SEMINAR TOPICS
I Semester 1979-80

Generation and Synthetic Utility of Carbanions Stabilized by Divalent Sulfur
Peter Becker

The Design, Synthesis, and Biology of Intercalating Agents
David W. Robertson

Phosphorus Compounds
Stephen D. Harper

Vanadium- and Molybdenum-Catalyzed Epoxidations of Olefins with Alkyl Hydroperoxides
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Detection and Characterization of Certain Carbon Diradicals Via ESR and CIDNP
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Enzymic Catalysis in Organic Synthesis
Venkatesalu Bakthavachalam

Regioselectivity in the Reactions of Hetero-Substituted Allylic Carbanions
Dale Kempf
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<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation and Synthetic Utility of Carbanions Stabilized by</td>
<td>Peter Becker</td>
</tr>
<tr>
<td>Divalent Sulfur</td>
<td></td>
</tr>
<tr>
<td>The Design, Synthesis, and Biology of Intercalating Agents</td>
<td>David W. Robertson</td>
</tr>
<tr>
<td>Modification of Olefins with Organo-Selenium Reagents</td>
<td>Larry D. Boardman</td>
</tr>
<tr>
<td>Synthetic Methods for the Preparation of</td>
<td>Ronald S. Michalak</td>
</tr>
<tr>
<td>Sterically Hindered Olefins</td>
<td></td>
</tr>
<tr>
<td>Mechanistic Considerations in 1,3-Dipolar Cycloadditions</td>
<td>Clark Cummins</td>
</tr>
<tr>
<td>Applications of Lasers in Organic Chemistry</td>
<td>Rick Gdanski</td>
</tr>
<tr>
<td>Magnetic Field Effects on Chemical Reactions in Solution</td>
<td>Paul Gelburd</td>
</tr>
<tr>
<td>Synthetic Approaches to Biotin</td>
<td>Jack Muskopf</td>
</tr>
<tr>
<td>Stable Hexacoordinate Organo-Phosphorus Compounds</td>
<td>Stephen D. Harper</td>
</tr>
<tr>
<td>Vanadium- and Molybdenum-Catalyzed Epoxidations of Olefins with Alkyl</td>
<td>John R. Hurst</td>
</tr>
<tr>
<td>Hydroperoxides</td>
<td></td>
</tr>
<tr>
<td>Detection and Characterization of Certain Carbon Diradicals Via ESR</td>
<td>G. H. Slocum</td>
</tr>
<tr>
<td>and CIDNP</td>
<td></td>
</tr>
<tr>
<td>Enzymic Catalysis in Organic Synthesis</td>
<td>Venkatesalu Bakthavachalam</td>
</tr>
<tr>
<td>Regioselectivity in the Reactions of Hetero-Substituted Allylic</td>
<td>Dale Kempf</td>
</tr>
<tr>
<td>Carbanions</td>
<td></td>
</tr>
</tbody>
</table>
Modern Methods for the Deoxygenation of Alcohols.................................96
William Stevenson

Enantiomerically Unusual Biomolecules..............................................104
Anthony W. Czarnik

Transition State Analogs as Enzyme Inhibitors..................................108
David Kinder
GENERATION AND SYNTHEtic UTILITY OF CARBANIONS
STABILIZED BY DIVALENT SULFUR

Reported by Peter Becker

September 6, 1979

Organometallic compounds stabilized by an adjacent sulfur atom are well known and synthetically useful. This survey is limited to carbanions stabilized by a single divalent sulfur atom.

Thioanisole was first metallated on the methyl group by Gilman and Webb by reaction with n-butyllithium at elevated temperatures; however, cleavage and ring metallation were serious side reactions. Corey found that addition of 1,4-diazabicyclooctane increased the yield of 1.2 Peterson formed 2 from dimethylsulfide using n-butyllithium/tetramethyl-ethylenediamine.3 Recently Dolak and Bryson deprotonated isobutylyphenyl sulfide with tert-butyllithium in tetrahydrofuran/hexamethylphosphoric triamide.4 Exchange with boron,5 sulfur,6 selenium,7 and tin8 also gives α-lithio sulfides.

\[
\begin{align*}
R-S-\text{CH}_2\text{Li} & \quad R-S\overset{\alpha}{\text{Li}} \quad X^- \\
1 \quad R = \text{Ph} & \quad 2 \quad R = \text{Me} & \quad 3 & \quad 4 \\
\end{align*}
\]

Reaction of α-lithiosulfides with a variety of electrophiles gives the expected products in good yield; e.g. 2 with carbon dioxide gives 2-methylthioacetic acid.9 Methylation of ketones10 has been performed with 1, and 1 along with higher homologs has been used in the synthesis of epoxides.11 Homologation of trialkyl boranes12 has been effected with 2, as well as the synthesis of terminal alkynes from carboxylic acids.13 Trost has formed cyclobutanones14 and cyclopentenes15 from adducts of phenylthiyclopentyl lithium with ketones.

Allyl and benzyl sulfides are more readily metallated, and even the dianions of allyl and benzyl thiol16 have been reported. Trialkyl borane complexes17 and complexation with heteroatoms18 have been used to direct α-alkylation of ambient allyl anion 3. However, the copper reagent gives predominantly γ-alkylation.19 Reported syntheses of terpenes,20 jasmonoids21 and prostaglandin F\textsubscript{2α}22 employed species 3. Cecropia juvenile hormones have been made via dihydrothiapyrans.23 Alkylation followed by sigmatropic rearrangement has proven useful.24

Metallated vinyl sulfides serve as acyl anion equivalents and have been prepared by addition of organometallic reagents to acetylenic sulfides and thioketenes and transmetallation.25 Direct proton abstraction is the most widely used route and there have been a number of recent examples.26 Metallation of 1,3-dien-1-yl sulfides has also been reported.27 Higher homologs have been metallated in the α-position.28

Derivatives of thiols such as thioumidates, dithiocarbonates and thioesters have been deprotonated on the sulfur-bearing carbon and are thought to be dipole stabilized.29 Mono and dithiocarbamates also have been deprotonated.30 The above compounds are generally limited to the methyl and allyl cases; however, α-lithioisopropyl 2,4,6-trisopropylthiobenzoate has been formed in good yield.
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THE DESIGN, SYNTHESIS, AND BIOLOGY OF DNA INTERCALATING AGENTS

Reported by David W. Robertson		September 27, 1979

Intercalation is the noncovalent insertion of planar aromatic molecules between two successive base pairs of double-helical DNA. Since Lerman's classic delineation of intercalation\(^1\) over two decades ago, many antitumor agents, mutagens, carcinogens, and teratogens have been found to exert their effects through intercalative binding to DNA. Because of the biological and clinical importance of intercalation, molecular biologists, oncologists, and chemists have intensively investigated the nature of this phenomenon. In this paper the evidence adduced for intercalation will be surveyed, and the design, synthesis, and biological applications of DNA intercalating agents will be examined.

Structural Requirements for Intercalation. Ethidium bromide (1), a phenanthridinium trypanocide, and proflavin (2), a powerful frameshift mutagen, are archetypical intercalators (Figure 1). Both inhibit DNA and RNA synthesis\(^2\) and are two of the more widely studied intercalators. As these two examples indicate, molecules which intercalate are planar aromatic molecules; large deviations from molecular planarity in the form of bulky substituents such as in 2,7-di-t-butylproflavin\(^3\) prevent intercalation. In addition to the endocyclic nitrogens which most high-affinity intercalators possess, many intercalators also contain exocyclic amine groups. These, if positioned properly, result in enhanced binding affinity.\(^4\)

Figure 1

Methods by Which Intercalation and the Resultant DNA Deformations are Studied. In the normal DNA duplex, the adjacent parallel base pairs are in van der Waals contact with one another. A planar molecule is accommodated in the helix by a local unwinding of the deoxyribose backbone; this separates the base pairs sufficiently to allow the insertion of the intercalator while still maintaining the integrity of the interbase Watson-Crick hydrogen bonding. The DNA-intercalator complex is stabilized by many physical processes; hydrophobic interactions, electronic interactions between the \(\pi\)-clouds of the intercalator and DNA bases, and hydrogen bonding have all been shown to contribute to the stabilization of the complex. Because intercalative interactions perturb the physical and chemical characteristics of both the DNA and the intercalator, a number of physicochemical probes can be used to examine the interaction of an intercalator with DNA.

Fluorescence and Visible Spectroscopy. Upon intercalation of ethidium bromide into DNA, hypochromatic and bathochromic shifts are produced in the visible spectrum of ethidium.\(^5\) When the intercalator is treated with
increasing concentrations of DNA, the absorbance spectrum of the drug shifts progressively towards a limit which represents the spectrum of the drug when fully intercalated (Figure 2). The curves pass through a well-defined isosbestic point, indicating that two forms of the drug, free and bound, are contributing to the absorbance.

**Figure 2**

![Absorbance spectrum](image)

From a combination of the visible spectrum and a Scatchard plot, the association constant and number of binding sites in the DNA can be estimated. For ethidium bromide the approximate association constant is $5 \times 10^7$ M$^{-1}$, with up to one ethidium per two base pairs being bound. The nonlinearity of the Scatchard plots and many other lines of evidence indicate that two types of binding are possible. After the high-affinity intercalative sites are exhausted, more positively charged ethidium molecules can interact with the negatively charged phosphates of the DNA. At a ratio of one drug per nucleotide residue, an electrostatically neutral complex precipitates.

When ethidium is complexed with DNA there is a dramatic increase in the fluorescence of the intercalator (Figure 3). The most plausible explanation for the fluorescence enhancement is the immersion of the ethidium into a hydrophobic region of the nucleic acid upon intercalation. This reduces the rate of excited state-solvent proton transfer, and increases the fluorescence lifetime by a factor of 12.

**Figure 3**

![Fluorescence intensity](image)

**NMR Spectroscopy.** Numerous $^1$H- and $^3$P-NMR experiments have been conducted on mixtures of complementary oligonucleotides and intercalators. When 9-aminoacridine in D$_2$O is titrated with increasing concentrations of dGpC, the nonexchangeable protons experience a linear upfield shift until a 1:2 acridine-dinucleotide stoichiometry is reached (Figure 4). This suggests the formation of a minihelix with the acridine sandwiched between...
the base pairs. In an ethidium bromide-(dCdGdCdG)$_2$ complex the phenanthridine ring protons shift upfield by about 0.9 ppm (H-2, H-4, H-7, H-9) and > 0.5 ppm (H-1, H-10) relative to the corresponding protons in uncomplexed ethidium.$^{12}$ Calculated values for the upfield shifts based upon the atomic diamagnetic anisotropy and ring current contributions compare favorably with the experimentally determined values.

Circular Dichroism and X-Ray Studies. When ethidium is mixed with double-helical DNA, circular dichroism is induced in the nonchiral ethidium.$^{7-9}$ Various dichroism studies have indicated that the plane of the intercalator is approximately parallel to the planes of the adjacent base pairs.

Complexes of intercalators and complementary oligonucleotides can sometimes be crystallized, allowing the direct visualization of intercalative binding in a miniature double helix.$^{13}$ All the X-ray studies confirm the postulates which were based on spectroscopic data.

Hydrodynamics. Intercalation, because of the necessary local unwinding of the helix, results in a lengthening and stiffening of the DNA molecule. This causes the intercalated DNA to become more rod-like than its pristine counterpart; as a consequence the intrinsic viscosity of DNA solutions is increased.$^1$ Because the additional length due to an intercalator is approximately the same as that of an additional base pair and most intercalators are of less molecular weight than a base pair, the average molecular weight per unit length of the DNA decreases; this results in a decrease of the sedimentation coefficient.$^1$

A unique method of studying intercalation is the interaction of the intercalating agent with covalently closed, supercoiled DNA.$^{14}$ These DNAs display large changes in their supercoiling as a result of local intercalative helix unwinding.$^4,15$ As increasing concentrations of intercalator are added, the right-handed supercoiling decreases until open circles are obtained. Additional intercalating agent results in more unwinding until torsional strains produce left-handed supercoils (Figure 5). The progress of the titra-
tion is most conveniently monitored by changes in the sedimentation coefficient of the DNA (Figure 6). All known intercalating agents remove and reverse the supercoils of closed circular duplex DNA.

**Figure 6**

Intercalative Photoaffinity Labelling Reagents. Intercalators such as ethidium bromide have been widely used to probe numerous biological structures such as tRNA, 5S-RNA, and chromatin; they have also been of great utility in studies of biological processes such as DNA replication and transcription, and the mechanism of frameshift mutagenesis. One of the major disadvantages of using noncovalently attached intercalators in the study of biological structures and processes is that during the time of a biological or physical assay the intercalators can move from site to site. In in vivo studies, cell fractionation techniques can rearrange concentration gradients and drug distributions among subcellular compartments. This problem can be circumvented by the use of intercalating agents which can be covalently attached to the DNA or juxtaposed proteins. Photoaffinity labelling is a technique which permits this covalent attachment. At least two different types of intercalative photoaffinity labels have been developed: the furucoumarins (Figure 7) and azide analogs of ethidium and acridine.

**Figure 7**

The furucoumarins are a group of naturally occurring and synthetic compounds which manifest interesting photobiological effects such as skin sensitization. They have been used therapeutically since antiquity; the fruit and seed extracts used by the ancient Egyptians to treat vitiligo contained furucoumarins. A more recent medicinal application is the photochemotherapy of psoriasis and other skin diseases.

The mechanism by which furucoumarins exert their photobiological effects is photoreaction with DNA; a linear relationship normally exists between the
biological effects and the extent of photoreaction.\textsuperscript{21} In the absence of electromagnetic excitation there is no disruption of cellular processes.

Furocoumarins intercalate into DNA and form cyclobutane adducts with the pyrimidine bases in DNA when the complex is irradiated with 365 nm light.\textsuperscript{19} The linear furocoumarins, the psoralens (Figure 7), are capable of forming either monofunctional or difunctional adducts with DNA. The difunctional adducts are due to the reaction of both the 3,4 and 4',5' double bonds with pyrimidine bases in each strand of duplex DNA. This crosslinks the DNA strands and prevents them from becoming separated even under conditions which normally denature DNA. The crosslinking has been demonstrated by denaturation-renaturation kinetics\textsuperscript{22} and by electron microscope studies.\textsuperscript{23} Cole has shown that the inhibition of certain bacterial functions by psoralin is approximately equal to the rate of formation of a single psoralen cross-link per DNA molecule.\textsuperscript{24}

Numerous derivatives of psoralen have been prepared in order to optimize their DNA interaction characteristics. Hearst and Rapoport reported\textsuperscript{25} that 4'-aminomethyl-4,5',8-trimethylpsoralen is the best derivative for photo-reaction with DNA. It can bind to DNA to the extent of one drug molecule per five base pairs with a 65% photoattachment efficiency.

The angular furocoumarins, the angelicins (Figure 7), form only monofunctional adducts and have a low ability to produce photosensitized effects.\textsuperscript{19} The angelicins, however, may be the furocoumarins of choice if inhibition of DNA or RNA synthesis is the only desired biological effect. Crosslinking is a very severe type of damage to a cell's genome and often leads to undesirable results.

9-Azidoacridine, another type of intercalative photoaffinity label, was prepared to help elucidate the mechanism of 9-aminoacridine's frameshift mutagenicity.\textsuperscript{26} Surprisingly, 9-azidoacridine is not a frameshift mutagen; it is a base pair substitution mutagen with or without photolytic activation. Placing the azide moiety at other positions on 9-aminoacridine would perhaps yield a photoaffinity label which still maintains the frameshift mutagenicity of the parent compound.

A more suitable photoaffinity label for the frameshift mutagen studies is the fluorescent intercalator 8-azidoethidium bromide.\textsuperscript{17,18,27} Structure-activity relationships of various phenanthridinium analogs of ethidium bromide indicated that the 8-aminogroup could be modified with little change in its interaction with DNA.\textsuperscript{4} This was found to be true with 8-azidoethidium bromide. In the dark, 8-azidoethidium bromide and ethidium bromide are competitive inhibitors in DNA binding studies and cause similar perturbations in the hydrodynamic properties of native DNA. The azide analog binds strongly to DNA ($K_a = 2-3 \times 10^5 \text{ M}^{-1}$), and can be photoattached to DNA with efficiencies approaching 75%.\textsuperscript{27} Unlike 9-azidoacridine, 8-azidoethidium bromide behaves as a frameshift mutagen both before and after covalent attachment to DNA.

**Antibiotic Intercalators.** Many naturally occurring antibiotics have been shown to exert their effects through intercalative binding to DNA. The actinomycins\textsuperscript{28,29} quinomycins,\textsuperscript{30} and triostins\textsuperscript{31} all intercalate into DNA with very high affinity. The two most heavily studied intercalators are actinomycin D (5, Figure 8) and echinomycin (6), a member of the quinomycin antibiotic family. Both of these compounds differ from previously mentioned intercalators in that they have peptide moieties, and
after incercalation of the chromophore, these peptides lie in the minor groove of the DNA. Through their hydrogen bonding and hydrophobic interactions with various components of the helix, the peptides enhance the binding affinity of the intercalators to the DNA and contribute some degree of sequence specificity.

Figure 8

actinomycin D (5)

Echinomycin is unique in that both quinoxaline rings can intercalate simultaneously into DNA. The helix unwinding angle is 1.82 times that of ethidium and the molar quantity of echinomycin required to unwind supercoiled
DNA to uncoiled circles is one-half the amount of ethidium required. The antibiotic lengthens the helix 6.3 Å per molecule bound, whereas a monofunctional intercalator lengthens the helix by 3.35 Å.

NMR studies and model building and semiempirical potential energy calculations for echinomycin indicate that in solution the two quinoxaline chromophores are held in a syn orientation by the octapeptide lactone; this results in a rigid, tweezer-like molecular conformation. The rings are almost parallel to each other and are separated by a distance of 10.2 Å, which is the exact value required to accommodate two stacked base pairs between them.

**Synthetic Polyintercalators.** DNA is the only pharmacological receptor which has been defined to atomic resolution. This, theoretically, should allow the design and synthesis of agents which possess optimal DNA interaction characteristics. Following Nature's model, echinomycin, polyintercalators have been synthesized in order to obtain intercalators with the highest possible affinity for DNA; provided entropic and steric factors are not unfavorable, the binding affinity should increase with each additional intercalating subunit. In addition, the possibility exists that these synthetic polyintercalators will exhibit some degree of sequence specificity in their interaction with DNA, a phenomenon lacking with most monointercalators. The bulk of the synthetic and biological work in the area has been on dimeric intercalators which have been prepared by linking monomeric intercalators with straight-chain paraffins or polyamines (polyamines are natural constituents of many forms of life, and because of their polycationic nature they bind tightly to nucleic acids).

Ethidium and its methyl analog methidium, acridines, quinaldines, caffeine, anthracyclines, and ellipticines have all been used to prepare homodimeric intercalators. In addition, an acridine-ethidium heterodimer has been reported.

By standard methodology Dervan and Becker have synthesized a p-carboxyethidium dimer using the polyamine spermine as the connecting chain. The product, bis(methidium)spermine (8, Fig. 9), was shown to remove and reverse the supercoils of PM2 DNA, and the molecule possesses an unwinding angle 1.5-fold greater than that of ethidium. Since previous studies have shown that substitution of a methyl for the ethyl group or addition of a p-carboxyl group to ethidium has little effect on the unwinding angle, the value for the dimer may reflect equal contributions from mono- and bisintercalated species. From fluorescence and stoichiometry of binding studies the workers concluded that the dimer does bisintercalate and has a binding affinity at least 1,000 times that of ethidium.

Kuhlmann et al. have synthesized a m-carboxymethidium and dimerized it by amide linkage to 1,5-diaminopentane. The dimer (9 in Figure 9) exhibits intramolecular stacking of the two chromophores. From spectroscopic and hydrodynamic studies it was shown to be a bisintercalator with a much higher affinity for DNA than ethidium. Despite its high affinity for DNA, it is a poorer inhibitor of nucleic acid synthesis in L1210 cells than ethidium. This may be related to a low cellular or nuclear uptake owing to the compound's double positive charge.

An ethidium homodimer (10, Figure 9) and an acridine-ethidium heterodimer (11) were synthesized by linking the monomers via the phenanthridinium's quaternary nitrogen. By a combination of NMR and fluorescent spectroscopy and ring current calculations, the compounds were found to
Figure 9

Figure 10

exist in a temperature- and pH-dependent equilibrium between folded and unfolded conformations (Figure 10). These compounds do not bisintercalate.

Much of the study of bisintercalators has involved acridine homodimers. Various bis(9-acridyl)polyamines have been prepared, and a homologous series of diacridines connected by the amino groups of the diamines NH₂(CH₂)ₙNH₂ (where n = 2, 3, 4, 6, 8, 10, 12, 14, 16, 18) has been synthesized (12 in Figure 9). In the latter compounds, bifunctional intercalation occurs when six methylene units separate the acridines. The diacridines of shorter chain length are monofunctional intercalators.

The activity of the homologous series against P-388 tumor cells in mice was then determined. Maximal activity is attained when the chain length is six carbons; longer connecting chains are increasingly toxic to the host (Figure 11). Spermine diacridine at low concentrations inhibits RNA polymerase by preferentially inhibiting chain initiation, in marked contrast to actinomycin D which inhibits chain elongation.
Whitlock and Chen have synthesized\textsuperscript{44} a series of caffeine dimers linked by rigid diyne chains. This decreases the amount of self-association of the two chromophores which was seen with the ethidium dimers. Since the self-association must be disrupted for intercalation to occur,\textsuperscript{35} bifunctional intercalators should possibly be constructed with rigid connecting chains in order to optimize the free energy of DNA binding.

**Conclusion.** Despite the large amount of work which has been reported to date, many aspects of intercalation are still enigmatic. The number of base pairs affected by intercalation, the differential effect of intercalation on the recognition of nucleic acids by various proteins, and the correlation between biological activity and the structure of the intercalative complex are still unknown. The answers to these and other questions concerning intercalation await the synthesis and physicochemical characterization of many other intercalating agents and is a goal which will require the union of synthetic organic chemistry and molecular biology.

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MODIFICATION OF OLEFINs WITH ORGANOSELENIUM REAGENTS

Reported by Larry D. Boardman October 4, 1979

In 1970 Jones, Mundy, and Whitehouse observed that selenoxides underwent clean syn elimination to form olefins. With this fact at hand Sharpless and Reich opened the door to modern organoselenium chemistry in 1973 with the conversion of epoxides to allylic alcohols and the preparation of α,β-unsaturated ketones and esters, respectively, via organoselenium intermediates. Organoselenium methodology has since undergone a remarkable growth and diversification and now occupies an important position in the field of organic synthesis. This report reviews the elaboration of olefinic substrates by organoselenium reagents, an area that recently has increasingly attracted the attention of the investigative community.

A wide variety of organoselenium reagents has been prepared, and selenofunctionalization of organic molecules has been refined to a high degree. A large number of important synthetic transformations can be achieved by taking advantage of the properties of organic selenium compounds. As expected, the chemistry of selenium parallels that of sulfur to a certain extent; however, the differences between the two elements often allow specific conversions to be accomplished in circumstances under which the analogous sulfur reaction might proceed only with difficulty or not at all. The unique properties of selenium also manifest themselves in reactions that have no counterpart in sulfur chemistry. Reich in his recent review draws attention to some of the key differences between the chemistries of sulfur and selenium and emphasizes organoselenium transformations that capitalize upon these differences.

At the heart of organoselenium chemistry is the selenoxide elimination (Eq. 1). Introduction of an arylseleno moiety followed by oxidation and elimination of the corresponding aryl selenenic acid has been developed and refined to the point that it is now a standard means of introducing unsaturation into organic molecules. Oxidation has been accomplished with a number of reagents: sodium periodate, peracids, hydrogen peroxide, ozone, and more recently tert-butyl hydroperoxide. Thermal elimination of sulfoxides is also known; however, pyrolysis at 50° to 110° is required whereas aryl selenoxides decompose cleanly under neutral conditions at room temperature. The elimination is stereospecifically syn and, in general, (E)-olefins are obtained where possible. The regiochemistry of the fragmentation is also predictable, the ease of hydrogen abstraction following the order allylic > propargylic > benzylic > methyl > methylene >> methine. Elimination is generally away from an electronegative substituent β to the selenoxide function, the above order notwithstanding (Eq. 1).
Addition of Aryl Selenenic Acid Derivatives, ArSeX. The first additions of selenenic acid derivatives to alkenes were reported in 1958 by Hölze and Jenny; however, the harsh reaction conditions and difficultly prepared starting materials detracted from the synthetic utility of their approach. More useful was the discovery by Clive in 1974 that benzeneselenenyl bromide reacts with alkenes in the presence of silver trifluoroacetate to give \( \beta \)-trifluoroacetoxy selenides. Mild hydrolysis with aqueous sodium bicarbonate afforded the corresponding \( \beta \)-hydroxy selenides in excellent yield (Eq. 2).

\[
\begin{align*}
\text{PhSeBr} & \underset{\text{AgO}_2\text{CCl}_3}{\longrightarrow} \text{PhSeO}_2\text{CCl}_3 \quad & \text{NaHCO}_3 & \underset{\text{H}_2\text{O}}{\longrightarrow} \text{PhSeOH} \\
\end{align*}
\]

Experiments with cyclic olefins gave exclusively products arising from \textit{anti} addition suggesting the intermediacy of the seleniranium ion \( 1 \), which is then captured by an external nucleophile (Eq. 3). This species is not without analogy (e.g., cyclic halonium, mercurinium, and sulfonium ions are well known), and the characterization by Schmid and Garratt of several hexafluorophosphate and hexafluoroantimonate salts of seleniranium ions lends further support to this proposal. Initial capture of \( 1 \) by bromide is, however, open to question for Reich has shown that benzeneselenenyl trifluoroacetate is formed upon admixture of benzeneselenenyl bromide and silver trifluoroacetate and adds to olefins rapidly and quantitatively. Many other workers have since noted \textit{anti} stereospecificity, and the above mechanism is generally accepted. In certain instances, however, non-stereospecific addition can be observed; addition of benzeneselenenyl chloride to 3,4-dihydro-2H-pyran, for example, gives two products, 3 and 4, arising from the capture of chloride by the resonance stabilized oxacarbonium ion \( 2 \) (Eq. 4).

\[
\begin{align*}
\text{PhSeCl} & \underset{\text{O}_2\text{CCl}_3}{\longrightarrow} \text{PhSeO}_2\text{CCl}_3 \\
\end{align*}
\]
The regiochemistry of these additions has also been investigated. Poor regioselectivity was noted by Reich in the addition of benzeneselenenyl trifluoroacetate to unsymmetrical olefins. Raucher observed that the addition of benzeneselenenyl chloride to terminal olefins initially gives anti-Markownikoff adducts which isomerize on standing to the thermodynamically more stable Markownikoff isomers (Eq. 5). Internal alkenes, as well as styrene, lead to only Markownikoff products. The observed regiochemistry is obviously a function of both steric and electronic effects, and the relative importance of each must be considered before the course of a specific reaction can be predicted.

\[
\begin{align*}
R\equiv & \quad \rightarrow \quad \text{R} & \quad \text{Cl} & \quad \leftarrow \quad \text{R} & \quad \text{SePh} & \quad (5) \\
& & & & & \\
& & & & & \\
\text{5} & & & & & \\
& & & & & \\
& & & & & \\
\text{6} & & & & & \\
& & & & & \\
& & & & & \\
\end{align*}
\]

Selenenic acid derivatives other than halides and acetates also add to olefins, and the utility of the β-functionalized selenides thus formed is found in their further elaboration into synthetically important compounds. Benzeneselenenic acid can be generated in situ by the action of hypophosphorous acid on seleninic acids, or more conveniently by the comproportionation of benzeneseleninic acid and diphenyldiselenide, and adds readily to olefins constituting an alternative route to β-hydroxy selenides. This functionality has also been introduced by Petrzilka; addition of benzeneselenenyl bromide to ethyl vinyl ether in ethanol followed by hydrolysis of the resulting diethyl acetal yields phenylselenoacetaldehyde which may be alkylated with a Grignard reagent. Miyoshi obtained β-acetoxy selenides from the reaction of dimethyl selenoxide with olefins in acetic acid, and the β-alkoxy compounds were prepared by Uemura by reacting alkenes with phenyl selenocyanate in alcoholic solvents in the presence of copper or nickel halides.

Elimination of benzeneselenenic acid from these β-hydroxy, acetoxy, and alkoxy selenides affords a mild, convenient route to allylic alcohols and their derivatives. In a related reaction, Petrzilka observed the Claisen rearrangement of the allyl ethyl ketene acetals generated by the selenoxide fragmentation of 7. These compounds were obtained from the reaction of benzeneselenenyl bromide with ethyl vinyl ether in the presence of the appropriate allyl alcohol (Eq. 6).
β-Hydroxy selenides are potentially important intermediates; in addition to allylic alcohols, they can be converted into simple alcohols, epoxides, olefins, bromohydrins, phenylseleno ketones, and vinyl selenides. The synthetic potential of these transformations is apparent; the preparation of (+)-crinamine and related compounds by Isobe and co-workers is but one example.

Phenyl vinyl selenides can also be prepared directly from olefins by the addition of benzeneselenenyl bromide to terminal double bonds followed by dehydrohalogenation as described by Raucher. Proper choice of reaction conditions permits control of both the regio- and stereochemistry of the elimination. Once prepared, these compounds can be subjected to further transformations. Vinyl and allyl bromides can be obtained simply and in good yield. Vinyl selenides can also be employed as \( \text{CH} = \text{CH}^- \) synthons; reaction with an alkyllithium yields a phenylseleno stabilized carbanion which may be trapped by an appropriate electrophile (Eq. 7). Selenoxide elimination affords the (E)-olefin in good yield.

\[
\begin{align*}
\text{CH}_2 = \text{CHSePh} & \xrightarrow{\text{RLi}} \text{CHSePh} \\
& \xrightarrow{\text{Li}} \text{RCH}_2\text{CHSePh} \\
& \xrightarrow{\text{[O]}} \text{E} \\
& \xleftarrow{} \text{RCH}_2\text{CHSePh}
\end{align*}
\]

Another functionalization that can be carried out by the addition of organoselenium reagents to olefins is the preparation of \( \sigma \)-phenylseleno ketones which has been accomplished in a number of ways. These compounds are useful intermediates, and their synthetic versatility has been amply demonstrated.

