposed mechanism for

**Table III** Asymmetric Reduction of Aldehydes Catalyzed by (S)-8

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Equiv of catalyst</th>
<th>Product$^a$ config, % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_5$CHO</td>
<td>0.3</td>
<td>S (95)</td>
</tr>
<tr>
<td>2</td>
<td>C$_6$H$_5$CHO</td>
<td>0.1</td>
<td>S (90)</td>
</tr>
<tr>
<td>3</td>
<td>p-BrC$_6$H$_5$CHO</td>
<td>0.3</td>
<td>S (91)</td>
</tr>
<tr>
<td>4</td>
<td>p-MeOC$_6$H$_5$CHO</td>
<td>0.3</td>
<td>S (82)</td>
</tr>
<tr>
<td>5</td>
<td>2-Octanal</td>
<td>0.3</td>
<td>S (90)</td>
</tr>
<tr>
<td>6</td>
<td>Cyclo-C$<em>6$H$</em>{11}$CHO</td>
<td>0.3</td>
<td>S (92)</td>
</tr>
</tbody>
</table>

$^a$ The yield is more than 90% in each case after purification by flash chromatography.
the CBS process and is predicted for all entries in Table III. The use of catecholborane in place of borane makes it possible to operate CBS reduction at a much lower temperature without loss of enantioselectivity.

Reduction of \( \alpha,\beta \)-Enones and Other Interesting Substrates

The original CBS procedure involving 3 or 4 as catalyst and borane as stoichiometric reductant is subject to the interference by functionality which is sensitive to borane (e.g. olefins or amides) and loses enantioselectivity at lower temperatures. In contrast, the catecholborane procedure functions well at low temperature thus allowing considerably enhanced enantioselectivity with important types of substrates such as \( \alpha,\beta \)-enones. Table IV summarizes the results with such substrates. \(^{17c}\) But the stereochemistry reported in the last two cases seems contradictory to Corey's mechanistic model.

**Table IV Asymmetric Reduction of \( \alpha,\beta \)-Enones and Some Other Ketones**

<table>
<thead>
<tr>
<th>Ketone</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute config</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>% ee</td>
<td>92</td>
<td>86</td>
<td>91</td>
<td>93</td>
<td>81</td>
<td>90</td>
<td>94a</td>
</tr>
</tbody>
</table>

a One recrystallization of the crude product from ether-hexane afforded pure carbinol.

\[
\text{Ketone} + (S)^{-}\text{BH} \quad \text{[R]} \quad 0.1 \text{equiv} \quad \text{toluene} \quad 15h \quad \text{70°F} \quad \text{R} \quad \text{R} \quad \text{R} \\
\]

From all of the experimental results shown above, it is clear that the catalytic enantioselective CBS reduction has a number of advantages: \(^{3b}\) (1) wide scope, (2) generally predictable absolute stereochemistry, (3) ready availability of the chiral catalyst in either enantiomeric form, (4) easy and efficient recoverability of the chiral amino alcohol (catalyst precursor), (5) high yields and experimental simplicity, and (6) economy.

**APPLICATIONS**

Since its discovery, the CBS process has been used as a key step to establish desired stereochemistry in the synthesis of several therapeutically important molecules. Recent applications of the CBS reduction include the enantioselective synthesis of prostaglandins, \(^{15}\) ginkgolides A and B, \(^{18,19}\) forskolin, \(^{20}\) anti-PAF 2,5-diarylfuran, \(^{21}\) fluoxetine as both pure \( R \) and \( S \) enantiomers, \(^{22}\) and \( R- \) and \( S- \) isoproterenol (\( \beta \)-stimulants and \( \beta \)-blockers). \(^{23}\) One of the most
challenging problems in the area of prostaglandin synthesis has been the development of synthetic approaches which control stereochemistry, particularly at C-15. The chiral ester keto lactone shown below, a standard intermediate in prostaglandin synthesis, underwent enantioselective reduction of the keto group upon treatment with borane and 0.1 equiv of 4 as catalyst to give the 15-R alcohol preferentially in a ratio of 91:9 (Scheme III). With the use of the enantiomer of 4 as catalyst, the opposite stereochemical preference was observed with the diastereomeric 15-S predominating in a ratio of 90:10.15

**Scheme III**

The power and outstanding utility of the CBS method has also been seen in the synthesis of the naturally occurring form of ginkgolide B, a potent antagonist of platelet activating factor (PAF). Scheme IV illustrates an efficient enantioselective route to an intermediate on the pathway of the total synthesis. A key step in this transformation was the highly enantioselective borane reduction of the starting cyclopentenone catalyzed by the chiral oxazaborolidine 4. This methodology provides an excellent route to chiral allylic alcohols.19

**Scheme IV**

**CONCLUSION**

The recent progress in catalytic and highly enantioselective methodology for reduction of carbonyl compounds, mainly of ketones, is very impressive and encouraging. Corey's enzyme-
like catalysts and the outstanding utility of the CBS process would seem to suggest that the rational
design of a structurally defined chiral catalyst, which works in a known way, is quite possible and
perhaps is an important field of chemistry for the years to come. It can be predicted that new
synthetic methods emerging from such efforts will be of great value.

REFERENCES
SYNTHETIC AND MECHANISTIC ASPECTS OF ASYMMETRIC ALLYLBORATION

Reported by Sriram Shankar

December 5, 1991

INTRODUCTION

Until the last decade, little work had been reported concerning the generation of stereogenic centers in acyclic compounds. Stereoselective synthesis belonged to the domain of alicyclic and heterocyclic chemistry, being concerned in particular with the generation of stereogenic centers of desired configuration during the synthesis of alkaloids, steroids and sugars. Many advances have been made since and innumerable methods are now available to achieve the same. Special attention has been given to those reactions in which new carbon-carbon bonds are formed via aldol reaction (M = Li, X = O in Scheme I).

Scheme I

In the aldol reaction (X=O, in Scheme I), two prochiral components - the aldehyde and the enolate - are allowed to react. Hence two diastereomeric products - the erythro adduct 2 and the threo adduct 5 - may result. This motivated the research for stereoselective synthetic methods, which lead to either the threo or the erythro product in high yield. It has therefore been the aim of several investigators to develop pairs of stereoisomeric reagents 1 and 4 which are capable of converting aldehydes stereoselectively to the adducts 2 and 5, respectively.

# The terms 'erythro' and 'threo' are used in the sense defined by Heathcock and Maskens. The usage is, however, contrary to the rules defined by Beilstein or Chem. Abstracts.

Copyright © 1991 by Sriram Shankar
Table I. Examples of Allylmetal-Aldehyde Condensations$^{8a, b}$

<table>
<thead>
<tr>
<th>Metal</th>
<th>E/Z Ratio</th>
<th>Conditions</th>
<th>Syn/Anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiMe$_3$</td>
<td>99/1</td>
<td>TiCl$_4$ / CH$_2$Cl$_2$ / -78°C</td>
<td>97/3</td>
</tr>
<tr>
<td>SnBu$_3$</td>
<td>100/0</td>
<td>BF$_3$OEt$_2$ / CH$_2$Cl$_2$ / -78°C</td>
<td>98/2</td>
</tr>
<tr>
<td>SnBu$_3$</td>
<td>0/100</td>
<td>BF$_3$OEt$_2$ / CH$_2$Cl$_2$ / -78°C</td>
<td>99/1</td>
</tr>
<tr>
<td>(RO)$_2$B</td>
<td>95/5</td>
<td>Hexane / -78°C</td>
<td>1/99</td>
</tr>
<tr>
<td>(RO)$_2$B</td>
<td>5/95</td>
<td>Hexane / -78°C</td>
<td>99/1</td>
</tr>
<tr>
<td>L$_2$CrCl$_2$</td>
<td>100/0</td>
<td>THF / R. T.</td>
<td>0/100</td>
</tr>
<tr>
<td>ZrCpCl$_2$</td>
<td>E</td>
<td>THF / -78°C</td>
<td>14/86</td>
</tr>
<tr>
<td>TiCpCl$_2$</td>
<td>E</td>
<td>THF / -78°C</td>
<td>19/81</td>
</tr>
</tbody>
</table>

WHY BORON

Several allylmetals are available that can give the desired products with high selectivity (Table I). It is opined that a useful reagent of this type must fulfil these requirements$^{8a}$: (i) each of the stereomeric synthons 1 and 4 should be conveniently available, (ii) the stereomeric synthons 1 and 4 should not equilibrate under the reaction conditions, (iii) each of the synthons 1 and 4 should add diastereospecifically to aldehydes forming only one of the adducts 2 or 5, (iv) the addition of 1 and 4 to the aldehydes should be irreversible, (v) the structural elements R and X in Scheme I should allow for easy transformation of the adducts into an aldol, eg 2$\rightarrow$3, (vi) chiral modifications of the reagents 1 and 4 should be achieved easily.

Lithium enolates (M = Li, X = O in Scheme I) having special substituents R fulfil most of these requirements satisfactorily and have been subsequently used in total synthesis of methymycin and monensin$^{1a, 3, 5}$. Crotylchromium reagents add diastereoselectively and irreversibly, and have the advantage of being easily manipulated so as to allow further transformations. In general all crotylmetal reagents undergo diastereoselective and irreversible addition to aldehydes, but some of them are either not conveniently available or have a high rate of E/Z isomerisation. Only germanium and silicon derivatives possess sufficient E/Z stability. However, their reactions with carbonyl compounds require either high temperatures or strong Lewis acids. In contrast, the crotylboronates, (M = B, X = CH$_2$ and R = H in Scheme I) are considerably more reactive and their reaction with aldehydes occur at or below ambient temperatures. Their ability to give high diastereoselectivities is well documented. The reaction is believed to proceed via a cyclic transition state and it has been recognised that their compacted transition state, owing to a shorter B-C
distance (1.5 - 1.6 Å), as compared to normal M-C bond distances (1.9 - 2.2 Å), allows for enhanced manifestations of A^1,2 and A^1,3 interactions, leading to greater selectivity. There is extensive knowledge on the synthesis of isomeric forms of the crotylboranes 1 and 4. Given these facts, crotylboron reagents should be almost ideal reagents for diastereoselective C-C bond formation.

**PREPARATION OF (Z)- AND (E)- CROTYLBORONATES**

(E)- and (Z)-Crotylboron derivatives 6 and 8 equilibrate via borotropic rearrangement involving the 1-methylallyl compound 7 as an intermediate (Scheme II). Dialkylcrotylboron compounds are fluxional molecules at room temperature, the rate of rearrangement decreasing with increasing π-donor property of the substituents on boron. Whereas one oxygen is insufficient to suppress the borotropic rearrangement at -20°C, one amino substituent renders it stable up to 150 °C. Compounds 7b and 7c fail to rearrange to 6 below 170 °C. Crotylboronates such as 6d and 8d are configurationally less stable but can be handled at room temperature. Consequently, and for other reasons, they are handled at sub-ambient temperatures.

**Scheme II**

(E)- and (Z)-Crotylboronates could be synthesized by the method of Schlosser (Scheme III)^4. Another route to (Z)-2-alkenyl-1-boronates has been described by Brown.6 (E)-Crotylboronates could also be synthesized using crotylmagnesium reagents.4a

**Scheme III**
CONTROL OF DIASTEREOSELECTIVITY

The control of stereochemistry during C-C bond formation is of paramount importance in synthesis. Four diastereomeric products may be produced in an condensation with carbonyl substrates. Considerable effort has gone into the selective synthesis of each isomer. To do so by using crotylmetal or aldol chemistry requires the control of two independent stereochemical problems: (i) C3, C4-anti or -syn stereochemistry generated in concert with the new C-C bond., and (ii) the aldehyde diastereofacial selectivity issue that determines the relationship of the newly formed C3 and C4 stereocenters to the center C5 originally present in the chiral substrate (Scheme I).

The first issue is easily tackled, as numerous allylmetal and aldol reagents are now available that react with aldehydes with high diastereoselectivity. It is clear that as long as the reagents used react via a cyclic transition state, the problem settles to just selecting the species with the appropriate double bond or enolate geometry. It is now well established that the reagents with an E-configuration give the C3-C4 anti relationship and the reagents with a Z-configuration give the 3,4-syn diastereomer.

The control of aldehyde diastereofacial selectivity is difficult to achieve, however, and recourse to the renowned strategy of double asymmetric synthesis is generally required. Several researchers have focused on strategies involving the concept of double asymmetric synthesis and several chiral allyl metal reagents have been developed for the application in aldol-like construction of natural products of propiogenic/acetogenic origin.

REACTION WITH ACHIRAL ALDEHYDES

Studies on allylboration were performed by Roush using auxiliaries 9-11,2a-c

\[
\begin{align*}
\text{9} & \quad \text{10} & \quad \text{11}
\end{align*}
\]

It has been established that best selectivities were acheived when the reactions with aliphatic aldehydes were performed in toluene (THF for aromatic aldehydes) at -78° C in the presence of 4-Å molecular sieves.2b The results were identical with all commercially available tartrate esters. The simple diastereoselectivity realized in these asymmetric crotylboronation reactions is excellent in a vast majority of cases, with the diastereoselectivity closely paralleling the isomeric purity of the crotylboronates (Table II).
Scheme IV

\[ \text{RCHO} \rightarrow \text{OH} + \text{OH} \]

Table II (Scheme IV). Examples of Achiral Aldehyde-Allylmethyl Condensations.

<table>
<thead>
<tr>
<th>RCHO</th>
<th>reagent</th>
<th>purity</th>
<th>reaction time</th>
<th>anti : syn</th>
<th>( 18:19 )</th>
<th>( 18 )</th>
<th>( 19 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td>10</td>
<td>99.4</td>
<td>3h (87%)</td>
<td>&gt;99:1</td>
<td>88</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17a</td>
<td>11</td>
<td>99.6</td>
<td>6h (70%)</td>
<td>1: &gt;99</td>
<td>-</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>17b</td>
<td>10</td>
<td>99</td>
<td>3h (86%)</td>
<td>&gt;99:1</td>
<td>84</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17c</td>
<td>10</td>
<td>98</td>
<td>4h(100%)(-95°C)</td>
<td>&gt;99:1</td>
<td>91</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17c</td>
<td>10</td>
<td>99</td>
<td>1h (96%)(23°C)</td>
<td>&gt;99:1</td>
<td>46</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17c</td>
<td>11</td>
<td>99</td>
<td>6h (90%)</td>
<td>2:98</td>
<td>-</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>17d</td>
<td>11</td>
<td>98</td>
<td>4h (68%)</td>
<td>2: &gt;98</td>
<td>-</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>17e</td>
<td>10</td>
<td>99.5</td>
<td>7d (66%)</td>
<td>1: &gt;99</td>
<td>-</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>17f</td>
<td>10</td>
<td>99</td>
<td>4h (91%)</td>
<td>&gt;99:1</td>
<td>74</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17g</td>
<td>10</td>
<td>99.3</td>
<td>3h (91%) (THF)</td>
<td>&gt;99:1</td>
<td>66</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

\( ^{a} \)All reactions were performed at -78°C in toluene unless indicated otherwise.

The asymmetric inductions realised with 9-11 are consistent with major product formation via the transition state A. It is explained that the transition state structure A is favored as a consequence of n-n electronic repulsive interaction involving the aldehydic oxygen atom and the β-face ester group, that destabilizes B relative to A. The origin of asymmetry is therefore stereoelectronic in nature (Scheme V) \(^{2a}\).

Scheme V

Other studies by Brown and co-workers have led to the development of reagents 12-15, that provided enantioselectivities of 94-99%.\(^{2e-g}\) These are easily synthesized from (+)- and (-)-
pinene and (+)-3-carene,

2-\textsuperscript{d}Icr\textsubscript{2}BA11 (15) possesses a relatively hindered boron atom flanked on both sides by substituents and therefore gave homoallylic alcohols with the highest enantiomeric purities. A composite study of allylboration using 13, 14 and 15 is shown (table III).

**Table III.** Comparison of the Asymmetric Allylborations of Representative Aldehydes with Chiral B-Allyldialkylboranes 13-15 at -78°C.

<table>
<thead>
<tr>
<th>aldehyde</th>
<th>alcohol</th>
<th>reagent</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaldehyde</td>
<td>4-penten-2-ol</td>
<td>R</td>
<td>92</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>propionaldehyde</td>
<td>5-hexen-3-ol</td>
<td>R</td>
<td>86</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>n-butyraldehyde</td>
<td>1-hepten-4-ol</td>
<td>R</td>
<td>86</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>isobutyraldehyde</td>
<td>2-methyl-5-hexen-3-ol</td>
<td>S</td>
<td>88</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>acrolein</td>
<td>1,5-hexadien-3-ol</td>
<td>S</td>
<td>92</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>benzaldehyde</td>
<td>1-phenyl-3-buten-1-ol</td>
<td>S</td>
<td>94</td>
<td>87</td>
<td>95</td>
</tr>
</tbody>
</table>

**DOUBLE ASYMMETRIC INDUCTION**

Table IV summarizes the results of the reactions of 9 and 26 with \(\alpha,\beta\)-dialkoxyaldehydes (20 and 23).

**Table IV.** Examples of Chiral Aldehyde- Allylmetal Condensations

<table>
<thead>
<tr>
<th>reagent</th>
<th>diol</th>
<th>conditions</th>
<th>product ratio(yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>diol</td>
<td>CH(_2)Cl(_2), (-78^\circ)C</td>
<td>96:4 (91%)</td>
</tr>
<tr>
<td>26</td>
<td>pinacol</td>
<td>CH(_2)Cl(_2), 78^\circ)C</td>
<td>80:20 (75%)</td>
</tr>
<tr>
<td>26</td>
<td>pinacol</td>
<td>toluene, 78^\circ)C</td>
<td>71:29</td>
</tr>
<tr>
<td>(+)-9</td>
<td>(-)-DIPT</td>
<td>toluene, 78^\circ)C</td>
<td>8:92</td>
</tr>
<tr>
<td>Reagent</td>
<td>Diol</td>
<td>Conditions</td>
<td>Product Ratio/Yield</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>(+)-9</td>
<td>(-)-DIPT</td>
<td>CH₂Cl₂, -78°C</td>
<td>98:2 (94%)</td>
</tr>
<tr>
<td>26</td>
<td>pinacol</td>
<td>CH₂Cl₂, -78°C</td>
<td>90:10 (85%)</td>
</tr>
<tr>
<td>(-)-9</td>
<td>(+)-DIPT</td>
<td>CH₂Cl₂, -78°C</td>
<td>71:29</td>
</tr>
</tbody>
</table>

26 is the boronate derived from pinacol.

It is noteworthy that the tartrate ester residue effectively enhances (matched) or overrides (mismatched) the intrinsic facial selectivity of 20 and 23, as measured in reactions with achiral pinacol boronate 26, thereby making possible a hitherto unprecedented, highly selective route to 21-24. Thus, whereas glyceraldehyde acetonide shows only moderate preferences in reaction with 26 (80:20 or 71:29, depending on solvent), selectivity for threo 21 is enhanced to 96:4 with (-)-9 prepared from (+)-DIPT. With pure (+)-9 prepared using its antipode, (-)-DIPT, a 92:8 selectivity is observed. Similar trends are observed using 23. These examples include some of the most powerful cases of matched and mismatched selectivities for 21 - 24 reported thus far.  

Other chiral auxiliaries have been used with comparable to lower efficacy.

CONCLUSION:

Crotylboronates 9-15 are easily prepared in high isomeric purity from commercially available starting materials, and undergo highly diastereo- and enantioselective additions to aliphatic, aromatic and α,β-unsaturated aldehydes. It is possible to get even higher diastereoselectivities. employing double asymmetric induction. The successful synthesis of several natural products such as rifamycin, olivin, Prelog-Djerrassi lactone and other macrolides bear testimony to the efficacy and applicability of this reaction.

REFERENCES


CURRENT PROGRESS IN THE PREPARATION OF CHIRAL SULFOXIDES

Reported by Hua Du

December 9, 1991

INTRODUCTION

Chiral sulfoxides are sometimes found as natural products with a defined stereochemistry at sulfur such as in carpetimycin A, 1, and sparsomycin, 2,1,2

![Chemical Structures]

Chiral sulfoxides are also frequently used as removable chiral auxiliaries in organic synthesis for the stereocontrolled formation of asymmetric centers.3 Conjugate additions of organometallic reagents to sulfoxide-substituted unsaturated carbonyls have been extensively studied by Posner.4 The transfer of chirality from the sulfoxide sulfur atom to the β-carbon atom during organometallic β addition, followed by removal of sulfur, produces β-substituted cyclopentanones in high optical purity. Complete control of absolute stereochemistry in the preparation of 4 allows one to prepare an optically pure steroid by a very short route starting from sulfoxide 3 (Scheme I).5

Optically active sulfoxide-stabilized carbanions can be substituted with high diastereoselectivity. For example, sulfoxide 5 gives aldol-type condensation with aldehydes. After desulfurization, the products (6) are obtained in good yields with 91% e.e. for R=OrBu, R'=Ph6 and 99% e.e. for R=NMe2, R'=Me.7 It is found that reactions at positions remote from the chiral sulfur center can also proceed with high diastereoselectivity. For example, chiral α,β-unsaturated β-keto sulfoxides are convenient intermediates for the synthesis of both enantiomers of allylic alcohols in high enantioselectivities; through reduction with LiAlH4 or DIBAL; both enantiomers of 8 are prepared with 90% e.e.8 Sulfoxide-mediated hydroxylation by osmium tetroxide of a remote olefin allows the clean preparation of 10.9

High enantioselectivity can be achieved in the [2,3] sigmatropic rearrangement of allylic sulfoxides. The fact that the sulenate esters formed can be converted to the corresponding allyl alcohols by treatment with trimethyl phosphite has made it possible to exploit [2, 3] sigmatropic rearrangement of chiral allyl sulfoxides for the asymmetric synthesis of chiral allyl alcohols.10
most successful example is the synthesis of spirocyclic alcohol 12 with 90% e.e. from allylic sulfoxide 11.\textsuperscript{10} The final example which illustrates the potential of chiral sulfoxides in asymmetric synthesis is the Diels-Alder reaction. The cycloaddition between cyclopentadiene and vinyl sulfoxide 13 affords the endo product 14 with 86% d.e.\textsuperscript{11}

Scheme I

The above reactions and others\textsuperscript{12} make chiral sulfoxides of great interest. Therefore, the development of a general method for the preparation of chiral sulfoxides with high enantiomeric purity is the goal of current research. The known methods (excluding resolution) can be divided into two classes: nucleophilic displacement on an electrophilic sulfur with established chirality and asymmetric oxidation of sulfides. This abstract will focus on recent improvements of those two methods.

PREPARATION OF CHIRAL SULFOXIDES
Nucleophilic Displacement

A widely used approach to chiral sulfoxides is the method developed by Andersen in 1962. It is based on the conversion of chiral sulfinates into sulfoxides with Grignard reagents. A convenient starting sulfinate is (-)-menthyl p-tolyl sulfinate (15) for reaction with a Grignard reagent to give 16. Both enantiomers are commercially available (Aldrich). The reaction proceeds with inversion of configuration at sulfur, as established by Mislow and other investigators.

The Andersen sulfoxide synthesis is general in scope and a large number of chiral alkyl aryl and diaryl sulfoxides have become available from 15 and other optically active sulfinates. The synthesis of chiral dialkyl sulfoxides of high optical purity, using the required menthyl alkylsulfinates, has not been successful because the sulfinates are oils and attempts to separate them have not succeeded. In 1984 Andersen found that substitution of cholesterol for menthol leads to crystalline cholesteryl methanesulfinates which can be separated by crystallization and which, upon treatment with alkyl Grignard reagents, afford alkyl methyl sulfoxides of high enantiomeric purity. Yields of separated epimers are too low (3.5% and 0.7%) for large scale preparation.

Recently, approaches to the synthesis of enantiomerically pure dialkyl sulfoxides that involve nucleophilic additions to diastereomerically pure sulfites have been developed. Two consecutive substitution reactions at sulfur are performed to convert the sulfites to sulfoxides.

In 1991, Kagan proposed such a new method, which is based on the use of the chiral cyclic sulfite 17 as a starting material. The preparation of 17 involves treatment of the chiral 1, 2-diol with SOCl₂. This gives 17 as the favored diastereomer (d.e.>80%) in 70% yield after crystallization.

Scheme II
There are two possible routes for ring cleavage to occur in the first nucleophilic substitution of 17 (Scheme II). When a bulky Grignard reagent (R^1=t-buty|l, mesity|l) is used, the regioselective cleavage mainly gives sulfinate 19. When a linear alkyl or vinyl Grignard reagent is used (R^1=Et, n-octyl, or vinyl), however, the sulfinate 18 is the major product. Organolithium reagents are less regioselective and overreact to afford symmetrical sulfoxides. The selective synthesis can be interpreted through the formation of trigonal bipyramidal transition structures A and B (Scheme III). In intermediate A, the bulky group (O-CPh2) places itself in the equatorial position. In this species, the incoming and leaving groups are both in apical positions and ring cleavage occurs giving sulfinate 18. When the incoming nucleophile is bulky it severely interacts with the O-CPh2 group linked to equatorial oxygen. The alternative intermediate B where the O-CPh2 is apical becomes favored, and as a consequence the alternative sulfinate 19 is produced.

Scheme III

By using 2 molar equiv of organometallic reagents the sulfoxides 20 or 21 are produced with 100% e.e. and isolated in quantitative yield. Grignard or organolithium reagents are equally suitable for the second nucleophilic displacement reaction. This method is especially convenient for the preparation of t-buty|l sulfoxides.

Snyder reported in 1991 the sequential displacement reactions by organometallic reagents of 1, 2, 3-oxathiazolidine-S-oxides to afford the corresponding chiral sulfoxides.17 Aminosulfite 23 can be prepared along with its diastereomer from (-)-ephedrine 22 and thionyl chloride in a 9:1 ratio. The addition of freshly prepared Grignard reagents to 23 in toluene leads to the production of sulfinamides 24 in excellent yields, and with diastereoselectivity up to 99%. Using THF as the
solvent with organolithium reagents, as originally reported by Wudl and Lee,\textsuperscript{18} leads to a significant decrease in diastereoselectivity and older Grignard reagents lead to increased epimerization at sulfur.

The addition of AlMe\textsubscript{3} to the intermediate sulfinamide 24, followed by subsequent addition of the Grignard reagent, gives good yields of the desired sulfoxides with excellent enantioselectivity, \(>99\%\) e.e..

The use of AlMe\textsubscript{3} to form the intermediate dimethylaluminum alkoxide 25 serves two purposes. First, the use of two equivalents of organometallic reagent in the ephedrine displacement from the sulfonamide is unnecessary. Second, the displacement of ephedrine is accelerated without racemization as the aluminum chelates between the oxygen anion and the nitrogen, which is the leaving group.

Optically pure dialkyl and alkyl aryl chiral sulfoxides can be prepared by this approach. Both enantiomers can be produced either by reversing the order of organometallic displacement or by using the (+)-enantiomer of ephedrine as the auxiliary, which is also commercially available. The only limitations are in the formation of \(t\)-butyl phenyl and aryl phenyl sulfoxides, due to the formation of diphenyl sulfoxide as the main product upon phenyl Grignard addition to 23. \(t\)-Butyl phenyl sulfoxide can be formed with 100\% e.e. by Kagan's cyclic sulfite method and aryl phenyl sulfoxides can be conveniently prepared by the Andersen method.

**Asymmetric Oxidation**

An attractive alternative to these nucleophilic displacement reactions is the asymmetric oxidation of sulfides. Not only can the sulfoxide be formed in one step, but the synthesis of some chiral sulfoxides not available by the Andersen procedure can also be realized. The introduction of chirality at sulfur can be carried out by using sulfides with chiral alkyl backbones or by using chiral oxidizing reagents.

Oxidation of chiral sulfides by mCPBA has been efficiently employed in some specific cases. In 1986, Lucchi and Lucchini reported the self-induced diastereoselective oxidation of vinyl sulfides bearing a chiral hydroxyl group as a way of preparation of chiral sulfoxides.\textsuperscript{19} The chiral sulfide 27 is prepared by stereoselective Michael addition of the isobornyl derivative to acetylenes. The high diastereoselectivity (d.e.\(>80\%\)) observed in the oxidation with mCPBA in dry dichloromethane can be explained on the basis of the work by Glass,\textsuperscript{20} which has shown that the
sulfoxide oxygen is on the same side as the hydroxyl group. This specificity is attributed to hydrogen bonding between the substrate hydroxyl group and the percarboxylic acid.

In 1988, Haynes and Ridley effectively utilized the foregoing concepts to prepare a number of camphor derived, optically active allyl and alkyl sulfoxides. The starting sulfides are treated with 1 equiv of mCPBA. Analysis of the crude products by HPLC and/or ¹H NMR indicates the sulfides are cleanly converted into the exo-3-(allylsulfinyl)- and exo-3-(alkylsulfinyl) isoborneol derivatives (31) in good yields.

This type of oxidation has a limitation in that the chiral backbone can not be removed for further elaboration.

In 1984, Kagan reported a simple method for the asymmetric oxidation of a wide variety of sulfides. This method is based on a modification of the Sharpless reagent (Ti(O-i-Pr)₄/(+)-DET/r-BuOOH = 1/1/2) for asymmetric epoxidation of allylic alcohols. In order to obtain a complex active in asymmetric oxidation of sulfides, 1 mol eq of water (with respect to titanium) was used to partially deactivate the Sharpless reagent. Subsequent treatment of sulfides such as aryl-S-CH₃ gives the corresponding sulfoxides with e.e. up to 95%-96%. The chemical yield is satisfactory (90%) and sulfone formation is avoided.

Independently, Modena found that a large excess of (+)-DET modifies the Sharpless reagent to give an asymmetric oxidant system for prochiral sulfides. The p-tolyl methyl sulfoxides were successfully prepared in 60% isolated yield with 88% e.e.. Unfortunately, these modified Sharpless reagents are less useful for the synthesis of dialkyl sulfoxides.

(-)-α,α-Dichlorocamphorsulfonyloxaziridine (32) represents another type of efficient asymmetric oxidizing reagent which has recently been used by Davis for the synthesis of chiral sulfoxides. Some typical examples are shown in Table I along with a comparison of e.e.'s obtained using Kagan's modified Sharpless reagent.
Catalytic oxidation is also possible using some transition metal complexes with chiral ligands. High catalytic yields could be obtained but the ee's remained low to moderate.\textsuperscript{25}

Enzymatic oxidations have been exploited in the preparation of chiral sulfoxides, with high enantioselectivities in specific cases.\textsuperscript{26} In 1984, Ohta reported high optical purity and a strong preference for production of the R enantiomer when enzymatic oxidation of alkyl aryl sulfides was carried out with \textit{Corynebacterium equi}.\textsuperscript{27} In most cases, however, detectable amounts of sulfone were formed.

Colonna has reported that chloroperoxidase catalysed oxidation of ethyl aryl sulfides afforded the corresponding sulfoxides with R absolute configuration in moderate to excellent e.e..\textsuperscript{28} He has also reported that oxidation of aryl alkyl sulfides at 4 °C by dioxiranes in the presence of bovine serum albumin (BSA) affords the corresponding sulfoxides in up to 89% e.e..\textsuperscript{29}

\section*{CONCLUSION}
Chiral sulfoxides are useful auxiliaries in asymmetric synthesis. The preparation of various chiral sulfoxides with high enantiomeric purity has been achieved through a variety of methods. Aryl alkyl and diaryl sulfoxides can be conveniently prepared by the classical Andersen method or by asymmetric oxidation. Modified Sharpless reagents are highly effective for preparation of aryl methyl sulfoxides. Oxaziridines are more general for the synthesis of aryl alkyl sulfoxides. Dialkyl sulfoxides, which have been difficult to prepare for a long time, are now easy to synthesize by the cyclic sulfite and cyclic aminosulfinate methods.

\section*{REFERENCES}
(6) Solladie, G. Synthesis, 1981, 185-196
(23) Modena, G.; Furia, F. D.; Seraglia, R. Synthesis 1984, 325-326


ASYMMETRIC SYNTHESIS OF \(\alpha, \alpha\)-DISUBSTITUTED \(\alpha\)-AMINO ACIDS

Reported by Li Deng

December 12, 1991

INTRODUCTION

Non-proteinogenic amino acids have been the focus of considerable research effort during the last decade.\(^1\)\(^2\)\(^3\) In particular, \(\alpha, \alpha\)-disubstituted \(\alpha\)-amino acids have drawn considerable attention. For example, this class of amino acids has been employed in the preparation of effective enzyme inhibitors, e.g., \(\alpha\)-substituted analogs of ornithine\(^1\), glutamate\(^1\) dopa.\(^4\) In addition an important class of antibiotics, exemplified by alamethicins, trichorzianines, and antiamoebins has been identified to be peptides rich in Aib (\(\alpha\)-aminoisobutyric acid).\(^5\)\(^a\)\(^d\) These peptides demonstrate remarkable pore-forming activity and much effort has been focused on the effect of Aib residues on the stabilization of the folded conformation of these physiologically active peptides.\(^5\)\(^e\)\(^f\) These studies help to guide the development of conformationally constrained analogues of biologically active peptides.\(^5\)\(^g\)

The asymmetric synthesis of \(\alpha, \alpha\)-disubstituted \(\alpha\)-amino acids presents a challenging synthetic problem as it involves the construction of stereogenic quaternary carbon centers. Moreover, only limited examples of \(\alpha\)-alkylated amino acids obtained by enzymatic optical resolution technology exist in the literature.\(^6\) These factors have made these amino acids highly pursued synthetic targets.\(^6\)\(^7\) Asymmetric syntheses of \(\alpha, \alpha\)-disubstituted \(\alpha\)-amino acids based on "heterocycle templates" have emerged as the most versatile and successful strategies developed to date. Such heterocycle templates include bis-lactim ethers (1), imidazolidinones (2), \(\beta\)-lactams (3) and diphenyl oxazinones (4). Discussion of the applications of these templates in the synthesis of optically active \(\alpha, \alpha\)-disubstituted-\(\alpha\)-amino acids is the focus of this seminar.

I. BIS-LACTIM ETHERS

Natural L-amino acids and their antipodes are readily available chiral materials Schöllkopf and coworkers\(^8\) developed bis-lactim ethers which are versatile heterocycle templates

Copyright © 1991 by Li Deng
derived from natural amino acids. The preparation of the bis-lactim ether begins with formation of the diketopiperazine by coupling of two amino acids, followed by the reaction of the diketopiperazine with trimethyloxonium tetrafluoroborate to afford the bis-lactim ether 6 (Scheme I). Treatment of 6 with strong base followed by electrophilic alkylation leads to 7 diastereoselectively. The methyl ester of the desired amino acid is released upon hydrolysis of 7 with HCl. The symmetry of the bis-lactim ether (6) has an advantage because the regioselectivity of deprotonation is not a concern. The disadvantage of the process is that two equivalents of chiral starting amino acid are invested, but only one equivalent of desired amino acid is gained. Numerous ω,ω-disubstituted ω-amino acids have been prepared successfully from bis-lactim ethers derived from alanine and leucine.

Scheme I

Scheme II

In order to circumvent the loss of homochiral material in symmetric bis-lactim ethers, Schöllkopf developed mixed bis-lactim ethers.9 These reagents incorporate two different amino acids, such as optically active L- or D-valine (9) and D, L-alanine ethyl ester (Scheme II). The resulting bis-lactim ether (10) is formed as a 1:1 diastereomeric mixture, but this is not a concern since the stereochemically undefined center is converted into a planar carbanion in the next step. The key to the success of this system relies on the high regioselectivity of deprotonation of 10. The heterocyclic anion obtained from 10 undergoes several types of nucleophilic reactions including aldol reactions,9 alkylation,10 Michael type reactions11,12 and arylation.13 Therefore, a variety of alkyl groups can be incorporated into the amino acid by this method. In general, excellent stereocontrol (de's > 95 %) on the ω-carbon is realized in these reactions, however, on the β-carbon it is only moderate (de's around 50%). The amino acid is obtained by hydrolysis of 11. The regioselective deprotonation of the heterocycle relies on the stereochemically undefined center being as unhindered as possible. Thererfore, asymmetric synthesis based on these
heterocyclic templates is largely limited to the preparation of α-methylated amino acids. It should also be noted that the final hydrolysis step to release the dialkyl amino acid from the bis-lactim ethers is sometimes problematic due to the sterically hindered quaternary α-carbon.

II. OXAZOLIDINONES AND IMIDAZOLIDINONES-RELATED TEMPLATES

Seebach and coworkers have developed a variety of chiral enolate precursors based on imidazolidinones and oxazolidinones. The first system reported\textsuperscript{14,15} was the bicyclic heterocycle 14, which was prepared from L-proline and pivaldehyde as a single diastereomer (Scheme III). Treatment of heterocycle 14 with lithium diisopropylamide at low temperature generated the enolate, which was alkylated to form 15. The configuration at the α–carbon is retained during the alkylation step. The stereogenic center in proline directs the stereochemistry of the newly formed stereogenic center in the bicyclic aminal, which is then made planar in the next step to form the enolate. This interesting stereocchernical outcome is termed as "self-reproduction of chirality". Seebach proposed conformation 17 to explain the stereoselectivity in the electrophilic reaction. It was believed that the hydrogen on the stereogenic center is oriented in a pseudoaxial position and thus shields one face of the enolate. Electrophilic attack then takes place anti to the hydrogen. A wide range of electrophiles participated in functionalization of this system in good yields (70-90%) and virtually complete diastereoselectivity (de's > 99%). Hydrolysis of the heterocyclic template (15) to release the homologated amino acid (16) is the most difficult step and often requires drastic conditions. This presents a severe problem, especially in the presence of a bulkier α-R group.

The imidazolidinone heterocycle, Boc-BMI (19), is one of the most successful glycine incorporated templates.\textsuperscript{16,17} The general approach is summarized in Scheme IV. The one deprotonation site in 19 is the most important feature of the template because regioselectivity is not a concern. Consequently there is tremendous potential for the development of a two step dialklylation procedure. Both enantiomers of the desired α,α-disubstituted amino acid (23) can be
prepared from any antipode of Boc-BMI. As mentioned earlier, however, the drastic hydrolysis conditions continues as a problem. In some cases, the hydrolysis even completely fails to release the desired amino acids from the templates.

Scheme IV

\[ \text{Scheme IV} \]

\[ \text{Scheme V} \]

III. β-LACTAM SYNTHON METHOD

Recently, Ojima and collaborators developed several β-lactam related templates to make α,α-disubstituted α-amino acids. The first system reported\(^{18}\) was the 4-phenyl substituted β-lactam 24. As shown in Scheme V, the benzylidene Schiff base 24 was metalated with lithium hexamethyldisilazide to give the chelated enolate 25. Electrophilic alkylation occurred in a stereoselective manner (de's>98%) anti to the 4-phenyl group to form 26. This alkylated template readily underwent hydrogenolysis or Birch reduction to yield the α-alkylated phenyl alanine amide 27. The 4-phenyl group is critical for the diastereoselective alkylation as well as for reductive cleavage, which restricts this β-lactam template to the production of α-alkylated phenylalanine related amino acids or amides. The chiral starting material is also incorporated into the product.

A more versatile method of dialkylation of a β-lactam-related glycinate was reported by Ojima and Qiu (Scheme VI).\(^{19,20}\) A protected glycine residue was incorporated at N-1 of a β-lactam ring. They propose that the enolate forms a seven-membered chelate (28a) which directs electrophilic attack anti to the 4-phenyl group (de's >96%). The stereochemistry at the
quaternary center can be controlled simply by changing the order of the alkylations. The dialkylated β-lactam 31 can be readily converted to the dipeptide 32 in good yield via reductive cleavage as mentioned above, after which hydrolysis affords the free amino acid. Very few examples releasing the amino acids are provided by the authors. In a modified β-lactam system hydrolysis to cleave the CO-N bond in β-lactam rings to produce optically pure diamino acids was reported very recently by Ojima.21

Scheme VI

IV. DIPHENYLOXAZINONE

In 1968 Kagan and coworkers reported22 an asymmetric synthesis of β-methyl aspartate (Scheme VII). The key step is the highly diastereoselective hydrogenation of unsaturated ester 34 to form 35. Williams and coworkers23 realized later the tremendous potential of a glycinate system based on this heterocycle and developed useful asymmetric syntheses of various α-amino acids based on diphenyloxazinones (4).

Scheme VII

The 5,6-diphenyloxazinone 37 can be prepared from the readily available, optically pure 2-amino-1,2-diphenylethanol in greater than 60% overall yield. The general procedure24,25 for
asymmetric synthesis of $\alpha,\alpha$-disubstituted $\alpha$-amino acids starting from 37 is illustrated in Scheme VIII. The oxazinone 37 forms an enolate when treated with strong base, on which alkylation proceeds in a highly diastereoselective manner (de's > 99%) to provide 38. The phenyl group at C-5 of 37 presumably occupies a pseudoaxial position, which shields the C-3 position from electrophilic attack on the same face. Reductive cleavage of 39 by catalytic hydrogenation or by dissolving metal reduction readily liberates the amino acid. Consequently, both enantiomers of amino acid 40 can be readily prepared respectively from two antipodes of the diphenyloxazinone 37.

An extremely important advantage of this template is the mild reductive cleavage to release the amino acid. Although the chiral auxiliary is sacrificed during this step, the mild reduction circumvents difficulties observed in other systems that require drastic hydrolysis conditions. Another advantage of this system is that the N-Boc protected amino acids are prepared directly from the templates, while acylating $\alpha,\alpha$-dialkylated amino acids is often difficult to achieve due to hindrance at the $\alpha$-carbon.

Scheme IX

\[ R_1 = -\text{CH}_2\text{CH}_2\text{CHCH}_2 \]
\[ R_2 = -\text{CH}_2\text{OMe} \]
The utility of this template has recently been demonstrated in the asymmetric synthesis of 2,6-diamino-6-(hydroxymethyl) pimelic acids, 45 and 46 (Scheme IX).\textsuperscript{26} The stereochemistry at the quaternary C-6 was not known prior to this synthesis; thus the crucial task of establishing the correct stereochemistry at C-6 was accomplished by sequential enolate alkylation of 42 (Scheme IX). Therefore, both R and S isomers at C-6 were constructed with proper antipodes of 42. Thus, the stereochemistry at C-6 was established along with the correlation of the natural diamino acid to 45 and 46. Recently, Williams et al achieved the asymmetric synthesis of 1-aminocyclopropane-1-carboxylic acid derivatives, 47, by using the same template.\textsuperscript{27}

\[ \text{CONCLUSION} \]

Construction of the quaternary chiral carbon in \( \alpha,\alpha \)-disubstituted \( \alpha \)-amino acids has been accomplished by "heterocycle template" approaches. In practice, the criteria to judge the best method depend on the nature of the amino acid, as well as the purpose and the scale of the synthesis. It is expected that future approaches and refinement of the existing systems will emphasize introducing side chains with more diverse structure and functionality, as well as extending stereochemical control beyond the \( \alpha \)-carbon.

\[ \text{REFERENCES} \]


(25) Williams, R. M. personal communication to L. D.


ORGANIC SEMINAR ABSTRACTS
1991-92, SEMESTER II

University of Illinois

Department of Chemistry
Box 68 Roger Adams Laboratory
1209 West California Street
Urbana, Illinois 61801-3731

June, 1992

Copyright © by The Board of Trustees of the University of Illinois
NOTICE: Return or renew all Library Materials! The Minimum Fee for each Lost Book is $50.00.

The person charging this material is responsible for its return to the library from which it was withdrawn on or before the Latest Date stamped below.

Theft, mutilation, and underlining of books are reasons for disciplinary action and may result in dismissal from the University.

To renew call Telephone Center, 333-8400

UNIVERSITY OF ILLINOIS LIBRARY AT URBANA-CHAMPAIGN
<table>
<thead>
<tr>
<th>SEMINAR TOPICS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Semester II, 1991-92</td>
<td>Page</td>
</tr>
<tr>
<td>Mechanism of the Primary Event of Bacterial Photosynthesis</td>
<td>1</td>
</tr>
<tr>
<td>Yifan Zhang</td>
<td></td>
</tr>
<tr>
<td>The Diels-Alder Reaction: Rate Accelerations in Aqueous Media</td>
<td>9</td>
</tr>
<tr>
<td>Shaun R. Selness</td>
<td></td>
</tr>
<tr>
<td>Radical Clock Investigations of Cytochrome P-450</td>
<td>17</td>
</tr>
<tr>
<td>Edward E. Fenlon</td>
<td></td>
</tr>
<tr>
<td>Living Ring-Opening Metathesis Polymerization Catalyzed by Homogeneous</td>
<td>25</td>
</tr>
<tr>
<td>Transition Metal Complexes</td>
<td>William A. Reinerth</td>
</tr>
<tr>
<td>Stereocchemical Aspects of Asymmetric Aldol Condensations Proceeding via</td>
<td>33</td>
</tr>
<tr>
<td>Titanium Enolates</td>
<td>Donald A. Seielstad</td>
</tr>
<tr>
<td>Dioxiranes as Selective Oxidizing Agents</td>
<td>41</td>
</tr>
<tr>
<td>James B. Day</td>
<td></td>
</tr>
<tr>
<td>FK506 and Rapamycin: Immunosuppressive Ligands of FK506 Binding Protein</td>
<td>50</td>
</tr>
<tr>
<td>Ken C. Rix</td>
<td></td>
</tr>
<tr>
<td>Photocatalytic Oxidations of Chlorophenols on TiO2 Surface - Mechanism of</td>
<td>59</td>
</tr>
<tr>
<td>the Primary Events</td>
<td>Nenad Koska</td>
</tr>
<tr>
<td>[3+2] Cycloadditions of Trimethylenemethane-Palladium Complexes</td>
<td>67</td>
</tr>
<tr>
<td>Steve Lee</td>
<td></td>
</tr>
<tr>
<td>Cieplak Model for the Addition to Exocyclic Double Bonds</td>
<td>75</td>
</tr>
<tr>
<td>Stephen C. Wilkie</td>
<td></td>
</tr>
</tbody>
</table>
MECHANISM OF THE PRIMARY EVENT OF BACTERIAL PHOTOSYNTHESIS

Reported by Yifan Zhang

January 20, 1992

INTRODUCTION

Photosynthesis is the most important process responsible for the maintenance of the earth's environment. It produces the oxygen we breathe as well as the oxygen for the combustion of fuels. The heart of photosynthesis is the absorption of sunlight and the subsequent conversion of that energy to chemical potential energy at the reaction center as a long-lived transmembrane charge separation produced by photoinitiated electron transfer. Although great progress has been made in understanding this process, many issues about the chemistry of reaction center are still unresolved. In this report, we will examine the issue of the electron transfer from the primary donor to an intermediate acceptor during the first 3 picoseconds after absorption of sunlight. The focus of this report is the mechanism of electron transfer in bacterial photosynthesis.

BACKGROUND

Bacteria use a different and simpler photosynthetic pathway to convert and store solar energy as chemical potential energy than do green plants. The initial photochemical process of bacterial photosynthesis is an electron transfer reaction which takes place in a specialized, membrane-bound pigment protein complex known as the reaction center.

Pure and photochemically active bacterial reaction center (RC) was first isolated from purple bacterium Rhodobacter sphaeroides (Rb. sphaeroides) by Reed and Clayton in 1968 using detergent fractionation. Since then, it has been established that all of the isolated and analyzed bacterial photosynthetic RCs contain three polypeptides which collectively bind six pigment molecules, four bacteriochlorophyll molecules (a or b) and two bacteriopheophytin molecules (a or b), along with two quinone molecules and one nonheme iron ion. The structures of bacteriochlorophyll and bacteriopheophytin are shown as B and H.

X-ray crystallographic investigation of the reaction center of bacterium Rhodopseudomonas viridis (Rps. viridis) by Deisenhofer and Michel in 1984, and later the determination of the crystal structure of Rb. sphaeroides R-26 by other groups stimulated an avalanche of research in this area. The X-ray data clearly revealed the spatial arrangement of the non-protein organic molecules in the reaction center.

Copyright © 1992 by Yifan Zhang
In this figure, P stands for the dimer of bacteriochlorophylls, B and H represent bacteriochlorophyll and bacteriopheophytin respectively, and Q refers to the quinone. It is clear now that all of the molecules in the reaction center are bound to the L and M polypeptides in which L and M stand for light and medium molecular weight protein components. The structures of bacteriochlorophyll and bacteriopheophytin are listed in the following figure.

The X-ray results confirmed the well established idea that the primary electron donor is a dimer of bacteriochlorophylls, called the special pair (P), and one bacteriopheophytin (H) is an intermediate electron acceptor between the special pair and a primary electron acceptor quinone $Q_1$. 
The assignment of the peaks in the absorption spectra of isolated bacterial reaction centers has been accomplished both experimentally and theoretically. The Q_y band occurs in the 750-1000 nm region, which is the lowest energy band due to S_0 to S_1 electronic transition of chromophores in the RC. It is also the most important for study of the primary electron transfer. The Q_x band is followed by Q_y and occurs in the 500-600 nm region. It is the high energy band due to S_0 to S_2 electronic transition of chromophores in the RC.

For the Rps viridis reaction center, P absorbs around 960 nm (Q_y), B around 830 nm (Q_y), H around 800 nm (Q_y) and 540 nm (Q_x). The four B molecules each have a Q_x absorption band around 600 nm. As for Rb. sphaeroides, the Q_y band of P is around 860nm, Q_y of B is around 800 nm and H absorb around 760 nm(Q_y) and 540 nm (Q_x). The four B molecules each have a Q_x band similar to Rps viridis reaction center at about 600 nm.

As more detailed information on the molecular structure of the reaction center has emerged, and with the development of laser flash photolysis, it has become possible to explore the dynamics of the primary event of bacterial photosynthesis on a sub-picosecond time scale. The primary step of bacterial photosynthesis is restricted to the L branch in the reaction center and the electron transfer sequence has been verified by time-resolved transient absorption spectroscopy as follows:

\[
\begin{align*}
P & \xrightarrow{\text{hv}} 1P^* \xrightarrow{3 \text{ps}} P^+H \xrightarrow{200 \text{ps}} P^+Q_1^- \xrightarrow{100 \mu s} P^+Q_2^-
\end{align*}
\]

**ELECTRON TRANSFER AND BACTERIOCHLOROPHYLL B**

Because of the large edge-to-edge distance of more than 10Å between the donor special pair (P) and the intermediate acceptor bacteriopheophytin (H) in the reaction center, the electron transfer in bacterial photosynthesis is usually described in terms of nonclassical nonadiabatic electron transfer theory. This approach treats electron transfer as a radiationless transition from the reactant to the product potential energy surface. The rate of electron transfer can thus be described in terms of Fermi's "Golden Rule" by:

\[
K_{et} = (4\pi^2/h)V^2F
\]

where V is the electronic coupling matrix element and F is a thermally averaged nuclear Franck-Condon factor. The Franck-Condon factor represents the overlap of vibrational wavefunctions of the reactant and product states which consist of the donor, acceptor and their surrounding environment. The magnitude of the Franck-Condon factor mainly depends on the free energy change for the electron transfer, and the reorganization energy \(\lambda\). The electronic coupling
factor is dictated primarily by the overlap of the donor and acceptor wavefunctions. The electronic coupling is distance dependent and its magnitude decreases exponentially with the increasing distance between the donor and the acceptor. In order to have fast electron transfer, there must be an effective electronic overlap and a favorable free energy change.

The electron transfer rate of about 3 picoseconds between the special pair (P) and bacteriopheophytin (H) in the reaction center was established by time-resolved transient absorption spectroscopy. The elucidation of the spatial organization of the reaction center by X-ray structure left unanswered the role of the accessory bacteriochlorophyll B, which is located between P and H, in this fast electron transfer. Direct electron transfer from the primary donor (special pair P) to the intermediate acceptor (bacteriopheophytin H) can be ruled out easily by theoretical calculations. Assuming the optimum Franck-Condon factor, theoretical calculations give a predicted rate which is much slower than that observed experimentally. The question of how the electron transfer in this primary event can then be exceptionally fast is raised. The most plausible answer is that B plays a special role, which enhances the rate of electron transfer. However, the specific effect of B has not be established and is a matter of controversy.

SUPEREXCHANGE OR TWO-STEP MECHANISM?

Several mechanisms have been proposed to explain the experimental data, but the most commonly discussed mechanisms are superexchange mechanism (virtual transfer) and a two-step mechanism which proceeds through an intermediate.

The superexchange mechanism proposes that the direct electron transfer from the excited singlet state $1P^*$ to H is mediated by coupling of the virtual vibronic states of $P^+B\cdot H$. The electron uses the orbitals on B as a bridge between the $1P^*$ and H, and electronic coupling between $1P^*$ and H is enhanced by mixing with the state $P^+B\cdot H$. Although B is involved in the electron transfer in this mechanism, it is not a true intermediate. It is assumed that the energy of $1P^*$ is lower than of $P^+B\cdot H$ state at the nuclear configuration of the transition state.

$$1P^+BH \xrightarrow{k} P^+BH^-$$

The two-step sequential mechanism involves formation of an explicit intermediate state $P^+B\cdot H$. In the two-step mechanism, the electron hops from $1P^*$ to B with a rate constant $k_1$, forming $P^+B\cdot H$ as a discrete intermediate, followed by a second electron hopping from $B^-$ to H with a rate constant $k_2$ to form $P^+BH^-$. It is postulated that $k_2 > k_1$. No back electron transfer occurs in this process.
The energy state of P\textsuperscript{+}B-H is presumably located between \textsuperscript{1}P\textsuperscript{*} and P\textsuperscript{+}BH\textsuperscript{-}.

The two proposed mechanisms may be distinguished by experiments designed to detect the intermediate P\textsuperscript{+}B-H. The most direct approach is to study this charge separation in the reaction center by time-resolved absorption spectroscopy. By monitoring the changes in the absorption bands of the components in the reaction center, the kinetics of this electron transfer can be deduced. If the intermediate P\textsuperscript{+}B-H is resolved kinetically, the superexchange mechanism can be rejected. However, the results to date are contradictory.

**KINETICS RESULTS OF TWO-STEP MECHANISM**

The basis for confirmation of the two-step mechanism is the detection of the intermediate state P\textsuperscript{+}B-H. In 1978, Shuvalov et al. reported the detection of P\textsuperscript{+}B-H in the reaction center of *Rhodospirillum rubrum* by picosecond spectroscopy with a pulse duration of 30 ps.\textsuperscript{13} They reported that P\textsuperscript{+}B-H is initially formed in about 15 ps and subsequently transfers an electron to H in about 30 ps.

Zinth's group, using femtosecond technique on *Rps. viridis* reaction center at 620 nm (a wavelength at which all four bacteriochlorophyll molecules absorb), have observed a transient absorption change at 620 nm, and kinetically resolved the intermediate P\textsuperscript{+}B-H.\textsuperscript{14} They report that this intermediate is formed in 1 ps and donates an electron to H in about 5 ps.

Other groups have used femtosecond spectroscopy and have also detected the intermediate state.\textsuperscript{15} Nevertheless, the two-step mechanism was supported by the recent result of Holzapfel and coworkers.\textsuperscript{16} By directly exciting the primary donor of *Rb. sphaeroides* at room temperature and monitoring different wavelength, they found that the primary electron transfer involved two time constants 3.5 \pm 0.4 ps and 0.9 \pm 0.3 ps. These results suggest that a discrete 3.5 ps electron transfer to bridging bacteriochlorophyll (B) is followed by a 0.9 ps electron transfer to bacteriopheophytin (H). All results to date favor the two-step mechanism due to the detection of intermediate P\textsuperscript{+}B-H.

**EVIDENCE FOR THE SUPEREXCHANGE MECHANISM**

On the other hand, those who support the superexchange mechanism claim that the intermediate P\textsuperscript{+}B-H cannot be resolved kinetically. Martin and coworkers excited the near-infrared (800-930 nm) absorption bands of special pair (P), bacteriochlorophyll (B) and bacteriopheophytin (H) with laser pulses of 150 fsec and monitored at different wavelengths.
They found that the oxidation of P and reduction of H in reaction centers of both *Rb. sphaeroides* R-26 and *Rps. viridis* occurred simultaneously with a time constant of $2.8 \pm 0.2$ ps at room temperature. They failed to detect bleaching of intermediate B absorption in the 100 fs to 2.8 ps region. Also, at low temperature (10 K), the intermediate $\text{P}^+\text{B}^-\text{H}$ could not be resolved. Their findings seemed to constitute compelling evidence against the two-step mechanism.

Kirmaier and Holten later measured the initial electron transfer rate in *Rb. capsulatus* reaction center using 350 fsec pulses at 870 nm. They concluded that if the intermediate state $\text{P}^+\text{B}^-\text{H}$ is formed, its transient concentration is extremely small, thus favoring the superexchange mechanism. In addition, Kirmaier and Holten report that the rate of electron transfer in the initial charge separation is a function of the detection wavelength. They propose this to be due to a distribution of reaction centers which encompass roughly a 3-fold variation of the rates of electron transfer at room temperature. Some fraction of the reaction centers carry out electron transfer with faster rate; some, with a comparatively slower rate; the majority, with intermediate rate. Their results are inconsistent with the assignment of 1 ps component to the $\text{P}^+\text{B}^-\text{H}$ intermediate made by Holzapfel et al. Kirmaier and Holten suggest that the complexity of the initial charge separation may be due to the distribution of reaction centers with an associated distribution of rates.

Most surprisingly, under essentially the same experimental conditions as Holzapfel, Kirmaier and Holten measured the time-resolved photodichroism spectra on *Rb. sphaeroides* R-26 reaction center in the anion region of $\text{B}^-$ and $\text{H}^-$ between 620 nm and 740 nm, and failed to resolve clearly the formation of a reduced $\text{B}^-$ species. These kinetic results seems to provide strong evidence against a mechanism in which B is a distinct, kinetically resolved intermediate electron acceptor between P and H.

Other experimental approaches also have been used to distinguish the two electron transfer mechanisms. For example, Lockhart et al. used an electric field to induce fluorescence anisotropy in *Rb. sphaeroides* reaction center. Their results suggest that the intermediate state whose electric dipole moment competes with fluorescence from $^1\text{P}^*$ has a permanent electric dipole moment oriented as expected for $\text{P}^+\text{H}^+$ but not for $\text{P}^+\text{B}^-$. The electric field effects on the fluorescence polarization indicated that the charge separation is via the superexchange mechanism.

**ASSESSMENT OF RESULTS**

Although femtosecond spectroscopy has improved the time resolution and eliminated the possibility of unreliable data due to the use of long pulses such as was the case for Shuvalov's experiment, the experimental results still seem to conflict in assessing the two
mechanisms. The main problem is the uncertainty in the transient spectral assignments. Exciton coupling among all the pigments in the reaction center has complicated the absorption bands of the special pair (P), bacteriochlorophyll (B) and bacteriopheophytin (H) in the desired region. It is very difficult to excite an individual band and not affect the others. Martin's experiments show the existence of an ambiguity in discriminating between a transient bleaching of B due to the formation either of B*, the excited state of B, or of B−; the bleaching of B state when the B band is excited. In addition, their results of no significant contribution of the intermediate state P+B·H as a spectrally or kinetically resolvable intermediate when P was directly excited contradict Zinth's result. Although some optimized experimental conditions such as directly exciting P band rather than B and H bands have been used, Holzapfel and Kirmaier's experiments are contradictory in explaining the possibility of intermediate P+B·H. This difference may be in part attributed to the inhomogeneous distribution of the reaction center with slightly differing spectral and kinetic properties, particularly at room temperature.

However, the results from transient absorption spectroscopy have shown that the formation of P+B·H does not necessarily mean that this intermediate can be observed provided that the depletion of this intermediate state is very rapid. The critical issue is the magnitudes of k₂ and k₁ in the two-step mechanism. Holzapfel's kinetic results clearly show that k₂ is greater than k₁. Although favoring the superexchange mechanism, Martin's and Kirmaier's experiments still cannot exclude the two-step mechanism due to the existence of the small concentration of P+B·H below the limit of detectability. Both Martin and Kirmaier's experiments set large lower limits on the ratio of k₂/k₁ and claimed that the two-step mechanism will exist with the ratio of k₂/k₁ greater than 70 and 21 respectively. So, the operation of the superexchange mechanism by itself can not rule out the existence of P+B·H.

Theoretical studies may give additional insight into the mechanism of this fast electron transfer. Recently, a neutral position has been taken by Bixon and coworkers in which the mechanism is a superposition of both superexchange and two-step mechanism.23 Joseph and coworkers calculated that in an electron transfer which occurs predominantly by a virtual process, some small, but nonzero transient population can be developed.24 In other words, 5-10% bleaching is possible for virtual transfer experimentally. If this is true, Holzapfel's result which allowed 15% maximal transient population of intermediate state seems less compelling.

CONCLUSION

Although experimental and theoretical work has been done to distinguish between the two mechanisms of the primary event in the bacterial photosynthesis, it is still unclear which mechanism is predominant. Both mechanisms have experimental and theoretical support, and it is very difficult to say at present which one is the primary electron transfer mechanism. The
main difficulty is the uncertainty caused by the use of spectroscopy to observe a transient signal which is overlapped by other bands. It is expected that future experimental approaches will introduce spectroscopic techniques specific for pigment groups in the reaction center, so that the transient absorption of the specific pigment can be followed accurately.

REFERENCES

(1) (a) Norris, J. R.; Schiffer, M. C&EN 1990, July 30, 27-37 (b) Borman, S. C&EN 1990, October 8, 27-31
INTRODUCTION

The Diels-Alder reaction has been employed extensively by synthetic organic chemists in the production of many natural products, biologically active compounds and synthetically challenging targets. The reaction is highly regioselective and stereoselective and can be used to generate four contiguous stereogenic centers. Because of the reaction's synthetic utility, much work has gone into optimizing the reaction conditions. Remarkable rate accelerations and improved regio- and stereoselectivities have been observed with Lewis acid catalysts. However, early studies on solvent effects suggested that solvent polarity and composition had only moderate effects on the rate of reaction. Of the solvents studied water was omitted either because of solubility problems or because of educt sensitivity to water. In 1980, Breslow reported the acceleration of several Diels-Alder reactions in water. A representative example is the reaction between cyclopentadiene, and butenone. This reaction is 733 times faster in water than in 2,2,4-trimethylpentane and 58 times faster in water than in methanol which correspond to $\Delta \Delta G^\ddagger$s of 3.9 and 1.3 kcal mol$^{-1}$ respectively.

\[
\text{1} + \text{2} \xrightarrow{20 ^\circ C} \text{3}
\]

In the last ten years there have been a number of applications of aqueous media to Diels-Alder reactions which are of synthetic value. Several proposals have been developed to explain observed rate enhancements of Diels-Alder reactions in water. These include hydrophobic association, micellar catalysis, and high internal solvent pressure. The current paper will discuss several synthetic applications of aqueous media to Diels-Alder chemistry and the proposed interactions responsible for the observed rate enhancements.

APPLICATIONS

Grieco, Yoshida and Garner have observed that dienes such as 4 (R = Na) react faster in
aqueous solutions than their ester analogs (R = Et) react in conventional organic solvents. The reaction of 4 (R = Na) with 5 in water at ambient temperature produces the adducts 6 and 7 in a 3:1 ratio and a 99% yield after 5 h. In contrast, the reaction of 4 (R = Et) with 5 proceeds in benzene at ambient temperature giving rise to a 52% yield, after 288 h, of 6 and 7 in a 1:1.2 ratio.\textsuperscript{7b}

\begin{center}
\begin{tabular}{c}
4 \quad + \quad 5 \\
\rightarrow \\
6 \quad + \quad 7
\end{tabular}
\end{center}

The reaction in water compares favorably with the neat reaction (R = H) as well. After 30 h at ambient temperature, a 80% yield of 6 and 7 is obtained in a ratio of 1.4:1.

Grieco has demonstrated that excellent regiochemical control can be achieved in aqueous media.\textsuperscript{7b} Quinones 8 and 11 react with 9 to yield the adducts 10 and 12 as shown below. The initially formed cis adducts were shown to equilibrate under the reaction conditions to form the more stable trans adducts. The reaction of methyl (E)-3,5-hexadiene (13) and 8 or 11 in solvents such as toluene does not proceed at an appreciable rate at ambient temperature. After 1 week only a small amount of 10 was formed in the reaction of 13 and 8 under these conditions.

\begin{center}
\begin{tabular}{c}
8 \quad + \quad 9 \\
\rightarrow \\
10
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c}
11 \quad + \quad 9 \\
\rightarrow \\
12
\end{tabular}
\end{center}

The scope of aqueous Diels-Alder reactions has been expanded to include derivatives of dienes such as 14 and 15.\textsuperscript{9} For example the reaction of 14 with 8 in water at room temperature results in a 95% isolated yield, after 0.5 h, of 16. The double bond, which is initially exocyclic, is
isomerized to the endocyclic position under the reaction conditions. The same reaction in benzene with the methyl ester of 14 requires heating at 50 °C for 21 h to achieve a 96% yield of 16.

Dienyl ammonium chlorides have been employed as dienes successfully. The condensation of the hydrochloride salts of dienyl amines 17 and 18 with substituted benzoquinones resulted in moderate to excellent yields of the tricyclic imines 19 (n = 1,2) formed upon intramolecular condensation of the free amine in the Diels-Alder adduct with a keto group of the quinone skeleton.

The condensation of (E)-4,6-heptadienyl amine with substituted benzoquinones yielded only degradation products. However, Diels-Alder adducts were isolated if the initially formed free amine was trapped with acetic anhydride. One of the drawbacks of the method is that common dienophiles such as acrolein, methacrolein, methyl vinyl ketone and methyl acrylate are subject to polymerization and 1,4 additions under the acidic reaction conditions. Polymerization and 1,4 additions also complicate reactions of the free amines with dienophiles in water or hydrocarbon solvents.

Both Waldman and Grieco have reported cycloadditions of iminium salts with dienes in aqueous solution. Previously, the condensations of imines with dienes required Lewis acid catalysis and a highly reactive diene. The iminium salts are generated in situ by the condensation of the ammonium salt and formaldehyde in water. Typically, temperatures of 25-55 °C are employed and the reactions are carried out in sealed ampules. Even relatively unactivated iminium salts such as 20 and 22 undergo cycloadditions.
The preceding examples illustrate several of the synthetic advantages of the use of aqueous media for Diels-Alder reactions. Because Diels-Alder reactions usually occur with large decreases in entropy, lower temperatures reduce the unfavorable entropic effect.\textsuperscript{3a} As shown, low to moderate temperatures generally are employed and the reaction times are reasonable when compared to those in conventional solvents. Endo/exo selectivities often are improved or even reversed in aqueous solutions. This improved selectivity has been applied in the preparation of several biologically active compounds.\textsuperscript{14}

The technique, however, is limited by the solubility of the reactants. Though Grieco has resolved this issue by employing dienes with carboxylate and ammonium salt functional groups, many common dienes do not have such functionality. However, the absence of ionizable groups does not exclude a diene from application of the method. Breslow has demonstrated that dilute aqueous solutions of cyclopentadiene can be used successfully in Diels-Alder reactions.\textsuperscript{4} Another limitation results from the water sensitivity of the reactants. Reactions employing dienes such as Danishefsky’s diene could suffer from competing decomposition.

**SOLVENT EFFECTS**

In order to evaluate solvent effects on the rates of Diels-Alder reactions, a mechanistic framework needs to be established. The mechanism is considered to be a synchronous one, though not necessarily symmetric.\textsuperscript{15} Retention of stereochemistry and previously reported small solvent effects support a concerted mechanism, but two-step mechanisms are not excluded by such observations. The negative $\Delta G^\ddagger$ values observed for many Diels-Alder reactions further support a concerted mechanism.\textsuperscript{15b} The formation of a zwitterionic intermediate is excluded by the small $p$-values measured for most Diels-Alder reactions. However, the formation of a diradical intermediate cannot be excluded and $p$-values for the reaction in water have not been reported. Although a rigorous examination of the reaction mechanism in water has not been reported the following discussion assumes that the mechanism is concerted.

**Hydrophobic Association.** Breslow’s initial reports indicated a pronounced rate enhancement of several Diels-Alder reactions in water relative to several solvents (Table I).\textsuperscript{4,16} He
proposed a hydrophobic packing model to explain these observed rate enhancements. However, the physical interactions responsible for the observed effects have not been rigorously established.

**Table I.** Second-Order Rate Constants for the Diels-Alder Reaction of Cyclopentadiene with Methyl Vinyl Ketone in Selected Solvents

<table>
<thead>
<tr>
<th>solvent</th>
<th>$k_2 \times 10^5$ M$^{-1}$ s$^{-1}$ (20 °C)</th>
<th>$k_{rel}$</th>
<th>$\Delta\Delta G$ (kcal mol$^{-1}$) relative to water</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,2,4-trimethylpentane</td>
<td>$5.9 \pm 0.3$</td>
<td>1.0</td>
<td>+3.9</td>
<td>a</td>
</tr>
<tr>
<td>methanol</td>
<td>75.5</td>
<td>12.8</td>
<td>+2.4</td>
<td>a</td>
</tr>
<tr>
<td>formamide</td>
<td>$318 \pm 4$</td>
<td>53.9</td>
<td>+1.5</td>
<td>b</td>
</tr>
<tr>
<td>ethylene glycol</td>
<td>480</td>
<td>81.4</td>
<td>+1.3</td>
<td>b</td>
</tr>
<tr>
<td>water</td>
<td>$4400 \pm 70$</td>
<td>745.8</td>
<td>0.0</td>
<td>a</td>
</tr>
</tbody>
</table>

aReference 4. bReference 16.

Of the proposed models the hydrophobic association model is the most easily visualized yet the most difficult to establish experimentally. Qualitatively, the model is based on association of the diene and the dienophile in a structure which minimizes unfavorable ordering of the solvent in the transition state. The model assumes that solvation of the individual educts requires a more structured solvent cage than the more compact transition structure. Based on this model the rate acceleration is entropic in origin and the energy of the transition structure is lowered relative to the transition structure in an organic solvent. An increase of the ground state energy in water relative to the ground state energy in an organic solvent would result in a rate acceleration in water and could be measured by the difference in heats of solution in each solvent. A more likely explanation includes contributions from both effects.

Engberts discusses the rate enhancements in terms of enforced hydrophobic interactions.\(^5\) Not only is association of the reactants favored, but their relative orientations are such as to favor product formation. This association is consistent with a model in which solute-solute interactions replace solute-solvent interactions. Water's low molecular polarizability weakens the London dispersion interactions between the solutes and the solvent.\(^5\) Therefore, desolvation during the activation process in water is less costly, in terms of $\Delta^\ddagger H$, than in polarizable organic solvents. The solvation of an individual solute in water is entropically disfavored due to the formation of a structured hydration shell. Association of the reactants minimizes the exposed hydrophobic surface, thus increasing the entropy of activation relative to the starting material. This implies that the reduced Gibbs free energy of activation in water is a manifestation of favorable contributions from both the enthalpy and the entropy of activation. Experimentally, this rationalization is supported by the activation parameters determined for the reaction of 1 with several dienophiles in water and propanol (Table II).\(^5\)
Table II. Isobaric Activation Parameters for the Reaction of Cyclopentadiene with Several Dienophiles in water and propanol at 25 °C

<table>
<thead>
<tr>
<th>reaction</th>
<th>solvent</th>
<th>$k_2$, dm$^3$ mol$^{-1}$ s$^{-1}$</th>
<th>$\Delta$G, kJ mol$^{-1}$</th>
<th>$\Delta$H, kJ mol$^{-1}$</th>
<th>-$T\Delta$S, kJ mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 + 2</td>
<td>1-propanol</td>
<td>0.912 x $10^{-3}$</td>
<td>90.37</td>
<td>45.1 (0.7)</td>
<td>45.3 (0.7)</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>51.9 x $10^{-3}$</td>
<td>80.35</td>
<td>39.4 (0.7)</td>
<td>40.9 (0.7)</td>
</tr>
<tr>
<td>1 + 27</td>
<td>1-propanol</td>
<td>0.792 x $10^{-3}$</td>
<td>90.82</td>
<td>45.8 (0.5)</td>
<td>45.0 (0.6)</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>48.9 x $10^{-3}$</td>
<td>80.50</td>
<td>41.5 (0.6)</td>
<td>39.0 (0.6)</td>
</tr>
<tr>
<td>1 + 28a</td>
<td>1-propanol</td>
<td>17.6 x $10^{-3}$</td>
<td>83.05</td>
<td>42.9 (0.6)</td>
<td>40.1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>4.28</td>
<td>69.42</td>
<td>36.6 (0.4)</td>
<td>32.8 (0.5)</td>
</tr>
<tr>
<td>1 + 28b</td>
<td>1-propanol</td>
<td>32.2 x $10^{-3}$</td>
<td>81.54</td>
<td>44.2 (0.5)</td>
<td>37.3 (0.6)</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>4.33</td>
<td>69.39</td>
<td>44.2 (0.8)</td>
<td>25.2 (0.8)</td>
</tr>
<tr>
<td>1 + 28c</td>
<td>1-propanol</td>
<td>14.9 x $10^{-3}$</td>
<td>83.44</td>
<td>43.3 (1.0)</td>
<td>40.2 (1.0)</td>
</tr>
<tr>
<td></td>
<td>water</td>
<td>5.26</td>
<td>68.91</td>
<td>40.5 (0.7)</td>
<td>28.4 (0.7)</td>
</tr>
</tbody>
</table>

Micellar Catalysis. Grieco has proposed that micellar catalysis is responsible for the observed rate accelerations in water. In his model the diene is associated in micellar aggregates and the relatively hydrophobic dienophile is preferentially solvated by the micelles. Increases in the observed rates of reaction can be attributed to a preferred orientation of the educts within a micelle, thus lowering the entropy of activation for the cycloaddition. In support of this model Grieco has reported that the rate decreases significantly if the nominal concentration of the diene is below a given concentration. This is consistent with the existence of a critical micelle concentration (cmc), below which micellar formation does not occur. However, the actual detection of micellar formation in the systems studied has not been addressed by Grieco.

As previously noted, the dienes used by Grieco are structurally similar to detergents. The hydrocarbon chains are shorter than typical detergents but this does not exclude the possibility of micellar formation. This model is limited to reactions of ionic dienes with hydrophobic dienophiles and cannot explain the reactivity of dienes such as cyclopentadiene in true solution with a variety of dienophiles. Schneider and Sangwan have established that the rate accelerations of the condensation of cyclopentadiene with several maleates and fumarates occur at concentrations of the diene at which the UV extinction coefficients obey the Lambert-Beer law. Micellar formation is commonly determined by the detection of dispersion in the UV absorption spectrum of a solution.
High Internal Solvent Pressure. Grieco has proposed that there is a direct relationship between the observed rate enhancements when high pressure is applied to Diels-Alder reactions and the observed rate enhancements in water, a solvent possessing a high internal pressure. The model is based on the information that reactions with negative $\Delta^+V$s are accelerated by pressures greater than atmospheric pressure. Both techniques result in higher endo/exo selectivities, which is consistent with the endo transition structure having a more negative $\Delta^+V$ than the exo transition structure. As shown by Tietze, the endo/exo selectivity of the hetero-Diels-Alder reaction between an enamino ketone and ethyl vinyl ether can be increased by the application of high external pressure. From the dependence of $\ln(\text{endo/exo})$ on pressure Tietze determined that $\Delta^+V_{\text{endo}}$ was more negative than $\Delta^+V_{\text{exo}}$ by $5.8 \pm 0.5 \text{ cm}^3 \text{ mol}^{-1}$ for the indicated reaction. Prinzbach has shown also that the regioselectivity of cycloadditions of substituted acetylenes to several syn-o,o'-dibenzences can be influenced by the application of high external pressure.

In support of his proposal, Grieco has examined the effect of 5.0 M lithium perchlorate in diethyl ether on several Diels-Alder reactions. Improved yields and endo/exo selectivities were obtained. However, a rigorous kinetic study was not conducted and the possibility of lithium ion catalysis was not considered. Recently, Foreman and Dailey have shown that the rate of reaction of 1,3-diphenylisobenzofuran with styrene is unaffected by 5.0 M lithium perchlorate diethyl ether compared to pure diethyl ether. If internal pressure were a factor rate accelerations would be expected even for Diels-Alder reactions lacking a Lewis base. It has been demonstrated, for the condensation of acrylonitrile with 9,10-dimethylanthracene, that there is a linear correlation between the second order rate constants and the concentration of LiClO$_4$. This is consistent with lithium ion catalysis and suggests internal pressure is not responsible for the rate accelerations.

CONCLUSION

Diels-Alder reactions can be conducted under relatively mild conditions and reactions are often carried out at ambient temperatures. Thus, the application can offer significant advantages over conventional solvents in terms of rate and selectivity. However, a physically meaningful rationale for the observed rate enhancements in water is difficult to establish rigorously. Hydrophobic interactions are often invoked to explain such phenomena but the nature of these interactions is poorly understood. Jorgensen has attempted several computational studies on the reaction of cyclopentadiene with methyl vinyl ketone. He has proposed that there is a significant nonhydrophobic contribution to the observed rate enhancements. This nonhydrophobic component is attributed to a more polarized transition state than the ground state and, thus, stronger hydrogen bonding to the carbonyl oxygen in the transition state. Other proposals such as micellar
catalysis and high internal solvent pressure have not been well established. This lack of understanding has not limited the synthetic utility of the technique as demonstrated by Grieco and Waldman.8,9,11,12

REFERENCES

INTRODUCTION

The role of radical intermediates in enzymatic catalysis has been the subject of much debate.1 There are three general methods available for the detection of radical intermediates: (1) indirect detection via a substrate that undergoes a radical rearrangement, (2) "spin trapping" to transform a transient radical into a long lived EPR-visable species, or (3) direct observation spectroscopically. This report will concentrate on the use of "radical clocks"\(^2\) incorporated into the substrate molecule to investigate the reaction pathway of cytochrome P-450 hydroxylation of alkanes.

BACKGROUND

The cytochrome P-450 enzymes are a ubiquitous family that use heme, NADPH, and molecular oxygen to hydroxylate unactivated C-H bonds.3 In humans this enzyme is involved in the synthesis of steroids, detoxification of foreign substances, and the activation of carcinogens.4 The catalytic cycle of P-450 is shown in Scheme I. This report will focus on the rate, stereo-

Scheme I

\[
\begin{align*}
[Fe^{III}] & \quad \text{[Fe]}^{III} \\
\text{ROH} & \quad \text{[FeIV=O]} \\
\text{H}_2\text{O} & \quad \text{[Fe}^{II}-\text{O}_2] \\
\text{[Fe}^{III}] & \quad \text{[Fe}]^{III} \quad \text{[RH]} \\
\text{O}_2 & \quad \text{[Fe}^{II}-\text{O}_2] \\
\end{align*}
\]

chemistry, and mechanism of step (e). This process has been extensively studied, and the current evidence (vide infra) supports a nonconcerted process that involves hydrogen atom abstraction by the high-spin oxoiron(IV) porphyrinate species followed closely by the so called "oxygen rebound" step (eq 1).5

\[
\begin{align*}
\text{R-H} & \quad \text{O}^{\text{Fe IV}} \quad \text{Fe IV} \\
\text{abstraction} & \quad \text{R'} \\
\text{HO-Fe IV} & \quad \text{Fe IV} \\
\text{rebound} & \quad \text{R-OH} \\
\end{align*}
\]

Copyright © 1992 by Edward E. Fenlon
The prototypic radical clock rearrangement is that of the methylcyclopropylcarbinyl radical (1') to the 3-butenyl radical (2') (eq. 2). The rate of this rearrangement has been established with good agreement by many different methods. For example, low temperature EPR experiments on 1' and on 1,1-dideuterio-3-butenyl radical (CH2=CHCH2CD2•) have been used to calculate \( k_1 \) and \( k_{-1} \), respectively. Methylcyclopropane and various derivatives of it have been used in the studies that are the basis of this report. Calibrated radical clocks can be used to study the rate and mechanism of both chemical and enzymatic reactions. To be successful, the rearrangement rate (\( k_r \)) should be similar (±10^2) to the rate of the reaction being studied, and the rearrangement must be effectively irreversible. The rate of enzymatic oxygen rebound can be determined by choosing a probe substrate that generates a single radical (unrearranged radical, U*) which can be hydroxylated in the oxygen rebound step, or rearrange to form another radical (R*), which in turn can be hydroxylated (Scheme II). The rebound rate, \( k_{OH} \), then can be calculated by equation 3, where \( k_r \) is the known radical rearrangement rate at 37 °C and [UOH]/[ROH] is the ratio of unrearranged to rearranged alcohol products from the enzymatic reaction.

\[
k_{OH} = k_r \frac{[UOH]}{[ROH]}
\]

**OXYGEN REBOUND RATE**

The first estimate of the oxygen rebound rate in microsomal cytochrome P-450 was reported by Ortiz de Montellano and Stearns in 1987. They employed methylcyclopropane (1), nortricyclane (3), and bicyclo[2.1.0]pentane (4) as radical probes. The sole product when 1 was
incubated with P-450 was cyclopropylmethanol (1-OH), as evidenced by gas chromatography (GC). Incubation of 3 with P-450 also resulted in only one product, nortricyclanol (3-OH) in this case. No rearrangement is observed with these clocks.

Incubation of bicyclo[2.1.0]pentane (4) with the enzyme gave two GC detectable metabolites. The first product was a rearrangement product, 3-cyclopenten-1-ol (5-OH). The second product was identified as the "normal" hydroxylation product, endo-2-hydroxy-bicyclo[2.1.0]pentane (4-OH). The ratio of 5-OH to 4-OH ranged from 1:6 to 1:10. At the time of this study 4' was known to rearrange faster than 1', but the rate had not been determined. These results prompted the researchers to conclude that (1) the hydroxylation is not concerted, (2) that a carbon free radical is an intermediate, and (3) that the rate of the "oxygen rebound" step is estimated to be on the same order as the rearrangement of 4'.

In order to obtain a more accurate value for this oxygen rebound rate, the Ingold group calibrated the rearrangement of 4' and several other very fast cyclopropylmethyl radical clocks. The nitroxide radical trapping method using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was employed.11 They then investigated the hydroxylation of these substrates by cytochrome P-450.12 The rearrangement rates at 37°C, product ratios (UOH:ROH), and the calculated (equation 3) "oxygen rebound" rate ($k_{OH}$) for eight clocks were determined. Representative examples are summarized in the Table. The products were identified by GC/mass spectrometry (MS) comparisons to authentic materials. The detection limit was ca. 0.5-1.0% of the major product.

Only unrearranged alcohols were detected from 6' and other relatively slow clocks, which

<table>
<thead>
<tr>
<th>U'</th>
<th>$k^{37°C}$ $(10^8 s^{-1})$</th>
<th>R'</th>
<th>Products [UOH:ROH]</th>
<th>$k_{OH}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6'</td>
<td>0.8</td>
<td>7'</td>
<td>&gt;100:1</td>
<td>&gt;1 x 10$^{10}$</td>
</tr>
<tr>
<td>8'</td>
<td>1.6</td>
<td>9'</td>
<td>95 (±16):1</td>
<td>1.5 x 10$^{10}$</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>10'</td>
<td>90 (±15):1</td>
<td>1.6 x 10$^{10}$</td>
</tr>
<tr>
<td>11'</td>
<td>8.0</td>
<td>9'</td>
<td>24 (±5):1</td>
<td>1.9 x 10$^{10}$</td>
</tr>
<tr>
<td></td>
<td>2.3</td>
<td>10'</td>
<td>77 (±9):1</td>
<td>1.8 x 10$^{10}$</td>
</tr>
<tr>
<td>12'</td>
<td>20</td>
<td>13'</td>
<td>100:0.8</td>
<td>2.5 x 10$^{11}$</td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>14'</td>
<td>&gt;200:1</td>
<td>&gt;5 x 10$^{10}$</td>
</tr>
</tbody>
</table>
is expected. The observation that P-450 produces rearranged alcohols from the faster clocks 4', 8', and 11' again shows that the enzyme hydroxylation is not concerted and that the enzymatic intermediate is a carbon radical. It is important to remember that proper controls are always required when using this method.\textsuperscript{13} For example, it was found that under the physiological conditions employed, the enzymatic product 4-OH underwent a slow polar rearrangement to 5-OH. Earlier it was found that a very small amount of 5-OH was formed from 4-OH under the GC conditions.\textsuperscript{10} Bowery and Ingold point out that cationic intermediates of methylcyclopropanes would give methylcyclobutanols as rearrangement products (eq 4), since this rearrangement is

\[
\begin{align*}
\text{(4)}
\end{align*}
\]

know to be very fast;\textsuperscript{14} however, no such products are detected. The microsomal hydroxylation of 
\textit{trans} and \textit{cis} 1,2-dimethyl cyclopropanes 8 and 11, resulted in the same ratios of rearranged alcohols as the TEMPO trapping reaction in solution did. The important implication of this result is that when radicals 8' and 11' are formed in the enzyme active site, they undergo ring opening in exactly the same manner as they do when generated in solution. Therefore, with these substrates it is concluded that the radicals are not significantly influenced by the confines of the active site, and the four rate constants that were measured for the "oxygen rebound" are indeed valid.

Two clocks gave unexpected results. Radicals derived from 1,1,2,2-tetramethylcyclopropane (12') and hexamethylcyclopropane (15') were shown to undergo very fast radical ring opening in solution, yet significant quantities of rearranged alcohols were not detected in the enzymatic reaction as would be expected. The authors offer several possible explanations for these anomalies. The possibility that 16' had undergone a disproportionation reaction with the hydroxyferryl complex was ruled out because the expected product, 2,3,3,4-tetramethyl-1,4-pentadiene (17) was not detected (eq 5). Other possibilities include: (a) a decrease in the effective

\[
\begin{align*}
\text{(5)}
\end{align*}
\]

rate of ring opening, (b) a reaction of the rearranged radical with an organic group of the enzyme, (c) tighter binding of the more bulky substrate might cause a much faster oxygen rebound, and (d) a change in the mechanism, e.g. a concerted oxene insertion. The possibility that different P-450 strains may be oxidizing these more bulky substrates is discussed, but the authors propose that factors (a) and (b) are most plausible.
Potentially there are several sources of a slower effective rate of ring opening. The steric constraints of the active site could hinder the ring opening as well as accelerate the rate of ring closure for these bulkier substrates. The ring opening rearrangement removes the carbon radical from the proximity of the FeOH center, therefore the substrate must turn around in the active site before it can react with the FeOH. With larger substrates it is possible that the constrictive nature of the hydrophobic pocket could hinder this process. The concept of a "round trip" radical probe was recently put forward by Branchaud et al.\textsuperscript{15} to address problems such as these. A "round trip" probe would undergo radical-mediated skeletal rearrangements in such a way that in the end the resultant radical is on the original carbon that underwent hydrogen abstraction.

**MECHANISM**

Three mechanistic possibilities for the oxygen rebound step are shown in equations 9-11. The first is a bimolecular homolytic substitution (S\textsubscript{H2}). The second involves formation of an Fe\textsuperscript{V} species followed by reductive elimination. The third involves loss of hydroxyl radical in a rate determining step, followed by a fast recombination step. The third mechanism seems unlikely for several reasons. The fact that different oxygen rebound rates are seen with different substrates (Table) is inconsistent with a rate determining step involving only the iron center.\textsuperscript{18} One would also expect that the liberation of free hydroxy radical would be detrimental to the enzyme. Bowery et al.\textsuperscript{11b,18} favor the S\textsubscript{H2} mechanism over the carbon-iron alternative for simplicity and because of the hindered active site environment. Distinguishing eq 9 from eq 10 is not trivial.

The distinction of carbon radical vs. organoiron intermediate has been investigated in other enzymes. Corey and Nagata\textsuperscript{19} studied the enzymatic lipoxygenation of fatty acids and offer three experimental observations which are interpreted as favoring the sequence shown in equation 12.
First, the total turnover number (TTN) of the enzyme, a measure of self-inactivation, was found to decrease when arachidonate analogues with extended conjugation were used. Substrates with extended conjugation should accelerate a radical process because the C-H bond dissociation energy is lowered, and the more stabilized radical should less readily attack the enzyme. A lower $V_{\text{max}}$ and TTN can be explained by an organoiron intermediate however. Greater homolysis of the Fe-C bond is expected because a more stable radical is formed, this radical can then attack and deactivate the enzyme. The second observation is that the distribution of products varied with $O_2$ pressure when the analogues with increased conjugation were used. This is attributed to capture of organoiron species at C-17 and C-19 in addition to the usual C-15 oxidation site. The third observation involves a cyclopropyl radical clock substrate. In the enzyme reaction, 14% ring opened products are detected, but Corey discounts this finding by contrasting it to a peroxide-induced oxidation in solution which produced only ring opened products. It has been proposed in the literature\textsuperscript{20} and in this report, however, that such comparisons are invalid.

**BICYCLO[2.1.0]PENTANE STEREOSELECTIVITY**

Deuterium labeling experiments by Ortiz de Montellano and Stearns\textsuperscript{10} showed that only the endo-H(D) of bicyclo[2.1.0]pentane was removed and all unrearranged products (20 and 21) had the endo- stereochemistry (eq 6). They reported no deuterium isotope effect for this reaction.

$$\text{18D} + \text{19D} \xrightarrow{P-450} \text{20D} + \text{21D} + \text{22D} + \text{23D} \quad (6)$$

These results prompted both the Ingold group,\textsuperscript{11,12} and the Newcomb group\textsuperscript{16} to further investigate this diastereoselectivity with different methods.

As mentioned, the Ingold group used the nitroxide radical trapping method using TEMPO to calibrate these rearrangements.\textsuperscript{11b} The trapping of $4'$ in solution gave very different stereochemistry when compared to the enzyme hydroxylation. The TEMPO trapping gave an exo:endo ratio of ca. 2 (eq 7), cf. 100% endo in the enzymatic reaction.\textsuperscript{10,12} Their enzymatic results
agreed with the earlier report in that no intramolecular isotope effect was seen, but a small intermolecular deuterium isotope effect between 1.3-1.7 was observed. The endo selectivity could simply be attributed to the chiral environment of the active site, but further investigation of this issue was nevertheless undertaken by others.

Newcomb et. al. studied the trapping of 4' using (((2-thioxopyridinyl)-oxy)carbonyl)) (PTOC) as the radical precursor with H(D)-atom donors: t-BuSH, PhSH(D), 2,6-dimethylthiophenol(SH, SD), and PhSeH(D). Trapping with PhSD at -78 °C showed a ΔΔG° of ca. 1.1 kcal/mol in favor of the endo-2-D product as evidenced by 2H NMR (eq 8). Similar selectivities (93:7) were seen at 1.5 °C as well, although 37% of the ring opened product was detected at this higher temperature. When isomerically pure samples of the exo- or endo-PTOC precursor were used the same endolexo product ratio was observed, establishing that 4' had reached equilibrium before trapping. The effect of steric factors was addressed by comparing the trapping rate of PhSH and 2,6-dimethylthiophenol with 1' and 4'. Although 4' could be considered to have greater steric bulk, no significant difference was observed. The deuterium kinetic isotope effect for trapping was determined to be in the range of 1.5-1.85.

It was noted that the origin of the diastereoselective formation of the endo-product in the enzymatic reaction is complex. Steric effects are presumably the dominate factor in radical coupling reactions and this could explain the exo-preference by TEMPO in solution. The selectivity observed with PhSD is attributed stereoelectronic factors. The weaker endo-C2-X bond ( X= CO2* or H ) is attributed to conjugation of its antibonding orbital with the C1-C4 bond by Newcomb et. al. Bowery and Ingold explain this in terms of better orbital overlap of the endo-C2-X with the Walsh π-orbitals of the cyclopropane ring. Newcomb's results do not rule out a role by the active site environment, but they do suggest that stereoelectronic effects within the bicyclo[2.1.0]pentane system alone could account for much of the observed selectivity of both reactions (abstraction and oxygen rebound) in the P-450 studies.
CONCLUSION

The characterization of radical intermediates sequestered in an enzymatic active site is an important and challenging task. This report has shown how radical clocks can facilitate this study for the case of cytochrome P-450 hydroxylation of unactivated C-H bonds. The results of the radical clock method implicate a nonconcerted process with a carbon radical intermediate. The oxygen rebound rate has been measured to be on the order of \(10^{10}-10^{11} \text{ s}^{-1}\) depending on the substrate. The method also helps rule out a free hydroxy radical mechanism. Thus far, however, it has been less helpful in distinguishing between \(\text{S}_\text{H}2\) vs. organoiron mechanistic paths or for determining the origin of the observed stereoselectivity of the enzyme.

REFERENCES

(17) Li, J. University of Illinois Student Seminar 1989, fall, 89-98.
LIVING RING-OPENING METATHESIS POLYMERIZATION CATALYZED BY HOMOGENEOUS TRANSITION METAL COMPLEXES

Reported by William A. Reinerth  February 27, 1992

INTRODUCTION

Ring-opening metathesis polymerization (ROMP) by transition metal complexes has been known for over three decades, however, only within the last ten years has an extensive understanding of this reaction been developed. With this understanding has come the ability to rationally design new catalysts that will polymerize a variety of monomers containing different functional groups and incorporate these monomers into block copolymers. Unlike classical ROMP catalysts that often form linear and cyclic oligomers, these "living" catalyst systems can form polymers having very narrow molecular weight distributions. Living ROMP catalysts which can tolerate diverse functionality and produce nearly monodisperse polymers, should allow control of bulk properties through manipulations at the molecular level.

This paper will discuss the mechanism of ROMP and polymer microstructure as well as the recent advances in ROMP catalysis by a variety of transition metal complexes.

MECHANISM AND POLYMER MICROSTRUCTURE

Mechanism

ROMP is a special case of olefin metathesis in which the reacting olefin is contained in a ring. The currently accepted mechanism for olefin metathesis proposed by Herrison and Chauvin in 1970 involves reaction of a metal-alkylidene with an olefin to yield a metallacyclobutane intermediate. This intermediate then rearranges to yield a new alkylidene and olefin. The application of this mechanism to a cyclic olefin is shown in Scheme I.

Scheme I

The metal-alkylidene and olefin undergo a [2+2] cycloaddition to generate the metallacycle which then rearranges to form the ring-opened alkylidene. Addition of more monomer to this species yields a living polymer. The transition metal can be cleaved from the organic fragment in a Wittig-like reaction with a carbonyl compound to give the free polymer and a metal-oxo species.
Theoretical calculations have shown that metallacycle formation is an endothermic process when the reacting alkylidene is the only multiply bonded ligand attached to the metal center. However, when another multiply bonded ligand, such as an oxo, is present, formation of a metallacyclobutane is exothermic by over 20 kcal/mol. This stabilization results from formation of a stronger metal-ligand bond to the "spectator" multiply bonded ligand upon cleavage of the metal-alkylidene double bond in formation of the metallacycle as illustrated in Scheme I.3 The spectator oxo effect, as it is called, has been of key importance in the design of olefin metathesis and ROMP catalysts.2,6

**Polymer Microstructure**

An understanding of the microstructures of polymers produced by ROMP catalysts is necessary in order to produce materials with specific properties. The microstructure of the polymer provides information about the geometry of monomer approach to the catalyst and to the living polymer and control over the microstructure of a polymer provides control over the bulk properties of the material. The three aspects of polymer microstructure that are of primary importance are double bond isomerism, tacticity, and regiochemistry of monomer addition.

Double bond isomerism deals simply with the orientation, cis or trans, of substituents on the carbon-carbon double bonds in the polymer backbone formed upon ring opening. Tacticity refers to the asymmetric centers formed upon polymerization of a prochiral cyclic olefin. If adjacent asymmetric centers have the same configuration, this is an $r$, or racemic, dyad, while if they have opposite configurations this is an $m$, or meso, dyad. A polymer consisting of completely $r$ dyads would be syndiotactic, while one comprised of entirely $m$ dyads would be isotactic. A random distribution of $m$ and $r$ dyads would result in an atactic polymer. The third aspect of polymer microstructure, regiochemistry of monomer addition, is a factor when an unsymmetric monomer is polymerized. This lack of symmetry creates the possibility of having three additional types of polymers based on the sequence with which subsequent monomers add. These sequences are described as head/tail, head/head, and tail/tail.1,7,8

**CATALYSIS BY MOLYBDENUM AND TUNGSTEN IMIDO-ALKYLIDENES**

The spectator oxo effect has been utilized to prepare several transition metal oxo-alkylidene complexes that act as catalysts for olefin metathesis and ROMP.9 However, because the metallacyclobutane is much lower in energy than the oxo-alkylidene,5 a Lewis acid is required for the metallacycle to rearrange to products. Schrock2,7,10 and Grubbs10a,11 have utilized the weaker spectator effect of an imido ligand to develop Lewis acid free olefin metathesis and ROMP catalysts based on molybdenum and tungsten.

The catalysts that they developed, $M$(CHR)(NAr)(OR')$_2$ ($M$=Mo, W; Ar=2,6-diisopropylphenyl; R=CMe$_3$, CMe$_2$Ph; R'=CMe$_3$, CMe$_2$CF$_3$, CMe(CF$_3$)$_2$), can be synthesized in
moderate yields in four steps. These catalysts will polymerize a variety of strained, cyclic olefins including 2,3-disubstituted norbornadienes, 7-oxanorbornadienes, cyclobutene, cyclooctatetraene (COT), and 7,8-bis(trifluoromethyl)tricyclo[4.2.2.0²⁵]deca-3,7,9-triene (TCDT) shown in Figure 1, to give homopolymers and block copolymers with polydispersities as low as 1.02.

The exact catalyst employed depends on the monomer, but generally the molybdenum catalysts when R=R'=CMe₃ are the most useful for ROMP. These catalysts are not as active as the tungsten-based catalysts. The Mo catalysts are more tolerant of functionality and less prone to react with acyclic olefins in the living polymer to form linear and cyclic oligomers than are the W catalysts.

The olefin TCDT is an interesting monomer for ROMP because it can be used to prepare polyenes containing up to 15 conjugated double bonds in a controlled manner as illustrated in Scheme II. Polymerization of TCDT by W(CHCMe₃)(NAr)(OCMe₃)₂ yields a living polymer that will, after end capping and upon heating, undergo a retro Diels-Alder reaction to eliminate hexafluoroorthoxylene and generate polyenes of various lengths.

Much interest has focused on the ROMP of COT and substituted COTs because ring-opened COT is isostructural with polyacetylene. Electronically conductive polymers like polyacetylene have potential applications in electronics, nonlinear optics, and solar energy.
conversion systems. Recent work has resulted in the preparation of poly-trimethylsilyl-COT which is easily handled and, upon doping with iodine, has been employed in Schottky barrier type solar cells. Cyclooctatetraene substituted with chiral alkyl groups has been polymerized to form soluble polyacetylene derivatives with effective conjugation lengths of at least 20 double bonds. The chiral side chains cause the polymer chain to twist in predominantly one screw sense making the polymer a disymmetric chromophore.

Scheme II

\[
W(CHCMe_3)(NAr)(OCMe_3)_2 + \text{1} \rightarrow \text{2}
\]

\( \text{Ar=2,6-diisopropylphenyl} \)

Recently, Grubbs and coworkers examined the polymerization of cyclobutene by \( W(CHCMe_3)(NAr)(OCMe_3)_2 \). They found that \( W(CHCMe_3)(NAr)(OCMe_3)_2 \) catalyzes the living ROMP of cyclobutene in the presence of \( \text{PMe}_3 \) to yield polybutadiene with a polydispersity of 1.03. In the absence of a Lewis base a polydispersity of greater than two is obtained for polymerization of cyclobutene. The phosphine appears to bind more strongly to the propagating alkylidene that to the initial catalyst which slows propagation and results in a more controlled...
polymerization. Coordination of a Lewis base to the propagating alkylidene also seems to suppress back-biting reactions relative to the polymerization of cyclobutene in the absence of a Lewis base.

A major problem with all living ROMP catalyst systems is the capping process. The living polymer is capped in a Wittig-like reaction with a carbonyl compound to yield a metal-oxo species that is incapable of continuing the polymerization. Schrock and coworkers has investigated methods of chain-transfer so that the living polymer can be cleaved using a strained olefin to form the capped polymer and a different alkylidene that can continue the polymerization.\textsuperscript{15} His approach has been to use a derivatized cyclopentene as a chain-transfer agent. A properly substituted cyclopentene should be ring-opened by the living polymer and then intramolecularly eliminate the cyclohexene-capped polymer and generate a new alkylidene species as shown in Scheme III. Schrock has found that cyclopentenes are not strained enough to undergo chain-transfer rapidly and quantitatively. More highly strained cyclic olefins will be necessary if chain-transfer is to be a viable method for capping and regenerating ROMP catalysts.

**Scheme III**

\[
\begin{align*}
\text{Catalysis by Titanacyclobutanes} \\
\text{Grubbs and coworkers have developed a series of titanacyclobutanes that are capable of polymerizing several norbornenes in a living manner.}\textsuperscript{8,16} \text{ Reaction of Tebbe's reagent with strained cyclic olefins forms these titanacyclobutanes in moderate yields. Living ROMP of a number of substituted norbornenes catalyzed by these complexes yield polynorbornenes with polydispersities as low as 1.03. In preparing block copolymers using titanacyclobutanes, Grubbs has found that the order of monomer addition can greatly affect the molecular weight distribution of the resulting polymer.}\textsuperscript{17}
\end{align*}
\]
Anslyn and Grubbs have examined the mechanism by which these titanacyclobutanes cleave to form the reactive species. There has been some controversy between several theoretical groups that have examined this cleavage reaction. The controversy is over whether the reactive intermediate produced by metallacycle cleavage is a free titanocene methylidene or a titanocene methylidene-olefin complex. From Grubbs' mechanistic study it appears that a titanocene methylidene-olefin complex is the reactive entity. It is believed that an incoming olefin displaces the olefin bound to the titanium center in an Sn2 process. The possibility that the bound olefin dissociates prior to attack by the incoming olefin in an Sn1-type process has not yet been completely eliminated.

**OTHER CATALYST SYSTEMS**

Classical ROMP catalytic systems employed Lewis acids such as alkylaluminum reagents, but the role of the Lewis acid is still undetermined in many systems. The role of Lewis acids in recent homogeneous systems is also a subject of debate. Lewis acids have been proposed to coordinate to the oxo ligand of a transition metal complex to either induce initial α elimination to form an active oxo-alkylidene complex, promote electrophilic attack on the incoming olefin by the alkylidene, or promote cleavage of the metallacyclobutane intermediate. Other researchers have proposed that the Lewis acid removes an anionic ligand to generate a reactive cationic complex or possibly that it binds to the alkylidene ligand to protect it both sterically and electronically.

Most Lewis acid assisted catalysts that have developed recently have been examined as catalysts for simple olefin metathesis but information regarding their ability to do ROMP is lacking. Osborn has reported the first direct observation of the interconversion of the chain-propagating alkylidene and the metallacyclobutane in the polymerization of norbornene by W(CHCMe3)(OCH2CMe3)Br2 assisted by GaBr3. Boncella and coworkers have developed a W(VI) oxo-alkylidene complex which, in combination with AlCl3, catalyzes the ring-opening polymerizations of norbornene and cyclooctene, but polydispersities are moderate at best. The unique aspect of this catalyst is its insensitivity to air and moisture over the course of the polymerization. Recently, Herrmann has reported the ROMP of norbornene using methyltrioxorhenium with alkylaluminumchlorides. Methyltrioxorhenium is stable in the presence of both air and water but polynorbornene produced using this catalyst system has moderate polydispersities at best.

Schrock has reported the polymerization of norbornene by the tantalum(V) complex Ta(CHCMe3)(OR)3(THF) (R=2,6-diisopropylphenyl). If the polymerization is stopped at 75% completion, a polydispersity of 1.04 is obtained for the polynorbornene. The ROMP of a few
substituted norbornenes has been reported by Basset using a Lewis acid free W(VI) catalyst. but no data on the resulting polymers has been provided.25

CONCLUSION
The past decade has witnessed an explosion in the field of living ROMP catalysis. There are now homogeneous catalysts that are capable of polymerizing a wide variety of cyclic olefins in a controlled manner. These catalysts can tolerate functionality and are stable over the course of the polymerization. Sensitivity to air and water as well as termination of the polymerization upon capping are drawbacks of these catalyst systems. The next steps in ROMP catalysis are the application of the current systems to the development of new, potentially useful materials as well as the development of improved catalysts.

REFERENCES


STEREOCHEMICAL ASPECTS OF ASYMMETRIC ALDOL CONDENSATIONS PROCEEDING VIA TITANIUM ENOLATES

Reported by Donald A. Seielstad March 16, 1992

INTRODUCTION

The aldol condensation constitutes one of the fundamentally most important carbon-carbon bond forming reactions in both biosynthesis and synthetic organic chemistry. The full utility of this reaction may be realized by its ability to stereoselectively generate vicinal asymmetric centers in the construction of β-hydroxycarbonyl compounds of the general structure 1, from achiral enolate and aldehyde precursors (Scheme I). A primary focus of aldol research has been the control of absolute stereoselectivity at these two centers. Contributions from a number of researchers have provided useful correlations between enolate geometry, enolate metal counterion, metal ligands, solvent, enolization base, and enolate and aldehyde substituents and the stereochemical outcome of the reaction. The development of predictive transition-state models based on steric and stereoelectronic factors for boron enolate systems which display very high stereoselectivities is an indication of the refinement possible using the above correlations.

Scheme I

Since their first reported use in aldol condensations, zirconium and titanium enolates have displayed unique features that distinguish them from the extensively studied alkali and alkaline earth metal enolates. These group IIB enolates have demonstrated an ability to preferentially yield syn-aldol products independent of the Z or E geometry of the enolate. Both extended and cyclic transition-state structures have been proposed to explain the observed aldol product diastereoselectivities, yet the predictive abilities of any of these models remains poor and there continues to be disagreement as to the validity of the different models.

ALDOL DIASTEREOSELECTIVITY

In general, aldol condensations of enolates or aldehydes containing a stereogenic center may produce four possible diastereomers, as shown in Scheme I. The reaction may be
characterized on the basis of the observed product diastereoselectivity (S₁ S₂ vs. A₁ A₂) or enantioselectivity of the newly created stereogenic centers. Enolates have been generated from a variety of metal counterions, including Li, B, Si, and Sn and these reactants result in stereochemical aldol product distributions that can be classified into one of three general groups. Type 1 aldol condensations, typically observed for group IA, IIA, and IIIA metal enolates, yield aldol product syn:anti ratios which directly reflect the Z:E ratio of the original enolate. In the absence of severe steric bulk, Z-enolates yield syn products while E-enolates yield anti products. A closed, six-membered chairlike transition-state structure originally proposed by Zimmerman and Traxler, in which 1,3-diaxial and aldehyde-ligand interactions are minimized, has been used to rationalize these results (Figure 1). Anomalous product distributions are occasionally observed for these enolates which may result from equivalent transition-state energies, competitive reaction kinetics, or solvation and aggregation effects. Type 2 aldol condensations display syn-diastereoselectivity independent of enolate Z- or E-geometry and have been demonstrated for silyl and stannyl-enol ethers, boron, titanium, and zirconium enolates. Type 3 aldol reactions, those which yield predominantly anti-products independent of enolate geometry, have been obtained using a variety of reagents and conditions, including ketene acetal substrates and chiral auxiliaries.

![Figure 1: Zimmerman-Traxler transition-state model](image)

The ability of titanium (IV) to form tetra-, hexa-, and octa-coordination complexes, as well as its unusual type 2 aldol behavior, makes this a unique and potentially versatile counterion for use in aldol condensations. This report will discuss recent advances in the applications of titanium and zirconium enolates to stereoselective aldol condensations, reevaluate some earlier results in light of recent findings, and examine the various transition-state (TS) models proposed in an effort to provide a model which rationalizes the observed stereoselectivities and possesses some degree of predictive value.

ZIRCONIUM AND TITANIUM ENOLATES

Zirconium enolates, first reported in 1980, were shown to undergo kinetic aldol condensations with representative aldehydes to yield syn-selective products in good yields with very good diastereoselection. These zirconocene enolates were generated from the corresponding lithium enolates via transmetallation using Cp₂ZrCl₂ with no demonstrated loss of enolate stereochemistry. In nearly all cases, experiments were performed to determine that kinetic, and not
thermodynamic, control applied under the reported conditions. Kinetic control is required for valid interpretation of the observed selectivities in terms of TS models. Product stereochemistry was assigned primarily by NMR data, or by analogy or derivatization to known products; occasionally X-ray crystallographic data of purified products was used. Product distributions were determined on crude or purified reaction mixtures using GC, HPLC, or NMR analysis.

As shown in Table I, various ketone, ester, and amide Z- and E-enolate mixtures, as well as stereochemically pure E-enolates of cyclic ketones, afforded predominantly syn-products. This is clearly contrary to the kinetic products expected from the Zimmerman-Traxler transition-state model. Evans and McGee have suggested that a modified pericyclic TS model be used to account for the observed product stereochemistry.\(^3\) The high syn-selectivity is proposed to result from Z-enolates reacting via the Zimmerman TS (3a) and E-enolates reacting preferentially via a boat-like TS (3b), as shown in Figure 2. Steric interactions between the zirconium cyclopentadienyl ligands and the E-enolate substituents result in a preference for the boat-like TS manifold over the chair-like TS. Alternatively, Yamamoto has proposed that syn-product selectivity results from an extended transition state, yet offers no further rationale for this conclusion.\(^3\)

**Table I**: Aldol Condensations of Lithium, Zirconium, and Titanium Enolates with Benzaldehyde

<table>
<thead>
<tr>
<th>Enolate</th>
<th>Enolate Ratio</th>
<th>Product Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z : E</td>
<td>syn:anti (Li) syn:anti (Zr) syn:anti (Ti)</td>
</tr>
<tr>
<td>OM</td>
<td>5 : 95 (^3)</td>
<td>74:26 (-Ti(NEt(_2))(_3)) (^3) 81:19 (-TiCl(_3)) (^3)</td>
</tr>
<tr>
<td></td>
<td>92 : 8 (^3)</td>
<td>44 : 56 (^3) 88 : 12 (^3)</td>
</tr>
<tr>
<td></td>
<td>36 : 64 (^3)</td>
<td>30 : 70</td>
</tr>
<tr>
<td>OM</td>
<td>5 : 95 (^4)</td>
<td>52 : 48 (^4) 87 : 13 (^4)</td>
</tr>
<tr>
<td></td>
<td>95 : 5 (^4)</td>
<td>60 : 40 (^4) 95 : 5 (^4) 2:98 (-TiC(_2)Cl) (^3)</td>
</tr>
<tr>
<td>OM</td>
<td>0 : 100</td>
<td>48 : 52 (^4) 72 : 28 (^4) 97:3 (-Ti(NEt(_2))(_3)) (^3) 92:8 (-Ti(NMe(_2))(_3)) 86:14 (-Ti(OiPr)(_3)) 89:11 (-TiCl(_3)) (^3)</td>
</tr>
<tr>
<td>OM</td>
<td>74 : 26 (^4)</td>
<td>85:15 (-Ti(NEt(_2))(_3)) (^3)</td>
</tr>
</tbody>
</table>

In 1981, Reetz and Peter reported the first application of titanium triisopropoxide and tris(dialkylamide) enolates of acyclic and C\(_5\)-C\(_7\) cyclic ketones which demonstrated better syn-diastereoselection than the zirconocene enolates, independent of enolate geometry.\(^4\) No consistent difference in selectivity was observed in replacing the isopropoxide ligands on titanium with dimethylamide ligands, suggesting that electronic effects at titanium had little or no influence on simple diastereoselectivity. Pericyclic (Figure 2) or acyclic\(^1\) (Figure 3) TS structures were suggested to account for the observed results, with steric effects of the enolate substituent causing
a shift in preference from chair to boat and the resultant improvement in syn-selectivity.

Figure 2: Proposed Cyclic Transition State Models Applied to Titanium and Zirconium Enolates

Figure 3: Proposed Acyclic Transition State Models for Aldol Condensations

Kinetically controlled syn-selective aldol condensations using trichlorotitanium enolates of both cyclic and acyclic ketones were observed by Nakamura who claims that an open TS is highly unlikely owing to the strong Lewis acidic character of the TiCl₃-enolate. Instead, a variety of cyclic TS hypotheses were discussed. The syn-selective chair (2b, 2d) and parallel-boat (4) TS structures were rejected based upon steric constraints between axial substituents and observed product selectivities for the cyclic E-enolates, while an energetically favorable tilt-boat (5), which results from the comparatively longer Ti-O bond length and reduced O-Ti-O bond angle, is proposed to be of slightly lower energy than the chair TS. This structure, as compared to a parallel-boat, is relatively free of steric strain and delivers the enolate at the aldehyde carbon in accordance with the accepted Burgi-Dunitz trajectory. In addition, this tilt-boat may account for the observed increase in anti-selectivity of the corresponding lithium and boron enolates of various substituted cyclohexanones. Metal-oxygen bond lengths or secondary orbital overlap favoring an "endo" arrangement of reactants may rationalize the origin of preference for this tilt-boat TS. Geometric descriptions of the twist- and tilt-boats are incomplete at best; these model structures may indeed be identical or simply opposing distortions of a parallel-boat structure.

ADVERSE LITHIUM EFFECT

The typical procedure for generating titanium and zirconium enolates via transmetallation of the lithium enolate utilizes stoichiometric L₃TiCl reagent per equivalent LDA added for enolization. It was recently reported that excess ClTi(OiPr)₃ resulted in a substantial increase in diastereo-selectivities, and that this effect saturated at ~2-3 equivalents per equivalent LDA used. It is
postulated that one excess equivalent of titanium reagent is necessary to complex the lithium salt displaced upon transmetallation; additional reagent is considered to shift the equilibrium of the lithium-titanium-ate enolate complex (7) toward the free titanium-ate complex (8b), as is shown in Scheme II. In the absence of excess titanium, loss of selectivity may result from reaction through the lithium enolate (6) or Li:Ti-complex (7) reaction manifolds (see Scheme II). Further evidence in support of this adverse lithium effect was demonstrated when 12-crown-4 was added to solutions of titanium enolates generated using only one equivalent of the titanium reagent. Up to a 30-fold increase in diastereofacial selectivity was observed, which mimicked selectivities obtained when a three-fold excess of titanium reagent was added. These findings may account for low syn-selectivities or anomalous reversals previously reported for titanium enolates. Previously published results and conclusions should be judiciously scrutinized and evaluated prior to incorporation into working TS models.

**Scheme II**

![Scheme II](image)

**CHIRAL AUXILIARIES**

A variety of chiral auxiliaries, including N-acyl oxazolidinones and chiral camphor derivatives,\(^\text{15}\) have been investigated both as probes of transition state structure and for their ability to induce asymmetry in the aldol condensation. These reagents, as described by Masamune,\(^\text{16}\) have been used by Evans\(^\text{6a}\) and others to substantially improve the diastereofacial selectivities of boron enolate aldol additions. In recent years, nearly all research on titanium enolate aldol reactions has incorporated chiral enolates or chiral auxiliaries to enhance product selectivity.

Siegel and Thornton have investigated titanium enolates of a chiral α-siloxy ketone (9) and have demonstrated excellent selectivities with representative aldehydes.\(^\text{14}\) The major product (10b S\(_2^2\) adduct) was found to be identical to the major enantiomer obtained in the corresponding boron-mediated aldol reaction.\(^\text{6c}\) These results cannot be explained by chelation of the bulky α-siloxy group by titanium, an effect previously observed for lithium enolates\(^\text{17}\) and other titanium reagents,\(^\text{18}\) as chelation would result in the opposite product stereochemistry (Scheme III). Furthermore, in studying the steric influence of α-siloxy groups in aldol condensations, Panyachotipun and Thornton observed variable diastereoselectivity for α-siloxy lithium enolates, while product selectivity for α-siloxy titanium enolates remained uniformly high regardless of siloxy group size.\(^\text{19}\) A non-chelated chair-like TS, which appears insensitive to siloxy group size, was offered to rationalize these observations for α-siloxy titanium enolates (Scheme III).
Scheme III

An alternate procedure to lithium transmetallation has been used by Harrison\textsuperscript{20a} and Evans, \textit{et al.},\textsuperscript{20b} to generate trichlorotitanium enolates of amides and ketones using TiCl\textsubscript{4} and Et\textsubscript{3}N or i-Pr\textsubscript{2}NEt. Under these conditions, unhindered carbonyls self-condensation and primary alkyl esters do not readily enolize. Evans has demonstrated high \textit{syn}-selectivities using chiral \textit{N}-acyl oxazolidinone- and sultam-derived titanium enolates. In a study of diastereoselective aldol reactions of \textbeta{}-ketoimide-derived enolates (12a,b) generated using TiCl\textsubscript{4} or Sn(OTf\textsubscript{2}), enolization occurred exclusively at C-4. Product stereochemistry was determined predominantly by the methyl substituent stereochemistry at C-2, with only minor contributions from the oxazolidinone geometry. The proposed chair TS structure (Scheme IV) possesses an octahedral titanium center resulting from chelation to both propionyl oxygens and the aldehyde carbonyl.

Scheme IV

Another remarkable example of reversal of product selectivity postulated to result from oxygen chelation by the enolate titanium counterion was demonstrated using enolates derived from (S)-\textit{N}-propionyl-4-isopropyl-2-oxazolidinone.\textsuperscript{21} The reversal in product stereochemistry upon replacing boron with titanium is consistent with a chair-like TS containing an octahedral titanium complex coordinated to the oxazolidinone carbonyl, or a tetrahedral boron center which is
incapable of coordinating with the oxazolidinone (Scheme V).

**Scheme V**

SOLVENT EFFECTS

The oxygen chelating and multiple coordination characteristics of titanium (IV) may clearly influence steric and stereoelectronic effects of the aldol TS, yet these interactions are presently only poorly understood. Solvation and aggregation effects have been proposed to account for the product selectivities observed for some lithium enolates and are now being explored as they relate to titanium enolates. A solvent chelation effect has been proposed to account for the five-fold increase in selectivity observed for the acyloxazolidinone-derived titanium enolates in changing solvent from THF to diethyl ether. It is proposed that stoichiometric binding of THF to titanium in the TS lowers the observed selectivity by interfering with chelation control via the carbonyl of the chiral auxiliary. Other investigators have also observed improved selectivities when Ti-mediated aldols are performed in weakly coordinating solvents, such as i-Pr₂O and Et₂O, instead of THF. Additionally, a substantial increase in product selectivity has been observed upon lowering Ti-enolate concentration from 0.17M to 0.08M, an effect which diminishes with increasing α-aldehyde substitution. No explanation is offered to account for the increase in selectivity observed upon dilution for the less-substituted aldehydes.

CONCLUSIONS

Titanium and zirconium enolates have demonstrated high syn-selectivities, independent of enolate geometry, for aldol condensations using a variety of representative aldehydes and enolates. The high stereoselectivities attainable with these reagents, in conjunction with their low cost, ease of handling, work-up, and disposal, suggest that these reagents would serve as excellent compliments to bulky or chiral boron enolates in the synthesis of highly syn-selective aldol products. The chelating abilities of titanium have been used advantageously to obtain high product selectivities; and factors such as solvent, lithium ion, enolate concentration, aldehyde and enolate substituents, chiral auxiliaries, titanium Lewis acidity, and metal ligands have all been shown to significantly influence aldol stereoselectivity.

The observed adverse lithium ion effect may warrant repeating early experiments using different procedures in order to help clarify low selectivities or unexplained reversals. Additional efforts should be directed toward examining chiral E- and Z-enolates, and unexplained anomalies are still observed for α-unsubstituted Ti-enolates. In spite of the clear advances made in
controlling and improving product selectivity, much is still unknown about the transition state or the origin of the observed aldol syn-selectivity. Continued work is needed in order to understand and unify the diverse array of extended and cyclic TS models currently proposed.

REFERENCES


DIOXIRANES AS SELECTIVE OXIDIZING AGENTS

Reported by James B. Day

INTRODUCTION

The recent emergence of stable dioxirane compounds provides synthetic chemists with a new reagent for performing oxidations under relatively mild conditions. The use of dioxiranes 1-3 has led to the preparation and isolation of unstable epoxides in high yields and provided a variety of useful oxidations which include the oxidation of carbon-hydrogen bonds. The mechanistic studies done to date indicate that dioxirane is essentially electrophilic in nature and that the oxidations proceed through bimolecular transition states.

The dioxirane structure was first proposed as an intermediate in the famous Baeyer-Villiger reaction by the investigators for whom the reaction was named, although later O\(^{18}\) labeling experiments discounted this proposal.\(^{1,2}\) In 1985 Murray reported a simple procedure for preparing dimethyldioxirane as a stable solution in acetone and physical organic and spectroscopic studies have proven the presence of the dioxirane species.\(^{3a}\) A detailed history of dioxiranes prior to 1989 can be found in two reviews by Murray and Adam.\(^{3b,4}\) This paper will focus primarily on more recent investigations of synthetic methodology, applications, and the reaction mechanisms of oxidations with dioxiranes.

\[
\begin{align*}
1 & : R_1 = R_2 = CH_3 \\
2 & : R_1 = CF_3, R_2 = CH_3 \\
3 & : R_1 = R_2 = CH_2 - (CH_2) \_3 - CH_2
\end{align*}
\]

SYNTHETIC METHODOLOGY

Oxidation of Olefins to Epoxides

The distinguishing feature of dioxirane epoxidations is the mild reaction conditions with which they are employed. Dioxiranes, in general, are used at pH neutral conditions and low temperatures. This is in contrast to other more familiar epoxidation techniques which employ per oxy acids or alkaline peroxides. Exploitation with dioxirane has lead to the relatively easy

Copyright © 1992 by James B. Day
isolation of several epoxides which are proven to be difficult to isolate. Epoxidation of silylenol ethers is a notable example (Entry A, Table I).\(^5\) Treatment of these compound with dimethyldioxirane at low temperature yields the stable \(\alpha\)-\(\beta\) epoxide silyl ether which rearranges with warming to the \(\alpha\)-siloxy-ketone - the observed product of typical peracid oxidations. Another example is the epoxidation and isolation of enol phosphates (Entries B, Table I).\(^6\) Dioxiranes have also been used to epoxidize \(\alpha\)-\(\beta\) unsaturated carbonyls (Entries C and D, Table I).\(^7\) The products of these reactions have traditionally been prepared under relatively harsh conditions with alkaline peroxides. The use of dioxiranes for epoxidations of compounds with ketones does not typically lead to Baeyer-Villiger rearrangement products. Crandall has applied dioxirane chemistry extensively to the di-epoxidation of allenes (Entry E, Table I).\(^8\)

**Table I.** Epoxidations of olefins with Dimethyl dioxirane in methylene chloride

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><img src="image1" alt="A" /></td>
<td>-40°C/3h</td>
<td>99%</td>
</tr>
<tr>
<td>B</td>
<td><img src="image2" alt="B" /></td>
<td>-10°C/2.5h</td>
<td>100%</td>
</tr>
<tr>
<td>C</td>
<td><img src="image3" alt="C" /></td>
<td>20°C/20h</td>
<td>94%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td><img src="image4" alt="D" /></td>
<td>20°C/20h</td>
<td>86%</td>
</tr>
<tr>
<td>E</td>
<td><img src="image5" alt="E" /></td>
<td>-50°C/0.5h(^a)</td>
<td>44%</td>
</tr>
</tbody>
</table>

\(^a\) acetone as solvent

**Oxidations of Carbon Hydrogen Bonds**

Methyl(trifluoromethyl)dioxirane (2) has been used extensively to oxidize non-activated carbon-hydrogen bonds and substantial information about the oxidations has been compiled.\(^9\) Representative examples are shown in Table 2. The general conclusion Curci makes is that tertiary C-H bonds are more reactive than secondary, while primary carbons are essentially unreactive (Entry A, Table II). The oxidation of methylene carbons, in some cases, yields ketones which apparently result from further oxidation of the initially formed alcohol (Entry A and B, Table II). Further investigations have confirmed the oxidation of alcohols.\(^10\) The observance of selectivity for oxidation makes dioxirane attractive when compared to other techniques such as the use of hydroxy radicals or ozone.
Oxidations of Other Compounds

Murray and co-workers have developed extensive methodology for the oxidations of amines. Products include nitro compounds, nitrogen oxides, nitrones, hydroxyl amines, and nitroxides. Sulfides and sulfoxides are conveniently oxidized by dioxirane and Adam has recently demonstrated the utility of I to oxidize thioesters to α-oxo sulfones. Dioxiranes have also been used to generate α-hydroxy ketones from enolates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Product Ratio</th>
<th>Conditionsa</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td>41</td>
<td>-22°C/70min</td>
<td>98%</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td>41</td>
<td>-22°C/2min</td>
<td>97%</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td>58:42</td>
<td>-22°C/1min</td>
<td>98%</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td>94:1b</td>
<td>-24°C/60min</td>
<td>95%</td>
</tr>
</tbody>
</table>

a) Solvent is methylene chloride  b) Other 5% is dihydroxy adamantane

SYNTHETIC APPLICATIONS

Dimethyl dioxirane was the reagent of choice for the preparation of the proposed insect juvenile hormone primary metabolite 6 (Scheme I). Messeguer found that treatment of the diol 4 with MCPBA did not yield the epoxide, but did lead to the acid catalyzed formation of the tetrahydropyran 5. The use of I accomplished the epoxidation and the desired product 6 was isolated. The epoxidation of the α,β-unsaturated ester did not occur under a relatively short reaction time of 5 min, but could be achieved if the reaction was carried out over 72 hours.

Danishefsky has used dimethyl dioxirane to epoxidize D-glucal derivatives stereospecifically to form the cyclic 1α,2α epoxides 7. The resulting epoxide has been used as
a stereospecific β-glycosal donor in several syntheses. Attempts to perform the oxidation with MCPBA reportedly gave poor results due to the acidic reaction conditions.\textsuperscript{15a,b}

Scheme I

![Scheme I](image)

The epoxide of aflatoxin B\textsubscript{1}, which is believed to be the active intermediate in the formation of covalent adducts with DNA, could not be isolated using peroxo acid techniques.\textsuperscript{16} Treatment of aflatoxin with dimethyl dioxirane afforded the characterizable epoxide as the only product in 15 minutes at room temperature.

Other examples of the advantages of using dioxirane range from the polyfunctionalization of adamantanes\textsuperscript{17} to the isolation of flavones and precocene epoxides.\textsuperscript{18}

Dioxiranes are limited in that they are not presently available commercially and must be prepared. These preparations (in situ or isolated solutions) are typically dilute (0.08-0.12M for 1; 0.6-0.8M for 2 and 3 as isolated solutions). This makes large scale preparations impractical.

**MECHANISM**

**Reaction Order**

In 1979 Curci and Edwards proved the presence of the dioxirane as the reacting species through kinetic studies which determined that the reactions were bimolecular.\textsuperscript{19} Baumstark determined the rate constant for the epoxidation of 17 olefins and found the observed reaction rates to be overall second order.\textsuperscript{20} The rate constants for these compounds using dimethyl dioxirane varied as much as 0.57M\textsuperscript{-1}s\textsuperscript{-1} for 4-methoxystyrene to 0.016M\textsuperscript{-1}s\textsuperscript{-1} for 3-methyl-1-butene-3-ol for typical examples.
Transition State

The structure of the transition state is still uncertain. There are currently two orientations thought to be possible for the transition state: the planar "butterfly" orientation, which closely resembles the proposed intermediate in per oxy acid epoxidations, or the "spiro" configuration as seen in Figure 1.\textsuperscript{21} Evidence supporting the spiro orientation has been presented based upon steric arguments.

![Figure 1](butterfly.png)  
**Butterfly**

![Figure 2](spiro.png)  
**Spiro**

Electrophilic/Nucleophilic Character

A growing body of evidence indicates that dioxiranes act as electrophiles in epoxidations. Adam compared dimethyl dioxirane with t-butyl peroxide anion and m-chloroperoxybenzoic acid (MCPBA) using 5-thianthrene oxide 8 as a diagnostic reagent (Scheme II).\textsuperscript{4} Electrophilic reagents were assumed to produce the 5,10 dioxide 9 while nucleophilic reagents preferentially oxidize the sulfoxide and lead to the 5,5 dioxide 10. The nucleophilic character of the reagent (X\textsubscript{nu}) is assigned a numerical value between the value 0 and 1 based upon the product ratios with a pure nucleophile receiving a 1, while 0 indicates a purely electrophilic reagent. The results of this study were taken to show that dimethyl dioxirane has an X\textsubscript{nu} of 0.68 to 0.85, depending on solvent systems, whereas MCPBA and t-BuOO\textsuperscript{-} have X\textsubscript{nu} values of 0.36 and 0.97 respectively. This analysis may be questionable because of the results obtained in studies using p-substituted aryl methyl sulfides. Murray found the \( p \) value for dimethyl dioxirane to be -0.76 whereas MCPBA had a value of -0.55.\textsuperscript{22} Dimethyl dioxirane appears more electrophilic than MCPBA for sulfide to sulfoxide conversion in this case. The ability for dioxiranes to have some nucleophilic character, however, is an attractive explanation when considering the epoxidations of electron deficient olefins.

In addition to determining rates, Baumstark showed that the epoxidation of p-substituted styrenes with dimethyl dioxirane gave a \( p^* \) value of -0.90,\textsuperscript{20} again indicating an electrophilic
nature in the dioxirane. Baumstark also found that increasing water concentrations increased the rate of epoxidation of p-methoxystyrene. This was reported to possibly be the result of a polar solvent effect on a charged transition state, although the possibility of a hydrogen bonding catalytic effect was not excluded.

Scheme II

Epoxidation of the deuterium substituted 4,4-dimethyldihydropyran 11 and 12 showed the expected secondary kinetic isotope effects for a sp² to sp³ re-hybridization in the transition states. The results indicate that a higher degree of rehybridization occurs at the β-carbon to oxygen as compared to the α position (k_H/k_D : 12 = 0.773 ± 0.029 and 11 ± 0.847 = 0.043 at 25°C; 12 = 0.681 ± 0.032 and 11 = 0.898 ± 0.036 at -78°C). This undoubtedly is the result of greater degree of bond formation at the β-carbon possibly due to a resonance contribution from the oxygen lone pair in the transition state (Figure 3). The observed effect at the α-carbon indicates that there is some bond formation in the transition state and indicates some degree of concerted addition across the double bond.

Figure 3

Carbon-Hydrogen Oxidation Mechanism

Curci and coworkers have provided a significant body of evidence that would indicate that radical or cationic intermediates are not present. By choosing appropriate substrates and analyzing the products, evidence is provided that discounts hydride or hydrogen atom extraction.
Adam found solvent effects in the oxidation of the chiral (S)-(−)-2-Phenyl-2-butanol (Entry D, Table II). The observance of a polar solvent effect lead to the conclusion that a concerted radical process (Figure 2) could be occurring. The absolute retention of configuration and a lack of side products tend to discount step wise extraction mechanisms.

**Dioxirane Analogs**

Shortly after the technique for the preparation of dimethyl dioxirane was established, a number of analogs were reported. Curci and coworkers concluded that methyl(trifluoromethyl) dioxirane was 200 fold more reactive than dimethyl dioxirane in oxidation of alcohols to carbonyl compounds, while being approximately 600 fold more reactive in direct carbon hydrogen oxidation. In a rate comparison of epoxidation of cis-stilbenes by pentamethylene dioxirane 3 and dimethyl dioxirane 1, Murray concluded that 3 was roughly six times more reactive than 1 at effecting the epoxidation. Dimethyl dioxirane and methyl(trifluoromethyl) dioxirane represent the most common examples of dioxiranes while pentamethylene dioxirane represents a more recently prepared dioxirane.

**Steric Effects**

Recent evidence indicates that dioxiranes reactions can be influenced by steric factors. Dimethyl dioxirane was shown to effect a carbon-hydrogen oxidation preferentially to olefin epoxidation in the case of 3,3-dimethyl-1,2-bis(trimethylsilyl)cyclopropene (13). The lack of epoxidation product is assumed to be due to steric hindrance by the silyl groups.

The preferential oxidation of the 3-hydroxy and the 7-methylene groups in the 4,4-dimethyl Δ⁵ analog of cholesterol 14 over the double bond is reported to occur as a result of steric congestion around this position. Curci has reported similar findings with steroids. As seen earlier, Danishefsky has demonstrated the ability to direct facial epoxidation on cyclic alkenes 7. Danishefsky rules out a hydroxyl directing effect in dioxirane epoxidations in this study.
The use of asymmetric dioxiranes or dioxiranes with chiral auxiliaries to obtain enantio-enriched products appears to be limited to studies done by Curci which show low enantioselectivities using asymmetric ketones as the dioxirane precursor. Another report of the oxidation of methyl phenyl sulfides with dimethyl dioxirane in the presence of bovine serum albumin gives better results with an enantiomeric excess upwards of 89%.

CONCLUSION

From a synthetic standpoint, dioxiranes offer a useful method for effecting the preparation of highly labile epoxides. The mechanistic data to date indicate that dioxirane reacts primarily as an electrophilic epoxidizing reagent while the ability of dioxiranes to effect epoxidation of electron poor olefins would indicate some capacity to act as a nucleophile. The issue of whether the transition state is in the butterfly or spiro configuration is still under investigation with the evidence to date favoring the spiro structure. The data for carbon-hydrogen oxidation indicate that a concerted radical mechanism is likely.

REFERENCES

(1) Baeyer, A. V.; Villiger, V. Ber. 1899, 32, 3625.
FK506 and Rapamycin: Immunosuppressive Ligands of FK506 Binding Protein

Reported by Ken C. Rix  
April 20, 1992

Introduction

FK506 and rapamycin (Figure 1) are two new members of a growing class of immunophilin ligands which possess the ability to suppress immune response in vivo by inhibiting T lymphocyte cell activation. FK506 was isolated from Streptomyces tsukubaensis\(^1\) and rapamycin was isolated from Streptomyces hygroscopicus\(^2\) both in relatively high yield giving 9.2 mg of FK506 and 30 mg of rapamycin per liter of fermentation broth.

![Figure 1. Structures of FK506 and rapamycin](image)

Immunophilins are highly soluble cytosolic proteins in the 10-30 Kd range which play an integral role in the signaling processes that lead to the activation of T cells. T lymphocyte cells control immune response in higher animals and are activated by surface receptors. This results in a signal which is transduced to the nucleus leading to T cell activation. Much is known about the surface and nuclear events, however, the mechanism of signal transduction through the cytoplasm has long been a mystery. Immunophilin ligands serve as probes into the mechanism of these signal transduction pathways.

FK506 and rapamycin inhibit separate T cell activation pathways. FK506 inhibits T cell receptor mediated signal transduction. This signaling pathway begins when an antigen is presented to a T cell receptor on the surface of the lymphocyte beginning a signaling cascade. The TCR signal is then transduced through the cytoplasm to the nucleus leading to the transcription and

Copyright © 1992 by Ken C. Rix
translation of genes coding for early T cell activation proteins such as interleukin-2 (IL-2) and interleukin-2 surface receptors.\textsuperscript{3,4}

Rapamycin inhibits the next step in T cell activation which involves lymphokine receptor mediated signal transduction leading to cell proliferation. This pathway begins when IL-2 is presented to an IL-2 receptor on the surface of the lymphocyte beginning a signaling cascade. The LKR signal is then transduced through the cytoplasm to the nucleus where T cell activation genes are transcribed and eventually translated leading to cell proliferation.\textsuperscript{3,4}

All known immunophilins are cis-trans isomerases (rotamases), that is, they catalyze the interconversion of the cis and trans rotamers of peptidyl-prolyl amide bonds as shown in Scheme 1.\textsuperscript{5-9} FK506 and rapamycin both bind to the immunophilin FK506 binding protein (FKBP) with binding constants of 0.4 nM and 0.2 nM, respectively, causing potent inhibition of FKBP’s rotamase activity.\textsuperscript{7-10} However, inhibition of rotamase activity is an insufficient explanation for mediation of immunosuppression because the median inhibitory concentration of FK506 and rapamycin of $\approx 0.5$ nM is about ten times lower than the cytoplasmic concentration of FKBP. Therefore, FK506 and rapamycin inhibit T cell activation when only one tenth of the FKBP binding sites are occupied. Furthermore, FK506 and rapamycin each inhibit one another’s activity but only when the antagonist is present in about a ten fold excess. These observations can be understood when considering that cytoplasmic signal transduction is calcium dependent and that immunophilin-ligand complexes are known to bind to the calcium binding proteins calmodulin and calcineurin. Calmodulin is a 17 Kd protein which mediates the effects of calcium ions on cell functions. Calcineurin is a protein phosphatase which can bind calmodulin. Protein phosphatases are known to play a role in signal transduction. The phosphatase activity of calcineurin is inhibited after it is bound to the immunophilin-ligand complex. It is this inhibition of phosphatase activity which is speculated to mediate the immunosuppressive activity of immunophilin ligands.\textsuperscript{11} Thus, FK506 and rapamycin act as "pro-drugs" and the ligand-immunophilin complex is the actual bioactive agent. This explains the ten fold excess of antagonist required for the inhibition of the immunosuppressive activity of FK506 or rapamycin due to the unoccupied receptor sites.
The first compound discovered in this class of immunophilin ligands was cyclosporin A (CsA) which binds to and inhibits the rotamase activity of cyclophilin, an 18 Kd protein previously called peptidyl-prolyl isomerase.\textsuperscript{5,6} CsA was a landmark discovery in the field of immune suppression affording unprecedented success in organ transplant surgery and in the treatment of autoimmune disorders. FK506 and rapamycin hold great interest due to their 10-100 fold greater potency than CsA and unique spectra of side effects.\textsuperscript{12}

**FK506 BINDING PROTEIN**

FKBP is a highly soluble, 12 Kd, cytosolic protein comprised of 108 amino acid residues. FKBP is an abundant protein comprising about 0.5% of the total cytoplasmic protein in most cell lines, and is also quite ubiquitous having been isolated from a wide range of organisms from the higher to the lower eukaryotes.\textsuperscript{9,13,14} The gene coding for FKBP is highly conserved as shown by the 65% sequence homology between this gene in \textit{Saccharomyces cerevisiae} and in the human species.\textsuperscript{14} Due to its abundancy and its highly conserved nature, FKBP is thought to be involved in a number of different biochemical cellular processes.

The primary sequence of FKBP was determined by the Edman degradation technique and corroborated by an extensive NMR investigation of FKBP conducted by Schreiber et al. which also lead to the determination of the secondary and tertiary structure of the immunophilin. The sequence of FKBP was determined by homo- and heteronuclear NMR techniques including \textsuperscript{15}N-\textsuperscript{1}H heteronuclear shift correlation spectroscopy (COSY) and heteronuclear multiple-quantum coherence spectroscopy (HMQC) experiments. Almost all carbon, proton and nitrogen chemical shift assignments were made resulting in the identification of 96 amide based spin systems which were connected by Nuclear Overhauser Effect Correlation Spectroscopy (NOESY) into partial sequences which were mapped onto the known sequence. Medium and long range NOE spectroscopy was used to assign the secondary structure of the protein. The tertiary structure was determined by long range side chain NOEs.\textsuperscript{15-17}

Distance constraints derived from NOESY cross peak magnitudes and angle constraints based on analysis of coupling constants were used in restrained molecular dynamics simulations leading to a determination of the three dimensional structure of FKBP. FKBP is composed of a large antiparallel five stranded \(\beta\) sheet which packs against an \(\alpha\) helix formed by residues 59 to 65. The \(\beta\) sheet wraps around the \(\alpha\) helix with a right handed twist forming a hydrophobic cavity which serves as the active site both for binding and rotamase activity.

For use in their extended research on FK506 and rapamycin, Schreiber et al. executed the molecular cloning and overexpression of human recombinant FKBP (rFKBP). The coding sequence for human FKBP was placed into the genome of \textit{Escherichia coli} using the plasmid expression vector pHN1 leading to the abundant production of fully active rFKBP.\textsuperscript{18-20}
The mechanism of rotamer interconversion by FKBP has been studied by NMR techniques. The α-keto carbonyl functionality at carbons 8 and 9 of FK506 and rapamycin would be expected to be very electrophilic and, with the adjacent homoprolyl ring, mimics a peptide substrate. The synthesis\(^{21}\) of \([8,9-^{13}\text{C}]\text{FK506}\) and subsequent \(^{13}\text{C}\) NMR analysis\(^{22}\) of its complex with rFKBP discredits formation of a tetrahedral adduct due to the lack of \(^{13}\text{C}\) resonances in the 90 to 130 ppm range. Furthermore, the presence of only one set of signals in this study leads to the conclusion that only one rotamer of FK506 is bound to FKBP. The labelled FK506 was recovered after denaturation of the rFKBP in nearly quantitative yield indicating that only noncovalent interactions occur in the complex.

**MOLECULAR RECOGNITION**

FK506 and rapamycin have many of the structural characteristics of a peptide substrate indicating these ligands may bind to FKBP due to peptidomimicry. The dicarbonyl and homoprolyl ring functionalities of FK506 and rapamycin apparently emulate the peptidyl-prolyl amide bond of an endogenous peptide ligand. It has been proposed that FKBP interconverts the rotamers of this endogenous ligand through noncovalent stabilization of a twisted amide bond, that is, through the stabilization of the transition state for rotamer interconversion.\(^{22-24}\) Such a transition state for a peptidyl-prolyl substrate would have the carbonyl of the amide bond rotated from the normal planar conformation to a position perpendicular to the prolyl ring as shown in Figure 2 on the right. The solution structure of FK506 shows that the adjacent carbonyls at C8 and C9 are perpendicular to one another due to \(\text{A}^{1-3}\) strain. This causes the carbonyl at C9 to be perpendicular to the homoprolyl ring, as shown in Figure 2 on the left, simulating the twisted amide bond of a peptidyl-prolyl substrate.\(^{22}\)

![Substructure of FK506](image1.png)  ![Twisted peptidyl-prolyl amide bond](image2.png)

**Figure 2.** FK506 as a twisted amide surrogate
The peptidomimicry of FK506 and rapamycin as shown in Figure 3 is evidenced by the catalytic efficiencies of a series of tetrapeptide substrates for the rotamase activity of rFKBP.

\[
\text{Leu-Pro peptide substructure} \quad \text{Ligand dicarbonyl substructure}
\]

**Figure 3.** Peptidomimicry of FKBP ligands

showing that a leucine-proline amide bond undergoes the fastest rate of rotamer interconversion.\(^{23}\) The dicarbonyl region of FK506 resembles a such a peptide substrate leading to the conclusion that FK506 is a leucine-proline twisted amide mimic.

Schreiber et al. conducted a \(^1\)H NMR study of the FK506- and rapamycin-FKBP complexes employing selectively deuterated FKBP which was overexpressed in *E. coli* supplied with only four protonated amino acids during growth: Tryptophan, tyrosine, proline and valine; all other amino acids were deuterated. The \(^1\)H resonances of the pipecolinyl rings of both FK506 and rapamycin were shown to move significantly upfield upon complexation with selectively deuterated FKBP. The two spectra of the respective ligand-FKBP complexes were also very similar in this upfield region arguing that rapamycin and FK506 bind to FKBP with similar structural elements.\(^{25}\)

The proposed binding pocket of FKBP is rich with aromatic residues which would account for the shielding of the pipecolinyl ring. Furthermore, NOESY NMR showed a connectivity between Try 59 and the protons on the pipecolinyl ring on the opposite side of the axial acyloxy group. The highly conserved nature of the aromatic residues near the binding pocket of FKBP, such as W59, Y82 and F99, also validates the importance of these hydrophobic residues towards substrate binding.\(^{25}\)

The structures of the FKBP-FK506\(^{26}\) and the FKBP-rapamycin\(^{27}\) complexes were both determined at 1.7-Å resolution by X-ray crystallographic techniques and correspond well with the results of the NMR analyses. FK506 and rapamycin bind to FKBP with very similar structural features and, in fact, the ester, pipecolinyl ring and dicarbonyl functionalities of the two ligands are nearly superimposable in the two complexes. In each case, the pipecolinyl ring is deeply buried in the protein residing in the back of the binding pocket between the \(\alpha\) helix and the \(\beta\) sheet. FK506 is largely immersed into the protein with only the allyl and cyclohexyl groups being exposed to
solvent. Rapamycin, however, is buried in the protein from the pyranose ring to the C28 hydroxyl including the cyclohexyl group with the triene functionality exposed.

The FK506-FKBP complex involves five hydrogen bonds which aid in binding including a pair to the C24 hydroxyl and ones to the C8 amide oxygen, to the C1 lactone carbonyl, and to the C10 hemiketal hydroxyl.26 The rapamycin-FKBP complex involves these same five hydrogen bonds with the C28 of rapamycin corresponding to the C24 of FK506.27 However, rapamycin lacks the double bond which binds the cyclohexyl group to the macrocycle in FK506 allowing the cyclohexyl group to freely rotate in rapamycin affording an additional hydrogen bond from Gln 53 to the C40 hydroxyl. In both complexes, no hydrogen bonds to the C9 carbonyl are found as might be expected if these ligands are viewed as twisted amide mimics. However, the C9 carbonyl interacts with three e-hydrogens - one from each of the conserved, aromatic residues Tyr 26, Phe 99 and Phe 36 - arguing that these residues play a role in the stabilization of the transition state for rotamer interconversion.26

Rapamycin's larger FKBP binding constant relative to that of FK506 can be understood when considering the structural aspects of ligand complexation. In solution, the cis rotamer of FK506 predominates,28 but the trans rotamer is bound to FKBP,26 whereas the trans rotamer of rapamycin is seen both in solution and in the bound form.27 Furthermore, unlike rapamycin, a change in the orientation of the pyranose ring of FK506 is observed upon complexation. These observations explain rapamycin's greater affinity for FKBP based on the greater preorganization for binding seen in rapamycin and the additional hydrogen bond to the C40 hydroxyl in which rapamycin is able to engage.

The structural similarities between the FK506-FKBP and the rapamycin-FKBP binding complexes along with the concomitant dissimilarities in the mode of action of the two ligands argues that FK506 and rapamycin act as dual domain agents possessing distinct binding and

---

**Figure 4.** Dual domains of FK506 and rapamycin
effector domains. The binding domain is involved in molecular recognition by FKBP while the effector domain determines which signal transduction pathway is inhibited.

This view of immunophilin ligands as dual domain agents suggests the opportunity to engineer immunosuppressive compounds with distinct effector cassettes attached to their respective binding domains which in turn inhibit distinct signal transduction pathways.

BINDING DOMAIN ANALOGUES

In order to test the dual domain hypothesis and to determine the structure-activity relationships regarding ligand complexation, Schreiber et al. synthesized three FK506 analogues possessing only the binding domain and various conformational constraints.\textsuperscript{29,30} FK506 Binding Domain

(506BD) was modeled after the solid state conformation of FK506 in which the cis isomer is found.\textsuperscript{29} 506BD was constructed with a macroring constraint from C16 to C25 consisting of a trans enoate group acting as a scaffolding element which fixes the distance between the ends of the binding domain limiting conformational freedom. This macroring constraint favors the cis rotamer of 506BD 8:1 in solution as determined by the analysis of coupling constants for the pyranose ring protons and the chemical shift values for the pipercolinyl ring protons α to the nitrogen. As in FK506, the keto carbonyl of 506BD is perpendicular to the adjacent amide carbonyl due to A\textsuperscript{1,3} strain.\textsuperscript{30} The pyranose ring was assumed to be important towards binding based on studies of tetrapeptide binding to FKBP.\textsuperscript{23} An isopropyl substituent was placed on C16 of 506BD to limit rotation around the C15-C16 bond mimicking a similar constraint found in FK506.\textsuperscript{29}

506BD showed no immunosuppressive activity in accord with the dual domain hypothesis. Although 506BD had a 20 nM FKBP binding constant, 506BD lacks the effector domain which presumably plays an integral role in the binding of calmodulin and calcineurin by the
immunophilin-ligand complex. Thus, because 506BD cannot bind calmodulin and calcineurin, it subsequently shows no immunosuppression. 506BD inhibits the actions of both FK506 and rapamycin when present in approximately 100 fold excess.\textsuperscript{30} This high inhibitory concentration of 506BD is explained by its ten fold weaker binding constant to FKBP compared to FK506 and by the ten fold greater abundance of unbound FKBP than that of bound FKBP \textit{in vivo}. Therefore, 506BD must first occupy the empty FKBP binding sites before antagonism is observed.

An analogue of 506BD was synthesized which lacks the cyclohexyl substituent (Des-CyH 506BD) to determine the importance of this group concerning ligand binding. Des-CyH 506BD had a 1.8 mM binding constant to FKBP indicating the necessity of the cyclohexyl group towards binding. An acyclic analogue (Acyclic 506BD) was also synthesized which had a very low binding constant indicating the importance of the macroring constraint.\textsuperscript{30}

The synthesis of 506BD demonstrates the utility of modeling new ligands which are specific for a given enzyme based on the structural features seen in a known ligand. The relatively high binding constant of 506BD indicates the importance towards complexation of not only ligand functionality but also of ligand conformation.

CONCLUSION

The study of FK506 and rapamycin as immunophilin ligands has shed some light on the "black box" of cytoplasmic signal transduction leading to T cell activation. Apparently, the binding domains of FK506 and rapamycin emulate a small endogenous ligand in which a peptidyl-prolyl amide bond is interconverted through transition state stabilization. The binding domains of FK506 and rapamycin are attached to distinct effector domains which enable FK506 and rapamycin to bind to calmodulin and calcineurin, thereby inhibiting the phosphatase activity of calcineurin and in turn effecting the observed immunosuppression. Thus, FK506 and rapamycin are actually "prodrugs" and the ligand-immunophilin complex is the bioactive agent. The study of FK506 and rapamycin has also contributed to the understanding of ligand binding sites and molecular modeling with their implications towards rational drug design. The synthesis of 506BD represents the beginning of a structure-activity relationship study and demonstrates the practicality of a ligand structure based approach to enzyme ligand modeling.

REFERENCES

PHOTOCATALYTIC OXIDATIONS OF CHLOROPHENOLS ON TiO$_2$
SURFACE - MECHANISM OF THE PRIMARY EVENTS

Reported by Nenad Koska        April 30, 1992

INTRODUCTION

Water pollution is one of the major problems which is facing society today. New and efficient methods for waste water decontamination that are more general and cost effective than the presently employed techniques are needed. Since many of the materials which are considered pollutants are organic compounds an approach which has drawn a lot of attention is oxidation of organic contaminants by means of heterogeneous photocatalytic oxidation on semiconductor surfaces.\(^1\) A variety of organic contaminants can be transformed to innocuous CO$_2$ and other harmless inorganic products by the use of this approach. The photocatalytic oxidation of contaminants C$_x$H$_y$X$_z$ to benign products which is termed mineralization is shown below. It is worth mentioning that this method is not limited to organic contaminants, but also applies to removal of diverse inorganic pollutants.\(^1\)

\[
C_x H_y X_z \xrightarrow{h\nu, \text{TiO}_2, \text{O}_2, \text{H}_2\text{O}} x\text{CO}_2 + \frac{1}{2} y\text{H}_2\text{O} + z\text{HX}
\]

There are few semiconducting materials which satisfy requirements for prospective commercial application as photocatalyst.\(^1\) Strikingly, TiO$_2$ emerges as the most promising photocatalyst due to its high photocatalytic efficiency in the mineralization of a variety of organic contaminants, its stability under a wide spectrum of conditions, and its low price.\(^1,2\) This paper will focus on the mechanism of oxidation of organic compounds on TiO$_2$ surface under photocatalytic conditions. Since chlorinated phenols represent a significant class of water pollutants, numerous publications have dealt with their photocatalyzed degradation, so this report will represent the mechanism in the light of this class.\(^1,2,7-9,11,14,16\) It appears that, on basis of similarities in kinetics and observed intermediates, the primary events for a much broader class of organic compounds share the same features.

Copyright © 1992 by Nenad Koska
MECHANISM

Photocatalytic oxidation of aromatic molecules on TiO\textsubscript{2} surface is a complex, heterogeneous multistep process. To date much work has been dedicated to the study of primary processes and formation of the first few intermediates in the process.\textsuperscript{1,3a,3b} The subsequent steps which provide mineralization have not received much attention. A plausible mechanism would need to account for the stoichiometry of the reaction which requires dioxygen and water, the catalytic nature of the process, the intermediates observed and the kinetics.

Photoactivation Of TiO\textsubscript{2} Surface

Upon irradiation of TiO\textsubscript{2} with near UV light electrons from valence bands are excited to conductance bands forming electron-hole pairs, as shown in Scheme I. In a few nanoseconds electrons (e\textsuperscript{-} \textsubscript{cb}) are trapped by Ti\textsuperscript{4+} near or at the surface forming [TiO\textsubscript{2}......e\textsuperscript{-}] center.\textsuperscript{3a} In addition Serpone and coworkers suggest that in aqueous solution holes (h\textsuperscript{+} \textsubscript{vb}) are trapped by hydroxyl anions at the surface forming [TiO\textsubscript{2}......OH\textsuperscript{-}] adducts.\textsuperscript{3b} In the absence of other available processes fast recombination of these two trapped species will occur recovering original unexcited species and releasing absorbed energy in the form of heat.
Formation of trapped hole. Detection of the [ TiO₂⋯OH⁻] adduct is a major advance in the study of photoprocesses on TiO₂ surface in aqueous media.³ In their work Serpone and Meisel used transparent colloidal solutions of TiO₂ which have much better defined optical properties than the traditionally used suspensions thus allowing application of sophisticated spectroscopic techniques. They irradiated a N₂O saturated aqueous solution of TiO₂ with high energy electrons in order to generate hydroxyl radicals (eq 1 and eq 2) and spectroscopically followed formation and decay of transient species formed in reaction of hydroxyl radicals with TiO₂ particles (eq 3) at 370 nm.

\[
\begin{align*}
\text{H}_2\text{O} & \xrightarrow{\text{high energy } e^-} \text{OH}^-, \text{H}^+, e^-_{(aq)}, \text{H}_2, \text{H}_2\text{O}_2 & \quad (1) \\
\text{N}_2\text{O} + e^-_{(aq)} + \text{H}_2\text{O} & \rightarrow \text{OH}^- + \text{OH}^- + \text{N}_2 & \quad (2) \\
\text{TiO}_2 + \text{OH}^- & \rightarrow [\text{TiO}_2\cdots\text{OH}^-] & \quad (3)
\end{align*}
\]

They found the growth rate of newly formed species to be linearly dependant on [TiO₂⁻] concentration with \( k = 6.0 \times 10^{11} \text{ mol}^{-1}\text{s}^{-1} \) which is close to diffusion control. The species decays at a much slower rate \( k = 1.52 \times 10^9 \text{ mol}^{-1} \text{s}^{-1} \). When monitored at different wavelengths species forms and decays at the same rate as at 370 nm indicating the presence of just one kind of species. The authors suggest that that species is [TiO₂⋯OH⁻] and in further experiments they oxidize thiocyanate anion in surface dependent fashion consistent with the existence of surface bound hydroxyl radical with an estimated redox potential at 1.5 V approximately 1.3 eV above valence band.

Role of dioxygen. It has been observed that oxidation of organic substrates does not occur in the absence of dioxygen.⁴ The primary role of dioxygen is in scavenging trapped electrons, thus preventing recombination process. Also in the case of some aromatic compounds dioxygen might have an additional role in further decomposition of oxidized intermediates.⁴,¹⁴ Dioxygen is intimately involved in processes on the surface as shown by Bideau and coworkers, where reaction rates show dependence on dioxygen concentration on the TiO₂ surface, thus indicating a need for the absorbed dioxygen.⁵ Superoxide ion radical \( \text{O}_2^{\cdot-} \) produced in scavenging of trapped electrons, will subsequently produce hydrogen peroxide as proposed by Matthews and others (eq 4 - eq 8).⁴,⁶ Hydrogen peroxide does not participate in the photocatalyzed oxidations on TiO₂ surface as shown by Matthews.⁴
Hydroxylation of chlorophenols

**Langmuir-Hinselwood kinetic model.** The Langmuir-Hinselwood kinetic model has been successfully applied to the interpretation of a variety of TiO_2 photocatalyzed reactions. Briefly, the model enables the calculation of rates and the binding constants in liquid-solid heterogeneous systems. The kinetics of these reactions are often complicated due to solvent adsorption as well as the adsorption of different intermediates. Modifications which were used in order to account for these effects in the simple form of the rate law are concentration and binding constants of the intermediates and the other species which compete for the reactive sites on the TiO_2 surface.

**Transfer of hydroxyl radical.** The step which follows photoactivation of the TiO_2 surface is the transfer of hydroxyl radical from the trapped hole to organic substrate. This step is shown for hydroxylation of 4-chloro phenol (1) in Scheme II.

Serpone reports that six intermediates can be detected in photocatalytic oxidation of 1, the major one being hydroquinone (3). Apparently the reaction takes place on the surface of TiO_2.
because kinetics of the reaction fit Langmuir-Hinselwood model. However, the complexity of the system which includes the solvent, substrate and different intermediates has prevented quantitative treatment of data. Hydroquinone (3), which has been referenced as an intermediate by Serpone is a result of the attack by absorbed hydroxyl radical followed by scission of C-Cl bond. Spectroscopical detection of the initial radical adduct 2 is almost impossible in this reaction due to the physical character of the system. However, Getoff and Solar observe 2 in radiolysis studies, where reactive species is hydroxyl radical. They propose the same pathway for decay of 2 which is scission of C-Cl bond.

Other identified intermediates are benzoquinone (4) and dihydroxychlorobenzene (5). Explanations for formation of 4 and 5 are mostly speculative. Serpone and Pelizzeti have proposed in their earlier work that benzoquinone is formed from via semiquinone radical. To account for dihydroxychlorobenzene Pichat suggests dismutation of initially formed radical adduct as a minor pathway. In the same paper Pichat indicates photoinstability of benzoquinone and suggests presence of photoprocesses which are not photocatalytic.

The first step, addition of hydroxyl radical seems to be best understood especially after studies on the nature of the hole species by Serpone and Meisel. Additional proof for the existence of hydroxyl radicals has been offered by different groups for related reactions. EPR spectra, rate suppressions or complete inhibitions by hydroxyl radical scavengers point to the hydroxyl radical as reactive species. The identified intermediates in this reaction as well as in reaction with other aromatic compounds, and regio-isomers formed are consistent with the electrophilic attack of hydroxyl radical. The kinetic studies show that hydroxyl radical is formed and transferred on the surface of the photocatalyst. This appears to be the dominant pathway to hydroxyl radical. The hydrogen peroxide which is formed in reaction has too low extinction coefficient to give a significant amount of photoproduced hydroxyl radical and it has been shown that addition of hydrogen peroxide to the reaction mixture has no effect on the reaction rate.

**Table I. Initial Rates of Chlorophenols Decomposition**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>( r_0 ) (( \mu \text{mol h}^{-1} ))</th>
<th>( t_{1/2} ) (min)</th>
<th>( t_{99%} ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-chlorophenol</td>
<td>4.30</td>
<td>26.5</td>
<td>80</td>
</tr>
<tr>
<td>3-chlorophenol</td>
<td>4.10</td>
<td>37.5</td>
<td>110</td>
</tr>
<tr>
<td>2-chlorophenol</td>
<td>4.20</td>
<td>34</td>
<td>120</td>
</tr>
</tbody>
</table>

a) source : ref 14  b) \( C_0 = 20 \text{ mg/L} \)
Pichat's study\textsuperscript{14} of photocatalytic degradation of 2-chlorophenol and 3-chlorophenol on TiO\textsubscript{2} indicate analogous mechanism to the one proposed for 4-chlorophenol. The initial rates (r\textsubscript{0}) half-lives and times required for 99% decomposition of these three chlorophenols are given in the Table I.

SECONDARY PROCESSES
Processes which follow the formation of primary intermediates and which result in complete decomposition of the original substrate are not well understood due to the difficulties in identification of a number of secondary intermediates which are present in low concentrations and strongly bound to the photocatalyst surface. Also, photo-processes which are not catalytic in nature have been suggested as one of the pathways of degradation of primary intermediates. The mechanisms proposed for this stage of the degradation process are mostly speculative. However, there are two observations which are worth noting: carbonyl compounds are observed\textsuperscript{14} and the initial drop in pH is larger than what can be expected from amount of HCl released, implying the presence of carboxylic acids.\textsuperscript{7,9}

EFFECT OF pH ON INITIAL RATES
The general pattern of pH effect on initial rates can be summarized as follows: in the regions of very low pH values the initial rates are diminished and pH dependent; in the region of medium pH values rates are fairly constant and pH independent and in the region of high pH values initial rates are significantly increased and pH dependent. Chlorophenols follow this general behavior, with the pH independant region from pH=3-9. To account for these effects of pH, two explanations have been suggested. One explains the effect in terms of changing absorption/desorption properties of the species involved in the processes on the surface.\textsuperscript{7} The other explanation would be that generation of hydroxyl radical is decreased by depletion of hydroxyl ions under conditions of very low pH values and increased under conditions of high pH values.\textsuperscript{14} The latter suggestion does not appear to explain pH independant region. A mode in which both interactions are operating is also possible, so further kinetic studies will be needed to determine the nature of the pH effect.

EFFECT OF COMMON INORGANIC ANIONS
The presence of common inorganic anions can reduce rates of photocatalyzed oxidations of organic molecules on TiO\textsubscript{2} surface. Common inorganic anions such as: chloride, sulphate, nitrate and phosphate can be found in waste waters, so from a practical point of view their effect on photocatalytic activity is very important. Presently, there are no studies of the influence of these inorganic anions on the photocatalyzed oxidations of chlorophenols. However, the studies
which were done investigated effects on quite diverse substrates, gave very similar conclusions thus giving a basis for assumption that same effect might be expected in case of chlorophenols.\textsuperscript{15} Results of studies done by Matthews and coworkers indicate that chlorides, sulphates and phosphates markedly reduce photocatalytic activity of TiO$_2$ at millimolar concentration. However, the initial effect quickly becomes concentration independent and the photocatalyst still renders significant activity even in the presence of high concentrations of these anions. Nitrate and perchlorate anions do not affect activity of the photocatalyst, therefore indicating absence of any common salt effect. Matthews has tested a few kinetic models and has suggested that the reduction of catalytic activity is the result of scavenging (eq\textsuperscript{9}-eq\textsuperscript{10}) of hydroxyl radicals by sulfate and dihydrogenphosphate anions. Residual activity of the photocatalyst is then ascribed to the newly formed radicals which are able to oxidize organic substrates (eq\textsuperscript{11}).

\begin{align}
\text{[TiO}_2\text{-OH}^-] & + \text{SO}_4^{2-} \rightarrow \text{TiO}_2\text{ (solid)} + \text{OH}^- + \text{SO}_4^{2-} \quad (9) \\
\text{[TiO}_2\text{-OH}^-] & + \text{H}_2\text{PO}_4^- \rightarrow \text{TiO}_2\text{ (solid)} + \text{OH}^- + \text{H}_2\text{PO}_4^- \quad (10) \\
\text{SO}_4^{2-} / \text{H}_2\text{PO}_4^- + \text{S} & \rightarrow \rightarrow \rightarrow \text{CO}_2 \quad (11)
\end{align}

**PHOTOCATALYZED OXIDATIONS OF OTHER ORGANIC COMPOUNDS ON TiO$_2$ SURFACE**

Many of organic compounds have been successfuely mineralized by photocatalyzed oxidations on TiO$_2$ surface.\textsuperscript{1,2,16} It appears that formation of primary intermediates via hydroxyl radical transfer on TiO$_2$ surface is the common process, especially for aromatic compounds. However, primary intermediates degrade in quite unique ways due to the differences in absorption/desorption properties, photostability and availability of other processes. Primary steps in the decomposition of 4-chlorophenol which is presented in this paper is quite typical for the whole class of aromatic compounds.

**CONCLUSION**

Photocatalytic processes on the TiO$_2$ surface have received considerable attention over the last ten years. The degradation of numerous compounds have been investigated. Recently, there have been several studies dedicated to elucidate the mechanism of these processes which resulted in significant understanding of the primary events.

Photocatalyzed oxidations on TiO$_2$ as a method of decontamination of waste waters is a process with a bright future. The generality of the approach, low cost, and high activity under a variety of conditions surely support this claim. However, optimization of the process employing this type of degradation will require better understanding of the mechanism, especially that of
secondary processes. Newly developed research techniques which employ much better optically defined transparent colloidal TiO$_2$ solutions are promising and may contribute to the better understanding of the process in the future.

REFERENCES


(16) Pelizzetti, E.; Serpone, N. Homogenous and Heterogeneous Photocatalysis; D.Reidel Publishing Company; Dordecht, 1986, pp 651-656

[3+2] CYCLOADDITIONS OF TRIMETHYLENEMETHANE-PALLADIUM COMPLEXES

Reported by Steven Lee
April 23, 1992

Introduction

In the field of cycloaddition chemistry, the Diels-Alder [4+2] reaction holds a prominent position as one of the most thoroughly investigated reactions in terms of utility, regio- and stereoselectivity, reactivity, and mechanism. Because it is well understood, organic chemists can apply this reaction towards the synthesis of six-membered rings with almost infallible predictability. Unfortunately, there has been no corresponding procedure for the formation of five-membered rings. Although there are several five-membered ring syntheses available, none possesses the high yields and selectivity of the Diels-Alder reaction. However, recent investigations of [3+2] cycloadditions of α,α'-bifunctionalized reagents 1 with double bonds have revealed a potentially powerful sequence of steps to give the five-membered rings 3. The sequence is shown in Scheme I.

Scheme I: [3+2] Cycloaddition Sequence for the Trimethylenemethane-Palladium Complex

Reaction of 1 with an organometallic catalyst is considered to form the reactive species 2, a trimethylenemethane (TMM) metal complex. This in turn cyclizes with an unsaturated system to yield 3. This report will discuss the reactions and mechanism of the [3+2] cycloaddition of the TMM-Pd complex 2 with double bonds to form five-membered carbocyclic and heterocyclic rings.

The [3+2] Cycloaddition Reaction with Carbon-Carbon Double Bonds

The [3+2] cycloaddition is well-established for reactions which involve a heteroatomic 1,3-dipole and an unsaturated dipolarophile. However, the reactions have been confined to the preparation of heterocycles only.
Recent work by Trost has significantly extended the former [3+2] cycloaddition, as shown in Scheme II. The most common TMM metal complex 5 can be formed by reacting the \( \alpha \)-acetoxyallyl silane 4 with a Pd(0) catalyst. This complex then reacts with an alkene 6 activated with an electron withdrawing carbonyl, sulfonyl, or cyano group to form substituted methylenecyclopentanes 7. Reaction with an electron rich olefin yields no reaction.

**Scheme II**: The Typical TMM Reaction

![Diagram of TMM Reaction]

The simplest and most studied TMM precursor is 2-((trimethylsilyl)methyl)-3-acetoxy-1-propene, 4. The allyl silyl group behaves as a carbanion equivalent and the acetoxy group as a carbocation. Replacing the silyl group for a stannyl group - usually found to lead to a more reactive carbocation - results in lower yields, presumably because this precursor is unstable. Other electron withdrawing groups, besides the acetoxy group, such as sulfonyl and cyano groups have been used successfully in similar precursors to give TMM equivalents.

Two catalytic systems have been reported frequently. The first was 1-4 mol % tetrakis(triphenylphosphine)palladium ((Ph\( _3 \)P)\( _4 \)Pd) with 3-9 mol % bis(diphenylphosphino)-ethane (DPPE, Ph\( _2 \)PCH\( _2 \)CH\( _2 \)PPh\( _2 \)). Without DPPE, yields were slightly lower. The second catalytic system was generated in situ from palladium(II)acetate with 6-8 equivalents of triisopropylphosphite ((O-i-Pr)\( _3 \)P) relative to Pd. The reactive catalyst is considered to be a (O-i-Pr)\( _3 \)PnPd species, where n = 3 or 4. The evidence for this assignment is that no cycloaddition reaction occurs with Pd(OAc)\( _2 \) only, and there is precedence of the in situ generation of Pd(0) species. This second catalyst has been shown to generally improve yields of the cycloaddition and lower the amount of side products.

Table I shows typical reactions of 4 with several olefins. Entry 1 shows that the electron poor olefin is reacted without detection of product from reaction at the unactivated olefin. Entries 2, 3 and 4 reveal that the stereochemistry of the dipolarophile is largely maintained in the product, but the \textit{trans} isomers do show a higher stereoselectivity. Entries 2 and 3 also show that solvent makes a difference in yields, with THF giving slightly higher yields than toluene. The fact that different catalysts play a strong role in the yields of the products is seen in all entries. Reaction conditions A were used in the initial trials and gave moderate to good reactivity. Reaction conditions B were used more recently and have shown better results in higher yields and selectivity.
Table I: Reactions of 4 with Alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Reaction Conditions</th>
<th>Products</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>A, THF reflux</td>
<td>4 : 1</td>
<td>75 %</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>4 : 1</td>
<td>98 %</td>
<td>4b</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>A, THF reflux</td>
<td>&gt;99 : 1</td>
<td>32 %</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A, PhCH₃, 100°C</td>
<td>&gt;99 : 1</td>
<td>10 %</td>
<td>6b</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>A, THF reflux</td>
<td>1 : 1.3</td>
<td>60 %</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A, PhCH₃, 100°C</td>
<td>1 : 25</td>
<td>50 %</td>
<td>6b</td>
</tr>
<tr>
<td>4</td>
<td>Ph(CH₂)₂</td>
<td>B</td>
<td>&gt;99 : 1</td>
<td>95 %</td>
<td>4a</td>
</tr>
<tr>
<td></td>
<td>Ph(CH₂)₂</td>
<td>B</td>
<td>2 : 98</td>
<td>93%</td>
<td>4a</td>
</tr>
</tbody>
</table>

*a: E = CO₂Me. b: Reaction conditions A: 3.8-8.8 mol % (Ph₃P)₄Pd and 1.5-3.9 mol % DPPE; conditions B: 0.1-5 mol % (OAc)₂Pd and 6-8 equivalent relative to Pd of (iPrO)₃P. b: reaction time of 210 hrs.*

The Mechanism of Cycloaddition

The mechanism of the TMM cycloaddition is considered to be a stepwise mechanism because of the loss of geometry in the products with respect to the alkene. The mechanism proposed by Trost is shown in Scheme III for the reaction between 4 and a cis isomer of an alkene 6.⁴

In the first step, the nucleophilic Pd(0) catalyst attacks the precursor 4 and the acetoxy group leaves. The Pd then shifts from a σ bond to an allyl complex. In the next step, the acetoxy group adds to and removes the silyl group to leave a TMM-Pd complex, which could have two different structures, 10a or 10b. The reactive complex attacks the π bond of 6 and forms the zwitterionic species 11. From this species, the reaction has two options. The reaction can complete the cyclization without rotation of the carbon-carbon bond of 11 so that the original cis geometry is retained as in 12a. The second option would be to rotate about the σ carbon-carbon bond of 11 in order to relieve the steric hindrance between the two cis groups into 11b and then complete the cyclization to form the trans product 12b.

The nature of TMM-metal complexes have been well studied since the first isolation of the TMM-Fe complex by Emerson in 1966.⁷⁻⁹ X-ray diffraction studies of the iron complex indicated a neutral π⁴ complex where the metal is equally bonded to all four carbons as in 10b.⁷a Similar results were obtained with Mo, Os, Ru and Ir complexes.⁷d,e However, the Pd complex
has been too elusive to be directly observed. Theoretical molecular orbital calculations of the Pd complex imply that it is more stable when Pd is bonded to only three carbons as in a zwitterionic \( \eta^3 \) allyl complex 10a, where there are three equivalent carbons with one carbon remaining as a carbanion.\(^{10}\) However, none of this data supplies any evidence for the actual reactive complex in the mechanism. Logic would simply dictate that the reactive species should be 10a because it contains a carbanion and since the TMM-Pd has been shown to react exclusively with electron deficient alkenes only.

**Scheme III: Proposed Mechanism**

![Scheme III: Proposed Mechanism](image)

Labeling studies provide further evidence for a \( \eta^3 \) TMM-Pd complex.\(^{10}\) The precursor 4 labeled with deuterium at the allyl position next to the acetoxy group reacted with the fast trap sodium dimethyl malonate to yield scrambling over only two of the methylene groups. This would indicate that the reactive complex has only two equivalent methylene groups and not three. Reaction with a slow trap like cyclopentenone shows scrambling through out all three methylene groups. This would indicate that both the silyl and acetoxy group are removed in separate steps before the cyclization. This evidence is consistent with the proposed mechanism with an \( \eta^3 \) TMM-Pd complex.

When additional alkyl substituents are placed on the TMM precursor, the products of the reactions imply the same mechanism.\(^{11}\) Placing one alkyl group at either \( \alpha \)-allyl position strongly favors one regioisomer independent of the original position of the alkyl group on the
precursor. The major product places the alkyl group at the allyl and not the vinylic position. Thus the data currently is consistent with the mechanism proposed in Scheme III.

The Intramolecular Cycloaddition Reaction

The reactions discussed above have all been intermolecular reactions, but new results explore the possibilities of the intramolecular alternative. A general sample of intramolecular reactions is presented in Table II.

Table II: Intramolecular Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Products</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcO&lt;sub&gt;n&lt;/sub&gt;</td>
<td>A, DME or THF, BSA</td>
<td>65%</td>
<td>12a</td>
</tr>
<tr>
<td></td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;n&lt;/sub&gt;</td>
<td></td>
<td>1.2 : 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>n = 2 trans</td>
<td>B, THF, BSA</td>
<td>73%</td>
<td>12a</td>
</tr>
<tr>
<td>3</td>
<td>n = 2 cis</td>
<td>B, THF, BSA</td>
<td>67%</td>
<td>12a</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>B, THF</td>
<td>62 - 78%</td>
<td>12b</td>
</tr>
</tbody>
</table>

a: E = CO<sub>2</sub>Me, SO<sub>2</sub>Me. b: Reaction conditions A (Ph<sub>3</sub>P)<sub>4</sub>Pd/DPPE; B (OAc)<sub>2</sub>Pd/(O-i-Pr)<sub>3</sub>. c: BSA - N,O-bis(trimethylsilyl)acetamide. d: Yields shown are for the cycloadducts only.

The reactions were carried out with both types of catalytic systems to afford bicyclic and tricyclic products. The formation of [3.3.0] bicyclic structures, entry 1, resulted in only one cycloadduct in 65% yield, along with the elimination product. Only the cis cyclic product is seen, as would be expected for small-membered rings. The addition of BSA reduced the amount of elimination product. When [4.3.0] bicyclics were formed, entries 2 and 3, the elimination product was only a minor product, but two diastereomers were formed. Entry 2 started with a trans dipolarophile and the major product maintained its geometry. However, when the corresponding cis isomer was used as shown in entry 3, the product which maintained the geometry was the minor one. When larger bicyclic rings were attempted, only elimination
products were formed. Entry 4 shows that tricyclic products can also be formed in good yields, with a ring as large as a 12-membered component.

The Cycloadditon Reaction with Heteroatomic Double Bonds

These reactions discussed above have been with carbon-carbon double bonds to yield cyclopentanes, but reactions with heteroatomic double bonds have also been shown to occur. They are shown in Table III. The change in dipolarophiles also involves a change in the catalyst. Precursor 4 has been shown to react with aldehydes using the Pd(0) catalyst and a tin co-catalyst as in entries 1 and 2. Tin is considered to act as a Lewis acid to increase the rate of nucleophilic attack to the aldehyde.

**Table III: Reaction of 4 with Aldehydes and Imines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heteroatomic Double Bond</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph=CH2</td>
<td>5 mol % Pd(OAc)2, 25 mol % Ph3P, 20 mol % n-Bu3SnOAc</td>
<td>![Product 1]</td>
<td>89 %</td>
<td>13b</td>
</tr>
<tr>
<td>2</td>
<td>![Heteroatomic Double Bond 2]</td>
<td></td>
<td>![Product 2]</td>
<td>94 %</td>
<td>13b</td>
</tr>
<tr>
<td>3</td>
<td>Ph=NPh</td>
<td>5 mol % Pd(PPh3)4, PhCH3 reflux 12 hrs</td>
<td>![Product 3]</td>
<td>19 %</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>![Heteroatomic Double Bond 4]</td>
<td></td>
<td>![Product 4]</td>
<td>77 %</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Ph=CH(NPh)</td>
<td>5 mol % Ni[P(OEt)3]4, PhCH3 reflux 12 hrs</td>
<td>![Product 5]</td>
<td>69 %</td>
<td>14</td>
</tr>
</tbody>
</table>

Reaction of the methylsulfonyl analogue of the TMM precursor 4, with imines produces pyrrolidones as shown in entries 3 - 5. Entry 3 shows that use of the Pd catalyst results in a low yield. But a nickel catalyst, as shown in entry 4, gives a much higher yield. Entry 5 shows that the nickel catalyst yields the [3+2] imine cycloadduct in good yield without any detection of cyclization with the olefin or of the [3+4] cycloadduct. The nickel catalyst remarkably has also been shown to catalyze reactions with electron deficient olefins in good yields.
The Cycloaddition Reaction with Other Precursors

The reactions discussed so far have been limited to those with the TMM-metal complexes in [3+2] cycloaddition. However, numerous other related reactions have been reported.\textsuperscript{15} Use of heteroatomic TMM analogues have recently exhibited success.\textsuperscript{16} The [3+4] cycloaddition with dienes have also been shown to occur, but with only slightly higher chemoselectivity over the [3+2] cycloaddition.\textsuperscript{17} Methylene cyclopropane also provides some interesting chemistry, although it undergoes a [2+2] cycloaddition with double bonds.\textsuperscript{18} Metallocyclobutane have recently been thought to be a precursor to the TMM-metal complex, however only synthesis of the precursors has been completed as of yet.\textsuperscript{19}

Conclusion

The need for simple synthetic routes towards cyclopentane derivatives is suggested by the countless examples of natural products and biologically active compounds with five-membered rings. Although there are several methods of producing these compounds, the [3+2] cycloaddition of TMM-Pd complexes offers a unique, efficient method with a versatile range of possibilities. The use of a TMM complex, as opposed to an allyl analogue, has the advantage of installing an exocyclic double bond in methylene cyclopentane, which can be used for further elaboration. For instance, the double bond can be isomerized into the ring or oxidatively cleaved into a carbonyl which can be alkylated at its $\alpha$ positions. The use of the intramolecular version extends the applicability even further by its ability to form multicyclic structures. The reaction is also synthetically efficient in terms of atom economy because only the two components of the cycloaddition and a catalytic system is required. This reaction can be expanded beyond other cycloadditions, beyond other TMM precursors, and beyond other transition metals. Thus the possibilities seem to be limited only by nature and the chemist's imagination.

References


(17) Trost, B. M.; Nanninga, T. N.; Chan, D. M. T. Organometallics. 1982, 1, 1543.


CIEPLAK MODEL FOR THE ADDITION TO EXOCYCLIC DOUBLE BONDS

Reported by Stephen C. Wilkie April 27, 1992

INTRODUCTION

A variety of models which can be used to understand and predict the course of stereoselective additions to carbonyl and methylene groups have been put forward and debated in the past 50 years. The earliest models dealt with steric interactions, for nucleophilic additions to carbonyl groups, but further experimentation suggested those models were incomplete and others were suggested. However, none of the models could successfully predict the stereochemical results observed. Recently, a stereoelectronically based model developed by Cieplak has proven to be fairly successful at predicting the stereochemistry of the products of nucleophilic addition to carbonyl groups and electrophilic addition to exocyclic methylene groups. The accuracy and usefulness of Cieplak's model is a matter of current debate. This report will focus on the Cieplak model and address the controversy surrounding it.

BACKGROUND

Work on the stereoselective reductions of carbonyls, and attempts to explain the results of these reductions first came into prominence in the early 1950's. This early work by Dauben, Cram, Karabatsos, and Felkin dealt exclusively with the steric interactions associated with the reductions of carbonyls. In the Cram and Karabatsos models, shown in 1 and 2, the nucleophile adds from the side of the small group. Due to the steric interactions associated with nucleophilic attack in the transition state this is considered the lowest energy trajectory for attack. While Felkin also believed that attack came from the side of the small group, he also stated that to ease steric strain in the transition state the large group should be as distant as possible from the incoming nucleophile. Thus, Felkin postulated that major attack will take place antiperiplanar to the largest group, as shown in 3. Work on the reduction of cyclic ketones, such as cyclohexanones, however gave products that were not consistent with the models.

Further efforts due to Anh and Klein led to proposals which included stereoelectronic factors in predicting the favored enantiomeric product. Klein's model for cyclohexanones was based on the assumption that interactions with the C-C bonds electronically differentiates the faces of the carbonyl group. Thus, electrophiles will be expected to attack from the side with the highest HOMO and nucleophiles from the direction of the lowest LUMO. However it was shown that in most cases for both...
electrophiles and nucleophiles attack came from the equatorial side, casting doubt on the Klein proposal. Anh improved on the Felkin model by adding a stereoelectronic component. In Felkin's model, the nucleophile attacks antiperiplanar to the largest group. Anh stated that instead of the sterically largest group the antiperiplanar group should be the one with the lowest σ* orbital. The Felkin-Anh model, as it is called, is probably the most accepted model for nucleophilic addition to the carbonyl group to date. However, the search for a better model continued.

Cieplak, in 1981, developed his model for the prediction of the stereochemical results of reductions of cyclic carbonyl groups. The Cieplak model is based on the stabilization of the electron deficient incipient carbon-nucleophile bond. Given the stretched and polarized nature of this incipient bond, Cieplak expects it to have a low-lying σ* orbital. Thus, as shown in the kinetic anomeric effect the major product will come from attack at the carbonyl from the direction which gives the greatest stabilization of the incipient bond. Therefore, the electron donation by the antiperiplanar bond will stabilize the low-lying σ* orbital of the incipient bond and define the preferred direction of attack by the incoming nucleophile. Due to microscopic reversibility, this donation into the antibonding σ* orbital, which we would expect to stabilize bond breaking will also stabilize bond making. The Cieplak model should apply to both electrophilic and nucleophilic additions. This abstract will discuss the Cieplak model and the controversy surrounding it.

NUCLEOPHILIC REACTIONS CONSISTENT WITH THE CIEPLAK MODEL

As with most models for reductions of carbonyl groups, the Cieplak model must balance stereoelectronic factors with the steric influences associated with nucleophilic attack. Most of the experimentation done to test the Cieplak model has utilized cyclohexanone, 2-adamantanone, and 7-norbornanone because these systems have small steric bias, well defined structures which allow a clear identification of the antiperiplanar bonds, and straight forward determination of product stereochemistry.

Despite the fact it does have the most steric bias of the three systems shown, the cyclohexanone system is the most common system studied. The antiperiplanar bonds for
axial and equatorial attack are respectively, the axial C\textsubscript{2} and C\textsubscript{6} carbon-hydrogen bonds, shown in 4, and the C\textsubscript{2}C\textsubscript{3} and C\textsubscript{5}C\textsubscript{6} bonds, shown in 5. The Baker-Nathan order of electron donors, which states that a carbon-hydrogen bond is a better donor than a carbon-carbon bond (*vide infra*)\(^6\) and is the basis of electron donating ability in the Cieplak model, predicts the stereoelectronic product should come from axial attack. The predicted product if steric effects dominate, on the other hand, should come from equatorial attack. Thus, the stereochemistry of the major product is determined by a combination of electron donation and steric factors, with the corresponding product attributed to whichever factor dominates in that case. By changing the C-3 substituents 6 from electron donating to electron withdrawing the electron donation ability of the C\textsubscript{2}C\textsubscript{3} bonds, and hence the axial/equatorial ratio, should change if the Cieplak effect is important. Since the C-3 substituents will prefer the equatorial position, they will have little steric effect. Experimentally, the axial/equatorial product ratio varies as the C-3 groups change, as shown in Table I. With electron donating substituents such as Si(CH\textsubscript{3})\textsubscript{3} and t-Bu, there is about a 85% equatorial attack by methyl lithium. With electron withdrawing substituents, the percent of equatorial attack by methyl lithium decreases, in the case of CF\textsubscript{3} 50% is observed.\(^3\) Therefore, while the major product is inconsistent with the Cieplak model, due to dominating steric factors, the observed trend for 3-substituted cyclohexanones does follow the Cieplak predicted results. While the ΔΔG\textsuperscript{‡} values are quite small the trend observed in the axial/equatorial product ratios is significant.

![Diagram](image)

**Table I.** Addition of Methyl Lithium to Selected 3-substituted Cyclohexanones, R= CH\textsubscript{3}.

<table>
<thead>
<tr>
<th>X</th>
<th>% 7 (ax)</th>
<th>% 8 (eq)</th>
<th>ΔΔG\textsuperscript{‡} (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si(CH\textsubscript{3})\textsubscript{3}</td>
<td>15</td>
<td>85</td>
<td>0.11</td>
</tr>
<tr>
<td>t-Bu</td>
<td>19</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>34</td>
<td>66</td>
<td>-0.30</td>
</tr>
<tr>
<td>CF\textsubscript{3}</td>
<td>50</td>
<td>50</td>
<td>-0.56</td>
</tr>
</tbody>
</table>
While cyclohexanone is one of the most frequently used systems for study, it is not an ideal system because of its steric bias. A better system is a 2-adamantanone, which contains the same steric effects for attack for either face of the carbonyl. As with cyclohexanones the conformational rigidity allows easy identification of the antiperiplanar bonds and C-5 substituents can affect the electronics of the C1C9 and C3C4 bonds, which are the bonds antiperiplanar to anti attack 9. Changes in the electron donating power of the C-5 substituents should result in changes of the ratio of the alcohol products. Given the distance over which the electronic effects must occur, the observed affects are not large but a definite trend is observed. Electron donating substituents, such as OH and Sn(CH3)3, result in around 60% of the Z alcohol from anti attack. Electron withdrawing groups change this ratio, up to 61% E alcohol from syn attack, Table II.7

![Reaction Scheme](image)

**Table II.** Reduction of Selected 5-substituted 2-Adamantanones by Sodium Borohydride.

<table>
<thead>
<tr>
<th>X</th>
<th>% 10 (anti)</th>
<th>% 11 (syn)</th>
<th>ΔΔG‡ (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sn(CH3)3</td>
<td>63</td>
<td>37</td>
<td>0.14</td>
</tr>
<tr>
<td>OH</td>
<td>57</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>42</td>
<td>58</td>
<td>-0.33</td>
</tr>
<tr>
<td>CF3</td>
<td>41</td>
<td>59</td>
<td>-0.35</td>
</tr>
<tr>
<td>CO2CH3</td>
<td>39</td>
<td>61</td>
<td>-0.39</td>
</tr>
</tbody>
</table>

Other systems which closely resemble the 2-adamantanones are the three 5-azaadamantan-2-one analogs 12-14, which have been synthesized and used to study the Cieplak effect. The structures of all three have been shown to be similar to the 2-adamantanone skeleton studied previously. The sodium borohydride reduction of all three gave an E/Z product ratio determined to be around 90/10 in all three cases. In order to test for effects caused by the charge of the aza groups these reductions were also carried out in water, which should solvate the charge and minimize any charge effects. However, these reductions proved to give similar results to the reductions in THF.8 Given the electron withdrawing nature of the aza groups, these results support the Cieplak model.
The 7-norbornanone system 15 has been used to study the Cieplak model.\(^2\) In fact, the geometry of the electron withdrawing and donating groups with respect to the antiperiplanar bonds should give a wider range of anti/syn attack ratios than for the 2-adamantanone systems. The 2,3-endo, endo substituents should alter the stereoelectronics of the addition without altering the steric effects. A variety of electron withdrawing and donating groups have been put in these positions and the effect on the product ratio has been investigated. The placement of electron withdrawing groups in these positions has produced 16% product from anti attack. When the electron donating ability of the groups increased, the product from anti attack increased, going up to 80% for two ethyl groups, Table III.\(^9\) Once again, these results agree with that predicted by the Cieplak model.

**Table III.** Reduction of Selected 2,3-endo, endo-disubstituted 7-Norbornanones by Sodium Borohydride.

<table>
<thead>
<tr>
<th>X</th>
<th>% 16 (syn)</th>
<th>% 17 (anti)</th>
<th>(\Delta G^\ddagger) (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO(_2)CH(_3)</td>
<td>84</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>CH(_2)OCH(_3)</td>
<td>40</td>
<td>60</td>
<td>-1.32</td>
</tr>
<tr>
<td>-CH=CH(_2)</td>
<td>36</td>
<td>64</td>
<td>-1.41</td>
</tr>
<tr>
<td>CH(_2)CH(_3)</td>
<td>20</td>
<td>80</td>
<td>-1.85</td>
</tr>
</tbody>
</table>

**ELECTROPHILIC REACTIONS CONSISTENT WITH THE CIEPLAK MODEL**

Under the Cieplak model, the same factors that govern nucleophilic addition should apply to electrophilic addition. In order to study electrophilic attack, exocyclic methylene analogs of the cyclohexane, adamantane, and norbornane systems were reacted with either mercuric acetate or \(m\)-chloroperoxybenzoic acid (\(m\)CPBA) to give the corresponding methyl carbinols following workup. The direction of attack was determined by analysis of the enantiomers after conversion to the methyl carbinols.
As with nucleophiles the Cieplak model correctly predicts the trends observed with electrophiles. As shown for the methylenecyclohexane systems 18, electron donating substituents give predominately equatorial attack, while electron withdrawing groups give predominantly axial attack, Table IV.\(^\text{10}\)

![Reaction Diagram]

**Table IV.** Electrophilic Addition to Selected 3-substituted Methylenecyclohexanes.

<table>
<thead>
<tr>
<th>X</th>
<th>% 19 (ax)</th>
<th>% 20 (eq)</th>
<th>ΔΔG(^\ddagger) (kcal)</th>
<th>% 19 (ax)</th>
<th>% 20 (eq)</th>
<th>ΔΔG(^\ddagger) (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si(CH(_3))(_3)</td>
<td>40</td>
<td>60</td>
<td>0.40</td>
<td>52</td>
<td>48</td>
<td>0.18</td>
</tr>
<tr>
<td>t-Bu</td>
<td>58</td>
<td>42</td>
<td>0</td>
<td>60</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>p-C(_6)H(_4)CF(_3)</td>
<td>70</td>
<td>30</td>
<td>-0.28</td>
<td>75</td>
<td>25</td>
<td>-0.38</td>
</tr>
<tr>
<td>CF(_3)</td>
<td>92</td>
<td>8</td>
<td>-1.14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A study of the reaction of 5-fluoro-2-methyleneadamantanes with \(m\)CPBA has also been reported. For this system with the electron withdrawing fluorine group a preference for the syn attack has been determined. This matches the results expected for the Cieplak model.\(^\text{11}\)

Some work with the similarly sterically unbiased 7-methylenenorbornane system has been done. Only ester and ethyl groups in the 2,3-endo, endo positions have been used for studying this system. However, since these cases did prove to be the two extremes for nucleophilic addition to the 7-norbornanone system they should be a good test of the application of the Cieplak model to electrophilic reactions. For the \(m\)CPBA epoxidation this has indeed proved to be the case, with the electron withdrawing ester groups a 74/26 syn/anti attack ratio is observed in the products. For the electron donating ethyl groups a 30/70 syn/anti attack ratio was produced.\(^\text{12}\)

This experimental evidence for both nucleophilic and electrophilic addition to carbonyl groups and olefins respectively lends support to the Cieplak model. In sterically unbiased cases the Cieplak model not only predicts the correct products, but the trends observed upon changing the stereoelectronics of the antiperiplanar bonds. The variety of nucleophilic and electrophilic reagents used, show that the model is not reagent specific and suggests it is general.
EXCEPTIONS TO THE CIEPLAK MODEL

Despite its success the Cieplak model is not without its limitations. One of the most fundamental disputes about the Cieplak model came from its dependence on the Baker-Nathan order of electron donors. There have been a number of publications reporting evidence disputing the Baker-Nathan order based on experimental evidence inconsistent with the Baker-Nathan order of carbon-hydrogen bonds being better electron donors than carbon-carbon bonds. Although none of these results have unquestionably proven the Baker-Nathan order wrong, serious doubts have been cast on the exact order of electron donation. If the Baker-Nathan order of electron donation is incorrect the premise of the Cieplak model would be destroyed.

Recently Houk has published experimental work on ketone reductions which he believes contradicts the Cieplak model. One example from Houk's work is the reduction of the benzocycloheptenone 21. The ground state of 21 has been shown to adopt a "chair-like" conformation 21, which is similar to that of cyclohexane. The Cieplak model would predict that the major product be that from axial attack. However, Houk has shown that reduction of benzocycloheptenone 21 with lithium aluminum hydride (LAH) proceeds predominantly from the equatorial direction. Le Noble has explained this result by consideration of a transition state such as 22. If delocalized as shown, the axial face will be much more sterically crowded than the equatorial face. Thus Le Noble claims the results obtained are not contradictory to the Cieplak model because there is another factor which overrides that of electron donation.

Another limitation of the Cieplak model was suggested by Hutchins in his study on the hydride reduction of cyclohexyl imines and enamines. Hutchins data show a wide range of results with no obvious trends, and a predominance of the anti-Cieplak product arising from equatorial attack. Given that these molecules contain exocyclic double bonds in the ground or transition states, the expected product would be the axial attack product as predicted by the Cieplak model. However, taking into account the increased sterics from the two nitrogen R groups it could be that steric effects are the dominant factor in these cases, so these are not results contradictory to the Cieplak model. A number of other exceptions to the model have also been reported.
The small ratios between the products in the tests of the Cieplak model is a point of concern. While the ratios themselves are quite small, definite trends have been observed to follow the predictions of the Cieplak model. In an attempt to address the problems of small ratios, new compounds, such as those designed by le Noble and discussed in the nucleophilic addition section, are being studied.8,9,12

CONCLUSION

The Cieplak2 model is one of the most recent in a long line of models which attempt to predict the stereoselectivity of additions to carbonyls or methylenes. It has proven to provide an effective rational for the test systems of cyclohexane, adamantane, and norbornane. While the Cieplak model has proven to be effective in three cases, there is still some doubt as to its usefulness. Perhaps the most serious theoretical question about the Cieplak model is that of its basic premise, the correct order of the Baker-Nathan effect.6 In summary, the Cieplak model appears to be the best of the current models for nucleophilic or electrophilic addition reactions. Nonetheless is has limitations which will need to be addressed before it will be more universally accepted.

REFERENCES


ORGANIC SEMINAR ABSTRACTS
1992-93, SEMESTER I

University of Illinois

Department of Chemistry
Box 68 Roger Adams Laboratory
1209 West California Street
Urbana, Illinois 61801-3731

February, 1993

Copyright © by The Board of Trustees of the University of Illinois
NOTICE: Return or renew all Library Materials! The Minimum Fee for each Lost Book is $50.00.

The person charging this material is responsible for its return to the library from which it was withdrawn on or before the Latest Date stamped below.

Theft, mutilation, and underlining of books are reasons for disciplinary action and may result in dismissal from the University.

To renew call Telephone Center, 333-8400

UNIVERSITY OF ILLINOIS LIBRARY AT URBANA-CHAMPAIGN
**SEMINAR TOPICS**

**Semester II, 1991-92**

<table>
<thead>
<tr>
<th>Non-Linear Effects in Organic Synthesis</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Jonathan Brice</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Three Contrasting Syntheses of the Denticulatins</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Todd Spradau</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ziegler-Natta Polymerization Using Chiral Zirconocene Reagents</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennifer M. Galvin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structural Features of Efficient Nonlinear Optical Materials: Conjugated, Donor-Acceptor, Organic Molecules</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas Bedard</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selectivity and Mechanism in the Friedel-Crafts Alkylation of Benzene and Related Substrates</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patrick L. Spence</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selective Zirconium-Catalyzed Carbomagnesation of Alkenes</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luis E. Martínez, Jr.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thermal Organic Reactions in Thermotropic Liquid Crystalline Solvents</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jana L. Westran</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate Analogs and Enzyme Inhibitors as Mechanistic Probes of Oxidosqualene Cyclase</th>
<th>57</th>
</tr>
</thead>
<tbody>
<tr>
<td>James B. Day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chiral Recognition of Organic Substrates by Designed Organic Receptors</th>
<th>61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuelong Liu</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recent Studies on the Mechanism and Stereoselectivity of the Oxy-Cope Rearrangement</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhan-Qi Ho</td>
<td></td>
</tr>
</tbody>
</table>
NON-LINEAR EFFECTS IN ORGANIC SYNTHESIS

Reported by L. Jonathan Brice  
September 17, 1992

INTRODUCTION

In an achiral environment, enantiomers display identical chemical behavior and diastereomers need not. However, the interactions of scalemic mixtures to form dimers may give rise to intermediates in asymmetric reactions that exhibit differential physical and chemical behaviors. The idea of aggregate formation and phenomenological divergence, formalized by Feringa and Wynberg, is termed enantiomeric recognition and has powerful implications, one of which is the ability of a catalyst with very low enantiomeric excess (ee) to catalyze product formation in very high ee. This concept, termed asymmetric or chiral amplification, was first studied by Kagan, and encompassed two known systems. In only 6 years, this field has grown to include many types of systems, mostly because of its mechanistic value and synthetic promise.

NON-LINEAR EFFECTS

As stated by Kagan, if the chiral auxiliary is scalemic, and no interaction among chiral ligands occurs, the theoretical enantiomeric excess (ee_{max}) in these "ideal" systems is linearly related to ee_{product} and ee_{aux} by the relation:

$$ee_{max} = ee_{product} / ee_{aux}$$

If the reacting complex involves two ligands or is dependent on a process involving oligomerization of auxiliaries, there may exist (in a scalemic mix) three discrete complexes (Figure 1): enantiomeric complexes 1 and 3 (homochiral complexes), and complex 2, a heterochiral complex, diastereomeric to complexes 1 and 3. This has two consequences:

1) The heterochiral complex may exhibit different reactivity than the homochiral complex
2) The heterochiral complex will produce a racemate

Copyright © 1992 by L. Jonathan Brice
If the heterochiral dimer is less reactive than the homochiral dimers, the relation of ee\_{product} to ee\_{aux} deviates positively from linearity, affording products in higher ee than predicted by linear behavior. If the heterochiral dimer is more reactive, the system deviates negatively from linearity. It is the former case, known as asymmetric amplification, that is of synthetic utility and current interest.

**DIALKYL ZINCS**

Dialkyl zinc compounds that are linear sp hybridized are monomeric in solution. Though unreactive towards carbonyl groups, if one of the alkyl moieties is replaced by an electronegative heteroatom, the remaining alkyl substituent will add to a carbonyl group. Their catalytic efficiency was discovered by Oguni\textsuperscript{3}, and their potential as nonlinear auxiliaries revealed in 1988. Since then, they have been prime targets for development of systems displaying non-linear behavior. It has been shown that tert-\(\beta\)-amino alcohols give rate enhancements of 30-100 fold as opposed to other types of heteroatomic ligands. The best ligand for chiral amplification to date, (-)-3\textsuperscript{exo} (dimethylamino)isoborneol (DAIB) (1) (Figure 2) was discovered by Noyori\textsuperscript{4}. It was found that 1: 1.1: 0.02 (PhCHO: Et\textsubscript{2}Zn: 1) catalyzes the ethylation of p-substituted and aliphatic aldehydes in good chemical yields (80-97%) and optical purities (91-99% ee) (Scheme I). Significantly, it was discovered that using equimolar amounts of PhCHO:R\textsubscript{2}Zn:DAIB, gives a benzyl alcohol instead of the ethylated product. The ratio of R\textsubscript{2}Zn:DAIB must be >1 for ethylation to occur, implying that two alkylzinc moieties participate in the alkylation. While not a chiral system, the catalytic efficiency and stereoselectivity of the system led Noyori to develop one.

Oguni\textsuperscript{5} demonstrated the nonlinear behavior of a dialkyl zinc system using 1-piperidine-3,3-dimethyl-2-butanol (PDB) 2 as a chiral ligand. With 2: R\textsubscript{2}Zn:benzaldehyde (0.02: 1.1: 1) of various optical purity, Oguni observed asymmetric amplification as shown in Table I. Noyori\textsuperscript{6}
discovered a substantial positive nonlinear effect for the DAIB system, and focused on the reaction mechanism and intermediates in an attempt to account for its origins. The participation

Table I. Amplification Phenomenon in a Dialkylzinc-PDB System (Oguni, 1988)

<table>
<thead>
<tr>
<th>% ee catalyst</th>
<th>% yield</th>
<th>% ee product</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>82</td>
<td>36</td>
</tr>
<tr>
<td>6.5</td>
<td>95</td>
<td>74</td>
</tr>
<tr>
<td>20.5</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>59.8 (and greater)</td>
<td>95</td>
<td>92</td>
</tr>
</tbody>
</table>

of two alkyl zinc moieties in the alkylation, as well as the existence of the dimeric catalyst precursor 3 was postulated. Significant mechanistic findings (Scheme II) included the equilibration of 4, 5, and 6, generated from the dimer 3. The accessibility of the catalyst/substrate complex 5 from either of the initially formed "di-zinc" species 4 and 6, which is crucial since a significant competing pathway from 4 would likely erode the amplification phenomenon. Moreover, the pre-catalytic dimer 3, whose breakdown upon exposure to other components in the catalytic cycle provides the reactive intermediate 5 is a dimeric form of the Zn/DAIB complex. As such, Noyori was able to rationalize the substantial positive non-linear effects of this system by comparing the relative stability of homo and heterochiral dimer 3.

Scheme II. Mechanism of DAIB mediated alkylation (Noyori, 1989)

Bolm used the C2 symmetric 2,2'-bipyridyl chiral auxiliary 7 for ethylation of various aldehydes (Scheme III). Structure reactivity surveys of this ligand showed that a free hydroxyl
is necessary for high ee. With the ratio of (7: Et2Zn: aldehyde 0.05: 1.1: 1, product of 90% ee and 92% chemical yield were obtained. Structure reactivity experiments suggested that 8 might be an efficient ligand, and in 5 mol% at 0°C in hexane with benzaldehyde it gave enriched ethyl phenyl carbinol (Table 2).

**Table 2 Amplification Values Using (8)**

<table>
<thead>
<tr>
<th>ee(%) (8)</th>
<th>ee product (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>9.2</td>
<td>74.7</td>
<td>28</td>
</tr>
<tr>
<td>14.8</td>
<td>86.6</td>
<td>49</td>
</tr>
<tr>
<td>29.8</td>
<td>87.7</td>
<td>84</td>
</tr>
<tr>
<td>&gt;99</td>
<td>85.7</td>
<td>83</td>
</tr>
</tbody>
</table>

Equimolar amounts of the ligand (8) and diethylzinc were shown to form dimeric species, insoluble in hexane, differing in stability depending on the optical purity of the starting ligand. On the basis of MS and NMR spectral data, Bolm concluded the homochiral dimer of 8 suffered severe steric compression, and together with an X-ray structure determination of the meso dimer, was able to hypothesize a structure for the homochiral dimer.