β-Hydroxy selenides may be oxidized to 1-phenylseleno-2-alkanones by a modification of the Corey-Kim oxidation, and Raucher obtained these compounds regiospecifically by treating his 2-bromoalkyl phenyl selenides with silver hexafluorophosphate in dimethyl sulfoxide in a modification of the Kornblum oxidation. Tsuji accomplished the same conversion by reaction of terminal olefins with benzeneselenenyl bromide in ethanol followed by periodate oxidation and reflux in toluene. Treatment of olefins with diphenyldiselenide, bromine, and hexabutyldistannoxane also yields \( \sigma \)-phenylseleno ketones as shown by Kuwajima, who also prepared these systems by a reaction that may involve addition of the elements of diphenylselenenonic anhydride to the olefinic bond.

Cyclofunctionalization. In addition to capture of the initially formed seleniranium ion by an external nucleophile such as halide or acetate, intramolecular capture is possible, a process christened cyclofunctionalization by Clive. The reaction was originally observed by Campos and Petragnani but was not developed as a synthetic tool until recently.

Nicolaou and Clive demonstrated the use of benzeneselenenyl chloride for the formation of bicyclic lactones, termed phenylseleno
deprotonation, in organic media under very mild conditions; the phenylseleno derivatives prepared thus may be reductively or oxidatively modified (Eq. 8). The same overall conversion may be carried out in principle with the halogens, as well as other reagents, through an analogous mechanism; however, the aqueous, basic media usually used
and the rather severe conditions necessary for further elaboration of the halo lactones thus formed impose restrictions on the applicability of halolactonization.

![Chemical structure](image)

Many other transformations of this general type are possible. Bicyclic ethers can be prepared from the appropriate olefinic alcohols, and the synthesis of ring-fused tetrahydrofurans is particularly important in view of the widespread occurrence of this ring system among natural products. Nicolaou, for example, has applied this methodology to the preparation of several prostacyclin isomers and analogs, and Lysenko and co-workers have exploited the process in their synthesis of muscarine analogs. In another example, Petzilka obtained the phenylseleno acetal from the cyclization of 8. Selenoxide fragmentation and spontaneous Claisen rearrangement afforded (+)-phoracanthrolide J (10a in Eq. 9).

![Chemical structure](image)
Both simple phenols and anilines undergo rapid para-substitution by the electrophilic benzeneselenenyl chloride and in the latter case attack at nitrogen as well; however, ortho-alkenyl phenols can be cyclized to 2,3-dihydrobenzofuran and 3,4-dihydro-2H-benzo[b]pyran derivatives (Eq. 10).31

![Chemical structure](image)

and nitrogen heterocycles can be prepared by cyclofunctionalization of olefinic urethanes (Eq. 11).41

![Chemical structure](image)

Carbon-carbon bond formation has also been recently achieved in this manner. Clive42 obtained the substituted hydrindan 11 by the reaction of benzeneselenenyl chloride with 1,5-cyclononadiene in acetic acid (Eq. 12). Hydrolysis of the acetyl group followed by reduction of the benzeneseleneno function by triphenyltin hydride43 afforded the alcohol 12 in 61% overall yield.

![Chemical structure](image)

Cyclofunctionalization also holds potential for selective protection-deprotection operations; Nicolaou33 has observed that reversion can be accomplished by treatment of the cyclized compounds with sodium in liquid ammonia (Eq. 13).

![Chemical structure](image)

**Epoxidation.** Another important modification of olefins mediated by organoselenium compounds is epoxidation. The process was initially observed as a side reaction in certain selenoxide eliminations.44-46
Grieco,\textsuperscript{45} for example, noted a product composition as a function of the number of equivalents of oxidizing agent employed when carrying out the selenoxide fragmentation of 13 (Eq. 14).

\begin{equation}
\text{SePh} \quad \text{H}_2\text{O}_2 \quad \text{H}_2\text{Se} \quad \text{H}_2\text{O} \quad \text{O} \\
\text{13} \quad 2 \, \text{eq. H}_2\text{O}_2: \quad 93\% \quad 0\% \\
\quad 8 \, \text{eq. H}_2\text{O}_2: \quad 18\% \quad 30\%
\end{equation}

Once eliminated, benzeneselenenic acid, as observed by Sharpless,\textsuperscript{2} may be further oxidized to benzeneseleninic acid. Grieco\textsuperscript{45} postulated oxidation of this species to benzeneperoxyseleminic acid in the presence of excess hydrogen peroxide (Eq. 15) and proposed this as the active reagent responsible for the epoxidation. As benzeneseleninic acid is regenerated in the reaction, the overall process is catalytic with respect to the selenium reagent. Appropriate conditions for avoiding this oxidation when desired have been designed by Reich\textsuperscript{47} while Hori and Sharpless\textsuperscript{6} have developed useful synthetic procedures for the epoxidation of olefins with arylperoxyseleninic acids. Dichloromethane was found to be the best solvent and o-nitrophenylseleninic acid, 14, and 2,4-dinitrophenylseleninic acid, 15, the most effective catalysts (Eq. 16).

\begin{equation}
\text{R} \quad ^\text{O} \quad \text{SeOH} \quad \text{H}_2\text{O}_2 \quad \text{H}_2\text{Se} \quad \text{H}_2\text{O} \quad \text{O} \\
\text{14} \quad \text{R}_1 = \text{NO}_2, \, \text{R}_2 = \text{H} \quad \text{90\%} \\
\text{15} \quad \text{R}_1 = \text{R}_2 = \text{NO}_2
\end{equation}

Unlike carboxylic peracids and alkyl hydroperoxides in the presence of vanadium or molybdenum catalysts, little or no regioselectivity is observed in the epoxidation of allylic dieneols with arylperoxyseleninic acids.
In summary, many important transformations are possible through the action of organoselenium reagents on olefins. Addition of aryl selenenic acid derivatives to double bonds provides a convenient route to several important synthetic intermediates, and, although the methodology is still young, cyclofunctionalization and epoxidation may provide important new answers to old problems.

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SYNTHETIC METHODS FOR THE PREPARATION OF
STERICALLY HINDERED OLEFINS

Reported by Ronald S. Michalak
October 22, 1979

Introduction. Conventional synthetic routes to olefins are seriously affected by steric hindrance. Although the Wittig reaction is frequently used for the preparation of disubstituted olefins, yields decrease for trisubstituted olefins and are generally very low for tetrasubstituted olefins. Photochemical pinacol coupling of aromatic carbonyl compounds is reversible; consequently, yields of products decrease as steric hindrance increases. Elimination reactions provide another important route to olefins. However, previously developed methods are plagued by inaccessibility of intermediates as substitution increases. This paper will discuss some of the more recently developed methods for the preparation of olefins which have special application to highly substituted and sterically hindered olefins. Chemists are interested in hindered alkenes because as the double bond of an olefin becomes more hindered, it is less accessible to electrophiles. Also, the steric hindrance which is introduced by bulky substituents can cause a weakening of the double bond, which is manifested in abnormally long bond lengths and less interaction between the orbitals in the π bond.

Olefins via Titanium Based Reagents. Several transition metal-based reagents (for example, W, Mg, and Al) have been reported to couple aryl and diaryl ketones, but fail to couple dialkyl ketones due to their higher reduction potentials. Reductive coupling of carbonyl compounds by some of these reagents was discussed in a previous departmental seminar. Presently, the transition metal based reagent used most frequently is TiCl₄/LiAlH₄, which was reported by McMurray and Fleming in 1974 (Eq. 1).

\[
2 \text{R}_2\text{C}=\text{O} + 4\text{TiCl}_3 \rightarrow 2\text{R}_2\text{C}=\text{CR}_2
\]

\[
\text{R} = \text{aryl, alkyl}
\]

The reaction generally proceeds in high yields for symmetrical olefins. Unsymmetrical dialkyl ketones are expected to give mixtures of the three possible products unless one of the ketones is in excess. When acetone is used in excess, good yields of unsymmetrical olefins have been realized (Table 1). When the diaryl ketones, benzophenone and fluorenone, are coupled with dialkyl ketones, unsymmetrical olefins are obtained in good yield (Table 2).

Table 1. Reductive Coupling Between Acetone and Other Ketones (Acetone/Ketone = 4/1) with TiCl₄/Li

<table>
<thead>
<tr>
<th>Ketone + Acetone</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamantanone</td>
<td>Isopropylidenedadamantanone</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Adamantylidenedadamantanone</td>
<td>12</td>
</tr>
<tr>
<td>Acetophenone</td>
<td>2-Methyl-3-phenyl-2-butene</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>2,3-Diphenyl-2-butene</td>
<td>16</td>
</tr>
<tr>
<td>Benzophenone</td>
<td>1,1-Diphenyl-2-methylpropene</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Tetraphenylethylene</td>
<td>trace</td>
</tr>
<tr>
<td>Cycloheptanone</td>
<td>Isopropylidenecycloheptanone</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Cycloheptylidenecycloheptanone</td>
<td>26</td>
</tr>
</tbody>
</table>
Table 2. Reductive Coupling Between Diaryl Ketones and Other Ketones (Ratio of Ketones 1:1) with TiCl₃/Li

<table>
<thead>
<tr>
<th>Ketones</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzophenone</td>
<td><img src="image" alt="Benzophenone structure" /></td>
<td>78</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td><img src="image" alt="Cyclohexanone structure" /></td>
<td>19</td>
</tr>
<tr>
<td>Fluorenone + Cycloheptanone</td>
<td><img src="image" alt="Fluorenone structure" /></td>
<td>77</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Cycloheptanone structure" /></td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Bifluorenylidene</td>
<td>7</td>
</tr>
<tr>
<td>Fluorenone + Acetophenone</td>
<td><img src="image" alt="Fluorenone structure" /></td>
<td>70</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Acetophenone structure" /></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Bifluorenylidene</td>
<td>8</td>
</tr>
</tbody>
</table>

Since the reduction potential of these diarylketones is 1.0-1.5 V less negative (a change in reduction potential of 1.0 V corresponds to a free energy change of 23 kcal/mole) than the dialkyl ketones, one would expect an anion radical\(^9\) coupling mechanism to effect predominantly symmetrical coupling. This mechanism is similar to that proposed for the reductive coupling of carbonyl compounds by other metals such as Al, Zn, and Mg.\(^2\) An alternative mechanism assumes the initially formed anion-radical is reduced further to a dianion, which undergoes nucleophilic addition to the dialkyl ketone.\(^8\) The second reduction potential of benzophenone and fluorenone is less negative than the first reduction potential of the dialkyl ketones. The evidence against a radical-anion mechanism in the case of diaryl-dialkyl couplings does not exclude an anion radical mechanism in the case of dialkyl couplings, where reduction potentials may be too high for the formation of dianions.\(^2\)

Through a series of experiments, McMurray has ascertained that the reduction of the intermediate pinacol occurs on the active surface of a titanium particle in a heterogenous process.\(^8\) Olefins 1-4 have been synthesized by the use of titanium-based reagents.
Olefins via Reduction of vic-Dinitro Compounds. A promising new method for the preparation of highly substituted olefins involves the coupling of nitro compounds to vicinal dinitro compounds (Eq. 2). Treatment with a mild reducing agent (for example, Na₂S, Ca/Hg, or NaS(J)) then yields the olefin. Unsymmetrical olefins can be prepared by employing an α-α dinitro compound in Eq. 2. Use of the milder reducing agent Ca/Hg amalgam allows the synthesis of olefins with ester, cyano, keto, and ether functionalities. The synthesis of bifluoroenylidene via reduction of the vic-dinitro intermediate with SnCl₂ has been reported. The preparation of α,β-unsaturated nitriles or esters has been accomplished by the reaction of an anion of α-cyanosulfones or α-ethoxy carbonylsulfones with α,α-dinitro compounds (Eq. 3).

The mechanism proposed for these couplings involves radical-anion intermediates and it is not expected that this method will provide very highly hindered alkenes, because many crowded radicals, such as triisopropyl-tert-butyl, di-, and tri-tert-butylmethyl radicals (10, 11, and 12, respectively) are resistant to dimerization and decay by other paths. However, this approach may prove superior to pinacol coupling when functional groups sensitive to reduction are present.

Decarboxylative Dehydration of β-Hydroxy Acids. A method which has been used to synthesize cycloalkylenedicycloalkanes involves the reaction of a carboxylate dianion with a cycloalkanone to yield a β-hydroxy acid. The β-hydroxy acids can be cyclized to the β-lactones which lose CO₂ upon thermolysis to form the olefins. Elimination to the olefin may also occur without formation of a β-lactone by reaction of 14 with a solution of DMF-acetal (N,N-dimethyl formamide dimethyl acetal).
Cycloalkylidenecycloalkanes with ring sizes 4–8 have been prepared in good yield (Table 3). An advantage of this method is the ease of formation of unsymmetrical olefins. Unfortunately, as steric bulk around the ketone carbonyl increases, enolate formation predominates in the initial step. If enolate formation is blocked by α-substituents such as spirocyclopropyl groups, successful formation of the β-hydroxy acid occurs, albeit in lower yields.\(^{17}\)

### Table 3. Cycloalkylidenecycloalkanes via β-Hydroxy Acids

<table>
<thead>
<tr>
<th>m</th>
<th>n</th>
<th>Yields (from cyclokanone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>62</td>
</tr>
</tbody>
</table>

Olefins via \(\Delta^3\)-1,3,4-Thiadiazolines. The loss of nitrogen and sulfur from \(\Delta^3\)-1,3,4-thiadiazolines has provided access to the most highly hindered olefins to date. It has long been known that diazo compounds react with thiketones to give episulfides by loss of \(\text{N}_2\).\(^{19}\) Thidiazoline intermediates were postulated but not isolated or confirmed. A stable thidiazoline, \(\text{16}\), was isolated in 1969 and was prepared by the reaction of hexafluorothioacetone and bis(trifluoromethyl)diazomethane.\(^{20}\) Other heterocycles, such as \(\text{17}, \text{18},\) and \(\text{19}\), were investigated as precursors to olefins and were found to be unsatisfactory.\(^{21}\)
One method for preparing thiadiazolines is to form the azine first with hydrazine. Allowing the azine to react with \( \text{H}_2\text{S} \) provides the 1,3,4-thiadiazolidines, which are oxidized with \( \text{Pb(OAc)}_4 \) or diethyl azodicarboxylate (Scheme I). This method produces mixtures of olefins if unsymmetrical ketones are used. Another drawback is that as the \( \text{R} \) groups become more bulky, the equilibrium between the thiadiazolidines 21 and the azine (+\( \text{H}_2\text{S} \)) lies too far on the side of dissociation. 22

Scheme I

\[
\begin{array}{c}
\text{R} \quad \text{C=O} \quad \text{N}_2\text{H}_4 \\
\text{R} = \text{aryl, alkyl}
\end{array}
\]

\[
\text{R} \quad \text{C=N-N=C} \quad \text{R'} \\
\text{R} \quad \text{C=N=O} \quad \text{R'}
\]

\[
\text{R} \quad \text{S} \quad \text{R'} \\
\text{R} \quad \text{S} \quad \text{R'}
\]

An alternative route to \( \Delta^3 \)-1,3,4-thiadiazoline formation is the addition of a diazo compound to a thiketone. There has been some confusion in the literature as to whether the symmetrical 1,3,4- or the unsymmetrical 1,2,3-thiadiazoline is formed. 34 Middleton established that 16 was symmetrical by NMR evidence. 20 Also, the reaction of di-tert-butyl thiketone and diphenyl diazomethane afforded the same adduct as the product of the reaction of thiobenzophenone and di-tert-butyl diazomethane (Scheme II). This is only possible if the symmetrical 24 is formed, it being assumed that no rearrangement has occurred.
The stereochemistry of the extrusion has been studied. Trans di-tert-butyl thiadiazoline gave almost exclusively the cis-episulfide, the product expected from conrotatory ring closure (Eq. 5). The episulfides can be converted to the olefin with retention of stereochemistry by reduction with a variety of reagents, including nBuLi, phosphine sulfides, and MeI.

In the case of dicyclohexylepisulfide, the sulfur atom adopts the pseudoaxial position. Olefins through have been synthesized via thiadiazolines.

In the search for new antibacterial cephalosporins, the addition of diazoethane and 2-diazopropane to produced the 4-alkylidene-2-azetidinones and after desulfurization (Eq. 6).
The reaction of isomeric sulfines with diazo compounds proceeds in a stereospecific manner. Unfortunately, the thia-diazoline-1-oxides generally do not give the episulfoxides upon thermolysis, but undergo retro-cycloaddition to starting materials.\(^{28}\)

A desire to extend the scope of this method prompted Barton to examine \(\Delta^3\)-1,3,4,-selenadiazolines as precursors to hindered olefins.\(^{33}\) Since the radius of the selenium atom is larger than that of sulfur, the hindered carbon centers would be held farther apart in a selenadiazoline than in a thia-diazoline. Previously unknown saturated monomeric selenoketones were prepared and reacted more readily with diazo compounds than the analogous thiones. Attempts to prepare tetra-\(\text{tert}\)-butylethylene by this method failed, and in fact more highly hindered olefins could not be prepared via selenadiazolines.

It is interesting to examine the steric limitations of these methods. The synthesis of tetra-\(\text{tert}\)-butyl ethylene has not yet been reported. The attempted synthesis of olefins \(\text{40}\) and \(\text{41}\) via thia-diazolines gave exchange products \(\text{32}\) and \(\text{33}\), indicating formation of the intermediate thia-diazoline which underwent cycloreversion faster than elimination of nitrogen. McMurray's method has failed to produce olefins \(\text{27, 41, 42}\), or tetra-\(\text{tert}\)-butyl ethylene; however, \(\text{27}\) was synthesized in 68% yield via thia-diazolines.\(^{33}\) The phenyl rings in \(\text{27}\) are twisted out of the plane by 61° and 59°. When the meta positions are linked together as in olefin \(\text{43}\), the phenyl rings might be forced to adopt a more planar configuration. The attempted synthesis of \(\text{43}\) via thia-diazolines failed.\(^{35}\)

Physical and Chemical Properties. The X-ray crystallographic structures of crowded olefins \(\text{4, 38, 24, 39, 32, 40, 33, 30}\) and \(\text{44}\) have been reported. Among this group the olefins which has the largest double bond twist is \(\text{44}\), with a twist angle of 40°. Tetra-\(\text{tert}\)-butylethylene has been calculated to have a double bond torsion angle of 75°.\(^{42}\) The thermo-chromic behavior of bianthrones is postulated to occur via metastable intermediates which are torsionally strained at the C=C bond.\(^{48}\)
Brominium ions have long been postulated as intermediates in the electrophilic addition of bromine to olefins. The first example of an isolable, stable bromonium perbromide, 45, was obtained by the bromination of 4. A stable 1,2-dioxetane was isolated from the reaction of 4 and O₃. Tetraeneopentylethylene is stable to Br₂/CCl₄. The barrier to rotation in tetraisopropylethylene and tetraeneopentylethylene calculated from observed line broadening in the NMR spectra is 17 and 22 kcal/mole, respectively.

The NMR, UV, Raman, and photoelectron spectra of alkenes bearing bulky substituents have been examined. Olefin 34 has the lowest carbon-carbon double bond stretching frequency (1540 cm⁻¹) and the longest wavelength (λ_max = 203.0 nm, ε = 15,100) yet reported for an isolated alkene.

Conclusion. The past ten years have seen considerable development in the variety of synthetic methods available for the preparation of olefins bearing bulky substituents and in their application to olefin synthesis. The extension of these methods to produce more highly hindered olefins, such as tetra-tert-butylethylene, remains as an interesting challenge in organic chemistry.

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MECHANISTIC CONSIDERATIONS IN 1,3-DIPOLAR CYCLOADDITIONS

Reported by Clark Cummins
October 29, 1979

1,3-dipolar (or [3+2]) cycloadditions have been known for a long time,¹ and various synthetic applications have been studied in depth.² In 1963 Huisgen first addressed the mechanism of these reactions.³ His studies showed a negligible dependence of reaction rate on solvent polarity (values of the relative rate constant in any one reaction decreasing by no more than a factor of 6, and increasing no more than a factor of 10). Calculations revealed large negative entropies of activation on the order of -20 to -40 eu, and moderate enthalpies of activation on the order of 10 to 20 kcal/mole. These data, coupled with the stereospecificity of addition to cis-trans isomeric dipolarophiles (usually at least 97%), led Huisgen to postulate a concerted mechanism for 1,3-dipolar cycloadditions. In 1968, Firestone reinterpreted the evidence in terms of a stepwise, diradical mechanism.⁴ He refuted Huisgen's explanation of rate and stereochemical effects, claiming inconsistency with a concerted mechanism but agreement with predictions of a diradical mechanism. Firestone also explained the regiochemistry of the cycloaddition in terms of formation of the most stable diradical. This led to a debate between Huisgen⁵ and Firestone⁶ on the concerted vs. diradical mechanism. In the end, Huisgen concluded that the bulk of the evidence favored a concerted addition, while Firestone maintained that the results were best explained by 1,5-diradical intermediates.

Harcourt and co-workers have attempted to reconcile these two mechanistic proposals using Linnett structures and valence bond theory.⁷ By considering a "long-bond", or spin-paired 1,3-diradical as an important contributor to the ground state of the dipole, they proposed a concerted diradical mechanism, with increased valence in the transition state, possibilities that both Huisgen and Firestone overlooked. Harcourt thus treats Firestone's 1,5 spin-paired diradical as a modification of a more general reaction mechanism. Firestone has also applied Linnett structures⁸ in some of his arguments.⁶a,b

One of the major questions about 1,3-dipolar cycloadditions is the origin of their regioselectivity. A number of groups have addressed this problem theoretically,⁹ using frontier orbitals, primary-secondary orbital interactions, and perturbation theory. CNDO/2 and EH methods have been used to generate frontier orbital energies and coefficients for 1,3-dipoles and dipolarophiles, and a qualitative understanding of the effect of substituents has been deduced. Utilizing perturbation theory, correlation of the energies of the interacting frontier orbitals, combined with terminal atom coefficients and the resonance integral of the addends, has led to rationalization of the regiochemistry of olefin cyclizations with azides, diazoalkanes, nitrones, nitrile oxides, and many other 1,3-dipoles. This approach has also met with success in a number of other investigations.¹⁰

The molecular orbital approach has helped in the understanding of 1,3-dipolar cycloadditions, but no clear-cut rules are yet available. Padwa and co-workers have extensively studied the photochemistry of azirines,¹¹ and the 1,3-dipolar cycloadditions of the generated nitrile ylides. Their results led them to postulate a stepwise mechanism for the addition.¹¹b,d Other workers have interpreted their own results in terms
of a concerted reaction. Work on 1,3-dipolar cycloadditions and related reactions continues, and may soon provide further insight into this mechanistic dichotomy.

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APPLICATIONS OF LASERS IN ORGANIC CHEMISTRY

Reported by Rick Gdanski  November 1, 1979

The advent of lasers has made available high-power light sources having very narrow band widths. The ability to tune a laser to a certain frequency has prompted experiments in selective excitation of molecules in the hope of observing new or unusual chemistry. Significant progress has been made in recent years in understanding laser-induced processes from physical and theoretical investigations of many small inorganic molecules. The two major areas of interest are vibrational and electronic excitation. Lasers are also used as specific frequency light sources for obtaining emission and absorption spectra.

In the field of vibrational excitation it was hoped that excitation of a specific bond with an infrared laser would result in cleavage of that bond before the energy could be distributed throughout the molecule. Experiments have shown that this is not the case except possibly for one 44 atom inorganic molecule studied in the gas phase. That is, the vibrational energy is distributed to all other vibrational modes on a picosecond \((10^{-12} \text{ sec})\) time scale. Intramolecular relaxation of the vibrational energy to rotational and translational is much slower. Intermolecular relaxation of vibrational energy is dependent on the number of collisions between the molecules and is also very fast. As a result of these fast relaxation processes, it is necessary to conduct these unimolecular reactions in the gas phase at pressures ranging from \(10^{-5}\) to \(10^2\) Torr. Even at very low pressures the bond in the vibrationally hot molecule which cleaves is the weakest one, regardless of which bond was excited.

However, with a judicious choice of the IR laser frequency, it may be possible to excite only one component of a multi-component gas phase mixture. If the excited compound undergoes a unimolecular decomposition before it collides with the second compound, a compound-specific reaction could be observed. This method has been used to accomplish isotope enrichment by tuning the laser to a \(^{10}\text{BCl}_3\) infrared absorption band and scavenging the dissociation products with molecular oxygen. The isomerization of hexadienes has been investigated for the possibilities of irradiating an isomer at one frequency and generating another isomer which did not absorb at that frequency. Although the investigation met with only limited success owing to partial overlap of the IR bands, the method should be effective when two isomers have clearly separated IR bands. An investigation of the competitive dehydration of ethanol and 2-propanol in the presence of HBr is a striking example of directing a reaction with an IR laser. When ethanol, 2-propanol, and HBr at a total pressure of 1.25 Torr were heated at 300°C for 20 min., a 98:2 mixture of propylene and ethylene was obtained. When ethanol was specifically irradiated in the presence of an equal amount of 2-propanol at a total pressure of 0.2 Torr, a 9:91 mixture of propylene and ethylene was obtained. When 2-propanol was specifically irradiated in a similar mixture, the product distribution was 92% propylene and 8% ethylene.

It is also possible to use an IR laser to effect "high temperature" reactions at room temperature. For example, SiF\(_4\) can be specifically irradiated at pressures that allow fast intermolecular energy transfer to reactants (10 to 50 Torr) whereby SiF\(_4\) acts as a thermal sensitizer.
a unimolecular reaction is fast compared to the rate of collision with the reaction vessel walls, a thermal reaction can be observed without the need for a high temperature oven. This method has been demonstrated in the retro-Diels-Alder reactions of norbornadiene, cyclohexene, 4-vinylhexene, d-limonene, and 2,3-dihydropyran to give the corresponding dienes and dienophiles in excellent yields. A comparison of the literature results the thermolysis of cyclohexene with the results for the laser method indicates that the latter was much cleaner owing to fewer secondary decompositions. Infrared lasers have also been used in mechanistic investigations. For example, specific irradiation of cis-3,4-dichlorocyclobutene gave exclusively cis,trans-1,4-dichloro-1,3-butadiene as predicted by orbital symmetry considerations even though the molecule was not at true thermal equilibrium.

The use of ultraviolet lasers for electronic excitation and flash photolysis has lent itself well to investigations in solution. In general, these lasers are used in conjunction with another light source to measure the absorption spectrum or the absorption decay of a transient intermediate. When a triggering mechanism is used in conjunction with a very short laser pulse, high time-resolution on the order of picoseconds can be achieved. This method has been used to measure the kinetics of protonation and deprotonation of the singlet excited state of 2-naphthol-6-sulfonate and its anion in water. In this case the fluorescence rise time was monitored as a function of pH. Regression analysis of the data gave the rates of protonation and deprotonation from which a pKa of 1.9 was calculated for the excited state as compared to 9.1 for the ground state. The electronic absorption spectrum of the key intermediate in the transamination of a pyridoxal-amino acid complex has been measured by using the time-resolution capabilities of a laser. Nanosecond time-resolution has been employed to measure the absolute rates of reaction of tert-butoxy radicals with various organic substrates. The radicals were formed by flash laser photolysis of di-tert-butyl peroxide, and the kinetics were followed by the rise in absorption of radicals formed by hydrogen atom abstraction as a function of time. The relative rates obtained agreed well with the literature. The absolute rates were found to be much higher than had been previously suggested. The isomerization of retinals, the flash photolysis of hemochromes, and the flash photolysis of benzyl phenyl ketone have also been investigated with the aid of the time-resolution capabilities of lasers.

The use of lasers in organic chemistry is still in its preliminary stages. Infrared lasers are limited to gas phase studies and are of limited utility in organic chemistry. Ultraviolet lasers have been found to be well suited to investigations in solution and are appearing in an increasing number of laboratories. The capability of an infrared laser to induce a thermal reaction in the gas phase at room temperature could be adapted to a flow system for a continuous gas phase reaction. The utility of ultraviolet lasers in the investigation of very fast processes or in the detection of short lived intermediates is becoming a well-established method and is an increasingly powerful tool for physical organic chemists.

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2. See ref. 1b, pp. 37-111.
MAGNETIC FIELD EFFECTS ON CHEMICAL REACTIONS IN SOLUTION

Reported by Paul Gelbudt November 8, 1979

Magnetic field effects on chemical reactions have interested chemists since the beginning of the century. Early work, however, was plagued by the lack of a coherent theory to unify the substantially different results. A typical example was reported by Rosenthal.\(^1\) His report of a magnetic field effect on starch hydrolysis was soon refuted by Cegielsky and Heimrod.\(^2\) Later, Selwood stated that several magnetic field effects were due to thermal agitation of the solution.\(^3\) The most poignant statement of this early era was made by Mulay and Mulay\(^4\) concerning the extensive work of Shchukarev:\(^5\) 

"...after finding that the phenomena of the action of a magnetic field on chemical reactions (were) more complicated than he had originally suspected, and that they were too complex for individual observation, he decided to give up his study of the phenomena and to retract his former statements."

Recently, due to extensive work with chemically induced dynamic nuclear polarization (CIDNP),\(^6\) a viable theory has appeared to explain magnetic field effects.\(^7\) This report will present a review of the theory behind high and low field magnetic effects on chemical processes in solution. Specific examples of these effects on neutral radicals, radical ions, and chemiluminescence reactions will be expounded.