In hexane at 0°C, a positive nonlinear effect was observed, 14% ee of ligand (8) giving products in 87% ee, the ee\textsubscript{max} for the reaction. Bolm rationalized the amplification phenomenon in a manner similar to Noyori, with the greater relative stability of the heterochiral ligand dimer responsible for sequestering the minor enantiomer. While the ee\textsubscript{max} value is less than in alkyl zinc systems, it is interesting that the nonlinear effects persevere through substantial steric diversity, as evidenced by the differing steric environments around the nitrogen atoms of the
Noyori, Oguni, and Bolm systems. It is this leeway that may allow for the rational design of ligands which exhibit positive nonlinear effects.

**Scheme IV**

\[
\begin{align*}
\text{Ar} & : \text{Ph} \\
\text{ZnEt} & : \text{Et} \\
\text{Ni(acac)}_2 & : \text{Ni}
\end{align*}
\]

For organozinc conjugate additions, Bolm\(^8\) observed large positive nonlinear effects in the nickel mediated ethylation of chalcone (Scheme IV) with the use of pyridyl ligands 8 and 9. Addition products were obtained in good chemical yield with ee up to 86%. It is interesting to note, in contrast to the 1,2 additions with this ligand, a polar solvent such as CH\(_3\)CN is necessary for a high ee in this case.

**Tanaka \(^9\),** obtained a synthetically useful amplification in the addition of the alkoxy cuprate (10) (Scheme V) derived from (1R,2R,3S,4S)-3-[(1-methylpyrrol-2-yl) methylamino]-1,7,7-trimethyl bicyclo[2.2.1]heptan-2-ol (MPATH). When

**Scheme V**

\[
\begin{align*}
\text{CuMe}_2\text{Li}_2 & : \text{Cu} \\
\text{O} & : \text{O}
\end{align*}
\]

the cuprate reagent was generated from MPATH with 80% ee, methylation of (11) to (R)-mucone (12) was formed in 93% ee. Again, the dimeric nature of the precatalyst species is cited as the origin of the amplification phenomenon, but the absence of kinetic data for this system and lack of physical data on the intermediates prevent firm conclusions.

Bolm\(^10\) observed a positive nonlinear effect with 8 for the nickel-mediated conjugated addition of diethylzinc to the chalcone in Scheme II. Both the ligand and nickel catalyst concentrations are important. Increasing the metal to ligand (10% ee) ratio from 1:10 mol % (compared to Et\(_2\)Zn) to 1:30 led to an ee increase from 30 to 44%. Increasing the overall concentration to 4:40 mol % gave an ee of 64% (with ligand ee = 16%). The ee of the product was found to decrease over time, implying that there is some non selective mechanism operating
that bypasses the ligand partitioning event. Use of 8 (19% ee) gave an 87% ee after 15 min but only 78 after 45 min. Bolm rationalizes the amplifying phenomenon, in contrast to Noyori and Oguni, by precatalyst association with one metal atom, and the less stable diastereotopic complex becoming the catalyst (Figure 2).

![Figure 2](image)

**THE HAJOS-PARRISH REACTION**

Non-linear effects are observed in the Hajos-Parrish cyclization, and have been used to support aspects of various mechanistic proposals (Scheme VI). Agami\(^{11}\) reports evidence of participation of two proline molecules in the transition state of the reaction. The second proline molecule in thought not influence the stereochemical outcome. However, its stereochemistry does create diastereotopic reactive conformations that may influence the reaction rate; the four possible complexes (Figure 3) are shown (18,19, 20, 21). The non linear effect is cited as proof that two proline molecules are involved in the transition state, in agreement later work Agami\(^{12}\)

![Figure 3](image)
Other Systems

The systems reviewed above have been the most thoroughly studied, but do not represent the entire scope of reactions observed to display nonlinear behavior. Nakai\textsuperscript{13} reports that titanium complex 22 (31\% ee) in 1 mol \% (compared to ester gave the amplification (Table 3) in the glyoxalate-ene reaction (Scheme VII):

Scheme VII

![Scheme VII](image)

Table 3 Amplification values in glyoxylate-ene reaction using (22)

<table>
<thead>
<tr>
<th>ee 22 (%)</th>
<th>ee 23 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>60</td>
</tr>
<tr>
<td>25</td>
<td>91</td>
</tr>
<tr>
<td>100</td>
<td>92</td>
</tr>
</tbody>
</table>

Oguni\textsuperscript{14} reports a modest non-linear effect in the trimethylsilylcyanation of benzaldehyde (Scheme VIII) using the titanium reagent 24 (Table 4):

Scheme VIII

![Scheme VIII](image)

Table 4 Amplification values for silylcyanation reaction using (24)

<table>
<thead>
<tr>
<th>ee 24 (%)</th>
<th>ee 25 (%)</th>
<th>ee 25 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>27</td>
<td>65</td>
</tr>
<tr>
<td>25</td>
<td>50</td>
<td>78</td>
</tr>
<tr>
<td>50</td>
<td>70</td>
<td>83</td>
</tr>
</tbody>
</table>
Rossiter has observed a slight amplification (ee auxiliary 84%, ee product 94%) for and (S)-MAPP cuprates.

Conclusion

The methodology of asymmetric reactions is at the forefront of organic research. The above examples represent the state of the art in this area. Although these reactions must meet all the requirements for a synthetically useful catalytic system as well as the additional requirements of some mechanism of ligand partitioning, the boon of being able to bypass expensive or difficult resolutions may allow for the design of more challenging (and efficient) ligands. The negative nonlinear effects prove useful as mechanistic tools, giving one direct access into the dynamics of the transition state. In either case, the understanding of the steric and kinetic factors that give rise to these effects give the experimental chemist a powerful tool for either synthetic methodology of mechanistic elucidation

References

THREE CONTRASTING SYNTHESSES OF THE DENTICULATINS

Reported by Todd Spradau September 24, 1992

INTRODUCTION

Denticulatins A and B, polypropionate metabolites from the marine mollusk Siphonaria denticulata, belong to a class of molecules that often exhibit high antibacterial activity. Many groups are therefore interested in developing efficient methodologies towards the construction of such polyketides. Though the denticulatins themselves show little antimicrobial activity, and their natural function remains a mystery, they are worthwhile synthetic targets because they can put such strategies to the test. Three total syntheses have recently appeared in the literature, and they serve to illustrate the various methods of acyclic stereocontrol used by these groups.1-3

THE ZIEGLER SYNTHESIS

In a 1990 denticulatin total synthesis, Ziegler was able to demonstrate the effectiveness of his 3-methyl-γ-butyrolactone strategy for the construction of polypropionate-derived natural products (PPDNPs).2,4 The synthesis utilized substrate control for the introduction of asymmetric centers quite elegantly, but required 41 steps and produced the denticulatins as a mixture in a 0.2% overall yield.2

Stereocenters four through eight were installed by means of substrate control of stereoselectivity. Lactone 4 was prepared by Claisen rearrangement of the adduct formed from alcohol 2 and the diethylorthoester of lactone 3 via the chair-like transition state shown (Scheme I).4 This preferred transition state produced 4 in 100% enantiomeric excess (ee), with the only impurity being a diastereomer resulting from lactone 3 being less than enantiomerically pure.4

Scheme I

As for the general utility of this step, the anti-anti stereochemistry produced in 4 is by far the most readily attained. The anti-syn isomer (anti within the lactone ring) of simple lactones

Copyright © 1992 by Todd Spradau
like 4 can be obtained with ≥ 97% diastereomeric excess (de) by thermodynamic equilibration of the product mixture obtained from rearrangement of the starting lactone (e.g. 3) with the other enantiomer of the alcohol (e.g. ent 2). However, this base-catalyzed epimerization does not always favor the trans lactone to such a high degree. The syn-anti isomer is available only via a five-step iodolactonization/thermodynamic equilibration procedure which again gives good selectivity (≥ 97%) in favorable cases, but is less dependable with increased substrate complexity. The syn-syn isomer is not available via this methodology.

Criegee rearrangement provided a route to replace the carbonyl group of lactone 4 with a hydroxyl group with retention of configuration, and subsequent manipulations would have allowed formation of lactone 6 (Scheme II), an analog of 3. It was hoped that a second Claisen iteration could provide stereocenters four and five, but this proved impossible, as the diethylortholactone of 6 was unattainable. Ziegler turned this seeming failure into an advantage, though, since the Ireland-Claisen rearrangement proved an excellent iterative tool.

Scheme II

As shown in Scheme III, protected diol 5 could be elaborated to ester 7 employing ent 2. The stereoselective Ireland-Claisen rearrangement provided the acid 8 as a 97:3 mixture of C5 epimers, and probably enhanced the scope of the overall strategy as well, since proper selection of enolate geometry and alcohol stereochemistry can provide all stereochemical relationships (including syn-syn), regardless of the configuration of the original centers.

Scheme III
The installation of the final stereocenter, C10, was poorly controlled. Ketone 14 (Scheme IV), was prepared without incident using the only reagent-controlled reaction of the synthesis. However, aldol condensation with 10 led to a meager 2.7:1 selectivity between C10 epimers, and even "careful rechromatography" resulted in only a ~5:1 mixture. Furthermore, the final deprotection/cyclization step could not be carried to more than 50% completion without recovering mainly elimination products, and C10 epimerization was unavoidable. Thus a synthesis that began with elegant control of stereochemistry ended a modest success.

**Scheme IV**

\[
\begin{align*}
\text{OMe} & \quad \text{3 steps from propionaldehyde} \\
\text{12} & \quad \text{1, LDA} \\
\text{13} & \quad \text{2, Cu(OAc)}_2 \\
\text{14} & \quad 54\%, 89\% ee
\end{align*}
\]

**THE HOFFMANN SYNTHESIS**

The second published synthesis of the denticulatins appeared in the form of a 1991 article by R.W. Hoffmann. He also used these PPDNPs as vehicles to demonstrate the capabilities of the methodology developed in his group. The strategy of Hoffmann can be succinctly described in three words: Iterative asymmetric crotylboronations. Three such reactions served to install stereocenters C4-C8 of the denticulatin chain in the form of aldehyde 15 (Scheme V), which, when combined with ketone 14, yielded a slightly less oxidized version of the denticulatins. Though these building blocks were similar to those used by Ziegler, Hoffmann's strategy for their construction was quite different from Ziegler's with respect to substrate vs. reagent control of stereoselectivity during the installation of the requisite asymmetric centers.

**Scheme V**

The first stereogenic center installed, C4, resulted from a chiral (Z)-pentenylboronate addition to propionaldehyde (Scheme VI). The observed stereocontrol arose from three factors: (a) the reaction proceeded via a chair-like transition state, a general rule with respect to crotylboration, (b) the (Z)-boronate led stereoselectively to the syn product, and (c) the α-methyl group in the boronate adopted a pseudo-equatorial arrangement in the transition state. Subsequent protection and ozonolysis set the stage for another iteration.
Scheme VI

The second stereoselective chain extension had the added complexity of a chiral substrate (18), but the synthetic challenge was relatively minor, as the new stereocenters were to have a Cram relationship to C4, and 18 provided a 1.2 kcal/mol asymmetric induction in that direction. Thus, the reagent, this time a simple (E)-crotyle boronate (Scheme VII), served only to enhance the Cram preference inherent to the substrate, and to provide an anti relationship between C5 and C6. The E-geometry of the crotyleboronate enforced both of these traits.

Scheme VII

Installation of C7 and C8 provided an imposing challenge for the crotyleboration technology, as success demanded that the reagent overcome a ≥ 3 kcal/mol asymmetric induction of the substrate aldehyde 21. This challenge could not be met by the chiral (E)-(α-chlorocrotyl)boronates used previously by Hoffmann, and the more powerful (E)-(α-methoxycrotyl)boronate reagent, 22, was developed (Scheme VIII). As before, this reagent prefers a chair-like transition state, but in marked contrast to the (Z)-pentenylboronates used previously, the α-methoxy group adopts a pseudoaxial position. Thus, a reaction that produced 90% of the undesired (Cram) diastereomer with the α-chloro reagent, yielded a 3:1 mixture in favor of the desired product 23 when the new α-methoxyboronate was used. This result does not compare favorably to the >96% de Ziegler obtained when installing the same three stereocenters (C6-C8).
Though the technology for installing the anti/anti-Cram stereochemistry is still less than ideal, the addition of the (E)-(α-methoxycrotyl)boronates to the existing group of crotylboronate reagents makes the Hoffmann strategy for the iterative synthesis of PPDNP's quite generally useful. The (Z)-pentenyloboronates exhibit the ability to provide syn diastereoselectivity in both the Cram and anti-Cram sense as desired, and the (E)-(α-methoxycrotyl)boronates can give the same high selectivity, but of the anti variety as long as the asymmetric induction of the aldehyde is not prohibitively large.

Hoffmann's synthetic scheme continued with the synthesis of ketone fragment 14. While this was the only place Ziegler resorted to reagent control for stereoselectivity, Hoffmann utilized his only substrate-controlled reaction, a Claisen rearrangement (Scheme IX).

**Scheme IX**

![Scheme IX](image)

Though the aldol coupling between 14 and 24 could be accomplished without incident, subsequent attempts to liberate the protected C3, C5, and C7 hydroxyl groups, regardless of the order of deprotection, led to decomposition, elimination, and/or epimerization in all cases. Evidently the p-methoxybenzylidene protecting group for the C5-C7 diol was less than ideal.

Rather than go back and change to the more labile p-methoxyacetophenylidene derivative used (somewhat) successfully by Ziegler, Hoffmann decided to make the C3-C7 acetal 29 with the expectation that it would isomerize to the thermodynamically more stable denticulatin conformation (Scheme X). Thus, intermediate 20 was converted to 29, oxidized to the diketone, and another attempt was made at removing the p-methoxybenzyl protecting group. This could be successfully accomplished only by deactivating the C9 and C11 carbonyl groups via enolization at C10, thus sacrificing this stereochemistry. Subsequent thermodynamically driven rearrangement provided denticulatins A and B as another C10-isomeric mixture.

**Scheme X**

![Scheme X](image)
THE PATERSON SYNTHESIS

The final denticulatin synthesis to be discussed here appeared in a 1992 article by Ian Paterson. He, too, utilized these PPDNP's to illustrate his general strategy regarding the synthesis of molecules of this type. Specifically, in a paper accompanying the synthesis, a universal plan towards the preparation of stereopentads 30 (Scheme XI), ubiquitous in PPDNP's was presented. With this in mind, his retrosynthetic scheme unfolded as shown.

Scheme XI

Though the (Z)-enolate of 31 shows no asymmetric induction during aldol condensations, it was found that its (E)-enolate, prepared using achiral (c-C6H11)2BCl, leads to highly stereoselective substrate-controlled anti aldol condensations. This reaction was expected to provide the required denticulatin precursor 33 (Scheme XII).

Scheme XII

Ketone reduction in 33 with chelation control of diastereoselectivity was attempted as planned using n-Bu2BOMe as the chelating agent. Instead of giving the predicted syn diol 34 (Scheme XIII), a 1:1 mixture of stereoisomers resulted, indicating that the reaction proceeded through transition state TS-2 as well as the desired TS-1. The problem was creatively solved by doing the reduction on the aldol adduct 32 before workup. Thus, the dicyclopentylboronate formed the directing chelate, and the reaction was driven through TS-1 to the required product 34. The elimination of the pseudo 1,3-diaxial interaction between R and L present in TS-2 was probably the main reason for the increase in reduction stereoselectivity when L=(c-C6H11), but the other asymmetric center α to the carbonyl group may have played a supporting role. The bulky cyclopentyl ligand may not only have made the chair in TS-1 favored, but could also have
pushed the -CH₂OBn group down, antiperiplanar to the forming C-H bond, thus preventing the "normal" Felkin-Ahn side chain rotamer from diluting the stereoselectivity of the reaction.

Scheme XIII

Syn diol 34 thus obtained, Paterson made use of the hindsight provided by Ziegler and Hoffmann and chose t-Bu₂Si(OTf)₂ to form the protecting acetal. This step preceded a very selective hydroboration reaction using simply BH₃•SMe₂. The reaction apparently proceeded starting from the most stable rotamer of the protected allylic alcohol 35 (Scheme XIV). In this conformation, the equatorial methyl group at C₆ projects over the rear face of the alkene, thus forcing BH₃ to attack from the front face.

Scheme XIV

Benzyl deprotection, oxidation to the ketoaldehyde, and a chemoselective Grignard alkylation provided 37 (Scheme XV). The titanium-mediated coupling of 37 and 38 proceeded
very well. The condensation was completely diastereofacially selective, giving a mixture due only to the enantiomeric impurity contained in \( 38.1 \). It is possible that the reaction occurred through a transition state such as TS-2, which is favored over TS-1 because the latter has three axial substituents projecting over the top of the forming bonds. TS-2 has only one such axial hydrogen. One can imagine titanium coordination via the other (axial) lone pair of the C7 oxygen, but counter-clockwise ring rotation from the configuration shown in TS-2 would project the entire ring over the forming bonds, and such a transition state would clearly be disfavored. A similar scenario would result with respect to TS-1, but in this case the ring would cover the chloride ligands on titanium, and so this transition state would be disfavored on steric grounds.

The synthesis was completed with a double oxidation of C3 and C11 followed by the first trouble-free deprotection/rearrangement sequence reported thus far (Scheme XVI). Pure denticulatin B resulted.

**Scheme XVI**

CONCLUSION

Ziegler and Paterson relied almost exclusively on substrate control of stereoselectivity to provide the requisite denticulatin stereogenic centers, while Hoffmann preferred reagent control. The diverse paths taken by these authors to achieve the same end is indicative of the creative freedom present in organic chemistry.

REFERENCES

ZIEGLER-NATTA POLYMERIZATION USING
CHIRAL ZIRCONOCENE REAGENTS

Reported by Jennifer M. Galvin October 1, 1992

INTRODUCTION

Ziegler-Natta polymerization uses transition metal catalysts to polymerize ethylene or other α-olefins. These types of catalysts act under low pressures and can produce high molecular weight polymers.\(^1\) Isotactic polypropylene produced by this method is of great commercial interest due to its greater tensile strength, compared to atactic polypropylene,\(^2\) and due to its potentially interesting electronic and optical properties. Recently, asymmetric group IV metallocene complexes have been used as Ziegler-Natta catalysts to produce highly isotactic\(^3\) or syndiotactic\(^4\) polymers. Asymmetric zirconocene reagents together with methylalumoxane (MAO) co-catalysts have been useful in polymer production and have been extensively studied.

BACKGROUND

Simple zirconocene-methylalumoxane (MAO) systems can produce purely atactic polypropylene.\(^5\) Modification of this system by addition of chiral ligands to the zirconium center allows the production of highly isotactic or highly syndiotactic polypropylene, as well as other oligomerization products.

Figure 1

Tetrahydroindenyl zirconium\(^6\) and titanium complexes\(^7\) were first synthesized in the early 1980's (Figure 1). Reaction of these complexes with methylalumoxane--polymeric arrays of CH\(_3\)-Al-O units--provides the active catalyst. These were first shown to have interesting polymerization characteristics by Ewen in 1984 for the titanium system,\(^8\) and by Kaminsky in 1985 for the zirconium system.\(^9\) Ewen found that the racemic titanocene complex (1) produces up to 63% isotactic polypropylene with molecular weight greater than 100,000. The racemic zirconocene complex (2), in conjunction with MAO, can produce polymers with a molecular weight of greater than 150,000, and isotacticity greater than 90%, depending on reaction conditions (Table I).

Copyright © 1992 by Jennifer M. Galvin
Optimization of reaction conditions has yielded polypropylene with an isotacticity index of greater than 99%. This system also produces isotactic polypropylene with a molecular weight distribution, \( M_w/M_n \), narrower than is now achieved with commercial catalysts. Resolution of 2 by reaction with (S)-BINAP or o-acyl-mandelic acid gives optically pure catalyst precursors that have interesting synthetic applications.

Table I  Polymerization of polypropylene using zirconocene-MAO catalysts

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Temperature °C</th>
<th>Activity kg/mol - hr</th>
<th>( M_w )</th>
<th>( M_w/M_n )</th>
<th>Isotacticity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-10</td>
<td>300</td>
<td>305,000</td>
<td>2.6</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>880</td>
<td>144,000</td>
<td>2.4</td>
<td>88.1</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>2900</td>
<td>62,000</td>
<td>2.0</td>
<td>87.3</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>4750</td>
<td>45,000</td>
<td>1.9</td>
<td>86.0</td>
</tr>
</tbody>
</table>

a: data for catalyst 2 from reference 3

**NATURE OF THE CATALYTIC SPECIES**

Zirconocene 2 and related group IV metallocenes are not the active polymerization catalysts, but catalyst precursors. Reaction with MAO produces the active catalytic form. There is considerable evidence that this reaction produces cationic \( L_2MCH_3^+ \) or \( L_2MH^+ \) species which are the actual catalysts (Scheme I). Polymerization requires between 6 and 20 aluminum atoms per zirconium atom. Reduction in the amount of alumoxane causes drastic reduction catalyst activity. After the production of the cationic metal complex, MAO acts as a remote counter ion, which is not directly involved in the catalytic cycle, except as a possible chain termination pathway.

Scheme I

Model cationic zirconocene complexes have been synthesized to show that they can initiate polymerization directly (Figure 2). Marks has synthesized and isolated zirconocene complex 4, which gives both polyethylene and atactic polypropylene. Similarly, a cationic zirconium complex (5) synthesized by Jordan also produces polyethylene.

![Figure 2](image-url)
Spectroscopic studies also support the presence of a cationic catalyst. X-ray photo-electron spectroscopy has shown that three different catalyst precursors give products with the same binding energy upon reaction with MAO. Results from numerous NMR spectroscopy experiments also imply that cationic zirconocenes are the active catalytic species.

STEREOCONTROL AND SOURCE OF ISOTACTICITY

It is generally held that Ziegler-Natta polymerization occurs in two discrete steps: olefin coordination, followed by insertion into the polymer chain. The growing polymer chain migrates from one side of the metal center to the other with each insertion. In this mechanism, there are two main ways to induce tacticity: enantiomorphc-site control or chain-based control. In enantiomorphc-site control, asymmetry of the metal center is responsible for control of polymer tacticity. In chain-based control, the stereochemistry of the growing polymer chain controls the tacticity. The two main mechanisms of induction lead to different types of isotactic polymers, which may be differentiated by statistical models of pentad distributions (Scheme II). Isotactic polypropylene with structure 7 fits a Bernoullian model, and results from chain-based control, with the last inserted monomer controlling the stereochemistry of the next insertion. Misinsertions of an olefin unit cause “block” irregularities until the next misinsertion. Polypropylene with structure 6 is an example of enantiomorphc-site-based control. Any stereochemical “mistakes” are corrected in the next insertion, and not propagated to form the block-like structures shown in 7. Ewen was the first to show that 1 yielded isotactic polypropylene with pentad structures corresponding to enantiomorphc site control. It is generally held that the rest of the Group IV metallocenes also follow site-based control.

Scheme II

Because of the site-based control mechanism, ligand shape is important for determining chain tacticity. The C2 nature of the ligand system of 2 yields isotactic polymers. Even though the polymer chain migrates with each insertion, the ligand provides the same environment with respect to olefin coordination. In this way, the same face of the olefin is inserted to the polymer with every monomer addition. Ewen has developed a non-C2-symmetric hafnocene system for the production of syndiotactic polypropylene (Figure 3). In this case, opposite faces of the olefin are inserted with each successive step, yielding syndiotactic polymers.
Absolute facial selectivity of 3 was determined by oligomerization experiments. In an initial study by Pino, it was found that reaction of olefins in the presence of H2 produced optically active oligomers. Optical rotation of the products gave their absolute configuration, and suggested olefin coordination occurred preferentially for the Re face. This led to the rationalization that the olefin must bind in a “1,2” sense with the growing polymer chain always occupying the empty quadrant, Q2 (Scheme III Note: opposite enantiomer of catalyst is shown).

Further studies using D2 as the oligomerization gas led to a more detailed picture of olefin insertion and chain growth. Oligomerization of 1-pentene in the presence of deuterium, followed by fractionation lead to several optically active products. Dideuteriopentanes had a positive optical rotation, corresponding to an R configuration at carbon 2. This implies that olefin insertion into an M-D bond occurs from the Re face. Deuterated dimers showed that insertion of the olefin into an M-C5H11 bond proceeds primarily from the Si face of the olefin. This implies that olefin coordination to the metal center changes depending on the nature of the other substituent on the metal. In the case of the initial insertion into an M-D bond, the olefin occupies the “least crowded position.” In following steps, the growing polymer chain occupies the empty quadrant, Q2, and the olefin coordinates to the next least crowded position, Q1.

Scheme III

In general, these experiments show that olefin coordination and polymerization are quite sensitive to the steric environment around the metal center. Recent studies have used this
information to design new polymerization catalysts with more sterically demanding ligands to improve selectivity.\textsuperscript{19}

**MECHANISM OF POLYMERIZATION**

Though polymerization is thought to occur in two steps, the actual mechanistic course of the reaction has been widely debated. In particular, there is much controversy over the role of \(\alpha\) hydrogens on the polymer chain. One popular model is that derived by Cosee.\textsuperscript{20} In this mechanism, the incoming olefin is complexed to a vacant coordination site on the metal. This is followed by migration of the polymer chain, through a four-membered, cyclic transition state. This regenerates the empty coordination site, and allows for further chain growth (Scheme IV). A modification of this mechanism invoking an \(\alpha\)-agostic interaction between the growing polymer chain and the metal has been suggested by Green and Brookhart (Scheme V).\textsuperscript{21}

Evidence for both mechanisms has been gathered for the zirconocene polymerization system.

**Scheme IV**

\[
\begin{align*}
\text{P} \\ \\
\text{M} & - \text{empty coordination site} \\
\end{align*}
\]

Computation results for both the titanium and zirconium complexes have shown that the Cossee mechanism is the lowest energy pathway. However, computation has also shown that \(\alpha\)-agostic mechanisms are possible, and cannot be ruled out.

Jolly and Marynick performed calculations on a \(\text{Cp}_2\text{TiCH}_3^+\)-ethylene system at the 4-31G* level, with MP2 corrections.\textsuperscript{22} Calculations related to the \(\alpha\)-agostic interactions show that though these may lower the reaction barrier, non-bonded and steric interactions are also important, and may override any energy gains made by the agostic interaction. High level calculations were performed by Rappe on catalyst 2.\textsuperscript{2} This study had a two-fold purpose: first, to investigate the mechanism of polymerization, and second, to look at the energetics of olefin binding with respect to overall stereocontrol. Calculations related to the mechanism of polymerization showed that a metallocyclic transition state is likely, but, that there is the potential of an electrostatic interaction between an \(\alpha\) H on the growing polymer chain and the
metal. Isotactic polymers were also shown to be energetically favorable. For the first propylene insertion into a Zr-CH3 bond, the activated complex leading to the isotactic structure is favored by 3 kcal/mol. Insertion of the second and third olefins also favor the isotactic structures by 6 kcal/mol and 5 kcal/mol, respectively.

Though calculations show that a Cossee mechanism is possible for metallocene polymerization, they give no definitive conclusions. A number of elegant isotope studies show that an α-agostic mechanism may be important.

α-Agostic Mechanisms

Scheme V

α-Agostic interactions imply the presence of a hydrogen bridge. If this bridge is present in the rate limiting polymerization step, it could be seen by isotope effects. Grubbs first used this type of experiment to probe the mechanism of a titanium polymerization system. Though the Grubbs system showed no such effects, similar methodology has been applied to other experiments.

Bercaw has designed a Ziegler-Natta polymerization catalyst containing scandium. Reaction of trans, trans-1,6-dideuterio-1,5 hexadiene with 10 yielded a racemic scandium alkyl complex. Cyclization takes place through a cis ring transition state to alleviate ring strain. Analysis shows that two different conformations are possible, and if agostic interactions are important, there is a preference for H to occupy the bridging position. This would lead to an unequal ratio of products 11 and 12. Indeed, products 11 and 12 were formed in a ratio of 1.19:1, thus favoring the mechanism shown (Scheme VI).

Brintzinger has also noted agostic interactions. Reactions of zirconocene dichloride with trans-1-deuterio-1-hexene yielded 6-deuterio-5-deuteriomethyl-undecane in a 13:14 ratio of 1.3:1. Preference for H to occupy the agostic bridge was used to rationalize these results. Without agostic interactions, a product mixture of 1:1 would be expected (Scheme VII).
Though these two experiments seem to support the Brookhart-Green mechanism, the evidence is not universal. Repetition of Bercaw’s cyclization experiment with zirconocene dichloride showed no isotope effects. Bercaw has also done further labeling studies with \( \text{10} \), but was unable to give further support to an agostic mechanism.

CONCLUSION

Group IV metallocene catalysts are quite useful in producing isotactic polypropylene. Even though they produce polymers with commercially important properties, presence of the MAO co-catalyst hinders widespread commercial use. Studies related to the mechanism of polymerization and to the origin of stereocontrol have identified important features in producing polymers of desired conformation, but there is still no definitive mechanism for polymerization. Further study in this area would be useful, because a greater understanding of the mechanism of polymerization could lead to better catalysts. Even though this mechanism is not fully understood, metallocene catalysts have been used to make interesting polymers, and may find use as hydrogenation catalysts to make optically active alkanes and imines.
REFERENCES

INTRODUCTION

Since the earliest observations of nonlinear optical (NLO) phenomena, shortly after the advent of lasers in 1960, research efforts have focused on creating new materials which are both capable of exhibiting large nonlinearities and are amenable to incorporation into NLO devices. Much current interest focuses on the development of organic materials, largely due to their rapid NLO response times, inherent design flexibility through functional group manipulation, and ease of processability into oriented structures, such as thin films. The efficiency of a particular NLO response, second harmonic generation for example, is directly related to the molecular hyperpolarizability ($\beta$) and to the arrangement of molecules in a bulk sample. Thus, design of efficient, organic NLO materials presents two related problems: the creation of chromophores exhibiting large $\beta$ values and their subsequent orientation. Aromatics substituted with donor and acceptor groups have been known to exhibit large $\beta$ values for some time. Due to the sensitivity of the electric field induced second harmonic generation (EFISH) experiment which measures $\beta$ to experimental variables $^{2,3a}$, a detailed correlation of specific structural features to second order hyperpolarizabilities awaited a systematically varied and internally consistent data set. Such a set of measurements has recently accumulated and will serve as the basis of this abstract.$^3$

TWO-STATE MODEL

It was recognized through early measurements performed on mono- and disubstituted benzene derivatives that donor-acceptor substituted aromatics exhibited significantly larger $\beta$ values than the algebraic sums of their constituent moieties. Oudar and Chemla proposed a two-state model which has been widely applied to conjugated organic systems, due largely to its simplicity and qualitative accuracy.$^4$ This model, based on perturbation theory, asserts that $\beta$ results largely from a single charge-transfer excited state. Electrons in the $\pi$-system are thus perturbed between a ground and a low-lying charge-transfer resonance structure through the action of a strong oscillating electric field, as in Scheme I. Hyperpolarizabilities are predicted by this model to be related to the transition dipole moment, $u_{ge}$, the difference in dipole moment between ground and charge-transfer states, $\Delta\mu_{ge}$, and the energy of the charge-transfer transition,

Scheme I

Copyright © 1992 by Thomas C. Bedard
$E_{ct}$ (Equation 1). Efficient organic NLO chromophores are thus predicted to have low energy

$$
\beta \equiv \beta_{\text{ct}} \quad \alpha \quad \Delta \mu_{\text{po}} \cdot u_{\text{ag}} \quad \frac{\Delta \mu_{\text{po}} \cdot f}{E_{ct}^3} \quad \frac{\Delta \mu_{\text{po}} \cdot f}{E_{ct}^3}
$$

charge-transfer transitions, large charge displacements between the ground and excited states, and efficient orbital overlap between the two states. The transition dipole moment is a measure of the probability of transition between ground and excited states and is related to the extinction coefficient of the charge-transfer band through the oscillator strength, $f$.

The two-state model is only an approximation. Despite good agreement between calculated $\beta_{\text{ct}}$ and EFISH hyperpolarizabilities for many conjugated organics, two main shortcomings are noteworthy. The model treats the transition dipole moment, the difference in dipole moment, and the charge-transfer energy as separate entities, even though it is likely that these quantities exhibit a systematic interdependence. Indeed, Cheng recently proposed such a dependence based on hyperpolarizability measurements.\(^3a\) This will be important when correlating specific structural features with measured $\beta$ values. Stiegman also recently demonstrated the contribution to hyperpolarizabilities from additional electronic transitions other than to a single low-lying charge-transfer state as the model assumes.\(^5\) These dispersive enhancements have been proposed as another means of increasing $\beta$ values through proper exploitation of the well known efficiency/transparency trade off.

**STRUCTURAL EFFECTS ON $\beta$ VALUES**

**Donor-Acceptor Strengths**

Cheng and coworkers\(^3\) have provided a relative ordering of the donor/acceptor strengths of various functional groups based on the hyperpolarizabilities of mono-substituted as well as 1,4- and 4,4'-disubstituted benzenes and stilbenes, respectively (Table I). The relative effectiveness of donor substituents observed in increasing order of efficiency is Me < Br < OH < OPh < SMe < N2H3 < NH2 < NMe2 and that of acceptors is SO2CH3 < SO2F < CN < CHO < COCF3 < NO=NO2 < CHC(CN)2 < CC(CN)3, in good agreement with those proposed previously.\(^10\) Almost intuitively, stronger donor-acceptor pairs exhibit higher $\beta$ values than do weak combinations in disubstituted derivatives. For those substituents studied, acceptor groups appear to have greater impact on the magnitude of $\beta$ than do donor groups. This is evidenced by the negligible $\beta$ values obtained for most donor monosubstituted benzenes versus those ranging from zero to three for acceptor substituted benzenes. Additional support is provided by the variance in the methoxy versus nitro disubstituted stilbene series which vary by factors of 4.9 and 11.2, respectively. While the generality of this principle remains to be demonstrated, particularly for sp\(^2\) hybridized donor substituents, it seems reasonable given the directional
nature of the charge-transfer process in which charge terminates on the acceptor group. Both Ulman and Cheng noted a good correlation between β values and Hammett σp⁺ and σp⁻ values in both the para disubstituted nitro and methoxybenzene series, but poorer correlation with stilbene derivatives.3a,6 The latter may be due to additional contributions to β from low-lying energy transitions. Different solvents were employed for some of the examples in Table I, an effect which has been shown to influence the absolute magnitudes of β.7 However, qualitatively these substituent effects agree with other reported examples10 and appear to provide important information concerning the design of effective NLO chromophores. Strong donor-acceptor combinations generally provide larger β values. Multiple substitution appears most effective for weak donors, apparently due to the geometrical considerations discussed below.3a,8

Geometry Effects

A correlation between hyperpolarizabilities and coincidence of the molecular dipole axis with the charge-transfer axis was also noted by Cheng.3 Para disubstituted benzenes had dramatically higher β values than ortho and meta isomers; that is para >> ortho = meta. Similar results were observed for a series of nitro-methoxy-disubstituted stilbenes and both sets of results are shown in Table II. A particularly vivid example is provided by comparison of 1 and 2 (Figure 1). An additional nitro group added to the acceptor portion of a stilbene derivative, in an attempt to improve its acceptor capability, actually results in a decrease of the measured β. It is reasonable to expect a large geometrical contribution of the nitro groups to the molecular dipole axis direction while the charge-transfer axis should remain largely along the axis defined by the double bond connecting the two benzene units. Therefore, the charge-transfer axis in 1 coincides more closely with the dipole axis than in 2. Since the EFISH technique only measures the components of β projected along the dipole axis, the larger value observed for 1 over 2 is likely to be a result of the measurement technique.2 It is certain that those portions of β not aligned with the dipole axis remain undetected, although the largest hyperpolarizability tensor

---

**Table I. Effect of donor-acceptor strengths on β values (β *10⁻³⁰ esu)**

<table>
<thead>
<tr>
<th>X</th>
<th>β</th>
<th>Studies performed in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>p-dioxane unless indicated</td>
</tr>
<tr>
<td>X</td>
<td>β</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>2.1</td>
<td>acetone</td>
</tr>
<tr>
<td>Br</td>
<td>3.3</td>
<td>CHCl₃</td>
</tr>
<tr>
<td>OH</td>
<td>3.0</td>
<td>CH₂Cl₂</td>
</tr>
<tr>
<td>OMe</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>SMe</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>NH₂</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>NMe₂</td>
<td>9.2</td>
<td></td>
</tr>
</tbody>
</table>

---

*Note: Values are in 10⁻³⁰ esu, with X representing different functional groups.*
Table II. Geometrical dependence of donor-acceptor groups on $\beta$ values ($\beta*10^{-30}$ esu)

<table>
<thead>
<tr>
<th>X</th>
<th>ortho</th>
<th>meta</th>
<th>para</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>1.0$^a$</td>
<td>1.5$^a$</td>
<td>2.1$^b$</td>
</tr>
<tr>
<td>OH</td>
<td>1.2$^b$</td>
<td>0.8$^b$</td>
<td>3.0$^b$</td>
</tr>
<tr>
<td>OMe</td>
<td>1.4$^a$</td>
<td>1.6$^b$</td>
<td>6.1$^b$</td>
</tr>
<tr>
<td>NH$_2$</td>
<td>2.5$^b$</td>
<td>1.9$^b$</td>
<td>9.2$^c$</td>
</tr>
</tbody>
</table>

Studies performed in
CHCl$_3$ unless indicated
$n$eat $^b$p-dioxane $^c$acetone

<table>
<thead>
<tr>
<th>X</th>
<th>NO$_2$</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-OMe</td>
<td>2'</td>
<td>4.4</td>
</tr>
<tr>
<td>4-OMe</td>
<td>2'</td>
<td>3.8</td>
</tr>
<tr>
<td>2-OMe</td>
<td>3'</td>
<td>5.5</td>
</tr>
<tr>
<td>4-OMe</td>
<td>3'</td>
<td>5.3$^b$</td>
</tr>
<tr>
<td>2-OMe</td>
<td>4'</td>
<td>22.0</td>
</tr>
<tr>
<td>3-OMe</td>
<td>4'</td>
<td>21.0</td>
</tr>
<tr>
<td>4-OMe</td>
<td>4'</td>
<td>34.0</td>
</tr>
<tr>
<td>2-Br</td>
<td>4'</td>
<td>12.0</td>
</tr>
<tr>
<td>3-Br</td>
<td>4'</td>
<td>14.0</td>
</tr>
<tr>
<td>4-Br</td>
<td>4'</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Figure 1. Coincidence of charge transfer and molecular dipole axes in 1 and 2.

Components should lie along the charge-transfer axis. Since in most cases the dipole and charge-transfer axes do not appear to vary by more than 60°, the results obtained by Cheng do provide at least a qualitative sense of the importance of geometry on $\beta$. This point is further evidenced by the observation that reversal of donor and acceptor positions in 2-methoxy-4'-nitrostilbene and 4-methoxy-2'-nitrostilbene results in molecules which provide dramatically differing $\beta$ values of 22.0 and 3.8 x10$^{-30}$ esu, respectively. From the significant increase in $\beta$ observed when the nitro group is placed in the 4'-position versus either the 2'- or 3'-, and the relative invariance of $\beta$ values with respect to the position of the methoxy group, it can be inferred that the placement of acceptor groups is more critical to $\beta$ than placement of donor groups. The magnitude of this dependence is again expected to be substituent specific. It is observed that 2,4-dimethoxy-4'-nitrostilbene has a $\beta$ value 15% larger than 2-methoxy-4'-nitrostilbene. These results suggest that the use of multiple substituents to increase donor or acceptor capabilities should favor substituents, particularly weak donors, which do not significantly alter the molecular dipole axis. If hyperpolarizabilities obtained from EFISH measurements are treated as a theoretical maximum to be approached in a solid state orientation of chromophores, the results indicate another
important design criteria concerning the location of substituent groups for NLO organic molecules.

**Conjugation Effects**

It was generally expected from early theory and measurements that increasing conjugation length would lead to larger hyperpolarizabilities, presumably resulting from an increased magnitude of charge separation.\(^4\) It is found experimentally that addition of conjugation units to benzene does result in an increase of \(\beta\), as evidenced by comparison of examples in Table III.\(^3,9\) From these data, styryl extensions are seen to cause larger increases in

**Table III. Effect of conjugation extension on \(\beta\) values (\(\beta\times 10^{-30}\) esu)**

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>(\beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO(_2)</td>
<td>NMe(_2)</td>
<td>12.0(^a)</td>
</tr>
<tr>
<td>NMe(_2)</td>
<td>NO(_2)</td>
<td>12.0(^a)</td>
</tr>
<tr>
<td>CN</td>
<td>MeO</td>
<td>1.9(^b)</td>
</tr>
<tr>
<td>CN</td>
<td>NMe(_2)</td>
<td>5.0(^b)</td>
</tr>
</tbody>
</table>

Studies performed in CHCl\(_3\) unless indicated. \(^a\)acetone  \(^b\)dioxane

\(\beta\) than vinyl extensions. Attempts to correlate hyperpolarizabilities with absolute conjugation length have been made, but suffer from many complicating factors including solution conformation, solubility, differences in experimental procedures, and differences in counting schemes for different conjugation units.\(^3b,9\) When a correction for the increase per unit volume is made, the vinyl group is generally considered more efficient, as predicted by Morley.\(^10\) Thus, although their magnitudes are dependent on the nature of the extension, increases in hyperpolarizabilities are expected with increasing conjugation length.

The importance of the extension unit can be seen in Table IV. Despite the structural similarity between stilbene and \(\alpha,\omega\)-diphenylacetylenes, \(\beta\) values for the latter are reduced by about 50%. Therefore, acetylenic units are considered less efficient structures than olefins for increasing hyperpolarizabilities. This observation has been explained as the result of differing overlap efficiencies associated with two different sets of p-orbitals on the linker between phenyl units. Longer C-C bond distances between the phenyl unit and sp-acetylenic versus the \(sp^2\) ethylenic carbons and have also been proposed, based on structural data obtained by Graham.\(^5b\)

Aza substitution for ethylenic or either 2- or 3-positions of stilbene derivatives were detrimental to \(\beta\) values, reducing them in all cases studied by as much as 80%. This has been
Table IV. Effect of extension unit on β values (β*10^{-30} esu)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 = n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHO</td>
<td>MeO</td>
<td>2.2</td>
<td>12.0</td>
<td>28.0</td>
<td>42.0</td>
<td>-----</td>
</tr>
<tr>
<td>NO₂</td>
<td>NMe₂</td>
<td>50.0</td>
<td>73.0</td>
<td>107.0</td>
<td>131.0</td>
<td>190 ± 50</td>
</tr>
<tr>
<td>NO₂</td>
<td>SMe</td>
<td>----</td>
<td>34.0</td>
<td>55.0</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>NO₂</td>
<td>NH₂</td>
<td>7.8</td>
<td>22.0</td>
<td>24.0</td>
<td>41.0</td>
<td>----</td>
</tr>
<tr>
<td>NO₂</td>
<td>SMe</td>
<td>20.0</td>
<td>20.0</td>
<td>17.0</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>CN</td>
<td>SMe</td>
<td>15.0</td>
<td>15.0</td>
<td>17.0</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>NO₂</td>
<td>NH₂</td>
<td>----</td>
<td>10.0</td>
<td>24.0</td>
<td>16.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Studies performed in CHCl₃ unless indicated *neat bNMP cNMP: reported as product uB

cited as additional support for the importance of overlap efficiency, although geometrical arguments concerning the effect of heteroatom substitution in these derivatives should not be neglected. Polyphenyl derivatives are seen to reach a maximum β value at n = 2 to 3 phenyl units in cases studied, contrary to computational predictions of planar polyphenyls. This discrepancy is explained in terms of a cumulative decrease in overlap efficiency between consecutive phenyl units assumed to be twisted away from planarity by 20-30° at each ring junction in solution. This explanation is supported by the observation that fluorene analogs, with their more planar ring junction and therefore more efficient orbital overlap, exhibit consistently higher β values than the corresponding biphenyl derivatives. The difference in β values for fluorenes and biphenyls are seen to converge with increasing donor-acceptor strength, as shown in Table V. This observation may be explained as the result of larger charge-transfer electronic contributions to the ground state resulting in more nearly planar conjugation.

Table V. Effect of conjugation planarity on β values (β*10^{-30} esu)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>X—CH₂—Y</th>
<th>X—CH₂—Y</th>
<th>%Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>H</td>
<td>3.0</td>
<td>1.9</td>
<td>57</td>
</tr>
<tr>
<td>NO₂</td>
<td>Br</td>
<td>6.0</td>
<td>4.4</td>
<td>36</td>
</tr>
<tr>
<td>NO₂</td>
<td>OMe</td>
<td>11.0</td>
<td>9.2</td>
<td>12</td>
</tr>
<tr>
<td>NO₂</td>
<td>NMe₂</td>
<td>55.0*</td>
<td>50.0*</td>
<td>10</td>
</tr>
</tbody>
</table>

Studies performed in p-dioxane unless indicated *CHCl₃

Hyperpolarizabilities are expected to increase with conjugation length, but the magnitude is dependent on several factors including the type of extension, orbital overlap efficiency, and
conjugation planarity. When the efficiency per unit volume is considered, the order of group efficiencies is vinylc>phenyl>acetylenic for conjugation extension. Heteroatom substitutions had largely detrimental effects on $\beta$ in derivatives studied.

Aromaticity

The two-state model predicts that $\beta$ is dominated by a single charge-transfer transition, within the limitations mentioned previously. This qualitatively accurate approximation (Scheme I) indicates a loss of aromatic stabilization on proceeding from the aromatic to quinonal resonance forms. A logical design feature of NLO chromophores is then to reduce this loss by either ground state destabilization or excited state stabilization. Both approaches have been pursued.$^{3b,c}$ As seen in Table VI, replacement of a phenyl ring in the stilbene backbone with either thiophene or furan rings results in an increase of $\beta$. This gain has been attributed to the lower aromaticity of thiophene and furan which are estimated at 29 and 16 kcal/mol, respectively. Interestingly, on the basis of resonance energies alone, furan is expected to result in higher $\beta$ enhancement. That this is not observed may be indicative of the delicate balance between the quantities of Equation 1 as proposed by Marder.$^{3c}$ Charge transfer excited state stabilization has also been employed through the use of dimethylaminoindoaniline derivatives which possess aromatic and quinonal rings in both the ground and excited states, as shown in Scheme II. The success of this approach is evident in the large $\beta$ values measured for these

Table VI. Effect of aromaticity on $\beta$ values ($\beta*10^{-30}$ esu)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe$_2$-C$_6$H$_4$</td>
<td>73</td>
</tr>
<tr>
<td>NMe$_2$-C$_6$H$_5$O</td>
<td>83</td>
</tr>
<tr>
<td>NMe$_2$-C$_6$H$_5$S</td>
<td>98</td>
</tr>
<tr>
<td>NMe$_2$-C$_6$H$_5$N$_2$</td>
<td>91</td>
</tr>
<tr>
<td>NMe$_2$-C$_6$H$_5$N$_2$O</td>
<td>190</td>
</tr>
</tbody>
</table>

Studies performed in CHCl$_3$

Scheme II
compounds. The importance of energetic considerations between ground and excited states in organic NLO design is evident.

CONCLUSION

Several design principles for efficient chromophores exhibiting second order NLO behavior have emerged, due in large part to a growing database of reasonably accurate, experimentally determined, hyperpolarizability measurements. These principles can be explained in terms of a simple two-level model. Superior NLO chromophores to date\(^{(11)}\) have incorporated several design features including properly aligned, strong donor-acceptor combinations as well as efficient orbital overlap. Energetic considerations between ground and charge-transfer excited states are also of great importance. Since development of NLO devices will ultimately rely upon bulk properties of properly oriented chromophores, much work for the organic chemist remains.

REFERENCES


SELECTIVITY AND MECHANISM IN THE FRIEDEL-CRAFTS ALKYLATION OF BENZENE AND RELATED SUBSTRATES

Reported by Patrick L. Spence

October 22, 1992

INTRODUCTION

The Friedel-Crafts alkylation reaction has been known for well over 100 years. Until the 1960's, the Friedel-Crafts alkylation reaction was believed to proceed through a carbocation intermediate. Accordingly, it was thought that stereochemical details of the reactants would be lost in the alkylated product.

In 1962 Sharman demonstrated that Friedel-Crafts alkylation reactions of primary substrates proceed with partial displacement to give primary alkylated products, thus implying that the possibility for stereoselection exists. Study of the stereochemistry in the Friedel-Crafts alkylation reaction is desired for the practical application of this reaction in the synthesis of optically active compounds.

CHIRAL CYCLIC ALKYLATING AGENTS

In 1967, Brauman alkylated benzene (2) with optically active valerolactone (1) in the presence of aluminum chloride. 2-phenylbutyric acid (3) was produced in 55% yield with 40% overall net inversion of configuration. The formation of 3 with significant stereoselectivity was the first reported practical stereoselective Friedel-Crafts alkylation reaction.

Brauman performed a series of experiments to determine what affected the observed selectivity. He isolated unreacted starting material and product at various intervals during the course of the reaction, observing the optical purity of each (see Table I). Based on these data, Brauman concluded that 3 is not racemized under the reaction conditions, but 1 is, even in the absence of 2. Lowering the concentration of benzene causes the lactone to racemize to a greater extent during the course of the reaction.
Table I. Stereochemical course of the alkylation of 2 with 1.

<table>
<thead>
<tr>
<th>Run</th>
<th>Solvent</th>
<th>Time (sec)</th>
<th>% Conversion</th>
<th>% (1) Optical Activity Lost</th>
<th>% (3) Optical Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>7200</td>
<td>100</td>
<td>---</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>82</td>
<td>46</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>2 (1.9M) + CS₂</td>
<td>4800</td>
<td>100</td>
<td>---</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>2 (1.9M) + CS₂</td>
<td>143</td>
<td>26</td>
<td>18</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>2 (1.9M) + CS₂</td>
<td>415</td>
<td>70</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>CS₂</td>
<td>143</td>
<td>---</td>
<td>56</td>
<td>---</td>
</tr>
</tbody>
</table>

A mechanism was proposed (Scheme I), in which an intermediate species $X^*$ is suggested to be capable of maintaining the stereochemical integrity of 1.

Scheme I

A structure for $X^*$ is shown in Figure I. Brauman stresses that this is not the only possible structure for the proposed intermediate. It does, however, provide for the stereoselectivity observed in the reaction due to the proposed proximity of the leaving group to the carbocationic center. This maintains a chiral environment for reaction with benzene.

Figure I. One possible structure of $X^*$, as described by Brauman.
Following the work of Brauman,\textsuperscript{3a-b} others began exploring the use of optically active cyclic alkylation agents in the Friedel-Crafts reaction. Suga and co-workers studied the alkylation of benzene with optically active cyclic ethers,\textsuperscript{4a-c} obtaining modest to excellent optical and poor to modest chemical yields (see Table II).

**Table II.** Enantioselectivities observed in the alkylation of 2 with chiral cyclic ethers.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Optical Yield</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AlCl₃ / 20-30°C</td>
<td></td>
<td>35%</td>
<td>&gt;50%</td>
<td>3b</td>
</tr>
<tr>
<td></td>
<td>AlCl₃ / -5°C</td>
<td></td>
<td>100%</td>
<td>56%</td>
<td>4a</td>
</tr>
<tr>
<td></td>
<td>AlCl₃ / 0°C</td>
<td></td>
<td>100%</td>
<td>14%</td>
<td>4b</td>
</tr>
<tr>
<td></td>
<td>SnCl₄ / -10°C</td>
<td></td>
<td>62%</td>
<td>12%</td>
<td>4c</td>
</tr>
</tbody>
</table>

Suga rationalized the decreased selectivity for 2-methyloxetane (62\%) by invoking competing pathways leading to the alkylated product. One pathway involves S\textsubscript{N}2-like attack on C-2 of the oxetane ring by benzene, while the other involves racemization through the carbocation produced after Lewis acid opening of the oxetane ring.

\(\alpha\)-aryl substituted amino acids have been synthesized using the cyclic bislactim ether (4) by Schöllkopf in the alkylation of anisole (5).\textsuperscript{5} The optical purity observed in this reaction (Scheme II) was excellent (90\%). The chemical yield is fair (57\% for the isomer shown), but as with many Friedel-Crafts reactions, other regioisomers are formed in competition. As expected, this problem is amplified as the aromatic group becomes larger and/or more substituted.
Schöllkopf proposes an $S_N1$-type mechanism for this reaction. Following chloride ion departure, a chiral cation (7) is formed, which may have a steric bias for reaction from the face which is trans to the bulky isopropyl group (Figure II).

Figure II. Chiral glycine cation equivalent proposed by Schöllkopf.

In another example of amino acid synthesis, Kronenthal and co-workers utilized 4-substituted (N-protected) proline derivatives in a stereospecific alkylation of benzene. They observed that the optical yield of 9 was >98% with 90.5% chemical yield, even when the reaction is run on a 100 kg scale.

CHIRAL ACYCLIC ALKYLATED AGENTS

The first successful application of chiral acyclic alkylating agents in the Friedel-Crafts reaction was performed by Suga and co-workers (Scheme III). Under optimum conditions, the maximum optical yield Suga achieved was 54%, with a chemical yield of 20% (10c at 30°C).

Scheme III
Suga alleges that the selectivity hinges on six-membered quasi-ring structures which act as the alkylating agents (see Figure III). Therefore, the stereoselectivity can be rationalized through a comparison of ring structure stabilities. Furthermore, the stereoselectivity is proposed to be dependent on the "tightness" of the ion pair formed after chloride departure. Suga does not, however, present any physical evidence for the formation of complexes 12a-d. In addition, there may be some uncertainty as to whether or not complexes such as 12c or 12d are formed in solution.

![Figure III. Six-membered cyclic aluminum complexes proposed by Suga and co-workers.](image)

Effenberger studied the alkylation of benzene with chiral threonine and allothreonine trifluoromethanesulfonates in the presence of trifluoromethanesulfonic acid (Scheme IV), in an effort to synthesize β-substituted-α-amino acids of high optical purity. High diastereoselection was observed for alkylations with threonine derivatives (≥94%), while low diastereoselection was observed for the allothreonine derivatives (20%). In both cases, however, the overall chemical yields were 20-40% (60-80% elimination). This selectivity was rationalized on the basis of the hindered rotation of the carbocation produced after triflate departure (see Figure IV). Experimental evidence to support this hypothesis involved two simple experiments. First, the N-
protected amino functionality was removed and the chiral ester obtained was subjected to the alkylation conditions. The product obtained was racemic. Second, the ester functionality was removed and the chiral N-protected aminotrifluorosulfonate was allowed to react. The alkylated product was isolated in 56% e.e., thus establishing that the N-phthaloyl group plays an important role in the selectivity of this reaction.

![Threonine](image1.png)

**Figure IV.** Rationale for selectivity observed by Effenberger.

The synthesis of non-steroidal anti-inflammatory drugs was the goal which prompted Piccolo to alkylate many aromatic compounds with derivatives of optically active 2-hydroxyproprio- and butanoates (Scheme V). Optical yields ranged between 61% (X = Tol, Ar = p-Cl-Ph, R = C2H5, n = 0) and >99% (X = Cl, Ar = Ph, R = CH3, n = 0), with chemical yields of 20% (mixture of three isomers) and 70%, respectively. The selectivity observed was proposed to be dependent on the stability of an aluminum chelated structure (Figure V) similar to that proposed by Suga. Again, no evidence was provided to account for the mechanism. Piccolo does not specify the nature of aluminum species, or in what form it exists in solution.

**Scheme V**

\[
\begin{align*}
XO_2SO + ArH &\rightarrow AlCl_3 \rightarrow XO_2SO
\end{align*}
\]

\[
\begin{align*}
X = CH_3, Cl, Tol, CF_3 \\
Ar = Ph, Tol, Naphthalene, p-Cl-Ph \\
n = 0,1 \\
R = CH_3, C_2H_5
\end{align*}
\]
Figure V. Aluminum chelated structure proposed by Piccolo.

ALKYLATIONS OF PHENOLIC SYSTEMS

Bigi and others have done important work in the area of asymmetric Friedel-Crafts regioselective ortho-hydroxy alkylation of phenolic systems. The reaction is useful because one can use chiral alkylating agents, chiral Lewis acids (derived from alcohols in the chiral pool), or a combination of the two, as shown in Scheme VI.\textsuperscript{12}

Scheme VI

![Scheme VI diagram]

Erker has described a catalytic version of the asymmetric ortho-hydroxylation of phenols in which a camphor-derived zirconium complex is used (Figure VI).\textsuperscript{13} Typically, 1-5 mol\% of catalyst is required for the reaction which can be run on a preparative scale obtaining 56\% isolated yield and >80\% enantiomeric excess.

Figure VI. Camphor derived zirconium catalyst as described by Erker.
CONCLUSION

The asymmetric Friedel-Crafts reaction has shown utility in the synthesis of β-substituted α-amino acids,9 non-steroidal anti-inflammatory drugs (i.e. ibuprofen was synthesized by Piccolo in 50% chemical and 98% optical yield)10, α-aryl glycine esters,5 and other aryl substituted carboxylic acids and esters.1,3,4,7,12

The stereochemical course of the reaction appears to depend on the leaving group employed, structural features of the alkylating agent (i.e. cyclic, chelated, etc.), temperature, and the solvent. The main limitation of the stereoselective Friedel-Crafts reaction, as stated earlier, is not that of stereochemistry but of regiochemistry. If the regiochemical outcome of a reaction is known or biased towards one product, this reaction will be of definite practical value in the synthesis of optically active compounds.

REFERENCES

SELECTIVE ZIRCONIUM-CATALYZED CARBOMAGNESATION OF ALKENES

Reported by Luis E. Martínez Jr. October 29, 1992

INTRODUCTION

Selective carbon-carbon bond forming reactions have been at the forefront of recent advances in organic chemistry, particularly the area of organozirconium chemistry.¹ In contrast to the more active areas of catalytic organozirconium chemistry, the zirconium-catalyzed carbomagnesation of olefins has been relatively less developed. Within the past year, however, a considerable amount of attention has been focused on the regio- and diastereoselectivity of the zirconium-catalyzed carbomagnesation of various alkenes.

BACKGROUND

Dzhemilev reported the first zirconium-catalyzed carbomagnesations of unfunctionalized alkenes during attempts to prepare higher-order organomagnesium compounds.² He observed that the carbometallation of 1-hexene, 1-octene, 1-decene, and allylbenzene with Et₂Mg is catalyzed by zirconocene dichloride (C₉H₆ZrCl₂) and results in the corresponding primary organomagnesium compound. The reaction is highly regioselective, with exclusive β-alkylation, and proceeds in excellent yield under very mild conditions. Dzhemilev, et al.³ have found that this transformation could also be applied to a variety of functionalized α-olefins (Scheme I).

Scheme I

\[
\begin{align*}
\text{R-} & \quad + \quad \text{excess } \text{Et}_2\text{Mg} \quad \xrightarrow{\text{cat. } \text{Cp}_2\text{ZrCl}_2} \quad \text{Et}_2\text{O}, 20-25 ^\circ\text{C} \quad \rightarrow \\
\text{Et}^\text{MgEt} & \quad \text{R-} \quad \text{R'} \quad \text{MgEt}
\end{align*}
\]

Carbomagnesations of polyenes occur chemeoselectively at the terminal olefin without isomerization of internal double bonds. The regioselectivity of the carbomagnesation is unaffected by varying the allylic substituent. However, a decrease in reactivity is observed using heteroatom substituted vinylic substrates, such as enamines and enol ethers. Homoallylic alcohols were found to be completely unreactive under identical conditions. In
these carbomagnesation reactions, Et$_2$Mg was found to be a superior reagent relative to alkylmagnesium halides, which gave lower yields and both regioisomers. Further synthetic use of the zirconium-catalyzed carbomagnesation of alkenes and investigations of the reaction mechanism remained underdeveloped until 1991.

UNFUNCTIONALIZED ALKYL-ALKENE COUPLING

Hoveyda$^4$, Negishi$^5$, and Waymouth$^6$ independently found that dialkylmagnesium Grignard reagents are not necessary; carbomagnesations with alkyl magnesium halides are effective and proceed with excellent regiocontrol (<99:1). Both Hoveyda and Negishi expanded the utility of this reaction by trapping the newly resulting Grignard reagent with electrophiles, resulting in either double alkylation or hydroxylation products in moderate to good yields (Scheme II).

Scheme II

![Scheme II](image)

Mechanism

Negishi undertook a series of deuterium labeling experiments, to elucidate the mechanism of the carbomagnesation, by quenching reaction mixtures with D$_2$SO$_4$ / D$_2$O. Under stoichiometric conditions (1:1, Cp$_2$ZrCl$_2$:EtMgX), 1 is produced with deuterium incorporation of >90% in the terminal CH$_2$D group and >98% in the 3'-CH$_2$D group. Under catalytic conditions (5 mol% Cp$_2$ZrCl$_2$, 3 eq. EtMgX), 2 was isolated with >90% D incorporation only at the terminal 3-methyl carbon atom, deuterium incorporation at the 1-methyl carbon atom was negligible (<2%). Metallocyclopentane 3 and the organomagnesium 4 were proposed as precursors for the formation of 1 and 2, respectively.
Zirconium cyclopropane 5 was implicated in the catalytic carbomagnesation. In solution, transmetallation of Cp₂ZrCl₂ with ethyl Grignard reagent forms Cp₂ZrEt₂. Under catalytic conditions, Cp₂ZrEt₂ undergoes β-elimination followed by reductive elimination to form zirconium cyclopropane 5. However, Negishi and Hoveyda both report that carbomagnesation does not occur with the use of a methyl Grignard reagent.

The intermediacy of 3 in the catalytic cycle was also inferred. When pre-formed 3 reacts with 1 eq. of EtMgBr and is quenched with D₂SO₄ / D₂O, 2 is isolated. Subsequent conversion of 5 to 3 by olefin insertion was implicated by the isolation of a Cp₂Zr(CH₂CH₂)P(CH₃)₃ adduct by adding P(CH₃)₃ to a solution of pre-formed 3 and 1 eq. of EtMgBr.⁵

Negishi proposes that under catalytic conditions, metallocyclopropane 5 undergoes olefin insertion to form metallocyclopentane 3. Subsequently, metallocyclopentane 3 reacts with excess EtMgBr in solution, to give zirconate complex 6. He states the observed regioselectivity of the reaction is steric in origin with the conversion of 6 to 7 strongly favored to the conversion of 6 to 8 (Scheme III).

Scheme III
Consequently, 8 may not be formed. If 8 was to form and the conversion of 6 to 8 was reversible, a Curtin-Hammett situation would be in operation. In this case, one might expect intermediate 8 to be more reactive than 7 due to steric congestion; however, the observed product formed can only be derived from 7. The factors accounting for the enhanced reactivity of 7 with respect to 8 are as of yet unkown.

**ALKYL COUPLING TO ALLYLIC AND HOMOALLYLIC ALCOHOLS AND ETHERS**

Hoveyda has further expanded the scope of carbomagnesation by showing that allylic alcohols and ethers are also suitable substrates.\(^4\) Cis-diols can be formed with excellent diastereoselectivity via the zirconium-catalyzed ethylmagnesation of allylic alcohols, followed by reaction with trimethylborate and hydrogen peroxide. In contrast, ethylmagnesation of allylic ethers proceeded with good, but opposite, selectivity to the anti diastereomers. When a THF/ether mixture was used as the solvent, a decrease in selectivity was observed for the alcohol but not the ethers (Table I). Similar trends in diastereoselectivities were also observed in the carbomagnesation of homoallylic alcohols and ethers.\(^7\)

**Table I**

<table>
<thead>
<tr>
<th>R</th>
<th>Solvent</th>
<th>10:11</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Et₂O</td>
<td>95:5</td>
</tr>
<tr>
<td></td>
<td>50%Et₂O/THF</td>
<td>73:27</td>
</tr>
<tr>
<td>Me</td>
<td>Et₂O</td>
<td>11:89</td>
</tr>
<tr>
<td></td>
<td>50%Et₂O/THF</td>
<td>11:89</td>
</tr>
<tr>
<td>MEM</td>
<td>Et₂O</td>
<td>10:90</td>
</tr>
</tbody>
</table>

These results suggest that chelate controlled delivery may be responsible for the high syn selectivity observed in carbomagnesation of alcohols. In the reaction of alcohols in THF, chelation of the magnesium alkoxide may be hindered due to effective coordination of THF to the metal. The diastereoselectivity of the carbomagnesation of the allylic ethers was observed to be unaffected by the presence of THF. Consequently, the carbomagnesation of the allylic ethers are postulated not to involve chelation of the substrate by the transition metal complex and formation of the anti-diol is favored.
Mechanistic Implications

Although the metallocyclopentanes suggested by Negishi are reasonable intermediates, Hoveyda argues that simple olefin insertion into a zirconacyclopropane alone cannot account for the observed levels of selectivity and reactivity in the carbomagnesation of allylic and homoallylic alcohols and ethers. The carbomagnesation of endo-5-nobornen-2-ol was studied in order to investigate the mechanism and the factors important for the observed diastereoselectivity.8

Zirconium-catalyzed carbomagnesations of endo-5-nobornen-2-ol with n-butyl magnesium chloride and n-propyl magnesium chloride produce sec-butyl and isopropyl substituted products, respectively. Carbomagnesations with CH2CD2MgBr under catalytic conditions resulted in significant deuterium scrambling on C1’ and C2’ of the alkylated products (Scheme IV). These results suggest that a zirconacyclopropane, similar to 5, acts as a nucleophilic alkylating agent.

Scheme IV

![Scheme IV diagram]

The difference in the reactivity and selectivity between the stoichiometric and catalytic versions of the experiment was determined by varying the concentration of Grignard reagent and Cp2ZrCl2. In reactions of varying concentrations of Cp2ZrCl2 and constant Grignard reagent, the consistent formation of a 70:30 ratio of regioisomers in 35-60% conversion was observed. However, in reactions where the concentration of Grignard reagent was varied with respect to Cp2ZrCl2, a dramatic increase in alkylation regioselectivity (97:3) and conversion (100%) was observed.

Therefore, the key to understanding the selectivity and reactivity of the reaction lies with the presence of excess Grignard reagent. Hoveyda proposes that excess Grignard reagent effects the selective formation of a metallocyclopentane by generating zirconate complex 13, which is more susceptible to ligand exchange than 12. Subsequent displacement of the alkene ligand from 13 with substrate leads to the formation of a zirconocene complex 14 of the reacting alkene.
Chelation of complex 13 with the heteroatom of a substrate having a proximal alkene allows the stereoselective association of the zirconium with the reacting alkene. With the parent zirconocene 12, such an association and internal delivery is not possible. To account for these observations, Hoveyda proposes the following mechanism (Scheme V) invoking pre-association of the transition metal with the alkene and the presence of two zirconocene complexes.

Scheme V

Hoveyda argues that since both chelation and excess Grignard are important for high selectivity, internal association of excess Grignard with the heteroatom and the proximal alkene could account for the regioselectivity. Such a complex would involve a magnesium salt complex similar to 17 and would consequently be affected by changes in the concentration of magnesium salts. Zirconium-catalyzed carbomagnesations of cyclic homoallylic alcohols and ethers, however, are independent of the concentration of added magnesium salts. In addition, carbomagnesation occurs with similar efficiency and selectivity using dialkylmagnesium reagents instead of alkylmagnesium halides.

ASYMMETRIC CARBOMAGNESATION

An obvious extension of this zirconium-catalyzed carbomagnesation would be to attempt an asymmetric version. Already, $C_2$ symmetric zirconocenes have been developed for the generation of homogeneous Ziegler Natta catalysts for the stereoselective polymerization of propene. Hoveyda and co-workers have found that Brintzinger's ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl) zirconium dichloride (R)-22, is an effective catalyst for asymmetric carbomagnesations. Reactions with (S)-1-decen-3-ol exhibited high levels of double diastereodifferentiation with 22 while reactions with the (R) enantiomer gave little or no
diastereodifferentiation. A mechanism similar to Scheme IV, involving the pre-association of zirconocene 22 with both the reacting alkene and the neighboring heteroatom is consistent with diastereoselectivity arising from stereochemically matched and mis-matched cases.

CONCLUSION

It has been demonstrated that the zirconocene catalyzed carbomagnesation of alkenes has potential as a useful synthetic method. These reactions permit the unprecedented regioselective alkylation of an unfunctionalized terminal olefin in a simple one-pot procedure. The extremely mild reaction conditions, short reaction times, high regioselectivities, and high diastereoselectivities with allylic and homoallylic substituted alkenes illustrate the practicality of these reactions. In addition, the ability to use chiral zirconocene catalysts for highly selective asymmetric carbomagnesations has been demonstrated.

REFERENCES

THERMAL ORGANIC REACTIONS IN THERMOTROPIC LIQUID CRYSTALLINE SOLVENTS

Reported by Jana L. Westran

November 16, 1992

INTRODUCTION

Liquid crystals\(^1\) have been known for a long time\(^2\) but it has only been in the last 25 years that their influence on organic reactions has been studied. Thermotropic liquid crystals are intermediate between solids and isotropic liquids, and as such, possess some properties of both. Liquid crystals have an ordered arrangement of molecules yet possess a conformational flexibility that allows molecular motion. Although the first observation of the influence of liquid crystalline solvents on dissolved solute molecules was reported by Svedberg\(^3\) in 1916, no further work was reported for another 50 years. The organizational properties available from thermotropic liquid crystalline solvents have recently been utilized to influence the course of thermal reactions.\(^4\)

BACKGROUND

Asymmetric Induction

Asymmetric induction by liquid crystalline solvents was a very controversial area of study for some time. Attempts at asymmetric induction were reported by many groups. The chiral twist of cholesteric liquid crystals was thought to have an influence on the course of several types of reactions, however, positive results achieved in one laboratory could not be reproduced in other laboratories. Verbit reported the asymmetric decarboxylation of ethylphenylmalonic acid to yield 2-phenylbutanoic acid with 18\% enantiomeric excess.\(^5\) They hypothesized that a shorter helical pitch in the liquid crystal would result in a product of higher optical purity. The study of the equilibration of interconvertible isomers of sulfoxides by Pirkle\(^6\) did not seem to support this hypothesis. These experiments, as well as others,\(^7\) were repeated by Kagan\(^8\) who did not find significant optical activity in any of the products. Kagan concluded that liquid crystals would never induce more asymmetry in a dissolved solute than can be achieved in isotropic chiral solvents except possibly in cases where strong and specific interactions between the solvent and solute were present.

The absence of asymmetric induction by cholesteric liquid crystals was explained by examining the structures thought to be the cause of the transferred optical activity. The helical pitch of most cholesteric liquid crystals is typically greater than 3000 Å.\(^8\) Thus the local environment of the reacting solute molecules includes only a very small portion of this twist. Only very large solute molecules would be able to detect enough of the twist to be influenced by it. In this case the solute molecules would tend to disrupt the ordering of the mesophase thereby making the solvent more nearly isotropic. It is now generally accepted that liquid crystalline solvents cannot be used...
to induce a significant amount of optical activity in solute molecules. The organization present on the molecular level, however, was still looked upon as a promising method of affecting transition state geometries and, therefore, product distributions.

**Rearrangements**

Liquid crystals are arranged so that the long axes of molecules are parallel. If a solute molecule has a long axis, the order of the solvent could force the solute molecules to orient themselves in the same manner as the solvent. If a reacting molecule can go through two or more different transition states to products, it would be expected that the transition state that best fit into the ordered solvent would be stabilized and therefore facilitate a higher relative yield of that product. Rod-like transition states should be favored over box-like transition states as they would require less reorganization of the surrounding solvent molecules. The results of several groups reporting on the Diels-Alder\(^9\) and Claisen rearrangements\(^{10}\) of benzene derivative substrates prior to the late 1980's did not support this hypothesis.

![Higher Energy vs Lower Energy](image)

**Isomerizations**

Isomerization reactions were studied in various liquid crystalline solvents. Results of kinetic studies were used by Weiss to help determine the mechanism of the syn to anti isomerization of azobenzene\(^{11}\). Two different mechanisms are possible: inversion, which would require very little solvent reorganization; and rotation, which would require a great deal of solvent reorganization and therefore should have a large positive $\Delta S^\ddagger$ relative to isotropic solvents. The activation parameters were calculated for fifteen 2- and 6-substituted low bipolarity azobenzenes in several liquid crystalline and isotropic solvents and it was found that these reactions showed little dependence on solvent order. Weiss concluded, therefore, that the isomerization was via an inversion mechanism.

Other isomerization reactions were studied and led workers to believe that solvent order can affect unimolecular reactions. The rate of racemization of 1,1'-binaphthyl (BN) was studied in one cholesteric\(^{12}\) and several nematic\(^{13}\) phases by Weiss and coworkers. It was found that BN racemized faster in the ordered solvents than in isotropic solvents. Samori\(^{14}\) studied the rearrangements of linalool and limonene and found that the reaction products and their ratios changed dramatically when liquid crystalline solvents were used.
Two well studied isomerization reactions are the quaternization of p-(dimethylamino)benzenesulfonate (methyl sulfonate ester, MSE) and allyl p-(dimethylamino)benzenesulfonate (allyl sulfonate ester, ASE) (Scheme I).\textsuperscript{15} Both are stable indefinitely in isotropic solvents while MSE rearranges to the zwitterion in the pure solid state or pure melt. ASE only undergoes rearrangement in the pure melt. Both MSE and ASE undergo isomerization to the zwitterion in liquid crystalline solvents at a faster rate, under the same conditions of temperature and time, than by any other method.

Scheme I

\begin{align*}
\text{MSE} \quad & \quad \text{AZWI} \\
\text{ASE} \quad & \quad \text{AZWI}
\end{align*}

Further kinetic studies\textsuperscript{16} on ASE and MSE quaternization reactions revealed a sigmoidal rate dependence on total solute concentration which was explained by a very sudden loss of solvent cooperative effects on the reaction. There is an unusual curvature to the second order Arrhenius plot. The authors postulate that the degree of smectic assistance varies with temperature and this effect is superimposed on the normal Arrhenius behavior. Recall that this reaction does not occur in isotropic solvents and is much slower in the pure solid and melt. The smectic phase has a catalytic effect on the reaction. At very high solute concentrations, optical microscopy shows that solute aggregation occurs and therefore the rate drops giving the sigmoidal plot.

One explanation for a curved Arrhenius plot is that there are two competing reaction mechanisms that dominate in two different temperature ranges. In this case the temperature range is quite small (\(-33 \text{ to } 43 \degree C\)) and two different mechanisms seem unlikely to the authors. They propose that this effect is due to the existence of two different solubilization sites within the liquid crystal. Linear dichroism\textsuperscript{17} measurements show two maxima (263 and 277 nm) which are interpreted as two different sites within the smectic structure of the solvent. These two sites are postulated to be the rigid cores and the flexible alkyl chains.

Study of isomerization reactions show that it is possible to affect reactions of solutes dissolved in liquid crystals. Once it was shown that the order of the solvent could affect reactivity in some cases, it remained to be understood why in other cases, particularly bimolecular cases, no apparent effects were noted. Some basis for understanding these problems recently came from work in a related field.
SOLUBILIZATION

Recent work directed toward the study of photochemical reactions in liquid crystalline solvents revealed that benzene derivatives actually have a much lower solubility in the liquid crystalline solvents than previously thought.\textsuperscript{18,19} Microscopy and other methods used in the past were unable to detect the complicated mixtures that were actually present. For the CCH-\(n\) series of liquid crystals (Figure 1) the solubility of 1 (for example) was found to be less than 1\% by \(^2\)H NMR studies. What previously had been regarded as a smectic phase was actually a mixture of smectic, solute enriched nematic,\textsuperscript{18} and (below 35 °C) a highly concentrated isotropic liquid.\textsuperscript{19} This attenuates the product differences predicted for the smectic phase.\textsuperscript{20} The reacting molecules actually present in the smectic phase were affected by the surrounding order and predominantly give the expected product. Those solute molecules in a less ordered microphase would, however, give results more similar to those found for isotropic solvents. The two product distributions were mixed when the products were isolated and analyzed. The authors claim this to be one possible reason that previous studies found only very small effects.\textsuperscript{21}

![Chemical structure](image)

Figure 1

RECENT PROGRESS

Very recently the results of the solubilization studies have been applied to new work on thermal organic reactions in liquid crystalline solvents. Bimolecular pericyclic reactions have been studied and dimerization kinetics and nitroxyl radical reduction kinetics have been modeled in the mesophase and in the pretransitional temperature region.

Pericyclic Reactions

Leigh and Mitchell recently reported\textsuperscript{22} the first clear example of the use of cholesteric liquid crystalline solvents to influence the reactivity of solutes toward transition states that are compatible with the weakly ordered solvent matrix. Cholesta-5,7-dien-3\(\beta\)-yl acetate (2) is known to undergo ene and Diels-Alder reactions with electrophiles in isotropic media (Scheme II). In this study it was shown that the use of cholesteric or nematic liquid crystals as solvents caused the yield of one of the minor products (6) to be significantly increased. Inspection of the transition states leading to the different products shows that the structure leading to the ene adduct (5) and the Diels-Alder
adduct (4) have the long axes of the molecules perpendicular to each other. Formation of (6) occurs with the two molecules aligned parallel to each other. The ordering of the liquid crystalline solvents would be disturbed least when reaction occurred via the transition state leading to (6). Solvent order and the activation enthalpy will favor the parallel transition states whereas the activation entropy should favor the perpendicular transition states, consequently this is not the only product seen. Further reports indicate that the results with other electrophiles and in several different cholesteric media support this interpretation. It should be stressed, however, that no new products were detected; minor products in isotropic solvents are enhanced.

Scheme II

![Scheme II](image)

Scheme III

![Scheme III](image)

$R_1 = \text{Phenethyl, Ph, p-MeO-Ph, Me, n-Pro}$
$R_2 = \text{Me, n-Bu, MeOCH}_2\text{CH}_2, \text{Phenethyl}$
Kunieda found that when liquid crystalline cholesteric fumarates are used as both dienophiles and solvents in the uncatalyzed cycloaddition reactions with 2,6-dialkoxyanthracenes, a highly regioselective (70% d.e.) formation of the syn-adducts was found (Scheme III). In isotropic media such as xylene or mesitylene, the reaction gives four diastereomeric products with no regiochemical or diastereoochemical selectivity. Further reports indicated that reactions of trans-4-cyclohexylcyclohexyl fumarates with 2,6-dibutoxy- and 2,6-bis(decyloxy)anthracenes in the cholesteric solvent CDCB give even larger diastereoselectivities (up to 90% d.e.). These studies demonstrate that the anisotropic order imposed by the liquid crystalline dienophiles can result in a regiochemically controlled bimolecular Diels-Alder reaction.

**Mathematical Models**

Batyuk and Sergeev have studied two reactions in liquid crystalline solvents and have formulated a model to predict the behavior of solutes in these solvents. These models are also being developed to aid in forecasting the feasibility of stereospecific synthesis.

The kinetics of the reduction of several nitroxy radicals with hydrazobenzene and diphenylcarbazone was studied in both the isotropic and nematic phases of MBBA. Previous studies and observations in the liquid crystalline phase were used to formulate relationships between the parameters of the reaction. Overall, three methods were proposed to account for the influence of the nematic ordering over the reaction. It was concluded that the relative increase of the experimental rate constant in the nematic phase was associated with a decrease in the reaction activation energy due to the stabilization of the transition state by the nematic solvent.

Once the relationships were determined, the group investigated how well they could predict the behavior of another system: the dimerization of 2-methyl-2-nitrosopropane. Based on four data points, they claim that at high temperatures the deviation between the predicted and experimental data increases slightly but the correlation is very good. The deviations are explained by the choice of a poor approximation of one parameter in the equations. They conclude that in some cases their model can be used for the description of chemical kinetics in nematic liquid crystalline systems.

**CONCLUSIONS**

Even though early results did not show much promise, utilizing the order of liquid crystalline solvents as an organizing force for thermal organic reactions has yielded promising results. Developments in the related photochemical field shed light on the fact that past failures could possibly be attributed to poor solubilization of the solutes in the liquid crystalline phase. With closer attention to solubilization and a proper matching of solute and solvent structure, a higher degree of solvent influence is detected. As further work in this area develops it is possible that minor reaction products will become the major ones (and therefore be of greater utility to
REFERENCES


(2) Discovery: Reinitzer F.; *Monatsh. Chem.*, 1888, 9, 421.


Liquid Crystals Used in These Studies

CnP  \( R = \text{CH}_2\text{CH}_3 \\
CnB  \( R = \text{C}_6\text{H}_5 \\
CnT  \( R = \text{p-H}_3\text{C-C}_6\text{H}_4 \\
ChCB \( R = \text{p-Cl-C}_6\text{H}_4 \\
CDCB \( R = 2\text{-Cl}_4\text{-Cl-C}_6\text{H}_3 \\

\[ \text{H(CH}_2)_5\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{(CH}_2)_3\text{H} \]
INTRODUCTION

Since the first investigations into the oxidation and cyclization of squalene\(^1\) to lanosterol (in animals and fungi) and cycloartenol (in higher phototropic plants), chemists have been fascinated with the mechanistic aspects of the enzyme responsible - oxidosqualene cyclase (OSC). Understanding the role of OSC in forming sterols precursors poses significant synthetic and mechanistic challenges and has practical implications as well. For instance, since lanosterol is the precursor of cholesterol, the ability to inhibit its formation has obvious merit. Currently compounds such as mevinolin\(^2\) and compactin\(^3\) are used to reduce serum cholesterol levels in humans by inhibiting HMG-CoA reductase. The inhibition of HMG-CoA reductase occurs well before the formation of squalene in the biosynthetic pathway and prevents the formation of other biologically important compounds in addition to squalene. An understanding of the mechanistic aspects of OSC will provide the prerequisites for rational inhibitor design.

DISCUSSION

The first studies of the cyclization of squalene involved feeding experiments which indicated the folding shown (Scheme 1) followed by the H/CH\(_3\) rearrangements which lead to the observed carbon atom arrangement. The original cyclization model proposed the formation of the ABCD ring system through a series of transient carbonium ions leading to the intermediate cation at C(20) (2). This step was followed by the H/CH\(_3\) rearrangement.\(^4\)\(^{a,b}\) At that time it was assumed that the cyclization was initiated by the transfer of a suitable electrophile such as a hydroxonium cation to the C(2) olefin of squalene with concomitant formation of the ring nucleus.\(^4\) Later, it was demonstrated that oxidosqualene (1b) was the active substrate for OSC and that a different enzyme, squalene epoxidase, was responsible for oxidosqualene formation.\(^5\)\(^,\)\(^6\) A considerable amount of early work was focussed on substrate analogs in an effort to elucidate the enzymes mechanistic aspects. Oxidosqualene was modified in a number of ways.

Copyright © 1992 by James B. Day
The most notable was a series of analogs with deleted methyl substituents. These experiments demonstrated that the C-6, C-10, C-15 methyl groups are not necessary for cyclization and rearrangement (when C-10 and C-15 were simultaneously missing the H/CH$_3$ shifts did not occur). The enzyme prefers substrates that are bis alkylated at C-2 with the incipient 4α substituant in the tetracycle having a degree of flexibility with respect to size and functionality.

**Scheme 1**

![Scheme 1](image)

The typical enzyme source for most experiments has been sedimented microsomes from animals, plants, and baker's yeast (*Saccharomyces cerevisiae*). Microsomal OSC from rat liver has been shown to be an internally bound membrane protein whose function depends to some degree on the membrane. Kinetic data for reactions using microsome suspensions are complex due to the heterogenous conditions. OSC has been isolated from the membrane by the use of detergents such as deoxycholate, however, it has been demonstrated that these detergents alter the rate of cyclization of the membrane free enzymes. More recently the pure enzyme has been obtained chromatographically from baker's yeast using a substrate analog as the stationary phase. Even though this circumvents the problems associated with detergents, the enzyme dependence on the membrane remains unresolved.

More recently, studies of OSC have focused on the development of inhibitors whose design is based upon on proposed high energy intermediates. The first such intermediate is represented by a series of C(2) aza analogs (quaternary amines and N-oxides) of squalene (4a-4e) which have demonstrated relatively high inhibitory potential. The rationale for their potency is based on the assumption that the mechanism of epoxide opening is somewhere between classical $S_N$1 (protonated epoxide opening forming a C(2) cation) and $S_N$2 (epoxide opening with the C(6) double bond acting as nucleophile at C(2)). The charge developed at C(2) is mimicked...
by these analogs. Interestingly, one of the most effective inhibitors to date is the substrate analog iminosqualene (1b). Other aza analog inhibitors simulate cations at ring closures for the A(5) and B rings. These compounds have demonstrated inhibition potential and support the assumption that the cyclization may not be fully concerted, but instead may be stepwise with enzymatically stabilized intermediates. 4,4,10β-Trimethyl-trans-decal-3β-ol analog (TMD) is a neutral carbocycle that imitates the AB ring system and is currently being investigated for therapeutic development.

The classic model for cyclization places the side chain at C(17) in the β orientation and assumes that the H/CH₃ rearrangement leads to the α-orientation observed in the product. Experiments which have trapped the C(20) cation intermediate without the rearrangement have shown the C(17) side chain to be α oriented. This raises questions about the orientation of the side chain during D ring formation and challenges the classic cyclization mechanism.

REFERENCES


CHIRAL RECOGNITION OF ORGANIC SUBSTRATES BY DESIGNED ORGANIC RECEPTORS

Reported by Yuelong Liu November 23, 1992

INTRODUCTION

Chiral recognition in designed complexes has attracted increasing interest in recent years due to the recognized fact that successful developments in this research area promise to provide new methods for enantiomeric separation,¹,a transport¹,b and even new reagents for asymmetric synthesis and catalysis.² This seminar will discuss recent work toward enantioselective complexation of designed organic receptors with chiral organic substrates in solution.

CHIRAL RECEPTORS FOR ENANTIOMERIC RECOGNITION OF ORGANIC CATIONS

One area of recent interest is the enantioselective recognition of ammonium salts of organic amines and amino acids and esters by chiral macrocyclic receptors,³-⁴ mainly chiral crown ethers.⁵ Several research groups have carried out work involving these chiral recognition systems. Cram and his co-workers carried out some of the most significant and elegant work in this area. They described the first chiral crown ethers exhibiting enantiomeric recognition towards cationic salts of organic amines and amino acids in 1973,⁶ and their systematic efforts and scrutiny resulted in enantioselective solvent extraction techniques, chromatographic separation and liquid membrane transport of enantiomers of ammonium salts of a series of amines and amino acids and esters.⁷ In the liquid-liquid extraction, enantiomeric distribution constants (EDC) as high as 30 were observed,⁸ which corresponds to ΔΔG = 1.9 kcal/mol. Equally significantly, the observed sense of selectivity can be rationalized by chiral recognition models.⁷

One of the most characteristic structure features of synthetic receptors reported so far is the use of large rings. This is not surprising since macrocyclic linkage can function to preorganize a receptor to reduce the number of its non-contributing conformations and to favor its binding conformation(s) which might otherwise be disfavored both entropically and enthalpically in the corresponding acyclic receptors.⁷,⁹ However, forming large rings is not the only way to establish preorganization in designed receptors. Such preorganization can also be achieved by forming normal-size rings and incorporating...
conformational locking mechanisms.

Following this approach, Still and co-workers recently developed a different kind of preorganized receptors, podand ionophores constructed by linking tetrahydropyran (THP) rings. Two such receptors are shown in Fig.1, which are much less conformationally heterogeneous and better preorganized than the corresponding acyclic glyme ethers. In contrast to 1 which has approximately $10^3$ distinct conformations within 3 kcal/mol of the global minimum energy conformation, 2 has only about 25. The

![Figure 1](image_url)

Figure 1

dramatic decrease in conformational flexibility results from the highly restricted rotation about all bonds except those linking the chair-like THP rings. Conformational flexibility can be reduced further by adding certain methyl substituents which operate as a kind of conformational lock as shown in 3. The locking mechanism works by favoring certain conformations of the inter-ring bonds and disfavoring those having 1,3-syn (+gauche, -gauche) pentane-like CH$_3$/CH$_2$ interactions by 4.9 kcal/mol, and 1,3-syn CH$_3$/O interactions by 1.0 kcal/mol. Thus 3 has a single low energy conformation capable of binding a cation when two or more THP ring oxygens are within the lowest 3 kcal/mol of the minimum energy structure. This conformation is the one found in the X-ray structure of 3 (Figure 2). Here preorganized 3 is in a favorable binding geometry in which the four oxygens form an ion binding site much like that found in the crystal structure of potassium 18-crown-6 complex. In addition, this preorganized conformation possesses C$_2$ symmetry and an open cation binding site within a chiral environment. The THP rings in this structure are perpendicular to the best plane of the four ligating oxygens.

As such, it is expected to bind substrates such as chiral organic ammonium ions enantioselectively. Table I summarizes the enantioselective binding properties of the
podands 2 and 3 (in the enantiomeric form) with various ammonium salts. As expected, 3 is significantly more enantioselective than the conformationally less rigid and less preorganized 2, whose poor selectivity reflects a number of contributing conformations. On going from 2 to 3 with the phenylethyl ammonium substrate, enantioselectivity doubled and changed from R- to S-selectivity. Whereas little or no enantioselectivity was observed with 2 and amino acid esters, 3 preferentially bond the S enantiomer of each of

<table>
<thead>
<tr>
<th>Table I Enantioselective complexation of receptors 2 and 3 with ammonium salts of chiral amines and aminoacid methyl esters, determined by liquid-liquid extractions</th>
<th>Ammonium salts of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor</td>
<td>α-PEA</td>
</tr>
<tr>
<td>2</td>
<td>20% ee (R)</td>
</tr>
<tr>
<td>3</td>
<td>42% ee (s)</td>
</tr>
</tbody>
</table>

the amino acid methyl esters examined with selectivities ranging between 34-40% ee.

The mode of binding of 3 with (S)-phenylethyl ammonium perchlorate was determined by X-ray crystallographic methods and the structure of the complex is shown in Fig. 2. From the crystal structure, it can be seen that two of the ammonium hydrogens form H-bonds to the ionophore while the third is directed toward the perchlorate counterion. The two ammonium hydrogens appear to be bound primarily to the central two THP ring oxygens with O-H distances of 2.0 and 2.2 Å. The two terminal THP ring oxygens also appear to be involved in H-bonding with O-H distances being about 2.5Å each. The phenyl group of the substrate lies across the face of one of the THP rings at a C-C distance of about 3.9 Å, which is appropriate for van der Waals association.
CHIRAL RECEPTORS FOR ORGANIC ANIONS

In contrast to the well studied host-guest chemistry of cations, reports on anion-binding receptors are far fewer in number. One of the most common ways to complex a negatively charged substrate is by means of positively charged or electron-deficient binding sites. This may be accomplished either by quaternary ammonium salts or by protonated receptors such as polyprotonated cyclic polyamines. Driving forces for such complexation are electrostatic interactions and hydrogen bonding. A particularly attractive module for binding carboxylate anions would be the guanidinium moiety which is known to participate in anion binding in proteins. Chiral receptors with a guanidinium group incorporated into a rigid bicyclic frame work as shown in Fig. 3 have been of recent interest to several research groups.

Guanidinium receptors are particularly promising and interesting for enantioselective recognition of chiral carboxylate anions including amino acids. First, the guanidinium group with pKa=13.5 remains protonated over a much wider range of pH than does the ammonium group, and it interacts with carboxylate anions by ion pairing assisted by two parallel ionic hydrogen bonds. Second, the incorporation of the guanidinium structure into a bicyclic system leaves only one side open for non-covalent interaction with carboxylates. Therefore, the relative position, orientation and distance of the receptor and substrate can be very well defined. Third, possibilities of introducing chirality by placing various substituents at the α,α′ positions may couple the guanidinium group with other interaction sites complementary to those present in a targeted substrate.

A high level of enantioselectivity may be achievable with this system. Mendoza and Lehn recently reported enantioselective recognition of chiral aromatic carboxylate anions by an optically active receptor containing the rigid guanidinium binding subunit (Figure 4). Both enantiomers and 4-RR were synthesized from L- and D-asparagine in ten steps, respectively. In liquid-liquid extraction experiments for chiral recognition study

Figure 3 Model receptors designed for chiral carboxylate anions
with 4, the N-acetyl derivative of sodium tryptophan was chosen because it contains two complementary functionalities (a carboxylate and a π-donor indole ring) and the N-acetyl group which may interact sterically with the receptor aromatic side arm not involved in the π-π stacking. Extraction of an excess of the racemic salts with 4-SS chloride afforded two diasteromeric salts with an enantiomeric excess of ca. 30-40% for the L-tryptophan derivative. A similar ee for the D-tryptophan derivative was obtained when an excess of the racemic sodium salts was extracted with the enantiomeric receptor 4-RR. This represents the first example of enantioselective recognition of chiral carboxylate anions by a designed receptor.

Receptor 4, however, is unable to extract free amino acids in zwitterionic form from neutral aqueous solutions. The design of a model receptor for amino acids in the strongly solvated zwitterionic form is still a challenging problem, since electron densities at the carboxylate and the ammonium functionalities are greatly affected by distance, causing the binding forces of complementary groups of the receptor to be less effective for the complexation. Most work so far has been performed with single-charged substrates under either acidic (for amino acids and esters), or basic (for carboxylate salts) conditions.

Very recently, based on the three-point rule for chiral recognition and principles of preorganization and complementarity, Mendoza et al. designed a more enantioselective receptor 5 (Figure 5) for free amino acids in zwitterionic form. In 5, binding functionalities were preorganized and complementary to those of zwitterionic amino acids: while the guanidinium group and the crown ether subunit were designed for the complementary carboxylate and ammonium respectively, the aromatic planar surface of the naphthalene system was incorporated for an additional selective π-π stacking interaction with the side chain of aromatic amino acids. Chiral recognition of amino acids in their zwitterionic form by 5 was determined by liquid-liquid extraction experiments. Extraction
of an excess of racemic samples of Phe and Trp with 5 gave a >99.5% ee for L-Trp and
>98% ee for L-Phe, respectively. This high level of enantioselectivity can be explained by
the three simultaneous interactions and complementarity between the substrate and the
receptor (Figure 6).

CHIRAL RECEPTORS FOR ORGANIC NEUTRAL SUBSTRATES

Among the recently developed receptors\textsuperscript{14-16} that show a measurable difference in
the binding energies (\(\Delta\Delta G\)) with enantiomeric substrates are those\textsuperscript{15} reported by Still and
his co-workers. They are di- or tri-macroyclic receptors mainly employing multiple H-
bonding for chiral recognition of amides of enantiomeric amines or amino acids. In these
receptors, cyclophane linkages, bridged macrocyclic structures, and incorporated C\textsubscript{2} or C\textsubscript{3}
symmetry all operate to reduce conformational heterogeneity. Increased conformational
rigidity provides enhanced enantioselectivity. Enantioselectivities expressed in \(\Delta\Delta G\) as
high as 3.0 kcal / mol were achieved, which are among the highest seen in the designed
organic receptors yet prepared, although the pictures of the chiral recognition mechanism in
some cases are not quite clear so far.
A more elegant example, which demonstrates the power of preorganization and complementarity in enhancing enantioselectivity, was reported by Rebek and co-workers. Chiral receptor 6 (Figure 7), with lactam functionalities being preorganized within its cleft, exhibits high enantioselectivity toward the enantiomers of lactams 7 and 8. In H\textsuperscript{1} NMR titration experiments with cyclo-L-leucylglycine 7 and receptors 6, an association constant of 73000 M\textsuperscript{-1} was determined for one enantiomer while the corresponding value for the other was only 2900 M\textsuperscript{-1}, which indicates a value of ΔΔG to be nearly 2.0 kcal/mol.

The enantioselectivity of 6 toward cyclo-L-leucyl-L-leucine 8 was determined to be even higher, with ΔΔG being 2.7 kcal/mol.

A rationale for the observed high enantioselectivity is given in the proposed structure for the more stable complex in which the stereochemical preferences are seen quite clearly (Figure 8). With the appropriate match, four H-bonds can be formed simultaneously without unfavorable steric interaction between the R group of the substrate and the aryl chiral barrier wall of the receptor. So the complementarity in terms of stereochemistry and binding sites are expressed in an almost ideal fashion between the substrate and the preorganized receptor.
CONCLUSION

Conformational rigidity (homogeneity) and preorganization of a receptor are among the most crucial factors in determining the level of its intrinsic enantioselectivity. The function of conformational rigidity is to preorganize its interaction sites in a favorable arrangement for chiral recognition by reducing the number or population of non-contributing conformations, and preorganization may be achieved in different ways. Furthermore, by use of principles of preorganization and complementarity, highly enantioselective receptors may be designed in a rational fashion for targeted substrates of interest.

REFERENCES

RECENT STUDIES ON THE MECHANISM AND STEREOSELECTIVITY OF THE OXY-COPE REARRANGEMENT

Reported by Zhan-Qi Ho

December 3, 1992

INTRODUCTION

Sigmatropic rearrangements provide useful synthetic methods for carbon-carbon formation.\(^1,2\) Of these, the oxy-Cope rearrangement has drawn considerable attention because of its broad synthetic application.\(^1,3,4\) Oxy-Cope rearrangements are thermal reactions,\(^5\) and rate accelerations up to \(10^7\) can be obtained by conversion of the hydroxy group to the potassium alkoxide.\(^5\) Therefore, it is possible for the reaction temperature to be decreased to such an extent that many sensitive functional groups may be tolerated. Both the thermal and anionic oxy-Cope rearrangements are essentially irreversible.\(^7\) It is this irreversibility that distinguishes them from the classical Cope rearrangements of 1,5-hexadienes.

BACKGROUND

The oxy-Cope rearrangement shows exceptional stereoselectivity\(^8\) that has been used in the construction of complex molecules with six or more stereogenic centers\(^1,9\) without the need for an external chiral auxiliary. Furthermore, the high diastereoselectivity of the reactions can often be predicted by conformational analysis of the highly ordered cyclic transition state of the oxy-Cope rearrangement.\(^1,7\)\(^1\) The preferred conformation of the cyclic transition state is usually chair-like;\(^1,7,10\) Doering and Roth's classic work\(^10\) on the Cope rearrangement suggests that the chair transition-state is about 6 kcal/mol lower in energy than that of the boat. In simple aliphatic dienes, the energy difference between the chair and boat transition states varies from 5 to 10 kcal/mol.\(^11,12\)

The stereochemistry of the rearrangement product can be predicted by assuming that the bulkiest substituents will reside in the less congested quasi-equatorial positions. However, structurally-enforced boat rearrangements are also energetically possible, and, in fact, they are known to occur in some polycyclic cases.\(^14\)

The mechanistic details of the Cope and oxy-Cope rearrangement continue to attract interest.\(^8,15\) Current studies\(^16-20\) have focused on: (a) the timing of the bond-making and bond-breaking steps, (b) the structure of the transition state, and (c) the effect of substituents on the rate of rearrangement. A crucial issue is which of the two limiting possibilities, an allyl radical pair or the cyclohexane-1,4-diyl intermediate,\(^18\), could more
precisely represent or contribute to the structure of the transition state. In spite of some remaining uncertainties,\textsuperscript{11, 18} it is generally accepted that the reaction proceeds via an early chair-like transition state\textsuperscript{10, 12(a), 19} with more cleavage of the C3-C4 bond than the bond formation at C1 and C6.\textsuperscript{17, 18, 20} (Scheme I)

Scheme I

\[
\begin{array}{c}
\text{1} \quad \text{2} \quad \text{3} \\
\text{4} \quad \text{5} \quad \text{6}
\end{array}
\rightarrow
\begin{array}{c}
\text{1} \quad \text{2} \quad \text{3} \\
\text{4} \quad \text{5} \quad \text{6}
\end{array}
\]

\[\dagger\]

\[
\begin{array}{c}
\text{1} \quad \text{2} \quad \text{3} \\
\text{4} \quad \text{5} \quad \text{6}
\end{array}
\rightarrow
\begin{array}{c}
\text{1} \quad \text{2} \quad \text{3} \\
\text{4} \quad \text{5} \quad \text{6}
\end{array}
\]

\textbf{STEREOCHEMISTRY OF THE OXY-COPE REARRANGEMENT}

The high stereoselectivity of the oxy-Cope rearrangement can be illustrated by considering Evans' stereoselective synthesis of (±)-juvabinone (scheme II).\textsuperscript{21}

Scheme II

\textbf{reaction conditions:} (1) KH, 18-crown-6, RT, THF (2) H\textsubscript{2}O

As shown in Scheme II, rearrangement of 1,5-diene-3-alkoxides 1 and 2 leads to exclusive formation of 3 and 4 in set I; on the other hand, dienol 5, 6 afforded only 7 and 8 in set II. The absence of the crossover products demonstrates that the rearrangements do not proceed via common diradical intermediate.
In order to study the E / Z stereoselectivity of the acyclic anionic oxy-Cope rearrangement, Nakai and co-workers have evaluated the rearrangements of 3-methyl-1,5-heptadien-4-ols (Scheme III).

Scheme III

\[
\begin{align*}
13 & \quad 14 \quad 15 \quad 16 \\
\text{HO} & \quad \text{HO} & \quad \text{HO} & \quad \text{HO} \\
\text{KOH, 18-crown-6} & \quad \text{THF, RT, 4 h} & \quad \text{K-O} & \quad \text{O-K} \\
\hline
13 & \quad 14 \quad 15 \quad 16 \\
99 & \quad 90 & \quad 20 & \quad 65 \\
1 & \quad 10 & \quad 80 & \quad 35 \\
\end{align*}
\]

It was found that the selectivity in the rearrangements of the E isomers decreases in the following order: 13 > 14 > 16 > 15. They proposed a chair-like transition state model in which the following two considerations determine the E / Z stereoselectivity: (1) the fewer the total number of pseudo-axial substituents in the transition state, the more favorable the transition structure; (2) a pseudo-1,3-diaxial interaction between the oxyanion and methyl group in the transition state is destabilizing. Furthermore, if one of the two possible chair-like transition structures has a 1,3 diaxial interaction, the reaction occurs with high E / Z stereoselectivity.