**Theory of Magnetic Field Effects on Chemical Reactions.** The basic premise of the theory of magnetic field effects is that the reactivity of radical pairs depends upon the spin states of their electrons and nuclei. This is quite remarkable since these interactions are of the order of 10–20 gauss (\(\sim 10^{-2}\) cm\(^{-1}\); \(\sim 10^{-6}\) kcal/mol). These small energy differences clearly cannot be the source of any equilibrium, electronic, or product distribution effects, which all involve activation energies of 0.5–50 kcal/mol. We could realize this effect if the spin state of the system affected the frequency factor, \(A\), in Eq. 1, where \(A\) is the probability that a collision will produce a bond.

\[
k(\text{sec}^{-1}) = A \exp \left( -\frac{E_a}{RT} \right)
\]

To explain this effect, consider the homolysis of a bond in the molecule A–B to give a pair of doublets \(^2\!A^\text{'}\) and \(^2\!B^\text{'}\). If AB was initially in the singlet state (electron spins paired – Pauli Principle), the spins of the radicals will still be 180° out of phase (see Figure 1). If there is no perturbation of the system the electrons will remain correlated in the overall singlet state \(^1(2A'\cdots 2B')\). However, the radicals are 6 – 7\(\AA\) apart in the solvent cage. At this distance the electron exchange integral, \(J\), is very small. A spin flip may easily occur to form the triplet phased radical pair \(^3(2A'\cdots 2B')\). Diffusion from the solvent cage may occur from either the singlet or triplet phased pair. Eventually, each radical will combine randomly with another radical...Since there are three possible triplet orientations compared to one singlet, we expect to see a statistical average of 3:1 triplet to singlet. This is homogeneous recombination. In juxtaposition, the probability of the radicals re-encountering each other in the solvent cage is very high.\(^10\)–\(^12\) If they re-encounter, they may form a bond, i.e. geminate recombination to give the cage product. The bond will form, however, only if the radicals are singlet phased.\(^10\) Therefore, the rate of recombination is strongly affected by the spin state.
The singlet phased state will manifest a larger frequency factor, \( A \), in Eq. 1 (but not \( E_a \)) than the triplet.

![Diagram of singlet, mixed, and triplet states](image)

If a mechanism exists which can promote singlet to triplet transitions a decrease in the geminate product is expected. Magnetic field effects arise from just such a mechanism. In the singlet state the spin vectors of electrons (1) and (2) are \( S_1 \) and \( S_2 \). The spin vectors possess values of \( \beta(\pm \frac{1}{2}) \) and \( \alpha(-\frac{1}{2}) \) and precess along the magnetic field axis \( B_z \) (Figure 1).

In the singlet state, \( S_1 \) and \( S_2 \) point in opposite directions and are always 180° out of phase. If the precession frequencies of the two spins differ by \( \Delta \omega \) the time for the singlet-triplet rephasing is of the order of \( \pi/\omega \). The difference, \( \Delta \omega \), is due to different local fields which the spins experience. Spin-orbit coupling and hyperfine coupling at the different radical centers cause this difference. For a system of two electrons, 1 and 2, with differing g-factors and hyperfine coupling constants, \( a \), the difference in precessional rates, \( \Delta \omega \), is:

\[
\Delta \omega \overset{\approx}{=} \Delta g \beta B_2 \hbar^{-1} \pm (a_1 - a_2) I
\]

For radicals with differing \( \Delta g \)-values, the difference of the precession frequencies is \( \Delta \omega \overset{\approx}{=} (g_1 \beta B - g_2 \beta B)/\hbar \) where \( \beta \) is the Bohr magneton and \( g_1 \) and \( g_2 \) are the two g-values. To rephase the spins in a 100 kG field with \( \Delta g \overset{\approx}{=} 10^{-3} \) (typical of organic radicals) a time of \( 3 \times 10^{-8} \) sec is required. This is comparable to cage lifetime.

The effect of the magnetic field on radical reactions can now be predicted. At high field strengths (approximately 1kG) the \( \Delta g \) effect predominates.\(^{13}\) As the field increases, the precession frequency, \( \Delta \omega \), increases and the rephasing time \( \pi/\omega \) decreases. At low field strengths (100-1000 gauss) the nuclear hyperfine interactions control the rephasing process (Eq. 2). When no external magnetic field, \( B_z \), is present, the three triplet levels are degenerate. Transitions due to spin-orbit coupling or hyperfine interactions, \( B_{x,y} \), will occur with equal probability to all three states (\( T_0, T_\pm \))(Figure 2). When the field is applied, the degeneracy is lifted.
The higher the applied field, the more the levels are separated (Figure 3). Since the probability of transitions between two levels depends inversely on their difference in energies, transitions to both the $T_+$ and $T_-$ levels decrease in a magnetic field.

Ipsa facto, the yield of cage products should be increased in the presence of a magnetic field. As the applied field increases, however, a decrease in the cage product yield should begin because the field can more effectively promote the $S-T_0$ transition due to the $\Delta g$ effect (Figure 4).

**Figure 3.** $B_{1/2}$ is the field strength at which the magnetic effect is half its maximum value (vide infra).

With the advent of high speed computers, many excellent, quantitative treatments of these effects have appeared.

briefly, to treat these systems, a statistically based model of diffusion is inserted into an
analytical expression of the initial energetics of the species, exchange interactions, and reaction rates. The diffusion model developed by Noyes is coupled with the stochastic Liouville equation. An expansion series of this relationship provides solutions with an accuracy of the order of a percent.

**Magnetic Field Effects on Radical Ions.** Recent advances in nanosecond laser spectroscopy has allowed the direct observation of magnetic field effects within the lifetime of the radical ion pair. These time resolved experiments have shown that magnetic field phenomena can serve as sensitive probes of the energetics of many photochemical and chemiluminescence reactions. Direct effects on product distribution have also been demonstrated.

Time-dependent field effects on geminate recombination in polar solvents have been extensively studied. The fluorescence quenching of an aromatic acceptor (A) in its excited singlet state, by an appropriate donor (D), leads to a singlet radical ion pair. A general mechanism is presented in Scheme I. Internal conversion to the singlet ground state may occur, but because of its large exothermicity in polar solvents, the reaction is expected to be slow. This has been shown recently for the pyrene (1) + N,N-dimethylaniline (2) system. The singlet phased radical ion pair may then annihilate in the solvent cage to yield the excited singlet state of the aromatic hydrocarbon which may fluoresce. If inter-

![Scheme I](image)

system crossing to the triplet occurs rapidly from the radical ion pair (due to hyperfine interactions available -HFI), the triplet excited state of A can be formed (Scheme I). Delayed fluorescence may now occur if ³A encounters another ³A (Eq. 3).

\[ ³A + ³A \rightarrow ¹A + A \rightarrow \text{light} \]

Weller et al. generated singlet phased radical ion pairs via rapid photoinduced electron transfer. For the system pyrene (1) + 3,5-dimethoxy-N,N-dimethylaniline (3), recombination from the radical ions is energetically allowed to the triplet excited state but not the singlet excited state (Scheme II).
The recombination can be followed spectroscopically as delayed fluorescence due to triplet-triplet annihilation of \( ^31^* + ^31^* \) on the nanosecond time scale. The system has been resolved into a fast geminate (\( \sim 10 \) ns) and a slow homogeneous (\( \sim 1000 \) ns) process. The fast geminate recombination entails initial separation of the radical ions and then fast re-encounter still within the solvent cage. This process is strongly influenced by the solvent medium.\(^{18}\) The less viscous the solvent, the more likely the radical ions may encounter members of other pairs and recombine. In the slow homogeneous phase of the reaction, higher triplet to singlet ratios are observed compared to the fast phase. Random spin alignment in the slow phase accounts for this observation; 75% of the encounters are in the triplet state while 25% are in the singlet state. In the fast phase of the reaction, triplet products are also observed.\(^{10,12}\) Since the radical ion pairs are generated from singlet precursors, a spin flip must occur in order to observe triplet products. The rapid change of the electron spin multiplicity can be induced by hyperfine interactions with the nuclear spin.\(^{24}\)

The existence of the hyperfine mechanism in radical pairs has been demonstrated in many systems by electron and nuclear spin polarization in ESR and CIDNP spectra.\(^{6d}\) Magnetic field effects at the nanosecond time scale, however, premit the most direct evidence for this mechanism. Since a magnetic field lifts the degeneracy of the \( T_o \) and \( T_+ \) states, the \( S \rightarrow T_+ \) transition probability is reduced. This results in a lowering of the overall singlet to triplet transition probability and hence of the triplet yield. Weller, et al., observed an 80% decrease in the yield of fast triplet products at fields up to 500 G compared to its zero field value. This observation supports their conclusion that formation of fast triplet products occurs via hyperfine interactions in the radical pair.

Further evidence for the importance of hyperfine interactions was presented by Werner, Staerk, and Weller.\(^{18}\) Theoretical and experimental studies have shown that the field strength at which the magnetic effect takes half its maximum value \( (B_k) \), (see Figure 4), for geminate triplet yield, is nearly independent of the diffusion, recombination rate, and spin motion of radical pairs in solution.\(^{26-28}\) Changes in \( B_k \) arise solely from changes in the hyperfine coupling constants of the radical pair.\(^{29}\) Werner, et al., utilized this fact by replacing their donor dimethylaniline (2) with dimethoxy-dimethylaniline (3). Due to the electron donating effect of the methoxy groups in 3, the coupling constant of the nitrogen is smaller than in 2. This should lead to a smaller \( B_k \) for the \( 1/3 \) system. A \( B_k \) of 55 G is found for the \( 1/2 \) system. As expected, the value for the \( 1/3 \) system is lower, \( B_k = 45 \) G.

The second half of Equation 2 can be modified to include changes from differing isotopic compositions. The hyperfine coupling effect then becomes:
\[
\text{hyperfine effect} \propto \sum_{i} A_i S_i I_i + \sum_{j} A_j S_j I_j
\]  
(4)

where \( A = \frac{4\pi}{3g\beta_n^2\beta_p^2} \) and \( S_1 \) and \( S_2 \) denote different isotopic interaction of two unpaired electrons with the nuclear moments \( I \) of radicals 1 and 2. From Eq. 4, we can expect a change in \( B_\perp \) when the isotopic composition is changed. Werner has found this to be true. When proceeding from \( \frac{1}{2} \) to \( \frac{1-d_{10}}{2} - d_{11} \) the \( B_\perp \) value is reduced by a factor of 2. A quantitative theory of this effect is presented by Haberkorn.\(^{14}\) Experimental data is also presented. Bube, Haberkorn, and Michel-Beyerle\(^{20}\) examined the magnetic field effect upon deuteration of anthracene (4) with \( N,N \)-diethyl-aniline (5) as donor in acetonitrile. Table 1 presents the pertinent values for the different nuclei.

<table>
<thead>
<tr>
<th>H</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>( \frac{1}{2} )</td>
</tr>
<tr>
<td>A</td>
<td>5.585</td>
</tr>
<tr>
<td>( B_\perp )</td>
<td>75( \pm )3G ((C_{14}H_{10}))</td>
</tr>
</tbody>
</table>

As a result, the half-width field, \( B_\perp \), decreased by \( \sim 17\% \) for the deuterated species.

Such isotope effects confirm the role of the hyperfine mechanism in spin-selective radical ion reactions. Recently, these effects have been used for isotope enrichment. An increase in the \( ^{13}\)C/\(^{12}\)C ratio has been observed in the photolysis of aromatic ketones and peroxides.\(^{31}\)

Spin-state dependence of recombination of radical ions formed initially in the triplet state show predictable results analogous to the singlet phased systems.\(^{32}\) Electron transfer from DABCO (diazabicyclooctane) to triplet fluorenone (6), results in the triplet phased radical ion pair,\(^{33}\) (Scheme III):\(^{32}\)
Such reactions via electron transfer have recently received considerable attention from the chemical and biochemical communities. Faulkner, et al., have done extensive work on charged ions generated electrochemically in solution. When anthracene (4) radical cations and anions, A\(^+\) and A\(^-\), generated by electrolysis at a single microelectrode, diffuse together, electron transfer occurs. This leads to \(^{3}\text{A*} + \text{A}\). Two such excited triplet molecules may encounter each other. Annihilation generates the excited singlet anthracene molecule. The excited singlet molecule may now relax to the ground state and emit a photon in the process. The appearance of light by this redox mechanism is referred to as electrogenerated chemiluminescence (ECL). The process can be summarized as:

\[
\begin{align*}
\text{reduction:} & \quad A + e^- \rightarrow A^- \\
\text{oxidation:} & \quad A - e^- \rightarrow A^+ \\
\text{electron transfer:} & \quad A^- + A^+ \rightarrow ^{3}\text{A}^* + \text{A} \\
\text{triplet-triplet annihilation:} & \quad ^{3}\text{A}^* + ^{3}\text{A}^* \rightarrow ^{1}\text{A}^* + ^{1}\text{A} \\
\text{fluorescence:} & \quad ^{1}\text{A}^* \rightarrow \text{A} + \text{light}
\end{align*}
\]

The magnetic field effect arises in the triplet-triplet annihilation step (TTA). When two triplets encounter each other, the overall spin state may be singlet, or quintet (±2,±1,0). The overall singlet phased pair can go on to produce the excited singlet state (and singlet ground state) of anthracene upon their first encounter. If, however, they are in the overall quintet state, their encounter will be unproductive. They may, however, rephase into the overall singlet under the influence of different hyperfine interactions (similar to two doublets, cf. second paragraph of this
Fluorescence is now permitted. In the presence of a magnetic field, this rephasing is inhibited since the five quintet orientations are no longer degenerate. In this way the field will inhibit the fluorescence yield. Numerous experimental observations of this effect have been reported.\textsuperscript{36,37} However, a reversal of this effect was noted upon the addition of doublets (radical ions). These results suggest a competition between quenching by doublets and TTA.\textsuperscript{35,38} The mechanism in Scheme IV can now be modified:

\[
\text{Scheme V}
\]

\[
\begin{align*}
^2\text{Ac}^* \ldots ^2\text{D}^+ & \quad \rightarrow \quad ^3\text{Ac}^* + ^1\text{D} \\
+ ^3\text{Ac}^* & \quad \downarrow \\
^1\text{Ac}^* & \quad \rightarrow \quad \text{light} + ^1\text{Ac}
\end{align*}
\]

where Ac and D represent an appropriate acceptor and donor, respectively: R is a radical ion, generated in situ, that can intercept the triplet before it annihilates (the fluorescence yield is then reduced).

If it is energetically feasible, the excited singlet state of the emitting species may be formed directly from the electron transfer step.\textsuperscript{39} Faulkner has labelled this mechanism the S-route while triplet-triplet annihilation is the T-route. This leads to a delineation of the magnetic field effects in ECL. For an energy sufficient system, S-route, we expect to see no magnetic field effect while for an energy deficient system, T-route, we expect an increase in the fluorescence yield in a magnetic field. We can expect no effect for S-route systems presumably because intersystem crossing to the triplet phased radical ion pair is slow compared to formation of $^1\text{A}^*$ by electron transfer. This delineation has been verified experimentally\textsuperscript{34b} and theoretically.\textsuperscript{40}

This interpretation of ECL has unfortunately exposed some inconsistencies in the theory of ECL or magnetic field effects. Faulkner and Morris,\textsuperscript{40,41} have examined various systems to determine the generality of the S-route and T-route systems. The fluoranthene (7) and tri-p-tolylamine (8) system was found to be the archetypical T-route example. They found a linear relationship between ECL intensity and radical ion annihilation, and a magnetic field enhanced fluorescence. The thianthrene (9)/2,5-diphenyl-1,3,4-oxadiazole (10) system was known to be an energy sufficient system.\textsuperscript{42} It shows no magnetic field effect.
yet exhibited T-route kinetics. Morris$^{40}$ introduces the Marcus theory of electron transfer$^{43}$ as an explanation for the anomalous kinetic data. No satisfactory theory can explain the lack of a magnetic field effect.

The recent work by Faulkner and Morris, demonstrates that further investigation is needed into the magnetic field effects on ECL reactions. For ECL, magnetic field effects should not be used as the sole diagnostic tool. However, for other light producing reactions, magnetic field effects can easily serve as a sensitive probe for the reaction dynamics.

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17. The mathematics are quite rigorous and very involved. For a well presented treatment, see Haberkorn, ref. 14c.
35. For instance, see: Ref. 34b and references cited therein.
SYNTHETIC APPROACHES TO BIOTIN

Reported by Jack Muskopf

The vitamin biotin has been of interest to biologists, nutritionists, and chemists for over eighty years. Recent disclosures of the importance of biotin in animal health and nutrition have fostered a renewed interest on the part of organic chemists to develop novel and more efficient syntheses of the vitamin. Currently, the only viable method for producing useful quantities of biotin is by chemical synthesis. This review will describe briefly the chemistry of biotin and will survey, in more detail, recent stereospecific syntheses.

Isolation and Identification. In 1935, Kögl\(^1\) reported the isolation of small amounts of a crystalline compound from egg yolk which promoted the growth of yeast. This compound, named biotin, was later found by György\(^3\) to be the same factor which cured and prevented the "egg-white" syndrome in rats.\(^4\)

The structure of biotin was elucidated in 1942 by du Vigneaud and co-workers, who based their conclusions on chemical transformations of the natural product.\(^5,6\) In 1943, Folkers\(^7,8\) reported the first total synthesis of (+)-biotin (vide infra) which confirmed the earlier structural assignment. The relative configuration at the three contiguous asymmetric centers in biotin was determined in 1956 by X-ray crystallographic analysis.\(^9a\) Later X-ray studies established the absolute configuration shown in 1.\(^9b\)

![Biotin structure](image)

Biochemistry. Since the discovery that acetyl-CoA carboxylase contains the vitamin as a prosthetic group,\(^10\) biotin has been shown to be a co-factor for a number of carboxylases, transcarboxylases and decarboxylases.\(^11\) These enzymes require devalent metal ions, such as magnesium or manganese, and, in addition, the carboxylases are ATP-dependent and utilize bicarbonate as the source of CO\(_2\).

An understanding of the mode of action of biotin in carboxylase systems has been gained through model reactions, identification of intermediates, isotope exchange experiments, and investigation of the kinetics.\(^11,12\) For example, the enzyme acetyl-CoA carboxylase consists of three separate proteins: biotin carboxylase, carboxyl transferase, and the biotin-containing carboxyl carrier protein (CCP).\(^13\) Biotin, covalently attached as an amide through an ε-amino lysine residue of the CCP, migrates from the active site on biotin carboxylase to the active site on carboxyl transferase. The reactive group of the CCP-bound biotin is the ureido-1'-N.\(^14\) The overall process for the carboxylation of acetyl-CoA by acetyl-CoA carboxylase is shown in Eq. 1.
Biosynthesis. The biosynthesis of biotin from pimelic acid (2) has been studied and four of the five enzymatic steps have been resolved (Eq. 2).\(^{15}\) Pimelyl-CoA (3), synthesized from 2 by pimelyl-CoA synthetase in a reaction requiring Mg(II), CoASH and ATP, is condensed with L-alanine to form 4 in a step catalyzed by an enzyme requiring pyridoxal 5'-phosphate (PLP) as a coenzyme. Reductive amination of amino ketone 4 affords diamine 5, a reaction catalyzed by an aminotransferase which requires both PLP as a coenzyme and $\text{S}$-adenosyl-$\text{L}$-methionine (SAM) as the amine donor. Dethiobiotin (6) is formed from 5 in a reaction requiring ATP, CO\(_2\), Mg(II) and dethiobiotin synthetase.

\[
\text{R} \equiv \text{CH}\_2\text{CO}_2\text{H} \quad \text{ATP} \quad \text{ADP} + \text{P}\_i \quad \text{R} \equiv \text{CH}\_2\text{COSCoA} \quad \text{CH}_3\text{CHCO}_2\text{H} \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{NH}_2
\]

The conversion of 6 to biotin is poorly understood at present and has been the subject of a recent report by Parry.\(^{16}\) Results from the incorporation of isotopically labeled dethiobiotin into Aspergillus niger led to the conclusion that the introduction of sulfur takes place with the loss of one hydrogen at C-2 and C-5. The stereochemistry of hydrogen loss from C-2 of dethiobiotin and the order of functionalization of C-5 and C-2 have not been determined.

Total Synthesis of Biotin. Biotin has been the synthetic goal of many groups both in industrial and academic settings. Although this review is primarily concerned with the recent syntheses of biotin, a brief survey of the earlier approaches has been included for comparison.

Folkers and co-workers were the first to prepare synthetic samples of biotin, thereby confirming the structure of natural biotin.\(^{7}\) In a series of articles they described a nonstereospecific synthesis of (+)-biotin from L-cystine and chloroacetic acid via the key intermediate 7.\(^{8,17}\) The resolution of (+)-biotin from the racemic mixture was achieved in 64% yield by crystallization of the L(+)-arginine salt.\(^{17d}\)
In 1945 Grüssner and co-workers reported a non-stereospecific preparation of \((\pm)-\text{biotin}\) in low yield.\(^1\)\(^8\) The substituted tetrahydrothiophene \(^8\), originally prepared by von Schmid,\(^1\)\(^9\) was converted to the diester \(^9\) in four steps (Eq. 3). The important steps in the pathway from \(^9\) to \((\pm)-\text{biotin}\) were Curtius rearrangement of the corresponding diazide to give \(^10\) and addition of the fifth carbon to the sidechain using cyanide displacement of an alkyl bromide. Intermediates prepared after \(^9\) were not purified and any unwanted diastereomers formed were removed by crystallization.

\[
\begin{align*}
\begin{array}{c}
\text{CH}_2\text{O}_2\text{C} & \quad \text{4 steps} & \quad 30\% \\
\text{CH}_3\text{O}_2\text{C} & \quad \text{3 steps} & \quad \text{EtO}_2\text{CNH} \\
\text{(CH}_2\text{O}_2\text{C})_4\text{OCH}_3 & \quad \text{5 steps} & \quad \text{0.3\% from} \\
\end{array}
\end{align*}
\]

(Eq. 3)

About this same time Baker and co-workers\(^2\)\(^0\) reported a synthesis of \((\pm)-\text{biotin}\) that required no fractional crystallizations in order to separate diastereomers. From pimelic acid, they prepared the trans triacid \(^11\) with the stereochemistry at C-2 unspecified (Eq. 4). The trans urea acid \(^12\), available from \(^11\) by selective Curtius rearrangement, was epimerized and cyclized to the cis uracil \(^13\) by reaction with sodium acetate in acetic anhydride. Reaction of the anilide of \(^13\) with hydrazine followed by conversion to the azide led to the rearranged product \(^14\). Hydrolysis of \(^14\) and reaction with phosgene completed the synthesis of \((\pm)-\text{biotin}\) in an overall yield of 1.7% from pimelic acid.

\[
\begin{align*}
\begin{array}{c}
\text{CO}_2\text{H} & \quad \text{3 steps} & \quad 36\% \\
\text{CO}_2\text{H} & \quad \text{65\%} \\
\text{(CH}_2\text{O}_2\text{C})_4\text{CO}_2\text{H} & \quad \text{3 steps} & \quad \text{52\%} \\
\end{array}
\end{align*}
\]

(Eq. 4)

The need for a more practical synthesis of \((\pm)-\text{biotin}\) led Cheney and Piening to develop a synthetic route to the tetradehydrobiotin \(^15\),\(^2\)\(^1\)\(^a\)

At the time the authors did not report any method for the reduction of \(^15\) to the all-cis \((\pm)-\text{biotin}\), although a later patent describes the hydrogenation of \(^15\) in unspecified yield at 200°C and 2700 psi using a molybdenum trisulfide-alumina gel catalyst.\(^2\)\(^1\)\(^b\)
An industrial preparation patented in 1950 by Goldberg and Sternbach\textsuperscript{22} originates from \textit{meso}-diaminosuccinic acid, \textit{16}, which corresponds to the \textit{cis}-structure of the two nitrogens in biotin. Resolution of an intermediate sulfonium salt as a \textit{d}-camphorsulfonate permitted direct production of \textit{(+)}- and \textit{(-)}-biotin.

In recent years there has been an increase in the use of readily available carbohydrates as starting materials for the total synthesis of many different types of natural products.\textsuperscript{23} In 1975 Ohru and Emoto reported a stereospecific synthesis of \textit{(+)}-biotin from the bis isopropylidene mannofuranose \textit{17} (Eq. 5).\textsuperscript{24} The three chiral centers present in \textit{(+)}-biotin are already present in \textit{17}. The aldehyde \textit{18}, prepared in 3 steps from \textit{17}, was condensed with excess methyl 4-triphenylphosphoranylidene-2-butenoate, and the resulting diene ester was hydrolyzed after hydrogenation and subsequently reduced with sodium borohydride to give the diol \textit{19}. The reaction of the dimesylate of \textit{19} with sodium sulfide afforded a tetrahydrothiophene derivative which was hydrolyzed with 92% formic acid to diol \textit{20}. Preparation of the all-\textit{cis} diazide \textit{21} was accomplished by \textit{S}\textsubscript{N}2 displacement of the dimesylate of \textit{20} with sodium azide. Catalytic reduction followed by hydrolysis and reaction with phosgene gave \textit{(+)}-biotin.

\begin{equation}
\begin{array}{c}
\text{CHO} \\
\text{CH}_3\text{Ph}
\end{array} \quad \xrightarrow{4 \text{ steps}} \quad \begin{array}{c}
\text{OH} \\
\text{CH}_2\text{Ph}
\end{array}
\quad \text{(Equation 5)}
\end{equation}

A similar synthesis of \textit{(+)}-biotin was reported by Ogawa, Kawano and Matsui.\textsuperscript{25} The authors first prepared the imidazolone ring and left the closure of the tetrahydrothiophene ring for last (Eq. 6). This order is similar to what is believed to be the pathway of biosynthesis.
A stereospecific synthesis of (+)-biotin was achieved by Confalone and co-workers at Hoffmann-La Roche from the amino acid L(+)-cysteine (22 in Eq. 7). The reactive functionality in 22 was blocked by condensation with benzaldehyde and methyl chloroformate to give thiazoline 23. Selective reduction with diborane followed by Collins oxidation gave the aldehyde 24 which afforded the vinyl alcohol 25 upon reaction with vinyl magnesium bromide. This compound underwent Claisen rearrangement to trans olefin 26. Bromination of 26 with pyridinium hydrobromide perbromide in methanol gave bromo carbamate 27 in 47% yield which was hydrolyzed quantitatively to the amine hydrobromide 28.

Heating bromo amine hydrobromide 28 in acetic acid set up an equilibrium between 28 and 30 via the aziridine 29. Bromo amine 30 cyclized to the crystalline trans bromo lactam 31 in quantitative yield (Eq. 8).

Unfortunately, bromo lactam 31 gave only poor yields of the desired cis azide. Hydrogenation of the azide and hydrolysis of the lactam, followed by reaction with phosgene, produced the methyl ester of (+)-bisnorbiotin. The addition of two carbons to the sidechain was performed in the manner of Goldberg and Sternbach.

In a recent communication, Field reported a synthesis of (+)-biotin from methyl 6-oxohexanoate (32) which gives the vitamin in 7.2% overall yield. Its success depended upon both the easy resolution of intermediate nitro acid 33 or nitro ketone 37 and the virtually stereospecific catalytic hydrogenation of 39. Nitro acid 33 was prepared from 32 by
condensation with nitromethane, dehydration with magnesium sulfate, and addition of thioglycolic acid (Eq. 9). Fractional crystallization of the (+)-α-methylbenzylamine salt 34 in ethyl acetate gave the (S) enantiomer of 33 as required for the synthesis of (+)-biotin. Conversion of 34 to the dicyclohexyl amine salt 35 and esterification with phenol furnished the phenyl ester 36. Cyclization of 36 to nitro ketone 37 was effected by reaction with (-)-α-methylbenzylamine in ethyl acetate. Catalytic hydrogenation, followed by reaction with potassium cyanate and alkaline hydrolysis provided the bicyclic urea 38 which was acetylated and dehydrated to 39. Hydrogenation and hydrolysis of 39 afforded (+)-biotin.

\[
\begin{align*}
\text{CHO}-(\text{CH}_2)_4\text{CO}_2\text{CH}_3 & \rightarrow \text{RO} \quad \text{NO}_2 \quad \text{CO}_2\text{CH}_3 \rightarrow 75\% \quad \text{R} = (-)-\alpha-\text{MBA} \\
32 & \quad 33 \quad R = H \\
34 & \quad R = \text{MBA-α- (+)}H^+ \\
35 & \quad R = \text{HDCA}^+ \\
36 & \quad R = \phi \\
26\% \text{ from } 32
\end{align*}
\]

Confalone and co-workers have recently utilized an intramolecular \([3+2]\) cycloaddition of the olefinic nitrile oxide 40 in a stereospecific synthesis of amino alcohol 42 which was converted to (+)-biotin in five steps (Eq. 10). Amino alcohol 42 was formed by the stereospecific reduction of the cycloaddition adduct 41 with lithium aluminium hydride and converted to the anti oxime 43 via the urethane ketone. Beckman rearrangement of 43 afforded the all-cis bicyclic lactam 44 in low yield which was easily converted to (+)-biotin.

\[
\begin{align*}
\begin{array}{c}
\text{CHO}-(\text{CH}_2)_4\text{CO}_2\text{CH}_3 \\
\text{NH}_2 \\
\text{NH}
\end{array}
& \rightarrow
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{NH}_2 \\
\text{OH}
\end{array}
& \rightarrow
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{NH}_2 \\
\text{OH}
\end{array}
& \rightarrow
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{NH}_2 \\
\text{OH}
\end{array}
& \rightarrow
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{NH}_2 \\
\text{OH}
\end{array}
& \rightarrow
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{NH}_2 \\
\text{OH}
\end{array}
& \rightarrow
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{NH}_2 \\
\text{OH}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{40} & \rightarrow \text{41} & \rightarrow \text{42} \\
\text{43} & \rightarrow \text{44} & \rightarrow (+)-\text{biotin}
\end{align*}
\]
A total synthesis of (±)-biotin reported by Marquet and co-workers\textsuperscript{29} took advantage of the high stereoselectivity of the alkylation of chiral sulfoxides. Bory and Marquet had previously shown that methylation of the anions of six-membered cyclic sulfoxides occurred exclusively \textit{trans} to the S→O bond.\textsuperscript{30} They assumed correctly that this empirical rule would also be true for five-membered cyclic sulfoxides. The starting material was meso-dibromosuccinic acid (45) and, in the manner of Goldberg and Steinbach, they prepared the diacid 46 which was converted to the tetrahydrothiophene 47 in three steps (Eq. 11). The sulfide 47 was oxidized to the sulfoxide 48 with the S→O bond \textit{cis} to the hydrogens at C-3 and C-4 by reaction with sodium metaperiodate in aqueous methanol. The lithio derivative of 48 was alkylated smoothly with tert-butyl 5-iodopentanoate. Reduction of the product with titanium(III) chloride gave the benzylated derivative 49 which was hydrolyzed to (±)-biotin.

Marx and co-workers\textsuperscript{31} focused on the formation of the thienofuroxan ring system 54 and its reduction to 55 as a means of introducing the functionality about the tetrahydrothiophene ring of biotin (Eq. 12). The dinitro sulfide 52, formed in good yield from the conjugate addition of 2-nitroethanethiol (51) to methyl 7-nitro-6-heptenoate (50), furnished the thionofuroxan 54 under dehydrating conditions. Bis-nitrile oxide 53 is presumably an intermediate in the cyclization. The thienofuroxan 54 was reduced to ene diamide 55 by activated zinc in dimethoxyethane-tri-
fluoroacetic acid which afforded the cis urethane 56 by catalytic hydrogenation. (±)-Biotin was obtained from 56 by hydrolysis and reaction with phosgene.

Confalone and co-workers have reported a stereospecific synthesis of (±)-biotin which incorporates an efficient reduction of the thiophene derivative 60 producing the requisite all-cis conformation at C-2, C-3 and C-4 in the precursor 61 (Eq. 13). Thiophene 58 was prepared by reaction of the oxime of ketone 57 with hydrogen chloride. Cyclization to the mixed imido anhydride 59 afforded protection of the sidechain carboxyl group prior to Curtius rearrangement in methanol. The mixed diurethan was hydrogenated at 50°C and 1800 psi with 10% palladium on carbon as catalyst to the all-cis acid 61. The need for phosgene was obviated because hydrolysis of 61 in aqueous barium hydroxide furnished (±)-biotin directly. The overall yield of biotin from 57 was 37%.

Another approach to (±)-biotin developed by the Confalone group involves the stereospecific hydrogenation of 2,5-dihydrothiophene 63 to the all-cis tetrahydrothiophene 64 (Eq. 14). The acid 62, obtained from ketone 57 in 83% yield after six steps, underwent Curtius rearrangement to the imido urethane 63 which was hydrogenated to 64 by the same conditions used in the previous synthesis. Hydrolysis of 64 afforded (±)-biotin in 39% yield from 57.

A synthesis of (±)-biotin developed by Zavylov and co-workers concluded with the hydrogenation of the thiophene 66 to (±)-biotin in poor yield (Eq. 15). Bromo imidazolone 65 was prepared according to the
literature method of Dushinsky and Dolan.\textsuperscript{34} Reaction of 65 with potassium thioacetate followed by alkaline hydrolysis afforded 66 which was reduced to (±)-biotin in 10\% yield by reaction with triethylsilane in trifluoroacetic acid.

\begin{equation}
\text{CH}_3\text{CCH}_2\text{COEt} \xrightarrow{5 \text{ steps}} \text{AcN} \xrightarrow{2 \text{ steps}} \text{H}_2\text{N} \text{NN} \text{H} \xrightarrow{23\%} \text{R} \xrightarrow{13\%}
\end{equation}

(15)

In summary, a number of efficient and stereospecific syntheses of biotin have been reported since 1975. Novel reactions have been used in many cases to introduce the requisite asymmetry at C-2, C-3 and C-4. In addition, several of the recent approaches have the potential of being exploited industrially.

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STABLE HEXACOORDINATE ORGANOPHOSPHORUS COMPOUNDS

Reported by Stephen D. Harper

November 15, 1979

The ability of phosphorus to expand its octet has permitted the synthesis and characterization of stable compounds in which six atoms are bonded directly to a negatively charged phosphorus. This abstract shall review the chemistry of all such hexacoordinate species except those containing halogen ligands or possessing a zwitterionic structure.¹

Several synthetic routes to hexacoordinate phosphorus compounds have been developed. One common approach involves the reaction of a pentacoordinate species with an alcohol,²⁻⁷ phenol,³,⁶,⁸⁻¹³ or amine¹⁴ in the presence of base or with a metallosubstituted biphenyl.¹⁵ The phosphorane may have one or more leaving groups, in which case more than one ligand is added to the phosphorus. An example of this synthetic approach appears in Figure 1. Phosphorane 1 reacts with one equivalent of catechol to yield the hexacoordinate species 2.³ The dimethylamine liberated from the phosphorane serves as the base in this reaction and is incorporated as the counterion in the product.

**Figure 1**

Phosphoryl chlorides react with catechols in the presence of tertiary amines to yield tris(o-arylenedioxy)phosphate anions.¹⁶,¹⁷ Hexacoordinate compounds containing hydrogen directly attached to phosphorus are obtained upon reaction of (RO)₂PR' species with catechols and tertiary amines.¹⁸⁻²⁰

Many of the first hexacoordinate organophosphorus compounds to be isolated were formed in the reaction of bis(2,2'-biphenylene)phosphonium iodides with either 2,2'-dilithiobiphenyls²¹⁻²⁴ or arylenediolates.²⁵ Figure 2 illustrates a reaction of this type.²⁵

**Figure 2**
Other less extensively exploited routes to P(VI) species have also been described.\textsuperscript{26-28}

The structures of two hexacoordinate phosphorus compounds have been determined by X-ray crystallography.\textsuperscript{29,30} Only small deviations from an octahedral geometry were noted. These two compounds exhibit $^{31}\text{P}$ NMR chemical shifts considerably upfield from 85\% H$_3$PO$_4$ due to shielding of the negatively charged hypervalent phosphorus. This property has been very useful in determining whether other isolated species are also hexacoordinate.

The octahedral geometry about phosphorus creates a chiral center if the ligands are bidentate or non-equivalent. Hellwinkel separated the two enantiomers (5 and 6) of bis(2,2'-biphenylene)phosphonium tris(2,2'-biphenylene)phosphate via their methyl brucinium salts.\textsuperscript{21} Circular dichroism and electron absorption spectra were used to determine the absolute configuration.\textsuperscript{31} Optically active $\alpha$-hydroxy acids react with phosphoranes to yield diastereomeric mixtures of P(VI) species.\textsuperscript{4} The optically pure diastereomers epimerize in solution.\textsuperscript{32,33} Other aspects of hexacoordinate phosphorus stereochemistry have also been examined.\textsuperscript{11,23,24,34}

Hexacoordinate phosphorus compounds display a wide range of stabilities. Bis(2,2'-biphenylene)phosphonium tris(2,2'-biphenylene)phosphate is stable in boiling water\textsuperscript{15} and does not exchange labelled phosphorus between the counter ions up to 130\textdegree{}C.\textsuperscript{35} In general, the structural features of the ligands which enhance the stability of phosphoranes also increase the stability of P(VI) compounds. Bidentate ligands provide greater stability than do monodentate ligands. Hexaphenoxy\textsuperscript{12} and hexamethoxy\textsuperscript{7} phosphate anions have been observed by NMR, but have not been isolated. Five-membered rings are more readily introduced than are six-membered rings.\textsuperscript{2,4,25}

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The epoxidation of olefins with alkyl hydroperoxides in the presence of certain transition metals is well-known. Metals which are likely to be active catalysts must meet three criteria: they must be relatively small, highly charged atoms with at least some low-lying vacant d-orbitals; they must be stable under strongly oxidizing conditions; and they must be labile to substitution. Of the few metals that meet these requirements, V$^{5+}$ and Mo$^{6+}$ have received the majority of attention. V$^{5+}$ and Mo$^{6+}$ are almost always generated in situ by addition of VO(acetylacetonate)$_2$ or MO(CO)$_6$, and subsequent oxidation. This review deals with the development of olefin epoxidations employing alkyl hydroperoxides and these two metals.

Simple Olefins. In 1968, Gould, Hiatt, and Irwin$^2$ reported an extensive study on the epoxidation of cyclohexene with VO(acetylacetonate)$_2$ (VO(acac)$_2$) and tert-butyl hydroperoxide (TBHP), as a model for simple olefins. Their study shows the reaction rate to be linearly dependent on both the catalyst and olefin concentrations. The concentration of the TBHP, however, has a non-linear effect on the rate. At low peroxide concentrations the rate is apparently first order in peroxide, but at higher concentration it approaches a limiting value which is proportional to the catalyst concentration. The data are in good agreement with Eq. 1, which is based on the assumption that a 1:1 complex of the peroxide and the catalyst is responsible for the oxidation.

$$\text{rate} = \frac{k[V]_o}{(1/([P]K) + 1)}$$

where

$[V]_o$ = initial concentration of catalyst

$[P]$ = peroxide concentration

$K$ = association constant of the complex

$k$ = a proportionality constant

A plot of rate/$[P]$ vs. rate was linear and gave values for k and K at different temperatures. An Arrhenius plot gave the activation parameters $\Delta H^\ddagger = 12.7 \pm 0.4$ kcal/mol, and $\Delta S^\ddagger = -19.9 \pm 1.9$ eu. Added tert-butyl alcohol inhibited the reaction drastically, and the authors speculated that the alcohol was forming one or more inactive complexes with the vanadium. The kinetic data of the inhibited reaction are well modeled by Eq. 2.

$$\text{rate} = \frac{k[V]_o}{1/([P]K[K_1'[A] + K_1[A]^2 + 1]) + 1}$$

where

$[A]$ = concentration of alcohol

$K_1$ = association constant for VA

$K_1'$ = association constant for VA$_2$
The association constants were determined to be $K_i = 119 \text{ M}^{-1}$ and $K_i' = 2.1 \times 10^4 \text{ M}^{-2}$.

Most importantly, their data indicate that 1 molecule each of peroxide, catalyst, and olefin are involved in the transition state. Since a ter-molecular transition state is unlikely, the transition state probably involves the olefin and a peroxide-catalyst complex.

Linden and Farona$^3$ have reported that improved yields in the epoxidation of some simple olefins result when the vanadium catalyst is incorporated on an insoluble polymer. For example, the oxidation of cyclohexene to its oxide with the polymer-bound catalyst occurs in 74% yield (on peroxide consumed) at 80°C, whereas the homogenous catalyst affords only 10-12% of the epoxide. Sharpless et al.$^4$ have found that addition of small amounts of anhydrous disodium hydrogen phosphate (Na$_2$HPO$_4$) reduces the amount of diols formed by ring opening of the epoxides, and thus improves the yield.

**Peroxomolybdenum Compounds as Possible Intermediates.** The discovery by Mimoun, de Roch, and Sajus$^6$ that 1 and similar peroxomolybdenum compounds stoichiometrically epoxidize olefins led them to speculate that a similar compound was involved in the molybdenum-catalyzed oxidation with TBHP.

![Diagram](image_url)

\[ 1 \quad (\text{HMPA} = \text{hexamethylphosphoramide}) \]

Chong and Sharpless$^7$ have investigated the possibility of such an intermediate but were unable to isolate any peroxomolybdenum compounds such as 1 when HMPA was added at different stages of the reaction. They performed an $^{18}$O labeling experiment which demonstrated that a compound such as 1 is not involved in the epoxidation. Since the oxo-oxygen of the catalyst readily exchanges with $H_2^{18}O$, these workers carried out the epoxidation in the presence of labeled water, and the results in Scheme I

**Scheme I**

\[ \begin{array}{c}
\text{O} \quad \text{H} \\
\text{Mo} \\
\text{O} \quad \text{HMPA} \\
\end{array} \]

\[ + \quad \text{TBHP} \quad \text{dioxane, } H_2O^* \quad \text{VO(acac)} \quad 25^\circ C, \quad 12^h \\
\text{no label} \quad \text{no label} \\
\]

\[ \begin{array}{c}
\text{O} \quad \text{H} \\
\text{H} \quad \text{H} \\
\end{array} \quad \text{no label} \quad \text{74% incorporation} \]

\[ \begin{array}{c}
\text{O} \quad \text{H} \\
\text{H} \quad \text{H} \quad \text{H} \\
\end{array} \quad \text{same as above} \quad \text{68% incorporation} \]
were obtained. The two mechanisms which would be likely to produce the peroxy species (Scheme 27) both would lead to the incorporation of labeled oxygen in the reaction products. The first involves oxo-oxygen incorporation in the peroxy linkage, and the second involves incorporation in the tert-butyl alcohol. Although incorporation of $^{18}O$ into the tert-butyl alcohol occurred in the Mo(CO)$_6$-catalyzed reaction, tert-butyl alcohol itself was shown to exchange extensively under the conditions of the reaction. Since the oxo-oxygen is not involved in the epoxidation, the alkyl peroxide must be directly involved in the epoxidation step. An assumption inherent in this conclusion is that the molybdenum and vanadium-catalyzed oxidations have similar mechanisms. This may not be the case since the reactivity of some olefins is significantly different with the two catalysts.

**Scheme 2**

Dienes and Substituted Olefins. Sheng and Zajacek$^8$ have reported the epoxidation of a number of dienes and substituted olefins. The reactivity of non-conjugated dienes is similar to that of mono-olefins, in that the reactivity increases with increasing substitution. For example, oxidation of 1,4-hexadiene gives predominantly the internal epoxide. The ratio of internal epoxide to external epoxide was 11:1 from the oxidation of cis-1,4-hexadiene with cumene hydroperoxide and Mo(CO)$_6$, and the ratio from the trans isomer was 6:1. For conjugated dienes the reactivity is diminished slightly, but the preference for reaction at the more substituted site is retained. Thus, isoprene is epoxidized 4 times faster at the more substituted double bond than at the less substituted one with TBHP and Mo(CO)$_6$. Epoxidation of allylic compounds, such as allylic ethers and halides, is slower and less efficient than that of the non-conjugated dienes, probably owing to the inductive properties of the electronegative allylic substituent. For example, epoxidation of allyl ethyl ether proceeded in only 77% yield, while the mono-epoxide of cis-1,4-hexadiene was obtained in 90% yield. A ratio of olefin to hydroperoxide greater than 2:1 increased the yields of the epoxides of the allylic compounds.

Allylic alcohols, on the other hand, displayed a significantly different pattern of reactivity. This special reactivity has been the object of much interest.

**Epoxidation of Allylic Alcohols.** With other olefinic compounds, the molybdenum catalyst gave higher yields than the vanadium catalyst, but the reverse was true for allylic alcohols.$^8$ The vanadium-catalyzed epoxidation of allyl alcohol is much faster than that of simple olefins, and the reaction could even be carried out with an excess of hydroperoxide, in contrast to other allylic compounds. This exceptional reactivity has been attributed to a complexation of the alcohol with the activated catalyst.
Chong and Sharpless\textsuperscript{7} have suggested some possible transition states for the metal-catalyzed epoxidation, which are shown in Scheme 3. Complexation with the allylic alcohol is geometrically impossible in 2 and 3, whereas 4 and 5 seem to be ideally situated for the complexation. For this reason, they suggest that the peroxide is coordinated to the vanadium at the oxygen furthest from the alkyl group.

\textbf{Scheme 3}

\begin{align*}
\text{2} & \quad \text{3} \\
\text{4} & \quad \text{5}
\end{align*}

Sharpless and Michaelson\textsuperscript{9} have demonstrated that the increased reactivity of allylic alcohols can be utilized to effect selective oxidations which might be difficult to realize with other reagents. Some examples are shown in Table 1.\textsuperscript{9}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\text{Reagent} & \text{% Yield} \\
\hline
\text{VO(acac)}_2 \quad \text{TBHP} & 98 \\
\text{VO(acac)}_2 \quad \text{TBHP} & 95 \\
\text{VO(acac)}_2 \quad \text{TBHP} & >95 \\
\text{Mo(CO)}_4 \quad \text{TBHP} & 98 \\
\hline
\end{tabular}
\caption{Table 1}
\end{table}

The reaction of the homo-allyl alcohol 6 is also faster than cyclohexene, and, furthermore, is stereospecific. The rate acceleration can be seen in Table 2.\textsuperscript{9}
In the epoxidation of cis-cycloalk-2-enols, Dehnel and Whitman\textsuperscript{10} and Itoh, Jitsukawa, Kaneda, and Teranishi\textsuperscript{11} have reported that the VO(acac)$_2$-catalyzed epoxidations display higher cis selectivity than those of peracids. Most notably, the vanadium-catalyzed reaction gives cis stereochemistry for cis-cycloalkenols with 6-9 members, while the peracid oxidation shifts from cis preference with 6-membered rings to a trans preference with 8- and 9-membered rings.\textsuperscript{10,11} The conformationally fixed cis- and trans-5-tert-butylcylohex-2-enols were epoxidized with the vanadium catalyst.\textsuperscript{10,11} The pseudo-axial alcohol underwent epoxidation 34 times faster\textsuperscript{10} and with greater cis-stereoselectivity\textsuperscript{11} than the pseudo-equatorial isomer. Oxidation of the alcohol to an unsaturated ketone becomes the dominant reaction of the pseudo-equatorial case.\textsuperscript{10,11}

In contrast, the peracid oxidation showed higher selectivity in the pseudo-equatorial case.\textsuperscript{11} Accordingly, Teranishi \textit{et al.} suggested that the preferred transition state geometry for the peracid oxidation is similar to that of the pseudo-equatorial alcohol, while the transition state geometry for the vanadium-catalyzed reaction is similar to the pseudo-axial alcohol.

Teranishi \textit{et al.}\textsuperscript{11} have also reported the epoxidation of some cyclic trans-allylic alcohols, and the vanadium-catalyzed oxidation retained its preference for cis stereoselectivity. A notable exception is 1R*,2R*-cyclooct-2-enol, which gives the trans epoxy alcohol.

In the oxidation of some acyclic allylic alcohols, Rossiter, Verhoeven, and Sharpless\textsuperscript{12} have demonstrated that the vanadium and molybdenum catalysts offer improved stereoselectivity over peracids (Table 3).\textsuperscript{12}

(continued on next page)
Table 3. Yields of Erythro Epoxy Alcohol Formed by Various Methods

<table>
<thead>
<tr>
<th></th>
<th>MCBPA†</th>
<th>Mo⁺⁶/TBHP*</th>
<th>V⁺⁵/TBHP*</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>39</td>
<td>58</td>
<td>80 (typical)</td>
</tr>
<tr>
<td><img src="image2" alt="Structure" /></td>
<td>59</td>
<td>84</td>
<td>98 (typical)</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>36</td>
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<td>71</td>
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<td>5</td>
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<tr>
<td><img src="image5" alt="Structure" /></td>
<td>5</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>

†MCBPA = m-chloroperbenzoic acid  
*TBHP = tert-butyl hydroperoxide

Furthermore, the pattern of reactivity is dependent on the olefin substitution. To account for the effect of substitution on the relative yields of the threo and erythro isomers, they have suggested optimal double bond-alcohol dihedral angles for the epoxidations with VO(acac)₂ and tert-butyl hydroperoxide, and m-chloroperbenzoic acid (Table 4).

Table 4. Optimal Partial Geometries for Epoxidation

<table>
<thead>
<tr>
<th>For threo</th>
<th>For erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image6" alt="Diagram" /></td>
<td><img src="image7" alt="Diagram" /></td>
</tr>
<tr>
<td><img src="image8" alt="Diagram" /></td>
<td><img src="image9" alt="Diagram" /></td>
</tr>
</tbody>
</table>

For V⁺⁵/tert-butyl hydroperoxide  
For peracids
For the epoxidation with V$^{4+}$ and tert-butyl hydroperoxide, alcohols 7–9 have significant steric interactions in the threo transition state (12); thus the reaction occurs predominantly via the erythro transition state (13). Alcohols 10 and 11 have R$_1$ and R$_3$ groups which destabilize the erythro transition state (13). These transition state models predict greater stereoselectivity for the V$^{4+}$ and tert-butyl hydroperoxide oxidation of alcohols 7–9 and greater selectivity for the peracid oxidation of alcohols 10 and 11.

Tanaka, Yamamoto, and Nozaki$^{13}$ have shown this stereoselectivity to be synthetically useful in the conversion of the bis-allylic alcohol 16 to the farnesol homologue 17. These compounds are intermediates in the synthesis of dl-C$_{18}$ Cecropia juvenile hormone from farnesol.$^{14}$

The stereoselective $S_N'$ alkylation of 16, which was previously accomplished by non-stereoselective methods, was carried out as shown in Scheme 4.$^{13}$

Scheme 4

The enhanced reactivity of allylic alcohols and the likelihood that they are coordinated to the catalyst during epoxidation led some researchers to investigate the possibility that asymmetric induction might be achieved by using a catalyst with a chiral ligand. Michaelson, Palermo, and Sharpless$^{15}$ employed chiral hydroxamic acids as the ligand. Although molybdenum complexes gave poor results (<2% enantiomeric excess), vanadium complexes generated in situ have induced chirality up to 80% of the
theoretical limit in the products of reaction.\textsuperscript{16} This represents a substantial improvement over the 25\% e.e. reported by Wynberg \textit{et al.}\textsuperscript{17} with chiral phase transfer agents. Sharpless \textit{et al.}\textsuperscript{15} suggest \textsuperscript{18} as a possible intermediate for the reaction (Scheme V).

\textbf{Scheme V}

\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{OH} & \quad \text{OH}
\end{align*}

\begin{align*}
\text{1\% V}^+\text{s, 2 tert-butyl hydroperoxide} & \quad \text{Ph-CH_3, -20°C, 5 days} \\
\text{Ph} & \quad \text{Ph}
\end{align*}

\begin{align*}
\text{95\% (80\% e.e.)}
\end{align*}

It is evident that vanadium- and molybdenum-catalyzed epoxidations with alkyl hydroperoxides can be useful in synthesis. For many cases the reaction proceeds with greater chemo- and stereoselectivity and in better yield than epoxidation with peroxy acids.

\section*{BIBLIOGRAPHY}

DETECTION AND CHARACTERIZATION OF CERTAIN CARBON DIRADICALS
VIA ESR AND CIDNP

Reported by G. H. Slocum November 26, 1979

Carbon diradicals have been proposed as reactive intermediates in chemical reactions for some time. The past decade has seen the development of electron spin resonance (ESR) and chemically induced dynamic nuclear polarization (CIDNP) as probes for examining these short-lived intermediates. This report will deal with the application of these two techniques to the study of certain diradicals in which the two radical sites are on carbons separated by a carbon chain.

The basic principles of the application of ESR to organic radicals are presented in a monograph by Wertz and Bolton.1 In a diradical, in which the radical sites are separated by a long saturated chain, the unpaired electrons will not be coupled to each other and the ESR spectrum observed will be that of two isolated carbon monoradicals. In most diradicals, however, there is considerable interaction, either through bond or through space, and spectra of triplet species are observed. ESR spectra of triplets are generally obtained by generating the diradical in a rigid matrix which serves to isolate the triplet species, inhibiting intermolecular reaction. This method increases the lifetime of the diradical intermediate and allows a measurable steady state concentration to exist. While well-resolved ESR spectra of several diradicals have been obtained, the properties of diradicals at the low temperatures usually used in matrix formation may differ significantly from those in solution phase at normal temperatures.

The simplest carbon diradical is the 1,3-diradical, trimethylene, which has been proposed2 as an intermediate in the stereoisomerization of cyclopropane. Although the extremely short lifetime of this diradical has prevented the observation of its ESR spectrum, the spectra of related 1,3-diradicals have been recorded. Closs3 has reported the spectrum of the diradical produced by the photolysis of 2,3-diazabicyclo[2.2.1]heptene-2, 1, in a cyclohexane matrix at 5.5K. The splitting pattern in the spectrum matched that predicted for a triplet species randomly oriented in a rigid matrix. The D value from the spectrum was $|D| = 0.084$ cm$^{-1}$ and the E value was $|E| = 0.002$ cm$^{-1}$. These are in reasonable agreement with the D and E values predicted for a diradical with specified geometry, represented by structure 2. The D and E values are a measure of the distance between and orientation of the two radical sites. In order to exclude the possibility that the spectrum arose from a diradical derived from the bicyclic compound, 1, by cleavage of a single C-N bond, Closs examined the spectrum of the diradical from 1-d$_6$. The narrowing of the lines in the ESR spectrum was attributed to the lower hyperfine coupling of deuterium, and eliminated the possibility of coupling with nitrogen nuclei. The spectrum persisted down to 1.3K, suggesting that diradical 2 has a triplet ground state.
Photolysis of tricyclic azo compound 3 at 77K produced an ESR spectrum attributed\(^4\) to diradical 4. This spectrum also exhibited the splitting pattern expected for a randomly oriented triplet species in a rigid matrix. The D and E values obtained in the spectrum were in reasonable agreement with those expected for the proposed structure.

A 1,3-diradical of theoretical interest is trimethylenemethane, 5. Dowd\(^5\) reviewed the literature of the ESR of 5 in 1972. Berson\(^6\) has discussed the chemistry of ethano-bridged trimethylene methane analogs, 6, and cites some of the more recent ESR results. Both trimethylenemethane and its bridge analog exhibit triplet spectra. Irradiation of a single crystal of 3-methylenecyclobutanone, 7, at 77K in an ESR spectrometer produced a spectrum consisting of a doublet of septets,\(^7\) consistent with a triplet species regularly oriented in a rigid matrix with six equivalent protons.

Considerable effort has been expended to establish that the spectrum arises from a ground state triplet, in agreement with theoretical predictions, rather than from a low-lying, thermally populated triplet. One approach used to distinguish these two alternatives is to study the relationship of the intensity of the ESR signal as a function of temperature. The Curie law predicts that the intensity of the ESR signal for a ground state triplet will be inversely proportional to the absolute temperature. A study\(^8\) of the temperature-intensity data from the irradiation of methylenecyclobutanone, 7, in a methylcyclohexane glass over the range of 20 to 80K indicated that trimethylenemethane was indeed a ground state triplet. The temperature dependence of the intensity of the ESR spectra of the bridged analogs\(^9\) led to the conclusion that they, too, have triplet ground states.
This method must be used with care, however. Another diradical predicted to have a triplet ground state is 1,8-naphthoquinodimethane, 8. The temperature dependence of the intensities of the ESR spectra of diradicals 8, 10, and 12 have been studied.\textsuperscript{10-12} The ESR intensities for these radicals were not found to vary inversely over certain ranges. Instead those intensities were found to vary according to the following equation:

\[
I = \frac{\left(\exp - \Delta E/RT\right)/(1 + 3\exp - \Delta E/RT)}{T}
\]

In this equation, \(I\) is the intensity, \(T\) is the absolute temperature, and \(\Delta E\) is the energy difference between a singlet ground state and a low lying triplet state. Analyses of the different temperature-intensity data predict \(\Delta E\) between singlet ground states and triplet excited states of 8, 10, and 12 of 40 cal/mol, 200 cal/mol, and 640 cal/mol, respectively. Later reports\textsuperscript{13} of a simple inverse dependence between temperature and intensity over a broader range led to the conclusion that diradicals 8, 10, and 12 either had triplet ground states or triplet states lying only a few cal/mol above the ground state.

Platz\textsuperscript{14} reported the ESR spectrum of a triplet species resulting from the photolysis of the diazo compound 14. The spectrum was identical with the spectrum of 8. Temperature-intensity data in this report support a ground state triplet.

\[
\begin{align*}
\text{8} & \xrightarrow{hv} \text{9} \\
\text{14} & \xrightarrow{hv} \text{10} \\
& \xrightarrow{hv} \text{11} \\
\text{12} & \xrightarrow{hv} \text{13}
\end{align*}
\]

Closs\textsuperscript{15,16} reported ESR spectra for diradicals 15 and 16, produced by photolysis of pyrazoline 17 in a pentane-isopentane glass at 77K. A D value of 0.1069 for 15 (R = CN) is indicative of contribution to the structure of 15 from resonance contributors a and b. The D value of di-radical 16, however, was consistent with the formal 1,5-diradical structure shown.
The difference in the properties of diradicals in matrix-isolated conditions and solution phase is illustrated in a report\textsuperscript{17} that photolysis of three to seven carbon cycloalkanones in an adamantane matrix over the range 123 to 296K did not produce any species with a triplet or diradical ESR spectrum. The observation of CIDNP signals from the photolysis of cycloheptanone, however, implicates a diradical intermediate as is generally proposed in the Norrish I photocleavage of this cycloalkanone. Thus, CIDNP appears to be the method of choice for the investigation of some diradicals in solution.

There are two mechanisms by which a CIDNP\textsuperscript{18} effect may be produced in the reaction of a diradical intermediate. The first mechanism is essentially the radical pair mechanism proposed independently by Kaptein\textsuperscript{19} and Closs\textsuperscript{20} in 1969. A diradical is formed either in the pure singlet or pure triplet state with the electron spins coupled. As the distance between the carbons is increased, the exchange coupling falls toward zero, and the singlet state becomes nearly degenerate with the triplet state. This allows mixing of the states through either a difference of g factors for the two electrons or for a difference in hyperfine interactions. If there is hyperfine splitting by a nucleus having a spin of \( \pm 1/2 \) or \(-1/2\), the rephasing frequency for the electrons will differ for the two nuclear spin states. As a consequence, the singlet will be enriched in one nuclear spin state and the triplet will be enriched in the other. If the diradical now undergoes two competing reactions, one of which requires the diradical to be in its singlet state, such as recombination or disproportionation, the other of which is spin independent, there will be spin selection. The nuclear spin state favored in the singlet will predominate the singlet derived product. Similarly, the enrichment of the other nuclear spin state in the triplet will be carried over into the spin-independent products. If the reaction is performed in the cavity of an NMR spectrometer, the spectrum will show enhanced absorption or emission for the lines in the spectrum corresponding to the protons the spins of which effected the singlet triplet mixing. "Radical pair mechanism" will be used to refer to this mechanism.

The other mechanism, proposed subsequently by Closs,\textsuperscript{21} will be called the "diradical mechanism" because it was developed to account for CIDNP effects unique to diradicals. When the singlet state, \( S_0 \), and the triplet state, \( T_0 \) (\( M = 0 \)), are not degenerate due to residual exchange coupling, \( J \), a degeneracy of one of the other triplet states, \( T_{\pm} \) (\( M = \pm 1 \)), may be imposed by adjusting the magnetic field, \( H_0 \), such that

\[
g \beta H_0 = <2|J|>.
\]

In this equation, \( g \) is the g-factor for the electron, \( \beta \) is the Bohr magnetron for the electron, and \( <2|J|> \) is the mean value of \( 2J \). This allows mixing of the singlet state with either of the \( T_+ \) or \( T_- \) states with which it is degenerate. Since the total spin angular momentum must be conserved, an electronic spin flip must be accompanied by a nuclear spin flip. Therefore, when a \( T_+ \) state of a diradical is depopulated by crossing to \( S_0 \) and is followed by self reaction, there is a depopulation of one nuclear spin state. This process gives rise to a non-equilibrium spin population in the products, which manifests itself as enhanced absorption or emission in the NMR spectrum. This mechanism does not require a competing reaction for spin selection, as does the radical pair mechanism. CIDNP effects produced by the diradical mechanism will be either solely enhanced absorp-
tion or emission in all of the peaks, rather than the mixed enhanced absorption-emission characteristic of the radical pair mechanism.