They investigated the diastereoselectivity in the anionic oxy-Cope rearrangement of substituted 3,4-erythro-1,5-dien-3-ol. The resulting 3,4-anti dimethyl enal is a key intermediate in a total synthesis of (+)-faranol, the trail pheromone of the Pharaoh's ant. The 91 % stereoselectivity of the reaction is consistent with a chair-like transition state with both oxyanion and alkyl group in equatorial positions.
THE EFFECT OF EQUATORIAL / AXIAL ORIENTATION OF THE OXYANION ON THE CHIRALITY TRANSFER

The stereochemical preference of oxyanionic bond (C-O⁻) conformation in the transition state of the anionic oxy-Cope rearrangement has an important influence on the chirality transfer. However, it is not clear whether the oxyanionic bond in a pseudo-equatorial or pseudo-axial position in the chair-like transition state would lead to maximum chirality transfer. In some cases the rearrangement occurs with the oxyanion in a pseudo-equatorial position as in Evans' juvabione synthesis (9 and 10 in Scheme II). In others, the rearrangement proceeds with the oxyanion in a pseudo-axial position (Scheme IV).

Scheme IV

Lee and co-workers have studied the reaction in Scheme V. Based on the stereoselectivity of the product, they proposed that the rearrangement proceeds via a chair-like transition state with the oxyanion in the pseudo-equatorial position.

Paquette and Maynard have investigated the oxy-Cope rearrangement of optically pure (3R, 5E)- and (3R, 5Z)-1,5-heptadiene-3-ols (Scheme VI). In these rearrangements, π-facial selectivity is absent, and the difference in activation energies for the two chair-like transition states comes only from the oxyanion orientation. They observed that
about 60% of the product related to the transition state with the oxyanion in the equatorial position.

Scheme VI

reaction conditions: (a) KH, 18-crown-6, 50°C, THF (b) H₂O

Scheme VII

reaction conditions: (a) KH, 18-crown-6, 50 °C, THF (b) H₂O
Paquette and Maynard have also studied tendocyclic dienols 17-22, in which the ring would influence the π-facial selectivity (Scheme VII). This is a stringent test for the effect of the orientation of the oxyanion on the stereoselectivity of oxy-Cope rearrangements in the presence of the stereocontrolling factors. The observation of a
significant stereoselectivity for rearrangement of compounds 17, 19, and 22 has been explained by the following considerations:

(1) For endocyclic compounds, such as 17, the axial orientation of the oxyanion would introduce a 1,3-steric interaction (Scheme VIII), which is much less severe than it is in the acyclic cases. It is this 1,3-steric interaction that destabilizes one of the two possible chair-like transition structures and, therefore, enhances the stereoselectivity.

Scheme VIII

(2) It is known,26 from the study of Claisen rearrangements, that pseudo-axial bond making is preferred for the cyclohexene molecule due to the stereoelectronic effect (Scheme IX).

Scheme IX

Therefore, in the reactions 17 and 18 (Scheme VII), maximum chirality transfer occurs when the oxyanion is in an equatorial position and the newly formed C-C bond is axial. In the reactions 19-22 (Scheme VII), maximum chirality transfer occurs when the oxyanion is in the equatorial position of a chair-like transition state and bond formation takes place on the direction required sterically and/or stereoelectronically, i.e. exo bond formation for norbornenyl and endo bond formation for camphenyl ring. If the oxyanion is restricted to the axial position in a chair-like transition state, it causes 1,3-diaxial interaction, and lower the stereoselectivity.

CONCLUSION

In acyclic anionic oxy-Cope rearrangements, the chirality of the starting material transferred to product can be predicted by a simple chair-like transition state model. The chirality transfer in anionic oxy-Cope rearrangements is influenced by the orientation of the oxyanion in the transition state, and the pseudo-equatorial position of this group is usually preferred. However, this effect can be overridden by stereoelectronic and/or steric factors.
In endocyclic ring cases, such as t-butylcyclohexenyl, norbornenyl, and camphenyl dienols (Scheme VII), maximum chirality transfer occurs when the oxyanion can adopt an equatorial position in a chair-like transition state, and the C-C bond formation takes place in the sterically or stereoelectronically favored direction.

REFERENCES

NOTICE: Return or renew all Library Materials! The Minimum Fee for each Lost Book is $50.00.

The person charging this material is responsible for its return to the library from which it was withdrawn on or before the Latest Date stamped below.

Theft, mutilation, and underlining of books are reasons for disciplinary action and may result in dismissal from the University.

To renew call Telephone Center, 333-8400

UNIVERSITY OF ILLINOIS LIBRARY AT URBANA-CHAMPAIGN

28 1897

L101—O-1096
# SEMINAR TOPICS

**Semester II, 1992-93**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Advances in Elucidation of the Structures of Lithium Amides</td>
<td>1</td>
</tr>
<tr>
<td>Atli Thorarensen</td>
<td></td>
</tr>
<tr>
<td>Manganese(III) Acetate-Induced Cyclizations</td>
<td>9</td>
</tr>
<tr>
<td>Charles S. Elmore</td>
<td></td>
</tr>
<tr>
<td>7-Oxanorbornene Systems as Carbohydrate Synthons</td>
<td>17</td>
</tr>
<tr>
<td>Corinne T. Mazur</td>
<td></td>
</tr>
<tr>
<td>Syntheses of Carbapenems: A Unique Class of β-Lactam Antibiotics</td>
<td>25</td>
</tr>
<tr>
<td>Sankaran Thayumanavan</td>
<td></td>
</tr>
<tr>
<td>Recent Advances in the Design and Synthesis of Cyclic Glutamate Analog: Novel Competitive Antagonists of the NMDA Receptor</td>
<td>33</td>
</tr>
<tr>
<td>Andrew Scribner</td>
<td></td>
</tr>
<tr>
<td>Aspects of the Biological Assembly of Tetrapyrroles</td>
<td>41</td>
</tr>
<tr>
<td>Jim McGuire</td>
<td></td>
</tr>
<tr>
<td>Electrophilic Additions Using Silicon Substituents as Directing Groups</td>
<td>49</td>
</tr>
<tr>
<td>Christopher W. Derstine</td>
<td></td>
</tr>
<tr>
<td>Synthetic Approaches Towards Taxane Diterpenes</td>
<td>57</td>
</tr>
<tr>
<td>Suk Bok Chang</td>
<td></td>
</tr>
<tr>
<td>Palladium Catalyzed Tandem Cyclization Reactions</td>
<td>65</td>
</tr>
<tr>
<td>Sriram Shankar</td>
<td></td>
</tr>
<tr>
<td>Nickel(O)-Catalyzed [4+4] Cycloadditions</td>
<td>73</td>
</tr>
<tr>
<td>Lawrence David Robinett</td>
<td></td>
</tr>
</tbody>
</table>
RECENT ADVANCES IN ELUCIDATION OF THE STRUCTURES OF LITHIUM AMIDES

Reported by Atli Thorarensen

January 14, 1993

INTRODUCTION

Lithium amides have been demonstrated to be useful as versatile, non-nucleophilic, strong bases in a variety of important organic reactions. In order to achieve improved yield and selectivity in carbon-carbon bond forming reactions that employ lithium amides, it is essential to have a thorough understanding of these reactive species; in particular, it is important to know their structure in solution. A point of key interest in this regard is the degree of aggregation they demonstrate in solution, i.e., monomer, dimer or higher aggregates. In order to understand the origin of selectivity in reactions that employ a lithium amide, one must know what controls the degree of aggregation, such as steric interactions, solvent effects or other factors. Methods available for structure elucidation include X-ray crystallography, spectroscopy and a combination of techniques to measure colligative properties. All of these methods are important tools, since the structure in the solid state may be vastly different from the structure in solution. This review will focus on recent reports that elucidate lithium amide structures in solution and in the solid state.

FACTORS THAT CONTROL THE AGGREGATION STATE OF LITHIUM AMIDES

While numerous organolithium compounds have been studied in the solid state, very limited information about their solution structure is available. In general, organolithium compounds in the solid state have coordination numbers from 2 to 7 at lithium, and many of them exist as clusters such as cubic tetramers (Figure 1). What differentiates lithium amides from other organolithium compounds is the sp\(^3\) hybridization on nitrogen. The sp\(^3\) hybridization places the alkyl groups perpendicular to the square planar arrangement that contains nitrogen and lithium. This prevents cluster formation by stacking, and promotes formation of either larger cyclic oligomers or, if the alkyl groups are small or planar, ladder type structures by edge to edge contact of smaller oligomers.

Effect of Solvent

The solvent used for lithium amide generation is the main factor controlling the degree of aggregation. Generally, in coordinating solvents such as tetrahydrofuran (THF), the dimer is the major component, and higher order aggregates are usually not detected. However, in solvents
that are non-coordinating (non Lewis bases) such as hexane or benzene, lithium amides tend to form higher order aggregates. Because it is experimentally difficult to determine the coordination of solvent to lithium in solution, information obtained from solid state experiments has been the most informative. Numerous structures of lithium amides crystallized from solution containing a Lewis base coordinated to lithium are known. Monomers, dimers and partial ladder structure have been observed, depending on the size of the alkyl group and the coordinating solvent. When ligands such as diethyl ether, THF, or HMPA are employed, only cyclic dimers with one coordinating ligand on each lithium are known.

Size of the Alkyl Group

The influence of the steric size of the alkyl group on the aggregation of lithium amides in coordinating solvents has mainly been studied by vapor pressure barometry and $^{13}$C NMR. Lithium indolide was employed as the reference compound in this study. At 17 °C, vapor pressure barometry predicts a degree of association (n) of 1.8-1.9 in THF. Therefore, the chemical shift of the para carbon (δ 108.1) was assigned to be that of a dimer. For other lithium amides, the change in chemical shift of the para carbon (Δ 1-2 ppm) downfield at higher temperature was attributed to a reduction in solvation, while an upfield shift (Δ 4-5 ppm) was considered to correspond to a decrease in aggregation. Within these series of amides, the chemical shift of the para carbon is assumed to be consistant with the type of aggregation and solvation. In diethyl ether, lithium amides with the general formula RPhNLi, (R = Me, i-Pr, or t-Bu) were all found to be bisolvated dimers based on their $^{13}$C NMR chemical shifts. In THF, below -50 °C, it is apparent that as the size of the alkyl group increases, the monomer becomes preferred over the dimer (Table I.). The assignment of solvation state has been supported by measurement of the $^7$Li quadruple splitting constant.

LITHIUM DIISOPROPYLAMIDE

Solid State Structure

Recently, lithium diisopropylamide (LDA) has been crystallized as a polymer from a mixture of hexane and tetramethylendiamine (TMEDA). By X-ray crystallographic analysis, this LDA polymer exhibited a helical structure having four amide units per turn. No solvent
Table I. Chemical Shift of Lithium Alkylanilides with Various Alkyl Groups in THF.\textsuperscript{3}

<table>
<thead>
<tr>
<th>Alkyl group</th>
<th>$\delta$ [ppm] $C_{\text{para}}$ at -100 °C</th>
<th>$\delta$ [ppm] $C_{\text{para}}$ at 26 °C</th>
<th>Concentration [M]</th>
<th>Aggregate</th>
</tr>
</thead>
<tbody>
<tr>
<td>indolide</td>
<td>107.5</td>
<td>108.1</td>
<td>0.73</td>
<td>dimer</td>
</tr>
<tr>
<td>Me</td>
<td>108.0\textsuperscript{a}</td>
<td>108.4</td>
<td>0.16</td>
<td>dimer</td>
</tr>
<tr>
<td>$n$-Bu</td>
<td>103.8 / 107.7\textsuperscript{b}</td>
<td>108.1</td>
<td>0.31</td>
<td>monomer/dimer</td>
</tr>
<tr>
<td>$i$-Pr</td>
<td>103.6</td>
<td>106.1</td>
<td>0.11</td>
<td>monomer</td>
</tr>
<tr>
<td>$t$-Bu</td>
<td>103.1</td>
<td>104.6</td>
<td>0.31</td>
<td>monomer</td>
</tr>
</tbody>
</table>

a) At -60 °C due to poor solubility, b) At -100 °C monomer/dimer ratio 2.8/1

coordinated to the lithium amide was detected. Other crystal structures of LDA are dimers in which the lithiums are coordinated to THF or to TMEDA. Due to its bidentate nature, TMEDA links dimers together, forming a polymeric LDA dimer with only one solvent molecule coordinated to each lithium.\textsuperscript{6} It is important to note that by using different procedures, vastly different structures of polymeric LDA and TMEDA dimer were obtained from a hexane TMEDA solution. The structures of the dimers are very similar to other dimeric lithium amides, and a good example would be the structure of the (LDA-THF)$_2$ dimer 1 (Figure 2).\textsuperscript{7} This dimer forms a planar ring with a N-Li-N bond angle of 72°. The average N-Li bond distance is 2.0 Å. The isopropyl groups are roughly perpendicular to the plane of N$_2$L$_2$ ring, while the THF molecules lie close to that plane to minimize steric interactions.

![Figure 2](image-url) Solid state structure of (LDA-THF)$_2$ dimer 1.\textsuperscript{7}

Solution Structure of LDA

In 1984, the first information on the solution structure of LDA in a coordinating solvent was determined by cryoscopic measurement in THF. The degree of aggregation (n) was determined to be between 1.5 and 1.6, depending on the concentration.\textsuperscript{8} By using isotopically doubly labeled material in $^6$Li and $^{15}$N NMR experiments, the workers showed that the only
detectable species over a large temperature range (0 to -106 °C) in THF was a cyclic oligomer. This finding is contradictory to the result from cryoscopic studies.9

To distinguish dimers from higher oligomers, an inverse detection 15N homonuclear zero quantum NMR spectroscopy experiment has been developed.10 Using this method, workers showed that at -95 °C LDA exists as a dimer and not as higher oligomers. In neat TMEDA at -50 °C, LDA exists exclusively as a dimer, as determined by both methods.6 The formation of the solvated dimer is very dependent on both concentration and temperature, with solvation being disfavored at low concentrations of TMEDA and at higher temperatures. Based on the fact that dimethylethylamine (DMEA) showed an equal capacity to solvate the dimer and exhibited a similar $K_{\text{eq}}$ constant, the investigators concluded that TMEDA is only solvating as a $\eta^1$ ligand. By 13C NMR the affinity of TMEDA as a ligand for lithium has been shown to be less than that of THF, irrespective of temperature. However, HMPA has been shown to have greater affinity for lithium than THF. By analysis of Li-P spin coupling the workers found that the addition of 0.5 equivalent of HMPA to a THF solvated LDA dimer, resulted in the formation of a mixed dimer in which only one lithium is solvated by HMPA.11 With addition of a further 0.5 equivalent of HMPA, an HMPA solvated dimer with one HMPA per Li was formed. Further addition of up to 5 equivalents HMPA does not result in measurable de-aggregation of the dimer; the equivalents beyond one are seen as free HMPA in 31P NMR.

LDA in hexane has been shown to exist as a mixture of five oligomers, over a large temperature range (-100 to 25 °C), as determined by 6Li NMR.12 Based on double labelling experiments, the oligomer resonances were assigned as a dimer and higher cyclic aggregates. However, severe overlap of resonances limits the extent of analysis possible.

**LITHIUM TETRAMETHYLPIPERIDIDE**

Lithium tetramethylpiperidide (LiTMP) forms a tetrameric planar ring in the solid state when crystallized from pentane (Figure 3); this is the only known tetrameric lithium amide.13 The cyclic array of lithium and nitrogen forms a planar eight-membered ring with bi coordinate lithium. This is consistent with other crystal structures of lithium amides crystallized from non-coordinating solvents. Interestingly, LiTMP has been shown to exist as an equilibrium mixture of dimer and monomer at -50 °C in THF, as judged by 7Li NMR (Scheme I).14 This assignment has been further proven by a double labeling NMR experiment.15 Also, at -115 °C, it has been shown that the LiTMP dimer exists only in conformation 4 and not 5; this was shown by 13C NMR, where the axial and equatorial methyl groups are separate signals, and in a 6Li NMR experiment where only one resonance was observed. This conclusion was further supported by the use of lithium 2,2,4,6,6 pentamethylpiperidide (LiPMP), which forms a conformationally locked system and, therefore, requires deaggregation to be converted between the $C_{2h}$ and $C_{2v}$
Figure 3. Solid state structure of LiTMP 2 obtained from pentane\(^{13}\).

conformations. The finding of only one \(^{6}\text{Li}\) resonance as a doublet of doublets excluded the \(C_{2v}\) conformation, which would have given two triplets. HMPA has a different effect on LiTMP than LDA, probably due to the monomer/dimer equilibrium observed with LiTMP.\(^{11}\) HMPA at 0.5 equiv. forms the mixed solvated dimer 4, as seen in \(^{6}\text{Li}\) NMR with one lithium as a singlet and one showing coupling to a phosphorus nucleus. As the concentration of HMPA is increased, a complicated mixture of species was identified, including open dimer 6 and the ion pair 7. From these observations the investigator drew the conclusion that HMPA does not significantly deaggregate the lithium amide, but rather helps to separate ions pairs.

Scheme I

\[
\begin{align*}
\text{Li}^+ & \quad +X \\
\text{Li}^+ & \quad -X \\
\text{Li}^+ & \quad X
\end{align*}
\]

\(X = \text{HMPA, THF}\)

\(Y = \text{HMPA}\)

LITHIUM PYRROLIDE

The other interesting type of structure is the partial ladder which is only known for lithium pyrrolidine complexed to TMEDA (8) and N,N,N',N','N''-pentamethyldiethylenetriamine (PMEDA 9), and lithium piperidide complexed to piperidine (Figure 4).\(^{16,17}\) The common feature of a partial ladder is that the lithium atom on the edges of the ladder are bi- or trisolvated, while the internal lithium atoms are not coordinated to solvent. The Li-N-Li angles in
the central rings are only slightly altered from that of the only known solvent-free dimer \[ \text{LiN(SiMe}_3)\text{(2,6-i-Pr}_2\text{C}_6\text{H}_3)\text{]}_2 \] of 73.7°. However, in the outer rings, a considerable distortion of the angles is observed.

Cryoscopic measurement of lithium pyrrolidine complexed with TMEDA in benzene indicates a degree of aggregation of 2.0 to 2.1, depending on concentration. \(^7\text{Li}\) and \(^6\text{Li}\) (natural abundance) NMR showed two resonances, where the major component was attributed to a dimer and the minor to a higher aggregate. Different results were obtained when lithium pyrrolidine was complexed to PMEDA, where the cryoscopic measurement showed a complicated behavior. The degree of aggregation varied from less than 2 at 0.09 M to 5.5 at 0.17 M. \(^7\text{Li}\) and \(^6\text{Li}\) (natural abundance) NMR showed a complicated pattern of signals dependent on concentration. At high concentration, three resonances were observed and assigned as a partial ladder similar to that found in the solid state (9). The high degree of aggregation was attributed to the fact that the tridentate amine is only dicoordinate in one ladder and monocoordinate in the next one; this connects ladders together to give the high aggregation state.

\[
\text{Figure 4. Solid state ladder type structures of pyrrolidine complexed with TMEDA, 8, and PMEDA, 9.}\]

**STRUCTURE PREDICTED BY THEORY**

Considerable efforts have been devoted to studying the nature of bonding and relative stability of the \(\text{LiNH}_2\) species over the past few years.\(^2\text{d,19}\) Several ab initio calculations have been performed on \(\text{LiNH}_2\). The result has been that trimeric oligomers are more stable than dimers in non-coordinating solvent, due to a more favorable N-Li-N bond angle which reduces repulsion. Also, it has been shown that conformations with alkyl groups perpendicular to the \(\text{N}_2\text{Li}_2\) plane are more stable than those in plane, a result of better Li-N orbital overlap. The bonding in these species is mainly electrostatic, as predicted by natural population ab initio calculations at the 6-31G* basis set on \(\text{Li-NH}_2\), where lithium has a +0.9 charge.\(^2\text{0}\) The ab initio calculations are limited to simple molecules, so that steric factors due to the size of the alkyl groups or the solvent are not included in the calculations.
A extensive MNDO (Modified Neglect of Diatomic Overlap) study has been performed on the solvation of LDA and LiTMP. These calculations suggest that solvation is very dependent on the steric size of the alkyl group and solvent molecule (Table II.) Only in the case of lithium dimethylamide was solvation by more than one ligand per Li exothermic, and then only in the case of a very small ligand such as water. The stability of solvated cyclic dimers suggests that as the steric size of the R groups increases, the cyclic dimer becomes less stable relative to the monomer, the open dimer or the ion pair.

**Table II: Heats of Solvation of Lithium Amide Dimers**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>(Me₂NLi)₂ [kcal/mole]</th>
<th>(LDA)₂ [kcal/mole]</th>
<th>(LiTMP)₂ [kcal/mole]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>-6.8</td>
<td>-1.4</td>
<td>-5.0</td>
</tr>
<tr>
<td>Et₂O</td>
<td>-4.8</td>
<td>1.4</td>
<td>-1.3</td>
</tr>
<tr>
<td>THF</td>
<td>-4.8</td>
<td>1.4</td>
<td>-1.4</td>
</tr>
<tr>
<td>(H₂N)₃PO</td>
<td>-8.4</td>
<td>-2.4</td>
<td>-5.1</td>
</tr>
<tr>
<td>HMPA</td>
<td>-7.3</td>
<td>0.0</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

**CONCLUSION**

The study of the solution structure of lithium amides has only recently been addressed in detail. In the case of cyclic lithium amides with an amine as a coordinating ligand, a higher order aggregate is observed, corresponding to a partial ladder structure. Lithium amides mainly exist as dimers in coordinating solvents. HMPA has the strongest affinity for coordination to lithium, followed by THF, while TMEDA shows the poorest ability to coordinate. Additives such as HMPA or TMEDA do not de-aggregate the dimers to a measurable extent, but rather a very delicate balance between the size of the alkyl groups on nitrogen and the ligand coordinated to lithium determines whether the dimer exists in an equilibrium with the monomer. The fact that the additive shows no different behavior from THF on LDA raises the question as to what role they play in reactions that utilize them to change selectivity. Further investigations are necessary to determine how the additive controls the structure and reactivity of the amide, which in turn controls the yield and selectivity of a reaction.

**REFERENCES**


(7) Williard, P. G.; Salvino, J. M. J. Org. Chem. in press. I thank Professor Williard for a copy of the manuscript and coordinates prior to publication.


MANGANESE(III) ACETATE-INDUCED CYCLIZATIONS

Reported by Charles S. Elmore

February 18, 1993

INTRODUCTION

The manganese(III) acetate-induced lactonization, discovered in 1968 by Dessau and Heiba, and Finkbauer and Bush, has been extensively studied over the last 25 years.\(^1\) The mechanism of the lactonization was first proposed by Heiba and coworkers and has subsequently been refined by several other research groups.\(^2\) Although the reaction originated strictly as a method for the generation of \(\gamma\) lactones, recently manganese(III) acetate has been studied as a means of inducing intramolecular free radical cyclization. Its primary advantage over other initiators is that the reaction is terminated by elimination to form an olefin product, which allows for easier manipulations of the cyclic system for further functionalization.

BACKGROUND

In 1968 several researchers discovered that manganese(III) acetate induces the formal addition of acetic acid across a carbon carbon double bond to form \(\gamma\) lactones.\(^1\) This reaction was extended to include the reaction of \(\beta\)-dicarbonyl compounds with alkenes to give cyclic products (Figure I).\(^3\)

Figure I

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Mn(OAc)}_3 \\
\text{HOAc, } \Delta & \quad \text{H}_3\text{C} \quad \text{79\%} \\
\text{H}_3\text{C} & \quad \\text{COOMe} \\
\text{Cu(OAc)}_2 & \quad \text{86\%}
\end{align*}
\]

X-ray crystallographic analysis has shown that manganese(III) acetate exists as a triangle of manganese(III) atoms centered about an oxygen atom, with two acetate
ligands bridging between each manganese atom; two acetate ligands and one acetic acid ligand are coordinated to each manganese atom. Manganese(III) acetate does not exist as Mn(OAc)₃, instead it has a molecular formula of [Mn₃(OAc)₆(HOAc)₂O][OAc] (Figure II). Studies on its solution structure have been limited, but Hessel has shown that in solution it behaves as the ion pair. ⁴

Figure II

The final step in the reactions of manganese(III) acetate with β dicarbonyl compounds and alkenes is the oxidation of a radical to an olefin. Tertiary radicals are stable enough that manganese(III) acetate catalyzed oxidation to the olefin occurs with little or no side products observed. However, with secondary and primary radicals, dimerization and proton abstraction from the solvent can become important side reactions.⁵ To suppress these side reactions, copper (II) acetate is added. It reacts more rapidly than the manganese(III) acetate with the primary and secondary radicals, thereby

Scheme I
eliminating many side reactions. The reaction proceeds as follows: Copper(II) acetate is known to react with radicals to form an organocuprate; this cuprate then disproportionates to form copper(I) acetate, acetic acid, and an alkene (Scheme I). Since the copper(I) acetate formed is rapidly converted into copper(II) acetate by the manganese(III) acetate, only a catalytic amount of copper(II) acetate is needed, while two equivalents of manganese(III) acetate are required.

THE MECHANISM OF THE MANGANESE(III) ACETATE LACTONIZATION

The lactonization of alkenes by manganese(III) acetate is an important synthetic method. There have been many mechanistic studies, which have led to a fairly good understanding of the mechanism (Scheme II). Heiba initially proposed a mechanism involving both cations and radicals; however, Fristad has shown that cations are not involved in the cyclization.

Using alpha substituted acetic acid derivatives (X-CH₂-COOH), Fristad observed a linear relationship between pKa of the alpha proton and the rate of the lactonization; this indicates that the rate determining step is a deprotonation - the enolization of the acid. The oxygens of the acetic acid coordinate in a bidentate fashion with the manganese(III) acetate. This results in further polarization of the oxygen-carbon
bond and assists the loss of an alpha proton to form the enolate. An electron is then transferred from the acetate to the manganese cation, yielding a radical, which then adds to the alkene and cyclizes. The radical formed after addition to the alkene can be in two forms: either still bound to the manganese, or as a free radical in solution. Fristad has presented evidence for the existence of an equilibrium of the two forms in solution. Dilution and steric crowding favor the uncomplexed free radical in solution.\(^7,8\)

**OXIDATION OF β KETO ESTERS AND ACIDS**

The potential of forming multiple fused ring systems using manganese(III) acetate was recognized soon after the initial discovery of the lactonization reaction, but surprisingly little research was done on this until recently. Nevertheless, in the last ten years, the synthetic utility of the reaction has been greatly expanded to include the formation of complicated ring systems.\(^9\)

The mechanism of the reaction of β dicarbonyl compounds with manganese(III) acetate and alkenes, although related to that of the reaction of acetic acid, is different in detail (Scheme III).\(^8,9\) While electron withdrawing substituents alpha to the carbonyl

**Scheme III**

accelerate the reaction of acetic acid with manganese(III) acetate and alkenes, electron donating groups alpha to the two carbonyl groups speed the reaction of β dicarbonyls.\(^10\)
This difference in the substituent effects on the rate of reaction probably reflects a change in the rate determining step of the reaction. As malonic ester derivatives are much more easily enolizable than acetic acid derivatives, it is not surprising that a different step becomes rate determining. The next step, oxidation of the carbonyl carbon by transfer of an electron from the enolate to the manganese, is probably the rate determining step with the malonates. Electron donating groups at the alpha carbon should increase radical stability, thereby accelerating the reaction.\textsuperscript{8}

To determine if the radical was complexed to the manganese or was a free radical in solution, the products obtained from the manganese(III) acetate induced cyclization of several different $\beta$ dicarboxyls and the products of a halogen atom transfer free radical cyclization were compared (Scheme IV). The atom transfer reaction is known to proceed through uncomplexed free radicals; so if the product ratios were comparable, then it would be logical to conclude that the reactions proceed through the same intermediate. The ratio of endo to exo product and the stereochemistry of the products were nearly identical in all cases.\textsuperscript{8} Therefore, it was concluded that the free radical dissociates from the manganese after formation. It is only then that it forms cyclic products.

Scheme IV

Unsubstituted dicarboxyl compounds react with a similar mechanism, except that the initial radical formation involves the alkene.\textsuperscript{8,10} Oxidation of the compounds is
slowed immensely in the absence of alkene. The reaction of methyl acetoacetate takes place in eight hours in the presence of 2-methyl-2-pentene, but it was not complete in over two days in the absence of the alkene. Ethyl methylacetoacetate, on the other hand, completely reduced the manganese(III) acetate in eight hours, regardless of whether alkene was present or not. Initial coordination of the alkene to the manganese and subsequent reaction with the radical, or assistance by the alkene in the dissociation from the manganese are both possible explanations for the results of the unsubstituted dicarbonyl compounds.8

LIMITATIONS ON THE MANGANESE(III) ACETATE-INDUCED CYCLIZATIONS

Steric effects can play a dominant role in the manganese(III) acetate-induced cyclizations. In an attempt to show the utility of the manganese-induced lactonizations, Paquette synthesized 14-epiupial using a manganese-initiated cyclization (Scheme V).11 The cyclization proceeded with excellent stereocontrol and in a moderate yield. However, when Paquette attempted to extend this reaction to the synthesis of (+)-upial, he was less successful. Apparently the steric interaction between the diastereotopic methyl group and the bridgehead carbon was enough to greatly reduce the efficiency cyclization of the potential (+)-upial precursor. This result was not predicted, and it indicates that the cyclization is extremely sensitive to steric constraints.

Scheme V
The solvent used in most of these reactions, acetic acid, limits its application to acid-stable compounds. Recently, Snider has shown that the same products are formed when ethanol is used as the solvent for the reaction of with manganese(III) acetate, alkenes, and β dicarbonyl compounds. He was able to demonstrate the viability of the reaction for acid-sensitive compounds by cyclizing acid sensitive enol ethers (Scheme VI). However, the reaction rate in ethanol is slower than in acetic acid.

Scheme VI

![Scheme VI Diagram]

Overoxidation of the substrate is another common problem encountered in manganese(III) acetate oxidation of alpha unsubstituted β dicarbonyl compounds. The product of this reaction contains a enolizable proton which can be further oxidized to form unwanted products such as dimers and polymers. The use of α chloro-substituted β dicarbonyl compounds has been the main method for preventing oxidation of the product. The chloride prevents the enolization of the carbonyl, and thus prevents further oxidation. The chloride is then removed if an unsubstituted alpha carbon is desired.

CONCLUSION

The manganese(III) acetate-induced cyclization reactions described in this paper form a powerful method of forming lactones and polycyclic systems. They provide a method of synthesizing lactones and substituted lactones from alkenes and also allow tandem and triple cyclizations from acyclic precursors. The stereocontrol is usually good, and asymmetric cyclizations have been achieved using chiral directing groups.
REFERENCES


7-OXANORBORNE SYSTEMS AS CARBOHYDRATE SYNTONS

Reported by Corinne T. Mazur

February 25, 1993

INTRODUCTION

Synthetic endeavors in carbohydrate chemistry have been hindered by expensive starting materials and complicated protecting group strategies. Methodology which introduces the desired functionality stepwise and stereospecifically would provide access to a variety of deoxy-, amino-, carbocyclic sugars or other potentially bioactive carbohydrate analogs. Several researchers have proposed "chirons", or chiral synthons, containing latent functionality and stereochemical information.\(^1\) An example is the 7-oxabicyclo[2.2.1]hept-5-ene-2-yl system.

Vogel offered two basic sets of templates, 1 and 2.\(^2\) These systems are precursors to natural and unnatural carbohydrates and derivatives, including D- and L-hexoses and pentoses and their deoxy derivatives,\(^2\) C-nucleosides,\(^3,4\) shikimates,\(^5\) and novel octoses.\(^6\)

SYNTHESIS AND OPTICAL RESOLUTION

The oxabicycloheptene system may be obtained by a simple Diels Alder reaction of furan and a suitable dienophile. Koizumi found that the asymmetric cycloaddition of furan and optically active (S)\(^{-}\)-3-(2-pyridylsulfinyl)acrylate 3 diastereoselectively affords oxabicyclic ester 4,\(^5\) providing access to intermediates in the shikimic acid pathway (Scheme I).\(^7\) The dienophile contains two chiral auxiliaries; the effect of the sulfinyl group dominates.\(^7\)

Scheme I

Acrylic acid and furan yield an adduct which Ogawa used to synthesize "pseudosugars", or carbocyclic sugar analogs.\(^8\) Upon treatment of the racemate with \((R)-(+)\)-\(\alpha\)-methylbenzylamine and subsequent separation, he correlated the \((-)\)-acid adduct with the D-series of sugars and the \((+)\)-adduct with the L-series.

Vogel obtained optically pure templates from the reaction of furan and \((-)\)-1-cyanovinyl camphanate (5, Scheme II).\(^9\) The desired diastereomer 6 can be isolated in

Copyright © 1993 by Corinne T. Mazur
98% de. The chiral auxiliary is recovered after saponification and can be efficiently recycled. Treatment of the crystalline adduct 6 with formalin gives (+)-ketone 7. Resolution of a cyanoacetate-furan adduct can be accomplished by the diastereoselective formation of a brucine complex.\(^\text{10}\) A mixture of 7 and its enantiomer has been separated by enzymatic methods.\(^\text{11}\) The reduced endo alcohol is converted to its butyl ester and treated with Candida cylindracea lipase.

Scheme II

\[
\begin{array}{cccc}
\text{NC} & \text{OR}^* & \xrightarrow{\text{ZnI}_2} & \text{CN} \\
\text{OR}^* = (-)-\text{camphanate} & 6 & \xrightarrow{\text{K}_2\text{CO}_3, \text{formalin}} & (+)
\end{array}
\]

**SOURCES OF CONTROL IN THE OXANORBORNE SYNTON**

The oxanorbornyl system contains elements of regiochemical and stereochemical control that include: 1) selective addition to the exo face of the olefin; 2) Wagner-Meerwein rearrangements of the oxanorbornyl skeleton; 3) reverse cyclization reactions; 4) regioselective olefin addition; 5) selective oxygen bridge opening; and 6) enolate and aldol chemistry at C(3), adjacent to the carbonyl functionality. Many synthetic approaches to carbohydrates exploit these features.

**Face Selectivity Of Olefin Addition**

Similar to norbornene, the rigid 7-oxa-norbornene skeleton is characterized by the near perpendicular relationship of the plane defined by C(2), C(3), C(5), C(6) and the C(1), O, C(4) plane, and the distorted sp\(^3\) hybridized bridgehead carbons. Yet, the oxygen bridge, while maintaining the exo face selectivity of olefin addition, is more functional and versatile than the methylene bridge of norbornene. The exo face of the olefin presents the least hindered path for attack in [2.2.1] bicyclic systems. Exo-face selectivity has also been explained by the "torsional effect".\(^\text{12,13}\) Endo attack requires the olefinic C-H bonds and the bridgehead hydrogens to eclipse; staggering in the cycloaddition transition state favors approach from the exo-face. A molecular orbital perturbation theory explaining the exo face preference has also been proposed by Fukui et al.\(^\text{14}\) Epoxidation and osmylation of the oxanorbornene illustrate this selectivity (Scheme III). The former establishes a cis relationship of the hydroxyl groups at C(2) and C(3) in the target carbohydrate; the latter results in a trans relationship of groups at these positions.
Wagner-Meerwein Rearrangement

Oxabicyclo epoxide 8 undergoes a facile Wagner-Meerwein rearrangement in a manner similar to norbornanes (Scheme IV). Vogel has used acid-catalyzed rearrangements of this type to obtain lyxose analog 9 and other poly-oxygenated derivatives. The rearrangement consists of a 1,2 shift of a C-C single bond, which achieves carbocation stabilization by oxo-carbonium ion formation. In the oxabicyclo epoxides, the preferred rearrangement path is determined by the effect that the substituents X and Y have on the migratory aptitude C(2).\textsuperscript{15,16} A 1,2 shift of the C(1)-C(2) bond in the 5,6 epoxide of ketone 1, opens the epoxide and the carbonium ion intermediate is trapped. On the other hand, the C(3)-C(4) bond shifts in the corresponding cyanoacetate. These results indicate that migratory aptitude of the C(2) or C(3) center decreases in the order acyl > alkyl > alkyl α-substituted with electron withdrawing groups. Vogel attributes the high migratory aptitude of the acyl group to the polarizability of the carbonyl non-bonding electrons.\textsuperscript{16} In the norbornyl system, substitution with electron withdrawing groups also disfavors Wagner-Meerwein rearrangement.\textsuperscript{17} A similar preference for the 1,2 shift of a simple alkyl group over one bearing an electron withdrawing group is observed under acidic Prevost conditions.\textsuperscript{18}
Reverse Cyclizations

The effects of oxygen substitution in the 6 and 7 positions of norbornyl systems have been studied. The influence of O(7) on the electronic structure and reactivity of 7-oxa-bicycloheptene-2-yl derivatives was demonstrated by Rodrigo. He found that reverse Michael and reverse aldol reactions occur upon treatment with base and acid, respectively (Scheme V).

Scheme V

Aldehyde 10 and ketone 11 undergo acid catalyzed C(1)-C(2) retro-aldol cleavage to the furan. Under basic conditions, nitrile 12 and ester 13 yield the corresponding cyclohexadienols via retro-Michael cleavage. These 5-endo-trig retro cyclizations are generally disfavored. However, a frontier orbital analysis of the oxanorbornene system can account for the alternate ring openings observed. In the protonated aldehyde or ketone, the retro-aldol reaction is activated by donation of electron density from a lone pair on the bridging oxygen into the C(1)-C(2) LUMO, favoring C(1)-C(2) cleavage to the oxygen heterocycle. The HOMO of the ester or nitrile lithium enolate is properly aligned for overlap with the C(1)-O antibonding orbital. Pi bond character develops between C(1) and C(2), lengthening the C(1)-O bond, followed by the retro-Michael cleavage to the six-membered ring. The retro-Michael reaction of the nitrile 12 followed by osmylation yields racemic shikimic acid (14). These transformations performed in the reverse order on the methyl ester 13 afford (±)-5-epi-shikimic acid 15 after deprotection.

Regioselective Electrophilic Olefin Addition

Cyclic cation 16 is initially formed by the addition of an electrophile to the exo face of the oxanorbornene (Scheme VI). Subsequent nucleophilic attack by a counter ion occurs from the endo face. Counter ion substitution occurs at C(6) in the bicyclic ketone 1 and at C(5) in the cyanoacetate 2. C(2) Substituents either stabilize or destabilize the positive
charge which develops as the cation breaks down. Nonbonding electrons of the carbonyl group in the ketone derivative delocalize into the C(1)-C(2) bond. Regioselectivity observed in the cyanoacetates is reversed. These disubstituted derivatives favor C(6) electrophile addition and accompanying positive charge formation distal to the electron withdrawing nitrile group. An alternative explanation for the selectivity is that the C(2) endo substituent in the cyanoacetate presents steric interference to the incoming counter ion. Arjona proposed that C(2) endo substituents disfavor counter ion attack at the adjacent C(6) position.

Scheme VI

Selectivity In Oxygen Bridge Cleavage
Regioselectivity in the oxygen ring-opening reactions of oxanorbornene is integral to revealing the stereochemical information contained within this template. Acid-catalyzed hydrolysis proceeds via protonation of the oxygen bridge, liberating key oxygenated intermediates. Successful reductive oxygen bridge opening has also been achieved. Recent research efforts have focused on Sn2' ring opening reactions with organometallic reagents. Alkyl addition occurs from the exo face of the olefin. Two ring opened products are possible in unsymmetrically substituted systems (Scheme VII).

Scheme VII

The factors which control selectivity include the nature of the organometallic reagent, remote oxygen substituents in the oxa-bicyclic heptene, and ring strain. Arjona demonstrated that the regioselectivity of attack by alkyllithium compounds on the oxanorbornene is not dependent on the orientation of a C(2) hydroxyl (Scheme VIII). The exo and endo isomers with variable C(2) alkyl substitution undergo addition at C(5) to
give similar yields of the ring-opened product. However, replacement of the hydroxyl with a methyl alcohol substituent gives a mixture of ring opened products. The endo isomer favors C(1)-O cleavage (Scheme VIII). Apparently, the methylene group provides freedom for directing olefin addition. Alignment of the endo-methyl alchol lone pair permits electron density donation into the C(1)-O antibonding orbital. Conversely, the lone pair of the exo oxygen substituent cannot align with the C-O antibonding orbital properly, with the result that no regioselectivity is observed.

Scheme VIII

Lautens found that SN2' hydride addition occurs in the reaction of substituted oxabicycloheptenes with magnesium dibromide and an organolithium species containing β-hydrogens. Metal exchange gives the organomagnesium species from which hydride transfer occurs.

These ring openings, accomplished by the addition of hydride or simple alkyl substituents, are important to elucidating regiocontrol in the oxanorbornene system, but do not offer much versatility to the synthetic carbohydrate chemist, as the products lack functionality. An alternate method of control involves a phenyl sulfonyl directing element. This electron withdrawing group moderates ring opening by directing deprotonation and subsequent β-elimination toward the oxygen bridgehead carbon or by stabilizing the carbanion generated during SN2' ring opening (Scheme IX). Desulfonylation followed by stereospecific hydroxylation of the olefin and finally deprotection affords cyclitols and pseudo sugars.

Scheme IX
Enolate And Aldol Chemistry At C(3)

Template ketone 1 undergoes Baeyer-Villiger oxidation to the lactone 20 upon treatment with MCPBA (Scheme X). Epoxidation of the corresponding silyl enolate 21 stereospecifically provides α-hydroxy ketone 22.

Scheme X

\[
\begin{aligned}
\text{20} & \xrightarrow{\text{LDA, THF, TMSCl}} \text{21} & \xrightarrow{\text{MCPBA}} \text{22}
\end{aligned}
\]

Vogel has outlined a route to octoses using the silyl enolate 23, obtained from the acetonide of dihydroxylated ketone 1, and protected L-glyceraldehyde 24 (Scheme XI). Octoses 25 and 26 are accessible by this route. Isomeric sugars are available from the (+)-enolate.

Scheme XI

CONCLUSION

The increasing diversity of carbohydrates and their derivatives has stimulated a search for new synthetic methodologies. Protecting group strategies are frequently used to control reaction selectivity but this approach is often fraught with difficulties. The diverse and intrinsic selectivity of these oxanorbornenes provides a multitude of means for the rational introduction of functionality at contiguous stereocenters in a target molecule under conditions of high stereo- and regioselectivity. Researchers have exhaustively manipulated this particular bicyclic chiron. Future efforts should be directed toward the identification and development of new templates.

REFERENCES

INTRODUCTION

Carbapenems were first recognized in the year 1976 with the isolation and structural identification of (+)-thienamycin (1) in the fermentation broth of the soil microorganism *Streptomyces Cattelaya* by the research groups at Merck, Sharpe and Dohme.\(^1,2\) The superiority of thienamycin over the penicillins and cephalosporins available in the mid 1970's is highlighted by the broad spectrum of thienamycin activity against Gram positive and Gram negative bacteria, especially the activity against *Pseudomonas* and the resistance to degradation by β-lactamases.

In spite of a broad spectrum antibiotic activity, poor chemical stability and susceptibility to the mammalian enzyme renal dehydropeptidase I compromise the use of thienamycin use as a parentally administered drug.\(^3\) In efforts to overcome these problems, several antibiotics with structural modifications on the side chain at the C-2 and C-6 positions of thienamycin (1) were synthesized and analyzed.\(^4\) The formimidoyl derivative of thienamycin, imipenem (2), showed both enhanced chemical stability and antipseudomonal activity.\(^4c\) Imipenem was launched as a drug in combination with cilastatin, a renal dehydropeptidase I inhibitor. However, 1-β-methylcarbapenems such as L-646591 (3) by Merck,\(^5\) SM-7338 (4) by Sumitomo,\(^6\) and L-10627 (5) by Lederle\(^7\) were reported to have all the major antibacterial characteristics of imipenem and also considerable stability to renal dehydropeptidase I. The 1-β-methylcarbapenems 4 and 5, are currently under clinical trials.
In addition to the synthetic challenge involved in the construction of these molecules with three or more stereogenic centers, this class of β-lactam antibiotics is of great interest because of their great medicinal importance. The world's market for antibiotics in the year 1992 was $9 billion, of which β-lactam antibiotics represent about $5 billion.8

In this abstract, different approaches towards syntheses of carbapenems are discussed. The syntheses and use of compounds 6 and 7 as key synthetic intermediates for the carbapenems will be emphasized.

SYNTHESSES OF CARBAPENEM SYNTHETIC INTERMEDIATES 6 AND 7

Cycloaddition Route

The azetidinone synthetic intermediate, 6, was synthesized by a [2+2] cycloaddition between the imine 8 synthesized from (S)-methyl-3-hydroxy-2-methylpropionate and the acetyl ketene equivalent 9 (Scheme I).9 The key step in this syntheses is the diastereoselective construction of the trans substituted β-lactam ring. The trans disposition and the chirality of the imine cause the facial selectivity in the approach of the ketene.

The reduction of the keto group of 10 with K-selectride proceeds with 16:1 diastereoselectivity (Scheme I). This selectivity is attributed to the preferred β-side attack of the hydride ion upon the syn-chelated conformer of the substrate in which the potassium ion is complexed by the β-dione system.10 In addition, the minor diastereomer after reduction can be converted via Mitsonobu inversion of the hydroxy group to the desired product.

The intermediates 6 and 7 were also synthesized by [2+2] additions using isocyanates11a,b and [3+2] cycloadditions of nitrones.11c
Enolate-Imin Condensation

β-lactam intermediates 6 and 7 have been prepared by an aldol type condensation between a chiral enolate derived from ethyl (S)-3-hydroxybutanoate (12) and an N-silyl protected imine 14 (Scheme II). The key step in this synthesis is the condensation of the enolate and the imine. The selectivity in this reaction is considered to be controlled by the chelated enolate intermediate 13, which directs the attack from the face opposite to the methyl group of 13. This chelation control yields the cis-β-lactam 15 as the major product.

Scheme II

In almost all of the subsequent reactions leading to carbapenems, the azetidinone intermediates 7 and 16 are considered to involve an acyl imine intermediate 17 formed by the elimination of acetic acid. Therefore, the configuration at C-5 of 16 is not critical. However, when (R)-12 is the starting material, the enantiomer of 15 is formed. So, the configuration at C-6 has to be inverted, this has proven to be more difficult.

The condensation using lithium enolates with silyl imines was satisfactory only for non-enolizable imines. For enolizable imines, boron enolates\textsuperscript{12c} and silicon enolates\textsuperscript{12d-f} were used, however, the yields in these reactions were low. Therefore, despite their limitation to non-enolizable imines, lithium enolates were preferable.

From Penicillin Derivatives

Synthesis of the intermediate 7 from commercially available methyl-6-aminopenicillinate (18) was accomplished in reasonable yield (Scheme III).\textsuperscript{13} The key strategy in this synthetic scheme is to exploit the stereochemistry previously set at C-5 of the starting material to obtain the desired stereochemistry at C-6 of the product. While the thiazolidine ring opening (21→22) proceeded efficiently with Hg(OAc)$_2$, the use of mercuric acetate in industrial manufacture is of
environmental concern and alternate routes were sought. Endo\textsuperscript{13b} obtained 7 in moderate yield from anhydropenicillin using chlorine followed by acetic acid instead of mercuric acetate.

Scheme III

Carbapenem intermediates were also synthesized from L-threonine,\textsuperscript{14a} L-aspartic acid,\textsuperscript{14b} and (R)-butane-1,3-diol\textsuperscript{14c} among others.\textsuperscript{4a,b,12f,14d} The acetoxyazetidinone intermediate 7 was also synthesized by Murasahi’s ruthenium catalyzed oxidation method.\textsuperscript{14e} This process is one of the common processes used in industry. BINAP-ruthenium(II) catalyzed hydrogenation was also used for the syntheses of the intermediate 6.\textsuperscript{14f}

The enolate-imine condensation approach (Scheme II) has the drawback of not being a good synthetic process for the industry. Even though an electrochemical oxidation method avoids the use of mercuric sulfate in the reaction, the number of steps involved makes this process less attractive for industry.\textsuperscript{14g} Despite the ready availability of the starting material and the simplicity of the synthetic strategy, the penicillin route (Scheme III) is also not a viable process for industry, as this route also uses mercuric acetate for the synthesis of the intermediate 7. In addition, if one is concerned about the carbon atom economy, the penicillin route is disadvantageous, since half of the starting atoms are wasted. The imine-ketene cycloaddition route (Scheme I) uses pyridinium dichromate for oxidation in the final step. Chromate based oxidants are also undesirable for large scale industrial usage. Even though environmentally safe alternate oxidation method could be utilized, the low yield and moderate diastereoselectivity of the cycloaddition step adds to the disadvantage of this route. However, in industry today, the most commonly used process to synthesize 7 is the [2+2] cycloaddition of hydroxy protected silyl enolate of chiral 3-hydroxybutanal and chlorosulfonylisocyanate.\textsuperscript{15} This route seems to be the most elegant and efficient process, since the intermediate 7 can be synthesized in just two steps.
SYNTHESSES OF THE INTERMEDIATE 6 FROM 7
From the Enolates of Propionic Acid Derivatives

The intermediate 6 was also synthesized from 7 and the enolate of propionic acid derivatives. The most commonly used enolates were of tin, zinc, and boron. The aldol type reaction of 4-(S)-isopropyl-1,3-thiazolidone-2-thione (23) with 24 gave the β-methyl diastereomer of 25 as the major product (Scheme IV). The selectivity was explained by a six-membered ring transition state involving Sn(II) chelation (Figure 1). Structure I is considered to be favored over II due to 1,3-diaxial type of interaction between the 4- and the 5-membered ring in II. Zinc and boron enolates result in comparable yields and selectivities. A common procedure used in industry to synthesize 6 involves asymmetric hydrogenation of allylic alcohols in the presence of ruthenium catalysts.

SYNTHESSES OF CARBAPENEMS FROM INTERMEDIATE 6

One route to carbapenems from the intermediate 6 is an intramolecular Wittig reaction of trialkoxyphosphorane with thiol esters (28→1) (Scheme V). The key strategy is the completion of the [3.2.0] bicyclic system in the final steps of the syntheses.

Scheme V
Merck researchers developed a procedure which involved a diazo compound 30 as the key intermediate in the synthesis. In this procedure, the C-2 thiol side chain is introduced after construction of the bicyclic system (Scheme VI).5,21

**Scheme VI**

Cyanamid's patented procedure using an α-keto ester intermediate 34 demonstrates an alternate to the above mentioned procedures. In this procedure, the C-2 substituents are introduced in the earlier stages of the synthesis (Scheme VII).7

**Scheme VII**

Several synthetic schemes involving the intramolecular Wittig ring closure result in low yields of the desired product due to the possible formation of the carbene intermediate in the reaction. The Merck procedure is particularly advantageous when compounds are synthesized on a small scale for the study of structure-activity relationships. It is a fast and efficient process to
give compounds which could be used to test the activity of different modifications of the side chain of the C-2 carbon as bulk quantities of 31 can be prepared using this procedure.

CONCLUSION

The three different approaches for the syntheses of carbapenems complement each other. The Cyanamid approach is the best, mainly because of the mild reaction conditions involved. For synthesizing the key carbapenem intermediates, the cycloaddition approaches are better, because of the safety and efficiency of the processes.

Even though an enormous effort has gone into the syntheses and development of carbapenems over the past decade, much still remains to be investigated. The identification of new bacterial strains and β-lactamases are increasing over time, so, several antibiotics which were found to be highly active initially were found to lose their activity over time. For human beings to win this race against nature, there is a need for the continued development of more new and effective antibiotics.

REFERENCES


(8) D.M. Paisley, Notes from "New Drug Science (CHEM 391A)", University of Illinois, Urbana, 1992.
(15) Lee, Ving J. personal communications.
(19) For a related asymmetric hydrogenation of the corresponding α,β-unsaturated ester see: C.A. 1989, 110:231338x.
RECENT ADVANCES IN THE DESIGN AND SYNTHESIS OF CYCLIC GLUTAMATE ANALOGS: NOVEL COMPETITIVE ANTAGONISTS OF THE NMDA RECEPTOR

Reported by Andrew Scribner

March 4, 1993

INTRODUCTION

L-Glutamate (1) is widely considered the most predominant excitatory neurotransmitter of the vertebrate brain.\(^1\) Regulated neuronal release and uptake of glutamate is crucial for the maintenance of proper cerebral function. Intercellular excesses of glutamate can lead to the over-excitation of neurons, a process called excitotoxicity, which can result in neuronal death and ultimately to the irreversible loss of memory and cognitive function. This is thought to be a major destructive mechanism in a broad range of mental disorders, which include Alzheimer's disease, Parkinson's disease, Huntington's chorea, epilepsy, schizophrenia, ischemia and/or inoxia resulting from stroke, and AIDS-induced dementia.\(^2\) There has been much effort within the past two decades aimed at diminishing the deleterious effects of excessive intercellular glutamate. One approach which has received much attention in recent years involves the design and synthesis of glutamate antagonists.

There are five post-synaptic receptors through which glutamate is known to mediate its effects, the most well-understood being the N-methyl-D-aspartate (NMDA) receptor, so named for the agonist which binds to it with high affinity (2).\(^3\) NMDA receptors are highly concentrated in the neurons of the hippocampus, the region of the brain associated with learning and memory. A salient feature of the NMDA receptor is its gated ion channel permeable to calcium. Maintenance of intracellular calcium is required to sustain synaptic plasticity, by which neurons are able to properly integrate incoming signals and establish appropriate synaptic connections. Within the receptor are several sites targeted for antagonists. These sites include binding pockets within the ion channel for zinc, magnesium, and phenylcyclidine, as well as distinct sites for polyamines, glycine, and NMDA itself. This NMDA site coincides with the site to which glutamate binds, as one might expect due to their similar structures. There has been much recent literature devoted to the design and preparation of competitive antagonists, which bind to the NMDA site, as well as noncompetitive antagonists, which bind to one of the other sites. Behavioral differences between the two suggest a more favorable side-effect profile for the former class.

Copyright © 1993 by Andrew Scribner
RATIONALE IN DESIGNING COMPETITIVE ANTAGONISTS

Watkins and coworkers tested a variety of straight chain analogs of glutamate and aspartate for agonist and antagonist activity.\textsuperscript{3a} The structure of the substrates was varied with regard to stereochemistry of the $\alpha$-carbon, length of the alkyl chain, and acidic functionality distal to the amino acid moiety. The following trends were observed: agonist activity was optimized in L-amino acids possessing alkyl chains up to six carbons long, with the preferred order of distal acid being -$\text{CO}_2\text{H}$ > -$\text{SO}_3\text{H}$ > -$\text{PO}_3\text{H}_2$. Antagonist activity, on the other hand, was favored in D-amino acids with alkyl chains containing five or seven carbons, with the preferred order of distal functionality being -$\text{PO}_3\text{H}_2$ > -$\text{CO}_2\text{H}$ > -$\text{SO}_3\text{H}$.

From these studies, the first potent in vitro competitive NMDA antagonists were found to be D-2-amino-5-phosphonopentanoate (3, D-AP5) and D-2-amino-7-phosphonoheptanoate (4, D-AP7) (Table I). It is not well understood why only the five and seven carbon alkyl chain length compounds had high affinity, and not the corresponding six carbon analog. There could be either two separate binding sites for the phosphonic acid moiety of each compound, or just one site within which D-AP7 can adopt a somewhat compressed, stable conformation allowing its phosphonate to be approximately the same distance from the amino and carboxyl groups as it is in D-AP5.

![Chemical structures of AP5 and AP7](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_i[\mu\text{M}]$ vs. [$^3\text{H}$] D-AP5</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-AP5</td>
<td>40</td>
</tr>
<tr>
<td>D-AP5 (3)</td>
<td>0.62</td>
</tr>
<tr>
<td>DL-AP6</td>
<td>42</td>
</tr>
<tr>
<td>L-AP7</td>
<td>28</td>
</tr>
<tr>
<td>D-AP7 (4)</td>
<td>1.7</td>
</tr>
<tr>
<td>DL-AP8</td>
<td>640</td>
</tr>
</tbody>
</table>

By designing glutamate analogs which possess at least one ring structure within the skeleton of the molecule, one could rigidly fix the distance between the phosphonate and the amino and carboxyl groups to improve knowledge of the binding site. Such studies have been undertaken in recent years with glutamate analogs containing piperazine, piperidine, phenyl, and isoquinoline ring structures. Presented herein are some key synthetic steps along with the biological activities of such compounds, ultimately leading toward the design of a pharmacophore.
PIPERAZINE ANALOGS

Recently Aebischer and coworkers have selectively prepared both enantiomers of CPP (5) and CPP-ene (6), and have shown that antagonist activity resides predominantly in the D-amino acid forms of each, roughly to the same extent as the corresponding acyclic analog, AP7 (Table II). Moreover, the appreciable binding of both suggests a fair degree of steric tolerance at the amino terminus within the binding pocket.

Table II. Binding Affinities of CPP and CPP-ene.

<table>
<thead>
<tr>
<th>Compound</th>
<th>K_i[μM] vs. [3H] CPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-5</td>
<td>0.14 ± 0.02</td>
</tr>
<tr>
<td>L-5</td>
<td>2.33 ± 0.40</td>
</tr>
<tr>
<td>DL-5</td>
<td>0.28 ± 0.04</td>
</tr>
<tr>
<td>D-6</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>L-6</td>
<td>0.60 ± 0.12</td>
</tr>
</tbody>
</table>

Hays, Bigge and coworkers have prepared racemic analogs of CPP which vary the length and functionality of the alkyl chain (Table III). Syntheses generally involved 4-N nucleophilic displacement of an alkyl halide possessing the appropriate phosphonate while the 1-N and 2-carboxyl were protected. Although the analogs of AP5 and AP7 were found to be the most potent, their order of potency was reversed. This decrease in potency for the AP5 analog may be due to electrostatic repulsion between the 4-N lone pair and the phosphonate, or perhaps simply due to the limited lipophilicity of the molecule.

Table III. Binding Affinities of Select Potent CPP Analogs.

<table>
<thead>
<tr>
<th>R</th>
<th>IC_{50}[μM] vs. [3H] CPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂PO₃H₂</td>
<td>0.32 ± 0.09</td>
</tr>
<tr>
<td>(CH₂)₂PO₃H₂</td>
<td>9.8 ± 0.84</td>
</tr>
<tr>
<td>(CH₂)₃PO₃H₂</td>
<td>0.079 ± 0.007</td>
</tr>
<tr>
<td>(CH₂)₄PO₃H₂</td>
<td>48.0 ± 7.4</td>
</tr>
</tbody>
</table>
PIPERIDINE ANALOGS

Both Hutchinson and coworkers and Ornstein and coworkers developed piperidine analogs of AP5 and AP7 which rigidly fix the four or five carbons branching from the amino acid terminus, and introduce a new stereogenic center at the 4-position.6 7 The 3-substituted and 4-substituted piperidines lock the phosphonate in folded and extended conformations, respectively. Ornstein also developed similar syntheses of corresponding compounds with a tetrazole bioisostere substituting for the phosphonate.8 The advantage of the tetrazole is that it may further increase bioavailability, and have a shorter duration of activity, which is preferable for the treatment of acute conditions such as cerebral ischemia.

Key steps in Ornstein's synthesis of the 4-substituted phosphonates are depicted in Scheme I. Reissert-Henze chemistry afforded the 2-nitrile from the 4-substituted pyridine, followed by deprotection and reductive hydrogenation to yield the 2,4-cis-substituted piperidines. For the tetrazoles, Horner-Emmons chemistry was used to introduce an alkyl nitrile group onto the ring; reaction of the nitrile with azidotri-n-butylstannane afforded the tetrazole. Separation of cis diastereosomers occurred via derivatization and subsequent resolution with di-p-toluoyltartaric acid. Here the D-isomer (2R,4S) showed greatly enhanced activity over the L-isomer, consistent with activity displayed in known antagonists thus far.

Scheme I

Binding data (Table IV) reveal that the 4-substituted AP5 and AP7 analogs bind comparably to the piperazyl analogs -- in fact, quite better in the case of AP5 for aforementioned reasons. It is noted that the 3-substituted analogs displayed rather limited activity, suggesting an extended conformation may be preferable for AP5. The tetrazoles with appropriate stereochemistry also show promise as AP5-like antagonists, and in particular are noted for their shorter duration of action (4 hr vs. > 12 hr for corresponding phosphonates). None of the pyridines showed any activity, suggesting the need for either a proton and/or a more basic nitrogen at the amine terminus.

PHENYL-SPACED ANALOGS

Johnson, Bigge, and coworkers have prepared a series of ortho, meta, and para substituted (phosphonoalkyl)phenylglycine and phenylalanine derivatives.9 Such analogs restrict from four to
six atoms in the backbone into a planar formation, limiting the spatial arrangement of the distal acid moieties.

Table IV. Binding Affinities of Select 3- and 4-Substituted Piperidines.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>IC₅₀[μM] vs. [³H]CPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂PO₃H₂</td>
<td>H</td>
<td>0.095 ± 0.028</td>
</tr>
<tr>
<td>(CH₂)₂PO₃H₂</td>
<td>H</td>
<td>6.600 ± 1.279</td>
</tr>
<tr>
<td>(CH₂)₃PO₃H₂</td>
<td>H</td>
<td>0.120 ± 0.019</td>
</tr>
<tr>
<td>(CH₂)₄PO₃H₂</td>
<td>H</td>
<td>&lt;50% inhibition</td>
</tr>
<tr>
<td>H</td>
<td>(CH₂)₂PO₃H₂</td>
<td>1.000 ± 0.226</td>
</tr>
<tr>
<td>(2R, 4S)CH₂N₄H</td>
<td>H</td>
<td>0.067 ± 0.006</td>
</tr>
<tr>
<td>(2S, 4R)CH₂N₄H</td>
<td>H</td>
<td>2.393 ± 0.368</td>
</tr>
</tbody>
</table>

The phosphonic acids were commonly introduced into the aryl compounds by nucleophilic displacement of an alkyl halide or mesylate. Alternatively, palladium(0)-catalyzed or palladium(II)-catalyzed displacement of an aryl bromide occurred with diethylphosphite or diethylvinylphosphonoate, respectively (Scheme II). Masked amino acid functionalities were introduced directly onto aryl rings either by traditional Strecker-style synthesis via α-amino nitriles or by amidoalkylation with α-hydroxyhippuric acid. Alternatively, acetamidomalonate in base could nucleophically displace an alkyl bromide, ultimately providing an alkyl amino acid.

Scheme II

Binding affinities for select compounds are given in Table V. In fact, no other compounds showed appreciable binding affinity. It is observed that the AP5, -6, and -7 trend does not appear to hold for the meta substituted compounds, as the AP6 analog shows the highest affinity of the
three. This strongly suggests that selectivity based on alkyl chain length is superceded by spacial orientation. The moderate affinities of the two para-substituted compounds show that the presence of an aryl ring in the backbone can be tolerated within the receptor. Nevertheless, the location of the ring relative to the two terminal acidic functionalities is critical.

<table>
<thead>
<tr>
<th>Table V. Binding Affinities of Select Phenyl-Spaced Phosphonates.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Substituent</td>
</tr>
<tr>
<td>p</td>
</tr>
<tr>
<td>p</td>
</tr>
<tr>
<td>m</td>
</tr>
<tr>
<td>m</td>
</tr>
<tr>
<td>m</td>
</tr>
<tr>
<td>o</td>
</tr>
</tbody>
</table>

Bigge and coworkers have more recently prepared N-phosphonoalkyl-, N-phosphonoalkenyl-, and N-(phosphonoalkyl)phenyl-spaced α-amino acids, employing synthetic chemistry quite similar to their phenylalanines and -glycines (data not shown). Compounds with phosphonates directly bonded to aryl rings showed low affinity. Ortho-phenyl spacers tended to show low affinity, as did derivatives with a phenyl ring attached directly to the amine. In general, high affinities were shown in molecules in which the carboxyl and phosphonic acid moieties appear to be folded on the same side of the molecule.

**ISOQUINOLINE ANALOGS**

The hydroisoquinoline nucleus imposes rigidity along the entire AP7 backbone. Decahydroisoquinolines can be prepared with distinct spatial orientations due to the four stereogenic centers. In this system, Ornstein has prepared several 1- and 3-carboxyl, 6-functionalized decahydroisoquinolines. Thus far, he has prepared L-amino acids possessing phosphonate, carboxylate, and tetrazole distal functionalities.

Cis and trans ring junctures were established by appropriate reduction conditions of the enone precursor (Scheme III). Hydrogenation over palladium and carbon afforded the cis product, whereas dissolving metal reduction provided the trans product. Stereochemical assignments were made based on ¹H NMR studies and resolution with the α-methylbenzylamine salt of the corresponding acid. Appropriate functionalities were incorporated via Horner-Emmons chemistry as in Ornstein's piperidine syntheses.
Scheme III

The binding affinities of the most potent compounds are shown in Table VI. It is observed that the preferred order of distal functionality is -PO₃H₂ > -CN₄H > -CO₂H, with equatorial substitution preferred to axial. The excellent binding of the equatorial phosphonate suggests not only that such a folded conformation is optimal for AP7, but that steric bulk along the entire backbone can still be accommodated within the binding site.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>IC₅₀[μM] vs. [³H] CGS19755</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂PO₃H₂</td>
<td>H</td>
<td>0.055 ± 0.014</td>
</tr>
<tr>
<td>CH₂CN₄H</td>
<td>H</td>
<td>0.856 ± 0.136</td>
</tr>
<tr>
<td>CH₂CO₂H</td>
<td>H</td>
<td>4.298 ± 0.598</td>
</tr>
<tr>
<td>H</td>
<td>CH₂PO₃H₂</td>
<td>0.815 ± 0.205</td>
</tr>
<tr>
<td>H</td>
<td>CH₂CN₄H</td>
<td>3.380 ± 0.286</td>
</tr>
<tr>
<td>H</td>
<td>CH₂CO₂H</td>
<td>&gt; 10.0</td>
</tr>
</tbody>
</table>

Recently, Ortwine, Malone, Bigge and coworkers have prepared tetrahydroisoquinolines, which combine the conformational restraints of both piperidine and phenyl-spaced analogs. The amino acid functionality was introduced either by Reissert-Henze chemistry as described before, intramolecular amidolkylation, or nucleophilic displacement by acetamidomalonate. Binding data (not shown) still clearly suggests that the two acid functionalities prefer to be cis to one another, particularly in AP5 analogs. It is observed that the trade off between added steric bulk and increased lipophilicity still allows for binding.
CONCLUSION

Clearly, more work needs to be done in order to fully establish the parameters of the NMDA competitive antagonist pharmacophore. Nevertheless, cyclic glutamate analogs provide insight as to how an antagonist interacts within the receptor. In particular, they have demonstrated how functionalities relatively far apart in space prefer to be aligned once in the binding site. The competitive glutamate antagonists studied thus far suggest that AP5 analogs prefer an extended conformation while AP7 analogs prefer a slightly folded one, and both prefer to have the two acid functionalities cis to one another. In addition, there appears to be tolerance for the steric bulk of one or more rings along the backbone of the antagonist, although the location of the ring is crucial. Such information is useful for the further design of new antagonists which could potentially treat brain disorders associated with excessive intercellular glutamate.

REFERENCES

ASPECTS OF THE BIOLOGICAL ASSEMBLY OF TETRAPYRROLES

Reported by Jim McGuire

March 18, 1993

INTRODUCTION

The complexity, diversity and importance of tetrapyrroles found in living organisms is tremendous. The heme group, chlorophyll, cofactor F₄₃₀ and siroheme are all essential or important to living organisms. The most complex of the tetrapyrroles are the corrinoids, which include coenzyme and vitamin B₁₂.¹ Coenzyme B₁₂-mediated reactions involve homolytic bond cleavage followed by characteristic 1,2 shifts,² which are extremely important anabolic processes, while cobalamin (vitamin B₁₂) is an essential nutrient. In fact, the importance of vitamin B₁₂ is borne out by the estimation that it has existed for nearly four billion years, about twice as long as there has been oxygen on the planet.

Figure 1. Structures of vitamin and coenzyme B₁₂.

The biosynthesis of tetrapyrroles begins with the formation of 5-aminolevulinic acid (ALA) from glycine and succinyl CoA in photosynthetic bacteria, yeast and mammals. Other organisms actually reduce glutamyl tRNA to the corresponding aldehyde, which is converted to ALA.³ Aminolevulinic acid is condensed with itself by ALA dehydratase to form porphobilinogen (PBG). PBG is polymerized by porphobilinogen deaminase to produce hydroxymethylbilane (HMB), which is cyclized and rearranged by uroporphyrinogen III synthase to give uroporphyrinogen III (uro'gen III). Uro'gen III is the template for all known tetrapyrroles. In the absence of uro'gen III synthase, HMB cyclizes to uro'gen I.

Copyright © 1993 by Jim McGuire
Scheme I. Biosynthesis of porphobilinogen.

Scheme II. Biosynthesis of uroporphyrinogen III.

PORPHOBILINOGEN DEAMINASE

Structure

The structure of *E. coli* PBG deaminase (EC 4.3.1.8, also known as hydroxymethylbilane synthase or deaminase) has recently been solved by x-ray crystallography to 1.9 Å resolution. The protein, which has a large hydrophobic core, was shown to consist of three domains that define five walls of an imaginary cube. Domains 1 and 2 constitute the floor, ceiling and two sides. They are similar in their tertiary structure and related by an approximate C2 axis of symmetry. The third domain, which comprises the back wall, is the site of attachment of the dipyrrromethane cofactor and is postulated to serve as a linker for domains 1 and 2. The enzyme has only one catalytic site and must accommodate the growing polypyrrole chain during its construction by expanding the hydrophobic core by slight changes in domain 3. PBG deaminase contains a novel cofactor constructed from two molecules of its substrate and attached to the cysteine at position 242.
Catalytic cycle

In the catalytic cycle for PBG deaminase the first molecule of PBG is bound in the active site and then activated presumably by formation of a carbocation with loss of ammonia. The free α position of the cofactor then attacks C-11 of PBG to form the new carbon-carbon bond. The new compound is termed the ES1 complex. Three subsequent molecules are likewise added to form the ES2, ES3 and ES4 complexes. Finally, the PBG hexamer (ES4) is hydrolyzed to give hydroxymethylbilane and the active enzyme.

Scheme III. Catalytic cycle for PBG deaminase.

Electrospray Mass Spectrometry

The detection of the enzyme-substrate complexes had previously been done with native polyacrylamide gel electrophoresis (PAGE) or SDS-PAGE and fast protein liquid chromatography (FPLC). Recently, however, the enzyme, as well as ES1 through ES4, were directly detected by electrospray mass spectrometry (ESMS). Incubation of the enzyme for ten minutes with five equivalents of PBG followed by a methanol quench produced the following results:

Table I. Electrospray MS data for PBG deaminase and substrate complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Found (Da)</th>
<th>Calculated (Da)</th>
<th>Relative Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>34 271</td>
<td>34 290</td>
<td>100</td>
</tr>
<tr>
<td>ES1</td>
<td>34 477</td>
<td>34 479</td>
<td>27</td>
</tr>
<tr>
<td>ES2</td>
<td>34 689</td>
<td>34 688</td>
<td>62</td>
</tr>
<tr>
<td>ES3</td>
<td>34 902</td>
<td>34 898</td>
<td>31</td>
</tr>
<tr>
<td>ES4</td>
<td>35 104</td>
<td>35 107</td>
<td>69</td>
</tr>
</tbody>
</table>

It had been reported that ES2 is the most stable complex, and, indeed, after 30 minutes it was found to be the most plentiful. ESMS was able to accurately measure the masses of the compounds and to detect the ES4 complex, which had never been seen by PAGE or FPLC.
PBG Deaminase Mutants

Several arginines are important for catalytic activity, presumably due to interaction with the acidic side chains of the PBG molecules. Nine Arg residues that correspond to those at positions 11, 101, 131, 132, 149, 155, 176, 206 and 232 in *E. coli* are also conserved in the enzymes isolated from *Euglena gracilis, Bacillus subtilis, rats, mice and men*. Site-directed mutagenesis studies which replaced each of these amino acids with leucine or histidine revealed their importance in the *E. Coli* protein. R131L (Leu substituted for Arg-131), R131H, R132L and R132H were inactive because these proteins were unable to incorporate the cofactor. Interestingly, these two residues come at the end of a seven amino acid span that is conserved in all known enzymes (GTSSLRR). R11H, R155L and R155H required high substrate concentrations before any complexes were seen. Only moderate activity was exhibited by R149H, R176L, R176H, R232H. Evidently, the arginines are extremely important in the binding of PBG, both in the apoenzyme to assemble the cofactor and in the active enzyme, to help stabilize the negative charges on the side chain carboxyl groups of the substrate.

**Mechanism**

Scott and coworkers have recently synthesized a series of porphobilinogen analogs to help investigate the mechanism of PBG deaminase. The E2 or Elcb mechanisms offer the simplest explanation for the observed reaction. Incubation of the PBG deaminase with N-methyl-PBG, which should be inactive if deprotonation of the amine is a crucial step in the mechanism, produced only ES1 with no higher complexes. These results clearly show that the amino proton is not necessary for activation of C-11 in the E2 mechanism. The methyl group must, however, reduce the nucleophilicity of the free α carbon of the pyrrole and halt polymerization at ES1.

**Scheme IV. Elimination mechanisms for PBG deaminase.**
Carbocation formation by loss of ammonia and subsequent elimination or even an \( \text{S}_2 \) pathway were also possible. To differentiate between these two possibilities, C-11-methyl-PBG as well as the corresponding trifluoromethyl derivative were synthesized and tested under standard incubation conditions (15-20 min at pH 8.1 or 5.2). C-11-methyl-PBG reacted just a little slower than PBG itself. C-11-trifluoromethyl-PBG, however, gave no product under identical conditions. After 36 hours at pH 8.1 or 20 hours at pH 5.2, C-11-trifluoromethyl-PBG did produce an ES\( _1 \) complex. Therefore, the trifluoromethyl derivative reacts \( \approx 10^3 \) times slower than PBG.

![Figure 2. Structures of PBG analogs.](image)

The differences in reactivity are likely due to electronic effects since fluorine and hydrogen occupy roughly equal amounts of space. The trifluoromethyl group seems to destabilize a carbocation formed by loss of ammonia. The relative rates of solvolysis of 1-(N-methyl)-pyrrolyl-2,2,2-trifluoroethyl \( p \)-nitrobenzoate and 1-(N-methyl)-pyrrolyl-ethyl \( p \)-nitrobenzoate are shown below.\(^{11}\) Although run in different media they still suggest that the trifluoromethyl substituent will retard the reaction rate by over an order of magnitude. The same effect is seen for the methyl PBG compounds.

![Figure 3. Rates of solvolysis for 1-(N-methyl)-pyrrolyl-2,2,2-trifluoroethyl \( p \)-nitrobenzoate versus 1-(N-methyl)-pyrrolyl-ethyl \( p \)-nitrobenzoate.](image)

Battersby and his coworkers proved that HMB is formed from PBG with retention of stereochemistry at C-20,\(^ {12} \) which was C-11 of the first substrate molecule. This results either from an inversion at that center both during ES\( _1 \) formation and hydrolysis or from reaction at only one face of the molecule. An \( \text{S}_2 \) mechanism, however, does not adequately explain the empirical evidence. First, the rate retardation of the trifluoromethyl group would not be expected for an \( \text{S}_2 \) pathway. Second, the ammonium ion that is probably formed is not a good nucleofuge and would not be expected to be a good leaving group. And, third, the methyl group
on C-11 would be expected to significantly hamper the rate of an \( S_N2 \) process. All of the current experimental data suggest that PBG coupling is accomplished through an \( E1 \) mechanism.

**UROPORPHYRINOGEN III SYNTHASE**

Uro'gen III synthase (EC 4.2.1.75, also known as cosynthetase) catalyzes the cyclization and ring D inversion that produces uro'gen III from HMB. The structure of uro'gen III synthase is still unknown. It seems to be monomeric with an approximate molecular weight of 28 000 Da.\(^\text{13}\) The sequence of the protein was deduced from the DNA sequence of its gene and contains multiple arginines, as does PBG deaminase. Kinetic studies have shown uro'gen III synthase to be a relatively fast enzyme, which is probably necessitated by the instability of its substrate.

**Spiro Intermediate**

Several models have been proposed to explain the transformation of HMB to uro'gen III. The longest standing hypothesis is the so-called spiro intermediate,\(^\text{14}\) in which ring D is flipped over by formation of a spiro-pyrrolenine. This compound could arise from water loss to form an azafulvene ion in ring A followed by nucleophilic attack of C-16 on C-20. The spiro-pyrrolenine would then undergo fragmentation-recombination to form uro'gen III. Similar compounds undergo analogous fragmentation-recombination reactions in solution.\(^\text{15}\)

**Scheme V. Proposed spiro intermediate mechanism.**

Battersby and coworkers have synthesized some model spiro compounds to test as inhibitors of uro'gen III synthase. The dicyano analog was constructed first and shown by x-ray to have a relatively rigid conformation in which two of the pyrrole rings are essentially parallel to one another while the other one is perpendicular and points in the opposite direction.\(^\text{16}\) They next made a spiro lactam,\(^\text{17}\) which is unable to undergo fragmentation-recombination and should not be turned over by uro'gen III synthase. One of the two isomers isolated had a \( K_i \) of ~1 \( \mu \)M toward uro'gen III synthase. The active isomer was further purified into its enantiomers. One was found to inhibit the enzyme about 20 times better than the other. In fact the \( K_i \) for this isomer was an order of magnitude lower than the \( K_M \) for HMB. Although the details including
identity of the most active isomer remain unpublished, the experiments do provide solid evidence for the intermediacy of a spiro compound.

![Image of spiro model compounds]

**Figure 4.** Structures of spiro model compounds.

**Lactone Intermediate**

Scott has recently questioned the spiro intermediate hypothesis based on some $^{13}$C NMR experiments done at -24°C in ethylene glycol/buffer. Despite slowing the reaction down by three orders of magnitude and feeding several labeled isomers, no signals corresponding to the proposed quaternary (≈ 80 ppm) or adjacent methylene (≈ 35-40 ppm) carbons were observed. He then proposed the intermediacy of a lactone, which is formed from the acetate carboxyl group on ring D to C-20. The resulting macrolide can then undergo fragmentation-recombination to arrive at uro'gen III. No details on the experiment have been published. He also claims that the lactone intermediate explains the fact that synthetic bilanes lacking the acetic acid side chain on ring D are not converted to type III porphyrinogens by the enzyme. Furthermore, it is known that another synthetic bilane in which the propionate and acetate groups on ring D are switched does give both uro'gen I (rearranged product) and uro'gen III enzymatically.

**Scheme VI.** Proposed lactone intermediate mechanism.

![Image of proposed lactone intermediate mechanism]

**CONCLUSION**

Despite three decades of work, the mechanisms of PBG deaminase and uro'gen III synthase are still under debate. The recent x-ray structure of PBG deaminase along with the substrate analog work have helped to rule out some possible mechanisms, but the published
results are not fully compelling. An x-ray structure of the relatively stable ES2 complex, if possible, may help elucidate the exact mechanism of the enzyme. While the research presented here represents large strides toward completion of B12 biosynthesis, many questions about later steps remain unanswered. As the chemical synthesis of vitamin B12 stands as a landmark, the completed biosynthesis will also be monumental.

REFERENCES
ELECTROPHILIC ADDITIONS USING SILICON SUBSTITUENTS AS DIRECTING GROUPS

Reported by Christopher W. Derstine

March 25, 1993

INTRODUCTION

The electrophilic addition to allylsilanes with resulting elimination of the silyl group has been a topic of considerable investigation. Less studied are electrophilic additions to allylsilanes and their counterparts the β-silylenols and β-silylenolates, where the silyl group is retained. This review will cover recent accounts concerning electrophilic additions to enolates carrying a silyl group at the stereogenic β position and examine the directing effect the silane has from this spectator position, on the diastereoselectivity of these reactions. In addition, it will cover recent work on electrophilic additions to chiral allylsilanes.

β-SILYL carbonyl compounds

The first utilization of a stereogenic center carrying a β-silyl group for directing electrophilic attack on enols and enolates was described by Fleming in 1984.1,2 Figure 1 shows the basic system in which the β position is a stereogenic center carrying a large silane. Unless specifically stated otherwise, all of the studies which will be discussed were carried out using racemic β-silylcarbonyl compounds, so that only the diastereoselectivity of the reactions was studied.

Figure 1. Basic model of the β-silyl enolates.

Compounds like the example in Figure 1, were allowed to react with electrophiles to see whether there would be predictable diastereoselectivity during electrophilic attack. Possible directions of electrophilic attack are shown as A and B (Scheme I), where the predicted approach of the electrophile occurs anti to the large silyl group. Fleming has shown that if there is significant 1,3-allylic strain between the allylic proton and R2, then the transition state arising from approach A will be energetically favored over the transition state arising from B, increasing the diastereoselectivity of electrophilic attack and producing an excess of product 1.1,2
The two reactions in Scheme II illustrate a comparison between the electrophilic attack on the chiral $\beta$-silyl enolate formed from 3 ($R^1 = \text{Me}$) and the related $\beta$-phenyl chiral enolate derived from 6 ($R^1 = \text{Me}$). In the first reaction, the enolate is formed by silylcupration of the $\alpha,\beta$-unsaturated ester. Quenching with methyl iodide formed the methylated products 4 and 5 in a 91:9 ratio, where the major product 4 is the derived from electrophilic attack in the preferred sense A.\(^2\) In contrast, an earlier paper reported that alkylation of the enolate formed from 6 produces the methylated products 7 and 8 in only a 55:45 ratio.\(^3\) Obviously there is an increase in the diastereoselectivity of methylation when a silane is substituted at the $\beta$ position of the enolate, but whether it is because of the shear bulk of the silane, favoring attack from the opposite face, or a result of some type of electronic effect is still in question at this point.

Both Fleming and McGarvey have stated that they believe there must also be an electronic reason for high stereoselectivity in reactions where an electropositive group is substituted $\beta$ to a carbonyl.\(^1,4\) The electronic effect being considered is termed the $\beta$-silicon effect because it has been shown that a silyl group can stabilize positive charge in a $\beta$-silylcarbonium ion ($R_3\text{SiCH}_2\text{CH}_2^+$), but there is still some debate about how this effect operates.\(^5\) The $\sigma$ electrons in the Si-C bond are believed to overlap with the adjacent p orbital, stabilizing the positive charge. If this hyperconjugation is operating in the $\beta$-silylenolates, then the electronic effect should also support transition state A just as the allylic strain effect does. Transition states A and B allow the $\sigma$ electrons to be coplanar with the $\pi$ electrons, maximizing
orbital overlap and possibly enhancing the nucleophilicity of the enolate. So far the only experimental evidence indicates that no electronic enhancements are operating.\(^2\)

Fleming next investigated which parts of the enolate could be modified without drastically affecting the diastereoselectivity of alkylation. Group R\(^1\) in the structure in Figure 1, was modified to see if increased bulk at the stereogenic center would erode diastereoselectivity. The expectation is that as R\(^1\) increases in size, it may compete with the silane for the least hindered position in the reactive conformation, causing transition state A to be closer in energy to transition state B. It was found that the diastereoselectivity was highest with phenyl, but as expected, declined in the alkyl series as the group got larger: methyl > isopropyl > tert-butyl.\(^2\) Panek had demonstrated that if R\(^1\) was a substituted vinyl substituent, high diastereoselectivities for alkylation were also achieved.\(^6\) Fleming uses this observation to support his belief that the effective bulk of the phenyl group may not be so great because it is planar like the vinyl group.

Modification of the groups at R\(^2\) results in high diastereoselectivity with the alkylation of ketones (R\(^2\) = Me, Ph), esters (R\(^2\) = OMe) and amides (R\(^2\) = NMe\(_2\)), but selectivities were lower with aldehydes (R\(^2\) = H).\(^2\) The aldehydes are presumably lower in selectivity due to insufficient A\(^1,3\) strain, since R\(^2\) is a proton, with the result that neither of the rotamers, A or B, are strongly preferred. These studies also demonstrated that the enolate geometry (E or Z) did not have a measurable effect on the product distributions.

It was also discovered that diastereoselective alkylation of \(\beta\)-silyl enolates is possible even when R\(^3\) is another alkyl group, thus generating a quaternary center.\(^2\) If R\(^3\) is methyl or ethyl, diastereoselectivity was high, but with groups larger than ethyl, diastereoselectivity declines quickly. Finally, Fleming modified the substituents on the silane and found that the diastereoselectivities were affected in only a minor, but not consistent, fashion by increasing (t-BuPh\(_2\)Si) or decreasing (Me\(_3\)Si) the size of the silane.\(^2\)

Throughout Fleming's work the silane of choice is always the phenyldimethylsilane. This silane is especially useful because of a synthetic transformation which allows this silyl group to be replaced by a hydroxyl group with retention of stereochemistry.\(^7\) What was originally a two-step process, has recently been improved to a high yielding one-step procedure.\(^8\) The replacement is based on the aromatic desilation by some electrophile such as Br\(^+\) or Hg\(^{2+}\), followed by oxidative cleavage of the Si-C bond with peracid, as shown in Scheme III. This demonstrates the usefulness of silane chemistry in stereocontrolled formation of \(\beta\)-hydroxyesters or ketones, which are groups that may be useful in synthetic applications.

**Scheme III** Conversion of silyl group into a hydroxyl group.
After showing that both alkylations and protonations of the \( \beta \)-silylenolates were diastereoselective,\(^2\) Fleming examined the scope of the reaction using other electrophiles. The same high diastereoselectivities were formed with aldehydes such as acetaldehyde and benzaldehyde, as shown in Scheme IV, but as is evident from the connected table, enolate geometry now becomes important in determining the stereochemistry of the final products.\(^9\) Not only is there diastereoselectivity between C-3 and C-2, but there is equally high diastereoselectivity between C-3 and C-3'. The choice between diastereomer 11 or 12 is simply controlled by which enolate is used. The selectivity in these reactions was sufficient enough that 11 and 12 were the only products detectable by \(^1\)H NMR.\(^9\) Oxidative desilation of the aldol products 11 and 12 produces compounds with two new stereogenic centers. It has also been shown that if R\(^1\) is a phenyl group, selectivities remain high, indicating that other substituents at R\(^1\) may be tolerated. This reaction may also prove useful in synthetic applications.

**Scheme IV**

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Products from Z-10</th>
<th>Products from E-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>89:11 73</td>
<td>6:94 81</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>94:6 90</td>
<td>9:91 79</td>
</tr>
</tbody>
</table>

**ALLYLSILANES**

Another area which has received attention is electrophilic addition to allylsilanes where the silane is substituted at a stereogenic allylic center. The stereochemistry of these additions can be analyzed by transition states C and D shown in Scheme V. The electrophilic reagents which will be covered include osmium tetroxide, \( m \)-chloroperbenzoic acid (MCPBA), Yamamoto’s methylenating reagent and various hydroboranes.

**Scheme V**
Some initial reports indicated that allylsilanes such as C might not undergo electrophilic attack diastereoselectively. These accounts showed low selectivities in [3 + 2]-cycloadditions with C (R, R¹ = Me)¹⁰ and in osmylations and epoxidations with simple allylsilanes, such as the trimethylsilyl analog of E-15a in Scheme VI.¹¹ One other report, however, showed relatively high diastereoselectivity of epoxidation with the trimethylsilyl analog of E-15c.¹² On this basis, Fleming did a more thorough study to see if selectivities could be predictable. The results of his work¹³ are shown in Scheme VI, along with some earlier results by Vedejs (16a, 17a and 18a, 19a).¹¹ (The epoxides 18, 19 were not actually isolated, since the compounds were too unstable, so the epoxides were allowed to react with n-Bu₄NF to form the stable cis, or trans-allylic alcohols).

Scheme VI

In each of the three examples shown in Scheme VI, as the group R¹ gets larger, the attack becomes more diastereoselective in the sense of C. Diastereoselectivity for the same three reactions with Z-15 was considerably higher in almost every case. Thus, as was seen with the β-silylenolates, the larger the A¹,³ strain the higher the selectivities. It is interesting to note that in simple chiral allylic systems without silicon substituents, surprisingly high selectivities were achieved with epoxidations; however, the selectivities are not as consistently high as in epoxidations of compounds which contained a silyl group at the β position.¹⁴,¹⁵ Therefore, it might be argued that an electronic effect is responsible for high stereoselectivities in the allylsilanes, although this may still not be the case. Vedejs maintains that there is no hyperconjugative effect at work in the osmylation which produces 16a and 17a, because changing from the electropositive silane to an electronegative sulphone (PhSO₂⁻) had very little
effect on the diastereoselectivity of the reaction.\textsuperscript{11} One concern is that his ratio for \textit{16a}, \textit{17a} is so different from the rest of Fleming's but Fleming never comments on the validity of Vedejs' data.

Finally, Fleming has shown that the hydroborations of allylsilanes occur with high regioselectivity\textsuperscript{16,17} as well as high diastereoselectivities (Scheme VII).\textsuperscript{17,18} From compounds \textit{22-25} it is apparent that the regioselectivity of hydroboration is high and independent of the geometry of the alkene. Also it is clear that selectivities are greater when using the bulkier 9-BBN as the hydroborating agent. Compound \textit{27} demonstrates that the allylic silane is not enough of a directing influence to overcome the intrinsic preference for hydroboration at the less substituted end of the alkene. Yet, alkene \textit{26} shows that as bulk increases at the allylic position, it is possible to overcome the intrinsic preference of hydroboration by using 9-BBN. If only steric factors were at work, the regioselectivity of hydroboration of \textit{28} might not be expected to cause 100\% of the boron atoms to be positioned away from the silane. Therefore, once again the argument can be made that an electronic effect is working in these reactions, but in this case, this presumption has support from experimental work. Bryson placed compound \textit{28} and 2,3-dimethyl-2-butene in competition for a limiting amount of BH\textsubscript{3} and found that the alcohol derived from the more hindered silyl substituted molecule (\textit{28}) was formed in a 9:1 ratio to the alcohol derived from the unsubstituted competing molecule.\textsuperscript{19} Thus the silated alkene reacted nine times faster than the nonsilated version, demonstrating that a $\beta$-silicon effect is operating.

\textbf{Scheme VII} Regioslectivity in the hydroborations of allylsilanes with 9-BBN (bold numbers) and BH\textsubscript{3}•THF (numbers in parentheses).

\begin{center}
\begin{tabular}{c c c c c c}
\textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} \\
\textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} & \textbf{PhMe\textsubscript{2}Si} \\
\textbf{22} & \textbf{23} & \textbf{24} & \textbf{25} & \textbf{26} & \textbf{27} & \textbf{28} \\
\textit{>95 (83)} & \textit{<5 (17)} & \textit{<5 (20)} & \textit{<5 (20)} & \textit{<5 (20)} & \textit{1 (7)} & \textit{100 (0)} \\
\textit{>95 (83)} & \textit{<5 (17)} & \textit{<5 (20)} & \textit{<5 (20)} & \textit{<5 (20)} & \textit{1 (7)} & \textit{100 (0)} \\
\textit{74 (13)} & \textit{74 (13)} & \textit{74 (13)} & \textit{74 (13)} & \textit{74 (13)} & \textit{74 (13)} & \textit{74 (13)} \\
\textit{10 (87)} & \textit{10 (87)} & \textit{10 (87)} & \textit{10 (87)} & \textit{10 (87)} & \textit{10 (87)} & \textit{10 (87)} \\
\textit{1 (7)} & \textit{1 (7)} & \textit{1 (7)} & \textit{1 (7)} & \textit{1 (7)} & \textit{1 (7)} & \textit{1 (7)} \\
\textit{100 (0)} & \textit{100 (0)} & \textit{100 (0)} & \textit{100 (0)} & \textit{100 (0)} & \textit{100 (0)} & \textit{100 (0)} \\
\end{tabular}
\end{center}

Scheme VIII lists the diastereoselectivities of hydroboration as \textit{anti}:\textit{syn} ratios, where \textit{anti} corresponds to the approach of the electrophile as in \textit{C}, and \textit{syn} as the approach in \textit{D}.\textsuperscript{17,18} The diastereoselectivity of the hydroborations, unlike the regiochemistry, is dependent on the \textit{E} or \textit{Z} nature of the alkenes, as shown by the data for alkenes \textit{22} and \textit{23}. These cases also demonstrate that poor diastereoselectivity of \textit{E} alkenes using BH\textsubscript{3}, can be overcome by using the bulkier hydroborane 9-BBN. Another way to achieve higher selectivities with \textit{E} alkenes is to increase the size of the medium group on the stereogenic center from methyl to phenyl, as demonstrated
by alkenes 24 and 25. Again, A\textsuperscript{1,3} strain is important for high diastereoselectivities, and in this case, the size of the electrophile can influence the selectivity of attack.

Scheme VIII  Stereoselectivity in the hydroborations of allylsilanes shown as \textit{anti:syn} ratios with 9-BBN (bold numbers) and BH\textsubscript{3}-THF (numbers in parentheses).

PRACTICAL USE OF A SILANE AS A DIRECTING GROUP

Because this reaction is relatively new there are as yet, rather few examples in the literature where a silyl group is used as a directing group in a complex synthesis. One excellent example has recently appeared in which the directing effects of a silane in both an enolate and an allyl system is used within the same molecule (Scheme IX).\textsuperscript{20} The propargylic alcohol 29 is catalytically hydrosilated and then oxidized to give the \(\alpha,\beta\)-unsaturated ketone 31. Nucleophilic attack on the ketone produces the allylic alcohol 32, and a Sharpless kinetic resolution gives enantiomeric enrichment. After a Claisen rearrangement the enantiomerically enriched silyl compound 33 is obtained. Under direction of the b-silyl group, the enolate of compound 33 is then diastereoselectively methylated to form 34, and after reduction of the ester and protection of the resulting alcohol, the same silane is used to guide a diastereoselective epoxidation, which after an acid catalyzed elimination produces the triol derivative 36 as the only detectable isomer. This synthesis produces the silane precursor 33 in a number of high yielding steps, but the kinetic resolution of the allylic alcohol 32 introduces a serious inefficiency. One reason why silyl groups are not yet widely used for their directing effects may be that at present there are very few methods to synthesize enantiomerically enriched silyl substituted precursors in high yield.\textsuperscript{21,22}

Scheme IX  Synthesis of an enantiomerically enriched silyl compound and its use in synthesis.
CONCLUSION

The electrophilic addition to β-silylenolates and allylsilanes has been shown to occur with high diastereoselectivity. The necessary requirement to maintain high diastereoselectivities is significant A^1,3 strain so that there is a preferred low energy conformation in which the electrophile can attack. This is demonstrated in the higher selectivities for attack on ester enolates over aldehyde enolates and for higher selectivities with electrophilic additions to Z alkenes over E alkenes. In the cases where an electronic effect such as the β-silicon effect might be at work, it is expected that this will cooperate with the directing effect of the bulky silane and increase diastereoselectivity even more. An added feature to working with the phenyldimethyldilanes described is the ability to transform the silyl group with retention of configuration into a hydroxyl group. This opens the door to a variety of syntheses such as preparing 1,3 diols from the products of hydroboration of allylsilanes and preparing β-hydroxyesters from β-silylesters. When coupled with convenient methods for the synthesis of the chiral silane precursors, these methods may find wide utility in synthesis.

REFERENCES


SYNTHETIC APPROACHES TOWARDS TAXANE DITERPENES

Reported by Suk Bok Chang

April 15, 1993

INTRODUCTION

The taxane diterpenes are a group of biologically important substances isolated from various yew species (Taxas) that possess a unique carbon skeleton (1). Although the naturally occurring compounds bear differing degrees of oxygenation, some structural subgroups may be discerned.

For example, the taxane C-ring functionality increases in complexity from the simple allylic ester characteristic of Taxinine (2), 1 through a more oxidized version represented by Baccatin I (3), 2 to the elaborate 3-oxygenated oxetane incorporated in the C-ring of Taxol (4). 3 The remarkable success of taxol in advanced clinical trials 4 for the treatment of breast and ovarian cancer has prompted an intensive effort in the synthesis of this natural product and its derivatives.

Although a vast array of synthesis strategies to the taxane skeleton has been reported, 5 only modest success in the total synthesis of naturally occurring taxanes has been achieved. From a synthetic point of view, the following structural features make it difficult to construct the taxane carbon frames; (1) construction of an eight-membered ring system having a bridgehead sp² carbon, (2) stereocontrol of two functional groups at the C-9 and C-10 positions, and (3) control of the tricarbocyclic ring system in the endo-conformation.

Copyright © 1993 by Suk Bok Chang
The conformation of the central eight-membered ring plays an important role in synthetic strategies involving the introduction and manipulation of ring functionality leading to taxane natural products. In this abstract, different approaches towards syntheses of the tricyclic diterpenoid structure of the taxanes are discussed.

INTRAMOLECULAR DIELS-ALDER REACTION APPROACHES

Intramolecular Diels-Alder reactions have proven very useful in the synthesis of complex polycyclic compounds. The A-ring with its bridgehead olefin is perhaps one of the striking structural features of the taxane diterpenes, and is the most obvious object for intramolecular Diels-Alder chemistry. When the diene and dienophile are joined at the 2-position of the diene, the reaction can result in formation of a bridgehead alkene.

Intramolecular Diels-Alder cycloaddition has been extensively studied by Shea. The most recent of Shea’s work in the taxane area describes examples of an atropselective reaction that generates a C-aromatic taxane ring system (Scheme I). Conversion of disubstituted benzoic acid 5 to the trienone 7 was carried out in 54% overall yield. Diels-Alder cyclization of the trienone 7 was achieved under Et<sub>2</sub>AlCl catalysis to afford a single cycloadduct (endo 8). The endo conformational integrity was assured by the C-2 carbonyl and the C-4 bromine substituents. The barrier for interconversion to the exo-8 conformer was calculated to be 27.1 kcal/mol, so endo-8 is stable well above room temperature. This barrier is sufficiently large so that subsequent transformations on the aromatic cycloadduct are expected to be controlled by the folded endo conformation, with the delivery of reagents occurring from the convex face of the molecule. The diol 10 is of interest in that it contains the C-4 substitution pattern found in taxol, i.e. an α-oxygen functionality and β-oxymethyl groups. This represents the first report of the formation of this stereocenter during the course of a synthesis of the taxane system.
RING CONTRACTION STRATEGY

The application of new methodology for the formation of medium sized rings was the focus of Oishi and Funk's plan for the taxane diterpene synthesis. Oishi provided a general strategy for eight to twelve-membered ring construction that relied on the formation of lactam sulfoxides and sulfones through transannular acylation of their sulfur-stabilized carbanions.¹¹

Funk utilized his methodology for carbocycle construction that is based on a Claisen rearrangement-mediated ring contraction of macrocyclic lactones to the taxane model 16 (Scheme II).¹² To transform the acid derived from the hydrolysis of 13 into the corresponding

Scheme II

macrolide, the Mukaiyama protocol¹³ was employed and gave a separable mixture of lactone epimers in 63% yield. The lactone 14 could be converted to a ketene acetal 15 which underwent rearrangement to provide a single silyl ester 16 through a putative chair-like transition state. The key Claisen rearrangement occurred smoothly and cleanly induced the correct relative stereochemistry at C-1 and C-3 necessary for a taxane total synthesis. Funk's approach is especially noteworthy because it was the first efficient adaptation of a convergent strategy to the synthesis of a taxane skeletal model.

B-RING CLOSURE ROUTE

Kuwajima has investigated the condensation reaction of acetals with cyclic enones bearing (trimethylsilyl)methyl groups under the influence of SnCl₄.¹⁴ He has applied his modified methodology to make a taxane ring system with complete stereocontrol of two functional groups at sites corresponding to the C-9 and C-10 positions (Scheme III).¹⁵ The isomeric mixture of enol silyl ether 18 (Z:E=82:18) was prepared from the acetal 17 through several reactions in 36% overall yield. The reaction of 18 at -78 °C initially gave a mixture of two stereoisomers, but when
the reaction temperature was raised to -25 °C, the cis-isomer disappeared and the trans isomer 19 was obtained as a single product. He suggested that the origin of the stereochemical control was thermodynamic in nature (Figure 1). The reaction of 18 gave two stereoisomers 19 and 20 through A and B respectively at low temperature, but less stable cis product was isomerized to trans product at higher temperature. Lability of the 8-membered ring may account for such isomerization. Thermodynamically less stable cis-isomer 20 undergoes ring opening under the influence of TiCl₄ to form intermediate B, which would be isomerized to intermediate A and would be cyclized to give the more stable trans-isomer 19.

Kuwajima recently has extended even further his methodology to the synthesis of aromatic taxinine system which contains also the desired C-2 oxygenated functional group. This approach provides an efficient and unique ring closure method with complete stereocontrol of C-2, C-9 and C-10 positions.
FRAGMENTATION STRATEGY

Holton’s Approach

In his initial report, Holton described an efficient synthesis of the taxane ring system using an epoxy alcohol fragmentation reaction as a key step. Holton’s route proceeds from an optically active starting material, patchouline oxide 21, and requires only five steps of 53% overall yield (Scheme IV). Beginning with epoxide 21, he achieved an isomerization and hydroxy-directed epoxidation that gave an unstable epoxy alcohol 22, which underwent fragmentation in situ to provide keto alcohol 23. He has demonstrated that the epoxy alcohol fragmentation prefers to proceed with a syn-periplanar alignment of the breaking bonds, as shown in the fragmentation of 22. The simplicity and efficiency of this process signals the viability of ring fragmentation strategies for the synthesis of taxanes.