CIDNP was first observed from diradical products by Kaptein\textsuperscript{22} in the thermolysis of spiro diperoxide, \textsuperscript{18}. Kaptein was able to account for the CIDNP effects observed in the NMR signals of the product 1-decene in terms of the radical pair mechanism and Scheme I. Here the reaction pathway to "other products" provides the competing reaction for spin selection. The spectrum exhibited an emission-absorption multiplet effect. Kaptein\textsuperscript{23} later reported polarization in the signal for cyclodecane when the thermolysis was carried out in a low magnetic field. He was able to make qualitative observation on the \(S_0-T_+\) splitting and the effect of solvent on that splitting from the field dependence of the signal enhancement.

\begin{center}
**Scheme I**
\end{center}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{O\text{---O}}};
\node (b) at (1,0) {\text{O\text{---O}}};
\node (c) at (0.5,0.5) {\text{several steps}};
\node (d) at (2,0) {\text{CH}_2(\text{CH}_2)_n\text{CH}_2\cdot};
\node (e) at (3,0) {\text{(CH}_2\text{)}_{10}};
\node (f) at (4,0) {\text{CH}_2=\text{CH} (\text{CH}_2)_7\text{CH}_3};
\node (g) at (2.5,-1) {\text{other products}};
\draw[->] (a) -- (b);
\draw[->] (a) -- (c);
\draw[->] (c) -- (d);
\draw[->] (d) -- (e);
\draw[->] (e) -- (f);
\end{tikzpicture}
\end{center}

The diradical mechanism is operative in the photochemical ring cleavage of cycloalkanones. Closs irradiated a series of cycloalkanones, \textsuperscript{19} in Scheme II, in chloroform under the influence of both high field\textsuperscript{24} and a series of low fields.\textsuperscript{25} He observed emission in the signals for the \(\alpha\) and \(\beta\) protons on the cycloalkanones, \textsuperscript{19}, and in the olefinic and aldehyde protons of the unsaturated aldehyde, \textsuperscript{20}. From the intensities of the CIDNP signals from cycloheptanone (\(18, n=2\)) and the corresponding unsaturated aldehyde, Closs calculated a ratio of forward to reverse reaction of 0.33.

\begin{center}
**Scheme II**
\end{center}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{\text{CH}\text{---O\text{---CH}}} (\text{CH}_2)_n};
\node (b) at (1,0) {\text{hv}};
\node (c) at (2,0) {\text{\text{CH}}\text{---O} (\text{CH}_2)_{n+3}\text{CH}_2\cdot};
\node (d) at (3,0) {\text{CH}_2=\text{CH} (\text{CH}_2)_{n+2}\text{CHO}};
\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\end{tikzpicture}
\end{center}

19

20

From the field dependence of the maximum intensity of emission from the aldehyde peaks for the different cycloalkanones, Closs deduced the \(S_0-T_+\) splittings. He also calculated the life times of the diradicals from the width of the curves of the intensity vs. the field strength plot (Figure 1). Kaptein's\textsuperscript{26} investigation of the \(^{13}\text{C}\) CIDNP observed in cycloalkanone photolysis confirmed the splittings estimated by Closs, since the same magnetic field dependence of the maximum enhancement was
obtained. The broadening of the curves which Closs attributed to the relationship of the diradical lifetime to the splitting through the uncertainty principle, Kaptein assigned more reasonably to the hyperfine interaction on the basis of larger broadening with the $^{13}$C CIDNP than in $^1$H CIDNP consistent with the larger $^{13}$C hyperfine coupling constant.

Kaptein$^{27}$ reported that the photolysis of cycloalkanones in the presence of a radical scavenger produces a change from the diradical mechanism to the radical pair mechanism, provided scavenging can compete with electron spin relaxation. At low fields the diradical mechanism predominates and only emission is observed. At higher fields the radical pair mechanism becomes favored and enhanced absorption is observed. The field strength at which the polarization changes is dependent on the scavenger concentration and the diradical chain length. From the magnetic field dependence of the signals observed on photolysis of cycloalkanones in the presence of 2-methyl-2-propane-thiol, Kaptein calculated a scavenging rate constant of $5 \times 10^7$ M$^{-1}$ s$^{-1}$ for the thiol.

One of the major problems in CIDNP is in the assignment of reliable enhancement factors. A technique was recently reported which could improve this situation. Sagdeev$^{28}$ and co-workers observed CIDNP signals produced during the photolysis of cyclooctane by spin echo NNR. They calculated an enhancement factor of over $10^6$ from the intensity of the CIDNP signals and the light absorbed in one pulse. The polarization quantum yield, i.e., the probability of a nuclear spin flip after the absorption of a photon, calculated from this enhancement factor was 0.3.

Theoretically, CIDNP signals arising from the diradical mechanism may be observed from products of diradicals of any length by adjusting the magnetic field such that

$$g\beta H_0 \approx <2|J|>.$$  

Practically, however, the exchange coupling in 1,3-, 1,4- and 1,5-diradicals is large enough that a very high magnetic field would be
required to impose degeneracy on the $S_0-T$ pair. Closs\textsuperscript{3} has reported preliminary results of CIDNP arising from a 1,3-diradical. Although experimental details were not given, the degeneracy of the $S_0-T$ states appears to be fortuitous in this case. Development of very high field NMR spectrometers promises to expand the range of diradical intermediates which may be investigated by CIDNP.

BIBLIOGRAPHY

ENZYMIC CATALYSIS IN ORGANIC SYNTHSES

Reported by Venkatesalu Bakthavachalam

November 29, 1979

Should organic chemists meddle in biochemistry? You might well answer this question in the negative if you read the article entitled "The explanation of the secret of alcoholic fermentation" published in 1839. Clearly things have changed since the days of Liebig and Wöhler. The establishment of primary metabolic pathways, the isolation of many of the enzymes involved, and the understanding of the physical organic chemistry related to the mechanism of enzymic catalysis has lead to a number of bridges between the territory of biochemistry and organic chemistry. One aspect of this bridging, at least in the future, will perhaps be the use of enzymes in organic syntheses. The utilization of microorganisms to bring about structural transformations in the fields of steroids and antibiotics paved the way for the current investigations with isolated enzyme systems. The major values of enzymes in organic syntheses are their regio- and stereospecificity and the simple procedures normally required for the isolation of products. There are enzymes known which catalyze most of the common organic reactions such as oxidation-reduction, condensation, addition, decarboxylation, deamination, and halogenation. Even though enzymes are ordained by nature to catalyze specific reactions at specific sites, there exists a large number of enzymes which show a broad spectrum of substrate activity. The advent of insolubilized and immobilized enzymes has enhanced the efficiency and stability of the enzymes and their general utility to wider applications in organic chemistry. The purpose of this abstract is to survey those cell-free enzyme systems which have been utilized to synthesize organic compounds in preparative quantities and to examine the steps taken to overcome the practical difficulties posed by the enzymic reactions.

Practical Aspects of Enzymes as Synthetic Catalysts. Common criteria for choosing a reagent are its cost, availability, stability for storage, and, of course, its suitability for the reaction in question. It would be a tedious job for chemists to isolate enzymes in a pure state, but fortunately the range of commercially purified enzymes is rapidly widening. Many of these preparations require only mild refrigeration to guarantee months of service. Even crude preparations obtained by breaking open the cells of the source organism often possess adequate activity.

In order for an enzyme to be active, the protein should be in its active conformation. As would be expected, these molecules of high molecular weight have limited stability. With most enzymes, the range of stability reflects the fact that they have evolved to function in a predominantly aqueous environment at around 37°C. Accordingly, it is necessary to handle them under similarly mild conditions, so that the activity may be maintained. However, such an aqueous medium is a poor solvent for many organic compounds. Nevertheless, many enzymes tolerate significant quantities of organic solvents mixed with water; e.g., the stereospecific reduction of benzaldehydes to benzyl alcohols by Battersby was carried out in a 5% organic solvent-phosphate buffer medium with high dilution and excellent yields were obtained given sufficient time. Similarly, it has been shown recently that α-chymotrypsin retains its L-enantiomeric preference to a significant extent in aqueous solutions to which moderate (up to 40%) proportions of organic solvents, such as 2-propanol, dioxane or dimethylsulfoxide, have been added. Special cases are known in which reactions are run in predominantly organic media. Recently a novel approach to prepara-
tive enzymatic synthesis using a biphasic 'water-water-immiscible organic solvent' system has been demonstrated with the chymotrypsin catalyzed synthesis of N-acetyl-L-tryptophan ethyl ester. 8

Since enzymes are expensive, it would be desirable to recycle them in many runs of a reaction. The technique of immobilizing enzymes makes this practical. Various techniques for immobilization of enzymes are well documented in recent reviews. 9 However, it is worth mentioning the elegant work done by Whitesides. 10 A new general chemical immobilization procedure was used based upon the peptide coupling agents, N-hydroxysuccinimidoyl esters (Scheme I); the choice of reagents allows greater control of the chemical and physical properties of the immobilized enzymes, which were protected from inactivation during the immobilization by the addition of substrate and/or coenzyme to the reaction mixture. This method has been successfully employed to immobilize several synthetically useful enzymes.

Scheme I

Requirement for Coenzyme and Coenzyme Recycling. The requirement of coenzymes in many biosynthetic reactions places important restrictions on the use of these reactions for preparative scale syntheses. Although certain coenzymes act as true catalysts (that is, they are regenerated unchanged at the conclusion of reactions in which they are involved), others are involved as stoichiometric reagents. All of these coenzymes are expensive; estimated costs in $ per mole are ATP, 2,500; NAD+, 2,500; NADH, 18,000; NADP+, 60,000; NADPH, 250,000. This has been recognized for many years and some progress has been made by using only catalytic quantities of the appropriate coenzyme in conjunction with a system capable of continuously regenerating it in its active form. 11

Recently, more refined methods of coenzyme recycling have been reported. Redox reactions catalyzed by alcohol dehydrogenases consume nicotinamide coenzyme in stoichiometric amounts (Eq. 1).
Jones and co-workers\textsuperscript{12} employed H-transfer reactions between 1,4-dihydropyridines and NAD$^+$, and pyridinium salts and NADH (Eq. 2) for an efficient nicotinamide coenzyme regeneration during enzyme catalyzed carbonyl-reduction and hydroxyl-oxidation reactions.

\begin{equation}
\begin{array}{c}
  \text{1) } C=O + \text{NAD(P)H} \rightleftharpoons \text{CH(OH)} + \text{NAD(P)} \\
\end{array}
\end{equation}

By appropriate variation of substituents X, Y and R of 1 and 2, 1,4-dihydropyridine and pyridinium derivatives of higher and lower redox potentials than NAD$^+$ or NADH were prepared such that the equilibrium of Eq. 2 could be displaced in either direction as desired. Flavin mononucleotide (3) has been found to be a convenient reagent for in situ recycling of NAD$^+$ by the same group (Scheme II).\textsuperscript{13} FMN regeneration is now in routine use in Jones' laboratory.

![Scheme II](image)

Battersby and co-workers\textsuperscript{14} approached the problem in a different way. They used excess of ethanol for an enzymic regeneration of NAD$^+$ (Scheme III) in the preparation of chiral labeled alcohols from aldehydes. The same method has been reported to yield up to 50,000 recyclings by Lemiere and co-workers.\textsuperscript{15}
Whitesides and co-workers\textsuperscript{16} devised a new scheme for the enzymatic regeneration of ATP from ADP and AMP and demonstrated its practicality by the preparation of glucose-6-phosphate from glucose on a mole scale.\textsuperscript{17} The ultimate phosphate donor was acetyl phosphate, which is readily prepared from ketene and phosphoric acid (Scheme IV).\textsuperscript{18}

The coenzyme recycling is made more economical by the transformation of adenosine moieties of RNA into ATP and subsequent use, without isolation, in enzyme catalyzed phosphorylation reactions.\textsuperscript{19}

**Examples of Enzymes in Organic Syntheses.** Much has been written in the past few years concerning the potential of enzymes for synthetic operations.\textsuperscript{20} A review by Stuart\textsuperscript{21} examines the utilization of enzyme systems in syntheses and degradation of heterocyclic compounds. The following represent the successful applications of cell-free enzyme systems in organic syntheses.

**Enzymes Catalyzing Redox Reactions.** The chief value of alcohol dehydrogenase enzymes in syntheses is their stereospecificity.\textsuperscript{22} Of the wide range of conventional reagents available for redox reactions, only complex boranes are equal to the alcohol dehydrogenases in stereospecificity, and then only in cyclic systems.\textsuperscript{23} Many alcohol dehydrogenases are very selective, but both yeast and liver alcohol dehydrogenases have wide
tolerance for non-natural substrates including aliphatic, alicyclic, aromatic and heterocyclic carbonyl compounds. Many of these substrates can also have other unprotected functional groups which are not affected by the enzymic reagent.

Liver alcohol dehydrogenase has been widely used for the preparation of chiral labeled alcohols from aldehydes (Scheme III). This has been the starting point for many elegant investigations of the stereochemical course of biosynthetic reactions.

Jones has reported the preparation of chiral lactones using horse liver alcohol dehydrogenase (Schemes V and VI). The chiral active site of the enzyme promotes the selective oxidation of only one of the enantiotopic \(-\text{CH}_2\text{OH}\) groups of 4 leading to the formation of chiral lactone 5 in good yields with high optical purity.

Scheme V

![Chemical structure](image)

An even more elegant example is the use of the same system to effect the resolution of enantiomeric conformers of 1,2-disubstituted cyclohexane (6), a task which would be virtually impossible by non-enzymic means. When bound to the active site of the enzyme, the conformationally mobile substrates are, in effect, frozen, when a Michaelis enzyme-substrate complex is formed. Thus the enantiotopic hydroxymethyl groups become diastereotopic in the enzyme-substrate complex. The enzyme catalyzed oxidation of one side-chain only (the axial \(-\text{CH}_2\text{OH}\) in 6a) and the conformational equilibrium moves until eventually all the substrate has been converted into lactone 7 via conformer 6a (Scheme VI, next page).

Regiospecific oxidation of bishydroxy cycloalkanes, and stereospecific reduction of bicyclic and heterocyclic ketones have also been reported. The observed stereosepecificities are in agreement with the predictions based on the diamond lattice section analysis of the active site of HLADH.

For a chiral compound to be useful for stereochemical mechanistic studies, it is often necessary to prepare both enantiomers. In his classical synthesis of chiral labeled acetic acid, Arigoni used the opposite stereosepecificities of lactate dehydrogenase and glyoxalate reductase to prepare S and R enantiomers of labeled glycolic acid which were subsequently converted into acetic acid chemically.
Scheme VI

\[ \begin{align*}
6a & \quad \Leftrightarrow \quad 6b \\
\end{align*} \]

\[ \begin{align*}
6a & \quad \xrightarrow{\text{HLADH}} \quad 6b \\
\end{align*} \]

\[ \begin{align*}
6a & \quad \xrightarrow{\text{HLADH}} \quad 7 \\
\end{align*} \]

(79% yield, 100% optically pure)

Peroxidase, Chloroperoxidase and Xanthine Oxidase. Peroxidase-type enzymes have been used extensively to accomplish a variety of coupling reactions in natural products chemistry.\(^{32}\) Unfortunately, peroxidase catalyzed reactions often yield mixtures of products in low yields. Inubushi, for example, has found that a simple N-methyltetrahydroisoquinoline gave a mixture of dimers in low yield upon oxidation with peroxidase and hydrogen peroxide. However, peroxidase is capable of generating radicals in many molecules, and, if reactivity is limited by the structure of the substrate as it is in 8, then preparative yields can be obtained.\(^{34}\)

\[ \begin{align*}
8 & \quad \xrightarrow{\text{Peroxidase}} \quad 9 \\
\end{align*} \]

Is is usually difficult to oxidize electron-deficient heterocyclic compounds, but enzymes have developed useful reactivities. Xanthine oxidase catalyzed the oxidation of many heterocyclic compounds not closely related to xanthine, its natural substrate, and it has been described as omnivorous. Purines and pteridines are oxidized to the corresponding hydroxy compounds normally at the electron-deficient positions.\(^{35}\) Similarly, N-methylnicotinamide can be oxidized to the 6-oxo derivative.\(^{36}\) Recently, xanthine oxidase has been used for the preparation of lin-benzoxanthosine (10) and 7-(p-X-phenyl)pteridine diones (11) (next page).\(^{38}\) Xanthine oxidase has also been shown to oxidize crotonaldehyde in a variety of organic solvents at rates less than a tenth of the rate in homogeneous aqueous solutions.\(^{39}\)
Neidleman\textsuperscript{40} has reported some unusual halogenations catalyzed by the enzyme chloroperoxidase. Electron rich molecules are halogenated by the enzyme in the presence of hydrogen peroxide and an alkali metal halide. The electrophilic halogenating agent generated by the enzyme attacks the most electron rich positions by substitutions, as in thiazole \textsuperscript{12} or by addition, as in the steroid \textsuperscript{13}.

Enzymes Catalyzing Hydrolysis Reactions. Hydrolytic enzymes in their usual function have three possible applications in syntheses. First, they can provide extremely mild methods of removing protecting groups, such as amides and esters. For example, the esterase from orange peel selectively hydrolyzes acetate esters from a range of substrates including the sensitive β-lactam antibiotics (Scheme VII).\textsuperscript{41}

\textbf{Scheme VII}

A second contribution of hydrolases is selective protection when enzymes are used for deprotection. Selective ester hydrolysis by chymotrypsin and its use in nucleotide synthesis has been demonstrated.\textsuperscript{42} The third application of hydrolytic enzymes is their use in resolution and in determination of absolute configurations.\textsuperscript{43}
Phosphorylating Enzymes. Large scale enzymatic phosphorylation of glucose, creatine and glycerol has been reported by Whitesides. The general utility of his method is exemplified by the fact that recoverable, chemically immobilized enzymes were used in each case with coenzyme recycling.

Other Enzymes. There are a few other enzymes which have been employed in certain instances of syntheses. Perhaps the most outstanding is Khorana's synthesis of a gene. He used chemically synthesized polynucleotides as substrates and joined them together, using polynucleotide kinase and ligase, to give a complete gene. Rose took advantage of the indiscriminate nature of aldolase to prepare a number of hexose epoxides from dihydroxyacetones and a variety of aldehydes. Most published work pertaining to hydrogenation and dehydrogenation of carbon-carbon bonds refers to steroids. Battersby used the enzyme δ-aminolaevulinate dehydratase to prepare 13C-labeled samples of phorphobilinogen (14) in high yield.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{δ-aminolaevulinate} \\
\text{H} & \quad \text{dehydratase} \\
\text{CO}_2\text{H} & \quad \text{H}
\end{align*}
\]

\[\text{* = 13C}\]

This highly reactive pyrrole is notoriously difficult to synthesize chemically and the expense involved in 13C-labeling made an alternative route essential.

In all of the above examples one enzyme is used to catalyze a single chemical step. This contrasts with the biological situation where usually a group of several enzymes catalyze multiple transformations. This feature of enzymic catalysis has thus far only been exploited to a very limited extent in synthetic chemistry. A successful project of this type, recently reported, is the de novo synthesis of the decapptide antibiotic gramicidin S from its constituent amino acids using reactors containing several immobilized enzymes.

Conclusion. From the above examples, it is clear that the use of enzymes in organic syntheses is still a developing science. Experimental procedures for enzyme isolation, stabilization, and immobilization are sufficiently advanced that it is now practical for organic chemists to consider catalysis by cell-free enzymes as an integral, if relatively unexploited, technique in intermediate and large scale syntheses. Having higher selectivity than chemical means and being more amenable to control and modification than fermentation, enzymic synthesis holds promise in a number of areas of fine chemical synthesis, particularly in areas relevant to biologically active compounds.
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ORGANIC SEMINAR ABSTRACTS
BIBLIOGRAPHY

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REGIOSELECTIVITY IN THE REACTIONS OF HETERO-SUBSTITUTED ALLYLIC CARBANIONS

 Reported by Dale Kempf  December 3, 1979

The question of regioselectivity in the reactions of electrophiles with 1-substituted allylic carbanions (Eq. 1) to form $\alpha$ and $\gamma$ products is

$$\text{M}^+ \quad + \quad \text{E}^+ \quad \rightarrow \quad \begin{array}{c} \text{E} \\ \text{X} \end{array} \quad + \quad \begin{array}{c} \text{X} \\ \text{E} \end{array}$$

$\alpha$-attack $\gamma$-attack

of both theoretical and synthetic interest. The ratio of $\alpha$- to $\gamma$-attack is profoundly dependent on a variety of factors, including substituent atom, metal ion, solvation, type of electrophile, and steric effects. The intent of this review is to compile experimental data and discuss various explanations for the observed regioselectivity. The discussion will deal primarily with allylic carbanions bearing a single heteroatom substituent at the 1-position. Those to be included are carbanions in which $X=\text{SR}$, $\text{S}\text{O}$, $\text{OR}$, $\text{NR}_2$, $\text{Cl}$, $\text{Br}$, $\text{SiR}_3$, $\text{SeR}$ and $\text{Br}_2$; and $\text{M=Li}$, $\text{Mg}$, $\text{Cu}$, $\text{Zn}$, and $\text{Cd}$. Although the reactions of allylic carbanions having two or more such substituents are not covered, the factors affecting regioselectivity in these anions are probably similar.

**Formation.** The generation of 1-heterosubstituted allylic anions is normally accomplished by removal of the $\alpha$-proton of a 3-substituted propene with n-butyl or sec-butyllithium, often in conjunction with tetramethylethylenediamine (TMEDA) or hexamethylphosphoric triamide (HMPA). Lithium dialkylamides have also been employed. Kow and Rathke have reported the $\gamma$-deprotonation of vinyldialkylboranes to generate the allylic species. Finally, chloro-substituted allylic anions are most efficiently prepared by transmetalation of 3-chloroallyltriphenyllead with n-butyllithium. The preparative metalations have normally been performed in tetrahydrofuran (THF) at $-65^\circ\text{C}$ or lower owing to the high reactivity of both the alkyl lithium base and the resulting allylic carbanion. These conditions, with lithium as the metal, are the basis on which comparison of factors governing regioselectivity in electrophilic attack are to be made.

**Mechanisms of Electrophilic Attack.** The initial problem in describing the mechanism of attack on substituted allyl anions is that the structures of the organometallic species are not well described. Ab initio calculations on alkyl lithium have indicated that the cation is symmetrically placed above the planar anion. Substituents undoubtedly perturb this geometry, and, as with alkyl-substituted allyl organometallics, there is presumably a rapid equilibrium between $\alpha$- and $\gamma$-substituted structures (Eq. 2). Mixtures of $\alpha$ and $\gamma$ have been postulated to result from a
variety of competitive pathways: (1) Direct attack (either $S_{E2}$ or $S_{E2'}$) on the two isomers of Eq. 2 could lead to mixtures, depending on the relative rates of reaction with electrophiles.\(^{12}\) (2) Alkylation of cisoid (1) and transoid (2) allylphenylether anions, which are not in rapid equilibrium,

![Diagram]

has been postulated by Schlosser and co-workers\(^{13}\) to produce $\gamma$ and $\alpha$ products, respectively. (3) Competing $S_{E2}$ and $S_{E2'}$ mechanisms with a common organometallic species (Eq. 3) has also been suggested to account for mixtures of products.\(^{12,14}\) (4) Addition to carbonyl compounds, which often

![Diagram]

shows selectivity opposite that of alkylation, has been rationalized by formation of an "ate" complex followed by cycloaddition through a six-membered transition state (Eq. 4).\(^{12,14}\) Evidence against this mechanism in alkyl-substituted allyl anions has been presented, however.\(^{12,14b}\)

![Diagram]

(5) Another proposed competing reaction involves one-electron transfer to give a caged radical pair which then collapses to yield one of the observed products.\(^{14a,15}\) (6) Finally, with activated halides, halogen-metal exchange could occur to form an allyl halide and new organometallic reagent, and coupling could then occur.

A further mechanistic consideration is the question of kinetic vs. thermodynamic control. Renger and Seebach\(^2\) have reported that addition of carbanions from allyl nitrosamines to ketones is reversible and that regioselectivity can be explained in this way. The same phenomenon has been observed in the reaction of alkyl-substituted allyl organometallics with ketones\(^{15}\) and in the electrophilic capture of 1,1-dichloroallyllithium with several inorganic reagents.\(^{16a}\) Reversible alkylation has never been observed, however, and addition to ketones has been found to be irreversible in several allylic systems.\(^{10b,16}\) It is doubtful, therefore, that the regiochemistry of most hetero-substituted allyl carbanions can be explained in this manner.
Unfortunately, most studies in this area have dealt simply with product ratios, and few attempts to characterize the allyl organometallic species have been made.\textsuperscript{17} Systematic comparisons of product ratios, however, can provide useful information and possibly reveal reactivity trends. In accordance with the proposed mechanisms, different substituents, metal ions, solvents and electrophiles will profoundly affect these $\alpha:\gamma$ product ratios.

**Effects of Substituents on the Regioselectivity.** The 1-substituted allylic carbanions for which the most information is available are those derived from allyl sulfides ($X=SR$).\textsuperscript{18} Various substituents on sulfur have been employed, including phenyl\textsuperscript{19} and vinyl\textsuperscript{20} as well as saturated alkyl groups. Anions \textsuperscript{3} and \textsuperscript{4} resulting from metalation of the corresponding dihydrothiopyrans, have also been prepared. Reaction of the metalated sulfides with primary alkyl halides generally leads to between 2:1 and 10:1 mixtures of $\alpha$ and $\gamma$ products, respectively, indicating a definite preference for $\alpha$-attack.\textsuperscript{19,20} Reaction with aldehydes and ketones, however, shows high $\gamma$-selectivity\textsuperscript{19-22} except in the sterically hindered carbanion 5.\textsuperscript{23} Seebach and co-workers\textsuperscript{24} have succeeded in reversing the preference for $\alpha$-alkylation. Double deprotonation of allyl mercaptan yields a dianion (Eq. 5) which can be trapped initially at carbon and subsequently alkylated at sulfur. With the dianion, the opposite regiochemistry of alkylation and condensation with carbonyl compounds is eliminated, and both alkyl halides and carbonyl electrophiles show a preference for $\gamma$-attack, with $\alpha:\gamma$ ratios between 1:2 and 1:5.

Several examples of carbanions from allyl ethers have appeared. Evans and co-workers\textsuperscript{25} have reported 54-89% $\gamma$-selectivity in the reaction of 6 with 1-iodohexane. Still and McDonald\textsuperscript{26} improved the $\gamma$-preference for primary alkyl halides to 78% by use of triethyl- (7) and dimethyl-$n$-butylsilyl ethers. With cyclohexanone, $\alpha$-selectivity is normally encoun-
tered. Organolithium 7 yields 71% of the α-product while the trimethylsilyl ether exhibits 95% α-selectivity.\textsuperscript{26b} Reaction of 6 with cyclohexanone shows α-preference with R = t-Bu, Ph, but γ-preference with R = Me, Et. It appears, however, that in most cases, alkoxyallyl carbanions undergo preferable γ-attack on alkyl halides and addition of the α-carbon to carbonyl compounds, behavior opposite that of allyl sulfide anions. Interestingly, the organolithium 8 is in equilibrium with 7,\textsuperscript{26a,27} and has been trapped with highly reactive electrophiles. A similar rearrangement is found\textsuperscript{28} with anions from allyl phosphates and phosphorodiamides, the products of which can be further deprotonated to dianionic species.

N-Substituted allylic carbanions have been generated from a variety of compounds. The anions 9 - 11, derived from N-allyl-N-methylaniline,\textsuperscript{17,29} N-allylpiperidined\textsuperscript{30} and N-allylcarbazole,\textsuperscript{31} respectively, react with primary halides and chlorotrimethylsilane with >93% γ-selectivity. As with

\[ \text{Ph} \quad \text{Li}^+ \text{ or K}^+ \]
\[ \text{Me} \]
\[ \text{N} \]
\[ \text{9} \]
\[ \text{Li}^+ \]
\[ \text{O} \]
\[ \text{Li}^+ \]
\[ \text{Me} \]
\[ \text{Me} \]
\[ \text{N} \]
\[ \text{10} \]
\[ \text{Li}^+ \]
\[ \text{NO} \]
\[ \text{11} \]

S- and O-substituted anions, addition to aldehydes and ketones is radically different, and both 9 and 10 exhibit only a slight α-selectivity (50-60%) with these electrophiles.\textsuperscript{29a,30} In addition to amines, N-substituted allyl carbanions have been formed from N-allyl-N-methyl-bis(dimethylamino)phosphoramide,\textsuperscript{32} N-allyl amide anions,\textsuperscript{3} allylnitrosamines\textsuperscript{2} and an allyl urea,\textsuperscript{7} giving 12 - 15, respectively. Both 12 and 13 alkylate exclusively at the γ-position. The nitrosamine anion, however, undergoes regiospecific alkylation at the α-carbon.\textsuperscript{2} The lithio carbanion 15 has not been alkylated.

There have been few cases of allylic carbanions substituted by halogen. Recently, Wenkert and co-workers\textsuperscript{4} have reported a dimerization of allyl chloride and allyl bromide, with the allylic anion as a probable intermediate (Eq. 6). Allyl bromide yields only the α-product while allyl chloride gives an 8:1 α:γ ratio, both in low yield. Mauze has generated the 1-chloro-1-methylallyl anion by lithium-lead exchange, which is stable at -90° and can be trapped exclusively at the α-position with unhindered
ketones and aldehydes.\(^9\) \(\alpha\)-Attack on both alkyl halides and carbonyl compounds is in marked contrast to the previous \(S^-, N^-,\) or \(O\)-substituted carbanions, although only a limited amount of data on haloallyl anions is available. Seyferth and co-workers\(^{10b,c}\) have shown that addition of \(1,1\)-dichloroallyllithium to carbonyl compounds can be selectively \(\alpha\) or \(\gamma\), depending on the electrophile.