In 1988, Holton reported the first total synthesis of the enantiomer of the simplest natural taxane, taxusin, using the fragmentation methodology described above. From (-)-β-patchouline oxide, ent-taxusin was prepared in 32 distinct operations with an excellent overall yield of 21%.

Wender’s Approach

Wender had pursued an approach to the construction of polycycles possessing eight-membered rings based on the nickel catalyzed intramolecular cycloaddition of tethered 1,3-diene units. However, he recently published a new approach to the synthesis of a taxane ring system using a fragmentation reaction as a key step (Scheme V). His underlying strategy is to approach the tricyclic system through the convergence of variable A and C ring precursors in a process that produces the B ring, thus affording overall access to systematically varied ABC tricycles.

From the available air-oxidation product of pinene, verbenone 25, α-alkylation, 1,3-alkyl shift of C15 from C13 to C11 followed by ring fusion provided the tetracyclic alcohol 26 in 31% yield from 25. The strained four-membered ring system is expected to be labile to fragmentation.
Scheme V

As in the case of Holton's approach (Scheme 4), hydroxy-directed epoxidation of 26 using Ti(iPrO)4/t-BuOOH resulted in the stereocontrolled formation of an epoxide (not shown) in 70% yield. Due to the lability of this epoxide, it was directly treated with DABCO to effect fragmentation to the desired tricycle 27 in 80% yield. In analogy with the observation of Shea, the tricycle 27 exists at 25 °C as a 9:1 mixture of two slowly interconverting atropisomers (the endo conformer predominates). This strategy elegantly provides the tricyclic core of the taxanes with enantiomeric control in five steps from pinene.

SYNTHESIS OF OXETANE RING

In addition to the highly functionalized AB-ring system, taxol has another characteristic oxetane CD-ring. Compared to the numerous approaches for the synthesis of taxane diterpenoid rings, only a few methods to obtain the oxetane ring system have been reported.

Recently, Magee and Danishefsky published an efficient method to make an oxetane, although it is not connected to the taxane ring system. They noted that diketone 29 might be exploited to secure much of the functionality required for possible synthesis of taxol (Scheme VI). The relationship of angular methyl group and its vicinal ketone in 29 bear obvious homology with the corresponding C-7 and C-8 position of taxol respectively. Transformation of 29 to 30 was an adaptation of a reported procedure. Compound 30 needs introduction of both a C-fragment at
C-6 and O-fragment at C-7 to install the final oxetane ring. To achieve one carbon homologation a palladium catalyzed carbomethoxylation was used. Osmylation provided the required O-fragment at C-7 position. A sequence of selective silylation, triflation and subsequent alcohol-induced desilylation gave the desired oxetane ring system 34.

It should be noted that compound 34 was the first synthesized subunit containing the full component of oxygens corresponding to the CD-section of taxol.

SUMMARY

The synthesis of taxane diterpenes is a subject of current interest in both academic and industrial laboratories. Despite the efforts of at least thirty groups, the synthesis of this medicinally active product still remains a formidable challenge. The approaches illustrated here show a promising first step towards the practical synthesis of taxane diterpenes. There are several different approaches leading to the eight-membered ring formation. Among them, the strategy that utilizes fragmentation as a key step provides the desired ring system efficiently if the substrate is properly designed.

REFERENCES


INTRODUCTION:

The novel concept of atom economy\(^1\) is one that chemists around the world should consider in their quest for succinct and efficient synthesis. The literature is replete with established examples of such atom economical reactions, the Diels Alder and the Aldol reactions being the most prominent among them. Cyclization reactions that involve a simple isomerization of an acyclic substrate also provide the most effective utilization of starting materials.

For years, polyene cyclizations have been used as a tool in the synthesis of fused multi-ring systems.\(^2\) These reactions, which also go by the name of "tandem", "zipper" or "domino" reactions, are multiple consecutive cyclizations in which the rings are built in one step by proper construction of the polyene precursor, instead of a tedious, often circuitous, step-by-step route. Both cations and radicals have been used in the initiation of these polyene cyclizations.\(^3\) Biomimetic cascades of cations which follow the biogenetic isoprene rule were among the first reactions of this type to be studied.\(^4\) The most remarkable of these examples is the biogenetic four-fold cyclization of 2,3-oxidosqualene to lanosterol.\(^5\)

Tandem cyclizations have been initiated with a variety of electrophiles, beginning with the proto-typical protic acids, to now include Lewis acids, sulfenium ions and benzene selenenyl triflates.\(^6\) In the past decade, radical reactions have also been employed in carbon-carbon bond formation in natural product synthesis.\(^7a\) A good example of a tandem cyclization involving a radical rather than an ionic intermediate was developed by Curran (Scheme I).\(^7b\)

Scheme I

As is apparent, the driving force for these tandem cyclizations is the transformation of a \(\pi\) to a \(\sigma\) bond followed by the generation of a carbocation/radical of an equal or greater stablility. Thus, polycyclization of electron deficient intermediates (carbocations, radicals) has an inherent regiochemical proclivity towards propagation of this intermediate at the more substituted
terminus of a participating $\pi$ bond. In contrast, a cyclization resulting from the sequential intramolecular insertion of transition metal alkyls into $\pi$ bonds is expected to propagate by the insertion of the transition metal at the least substituted terminus.\(^8\) This was the origin of a technique involving transition metals, complementary to the cation/radical initiated polyene cyclization.

Polyene cyclizations were initially employed in the synthesis of cyclopentanes, largely in an endeavor to synthesize prostaglandins and related compounds such as prostracyclins. Concomitant with this was the identification of a large number of biologically significant cyclopentanoid systems, sometimes referred to as quinanes. An approach to the cyclopentanes appeared viable via a regiochemical palladium-catalyzed alkylation, followed by an intramolecular ene reaction (Scheme II).\(^9\)

**PROPOSED CATALYTIC CYCLE OF PROPAGATION**

Metals are known to activate otherwise unreactive substrates, and often, a metal template offers the opportunity for subtle regio- and stereo-chemical control. As observed (Scheme III), the palladocyclopentene \(1\) undergoes hydride migration via $\beta$-CH insertion of a "Pd" to give the bis-exomethylene cyclopentane \(2\). In contrast, the thermal reaction only yields the 1,4-diene \(3\).
This regioselectivity arises due to the conformational rigidity of the pseudopalladocyclopentene system and the absolute requirement of a cis-syn relationship of the C-H bond to the C-Pd bond; an optimal required dihedral angle of ca 0° is fulfilled only by Hb. By coordinating the remote double bond, the Pd acts like an enzyme in recognizing more of the molecule than just the reaction site. Thereby, it offers an opportunity to control the reaction cascade by recognition of remote reaction sites. This provides an easy access to polyfused and spirofused cyclic systems starting from acyclic alkenyl and alkynyl substrates.

Much investigation has gone into the identification of the mechanistic nuances of this reaction. Strong support for carbopalladation as a reaction pathway (Scheme IV) derives from the recognized formation of other metallo cyclopentenes. The catalytic Pd^{2+}-Pd^{4+} cycle, although, is not well represented in the literature.

Scheme IV

The alternate pathway, hydropalladation, which obviates the necessity to invoke a Pd^{4+} species (Scheme IV) involves the in situ formation of a hydridopalladium acetate by reaction of palladium acetate with the substrate. Further corroboration of this pathway comes from examples of cascade cyclization initiated by Pd^0 in the presence of acetic acid.

It is possible to conceive, as a consequence of these mechanistic interpretations, that the Pd catalyzed isomerization can yield 1,3 or 1,4-dienes, based on the fulfillment of the appropriate requirement discussed earlier, by an available allylic or vinylic proton. Such 1,3-dienes are good substrates to carry on further intermolecular Diels-Alder reactions. Using a dienyne such as 4 (Scheme V) permits these two steps to be performed in tandem, the product being obtained with

Scheme V

\[
\text{dba = dibenzylidene acetone, BHT = butylated hydroxy toluene}
\]
high chemo, regio and diastereoselectivity. In this case, the hydroxyl group plays the role of both a regiochemical control element (to favor dehydropalladation to the 1,3-diene) and a diastereoochemical control element for the cycloaddition reaction.\textsuperscript{11c,12} The 1,3 to 1,4 selectivity arises apparently from the inductive influence imposed by the adjacent hydroxyl group, that slows down or suppresses β-H elimination in that direction.

This reaction suggests that further cyclizations become possible when β-H elimination of the palladocycle is slowed or suppressed. Using this element of control, one can achieve an elegant one-step synthesis of [3.3.3]-propellane (Scheme VI).\textsuperscript{13}

Scheme VI

\[
\begin{array}{c}
\text{TBDMSO} \\
\text{Ph}_3\text{P}, \text{HOAc, 53 °C} \\
77\%
\end{array}
\]

Scheme VII

This process may in theory continue, limited only by the number of double bonds. The theory is vindicated by the construction of a novel spirofused pentacyclic system, that has been generated by zipping together six sites of unsaturation (Scheme VII).\textsuperscript{1,13} The nature of the ring system depends only on the position of the double bonds, which act like the teeth of a zipper; thus the name 'zipper reaction'.

Linear triquinanes 9, with exocyclic double bonds that offer further avenues for propagation, are easily prepared in high yields using dienyne 8 (Scheme VIII). The aza-analog provided the aza-triquinane in similar yields.\textsuperscript{13}

Scheme VIII

Using a 1,1-disubstituted double bond on the other hand, one obtains spirocyclic systems in high yields under similar reaction conditions (6, Scheme VII). Di-substituted acetylenes undergo this reaction with equal facility, and the nature of the acetylene substituent plays little role in the outcome of the reaction. Substitution in the pendant chain does not affect yields, although diastereoselection may be tempered (Table I).\textsuperscript{14}
Table I. Effect of acetylene substituent on yield of cyclization

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>R_a</th>
<th>R_b</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>57 %</td>
</tr>
<tr>
<td>COOCH_3</td>
<td>H</td>
<td>H</td>
<td>COOCH_3</td>
<td>75 %</td>
</tr>
<tr>
<td>CH_2OCH_3</td>
<td>Ph</td>
<td>H</td>
<td>CH_2OCH_3</td>
<td>70 %</td>
</tr>
</tbody>
</table>

VINYL HALIDES AND TRIFLATES AS INITIATORS OF CYCLIZATION

While Trost and workers have used acetylenes to trigger the Pd^{2+} catalyzed reactions, Negishi and Overman have recently employed oxidative addition of Pd(0) to vinyl halides and triflates to initiate polycyclization. This route offers the added dimension of site selective initiation of the reaction. The steroidal nucleus is thus easily generated from the substrate 12 to give 13 in 76% yield (Scheme IX). This remarkably high yielding reaction and others in its cadre suggest that 1,1-dialkyl-substituted alkenes and monoalkyl-substituted alkenes can serve as penultimate and terminal functional groups in cyclizations, respectively.

Scheme IX

A curious side reaction was observed by Negishi during his attempt to generate the tricyclic system 14 from the substrate 15, a viable pathway to capnellene and related natural products. Instead of the expected tricyclization product 14, a monomeric cyclization product 17.
was isolated in 56% yield. Evidently, the alkyl palladium 16 had inserted into the proximal double bond, giving an interesting cyclopropanated product. The cyclopropanation is useful by itself in the scope it provides to synthesize molecules such as masmarane\textsuperscript{15b} that contain a cyclopropyl ring, but it could also erode the efficacy of ring formation when cascade cyclization involves carbopalladation to a 1,1-disubstituted alkene. Studies by Negishi\textsuperscript{17} have shown that the exo mode carbopalladation of such alkenes as 15 give neopentyl-type alkylpalladium species 16, which could undergo cyclopropanation with a juxtaposed double bond. It is reasonable to expect that if the cyclopropylcarbinyl to homoallyl rearrangement or its reverse were to take place, a syn-coplanar arrangement of the C-Pd to the participating C-C bond is required. Under such conditions, if the cyclopropylcarbinyl palladium species is rigid and can undergo dehydropalladation, cyclopropanated products are observed. By contrast, if the cyclopropylcarbinyl palladium species is conformationally flexible, reversal to give a ring enlarged homoallyl palladium species is observed, which can subsequently give, by dehydropalladation, products that arise from apparent endo-cyclization.

TERMINATION OF CASCADE CYCLIZATIONS

While alkylpalladium complexes easily undergo decomplexation by β-hydride elimination to give the active palladium species, alkenyl palladium complexes sometimes undergo the not-so-facile 1,1-reductive elimination. In order to recycle the catalytic palladium species in such instances, a terminating step is incorporated. Such sources as proton donors, CO, alkenes have been developed, and a series of organometals have been screened for the termination step (Table II). Organozincs undergo cross coupling faster than carbopalladation and are seldom used in such a capacity. Other metals such as B, Al, Zr, Cu and Sn have been

Table II. Effect of metal in termination of cascade cyclization via cross coupling

<table>
<thead>
<tr>
<th>M</th>
<th>18 (%)</th>
<th>19 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnCl</td>
<td>19</td>
<td>68</td>
</tr>
<tr>
<td>ZrCp\textsubscript{2}Cl</td>
<td>84</td>
<td>≤3</td>
</tr>
<tr>
<td>SnMe\textsubscript{3}</td>
<td>69</td>
<td>≤3</td>
</tr>
<tr>
<td>Al\textsuperscript{1}Bu\textsubscript{3}</td>
<td>57</td>
<td>32</td>
</tr>
</tbody>
</table>
studied, and the results seem to indicate that cross coupling is dependent on both the metal and the organic ligand.\textsuperscript{15a}

**ZIRCONIUM-PROMOTED BICYCLIZATION**

Metals other than Pd have been known to catalyze alkylation and cross coupling.\textsuperscript{18} Intramolecular versions of allyl Grignard and zinc additions to olefinic systems are known.\textsuperscript{18} These so-called metallo-ene reactions, owing to their close resemblance to the Alder-ene reaction, are much more facile and expeditious than their thermal ene counterparts. The reactions are limited in their capability since they involve only terminal and strained olefinic enophile units. Most importantly, these organometals are incapable of sustaining a catalytic cycle, and polycyclization cannot be achieved. Nickel and platinum are known to facilitate mono-cyclizations, but their scope has not been extended to study polycyclizations as yet.\textsuperscript{18}

Metals such as Zr and Co have been studied as templates for polycyclization reactions, and it is becoming evident that each metal exhibits its own characteristic scope and limitations. For example, the Co-promoted bicyclizations is useful only for bicyclization-carbonylation.\textsuperscript{10b} The Zr-promoted reaction can produce organo-zirconium compounds, zirconacycles, that can be transformed to different compounds. Work done by Negishi, Buchwald, Nugent, Taber and Livinghouse reveal broad synthetic applicability and high levels of 'pair'-, regio- and stereoselectivities in these reactions.\textsuperscript{10d, 19}

The Zr-promoted bicyclization-carbonylation to products 20-25 starting from their corresponding non-racemic substrates is known to occur with high diastereo and enantioselectivities\textsuperscript{15a, 20}. By known reactions, 21 has been further extended to give pentalenic acid with high selectivity.

![Chemical structures](image)

**CONCLUSION**

Tandem cyclization may be heralded as a major frontier achieved, after convergent synthesis, in simplifying the synthesis of complex, polycyclic systems. The reactions are
efficient, proceed with high diastereo- and enantio-selectivities, and most vitally, exhibit high atom economy. The contra-thermodynamic bias in some of these reactions is an useful complementary tool to established methods. This chemistry shall be a harbinger of more studies as applied to natural product synthesis.

REFERENCES

NICKEL(0)-CATALYZED [4 + 4] CYCLOADDITIONS

Reported by Lawrence David Robinett

April 26, 1993

INTRODUCTION

Many natural products, *e.g.* taxanes, ophiobolins, fusicoccins, (+)-asteriscanolide, crispolide, vulgarolide, vinigrol, epoxysmenone, kalmanol, cotylenin, variecolin, pleuromutilin, contain eight-membered cyclic structures with varying numbers of stereo-defined centers. Both the regio- and stereodefinition in these natural products offer a tremendous synthetic challenge. Several approaches to the construction of eight-membered carbocycles are available, including thermal, photochemical, and metal catalyzed [4 + 4] cycloadditions. The opening of strained [4.2.0] bicyclic systems has been employed to approach some of these challenging targets. This strategy, however, is dependent upon a significant amount of asymmetric synthesis in the steps that precede the fragmentation; the stereochemistry of the product is defined in these steps. Of the [4 + 4] cycloadditions, nickel(0)-catalyzed [4 + 4] cycloadditions may at present offer the most useful route to these challenging targets, as this approach has the advantage of creating new stereocenters simultaneously with the formation of the eight-membered ring. Other possible organometallic catalysts exist, but none have been developed as extensively as the nickel(0) systems.

CYCLODIMERIZATION OF 1,3-DIENES

Butadiene

The cyclodimerization of 1,3-butadiene via nickel(0) catalysis was first reported in 1954 by Reed. As illustrated in Scheme I, Reed, using (Ph₃P)₂Ni(CO)₂ as the catalyst, obtained a 30-40% total yield of 1,5-cyclooctadiene (COD) at a 50-70% conversion of starting material. This reaction was further studied in the 1960's by Heimbach and Brenner. Cyclo-

Scheme I

The cyclodimerization of 1,3-butadiene was shown to be very dependent on the choice of ligand. With triphenylphosphine as the ligand and Ni(COD)₂ as the nickel(0) source, the product distribution was 64% 1, 27% 2, and 6% 3. Likewise, the distribution for tricyclohexyl-
phosphine was 41% 1, 40% 2, and 14% 3. By contrast, the use of P(O-o-biphenyl)3 yielded 96% 1, 3% 2, and less than 1% 3. This latter reaction was also four times as rapid as was the one with triphenylphosphine and 27 times as fast as the one with tricyclohexylphosphine.

**Substituted Butadienes**

Attempted cyclodimerizations of several substituted butadienes have been reported. Of particular interest are the cyclodimerizations of piperylene, isoprene, and 2,3-dimethylbutadiene. Reaction conditions for the cyclodimerizations of these substituted dienes employed by Heimbach and Wilke utilized Ni-P(O-o-biphenyl)3 as the catalyst and achieved full conversion of the diene. The product distributions for these substituted dienes were: for 2,3-dimethylbutadiene, 6.1% C8 ring and 86.3% C6 ring; for isoprene, 55.1% C8 ring and 34.8% C6 ring; and for piperylene, 90.9% C8 ring and 5.3% C6 ring. This compares to 1,3-butadiene which gave a 97.2% yield of COD and a 2.3% yield of the C6 ring. Clearly, the more substituted the diene, the less the propensity to form the C8 ring, resulting in a higher yield of the C6 ring. Cyclodimerization of 4 and 5 has also been accomplished by Brun, Tenaglia, and Waegell, as illustrated in Scheme II. However, attempts to cyclodimerize with 1,3-butadienyl acetate and methyl 2,4-hexadienoate failed.

**Scheme II**

\[
\begin{align*}
\text{4} & \xrightarrow{\text{Ni-PPh₃}} \text{COD} \\
\text{5} & \xrightarrow{\text{Ni-PPh₃}} \text{COD}
\end{align*}
\]

Studies were also performed on the potential codimerization of butadiene with substituted butadienes. Scheme III shows the results obtained for a representative selection of some of the substituted butadienes used. The production of COD from the cyclodimerization of 1,3-butadiene was minimized by maintaining a very low concentration of butadiene. By this approach a good yield of the desired mixed codimer was obtained in all cases. These experiments were also performed with substituted butadienes containing electron withdrawing groups, as illustrated in Scheme IV.

**MECHANISM OF CYCLODIMERIZATION**

In 1967, Heimbach and Brenner published the results of a study employing Ni-P(O-o-biphenyl)3 and 1,3-butadiene neat at 80 °C in 1967, showing that as the butadiene approached 100% conversion, the yield of COD increased at the expense of *cis*-1,2-
divinylcyclobutane (DVCB). The yield of 4-vinylcyclohexane (VCH) remained fairly constant throughout the course of the reaction. Both at 30% and at 85% conversion, the product ratio was 36% DVCB, 2.0% VCH, and 61% COD. But at 95% conversion, the product ratio had changed to 14% DVCB, 2.2% VCH, and 83% COD, and at 100% conversion, the product ratio was 0% DVCB, 2.4% VCH, and 97% COD. Assuming that the bis-π-allyl intermediate is formed as part of a stepwise mechanism, Heimbach and Brenner proposed (Scheme V) the equilibration between the σ-allyl-π-allyl intermediate and DVCB, and the non-reversible formation of COD and VCH as explanation for the observed data.

Nickel(0) Olefin Complexes

Jolly, Tkatchenko, and Wilke reported the isolation of both a white DVCB-Ni-P(C₆H₁₁)₃ and a yellow bis-1,3-butadiene-Ni-P(C₆H₁₁)₃ complex. These complexes were obtained by adding the appropriate olefin to a 1,5,9-cyclododecatriene-Ni-P(C₆H₁₁)₃ solution and cooling. The bis-1,3-butadiene-Ni-P(C₆H₁₁)₃ complex in a solution reacts with excess triphenylphosphine at 80 °C to form 65% 1,3-butadiene, with the remainder of the material forming a mixture of VCH, DVCB, and COD. However, at -78 °C the addition of CO to the
solution yields only VCH. Interestingly, when the DVCB-Ni-P(C₆H₁₁)₃ complex is allowed to react with CO at -78 °C, only DVCB is obtained. If, however, it is allowed to stand at room temperature for one hour, the isolated product is exclusively VCH. In addition, although the bis-butadiene complex is stable in toluene, the DVCB complex partially rearranges to the bis-butadiene complex. Based on these observations, Jolly, Tkatchenko, and Wilke propose the equilibration in solution as presented in Scheme VI.

**Scheme V**

![Scheme V Diagram](image)

**Scheme VI**

![Scheme VI Diagram](image)

**Identification of an Intermediate**

Brown, Golding, and Smith also isolated a yellow solid from a solution containing 1,3-butadiene and tricyclohexylphosphine at 0 - 20 °C. A comparison of the IR spectra of hexadeuterio-butadiene and the isolated yellow solid revealed a shift in absorbance bands from 2200 and 2350 cm⁻¹ to 2200 and 2100 cm⁻¹ for the complex. They attribute the lower energy absorbance band at 2100 cm⁻¹ to sp³-hybridized carbon-deuterium bonds. This corresponds to the σ-allyl portion of 6. As further reinforcement of this proposal, X-ray analysis by Barnett and Kruger showed the related complex with isoprene to be similar to the σ-allyl-π-allyl complex 6. Interestingly, the X-ray crystal structure shows the geometry around nickel to be roughly square planar. In the same paper, a claim is made that up to a 30% yield of butadiene can be obtained from the DVCB complex.

**DVCB Formation**

These data support a stepwise mechanism where, perhaps, the initial formation of a
complex similar to 6 is followed by equilibration with other intermediates which lead to the various cyclodimerization products. Mango proposes that a nickel(0)-mediated concerted [2 + 2] cycloaddition followed by rearrangement to 6 is the first step of the mechanism. However, Heimbach and Hey propose that only five of the possible 10 isomers of the [2 + 2] cycloaddition product are obtained from piperylene. None of the isomers expected from two molecules of cis-piperylene are obtained. The formation of the four-membered ring from two molecules of cis-piperylene is extremely slow, with the reaction of one molecule each of cis-piperylene and trans-piperylene being about 3 times as fast. The stereoselectivity suggested here is based on IR and $^1$H-NMR spectroscopic data of the [2 + 2] cycloaddition products.

**Rearrangement of DVCB**

Heimbach and Brenner reported a rate study on the conversion of DVCB to COD. The thermal Cope rearrangement was first order in butadiene, while the catalyzed rearrangement appeared to be zero order in butadiene. The thermal study was done at 80 °C and the catalyzed conversion at 24 °C. The catalyzed process was most rapid and efficient when Ni-P(O-o-biphenyl)$_3$ was used.

In 1977, Stephenson and Graham published a deuterium labeling study using cis, cis-1,4-dideuterio-butadiene. The study utilized Ni(COD)$_2$ as the nickel(0) source and triphenylphosphine as the ligand. It was observed that cis, cis-1,4-dideuterio-butadiene was quickly isomerized in the reaction to trans, trans-1,4-dideuterio-butadiene. Cope rearrangement of the tetradeterdio-DVCB to the substituted COD product resulted in isolation of only the trans, trans-3,4,7,8-tetradeterdio-1,5-cyclooctadiene. No cis, cis or cis, trans products were obtained. Based on this evidence, Stephenson and Graham proposed the reaction sequence shown in Scheme VII.

**Scheme VII**

**INTRAMOLECULAR [4 + 4] CYCLOADDITIONS**

Three basic classifications for the intramolecular reaction have been proposed by
Wender, et al.; (Figure 1). Of these, type A has been the most thoroughly studied. Scheme VIII illustrates the versatility and both the regio- and stereoselectivity of the nickel(0)-catalyzed [4 + 4] cycloaddition of type A. The cycloaddition produces a cis-fused ring juncture when the connecting tether between the two dienes has 3 carbons. In contrast, when the connecting tether has 4 carbons, the preferred geometry of the ring juncture is trans-fused.

Figure 1

Scheme VIII

Scheme IX depicts the efforts reported to date to accomplish the nickel(0)-catalyzed intramolecular [4 + 4] cycloaddition on structure type B. Attempts to perform the cycloaddition on 7 with Ni-PPh₃ as the catalyst gave low conversion of the bis-diene.
Alternate efforts with Ni-P(O-o-biphenyl)3 gave complete conversion with a 74% yield of substituted COD.

Scheme IX

Wender suggests that the stereochemical outcome is determined by the corresponding rates of breakdown of the diastereomeric syn-bis-π-allyl intermediates due to differences in energy of the related transition states. Figure 2 shows a mnemonic proposed by Wender et al., for the prediction of product for the intramolecular [4 + 4] cycloaddition, when a [6.4.0] bicyclic system is formed. Using this model, the equatorial/axial product ratio can be estimated based on the calculated difference in strain energy. The calculations show the ratio to be 1.2:1 when G is CN, 28:1 when G is CH3, 29:1 when G is CH2OAc, and 38:1 when G is CO2CH3. The experimental values for the ratios were; 1.5:1, 20:1, 21:1, and 70:1, respectively.

Figure 2

CONCLUSION

Nickel(0)-catalyzed [4 + 4] cycloaddition offers both regio- and stereochemical control for potential use in the synthesis of many natural products. Although the cycloaddition of structure type C has yet to be reported, one may hope that the successful cycloaddition for this sterically demanding structure type will soon be accomplished. Other ligand systems for Ni(0) could be explored. Still lacking is a study on the use of chiral ligands to induce stereochemical preferences in the co-dimerization of achiral substituted dienes, which may further extend the synthetic utility of this type of chemistry.
REFERENCES

(3) Tsuji, J. *Advances in Organometallic Chemistry* 1979, 17, 141.
(12) *ibid.*, 329.
ORGANIC SEMINAR ABSTRACTS
1993-94, SEMESTER I
University of Illinois

Department of Chemistry
Box 68 Roger Adams Laboratory
1209 West California Street
Urbana, Illinois 61801-3731

January, 1994

Copyright © by The Board of Trustees of the University of Illinois
NOTICE: Return or renew all Library Materials! The Minimum Fee for each Lost Book is $50.00.

The person charging this material is responsible for its return to the library from which it was withdrawn on or before the Latest Date stamped below.

Theft, mutilation, and underlining of books are reasons for disciplinary action and may result in dismissal from the University.

To renew call Telephone Center, 333-8400.

UNIVERSITY OF ILLINOIS LIBRARY AT URBANA-CHAMPAIGN
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toward an Organic Molecular Magnet</td>
<td>1</td>
</tr>
<tr>
<td>Michael B. Tollefson</td>
<td></td>
</tr>
<tr>
<td>Chromium and Tungsten Carbene Complexes in Organic Synthesis</td>
<td>9</td>
</tr>
<tr>
<td>Roy K. Horn</td>
<td></td>
</tr>
<tr>
<td>Magnetic Field Effects on Photochemically Generated Biradicals</td>
<td>17</td>
</tr>
<tr>
<td>David J. Owen</td>
<td></td>
</tr>
<tr>
<td>Applications of $\eta^6$ - Arene Chromium Tricarbonyl Complexes in Stereoselective Synthesis</td>
<td>25</td>
</tr>
<tr>
<td>Amit Basu</td>
<td></td>
</tr>
<tr>
<td>Microwave Heating in Organic Synthesis</td>
<td>33</td>
</tr>
<tr>
<td>Kevin S. Guigley</td>
<td></td>
</tr>
<tr>
<td>Structure, Design, and Application of Triple Helical DNA</td>
<td>41</td>
</tr>
<tr>
<td>Paul A. Thiessen</td>
<td></td>
</tr>
<tr>
<td>Recent Advances in Asymmetric Phase Transfer Catalysis</td>
<td>49</td>
</tr>
<tr>
<td>Julie A. Dixon</td>
<td></td>
</tr>
<tr>
<td>Asymmetric Protonations in Organic Chemistry</td>
<td>57</td>
</tr>
<tr>
<td>Brad Crawford</td>
<td></td>
</tr>
<tr>
<td>Utility of the Aza-Cope Mannich Reaction in the Total Synthesis of Alkaloids</td>
<td>65</td>
</tr>
<tr>
<td>Eric D. Hostetler</td>
<td></td>
</tr>
<tr>
<td>DNA Photolyase: Model Studies on the Mechanism of Electron Transfer</td>
<td>73</td>
</tr>
<tr>
<td>Susan M. Gasper</td>
<td></td>
</tr>
<tr>
<td>Catalytic Antibodies in Organic Synthesis: Recent Advances</td>
<td>81</td>
</tr>
<tr>
<td>Stephen P. O'Connor</td>
<td></td>
</tr>
<tr>
<td>The Use of Lithium Perchlorate to Promote Organic Reactions</td>
<td>89</td>
</tr>
<tr>
<td>Kathleen M. Bertini</td>
<td></td>
</tr>
<tr>
<td>From Rotaxanes to Molecular Trains - Just Chemist’s Toys?</td>
<td>97</td>
</tr>
<tr>
<td>Slawomir Z. Janicki</td>
<td></td>
</tr>
</tbody>
</table>
TOWARD AN ORGANIC MOLECULAR MAGNET

Reported by Michael B. Tollefson  September 9, 1993

INTRODUCTION

Organic molecular magnets have been discovered and are expected to have properties that could be important in many possible applications. They are projected to be low in weight, low in density, insulating, optically transparent, biocompatible and be made to be photoreactive.

Organic molecular magnets may lead to advances in magnetic recording design and optical disk design by increasing their data density. Organic magnets could be used as insulating photomagnetic switches and for useful biological applications such as magnetic imaging.

However, very few molecular magnets have been discovered to date. This abstract will present the theory behind ferromagnetism and various models to achieve an organic molecular magnet.

Paramagnetic substances carry a permanent magnetic moment whereas diamagnetic materials do not. Macroscopically paramagnetic spins are randomly aligned when no magnetic field is applied (Figure 1a).

![Figure 1](image-url)  

**Figure 1**: Schematic drawing of molecular spins for (a) paramagnetic, (b) ferromagnetic, (c) antiferromagnetic and (d) ferrimagnetic systems.

When a magnetic field (H) is applied the individual spins will line up giving a net magnetization (M). The magnetic susceptibility (χ) is a measure of how easily the dipoles will align and is defined by eq 1.

\[ \chi = \frac{M}{H} \]  

When heated, ferromagnetic, antiferromagnetic and ferrimagnetic substances become paramagnetic above a certain critical temperature. Ferromagnetism occurs when all molecular spins align parallel in the absence of a magnetic field (Figure 1b). The spins align antiparallel in an antiferromagnetic substance (Figure 1c). In a ferrimagnetic substance the spins of different magnitudes align antiparallel thereby creating a net magnetization (Figure 1d). In a ferromagnetic or ferrimagnetic substance there will be a spontaneous magnetization when there is no applied

Copyright © 1993 by Michael B. Tollefson
field. These bulk properties are the result of three dimensional interactions and do not exist at lower dimensions.

Curie's Law⁴ (eq 2) as derived from the thermodynamic expression for magnetization is given as

$$\chi = M / H = \frac{[Ng^2J(J+1)\mu_b^2]}{(3kT)} = \frac{C}{T}$$

(2)

where \(N\) is the number of atoms per unit volume, \(g\) is the spectroscopic splitting factor, \(J\) is the total angular momentum quantum number, \(\mu_b\) is the Bohr magneton, \(k\) is Boltzman's constant and \(C\) is Curie's constant (Figure 2a).⁶ The ground state molecular spin (\(S\)) can be determined by plotting the magnetization as a function of inverse temperature using Curie's Law.

In a ferromagnetic or antiferromagnetic substance the susceptibility deviates from Curie's Law (eq 2) due to the magnetization of the substance. Taking the spontaneous magnetization into account the Curie-Weiss Law⁷ (eq 3) can be derived for the paramagnetic region above the critical temperature where \(\theta\) is the Weiss Constant.

$$\chi = \frac{C}{(T - \theta)}$$

(3)

For a ferromagnet \(\theta > 0\) K, where the Weiss Constant \((\theta)\) is approximately equivalent to the ferromagnetic transition temperature \((T_c)\). For an antiferromagnet \(\theta < 0\) K, where the antiferromagnetic transition \((T_N)\) is approximately equivalent to \(-\theta\).⁷ By measuring the magnetic susceptibility above the critical temperature it can be determined whether a substance is ferromagnetic or antiferromagnetic by determining \(\theta\) (Figure 2).

**Figure 2:** Reciprocal magnetic susceptibilities plotted as a function of temperature for a (a) paramagnet, (b) ferromagnet and (c) antiferromagnet.

**LOW SPIN POLYMERIC FERROMAGNETS**

A number of ferromagnetic substances have been synthesized by pyrolysis of nitrogen containing compounds. The first purely organic ferromagnet was synthesized by Ovchinnikov⁸ by thermal polymerization of 1,4-bis-(2,2,6,6-tetramethyl-4-oxy-4-piperodyl-1-oxyl)butadiin to give
1 as one possible product. Only a small fraction of the product exhibits any magnetic phenomena. The magnetic saturation was found to be 0.1% of the predicted value indicating that only a small amount of material is involved in ferromagnetic interactions. Characterization of this material failed, therefore the nature of the magnetism is unknown. Pyrolysis of 2\textsuperscript{9} and 3\textsuperscript{10} also led to polymeric ferromagnets of unknown structure. Both products show a hysteresis curve\textsuperscript{7} indicating a stable ferromagnet at room temperature. Pyrolysis of a 1:1 mixture of 4 and 5 produce other stable organic ferromagnets.\textsuperscript{10} Unfortunately the structures of these magnetic substances have not been determined due to their highly impure, insoluble nature. Therefore the exact nature of the magnetic coupling and its relationship to molecular structure is not known.

\begin{center}
\includegraphics[width=\textwidth]{molecule.png}
\end{center}

**HIGH SPIN MOLECULAR SYSTEMS**

Metal ferromagnets have high spins due to degeneracies in their d and f orbitals. In organic molecules only s and p orbitals are available to produce a high spin molecule. Mataga\textsuperscript{11} proposed that polycarbene or polyradical structures could yield high spin molecules because of large degeneracies in their nonbonding molecular orbitals (NMBO) that would lead to an organic ferromagnet. On the basis of molecular orbital (MO) theory, Longuet-Higgins\textsuperscript{12} observed that the molecular spin of a polyradical could be predicted by marking every other atom so that no two marked atoms or two unmarked atoms are adjacent to each other.\textsuperscript{13} The predicted molecular spin is determined by taking the difference between the number of marked and unmarked atoms and dividing by two. This has proven to be a versatile and useful technique toward the design of high spin molecules.

On this basis Mataga\textsuperscript{11} suggested 6, 7 and 8 as possible candidates for an organic ferromagnet. Polycarbene 6 is one dimensional and very flexible while 7 and 8 are more rigid and may have a higher probability of the individual spins being held in a favorable orientation to allow the coupling of spins to yield a high spin molecule.

Itoh\textsuperscript{14} prepared 6 (n = 1) from the corresponding diazo compound and found a stable quintet ground state. Higher analogs of 6 have been synthesized by Iwamura and Itoh\textsuperscript{15} by photolysis of the corresponding diazo compounds in a 2-methyltetrahydofuran (MTHF) glass at 77 K for n = 2, 3, 4. The ground state molecular spins where found to be S = 3, 4, 5, respectively, however none of these molecules exhibit ferromagnetic coupling on the macroscopic
level. Apparently these systems do not have the three dimensional order required to achieve bulk ferromagnetic coupling.

Rajca\textsuperscript{16} synthesized polyradicals of type 9 (n = 0, 1, 2) by oxidation of the corresponding organolithium compound with iodine. Their ground state molecular spins were found to be $S = 2, 7/2$ and 5, respectively, as determined by electron spin resonance (ESR) spectroscopy. For these molecules weak antiferromagnetic interactions were detected. Iwamura\textsuperscript{17} constructed similar high spin molecules with carbenes replacing the radical centers (10). He synthesized 10 with n = 1 and 2 by photolysis of the corresponding diazo compound in MTHF at 11 K. The ground state molecular spins were determined to be $S = 6$ and 9, respectively, however, ferromagnetic coupling was not observed in 10.

One problem with the previously mentioned oligoradical and oligocarbene systems are their thermal stabilities. Other approaches toward organic molecular magnets involve the use of stable radical cations and nitroxide radicals.\textsuperscript{18} A second problem is that there is no order in the third dimension thereby preventing ferromagnetic coupling of the electron spins. Possible methods to obtain order in the third dimension through the use of bridges or by stacking induced by intermolecular interactions is being pursued.\textsuperscript{19}

McConnell\textsuperscript{20} suggested that it may be possible to induce three dimensional ordering by using odd alternant $\pi$ systems which contain positive and negative $\pi$ spin densities. The exchange interaction between these different spin densities in adjacent molecules may force the molecules into an ordered solid state leading to intermolecular coupling of molecular spins resulting in ferromagnetism.
Iwamura studied the effects of the third dimension by synthesizing different [2.2]paracyclophanes. He found pseudo-ortho (11) and pseudo-para (13) were ground state quintets while the pseudo-meta cyclophane (12) was a ground state singlet as determined by ESR measurements. Using MO theory, the π spin densities were calculated for each carbon and are represented below. The exchange interaction between π spin densities control the ground state multiplicity of these molecules. The observations for [2.2]paracyclophanes show the importance of order in the third dimension to enable ferromagnetic coupling of molecular spins and they correspond closely to McConnell's proposal. No bulk ferromagnetism was observed in these [2.2]paracyclophanes due to the lack of three dimensional ordering throughout the crystal lattice.

SOLID STATE ORDERING IN FERROMAGNETS

Ferromagnetism is a solid state phenomena that depends on the coupling of spins within three dimensions. Some investigators have been using low spin molecules and intermolecular interactions to create order in the crystal lattice thereby enabling ferromagnetic coupling in three dimensions.

4-Nitrophenyl nitronyl nitroxide (14a) was found to exhibit ferromagnetic behavior in the β phase. The orthorhombic β phase has a $T_c = 0.60$ K as indicated by heat capacity and susceptibility measurements. Crystallographic data shows the nitroxyl oxygens are in close proximity to the nitro nitrogen leading to ordered intermolecular ferromagnetic coupling. Antiferromagnetic interactions were observed in 14b and 14c illustrating the importance of the nitro group and its ability to interact with the nitroxide oxygen.

Recently Velciana synthesized the 4-hydroxy analog 14d. Hydrogen bonding is observed between one nitroxide group and a neighboring hydroxy group, which leads to an ordered solid state. Ferromagnetic interactions are evidenced by susceptibility data which give a positive Weiss temperature of 0.8 K. Further work is being undertaken to determine $T_c$.

Rassat synthesized adamantane 15 and showed it has a ferromagnetic transition at 1.48 K, the highest $T_c$ reported for a low spin organic molecule. The solid state structure shows that each nitroxide group has two other nitroxide groups in close proximity, which creates an ordered three dimensional network within the crystal. This ordering allows ferromagnetic coupling to occur intermolecularly throughout the crystal lattice. The spontaneous magnetization and
susceptibilities indicate that ferromagnetic interactions are present in 15.

\[ \text{Charge Transfer Approach} \]

McConnell\textsuperscript{26} suggested that ferromagnetic coupling could occur in an ionic donor-acceptor complex \((D^+A^-D^+A^-\ldots)\) if the donor or acceptor has a neutral triplet ground state (Figure 3a). Breslow\textsuperscript{27} extended McConnell’s idea by designing a donor-acceptor complexes that lead to the formation of a doubly charged triplet donor via further forward charge transfer (Figure 3b). Breslow reasoned that this should lead to a stronger donor-acceptor interaction thereby increasing the likelihood of alternating donor-acceptor stacking. Breslow\textsuperscript{27b} was able to produce 1:1 complexes of this type (16:17) and antiferromagnetic coupling was observed. Breslow’s mechanism fails because of larger singlet state degeneracies which are more energetically favorable leading to antiferromagnetic interactions throughout the lattice.\textsuperscript{28}

\[
\begin{align*}
\text{Figure 3: Charge Transfer Models. (a) McConnell (II) Model (b) Breslow Model}
\end{align*}
\]

Miller and Epstein\textsuperscript{29} have synthesized metallocene / tetracyanoethylene (TCNE) complexes of the type \([M(\text{Me5Cp})_2]^+\text{[TCNE]}^-\) using \(M = \text{Fe, Mn, Cr and Ni}\). Ground state configurations of the metallocene cations give \(S = 1/2, 1\) and \(3/2\) for \(M = \text{Fe, Mn and Cr}\), respectively. Their ferromagnetic transitions have been found to occur at 4.8 K, 8.8 K and 3.65 K, respectively. Miller and Epstein have also found that for \(M = \text{Ni}\), an antiferromagnetic material is formed.
Kahn$^{28}$ pointed out that if McConnell's charge transfer proposal$^{26}$ is correct, M = Ni would have been a ferromagnetic substance (Figure 4a). Kahn$^{28}$ utilizes McConnell's spin density model to explain the observed magnetic behavior. When M = Fe, Mn and Cr the electron density is localized on the metal (a$_{1g}$ and e$_{2g}$ orbitals) but for M = Ni there is cyclopentadiene ligand (Cp) electron density found in the e$_{1g}^*$ orbital (Figure 4b). The electron density on the metal induces a negative $\pi$ spin density on the Cp ligand while the TCNE$^{-}$ has a positive spin density due to its $\pi^*$ electron. This interaction corresponds to McConnell's first proposal and leads to ferromagnetic interactions because of large exchange interactions between Cp and TCNE. For M = Ni the e$_{1g}^*$ electron induces positive spin density on the Cp ligand resulting in an antiferromagnetic coupling between the Cp ligand and TCNE.

![Molecular Orbitals Diagrams For Metalloocene Complexes](image)

**Figure 4:** Molecular Orbitals Diagrams For Metalloocene Complexes. (a) M = Ni. (b) M = Fe.

**CONCLUSION**

There have been successes towards building an organic molecular magnet and a few are significant. High spin molecules have been constructed but they do not lead to ferromagnetic materials due to the lack of three dimensional ordering. Reports of ferromagnetism in low spin polymers have had little impact on the development of ferromagnets and their corresponding models because of their unknown chemical compositions, low reproducibility and poor yield of magnetic substances. The first real success has come using intermolecular interactions to dictate the solid state structure of nitrooxide compounds which exhibit ferromagnetism. These results indicate that consideration of three dimensional structure is extremely important in the successful design of ferromagnets. McConnell's spin density mechanism has been able to explain and to predict the ferromagnetic interactions discussed above. The development of high temperature ferromagnets will depend on the ability to construct high spin organic molecules that can become highly ordered in the solid phase through intermolecular interactions.

**REFERENCES**


New York, 1971; Ch 15 & 16.
INTRODUCTION

Since E.O. Fischer first isolated a group 6 pentacarbonylcarbene complex in 1964,1 considerable effort has been expended to develop these compounds as synthetically useful intermediates. Such compounds have been used to effect benzannulation,2 and to mediate the formation of cyclobutanones,3 cyclopentenones,4 and pyrroles.5 Recently, general methodology using chromium carbenes have been developed to synthesize amino acids, β-lactams, and pyrrolinones. Also, chiral metal complexes have been shown to effect stereoselection in Michael and Diels-Alder reactions.

REACTIVITY TRENDS

Metal carbenes complexes 1, which contain a low oxidation state metal and, typically, electron-withdrawing ligands, are known as Fischer carbenes. These compounds can be deprotonated α- to the carbene center by a strong base. In addition, Fischer carbenes contain a carbene carbon which is electrophilic.

The reactivity of Fischer carbenes is controlled not by charge distribution, but rather by orbital energies. Molecular orbital calculations5 and subsequent electron spin resonance studies8 have shown the complex to contain a LUMO localized mainly on the carbene carbon. Thus the initial site of reaction will tend to be the carbene center.

Fischer investigated the feasibility of using the C=Cr double bond as a C=Y (Y=O, S, Se) equivalent. He discovered that chromium alkoxycarbene complexes can be cleaved to yield the corresponding ester, thioester, or selenoester by treatment with O2, S8, or SeX.9 More recently, DMSO10 and Ce(IV) oxidants4 have been used as milder alternatives for conversion to carbonyl compounds. With cleavage methods, metal carbenes can be used as synthetic equivalents for aldehydes, amides, and esters.

SYNTHESIS

Fischer developed one of the widely used methods of synthesizing group 6 carbene complexes.11 Treatment of a metal hexacarbonyl according to Scheme I yields the alkoxycarbene
2. The aminocarbene complex 3 can be generated by treating 2 with an unhindered primary or secondary amine, such as dimethylamine. This route provides a wide range of metal carbene compounds; however, only alkoxy carbones stable to strongly basic conditions can be generated, and hindered aminocarbene complexes (e.g. derived from pyrrolidine) cannot be made.

Scheme I

A method developed by Hegedus allows for the more general synthesis of chromium aminocarbene complexes. Treatment of the amide 4 affords chiral carbenes in excellent yields, including hindered aminocarbenes such as the (S)-phenylglycine derivative 5 (Scheme II).

Scheme II

SYNTHETIC UTILITY

α-Amino Acids

The aminocarbene complexes generated by the Hegedus method have been used in the synthesis of α-amino acids. Photolysis of aminocarbene complexes in the presence of an alcohol, yields α-amino esters, which can then be cleaved to the corresponding acids (Table I).

Table I. Chiral Amino Acids

<table>
<thead>
<tr>
<th>compound</th>
<th>R</th>
<th>R'</th>
<th>yield of 7, %</th>
<th>de, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>Me</td>
<td>Me</td>
<td>96</td>
<td>≥93</td>
</tr>
<tr>
<td>6b</td>
<td>Me</td>
<td>t-Bu</td>
<td>77</td>
<td>≥93</td>
</tr>
<tr>
<td>6c</td>
<td>CH₂CO₂-t-Bu</td>
<td>Me</td>
<td>74</td>
<td>≥93</td>
</tr>
<tr>
<td>6d</td>
<td>CH₂CH₂CH=CH₂</td>
<td>Me</td>
<td>57⁵</td>
<td>≥95</td>
</tr>
<tr>
<td>6e</td>
<td>CH₂Ph</td>
<td>Me</td>
<td>81⁵</td>
<td>≥95</td>
</tr>
<tr>
<td>6f</td>
<td>CH₂Ph</td>
<td>t-Bu</td>
<td>60</td>
<td>≥93</td>
</tr>
</tbody>
</table>

⁵experiment done at 0 °C. All others performed at 25 °C
The reaction is believed to proceed through a metal-ketene intermediate, formed by the insertion of CO into the C=Cr bond. The observation that ketene complexes from thermal cyclization reactions of alkoxy carbene compounds have been isolated as intermediates supports this mechanism. Also, though no typical ketene byproducts such as dimers are observed, the intermediate complexes react with nucleophiles in the same manner as ketenes. With amino acids, the addition of methanol across the C=C double bond of the ketene is observed. Chromium carbenes also react photochemically with imines to produce β-lactams, and with olefins to form cyclobutanones.

For chiral carbenes, such as 6, the addition of the alcohol will occur on the less hindered face of the ketene, favoring the formation of a single diastereomer (Table I). Excellent diastereoselectivity is generally observed, and bulky alcohols tend to lower yields without improving stereoselectivity.

This method can be easily modified to produce $1,2$-$^{13}$C$_2$-enriched amino acids 8 (Scheme III). The yields are generally good (57-97%), with 60-70% $^{13}$C incorporation. The synthesis also is efficient in recovering expensive, unused $^{13}$C by converting the byproduct (O$^{13}$C)$_4$Cr(MeCN)$_2$ to Cr($^{13}$CO)$_6$, which can be used again to generate aminocarbenes.

Scheme III

β-Lactams

Hegedus has also used chromium aminocarbenes in the formation of optically active β-lactams (Scheme IV). Reaction proceeds photochemically through a ketene intermediate 9, which

Scheme IV

in turn adds to an imine to form the four-membered lactam ring 10. However, unlike a ketene addition to an olefin, which is a concerted [2 + 2] cycloaddition, an addition of 9 to imines
undergoes a stepwise cyclization process (Scheme V). Nucleophilic attack of the imine nitrogen onto the carbonyl carbon of the ketene (largest LUMO coefficient) forms a zwitterion, which can then undergo a conrotatory ring closure (c) to form the cis isomer or rearrange via (a) or (b) to give the trans isomer. Rearrangement tends to occur if R₃ stabilizes positive charge (e.g. aryl or alkoxy group) and promotes path (b), or if path (c) is slow, allowing the enolate to equilibrate (path (a)).

**Scheme V**

![Scheme diagram](image)

Excellent diastereoselectivity in this reaction may be achieved by using a chiral aminocarbene complex, thereby favoring attack from the least hindered face. Rearrangement is minimized by also using a cyclic imine, which cannot isomerize via pathway (b). The best results (75-95% yield, $\geq 97\%$ de) were obtained in the formation of compounds 10, with a sterically discriminating chiral auxiliary and cyclic imines.

**Nitrogen Ylides**

Although Hegedus focuses on the development of aminocarbene chemistry toward novel syntheses of natural products, other groups are concerned with its use in the synthesis of nitrogen-containing heterocycles. In work aimed towards developing methodology for polycyclic nitrogen compounds, Rudler discovered an unexpected rearrangement reaction of aminocarbenes to form pyrrolinones through a nitrogen ylide intermediate.

The nitrogen ylides 13a-f are isolated when the precursor carbene 11 is heated with diphenylacetylene in refluxing benzene (Table II). The reactivity of these compounds is consistent with other known nitrogen ylides, since treatment by strong acids yield quaternary ammonium salts, and treatment by alcohols yield amino esters. Furthermore, upon additional heating, compounds 13a-f lead to 14a-f, providing strong evidence that nitrogen ylides are intermediates in pyrrolinone formation.
Table II. Reaction of Aminocarbenes to Form Pyrrolinones

![Chemical structure]

<table>
<thead>
<tr>
<th>compound</th>
<th>R²</th>
<th>R-R¹</th>
<th>yield of 13, %</th>
<th>yield of 14, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>H</td>
<td>-(CH₂)₅-</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>11b</td>
<td>Me</td>
<td>-(CH₂)₅-</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>11c</td>
<td>Me</td>
<td>R = R¹ = Me</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>11d</td>
<td>Ph</td>
<td>R = R¹ = Me</td>
<td>55</td>
<td>52</td>
</tr>
<tr>
<td>11e</td>
<td>Me</td>
<td>R = Me, R¹ = cyclopropyl</td>
<td>57</td>
<td>79</td>
</tr>
<tr>
<td>11f</td>
<td>Ph</td>
<td>R = Me, R¹ = cyclopropyl</td>
<td>47</td>
<td>66</td>
</tr>
</tbody>
</table>

The pattern of rearrangement shown in Table II does not extend to aminocarbenes with alkenyl substituents on nitrogen. For the 3-pyrroline-derived aminocarbone (R²=Me), heating with diphenylacetylene gives the fused system 15 rather than the expected bridged system 14 (Figure 1). For the 1,2,3,6-tetrahydropyridine derivative (R²=Me), there is a mixture of products 16 and 17. Thus, rearrangement to 14 is observed only for complexes with saturated amines. Future work to functionalize the saturated amine ring with compatible substituents, such as alkyl or ether groups, would make this reaction more synthetically useful.

![Chemical structures 15, 16, 17]

Figure 1. Rearrangement Products from Alkenyl-Derived Aminocarbenes

Exploitation of Carbenes as C=O Equivalents

Interest has increased recently in the use of the C=Cr bond of carbene complexes as C=O equivalents. Research on the α-alkylation of complexes at the carbene center mostly focuses on expanding the available number of alkoxy- and aminocarbenes.²² The development of chromium carbenes as aldol reagents has led to the discovery that aminocarbenes effect diastereoselectivities comparable to those found in Lewis acid mediated reactions.²³ Research into the "enolate-like" chemistry of anionic carbene complexes has also led to their use in asymmetric Michael reactions (Scheme VI).
Wulff discovered that when chromium aminocarbene anions are combined with enones, they give rise to exclusive 1,4-addition. Furthermore, better diastereoselectivity is produced with addition to chiral enones compared to Lewis acid catalyzed methods. But perhaps the most useful application is the addition of chiral complexes to achiral enones (Table III). Optically active carbene anions 18a and 18b, with subsequent chromium cleavage by triflic acid, produce the desired Michael adduct in good diastereoselectivity and fair overall yield. Excellent diastereoselectivity results if there is a large steric differentiation in the enone (c.f. reaction of 18a with 19a and 19b).

Table III. Asymmetric Michael Reactions with Chiral Aminocarbenes

<table>
<thead>
<tr>
<th>nucleophile</th>
<th>enone</th>
<th>product 20</th>
<th>yield, %</th>
<th>ee, % (config.)</th>
<th>lit. yield, % (ee, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a</td>
<td>19a</td>
<td>R1R2=-(CH2)3-</td>
<td>59</td>
<td>65 (S)</td>
<td>82(88)</td>
</tr>
<tr>
<td>19b</td>
<td>19a</td>
<td>R1R2=-(CH3)2C(CH2)2-</td>
<td>51</td>
<td>95 (S)</td>
<td>-</td>
</tr>
<tr>
<td>19c</td>
<td>19a</td>
<td>R1R2=-(CH2)2-</td>
<td>46</td>
<td>64 (S)</td>
<td>80(98)</td>
</tr>
<tr>
<td>18b</td>
<td>19a</td>
<td>R1R2=-(CH2)3-</td>
<td>57</td>
<td>76 (R)</td>
<td>82(73)</td>
</tr>
</tbody>
</table>

When compared to Hua’s method of Michael additions with chiral phosphonyl anions such as 21, the aminocarbene complexes do not offer any obvious advantages. Reactions using the phosphonyl anions generally result in better yield and ee (Table III). However, the diastereoselectivities of the aminocarbene reactions are significant, since there are relatively few ways of adding unsubstituted enolate equivalents to simple cyclic enones.

Diels-Alder Reactions

The use of carbene complexes as C=O equivalents has also led to their development as dienophiles in Diels-Alder reactions. In these cases tungsten complexes are preferred, since they
do not exhibit the C=O insertion to form the ketenes observed in chromium complexes, and fewer side products result. Intermolecular Diels-Alder reactions with alkoxycarbenes give yields and stereoselectivities comparable to Lewis acid catalyzed reactions.\textsuperscript{27} Reactivity of the carbene dienophile depends on the heteroatom substituent on the carbene carbon. A destabilizing electron-withdrawing group such as acetate makes the complex more reactive compared to an electron-donating group, such as an alkoxy group.\textsuperscript{28} Also, unusually high exo selectivity is observed when aminocarbenes are used as dienophiles.

For some intramolecular Diels-Alder reactions, the carbene dienophile produced the desired adducts in good stereoselectivity, whereas the analogous compound 23 was unselective and the Lewis acid catalyzed reaction yielded no product (Table IV).\textsuperscript{29} Thus, not only is the carbene methodology comparable in utility to Lewis acid mediated Diels-Alder reactions, but perhaps even more versatile, yielding [4+2] cycloadducts for substrates not compatible with Lewis acids.

**Table IV. Comparison of Diels-Alder Reactions**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions, ( ^\circ\text{C}) (h)</th>
<th>Overall Yield to Esters, %</th>
<th>Endo:Exo Ratio</th>
<th>Yield Ce(^{4+}) Cleavage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>22-trans</td>
<td>(80) (36)</td>
<td>82</td>
<td>93:7</td>
<td>94</td>
</tr>
<tr>
<td>23-trans</td>
<td>(150) (45)</td>
<td>94</td>
<td>51:49</td>
<td>-</td>
</tr>
<tr>
<td>22-cis</td>
<td>(40) (48)</td>
<td>78</td>
<td>78:22</td>
<td>91</td>
</tr>
<tr>
<td>23-cis</td>
<td>(150) (45)</td>
<td>90</td>
<td>49:51</td>
<td>-</td>
</tr>
</tbody>
</table>

**CONCLUSION AND FUTURE WORK**

With the increasing accessibility of group 6 carbene complexes, there is a growing number of applications of these compounds in organic synthesis. Much like other pathways in organic methodology, those which involve group 6 carbenes provide enhancements of previous methods, as with Diels-Alder reactions, or improved ways to achieve target compounds, as with \(^{13}\text{C}_2\)-labeled amino acids. Given the success in developing enantioselective ways of generating chiral amino acids and \(\beta\)-lactams with carbene complexes, the investigation of chiral complexes for use in enantioselective Diels-Alder reactions would be worthwhile. In addition, since tungsten carbene complexes have been used in Diels-Alder reactions successfully, similar compounds may likely be developed for the ene reaction, and give rise to enantioselective carbene enophiles.
REFERENCES

MAGNETIC FIELD EFFECTS ON PHOTOCHEMICALLY GENERATED BIRADICALS

Reported by David J. Owen September 16, 1993

INTRODUCTION

Biradicals have been postulated as reactive intermediates for some time in numerous photochemical reactions. Many systems of current interest are believed to include these species as part of the reaction pathway. One such system under investigation is the di-π-methane rearrangement, which is believed to involve two biradical intermediates. Similarly, a 1,4-biradical is a postulated intermediate in the mechanism of the photocycloaddition of enones to alkenes. A classical example of the photochemical generation of biradicals involves the intramolecular hydrogen atom abstraction of excited ketones often leading to cyclization products (Scheme I). Owing to the numerous reactions which involve biradicals as intermediates, much work has been dedicated to establishing their chemical nature. One method which has recently gained much attention is the use of applied magnetic fields. This seminar will focus on how magnetic field effects have been used to further characterize biradicals generated in photochemical reactions.

Scheme I

BACKGROUND

Photochemical generation of biradicals has been carried out through direct irradiation of precursors such as aromatic and aliphatic ketones. Ketones which contain long chains with accessible hydrogens may undergo hydrogen abstraction yielding a biradical in a Norrish Type II reaction. If the excited ketone is suitably substituted at the carbonyl α-position, however, homolytic C-C bond cleavage may result by a Norrish Type I reaction. In the process, correlated radical pairs (from acyclic ketones) or biradicals (from cyclic homologs) are generated. Additionally, the irradiation of electron rich groups tethered by flexible methylene chains to electron deficient groups results in intramolecular electron transfer and the production of zwitterionic biradical moieties.

In all cases, the spin state of the resulting ground state biradical is of considerable
importance as it determines available reaction pathways. As dictated by selection rules, only singlet state biradicals may undergo direct recombination within the cage while triplet state biradicals must either intersystem cross to the singlet state or escape the cage and encounter a radical with an opposing spin before recombining. The spin state of a biradical is described by the relative orientations of its electronic spin vectors as they precess about the net magnetic field of the molecule, \( H_Z \) (which is a summation all the individual magnetic moments generated by spinning nuclei and electrons, Figure 1).\(^5\) A singlet arises from spin pairing, in which the two spin vectors are \( 180^\circ \) out-of-phase. This results in no net polarization \((M_s=0, S=0)\). In the triplet, the spins are parallel \((S=1)\), with three possible orientations and respective values for the magnetic quantum number, \( M_s \) \( (M_s=-1, 0, \text{ or } +1) \). In the absence of any magnetic fields the energies of the three triplet states are degenerate.

![Figure 1: Vectoral representation of spin states.](image)

**INTERSYSTEM CROSSING AND EXTERNAL MAGNETIC FIELDS**

The spin state of a biradical is not a static property as mechanisms exist for intersystem crossing (ISC) between the triplet and singlet states. Magnetic field effects are manifested by changes in the rate at which these crossings occur by affecting various mechanisms available for intersystem crossing. These include spin-orbit coupling, hyperfine coupling, \( \Delta g \) mechanism, and spin relaxation.

Spin-orbit coupling involves a coupling of the orbital motion of the electron to its spin magnetic moment. The orbital motion of the electron provides a "torque" which acts to flip the spin vector of the electron.\(^6\)\(^7\)\(^8\) To conserve angular momentum, the electron undergoes a simultaneous jump to an orthogonal orbital (i.e., \( P_x \rightarrow P_y \)) to compensate for the change in the spin angular momentum. For this mechanism to occur, the energetic difference between the two states, \( \Delta E_{ST} \), must not exceed the energetics of the coupling, \( E_{SO} \). In organic compounds containing only first row atoms this energy is relatively small \((-0.1 \text{ kcal})\).\(^9\) With additional "heavy atoms" present, the interaction becomes larger, and thus a greater singlet-triplet energy difference

...
is permissible. Salem and Rowland were the first to discuss spin-orbit coupling in biradicals; they concluded that an inverse dependence of spin-orbit coupling on the distance between the radical centers exists in biradicals.10

In the hyperfine mechanism, interactions between the nuclear and electronic spins can lead to intersystem crossing; however, the inherent weakness of this coupling requires near degeneracy of the singlet and triplet states for transition. When the exchange interaction, J (defined by the amount of spin spin interaction) between the two spins is small, the triplet and singlet states are nearly degenerate. Under these conditions, differences in local nuclear magnetic fields experienced by the electronic spins cause differences in their relative precessional frequencies, \( \omega \), about the net magnetic field, \( H_2 \). Thus, the phasing of the spins is no longer either 180° or 0° and a mixing between the \( T_0 \) and S states is possible. In addition, crossing between the \( T_{\pm} \) and S states is possible through a simultaneous nuclear and electronic spin flip, provided both states are nearly degenerate.11

In the presence of an external magnetic field, Zeeman splitting of the triplet sublevels removes their degeneracy. As a result, hyperfine coupling induced transitions are reduced to only S-T\( _0 \). If a significant exchange interaction exists, such that S and T\( _0 \) are not initially degenerate, an applied field may reduce the level of T\( _0 \) to where it is energetically degenerate with S. Once this occurs hyperfine coupling may induce a transition.

Similar to hyperfine coupling, the \( \Delta g \) mechanism involves an interaction between neighboring electron spins. These electron spins determine the environment "felt" by the spinning electron as reflected in its characteristic g-value.12 Differences in these values may lead to variations in relative precessional rates and consequently induce singlet-triplet intersystem crossing. Since this is a precessional difference, only S-T\( _0 \) crossings are possible. In the presence of only the Earth's magnetic field (\( \sim 1G \)) this mechanism is inconsequential. Only with very large external fields (\( \sim >10^5G \)) does it become effective.

Transverse and longitudinal relaxation of the spins of the biradical may lead to intersystem crossing in the relaxation mechanism.13 The loss of phase coherence induced by transverse relaxation leads to S-T\( _0 \) transitions at rate inversely proportional to the transverse relaxation time, \( T_2 \). Similarly, longitudinal relaxation, characterized by the parameter \( T_1 \), provides a means for S-T\( _{\pm} \) transitions. Unless they possess unusually short relaxation times, biradicals undergo this mechanism only if they have a sufficiently long lifetime (\( \sim >10^{-5}s \)).

**REPRESENTATIVE SYSTEMS**

Photolysis of dibenzyl ketone (DBK) in micellar media produces spin correlated radical pairs through \( \alpha \)-cleavage in a Norrish Type I fashion. Rapid loss of CO from the triplet excited state of DBK produces triplet pairs of benzyl radicals (Scheme II).14 This system introduces a
barrier to cage escape by localizing the benzyl radicals within the hydrophobic core of the micelle. Thus, intersystem crossing competes effectively with cage escape, and magnetic field effects are measurable.

Scheme II

Through laser flash photolysis and transient absorption of the formed benzyl radical pairs in aqueous solutions of cetyltrimethyl ammonium chloride (CTAC), Turro\textsuperscript{15} showed that the decay rate of the spin correlated radical pairs decreases upon application of 400 G fields. Likewise, a reduced cage effect, defined as the relative yield of the 1,2-diphenylethane cage product to DBK disappearance in the presence of Cu\textsuperscript{+2} benzyl radical scavengers, was observed in the presence of magnetic fields. Within CTAC micelles, a 1000 G field yielded a cage effect of 20\%, as compared to 30\% obtained in absence of an applied magnetic field.\textsuperscript{16} The reduced rate of intersystem crossing reduces the yield of in cage products. Nagakura \textit{et. al.} studied the decay rates of benzyl radicals from DBK photolysis in aqueous sodium dodecyl sulfate (SDS) and CTAC micelles. They observed a steady reduction in decay rates of correlated benzyl radical pairs in magnetic fields up to 150 G.\textsuperscript{17} Since this value was close to the calculated weighted average of hyperfine coupling, \(\alpha,\)\textsuperscript{18} the effect was attributed to hyperfine coupling. For fields above this value no additional effects should be observed.

In a further attempt to limit loss of correlation, Doubleday and Turro investigated the photoinitiated \(\alpha\)-cleavage of \(\alpha,\alpha'\)-diphenylcycloalkanones, \(1_n,\)\textsuperscript{19} Excitation of \(1_n\) with a 308 nm laser pulse produces biradical \(2_n\) in high yield via Norrish type I cleavage of the triplet excited state of the ketone. Rapid decarbonylation (<10 ns)\textsuperscript{20} produces the triplet methylene linked benzyl biradical, \(3_n.\) The decay of \(3_n,\) monitored by transient absorption at 320 nm, was governed by the rate limiting ISC, \(k_{ISC},\) to the singlet state, \(4_n\) (Scheme III). The rapid decarbonylation of \(2_n\) was assumed to be complete in less than 10 ns, even though the same authors had previously reported the decarbonylation rate of phenyldimethylacetyl radical (\(C_6H_5CCH_3CO^-\)) as \(4.9 \times 10^7\ \text{s}^{-1}\) (\(\tau = 20\ \text{ns}\)).\textsuperscript{20} In the same work, rate of loss of CO from phenyldimethylacetyl \([C_6H_5C(CH_3)_2CO^-]\) radical was given as \(1.5 \times 10^8\ \text{s}^{-1}\) (\(\tau = 6.7\ \text{ns}\)). However, the former radical would be expected to be the more suitable model to \(2_n\).
Application of various magnetic fields from 0 to 2 kG to long-chain biradicals, \(3_9, 11, 14\), led to an increase of \(k_{\text{ISC}}\) until a maximum value was obtained at a value given by \(H_{\text{max}}\) (Table I). A further increase in field strength eventually led to an asymptotic region with a rate \(k^\infty_{\text{ISC}}\) (only observed for \(n = 11\) and 14). For short chain lengths, \(3_4\) and \(3_5\), magnetic fields did not appreciably affect the observed decay rate. Due to a significant exchange between the spins of the radicals, a conformationally averaged singlet-triplet energy gap, \(\langle E_{\text{st}} \rangle\), exists. The value of \(H_{\text{max}}\) gives a measure of this gap as the applied field's induced Zeeman splitting creates a \(T_1-S\) degeneracy, so hyperfine initiated ISC may occur. For the short biradicals, \(3_4\) and \(3_5\), \(\langle E_{\text{st}} \rangle\) exceeds the Zeeman splitting at 2 kG. Because only one of the triplet sublevels is degenerate with the singlet at high fields, \(T_0-S\), the ratio of the asymptotic rate to that at zero applied field, \(k^\infty_{\text{ISC}} / k^0_{\text{ISC}}\), is expected to be 1/3. For long biradicals which showed an asymptote, \(3_{11, 14}\), ratios were found to be less than expected and were attributed to the presence of additional ISC mechanisms. Comparison of rates of ISC at high field, \(H = 2\) kG, to the "expected" \(T_1^{-1}\) value of 3-5 x 10\(^5\);\(^{21}\) led to the conclusion that the additional rate reduction is attributable to the relaxation mechanism. The expected values for \(T_1^{-1}\) employed by the authors were based on \(T_1\) measurements obtained for alkyl and semiquinoid radicals, leading to some question as to their applicability to the present system.

**Table I. Magnetic Field Data for Benzyl Biradicals, \(3_n\).**

<table>
<thead>
<tr>
<th>(n)</th>
<th>(H_{\text{max}}, \text{G})</th>
<th>(k_{\text{ISC}}, 10^6 \text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(H = 0)</td>
<td>(H = H_{\text{max}})</td>
</tr>
<tr>
<td>9</td>
<td>300 ± 100</td>
<td>1.58 ± 0.06</td>
</tr>
<tr>
<td>11</td>
<td>120 ± 80</td>
<td>3.7 ± 0.1</td>
</tr>
<tr>
<td>14</td>
<td>30 ± 15</td>
<td>6.9 ± 0.9</td>
</tr>
</tbody>
</table>

In the photolysis of aryl amino nitro aromatic methylene chain linked species, the nature of biradical intermediates and product yield dependencies were studied with applied magnetic fields.
Photolysis of N-[12-(4-nitro-1-naphthoxy)dodecyl]aniline, 5, leads to three major products with intermediate triplet and singlet biradicals (denoted by superscripts) as depicted in Scheme IV. The assignment of the triplet state to the initially formed biradical was based on the observed rule that photoexcited nitro compounds undergo rapid ISC from the excited singlet to the excited triplet state. In accordance with spin selection rules, the subsequently formed biradical must be in the triplet state.

Scheme IV

The formation of the nitroso aldehyde, 6, was attributed to an in cage mechanism involving intramolecular oxidative N-dealkylation of the donor amine group from the singlet biradical precursor. However, the mechanism of formation of the nitro aldehyde, 7, was assigned to a cage escape followed by an analogous intermolecular process. As a result, the relative abundance of 7 and 6 would be indicative of the nature of their biradical precursors. Yield ratios of the competing products, $R_b$, defined by $R_b = \Phi(\text{escape product, 7}) / \Phi(\text{cage product, 6})$ were obtained in the presence and absence of a 6.4 kG (Table II).

Table II

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$R_b$ (0 G)</th>
<th>$R_b$ (6.4 kG)</th>
<th>conversion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzene</td>
<td>0.17±0.02</td>
<td>0.59±0.07</td>
<td>35</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>0.36±0.03</td>
<td>0.60±0.08</td>
<td>30</td>
</tr>
</tbody>
</table>

In accordance with the mechanism, the yield of the escape product, derived from the triplet, is enhanced by the applied magnetic field due to a reduction in the hyperfine induced intersystem crossing. Nakagaki proposed that the nature of the biradical species is also dependent
on solvent. Based on a) previous transient absorption spectra of N-[12-(p-nitrophenoxy)dodecyl]aniline in acetonitrile and b) the low ionization potentials for N-alkyl anilines, a zwitterionic electron transfer product species was assigned to $^3$(biradical) for photolyses carried out in acetonitrile. In benzene, however, the lack of solvent stabilization of charged species would require a close association of two radical centers. If this were the case the resulting large exchange term, J, would preclude the observable magnetic field effects. Thus, the biradicals formed in benzene were proposed to be neutral and the result of hydrogen abstraction.

APPLICATIONS

Turro has pioneered the use of magnetic fields in conjunction with photoinitiated emulsion polymerization. By employing oil soluble DBK photoinitiator to SDS micellar solutions of styrene monomer, he was able to show the existence of a dramatic magnetic field effect on average molecular weights, $M_r$, and yields of polystyrene. Addition of a 1000 G external field caused $M_r$ to increase by a factor of five. Similar effects were observed on polymerizations of methyl methacrylate, MMA, initiated by DBK and other photoinitiators such as phenyl benzyl ketone (PBK) and 1,2 diphenyl-2-methylpropanone, DPMP (Table III). By application of the external field, intersystem crossing from the initially formed triplet to the singlet, in the case of DBK, is reduced, thus allowing more cage escape of the radical initiator. Escape of one of the radical initiators from the originally formed pair to other monomer laden micelles reduces the rate of termination and thus increases polymer weight.

Table III. Magnetic Field Effects on Emulsion Polymerization of Methyl Methacrylate, MMA.

<table>
<thead>
<tr>
<th>initiator</th>
<th>monomer</th>
<th>magnetic field, G</th>
<th>$M_r \times 10^6$</th>
<th>yield, %</th>
<th>polymerization time, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBK</td>
<td>MMA</td>
<td>0</td>
<td>4.6</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>DBK</td>
<td>MMA</td>
<td>100-5000</td>
<td>10.0</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>PBK</td>
<td>MMA</td>
<td>0</td>
<td>3.3</td>
<td>82</td>
<td>1.5</td>
</tr>
<tr>
<td>PBK</td>
<td>MMA</td>
<td>5000</td>
<td>5.5</td>
<td>84</td>
<td>1.5</td>
</tr>
<tr>
<td>DPMP</td>
<td>MMA</td>
<td>0</td>
<td>2.5</td>
<td>60</td>
<td>1.5</td>
</tr>
<tr>
<td>DPMP</td>
<td>MMA</td>
<td>5000</td>
<td>3.0</td>
<td>60</td>
<td>1.5</td>
</tr>
</tbody>
</table>

CONCLUSION

In the continuing effort to study the nature of suspected biradical intermediates and to prove their existence in reaction mechanisms, magnetic field studies have proven to be a useful tool. In combination with recent improvements in detection of transient species, they have been
instrumental in the assignment of intersystem crossing mechanisms employed by biradical species. In addition, applied fields may prove useful in directing reaction pathways. They have been utilized to induce reaction products and polymerization processes involving radical species.

REFERENCES

(7) Turro, N. J. Modern Molecular Photochemistry; Benjamin/Cummings: Menlo Park, 1978; Chapter 3.
(20) Turro, N. J.; Gould I.; Barretz, B. ibid. 1983, 87, 531.
APPLICATIONS OF η⁶- ARENE CHROMIUM TRICARBONYL COMPLEXES IN STEREOSELECTIVE SYNTHESIS

Reported by Amit Basu

September 27, 1993

INTRODUCTION

Arene chromium tricarbonyl complexes were first reported in 1957,¹ but their application to organic synthesis is a field that has only recently been developed.² The ease of preparation and wide range of reactivity of these complexes make them particularly attractive reagents for organic synthesis. These complexes can function as valuable intermediates in a synthetic sequence, and can often undergo transformations not readily accessible with the uncomplexed arene. Chromium complexation of an arene can also serve to enhance the stereochemical fidelity of reactions in which the free ligand exhibits poor stereoselection.³ In addition, ortho and meta unsymmetrically disubstituted complexes are chiral, and high diastereoselectivities are observed in reactions with these complexes. This review will focus on the impact of chromium complexation in affecting stereoselective transformations at positions α to the aromatic ring.

![Figure 1](image1.png) Schematic of complexation.  

![Figure 2](image2.png) Chiral disubstituted complexes

BACKGROUND

Properties of arene chromium tricarbonyl complexes

Complexation of the chromium tricarbonyl moiety exerts steric and electronic effects on both the ring and adjacent positions, as summarized in Figure 1. The complexed arene is rendered electron-deficient as a result of the electron-withdrawing properties of the chromium tricarbonyl fragment. This polarization is supported by various spectroscopic and physical measurements such as IR and dipole measurements.⁶ As a consequence of the electron deficiency of the arene, nucleophilic addition to the ring is facilitated,²c presenting an alternative to traditional electrophilic substitution as a means of aromatic functionalization, often with complementary regioselectivity. The electron deficiency of these complexes also enhances

Copyright © 1993 by Amit Basu
the kinetic acidity of the aryl protons, a feature that has also found synthetic applications.\textsuperscript{7}

Synthesis of arene chromium tricarbonyl complexes

Formation of an arene-chromium tricarbonyl complex is facile, and is most frequently accomplished by heating the arene with chromium hexacarbonyl in a solution of dibutyl ether and THF, or by arene transfer from \([\text{naphthalene-Cr(CO)}_3]\) in a sealed tube.\textsuperscript{6b} The complexes usually form bright yellow or red crystals that are air stable and easy to handle. Mild oxidation of the complexes by cerium(IV), iodine, or prolonged exposure to sunlight in air serves to liberate the arene.\textsuperscript{2a}

As previously mentioned, an ortho disubstituted complex is chiral, and can yield diastereomeric products in reactions involving the creation of a new stereocenter. A representation for the enantiomers of an ortho disubstituted complex is shown in Figure 2. Preparations of enantiomerically pure complexes have traditionally relied on resolution of diastereomeric derivatives via chromatography or recrystallization\textsuperscript{8}, but the advent of new methods of synthesis,\textsuperscript{9} as well as enzymatic resolution\textsuperscript{10} and diastereoselective complexation (Scheme I),\textsuperscript{11} continues to allow easier access to a wider variety of optically active complexes.

Scheme I

![Scheme I](image)

**NUCLEOPHILIC ADDITION**

Metal complexation shields one face of an arene such that nucleophilic addition occurs preferentially from the face opposite to the metal. Thus, reaction of complexed \(\alpha\)-tetralone with nucleophiles yields \textit{endo} alcohol complexes 5 and 6 with complete stereoselectivity.\textsuperscript{12}

Scheme II

![Scheme II](image)
Nucleophilic attack on o-substituted benzaldehyde complexes affords diastereomeric products with high stereoselectivities. Thus, addition of methylmagnesium iodide to enantiomerically pure 7 followed by decomplexation yields the alcohol 9 essentially enantiopure. The high stereoselectivity is rationalized via nucleophilic addition to the exo conformer of the carbonyl group, as shown in Scheme III, thereby reducing steric and dipole interactions in the transition state.

**Scheme III**

Even with electronically less demanding ortho substituents such as alkyl groups, the major products correspond to those of addition to the exo conformer. The selectivity can be explained by the unfavorable steric interactions between the substituent and the carbonyl functionality in the endo conformer. A variety of nucleophiles undergo diastereoselective addition to the carbonyl group of complexed benzaldehydes, with good to excellent ee's in cases where enantiomerically pure complexes are used. Solladie-Cavallo has successfully applied this methodology to the synthesis of ephedrine derivatives. Addition of tosylmethylisocyanide to (1R)-10 provides the oxazoline 11 as a single diastereomer. Decomplexation and reduction yields unnatural halostachine (12). The enantiomer of the corresponding primary amine had previously been synthesized from (2R)-10 by means of a Henry reaction with nitromethane. A Darzens condensation with α-chloroacetophenone to yield the corresponding trans-epoxides with high asymmetric induction (80 - 97 % ee) has also been reported.

**Scheme IV**

A limitation of this methodology is that it does not allow access to monosubstituted aromatic rings. An ortho silyl protecting group provides a convenient solution to this problem, since it can easily be removed by treatment with fluoride. The silyl group is introduced via an acetal-directed ortho-lithiation prior to chromium complexation, thus avoiding undesirable detours in the preparative sequence. The sense of approach is reversed with an o-trialkylsilyl group, as shown in Figure 3. This is believed to result from steric interactions that could arise...
between the nucleophile and the silyl substituents if attack were to occur on the energetically more favorable *exo* conformer. Complementary diastereoselectivity can be obtained by precomplexing the aldehyde with a Lewis acid. The effective steric bulk of the carbonyl group is increased due to complexation, increasing the steric repulsions of the *endo* conformer.

![Figure 3. Nucleophilic attack on ortho-silyl substituted benzaldehyde complexes.](image)

Cyclic enol ethers and $O,S$-ketene acetals have been used as nucleophiles in stereoselective aldol reactions in the presence of Lewis acid conditions to afford the *anti* adducts in moderate to high diastereoselectivities.$^{16}$

**STABILIZATION OF BENZYLIC CATIONS**

The ability of the chromium tricarbonyl moiety to stabilize benzylic cations was demonstrated in the faster solvolysis of the complexed benzyl chloride compared to its uncomplexed counterpart.$^{17}$ While two primary contributing resonance forms can be drawn for the cation, (Figure 4) calculations indicate that stabilization arises as a consequence of electron donation from the metal $d_{x^2-y^2}$ orbital to the LUMO of the benzyl ligand, which has its largest coefficient at the benzyl carbon.$^{18}$ As a result, rotation around the bond between the cation and the ring is restricted. This is consistent with $^{13}$C NMR studies, which indicate a large upfield shift in the resonance of the cationic carbon in the complex when compared to the uncomplexed cation.$^{19}$ Magnetic inequivalency due to restricted rotation gives rise to two separate resonances for the *ortho* carbons when $R \neq R'$.

![Figure 4. Two contributing resonances towards cation stabilization.](image)

The conformational rigidity of these cations can be harnessed for stereoselective transformations, as illustrated by the Ritter reaction of enantioenriched 1-phenylethanol in
acetonitrile, which yields the secondary amide with almost complete retention of stereochemistry. The reaction is thought to proceed via a transition state in which the nucleofuge is positioned anti to the chromium atom in a stereoelectronically favored orientation for overlap of the metal d-orbital with the developing carbon p-orbital.

The enhanced stability of benzylic carbocations has enabled their successful use in synthesis without competing side reactions. Good diastereoselectivities were observed for nucleophilic attack of trialkylaluminum and dialkylzinc reagents on cations derived from complexed tetralols. Electron-rich aromatic rings and \( \beta \)-dicarbonyl compounds also serve as efficient nucleophiles. In all cases, the major product formed results from nucleophilic attack to the distal face, irrespective of the initial configuration of the nucleofuge. Starting from the \( \alpha \)-tetralone complex 4 and inverting the order of nucleophilic addition and reduction provides access to both diastereomers 13a and 13b selectively as depicted in Scheme V.\(^{12a}\)

**Scheme V**

\[
\begin{align*}
4 & \xrightarrow{1. \text{LiAlH}_4} 5 \\
& \xrightarrow{2. \text{Ac}_2\text{O}} 13a \\
& \xrightarrow{\text{Me}_3\text{Al, TiCl}_4} 13b
\end{align*}
\]

Davies has applied this methodology towards syntheses of tetrahydroisoquinolines and tetrahydrobenzazepines. The key step involves the stereoselective cyclization of the cation derived from the benzylic alcohols 14 to yield enantiomerically pure cyclized products 15, as shown in Scheme VI. These results are in marked contrast with enantiomeric excesses of 6% and 54% respectively, obtained when the reactions are carried out with the uncomplexed alcohols.

**Scheme VI**

\[
\begin{align*}
14a \text{ - } n = 1 & \xrightarrow{1. \text{HBF}_4 \cdot \text{OMe}_2} 15a \text{ - } n = 1, 66\% \\
b \text{ - } n = 2 & \xrightarrow{2. [\text{O}]} 15b \text{ - } n = 2, 75\%
\end{align*}
\]

Zinc chloride assisted alkylation of silyl enol ethers using enantioenriched complexed benzyl
acetates has also been found to proceed with excellent stereochemical conservation.\(^{24}\)

Davies has extended the use of chromium complexes to stabilize benzylic oxocarbenium ions derived from acetals. Reaction of benzylic oxonium ions with various homoallylic alcohols in the presence of titanium tetrachloride yields the 2-aryl-4-chlorotetrahydropyrans 17a-d as single diastereomers (Scheme VII).\(^{25}\)

**Scheme VII**

\[
\begin{align*}
16a-d & \xrightarrow{\text{TiCl}_4} 17a-d \\
\end{align*}
\]

\[
\begin{array}{l}
a- X = \text{Me}, R = \text{Et}, R' = \text{H} (92\%) \\
b- X = \text{Me}, R = \text{H}, R' = \text{Et} (80\%) \\
c- X = \text{OMe}, R = \text{Et}, R' = \text{H} (83\%) \\
d- X = \text{OMe}, R = \text{H}, R' = \text{Et} (80\%)
\end{array}
\]

**STABILIZATION OF BENZYLIC ANIONS**

One of the unique features of arene chromium complexes is their 'hermaphroditic'\(^{26}\) nature, for they stabilize both benzylic cations and anions. The deprotonation of toluene-[Cr(CO)\(_3\)] by potassium tert-butoxide is an example.\(^{27}\) The stereocontrolling factors for manipulations of \(o\)-substituted benzylic anions are analogous to those of cations, and involve \textit{exo}-selective proton abstraction, hindered rotation around the C\(_{\text{ipso}}\) - C\(_{\alpha}\) bond, followed by electrophilic substitution from the face \textit{exo} to the metal. Deuterium labeling studies on \textit{endo} and \textit{exo} 1-methylindane complexes have shown that \textit{endo} deprotonation does not take place in these substrates.\(^{28}\) This has led to both anionic and cationic (vide supra) routes to manipulations of the tetrahydroisoquinoline skeleton.\(^{29}\)

Monosubstituted pyridines are stereochemically analogous to \textit{ortho} or \textit{meta} substituted benzenes since the heterocyclic nitrogen assumes the role of a second substituent and desymmetrizes the ring. Thus, deprotonation at the benzylic site of 18 followed by electrophilic substitution with allyl bromide yields 19 with good diastereoselectivity (Scheme VIII).\(^{30}\) The selectivity is envisaged to arise from a transition state involving lithium coordination with the nitrogen, along with \textit{exo} abstraction of a proton from the sterically least hindered conformer. Reaction of the anion derived from 18 with non-enolizable aldehydes provides the \textit{syn} adducts in good yield and complete diastereoselectivity.\(^{30}\)
Benzyl ethers typically undergo [1,2]-Wittig rearrangements upon lithiation at the benzylic position, but complexation of the ring suppresses this process, and the stabilized anion can be trapped with electrophiles.\(^1\) In an ortho-substituted complex, this can lead to diastereomeric products, usually with very good stereoselectivities. Thus, treatment of enantiopure 20 with tert-BuLi, followed by trapping with methyl iodide and subsequent decomplexation affords enantiomerically pure ether 22 (Scheme IX).\(^2\)

**CONCLUSION**

The use of chromium arene complexes has become a well developed and powerful methodology, and has been incorporated into a variety of total syntheses.\(^3\) The complexes are synthetically equivalent to the free arenes, yet they undergo reactions that the free arenes do not, allowing for increased versatility in arene formation. The ease of preparation, handling, and decomplexation makes the utilization of arene chromium tricarbonyls a particularly attractive methodology from an experimental perspective.

**REFERENCES**

1. Fischer, E. O.; Ötele, K. *Chem. Ber.* 1957, 90, 2532
5. Davies, S. G.; Donohoe, T. J. *Synlett* 1993, 323.
6. For a review of structural, physical and spectroscopic properties of arene chromium tricarbonyl complexes see: (a) Solladié-Cavallo, A. *Polyhedron* 1985, 4, 901. (b)


25. (a) Davies, S. G.; Donohoe, T. J.; Lister, M. A. Tetrahedron Asymmetry 1991, 2, 1085. (b) Davies, S. G.; Donohoe, T. J.; Lister, M. A. ibid. 1089.


MICROWAVE HEATING IN ORGANIC SYNTHESIS

Reported by Kevin S. Guigley September 23, 1993

INTRODUCTION
The esterification of benzoic acid with methanol under classic heating takes place in 8 hours with a 74% yield. Microwave heating produces a 76% yield within 5 minutes\(^1\). The reaction of Sodium 4-cyanophenoxide with benzyl chloride to produce 4-cyanophenyl benzyl ether classically results with a 65% yield in 12 hours. Microwave heating produces the same yield within 35 seconds\(^1\). Microwave heating provides the ability to perform chemical reactions with dramatic completion times. It has been implemented to reduce reaction times in several reactions in several different manners, such as with performing the reaction within a sealed Teflon vial\(^1\), or with a modified open reflux apparatus\(^2\). The reaction being performed neat or absorbed on alumina\(^3\). Reaction conditions held at atmospheric pressure or elevated pressures\(^4\) with proper choices of solvents for maximum heating rate and temperature\(^5\).

MICROWAVE HEATING
Microwaves produce heat by interacting with dipole moment of molecules resulting in vibrations of the molecule\(^6\). The dipole moment of the molecules attempts to align with the magnetic component of the microwave radiation. The magnetic component constantly oscillates because of the wave nature of light. The molecule attempts to oscillate with the wave producing a heating effect. With increasing dipole moment, the compound or molecule experiences greater oscillations. Water and acetic acid exhibit very high heating rates compared to hexane that exhibits little influence from microwaves\(^6\).

APPARATUS AND EQUIPMENT
Most microwave reactions are performed in standard consumer ovens. Though for precise temperature and pressure control, several modifications were reported. Performing reactions within any microwave requires special attention to the reaction vessel. Teflon screw cap bottles\(^1,7\) were used instead of glass vessels because the Teflon bottles do not heat in the microwave and can withstand the higher temperatures and pressures, up to 100 psi. These bottles can be equipped with pressure releasing caps which vent above 100 psi\(^6\). Some thick wall glass vessels were developed for temperatures higher than 400°C with precise pressure release values to prevent explosion\(^4\).

Several variations of microwave ovens perform these reactions with different emphasis as to the level of control. The rapid heating rates\(^1,8\) produce difficulties in exact temperature control of the reaction mixture. The temperature measurement itself proved troublesome
because metal and solvent based thermometers absorbs microwave energy distorting the measurement. One method involves placing samples of known melting point in sealed capillaries along with the reaction mixture\textsuperscript{7}. When a certain sample had melted, the temperature was known. Uncertainties arise with this method because microwaves can heat the sample giving inflated temperature readings.

A more efficient and expensive method requires the use of a fiber optic thermocouple. A phosphor paint applied to the reaction vessel emits light that correlates to temperature. This light is conducted out through a fiber optic cable to a detector\textsuperscript{9}. The phosphor paint has limited microwave adsorption and does not give inflated readings as the capillary method. These two methods only provide the temperature of the area in contact with the probe and do not take in account the overall temperature of the reaction mixture.

A more complex system involves the use of an infrared imaging system that produces an infrared image of the reaction vessel\textsuperscript{9}. The average temperature and observations of thermal gradients can be determined. The main point of all these methods is to minimize the heating of the temperature probe by the microwaves to obtain an accurate temperature measurement.

In a closed vial, the pressure inside the vial will be proportional to temperature. Several reaction vessels were developed with pressure transducers to measure the pressure that develops under microwave heating\textsuperscript{4}. This pressure provides an indirect measurement of temperature and cannot be used for kinetic studies. This method does provide an inexpensive method of determining heating rates of solvents by plotting the pressure with respect to time\textsuperscript{4}.

Control devices receiving input from either temperature\textsuperscript{9} or pressure\textsuperscript{4} probes can adjust the power flow of the microwave by either lowering the intensity\textsuperscript{9}, or pulsing the microwaves emitted\textsuperscript{4}. Constant temperature or pressure can then be obtained.

**APPLICATIONS**

The first interest in the use of the microwave ovens developed from the dramatic completion of reactions when compared to classical heating (Table I). These reactions proceeded with short reaction times because they were performed in sealed Teflon vials producing superheated conditions.

**Superheating Effects**

Solvents under microwave heating were found to boil 13-26\textdegree C above their conventional boiling points at atmospheric pressure\textsuperscript{2}. The results were determined with fiber optic thermocouple measurements and a microwave oven fitted with a round bottom flask leading outside the oven to an open reflux condenser. The temperature of ethanol (normal Bp 79\textdegree C) upon microwave heating peaks at 110\textdegree C where it begins to boil. The temperature lowers with start of refluxing but levels off to a constant 103\textdegree C that can be maintained for hours. Once the
microwave is terminated, the ethanol returns to its normally boiling point. Several solvents exhibit this superheating behavior, but water does not (Table II).

Table I. Examples of Microwave Enhanced Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Microwave</th>
<th>Classical</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCONH₂ → PhCOOH</td>
<td>10 min. (10) (99%)</td>
<td>1 hour (90%)</td>
</tr>
<tr>
<td>PhCOOH → PhCOOCH₃</td>
<td>5 min. (10) (76%)</td>
<td>8 hours (74%)</td>
</tr>
<tr>
<td>![Reaction diagram]</td>
<td>10 min. (7) (87%)</td>
<td>72 hours (90%)</td>
</tr>
</tbody>
</table>

Pits and scratches on the surface of the glass produce small crevices where the solvent does not occupy. The crevices provide sites for boiling. If the solvent has a low surface energy, it can occupy these crevices and prevent boiling and a higher temperature will be required for boiling to occur. If the solvent has a high surface energy, i.e., water, the wetting of the surface is limited and thus a more normal boiling point results².

Table II. Superheating Effects of Solvents²

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Normal B.p./°C</th>
<th>Microwave B.p./°C</th>
<th>Difference/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>100</td>
<td>104</td>
<td>4</td>
</tr>
<tr>
<td>Ethanol</td>
<td>79</td>
<td>103</td>
<td>24</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>66</td>
<td>81</td>
<td>15</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>40</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>81</td>
<td>107</td>
<td>26</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>132</td>
<td>150</td>
<td>18</td>
</tr>
</tbody>
</table>

Hydrosilylation

The hydrosilylation of 2-vinylpyridine with methylidichlorosilane in the presence of Copper(I) Chloride and TMEDA produced very low yield of dichloromethylsilane (1) (5%) and isolation was difficult (Scheme 1)¹⁰. The same reaction performed in the microwave produced an easier to obtain product that was isolated as the diethoxysilane derivative (2) in 75% yield¹⁰. This example depicts an uncommon reaction where the product is difficult to isolate using classical heating and relatively easy under microwave conditions.
Scheme I Hydrosilylation of 2-Vinylpyridine\textsuperscript{10}

\[
\text{MeSi(Cl}_2\text{H}} \xrightarrow{\text{CuCl, TMEDA}} \text{Py} \xrightarrow{\text{HC(OEt)}_3} \text{Py-Si(Me)Cl} \xrightarrow{\text{HC(OEt)}_2}
\]

Diels-Alder

This tandem ene/intramolecular Diels-Alder reaction (Scheme II) between 1,4-cyclohexadiene (1) and dimethylacetylene dicarboxylate (2) was discovered by Alder and Bong in 1952, but with low yield (Table III). Microwave heating produces a 82% yield in 6 minutes\textsuperscript{11}.

Scheme II The Alder-Bong Reaction\textsuperscript{12}

\[
\text{MeO}_2\text{C}==\text{CO}_2\text{Me}} \xrightarrow{\text{MeO}_2\text{C}==\text{CO}_2\text{Me}} \text{CO}_2\text{Me} \xrightarrow{\text{CO}_2\text{Me}} \text{CO}_2\text{Me}
\]

Table III. Comparison and Optimization of the Alder-Bong Reaction\textsuperscript{12}

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ene:Enophile</th>
<th>Time</th>
<th>Temp °C</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Literature</td>
<td>1.1 : 1</td>
<td>20 h</td>
<td>185</td>
<td>40 %</td>
</tr>
<tr>
<td>2. Microwave</td>
<td>15 : 1</td>
<td>6 min.</td>
<td>325 &lt; 361</td>
<td>82 %</td>
</tr>
<tr>
<td>3. Control</td>
<td>15 : 1</td>
<td>20 h</td>
<td>220</td>
<td>82 %</td>
</tr>
<tr>
<td>4. Control</td>
<td>15 : 1</td>
<td>15 min.</td>
<td>360</td>
<td>51 %</td>
</tr>
</tbody>
</table>

The results from this experiment and others\textsuperscript{1,7,11-13} suggested that reactions performed in the microwave are proceeding at higher rates and possibly being activated by the microwaves themselves.

The determination of the existence microwave activation of compounds provided the basis of the next example. The kinetics of the Diels-Alder reaction between Anthracene and Diethyl Maleate (Scheme III) was determined to see if the presence of the polar dieneophile would accelerate the reaction.

Scheme III Diels-Alder Reaction between Anthracene and Diethyl Maleate\textsuperscript{14,15}

\[
\text{Anthracene} + \text{CO}_2\text{Et} \xrightarrow{\text{CO}_2\text{Et}} \text{Anthracene-CO}_2\text{Et}
\]


Berlan reported that Scheme III reached 90% completion in 1.1 hours under microwave irradiation and 4 hours classically with both being heated at a constant 95°C \(^{14}\). The results suggest this reaction under microwave heating has a higher rate constant than classical heating. It was suggested that microwaves possible interact with the polar dieneophile and weaken the chemical bonds or an unknown "microwave effect" lowers the energy of activation. It should be noted Berlan's microwave was modified to vary the microwave output to maintain constant temperature using a fiber optic thermocouple.

Raner performed the same reaction with similar equipment except with the addition of a magnetic stirrer \(^{15}\). For each temperature, the rate constants for microwave and classical heating were the same within reasonable error (Table IV) suggesting there is no rate difference between the two heating methods. The differences between these two reports can be attributed to production of thermal gradients within the reaction mixture. Microwave ovens heat from the inside out resulting in the outside layers of solvent being at lower temperature than the inside. Only the outside layers transfer heat to the reaction container where the temperature measurement is made. The reaction proceeds at a higher temperature than measured resulting in the assumption that the kinetics were faster.

**Table IV. Second-Ordered Rate Constants for the Diels-Alder Reaction between Anthracene and Diethyl Maleate\(^{15}\)**

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>Microwave (k) (M^{-1}s^{-1})</th>
<th>Oil Bath (M^{-1}s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>(1.0 \times 10^{-5})</td>
<td>(9.6 \times 10^{-6})</td>
</tr>
<tr>
<td>150</td>
<td>(1.5 \times 10^{-5})</td>
<td>(1.3 \times 10^{-5})</td>
</tr>
<tr>
<td>160</td>
<td>(3.5 \times 10^{-5})</td>
<td>(2.9 \times 10^{-5})</td>
</tr>
<tr>
<td>170</td>
<td>(4.7 \times 10^{-5})</td>
<td>(4.4 \times 10^{-5})</td>
</tr>
</tbody>
</table>

Early reports indicated that microwaves produce faster rate kinetics \(^{11-13}\). Each of these reports contains one common error. The reaction mixture was not stirred producing thermal gradients. The microwave effect or the interaction of the microwave with polar molecules to produce bond vibrations or rotations is a common misconception. The frequencies at which polar molecules undergo rotational transitions are 12.2 GHz for OCS, and 51 GHz for CH3F \(^{14}\). Commercial microwave ovens emitted radiation at 2.54 GHz lower than first absorption of OCS. The microwave radiation vibrates the entire molecule increasing its internal energy and distributing equally into the rotational, vibrational, and translational energy levels \(^{14}\). An analogy of microwave heating is to place a model of a molecule upon a shaking table. The model will jump and change position but the table rattling does not produce a specific rotation or vibration.
Product Composition In a Diels-Alder Reaction

Microwave heating produces high temperatures and pressures that lead Gedye to study this Diels-Alder reaction between cyclopentadiene and methyl acrylate (Scheme IV)\(^8\). Gedye chose this reaction in particularly because the endo product is favored at lower temperatures under classical heating.

**Scheme IV** Diels-Alder Reaction between Cyclopentadiene and Methyl Acrylate\(^8\)

\[
\begin{align*}
\text{CO}_2\text{CH}_3 + \text{C}_5\text{H}_5\text{N} &\rightarrow \text{CO}_2\text{CH}_3 \\
\text{HOCH}_3 &
\end{align*}
\]

\(\text{endo}\) \(\text{exo}\)

**Table V.** Composition of the Reaction between Cyclopentadiene and Methyl Acrylate\(^8\)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>% endo classical</th>
<th>% endo microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>89.8</td>
<td>---</td>
</tr>
<tr>
<td>21</td>
<td>87.5</td>
<td>---</td>
</tr>
<tr>
<td>56</td>
<td>84.9</td>
<td>---</td>
</tr>
<tr>
<td>110</td>
<td>---</td>
<td>79.0</td>
</tr>
</tbody>
</table>

The reaction produced a lower percentage of the endo product (Table V), but not lower than expected for that temperature. The slightly lower endo composition confirms that reactions under microwave only proceed at higher temperatures and not with faster kinetics.

**Esterification**

Previous reports indicate that the formation and hydrolysis of esters proceed with faster kinetics under microwave radiation\(^13\). Raner studied the esterification of 2,4,6-trimethylbenzoic acid with 2-propanol for this reaction can be represented as this equilibrium (Scheme V)\(^16\).

**Scheme V** Equilibrium Esterification of Carboxylic Acid with iso-Propanol\(^16\)

\[
\begin{align*}
\text{ArCO}_2\text{H} &\rightarrow \text{ArCO}^+\text{OH}_2 \\
\text{fast} &\rightarrow \text{slow} \\
\text{fast} &\rightarrow \text{slow} \\
\text{fast} &\rightarrow \text{fast} \\
\text{fast} &\rightarrow \text{slow} \\
\end{align*}
\]

Raner performed this reaction by classical and microwave methods\(^16\). The reaction vessel used in the microwave segment did not provide a constant heating rate but a non-uniform heating curve. A computer program, LARKIN, was used to model the reaction with this heating curve. The Arrhenius parameters determined from the classical method were used in the
LARKIN calculated the concentration of the ester for the microwave reaction with respect to time. The experimental values coincided with the calculated values indicating that the concentration of the ester was a function of the temperature and not the form of heating\textsuperscript{16}.

<table>
<thead>
<tr>
<th>Table VI. Predicted and Actual Final Ester Concentration\textsuperscript{16}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reaction</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>

**Claisen Rearrangement**

The synthesis of bicyclic lactones from cyclic allylic alcohols could be effectively made with minimal side products by microwave heating\textsuperscript{17}. Jones attempted the Claisen rearrangement (Scheme VI) between 2-cyclohepten-1-ol and triethyl orthoacetate (TEOA) to produce the ester (1). Difficulties in separating the ester (1) from the acetate side product, (2), inspired Jones for an alternative approach. The implementation of microwave heating produces a dramatic increase in yield of the ester (1) (Table VI) and complete elimination of the acetate side product. The continued manipulation of the ester (1) by selenolactonization followed by oxidative elimination produces the bicyclic lactone.

**Scheme VI Synthesis of Bicyclic lactones\textsuperscript{17}**

![Scheme VI Synthesis of Bicyclic lactones](image)

(i) LiOH / THF (ii) PhSeCl / Et\textsubscript{3}N / CH\textsubscript{2}Cl\textsubscript{2} (iii) H\textsubscript{2}O\textsubscript{2} / THF

<table>
<thead>
<tr>
<th>Table VII. Claisen Rearrangement Reaction of 2-Cyclohepten-1-ol\textsuperscript{17}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heating Method</strong></td>
</tr>
<tr>
<td>Classical</td>
</tr>
<tr>
<td>Microwave</td>
</tr>
</tbody>
</table>
CONCLUSION

Reactions under microwave irradiation perform similarly to reactions under classical methods. These results are not spectacular but refute claims of reactions accelerated from other means besides temperature. Future reports that conclude the kinetics of microwave reactions are faster should be examined for errors in their apparatus. Though early papers were incorrect with the rate kinetics, they agree that reactions heated by microwaves have decreased reaction times and can be useful as an expedient approach to organic synthesis.

REFERENCES

STRUCTURE, DESIGN, AND APPLICATION
OF TRIPLE HELICAL DNA

Reported by Paul A. Thiessen
September 30, 1993

INTRODUCTION

Within the past five years, triple helical DNA, also known as triple stranded or triplex DNA, has emerged as a tool for highly sequence-selective recognition and cleavage of duplex DNA that is thousands to millions of bases long. Efforts to characterize the structure and stability of the triplex, and to explore the many factors that affect its stability will be described, followed by strategies for generalizing triplex formation to any duplex sequence, finally leading up to recent examples of how the triple helix can be applied to cleavage of DNA strands as long as a human genome.

STRUCTURE

Triple helical DNA is not a new discovery. As early as 1957, a paper was published in which two RNA oligoribonucleotides poly-A (adenylic acid) and poly-U (uridylic acid) formed a 1:2 complex.1a The authors of the paper postulated that a strand of poly-U bound into the major groove of the right-handed double helix of poly-A•poly-U. Very little further research was done on the structure until 30 years later when the search for chemical cleavage agents gave the triplex a new role.1b With the reemergence of the triple helix have come experiments to determine its structure by methods such as NMR, IR, UV, CD, and melting temperature studies. A high-resolution X-ray structure of a triplex has yet to be published.

In double helical DNA, the bases form complementary hydrogen bonding pairs between the purine adenosine (A) the pyrimidine thymidine (T), and between the purine guanosine (G) and the pyrimidine cytidine (C), in a pattern first described by Watson and Crick. The bases are connected by phosphodiesters at the 3' and 5' carbons of the ribose moiety, and the two strands come together in an antiparallel orientation. It is of interest to understand the hydrogen bonding and other structural features of the triple helix, especially as they compare to structure of the duplex.

There are two main categories of triplexes: pyrimidine•purine-pyrimidine and purine•purine-pyrimidine helices. The bullet symbol denotes a third base binding to one base of a Watson-Crick pair. The RNA poly-U•poly-A•poly-U triplex belongs to the pyr•pur-pyr category, as do the deoxyribonucleotide triplets shown in Figure 1, with T and protonated C (C+) bound to AT and GC Watson-Crick pairs, respectively.
NMR studies on pyr•pur-pyr triplexes\textsuperscript{2} confirmed the T•AT and C\textsuperscript{+•}GC base matching scheme. It was shown that in both a triplex formed from three separate strands,\textsuperscript{2a-b} and in a triplex formed from one strand that folds onto itself,\textsuperscript{2c} the third Hoogsteen-bound strand runs parallel to the purine Watson-Crick strand. The stability of binding is dependent on cation (usually Mg\textsuperscript{2+}, Na\textsuperscript{+}, or protonated spermine) concentration, temperature, and pH; the pH dependence is due primarily to the fact that the cytosine must be protonated to hydrogen bond correctly. IR\textsuperscript{3a-b} and NMR\textsuperscript{3c} analyses of pyr•pur-pyr helices showed that the triplex has B-form geometry and C2'-endo sugar conformation.

NMR studies of pur•pur-pyr helices\textsuperscript{4a,b} showed the existence of G•GC and A•AT triplets depicted in Figure 2. It was also reported that a T•AT tripllet in the center of an otherwise pur•pur-pyr sequence is favorable.\textsuperscript{4c} The third-strand bases are thought to be in the anti conformation,\textsuperscript{4d} wherein the purine moiety points away from the bulk of the sugar. The backbone has the C2'-endo sugar conformation. In the pur•pur-pyr structure, the third strand runs antiparallel to the purine Watson-Crick strand, and the stability of the helix is dependent on cation concentration and temperature. However, there is less dependence on pH compared to the pur•pur-pyr helix because no protonated bases are involved in the hydrogen bonding scheme.

To date, such detailed structural studies were only carried out on triplexes in which the third strand binds to a homopurine strand of the duplex, because no combination of natural bases has sufficient binding strength to form either a pur•pyr-pur or pyr•pyr-pur triplex. The closest
examples are NMR characterizations of a favorable G•TA triplet in the center of an otherwise pyr•pur-pyr triplet. However, the exact orientation and hydrogen bonding scheme of this triplet is still unknown.

TRIPLE HELIX STABILITY

To design sequences and conditions under which duplex recognition and binding can occur, it is important to understand the structure and stability of the triple helix, as well as the factors that affect the complex between a duplex and a third strand. In an elegant set of experiments, Dervan, et al. characterized the thermodynamic behavior of the 15 base pair (bp) pyrimidine strand 5'-TTTTTCTCTCTCTCT-3' (y15) bound to the purine strand of the 21-bp duplex 5'-GCTAAAAAGAGAGAGATCG-3' • 3'-CGATTTTTCTCTCTCTCTAGC-5' (u21•y21). UV mixing curves confirmed the 1:1:1 complex y15•u21•y21. UV absorbance vs. temperature profiles showed two transitions: a low temperature transition from triplex to duplex and single strand, and a higher temperature transition identified as duplex dissociation. Thus, the triplex was found to be qualitatively less stable than the "host" duplex. Detailed calorimetric experiments quantitate this observation; the results are shown in Table I.

The data in Table I indicate that the binding enthalpy for the triplex strand is lower than that for the duplex by an average of about 4.3 kcal/mol/base pair. An important point is that the relatively low stability of the triplex may be advantageous for selective binding: if association were too strong, single unfavorable base-pair "mismatches" would not prevent triplex formation; with weaker binding, single unfavorable interactions may be enough to destabilize the entire complex.

An experiment to quantitate the effect of a single mismatch showed that a C•AT or T•GC mismatch in an otherwise T•AT and C•GC 15-bp triplex reduces free energy of complexation by 2.5-3.0 kcal/mol, but shortening of the third strand by 4 base pairs lowers the free energy by only 1.1 kcal/mol. It was found for a similar sequence that if the pH was raised from 5.8 to 7.6, the triplex was destabilized by about 1.4 kcal/mol; when 5-methyl cytosine (m5C) is substituted for C (a strategy used to lessen the pH dependence), the binding was little improved.

The instability of base mismatches and their affect on the local structure of an intramolecular triplex was assayed qualitatively by monitoring which thymidine bases in the triplex sequence were susceptible to modification by permanganate, a reagent that reacts only with exposed thymidines. It was found that pH and base mismatches affect the stability of the structure. The strands are tight at pH ≤ 6, because all thymidines in the triple helical region remain unmodified. The same thymidines were modifiable at pH ≥ 6. However, even at pH ≤ 5, thymidines adjacent to a T•GC or C•AT mismatch were subject to reaction. These experiments
Table I. Thermodynamic Parameters for Dissociation of the y15•u21-y21 Triplex.

<table>
<thead>
<tr>
<th>Transition</th>
<th>Tm, °C</th>
<th>ΔH*, kcal/mol</th>
<th>ΔS*, cal/mol-K</th>
<th>ΔG*, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triplex→Duplex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>y15•u21•y21 → y15 + u21•y21</td>
<td>30.0</td>
<td>30.4 ± 2</td>
<td>97.6 ± 7</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>Duplex→Single</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>y15 + u21•y21 → y15 + u21 + y21</td>
<td>65.7</td>
<td>128 ± 8</td>
<td>370 ± 24</td>
<td>17.2 ± 1.6</td>
</tr>
<tr>
<td>Duplex→Single</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>u21•y21 → u21 + y21</td>
<td>64.7</td>
<td>133 ± 6</td>
<td>388 ± 15</td>
<td>17.2 ± 1.2</td>
</tr>
</tbody>
</table>

give evidence of local structural disruptions due to base pair mismatches and higher pH, which could account for the observed loss of binding enthalpy.

The triplex stability was also shown to depend on sequence.10 Within a pyr*pur-pyr stretch, it was found that: (1) T•AT is insensitive to triplets on either side; (2) triplexes containing C•GC triplets become less stable as the number of adjacent C•GC increased, probably due to charge repulsion; and (3) G•TA is most stable with T•AT on both sides, but is considerably less stable with a C•GC triplet adjacent on the 5' side (relative to the purine strand).

The above experiments show that there are many factors that need to be understood before rational design of stable helix sites can be achieved. Unfortunately, each of these experiments targets one specific factor; it has yet to be shown how the mutual interaction of all these elements of stability can be assimilated into a general scheme for constructing a triple helix around any given duplex sequence.

NONNATURAL BASES

To develop a general method of triplex construction, it is necessary to find bases that will bind strongly and selectively to all four bases in the duplex. It was found that a (purine)_n(pyrimidine)_m strand can recognize alternate strands of duplex DNA, with the same base pairings described above.11a The third strand always binds to the purine strand, but in a mixed tract on the duplex, the third strand "skips" between strands to continue its association with the purines. This type of structure was used to cause nonenzymatic ligation of the DNA in the presence of ligating agent N-cyanoimidazole by bringing two DNA ends, recognized by the respective pur*pur-pyr and pyr*pur-pyr motifs, into proximity.11b Thus, a stretch of
homopurines followed by homopyrimidines can be targeted for helix construction, but this technique does not extend recognition to a mixed sequence of pyrimidines and purines.

In the search for pyrimidine recognition, the natural base triplets were exhaustively tested.\textsuperscript{4c,12} The data in Table II show the stability of a series of pyr\textsuperscript{•}pur-pyr helixes that contain a central X\textsuperscript{•}YZ triplet, where X\textsuperscript{•}YZ is each of the 16 possible triplets.\textsuperscript{12a} The T\textsuperscript{•}AT and C\textsuperscript{+}•GC triplets are strong, though G\textsuperscript{•}TA is much weaker. Unfortunately, A does not recognize CG. Triplets with CG are very weak, and the pair is recognized by a third base (T or C) already being used to target a different base pair (AT or GC). Thus, within the natural bases, the desired scheme for strong and selective recognition of all four pairs is incomplete, because there is no permutation of triplets that allows each Watson-Crick pair to be recognized by a different third base.

Table II. Melting Temperatures (T\textsubscript{m}, °C) of a 13-bp Oligonucleotide Complexed to a 31-bp Duplex with X•YZ in the Center of the Sequence.\textsuperscript{12a} (Best match for YZ shown in bold type.)

<table>
<thead>
<tr>
<th>Y Z</th>
<th>X</th>
<th>AT</th>
<th>GC</th>
<th>TA</th>
<th>CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>37</td>
<td>25</td>
<td>15.5</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>16.5</td>
<td>38</td>
<td>11</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>21</td>
<td>29</td>
<td>26</td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>23.5</td>
<td>26</td>
<td>17.5</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

To find triplets with favorable and specific binding to all duplex base pairs, the search was extended to nonnatural bases.\textsuperscript{10,13} The bases examined to date are shown in Figure 3.

The abasic site Ø, wherein the heterocycle is simply replaced by a hydrogen, allows moderate stability when paired with CG or TA as one different triplet in a homo-T•AT sequence.\textsuperscript{13a} The abasic site binds CG as strongly as any natural base, but Ø•TA is worse than G•TA, and Ø•AT and Ø•GC completely destroy the triplex. Therefore, Ø is not likely to be useful as a natural base substitute, but it does give evidence that the base stacking, disrupted when one "step" of the stack is missing, is as important as hydrogen bonding.\textsuperscript{13a}

Another nonnatural base D\textsubscript{3} was found to favorably recognize CG and TA pairs in an otherwise pyr•pur-pyr sequence,\textsuperscript{10,13b} although only when the Watson-Crick pairs are flanked on the 3' side (relative to the purine strand) by AT and on the 5' side by either AT or GC. Because of this flanking sequence effect, as well as the lack of an apparent hydrogen bonding scheme for D\textsubscript{3}, it was postulated that D\textsubscript{3} recognizes local structural features beyond a single base pair.\textsuperscript{10} This new base extends recognition to all four natural base pairs within the pyr•pur-pyr motif, but unfortunately does not distinguish between CG and TA, and is subject to sequence limitations.
Figure 3. Nonnatural bases studied for improved matching of all four Watson-Crick base pairs.\textsuperscript{10,13} (R\textsubscript{D}=deoxyribose)

Because the juxtaposition of multiple positively charged C\textsuperscript{+}-GC triplets is unfavorable due to Coulombic repulsion, the base P1 was designed as a neutral recognizer of GC pairs.\textsuperscript{13c} This new base is as specific for GC as C\textsuperscript{+}, but allows stable triplex formation at a sequence containing 6 contiguous GC base pairs, which would be impossible with C\textsuperscript{+}. Also, since protonation is unnecessary, P1 is applicable over a broader pH range. Thus, P1 is a good replacement for C\textsuperscript{+} and extends the generality of recognition within the pyr-pur-pyr structure.

In the pur-pur-pyr motif, 2'-deoxynebularine (N) was shown to recognize CG and AT pairs.\textsuperscript{13d} The N-CG triplet is stronger than N-AT, but both are weaker than the previously known G-GC, A-AT, and T-AT triplets. With N-CG, three of four base pairs in a pur-pur-pyr sequence can be recognized, but it is unknown how many pyr-pur pairs can exist in a pur-pyr stretch without disrupting the pur-pur-pyr structure.\textsuperscript{13d}

The search for new nonnatural bases will undoubtedly continue until triplets are available that will strongly and specifically recognize all four base pairs in both pyr-pur-pyr and pur-pur-pyr structures. Once that goal is accomplished, it is likely that a triplex could be constructed around any duplex sequence.

APPLICATIONS TO DUPLEX DNA CLEAVAGE

Early experiments on the application of triplex structure design to cleavage of duplex DNA were reported. For most of the binding studies described above, an ETDA-Fe moiety was attached to the end of the triplex strand. Under oxidizing conditions, a hydroxyl radical is produced at the Fe site, which then cleaves the phosphate backbone. Unfortunately, the hydroxyl radical is nonspecific and diffusible, so specific cleavage between two bases is impossible. Also, yields by this process are low, only 5-25\% depending on DNA length. Different strategies are needed to cleave more efficiently and specifically.

One cleavage technique reported involves double-strand alkylation.\textsuperscript{14} In this technique, two triplex strands bind to two alternate strands of the duplex, but offset from each other (5'-end to 5'-end) so the triplex regions are separated by a few base pairs. An electrophilic (N-bromoacetyl) modified base is attached to the 5'-ends of the triplex strands; the electrophile specifically alkylates a guanosine two bases from the 5'-end of the third strand to which it is
attached. Thus, two guanosines near each other and between the triplex regions become covalently attached to the triplex strands. When warmed with base, the triplex dissociates and removes the modified guanosine from the backbone, cleaving both strands of the DNA and creating controllable sharp ends that can then be ligated to other complementary DNA fragments. In this way, a yeast chromosome of 340 000 base pairs was cleaved at only a single site in 85-90% yield.

A second, enzymatically assisted method was described in another publication. First, a sequence must be found that has a restriction enzyme site overlapped by a triplex oligonucleotide binding site. The paper described a method to screen for such sites. The duplex is equilibrated with the triplex strand, and then the complex is subjected to exhaustive enzymatic methylation by EcoRI methylase. The site covered by the triplex is protected from methylation. The triplex is disrupted and the third strand removed, then the duplex is cleaved by the restriction enzyme that can only react at the previously triplex-protected, unmethylated site. Using this technique, a yeast chromosome of 340 000 bp has been cleaved at one site in about 94% yield, and human chromosome-4 cleaved in 80% yield at one site on the 10 gigabase molecule.

CONCLUSION

Although not a new discovery, triple helical DNA is structurally interesting in the variety of structures it can adopt: pur-pur-pyr, pur-pur-pyr, alternate strand, or even a T-shaped structure in which free ends from two triplex third strands come together in a duplex perpendicular to the triplex sites. In vitro biochemical effects of triple helices have also been found such as the ability of a triplex to repress transcription, though probably by alteration of the flexibility of the DNA near the affected region, rather than site-specific inhibition. For now, though, the emphasis on triplex DNA research is on its application to highly specific gigabase DNA cleavage. As described above, a complete understanding of the factors that affect triplex formation is still missing, as are (nonnatural) bases that can recognize any duplex base pair. It is in this area that research will probably focus in the near future, moving towards detailed design criteria for triplex formation at any given sequence. But already, astonishing examples of genome cleavage have appeared that will provide motivation for scientists to continue developing strategies for application of triple helical DNA techniques.

REFERENCES


RECENT ADVANCES IN ASYMMETRIC PHASE TRANSFER CATALYSIS

Reported by Julie A. Dixon

INTRODUCTION

Phase transfer catalysis (PTC) was independently developed in the mid 1960's by the research groups of M. Makosza,1 A. Brändström,2 and C. M. Starks3. This biphasic reaction technique has found notable utility in alkylations, Michael type additions, epoxidations, as well as many other reactions.4 PTC offers several advantages over classical catalytic reaction methods such as the use of: inexpensive, non-anhydrous solvents; easier reaction workups; milder reaction conditions, lower reaction temperatures, and applicability to industrial scale.4,5,6 In addition to the advantages described above, PTC has been applied to the synthesis of optically active compounds using chiral catalysts. This abstract will provide a brief background on the general aspects of PTC and highlight the utilization of chiral phase transfer catalysts in organic synthesis.

GENERAL PRINCIPLES AND MECHANISM

Phase transfer catalysis allows a chemical reaction to take place between two species initially present in two different phases.5 The most common types of PTC are liquid-liquid PTC and solid-liquid PTC. Liquid-liquid PTC involves ionic reagents dissolved in an aqueous phase and a substrate dissolved in an organic phase. In solid-liquid PTC, the ionic reagent exists as a solid which is suspended in the substrate containing organic phase. Central to the success of PTC, is the choice of the catalyst. A wide variety of phase transfer catalysts have been employed, the most commonly used catalysts include: quaternary ammonium and phosphonium salts, crown ethers, cryptates, and open chain polyethers.4 For liquid-liquid PTC, quaternary ammonium salts are used most commonly because they are efficient and inexpensive. Starks proposed a general mechanism for a S_N2 displacement reaction between a water soluble nucleophile (M^+X^-) and an organic soluble electrophile (RY) using quaternary ammonium and phosphonium ions (Scheme I).3 The phase transfer catalyst (Q^+X^-) possess enough ionic character to be freely soluble in the aqueous phase; however, hydrophobic alkyl chains on the organic cation allow Q^+X^- to exist in the organic phase as a tight ion pair ([Q^+X^-]). Once [Q^+X^-] is in the organic phase, it undergoes a fast displacement with the electrophile (RY) to afford the desired product (RX). The new tight ion pair

Scheme I

<table>
<thead>
<tr>
<th>Organic phase</th>
<th>RX + [Q^+Y^-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interface</td>
<td>[Q^+X^-] + RY</td>
</tr>
<tr>
<td>Aquous phase</td>
<td>M^+X^- + Q^+Y^-</td>
</tr>
</tbody>
</table>

Copyright © 1993 by Julie A. Dixon
([IQ+Y-]), which is formed in the displacement reaction, returns to the aqueous layer so that it can pick up a new counter ion (X-) and continue the catalytic cycle.

When PTC is run under strongly basic conditions (PTC/OH) as in aqueous potassium or sodium hydroxide, an alternative mechanism as well as the extraction mechanism, maybe in operation. This alternative mechanism applies to reactions in which the anionic nucleophile (R-) is generated in situ by deprotonation. Makosza proposes the interfacial mechanism which is depicted in Scheme II. The following sequence of events take place: Step 1, a portion of the organic substrate (RH) present in the organic layer is near the interface and is deprotonated by the hydroxide ion in the aqueous phase; Step 2, the anion (R-) remains at the interface associated with M+ until the catalyst cation (Q+) is able to transport the organic anion into the organic phase as the tight ion pair [Q+R-], meanwhile the previous counterion X- of Q+ is released into the aqueous phase; Step 3, [Q+R-] reacts with the electrophile R'Y to form the product R-R' and a new ion pair [Q+Y-] is produced, which can continue the catalytic cycle.

**Scheme II**

![Scheme II Diagram](image)

In liquid-liquid PTC, hydration of the anion often occurs due to the co-extraction of water. This may suppress the desired reaction or promote side reactions. To solve this problem, solid-liquid PTC is employed (Scheme III). Crown ethers appear to be the catalyst of choice for this method. Because of its structure, the crown ether can approach the crystalline lattice of the solid base very closely. Once at the face of the crystalline lattice, the crown ether forms a complex with the cation with little cation displacement and the anion stays associated to the complex. Quaternary ammonium salts are more sterically encumbered around the cationic center so that interaction with the anion at the surface of the crystal is less favored.

**Scheme III**

![Scheme III Diagram](image)

**ASYMMETRIC PHASE TRANSFER CATALYSIS**

Phase transfer catalysis offers a simple one pot procedure for the synthesis of chiral non-racemic compounds through the use of chiral catalysts. Quaternary ammonium salts and crown ethers appear to be the most efficient chiral catalysts for asymmetric reactions. It has been found
for chiral quaternary ammonium salts, that an auxiliary polar group enhances anion-cation interaction and promotes asymmetric induction. A few of the more successful chiral quaternary ammonium catalysts derived from ephedrine and the cinchona alkaloids are shown below.

Asymmetric Alkylations

In 1975, Fiaud reported the first asymmetric phase transfer reaction which involved the alkylation of a β-keto ester with allyl bromide in the presence of (-) N-benzyl N-methylephedrine as the chiral PTC. However, the results were found to be erroneous due to the breakdown of the chiral catalyst into an optically active epoxide, whose large specific rotation which was mistaken for the chiral product. Asymmetric alkylations using chiral quaternary ammonium salts as phase transfer catalysts were only marginally successful until 1984. In that year, Dolling and coworkers demonstrated that methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone could be achieved in up to 94% enantiomeric excess in a 95% yield with the use of N-(p-(trifluoromethyl)benzyl) cinchoninium bromide (p-CF$_3$BCNB) as the chiral phase transfer catalyst (Scheme IV).

Scheme IV

Quaternary ammonium salts derived from cinchona alkaloids have also been employed as chiral catalysts in the synthesis of optically active α-amino acids. In 1989, O'Donnell and coworkers reported alkylation of a prochiral protected glycine derivative with allyl bromide in the presence of N-benzylcinchoninium chloride (BCNCI), resulting in 66% ee and 75% yield (Table I). Alternatively, the use of N-benzylcinchonidium chloride (BCDNCI) afforded the R enantiomer of the alkylated product in 64% ee and 85% yield. A variety of alkyl halides can be used, including allylic, benzylic, methyl, and primary halides. The ester moiety can also be varied. Changing the ester group and/or the alkylation agent has a dramatic effect on the enantiomeric
excess and chemical yields. The optically pure amino esters (>99% ee) could be obtained by recrystallization and subsequent deprotection.

**Table I.** Asymmetric Alkylation of N-Protected 4-Butyl Glycinate with Benzyl Bromide.

<table>
<thead>
<tr>
<th>catalyst</th>
<th>major enantiomer</th>
<th>% ee</th>
<th>chemical yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCNC1</td>
<td>R</td>
<td>66</td>
<td>75</td>
</tr>
<tr>
<td>BCDNC1</td>
<td>S</td>
<td>64</td>
<td>85</td>
</tr>
</tbody>
</table>

The utility of chiral phase transfer catalysis was further demonstrated in the synthesis of optically active \(\alpha\)-methyl amino acid derivatives (Table II).

Schiff's base derivatives of aromatic aldehydes and alanine 4-butyl ester were alkylated in 78-87% yield and 16- 50% ee under solid-liquid phase transfer conditions using BCNC1 as the chiral catalyst. Various amine protecting groups and alkylating agents were investigated to explore the effect of these variables on asymmetric induction. Under the basic conditions, the 4-chlorobenzylidene protecting group gave the best enantiomeric excess (46% ee). Unfortunately, there appears to be no general trend in the extent of asymmetric induction related to the electronic nature of the amine protecting group. A variety of activated alkyl halides can be used as the electrophile in the alkylation reaction.

**Table II.** Dependence of Aryl Group and Alkylating Agent.

<table>
<thead>
<tr>
<th>variable</th>
<th>chemical yield</th>
<th>% ee (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A imine group(^a)</td>
<td>4-ClC(_6)H(_4)-</td>
<td>78%</td>
</tr>
<tr>
<td>aryld</td>
<td>Ph-</td>
<td>78%</td>
</tr>
<tr>
<td>4-MeOC(_6)H(_4)-</td>
<td>80%</td>
<td>42%</td>
</tr>
<tr>
<td>1-Naphthyl-</td>
<td>82%</td>
<td>16%</td>
</tr>
<tr>
<td>B alkylating agent(^b) (R)</td>
<td>4-FC(_6)H(_4)CH(_2)Br</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>2-NapthylCH(_2)Br</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>PhCH(_2)Br</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>CH(_2)=CHCH(_2)Br</td>
<td>78%</td>
</tr>
</tbody>
</table>

\(\text{\(^a\) alkylating agent, 4-ClC\(_6\)H\(_4\)CH\(_2\)Br; \text{\(^b\) substrate, 4-ClC\(_6\)H\(_4\)-}}\)
However, the attempt to use a more hindered alkyl halide ($i$-BuBr) resulted in incomplete reactions. As with previous examples, the use of $N$-benzylcinchonidinium chloride allows access to the opposite product enantiomer with similar enantiomeric excess.

Additional examples of asymmetric alkylations have been reported for several different substrates. Various $\alpha$-aryl substituted ketones, esters, and lactones, along with oxindoles, have been reported to undergo asymmetric alkylation with cinchona alkaloids as the chiral phase transfer catalyst with comparable enantiomeric excesses. Also the synthesis of $\alpha$-substituted amino acids has been reported using chiral nickel(II) Schiff base complexes of glycine and alanine in 41-58% ee and in 69-83% yield.

**Asymmetric Michael Addition**

In 1986, Conn and coworkers reported an asymmetric Michael addition of 6,7-dichloro-5-methoxy-2-propylindanone to methyl vinyl ketone (MVK) using cinchona alkaloids as chiral phase transfer catalysts (Table III). When the reaction was carried out with 5.6 mol % of $N$-($p$-trifluoromethylbenzyl)cinchoninium bromide ($p$-CF$_3$BCNB), a 95% yield and 80% ee was obtained of the expected $S$ adduct. The best case for the $R$ adduct resulted in only a 52% ee using a slight modification of the $N$-($p$-trifluoromethylbenzyl) cinchonidinium bromide ($p$-CF$_3$BCDNB) catalyst.

**Table III. Asymmetric 1,4 Addition to Methy Vinyl Ketone.**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Major Enantiomer</th>
<th>Chemical Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$-CF$_3$BCNB</td>
<td>$S$</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>$p$-CF$_3$BCDNB</td>
<td>$R$</td>
<td>99</td>
<td>78</td>
</tr>
</tbody>
</table>

Asymmetric Michael reactions have been reported using $N$-methyl $N$-benzylephedrine as the phase transfer catalyst in solid-liquid PTC. Loupy and coworkers noted that higher enantioselectivities were obtained when the reaction was run without solvent, which they attribute to greater rigidification of the system. In the absence of solvent, reactive species are likely to be highly aggregated and thus demand more organization of the system, leading to increased selectivity. A survey of several different catalysts was performed for solid-liquid PTC. Ephedrine quaternary ammonium salts were found to give better selectivities than the quaternary ammonium salts derived from the cinchona alkaloids. Also, the results of a Hammett study
revealed that greater selectivity can be obtained if electron-donating groups are placed on the N-benzyl moiety of the ephedrine catalyst. The best catalyst for the Michael addition of diethylacetamidomalonate to chalcone was found to be N-methylephedrinium bromide 1 bearing an (S)-binaphthyl group (Scheme V). This reaction gave the 1,4-addition product in a 51% yield and 82% enantiomeric excess.

Scheme V

Chiral crown ethers have also been used as asymmetric phase transfer catalysts in Michael additions. In 1981, Cram reported Michael additions of a β-ketoester to methyl vinyl ketone, and two phenylacetic esters to methyl acrylate with enantiomeric excess of 60-99%. He employed crown ethers bearing one or two binaphthyl moieties (Figure 1). These crown ethers complex with potassium tert-butoxide, allowing the base to be transported into the organic phase so that it can deprotonate the esters.

Figure 1 Chiral Crown Ethers.

Yamamoto demonstrated that chiral crown ether potassium tert-butoxide complexes can be used to catalyze Michael additions of methyl phenylthioacetate to cyclopentenone in 41% ee (Scheme VI). The chiral crown ether 2, was synthesized in 3 steps from anthracene and dimethyl fumarate.

Scheme VI
Dehmlow has surveyed a series of chiral crown ethers for their ability to act as chiral phase transfer catalysts in Michael additions. Through this survey, Dehmlow makes the following observations on the effect of asymmetric induction: crown ethers with non-equivalent upper and lower faces are not useful, crowns with additional stereogenic centers and hydroxyl groups in side chains are not advantageous, and the possibility of reversal of product stereochemistry when exchanging potassium for sodium ions and increasing the number of side chains on the crown ether.

Other Asymmetric Reactions

Many other types of reactions have been carried out under asymmetric phase transfer conditions with limited success. One reaction that has achieved moderate success is epoxidation. This material was addressed in an earlier seminar on chiral phase transfer catalysts and will not be discussed. Reactions that have been recently carried out under asymmetric phase transfer conditions involving chiral catalysts derived from the cinchona alkaloids are discussed below. Miller and coworkers attempted to synthesize β-hydroxy-α-amino acids via an aldol condensation. Imine protected glycine esters were reacted with various aldehydes under basic PTC conditions with BCNC as the chiral catalyst to yield aldol products in 14-56% diastereomeric excess and 46-78% yield. The highest enantiomeric excess reported for any diastereomer was found to be only 12%.

An investigation was performed on the nucleophilic displacement of 1,2,4-triazole with KCN under PTC conditions using cinchona alkaloids. Despite considerable efforts, the desired product was obtained in only a 5.4% ee.

In 1988, Shioiri reported the first catalytic, enantioselective oxidation of achiral ketones with the use of molecular oxygen and p-CF_3BCNB as the phase transfer catalyst (Scheme VI). This reaction produced the α-hydroxy ketones in ee's ranging from 0-79% and yields ranging from 60-98%.

Scheme VI

![Scheme VI](image)

CONCLUSION

Asymmetric phase transfer catalysis is an important tool in the synthesis of chiral non-racemic compounds. However, it is not without limitations. For good asymmetric induction to
occur with the cinchona and ephedrine quaternary ammonium catalysts, one must have a fairly rigid substrate which includes phenyl substituents. The phenyl group is necessary for π-π interaction with the chiral catalyst. Few examples have appeared in the literature where good asymmetric induction was achieved with non-phenyl bearing substrates. These examples use chiral crown ethers and chiral nickel complexes as phase transfer catalysts. For future work, one could envision the development of a chiral catalyst which interacts with the substrates by means other than π-π interactions. This would allow for broader application of PTC in syntheses of chiral nonracemic compounds.

References

INTRODUCTION

The synthesis of asymmetric compounds is of current interest to most synthetic chemists. Consequently, extensive effort has gone into the development of diastereo- and enantioselective reactions. One such example is the asymmetric protonation of a prochiral intermediate. Asymmetric protonations can be classified as being either enantioselective or diastereoselective.\(^1\)

Each of these classes can be further divided into deracemizations or synthetic transformations.\(^2\) Deracemization is the process of transforming a racemate into a single enantiomer \textit{via} protonation of a prochiral intermediate. In diastereoselective deracemization, a chiral auxiliary directs the protonation of the intermediate and is subsequently removed, thus affording the scalemic product (if the second stereogenic center in the molecule does not belong to a chiral auxiliary, then the process is an epimerization). Asymmetric synthesis is a transformation in which a reactive intermediate is generated during the course of the reaction and is subsequently protonated to form a stereogenic center. Depicted below in Scheme I are examples of diastereoselective protonations including (1) an asymmetric synthesis\(^3\) (2) a deracemization\(^4\) and (3) a kinetic epimerization.\(^5\)

Scheme I

\[ \text{Scheme I} \]

A general approach to enantioselective protonation through deracemization is shown in Scheme II. Deprotonation of the racemic substrate affords a nucleophilic, prochiral intermediate,
i, which may then be selectively protonated on one enantioface through the use of a chiral proton source.

The following review will discuss diastereoselective protonations of molecules that are directed by internal chiral centers of the molecule or through a chiral auxiliary, as well as enantioselective asymmetric syntheses and deracemizations.

**Scheme II**

![Diagram of Scheme II]

**DIASTEREODIFFERENTIATING PROTONATIONS**

**Deracemization**

Diastereoselective deracemizations involve the protonation of an achiral intermediate that is covalently bonded to a chiral auxiliary. Previous work in this area has included protonations of optically active enenimes, oxazolines, and bis-lactam ethers. A typical example of this class of diastereodifferentiating protonations is the deracemization of 2-arylpionic acids, including such important compounds as the non-steroidal anti-inflammatory agents ibuprofen and naproxin. Larsen, Corley, et al., have converted the racemic acid (rac-1) into a prochiral ketene from which the optically active ester was obtained by addition of a chiral alcohol, pantolactone (Scheme III). The resulting enolate was then protonated by the hydroxyl proton of the pantolactone. Employment of R pantolactone yielded esters of the R configuration. The resulting esters could then be hydrolyzed to yield the desired carboxylic acids. Chemical yields were high and diastereomeric excesses (d.e.'s) were over 99%. The structural and electronic nature of the chiral proton source was found to be extremely important in these reactions, and the highest e.e.'s were obtained when the chiral proton source was an α-hydroxy ester.

**Scheme III**

![Diagram of Scheme III]
Hunig et al., used a different approach in the diastereoselective protonation of chiral, diisopinocampheylborane enolates. They used achiral acids and obtained e.e.'s of up to 50% (Scheme IV). Small, sterically unencumbered proton sources, (e.g. MeOH, CF₃CH₂OH) protonated the enolate unselectively, while the large and sterically encumbered t-BuOH was found to be unreactive. Employment of either acetic acid or trifluoroacetic acid, two sterically similar reagents, led to an enantiomeric enrichment of the product, but surprisingly, the trifluoroacetic acid yielded the S enantiomer while acetic acid yielded the R enantiomer preferentially. These results have been rationalized in terms of the diastereomeric transition states, Figure 1. It is believed that the carbonyl group of acetic acid forms a dative bond with the boron atom of the enolate. The resulting adduct can protonate the enolate on the re face through an eight-membered cyclic transition state. The carbonyl group of the trifluoroacetic acid is less nucleophilic, and the acid is a stronger proton source; consequently, the acid attacks the enol directly from the less hindered si' face.

![Scheme IV](image)

Figure 1. Diastereofacial differentiation in protonation of the enol boronate.

**Epimerizations**

An example of steric-approach-controlled, diastereoselective protonations is the kinetic protonation of 4-phenylnitro cyclohexane. Stoichiometric deprotonation of a diastereomeric mixture of 1-nitro-4-phenylcyclohexanes provided the nitronate which was subsequently protonated with a buffered solution of LiOAc/HOAc to yield the cis isomer in 37% yield. When using the sterically more demanding collidine/collidine-HCl buffer system as a proton source, the
cis isomer was selectively formed in 60% yield. Sterically encumbered proton sources were proposed to favor the cis isomer because of undesirable 3, 5-diaxial interactions which would inhibit the proton donor from attacking the top face of the molecule.

Asymmetric Synthesis

There are several examples of diastereoselective protonations in asymmetric synthesis. An example of diastereoselective asymmetric synthesis is the 1,4-additions of Grignard reagents to conjugated N-enoylsultams (Scheme V). Oppolzer et al. have created two contiguous stereocenters by performing a 1,4-addition followed by a diastereoselective protonation of the resulting enolate. In this sequence, the major product 3 was obtained in good chemical yields (50-80%) and excellent levels of diastereoselectivity (99% d.e.). The resulting sultam could be hydrolyzed with LiOOH to yield the optically active acid. Oppolzer and coworkers proposed that compound 5 was formed preferentially due to chelation of the synperiplanar SO₂ oxygen with the carbonyl oxygen by magnesium, selective formation of a Z-enolate, and the presence in the enolate of the nitrogen lone pair in the nodal plane of the π-system.

Scheme V

![Scheme V Image]

ENANTIODIFFERENTIATING PROTONATIONS

Deracemization

Enantiodifferentiating deracemizations are the most common (and extensively studied) type of asymmetric protonations. Early work on deracemizations was conducted by using (2R,3R)-O-O-diacyltartrates. Duhamel and coworkers converted carbonyl compounds into their enamines, and then selectively protonated the enamines with a chiral acid. Although the enantiomeric excesses (e.e.'s) were low (8-32%) the potential of this new method was recognized.

Chiral proton sources are the most common means of carrying out enantioselective deracemizations. Fehr et al., have used N-isopropylephedrine as the chiral proton source in the
deracemization of thiol esters\textsuperscript{18}, which are versatile chiral building blocks in the perfume industry (Scheme VI). After the thiolester was deprotonated with \( n\text{-BuLi} \) at \(-100\^\circ\text{C}\), excess (\(-\))\( N\)-isopropylephedrine was added, and the solution was allowed to warm. Subsequent quenching of the reaction affords chemical yields of approximately 80\%, and e.e.'s of 95\%. It has been proposed that \( N\)-isopropylephedrine forms a 1:1 complex with the thiolester enolate followed by an irreversible stereocontrolled carbon protonation \textit{via} a conformationally rigid transition state.

**Scheme VI**

![Scheme VI](image)

On the basis of Fehr's comments, and the work of Pete and coworkers\textsuperscript{19}, the following transition state has been proposed (Figure 2).

![Figure 2](image)

**Figure 2.** Proposed transition state for the asymmetric protonation of a thiolester enolate.

While studying the protonation of thiolester enolates, Fehr \textit{et al.}, noticed that above \(-80\^\circ\text{C}\), thiolester enolates underwent elimination of thiolate to form ketenes\textsuperscript{20}. They were able to add lithium thiolate selectively to the ketene and then quench the resulting enolate with \( N\)-isopropylephedrine (Scheme VII). By employing the lithium alkoxide of \( N\)-isopropylephedrine the reactions in Scheme VII were made catalytic. In the catalytic reaction, the aromatic thiol acts both as the nucleophile and as the proton source. High e.e.'s were only observed upon slow addition of the thiol; if the thiol was allowed to accumulate, it acted as an achiral proton source and competed with the \( N\)-isopropylephedrine, which led to an erosion in stereoselectivity. The
best selectivities observed in the catalytic process gave protonations in 85% chemical yield with 97% e.e. On the basis of the above observations, the authors proposed that three aspects of the chiral proton source are important for good selectivities. The best proton sources are (1) weakly acidic, (pK\textsubscript{A} 15-20); (2) they contain electron rich groups that have chelation or coordination ability, and (3) the proton to be donated is in a dissymmetric environment.

**Scheme VII**

Asymmetric Synthesis

Enantioselective protonations have found limited use in asymmetric synthesis. They have been used in the synthesis of chiral \( \alpha \)-ketones\textsuperscript{21}, and the electrochemical reductions of carbonyl compounds.\textsuperscript{22} One of the most recent examples of asymmetric protonations in asymmetric synthesis was performed by Fehr and coworkers in the synthesis of the two enantiomers of a damascone precursor.\textsuperscript{23} The critical step in the synthesis was the protonation of the prochiral intermediate 10 (Scheme VIII). Protonation of 10 with (-)-\( N \)-isopropylephedrine, yielded the \( S \) enantiomer of damascone in roughly 70% chemical yield and 70% e.e. When 10, was protonated with (-)-\( N \)-isopropylephedrine in the absence of lithium methoxide, (ie. the Grignard reaction was carried out on the previously isolated, lithium free ketene) the e.e. was only 16%. Clearly the lithium is forming a transient chiral complex with the enolate.

**Scheme VIII**
Although catalytic enantioselective asymmetric protonations are still unusual, they have been used in the photodeconjugation of α, β-unsaturated esters. Pete et al., have studied the photo deconjugation of many α-methyl α, β-unsaturated esters in the presence of catalytic amounts of various chiral β-amino alcohols, such as ephedrine and N-isopropylephedrine (Scheme IX). In this reaction, a dienol intermediate, ii, is generated, which forms a complex with the chiral β-amino alcohol. The β-amino alcohol then selectively protonates the enol to provide the β,γ-enone in up to 70% e.e. A relationship between the configuration of the amino group of the chiral proton source, and the configuration of the newly created stereogenic center has been established. In most cases, the use of R amino alcohol yields the (S)-α-methyl β,γ-unsaturated ester. It is also interesting to note that the presence of an alcohol moiety in the chiral proton source is necessary to obtain good e.e.'s, but the configuration of the alcohol is not important. Chiral β-amino alcohols derived from camphor have also been used. These rigid proton sources require an eclipsed conformation between the hydroxy and amino groups of the chiral proton source, and consequently give good chemical yields and selectivities of up to 91% e.e.

Scheme IX

CONCLUSION

Asymmetric protonations are a useful method for preparing diastereo- or enantioenriched compounds. They have been performed by using achiral proton sources and chiral enolates as well as chiral proton sources and achiral intermediates. Several generalizations can be made concerning the factors likely to give diastereoselectivities and enantioselectivities during asymmetric protonations. The ideal proton donor should: (1) have sterically demanding groups near the proton to be donated, (2) be weakly acidic, (3) contain electron rich groups which are capable of hydrogen bonding/coordinating to the substrate, and (4) the proton to be donated should be in an asymmetric environment. In the instances where all of the above criteria are not met, the optical purity of the product is attenuated.

In conclusion, asymmetric protonations are useful for the preparation of chiral, non-racemic carbonyl compounds via their enolates, kinetic epimerizations, and they are also useful for converting racemic mixtures into a single enantiomer.
References

UTILITY OF THE AZA-COPE MANNICH REACTION IN THE TOTAL SYNTHESIS OF ALKALOIDS

Reported by Eric D. Hostetler

October 21, 1993

INTRODUCTION

In the most general sense, an alkaloid is defined as any nonproteinaceous nitrogen containing compound isolated from nature. In addition to the pharmacological activity displayed by alkaloids, their complex and unusual structures have inspired great interest in developing methods to achieve their efficient total synthesis. This review will illustrate the power of the tandem aza-Cope rearrangement/Mannich cyclization as a general strategy which can be applied to many complex systems. Alternative strategies for the total synthesis of alkaloids from three families will be compared, highlighting the simplification brought about by the application of the aza-Cope Mannich reaction.

SCOPE AND MECHANISM

Overman envisioned the aza-Cope Mannich rearrangement as an attractive tool for carbon-carbon bond formation due to its mild reaction conditions, high stereospecificity, and the range of methods available for creating the initial iminium ion. An initial concern in the development of the aza-Cope Mannich reaction was the reversibility of the aza-Cope rearrangement. The rearrangement could be rendered irreversible by nucleophilic trapping of the product iminium ion. Overman accomplished this by incorporating an allylic alcohol (B) which became a nucleophilic enol upon rearrangement (C) (Scheme I). Even in the case where the initial iminium ion (B) is more stable due to aryl conjugation, the cyclized product is still formed in excellent yields. In cases where the amino alcohol is cyclic (A), the product results in a pyrrolidine annulation and expansion of the initial ring by one carbon (D). The identifiable retron that triggers the application of the aza-Cope Mannich reaction is a 3-acylpyrrolidine unit.

The aza-Cope Mannich reaction proceeds in a stereoselective manner for three reasons: (1) the aza-Cope rearrangement occurs through a chair-like transition state, (2) iminium ion...
substituents prefer to occupy pseudo-equatorial positions during rearrangement, and (3) the intramolecular Mannich cyclization occurs with great facility. For substituted cyclopentanes such as A, if the starting amine and vinyl groups are trans, the transformation should lead to a single cis-fused bicyclic product such as D. This is because only one chair-like transition state is available for the iminium ion rearrangement (Scheme I). Conversely, if the starting amine and vinyl groups are cis, the formation of a cis-fused product is not exclusive since there are four possible transition states (two "chair" and two "boat") through which iminium ion rearrangement can occur.

APPLICATION TO ALKALOID SYNTHESIS

Alkaloids were a natural choice for application of the aza-Cope Mannich reaction, since they often contain the pyrrolidine retin in their polycyclic skeletons. Overman has synthesized representative alkaloids from many different families, including 16-methoxytabersonine (1) from Aspidosperma, pancrace (2) from Amaryllidaceae, and strychnine (3) from Strychnos.

Aspidosperma: 16-Methoxytabersonine

Magnus' approach (Scheme II) to the synthesis of (-)-16-methoxytabersonine began with an indole synthesis, followed by selective formation of E-imine sulfide 10. Enantiomerically pure syn-acid chloride 11 was then condensed with imine 10 to form the amide, setting up an intramolecular Diels-Alder reaction. The norbornyl chiral auxiliary necessitates approach of the dieneophile from the α-face establishing the appropriate cis stereochemistry at the C-D ring junction. The chiral auxiliary forced the alkene to adopt a more restricted conformation, significantly increasing the yield (ca. 20%) of the key cyclization step to form amide 12. Treatment of the diastereomeric sulfoxides with TFAA generated the sulfonium ion, which is ideally poised for an intramolecular Pummerer-type reaction, creating the key sterically congested C(11)-C(12) bond of 13, which is quaternary at C(12) as well as part of a strained N-containing five membered ring. Removal of the chiral auxiliary by a retro-Diels-Alder reaction is facilitated by the strain of the ring system. This created the desired α,β-unsaturated amide 14 under mild conditions without destroying the sensitive ring system (a second retro-Diels-Alder is available; no SPh is eliminated). Unfortunately, cleavage of the SPh group could not be achieved without competitive reduction of the α,β-unsaturated amide. Alternatively, 13 could not be desulfurized first due to reduction of the norbornyl double bond, preventing the retro-Diels-Alder reaction.
Therefore, the double bond was deliberately reduced and then reintroduced by a thiolactam dehydrogenation procedure to provide 15. Vilsmeier formylation gave the aldehyde, which was oxidized to the acid and converted to the methyl ester. Deprotection of the indole amine afforded (-)-16-methoxytabersonine (1) in a total of eighteen steps and 3.4% overall yield.

Scheme II

One of the first alkaloids prepared by Overman using the aza-Cope Mannich as the key step was (+/-)-16-methoxytabersonine (1) (Scheme III). Bicyclic ketone 5 was synthesized from silyl enol ether 4 in five steps and 25% overall yield. The dianion of silyl cyanohydrin 6 attacked ketone of 5 from the more accessible convex α-face to give tetracyclic carbamate 7. This coupling established the aryl moiety early in the synthesis, whereas most approaches towards 16-methoxytabersonine incorporate this through a low-yielding Fischer indole procedure. A Wittig olefination followed by carbamate hydrolysis created the allylic alcohol necessary for the key aza-Cope Mannich reaction. Since the homoallylic secondary amine and the vinyl group are trans, rearrangement was expected to occur through a single chair-like transition state to give the cis-fused product. Reaction of 8 with paraformaldehyde gave the corresponding oxazolidine, which was cleaved in situ to provide the imine alcohol. Refluxing in toluene triggered aza-Cope Mannich rearrangement to yield pentacyclic imine 9 with complete stereocontrol in up to 90% yield. It is noteworthy that this single step formed three of the five rings of the alkaloid skeleton with complete stereocontrol. Additionally, the mildness of the reaction allowed the aniline to remain unprotected. Thus, imine formation to close the B-ring occurred in the same pot as the Mannich cyclization. Acylation of 9 completed the efficient total synthesis of (±)-16-methoxytabersonine (1) in eleven steps and 6% overall yield from silyl enol ether 4.
In Overman's approach, the aza-Cope Mannich reaction established several critical stereocenters in one step and in excellent yield: the critical C(11)-C(12) bond was made with the proper stereochemistry, the C-ring was created by the ring expansion caused by the Mannich cyclization, the C-D ring junction was formed with the correct cis stereochemistry, and the indole ring was closed. In comparison, Magnus' approach required introducing an activating sulfoxide group in order to form the key C(11)-C(12) bond, and its removal caused problems later in the synthesis. Magnus' strategy also required a low-yielding indole synthesis to make the necessary precursor. This caused Magnus synthesis to require seven more steps than Overman's and gave the product in about half the overall yield. Additionally, it took Magnus seven steps to arrive at the final product after the basic skeleton was formed, whereas Overman's approach required only one extra step after the aza-Cope Mannich reaction.

**Amaryllidaceae: Pancrachine**

Pancrachine contains a unique 5,11-methanomorphanthridine skeleton which has received relatively little attention synthetically. The primary synthetic challenge in pancrachine is the establishment of the stereochemistry at C(4a) and C(11). Hoshino's approach\(^7\) (Scheme IV) began with ring opening of cis-fused cyclic anhydride 17 by aryl Grignard 16 followed by Curtius rearrangement to produce carbamate 18. Dihydroxylation of 18 occurred stereoselectively to give the cis-diol, which was protected as the cis-diacetate. The configuration of the 1-carbon bridge at C(11) was established by a Wittig olefination followed by stereoselective hydroboration-oxidation occurring from the β-face to provide 19. Protection of the alcohol as an acetate preceded a
modified Pictet-Spengler cyclization to afford pentacyclic acetate 20. In the key step of the synthesis, cyclization was achieved by treatment of the alcohol with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) yielding hexacyclic amine 21. An additional six steps of functional group manipulation provided (±)-pancracine (2) in seventeen steps and 3% overall yield from cis-cyclic anhydride 17.

Scheme IV

(a) THF, 98%; (b) ClCO₂Et, Et₃N; NaN₃; t-BuOH, 94%; (c) TFA; TsCl, Et₃N, 71%; (d) OsO₄, NMO; Ac₂O, py, 93%; (e) Ph₃P=CH₂, 71%; (f) BH₃; NaOH, H₂O₂, 100%; (g) Ac₂O, py, 100%; (h) (CH₂)₅, Ac₂O, MeSO₃H, 81%; (i) NaOMe, 100%; (j) PhCH(OMe)₂, p-TsOH, 83%; (k) SMEAH, o-xylene, reflux, 91%.

Overman's approach⁸ (Scheme V) started with enantiomerically pure amino ketone (S)-21. Coupling of (S)-21 with alkynylcerium reagent 22 occurred with facial selectivity to yield the corresponding amino alcohol. Reduction of the alkyne with Red-Al provided trans-allylic alcohol 23, which is properly suited to undergo the key aza-Cope Mannich reaction. Because of the trans relationship of the amino and vinyl groups, the reaction could proceed through only one "chair-like" transition state affording the cis-fused hydroindolone 24. Pictet-Spengler cyclization gave

Scheme V

(a) 93%; (b) AgNO₃, 95%; (c) Red-Al, 100%; (d) CH₂O, CSA, 75%; (e) BF₃-OEt₂, 95%; (f) H₂ (50 psi), HCl, Pd/C, 99%; (g) CH₂O, Et₃N, HCl, 67%.
the pentacyclic ketone, which after functional group manipulation (seven steps) produced (-)-pancracine (2) in thirteen steps and 14% overall yield from (S)-21.

In Overman's strategy, the aza-Cope Mannich reaction formed the C and D rings stereoselectively, setting the critical stereochemistry at C(4a). This efficient procedure allowed the pentacyclic backbone of pancracine to be completed with only one additional step after the aza-Cope Mannich and four steps overall from precursors 21 and 22. In contrast, Hoshino's method required separate steps to set the C(11) stereochemistry and form the D ring, with additional necessary protections in between.

**Strychnos: Strychnine**

The total synthesis of racemic strychnine was first reported by Woodward in 1953.9 No other syntheses had been successful until 1989, when Magnus prepared10 strychnine in racemic form (Scheme VI) via the Wieland-Gumlich aldehyde 31, a degradation product of strychnine. Tetracyclic indole lactam 25 was formed by Pictet-Spengler condensation of tryptamine with dimethyl 2-ketoglutarate. The desired nine-membered ring intermediate was formed by chloroformate induced fragmentation of 25, followed by an additional five steps to create diastereomeric sulfoxides 26. Conjugate addition of the heteroatom stabilized amide enolate ion provided fromation of the F-ring of β-keto sulfoxide 27. The key C(11)-C(12) bond formation was achieved by oxidation of the tertiary amine to give the desired least strained iminium ion. Trapping of the iminium ion formed the heptacyclic α,β-unsaturated ester 28 with the desired stereochemistry. Conversion of 28 to protected γ-keto-alcohol 29 was accomplished in seven steps. α,β-Unsaturated nitrile 30 was formed by a Wadsworth-Emmons reaction, which was converted to Wieland-Gumlich aldehyde 31 in six additional steps. Conversion of 31 to (±)-strychnine (3) was accomplished using the method reported by Robinson.11 This completed the total synthesis of racemic strychnine in 27 steps and 0.1% overall yield from 25.

Overman's approach12 (Scheme VII) began with enantiomerically pure hydroxy acetate 32, which was converted into vinylstannane 33 in seven steps and 40% overall yield. Palladium catalyzed carbonylative coupling of 33 with triazone-protected aryl amine 34 gave ketone 35. Stereoselective epoxidation of 35 followed by Wittig methylation and desilylation provided epoxy alcohol 36. Conversion of 36 to the allylic trifluoroacetamide followed by cyclization with NaH and removal of the trifluoroacetyl group with KOH yielded azabicyclooctane 37. The key aza-Cope Mannich reaction was accomplished by heating 37 with paraformaldehyde and Na2SO4 in acetonitrile to afford diamine 38 in near quantitative yield with complete stereocontrol. This single step effectively set the proper stereochemistry of the basic strychnine skeleton while providing adequate functional handles to complete the synthesis in a straightforward manner. Acylation of 38 followed by hydrolysis to form the pentacyclic indole ring and subsequent reduction of the α,β-unsaturated ester followed by base promoted epimerization gave β-ester 39.
Scheme VI

Reduction of the ester provided cyclization affording Wieland-Gumlich aldehyde 31, which was converted to (-)-strychnine 3 by Robinson’s method. This sequence accomplished the first asymmetric total synthesis of strychnine in twenty steps and a remarkable 3% overall yield, nearly thirty times greater than the yield obtained by Magnus’ approach to racemic strychnine.

The aza-Cope Mannich reaction allowed Overman to form the D and E rings of strychnine, which contain the critical cis-fused ring juncture, in a single step with complete stereocontrol in near quantitative yield. Additionally, it allowed the basic pentacyclic Strycynos backbone to be assembled with only an additional hydrolysis and acylation, providing the necessary functionalities for completion of the synthesis of (-)-strychnine in only two additional steps. In contrast, Magnus’ strategy required the construction of a β-keto-sulfoxide moiety to form the F ring. Removal of the ketone and conversion of the sulfoxide to a ketal was necessary before formation of the D and E-rings. Equally as important are the fourteen additional steps that were required for Magnus to complete the synthesis. Because of the mildness of the aza-Cope Mannich, the necessary functional handles could be introduced before the key rearrangement, leaving the product poised for efficient conversion to the product.

CONCLUSION

The efficient production of 16-methoxytabersonine, pancracine, and strychnine illustrate the power of the aza-Cope rearrangement Mannich cyclization to provide solutions for the total syntheses of complex alkaloids. The mildness, stereoselectivity, and versatility of the reaction
allow it to be used as a strategy to solve many synthetic problems, rather than simply a problem specific transformation, which is the benchmark of a truly powerful methodology.

Scheme VII

![Scheme VII Diagram]

(a) 2.5% Pd2dba3, 22% Ph3As, CO (50 psi), LiCl, NMO, 80%; (b) i-BuO2H, Triton B, 91%; (c) Ph3P=CH2, 92%;
(d) TBAF, 100%; (e) MsCl, i-PrNEt; NH2CO2Me, NaH, DMF, 83%; (f) NaH; EtOH-H2O, 62%; (g) (CH2O)n, Na2SO4, 98%;
(h) LDA, NCCO2Me; HCl-MeOH, 70%; (i) Zn dust, H2SO4-MeOH, 80%; (j) NaOMe, 85%; (k) DIBAL, 76%; (l) CH2(CO2H)2, Ac2O, NaOAc, H2OAc, 65%.

REFERENCES

DNA PHOTOLYASE: MODEL STUDIES ON THE MECHANISM OF ELECTRON TRANSFER

Reported by Susan M. Gasper

November 4, 1993

INTRODUCTION

Pyrimidine-base dimers (cyclobutanes) are the major product in the irradiation of DNA with ultra-violet light. These dimers induce a slight kink in the double helix of DNA which is able to block replication and thus induce mutagenic and often lethal effects. Most organisms are equipped with repair enzymes that remove pyrimidine dimers from the DNA strand. DNA photolyase is a unique repair enzyme in that it utilizes a photon of visible light to induce monomerization. The cofactors of this enzyme have been identified and a mechanism for repair involving electron transfer has been proposed, although the direction of electron transfer and the details of dimer cleavage remain unknown. Studies of model systems in which electron donation to or from the dimer can be controlled provide insight regarding the possibility of dimer cleavage from the corresponding radical anions or cations. In addition to reviewing what is known about the mechanism of action of DNA photolyase, this seminar will provide a look at model systems and evaluate their relevance to the biological repair of cyclobutapyrimidines.

UV DAMAGE TO DNA AND REPAIR ENZYMES

Deoxyribonucleic acid (DNA) is an anionic polymer comprised of nucleoside bases connected to a poly-sugar-phosphate backbone. Since the sugar-phosphate backbone does not absorb UV light, the bases are the only components of DNA affected by UV irradiation. The main photoproducts that have been isolated and identified from cellular DNA are the cyclobutapyrimidines (Pyr<->Pyr), of which, the thymine dimers are the most prevalent and by far the most lethal. When DNA is irradiated at 280-320 nm, it is possible for adjacent pyrimidines on the same strand to undergo a photochemically allowed [π2s + π2s] cycloaddition to form what is referred to as a pyrimidine dimer.

Using thymine as a representative pyrimidine, it is obvious that there are four possible stereoconfigurations of Thy<->Thy. These are shown in Fig. 1. DNA imposes certain structural restraints upon the stereochemistry of Thy<->Thy formed. In double-stranded DNA, only the cis-syn isomer of the dimer is formed while in single-stranded or denatured DNA, formation of the trans-syn isomer is allowed, albeit in low yield.

Copyright © 1993 by Susan M. Gasper
The presence of pyrimidine dimers in DNA not only hinders replication but causes structural damage as well. In order to keep DNA functional, organisms have developed enzymes for repair. There are three main categories of repair enzymes that are capable of fixing Pyr<>Pyr in DNA. Base-excision and nucleotide-excision repair enzymes both affect removal of the damaged base through a process involving cleavage of the N-glycosidic bond. In order to restore DNA to its original form, however, the action of other enzymes is required. The last category of enzymes are those that directly reverse the chemical modifications to DNA, hence their name, direct repair enzymes. Among these, the most interesting and unique are the DNA photolyases. As mentioned briefly in the introduction, these enzymes mediate dimer cleavage through a light dependent step. Since the mechanism of DNA photolyase will be the main focus of this seminar, more details about the enzyme will be presented in the following section.

DNA PHOTOLYASE

Identities Of Cofactors

A number of photolyases have been isolated from various organisms and can be classified into two major groups on the basis of their UV absorption spectra. The first class of enzymes is characterized by a strong absorption between 360-390 nm. These include photolyases isolated from *E. coli* and *Saccharomyces cervisiae*. Sancar et al. identified one chromophore of *E. coli* photolyase in 1984 as flavin adenine dinucleotide (FAD) by a process involving denaturation of the enzyme, pH-dependent fluorescence studies, and thin layer chromatography (TLC). A second chromophore from this enzyme was identified in 1988. Jorns et al. suggested that enzyme absorption at 360 nm was due to a 7,8-dihydropterin substituted at positions 5 and 6 based on the reversibility of chromophore bleaching as well as chemical and physical similarity to known compounds. Denaturation of DNA photolyase and chromophore isolation allowed Johnson et al. to identify the pterin derivative as 5,10-methenyltetrahydrofolylpolyglutamate (5,10-MTHF). Identification of this chromophore was achieved through absorption and fluorescence spectroscopy and hydrolysis. The second class of enzymes exhibits an absorption maximum between 430-450 nm. Among this group are the photolyases of *A. nidulans* and *S.*
Similar to E. coli photolyase, the chromophores of A. nidulans enzyme were identified through a process involving denaturation and subsequent study of the released chromophores. In 1990, Eker et al. utilized fluorescence, TLC, and specific enzymatic reactions to confirm the A. nidulans chromophores as FAD and 7,8-didemethyl-8-OH-5-deazariboflavin (8-HDF). It is noteworthy that both classes of enzymes contain FAD. Thus, known photolyases can be separated into two classes on the basis of their second chromophore, either folate or deazaflavin.

**Figure 2.** DNA photolyase cofactors.

**Proposed Mechanism**

The available evidence regarding DNA photolyase-catalyzed splitting of Pyr$\leftrightarrow$Pyr suggests the mechanism outlined in Scheme I. Visible light is initially absorbed by the second cofactor (8-HDF or 5,10-MTHF). The excitation energy is then transferred to FAD which then sensitizes dimer splitting by an electron transfer (ET) process. Evidence to support the steps in Scheme I will be presented in detail in the following section.

**Scheme I**

**Quantum Yields Of Repair And Catalytically Active Forms**

The quantum yield for the light dependant dimer splitting by DNA photolyase can be defined as the following:

$$\phi_{\text{spl}} = \frac{\# \text{ dimers split}}{\# \text{ photons absorbed}}. \quad (1)$$

Quantum yields for dimer repair *in vivo* are high, with $\phi_{\text{spl}}$ approaching the theoretical maximum of 1. This is not surprising, as enzyme catalyzed reactions are usually very specific and efficient. Quite surprising, however, are the splitting quantum yields for *in vitro* repair. Isolated and purified E. coli photolyase was found to affect little dimer cleavage, as evidenced by $\phi_{\text{spl}} =$
0.07. To account for the discrepancy between in vivo and in vitro quantum yields, it was proposed that perhaps the isolated form of the enzyme is not the catalytically active form in vivo. Spectroscopic studies of purified enzyme have shown FAD to be present as a neutral semiquinone radical (FADH*, see Figure 3). Oxidation of this species leads to complete loss of activity. However, photoreduction to reduced flavin (FADred) allows dimer splitting to proceed with a ϕ_spl of 0.44. Since the quantum yield for FADred is closer to unity, it is likely that FADred is the catalytically active form of the flavin in vivo. Further evidence against FADH* as the in vivo form was obtained from an EPR study on whole cells containing photolyase. The presence of unpaired electrons, such as those in radicals, should be detectable by EPR. However, no EPR signal was observed in bacterial cells. These and other experiments led to the preliminary conclusion that the in vivo form of photolyase contained FADH2. More recent time-resolved EPR studies on the process of enzymatic photoreduction, however, point to FADH− as the catalytically active form. Thus, it is generally believed that the in vivo form of the enzyme contains a fully reduced flavin while the protonation state of the active flavin remains controversial.

Figure 3. Protonation and redox states of FAD.

MECHANISMS OF ENZYMATIC REPAIR
Photoreduction Of Purified Enzyme

Laser flash photolysis is a useful tool in the characterization of short lived intermediates. Several flash photolyses were performed in elucidating the nature of the transients involved in the photoreduction of purified enzyme. It was found that irradiation of enzyme-bound flavin radical in the absence of external electron donors produced FADred with a quantum yield of 0.1. This value is identical to those obtained in the presence of external electron donors, suggesting the presence of an electron donor in the enzyme, most probably an aromatic amino acid residue. Systematic replacement of tryptophan residues in the enzyme with phenylalanine by site-directed mutagenesis allowed for the identification of Trp-306 as the internal electron donor. Picosecond laser flash photolysis of E. coli enzyme containing the flavin radical but no folate showed the formation of two transients. A mechanism of photoreduction consistent with the picosecond experiment has been proposed and is illustrated in Scheme II, where E-FAD denotes
enzyme bound cofactor. Abstraction of an electron or a hydrogen atom from TrpH would result in generation of the TrpH radical cation or the neutral Trp radical. Recently, Heelis et al. obtained evidence for the presence of TrpH$^{+\cdot\cdot}$ by correlating predicted spin densities for TrpH$^+$ and TrpH$^{+\cdot\cdot}$ with observed EPR signals. Thus, the most recent evidence supports photoreduction involving electron transfer to generate FADH$^-$ as the catalytic form of DNA photolyase.

**Scheme II**

\[
\begin{align*}
\text{E-FADH}^* & \xrightarrow{h\nu} \text{E-}{^2}\text{FADH}^* \xrightarrow{\text{isc}} \text{E-}{^4}\text{FADH}^* + \text{TrpH} \quad \tau = 100 \text{ ps} \\
\text{E-FADH}^* + \text{TrpH} & \rightarrow \text{E-FADH}^- + \text{TrpH}^{+\cdot\cdot} \\
\text{E-FADH}_2 + \text{Trp}^* & \rightarrow \text{E-FADH}_2 + \text{Trp}^* \quad \tau = 1 \mu\text{s}
\end{align*}
\]

**Energy Transfer From Second Chromophore to Flavin**

In the elucidation of the function of the second chromophores in the enzymatic repair reaction, quantum yields for enzyme depleted in one or both chromophores were determined. It was found that E-FAD$_{\text{red}}$ was able to repair dimers in the absence of MTHF while E-MTHF in the absence of FAD$_{\text{red}}$ was unable to affect dimer cleavage. Also, E-MTHF-FAD$_{\text{red}}$ is known to have a significantly higher $\phi_{\text{spl}}$ than E-FAD$_{\text{red}}$.13 These results in conjunction with the fact that MTHF has a much higher extinction coefficient at photoreactivating wavelengths than FAD$_{\text{red}}$ suggest that the sole function of MTHF is as a light harvesting molecule. In 1991, Kim et al. provided direct evidence for energy transfer from MTHF to FAD$_{\text{red}}$ in a picosecond laser experiment.13 Transient absorption of E-MTHF 40 ps after the laser pulse was found to have $\lambda_{\text{max}} = 480$ nm. This transient had a lifetime of 480 ps and was assigned to the first excited singlet of MTHF. Irradiation of E-MTHF-FAD$_{\text{red}}$ at the same wavelength resulted in a transient spectrum identical to E-MTHF at 20 ps. The absorption at 480nm was found to decay with lifetime $\tau = 180$ ps concomitantly with the growth of a new band between 500-600 nm which has been assigned to the first excited singlet of FAD$_{\text{red}}$. Flourescence studies which further support energy transfer were published in the same paper.

**Scheme III**

\[
\begin{align*}
\text{E-FAD}_{\text{red}}^-\text{-MTHF} & \xrightarrow{h\nu} \text{E-FAD}_{\text{red}}^-*\text{-MTHF} \quad \tau = 180 \text{ ps}
\end{align*}
\]

**Electron Transfer Between Excited Flavin And Dimer**

A number of experimental and theoretical results have led to the popular belief that dimer cleavage is initiated by an electron transfer process. The fact that quantum yields for dimer repair are found to increase with a decrease in the oxidation state of the flavin suggests
that flavins in this system function as electron donors. Indirect evidence for an electron transfer mechanism involving the first excited singlet state of FAD<sub>red</sub> was obtained by Kim et al. in 1991 using time-resolved fluorescence. In the absence of dimer, E-FAD<sub>red</sub> was shown to have a fluorescence lifetime \( \tau_{\text{fl}} = 1.4 \text{ ns} \). In the presence of dimer, \( \tau_{\text{fl}} \) is reduced to 0.16 ns.\(^{13}\)

Direct evidence for electron transfer was presented by Okamura et al. in 1991.\(^{14}\) An *E. coli* DNA photolyase complexed with a deoxyuridine dimer was irradiated with a laser pulse and transient absorption spectra were recorded on a picosecond time scale. At 2 ns, the growth of a new absorption band at 400 nm is observed while photolysis of uncomplexed enzyme lacked new absorption bands at long delay times. The absorption band was attributed to an unidentified transient generated during dimer repair. Using time-resolved EPR, Kim et al. were able to detect the formation of a radical intermediate during dimer repair in a similar experiment, however, low resolution of the spectrum precluded transient identification.\(^{15}\)

Though these results support the fact that electron transfer between the excited flavin and the dimer is operative in DNA photolyase mediated cleavage of pyrimidine dimers, it is important to remember that the direction of electron transfer remains ambiguous due to the lack of identification of resulting intermediates.

**MODEL STUDIES**

**Quinone Sensitized Cleavage**

In the excited state, quinones are known to be electron abstractors. Therefore electron transfer should result in formation of the dimer radical cation. The earliest studies using anthraquinone-2-sulfonate as a sensitizer involved detection of monomer radical cations by photoChemically Induced Dynamic Nuclear Polarization, more commonly known as photoCIDNP. In a recent photoCIDNP study involving the anthraquinone-2-sulfonate sensitized splitting of dimethylthymine and thymine dimers, Young et al. were able to detect a radical cation intermediate in dimethylthymine dimer monomerization.\(^{16}\)

In 1990, Pac et al. performed a study of dimer splitting sensitized by *p*-chloranil.\(^{17}\) The dimers used in this experiment were three stereoisomers of 1,3-dimethylthymine: *cis*-syn, *trans*-syn, and *cis*-anti. Electron transfer from the dimer to triplet chloranil \( (^3\text{Chl}) \) is expected to result in the formation of dimer radical cation. The highest quantum yields for dimer splitting were obtained for the *trans*-syn and *cis*-syn dimers, where \( \varphi_{\text{spl}} = 0.39 \) and 0.34 respectively. The *cis*-anti dimer showed minimal splitting. The authors have invoked through-bond coupling to account for perturbation of the syn cyclobutane rings relative to the anti.

**Indole Sensitized Cleavage**

In contrast to quinones, indoles are known to be powerful electron donors in the excited state and dimer radical anions would be generated upon electron transfer. Rose et al. have done
As of in to DNA reduced, propagating mirrors basis variety CONCLUSIONS deprotonated flavins. However, $\phi_{spl}$ values are much lower than unity, suggesting the possibility of a competing process. Fluorescence lifetimes of free and linked indoles were measured and found to be significantly shorter for the latter, presumably due to electron transfer from indole to dimer.

In a study of a similar system two years later, Rose et al. reported a dramatic solvent dependence on the quantum yield of dimer splitting. As in the previous study, covalently linked dimer was found to quench indole fluorescence. Quantum yeilds for the splitting reaction were found to increase with a decrease in solvent polarity. This trend is rationalized as a slowing of the rate of back electron transfer in non-polar solvents.

**Flavin Sensitized Cleavage**

Model studies involving flavins as sensitizers for dimer cleavage are expected to be especially relevant to the biological system. In a study using protonated, oxidized flavins as electron abstractors, Rose and Hartman determined $\phi_{spl}$ values for the cis-syn and trans-syn dimethylthymine dimers. For the cis-syn dimer, $\phi_{spl}$ was found to be 0.35, while for the trans-syn dimer, a $\phi_{spl}$ of 1.5 was observed. The fact that $\phi_{spl}$ was greater than the theoretical maximum and that it increased in a quadratic manner with increasing dimer concentration, led to the postulation of a chain reaction mechanism involving monomer radical cations as the chain propagating species.

High $\phi_{spl}$ values and a quadratic dependance of $\phi_{spl}$ on dimer concentration led Rose and Hartman to invoke a similar chain reaction mechanism for dimer cleavage involving reduced flavins. In this case, however, monomer radical anions would be the chain propagating species. Since quantum yields for dimer splitting were high (maximum $\phi_{spl}$ of 1.4), the determination of a pH profile for the monomerization reaction was possible. Dimer splitting efficiency was found to follow a titration curve with low efficiencies at low pH, where the flavin is in the fully reduced, fully protonated form. At high pH, where the flavin is in the fully reduced, deprotonated form, splitting efficiency was seen to be eight times greater.

**CONCLUSIONS**

Many systems that mimic the sensitizer and substrate of the electron transfer process in DNA photolyase have been examined over the last twenty-five years. These studies employ a variety of mechanistic tools, ranging from laser flash photolysis to simple isotope effects. On the basis of the results in the studies used in this review, it is difficult to speculate what system mirrors the enzymatic one. Actual enzyme studies point toward a reduced flavin as the electron donor however, model studies in which dimer cleavage originates from the radical anion show low splitting efficiencies. It seems unlikely that the enzyme uses an oxidized flavin, based on the
inability of E-FAD\textsubscript{ox} to split dimers. At this point, a definite conclusions about the direction of electron transfer in the enzyme cannot be made, since details about the enzyme active site are unknown.

REFERENCES

CATALYTIC ANTIBODIES IN ORGANIC SYNTHESIS:
RECENT ADVANCES

Reported by Stephen P. O'Connor

November 15, 1993

INTRODUCTION

Enzymes catalyze the thousands of reactions responsible for the maintenance of life. Antibodies recognize and bind foreign objects as part of the immune response. In 1948, Linus Pauling\(^1\) realized that while enzymes function through binding and stabilizing transition states, antibodies function through binding and stabilizing ground states. Seeking a link between enzymes and antibodies, Woolley\(^2\) speculated in 1952 that antibodies might evolve into enzymes if repeatedly challenged by a particular substrate for a sufficient length of time. In 1968, Jencks\(^3\) suggested that an antibody for a molecule which resembles the transition state of a given reaction might catalyze that reaction. However, it was not until 1986 that this theory was successfully demonstrated in simultaneous reports from Lerner\(^4\,a,b\) and Schultz\(^4\,c\). One of the major obstacles to realizing this idea is the multitude of antibodies produced in response to a foreign molecule or cell. This "polyclonal" response greatly improves the chances of success in disease prevention, but unfortunately hinders the isolation of the single strains of "monoclonal" antibodies that bind single substrates. It was not until 1975\(^5\) that methods were devised for producing highly purified antibodies of virtually unlimited quantities. This development allowed the subsequent generation of antibodies possessing catalytic features, the so-called catalytic antibodies.

BACKGROUND

The Immune System

All vertebrates produce antibodies as part of the defense mechanism involved in protection from disease. Antibodies are made up of four peptide chains, two short (light) and two long (heavy), linked by disulfide bonds. The linkages are such that the molecules have a Y-shape, with the two arms of the Y functioning as the antigen-binding region. The white blood cells are the workhorses of the immune system and can be divided into two types: lymphocytes and phagocytes. The lymphocytes themselves are separated into two classes, the bone-marrow-derived B-lymphocytes and the thymus-derived T-lymphocytes. B-cell recognition of an antigen triggers antibody production. The T-cells are also involved in antigen recognition and antibody production, but play a major role in activating the various cells types of the immune system in response to the danger of infection. Part of this activation is stimulation of antibody synthesis by B-cells, but more importantly it involves an interaction

Copyright © 1993 by Stephen P. O'Connor
with the phagocytic cells, which engulf antigens and thus participate in removing them from the body.

**Monoclonal Antibodies**

The immune system recognition of a foreign molecule or cell leads to the production of a large variety antibodies. This represents a polyclonal antibody population, undesirable in terms of substrate selectivity. However, Kohler and Milstein\(^5\) discovered that if the spleen cells of immuno-stimulated mice were fused with "immortal" myeloma cells, the \textit{hybridoma} cells formed would produce large quantities of antibodies. Screening of the cells for those that produce the desired antibody would then allow the identification and isolation of the appropriate cultures.\(^6\) These cell lines could then be used to produce virtually unlimited quantities of pure \textit{monoclonal} antibodies.

**Catalytic Antibodies**

To make an antibody capable of catalyzing a particular reaction, a transition state must be proposed, a stable analog of that species is synthesized, and monoclonal antibodies to this transition state analog are produced and purified. Since the immune system cannot recognize small molecules due to either rapid excretion or metabolism, the proposed transition state analog is bound to an appropriate carrier protein known to elicit a strong immune response. In particular, bovine serum albumin (BSA) and keyhole limpet hemocyanin (KLH) exhibit this feature.\(^7\) In addition to having high immunogenicity, they have on their surfaces numerous points for attachment of the transition state analogs.

**SYNTHETIC APPLICATIONS**

The use of catalytic antibodies in synthesis up to 1989 has been reviewed previously.\(^8\) Developments in the application of catalytic antibodies to organic synthesis since that time will be shown.

**Enantioselective Protonation**

The enantioselective protonation of prochiral enol ether \(1\) followed by hydrolysis to provide aldehyde \(2\) in 96% enantiomeric excess (ee) was accomplished using an antibody elicited for the transition state analog \(3\) linked to KLH, Scheme I.\(^9\) The rate of reaction was increased 2500-fold over the background, unselective protonation/hydrolysis. Under catalysis by the same antibody, the \((E)\)-isomer of \(1\) provided the same isomer of \(2\) as had \((Z)\)-\(1\), but in 93% ee with a 290-fold rate enhancement. The protonated intermediate shown in the brackets is modeled by \(3\), with the \textit{cis}-isomer of \(1\) providing a better correlation to the antibody produced.
Scheme I

Glycosidic Hydrolysis

The same antibody used to catalyze the conversion of 1 to 2, above, also affected the acid-promoted hydrolysis of an activated glycosidic bond, as shown in Scheme II. The antibody catalyzed reaction for the conversion of 4 to 5 was 70 times as fast as the background rate for hydrolysis. The proposed transition state shown in the brackets is similar in shape, size, and charge location to hapten 3, and would be expected to be stabilized by favorable binding interactions with the antibody.

Scheme II

Rearrangement of a Peptide Bond

Catalytic antibodies have the potential to inactivate proteins or peptides through selective amide bond cleavage. Antibody recognition of the target peptide, followed by subsequent antibody-directed hydrolysis could accomplish this task. Efforts in this direction led to the development of catalytic antibodies that carried out the rearrangement of an asparaginyl-glycyl sequence (8) to the corresponding isoaspartyl-glycyl sequence (11), as shown in Scheme III. Cyclic phosphinate 13, the proposed transition state, was coupled KLH and the conjugate used to stimulate antibody production. The overall reaction shown above is a two-step process with the initial cyclization to succinimide intermediate 10 as the rate-
limiting step. There was no significant accumulation of 10, while phosphinate 13 effectively inhibited antibody catalysis of the reaction. One antibody catalyzed the conversion of the L-isomer of 9, and another worked for the D-isomer. A third antibody isolated was capable of processing either. These catalytic antibodies exhibited selectivities in producing 11 and 12 in ratios of 8.3, 3.4, and 16.4, respectively, for the conversion of the L-isomer of 9, while for the D-isomer, the corresponding ratios were 3.6, 1.4, and 1.2. The spontaneous, uncatalyzed ratio of 11 to 12 was 3.5. Thus, catalytic antibodies were made which had the ability to accelerate the rate limiting step of succinimide formation as well as to selectively control the direction of the ring opening.

Scheme III

Stereoselective Reduction of an $\alpha$-Keto Amide

The use of catalytic antibodies elicited to hapten 8 for the reduction of $\alpha$-keto amide 6, with sodium cyanoborohydride as the reducing agent, was investigated, Scheme IV.12

Scheme IV
The use of the \((S)-(\alpha\text{-methylbenzylamine})\) group in the keto amide facilitated analysis of the reaction stereoselectivity. The uncatalyzed sodium cyanoborohydride reduction gave a 56\% de of \((R)-7\). One of the catalytic antibodies obtained provided \((S)-7\) in greater than 99\% de.

**Aminoacylation**

If antibodies could be made to facilitate the aminoacylation of transfer-RNA's, unnatural amino acids could be used as building blocks in the biosynthesis of proteins. This would provide novel compounds for evaluation as well as assist in the study of protein biosynthesis. The phosphonate hapten 17 was used to mimic the acylation of the 3'-hydroxyl group of thymidine derivative 14 with alanyl ester 15, Scheme V.\(^{13}\) One antibody showed L-selective catalysis for the formation of ester 16 when \(R'' = \) phenyl or cyanomethyl, but not \(R'' = \) ethyl. Compound 15 as the cyanomethyl ester was studied further due to its greater water solubility. A rate acceleration of 2.1x10^{8}-fold over the uncatalyzed variant was observed. The D-alanyl derived isomer of 15 (\(R'' = \) cyanomethyl) was found to bind to the catalytic antibody with a \(K_m\) (Michaelis constant) similar to that of the L-isomer (\(K_m\)(L) = 1.3\(K_m\)(D)), but the \(k_{cat}\) (rate constant) for the L-isomer was 22 times as large. This indicates that the antibody has low selectivity in substrate binding but is highly efficient at distinguishing the diastereomeric transition states for the subsequent transesterification.

**Scheme V**

\[
\text{Scheme V}
\]

Enantioselective Epoxide Hydrolysis

The same catalytic antibody that was used in the enantioselective protonation and the glycosidic hydrolysis, both shown earlier, has also been used to catalyze an enantioselective epoxide hydrolysis.\(^{14}\) This antibody was produced using hapten 3, Scheme VI. Hydrolysis of 18 to yield 20, under acidic conditions, was speculated to occur through transition state 19. Proposed transition state 19 could be mimicked by the quaternary ammonium cation 3, which has a positively charged nitrogen in the correct position. A rate enhancement of 440-fold as
well as kinetic resolution of the racemic epoxide yielded the diol 20 of 87% ee. The antibody catalyzed hydrolysis of racemic 21, an acyclic analog, showed rate acceleration (100x), but no selectivity (0% ee). It appears that the two additional methylenes of 18 are required for kinetic resolution.

Scheme VI

6-Endo versus 5-Exo Epoxide Openings

Baldwin's rules for cyclization have been used to rationalize the course of ring closures. A 5-exo-Tet reaction is favored while the 6-endo-Tet version is disfavored. Antibody catalysis has been used to reverse this selectivity. Hapten 25, when coupled to KLH, provided catalytic antibodies capable of transforming the epoxy alcohol 22 via the normally disfavored pathway to product 23, Scheme VII.\footnote{15}

Scheme VII

Stabilization of the proposed 6-membered transition state 26 is suggested to account for the product distribution (in control experiments, with no antibody, only 24 was formed). In addition, only one isomer of 23 was formed, indicating that a kinetic resolution was occurring.
Houk et al.\textsuperscript{16} have performed ab initio calculations (RHF/6-31G\textsuperscript{*}) on transition state models to estimate the energy barriers that antibody catalysis must overcome to achieve such high yields of the unfavored product. The formation of the 5-exo product was calculated to be favored by 1.8 kcal/mol, which would lead to a 96/4 ratio of 5-exo/6-endo products. Thus, in order to achieve a similar excess of the 6-endo product over the 5-exo, the activation energy for the formation of the 6-endo compound must be lowered by the catalytic antibody by at least 3.6 kcal/mol more than the 5-exo activation energy is lowered.

**Exo versus Endo Diels-Alder Reaction\textsuperscript{17}**

The Diels-Alder reaction of diene 27a with N,N-dimethylacrylamide (28) in phosphate buffered saline at pH 7.4 (PBS) at 37°C provided cycloadducts 29 (endo) and 30 (exo) as an 85:15 mixture ($\Delta \Delta G^\ddagger = 1.1$ kcal/mol), by HPLC analysis, Scheme VIII. The reaction using the analogous methyl ester of 27b in toluene at 110°C gave an endo/exo ratio of 66/34 ($\Delta \Delta G^\ddagger = 0.5$ kcal/mol).

\begin{align*}
\text{Scheme VIII} \\
\begin{array}{c}
\text{NHR} \\
27 \\
+ \text{CONMe}_2 \\
28 \\
\rightarrow \\
\text{NHR} \\
29 \text{ (Endo)} \\
+ \text{CONMe}_2 \\
30 \text{ (Exo)}
\end{array}
\end{align*}

Antibodies were elicited to haptens 31 and 32 using BSA and KLH conjugates. The reactions between 27a and 28 in PBS at 37°C were carried out with a number of the catalytic antibodies produced. One antibody for hapten 31 catalyzed selective endo cyclization with the product formed in greater than 98% ee. Likewise, an antibody for hapten 32 promoted exo cyclization (no endo observed), also with greater than 98% enantioselectivity. Thus, the catalytic, diastereoselective, and enantioselective Diels-Alder reactions are possible, in both endo and exo modes, using antibodies derived from the appropriately designed hapten.
CONCLUSIONS

Catalytic antibodies have been shown to accelerate a wide range of reactions. High diastereoselectivities and enantioselectivities can be obtained with correctly structured haptens. In addition, kinetic resolution is often observed when racemic substrates are used. Catalytic antibodies hold great promise for the catalysis of reactions for which no enzyme counterpart exists.

REFERENCES

(1) Pauling, L. Am. Sci. 1948, 36, 51.
THE USE OF LITHIUM PERCHLORATE TO PROMOTE ORGANIC REACTIONS

Reported by Kathleen M. Bertini

November 18, 1993

INTRODUCTION

During the past four decades, lithium perchlorate (LiClO₄) has been used to promote several organic transformations, and recently emphasis has been placed on synthetically useful processes. LiClO₄ has been used extensively to increase the rates of reactions which proceed via ion pairs.¹ This salt has also been found to promote reactions which traditionally were not thought to involve ionic intermediates.² For example, LiClO₄ enhances the rates and selectivities of Diels-Alder reactions. This medium has also been applied to the efficient promotion of [1,3]-sigmatropic rearrangements, aldol condensations, and additions to α,β-unsaturated carbonyl compounds. A variety of explanations have been offered for the rate enhancements, and the salt may not have the same role in each reaction. This review will discuss the various reactions which have been promoted by LiClO₄ and the possible explanations for the rate enhancement in each case.

ION PAIRS AND SALT EFFECTS

Winstein thoroughly investigated the mechanistic details of the S_N1 reaction and has provided strong evidence for the concept of ion pairs.³ His work showed that there exists a range of ionic intermediates in the S_N1 reaction. Initially, the starting material dissociates into a contact ion pair 1 in which the cation and the leaving group are immediately adjacent. Further dissociation leads to a solvent separated ion pair 2 in which the ions are separated by a molecule of solvent. Finally, dissociation leads to the formation of free ions (eq 1). Each ion pair can recombine to give starting material.

\[
\text{RX} \rightleftharpoons R^+ X^- \rightleftharpoons R^+ || X^- \rightleftharpoons R^+ + X^- \quad (1)
\]

Winstein found that the addition of salts had diverse and dramatic effects on the rates of ionic reactions. The rate increase of an ionization reaction upon addition of a salt is termed "normal" salt effect if it simply results from the increase in dielectric constant. In reactions exemplifying this effect, the increase in rate is linearly dependent on LiClO₄ concentration.⁴ In some reactions, such as the acetalolysis of o-anisylethyl-p-toluenesulfonate,⁵ the expected linear correlation between reaction rate and salt concentration is preceded by a strong nonlinear dependence at low salt concentration. This phenomenon is termed "special" salt effect and is described by eq 2. The nonnucleophilic perchlorate anion is assumed to exchange cations with the
solvent separated ion pair and suppress its return to starting material. Numerous examples of the "normal" and "special" salt effects have been reported.¹

\[
R^+ || X^- + Li^+ClO_4^- \rightleftharpoons R^+ || ClO_4^- + Li^+Cl^-
\] (2)

LiClO₄ in diethyl ether (LPDE) has been demonstrated to have an even greater propensity to promote ionization than LiClO₄ in acetic acid. Pocker and co-workers have studied the kinetics of several reactions which proceed through ionic intermediates and have found evidence which is consistent with the presence of aggregates of LiClO₄ and diethyl ether.⁶ These aggregates stabilize the ionic intermediates formed in the reactions and thereby increase the rate of dissociation. For example, the dissociation constant of triphenylmethyl chloride increases by a factor of \(7 \times 10^9\) in 5.05 M LPDE as compared the reaction in pure diethyl ether.⁶

**LPDE AS A LEWIS ACID**

**Mechanistic Studies**

In addition to the remarkable effects LPDE has on ionization reactions, this medium has been shown to dramatically enhance the rates of Diels-Alder reactions. For example, the reaction between 1-phenyl-4-benzylidene-5-pyrazolone (3) and allyl vinyl ether (Scheme 1) is 300 times faster in 2.16 M LPDE than in pure diethyl ether.⁷ In this case and nearly all of the synthetically useful reactions involving LiClO₄, the lithium cation is suspected to act as a Lewis acid.

**Scheme I**

Righetti and co-workers carried out the reaction of heterodiene 3 with ethyl vinyl ether in five solvents containing different concentrations of LiClO₄.⁷ The kinetic data obtained in these studies indicate that lithium cation acts as a Lewis acid to promote the reaction, but the solvation of the cation is different in each solvent. The importance of the lithium cation was demonstrated by an experiment in which the Li⁺ sequestering crown ether, [12]crown-4, was added to the reaction mixture. A decreased rate in the formation of adduct 4 was observed when [12]crown-4 was present.

Forman and Dailey also provided evidence for Lewis acid promotion by the lithium cation in LPDE solutions.⁸ In their study, the second-order rate constant for the cycloaddition between
acrylonitrile (AN) and 9,10-dimethylanthracene (DMA) was measured under pseudo-first-order conditions using excess AN. In a plot of the rate constant of this reaction vs. LiClO₄ concentration a first-order dependence was found. The importance of the lithium cation was verified by carrying out the addition of AN and DMA in the presence of another salt with a weakly coordinating anion, lithium hexafluorophosphate. This salt behaved similarly to LiClO₄ and enhanced the rate of reaction. The existence of "normal" or "special" salt effects was ruled out by an experiment which demonstrated that n-Bu₄NCIO₄ had no effect on the rate of the Diels-Alder reaction.

Efficacy Of The Lithium Cation As A Lewis Acid

Although Li⁺ is known to be an effective Lewis acid in the gas phase, its efficacy in solution is limited. One reason is that LiClO₄ forms mono- and dietherates when dissolved in diethyl ether. Also, the nonnucleophilicity of the perchlorate anion in nondissociating solvents has been questioned recently. The assessment of the Lewis acidity of LPDE solutions has been accomplished by comparing it to other common Lewis acids. Pagni and co-workers demonstrated that other Lewis acids give better diastereoselectivities than LPDE for the reaction shown in Table I (R = (-)-menthyl). Furthermore, the endo/exo selectivity in the reaction between cyclopentadiene and dimethyl maleate increased from 8:1 in 6.0 M LPDE to 20:1 in the presence of AlCl₃. This evidence and the data from Table I suggest that Li⁺ in LPDE is a weaker Lewis acid than AlCl₃ and Et₂AlCl, and its Lewis acidity is comparable with the modest Lewis acid, Al₂O₃. Lewis acids usually increase the regio- and stereoselectivities of normal electron demand Diels-Alder reactions by binding to the dienophile and changing the coefficients of the atoms in the lowest unoccupied molecular orbital (LUMO). Stronger Lewis acids can bind to the dienophile more effectively and induce greater selectivity in the reaction.

![Diels-Alder reaction diagram]

Table I. Product Ratio for the Reaction of Cyclopentadiene with (-)-Dimenthyl Fumarate.

<table>
<thead>
<tr>
<th>conditions</th>
<th>6:7</th>
<th>conditions</th>
<th>6:7</th>
</tr>
</thead>
<tbody>
<tr>
<td>neat</td>
<td>1:1.08</td>
<td>10 mmol AlCl₃/Et₂O</td>
<td>2.25:1</td>
</tr>
<tr>
<td>1.0 M LPDE</td>
<td>1.35:1</td>
<td>unactivated Al₂O₃</td>
<td>1.32:1</td>
</tr>
<tr>
<td>3.0 M LPDE</td>
<td>1.52:1</td>
<td>activated (200 °C) Al₂O₃</td>
<td>1.40:1</td>
</tr>
<tr>
<td>5.0 M LPDE</td>
<td>1.40:1</td>
<td>Et₂AlCl in toluene (-20 °C)</td>
<td>21.2:1</td>
</tr>
</tbody>
</table>
SYNTHETIC APPLICATIONS

Diels-Alder Reaction

Braun and Sauer demonstrated in 1986 that the reaction of cyclopentadiene with methyl acrylate showed an increase in the endo/exo ratio with increasing LiClO₄ concentration in diethyl ether.¹¹ More recently, Grieco has demonstrated that high concentrations of LiClO₄ in diethyl ether provide a powerful medium for performing Diels-Alder reactions. One remarkable example of this reaction medium is the Diels-Alder reaction of furan with dienophile 8 (Scheme II).¹² This reaction is synthetically challenging because furan is normally an unreactive diene in Diels-Alder reactions, and the adduct undergoes cycloreversion at high temperatures. This reaction had previously been carried out at 15 kbar pressure for six hours,¹³ but in the presence of LiClO₄ the reaction proceeds at ambient pressure and temperature.

Scheme II

Grieco originally proposed that the increased rate of this reaction was due the internal solvent pressure exerted by LDPE. This explanation was discounted by Forman and Dailey⁸, who determined that the Diels-Alder reaction between styrene and 1,3-diphenylisobenzofuran, which is not catalyzed by Lewis acids, is also unaffected by LiClO₄ concentration. If the effect of LPDE were due to internal solvent pressure, all Diels-Alder reaction rates would be expected to increase because they all have a negative volume of activation.

Water has been used as a solvent to enhance the rate of Diels-Alder reactions,¹⁴ but these same reactions run in LPDE give somewhat better selectivities and yields. For example, reaction of cyclopentadiene with ethyl acrylate in water after five hours at room temperature gives the cycloadducts in 73% yield and in a 4:1 endo/exo ratio. In contrast the reaction carried out in LPDE at room temperature gives a 93% yield of the products in an endo/exo ratio of 8:1.¹² Another favorable feature of the LPDE reaction medium in comparison to water is that substrates sensitive to hydrolysis can be used in LPDE.

Other notable examples of Diels-Alder reactions promoted by LiClO₄ have been reported recently. Grieco has used this methodology to perform a regio- and stereoselective Diels-Alder reaction in the syntheses of quassinoid natural products.¹⁵ Reaction of dienophile 11 with diene 12 gave unsatisfactory results in hydrocarbon solvents but gave 73% yield of the desired isomer 13 with 5.0 M LiClO₄ in ethyl acetate (Scheme III).
Lucchi and Fabris have used LPDE to effect a cycloaddition of two equivalents of quadricyclane with $p$-benzoquinone to form interesting C$_2$ symmetric ketones.\textsuperscript{16} Quadricyclane decomposed when conventional Lewis acids were used in an attempt to catalyze the reaction. Earlier this year Reetz and Gansauer reported that a number of Diels-Alder reactions can be performed using catalytic amounts of LiClO$_4$ in dichloromethane.\textsuperscript{17} A notable example of this work is the reaction of the Danishefsky diene 14 with the $\alpha$-alkoxy aldehyde 15. The product corresponding to chelation control 16 was formed in preference to 17 in a ratio of 19:1 using LiClO$_4$ as a catalyst (Scheme IV). Similar diastereoselectivity has been achieved in this system using stoichiometric amounts of MgBr$_2$.\textsuperscript{18}

**Scheme IV**

![Scheme IV](image)

### [1,3]-Sigmatropic Rearrangements

The aliphatic Claisen rearrangement of allyl vinyl ethers is a thermal [3,3]-sigmatropic process. Grieco has reported that this reaction proceeds rapidly in water and has subsequently examined the effect of LPDE.\textsuperscript{19} Remarkably, however, products consistent with a [1,3]-sigmatropic rearrangement instead of the expected [3,3]-rearrangement were obtained (Scheme V). For example, when allyl vinyl ether 18 was heated in a water-methanol mixture, the Claisen rearrangement product 19 was isolated. However, when 18 was stirred in LPDE, a mixture of [1,3]-sigmatropic rearrangement products 20a and 20b were isolated in a 5:1 ratio. Seven additional allyl vinyl ethers were studied, and the [1,3]-sigmatropic rearrangement was found to be the major pathway in each instance. The [1,3]-sigmatropic rearrangement has been known to compete with the Claisen rearrangement in rare cases when the Claisen is energetically or sterically unfavored.\textsuperscript{20}

When the C-12 epimer of 18 was subjected to the reaction conditions shown in Scheme VI, 20a and 20b were isolated in the same ratio as previously reported. This observation is consistent with a nonconcerted pathway. Moreover, a crossover experiment indicated that the
substrates ionized and then recombined to form the rearranged products. Finally, when the allyl vinyl ether is monosubstituted in the allyl γ position, the recombination of the ions is not selective.21

Scheme V

The inability of 1.8 M n-Bu4NC104 to promote any sigmatropic process lends support to the idea of Lewis acid promotion by the lithium cation.19 Kinetic experiments showed that the rate constant of the rearrangement increases as the lithium cation concentration increases, although the dramatic non-linear increase observed suggests that Lewis acid promotion may not be the only operative mechanism. On the basis of these experiments and literature precedent,22 it is proposed that the Lewis acidic lithium cation promotes ionization, and that the charged intermediates are stabilized in the high dielectric medium.

Reactions Of Allylic Alcohols And Allylic Acetates

Both Grieco and Pearson have used LiClO4 to promote nucleophilic additions to allylic alcohols.23,24 The LiClO4 promoted reaction was found to be general for many substrates and nucleophiles.24 Experimental evidence suggests that these transformations proceed by a mechanism analogous to that described for the [1,3]-sigmatropic rearrangements; the lithium cation acts as a Lewis acid to promote ionization and LiClO4 stabilizes the ionic intermediates. Evidence to support this mechanistic proposal is shown in Scheme VII.24 Both allyl alcohols 21 and 22 react with silyl ketene acetal 23 to give the same product 24. No specific rate evidence was provided, but Grieco reported that reactions proceed more quickly in 2.0 M LPDE than in 1.0 M LPDE.23 Pearson used this methodology in his synthesis of (±)-γ-lycorane, and Grieco found a useful application for it in the synthesis of yuehchukene.25,26

Scheme VII
Addition Reactions

In 1991 Reetz and Bach discovered that LPDE promotes aldol reactions. Solutions containing a large excess of LiClO₄ induce reactions which are complete in one hour; however, catalytic amounts of LiClO₄ in diethyl ether required much longer reaction times.²⁷ It was recently reported that the catalytic activity of LiClO₄ is much greater in methylene chloride.²⁸ For example, the addition of the silyl ketene acetal 23 to benzaldehyde was complete within 15 minutes in the presence of 3 mol % LiClO₄. It was also found that the use of LiClO₄ in the reaction of 23 with chiral α-alkoxy aldehyde 13 results only in the product of chelation-controlled addition 25 (eq 3).²⁷ These results are comparable to a similar reaction promoted by TiCl₄ which gave the aldol adduct in 97% diastereoselectivity.²⁷ It is probable that the lithium cation acts as a Lewis acid to promote the formation of the aldol condensation product 25.

\[ 23 + 13 \xrightarrow{5 \text{M LPDE, 1 h}} 25 \]

LPDE has also been used successfully to promote additions to hindered α,β-unsaturated ketones and lactones.²⁹ Grieco reported that conjugate additions to hindered substrates which normally required high pressure can be carried out efficiently using LiClO₄ promotion. This methodology has been applied to the synthesis of (±)-sesbanimide A and B.²⁹b Allylstannations of aldehydes³⁰ as well as additions to quinones,³¹ aldimines, and oxiranes³² have also been promoted by LiClO₄. Each of these substrates contains a Lewis basic functional group; therefore, it is reasonable to propose that the Li⁺ is acting as a Lewis acid in each case.

CONCLUSION

LiClO₄ has been used to promote several synthetically important organic transformations. Reactions that were previously available only under high pressures can be performed in relatively mild conditions using this salt. A major disadvantage of this medium is that perchlorate salts can cause explosions in the presence of easily oxidized substrates.³³ Two principle mechanisms have been proposed in the LiClO₄ promoted reactions: stabilization of polarized transition states and Lewis acid catalysis. The reactions are usually carried out in high concentrations of LiClO₄ in diethyl ether but some can take place catalytically when methylene chloride is the solvent. Although excellent results are observed in this reaction medium, studies suggest that LiClO₄ is not as effective as conventional Lewis acids by comparison.
REFERENCES
FROM ROTAXANES TO MOLECULAR TRAINS - JUST CHEMIST'S TOYS?