Anions derived from allylsilanes were first reported by Corriu and co-workers.\(^{33}\) Again, as with halo-substituted anions, selectivity for both ketones and alkyl halides appears to be similar, although the data are limited in this case as well. Benzophenone, chlorotrimethylsilane, and methyl iodide react at the \(\gamma\)-position of anion \(\text{16,}^{33a,b} \text{ and 17 condenses with other ketones and aldehydes exclusively at the } \gamma\)-position.\(^{34}\)

The \(\gamma\)-silation of \(\text{18}\) has recently been employed by Corriu as a key step in the preparation of asymmetric disilacyclopentanes.\(^{33c}\)

Reich\(^5\) has generated allyl organometallics stabilized by the phenylseleno group. Alkylation of \(\text{19}\) produces ca. 80% of the \(\alpha\)-product, while a 15:85 \(\alpha:\gamma\) ratio is obtained with acetophenone. From the limited data available, the behavior of phenylseleno allyl carbanions appears to parallel that of allylthio anions.\(^5\) Kow and Rathke\(^6\) have reported that boron-stabilized anions (20) react with water and methyl iodide predominantly at the \(\alpha\)-carbon, but reaction with chlorotrimethylsilane and acetone occurs mainly at the \(\gamma\)-position. Steric factors are cited as an explanation for this difference; consequently, little is known regarding the effect of dialkylboron substitution on the regioselectivity.

Most explanations of substituent effects upon regioselectivity involve donor or acceptor abilities of the substituent group. Still and McDonald\(^{26b}\) have suggested that alkylation and protonation occur at the site of higher electron density and that carbonyl compounds react by a cyclic mechanism. Donor groups (OR, NR\(_2\), alkyl) create a greater charge density at the \(\gamma\)-carbon while acceptor groups (SR, BR\(_2\)) create a greater charge density at the \(\alpha\)-carbon.\(^{26b}\) To test this proposal further, this reviewer has performed MINDO/3 calculations on several model 1-substituted allyl anions.\(^{35}\)
Tables 1 and 2 list the calculated charge densities and the coefficients of the highest occupied molecular orbital for the carbon and substituent atoms of each of these models. A greater charge density is found at the γ-carbon in each case. α-Alkylation of allyl sulfide anions is consistent, however, with the larger HOMO coefficient at the α-carbon. When X = OR or NR₂, the α and γ-coefficients are very nearly the same, providing no basis for selectivity. The greater charge density at the γ-carbon, therefore, appears to be the important factor in the transition state and γ-alkylation is observed. When X = Cl, α-alkylation is predicted because of the greater HOMO coefficient at that carbon, while the thioallyl dianion (X = S⁻) would be expected to alkylate mainly at the γ-carbon on the basis of both the HOMO coefficients and the charge densities. Both of these predictions correspond to the observed behavior. With allylsilyl anions, however, the predictions break down and γ-alkylation is observed, possibly owing to overriding steric effects. The coefficients of the HOMO may explain the observation by Ahlbrecht¹⁷ that increasing the donor ability of the dialkylamino group of aminoallyl anions unexpectedly decreased the preference for γ-attack, although no quantitative data are available.

Additions to carbonyl compounds appear to depend more on the position of the metal than on orbital coefficients, and a cyclic mechanism appears to be reasonable in cases where the selectivity is opposite to that observed in alkylation. Seebach and co-workers have postulated²⁴ that a structure such as 21 for dialithiated allylmercaptan to explain the absence of trans products. In 21, the cyclic mechanism would not be expected, and addition to carbonyl compounds would be predicted by both charge density and HOMO coefficients to parallel alkylation at the γ-position, which is the observed preference.
Effects of Metals on Regioselectivity. Metals other than lithium often alter the regioselectivity of hetero-substituted allyl carbanions. Seebach and co-workers\textsuperscript{36} have found that addition of MgBr\textsubscript{2} to the allyl-mercaptan dianion reverses the selectivity of reaction with cyclopentanone from 65\% γ to 95\% α. Addition of MgBr\textsubscript{2} to the anion of an allylmethyl-piperidinyl urea (15) resulted in almost exclusive γ-attack with both alkyl halides and carbonyl compounds.\textsuperscript{7} In contrast, Corriu and co-workers,\textsuperscript{33b} found similar regioselectivity with the lithium and Grignard reagents of allyl silanes. Recently, the lithio derivative of an allylsilane in conjunction with MgBr\textsubscript{2} has been observed to react with different selectivity than the corresponding Grignard reagent.\textsuperscript{37} This phenomenon raises questions about the role of the metals in the reaction and has not yet been sufficiently studied.

The addition of CuI to anion 22 followed by alkylation with allylic halides has been reported by Yamamoto and co-workers\textsuperscript{38} to exhibit specific γ-attack on the nucleophile and Sn2\textsuperscript{'} attack on the halide. Reaction with acetone yields predominantly the α-product; therefore, selectivity opposite to that of the lithio reagent is observed. Upon low-temperature reaction of 22 with benzyl bromide, a moderate yield of bibenzyl was obtained, a possible indication of a radical mechanism.\textsuperscript{38}

α-Selectivity of >95\% has been observed in reactions of ketones with zinc derivatives of allyl ethers\textsuperscript{25,39} and allyl amines\textsuperscript{30} and the cadmium derivatives of allyl sulfides.\textsuperscript{40} Both metals promote selective γ-condensation of allylsilyl anions with acetophenone,\textsuperscript{37} and zinc has been found to give greater selectivity than cadmium in allyl ether carbanions.\textsuperscript{41} Only with sulfides is the regioselectivity reversed; in the other examples, zinc and cadmium simply enhance the selectivity observed with the lithio derivatives.

Effects of Solvation. The regioselectivity is also dependent upon the solvating ability of the solvent and/or additives. Tetrahydrofuran has been found to enhance the α- and γ-selectivity of allyl sulfides\textsuperscript{13} and amines,\textsuperscript{17} respectively, in comparison to hydrocarbon solvents. 1,4-Diazabicyclo[2,2,2] octane (DABCO) and TMEDA enhance the γ-selectivity in the reaction of acetone with the anion from an allyl sulfide,\textsuperscript{16} although TMEDA has also been reported to reduce the γ-selectivity with heptanal.\textsuperscript{19c} In both cases, the effects were small. HMPA, a better solvating agent, is also quite unpredictable, and both increased and decreased selectivities have been observed.\textsuperscript{16,24b,26b} Presumably, highly solvating agents cause dissociation of the ion pairs to solvent-separated ion pairs or free ions. The Sn2\textsuperscript{'} and cyclic mechanisms should not be favored, and the regioselectivity should be governed by charge densities and orbital interactions. Biellmann and co-workers\textsuperscript{16} found that a phenylthio-substituted carbanion in the presence of a highly solvating diamino polyether reacted with acetone at the α-position and with alkyl halides randomly at both α- and γ-positions. This behavior is consistent with solvent-separated or free ions. Ahlbrecht\textsuperscript{17} has examined the UV spectra of alkali allyldialkylamines in media of various solvating abilities and detected three different anionic species.

Effect of the Electrophile on Regioselectivity. The effect of different carbonyl compounds on the regiochemistry in reactions of 1,1-dichloroallyllithium has been studied by Seyferth and co-workers.\textsuperscript{10b,c}
Generally, ketones and aldehydes with electron-donating substituents afforded \( \alpha \)-products, and those with electron-withdrawing groups, \( \gamma \)-products. This behavior was explained by characterizing the \( \sigma \) - and \( \gamma \)-carbons as the soft and hard centers of the ambident nucleophile, respectively. However, MINDO/3 calculations on the dichloroallyl anion\(^7\) indicate a greater charge density at the \( \alpha \)-carbon, making it the harder center.\(^4\) The results can still be rationalized, however, by competing cyclic and \( \text{SP}^2 \)-like mechanisms.

Hard-soft effects have been observed in alkylations of allyl sulfide carbanions. Torii and co-workers\(^2\) have found that the anion (3) derived from \( \Delta^3 \)-dihydrothiopyran gives \( \alpha: \gamma \) ratios of 53:1, 11:1 and 2.4:1 upon reaction with \( n \)-butyl chloride, bromide and iodide, respectively. Similar behavior in 1,1-disubstituted allylic anions has been rationalized in terms of hard-soft interactions.\(^3\)

Controlling the Regiochemistry. Synthetic chemists, in efforts to achieve higher regioselectivity, have developed several methods of control in which the normal factors affecting the regiochemistry appear to be outweighed. Evans and Andrews\(^1\) and Mukaiyama\(^4\) have reported greater \( \alpha \)-selectivity with anions from heteroaromatic-substituted allyl sulfides and ethers than normally observed. Intramolecular chelation of the lithium to the heteroaromatic ring (Eq. 7) is presumed to be responsible for this effect. Anions from allylthio\(^8\) and dithiocarbamates\(^8\), and dithiocarbonate tosylhydrazones\(^9\) exhibit the same high \( \alpha \)-selectivity with both alkyl halides and carbonyl compounds. The kinetically favored \( \alpha \)-alkylation of allylnitrosamine anions\(^2\) could also be a result of intramolecular complexation.

\[
\begin{align*}
\text{N-S} - \text{C} & \quad \text{Li:B} \quad \text{E}^+ \\
& \quad \text{N-S} - \text{C} \quad \text{Li} \\
& \quad \text{N-S} - \text{C} \quad \text{E} \\
\end{align*}
\]

(7)

A second method controlling the regiochemistry, recently reported by Yamamoto and co-workers,\(^4\) involves prior formation of a \( \gamma \) "ate" complex by reaction of an allylthio carbanion with a trialkyl borane. Subsequent reaction with electrophiles followed by oxidation affords \( \alpha \)-products almost exclusively.

Still\(^4\) has reported the intramolecular alkylation of an allyl ether carbanion to form a vinyl oxetane (Eq. 8). Only \( \alpha \)-attack is observed because of the geometric requirements for nucleophilic attack, in spite of the formation of the more highly strained product.

\[
\begin{align*}
\text{O} - \text{C} - \text{O} & \quad \text{s-BuLi} \quad \text{TMEDA} \\
& \quad \text{O} - \text{C} - \text{O} \quad \text{Li}^+ \\
& \quad \text{O} - \text{C} - \text{O} \quad \text{H} \\
\end{align*}
\]

(8)

As illustrated in this review, the factors influencing the regioselectivity in the reactions of hetero-substituted allylic carbanions are quite varied and complex. Generalizations can be made in most cases, however, and the application of molecular orbital theory will hopefully bring more order and predictability to the matter.
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MODERN METHODS FOR THE DEOXYGENATION OF ALCOHOLS

Reported by William Stevenson  December 6, 1979

The alcohol functionality is one of the most important and ubiquitous in organic chemistry, occurring throughout the range of aliphatics, aromatics, and an enormous number of natural products. In many areas of synthetic chemistry deoxygenation reactions become necessary to effect the formal conversion R-OH → R-H without altering other functionalities present in the molecule. Understandably the development of efficient methods for the deoxygenation of alcohols has been the subject of much current interest in the field of organic chemistry, and considerable research in synthetic methodology has been directed towards this end. For the purposes of this review, reactions are classified by mechanistic type under one of the following headings - 1) hydride transfer, 2) hydrogenation or hydrogenolysis, 3) dissolving metal, 4) radical chain, or 5) photo-chemical.

The scope of the seminar includes both aliphatic alcohols and phenols; the deoxygenation of activated cases (e.g. allylic, benzylic) will not be discussed in detail, although references are given for these transformations. Furthermore, deoxygenation methods which involve initial oxidation of alcohols to ketones or aldehydes followed by carbonyl removal (e.g. by Clemmensen or Wolff-Kishner reductions) will not be included in this review, although such methods are often useful for primary and secondary alcohols. Throughout, emphasis will center on the more modern and most efficient methods of deoxygenation.

Deoxygenation by Hydride Transfer. Metal hydrides such as lithium aluminum hydride have frequently been used for deoxygenation of alcohols after initial conversion to the corresponding sulfonate or halide. 1-3 The scope of this procedure has generally been limited to primary alcohols; secondary and tertiary derivatives react poorly and give rise to large amounts of elimination products. 1a, 3a A major disadvantage is the high reactivity of metal hydrides toward other functional groups. 4

The scope of metal hydride deoxygenations has been significantly extended by the recent development of lithium triethylborohydride (Super Hydride) 3 and copper hydrides such as LiCuHR. 5 Relatively hindered primary alcohols and many secondary alcohols may be reduced by lithium triethylborohydride in good yield with far fewer elimination products. 3a The copper hydride reagents have been less extensively studied but show indications of similar utility and are also effective in the reduction of aromatic and vinyl halides 5a,b (Table 1). Other reducing agents of interest include borohydride "ate" complexes which reduce tertiary and activated halides selectively 6 and lithium aluminum hydride in the presence of transition metals which has been shown effective in reducing alkyl and aromatic halides. 1c

Undesirable reduction of functionalities is a common problem in metal hydride procedures. The general order of reactivity of the most commonly used reagents is as follows - LiAlH₄ > NaBH₄ > NaCNBH₃. Sodium cyanoborohydride shows a remarkable degree of selectivity which is dependent upon the pH of the reaction medium. 7a At pH > 6 alkyl halides, sulfonates, and iminium salts are the only groups reduced. A particularly good one-pot reduction of alcohols involving in situ generation of the
Table 1. Metal Hydride Reductions$^{3a,5a,5c}$

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent</th>
<th>Products</th>
<th>% Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexyltosylate</td>
<td>LiAlH$_4$</td>
<td>Cyclohexane</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclohexene</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclohexanol</td>
<td>19</td>
</tr>
<tr>
<td>Cyclohexyltosylate</td>
<td>LiBHEt$_3$</td>
<td>Cyclohexane</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclohexene</td>
<td>20</td>
</tr>
<tr>
<td>Cycloheptyltosylate</td>
<td>LiBHEt$_3$</td>
<td>Cycloheptane</td>
<td>100</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_2$-C(CH$_3$)$_2$-OTs</td>
<td>LiBHEt$_3$</td>
<td>CH$_3$(CH$_2$)$_3$C(CH$_3$)$_3$</td>
<td>81</td>
</tr>
<tr>
<td>Cyclohexyltosylate</td>
<td>LiCuHBu</td>
<td>Cyclohexane</td>
<td>80</td>
</tr>
<tr>
<td>endo-2-Norbornylmesylate</td>
<td>[CuI + LiAlH(OCH$_3$)$_3$]</td>
<td>Norbornane</td>
<td>99</td>
</tr>
<tr>
<td>exo-2-Norbornylmesylate</td>
<td>[CuI + LiAlH(OCH$_3$)$_3$]</td>
<td>Norbornane</td>
<td>75</td>
</tr>
</tbody>
</table>

$^a$Determined by gas chromatography

iodide is described by Hutchins et al.$^7b$ This reaction is most useful for relatively unhindered primary alcohols, 4-methyl, 4-hydroxymethylcyclohexene being reduced in only 58% yield.

Alcohols which form relatively stable carbonium ions may be deoxygenated directly in acidic media by hydride transfer reagents.$^8$ Examples of such systems include NaBH$_4$/CF$_3$COOH, R$_3$Si-H/BF$_3$, and (Ph$_3$P)$_2$PtR$_1$R$_2$/H$_2$/CF$_3$COOH. Yields are often excellent for allylic and benzylic cases but are not as good for tertiary alcohols. Other methods of deoxygenation give improved yields for those allylic alcohols especially prone towards rearrangement.$^9$

Hydrogenation and Hydrogenolysis Reactions. Dehydration of alcohols followed by hydrogenation is a standard method of deoxygenation. This method is most effective with tertiary alcohols which are easily dehydrated. The necessity of an acid catalyst and the possibility of molecular rearrangement are the major disadvantages of this method. And in this as in all deoxgenations involving hydrogenation, the presence of other functional groups capable of reduction may render the procedure undesirable.

Derivatization of alcohols followed by hydrogenolysis has been developed using several procedures and has been most commonly applied to phenols$^{10}$ (Scheme I, Table 2). Conversion of phenols to mercaptans via the O-aryldialkylthiocarbamates (Eq. 1) and subsequent hydrogenolysis is a very general method, proceeding in fair yield even for the hindered 2,3,5,6-tetramethylphenol.$^{10a}$ This method is, however, limited to those molecules which can withstand the rather severe pyrolysis temperatures necessary in the rearrangement step.

Hydrogenolysis of phenyltetrazolyl ethers (2) is a milder method which is compatible with ketone and aldehyde groups$^{10b}$ (Eq. 2). The conversion is generally more successful with relatively unhindered alcohols and allows selective deoxygenation in some cases.$^{10c}$ Deoxygenation via the isourea derivatives 3 has been demonstrated for aliphatic
Scheme I. Deoxygenation by Hydrogenolysis

\[
\begin{align*}
\text{Ar-OH} & \quad \xrightarrow{(\text{CH}_3)_2\text{NCSCl, NaH, DMF}} \quad \text{Ar-OCSN(\text{CH}_3)_2} \\
& \quad \xrightarrow{(130-300^\circ)} \\
\text{Ar-SCON(\text{CH}_3)_2} & \quad \xrightarrow{-\text{OH}} \quad \text{Ar-SH} \quad \xrightarrow{\text{RaNi}} \quad \text{Ar-H}
\end{align*}
\]

(1)

\[
\begin{align*}
\text{Ar-OH} + \text{Cl} & \quad \xrightarrow{\text{K}_2\text{CO}_3} \quad \text{Ar-O-C} \\
& \quad \xrightarrow{\text{H}_2/\text{Pd}} \\
\text{Ar-H} & \quad \xrightarrow{\text{O}} \quad \text{N} \quad \text{Ph} \\
& \quad \xrightarrow{\text{Ph}}
\end{align*}
\]

(2)

\[
\begin{align*}
\text{R-OH} + \text{R'}-\text{NCN-R'} & \quad \xrightarrow{\text{H}_2/\text{Pd}} \quad \text{R-O-C} \\
& \quad \xrightarrow{\text{R-H}} \\
\text{Ar-O-SO}_3\text{CH}_3 & \quad \xrightarrow{\text{H}_2/\text{Pd}} \quad \text{Ar-H}
\end{align*}
\]

(3)

(4)

(5)

Alcohols\textsuperscript{10d} and phenols\textsuperscript{10e,h} (Eq. 3). Yields are generally good to excellent; however, the reaction is sensitive to steric hindrance, and rearrangement occurs in some cases (i.e. isobornyl).

Hydrogenolysis of sulfonate esters 4 is also effective for many phenols but requires conditions which reduce aldehydes\textsuperscript{10f} (Eq. 4). Reduction of the aryl sulfate 5 shown in Eq. 5 also proceeds in generally good yield and has the advantage of alternate cleavage conditions.\textsuperscript{10g}
Table 2. Deoxygenation by Hydrogenolysis

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Equation</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Naphthol</td>
<td>Naphthalene</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>4-Methoxyphenol</td>
<td>Anisole</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>3</td>
<td>69(^a)</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>2,3,4,6-Tetramethylphenol</td>
<td>2,3,5,6-Tetramethylbenzene</td>
<td>1</td>
<td>45</td>
</tr>
</tbody>
</table>

\(^a\)Yield determined by gas chromatography; all other values are for pure isolated product.

**Dissolving Metal Reactions.** The most generally useful reaction of this class are those which involve cleavage of a phosphate ester. This reaction has been known since 1955,\(^{11, a}\) but its usefulness in deoxygenation was first shown by Ireland et al.\(^{11, b}\) using the \(N,N',N_1\)-tetramethylphosphordiamidate and diethylphosphate esters (Eq. 6). Yields are generally good for deoxygenation of alcohols, phenols, and enolates\(^{11}\) (Table 3).

\[
\text{R-OH} \xrightarrow{((\text{CH}_3)_2\text{N})_2\text{POCl}} \xrightarrow{n-\text{BuLi}} \text{R-OP}(\text{N(CH}_3)_2)_{\text{Li/ETNH}_2} \xrightarrow{\text{THF}} \text{R-H} \quad (6)
\]

Recently, treatment of alcohols with \(N,N\)-dimethylphosphoramidic dichloride followed by addition of dimethylamine has been found to be a particularly good way to derivatize hindered alcohols.\(^{11, f}\)

Several other alcohol derivatives have been cleaved by dissolving metals to effect deoxygenation; use of \(N,N\)-dimethylsulfamoyl derivatives has been found particularly valuable for secondary positions at which \(S_N2\) processes are hindered.\(^{12}\) Cleavage of carboxyl esters gives selective deoxygenation of tertiary and hindered secondary esters.\(^{13}\) Zinc reduction of primary and secondary tosylates or mesylates (via \textit{in situ} formation of the iodide) has been reported to give excellent yields of the hydrocarbons,\(^{14}\) and the reduction of thioesters\(^{15}\) and 2,4-diaminophenylethers\(^{16}\) has been used on occasion. Allylic and benzylic alcohols may often be directly deoxygenated in high yield by dissolving metals.\(^{17}\)

A common limitation of dissolving metal reactions is the relatively harsh conditions necessary for ester cleavage. Functionalities not compatible with the reaction conditions include aryl aldehydes, aryl esters and aryl chlorides. However, isolated esters, enolizable ketones, ethers, and isolated alkenes are usually compatible. Reduction of aromatics may also occur if the molecule has a high affinity for electrons (e.g. nitro-
Table 3. Dissolving Metal Reductions\textsuperscript{11c,d,12,13}

<table>
<thead>
<tr>
<th>Compound</th>
<th>Derivative</th>
<th>Cleavage Cond.</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Napthol</td>
<td>-PO(4OEt)$_2$</td>
<td>Ti/THF</td>
<td>74</td>
</tr>
<tr>
<td>2,6-Dimethylphenol</td>
<td>-PO(4OEt)$_2$</td>
<td>K/NH$_3$</td>
<td>92$^a$</td>
</tr>
<tr>
<td>2- Allyl-4-methylphenol</td>
<td>-PO(4OEt)$_2$</td>
<td>Li/NH$_3$</td>
<td>77</td>
</tr>
<tr>
<td>3-Acetylphenol</td>
<td>-PO(4OEt)$_2$</td>
<td>Na/NH$_3$</td>
<td>52</td>
</tr>
<tr>
<td>3β,4,4-Trimethyl-5α-cholestan-3α-ol</td>
<td>-SO$_2$N(CH$_3$)$_2$</td>
<td>Na/NH$_3$</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>-COR</td>
<td>Na/HMPA</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Yield determined by gas chromatography; all other yields are for pure isolated deoxygenated products.

phenol, naphthalene), but this problem may be minimized by adding "electron mops" such as sodium benzoate immediately prior to quenching\textsuperscript{11c} or by using highly activated titanium in place of a group 1A metal.\textsuperscript{11d} It should be noted that titanium is not a true dissolving metal as reduction is thought to occur on the surface of the metal and not in solution.

**Radical Chain Reactions.** D. H. Barton and co-workers have developed a deoxygenation procedure which involves derivatization of alcohols to O-alkyl thioesters followed by reduction with tributyltin hydride\textsuperscript{18} (Eq. 7). The reduction step is specific for secondary groups and is quite effective for the deoxygenation of hindered secondary alcohols. It is desirable to keep the concentration of the tin hydride as low as possible in order to favor fragmentation of the radical intermediate (7) over hydrogen abstraction (Scheme II).
A variation of the Barton procedure, involving conversion of 1,3-diols to cyclic thiocarbonates allows selective deoxygenation if the thiocarbonate ring is formed from a primary and secondary alcohol\textsuperscript{18b} (Scheme III). Treatment with tributyltin hydride gives secondary deoxygenation, evidently due to the greater stability of secondary over primary radicals; however, cleavage of the thiocarbonate ring with methyl iodide followed by reduction gives primary deoxygenation in high yield. Selectivity is low if the thiocarbonate ring is formed from two secondary alcohols.

Tributyltin hydride is also an excellent dehalogenating agent, thus providing a method of deoxygenation by initial conversion of alcohols to halides.\textsuperscript{4} Allylic, benzylic, and other alcohols which form relatively stable radicals may be deoxygenated by reduction of their carboxylic esters.\textsuperscript{19}

Trialkylsilanes have also been shown to be effective deoxygenating agents of primary and secondary alcohols via the corresponding chloroformates.\textsuperscript{20} This procedure is compatible with carbonyl functions, 2-pentanone being obtained in 69% yield from the chloroformate $\text{CH}_3\text{CO}(\text{CH}_2)_2\text{OCl}$.
Photochemical Deoxygenations. Photochemical cleavage of esters has been reported as a general method for deoxygenation of aliphatic alcohols. Yields are generally good, even for hindered secondary and tertiary alcohols, and the reaction conditions are compatible with alkene, alcohol, ether, acid, and acetal groups — ketones and halogens are reduced. Selectivity among di- and tri-esters is low, and multiple deoxygenation frequently occurs in this case.

Conclusion. As a result of the recent advances in synthetic methodology the organic chemist now has available a wide range of procedures for the deoxygenation of alcohols. Perhaps the greatest advances have been made in the reduction of rather hindered secondary alcohols and of phenols, systems for which no general method has traditionally been available. Quite hindered secondary alcohols may be efficiently deoxygenated by dissolving metals, radical processes and photochemical cleavage, while some of the more modern hydride reagents (Super Hydride) are also effective in many cases. Phenols may be most generally deoxygenated by one of the hydrogenolysis reactions, though dissolving metals are successful if the substrate does not have a great affinity for electrons. No doubt the area of alcohol deoxygenation will continue to advance both in scope of application and efficiency of reduction.

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ENANTIOMERICALLY UNUSUAL BIOMOLECULES

Reported by Anthony W. Czarnik
December 10, 1979

A high degree of optical asymmetry has been known to exist in compounds of biological origin nearly since the inception of plane-polarized light. Virtually every major class of biomolecules exhibits enantiomerism to varying extents. Sugars, amino acids, and phospholipids exist almost exclusively as one stereoisomer, while terpenoids, alkaloids, and other natural products will somewhat more frequently occur as several isomers. Interest in the enantiomerically unusual forms of these biomolecules (Figure 1) has recently become acute owing largely to their anticipated resistance to enzymatic degradation in living systems.

Figure 1. Enantiomeric Forms of Some Common Biomolecules

- L-alanine
- D-alanine
- D-glucose
- L-glucose
- (R)-α-glycerol phosphate
- (S)-α-glycerol phosphate

The reason that one of two enantiomers of a chiral compound should predominate in a biological system is by no means obvious. Many investigations have been reported to test various theories concerning stereochemical evolution. Asymmetric syntheses and decompositions using circularly polarized light are known. The interaction of racemic 2-butanol with asymmetric inorganic crystals of quartz leads to enantioselective dehydration of the chiral alcohol. In addition, a number of L-amino acids have been reported to bind preferentially to L-quartz and to bentonite, a colloidal hydrated aluminum silicate. The spontaneous resolution of some racemates has been observed to occur on crystallization and the implications to stereochemical evolution have been discussed. Efforts have also been made to correlate the now well-known asymmetry of β-decay to the induction of asymmetry in biomolecules. The successful enantio-
selective decomposition of amino acids exposed to β-sources (e.g. ⁹⁰⁰Sr) has been reported;¹⁰,¹¹ however, some controversy over the β-decay mechanism for the origin of optical activity exists.¹²

The preponderance of biologically-derived carbohydrates exist as the D-isomer, so termed because of their relationship to D-glyceraldehyde. While the enantiomeric L- forms of D-glucose and D-ribose have never been found in nature, L-rhamnose and L-arabinose occur in plants, L-fucose in blood, and L-galactose in snails. In addition, several bacterial antibiotics originating from the genus Streptomyces contain L-sugars.¹³ Recently, the synthesis of L-sucrose, the enantiomer of common table sugar, has been accomplished by Szarek and Jones from L-arabinose.¹⁴ The finding that L-sucrose is sweet (unlike L-glucose¹⁵ which is salty³⁸) makes it potentially useful as a non-nutritive sweetener.

The twenty or so common amino acids found in living systems exist mainly as the L-enantiomer. The isomeric D- amino acids are found in the cell walls of gram-positive bacteria and in over 25 naturally occurring antibiotics, including penicillin.¹³ An enzyme, alanine racemase, has been found in some bacteria which catalyzes the conversion of L-alanine to D-alanine.¹⁶ The concept that these D- amino acid-containing peptides are resistant to protease hydrolysis has been the motivation behind the synthesis of enantiometric and retroenantiogenic peptides (Figure 2).¹⁷ The enantiomers of oxytocin,¹⁸ bradykinin,¹⁹ angiotensin,²⁰ eledoisin,²¹ and MSH-pentapeptide²² have been synthesized. All were found to be biologically inactive with respect to the parent peptide.