Reported by Slawomir Z. Janicki

TOPOLOGY AND CHIRALITY

The vast majority of compounds organic chemists work with are held together by some kind of chemical bond - covalent, ionic or hydrogen, to name the most prevalent. There is, however a family of structures that defy our intuitive sense of bonding and related chirality. The elements of these structures interact with each other by mechanical means without any obligatory chemical bonding. The simplest one is a rotaxane which consists of an axle with bulky ends that hold a freely moving central ring. Higher order structures include catenane and related molecular knots of which the trefoil is the simplest one. The description of their structure and chirality belongs to the field of topology - a division of mathematics that describes connectivity only disregarding such structural properties as distance and angle. Topology regards all objects as flexible, thus a classical tetrakisubstituted carbon is not topologically chiral as it can deform to its mirror image without breaking a bond. Within the rules of of the topology D-glyceraldehyde can become planar and then transform into its L enantiomer. It involves a higher dimension of chirality and considers a structure chiral only when breaking a bond is necessary to transform it into its mirror image. Therefore the trefoil knot is chiral. The catenane itself is not chiral but becomes topologically chiral when its rings are given a direction.

Scheme I

The aesthetics of these structures appealed to organic chemists and their syntheses constituted a challenge. Over the last decade, however, developments in the field of organic material engineering made these supramolecular systems desirable, and their syntheses, therefore, became an important field of unnatural product chemistry. Today, their properties are investigated in more than a dozen research groups in organic, organometallic and polymer chemistry. In addition, catenanes and molecular knots are often found in DNA and are of interest.

Copyright © 1993 by Slawomir Z. Janicki
in genetic biochemistry.

SYNTHETIC METHODS

Statistical

The conceptually simplest synthesis of these structures involves statistical threading and/or winding of a chain-like structure during a chemical reaction. In this way a rotaxane may be made either by threading\(^3\) of a chain through a macrocyclic ring during the installation of its end cap or by winding of a bifunctional chain around a pre-assembled axle with subsequent cyclization. Similarly, catenanes can be synthesized by threading a bifunctional chain through a macrocyclic compound\(^4\) or by mutual winding of two bifunctional chains. Although this simple concept proved to be valid, it has little practical application. The required reaction conditions are mutually exclusive; therefore, the yields are very low. A high yield of macrocyclisation requires high dilution, but the crucial winding or threading process needs very high concentration because of its low probability. The first requirement is lifted in the synthesis of polymeric rotaxanes\(^5\) where high concentration is required to both thread and couple, thus allowing for the successful synthesis of novel polymers. The most obvious solution to the first problem is to use templates.

Templates

It is difficult to achieve high yields of cyclizations at high concentration; therefore, chemists concentrated their attention on providing conditions for successful winding and threading by a local rather than a global increase of concentration.

Covalent Bonds

One method to increase the local concentration is to provide the molecules with some means of interacting before the actual reaction occurs, thus removing some of the probability factors which lower the yields. The most obvious approach is to temporarily create a covalent bond between the parts and then destroy it after the construction is completed (Scheme II).\(^1\) Published synthetic routes are very long and arguous. During the 30 years of their development\(^6\) in Schill's group their effort resulted in only a handful of synthesized structures.

Scheme II

\[
\text{Diagram of Scheme II}
\]
Inclusion In Cyclodextrins

Cyclodextrins form stable inclusion complexes\(^7\) with hydrophobic molecules by shielding them from the hydrophilic environment. This allows preassembly of the ring and axle parts of a rotaxane\(^8,9\) followed by the installation the end caps on the relatively stable complex (Scheme III). As cyclodextrins have two distinct ends, it is possible to resolve cyclodextrin rotaxanes with two different caps\(^9\). When the chain is long enough,\(^10\) several cyclodextrin units may be threaded onto one axle giving oligo-cyclodextrin rotaxanes.

Scheme III

\[ \text{HO} \quad \text{COOH} \]

\[ \text{J}_l - \text{J}_t \]

\[ \text{Stacking} \]

One of the most successful approaches\(^11\) to-date uses the principle of \(\pi - \pi\) interactions between aromatic systems. Developed in the J. Fraser Stoddart research group the synthesis relies on the \(\pi - \pi\) stacking interaction between bis-pyridinium salt and \(p\)-dialkyloxybenzene.\(^12\) The preassembled system undergoes intramolecular alkylation at nitrogen\(^12,13,14,15\) or formation of a macrocyclic ether (Scheme IV).\(^16\)

Scheme IV

\[ 2 + 2 + 6 \rightarrow 7 \]
This self-assembly process allowed for facile construction (as it became more of an act of engineering rather than art) of a plethora of structures with interesting topology and behavior.\textsuperscript{12-19} The initial synthesis\textsuperscript{12} of [2]-catenane 7 (Scheme IV) was a one-pot one step reaction of five units: two of bipyridine 4, two of \textit{para}-bis(bromomethyl)benzene 5 (BBB) and bisparaphenylene-34-crown-10 6. Extension of the BBB unit to the \textit{p,p}'-bis(bromomethyl)-bisphenylene\textsuperscript{14} allows for inclusion of two crown ether units giving a [3]-catenane 8 (Scheme V).

\textbf{Scheme V}
Similar methodology was used to make rotaxane 9 (Scheme V).\textsuperscript{18} This bisporphyrin rotaxane was made as a model compound for a system in which the absorption of a photon triggers the movement of its ring unit. The rotaxane 9 has two degenerate sites suitable for complexation of the ring unit. It acts as a shuttle moving back and forth the two complexation sites. Assembling the four donor units in a cycle under high pressure allows the threading of two paraquat units onto one four-site ring producing\textsuperscript{15} a molecular train 10 in which the central ring moves around the larger cycle.

**Metal Complexes**

Several years ago Sokolov\textsuperscript{20} put forth the idea of using transition metals as a templates for the synthesis of a molecular knot, much like the alkali metals are used to synthesize crown ethers. Practical realization of this approach was first published by Sauvage.\textsuperscript{21} He used the copper(I) ion as the template and 2,9-disubstituted 1,10-phenantrolines as building blocks. The Pedersen synthesis of two crown ether units around the central complex completed the [2]-catenate. The resulting complex 11 (Scheme V) can be demetalated with aequous KCN to give the final free [2]-catenand 12. The X-ray structure of 12\textsuperscript{8} shows that the rings intersect in the polyether region, indicating that the molecule rearranges significantly after the release of the central copper ion. If the molecule is denied this opportunity, the demetalation occurs extremely slowly.\textsuperscript{22}

**Scheme VI**
It is possible to extend this approach to make [3]-catenands with polyether\textsuperscript{23} and bisalkyne\textsuperscript{24} bridges. The [3]-catenate and its higher homologs, up to [7]-catenate, were formed.\textsuperscript{24c}

Using bis-phenantroline units, Sauvage\textsuperscript{25} was able to perform the first synthesis of a trefoil molecular knot (Scheme VI). This was the only topologically chiral molecule synthesized.

APPLICATIONS

The use of the template-based synthesis allows for the assembly of many-body systems with a set of designed properties. One target system\textsuperscript{18,26} is an artificial electron cascade, similar to those found in photosynthetic systems. Model compounds were prepared by using both $\pi-\pi$ stacking\textsuperscript{18} and copper complex\textsuperscript{36} methodologies. The copper-based molecule 13 (Scheme VII)\textsuperscript{36} contains three different metal atoms: copper(I), complexed by the rotaxane system, zinc(II) and gold(III), complexed by two porphyrin units. When this molecule is excited with a laser pulse at the gold-complexing end, it rapidly transfers an electron from the gold porphyrin to the zinc porphyrin. It then slowly transfers the electron back to the gold end stepwise via the copper center. The advantage of using the rotaxane complex is that it is at least 8 orders of magnitude more thermodynamically\textsuperscript{26} stable than the open chain analog. Also its kinetic\textsuperscript{22} stability is two orders of magnitude larger.

Scheme VII
Numerous publications have described the synthesis of polymeric rotaxanes and catenanes with the objective of synthesizing a polymer with unique properties. Three goals of this synthesis have been described in the literature\(^\text{27}\): (1) increase in elasticity due to the non-covalent interaction of interlocking chains and rings; (2) change of solubility of a threaded polymer as compared to the unthreaded polymer and (3) the chance of preparing copolymers from immiscible polymers.\(^\text{28a}\)

The polymeric rotaxanes may exist in one of four possible forms: main chain (14 and 15) or side chain (16 and 17) (Scheme VIII).

**Scheme VIII**

![Scheme VIII](attachment:image.png)

Several types of backbone polymers (polyester,\(^\text{28a}\) polystyrene,\(^\text{28b}\) polysiloxane,\(^\text{28c}\) and polyacrylonitrile\(^\text{28d}\)) and threaded units (crown ethers,\(^\text{28a}\) cycopolysiloxane,\(^\text{28c}\) and cyclodextrins\(^\text{28e}\)) were employed. An example of such synthesis is shown on Scheme IX.\(^\text{28b}\) The polymerization of styrene 18 is initialized by the catalyst 19. The azo-initiator 19 decomposes thermally releasing nitrogen and two tertiary radicals. These radicals initiate chain reaction which is run in the presence of macrocyclic polyether 20. The threading occurs during polymerization, and the tertiary radicals formed from 19 serve as the cap ends. The resulting polymer had one crown ether unit per 1.5 styrene mer. The polymer has low average molecular weight, \(\sim 10\) kg/mol, which corresponds to \(\sim 15\) rotaxane units per chain.

In another example, 2,6-dimethyl-\(\beta\)-cyclodextrin (\(\text{Me}_2\)-\(\beta\)-CD) 21 (Scheme X) was threaded on the side chains of the copolymer 22. Subsequently the dangling ends of the side chains were capped with the amine 23. No extractable cyclodextrin was found in the product and nearly all side chains of 22 were functionalized. The cyclodextrin shielded the amide groups and did not allow the hydrogen bonds to form. This resulted in a polyrotaxane that was soluble in
ether while the parent copolymer 22 was not. Also, the viscosity of the polymer was significantly reduced.

Scheme IX

Scheme X
Similar polymers also exhibit increased solubility, decreased viscosity, and increased swelling capabilities.  

When the synthesis of polymeric rotaxanes is close to statistical, that is the preorganization interactions are small or negligible, the threading becomes more efficient when the ring size increases. For short chain rotaxanes, however, there are upper and lower limits to the threading efficiency. If the ring is too small, the axle can not fit inside. A very large ring would be too loose and slip around the cap. The situation is different with the polymeric rotaxanes whose structures resembles 14. In this case, the upper limit of the ring size has not been observed even with rings as large as >500 bonds. It is quite possible that rings of this size may undergo multithreading, that is multiple threads may run through one ring. This is a new type of mechanical crosslinking. Once the ring threads onto the polymer it has a chance to slip back or to move toward the center of the polymer. If the polymerization is still in process, the chain elongates, and the ring further "moves" toward the center. At some point the probability of dethreading is so small that no such effect is observed.

**SUMMARY**

The chemistry of catenanes, rotaxanes and molecular knots evolved from the challenge of synthesis for aesthetic values to the rapidly growing field of molecular engineering. The goals which have been realized were unachievable until just a few years ago. The growing number of publications in this area, now well above 200, shows the widespread interest in these fascinating structures.

**REFERENCES**


NOTICE: Return or renew all Library Materials! The Minimum Fee for each Lost Book is $50.00.

The person charging this material is responsible for its return to the library from which it was withdrawn on or before the Latest Date stamped below.

Theft, mutilation, and underlining of books are reasons for disciplinary action and may result in dismissal from the University.

To renew call Telephone Center, 333-8400

UNIVERSITY OF ILLINOIS LIBRARY AT URBANA-CHAMPAIGN
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereoselective Reactions of Chiral Allenes</td>
<td>1</td>
</tr>
<tr>
<td>Yong Sun Park</td>
<td></td>
</tr>
<tr>
<td>Arynes: Useful Intermediates in Organic Synthesis</td>
<td>9</td>
</tr>
<tr>
<td>Zhipei Wu</td>
<td></td>
</tr>
<tr>
<td>Reduction and Oxygenation of Organic Substrates with <em>Beauveria Sulfurescens</em></td>
<td>17</td>
</tr>
<tr>
<td>Zhengrong Kong</td>
<td></td>
</tr>
<tr>
<td>Methane Monoxygenase: Elucidation of an Organometallic Enzyme Mechanism</td>
<td>25</td>
</tr>
<tr>
<td>James V. Suggs</td>
<td></td>
</tr>
<tr>
<td>Synthesis, Characterization, and Properties of Ladder Polymers</td>
<td>33</td>
</tr>
<tr>
<td>Douglas J. Pesak</td>
<td></td>
</tr>
<tr>
<td>Dithioacetal S-Oxides in Organic Synthesis</td>
<td>41</td>
</tr>
<tr>
<td>Kevin Z. Gan</td>
<td></td>
</tr>
<tr>
<td>Preparation and Functionalization of Buckminsterfullerene</td>
<td>49</td>
</tr>
<tr>
<td>Scott A. Long</td>
<td></td>
</tr>
<tr>
<td>Enantioselective Catalysts for the Cyclopropanation of Olefins by Diazocompounds</td>
<td>57</td>
</tr>
<tr>
<td>Jennifer L. Hunt</td>
<td></td>
</tr>
<tr>
<td>Rapid Assembly of Oligosaccharides by Substrate-Controlled Strategy</td>
<td>65</td>
</tr>
<tr>
<td>Fanwen Zeng</td>
<td></td>
</tr>
<tr>
<td>Synthetic and Mechanistic Aspects of Cubane and Homocubane</td>
<td>73</td>
</tr>
<tr>
<td>Sergei V. Kolotuchin</td>
<td></td>
</tr>
<tr>
<td>Reductive Coupling of Carbonyl Groups with Carbon-Carbon Double Bonds Through Ketyl Radical Anions</td>
<td>81</td>
</tr>
<tr>
<td>Ali Koohang</td>
<td></td>
</tr>
<tr>
<td>Cyclization Techniques to Provide 14-Membered Carbocyclic Rings: Synthesis of Cembranoid Diterpenes</td>
<td>89</td>
</tr>
<tr>
<td>José J. Morales</td>
<td></td>
</tr>
<tr>
<td>From Templates to Self-Replicating Systems</td>
<td>97</td>
</tr>
<tr>
<td>Yue Wang</td>
<td></td>
</tr>
<tr>
<td>Synthesis of Heterocycles Using Oxygen Ylides</td>
<td>105</td>
</tr>
<tr>
<td>Brian Fink</td>
<td></td>
</tr>
</tbody>
</table>
STEREOSELECTIVE REACTIONS OF CHIRAL ALLENES

Reported by Yong Sun Park

January 27, 1994

INTRODUCTION

Allenes exhibit a wide variety of reactivities in many types of reactions and have become versatile intermediates for organic synthesis. In particular, chiral allenes bearing two different substituents on each side of the allene moiety can serve as useful precursors for the synthesis of complex chiral molecules. The recent development of general methods for the preparation of chiral, non-racemic allenes and the resolution of chiral allenes by chiral liquid chromatography on a preparative scale and chiral gas chromatography on an analytical scale have facilitated their use for synthetic applications as well as mechanistic investigations. This review will discuss recent work on the stereoselective reactions of chiral allenes in Diels-Alder reactions, nucleophilic additions to allenyl aldehydes and ketones, and electrophilic additions.

BACKGROUND

The central carbon of an allene is sp-hybridized with two sets of orthogonal p-orbitals which form bonds with the p-orbitals of the two terminal sp2-hybridized carbon atoms. Consequently, the resulting π-bonds are orthogonal to each other. Therefore, two different substituents attached to a terminal carbon of a chiral allene lie in a plane at right angles to the plane of the adjacent double bond. The chirality of the allene is maintained in the product of various types of stereoselective reactions by the facial selectivity controlled by the steric and electronic effects of two different out-of-plane substituents (Figure 1).

![Figure 1. Model of the Facial Selectivity in reactions of Chiral Allenes.](image)

STEREOSELECTIVE REACTIONS OF CHIRAL ALLENES

Catalytic Hydrogenation

In 1975, Crombie and co-workers found that the heterogeneous catalytic hydrogenation of
chiral allene proceeded with high stereoselectivity. The facial selectivity of the partial hydrogenation reaction of chiral allene was controlled by the two different size of the out of plane substituents. As shown in Scheme I, the H-side of the double bond can approach the surface of the catalyst closer than the CH₃-side of double bond. The (Z)-isomer comes from preferable H-side attack and was major product of the reaction in a ratio of 15:1.

Scheme I

Diels-Alder Reactions

Figure 2. Basic Model of a Vinyl Allene as Diene in Diels-Alder Reaction.

Intermolecular Diels-Alder reactions of vinyl allenes have the potential for regio- and stereochemical control as illustrated in Figure 2. The results in Scheme II show how A-X interactions can dominate the stereochemistry of the cycloadditions. In all cases, the major product arises from a transition state in which the A-X interaction is small (H-H), and only compounds in which A or X is a hydrogen are detected. When the two substituents at the allene terminus are different, X≠Y, the dienophile approaches the less hindered face of the diene and that results in control of the exocyclic double bond stereochemistry. As shown in Scheme II, the facial selectivity of the reactions are very high in the addition of both fumarate (99:1) and and maleic anhydride (98:2). When A≠B, the A-X interaction appears to control the exo/endo selectivity of the reaction. In the fumarate addition reaction, because one carbomethoxy group is always below the diene in the transition state, there is less or no inherent endo preference resulting from secondary orbital overlap. However, in the case of the maleic anhydride addition reaction, because the inherent endo preference can reinforce the endo selectivity of the A-X interaction, the endo/exo selectivity is higher than in the fumarate addition reaction (94: 4 vs. 82:17). When A≠C, it controls the regiochemistry as shown in Scheme II.
The activating influence of a carboxylate moiety on the allene framework makes chiral allenes excellent dienophiles in Diels-Alder reactions. It is expected that the 1:1 adduct would be preferentially obtained through the combination of the sterically favored approach owing to the axial asymmetry of the allene moiety and the effective secondary orbital interaction. Recently, Kanematsu\(^5\) reported that the Diels-Alder reaction of enantiomerically pure 1 with cyclopentadiene in the presence of aluminum chloride afforded the 1:1 adduct 2 in 96\% yield. As expected, 3, the enantiomer of 1, gave the 1:1 adduct 4 in 89\% yield (Scheme III).

An intramolecular Diels-Alder reaction with the vinyl allene acting as the diene has several advantages as a synthetic method for the asymmetric synthesis of highly functionalized adducts. The vinyl allenes are sterically ideally structured for undergoing completely exo selective intramolecular Diels-Alder reactions, due to the rigidity of the vinyl allene system. As shown in Scheme IV, the central chiral element of the propargylic alcohol is considered to be preserved, when the alcohol undergoes stereoselective [2,3]-sigmatropic shift to produce an allene intermediate. In the subsequent stereospecific intramolecular Diels-Alder reaction, the axial chiral element of an allene intermediate is also preserved to generate two central chiral elements of the product.\(^6\) This stereospecific reaction has potential for natural product synthesis and has been used in the synthesis of 4/6/5 tricyclic (+)-sterpurene(Scheme V)\(^7\) and the hexahydronaphthalene moiety of (+)-compactin.\(^8\)
Addition to Chiral Allenyl Aldehydes and Ketones

The facial selectivity of nucleophilic addition to an aldehyde or ketone is influenced by an adjacent stereocenter. In the case of chiral allenyl aldehydes and ketones, the magnitude of the directing effect might be expected to be small, because of the distance between the carbonyl center and the out-of-plane substituents. However, Marshall and co-workers recently reported highly diastereoselective addition reactions of Grignard reagents and L-Selectride to chiral allenyl aldehydes and ketones as shown in Table I.\textsuperscript{10} If one assumes a preferential s-trans transition state orientation of allenyl carbonyl group and considers the Bürgi-Dunitz approach of a nucleophile to a carbonyl carbon, the trajectory of approach is roughly parallel to the C-C bond between allene skeleton and substituents and the nucleophile prefers to attack the less hindered face of carbonyl group.\textsuperscript{9,11} When the bulky \( t\)-BuPh\(_2\)Si(DPS) group was used as a directing group, the nucleophilic reagents attack the carbonyl group with high stereoselectivity. Even MeMgBr adds with high diastereoselectivity. The selectivity decreases as the size of \( R^2 \) increases as expected. The steric directing effect apparently plays a major role in these diastereoselective addition reactions.
Table I. The Diastereoselective Additions to Chiral Allenyl Aldehydes and Ketones.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵M</th>
<th>Yield(%)</th>
<th>5:6</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-Bu</td>
<td>H</td>
<td>H</td>
<td>Bu</td>
<td>MeLi</td>
<td>95</td>
<td>55:45</td>
</tr>
<tr>
<td>t-Bu</td>
<td>H</td>
<td>H</td>
<td>Bu</td>
<td>i-PrMgBr</td>
<td>90</td>
<td>81:19</td>
</tr>
<tr>
<td>DPS</td>
<td>Bu</td>
<td>H</td>
<td>Me</td>
<td>MeMgBr</td>
<td>95</td>
<td>83:17</td>
</tr>
<tr>
<td>DPS</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>MeMgBr</td>
<td>90</td>
<td>96:4</td>
</tr>
<tr>
<td>DPS</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>EtMgBr</td>
<td>90</td>
<td>99:1</td>
</tr>
<tr>
<td>DPS</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>DIBAH</td>
<td>90</td>
<td>50:50</td>
</tr>
<tr>
<td>DPS</td>
<td>Bu</td>
<td>Me</td>
<td>Me</td>
<td>L-Selectride</td>
<td>90</td>
<td>84:16</td>
</tr>
<tr>
<td>DPS</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>L-Selectride</td>
<td>92</td>
<td>99:1</td>
</tr>
</tbody>
</table>

Electrophilic Addition to Chiral Allenes

The intramolecular addition of a nucleophilic species, such as an alcohol or an amine to a suitably positioned and activated allenyl group can lead to a variety of functionalized heterocycles. Mercury(II) and silver(I) ions have been used as electrophilic activating reagents. The metal ions are generally introduced on the more crowded face of the reactive double bond to form a bridged species, followed by backside attack of nucleophile. The product stereochemistry can be explained by nucleophilic attack of a hydroxyl or amino group from the least hindered side of the intermediate. This step is the rate- and product determining step. Treatment of 7 with silver tetrafluoroborate gave 8 and 9 in a ratio of 8:1 in 86% yield(Scheme VI). This aspect of chiral allene chemistry has been evaluated for a simple allenic amine 7 in the synthesis of (R)-coniine.12

Scheme VI

![Scheme VI](image)

It is well established that α-allenic alcohols cyclize stereospecifically to 2,5-dihydrofurans and this can be applied to the synthesis of hydrofuran subunits of natural products.13 The intramolecular cyclization of diol 10 with AgNO₃ afforded only the fused dihydrofuran 11 and the
spiro dihydrofuran 12 was not detected. The first step appears to be rate-determining step and the formation of the less crowded bridged species is favored due to the steric approach control during attack on the allenyl π system. The spiro compound 12 was obtained by protecting the secondary alcohol and cyclization with AgNO3.\(^\text{14}\)

**Scheme VII**

The epoxidation of allenes generally yields highly reactive allene oxides and/or bis-epoxides which lead to complex mixture of products. However, for some hindered allene bearing bulky substituents, peracid epoxidation can lead to isolable allene oxide and bis-epoxide. The peracid attack takes place at the more substituted double bond and on the sterically least hindered side of that double bond stereoselectively.\(^\text{15}\) As shown in scheme VIII, in the presence of excess oxidant, the allene 13 was transformed to rearrangement product enone 14, presumably via a transient bis-epoxide intermediate.\(^\text{10}\) The bulky DPS group would serve as effective steric directing group.

**Scheme VIII**

When an electrophile reacts with an allenic substrate bearing an electropositive substituent such as a silyl or a stannyl group, an electrophilic substitution reaction can take place. This reaction can proceed via $S\text{E}^2$\(^-\) by a syn or anti mechanism.\(^\text{16}\) With the two faces of the chiral allene sterically differentiated by the silyl and methyl group, the allenylsilane 15 reacted highly stereoselectively with the adamantyl cation to give the acetylenic products 16 and 17 in a ratio of 99:1 in 30% yield as shown in Scheme IX.\(^\text{17}\)
If one consider a steric effect of silyl group, the predicted approach of the electrophile is *anti* to the large silyl group. However, the observed enantioselectivity could arise from the steric bulk of the silyl group, the electronic effect of the silyl group, or a combination of both. A silyl group can stabilize positive charge in a β-silyl carbocation through hyperconjugation of the σ-electrons in the Si-C bond with the empty p-orbital of the cationic carbon. This hyperconjugation by an electron donating leaving group is considered to render the π-bond more nucleophilic and more concentrated on the *anti* side.\(^\text{18}\) This electronic effect should reinforce *anti* attack as does the steric effect.

**Scheme IX**

The allenyl silane 15 was treated also with isobutyraldehyde in the presence of titanium tetrachloride to give acetylenic alcohols.\(^\text{17}\) The diastereomers were produced in a ratio of 95:5 and the enantiomeric purity of the major diastereomer was 98% ee. These results show that the transfer of chiral element was very close to 100%. It can be suggested that the \(S_E2'\) reactions of allenylsilanes are stereospecifically *anti* and the addition of aldehyde to the allene was predominantly *syn*(C\(_4\)-C\(_5\)). The stereoselectivity of these reactions can be rationalized on the basis

**Scheme X**
of the transition state model in which the steric repulsion between the allenyl methyl and aldehydeisopropyl groups destabilizes transition state B and consequently A is favored. Marshall recently reported that chiral allenylstannanes can also undergo stereoselective Se2' additions to aldehydes in the presence of Lewis acids affording homopropargylic alcohols with excellent diastereoselectivity.

CONCLUSION

Chiral allenes have been shown to be very useful reagents for a variety of reactions proceeding with high stereoselectivity. In particular, intramolecular Diels-Alder reactions of cycloalkenylallenes and various electrophilic addition reactions provide versatile and convenient methods to construct a wide range of polycyclic compounds and potential intermediates for the syntheses of natural products with high stereoselectivities. In the case of Diels-Alder reactions and additions to allenyl carbonyl groups, the steric directing effect of the substituents of the allene appears to play a major role towards determining the facial selectivity. In the electrophilic substitution reactions, an electronic β-silicon effect might be at work in cooperation with the directing effect of the sterically bulky silyl group enforcing even greater stereoselectivity.

REFERENCES

ARYNES: USEFUL INTERMEDIATES IN ORGANIC SYNTHESIS

Reported by Zhipei Wu January 31, 1994

INTRODUCTION

After the benzyne molecule was first proposed by G. Wittig in 1942\(^1\) and the role of aryne intermediates in nucleophilic addition was demonstrated by J. D. Roberts in 1953,\(^2\) considerable work has been devoted to developing aryne intermediates as potent tools in organic synthesis. Arynes have been used to synthesize polycyclic compounds through nucleophilic additions\(^3\) and cycloadditions because of their high electrophilicity and dienophilicity.\(^4,5\) In addition, aryne chemistry under Flash Vaccum Pyrolysis (FVP) conditions has also been studied.\(^6\) In this discussion, emphasis will be placed on recent development in the applications of aryne intermediates for synthesis of polycyclic aromatic compounds and polyarenes.

GENERATION OF ARYNES

Classically, arynes have been generated by base-induced elimination of hydrogen halide from halobenzene,\(^2\) by the thermal decomposition of diazocarboxylate salts,\(^7\) or by the oxidation of 1-aminobenzotriazole in the presence of lead tetraacetate.\(^8\) In 1976, the preparation of aryne from phenyl benzenesulfonate and its derivatives by treatment with lithium tetramethylpiperidide was reported.\(^9\) The product yields, however, were not as high as when bromobenzene was used as the benzyne precursor. S. V. Luis and coworkers found that aryne can also be generated in the thermal decomposition of 2-carboxyphenyl p-toluenesulfonate.\(^10\) This compound and its sodium and potassium salts behave as better aryne precursors than the related metal o-halobenzoates, but apparently are not as useful as phenyldiazonium-2-carboxylate and diphenyldiodonium-2-carboxylate, the two most common sources for thermal decomposition to give aryne intermediates. In 1991, Suzuki et al. reported a new efficient protocol for aryne generation in which arynes are cleanly and rapidly generated by halogen-lithium exchange of ortho-haloaryl triflate with n-BuLi at -78°C.\(^11\) In the same year, Wickham et al. reported that the reactions of aryl triflates and LDA at -78°C proceed by elimination of triflic acid to form the corresponding arynes.\(^12\) This method provides the first general use of phenols as aryne precursors. In addition, arynes can be formed by FVP of phthalic anhydride, benzocyclobutenedione or 2-(3',3'-dimethyltriazenyl)benzoic acid.\(^6\) As this work is at an early stage, the mechanisms governing the reaction are not yet known. At present, the findings can be best understood by assuming that arynes generated by FVP undergo ring contraction to cyclopentadienylidene carbenes, although alternative routes may exist.

Copyright © 1994 by Zhipei Wu
NUCLEOPHILIC ADDITIONS TO ARYNE INTERMEDIATES
Annulations involving intramolecular aryne side-chain cyclization

Aryne side-chain cyclization was introduced independently by Huisgen and Bunnett in the 1960s,\textsuperscript{13} and this approach has been extensively developed in natural product synthesis. In 1988, Kessar applied this methodology to the preparation of several naturally occurring benzo[c]phenanthridine alkaloids exemplified by the synthesis of chelerythrine 1 (Scheme I).\textsuperscript{14} The key step for the preparation of 1 is joining the two aryl carbons by intramolecular addition of the anionically activated naphthalene to the aryne fragment 2.

Scheme I

Annulations involving intermolecular addition of functionalized nucleophiles by arynes

Two general aryne arylation methods fall into this category. The first involves the introduction of a functionalized carbanion which also can provide an electrophilic center to an aryne. The resulting aryl anion then undergoes an intramolecular addition to the electrophilic site to complete the annulation process. The synthetic usefulness of this method was first demonstrated by Caubere who prepared benzocyclobutenols by trapping arynes with five- to seven-membered cyclic sodium enolates (Scheme II).\textsuperscript{15} It is believed that the addition of the sodium enolate to the aryne generates both an aryl anion and an electrophilic carbonyl group, which combine to form the oxyanion 3. The oxyanion is then protonated to afford 4.

Scheme II
A second annulation method has been used in the synthesis of 4-alkyl- and 4-aryl derivatives of the isochroman-3-ones, 5, which are valuable precursors in the synthesis of condensed polynuclear aromatic compounds. The key step in this methodology is the introduction of a cyano side chain ortho to a methoxymethyl group by the addition of aliphatic or aromatic nitrile anions. Subsequent hydrolysis and cyclization of the products yield the corresponding isochroman-3-ones (Scheme III).\(^3\)

**Scheme III**

\[
\begin{align*}
\text{OMe} & \quad \text{RCHCN} \quad \text{OMe} \quad \text{HCl/HAc} \quad \text{MeO} \quad \text{R} \\
\text{CH}_2\text{OMe} & \quad \text{M=Na, Li; R=alkyl} \\
\end{align*}
\]

A tandem addition rearrangement was reported in 1988 by Khanapure and Biehl. These workers found that when they treated arylacetonitriles and 2-bromo-4-(methoxymethyl)anisole with LDA in THF, the reaction did not generate the expected product 6, but rather compound 7.\(^{16}\) The tandem addition rearrangement pathway was proposed to support the experimental results (Scheme IV).

**Scheme IV**

\[
\begin{align*}
\text{OMe} & \quad \text{Li} \quad \text{CN} \quad \text{OMe} \quad \text{Li} \quad \text{CN} \\
\text{MeOH}_2\text{C} & \quad \text{MeOH}_2\text{C} \\
\text{6} & \quad \text{Ar} \quad \text{Ar} \\
\end{align*}
\]

Aryl-aryl bond formation via Grignard generation and trapping of arynes

In 1985, Hart and Harada found that the reaction of Grignard reagents with polyhalogenated aromatics was shown to be extremely useful in aryl-aryl bond formation in \(p\)-terphenyl synthesis.\(^{17}\) A variety of aryl Grignard reagents react with 1,4-dibromo-2,5-
diiodobenzene to produce \( p \)-terphenyls (Scheme V). This reaction can also be applied to biaryl synthesis, particularly unsymmetric biaryl synthesis.

**Scheme V**

\[
\text{Ar=biaryl (54%), 1-naphthyl (30%), 2-naphthyl (35%), } p-\text{chlorobenzene (43%)}
\]

In the same year, Harada and Hart reported the synthesis of novel arenes via the multiple aryne sequence. This reaction utilizes excess aryl Grignard reagents and certain hexahalobenzenes to produce four new aryl-aryl bonds in a one-pot reaction (Scheme VI).\(^\text{18}\) Ghosh and Hart also found that triarylbenzenes can be prepared via tandem aryne reactions of aryl Grignards with polyhalobenzenes.\(^\text{19}\)

**Scheme VI**

**INTERMOLECULAR ARYNE CYCLOADDITION**

\( [4+2] \) Cycloaddition

Guitian and Castedo developed the use of arynes for the synthesis of isoquinoline alkaloids.\(^\text{20}\) The key step in their syntheses is an intermolecular Diels-Alder reaction between an appropriate diene and an aryne serving as a dienophile (Scheme VII).

**Scheme VII**

Rickborn and coworkers also found that aryne-isobenzofuran cycloaddition provides a very direct and convenient route to the carbon skeleton of various polycyclic aromatic hydrocarbons.\(^\text{21}\) For example, two unusual aromatic compounds, \( 8 \) and \( 9 \), were constructed
through the use of 5-bromoacenaphthene and 1-bromopyrene as aryne precursors, respectively.

Figure 1. Some products from aryne-isobenzofuran cycloaddition.

Rickborn et al. subsequently investigated the regioselectivity of cycloadducts of arynes with isobenzofuran derivatives. The reactions of compound 10 with four 3-substituted arynes (3-Me, OMe, Cl, and Br) were studied, and found to exhibit regioselectivity ranging from barely perceptible (Cl) to modest (OMe) (Table I). For all of these reactions, regardless of the nature of the substituent on the aryne, the major cycloadduct formed is 11, with the aryne substituent being proximal to the ethoxy group of the isobenzofuran derivatives. Since these cycloaddition reactions involve very reactive partners, that is, arynes are probably the most reactive dienophiles known, and isobenzofurans the most reactive isolable dienes, they imply a very low activation energy and an "early" transition state. It is still not clear whether the electronic or steric effects or both play an important role for the overall regioselectivity.

Table I. Regioselectivity of 3-Substituted Benzyne Reaction with 10

<table>
<thead>
<tr>
<th>R</th>
<th>Ratio (11:12)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>60:40</td>
<td>74</td>
</tr>
<tr>
<td>Cl</td>
<td>53:47</td>
<td>74</td>
</tr>
<tr>
<td>Br</td>
<td>63:37</td>
<td>62</td>
</tr>
<tr>
<td>OCH₃</td>
<td>80:20</td>
<td>52</td>
</tr>
</tbody>
</table>

[2+2] Cycloaddition
Although reaction via a concerted [4+2] mechanism is generally preferred in the reactions of arynes with a wide variety of dienes, for certain dienes [2+2] pathway will be favored.\textsuperscript{23} For example, cycloheptatriene appears to give product from a [2+2] mechanism (Scheme VIII).\textsuperscript{24} This example indicate that when a diene system is sufficiently distorted from planarity, stepwise [2+2] cycloaddition with benzyne becomes energetically favorable.

Scheme VIII

\[
\begin{array}{c}
\text{[3+2] Cycloaddition} \\
\text{The marked electrophilicity of the aryne is also evident in [3+2] cycloaddition. Arynes react with a variety of 1,3-dipoles as well as with several sulfur and selenium heterocycles to produce cycloadducts.}^{25a-d} \text{ An example of [3+2] cycloaddition was provided by Bryce et al. who reported the reaction of benzyne with 1,2,5-thiadiazole derivatives to give the corresponding 1,2-benzisothiazole derivatives (Scheme IX).}^{25c}
\end{array}
\]

Scheme IX

1,4-Dipolar Cycloaddition

1,4-Dipolar cycloaddition reactions have attracted much attention since they provide more streamlined approaches for the construction of polycyclic systems under mild conditions.\textsuperscript{26} Khanapure and Biehl developed a novel synthesis ofazaacridones using 1,4-dipolar aryne cycloaddition.\textsuperscript{27} The general strategy is outlined below (Scheme X).

Scheme X
SYNTHESES BASED ON INTRAMOLECULAR TRAPPING OF CYCLOPENTA-DIENYLIDENECARBENES

Arynes can be formed under FVP conditions from appropriate precursors, which then undergo ring contraction to cyclopentadienyldienecarbene. Pyrolysis of tetraphenylphthalic anhydride at 860°C under the vacuum pressure of 0.04 mm Hg produces the expected product 13 in high yield (Scheme XI). It is believed that the exocyclic carbene species produced from the aryne rearrangement inserts its carbene center into the C-H bond. Brown and Eastwood also extended the ring contraction and intramolecular trapping reaction to one heteroaryne system.6

Scheme XI

CONCLUSION

Arynes have been shown to be very useful intermediates in ring construction. In addition to the typical nucleophilic reactions and cycloadditions to make complex aromatic or polycyclic compounds, intramolecular reactions of aryne and exocyclic carbene species under FVP conditions offer new approaches to the synthesis of polycyclic hydrocarbons and heterocycles, particularly of those containing a five-membered ring. Also, further effort should be put for the study of the regioselectivity in aryne chemistry in order to get higher yield for the target compound.

REFERENCES

(1) Wittig, G. Naturwissenschaften, 1942, 30, 696-703.
(22) Pollart, D.J.; and Rickborn, B. J. Org. Chem. 1987, 52, 792-798.
INTRODUCTION

Many synthetic reactions, including those requiring diastereoselectivity and enantioselectivity, may be achieved by microbiological reactions. Recent work has shown that *Beauveria sulfurescens* provides good results in reductions and oxidations of organic substrates.\(^1\) Enantioselectivity of reduction and regioselectivity of oxygenation with *B. sulfurescens* are rationalized by empirical rules. This report will focus on the use of *B. sulfurescens* in the reductive and oxidative biotransformation of organic compounds.

MICROBIOLOGICAL REDUCTION

Reduction of \(\alpha, \beta\)-Unsaturated Ketones

A number of chemical methods have been developed for the reduction of \(\alpha, \beta\)-unsaturated ketones. For cyclohexenones, dissolving metal reduction in alcohol or ammonia media offers one major isomer. Hydrogenation with transition metal catalysis, which include chiral phosphine cobalt,\(^6\) iridium,\(^7\) rhodium,\(^8\) and ruthenium\(^9\) complexes as well as copper hydride,\(^10\) provide the saturated ketones but with low enantiomeric efficiencies. Other chemical methods are also available for reduction of \(\alpha, \beta\)-unsaturated ketones, but do not offer good enantioselectivity.\(^11\) Biological reduction with *B. sulfurescens* offers good selectivity and yield.\(^4\) Studies were performed on the reductions of acyclic and cyclic \(\alpha, \beta\)-unsaturated ketones of medium ring size. For \(\alpha, \beta\)-unsaturated ketones bearing only \(\alpha\)-alkyl substituents, the products are optically pure. Scheme I illustrates reduction of acyclic \(\alpha, \beta\)-unsaturated ketones.\(^12\) The

Scheme I

```
\[
\begin{align*}
\text{R}_1=\text{Me}, \text{n-Bu} & \quad \text{R}_2=\text{Me}, \text{Et, n-Pr} \\
\end{align*}
\]
```

corresponding saturated ketones are the main products from the reduction of \(\alpha, \beta\)-unsaturated ketones with only small amounts of the saturated alcohols obtained. Two new stereogenic centers are generated. The configuration of alcohol 3 at C-2 is different from that of ketone 2 for acyclic unsaturated ketones, whereas it is the same for cyclohexenones. This suggests that there may be different modes of reaction of the acyclic saturated alcohols 3. It is presumed that alcohol 3 does not arise from ketone 2 but from a \(\alpha, \beta\)-unsaturated alcohol, which arises from the
reduction of the carbonyl in a \( \alpha, \beta \)-unsaturated ketone. The configuration of the \( \alpha \)-position of 3 is consistent with Prelog's rule (Scheme II).\(^{13}\) For acyclic \( \alpha, \beta \)-unsaturated alcohols, the ethanoyl group is larger than the methyl group at position \( \alpha \) and the Prelog product should have the \( S \) configuration.

**Scheme II**

![Scheme II Diagram]

Long chain ketones provide small amounts of the alcohols. However, \( \alpha, \beta \)-unsaturated ketones with two substituents at the \( \beta \)-position of the double bond are not reduced and bulky \( \alpha \) groups slow down the reaction. These similar results are also observed for cyclic \( \alpha, \beta \)-unsaturated ketones, such as cyclopent-2-en-1-ones and cyclohex-2-en-1-ones. These reduced rates are attributed to stereocrowding at the \( \alpha \) and \( \beta \) positions, which inhibits the delivery of hydrogen. Reductions do take place when the molecule has less than ten carbon atoms with a small \( \alpha \)-substituent and a hydrogen atom on the \( \beta \)-position.

Reduction of cyclohexenones with *B. sulfurescens* provides cyclohexanones and small amounts of cyclohexanols. Reduction of cyclohexanones gives cyclohexanols. However, reduction of cyclopentenones yields only cyclopentanones. It is assumed that reduction of the double bond occurs faster than that of the carbonyl for cyclohexenones whereas reduction of the carbonyl is inhibited for cyclopentenone. These results, which are summerized in Scheme III,\(^{14}\) show that the addition of hydrogen to the double bond is *anti*.

**Scheme III**

![Scheme III Diagram]

The absolute configurations at both C-2 and C-3 in cyclic \( \alpha, \beta \)-unsaturated ketones are assigned by circular dichroism. Reduction of cyclic \( \alpha, \beta \)-unsaturated ketones which have deuterium labels also shows the stereochemistry of the reaction. As presented in Scheme IV,\(^{15,16}\) reduction of 2-deuteriocyclohex-2-en-1-one gave the \( R \) configuration at C-2 while reduction of 3-deuterio analogs provided the \( S \) configuration at C-3. These results show that the addition of hydrogen to the \( \alpha \) and \( \beta \) positions are from opposite sides.

**Scheme IV**

![Scheme IV Diagram]
In support of this anti addition, studies on the reduction of 2,3-dideuteriocyclohex-2-en-1-one were carried out. The product has the R configuration at C-2 and the S configuration at C-3, and the addition of hydrogen is anti. Presumably, anti addition also occurs for acyclic analogs since the reduction of acyclic α, β-unsaturated ketones generates an asymmetric carbon whose configuration is consistent with Prelog's rule.

**Reduction of The Carbonyl Group**

A number of methods for the enantioselective reduction of carbonyls have been developed using aluminum, boron and silicon hydrides, and catalytic reductions. Some methodologies provide good enantiomeric excesses and good yields, and most of these approaches require the syntheses of chiral hydrides or catalysts. Bioreduction of carbonyls with *B. sulfurescens* is a useful tool for the preparation of chiral alcohols.

*B. sulfurescens* is capable of reducing cyclohexanones to cyclohexanols. As illustrated in Scheme V, reaction of 2-methylcyclohexanones mainly provides one epimer of the saturated alcohols, the cis alcohols as the major products. These results indicate that the reduction of cyclohexanones is inhibited if there is a high strain in the alcohol, i.e. strong 1,3-diaxial interaction. Thus, it is concluded that the transition structure in the reduction of cyclohexanones resembles the product alcohol and that attack of hydrogen prefers the equatorial side. Reduction of other homologues shows that mainly one epimer is obtained, which does not follow Prelog's rule. This result is further supported by the reduction of (+)-carvone (6a, 6b) which gives 7a, 8a in 15% and 85% yield, and 7b, 8b in 40% and 60% yield, respectively (Scheme V). If these results are compared with those for the reduction of (+)-carvone with *Pseudomonas ovalis*, it is seen that reduction with *B. sulfurescens* is more stereoselective.

**Scheme V**

![Scheme V](image)

Aldehydes can be converted to alcohols by *B. sulfurescens*. Reduction of acyclic α, β-unsaturated aldehydes provides saturated alcohols and α, β-unsaturated alcohols, instead of saturated ketones. It is assumed that reduction of carbonyls occurs faster than that of the double bonds for α, β-unsaturated aldehydes, and the saturated alcohols arise from the reduction of the α, β-unsaturated alcohols.

Reduction of carbonyl compounds with *B. sulfurescens* produces a new asymmetric carbon. The enantioselectivity is consistent with the result rationalized by Prelog's rule.
synthetic application of \textit{B. sulfurescens} may be illustrated by the total synthesis of \textit{S}-fluoxetine 10 in which the key step is the generation of the stereogenetic center at benzylic position. Reduction of ethyl benzoyleacetate by microorganisms provided a much efficient approach compared to chemical methods.\textsuperscript{19,26,27} Reactions with Bakers yeast, \textit{B. sulfurescens} and \textit{Geotrichum candidum} gave the precursor of fluoxetine in excellent enantiomeric excesses and yields. As shown in Table I,\textsuperscript{28} reduction with \textit{B. sulfurescens} provided the enantiomer 9 in highest yield and with excellent enantiomeric excess.

**Table I.** Reduction of Ethyl Benzoyleacetate with Microorganisms

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>% yield</th>
<th>% ee</th>
<th>Absolute configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakers' yeast ((Saccharomycyes cerevesiae))</td>
<td>50-63</td>
<td>87-93</td>
<td>\textit{S}</td>
</tr>
<tr>
<td>\textit{Beauveria sulfurescens}</td>
<td>72</td>
<td>96</td>
<td>\textit{S}</td>
</tr>
<tr>
<td>\textit{Geotrichum candidum}</td>
<td></td>
<td></td>
<td>\textit{S}</td>
</tr>
<tr>
<td>Condition A</td>
<td>65</td>
<td>97</td>
<td>\textit{S}</td>
</tr>
<tr>
<td>Condition B</td>
<td>64</td>
<td>&gt;98</td>
<td>\textit{S}</td>
</tr>
</tbody>
</table>

The mechanism for the reduction with \textit{B. sulfurescens} is unknown. The reduction of isolated carbonyls presumably involves addition of the hydride to give the \textit{S} alcohol. Since \textit{\alpha, \beta}-unsaturated ketones are Michael acceptors, 1, 4-addition may be involved in the reduction to give the enolate. Asymmetric protonation of this enolate on the enzyme surface would provide the saturated ketone with high enantioselectivity. Because the \textit{\alpha}-carbon of the reduced double bond for \textit{\alpha, \beta}-unsaturated ketones has nucleophilic character whereas the \textit{\beta} and carbonyl carbons have electrophilic character, the reduction of the \textit{\beta}-position in double bond and the isolated carbonyl may be similar.

**MICROBIOLOGICAL OXIDATION**

Direct electrophilic hydroxylation of aromatic rings is difficult because the hydroxyl group activates the ring and may cause the reaction to go further. Hydroxylation with peroxides under catalysis can be an effective method.\textsuperscript{29-31} Highly selective oxidation of non-activated carbon atoms which are remote from heteroatoms are difficult for an organic reaction to achieve. The chemical Gif system only selectively oxidizes secondary carbon atoms.\textsuperscript{32} \textit{B. sulfurescens} is effective in one-step hydroxylation with high regiospecificity. It was first found to be useful for hydroxylation of steroids.\textsuperscript{33} Recent research has found that it is particularly effective in hydroxylation of various cyclic structures including aromatic rings. It is observed that hydroxylation is facilitated in the presence of a functional group in the structure, especially amides. Carbamates and N-arylpiiperidines have been selected as the reference compounds for
this study. Hydroxylation of other structure bearing a nucleophilic group are also documented.34,35

Carbamates

Scheme VI presents the result of hydroxylation of a series of carbamates bearing a urethane moiety.36 Substrates with a N-phenyl structure of anilinide carbamate undergo the hydroxylation with *B. sulfurescens*. Hydroxylation takes place at the para position on the phenyl ring when a small alkyl group (Me and iPr) is present. As the size of alkyl groups increases, hydroxylation occurs on both the cycloalkyl portion and the phenyl ring. In the presence of a very lipophilic substituent, substrates undergo multiple hydroxylations. Interestingly, no hydroxylation occurs on the phenyl ring when the alkyl is pentyl. The regiochemical selectivity in the hydroxylation on the cycloalkyl group is striking that the hydroxyl group is in *anti* configuration to the urethane moiety. But reaction is inhibited if C6H5OCONR1R2 structure is presented.

Scheme VI

A few factors may be assumed to explain these results. First, there is an interaction between the enzyme and the substrate such that the distance between the nucleophilic atom (O) and the hydroxylated site plays an important role. This distance factor was proposed by Fonken, *et al.*,37 based on the results of cyclododecanol and cyclododecane. It suggests that the distance between the site of oxygenation and the nucleophilic atom is approximately 5.5 Å. Secondly, the conjugation between N atom and the aromatic ring may be important. A different enzyme-substrate structure may exist due to a different stereoelectronic factor, which arises from the disturbance of the conjugation in N-phenyl substrates. This structure provides a better fit for the required distance between the carbonyl oxygen atom and the hydroxylated site for urethane substrates. Third, different alkyl groups provide different enzyme-substrate structures due to their lipophilicity. The positioning of the carbon skeleton is fixed by the internal shape of the
enzyme hydrophobic part, which gives the *anti* product. Further investigation of this *anti* preference was performed on adamantanes bearing an amide group (Scheme VII).38 If the substituent changes from urethane to amide, the *anti* propensity for hydroxylation is also seen. However, no hydroxylation occurs on the phenyl ring for the amide substrate.

**Scheme VII**

![Scheme VII](image)

**N-Arylpiperidine and Related Compounds**

Both the urethane and amide group have a carbonyl moiety. In order to examine the role of this carbonyl in oxygenation, the N-arylpiperidines and related compounds were studied. As shown in Table II,39 if there is an electron-withdrawing group *para* to the N atom, oxygenation occurs on the non-aromatic ring. When the phenyl has no substituent or an alkyl group at the *para* position, hydroxylation occurs on the aromatic ring or the side chain. This may be attributed to the distance factor. However, no *anti* preference was observed for these substrates. The distance between nitrogen atom and *para* position of phenyl ring or the side chain is optimal for these substrates 13, 17.

**Table II. Oxygenation of N-Arylpiperidines with *B. sulfurescens***

<table>
<thead>
<tr>
<th>Compound</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>20</td>
</tr>
<tr>
<td>14</td>
<td>NO₂</td>
<td>H</td>
<td>NO₂</td>
<td>OH</td>
<td>42</td>
</tr>
<tr>
<td>15</td>
<td>CN</td>
<td>H</td>
<td>CN</td>
<td>OH</td>
<td>34</td>
</tr>
<tr>
<td>16</td>
<td>Ac</td>
<td>H</td>
<td>Ac</td>
<td>OH</td>
<td>66</td>
</tr>
<tr>
<td>17</td>
<td>Et</td>
<td>H</td>
<td>CH₂CH₂OH</td>
<td>H</td>
<td>30</td>
</tr>
</tbody>
</table>

If the conjugation between the N atom and phenyl ring is disturbed, e.g. a methylene is inserted between the nitrogen atom and the phenyl ring for N-(acetophenyl)piperidine and N-(acetophenyl)pyrrolidine, no reaction occurs.39 It is assumed that an electron-rich substituent and the conjugation are essential for substrates. However, many substrates do undergo oxygenation without a phenyl group. The role of distance factor is further illustrated by
changing the heterocyclic portion of the molecule. As presented in Scheme VII, oxygenation takes place on the site where the optimal distance is reached.

**Scheme VII**

![Scheme VII](image)

In summary, a variety of substrates undergo hydroxylation with high regioselectivity for 13a-17a. Examination of the substrates that undergo hydroxylation reveals the optimal distance between N atom and the hydroxylated sites to be about 5.0-5.7 Å. This result supports the idea that there is an interaction between the nucleophilic atom and the active site in the enzyme which offers the orientation of the substrate.

The mechanism of the hydroxylation is not unambiguously established. It is assumed that a stepwise mechanism has to be involved in hydroxylation. As the first step, abstraction of a hydrogen atom at the hydroxylated site is presumed to give a free radical intermediate for the hydroxylation on cycloalkyl group whereas a radical cation may be involved for the hydroxylation on aromatic ring, which is stabilized by N atom. This radical is subsequently trapped by oxygen transfer. The stereochemistry of this transfer is governed by the internal shape of the active site in the enzyme, and the position and the reactivity of the radical. A hypothesis may be made that oxygen is delivered by the cytochrome P-450 enzymes, in which the oxo-iron species has two oxidation equivalents above ferric state, and the Fe-O orbital are capable of bearing unpaired electron density.40,41

**CONCLUSIONS AND FUTURE WORK**

*B. sulfurescens* provides ready means for the reduction of α, β-unsaturated ketones and isolated carbonyls, whereas chemical methodologies seem to be demanding. Most reactions offer products with excellent enantioselectivity and enantiospecificity. Introduction of a hydroxyl group on unactivated carbon atoms can be achieved by *B. sulfurescens*, while a similar organic reaction is difficult to carry out. *B. sulfurescens* proves to be a striking organism which offers useful techniques in the manipulation of organic synthesis. Further studies should be focused on the applications of *B. sulfurescens* to other substrates.

**REFERENCES**

METHANE MONOOXYGENASE: ELUCIDATION OF AN ORGANOMETALLIC ENZYME MECHANISM

Reported by James V. Suggs
February 17, 1994

INTRODUCTION

The methanotrophic bacteria utilize methane as their sole source of carbon and energy. They are ubiquitous in soil and marine sediments, where both methane and oxygen are present. They play an essential part in cycling carbon in the biosphere by oxidizing methane produced by anaerobic bacteria to carbon dioxide. The first and chemically most difficult step is the oxidation of methane to methanol, catalyzed by methane monooxygenase (MMO):

\[ \text{CH}_4 + \text{NADH} + \text{H}^+ + \text{O}_2 \xrightarrow{\text{MMO}} \text{CH}_3\text{OH} + \text{NAD}^+ + \text{H}_2\text{O} \]

Many other saturated and unsaturated hydrocarbons are oxidized by MMO, but do not support bacterial growth.

The ability of MMO to oxidize hydrocarbons other than methane has led to a number of applications of methanotrophic bacteria, including bioremediation of oil spills and the removal of trichloroethylene and other dangerous chlorinated hydrocarbons from ground water. An understanding of the mechanism of hydrocarbon oxidation by bacteria could lead to the development of newer catalysts for hydrocarbon oxidation and olefin epoxidation. The conversion of natural gas (methane) to methanol would greatly simplify its storage and transport, allowing its full utilization as an energy source.

Methane monooxygenase is generally isolated from one of two bacterial sources: *Methylosinus trichosporium* OB3b or *Methylococcus capsulatus* (Bath). MMOs from both sources have been characterized and found to be very similar to one another. When grown in media rich in copper, the monooxygenating enzyme is membrane bound. Otherwise, it is expressed as an unbound soluble protein. All studies thus far have been performed on the soluble monooxygenase, as the membrane bound form is difficult to isolate in active form. This seminar will be a review of efforts to elucidate the mechanism of MMO catalyzed oxidation of hydrocarbons.

STRUCTURE

Methane monooxygenase consists of three proteins: a hydroxylase, a reductase, and a coupling protein. The coupling protein has no metals or cofactors and is regulatory in nature. It has been shown that the coupling protein perturbs the environment of the
hydroxylase active site. The reductase contains a flavin cofactor and an iron-sulfur cluster. Its function is to accept two electrons from NADH and deliver them to the hydroxylase. The hydroxylase is a six polypeptide protein of $\alpha_2\beta_2\gamma_2$ stoichiometry and is the site of hydrocarbon oxidation. Mössbauer, electron spin resonance (ESR) and extended x-ray absorption fine structure studies have identified a non-heme dinuclear iron center in the active site of the hydroxylase. All three proteins are necessary for maximal catalytic rate, although the hydroxylase and reductase alone are capable of turnover, as is chemically reduced hydroxylase.

Until recently, the spectroscopic studies mentioned above provided the only clues to the structure of the enzyme active site. Recently, the 2.2 Å crystal structure of MMO hydroxylase from M. capsulatus (Bath) has been determined. A schematic representation of the dinuclear iron core is shown in Figure I. Both irons are pseudo-octahedral, and are linked by Glu 144, a bridging hydroxide, and a bridging acetate. It is believed that acetate is incorporated as a result of crystal growth in ammonium acetate buffer. The position of this exogenous acetate could show where the oxidized substrate sits before release from the active site.

![Figure I: Schematic representation of the dinuclear iron core](image)

The identities of the bridging hydroxide and the terminal water ligand could not be determined with X-ray crystallography, as this technique is insensitive to protons. The proton ENDOR spectra of mixed-valent Fe(II)-Fe(III) hydroxylase is consistent with a hydroxide ligand bridging two iron atoms, and a terminal water or hydroxide ligand on one iron atom. Furthermore, the ENDOR spectral characteristics of MMO compare well with those of the enzymes semimeth HrN3, which is known to contain an $[\text{Fe}_2(\text{OH})]^{4+}$ core, and aconitase, which has a terminal water ligand on an iron atom.

Each MMO hydroxylase has two active sites, one in each subunit. Each active site consists of a hydrophobic cavity, with the dinuclear iron center ligated with histidines and
carboxylates on one surface of the cavity. Possible binding sites for the reductase and coupling protein exist in canyons formed between the α and β subunits.3

The Inorganic Mechanism - The Iron Center

The reaction of methane with oxygen requires activation of a methane C-H bond and an oxygen O-O bond. The role of the dinuclear iron center in the active site is presumably to activate the oxygen, as iron has a low affinity for saturated hydrocarbon ligands. In order to elucidate the mechanism of action of MMO, it is necessary to identify the metal-oxygen interactions.

Electron spin resonance (ESR) studies11 have been widely used in identification of the redox state of the iron center.6 In ESR, transitions between electronic spin states are detected for unpaired electrons. The electronic spin states are coupled to the nuclear spin states of adjacent atoms, resulting in hyperfine splittings which can give information about other spin-active nuclei nearby. The g-factor reflects the ability of the electron's environment to exhibit an induced magnetic field.11

The dinuclear iron cluster of MMO hydroxylase can be stable in three redox states.6 The native form has an Fe(III)-Fe(III) iron cluster, the ESR spectrum of which shows only minor resonances associated with iron bound to the surface. Since this state of the enzyme is not ESR active, the two irons must be magnetically coupled through the hydroxo bridge. Partial reduction of the hydroxylase with sodium dithionate yields the mixed-valent form, Fe(II)-Fe(III), with ESR signals at g=1.94, 1.86 and 1.75 (gav=1.85). Full reduction of the diiron center, achieved by addition of proflavin, methyl viologen and dithionate, gave an Fe(II)-Fe(II) cluster with a g=15 signal in the ESR spectrum.12 An identical species is observed when the natural reducing system, NADH, reductase and coupling protein, is used. Addition of oxygen to the reduced MMO hydroxylase causes the disappearance of the g=15 signal without the appearance of gav=1.85, whereas exposure of the mixed-valent MMO hydroxylase to oxygen has no effect on the gav=1.85 signal.6 The g=15 signal was found to decay upon exposure to oxygen with a rate constant k=22 ± 5 s⁻¹ at 4 °C.13 These results indicate that only the fully reduced hydroxylase reacts with oxygen, and it is oxidized at least to the Fe(III)-Fe(III) state.

Ultraviolet and Mössbauer spectroscopic studies have also provided insights into the inorganic workings of the catalytic cycle. In rapid-scan stopped-flow spectroscopy, a solution of chemically reduced enzyme is rapidly mixed with an air-saturated solution with or without a substrate. UV spectra were obtained at 1 s intervals starting at 300 ms after mixing. At 4 °C the reactions were sufficiently slow that transient intermediates could be detected.13 When substrate was omitted from the oxygen-containing solution, an
intermediate with absorption maxima at 330 and 430 nm was observed, with a rate of formation of 1 s\(^{-1}\). By spraying the reaction mixture into isopentane at -140 °C after 4 s, this intermediate could be trapped, and its Mössbauer spectrum obtained.\(^{14}\) This spectrum contained signals from three species. About 30% of the iron clusters were found to be in the Fe(II)-Fe(II) state, with about 25% in the Fe(III)-Fe(III) state, corresponding to the fully reduced and native states of the enzyme. The remaining 45% of the iron clusters gave a well-defined doublet with spectral parameters consistent with an Fe(IV)-oxo unit. Both iron atoms were spectroscopically indistinguishable. This data, along with the observed diamagnetism of the intermediate, indicate that the cluster is in a magnetically coupled Fe(IV)-Fe(IV) state with one or more oxygen atoms bound to the iron.\(^{14}\)

The rate constants of 22 s\(^{-1}\) for disappearance of fully reduced MMO hydroxylase and 1 s\(^{-1}\) for appearance of the activated Fe(IV)-Fe(IV)-oxo state imply one or more non-chromophoric intermediates on the path from reduced to activated MMO.\(^{13}\) These intermediates have yet to be observed spectroscopically.

When nitrobenzene is used as a substrate for fully reduced enzyme in the stopped-flow rapid-scan experiments, \(p\)-nitrophenol (70%) and \(m\)-nitrophenol (30%) are the oxidation products. Appearance of a new intermediate \((\lambda_{\text{max}}=320 \text{ nm})\) was observed, concomitant with the decay of activated MMO \((k=200 \pm 10 \text{ M}^{-1}\text{s}^{-1})\). This intermediate was seen to decay with a rate constant of 0.02 ± 0.005 s\(^{-1}\). As this intermediate disappeared, \(p\)-nitrophenol \((\lambda_{\text{max}}=410 \text{ nm})\) was observed to appear at a similar rate. When furan or methane was used as the substrate, the Fe(IV)-Fe(IV) state decayed much faster than with nitrobenzene \((k=9000 \text{ and } 19000 \text{ M}^{-1}\text{s}^{-1} \text{ respectively})\), and no chromophoric intermediate was seen. These facts suggest that the intermediate represents product bound in the active site, and that its decay represents release of product into solution, and that if an intermediate exists between the activated MMO and product-bound MMO, it is very short-lived.\(^{13}\)

The activity of the iron centers in the catalytic cycle of MMO can now be summarized as shown in Scheme I. Since the turnover rate of the MMO system is 0.025 ± 0.002 s\(^{-1}\) at 4 °C, it is probable that the rate determining step is the slow release of product. It will be noted that unknowns still exist in the catalytic cycle. The structure of the activated intermediate is unknown, as are the identities of the intermediates between the reduced and activated and the activated and bound product states, which are represented by question marks in the scheme.
THE ORGANIC MECHANISM - THE HYDROCARBON SUBSTRATE

Many possibilities exist for the mechanism of the insertion of an Fe(IV)-Fe(IV)-activated oxygen atom into a C-H bond. One may envision a direct insertion, concerted formation of a carbon-iron bond followed by reductive elimination, or processes proceeding through cationic or radical intermediates. The nature of the intermediate has been studied through the use of various substrate probes and spin traps.

One simple way to obtain clues about an enzyme mechanism is to study the products of conversion of various substrates. MMO oxidizes alkanes to alcohols, and alkenes to mixtures of allylic alcohol and epoxide. There seems to be little difference in substrate specificity and conversion between MMOs isolated from M. capsulatus (Bath) and M. trichosporium OB3b. In general, the easiest C-H bond to break is oxidized, as exemplified by the conversion of 2-methylpropane to 2-methyl-2-propanol. For straight chain alkanes containing less than seven carbons, secondary alcohol products are favored. Steric effects also seem to play a role, as 2,3-dimethylpentane is converted to 3,4-dimethyl-2-pentanol. The above selectivities are inconsistent with any purely concerted reaction of a C-H bond, as such a process would show little preference for primary, secondary, or tertiary hydrogen atoms.

Stereochemical scrambling has been observed for a variety of substrates. One of the most elegant enzyme stereochemical probes, chiral ethane ([\(1-{^2}H_1, 1-{^3}H_1\)]-ethane) showed 66 ± 3% retention and 34 ± 3% inversion of stereochemistry upon oxidation to ethanol. Analysis was performed by \(^3\)H NMR on the ethanol samples and their (2R)-2-acetoxy-2-phenylethanoate derivatives. This inversion implies an unbound substrate intermediate, such as a radical or a carbocation. A radical is the more likely intermediate, as an ethyl carbocation is markedly unstable and has a high barrier to direct formation. The fact that complete racemization was not observed implies that this intermediate is not long
enough lived to equilibrate, or that the active site restrains inversion. Stereochemical scrambling has also been reported for cis-1,3- and cis-1,4-dimethylcyclohexanes\textsuperscript{16} and exo,exo,exo,exo-2,3,5,6-d\textsubscript{4}-norborne.\textsuperscript{18}

The allylic rearrangement of double bonds in oxidations of olefins to allylic alcohols has also been reported.\textsuperscript{16,18} β-Pinene, methylenecyclohexane, and 3,3,6,6,-\textsubscript{d\textsubscript{4}}-cyclohexene all show a significant amount of rearranged allylic alcohol upon enzymatic oxidation. These results are consistent with the intermediacy of a free radical or ion.

Use of a substituted cyclopropane as a substrate is another widely used method of detecting radical intermediates. Methylcyclopropane radicals rearrange rather quickly to the corresponding homoallylic radicals, which, in the active site of MMO would be hydroxylated to homoallylic alcohols (eq 1).\textsuperscript{19} Detection of ring-opened products is

\[
\Delta 
\begin{array}{c}
\text{R-H} \\
\text{k=1.2 \times 10^8} \\
\text{R} \\
\text{HO} \\
\end{array} 
\]

(1)

evidence for a radical intermediate. Unfortunately, the studies that have been performed thus far are inconclusive at best. Incubation of cyclopropylbenzene with MMO from \textit{M. capsulatus} (Bath) resulted in 30% ring-opened product.\textsuperscript{16} When oxidized by MMO from \textit{M. trichosporium} OB3b, 1,1-dimethylcyclopropane yielded 20% ring opened products,\textsuperscript{20} and \textit{trans}-2-phenylmethylcyclopropane gave 3% ring-opened products.\textsuperscript{15} However, when \textit{trans}-1,2-dimethylcyclopropane, bicyclo[2.1.0]pentane, \textit{trans}-2-phenylmethylcyclopropane and \textit{trans}-2-phenylmethylcyclopropane were incubated with the enzyme from \textit{M. capsulatus} (Bath), no rearranged products were observed.\textsuperscript{15} These results are disturbing, indeed, when one considers the rate constants of radical ring opening for the latter two are on the order of 10\textsuperscript{11} s\textsuperscript{-1}. A possible explanation for the observed lack of rearrangement may be that the active site constrains the probes from attaining a conformation optimal for rearrangement.

The results from the substrate probe studies above suggest that a radical intermediate may be formed in hydrocarbon oxidation by MMO. These radicals react too rapidly to be detected by ESR; however the technique of spin trapping can overcome this problem.\textsuperscript{21} Spin traps, usually nitrones, react with free radicals, giving nitroxide adducts, which have a lifetime long enough to allow detection by ESR. By comparison of hyperfine splittings with tabulated literature values, it is possible to "fingerprint" unknown radicals. By incubating DMPO (5,5-dimethyl-1-pyrroline-\textit{N}-oxide) or POBN [\textit{α}-(4-pyridyl-1-oxide)-\textit{N}-tert-butyl nitrone] with substrate R-H and MMO, it is possible to generate the corresponding trapped nitroxide DMPO-R or POBN-R, which can be observed by ESR
spectroscopy at 77 K. The adducts had hyperfine splitting constants consistent with those for adducts of carbon-based radicals, but inconsistent with those for adducts of oxygen based radicals. Furthermore, an extra hyperfine splitting was observed when $^{13}$CH$_3$OH was the substrate, indicating the radicals were substrate derived. There was no indication of an enzymic radical.\textsuperscript{21}

The observation of solely carbon-based radicals not only gives further evidence to suggest a radical intermediate in hydrocarbon oxidation, it also provides clues as to the identity of the unidentified iron-oxygen intermediate in Scheme I. The activation of oxygen does not proceed via generation of peroxide or hydroxide radicals, as these would be trapped by POBN or DMPO faster than a methyl radical.\textsuperscript{21} This observation, along with the facts that NADH and oxygen are consumed in a 1:1 ratio, and that peroxide can be used in the catalytic cycle instead of NADH and oxygen imply that this intermediate is an iron-bound peroxide species.

**CONCLUSION**

The mechanism of methane monooxygenase oxidation can now be summarized as in Scheme II. The di-ferric native state is reduced by NADH via the reductase protein, followed by reduction addition of molecular oxygen. The peroxo ligand thus formed probably hydrogen bonds to the hydroxo bridge. One oxygen atom is reduced to water, while the other becomes part of the activated form of the enzyme. The structure of this diferryl-oxo unit is currently unknown. The activated form then abstracts a hydrogen atom from the substrate, then donates a hydroxyl radical to the substrate radical. The rate determining step of the whole process is slow release of product into solution.

There still remains much work to be done in order for this mechanism to be put to use outside of a protein. The conflicting results of the cyclopropane ring opening studies
must be reconciled, and knowledge of the nature of the ferryl-oxo intermediate in Scheme II is vital. More important is development of a system to ligate a binuclear iron center so that its coordination environment is similar to that of the irons in the MMO hydroxylase-coupling protein complex. Alternatively, an inexpensive chemical reducing agent could be developed for use with the hydroxylase-coupling protein complex and oxygen for catalysis of oxidation in vitro.

REFERENCES

SYNTHESIS, CHARACTERIZATION, AND PROPERTIES OF LADDER POLYMERS

Reported by Douglas J. Pesak
February 21, 1994

INTRODUCTION

The goal of polymer science is to produce new and better materials. Researchers are actively exploring a class of macromolecules known as ladder polymers with this goal in mind. At least two definitions of the term "ladder polymer" exist, however, this abstract will focus on those polymers whose basic structure is defined as "[a polymer with] cyclic subunits, connected to each other by two links which are attached to different sites of the respective subunits" (structure (a), Figure 1). The first attempt at preparing a ladder-type polymeric structure by Staudinger in 1926, although unsuccessful, marked the beginning a research effort which has gained the attention of many investigators and has made significant advances in recent years. Numerous methods for preparing ladder polymers have been developed and researchers are now able to prepare a variety of processable high molecular weight ladder polymers. Applications in high performance materials, conducting polymers, and materials with non-linear optical (NLO) properties have been investigated.

![Figure 1.](image)

METHODS OF SYNTHESIS

The early attempts to prepare ladder structures employed a method termed "zipping up". Typically, a single strand polymer functionalized at regular intervals is prepared and then subjected to conditions whereby the functional groups react with one another in a propagating manner thus "zipping-up" the polymer to form a ladder structure (Scheme I). Statistically, one can never obtain a "perfect" ladder structure by this method. First, it is possible for any given polymer chain to start "zipping-up" at two different sites. This will produce gaps in the ladder. Second, interchain reactions can also occur resulting in crosslinked structures.
Another method involves the use of multifunctional monomers. Polycondensation is the most commonly employed process (Scheme II). This method has the advantage of being a single pot preparation, but it can result in crosslinking as a side reaction.

The limited success of the above methods necessitated the development of methods where these structural defects arising from statistical considerations could be eliminated. In the "lacing-up" process, a single strand polymer containing functionalized rings fused to the polymer backbone is subjected to conditions whereby the ladder structure is formed upon intramolecular reaction of the functional groups (Scheme III). The functional groups on the same ring are positioned so that they do not react. This eliminates defects of a statistical nature such as those found in the "zipping-up" method, however the possibility of crosslinking still exists.

Cycloaddition reactions offer another route to ladder polymers. The concerted nature of most cycloadditions eliminates not only the possibility of statistical defects, but also undesirable crosslinking reactions. A hypothetical reaction is shown in Scheme IV. The Diels-Alder reaction has proven to be quite valuable in producing polymers with ladder structures. Other more creative methods involving metal coordination or pyrolysis have also been used to make ladder polymers.
EARLY STUDIES

The goals of the early studies of ladder polymers were to prepare the polymer and obtain evidence for its formation. Evidence in support of the structures was presented, although lack of the powerful analytical techniques which are used today, precluded any definitive proof of structure. Also, many of the early ladder polymers exhibited poor solubility and thus eliminated any hope of processing them into useful films or fibers.

Staudinger was the first to attempt to prepare a ladder polymer. Successive Diels-Alder reactions of cyclopentadiene showed only limited success as only oligomers of up to 6 monomers were isolated and partially characterized. Also, the cycloaddition was thought to be of a [2+2] type rather than the [4+2] type. Of course it is known today that one cyclopentadiene molecule adds to another in a [4+2] fashion.

In the late 30's and early 40's Marvel et al. explored the first "zipping-up" process with poly(methyl vinyl ketone). It was observed that pyrolysis of the single strand polymer produced water which was attributed to an intramolecular "poly-aldol condensation" (Scheme V). Oddly enough, Marvel was not interested in the ladder polymer, rather he used the condensation to prove the structure of the poly(methyl vinyl ketone). A similar study of the pyrolysis of poly(acrylonitrile) was carried out in the 50's and 60's.

Scheme V

\[
\begin{align*}
\text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{CO} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H}
\end{align*}
\]

\[\Delta \quad -\text{H}_2\text{O} \quad \text{H}_2\text{O} \]

In the mid 60's, Marvel attempted to prepare a "perfect" ladder polymer by a clever "lacing up" process. Free radical polymerization of 4,4-Dimethyl-1,6-heptadiene-3,5-dione 1 gave the prepolymer 2. Oximation of one carbonyl per ring followed by dehydration gives the nearly "perfect" ladder structure (Scheme VI).

Scheme VI

\[
\begin{align*}
\text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{CO} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H}
\end{align*}
\]

\[\text{PhH, 65°C} \quad \text{AIBN} \quad \text{NH}_2\text{OH} \quad \text{220°C, vac quinoline} \]

The polymer was soluble in hot solvents which indicated minimal crosslinking, however, IR and elemental analysis suggested that the ladder formation was only 90% complete.

Stille et al. successfully employed the multifunctional condensation method in the preparation of a ladder type poly(quinoxaline) (PQL). Reaction of tetraaminobenzene and 2,5-
dihydroxyquinone at elevated temperature in a strongly acidic medium produced the desired aromatic ladder polymer (Scheme VII).

Scheme VII

The first successful cycloaddition polymerization was carried out by Bailey et al. in the mid 50's. Diels-Alder reaction of the 2-vinyl-1,3-butadiene and benzoquinone gave a snake-like ladder polymer (Scheme VIII).

Scheme VIII

Characterization of the polymer proved difficult due to its limited solubility. The fraction which was slightly soluble in camphor was found to have a molecular weight of only 440.

CURRENT RESEARCH IN LADDER POLYMERS

Modern research of ladder polymers now focuses on the synthesis of processible polymers without structural defects and the examination of some of the properties which they exhibit. Recently, Bein and Enzel examined a new method to affect the pyrolysis of poly(acrylonitrile) or PAN. The monomer was encapsulated in an inert zeolite host. Radical polymerization in the zeolite channels produced PAN of an acceptable molecular weight. Pyrolysis of the encapsulated polymer produced a partially graphitized naphthyridine structure. The purpose of synthesizing the polymer in the zeolite is to produce a well defined structure as opposed to the random coil type structure produced in solution polymerizations. It is believed that ordered polymer systems will show enhanced properties. This issue is discussed in more detail below.

Aryl-aryl cross coupling reactions have been used recently to prepare poly(p-phenylenes) of ladder structure. Mülken and Scherf were able to prepare polymer 6 in moderate yield in just three steps. Repetitive Suzuki coupling of the aryl diboronic acid 3 with aryl dibromide 4 produced the
single strand poly($p$-phenylene). Reaction of the polymer with Grignard reagent set up the structure for the Lewis acid catalyzed Friedel-Crafts ring closure and ladder formation (Scheme IX).

**Scheme IX**

![Chemical structure](image)

Number average molecular weights ($M_n$) of around 5000 were obtained for polymer 5. The ladder polymer 7 was completely soluble and no structural defects were detected by spectroscopic methods. Müllen prepared another polymer similar to 6 where the connectivity consisted of alternating *para* and *meta* phenylene linkages.\(^\text{15}\)

Schlüter has employed the Diels-Alder reaction with great success to the synthesis of novel ladder structures some of which have been extensively characterized.\(^\text{2, 17}\) One such example is shown in Scheme X. Soluble fractions of polymer were obtained with $M_n$ over 100,000, which corresponds to a degree of polymerization of approximately 150. Schlüter was even able to examine the stereochemistry of the polymerization by NMR and determined that the ratio of *exo* to *endo* addition was approximately 1:1.
Tsuda recently reported the Ni(0) catalyzed copolymerization of CO₂ or isocyanates with cyclic diynes to give novel ladder structures (Scheme XI) with \( M_n \) between 3000 and 13000 for the poly(2-pyrone)s and between 16000 and 63000 for poly(2-pyridone)\(_s\). Both polymers are soluble in a variety of solvents.

**Scheme XI**

\[
\text{(CH}_2\text{)}_n \quad \text{Ni}(0) \quad \text{(CH}_2\text{)}_m
\]

The mechanism of the reaction is proposed to proceed first by \( \pi \) coordination of two triple bonds to the Ni(0) followed by coordination of the CXO. The complex then forms a 5 membered and then a 7 membered metallacycle followed by reductive elimination of the catalyst (Scheme XII).

**Scheme XII**

**APPLICATIONS OF LADDER POLYMERS**

Chemists and engineers seem to have a very mature understanding of the synthesis, processing and application of countless single strand polymers. Why then do we need double stranded ladder polymers? What advantages might they possess over their single stranded analogs? The answer to this question lies in the predicted stability of ladder structures.

A polymer loses its useful properties when the molecular weight is decreased i.e. when chain scission occurs. This occurs when a single bond along the polymer backbone of a single strand polymer is broken by a chemical, thermal, or photolytic process. For the molecular weight of a ladder polymer to decrease, 2 bonds on different strands must break. Tessler carried out statistical studies on the degradation of single and double stranded polymers. Examination of the molecular weights of both single and double stranded polymers as a function of time with random bond cleavage
throughout the chain shows that ladder polymers lose weight at a much slower rate than single stranded polymers. It follows then that ladder polymers should exhibit enhanced thermal, photolytic, and chemical stability. Bailey compared the rates of hydrolysis of a ladder type polyester and its single strand analog and found that the ladder structure reacted at a much slower rate. Also, thermal gravimetric analysis showed that the double strand structure lost mass at a lower rate than the single stranded analog. A more modern example is that of BBL whose structure is shown below.

![Image of BBL, BBB, and PBI structures]

The mechanical properties of BBL are similar to that of BBB and PBI. TGA data also show similar characteristics, however, isothermal degradation experiments show that BBL loses weight more slowly than single stranded BBB and PBI over extended periods of time.

Researchers have shown interest in the use of ladder structures as conducting polymers and nonlinear optical materials. It is known that these properties are enhanced by good overlap of \( p \)-orbials in extended \( \pi \) systems, which should be facilitated by the rigid nature ladder polymers. Conductivities of conjugated ladder polymers vary widely depending on type, preparation, and dopant type and concentration. BBL films doped with potassium have shown conductivities of approximately 1 S/cm. Ion implantation doping of BBL has produced films with conductivities over 200 S/cm. Doped PTL films have been prepared with conductivities ranging from \( 10^{-5} \) to \( 10^{-1} \) S/cm. For comparison, typical conductivities of polycetylene and polypyrrole (two widely studied conducting polymers) are around 500 S/cm. Such conductive films could have applications in solid state batteries.

Nonlinear optical properties can be correlated with the higher order electric susceptibilities (\( \chi^{(n)} \) where \( n \geq 2 \)) of a solid in an applied external field. BBL films were shown to have third order susceptibilities of approximately \( 2 \times 10^{-9} \) esu at 532 nm. The \( \chi^{(3)} \) values decreased substantially at longer wavelengths. For comparison, semiconductors such as GaAs and Si have \( \chi^{(3)} \) values around \( 10^{-11} \) esu. NLO materials could be useful in optical based communications.
CONCLUSIONS AND FUTURE WORK

Several methods have been successfully employed in the preparation of ladder polymers. The development of synthetic methods and powerful analytical techniques as well as the understanding of certain structure/property relationships has allowed present day researchers to prepare and characterize soluble (processable) high molecular weight ladder polymers. The double stranded structure of these polymers has made them attractive materials for a number of applications. In order for these polymers to gain widespread use, the cost of producing them will have to decrease substantially as current syntheses require very specialized monomers.

REFERENCES

(1) Overberger, C. G.; Moore, J. A. Advances in Polymer Science 1970, 7, 113.
DITHIOACETAL S-OXIDES IN ORGANIC SYNTHESIS

Reported by Kevin Z. Gan February 28, 1994

INTRODUCTION

The dithioacetal S-oxide moiety has been widely used in organic synthesis as a synthon for the carbonyl anion. More importantly, the 2-acyl-1, 3-dithiane-1-oxide function shows high diastereoselectivity as a chiral auxiliary in enolate alkylation, Grignard addition, hydride reduction, cycloaddition and conjugate addition reactions. In this abstract, the synthetic applications of both acyclic and cyclic dithioacetal S-oxides will be discussed.

PREPARATIONS AND REMOVALS OF DITHIOACETAL S-OXIDES

Racemic dithioacetal S-oxides are made by oxidizing their dithioacetal precursors. Optically active cyclic and acyclic dithioacetal S-oxides are synthesized by either nucleophilic displacement reactions or direct asymmetric oxidations.

Syntheses of enantiomerically enriched dithioacetal S-oxides

The common way of generating optically pure acyclic dithioacetal S-oxides is nucleophilic displacement on enantiomerically pure menthylsulfinate esters. This reaction proceeds with clean inversion of configuration at sulfur (Scheme I). The enantiomeric purities are determined by 1H NMR with Eu(tfc)3 as the chiral shift reagent. The configurations of the products are characterized by comparing their CD spectra with those of known compounds.

Scheme I

The cyclic dithioacetal S-oxides are synthesized primarily by asymmetric oxidations of their dithioacetal precursors. Kagan's method using modified Sharpless' chiral reagent [Ti(O-iPr)4/(+)-diethyl tartrate/t-BuOOH/H2O=1:2:1:1] stoichiometrically gives enantiomeric excess of up to 99% (Table I) with 2-acyl-1, 3-dithiane-1-oxide. Optically active 1, 3-dithiane 1-oxide derivatives have also been obtained through kinetic resolutions and enzymatic oxidations.
Table I. Asymmetric oxidations of 1, 3-dithianes

\[
\begin{align*}
\text{S} & \quad \text{S} \\
R_1 & \quad R_2 \\
\text{H} & \quad \text{CO}_2\text{Et} \quad 30 & \quad \text{syn}\% & \quad 20 & \quad \text{anti \% ee} & \quad 30 & \quad \text{syn \% ee} \\
\text{Ph} & \quad \text{COMe} \quad 65 & \quad 6 & \quad 99 & \quad 57 \\
\text{Et} & \quad \text{COMe} \quad 61 & \quad 4 & \quad 81 & \quad 57
\end{align*}
\]

Removal of the dithioacetal S-oxide moiety

Dithioacetal S-oxides can be hydrolyzed under mild conditions using reagents such as NBS or NCS/AgNO₃.¹ The hydrolysis of the dithioacetal S-oxide function is often easier than the hydrolysis of dithioacetal.¹a However, some exceptions have been reported, in which the reductions of dithioacetal S-oxides to dithioacetals are needed for smooth hydrolysis.⁹

SYNTHETIC APPLICATIONS OF ACYCLIC DITHIOACETAL S-OXIDES

Applications as carbonyl anion equivalents

Besides dithioacetals, many carbonyl-anion equivalents have been developed, including α-trimethylsilyl selenide and phenylthiotrimethylsilylmethane.⁵ In comparison to these reagents, the carbanions of the dithioacetal S-oxides are good nucleophiles (Table II).⁶ For example, highly strained cyclobutanone is generated with good overall yield by this approach.

Table II. Nucleophilic reactions of acyclic dithioacetal S-oxides

<table>
<thead>
<tr>
<th>Base</th>
<th>Electrophile</th>
<th>Product</th>
<th>Total yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH</td>
<td>Mel</td>
<td>CH₃CHO</td>
<td>77</td>
</tr>
<tr>
<td>KH (2 eq.)</td>
<td>1, 3-ditosyloxypropane</td>
<td>Cyclobutanone</td>
<td>72</td>
</tr>
<tr>
<td>NaOH</td>
<td>PhCHO</td>
<td>PhCH₂CO₂Et*</td>
<td>68</td>
</tr>
</tbody>
</table>

* The hydrolysis was done with EtOH.
The α carbanions of dithioacetals give only 1, 2 additions to α, β-unsaturated carbonyl compounds in THF. On the other hand, the α carbanions of dithioacetal S-oxides can undergo conjugate additions and produce 1, 4-dicarbonyl compounds after hydrolysis. The total yields for acyclic diones are typically above 90%. In addition, the ketene thioacetal monoxides are good acceptors in Michael addition reactions with very good yield (usually 90%).

In comparison to the dithioacetals, the dithioacetal S-oxides are capable of conjugate addition and have comparable reactivities as nucleophiles. Moreover, the anions of S-oxides are more easily generated.

**Diastereoselective syntheses with chiral acyclic dithioacetal S-oxides**

All the work in this area has been done with compounds 2 obtained by the nucleophilic displacements of menthyl sulfinate esters (Scheme I). The chiral aldehyde 3 was generated with 70% ee when R₂ was phenyl and 46% ee when R₂ was benzyl group. In a similar reaction, a decrease in the diastereoselectivity (from 65:35 to 53:47) was observed when R₁ changes from p-tolyl to methyl group.

**Scheme II**

![Scheme II](image)

To rationalize these data, a chair form transition state 4 has been proposed. Because the most stable transition state is the one with R₂, R₁S and p-tolyl group equatorial, a decrease in diastereoselectivity is expected when R₂ changes from phenyl to benzyl group, which reduces the equatorial preference of R₂ at the β carbon (Scheme II). By the same logic, a decrease in selectivity is also expected when R₁ is changed from a p-tolyl group to a smaller methyl group because the equatorial preference of the alkylthio group is reduced.

The α carbanion of compound 2a (R₁=p-Tol) is also used in a diastereoselective Michael addition to cyclopentenone in the synthesis of prostanoic acid skeleton which is an intermediate in prostaglandin synthesis. The diastereomeric ratio was 92:8 favoring the desired isomer.
SYNTHETIC APPLICATIONS OF 1, 3-DITHIANE-1-OXIDES

1, 3-Dithiane-1-oxide derivatives are almost the only class of cyclic dithioacetal S-oxides used in synthesis. The 2-substituted 1, 3-dithiane-1-oxides are synthesized by the oxidations of their 2-substituted 1, 3-dithiane precursors.\textsuperscript{13,14} The first synthetic application of 1, 3-dithiane-1-oxide was reported by Carlson.\textsuperscript{10} The yields for the nucleophilic reactions of the \( \alpha \) carbanion of 1, 3-dithiane S-oxides were poor when n-BuLi was used.\textsuperscript{10} Much better yields ranging from 70\% to 90\% were obtained with LDA at -60°C.\textsuperscript{14} The 1, 3-dithiane-1-oxide moiety of the products which have various functional groups such as olefin, ketone, enone and alcohol can be selectively removed with \( N \)-halosuccinimides.

Conformations of 1, 3-dithiane-1-oxides

For 1, 3-dithiane-1-oxide, the ratio between the equatorial and the axial conformer is 85:15 (\( \Delta G = -0.63 \text{kcal/mol, } -80^\circ \text{C} )\textsuperscript{11} \)\textsuperscript{11} \( \text{H, } \text{\textsuperscript{13}C NMR and X-ray crystallographic studies showed the equatorial preference for the sulfoxide bond of 1, 3-dithiane-1-oxides is also affected by the substituents on the dithiane ring.} \)\textsuperscript{11-13} A factor which is often important to the conformational equilibrium is that the C-2 substituent also tends to be equatorial to be more stable.\textsuperscript{11,13}

Diastereoselectivities in the reactions of \( \alpha \)-carbanions

The diastereoselectivities of the 2-substituted 2-lithio-1, 3-dithiane-1-oxides appears to be substrate dependent (Table III).\textsuperscript{14} Obviously, the major diastereomeric products are often the ones with the electrophile being \( \text{cis} \) to sulfoxide oxygen. It is also observed that both \( \text{trans} \) or \( \text{cis} \) substrates (\( \text{trans} \) and \( \text{cis} \) refer to the sulfoxide and C-2 substituents) give the same diastereomeric ratios.\textsuperscript{15} This interesting phenomenon might suggest the existence of the equilibria between several lithiated carbanion intermediates.

\begin{table}[h]
\centering
\caption{Diastereoselective reactions of the \( \alpha \)-carbanions of 1, 3-dithiane-1-oxides}
\begin{tabular}{llll}
\hline
Substrate & \( R_1 \) & \( R_2 \) & \text{5a}\% & \text{5b}\% \\
\hline
\textit{trans} & Me & H (quenching) & 88 & 12 \\
\textit{cis} & Me & H (quenching) & 91 & 9 \\
\textit{trans} & Ph & H (quenching) & 100 & 0 \\
\textit{trans} or \textit{cis} & Ph & Me & 84 & 16 \\
\hline
\end{tabular}
\end{table}
Diastereoselective syntheses using 2-acyl-1, 3-dithiane-1-oxides

There are many examples for diastereoselective alkylations of enolates being attached to chiral auxiliaries. Among them, oxazolidones 6a and 6b, 2-anilinomethylpyrrolidine 7 and 1, 3-oxathiane derivatives 8a and 8b are good comparisons to the recently developed 2-acyl-1, 3-dithiane-1-oxide 9 (Table IV).

The data for enolate alkylations with 2-acyl-1, 3-dithiane-1-oxides as chiral auxiliaries are summarized in Table IV. The isomer ratios were determined by NMR and the configurations of the products are determined by 1H, 13C NMR and X-ray crystallography. The data show that very good diastereoselectivity can be achieved by 9 with certain substrate (R₁=Et, de>92%). This diastereoselectivity is higher than that obtained with 6a (R=Et, de=80%) in enolate methylation reaction. A set of reactive intermediates have been proposed to rationalize the same facial preference for both syn and anti substrates. In these proposed models, the chelation of the enolates with the metal ion and the conformation of the dithiane ring, which determines the orientation of the sulfoxide bond, play very important roles in the rationales for the observed diastereoselectivities.

Table IV. Enolate alkylations of 2-acyl 1, 3-dithiane-1-oxides

<table>
<thead>
<tr>
<th>Substrate*</th>
<th>R₁</th>
<th>de%</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti</td>
<td>Me</td>
<td>44</td>
</tr>
<tr>
<td>anti</td>
<td>Et</td>
<td>&gt;92</td>
</tr>
<tr>
<td>syn</td>
<td>Et</td>
<td>90</td>
</tr>
<tr>
<td>syn</td>
<td>i-Pr</td>
<td>50</td>
</tr>
</tbody>
</table>

* syn and anti are the relationship between the acyl group and the sulfoxide
The hydrolysis of 6a and 6b would generate carboxylic acid derivatives and the chiral auxiliaries could be recovered. In contrast, the hydrolysis of 9 generate chiral diketones and the auxiliaries are lost. A disadvantage for the derivatives of 6a and 6b is that two separate syntheses are needed for the complementary auxiliary 6a and 6b. On the contrary, both enantiomers of 9 can be prepared by the asymmetric oxidation reactions using (+) or (-) DET.3

The sequential trapping of the carbanion α to sulfoxide and the enolate of the acyl group of 9 (R1=H) has been applied to the synthesis of medium sized chiral cyclic 1, 2-diketones (Scheme III.).18 The diastereoselectivities were excellent (de>99%) when R was methyl group.

Scheme III

Additions of Grignard reagents to 2-acyl-2-alkyl-1, 3-dithiane-1-oxides 9 show even better diastereoselectivities than enolate alkylation reactions (de>99%).20 The data listed in Table V shows higher selectivity for syn isomers and lower selectivity for anti isomers when R1 is smaller. These trends are also observed with alkylation reactions suggesting that the stereoselectivities originate through a similar set of transition states. A competing attack of the Grignard reagent at the sulfoxide moiety to give ring opened keto-sulfoxides becomes important when the β carbonyl carbon is hindered because of larger C-2 substituents.

Table V. Additions of Grignard reagents to 2-acyl-1, 3-dithiane-1-oxides

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R1</th>
<th>Alcohol%</th>
<th>de%</th>
<th>Acyclic%</th>
</tr>
</thead>
<tbody>
<tr>
<td>syn</td>
<td>Me</td>
<td>95</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>syn</td>
<td>Et</td>
<td>15</td>
<td>81</td>
<td>18</td>
</tr>
<tr>
<td>anti</td>
<td>Me</td>
<td>95</td>
<td>88</td>
<td>0</td>
</tr>
<tr>
<td>anti</td>
<td>Et</td>
<td>75</td>
<td>92</td>
<td>0</td>
</tr>
</tbody>
</table>
The hydrolysis of the products of Grignard addition reactions of 7, 8a, 8b and 9 generate enantiomerically enriched α hydroxyl ketones or aldehydes. These reactions also have shown comparable diastereoselectivities: de is 95% for 8a (R=PhCH₂), 98% for 8b (EtMgBr as nucleophile) and >99% for 9 (Table V). The most remarkable advantage of 8a is that the chiral auxiliary is recoverable (>70% yield) after the hydrolysis. Although the 1, 3-dithiane-1-oxide moiety is lost in the hydrolysis, 9 is the least expensive one to prepare and the complementary chiral auxiliaries for the synthesis of both enantiomers of the final α hydroxyl ketone products can be easily obtained by asymmetric oxidation using (+) or (-) DET.

The β carbonyl group of 2-acyl-2-alkyl-1, 3-dithiane-1-oxides 9 can also be reduced with excellent diastereoselectivities using DIBAL (Table VI). The opposite diastereomeric preference observed with ZnCl₂ suggests a chelated transition state in the presence of ZnCl₂. In the non-chelated transition state, the orientation of the carbonyl group becomes important and determines the diastereoselectivity of the hydride transfer. The reduction of the carbonyl group of 8a with DIBAL is much less diastereoselective (de=30%).

Table VI. Reduction of β carbonyl group of 2-acyl-1, 3-dithiane-1-oxides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R₁</th>
<th>Reagent</th>
<th>Isomer ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>syn</td>
<td>Me</td>
<td>DIBAL</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>b</td>
<td>syn</td>
<td>Me</td>
<td>DIBAL/ZnCl₂</td>
<td>1:7</td>
</tr>
<tr>
<td>c</td>
<td>anti</td>
<td>Me</td>
<td>DIBAL</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>d</td>
<td>anti</td>
<td>Me</td>
<td>DIBAL/ZnCl₂</td>
<td>&lt;1:99</td>
</tr>
</tbody>
</table>

In addition to the reactions discussed above, 2-acyl-1, 3-dithiane-1-oxides can be applied to several other types of reactions with very good diastereoselectivities. These reactions include Mannich reactions with benzotriazole derivatives (de>99%), heterocycloaddition with Danishefsky's diene (Scheme IV) and the Michael addition reaction (low de%).

Scheme IV

CONCLUSION
Overall, dithioacetal S-oxides have useful applications as a carbonyl anion synthon. The 2-acyl-1, 3-dithiane-1-oxides are very good chiral auxiliaries with comparable or even better diastereoselectivities than several well-known chiral auxiliaries. However, a major weakness for the use of 1, 3-dithiane-1-oxide system is the conformational flexibility of the dithiane ring which is detrimental to facial selectivity. In addition, the chiral auxiliaries are lost upon hydrolysis.

REFERENCES
INTRODUCTION

The structure of \( \text{C}_60 \) (Figure 1) or buckminsterfullerene (named after Buckminster Fuller who first described geodesic domes) was first proposed by Kroto, Heath, O'Brien, Curl and Smalley in 1985.\(^1\) The basis for this proposal was the observance of a stable 60 atom cluster in mass spectral studies of carbon clusters. The structure was not confirmed until the method of Kratschmer, Huffman and coworkers provided enough \( \text{C}_60 \) for chemical analysis in 1990.\(^2\) The following year, Hawkins and coworkers obtained X-ray quality crystals of an osmium tetroxide adduct of \( \text{C}_60 \), and the spherical structure shown in Figure 1 was verified.\(^3\)

Since their discovery, \( \text{C}_60 \) and higher order fullerenes have been of great interest. The importance of functionalizing this new form of carbon was quickly recognized. In initial probes of its chemical reactivity, researchers found that reactions with \( \text{C}_60 \) gave largely polyfunctional products. However, it has been demonstrated that under controlled conditions, monoadducts of \( \text{C}_60 \) can be obtained. Possible applications of \( \text{C}_60 \) as polymers, superconductors, lubricants, and pharmaceuticals have been suggested.\(^4\) Recent work has shown that \( \text{C}_60 \) derivatives have biological activity. The focus of this abstract will be on the organic reactions of \( \text{C}_60 \) which yield monoadducts. These reactions have provided a foundation for chemically building on the fullerene core.

MOLECULAR AND PHYSICAL PROPERTIES

\( \text{C}_60 \) is a highly symmetrical molecule made up of sixty carbon atoms arranged in a truncated icosahedron, or soccer ball structure (Figure 1) with the point group \( \text{I}_h \), as evidenced by a single resonance in the \( ^{13}\text{C} \) NMR.\(^5\) This spherical structure is made up of twelve isolated pentagons and...
twenty hexagons. There are thirty double bonds in the sphere and according to X-ray structures the bonds between two six membered rings are shorter by 0.05Å on average than those bonds in the five membered rings.

Pure C₆₀ in its crystalline form has a mustard color and in solution it is a deep purple. Buckminsterfullerene has low solubility in most organic solvents but is soluble in toluene and benzene and is especially soluble in carbon disulfide. The reactions discussed below have been carried out largely in toluene and benzene. Functionalization of C₆₀ generally increases its solubility in more polar solvents depending on the functional group.

**PREPARATION AND ISOLATION**

The recent sudden growth in research on C₆₀ can be attributed to the development of a fullerene synthesis on the macroscopic scale by Kratschmer, Huffman and coworkers in 1990. The most abundant fullerenes from this preparation are C₆₀ and C₇₀, which are formed in about a 85:15 ratio. Since the early work, a number of economical methods for the preparation and isolation of fullerenes have appeared. These preparations all consist of vaporizing graphite electrodes by passing an electrical current through them under a reduced pressure of helium to produce fullerene soot. Of the more efficient preparations, the report by Olah and coworkers provides a modification on this procedure which allows the preparations of about 20 to 30 grams of soot per working day. The soot contains about 8-11% fullerenes and when extracted via a soxhlet extraction gives a mixture rich in fullerenes. A very recent advance in the purification of the fullerene extract, described by Diederich and coworkers, is the isolation of C₆₀ via a simple filtration through a charcoal/silica-gel plug to give C₆₀ containing 1-3% contamination by C₆₀O as the only impurity.

**FUNCTIONALIZATION**

**Characterization**

Characterization of isolated reaction products is usually done by ¹H and ¹³C NMR, UV/vis spectroscopy, and FAB mass spectrometry techniques. Since the C₆₀ structure contains hexagons and pentagons, it is conceivable that addition to the sphere could take place across a 6,6 ring juncture or a 6,5 ring juncture. The 6,6 and the 6,5 isomers can be differentiated by the number of resonances in the ¹³C NMR spectrum if a mirror plane of symmetry exists in the adduct. Within these isomers there can also be valence isomers in which the transannular bond is either open or closed. Analogous to the methano[10]annulenes, ¹³C NMR chemical shift of the bridgehead carbons are diagnostic, and differentiate between the opened and the closed valence isomers. The majority of additions to C₆₀ have been found to occur across the 6,6 bond with the transannular bond closed. The 6,5 open isomer has been detected only when a rearrangement has occurred. In the additions mentioned below, the reactions occur across a 6,6 ring juncture unless otherwise specified.
Early Reactions

Initial attempts at functionalization of C\textsubscript{60} led to the preparation of complex isomeric mixtures resulting from multiple additions to C\textsubscript{60}.	extsuperscript{12} These early reactions were aimed at determining the chemical reactivity. Buckminsterfullerene can be easily and reversibly reduced by six electrons as determined by cyclic voltammetry.	extsuperscript{13} Evidence supporting the ease of reduction is seen in the Birch reduction of C\textsubscript{60} to give C\textsubscript{60}H\textsubscript{36}.	extsuperscript{14} In contrast to reduction, oxidations were found to be difficult. Oxidation of C\textsubscript{60} to the epoxide C\textsubscript{60}O was achieved with dimethyldioxirane\textsuperscript{15} or through photo-oxidation in benzene.	extsuperscript{16}

Use of excess reagent in organolithium additions, Grignard additions, and halogenations all led to mixtures of adducts. As an example, passing chlorine gas through a sample of C\textsubscript{60} at 250 °C produces a mixture of polychlorinated products as evidenced by broad \textsuperscript{13}C NMR absorptions at 50-150 ppm.	extsuperscript{17} Although it was easy to functionalize C\textsubscript{60}, preparation of single functionalized isomers proved difficult in early studies.

Nucleophilic Additions

More recently methods for monofunctionalizing C\textsubscript{60} with t-BuLi and EtMgBr have appeared. Hirsch and coworkers have reported reacting C\textsubscript{60} with t-BuLi and EtMgBr to give the corresponding monoadducts C\textsubscript{60}Ht-Bu and C\textsubscript{60}HEt after acidic workup as shown by \textsuperscript{1}H NMR and UV/vis spectroscopy.	extsuperscript{18} The authors state that the product is one corresponding to addition across a 6,6 ring juncture in both cases, and it provides a general method for formation of monoadducts through nucleophilic additions.

Carbene Additions

Carbene additions have also been successful in yielding monoadducts. Diederich and coworkers show that reaction of C\textsubscript{60} with glycosylidene carbenes 2 gives the corresponding spiro monoadducts 3\textsubscript{a} and 3\textsubscript{b} (Scheme I) in good yields as shown by \textsuperscript{1}H and \textsuperscript{13}C NMR and UV/vis spectroscopy.	extsuperscript{19} Other examples of carbene additions include reaction with dichlorocarbene,\textsuperscript{20} and vinyl carbenes,\textsuperscript{21}

Scheme I

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_I.png}
\caption{Scheme I}
\end{figure}

a) R = Bn 55%
b) R = Piv 54%
4+2 Additions

Since the chemical reactivity of C\textsubscript{60} is analogous to that of an electron deficient alkene, it was tested in cycloaddition reactions. Diels Alder adducts were initially plagued with difficult mass spectral characterizations since they underwent a retro-Diels Alder reaction under these conditions. It was possible to obtain characterizable products by stabilizing the final product through aromatization. Rubin and coworkers have shown that reaction of C\textsubscript{60} with diene 4 (Scheme II) gives, after loss of CO, the corresponding aromatized product 5 as characterized by X-ray crystallography, UV/vis spectroscopy, \textsuperscript{1}H and \textsuperscript{13}C NMR. Diels Alder adducts of C\textsubscript{60} with cyclopentadiene\textsuperscript{23}, isobenzofuran\textsuperscript{24}, anthracene\textsuperscript{25}, 2-[(trimethylsilyl)oxy]-1,3-butadiene\textsuperscript{26} and orthoquinodimethanes\textsuperscript{27} have also been reported.

Scheme II

\[
\begin{array}{c}
\text{C}_{60} + \begin{array}{c}
\text{O} \\
\text{Ph}
\end{array} \text{Ph} \\
\text{O} \\
\text{Ph}
\end{array} \xrightarrow{\text{Toluene}} \begin{array}{c}
\text{Ph} \\
\text{CH}_3 \\
\text{Ph} \\
\text{CH}_3
\end{array}
\]

Ene Reaction

To date there has been only one report of an ene reaction with C\textsubscript{60}. Wu and coworkers report an ene reaction with 4-allylanisole to give, in low yield, the monoadduct as evidenced by FAB MS, FTIR, and \textsuperscript{1}H NMR.\textsuperscript{28} The new double bond in the product was \textit{trans} as shown by \textsuperscript{1}H NMR coupling constants. The product presumably arises from a chair-like transition state of the reactants.

3+2 Additions

Buckminsterfullerene has been shown to undergo reaction with nitrile oxides\textsuperscript{29}, azides\textsuperscript{30}, azomethine ylides\textsuperscript{31}, and diazo compounds\textsuperscript{32} to give the corresponding 3+2 adducts in acceptable yields. Of particular interest is the reaction of C\textsubscript{60} with diazomethane to give the organofullerene (C\textsubscript{61}R\textsubscript{2}) via the pyrazoline intermediate. The four possible isomers for this adduct are shown as 6, 7, 8, and 9 in Figure 2. The isomer formed in this reaction is compound 7.
Figure 2

Reaction of C$_{60}$ with substituted diazomethane compounds gives isomers 7 and 8 based on the $^{13}$C NMR spectrum as discussed above. Thermal equilibration of isomers 7 and 8, leads to isomer 8 only. Formation of isomers 7 and 8 followed by thermal equilibration to the thermodynamically more stable isomer 8 seems to be characteristic of reactions with diazo compounds except in the case of diazomethane.$^{33}$

It is interesting to note that reaction with benzyl azides affords two products. One product was unidentified and the other was the 6,5 open isomer as shown by $^{13}$C and $^{15}$N NMR spectroscopy. In this case, after thermal equilibration the 6,5 open isomer was found to be the thermodynamically most stable isomer. An explanation for the formation of different thermodynamically stable isomers in these diazo compounds remains unresolved.

2+2 Cycloadducts

A few examples of the formation of 2+2 cycloadducts of C$_{60}$ have been reported. Photochemically induced cycloaddition of cyclohexenone to C$_{60}$ gives the corresponding 2+2 product as a mixture of cis and trans isomers as shown by $^1$H and $^{13}$C NMR.$^{34}$ Another case of 2+2 photocycloaddition is the reaction of C$_{60}$ with N,N-diethylpropynylamine.$^{35}$ Buckminsterfullerene has also been shown to undergo 2+2 cycloaddition with benzyne,$^{36}$ which normally adds in a 4+2 manner, and dimethyleneketene acetals.$^{37}$

Reactions of Functionalized C$_{60}$

Once a foundation for the preparation of monofunctionalized C$_{60}$ has been established, the next logical step is to determine the reactions that can be performed on these organofullerenes in the presence of the fullerene core. Recently, several examples of functional group manipulations in the presence of the fullerene core have appeared in the literature. The most noteworthy is the work by Wudl and coworkers, who describe oxidation, and functionalization (Scheme III) of organofullerene 10 as well as reduction and C-C bond-forming reactions with organofullerene 12.$^{38}$
Not surprisingly, the authors report that C-C bond formation through nucleophilic additions with Grignards and alkyllithium reagents were unsuccessful due to competing reaction with the fullerene core.

Organofullerene 13, prepared by hydrolysis of the corresponding bis(acetamide) and treatment with succinic anhydride, has been shown to inhibit the HIV protease enzyme in vitro.\(^{39}\)

Other interesting examples of derivatizing an organofullerene include preparation of \(\alpha\)-amino acid derivatives,\(^{40}\) a fullerene peptide,\(^{41}\) a fullerene bound dendrimer,\(^{42}\) a fullerene derived polymer,\(^{43}\) and a derivative which showed photoinduced biochemical activity.\(^{44}\)

**BIS- AND POLYADDUCTS**

In the reactions described above, monoaadduct formation was accompanied by some amounts of bisadducts, and higher adducts. The second addition generally occurs on the opposite hemisphere of the molecule, but the number of positional isomers makes spectroscopic characterization complex. Hawkins and coworkers have had some success forming chiral bisadducts reacting osmium tetroxide in the presence of bulky chiral ligands with \(\text{C}_{60}\).\(^{45}\) Exchange of this chiral ligand with pyridine gives bisadducts which are chiral due to the substitution on the
sphere. Hirsh and coworkers have reported the isolation of two isomers of a bisadduct and two isomers of a tris adduct of C$_{60}$ with di(ethoxycarbonylmethylene).46

**OTHER FUNCTIONALIZATIONS**

A number of organometallic derivatives of Buckminsterfullerene have been prepared with complexation in an $\eta^2$ fashion.47 Another type of derivative is an endohedral complex of C$_{60}$.48 Since the cavity of C$_{60}$ is hollow with an internal radius of about 7 Å, one can imagine placing one or more atoms inside of the cavity. There are two different ways to accomplishing this task. The first is to prepare C$_{60}$ by the method previously mentioned, except that the graphite rods in the preparation must be doped with the atom to be incorporated inside the C$_{60}$ carbon cage. A second method used to introduce gasses, is to heat a C$_{60}$ sample at 600°C and high pressure in the presence of the gas of interest. Scuseria and coworkers report the theoretical existence of a window mechanism in which two carbon bonds are reversibly broken in C$_{60}$ to allow the atom to enter.49

**CONCLUSION**

It has been demonstrated that C$_{60}$ can be selectively functionalized to give monoaadducts through a variety of cycloaddition and nucleophilic addition reactions. The initial problem of assignment of the valence isomers of the methanofullerenes and fulleroids has been solved and the energetic preference of addition to the fullerene core has been shown to favor the 6,6 closed and 6,5 open isomers. Further manipulations can be carried out on the monoaadducts in the presence of the fullerene core to give novel compounds. Future work needs to be completed to elaborate the chemistry that can be performed on fullerene derivatives.

9. Fullerenes soot is a term used to describe a mixture of carbonaceous material including C$_{60}$, C$_{70}$ and higher fullerenes.
12. For leading references to early reactions with C$_{60}$ see reference 11.


ENANTIOSELECTIVE CATALYSTS FOR THE CYCLOPROPANATION OF OLEFINs BY DIAZO COMPOUNDS

Reported by Jennifer L. Hunt
March 21, 1994

INTRODUCTION

The cyclopropyl group is found in a large number of naturally occurring compounds of biological importance and is a synthetically useful intermediate in organic synthesis. The stereochemistry of the cyclopropane ring often plays an important role in its biological activity. For example, of the four stereoisomers of chrysanthemic acid, the pyrethroid insecticide, the (+)-trans isomer is the most toxic to insects. The importance of the stereochemistry of cyclopropanes has stimulated a great deal of interest in the synthesis of optically active cyclopropanes and several methods for their preparation have been developed. The approach which utilizes asymmetric copper or rhodium catalysts to perform the addition of the carbon of a diazo compound to an olefin is the most efficient method for the synthesis of trans-cyclopropanecarboxylates. This abstract will focus on the synthetic and mechanistic aspects of these cyclopropanation reactions.

GENERAL REACTION

The conversion of olefins to cyclopropanes by the decomposition of diazo compounds is a reaction that has been known for many years. The general reaction for styrene is shown in equation 1. Formation of cyclopropanes by the decomposition of diazo compounds using a metal catalyst such as copper or rhodium is more selective than decomposition by photolysis or pyrolysis. Replacement of the insoluble copper compounds originally used by soluble copper complexes made these reactions easier to study mechanistically.

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{N}_2\text{CHCO}_2\text{R} \\
\rightarrow & \\
\text{Ph} & \quad \text{H} & \quad \text{H} & \quad \text{COOR} & \quad \text{Ph} & \quad \text{H} & \quad \text{H} & \quad \text{COOR}
\end{align*}
\]

(COPPER(I) AND COPPER(II) COMPLEXES

Chiral Salicyaldimine Ligands

The first asymmetric catalyst utilized for the conversion of olefins to cyclopropanes by the metal catalyzed decomposition of diazo compounds was reported by Nozaki and coworkers in 1966. Decomposition of ethyl diazoacetate in the presence of styrene by the chiral catalyst bis[N-(R)-α-phenylethylsalicylaldiminate]copper(II) or its enantiomer gave both cis- and trans-2-phenylcyclopropanecarboxylate esters in less than 10% enantiomeric excess (ee). The chiral ligand was synthesized from α-phenethylamine and salicylaldehyde. The copper complex was prepared
by addition of a solution of Cu(OAc)$_2$·H$_2$O in methanol to a boiling solution of (S)- or (R)-N-salicyclidene-α-phenethylamine in ethyl acetate.$^9$

Aratani and coworkers conducted an extensive search for a more effective catalyst specifically for the synthesis of chrysanthemic acid.$^3$ The chiral ligands investigated were synthesized by reaction of an optically active amino acid ester with a Grignard reagent to give an amino alcohol which was then treated with salicylaldehyde to give a Schiff base. The copper complex 1 was formed upon treatment of the Schiff base with cupric acetate. The structure of 1 is dimeric as shown by X-ray analysis of the copper complex with R$_1$ = benzyl and R$_2$ = 2-butoxy-5-t-butyl-phenyl.$^3$

![Image of copper complex 1]

The reaction of 2,5-dimethyl-2,4-hexadiene with ethyl diazoacetate in the presence of copper catalysts of the type 1 was investigated (equation 2).

$$\text{N}_2\text{CHCOOR} \xrightarrow{\text{cat}} \text{COOR} + \text{COOR}$$  \hspace{1cm} (2)

As the size of R$_2$ increased, the enantioselectivity for both the cis and trans isomers increased. In contrast, increasing the size of R$_1$ was detrimental to the enantioselectivity of both isomers. The best results, a cis/trans ratio of 49:51 with ee's of 68% and 62% for the trans and cis isomers respectively, were obtained for 1a in which R$_1$ = methyl and R$_2$ = 5-t-butyl-2-octyloxy-phenyl. The size of the alkyl group on the diazoacetate also has an effect on the selectivity. As the size of the alkyl group increases, the diastereoselectivity as well as the enantioselectivity increases. For example, the use of the bulky l-menthyl diazoacetate changes the cis/trans ratio to 7:93 and the diastereomeric excess (de) for the trans isomer to 94%, but the de for the cis isomer drops to 46%. The trans isomer is generally formed with higher enantioselectivity. The selectivity also increases with increasing substitution on the double bond. Reaction of l-menthyl diazoacetate with styrene and 1,1-diphenylethylene gave the trans isomers in 69% and 75% de, respectively, compared to the 94% de obtained with 2,5-dimethyl-2,4-hexadiene. Similar copper(II) Schiff base catalysts have been described by Laidler and coworkers.$^{10}$ These catalysts give results similar to the Aratani catalysts.
Chiral Semicorrin Ligands

Pfaltz and coworkers introduced the use of semicorrin copper(II) complexes as precatalysts for the cyclopropanation of olefins in 1986. The semicorrin ligand 2 is easily prepared from D- or L-pyroglutamic acid which are both commercially available in an overall yield of 30 to 40%. The two ester functional groups can be modified in a variety of ways to give modified versions of the semicorrin ligand such as 3 and 4.

\[ \text{2} \quad \text{3} \quad \text{4} \]

The copper(II) catalysts are formed with 2 and 4 by reaction of the semicorrin with copper(II) acetate in methanol and the copper(II) adduct of 3 is formed by reaction of the semicorrin with copper(II) sulfate and sodium bicarbonate in a mixture of water and methylene chloride. X-ray analysis of the copper(II) adduct of 3 verifies that two semicorrin ligands are chelated to the copper with the four coordinating nitrogens arranged in a distorted tetrahedron about the metal. The bis(emicorrinato)copper(II) precatalysts are activated by heating in the presence of diazo compound or by adding phenylhydrazine at room temperature. The actual catalyst is thought to be a mono(emicorrinato)copper(I) complex. The reaction of styrene with ethyl diazoacetate in the presence of the copper(II) adducts of 2, 3, and 4 was investigated. The three catalysts give similar cis/trans ratios of approximately 25:75, but the copper(II) adduct of 3 proved to be much more enantioselective providing the trans isomer in 85% ee. As with the Aratani catalyst, bulky diazo esters give higher diastereoselectivities and enantioselectivities. For example, the use of d-menthyl diazoacetate gives a cis/trans ratio of 18:82 with the trans isomer in 97% de. Other terminal olefins such as butadiene and 1-heptene give similar selectivities.

Chiral Bis(oxazoline) Ligands

Masamune, Evans, and Pfaltz have reported the use of chiral bis(oxazoline) copper complexes for catalysis of the cyclopropanation of olefins. The bis(oxazoline) ligands are structurally related to the semicorrins and would be expected to give similar results. Masamune and coworkers synthesized bis(oxazolines) 5 and 6 by reaction of the corresponding amino alcohol with diethyl malonate to form N-(hydroxylalkyl)amides which were then cyclized by addition of dichlorodimethylstannane or by reaction of the corresponding amino alcohols with malono-bis-imidate in methylene chloride in the presence of triethylamine. The copper(II) complexes used as precatalysts were prepared by deprotonation of the ligands 5 and 6 with n-butyl lithium followed by addition of cupric chloride.
The precatalysts were activated by phenylhydrazine in the same manner as the copper(II) semicorrins. Copper(I) catalysts can also be prepared from by treating 5 and 6 with CuClO₄(CH₃CN)₄, CuOTf, or CuOtBu.¹⁴b In these complexes the bis(oxazoline) ligands act as neutral donors and no activation of the catalyst is required. The reaction of styrene with ethyl diazoacetate in the presence of copper(II) adducts of a variety of ligands was investigated. As the size of R increases the enatioselectivity increases. The best results, a cis/trans ratio of 25:75 with an ee of 90% for the trans isomer, were obtained for 5a where R = tBu.¹⁵a Like the other copper catalysts, the maximum diastereoselectivities and enantioselectivities are obtained with larger diazo esters. Reaction of styrene and 1-octene with l-menthyl diazoacetate catalyzed by the copper(II) adduct of 5a gave cyclopropane products with cis/trans ratios of 14:86 and 6:94 and de's for the trans isomer of 98% and 99% respectively. The selectivities observed for disubstituted olefins are slightly lower. For example, trans-4-octene gives only one product in 88% de and 2,3,3-trimethylbutene gives cyclopropane products in a cis/trans ratio of 5:95 and 80% de for the trans isomer.

This catalyst was unsatisfactory for cis-1,2-disubstituted and trisubstituted olefins; therefore, the reaction of 2,5-dimethyl-2,4-hexadiene with diazoacetates in the presence of a variety of copper catalysts was investigated.¹⁵b The best results were obtained with the bulky dicyclohexylmethyl diazoacetate which gave a cis/trans ratio 5:95 and an ee of 94% for the trans isomer using 6a, R = R' = phenyl, as the catalyst. Reaction of cis-4,4-dimethyl-2-pentene and 1,1-diphenylpentene with l-menthyl diazoacetate in the presence of the copper(I) adduct of 6a gave cis/trans ratios of 12:88 and 2:98 and de's for the trans isomer of 95% and 84% respectively.

Pfaltz and coworkers synthesized bis(oxazoline) 5 by the reaction of the corresponding amino alcohol with dimethyl malonate to form N-(hydroxylalkyl)amides which were then treated with SOCl₂ followed by base-induced cyclization.¹⁷ Many of the same R groups were studied and the results were consistent with the Masamune study.

Evans and coworkers synthesized representative bis(oxazolines) 5, 6, and 7 and prepared copper(I) trifluoromethanesulfonate complexes of these ligands.¹⁶a The reaction of styrene with ethyl diazoacetate in the presence of the copper(I) adducts of 5, 6, and 7 was investigated. The copper(I) adduct of 7a (R = tBu) gave the best selectivities. The cyclopropane products were obtained in a cis/trans ratio of 26:74 with an ee of 99% for the trans isomer. The size of the alkyl group on the diazoacetate greatly influences the selectivity in the same manner as previously
observed for the other catalysts. Use of the bulky diazoester derived from 2,5-di-tert-butyl-4-methylphenol (BHT) changed the 
\textit{cis}/\textit{trans} ratio to 6:94 while maintaining the ee of the \textit{trans} isomer at 99\%. The solid state structure of the copper(I) triflate adduct of 7a had been investigated by X-ray analysis and has been shown to exist as a helical polymer.\textsuperscript{16b}

\textbf{Chiral 5-Aza-Semicorrins}

Pfaltz has investigated the use of 5-aza-emicorrins, 8, which are structurally related to the semicorrin and bis(oxazoline) ligands.\textsuperscript{18} These ligands are prepared by treating the corresponding lactam with an excess of bis(trimethylsilyl)amine in the presence of a catalytic amount of \textit{p}-toluenesulfonic acid at 130\°C followed by alkylation with methyl iodide.

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

The copper(I) adduct of this neutral ligand is prepared in situ by addition of copper(I) triflate. When styrene was investigated, the best results were obtained for \( R = \text{CMe}_2\text{OSiMe}_2\text{t-Bu} \). Yields between 45 and 75\% were obtained with \textit{cis}/\textit{trans} ratios between 23:77 and 16:84 and ee's ranging from 95 to 98\% for the \textit{trans} isomer depending on the diazoester used in the reaction. The selectivity increased with increasing size of the alkyl of the diazoacetate.

\textbf{RHODIUM COMPLEXES}

Several attempts have been made to utilize rhodium catalysts with chiral ligands for the cyclopropanation of olefins. Poor selectivities are observed for chiral rhodium(II) carboxylate complexes with optical inductions of less than 12\%.\textsuperscript{19} Moderate to poor selectivities are observed for chiral rhodium(III) porphyrins which give cyclopropane products in 10\% to 60\% ee.\textsuperscript{20} Much higher selectivities are observed for the chiral rhodium(II) carboxamides developed by Doyle and coworkers.\textsuperscript{21} These complexes are prepared by exchange of the acetate ligands in \( \text{Rh}_2(\text{OAc})_4 \) with chiral oxazolidinone or pyrrolidone ligands in refluxing chlorobenzene.\textsuperscript{22} Of the four possible isomers, only the isomer placing the two nitrogen-donor atoms \textit{cis} is formed (Figure 1). The structure of several of these complexes has been verified by X-ray analysis.\textsuperscript{22} Of the catalysts investigated, 9a-c, 10, and 11a-c, the best results were obtained using 11a. The size of the alkyl group on the diazoacetate influences selectivities in the same manner as the copper catalysts previously discussed. Reaction of styrene and 3,3-dimethyl-1-butene with \textit{d}-menthyl diazoacetate catalyzed by 11a gave cyclopropane products with \textit{cis}/\textit{trans} ratios of 33:67 and 29:71 with de's for the \textit{trans} isomer of 48\% and 65\% respectively and de's for the \textit{cis} isomer of 86\% and 91\%
respectively. Selectivities for intermolecular cyclopropanation are not as high as those obtained by the use of the copper(I) adduct of 7a; however, intramolecular cyclopropanation reactions catalyzed by 11a proceed with much higher enantioselectivities than those previously observed. Allylic diazoacetates give γ-lactones in up to 94% ee, homoallylic diazoacetates give δ-lactones in up to 90% ee, and N-homoallylic diazoacetamides give δ-lactams in up to 90% ee. A polyethylene-bound version of 11a has been synthesized and gives similar selectivities to the unbound 11a. In addition, it can be recovered and reused up to 7 times with only slight decreases in selectivity.

**Figure 1**

![Diagram](image)

**MECHANISM**

The decomposition of diazo compounds by transition metals is believed to involve the formation of a transient electrophilic carbene which is then transferred to an electron rich substrate (Scheme IV). There is a substantial amount of indirect evidence that supports the existence of a metal carbene complex in this transformation. The formation of carbene dimers as side products in the reaction suggests the presence of carbene intermediates. The difference in the stereoselectivity observed for cyclopropane formation by the metal catalyzed decomposition of diazo compounds and by photolysis of diazo compounds, which is thought to form free carbenes, indicate that the metal-induced reactions involve a slightly different intermediate. Relative reactivities and selectivities observed in the Rh2(OAc)4-catalyzed cyclopropanation of alkenes with phenyl diazomethane correlate directly to the relative reactivities and selectivities observed in the stoichiometric cyclopropanation of alkenes by the stable metal carbene (CO)5WCHPh. There is also a linear correlation between the stereoselectivities observed for Rh2(OAc)4 catalyzed reactions of ethyl diazoacetate with a variety of olefins and the same reactions catalyzed by CuCl·P(O-i-Pr)3, Rh6(CO)16, and PdCl2·2PhCN. This suggests that the metal is involved in the product-forming step and that the reactions are mechanistically related. The transfer of chirality observed for chiral copper and rhodium catalysts also suggests that the catalyst is involved in the product-forming step. Transition state models describing the transfer of the carbene to the substrate have been proposed by Aratani, Pfaltz, Evans, and Doyle. These transition state models can be used...
to predict the stereochemistry of the products. Unfortunately, none of these models are applicable to all systems.

**Scheme IV**

![Scheme IV diagram]

**APPLICATIONS**

The synthesis of a few biologically important molecules using this approach has been reported. Chrysanthemic acid, a pyrethroid insecticide, has been synthesized from 2,5-dimethyl-2,4-hexadiene (equation 2) using both 1a and the copper(I) adduct of 6a. The copper(II) adduct of 3 has been used to synthesize 2-vinylcyclopropanecarboxylic acid, a building block for the synthesis of brown algae pheromones, from butadiene. An important precursor in the industrial synthesis of cilastatin, an *in-vivo* stabilizer of the antibiotic imipenem, can be obtained from isobutylene in 92% ee using Aratani's catalyst. In addition, trisubstituted cyclopropanes synthesized utilizing this approach have been used as rigid surrogates in conformational studies of oligopeptides.

**CONCLUSION**

Chiral copper and rhodium complexes are useful catalysts for the cyclopropanation of olefins by diazo esters. These complexes are easily prepared from readily available starting materials. Cyclopropanes are produced in high yields with excellent diastereoselectivity and enantioselectivity in many cases. The choice of catalyst depends on the olefin used in the reaction. The copper(II) salicyaldimine catalyst 1a is best for highly substituted olefins. The copper(I) bis(oxazoline) 7a gives the best selectivities for terminal olefins. The best results for intramolecular cyclopropanation are obtained by the dirhodium catalyst 11a.

**REFERENCES**

RAPID ASSEMBLY OF OLIGOSACCHARIDES BY SUBSTRATE-CONTROLLED STRATEGY

Reported by Fanwen Zeng

March 24, 1994

INTRODUCTION

A large number of biologically significant substances, for example glycoproteins and glycolipids, carry carbohydrate groups which are important in cell interaction processes. Carbohydrate residues also play a key role as the molecular recognition site and delivery system in some antitumor antibiotics. Because of their usefulness in biological studies involved in these roles and the scarcity of the carbohydrates, new chemical, enzymatic and chemo-enzymatic glycosylation methodologies have been developed recently.

Chemical O-glycosylation methodology is indispensable for the preparation of oligosaccharides with different glycosidic moieties and linkages. A traditional strategy for O-glycosylation involves differentiation of the hydroxyl groups by a number of highly selective protections and deprotections. A different strategy involves the coupling between an activated glycosyl donor equipped with a good leaving group at its anomeric carbon and the free hydroxyl group of a glycosyl acceptor. Subsequent activation of the new anomeric center allows for further elaboration, which requires mild conditions and should not affect the newly formed glycosidic bond. However, these manipulations are usually tedious and problematic. This seminar will present recent work which provides a new methodology to rapidly assemble oligosaccharides by a substrate-controlled strategy. In this approach, the reactivity of the glycosyl donor and the acceptor can be tuned by changing the nature of the substituents on the sugar ring or on the leaving group. Both elaborations avoid the anomeric carbon and have been proven to be valuable in natural product synthesis.

SUBSTRATE-CONTROLLED STRATEGY: GLYCOSIDE SUBSTITUENTS

n-Pentenyl Glycosides

The n-pentenyl glycoside (NPG) approach was introduced to carbohydrate chemistry by Fraser-Reid and coworkers when they observed an unexpected oxidative hydrolysis of a pent-4-enyl acetal 1 by N-bromosuccinimide (NBS).3 Bromomethyl tetrahydrofuran 2 was formed, instead of the desired bromohydrin 3, as shown in Scheme I. A generalized mechanism is summarized in Scheme II, and it was presumed to proceed by a cascade of cationic intermediates initiated by the 5(O)n-exo-tet opening of the cyclic bromonium ion 4. The resulting oxocarbenium ion 6 can be captured either by water, leading to the formation of hemiacetal 7.
Scheme I

![Chemical structure](image)

Scheme II

![Chemical structure](image)

(path a), or by an alcohol, leading to acetal 8 (path b). This latter acetal exchange can be applied to O-glycosylation if the alcohol employed is a glycosyl acceptor. The mild, neutral conditions of those reactions are useful for acid-sensitive glycosides. Further studies showed that C-2 esterified NPGs were hydrolyzed much slower than their C-2 etherified analogs, when NBS or iodonium dicollidine perchlorate (IDCP) was used as promoter, suggesting that the reactivity of a NPG can be controlled by the electronic nature of C-2 substitutions. Relatively electron-withdrawing groups decrease the reactivity of the corresponding NPG and electron-donating groups enhance the reactivity of the corresponding NPG. This substrate differentiation is referred to as the "armed/disarmed" effect and can be utilized in the selective and rapid preparation of oligosaccharides.

As shown in Scheme III, the "armed" NPG 9 is coupled with "disarmed" NPG 10 in the presence of IDCP forming disaccharide 11 exclusively. The α/β selectivity is solvent dependent and self-coupling of 10 is not observed. The disaccharide 11 is converted to 12 by the replacement of the O-acetyl with O-benzyl group and this rearmed disaccharide can be used directly in the next elaboration with 13 to form the trisaccharide 14. Further demonstration of this armed/disarmed effect by C-2 substituents is shown in the reactivity comparison between 2-deoxy NPG and 2-bromo NPG, in which the latter with a free hydroxyl group can function as a glycosyl acceptor to attack the fully protected former.
Scheme III

A mechanistic explanation\textsuperscript{5} of this highly substrate-specific reaction is shown in Scheme IV. The formations of cyclic bromonium ions and oxonium ions (abbreviated as 15/17) are considered to be reversible processes by analogy to the kinetic studies on the electrophile-promoted cyclization of $\gamma$-hydroxyalkenes.\textsuperscript{6} Therefore, it is reasonable to assume that the formation of the oxocarbenium ion is the rate-determining step. The inductive effect of relatively electron-withdrawing groups such as acetyl or bromo at C-2 disfavors the formation of the corresponding oxocarbenium ion compared to that of electron-donating substituents such as benzyl or hydrogen (18 vs. 16) both kinetically and thermodynamically. So cross-coupling product is observed through path a and path b which leads to self-coupling product is eliminated.

Scheme IV

The armed and disarmed phenomenon was also observed in cyclic protecting sugars and was attributed to a torsional effect.\textsuperscript{7} The estimated activation energy taken from the energy differences between ground state and reactive oxocarbenium ion was calculated by the PM3 semi-empirical method. There is an agreement between this activation energy and rate of oxidative hydrolysis of the corresponding NPG (Table I). The rationalization is that the origin of
this torsional strain effect is due to the unfavorable distorsion on the planarity of the forming oxocarbenium ion (C₅O₅-C₁C₂) by the cyclic protection. Indeed, coupling between 9 and a disarmed glycosyl acceptor 19b (P = H) equipped with a free hydroxyl group in IDCP afforded cross-coupling disaccharide in 52% yield and self condensation product of 19b was not detected.

Table I. Comparison Between Rate of Hydrolysis and Computed Activation Energy in Cyclic Protecting Sugars

<table>
<thead>
<tr>
<th></th>
<th>Hydrolysis (hrs) (NBS/H₂O)</th>
<th>Computed relative Eₐ (kcal) (β only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>3</td>
<td>0.0</td>
</tr>
<tr>
<td>19a (P = Bn)</td>
<td>6</td>
<td>6.5</td>
</tr>
<tr>
<td>20(β)</td>
<td>20</td>
<td>9.4</td>
</tr>
<tr>
<td>21 (1,2-trans only)</td>
<td>65</td>
<td>16.9</td>
</tr>
</tbody>
</table>

The weak reactivity of the disarmed 2-esterified NPGs with NBS or IDCP prevents their use as potential glycosyl donors. This is a disadvantage since 2-esterified sugars are widely used to form 1,2-trans glycosides via neighboring group participation. The search for stronger promoters to activate disarmed NPGs was successful when N-iodosuccinimide (NIS) with a catalytic amount of triflic acid (TfOH) or triethyisilyl triflate (TESOTf) was used as a reactant. As shown in Scheme V, the esterified NPG 20 can function as a glycosyl donor and form 1,2-trans glycosylation product 21. The combination of substrate-controlled and promoter-mediated strategies has allowed the rapid assembly of oligosaccharides. This approach was used in the synthesis of a glycan segment of nephritogenic glycopeptide.

Scheme V

Glycals

The armed/disarmed strategy was applied to the oxidative coupling of glycals, as demonstrated by Danishefsky. For glycals, the reactivity is controlled by the nature of the C-3
substituents as illustrated by compounds 22 vs. 23 (eq 1). In fact, C-4 substitution as shown by compounds 22 vs. 24 is sufficient to differentiate the substrates (eq 2). It should also be pointed out that this substrate-control is a competitive process, i.e., the disarmed glycal can also be a glycosyl donor in the absence of the armed glycal under the same condition. By mediation with IDCP (Scheme VI), the armed glycal donor 22 with three benzyl protections and no free hydroxyl group can be coupled with disarmed acceptors 23 and 24 with two benzoyl protections and one free hydroxyl group to form clean α-disaccharides 25-26. The high stereoselectivity observed in the products can be rationalized as favorable 1,2-diaxial attack on the presumed 1,2-iodonium ion intermediate. The α-disaccharides 25-26 can only function as glycosyl donors and were used directly to form trisaccharides stereoselectively without any rearming manipulations. The methodology was also applied to the synthesis of tetrasaccharides and ciclamycin 0.10b

Thioglycosides and Selenoglycosides11

The application of armed and disarmed approach to thioglycosides and selenoglycosides was explored by van Boom and coworkers.12 A partially esterified thio- or selenoglycoside with a free hydroxyl group can function as a glycosyl acceptor and react with a fully etherified corresponding substrate which functions as a glycosyl donor in the presence of IDCP, without self-coupling product detected. The α/β selectivity is dependent on substrate and solvent. Alternatively, glycosylation of fully esterified substrate can be achieved in NIS/TfOH with high 1,2-trans stereoselectivity. The strategy was applied to the synthesis of the glycan in a M. bovis BCG glycolipid.12c

2,6-Anhydro-2-thio and 2-Sulfinyl Glycosides

The recent demonstration of the armed and disarmed approach was achieved by Toshima13 with 2,6-anhydro-2-thio and 2-sulfinyl glycosides. The former is armed and the latter is disarmed. Simple redox manipulations between thio and sulfinyl functionality facilitate the
arming and disarming transformation. This glycoside is a potential 2,6-dideoxy sugar after being unmasked by hydrogenation. This method was used in the synthesis of the sugar components of avermectin b$_1$a (Scheme VII) and olivomycin A.

Scheme VII

![Scheme VII](image)

* TPS = t-butylidiphenylsilyl

SUBSTRATE-CONTROLLED STRATEGY: LEAVING GROUP SUBSTITUENT n-Pentenyl Glycosides

A further strategy to control substrate reactivity in glycoside synthesis involves modifications of the leaving group. Removal of a “trigger” such as the double bond in NPG or addition of a strongly deactivating group will convert the “active” form to its “latent” state. An ideal strategy is accompanied by the simple chemical transformation between active and latent states. The approach was realized when a NPG was conveniently dibrominated with bromine in the presence of Et$_4$NBr, this latent 4,5-dibromopentanyl glycoside can function as a glycosyl acceptor.$^{3c,6}$ Active n-pentenyl glycoside can be restored when needed as a glycosyl donor by a subsequently reductive debromination. This sidetracking technique was used in the synthesis of the nonasaccharide component of a glycoprotein.$^{14}$

Thioglycosides and Sulfoxide Glycosides

The reactivity of phenylthioglycosides can be mediated by para-substitution.$^{15}$ As shown in Table II, when dimethyl(methylthio)sulphonium triflate (DMTST) was used as a promoter, the $p$-methoxy compound 27b is reactive, while $p$-nitro derivative 27c is unreactive under the same conditions. However, the nitro group can easily be replaced with an acetamido group by reduction followed by acetylation and the resulting derivative 27d is as active as 27b. The activation of sulfanyl by a thiophilic promoter is the rate-determining step in the sialylation.

An elegant example of this substrate-controlled technique was demonstrated by Kahne with the glycosyl phenyl sulfoxides.$^{16}$ A one-step synthesis of the ciclamycin trisaccharide (Scheme VIII) was achieved by mixing glycosides 28, 29, 30 with a catalytic amount of TfOH. The thioglycoside 28 is inactive under these conditions while 29 is much more reactive than 30.
Table II

<table>
<thead>
<tr>
<th>Glycosides</th>
<th>Sovlent</th>
<th>Time(h)</th>
<th>%Yield</th>
<th>α/β</th>
</tr>
</thead>
<tbody>
<tr>
<td>27a R = Ph</td>
<td>CH₂Cl₂</td>
<td>24</td>
<td>81</td>
<td>55:45</td>
</tr>
<tr>
<td>27b R = p-MeO-Ph</td>
<td>CH₂Cl₂</td>
<td>8</td>
<td>80</td>
<td>50:50</td>
</tr>
<tr>
<td>27b R = p-MeO-Ph</td>
<td>CH₂Cl₂/MeCN (1:1)</td>
<td>0.5</td>
<td>73</td>
<td>70:30</td>
</tr>
<tr>
<td>27c R = p-NO₂-Ph</td>
<td>CH₂Cl₂/MeCN (1:1)</td>
<td>No Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27d R = p-NHAc-Ph</td>
<td>CH₂Cl₂/MeCN (1:1)</td>
<td>0.5</td>
<td>81</td>
<td>75:25</td>
</tr>
</tbody>
</table>

Therefore intermediate 31 is first formed with concurrent TMS deprotection. Further glycosylation with 30 affords trisaccharide 32 in 25% yield.

Scheme VIII

CONCLUSION AND FUTURE WORK

The armed/disarmed strategy for glycoside synthesis was originally demonstrated with esterified and etherified NPGs and was shown to have general applicability to other glycosyl donors including glycals, thioglycosides, selenoglycosides, and 2,6-anhydro-2-thio/sulfinyl glycosides. This substrate reactivity differentiation can be controlled to allow the rapid assembly of oligosaccharides in which the armed glycoside functions as a donor and the disarmed as an acceptor. On the other hand, the disarmed substrate is not completely inert and can be activated by a stronger promoter. Another way to control the reactivity of the glycoside is by varying the substituents present on the leaving group. Easy functionalization can turn on and off the reactivity of the substrate providing active and latent forms. In the near future, the emphasis of substrate-controlled strategies should be placed on the reactivity differentiation on the different
glycosyl donors with different promoters, while continuing efforts on the search for more efficient glycosyl donors. One would also expect progress on developing solid-state synthesis either by chemical or enzymatic methods.  

REFERENCES

SYNTHETIC AND MECHANISTIC ASPECTS OF CUBANE AND HOMOCUBANE

Reported by Sergei V. Kolotuchin

March 28, 1994

INTRODUCTION

Understanding the reactivity and bonding of molecules is central to the study of organic chemistry. Over the last thirty years saturated polycyclic cage molecules have attracted a great deal of attention because they offer a unique display of bent, twisted, strained and rehybridized carbon-carbon bonds. As a result of such "abuse," these molecules contain C-C-C bond angles that deviate significantly from the preferred carbon (sp$^3$) angle of 109.5° and possess unusual positive heats of formation compared to nonstrained analogs.

Cubane (pentacyclo-[4.2.0.0.2.5.3.8.0.7]-octane, 1) and homocubane (pentacyclo-[4.2.0.0.2.5.3.8.0.7]-nonane, 2) are representative examples of this large series of molecules. The strain energies, estimated by force field calculations, are about 166 kcal/mol for cubane and 121 kcal/mol for homocubane.$^{1,2a}$

![Cubane](image1.png)

![Homocubane](image2.png)

Figure 1

Despite its high enthalpy content cubane is kinetically stable because no symmetry-allowed pathway exists for its concerted thermal rearrangement to more stable products. A stepwise mechanism starting with a homolytic cleavage of one C-C bond followed by rearrangement of the cubyl diradical can be envisaged but stable fragments are not formed. Pyrolysis studies of cubane have shown that this process is high in energy, requiring 43 kcal/mol to break the first C-C bond.$^{3}$ Analogous studies on the less strained and less symmetrical homocubane have not been reported, but one might expect the conclusions to be the same.

This paper will be concerned with the following aspects: synthesis of the cage systems, their functionalization, and the discovery of cations and dehydrocompounds.

SYNTHETIC APPROACHES TO CUBANES AND HOMOCUBANES

The first synthesis of cubane (1) was reported in 1964 by Cole and Eaton.$^{4}$ The two main features of this synthesis are the intramolecular [2+2] photocyclization and the Favorskii
“semibenzilic” ring contraction. Synthesis of homocubanes follows essentially the same pathway. 5,6 Further attempts to synthesize cubanes and homocubanes made use of intramolecular [2+2] photocyclizations but obviated the need for a ring contraction. By this approach, homocubyl precursor 3 readily cyclizes to 4.

Scheme I

However appealing adaptation of this approach may seem for the synthesis of unsubstituted cubane (1), it has never been successful. One explanation for this observation was put forward by Osawa who argued that the relatively longer distance separating the two double bonds in the starting diene 5 (3.05Å vs. 2.87Å in 3) and the larger strain increase in cubane (72 kcal/mol vs. 65kcal/mol in homocubane 4) prevents the cyclization2b. This observation was supported by the work of Gleiter and Karcher in which they reduced the nonbonded distance between the unsaturation centers to ca. 2.8Å by the synthesis of 7 and cyclized it to the corresponding cubane derivative 9.7 This work prompted Osawa to further predict, based on MO calculations, that the number of atoms in the bridging chains between the double bonds in question will influence the outcome of the photocyclization. When the bridging chains have an even number of atoms (0, 2, 4, etc.) mixing of π and σ orbitals can render the process of suprafacial [2+2] cycloaddition symmetry-forbidden. This process is symmetry-allowed when the bridging chains have an odd number of atoms as in 7.8 To date, the only exception to this rule is the cycloaddition of syn-octakis-(trifluoromethyl)-diene 6 to afford the cubane 8 (Scheme I).9 An explanation of this fact based on MO theory has yet to be forwarded.

SUBSTITUTION ON THE CUBANE AND HOMOCUBANE FRAMEWORK

An interesting feature of cubane and homocubane chemistry is the methodology employed for direct substitution on the cubane framework. Cubyl and homocubyl carboxylic acids are the most versatile intermediates that serve as entry points into these systems. It is well documented
that these carboxylic acid groups can be successfully transformed into substituted cubanes and homocubanes, with the same substitution pattern, by known functional group transformations.

However, systematic and controlled substitution onto the cubane framework cubanes could be achieved only by directed metallation processes. For instance, it was shown that lithium tetramethylpiperidide (LiTMP) can ortho-lithiate cubane 10 reversibly to an extent of 3% (Scheme II).

**Scheme II**

The cubyl anion, thus formed, was trapped with mercury halides to drive the equilibrium. These mercurated cubanes were shown to be useful intermediates in cubane functionalization. They can be halogenated and transmetallated to cubyl lithium species.\(^{10a}\)

During this investigation a new process of mettallation was developed, which was called "directed ortho-magnesiation" by analogy to the directed ortho-lithiation. In this process TMPMgBr and Mg(TMP)\(_2\) were used as bases. In contrast to directed lithiation, whereupon only one Li-C bond is formed by lithium-hydrogen exchange, in directed magnesiation two such metal-hydrogen exchanges can occur in good yields. A wide range of electrophiles was used to quench the magnesium species to afford polysubstituted cubanes.\(^{10b,c}\) Unfortunately, no related examples were reported for mettallation of homocubanes.

**CUBYL AND HOMOCUBYL CATIONS.**

As Figure 2 illustrates there is only one cation for cubane and four different cations for homocubanes, because of the symmetry of these systems.

![Figure 2](image)

The carbocation center in 9-homocubyl cation 15 is a relatively non-strained, non-bridged methine. It was hypothesized that this carbocation could potentially undergo a degenerate 1,2 C-C Wagner-Meerwein rearrangement leading to complete scrambling of all methine units (Scheme III). This cation is similar to bulvalene whose methines are exchanged by a degenerate Cope
rearrangement. In practice, the anticipated rearrangement can be simply achieved by the solvolysis of 9-substituted homocubanes as shown by NMR studies.

**Scheme III**

Cubyl cation 11 and 4-homocubyl cation 14 seem unstable because their cationic centers reside on s-rich bridgehead exocyclic orbitals. Their geometry is far from being planar and the hyperconjugation with the neighboring methines would require high-energy, cubene-like structures.

In 1983 Rüchardt, et al., showed that 4-bromo-homocubane 16 solvolized in hexafluoro-2-propyl alcohol to the corresponding ether 17. A few years later it was independently reported that cubanes carrying good nucleofugal substituents could undergo remarkably rapid alcoholysis.

**Scheme IV**

Labeling studies established that during the methanolysis of cubyl triflate 18 (X = H) the methoxy group is attached to the same carbon atom as the original triflate group. There is, therefore, neither hydrogen scrambling nor rearrangement. Unfortunately, an attempt to observe the cubyl cation directly in super acids at low temperature failed. Substituent effects on the rate of solvolysis were also investigated. It was found that a 2-methyl substituent accelerates the reaction three-fold over the desmethylated compound, whereas a 4-methyl depresses the rate by two-fold. When compared to unsubstituted cubyl triflate, 4-chloro, -bromo, -iodo, -carbomethoxy and -methoxy groups decelerate the rate of solvolysis and 4-trimethylsilyl and -trimethylstannyl groups accelerate it 110 and 2800 fold, respectively. All of this experimental data and ab initio calculations suggest the non-classical nature of the cubyl cation. It is believed that the positive charge is delocalized by interaction with the strained C-C bonds in the cubane framework and
there is a positive bond order between the \( p \) orbital at the positively charged carbon atom and the \( p \) orbital aligned with it at each of the \( \beta \) carbon atoms. The \textit{ab initio} calculations suggest that the LUMO of the delocalized cubyl cation 11 is cylindrically symmetrical along the body diagonal of the cube.\(^{16}\) Therefore, any electron donation from substituent orbitals off this axis will be ineffective. This might be a possible explanation for the exceedingly slow solvolysis of 4-methoxy triflate 18 (\( X = \text{OMe} \)) which results from an electron-withdrawing effect of the methoxy group rather than its usual and powerful cation-stabilizing effect. For the same reason, hyperconjugative stabilization by a 4- methyl group is rendered ineffective by the off-axis positioning of the cation LUMO, while the geometry-independent electron withdrawing inductive effect of the methyl group remains significant. In other words, orbital alignment is not important for \( \sigma \) donation and, therefore, groups capable of \( \sigma \) donation should stabilize the cation and enhance the rate of solvolysis of its parent if there is the charge delocalization at the 4-position of the cubyl cation. An alternative explanation, proposed by Moriarty \textit{et al.}, which excludes the non-classical character of the cubyl cation invokes a through-space field effect for the destabilization of the cation to explain the substituent effects.\(^{17}\)

![Diagram](image)

\textbf{Figure 3}

The suggested delocalization of the positive charge may not be the only reason as to why the cubyl cation is more readily accessible than expected. An additional qualitative point worth mentioning is the bent bonding in cubane which reduces the pyramidalization angle from 90° to about 105° when it is defined by using orbital vectors rather than the internuclear lines. The latter qualitative considerations should also hold for 4-homocubyl cation 14 whose non-classical stabilization of the same nature was postulated.\(^{14}\) An explanation as to why cubyl cation 11 is more readily formed than 4-homocubyl cation 14 is yet to be forwarded.

Both 1- and 2-homocubylcations 12 and 13 are unknown, though the existence of the former was postulated.\(^{10}\)

\textbf{DEHYDROCUBANES AND DEHYDROHOMOCUBANES}

Can extra bonds, besides the bonds of the framework, be accommodated in cubane or homocubane? The answer to this intriguing question is yes as seen in four examples reported to date.

1,2-Dehydrocubane (cubene, 21) and homocub-4(5)-ene (25) are the most pyramidalized olefins known, with the calculated pyramidalization angle for cubene being 84°.\(^{19}\) The inter-
mediacy of cubene and homocub-4(5)-ene is strongly suggested by trapping experiments in a Diels-Alder reaction leading to adducts 23 and 27 respectively (Scheme V).\textsuperscript{19,20} In a related example, however, 1,4-cubanediyl (30) was produced upon codeposition of argon with 1,4-diodocubane 28 and potassium or cesium vapor. The structure of the products based on IR, UV, and ESR spectra of the products obtained strongly suggested its formation.\textsuperscript{21} Transient intermediacy of 30 in solution was also confirmed by the finding that treatment of 4-haloiodocubanes (e. g. 28) with tert-BuLi, n-BuLi or PhLi (reverse addition) gives rise to products

\textbf{Scheme V}

\[ \text{Scheme V} \]

\[ \begin{array}{c}
\text{20} \\
[1.5em] \text{21} \\
[1.5em] \text{22} \\
[1.5em] \text{23} \\
\end{array} \]

\[ \text{24} \\
[1.5em] \text{25} \\
[1.5em] \text{26} \\
[1.5em] \text{27} \\
\]

\( (e. g. \text{ acid 32}) \) whose origin can only be explained by invoking 1,4-dehydrocubane (Scheme VI).

\textbf{Scheme VI}

\[ \text{Scheme VI} \]

\[ \begin{array}{c}
\text{28} \\
[1.5em] \text{29} \\
[1.5em] \text{30} \\
[1.5em] \text{31} \\
[1.5em] \text{32} \\
\end{array} \]

The presence of the symmetrical intermediate was also supported by labeling experiments.\textsuperscript{22} \textit{Ab initio} calculations suggest the singlet state of diyl 30 to be 10 kcal/mole lower in energy than the corresponding triplet state which suggests a substantial through-bond interaction.\textsuperscript{23}

Force field calculations suggest that 1,3-dehydrocubane 33 is only 8.1 kcal/mole higher in energy than cubene 21 and there is a significant bonding between C1 and C3 (Scheme VII). The species 33 may, therefore, be prepared by dehalogenation of the corresponding diiodide.\textsuperscript{23} This preparation is analogous to the preparation of 2,4-dehydrohomocubane 35 in which 2,4-dihalo-homocubanes (e. g. 34) were treated with \textit{tert}-BuLi at -78 °C and subsequently quenched with D\textsubscript{2}O, affording homocubane 36.\textsuperscript{24}
The last of this series of dehydrocompounds is 1(9)-homocubene 40 (Scheme VIII) which is formed upon thermal or photochemical rearrangement of cubyl phenyl diazomethane 39 (R = Ph).

**Scheme VIII**

Jones *et. al.* showed that the same reaction can occur if R = H. The 1(9)-homocubene system contains the most twisted C-C double bond known and if rehybridization and pyramidalization did not occur the angle between the \( p \) orbitals of the unsaturated carbons would be 90°. This is an example of an anti-Bredt olefin. Because of the strain in the system it rearranges reversibly to the corresponding carbene 42 (Scheme VIII) and for unsubstituted 1(9)-homocubene (40, R = H) the equilibrium constant \( K \) has been determined to be close to unity at room temperature. Labeling studies strongly suggested that the rearrangement proceeds by a shift of the C-C bond in the homocubene which can best be rationalized by invoking a zwitterionic contributor as shown in 41 (Scheme VIII).

**CONCLUSION**

Studies of cubanes and homocubanes expand our knowledge about bonding and reactivity of organic molecules and reactive intermediates. The results of solvolysis studies of cubyl triflates and mesylates support the intermediacy of cubane carbocations that are surprisingly accessible. Trapping the lithiation products from 1,2- and 1,4-diiodocubane and 3-bromo-4-chlorohomocubane suggests the formation of the corresponding dehydrocompounds, including 1,2-cubene, the most pyramidalized olefin known. Because of unusual geometry, 1(9)-dehydro-
homocubane, the most twisted olefin known, undergoes a reversible olefin-carbene rearrangement with an equilibrium constant that is close to unity at room temperature. Future work needs to be done to elaborate the chemistry that can be done on these molecules.

REFERENCES


REDUCTIVE COUPLING OF CARBONYL GROUPS WITH CARBON-CARBON DOUBLE BONDS THROUGH KETYL RADICAL ANIONS

Reported by Ali Koohang

April 4, 1994

INTRODUCTION

The reductive coupling of carbonyl functionality with alkenes and alkynes through the intermediacy of ketyl radical anions has been investigated extensively by chemical, electrochemical, and photochemical methodologies. The synthetic utility of these reactions, particularly in the case of intramolecular cyclization of olefinic ketones, has led to the useful construction of four, five, and six membered ring structures. The most striking feature of these reactions is their high regio- and stereoselectivities. In general, ring formations in the reductive coupling reactions of olefinic ketones is consistent with Baldwin’s rules of cyclization and those observed in intramolecular free-radical cyclization.\(^1,2\) The chemical cyclization of olefinic ketones that was discovered through dissolving metal reduction has been improved by utilization of SmI\(_2\).\(^3,4\) Electrochemical cathodic couplings of ketones and olefins have been shown to provide an alternative methodology to construct cyclized alcohols in high yields and stereoselectivities.\(^5\) More recently, Cossy and coworkers have reported photochemical generation of bicyclic cyclopentanols through cyclization of \(\delta,\varepsilon\)-unsaturated ketones.\(^6\) This abstract will compare different approaches to the reductive coupling of ketyl radical anions with unsaturated groups, particularly alkenes, both inter- and intramolecularly.

ELECTROCHEMICAL CYCLIZATION OF OLEFINIC KETONES

Reductive cyclization of carbonyl groups with alkenes was first investigated by Shono and coworkers in 1971 electrochemically.\(^7\) They reported intramolecular cyclization of nonconjugated olefinic ketones to form tertiary alcohols stereoselectively. Electroreduction of 6-hepten-2-one (1a), in 5:1 mixture of dioxane/methanol containing tetraethylammonium tosylate as supporting electrolyte, with 3 F/mol of electricity afforded cis-1,2-dimethylcyclopentanol (2a) as exclusive diastereomer.\(^8\)

\[
\begin{align*}
\text{1a-h} & \rightarrow \begin{array}{c}
\text{2a-h} \\
\text{R'OHCH}_2\text{R'} & \text{R'OHCH}_2\text{R'} \\
\end{array} \\
\text{3a-h} & \end{align*}
\]

Alkylation of the terminal carbon atom of the alkene group did not prevent the intramolecular cyclization, however, a small amount of the acyclic alcohols 3g and 3h was produced perhaps due

copyright © 1994 Ali Koohang
to a two electron transfer process (Table I). Alkyl substitution on the inner carbon atom of the double bond, however, prevented the cyclization process, while a methyl or isopropyl substituent attached to the β position did not inhibit the cyclization.

Table I. Electroreduction of Olefinic Kerones 1a-h in Methanol/dioxane

<table>
<thead>
<tr>
<th>Ketone 1</th>
<th>% Yield</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>R'</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>a</td>
<td>Me</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>b</td>
<td>Et</td>
<td>88</td>
<td>0</td>
</tr>
<tr>
<td>c</td>
<td>i-Pr</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>d</td>
<td>n-Bu</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>e</td>
<td>n-Hex</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>f</td>
<td>Me</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>g</td>
<td>Me</td>
<td>78</td>
<td>5</td>
</tr>
<tr>
<td>h</td>
<td>Me</td>
<td>75</td>
<td>10</td>
</tr>
</tbody>
</table>

The preparation of six-membered ring compounds was also achieved by reducing appropriate olefinic ketones. For instance, the electroreduction of 7-octen-2-one (6) in methanol-dioxane afforded cis-1,2-dimethylcyclohexanol (7, 70%) and 7-octen-2-ol (8, 8%) as the acyclic byproduct, however, when DMF was substituted for methanol-dioxane, 7 was formed exclusively.

The high diastereoselectivity observed in the cyclization of olefinic ketones is attributed to the electrostatic repulsion between the negatively charged oxygen and the developing methylene radical in the ketyl radical anion intermediate. Secondary orbital overlap between the radical methylene and the alkyl group in the radical intermediate 5b is also suggested to influence in the stereochemical outcome of these reactions.
The Effect of Supporting Electrolyte and Solvent

The electrochemical cyclization reactions involving ketyl radical anions have also been studied by Kariv-Miller and coworkers. The reduction of 6-hepten-2-one (1a) in electrochemical cells was shown to be affected dramatically by the addition of a small amount of dimethylpyrrolidinium tetrafluoroborate (DMP⁺ BF₄⁻). Thus, a solution of 1a in DMF, in the absence of a catalyst, was immersed in TBA⁺BF₄⁻ as supporting electrolyte, and reduced at mercury (cathode) with 2 F/mol at -3.1 V (vs SCE) to afford the acyclic 6-hepten-2-ol (3a, 85%) as the only product. When catalytic amount of DMP⁺ or TEA⁺ was added to this solution, 1a was reduced at a more positive potential (-2.7 V) and the product was identified as cis-1,2-dimethylcyclopentanol (2a, 95%). Substitution of diglyme-H₂O (0.5%) as solvent, in the absence of catalyst, gave the acyclic product 3a as expected, however, the pinacol 4 was obtained in the presence of catalytic amount of DMP⁺ or TEA⁺. Cyclic voltamogram for the reduction of a DMF solution of 6-hepten-2-one (1a) in 0.1 M solution of TBA⁺BF₄⁻ as supporting electrolyte showed a peak at -3.1V characteristic of TBA⁺ alone. When 1.0 X 10⁻³ M DMP⁺ BF₄⁻ was added to the catholyte the voltamogram showed a reduction peak at a more positive potential (-2.7 V). These results suggested that in the presence of catalytic DMP⁺ or TEA⁺, the reduction of ketone involved only one electron transfer to the catalyst cation with participation of Hg to form a complex that would initiate the cyclization. When a protic solvent was used the protonation of ketyl radical anion led to the formation of pinacol product.

\[
\text{DMP}^+ + 1 \text{e}^- + n \text{Hg} \rightleftharpoons \text{DMP(Hg)}_n
\]

\[
\begin{align*}
\text{1a} & \rightarrow \text{DMP(Hg)}_n
\end{align*}
\]

\[
\begin{align*}
\text{R} & \text{O}^- \rightarrow \text{CH}_2 \\
\text{R} & \text{O}^- \rightarrow \text{CH}_2 \\
\text{OH} & \rightarrow \text{HO} \\
\text{OH} & \rightarrow \text{HO}
\end{align*}
\]

CHEMICAL CYCLIZATION OF OLEFINIC KETONES

The dissolving metal reduction of δ,ε-unsaturated ketones was first reported separately by Stork and Eakin in 1965. Upon addition of lithium to a solution of 6-heptyn-2-one in liquid ammonia-tetrahydrofuran, a mixture of cyclic and acyclic products were obtained in moderate yields.
from which the cyclic compound characterized as 1-methyl-2-methylene cyclopentanol was obtained. Whitesides and coworkers obtained cyclized five- and six-membered rings in good yields by carrying out several reactions of olefinic ketones in a mixture containing N,N-diethylacetamide-sodium-tert-butyl alcohol. For example, 6-hepten-2-one was converted to diastereomeric mixture of 1,2-dimethylcyclopentanol (65%). Intramolecular cyclization of 2,2-dimethyl-5-hexenal (9) was studied as a model compound during the total synthesis of Hypnophilin by Curran and coworkers. When the reduction was conducted with lithium in liquid ammonia a 1:1 mixture of 10 and 11 was obtained. The cyclized product, however, was formed with high diastereoselectivity (trans/cis = 7). Treatment of 9 with SmI2 in the presence of HMPA gave a mixture of cyclic diastereomers (10) and unidentified products.

\[
\begin{align*}
\text{Li/} \text{NH}_3 \quad \text{t}-\text{BuOH} & \quad \text{or SmI}_2 \quad \text{THF/ HMPA} \\
9 & \quad \xrightarrow{\text{Sml}} \\
\text{cis} + \text{trans} & \quad \frac{1}{1} \\
\end{align*}
\]

The chemical reductive coupling of activated olefins with aldehydes and ketones via SmI2 has been investigated by Fukuzawa and coworkers. Therefore, treatment of (E) 8-oxo-2-nonenoeate (12) with SmI2 in THF gave the bicyclic lactone 13 as a mixture of cis/trans (36/64), however, the trans selectivity increased tremendously (trans/cis = 250), when cycloalkanone 14, with a trans configuration about the olefin, was cyclized with SmI2. Electrochemical cyclization of 14, in comparison, was reported to afford a mixture of 15 and 16 that was increased from 11.4:1 at room temperature to 26:1 at -20 °C.

\[
\begin{align*}
\text{12} & \quad \xrightarrow{\text{Sml}} \quad \text{THF, 4h, reflux} \\
& \quad 56\% \\
\text{13} & \\
\end{align*}
\]

\[
\begin{align*}
\text{14} & \quad \xrightarrow{\text{Sml}} \\
& \quad 87\% \\
\text{15} + \text{16} & \\
\end{align*}
\]

Recently, Molander and McKie have examined the SmI2-induced reductive cyclization of unactivated olefinic ketones and obtained high yields and diastereoselectivities for a variety of substrates. They observed that in the presence of 8 equivalents of HMPA, 6-hepten-2-one was
They also obtained excellent results by reducing 7-octen-2-one to the corresponding cis-1,2-dimethylcyclohexanol product (cis/trans = 36). A summary of their results is shown in Table II.4

**Table II. Samarium Iodide-Promoted Cyclization of Olefinic Ketones**

<table>
<thead>
<tr>
<th>substrate</th>
<th>product</th>
<th>% isolated yield (diastereomeric ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{O}$</td>
<td>$\text{HO}$</td>
<td>$n=1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n=2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n=3$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n=1, m=1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n=2, m=1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n=1, m=2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n=2, m=2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n=0, m=2$</td>
</tr>
</tbody>
</table>

**PHOTOREDUCTIVE CYCLIZATION OF OLEFINIC KETONES**

The photochemically promoted cyclization of $\delta,\epsilon$-unsaturated ketones has been investigated by Cossy and coworkers as an alternative to the chemical and electrochemical methodologies.6 Thus, irradiation of $\delta,\epsilon$-olefinic cyclopentanone 17 and cyclohexanone 18 in HMPA with low pressure mercury lamps ($\lambda = 254$ nm) gave the bicyclic cyclopentanols 19 and 20 respectively,

while, 4-cyclooctenone (21) afforded bicyclo[3.3.0]cyclooctan-1-ol (22). In most cases, substitution of Et$_3$N/CH$_3$CN for HMPA led to the same products but in lower yields.
In general, the photochemical cyclization of δ,ε-unsaturated ketones provides a simple approach under mild conditions without further need for chemical reagents.

**Electroreductive Cyclization vs Michael-Initiated Ring Closure**

Electroreductive cyclization reactions (ERC) can be utilized to construct rings of size n-1 in contrast to those of size n in a normal Michael-initiated ring closure (MIRC) of the same substrates.\(^{16,17}\) During the electroreductive cyclization, the β carbon in the α,β-unsaturated ester becomes nucleophilic. Thus, treatment of the bromoalkylidenemalonate 23 with lithium sec-butylborohydride provided the cyclopentyl diester 24, whereas, an electrochemically promoted reduction of the same substrates afforded cyclobutyl diester 25.\(^{16}\)

**ADDITION OF KETYL RADICAL ANIONS TO AROMATIC RINGS**

Ketyl radical anions generated by electrochemical reduction can also undergo cyclization with π electrons in aromatic rings.\(^{18}\) Shono and coworkers reported the electroreduction of 5-phenyl-2-pentanone (26) in isopropyl alcohol by using a tin electrode as cathode and a carbon rod as anode immersed in Et\(_4\)NTOs as supporting electrolyte in a divided cell. The major product of this reaction was identified as a single diastereomer (27) by \(^1\)H- and \(^{13}\)C-NMR. The stereochemical assignment of 27 was accomplished by \(^1\)H- and \(^{13}\)C-NMR analysis of the saturated products that obtained from hydrogenation of 27 with H\(_2\) in the presence of Pd/C.
INTERMOLECULAR COUPLING OF KETONES WITH ALLYLIC ALCOHOLS

The electrochemically promoted intermolecular coupling of ketones with allylic alcohols provides high regio- and diastereoselectivities at the position $\gamma$ to the hydroxyl group to afford the corresponding 1,4-diols. For example, (3S, 5R)-2,3-dimethyl-2,5-nonanediol (31, 78 %) was obtained diastereoselectively, when 2-propanone (29) was coupled with trans-(R)-2-octen-4-ol (30) at the cathode electrode.

\[
\text{29} + \text{30} \xrightarrow{+e^-} \text{31} \quad 78\%
\]

The ease of coupling of the ketyl radical anion with the double bond was proposed to be directly related to the reduction of the radical intermediate 32. In the case of allylic alcohols, such as the coupling of 29 with 30, the carbanion 33 is rapidly neutralized by an intramolecular proton transfer from the allylic hydroxyl group, so that the second electron transfer to the radical 32 occurs with a reasonable rate.

The diastereoselective outcome of these coupling reactions was explained by examining different conformation. The stereo structure of these conformations were proposed to be fixed by the interaction of hydroxyl group and negatively charged oxygen. Thus, in the case of coupling of 27 with 30 three different intermediates were considered from which 34 was formed by coupling of the intermediate ketyl radical to the $si$-face of the double bond, whereas 35 and 36 were obtained through $re$-face attack. The formation of 35 and 36 was suggested to be less favorable due to the severe steric interaction between the alkyl groups in both structures.
CONCLUSION

Since 1965, a number of investigations have been focused on the reductive coupling of ketones with a variety of olefins by chemical, electrochemical, and photochemical methodologies. Intramolecular coupling of olefinic ketones can lead to the formation of highly regio- and stereoselective ring structures. Among different chemical methodologies, Sml2 in the presence of HMPA has been utilized as a powerful reagent to cyclize olefinic ketones with high stereoselectivities. The electrochemical and photochemical approaches are simple, inexpensive, selective and complementary to the chemical reactions.

REFERENCES

CYCLIZATION TECHNIQUES TO PROVIDE 14-MEMBERED CARBOCYCLIC RINGS: SYNTHESIS OF CEMBRANOID DITERPENES

Reported by José J. Morales
April 7, 1994

INTRODUCTION

In the three decades since their initial structural elucidation cembranoid diterpenes have been increasingly recognized as a major class of natural products. These natural products are characterized by the presence of a 14-membered carbocycle. They have been found in plants and terrestrial insects, but the most fascinating and biologically active cembranoids have been isolated from marine organisms. Many of them show marked cytotoxic, antiinflammatory, antitumor and other potentially useful physiological activities. Representative examples are: sarcophytol A (1), an antitumor agent isolated from the soft coral Sarcophyton glaucum; sinulariolide (2), a potent antineoplastic agent isolated from the soft coral Sinularia flexibilis, and lophotoxin (3), a furanocembranolide recognized to be a particularly powerful neuromuscular toxin isolated from a soft coral Lophogorgia species. The wide range of biological activities exhibited by cembranoid diterpenes in combination with their diversity of structures, and the lack of a general method for the construction of carbocycles of 12 or more members have made this family of natural products a challenging target for organic chemists.

Although a number of macrocyclization techniques have been developed for the construction of large membered carbocycles only a few have the promise of generality. In this report, successful routes toward the cembranoid skeleton are discussed. A new macrocyclization technique involving an intramolecular Lewis acid-promoted ene reaction which appears to be a fairly general one for the synthesis of carbocycles of 12 or more members is discussed in detail.

BIOMIMETIC TYPE CYCLIZATIONS

Cyclization of acyclic geranyl-geranyl pyrophosphate (OPP) via displacement of OPP is one of the most fundamental and important pathways in the biosynthesis of cyclic diterpenoids.
(Scheme I). Following this biogenetic line three kinds of biomimetic type cyclizations leading to 14-membered rings have been studied: alkylation of sulfur-stabilized carbanions, alkylation of protected cyanohydrins and Friedel-Crafts acylation of alkenes.

Scheme I

![](image)

Alkylation of Sulfur-Stabilized Carbanions.

The anion-induced cyclization via alkylation of sulfoo- or thioether-stabilized carbanions has been employed in several syntheses of cembranoid diterpenes. The synthesis of cembrene A (6) is a representative example of this cyclization technique. The crucial step, the intramolecular cyclization, took place upon addition of a slight excess of n-BuLi and DBU at -78 °C to a dilute solution of epoxide 5 in THF (Scheme II). Although this technique is straightforward, it has often encountered serious problems with double bond migration and isomerization during both the alkylation and desulfurization steps.

Scheme II

![](image)

a) excess n-BuLi, THF, DBU, -78 °C; b) Li, EtNH₂; c) prep. TLC, AgNO₃; d) SOCl₂, pyridine.

Alkylation of Protected Cyanohydrins.

In addition to sulfur-stabilized carbanion cyclizations, the intramolecular alkylation of protected cyanohydrins has been used in the synthesis of cembranoid diterpenes, particularly for simple cembrenes. This methodology has successfully been employed in the syntheses of sarcophytol A (1) and mukulol (Scheme III). Actually, two total syntheses of the former cembrene have recently been reported using this strategy but these differ in how the E, Z diene conjugated system was assembled. It is noteworthy that the intramolecular alkylation of protected cyanohydrins proceeded regioselectively at the α position without geometrical isomerization of the double bond.
Friedel-Crafts Acylations of Alkenes.

Cation-induced cyclizations have also effectively been used, along biogenetic lines, for the construction of the cembrane rings by means of intramolecular Friedel-Craft acylations (Scheme IV). The syntheses of two trail pheromones of the cembranoid type have been reported employing this methodology.\textsuperscript{8b} Intermediate 7 was employed in both syntheses and the cyclization proceeded with high selectivity for the 14-membered-ring formation in excellent yields, and no double bond isomerization was observed. However, a drawback of this technique is that the stereochemistry of the chiral center formed during the cyclization at the ring carbon bearing the isopropyl group is difficult to control.

Non-biomimetic type cyclizations of 14-membered rings such as ring expansion\textsuperscript{9}, ring contraction,\textsuperscript{10} allylmetal addition to aldehydes\textsuperscript{11,12}, intramolecular Horner-Emmons reactions\textsuperscript{13} and Lewis acid-promoted ene reactions,\textsuperscript{14} have been successfully employed for the cembranes. In addition, approaches based on radical macrocyclizations\textsuperscript{15}, and nickel-\textsuperscript{16} and titanium-induced\textsuperscript{17} cyclization methods have also been investigated.

Macroexpansion

A straightforward synthesis of (3Z)-cembrene A (10) based on an ingenious ring expansion methodology has been reported.\textsuperscript{9} The elaboration of the 14-membered ring was accomplished by an oxy Cope rearrangement of intermediate 9 (Scheme V), which was synthesized in four steps from (+)-carvone (8). This approach promises to be a general method for the preparation of chiral cembranoid diterpenes.
Scheme V

Ring contraction

Another interesting route employed in the synthesis of 14-membered rings consists of the [2,3] Wittig ring contraction of 17-membered propargylic ethers (Scheme VI). The formation of the carbon-carbon bond in this ring-contracting variant is facilitated by the proximity of the reacting centers imposed by the heterocyclic ring. Is interesting to note that the stereochemical outcome of the cyclization can be manipulated by simple choice of the reaction medium. The trans stereoisomer is favored in hexane-THF solvent, while in THF-HMPA solvent the cis stereoisomer is the major product.

Scheme VI

盟metal addition to aldehydes

The intramolecular addition of allyl organometallics to aldehydes has been used for cembrane synthesis. Diastereoselective macrocyclizations of 14-membered rings have been reported using Cr(II)-promoted reductive couplings and intramolecular coupling of α-alkoxyallylstannanes to aldehydes. Still's (±)-asperdiol synthesis is an example of this methodology. The macrocyclization was accomplished using the threo-selective Hiyama/Heathcock (CrCl₂, THF) to give a 4:1 mixture of the desired isomer and its diastereoisomer in 64 % yield (Scheme VII). Partial stereocontrol by the remote epoxide was observed. Marshall's synthesis of cembranolide made use of an intramolecular addition of α-alkoxyallylstannane to an aldehyde to obtain an 88/12 mixture of cis and trans diastereoisomers in 88 % yield (Scheme VIII). It has been shown that the syn product is formed enantiospecifically when chiral α-alkoxyallylstannanes are used.
Intramolecular Horner-Emmons reaction

Several syntheses of cembranoid diterpenes employing an intramolecular Horner-Emmons reaction have been reported. The approach is particularly useful when the geometry of one of the trisubstituted double bonds in the cembrane skeleton has to be controlled. For example, the successful synthesis of (±)-anisomelic acid (14) demonstrates the usefulness of this methodology. In this synthesis, the C-8, C-9 double bond is formed during the ring closure step by a Z-selective Horner-Emmons reaction. A yield of 71% of a 95/5 Z/E mixture was obtained in the cyclization step (Scheme IX).

Lewis Acid-Promoted Ene Cyclization

Lewis acid-catalyzed intramolecular ene reactions of unsaturated carbonyl compounds have been used frequently in organic synthesis for the formation of five-, six- and few conformationally constrained seven-membered rings, with control of the stereochemistry in the products. Two types of reactions, Type-I and Type-II ene reactions, are generally useful
In type-I reactions the carbonyl group forms a bond to the internal carbon of the double bond, while in Type-II ene reactions the carbonyl group forms a bond to the terminal carbon of the double bond. Recently, Marshall and coworkers have reported that certain acetylenic aldehydes undergo efficient type-I and type-II ene cyclizations in the presence of alkylaluminum chlorides to afford 12-, 14- and 16-membered propargylic alcohols.\textsuperscript{14}

**Scheme X**

\[
\text{Type-I} \quad \begin{array}{c}
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbullet}};
\node (b) at (1,0) {\text{\textbullet}};
\node (c) at (2,0) {\text{\textbullet}};
\node (d) at (3,0) {\text{\textbullet}};
\node (e) at (4,0) {\text{\textbullet}};
\node (f) at (5,0) {\text{\textbullet}};
\node (g) at (6,0) {\text{\textbullet}};
\node (h) at (7,0) {\text{\textbullet}};
\node (i) at (8,0) {\text{\textbullet}};
\node (j) at (9,0) {\text{\textbullet}};
\node (k) at (10,0) {\text{\textbullet}};
\node (l) at (11,0) {\text{\textbullet}};
\node (m) at (12,0) {\text{\textbullet}};
\node (n) at (13,0) {\text{\textbullet}};
\node (o) at (14,0) {\text{\textbullet}};
\node (p) at (15,0) {\text{\textbullet}};
\node (q) at (16,0) {\text{\textbullet}};
\node (r) at (17,0) {\text{\textbullet}};
\node (s) at (18,0) {\text{\textbullet}};
\node (t) at (19,0) {\text{\textbullet}};
\node (u) at (20,0) {\text{\textbullet}};
\node (v) at (21,0) {\text{\textbullet}};
\node (w) at (22,0) {\text{\textbullet}};
\node (x) at (23,0) {\text{\textbullet}};
\node (y) at (24,0) {\text{\textbullet}};
\node (z) at (25,0) {\text{\textbullet}};
\end{tikzpicture}}
\end{array}
\]

\[
\text{Type-II} \quad \begin{array}{c}
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbullet}};
\node (b) at (1,0) {\text{\textbullet}};
\node (c) at (2,0) {\text{\textbullet}};
\node (d) at (3,0) {\text{\textbullet}};
\node (e) at (4,0) {\text{\textbullet}};
\node (f) at (5,0) {\text{\textbullet}};
\node (g) at (6,0) {\text{\textbullet}};
\node (h) at (7,0) {\text{\textbullet}};
\node (i) at (8,0) {\text{\textbullet}};
\node (j) at (9,0) {\text{\textbullet}};
\node (k) at (10,0) {\text{\textbullet}};
\node (l) at (11,0) {\text{\textbullet}};
\node (m) at (12,0) {\text{\textbullet}};
\node (n) at (13,0) {\text{\textbullet}};
\node (o) at (14,0) {\text{\textbullet}};
\node (p) at (15,0) {\text{\textbullet}};
\node (q) at (16,0) {\text{\textbullet}};
\node (r) at (17,0) {\text{\textbullet}};
\node (s) at (18,0) {\text{\textbullet}};
\node (t) at (19,0) {\text{\textbullet}};
\node (u) at (20,0) {\text{\textbullet}};
\node (v) at (21,0) {\text{\textbullet}};
\node (w) at (22,0) {\text{\textbullet}};
\node (x) at (23,0) {\text{\textbullet}};
\node (y) at (24,0) {\text{\textbullet}};
\node (z) at (25,0) {\text{\textbullet}};
\end{tikzpicture}}
\end{array}
\]

The model system employed on Marshall’s study was ynal 15. The effectiveness of this intermediate on ring closure has previously been demonstrated by Marshall and co-workers on studies of intramolecular additions of α-alkoxyallylstannanes to aldehydes.\textsuperscript{12} Its reactivity on ring closure has, at least in part, been attributed to the high electrophilic nature of the ynal-Lewis acid complex and the entropic restrictions imposed by the alkyne and (E)-alkene linkages. The ynal 15 was easily prepared from farnesol using readily available reagents in few steps and good yields.

The crucial step, the cyclization of ynal 15, was performed with different Lewis acids and under a variety of reaction conditions. Slow addition of ynal 15 to a dilute solution of EtAlCl\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} at -78 °C gave the best results. A 1:1 mixture of cis and trans isomers 16 and 17 was obtained in 75-80 % yield. In addition, formation of oxetane 18, the 2 + 2 adduct, was observed (10 % yield). Cyclization with BF\textsubscript{3}•OEt\textsubscript{2} afforded a 5:1 mixture of cis/trans isomers but the observed yield was lower (40 - 50 % yield). It was observed that high diastereoselectivity could be obtained when a remote epoxide was present.

**Scheme XI**

\[
\text{\begin{tikzpicture}
\node (a) at (0,0) {\text{\textbullet}};
\node (b) at (1,0) {\text{\textbullet}};
\node (c) at (2,0) {\text{\textbullet}};
\node (d) at (3,0) {\text{\textbullet}};
\node (e) at (4,0) {\text{\textbullet}};
\node (f) at (5,0) {\text{\textbullet}};
\node (g) at (6,0) {\text{\textbullet}};
\node (h) at (7,0) {\text{\textbullet}};
\node (i) at (8,0) {\text{\textbullet}};
\node (j) at (9,0) {\text{\textbullet}};
\node (k) at (10,0) {\text{\textbullet}};
\node (l) at (11,0) {\text{\textbullet}};
\node (m) at (12,0) {\text{\textbullet}};
\node (n) at (13,0) {\text{\textbullet}};
\node (o) at (14,0) {\text{\textbullet}};
\node (p) at (15,0) {\text{\textbullet}};
\node (q) at (16,0) {\text{\textbullet}};
\node (r) at (17,0) {\text{\textbullet}};
\node (s) at (18,0) {\text{\textbullet}};
\node (t) at (19,0) {\text{\textbullet}};
\node (u) at (20,0) {\text{\textbullet}};
\node (v) at (21,0) {\text{\textbullet}};
\node (w) at (22,0) {\text{\textbullet}};
\node (x) at (23,0) {\text{\textbullet}};
\node (y) at (24,0) {\text{\textbullet}};
\node (z) at (25,0) {\text{\textbullet}};
\end{tikzpicture}}
\]

Further studies demonstrated that the catalyzed ene cyclization methodology (Type-I and Type-II) can be use for the construction of rings in the 12- to 16-membered range.
SUMMARY

Cembranoid diterpenes have been the focus of an extensive synthetic effort in the last decade because of the interesting structural features of the cembrane ring and the wide range of bioactivity recorded for these compounds. An interest in developing an efficient methodology for the construction of macrocycles have made this class of natural products a synthetic target for many research groups. These efforts have lead to a series of ring closure techniques that are useful for the synthesis, not only for 14-membered rings, but for other medium to large rings. Although many of these reactions were accomplished in good yields, poor stereoselectivity was a recurring problem.

REMAINING CHALLENGES

The rationalization of the stereochemical outcome of macrocyclic reactions by means of new molecular mechanics software should be developed, and will be a valuable tool to predict the stereochemistry of such reactions. In addition, through use of appropriate chiral reagents, such as a chiral Lewis acid in the intramolecular ene reaction, enantioenriched products could be realized from achiral substrates. The cembrane skeleton will continue to be a synthetic model for future investigations on ring closures.

REFERENCES


INTRODUCTION

In 1953, Watson and Crick proposed the double helical structure of DNA, and realized that its replication involved template synthesis. Their work led Todd to note the potential for a field of investigation where he pointed out that: "The use of one molecule as a template to guide and facilitate the synthesis of another... has not hitherto been attempted in the laboratory synthesis, although it seems probable that it is common in living systems." Since the 1960's, the expanding roles of templates in organic synthesis have been widely recognized. The definition for a chemical template was provided by Busch as a structure "which organizes an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms". As shown in Scheme I, the template binds the substrates R1 and R2 to bring them into a suitable position for the formation of the product, after which the template is usually removed and the cycle repeats. The organization of the substrates and templates involve electrostatic interactions, hydrogen bonding and π-π interactions.

Scheme I

This abstract will focus on the special area of template synthesis which is self-replicating systems that involve hydrogen bonding and π-π interactions in the organization step. If the template is identical to the product, it can catalyze the formation of itself, in other words, it can self-replicate. The fundamental feature of a self-replicating system is its self-complementarity in sizes, shapes and intermolecular forces involved in the recognition between the subunits.

Many researchers believe that evolution involved one or more original molecules that had the ability to replicate, thus ensuring the continuity of the genetic information. Self-replicating systems can provide chemical insight into this important process which may increase the understanding of the origin of life.
SELF-REPLICATING SYSTEMS BASED ON NUCLEOTIDES

In 1966, Naylor and Gilham reported the template-directed, nonenzymatic synthesis of oligonucleotides using polyadenylic acid as a template to achieve a favorable orientation of two thymidine oligonucleotides. Subsequent use of a water soluble carbodiimide as an activating reagent allowed the formation of thymidine deca- and dodecanucleotides.\textsuperscript{10}

This concept was further explored by von Kiedrowski who demonstrated in 1986 the first successful nonenzymatic self-replicating system using a DNA hexamer (Scheme II).\textsuperscript{11-13} Trideoxyribonucleotide 3'-phosphate 1 with its 5'-terminus protected as its methyl ether was activated in situ to give 1\textsuperscript{*}. Reaction between 1\textsuperscript{*} and a complementary trideoxyribonucleotide 3'-phosphate 2 with its 3'-terminus protected with o-chlorophenyl group, gave hexamer 3. Kinetic studies showed that the addition of 3 clearly enhanced the rate of its own formation indicating that it behaved as an autocatalyst and therefore this was a self-replicating system. Complex 1\textsuperscript{*}:2:3 was reversibly formed from 1\textsuperscript{*}, 2 and template 3 through base pairing. Formation of the phosphodiester bond between 1\textsuperscript{*} and 2 in 1\textsuperscript{*}:2:3 yielded a self-complementary duplex 3:3. This condensation was a slow process and shown to be the rate-determining step. Dissociation of 3:3 was an equilibrium process which gave free 3 for the new cycle. The rate of the template-directed condensation is expressed in Scheme II. Since at equilibrium, most of the template existed in the form of duplex 3:3, concentration of [3:3] should be only slightly different from half of the total template concentration [3]. Therefore, reaction order for 3:3 formation in terms of [3] is expected to be 1/2. This mechanism was shown to be consistent with the experimental results. The empirical "square root law" showed that the initial rate of template formation can be expressed as \( \frac{dC}{dt} = aC^{1/2} + b \) with a and b being the constants corresponding to autocatalytic and nonautocatalytic terms respectively and C being the concentration of the template.
Therefore, square root growth can be explained as a result of the fact that most of the 3 molecules present in the solution are tied up in the unbroken duplex.

In 1987, a self-replicating system based on an RNA tetramer was reported by Orgel.\textsuperscript{14} According to those kinetic studies, the product $\text{G}_{\text{NH}_2}\text{C}_{\text{NH}_2}\text{G}_{\text{NH}_2}\text{C}_3$ which was formed from the reaction of $\text{G}_{\text{NH}_2}\text{C}_{\text{NH}_2}$ and $\text{pG}_{\text{NH}_2}\text{C}_3$ acted as a template to catalyze its own formation. The reaction was also initiated by carbodiimide and $^{14}\text{C}$-labeled $\text{G}_{\text{NH}_2}\text{C}_{\text{NH}_2}$ was used so that the formation of product could be determined by scintillation counting. The rate of product formation in this system fits the square root law.

The above oligonucleotide systems involve reactions in aqueous solutions and the templates bind the substrates through base pairing. Another approach to self-replicating systems involves studies carried out in non-aqueous, non-polar organic solvents.

**NON-NATURAL TEMPLATE-DIRECTED SELF-REPLICATING SYSTEMS**

It is widely established that enzymes convert intermolecular reactions effectively into intramolecular ones by binding the substrates and placing the reacting groups in correct proximity. In 1989, Kelly reported an artificial template using the same feature (Scheme III).\textsuperscript{15}

**Scheme III**

\begin{center}
\includegraphics[width=\textwidth]{scheme_iii.png}
\end{center}

The ditopic template 4 bound the two substrates simultaneously through hydrogen bonding, giving the ternary complex 5 and placing the two potentially interacting groups in close proximity.
proximity. Bond formation followed by dissociation of template-product complex 6 completed the process with product 7 precipitated as its HBr salt. The product formation was accelerated in the presence of the template. Control experiments showed that no acceleration was observed with the monotopic template. Thus, 4 mimics naturally occurring enzymes.

The same concept was used in the development of synthetic self-replicating systems. In 1990, Rebek successfully designed a modified adenine-imide replicating system that mimics peptide bond formation. This system uses hydrogen bonding and π-π interactions, the stabilizing forces for double-stranded nucleic acids (Scheme IV).16-21

Scheme IV

The design of a naphthalene spacer and the use of a fully blocked sugar unit avoided the cis-"fold-shut" structure of the template. They served as a "bulge" to help the cis-amide open in a "jackknife" manner to the trans form which was crucial for replication to occur in this system.

Kinetic data showed that the reaction was autocatalytic and a fit with the square root law was observed. The mechanisms proposed for product formation are compared in Schemes IV and V. There are three pathways to the product: The first is the background bimolecular reaction (Pathway 1) of 8 and 9 with rate constant 0.023 M⁻¹min⁻¹ established by using the N-
methyl imide derivative of 9. An independent measurement by using 2,6-bis(acetylamino)pyridine 11 as an inhibitor (association constant with 9 is 450 M$^{-1}$) in the reaction of 8 and 9 was achieved and gave a consistent result. The second pathway (Pathway 2) involves a base-pairing or preassociative mechanism where 8 and 9 form the dimer 8:9 prior to the reaction. This dimer has an important role in the formation of 10 and the fact that 9 reacted 6.5-fold more rapidly with 8 than the N-methyl derivative under the same conditions provided strong evidence for this mechanism. Additional support for this mechanism came from the inhibition of reaction between 8 and 9 by 10. The third mechanism is the termolecular template process (Scheme V) suggested by the enhanced rate of reaction upon addition of 10. The close proximity of the reacting groups in 8:9:10 leads to the formation of duplex 10:10 which existed in equilibrium with free 10.

Scheme V

Based on the above mechanisms, kinetic modeling studies were performed. The result showed that although the background bimolecular reaction contributed only slightly to the
formation of the product, both the uncatalytic preassociative and the autocatalytic template mechanisms contributed substantially.

In replication systems, there are other biorelevant behaviors that they express. For evolution to occur at the molecular level, mistakes made that led to better replicators are necessary and environmental effects may favor new or other competitive processes.\textsuperscript{22} The features of reciprocity and mutation were demonstrated on synthetic models (Scheme VI).\textsuperscript{23}

\textbf{Scheme VI}

\begin{center}
\textbf{Reciprocity}
\end{center}

The three templates formed by the reactions of 11 and 12 in Scheme VI not only catalyzed their own formation, but also catalyzed the formation of each other. For example, the presence of 20% 11b during the reaction of 11c with 12 increased the rate of formation of the product by 18%. Such behavior is called cooperativity or reciprocity in biological terms.
However, this behavior may also be regarded as a lack of selectivity in the template-catalyzed replication.

Mutation

The template formed by 11a and 12 is shown to be more efficient than 11b+12 and 11c+12 because it can bind 12 in either Watson-Crick modes or Hoogsteen modes.\textsuperscript{24} In the latter two, the bulky groups on N-6 hindered the base-pairing in the Watson-Crick modes and forced them to bind in the Hoogsteen modes. In the preassociative process that initiated the reaction, the two reacting centers were more difficult to reach in Hoogsteen modes than in the Watson-Crick modes because of their spatial distance. In an experiment designed to study mutation, 11a and 11c competed for a limited amount of active ester. When the ester was consumed, the product replicators and amine solution was irradiated and the o-NO\textsubscript{2}-benzyloxy carbonyl group at N-6 of adenine in 11c was cleaved. The resulting photodeprotected system was a more efficient replicator. This reaction can be considered as mutation. It is interesting to note that irradiation is also considered as one of the possible causes for mutation in the prebiotic world due to its primary role as an energy source. In addition, this photochemical mutation is inheritable, that is, it catalyzed its own formation in subsequent generations.

Hybridization

In 1992, Rebek and coworkers synthesized another replicating system which was based on thymine-diaminotriazine derivatives.\textsuperscript{25-27} A competition experiment mimicked the hybridization process was carried out between the two systems and gave interesting results. One hybrid showed effective replication while the other did not show any replication at all.

CONCLUSION

The general features, kinetics, and mechanisms of self-replicating systems have been discussed. A chemical mutation model has also been demonstrated on synthetic systems. Current self-replicating molecules show less than exponential growth due to the fact that product molecules bind to themselves instead of to the reagents. According to Szathamáry,\textsuperscript{30} only exponentially growing templates could survive the competitions during evolution. Therefore, future work may include the development of replicating systems that can show exponential growth.\textsuperscript{31} In addition, it may be possible to design a new replicator that can recognize a prochiral center and thus asymmetrically replicate itself.

The application of the template effect in synthesis has been dramatically expanded over the past thirty years with chemical nonenzymatic self-replicating systems studied only recently. However, this interesting research area has a promising future. By studying these systems,
chemistry may challenge the complexity in biological systems and start a new era of research on understanding the origin of life.

REFERENCES

SYNTHESIS OF HETEROCYCLES USING OXYGEN YLIDES

Reported by Brian Fink

April 21, 1994

INTRODUCTION

Interest in the synthesis of oxygen heterocycles, which have wide spread occurrence in plant and marine natural products, has led to a variety of methods for their construction. Cycloadditions of 1,3-dipoles are a favored method for generating medium-sized heterocyclic rings due to the high degree of stereospecificity and wide range of functional group tolerance associated with the pericyclic reaction. Frontier molecular orbital (FMO) theory has been a valuable tool for predicting and explaining the relative rates and the regiochemical outcomes of reactions in many instances. Conceptually, the use of carbonyl ylides as the 1,3-dipolar components in concerted additions to π bonds provides a relatively simple strategy for constructing oxygenated heterocycles. Until recently, methodology for the mild, selective generation and subsequent reaction of carbonyl ylides has lagged behind that of other 1,3-dipoles. General aspects of carbonyl ylide reactions and their recent applications in the construction of oxygenated monocyclic and polycyclic systems will be discussed in this abstract.

BACKGROUND

The two most common methods for forming carbonyl ylides are illustrated in Scheme I.

Scheme I

![Scheme I](image_url)

The products from the thermal, conrotatory ring opening of epoxides (Method A) and subsequent addition of the putative acyclic dipole to a dipolarophile first suggested the intermediacy of these...
transient 1,3-dipoles. The requisite high temperatures and the need for strongly electron withdrawing substituents, however, restrict the synthetic utility of this method. Metal-catalyzed decomposition of α-diazoketones (Method B) is often milder, taking place at ambient temperature in neutral solvents, and represents a potentially more useful method for generating carbonyl ylides. Intramolecular attack of a suitably positioned carbonyl oxygen at the carbenoid center affords cyclic carbonyl ylides from acyclic precursors as shown in Scheme I. Subsequent addition of a dipolarophile affords polycyclic oxygenated heterocycles in a single step from acyclic starting materials.

Although they have been less studied than their nitrogen counterparts, carbonyl ylides should show similar reactivity. In reactions with π systems, FMO theory predicts that the important orbital interactions are between the HOMO(dipole)/LUMO(dipolarophile) (type I) or the LUMO(dipole)/HOMO(dipolarophile) (type III); the dominant reaction type results from the pair with the smaller HOMO/LUMO energy difference. Regiochemical outcomes are predicted by matching the larger coefficients on each interacting orbital. Carbonyl ylides, however, are characterized as type II dipoles; they are able to react in either a type I or type III manner. This crossover from HOMO(dipole) controlled to LUMO(dipole) controlled is the result of a small energy difference between the carbonyl ylide HOMO and LUMO. In general, the HOMO of the dipole is dominant for interactions with electron deficient dipolarophiles and heterodipolarophiles (type I) while the LUMO of the dipole becomes more important in reactions with electron rich dipolarophiles (type III).

FORMATION OF CARBONYL YLIDES FROM α-DIAZOKETONES

Ibata was among the first to show that the metal catalyzed decomposition of α-diazodiones, with Cu(acac)₂, could generate carbonyl ylides. Padwa and coworkers have more recently reported on the generation and subsequent reactivity of carbonyl ylides using Rh₂(OAc)₄ as a catalyst. Rhodium carbenoids derived from α-diazoketones are known to be highly reactive species, undergoing dimerization, C-H insertion, and cyclopropanation reactions in addition to ylide formation. The extent to which these processes compete with ylide formation is dependent on the rate at which the rhodium carbenoid cyclizes onto an adjacent carbonyl oxygen. Structural effects controlling the rate of cyclization are shown in Table I. Changes in product yield are assumed to reflect the relative rate of carbonyl ylide formation versus alternative reactions. Inspection of entries 1-4 demonstrates that carbonyl ylide formation is most efficient when forming five- or six-membered rings and becomes less efficient for larger sized rings. Competitive cyclization studies indicate that five-membered ring formation is approximately 0.12 kcal/mol more favorable than six-membered ring formation, which in turn is 0.4 kcal/mol more favorable than seven-membered ring formation.
Table I. Factors Influencing Ylide Formation

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>X</th>
<th>n</th>
<th>Yield 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>H</td>
<td>CH₂</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>CH₂</td>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>H</td>
<td>CH₂</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>H</td>
<td>CH₂</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>H</td>
<td>O</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>H</td>
<td>O</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>CO₂Et</td>
<td>O</td>
<td>1</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>CH₃</td>
<td>C(O)CH₃</td>
<td>O</td>
<td>1</td>
<td>75</td>
</tr>
</tbody>
</table>

The effect of heteroatom substitution in the tether was also examined by replacing the β-methylene with an internal ester. In contrast to the high yields of cycloaddition products from α-diazodiones, no products derived from carbonyl ylides were observed with the ester functionality (entries 5-6). The only products isolated were those derived from carbene insertion into the solvent and dimerization. Padwa proposed that this effect is due to the diminished electrophilic nature of the rhodium carbenoid. Thus, nucleophilic attack of the carbonyl oxygen is retarded to the point where competing side reactions dominate. When the carbenoid center is substituted by an additional electron withdrawing group, the cyclization-cycloaddition proceeds as expected. This appears to be a general effect, requiring strongly electron withdrawing substituent α to the diazocarbon (entries 7-8).

Incorporation of nitrogen at the β position in 1 to give an imide structure (X=N, n=0) should similarly reduce the rate of carbonyl ylide formation. However, the cyclized intermediate is now part of a resonance stabilized structure known as an isomunchnone 3 (Scheme II). Isomunchnonones were first successfully isolated by Ibata, and in some cases are stable for extended periods of time. These compounds have been shown to act as carbonyl ylides in [3+2] additions to dipolarophiles. With acetylenic dipolarophiles, however, the initial cycloadducts readily rearrange to form highly substituted furans or lactams as shown in Scheme II.
INTERMOLECULAR [3+2] CYCLOADDITIONS

Non-stabilized carbonyl ylides derived from cyclic and acyclic α-diazadiones react with a variety of electron rich and electron deficient dipolarophiles yielding cyclized products readily accounted for by FMO theory (see Table II).

Table II. [3+2] Cycloadditions to Carbonyl Ylides

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>4:5</th>
<th>4- endo:exo</th>
<th>5- endo:exo</th>
<th>Total yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>CO₂CH₃</td>
<td>2:1</td>
<td>1:3</td>
<td>1:2</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>C(O)CH₃</td>
<td>1:4</td>
<td>exo</td>
<td>1:6</td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td>CH₃</td>
<td>OC(O)CH₃</td>
<td>5 only</td>
<td>endo</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>OCH₂CH₃</td>
<td>5 only</td>
<td>endo</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

Reactions of carbonyl ylides with electron-deficient olefins generally proceed in good yield to give mainly the exo cycloadduct (entries 1-2), while electron-rich dipolarophiles give considerably lower yields of the 1:1 cycloadducts (entries 3-4). In reactions with electron-rich dipolarophiles, significant amounts of 2:1 and 3:1 adducts were isolated, arising from competitive carbonyl ylide cycloaddition across the carbonyl of the initially formed 1:1 adducts (4/5). Apparently, the larger HOMO-LUMO gap between the dipole and the dipolarophile reduces the reaction rate to a point where carbonyl ylide addition to the carbonyl group of the 1:1 adduct becomes competitive. Interestingly, these higher order adducts arise exclusively from the
5-exo adduct. Steric interactions prevent further reaction with the 5-endo isomer leaving it as the only 1:1 adduct isolated.\(^{15}\)

Although FMO theory is useful for rationalizing the regiochemical outcome of the cycloadditions, it does not explain the stereochemistry. From a FMO perspective,\(^1\) the transition state in which the dipolarophile approaches the planar carbonyl ylide in an endo fashion results in favorable secondary orbital overlap, yet for the above cases the exo isomer prevails. Padwa rationalized the predominance of the exo product as arising from dipole repulsion between the carbonyl groups of the approaching addends.\(^{14}\) It is clear from the results in Table II that the dominant interactions in the approach of dipole and dipolarophile are case specific, and this represents a significant restriction to the usefulness of bimolecular additions to carbonyl ylides.

**INTRAMOLECULAR [3+2] CYCLOADDITIONS**

Although few cases of intermolecular cycloadditions have been reported with unactivated alkenes, the intramolecular addition of tethered olefins has been well studied.\(^{16}\) These cases represent a unique method for the rapid generation of polycyclic oxygenated systems with the opportunity to control stereochemistry. Maier has shown that the intramolecular trapping of isomunchnones with tethered alkenes and alkynes may lead to enantiomeric pairs of fused piperidones \(^{8}\)\(^{17}\) and furan systems \(^{11}\)\(^{18}\) (Scheme III).

**Scheme III**

![Scheme III](image)

Furan 11 is of interest since it strongly resembles the annulated furan core of several furanosesquiterpenes known to show biological activity.\(^{19}\) Recently, the intramolecular cycloadditions of the related 3-oxidopyrilium compounds and 2-benzopyrilium-4-oxides have been studied by Sammes\(^{20a,b}\) and Wender.\(^{20c}\) Thermally induced fragmentation of an appropriately substituted 6-acetoxy-pyranone followed by intramolecular trapping leads to a variety of perhydroazulene systems, which are useful as intermediates in the synthesis of a number of natural products.\(^{21}\)
DIPOLE REARRANGEMENTS

The rearrangement of various dipoles has been the focus of relatively few studies. However, in suitably substituted systems, rearrangement from an initially formed carbonyl ylide to an azomethine ylide is readily achieved. For example, rearrangement of carbonyl ylide 12 to azomethine ylide 13, followed by trapping with dimethoxyacetylene dicarboxylate (DMAD), produces tricyclic compound 14, which undergoes a 1,3-shift to produce 15. Intermediate 15 has only been isolated in a few cases, as it rearranges and fragments in chloroform at room temperature to give 1,2-annulated-3,4,5-trisubstituted pyrroles in high yield.

Scheme IV

Acyclic starting materials may be used to give 1,2,3,4- and 3,4,5-substituted pyrroles and represent an alternative method to classical condensation routes to these products. Padwa has shown that the differences in the calculated heats of formation for carbonyl ylides and the corresponding azomethine ylides may be used to estimate the ease with which these rearrangements occur, providing reasonable predictability for these transformations.

CARBONYL YLIDES IN ELECTROCYCLIZATIONS

Although the majority of work with carbonyl ylides addresses their reactivity in [3+2] cycloadditions, Eberbach has shown that carbonyl ylides derived from 1,2-epoxy-3(Z)-hexen-5-ynes undergo 1,7-electrocyclization to produce a number of 2-vinyl furan derivatives. The proposed mechanism is shown below. Thermal ring opening of the epoxy hexenylene 15 leads to unsaturated carbonyl ylide 16, which preferentially undergoes 1,7-electrocyclization to cycloallene 17. Rearrangement of this strained intermediate to substituted 2-vinyl furans 18 and 19 proceeds by a formal 1,3-O-shift thought to involve radical or carbene intermediates.

Substituted furans are prepared in good yield with high degrees of stereoselectivity when $R_3$ is small (Table IV). When $R_3$ is large (entries 2-3), isomerization of the double bond during the rearrangement from 16 to 17 reduces the stereospecificity.
Table IV. Carbonyl Ylides in 1,7-Electrocyclizations

\[
\begin{array}{cccccc}
\text{entry} & R_1 & R_2 & R_3 & \text{Total Yield (\%)} & \text{18:19} \\
1 & H & Ph & H & 79 & 11:89 \\
2 & H & Ph & Ph & 89 & 47:53 \\
3 & H & Ph & Bu & 68 & 56:44 \\
4 & H & CH_3 & H & 77 & 10:90 \\
5 & -CH_2CH_2CH_2- & H & 65 & 11:89 \\
6 & -CH_2CH_2CH_2CH_2CH_2- & H & 70 & 12:88 \\
\end{array}
\]

It is also possible to carry out the reaction without the use of strongly electron withdrawing substituents, but temperatures in excess of 300 °C are necessary. Eberbach has shown that it is possible to construct a number of furan-containing products with this methodology, including furanophanes (2,5-annulated furans), 4,5-annulated furans, and furo[3,4-b]furans. Although high temperatures are required, the reactions proceed under neutral conditions, and may represent an alternative to more traditional furan syntheses employing strong acids and bases.

CONCLUSION

At present, carbonyl ylides represent an under-exploited class of 1,3-dipoles. The reasons for this may be the lack of regio- and stereoselectivity during the cycloaddition step and the need for electron withdrawing substituents at the ylide termini. Future work will need to develop mild, general methods for non-stabilized carbonyl ylide formation as well as methods for asymmetric induction during the cycloaddition steps. The most valuable applications of this methodology currently center on the rapid generation of complex polycyclic systems containing multiple stereogenic centers whose subsequent elaboration may find application in future natural products syntheses.
REFERENCES