Figure 2. Some Isomers of MSH-Pentapeptide

Natural MSH-pentapeptide:

L-His-L-Phe-L-Arg-L-Try-Gly

Enantio-MSH-pentapeptide:

D-His-D-Phe-D-Arg-D-Try-Gly

Retroenantio-MSH-Pentapeptide:

Gly-D-Try-D-Arg-D-Phe-D-His

The retroenantioiomer of a peptide results by both inverting each chiral center and reversing the sequence direction of a linear chain of amino acids. In 1969, Shemyakin et al. suggested that retroenantioiomers of biologically active peptides should themselves show activity owing to their close topological similarity to the parent peptides.²³ Both retroenantio-Gly⁵,¹⁰-gramicidin S²⁶ and retroenantio-antamanid²⁵ have been synthesized and do show activity comparable to their natural counterparts. However, the retroenantioiomers of bradykinin,²⁶ MSH-pentapeptide,²⁷ tuftsins,²⁸ somatostatin analogues,²⁹ desamino-gastrin C-terminal tetrapeptide,²⁸ and lutenizing hormone releasing factor³⁰ subsequently have been reported to be inactive. The basic premise of close topological similarity has been reinvestigated, and recently Freidinger and Weber have reported that there are innate differences in sidechain topology between a retroenantioiomer and its parent peptide based on computer models of cyclic peptides.³¹
Phospholipids are chiral biomolecules derived by enzymatic phosphorylation of glycerol, an achiral precursor. The α-glycerol phosphate which results has the (R)-configuration as shown by $^{14}$C-incorporation experiments.\textsuperscript{32} The interactions of (R)- and (S)-diacylphospholipids with cholesterol, a common membrane constituent, have been studied by pressure-area measurements\textsuperscript{33} and by $^1$H-NMR\textsuperscript{34} of the resulting lipid vesicles. This latter study indicates a stereospecific interaction between the hydrogen bond accepting carbonyl group of the lipid and the hydrogen bond donating hydroxyl group of cholesterol. In addition, initial findings by Arnett and co-workers also show clear differences between samples of (R)- and (R,S)-diacylphospholipids by $^{31}$P-NMR, $^1$H-NMR, and differential scanning calorimetry.\textsuperscript{35}

Natural products such as terpenoids or alkaloids often occur as a single enantiomer; yet, it is not uncommon to observe diastereomerism or enantiomerism within a series of compounds. An interesting example is found in the Strychnos alkaloid series (Figure 3) in which the presence of both (+)- and (−)-akuammicine raised difficult biosynthetic questions: e.g., did a separate pathway exist for each enantiomer? In 1973, Scott and Yeh resolved this problem by showing that dihydro-(+)- and (−)-akuammicine could be reversibly interconverted in vitro under simple thermal conditions and proposed a mechanism which accounted for the observed inversion at the three chiral centers of interest.\textsuperscript{36}

Figure 3. Enantiomers in the Strychnos alkaloid series\textsuperscript{35}

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TRANSITION STATE ANALOGS AS ENZYME INHIBITORS

Reported by David Kinder  

Transition state analogs are compounds which resemble the structure of the proposed transition states for enzyme catalyzed reaction. Because they are bound more tightly than substrate, the transition state analogs inhibit enzymatic reactions by forming a dead-end complex with the enzyme. Information from this binding can be used to support a proposed transition state structure for the reaction as well as to provide mechanistic information. Two types of transition state analogs that have yielded a wealth of information are those involving tetrahedral intermediates, and those involving two substrates, referred to now as bisubstrate analogs. These two types will be considered in this review.

Theory. Enzymes catalyze reactions by lowering the activation energy of the transition state. Pauling suggested that this lowering of the activation energy is the result of enzyme binding the transition state more tightly than substrate. Wolenden\(^1\) elaborated a scheme for studying the structure of the substrate as it approaches the transition state, and assumed that the substrate is bound more tightly to the catalytic site as the transition state is approached. The relationships derived from transition state theory are presented in Figure 1 for a single substrate reaction.\(^2\)

![Figure 1](image_url)

After derivation the following relationships may be obtained:

\[
\frac{k_e}{k_{ne}} = \frac{K_S}{K_{TX}} = \frac{K_{e+}}{K_{ne+}}
\]

(1)

where \(K_S\) is the equilibrium constant for the association of substrate with the enzyme, \(K_{e+}\) and \(K_{ne+}\) are equilibrium constants for the formation of the enzymatic and nonenzymatic transition states, respectively, \(K_{TX}\) is the association constant for the formation of the hypothetical activated complex, \(k_e\) and \(k_{ne}\) are first order rate constants for conversion of substrate to product for the catalyzed and uncatalyzed reactions, respectively, and \(K_{e+} = k_e(h/kT)\), where \(h\) and \(k\) are Planck's constant and Boltzmann's constant, respectively; \(T\) is absolute temperature. In the above scheme of enzymatic reactions, \(E\) is ground state enzyme, \(S\) and \(S^+\) are free substrate in the ground and the enzyme catalyzed transition state, \(ES^+\) is enzyme-substrate activated complex, \(ES\) is the enzyme-substrate complex, and \(P\) is product.

By comparison to non-enzymatic model reactions, enzymes lower activation energies by about 10 kcal or more which leads to rate enhancements \((k_e/k_{ne})\) on the order of \(10^8\) to \(10^{14}\). From the series of relationships
(\(K_{TX}/K_q\)) shown in Eq. 1, it follows that a molecule which closely resembles the actual transition state will be bound to the active site more tightly than normal substrate with a binding constant \(10^8\) to \(10^{14}\) greater than normal substrate.\(^2\),\(^3\)

**Design.** In practice, it is impossible to synthesize a perfect transition state analog, since that would involve synthesizing the transition state structure itself, and by its very nature it cannot be isolated and detected. Most, if not all, enzymatic reactions involve high energy intermediates that are bound to the enzyme. These intermediates are then converted to product after passing through a second (or more) transition state. According to the Hammond postulate these high energy intermediates are expected to resemble the transition state for the enzymatic reaction.\(^4\) Transition state analogs are usually designed to resemble the high energy intermediates, and are not expected to exhibit the theoretical binding enhancement. Thus, a transition state analog is distinguished from other potent inhibitors of an enzyme by its resemblance to the transition state structure. As experimental criteria, a transition state analog must be a specific and competitive inhibitor of the enzyme for which it is designed.

A plethora of transition state analogs have been prepared. Wolfenden\(^5\) lists the results of early attempts to design analogs as well as some compounds whose mode of inhibition has subsequently been explained in terms of their binding as transition state analogs. The transition state analogs considered in this paper were prepared for well-studied systems in which much was known about the transition state. In most cases, the transition state analog supports the proposed transition state.

**Tetrahedral Analogs**

**Deamination of Purines and Pyrimidines.** Deamination reactions of purines and pyrimidines are important steps in the biosynthesis of nucleosides as well as metabolism and urea. An example is the conversion of adenosine (1) to inosine (2), shown in Scheme I.

**Scheme I**

![Scheme I](image)

The simplest mechanism for this reaction involves the direct addition of water to form carbinol amine 3.\(^6\) The mechanism for cytidine deaminase,\(^6,7\) and guanase\(^8\) were presumed to be analogous. Transition state analogs have been prepared which resemble 3. One stereoisomer of photoadduct 4 of methanol with purine ribonucleoside was bound 200-fold more tightly than adenosine.\(^9\) The absolute configuration of the photoadduct was not determined, but enhanced binding was not observed for the other isomer. Two antibiotics,\(^10\) coformycin (5) and coidarabine (6), are potent inhibitors of adenosine deaminase and bear a remarkable resemblance to
the photoadduct 4. Taken together, the binding of 4, 5, and 6 support 3 as a model for the transition state.

More recently, analogs containing sulfur and phosphorus have been synthesized. Some examples of these compounds are shown in Figure 2. Phosphorus-oxygen and phosphorus-nitrogen bond lengths are about 10-15\% longer (0.1-0.2 Å) than the corresponding carbon-oxygen and carbon-nitrogen bonds. Sulfur bonds are about 0.1 Å longer. The effect of this increased length was presumed not to be seriously detrimental to the binding (cf. compounds 4–6). Inhibition studies were not performed on phosphorus compounds 7–9 and evaluation of their potential as transition state analogs cannot be made at this time (cf. 9 and 13 compound 13 is a known inhibitor of cytidine deaminase). Sulfur analogs 10 and 11 were bound to guanase about as tightly as substrate guanosine. However, this binding was non-competitive. Compounds 10 and 11 are therefore not transition state analogs for guanase.

**Figure 2**

**Xanthine Oxidase.** Xanthine oxidase catalyzes subsequent oxidations in the metabolism of adenine. The first oxidation affects the 6 position of hypoxanthine. Hypoxanthine is the product (following the removal of ribose) of the deamination of adenine. Xanthine oxidase utilizes oxygen
for catalysis. Several mechanisms have been proposed for xanthine oxidase reactions. One possible mechanism involves addition of water to hypoxanthine followed by coupled transfer of two protons and an electron pair to the enzyme as in Figure 3.

Figure 3

Compounds 10 and 12 which contain tetrahedral sulfur in the position being oxidized, were tested as inhibitors of xanthine oxidase. A positively charged molybdenum in the active site of the enzyme might be expected to increase binding of 10 and 12 since they contain a negative charge at neutral pH. However, no inhibition of xanthine oxidase was observed. Lack of inhibition would be consistent with a mechanism proposed by Olsen et al. in which an enzyme disulfide anion first attacks hypoxanthine followed by displacement by water. The negative charge present on the sulfur analog would then be repulsed by the negative charge in the active site. Lack of binding of these analogs may indicate that a mechanism other than covalent addition of water followed by oxidation is operative in xanthine oxidase catalysis.

Hydrolase Reactions Involving Tetrahedral Intermediates

Proteases. Proteases function by adding water across a peptide bond to generate an acid and amine. The mechanism for serine proteases involves two steps. The first step is addition of serine in the active site to the carbonyl of the peptide to form a tetrahedral intermediate. This is followed by collapse of the tetrahedral intermediate to form the amine and the acyl enzyme. The acyl enzyme is then hydrolyzed in the rate-limiting step to form carboxylic acid and regenerate enzyme.

Revel and Ball noticed that 1-serine in borate buffer reversibly inhibited γ-glutamyl transpeptidase (an enzyme involved in glutathione syntheses). Inhibition did not occur with other buffers. Szweczuk and Connell found that serine in borate buffer protected the enzyme from inactivation by iodoacetamide. Inactivation is caused by alkylation of a serine residue in the active site with iodoacetamide. A model for the active site of glutamyl transpeptidase has recently been proposed. A schematic drawing of the proposed active site with bound substrate is shown in Figure 4 for glutamic acid (A) and the serine-borate complex (B).

Boronic acids inhibit catalysis by subtilisin and chymotrypsin in a manner similar to the inhibition of glutamyl transpeptides by borate ion. Aldehydes are also known to inhibit these enzymes by a similar mechanism. 2-Phenylethaneboronic acid (14) and hydrocinnamaldehyde (15), as well as an analog (16) of hippuric acid (N-benzylyglycine), are potent protease inhibitors with binding constants $10^3 - 10^4$ greater than those of hippuric acid. Methyl hippurate is a substrate for proteolytic enzymes.


The boronic acid analogs are bound to the active site serine and hydrogen bonded to histidine[23] as shown in C in accord with the known mechanism for these proteases.11

An analogous intermediate (D) was proposed for the aldehydes. Confirming evidence has come from NMR studies[24,25] of aldehyde transition state analogs bound by enzyme. Further, trichloromethyl ketones[22] are bound by the enzyme in the unhydrated form suggesting that aldehydes also bind in the unhydrated form.

**Acetylcholine Esterase.** Acetylcholine esterase hydrolyzes the neurotransmitter acetylcholine (18) by a mechanism similar to that of serine proteases.26 Hydrolysis of the acyl enzyme intermediate is the overall rate-determining step.27 Borinic acid analog 19 is competitively bound about $10^3$ times greater than acetylcholine. It is interesting that 2-phenylethanolboronic acid[28] is also bound competitively and about 1 fold greater than acetylcholine despite the presence of a phenyl group in place of the charged trimethylammonium substituent. Presumably ketones[29] will form tetrahedral adducts with the serine in the active site, although they are not as susceptible to nucleophilic attack as aldehydes (cf. aldehyde protease inhibitors). Studies have been performed with trihalomethyl ketones because of the enhanced reactivity of the carbonyl group to nucleophiles. Trifluoromethyl ketone 20 was the most potent inhibitor of acetylcholine esterase and was bound by enzyme to form a very stable adduct. The enzyme could not be fully reactivated following 8 days of dialysis. The nonfluorinated compound 21 was bound by the enzyme $5 \times 10^4$ greater than acetylcholine, and its potential for use in studies of
the synapse is being investigated. Further, trifluoromethyl ketone inhibits the enzyme on a time-dependent basis related to dehydration of the carbonyl hydrate. Nonhalogenated compound, which does not readily form a hydrate, inhibits in a time-independent fashion, for which binding is 125 times greater than that observed for acetylcholine. These results are consistent with formation of a tetrahedral intermediate at the transition state. The results are also consistent with X-ray evidence that trichloromethyl ketones bind sublillisin as the tetrahedral hemiketal.

\[
\begin{align*}
18 & \quad \text{(CH}_3)_3N-\text{CH}_2\text{CH}_2-O-C-\text{CH}_3 \\
19 & \quad \text{(CH}_3)_3NCH_2-\text{CH}_2\text{CH}_2-B-\text{CH}_3 \\
20 & \quad \text{(CH}_3)_3N-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CCH}_3 \\
21 & \quad \text{(CH}_3)_3N-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CH}_3 \\
22 & \quad \text{(CH}_3)_3N-\text{CH}_2\text{CH}_2-0-\text{C-CH}_3
\end{align*}
\]

Thermolysin. Thermolysin is an endopeptidase isolated from B. Thermo-proteolyticus. Phosphoramidon \((23, K_i \text{ about } 10^{-9} \text{M}^{-1})\) is a potent inhibitor of thermolysin which is isolated for cultures of actinomycetes. Phosphoramidon contains a tetrahedral phosphorus in place of the scissile peptide bond and thus resembles the tetrahedral transition state for the hydrolysis reaction. A considerable amount of evidence concerning the mechanism of hydrolysis and mode of binding of substrates to the enzyme has been gained using phosphoramidon. The mechanism of action of thermolysin is thought to be similar to that of carboxypeptidase A. Phosphoramidon does not inhibit α-chymotrypsin or other proteases that have similar specificity, indicating a different mechanism is operative for these enzymes. Thermolysin has been crystallized with phosphoramidon in the active site. The X-ray crystallography structure shows that phosphoramidon is bound with a phosphate oxygen coordinated to the Zn ion in the active site in the same way as the tetrahedral intermediate would be coordinated after addition of water. The structure also shows a glutamate residue near the scissile bond which may facilitate general base catalysis. The sugar residue does not appreciably affect binding of phosphoramidon to thermolysin. When the sugar residue is removed from phosphoramidon, binding is only slightly increased. This result is consistent with dipeptide mapping studies that indicate the positon occupied by the sugar residue of phosphoramidon does not enter into binding of substrate.
Thus, studies with phosphoramidon support a mechanism for themolysin that involves general base catalysis and a tetrahedral intermediate.

Bisubstrate Analogs. Transition state analogs that resemble the transition state for the reaction of two substrates can be called bisubstrate analogs. Caution must be exercised in interpreting the binding data from a bisubstrate analog since favorable entropic contributions to binding are gained by connecting together the two substrates. An early bisubstrate analog, pyridoxyl-alanine (24), was found to inhibit pyridox-amine-pyruvate transaminase about 200-fold better than binding of either substrate alanine or pyridoxal. This was said to be consistent with a mechanism involving an enzyme bound Schiff base intermediate.

\[ \text{N-(Phosphonacetyl)-l-aspartate.} \]

The bisubstrate analog that has received the most attention is N-(phosphonacetyl)-l-aspartate (25, PALA), which inhibits aspartate transcarbamylase. This enzyme is involved in the first steps of pyrimidine biosynthesis. Figure 5 shows the substrates and products of the reaction, along with PALA. PALA evidently is bound on both the carbamyl phosphate and aspartate sites with an affinity 10^3 times greater than that of carbamyl phosphate, the most tightly bound of the substrates.

Important information has been gained concerning enzyme conformational changes as well as subunit interactions from studies with PALA. On binding PALA, the enzyme apparently adopts a conformation resembling the transition state complex. The sedimentation coefficient of the enzyme-PALA complex is increased by 1% over that of the native enzyme. An increase in sedimentation coefficient of 0.3% would be expected from binding of both substrates alone, and suggest that conformational changes are intimately involved in catalysis.

PALA has shown clinical promise as an antitumor agent. It has also been quite useful in the study of the sequence of reactions involved in uridine biosynthesis.
5-N-(Phosphonacyl)-L-ornithine. Similarity is seen between L-ornithine carbamyl transferase, which is involved in urea biosynthesis, and L-aspartate transcarbamylase. Transition state analogs similar to PALA have been prepared for ornithine carbamyl transferase. The most effective analog is 5-N-(phosphonacyl)-L-ornithine (26) which is bound 250-fold more tightly than carbamyl phosphate. Since the binding of 26 is not competitive with the binding of ornithine, an ordered mechanism is operative.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O}_2C-C-(CH_2)_3-N-C-CH_2-P-O^- & +NH_3 \\
\text{O} & \\
\end{align*}
\]

26

Kinase Reactions. Phosphate transfer reactions are important in biosynthesis as well as energy transfer and storage reactions. Creatine kinase catalyzes the transfer of phosphate from creatine phosphate to ADP. A bisubstrate analog has been used to study phosphate transfer by creatine kinase. The analog is a complex of creatine, MgADP, and nitrate that is formed in the active site. The planar nitrate ion is presumed to simulate a trigonal bipyramidal transition state for the transfer of phosphate as shown in Figure 6.

**Figure 6**

The planar anions HCO$_3^-$, HCO$_2^-$, and NO$_2^-$ were found to form inhibitory complexes while tetrahedral ions such as phosphate and sulfate were ineffective.

Recently the existence of two different binding sites on creatine kinase with different affinities for substrates has been revealed by phosphorus-NMR studies with the creatine-MgADP-nitrate complex. The second binding has a reduced affinity for substrates as well as for the transition state analog.

Creatine-MgADP-nitrate complex has also been useful in studying the function of Mg ion in the transfer of phosphate. The Mg ion was observed to coordinate to the nitrate ion. Infrared absorption spectroscopy was used to observed the coordination. The authors inferred that the Mg ion coordinates to the PO$_4^{2-}$ in the transition state for phosphate transfer. Further support for the trigonal bipyramidal transition state for phosphate transfer comes from studies with arginine kinase and adenylate kinase transition state analog complexes.
Conclusion. While the transition state of an enzymatic reaction may never be proven, much evidence can be gained in support of postulated transition states or against alternate transition states through the use of transition state analogs designed as enzyme inhibitors. The design of more potent enzyme inhibitors is being undertaken by many researchers in hopes that ambiguities concerning transition state and activated intermediate structures can be eliminated. Undoubtedly, this will require the synthesis of less easily prepared analogs and close collaboration between organic chemists and biochemists.

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14. See ref. 4, pg. 153.
ORGANIC SEMINAR ABSTRACTS

1980-81, Semester I

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SEMINAR TOPICS

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\(^6\)-Arenetricarbonyl-chromium(0) Complexes in Organic Synthesis.................................1
  Daniel Dess

Introduction of Sulfur into Organic Compounds for the Preparation of Thiols, Thiiranes and Thioketones.........................10
  Julie L. Rickard

Metathetical Reactions of Trivalent Pnictogens..........................................................20
  Scott A. Culley

Organotin Reagents: Versatile Intermediates for Organic Synthesis........................................29
  John Lloyd

Ozonations on Solid Supports.................................................................32
  Joan Z. Suits

Bis(Triphenylphosphine)Nickel Dichloride Catalyzed Grignard Substitution Reactions..................42
  Steve Ashburn

Permutational Isomerization in Hexacoordinate Derivatives of Non-metallic Elements..................52
  Ronald S. Michalak

Synthesis and Utility of Vinylsilanes in Organic Synthesis..............................................54
  Pam Albaugh-Robertson

Mechanistic Aspects of the Phototautomerism of Phenols and Aromatic Ketones.....................58
  Sander G. Mills

Two Dimensional Nuclear Magnetic Resonance and Some Applications in Organic Chemistry..........61
  Tuyen T. Nguyen

Asymmetric Catalytic Hydrogenation of Prochiral Amino Acid Precursors................................68
  Jack Muskopf

New 2-Substituted Allyl Anions: \(\beta\)' Lithiation of \(\alpha,\beta\)-Unsaturated Secondary Amides............70
  Dale Kempf
The Ugi Reaction.................................................................73
Jim Gloer

Solid State Organic Photocyclizations.......................................83
Barbara Murray

Interferons; Structures and Technologies....................................86
Gary Harbour

The Inhibition of Thymidylate Synthetase
by 5-Substituted Uridines................................................95
Marc d'Alarcao

The Chemistry of Tetracyanoethylene........................................104
A. Bashir-Hashemi

Remote Functionalization Reactions.........................................113
Venkatesalu Bakthavachalam

Hypervalent Hydrogen..........................................................117
Charles Perkins
\( \eta^6 \)-Arenetricarbonyl-chromium(0) Complexes in Organic Synthesis

Reported by Daniel Dess  
September 4, 1980

Introduction. Reactions that interchange or introduce substituent groups on aromatic rings are very important in organic chemistry. The most common method for introducing a substituent is electrophilic aromatic substitution. Nucleophilic aromatic substitution is also important. This method requires that a leaving group be present on the ring and usually requires that some electron withdrawing group also be present. Recently it has been observed that coordination of a chromium tricarbonyl unit to an aromatic ring via \( \Pi \) bonding increases the reactivity of the ring toward attack by nucleophiles.\(^2,3\) Unlike activating groups used in classical nucleophilic aromatic substitution, the chromium tricarbonyl unit is easily attached and removed.\(^2,3\) These \( \eta^6 \)-arenetricarbonylchromium(0) (\( \eta^6 \)-arene TCC) complexes have shown promise as useful reagents for the introduction of alkyl substituent groups on aromatic rings. This report will present the scope and limitations of this reaction and proposed mechanisms. Methods for synthesizing \( \eta^6 \)-arenetricarbonylchromium will also be outlined.

Preparation of \( \eta^6 \)-Arenetricarbonylchromium(0) Complexes. \( \eta^6 \)-benzenetricarbonylchromium was synthesized for the first time by combining dibenzene chromium and chromium hexacarbonyl in benzene in a sealed system at 220°.\(^4\) A simpler method has since been devised (Eq.1) in which chromium hexacarbonyl (2) and the aromatic compound (1) are heated at reflux at atmospheric pressure in diethylene glycol dimethyl ether, decalin or di-n-butyl ether\(^3,5\) (Eq.1). The reacting aromatic compound has also been used as the solvent. Aromatic compounds containing electron withdrawing substituents usually do not give good yields of \( \eta^6 \)-arene TCCs.\(^3\) Aromatic compounds with para substituents generally give poor yields also.\(^3\)

\[
\begin{array}{c}
\text{reflux} \\
\xrightarrow{\text{TCC}} \\
\end{array}
\]

\( \eta^6 \)-benzenetricarbonylchromium was synthesized for the first time by combining dibenzene chromium and chromium hexacarbonyl in benzene in a sealed system at 220°. \( \eta^6 \)-benzenetricarbonylchromium was synthesized for the first time by combining dibenzene chromium and chromium hexacarbonyl in benzene in a sealed system at 220°. \( \eta^6 \)-benzenetricarbonylchromium was synthesized for the first time by combining dibenzene chromium and chromium hexacarbonyl in benzene in a sealed system at 220°. A simpler method has since been devised (Eq.1) in which chromium hexacarbonyl (2) and the aromatic compound (1) are heated at reflux at atmospheric pressure in diethylene glycol dimethyl ether, decalin or di-n-butyl ether (Eq.1). The reacting aromatic compound has also been used as the solvent. Aromatic compounds containing electron withdrawing substituents usually do not give good yields of \( \eta^6 \)-arene TCCs. Aromatic compounds with para substituents generally give poor yields also.
$\eta^6$-Arene TCC are stable in air, and do not react rapidly with aqueous base or acid or reducing agents such as lithium aluminum hydride. Reaction with mild oxidizing agents such as manganese dioxide, cerium (IV), and iodine regenerates the aromatic compound, chromium (III) species, and carbon monoxide (Eq. 2). Reaction of the complexes with refluxing pyridine also regenerates the aromatic compound (Eq. 3).

$$\text{excess I}_2 \xrightarrow{\text{Et}_2\text{O}, 25^\circ\text{C, 3 hrs.}} \text{R} - \text{X} + \text{Cr(III)} + \text{CO}$$ (2)

$$\text{R} - \text{X} \xrightarrow{\text{pyridine reflux}} \text{R} - \text{X} + \text{Cr(py)_3(CO)_3}$$ (3)

The pKa of Cr(CO)$_3$C$_6$H$_5$COOH is 4.77. The pKa of p-nitro benzoic acid is 4.48. Thus the tricarbonyl chromium group exerts an electron withdrawing effect comparable to a para nitro group.

Reactions of $\eta^6$-Arene TCCs. $\eta^6$-Arene TCCs owe their synthetic utility to the fact that the chromium tricarbonyl unit is electron withdrawing and thus activates the ring to nucleophilic addition. Organolithium compounds react with 3a at 0°C in THF or THF/HMPA to give $\eta^5$-cyclohexadienyl TCCs.

$$\text{R} - \text{Li} \xrightarrow{0^\circ\text{C, THF or THF/HMPA}} \text{R} - \text{LiCH}_3\text{COO-t-Bu}$$

<table>
<thead>
<tr>
<th>Carbanion (6)</th>
<th>Product (6)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Li(CH$_3$)$_2$CCN</td>
<td>6a</td>
<td>93</td>
</tr>
<tr>
<td>b Li(CH$_3$)$_2$CCN</td>
<td>6b</td>
<td>94</td>
</tr>
<tr>
<td>c Li(CH$_3$)$_2$CCN</td>
<td>6c</td>
<td>71</td>
</tr>
<tr>
<td>d Li(CH$_3$)$_2$CCN</td>
<td>6d</td>
<td>97</td>
</tr>
<tr>
<td>e Li(CH$_3$)$_2$CCN</td>
<td>6e</td>
<td>87</td>
</tr>
</tbody>
</table>
These complexes are stable in solution under an inert atmosphere for long periods when kept at or below 0°C. They decompose rapidly upon exposure to water or oxidizing agents.

The proposed structure of the complexes is based on \(^1\)H NMR spectra for several different R groups. When R is 1,3-dithianyl, 5a is stable enough to isolate as a crystalline solid. X-ray diffraction studies of the crystal have confirmed the structure 5a.

Complex 5 undergoes several interesting reactions as illustrated in scheme 1. Addition of I\(_2\) to a solution of 5 in ether at 25°C gives the free aromatic ligand and chromium (III) species. The two step conversion of 3 to 6 is equivalent to formal nucleophilic displacement of hydride (Eq. 4). This sequence has been found to be a convenient method for synthesizing a wide variety of alkyl substituted aromatic compounds. Organolithium compounds that have been found to add to \(\eta^6\)-benzene TCC in high yield include the lithium salts of esters, nitriles, 1,3-dithiane acetals, and cyanohydrin-acetals.

**Scheme I**

![Scheme I Diagram](image)

Anomalous results have been reported for the reaction of n-butyl lithium and \(\eta^6\)-arene TCCs. While other carbanions added to the \(\Pi\) system of the arene, including tert-butyl lithium, n-butyl lithium acted as a base producing the lithiated species 7 (Eq. 5). Electrophiles...
react with 7a-d to produce new \( \eta^6 \)-arene TCC complexes with elaborated substituents. This reaction sequence has proved to be an efficient method for synthesizing \( \eta^6 \)-arene TCC complexes not available by the other method. At temperatures above \(-10^\circ C\), n-butyl lithium reacts with \( \eta^6 \)-phenyl lithium TCC (7a) to produce n-butyl benzene in high yield. No oxidation step is necessary to free the arene ligand (Eq. 6). Although

\[
\begin{align*}
\text{Cyclohexadienyl TCCs also undergo a ligand transfer reaction with} & \quad \text{the parent} \ \eta^6\text{-benzene TCC.} \\
\text{The ligand transfer reaction (Eq. 8) occurs} & \quad \text{more rapidly than the ligand exchange reaction (0.25 h at 0^\circ \text{C}). For this} \\
\text{reason it has been postulated that the transfer reaction occurs by direct}
\end{align*}
\]
interaction of the ligand on the exoface of 9 with the exoface of 3a. 

$\eta^5$-Cyclohexadienyl complexes react with protic acids to give products characteristic of the strength and amount of the acid used. When $\text{H}_2\text{O}$ is added to a solution of 5b, the products are 3a and 4b (Eq. 9). When D$_2$O is used, 4b is found to contain greater than 90% deuterium at the two position. Complex 3a is found to contain no significant amount of deuterium. As the ligand transfer reaction, this reaction occurs rapidly (1 h at 25°C). The rate of the reaction argues against rate limiting dissociation of 5b to 3a and 4b. It is thus more likely that water reacts directly with 5b. Similar results are obtained with other weak acids or with one equivalent of trifluoroacetic acid (TFA).

When 5b was treated with a five fold excess of TFA, followed by treatment with I$_2$ or NH$_4$OH, the cyclohexadienes 10a-c were obtained (Eq. 10).

Pathways considered for this reaction are illustrated in scheme 2. When the reaction was monitored by H$^1$ NMR no evidence for either pathway was obtained. The net 3 step conversion of 3a to 10a-c is the equivalent of the addition of R-H across an aromatic $\pi$-bond. This reaction, like the substitution reaction, has shown promise as a useful synthetic technique for the synthesis of cyclohexadienes and cyclohexenones.
\[ \eta^3\text{-cyclohexadienyl TCCs react with electrophiles to regenerate 3a.} \]

When 5b reacts with benzophenone, triphenyl carbenium fluoroborate, methyl iodide, or triisopropyl borane, 3a is regenerated in high yield (Eq. 11).

When electrophile is benzophenone, the electrophile ligand adduct, 11, 3-hydroxy-2,2-dimethyl-3,3-diphenylpropionitrile, is isolated in 93% yield. The reaction is over in 0.5 hr at 0°C. The observed rate indicates that the electrophile probably reacts directly with the complex rather than with the dissociated ligand. These reactions were part of an attempt to find an electrophile that would abstract preferentially the endo hydride and generate a new \( \eta^6 \)-arene TCC complex that could undergo the substitution reaction again. Such an electrophile would greatly extend the utility of \( \eta^6 \)-arene TCCs as synthetic intermediates. Highly elaborate aromatic compounds could be synthesized in a straightforward stepwise manner.

The synthetic utility of the substitution reaction can be extended by making use of the directing effects of substituents already on the ring. When a carbanion is allowed to react with \( \eta^6 \)-anisole TCC, the product is almost exclusively that of substitution meta to the methoxy group. A small amount of ortho substitution occurs but no para product is observed. Similar results are obtained when the substituent is methyl, ethyl, or dimethyl amino (Eq. 12). Preliminary results have shown that the trifluoromethyl, tert-butyl and trimethyl silyl groups favor para substitution. Substantial amounts of meta substitution occur in the presence of the trifluoromethyl and tert-butyl groups but no ortho products are obtained. When the substituent is chloro, mixtures of meta and ortho substituted products are obtained. Selectivity is low.
Presently no satisfactory proposal has been advanced to explain these directing effects. Preliminary attempts to explain the directing effects with models derived from molecular orbital theory have failed. The regiospecificity cannot be consistently explained on the basis of steric effects.

Halogen substituted η⁶-arene TCCs undergo two types of reactions with nucleophiles, the substitution reaction, as discussed earlier, and what appears to be direct nucleophilic displacement of halogen. Complexes 14 and 15 are the immediate products of the reaction between 3d and a carbanion. They are in equilibrium with 3d which is in equilibrium with 18. Complex 18 can irreversibly lose halide to form 19. Fluoride is lost as readily as chloride in this reaction. Groups such as methoxyl might also be expected to undergo displacement but this has not been observed. Methoxide does however efficiently replace chloride or fluoride. The net nucleophilic displacement of halogen has also shown promise as a useful synthetic technique.

When two substituents are present on a ring, their directing effects can oppose or reinforce each other. The directing effects of the methoxy groups in 21 oppose each other. The more sterically hindered product
is obtained preferentially. Apparently the tendency to avoid substitution para to a methoxy group is quite strong. When the less sterically demanding lithio cyano methane reacts with 21 only the 1,2,3 isomer is formed. In 23 the directing effects of the trimethyl silyl and methoxy groups reinforce each other. Only 25 is formed (82% yield).

Conclusion. Preliminary results have shown that \( \eta^6 \)-arene TCCs allow the facile introduction of alkyl substituents on aromatic rings. This method also allows the direct introduction of alkyl groups that could not be readily introduced by conventional methods. The substituent directing effects observed in \( \eta^6 \)-arene TCCs complement those observed in classical electrophilic aromatic substitution. Groups that direct ortho-para in electrophilic substitution direct meta in the \( \eta^6 \)-arene TCC addition reaction. \( \eta^6 \)-arene TCCs also allow formal addition of R-H across an aromatic \( \pi \)-bond. Thus \( \eta^6 \)-arene TCCs open up a whole new range of chemistry for aromatic compounds.

BIBLIOGRAPHY

INTRODUCTION OF SULFUR INTO ORGANIC COMPOUNDS FOR THE PREPARATION OF THIOLS, THIIRANES AND THIOKETONES.

Reported by Julie L. Rickard September 8, 1980

Introduction. Compounds containing sulfur are useful to the synthetic organic chemist as protecting groups. These compounds are also interesting because their chemistry is different from that of the oxygen containing compounds.

How does one introduce sulfur into an organic compounds? German chemists discovered methods in the nineteenth century which have become text-book preparations. This report will review the early standard methods and will outline recent developments in the preparation of thiols, thiiranes and thioketones.

Thiols. There are three standard preparations for thiols: hydrogen sulfide addition to an olefin (Method 1),\(^1\),\(^2\),\(^3\) hydrosulfide displacement of a halide or pseudohalide, (Method 2)\(^4\),\(^5\) and by alkylation of thiourea by alkyl halides followed by hydrolysis (Method 3).\(^5\) The series of reaction involving S-alkylation of thiourea is the father of most modern preparations of thiols.

N-Alkyl-2(1-H)-pyridothione\(^6\) (1) reacts with alkyl halides to give an intermediate salt (2) which is hydrolyzed under basic conditions (Method 4).\(^6\)

\[
\begin{align*}
\text{Method 4} \\
\text{N} = \text{N} \\
\text{R} = \text{R} \\
\text{S} = \text{S} \\
\text{X} = \text{X} \\
\text{OH}^- \\
\text{RSH}
\end{align*}
\]

The rate of formation of intermediate 2 from primary alkyl halides is four times faster than that from secondary alkyl halides when the alkyl halide and 1 are heated in refluxing ethanol in a one to one stoichiometry.\(^6\) However, initial reaction kinetics have not been studied. Secondary thiols are prepared in about 70% over all yield\(^6\) whereas in the thiourea case the yield of secondary thiols is not reported\(^5\) (see Table 1). This is the only reagent presently in the literature used to thiolate halo sugars;\(^6\) it is also used for the thiolation of α-halo ketones,\(^6\) and β-halo- and α-halocarboxylic esters.\(^6\)

N,N-Dialkyl dithiocarbamic acids and their salts\(^7\) are easily prepared (see Method 5). The N,N-dialkyl dithiocarbamate anion displaces chlorides\(^7\) where thiourea is not alkylated by chlorides.\(^5\) This method of preparation yields more thiol than does the hydrosulfide salt method (see Table 1).
Method 5

1) $\text{R}_2\text{NH} + \text{NaOH} + \text{CS}_2 \rightarrow \text{R}_2\text{N}^-\text{S}^-\text{Na}^+ + \text{H}_2\text{O}$

2) $\text{R}_2\text{N}^-\text{S}^-\text{Na}^+ + \text{RX} \rightarrow \text{R}-\text{S}^-\text{NR}_1$

   $X^- = \text{Cl}^-, \text{Br}^-, \text{I}^-$

3) $\text{R}_2\text{N}^-\text{S}^-\text{Na}^+ + 5 \text{NaOH} \rightarrow \text{RSH} + \text{Na}_2\text{S} + \text{Na}_2\text{CO}_3 + 2\text{H}_2\text{O}$

4) $\text{R}_2\text{N}^-\text{S}^-\text{Na}^+ + \text{H}_2\text{NNH}_2 \rightarrow \text{RSH} + \text{H}_2\text{NNH}_2\text{NR}_1$

The N,N-dialkyl dithiocarbamic acid ester (4) can be degraded in two ways; by means of sodium hydroxide in aqueous alcohol or by means of hydrazine in ethanol. This allows compounds which are alkali or water sensitive to be prepared.

Preparation of optically active thiols has been achieved using an enantiomeric mixture of the halide and an optically active derivative of O-alkyl dithiocarbamic acid (Method 6). Such derivatives are easily obtained from the optically active alcohol, sodium, and carbon disulfide. Once the diastereomers are separated the ester (5) is decomposed with morpholine. The yields of optically active thiol were approximately 17% with an optical purity of 97 to 99%.

N,N-Dimethylthiolformamide (6) has been used in the preparation of thiols. 6 is S-alkylated by an alkyl bromide or alkyl iodide, alkyl chlorides give no S-alkylation, and the intermediate is then solvolysed with methanol (Method 7) giving yields of 85-95% (see Table 1). Secondary halides did not give thiol.
Method 7

If in Method 3 acetylthiourea \((7, R' = \text{Me})\) or benzoylthiourea \((7, R' = \emptyset)\) is used instead of thiourea, there is no separate hydrolysis step necessary. Use of these activated thioureas allows alkali and water sensitive thiols to be generated. Acetylthiourea is preferred because one of the by-

Method 8

products ethyl acetate is more easily removed than the ethyl benzoate from benzoylthiourea\(^{5c}\) (Method 8, Eq. 2). This reaction serves to inactivate \(7\), thus making quantative yields of thiol unachievable.\(^{5c}\) Unfortunately, like thiourea, \(\beta\) elimination is possible. The reaction of 2-bromoethylamine hydrobromide \((2)\) with acetylthiourea \((7, R' = \text{Me})\) produces a polymer like that obtained from thiirane\(^{5c}\) (Method 8, Eq. 3).
Table 1. Yields of Thiol from Discussed Reaction Methods

<table>
<thead>
<tr>
<th>Thiol</th>
<th>Method 1</th>
<th>Method 2</th>
<th>Method 3</th>
<th>Method 4</th>
<th>Method 5</th>
<th>Method 6</th>
<th>Method 7</th>
<th>Method 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCHSH</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>HSH</td>
<td>49%</td>
<td>49%</td>
<td>79%</td>
<td>4%</td>
<td>5%</td>
<td>quant.</td>
<td>76%</td>
<td>5c%</td>
</tr>
<tr>
<td>HSH</td>
<td>70%</td>
<td>4%</td>
<td>90%</td>
<td>6%</td>
<td>82%</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSH</td>
<td>66%</td>
<td>4%</td>
<td></td>
<td>82%</td>
<td>6%</td>
<td>92%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>HSH</td>
<td>14%</td>
<td>4%</td>
<td></td>
<td>70%</td>
<td>6%</td>
<td></td>
<td>0%</td>
<td>10%</td>
</tr>
</tbody>
</table>

(a) calculated by olefin consumption
(b) 98% (-) isomer

Thiiranes. Thiiranes, unlike their oxygen analogues, have not been prepared in one step from the corresponding olefins. Sulfur monochloride adds to olefins to give \( \beta,\delta \)-dichloroalkylidisulfides which are subsequently reduced to yield thiiranes (Method 9). Another standard method of preparing thiiranes is by the reaction epoxides and one of the following: thiourea, thiocyanates or thiosulfates (Method 10). 1,3,4-oxadiazoles react with hydrogen sulfide constituting a standard preparation of tetraaryl thiiranes.

More recently iodine thiocyanate \(^1\) has been used to prepare thiiranes from olefins. \(^1\) Iodine thiocyanate (10), prepared from iodine and thiocyanogen (Method 11, Eq. 1), \(^1\) adds to the double bond of the cyclic olefin; \(^1\) the thiol is produced upon basic hydrolysis at room temperature \(^1\) (Method 11, Eq. 2).

Method 11

1) \( I_2 + (SCN)_2 \rightarrow 2ISCN \)

2) \( \text{Base} \)

This method gives yields which are better than the sulfur monochloride method, (see Table 3) however, it can only be used on cyclic alkenes. \(^2\) Iodine thiocyanate is also used to prepare 2\( \beta \),3\( \beta \)-Epithio-5\( \alpha \)-cholestane in 46\% yield from 2-cholestene. \(^2\)
Epoxides have been transformed into thiiranes by the use of phosphine sulfides.\textsuperscript{14} This method gives poorer yields than either the thiocyanate or thiophosphite methods (see Table 3), however, thiirane preparation is stereospecific.\textsuperscript{14} The best yields are obtained when trifluoroacetic acid is used for a catalyst.\textsuperscript{14} The only phosphine sulfides that have been used have been tri-t-butyl- or triphenylphosphine sulfides. Chan and Finkenbine believe the mechanism they have proposed (Method 12) can be substantiated by using an optically active phosphine sulfide.\textsuperscript{14} This work has not been completed.

In 1975 a series of reagents (of form 11)\textsuperscript{12a,15} was prepared to convert aldehydes and ketones to thiiranes.\textsuperscript{12a,15} These reagents add to the carbonyl carbon (Method 13, Eq. 1); the intermediates are acidified and hydrolysed under basic conditions (Method 13, Eq. 2).\textsuperscript{12a,15} The substituents used for \( R \) vary a great deal but those for \( R' \) can be phenyl, vinyl or hydrogen.\textsuperscript{12a} Other substituents have been used for \( R' \) but polymerization of reagent 11 occurs.\textsuperscript{12a} Yields of thiirane from this method range from 61 to 78%.
When R of 11 is 13 or 14 (see Table 2) the reaction is stereospecific.\textsuperscript{12a,15} When R is 15 there is no hydrolysis step needed.\textsuperscript{12a} Base sensitive compounds can be prepared in this manner. When R is 16 or 17 some ketones will form olefins rather than thiiranes.\textsuperscript{12a}

\begin{table}[h]
\centering
\caption{Alkyl Moieties For Reagents of Form 11}
\begin{tabular}{|c|c|c|c|c|}
\hline
13 & 14 & 15 & 16 & 17 \\
\hline
\includegraphics[width=0.2\textwidth]{image1} & \includegraphics[width=0.2\textwidth]{image2} & \includegraphics[width=0.2\textwidth]{image3} & \includegraphics[width=0.2\textwidth]{image4} & \includegraphics[width=0.2\textwidth]{image5} \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Yields of Thiiranes from Discussed Reaction Methods}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Thiiranes & Reaction Methods & 9 & 10 & 11 & 12 & 13 \\
\hline
 & & \% yield ref & \% yield ref & \% yield ref & \% yield ref & \% yield ref \\
\hline
 & & 36 & 11 & 70 & 1 & 40 & 12 & 50 & 14 \\
\hline
 & & 47 & 11 & 57 & 12 & 44 & 14 \\
\hline
Styrene thiirane & & 62 & 14 & 80 & 13a \\
\hline
 & & 58 & 12 & 73 & 15 \\
\hline
\end{tabular}
\end{table}

Thioketones. Hydrogen sulfide is also used in two standard preparations of thioketones. If compounds with geminal leaving groups and one of the following: hydrogen sulfide,\textsuperscript{11,16} thiocarboxylic acid,\textsuperscript{11,17a} 0-alkyldithiocarboxylic acid\textsuperscript{11,17} or thiourea,\textsuperscript{1} are heated to reflux in an alcoholic solution of thioketone results\textsuperscript{1} (Method 15). Hydrogen sulfide is also added to ketones in the presence of a catalytic amount of hydrochloric or hydrofluoric acid to prepare thioketones\textsuperscript{1,5a,16b,c,18} (Method 16).

Phosphorous pentasulfide has been used for the preparation of thioketones for many years.\textsuperscript{1} Reaction conditions have been changed and analogues have been prepared to try to improve the scope and the yield of this reaction.\textsuperscript{19} Phosphorous pentasulfide has been used with non-polar solvents but recently polar solvents have been used and carbonate or bicarbonate salts are being added to the reaction mixture.\textsuperscript{19} The reason for these changes can be seen in Method 17. Phosphorous pentasulfide is in equilibrium with a reactive
Method 17

1) \( \text{P}_4\text{S}_{10} \rightleftharpoons 2\text{SPS}_2^- + \text{PS}_2^+ \text{complexes} \)

2) \( \text{P}_4\text{S}_{10} + 2\text{CO}_2 \rightarrow 2\text{SPS}_2^- + 2\text{OPS}_2^- + 2\text{CO}_2 \)

3) \( \text{SPS}_2^- + \text{R}^1\text{CHO} \rightarrow \text{R}^1\text{S} + \text{OPS}_2^- \)

Ionic intermediate 18 if a polar solvent is used the equilibrium will favor the side of the intermediate. 16,18 Upon the addition of carbonate and subsequent loss of carbon dioxide, there is no longer an equilibrium, the reaction is driven to the products side. 19 The reaction rate is increased if \( \text{R} \) and \( \text{R}' \) (Method 17, Eq. 3) are electronegative; 19 this indicates nucleophilic attack on the carbonyl carbon. 19

Two reagents in the phosphorous pentasulfide family are silicon disulfide 20 (19) and boron sulfide. 20 The products from the reaction of these two compounds are insoluble complexes instead of acid anhydrides 20 observed in the reaction of phosphorous pentasulfide (Method 17). They react with ketones which release electrons toward the carbonyl group (Method 18, Eq. 1) indicating the initial reaction is at the carbonyl oxygen. 20 Compounds such as m-nitrobenzaldehyde give no reaction. 20 Cyclic \( \alpha,\beta \)-unsaturated ketones with hydroxy or alkoxy substituents in the \( \beta \) position, such as 20, form unreactive, insoluble complexes (21) (Method 18, Eq. 2). This makes silicon disulfide (19) unsuitable for the conversion of ketones such as 20 to thioketones. 20 Of silicon disulfide, phosphorous pentasulfide and boron sulfide, silicon disulfide is considered the mildest. 20
Boron sulfide is the most efficient of these three reagents and unlike phosphorous pentasulfide and silicon disulfide, it gives no byproducts.\textsuperscript{20} Low temperatures can be used for reaction with boron sulfide.\textsuperscript{20} Parallel experiments have been run with flavone and after one hour boron sulfide had almost completed the conversion to the thioflavone whereas with phosphorous pentasulfide and silicon disulfide the starting material was recovered quantitatively.

All three reagents give complex mixtures when enolizable hydrogen atoms are present in the ketone.\textsuperscript{20}

\textbf{Method 19}

\[
\begin{align*}
\text{MeO-} & + 23 \rightarrow \text{EtO} \quad \text{EtO} \quad \text{EtOH} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{SP(OEt)$_2$} \\
\text{S} & \quad \text{HOP(OEt)$_2$} \\
\end{align*}
\]

Derivatives of phosphorous pentasulfide have been prepared. P-methoxyphenylthionophosphine\textsuperscript{21} (22) has been used to produce thio ketones from ketones with fewer side reactions than phosphorous pentasulfide.\textsuperscript{21} The first example of any thiobenzylopyridines has been produced by the reaction of 22 and 3-benzoxylyridine.\textsuperscript{21} Yields of thioketone are better using 22 than phosphorous pentasulfide (see Table 4, Method 19).\textsuperscript{21} No mechanistic work has been done on this reaction.\textsuperscript{21}

\textit{O},\textit{O}-diethyl dithiophosphoric acid (23)\textsuperscript{16C,22} also reacts with ketones to form thioketones; the reaction is done at lower temperature and needs more time.\textsuperscript{22} Oae, Nakanishi and Tsujimoto suggest Method 19, Eq. 1 as the mechanism for the conversion of ketone to thioketone.\textsuperscript{22}

\textbf{Method 20}

\[
\begin{align*}
\text{CF$_3$Hg} & + \text{S} \rightarrow \text{CF$_3$F} \quad \text{CF$_3$F} \\
\text{CF$_3$} & \quad \text{CF$_3$} \\
\text{CF$_3$} & \quad \text{CF$_3$} \\
& \quad \text{S} \\
& \quad \text{S} \\
\end{align*}
\]
Elemental sulfur has also been used as a source of sulfur in some interesting thiokecone synthesis. Thiohexafluoroacetone\textsuperscript{23} is prepared from the dialkyl mercury and sulfur (Method 20).\textsuperscript{23} An excess of triphenyl phosphine causes dimerization.\textsuperscript{23} The mechanism suggested in Method 20 by Middleton, Howard and Sharkey involves nucleophilic attack of triphenyl phosphine on fluorine instead of sulfur.\textsuperscript{23} If polysulfides are involved \((n > 2)\) excess triphenylphosphine is necessary to remove the excess sulfur.\textsuperscript{23} Most perfluorothioke tones are prepared in this manner.

Sulfur is also introduced into hindered ketones by elemental sulfur. From the ketone the hydrazone (24) is prepared to which triphenyl dibromophosphine is added (Method 21).\textsuperscript{24} The triphenylphosphorylidene hydrazone (25) is melted with sulfur under a vacuum and the thioketone pumped out.\textsuperscript{24} This reaction is an analogue of Barton's selenoketone synthesis.\textsuperscript{24} The unoptimized yield of di-t-butylthione is 83\%.

\begin{center}
\textbf{Method 21}
\end{center}

\begin{center}
\begin{tabular}{c c c c}
\hline
Thioketone & Reaction Methods & \% yield & ref \\
\hline
\hline
\hline
\hline
thioflavone & 15 & 17a & 86 & 17b & 75 & 19 & 95 & 18b \\
\hline
\end{tabular}
\end{center}
Summary. S-alkylation of thiolating agents and subsequent decomposition of the formed complex serve as the primary method of preparation of thiols, thiiranes and thioketones. Thiolating reagents, recently developed, have resulted in higher yields and stereospecific products and the preparation of thiols, thiiranes, and thioketones which were unknown twenty years ago.

BIBLIOGRAPHY

Metathetical Reactions of Trivalent Pnictogens

Reported by Scott Anthony Culley
September 11, 1980

A metathetical reaction is simply an exchange of ligands or cationic and anionic pairs between atomic centers. The central atoms may be of the same element, same family, or different families. The exchanging ligands may be identical or distinct. Metathetical reactions are also referred to in the literature as exchange, redistribution, scrambling, reorganization and disproportionation reactions. The general scheme is given in Equation one, while specific metathetical reactions are seen in Equations two through five.

\[
R_nP_m^+ + R'_nP'_m^+ \rightleftharpoons R'_nR_{n-x}^+ + R_mR'_{m-x}^+
\]  

(1)

\[
\text{trivalent : } R_2P_N^+ + R_2P_N^+ \rightleftharpoons R_3P_N^+ + R_2P'_N^+ + R_2P_N^+ \rightleftharpoons R_3P_N^+ + R_2P'_N^+(
\]

(2)

\[
\text{pentavalent: } R_5P_N^+ + R_5P_N^+ \rightleftharpoons R_5P_N^+ + R_5P'_N^+ + R_5P_N^+ \rightleftharpoons R_5P_N^+ + R_5P'_N^+(
\]

(3)

\[
\text{mixed : } R_2P_N^+ + R_5P_N^+ \rightleftharpoons R_3P_N^+ + R_4P'_N^+
\]

(4)

\[
\text{redox : } 3R_{n-x}P_N^+ + (5-n)R_5P_N^+ \rightleftharpoons 3R_{5-n}P_N^+ + 2P_N^o + (3-n)P'_NX_3
\]

(5)

Although this review will focus upon metathetical reactions of trivalent pnictogens (group V elements) almost every family from the alkaline earths to the halogens exhibit some metathetical behavior. Metathetical reactions within the group V family provides a facile route to the substituted pnitides and in particular to the pnictogen halides. These compounds may then be allowed to react with various metals, grignard reagents, and organolithium compounds to yield symmetric or unsymmetric species (R1R2R3Bi not yet known). These trivalent species may then be allowed to react with various reagents to yield tetra, penta, and hexacoordinate pnictogens. In addition fluorophosphines which are easily prepared by metathetical reactions are finding wide use as coordinating ligands in transition metal complexes.

Mechanisms. Various pathways for metathetical reactions have been suggested. These are summarized in Schemes I and II.

The available kinetic data (mainly for antimony and arsenic) are summarized in Table 1. These data for an overall second order exchange reaction rules out most dissociative types of mechanisms since these would be first order. A second order dissociative mechanism is possible, however, if the second step is rate determining. Early workers in this field have studied the disproportionation of diphenylchlooroarsine and phenyldichloroarsine. The \( \Delta S^\# \) for these reactions is of the correct magnitude for a two center mechanism, but falls appreciably below that for suspected four center mechanisms.
Scheme I. Associative

1. Biphilic:

\[ R_3P_N + R'_3P'_N \rightarrow R\cdots P\cdots N/R' \rightarrow R'_{-}\text{migration} \]

\[ R' \rightarrow R'_{\text{migration}} \]

\[ \text{dissociation} \]

\[ \text{equilibrium} \]

\[ R'R_2P_N + RR'R'_2P'_N \]

2. Four Center Mechanism:

\[ R_3P_N + R'_3P'_N \rightarrow R'_{\text{migration}} \rightarrow R'R_2P_N + RR'R'_2P'_N \]

Scheme II. Dissociative

1. Radical, cationic, anionic: (only radical shown)

\[ R_3P_N \leftrightarrow R_2P_N^* + R^* \]

\[ R'_3P'_N \leftrightarrow R'_* + R'_2P'_N^* \]

\[ R_2P_N^* + R'_2P'_N^* \]

\[ R_2P_N^* + R'_2P'_N^* \]

2. Elimination of halogen

\[ R_PNX_2 \leftrightarrow R_PNX_2^* + X_2 \]

\[ R'_PNX_2 \leftrightarrow R'_PNX_2^* + R'_PNX_2 \]
3. Charge transfer:

\[
\begin{align*}
R_3P_N + R_4P'_N & \rightleftharpoons R_3P'_N + R_3P_N \\
\cdot & \rightleftharpoons R + \cdot \\
R + R_4P'_N & \rightleftharpoons RR_4P'_N \\
\cdot & \rightleftharpoons RR_2P'_N + R' \\
R_2P_N + R & \rightleftharpoons R'R_2P_N
\end{align*}
\]

Van Wazer\(^{10}\) has studied the metathetical reactions of arsenic by n.m.r. and has found the fastest exchange at arsenic centers \((k = 10^{21}/\text{sec.-mol.})\) occurs between halogen and dimethylamino substituents while exchange between

\[
\begin{array}{c}
2\phi_2\text{AsCl} \quad \frac{k_1}{k_2} \quad \phi_3\text{As} + \phi\text{AsCl}_2 \quad \text{(neat)} \\
2\phi\text{AsCl}_2 \quad \frac{k_3}{k_4} \quad \phi_2\text{AsCl} + \text{AsCl}_3 \quad \text{(neat)}
\end{array}
\]

<table>
<thead>
<tr>
<th>(k \times 10^3) (cc/sec.-mol.)</th>
<th>(E^*) (kcal./mol.)</th>
<th>(\Delta S^*) (e.u.)</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_1 = 0.89) (T = 252°C)</td>
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<td>(\Delta S^*_1 = -2.83)</td>
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<td>8</td>
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<tr>
<td>(k_4 = 56.6) (T = 256°C)</td>
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</table>
dimethylamino and methoxyl substituents is too slow to measure by n.m.r. line broadening techniques. This absolute order of reactivity seems to support a biphilic mechanism (at least for this element) since the fastest rate is observed for a good nucleophile, trisdimethylaminoarsine, reacting with a good electrophile, an arsenic trihalide. The slowest rate is observed for the reaction of two good nucleophiles with each other. The proposed intermediate in the biphilic reaction mechanism is a zwitterionic species. Since the transition state most likely lies late along the reaction coordinate it would be closest in energy to the zwitterionic intermediate. Features which stabilize the intermediate would be expected to also stabilize the transition state more than the starting materials and thus increase the rate of the reaction. The zwitterionic intermediates are seen in Figure 1.

Further evidence for a biphilic mechanism comes from the reactions of trialkyls of phosphorous and arsenic with organophosphines and arsines. Several authors have examined these reactions and report the isolation of crystalline adducts postulated to be salts of the general formula \([R_2P-P'R_3]X\). The exact nature of bonding in these adducts is unclear. Ramirez has reported the isolation of a solid material from the reaction of trimethylphosphine with diphenylchlorophosphine. Although he postulates an ionic structure the reported \(^{31}\text{P}\) n.m.r. data are also consistent with a phosphonium phosphorane (the intermediate in the biphilic mechanism). This species and the appropriate n.m.r. data are shown in Figure 2. Unfortunately no conductance measurements were reported. The X-ray crystal structure of this 1:1 adduct

\[ (\text{CH}_3)_3\text{P} + \phi_2\text{PCl} \xrightarrow{\text{R}} \text{CH}_3\text{P}^+\phi_2\text{PCl}^- \]

1:1 adduct, 2.5 M \(\text{CH}_2\text{Cl}_2\); shifts relative to \(\text{H}_3\text{PO}_4\) where positive sign indicates downfield shift.
has not yet been reported. Many other examples of arsonium and phosphonium salts are reported in the literature, however, at least in the cases of mono and dihalo pnictogen adducts the evidence does not support an ionic structure. The melting points are surprisingly low and solutions of some of the species have relatively low conductances. For example methyldichloroarsine and trimethylarsine react to give a solid which has a specific conductance of only 5.6 μmho/cm. (10^-5 M in nitromethane) and a melting point of 94-97°C. It is probably best formulated as a zwitterionic compound.

Despite the fact that the nature of bonding in these species is uncertain, it seems clear that the phosphorus and arsenic centers are acting both as a nucleophile and an electrophile and the ability of the substituents to metathesize depends in part on their ability to enhance electrophilic or nucleophilic character at the metathetical center.

Antimony: A Four Center Exchange. Van Wazer has studied the exchange reaction between trimethylstibine and trichloroantimony by NMR. The second order rate constants obtained in dimethylformamide at 72°C and 100°C were determined as well as the enthalpy and entropy of activation. The low entropy of activation (~25 e.u.) has been attributed to a four-center transition state. This ΔS° is in accord with that of other four-center transition states.

Thermodynamics. The available thermodynamic data (summarized in Table 2) indicate that almost all of the mixed products of metathetical reactions are favored to a greater extent than random exchange would predict. When the exchanging substituents on the pnictogen center are of the same class (i.e., both alkoxy groups) the equilibrium lies closest to a completely random equilibrium. When the exchanging substituents are of different classes, quite significant deviations from random exchange are observed. For example, in the dimethylaminofluorine system the equilibrium constant is 6.9 x 10^9.

<table>
<thead>
<tr>
<th>System</th>
<th>R</th>
<th>R'</th>
<th>K</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Statistical</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>P</td>
<td>OCH₃</td>
<td>OC₂H₅</td>
<td>6.9</td>
<td>19</td>
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<td></td>
<td>Cl</td>
<td>OΦ</td>
<td>5.9 x 10⁴</td>
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<tr>
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<td>(CH₃)₂N</td>
<td>OΦ</td>
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<tr>
<td></td>
<td>Cl</td>
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<td>As</td>
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<td>10</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
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<td>1.6 x 10⁴</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(CH₃)₂N</td>
<td>F</td>
<td>6.2 x 10⁹</td>
<td>10</td>
</tr>
</tbody>
</table>

Survey of Synthetically Useful Metathetical Reactions: Phosphorus. Numerous metathetical reactions between trivalent phosphorus compounds are known. Trihalophosphines metathesize although only mixed halophosphines containing fluoride are isolable. This may be due to the greater stability of the phosphorus fluoride bond (P-F > P-Cl > P-Br > P-I).
and the slower exchange rate of mixed halophosphines containing fluorine. Phosphorus trihalides metathesize with other phosphorus trihalides or other pnictogen trihalides to yield mixed halo- and pseudohalophosphines. Some of the phosphines which may be obtained by this route are PF$_2$Br, PFBr$_2$, PF$_2$Cl, PFCl$_2$, PF$_3$(NCO), PF(NCO)$_2$, and PF$_2$(NCS). A recent synthesis which provides a very convenient method of generating the gaseous chlorodifluorophosphine is outlined in Equation 6.

\[
(C_2H_5)$_2$N-PCl$\_2$ $\xrightarrow{\text{SbF}_3, \text{NaF}}$ (C$_2$H$_5$)$_2$NPF$_2$ $\xrightarrow{\text{PCl}_3}$ ClPF$_2$ \tag{6}
\]

Although trialkylphosphines (perfluoroalkyls are an exception, vide infra) have not been observed to metathesize with any pnictogen, dihalophosphines disproportionate to yield the monohalophosphine.

Arsenic and antimony trifluoride have found wide use as metathetical fluorinating agents. These reagents metathesize with phosphorus trichloride either in the presence or absence of a catalyst to produce good yields (ca. 85%) of phosphorus trifluoride as seen in Equation 7. These reagents also fluorinate dialkylamino and alkoxychlorophosphines as well as halophosphines with electronegative alkyl substituents in good yields (Equation 8). These reactions have been extensively reviewed by Schmutzler. Although trialkylphosphines do not metathesize, tris(trifluoromethyl)phosphine does metathesize. Emeléus indirectly observed this behavior in the reaction of white phosphorus with iodotrifluoromethane. Direct observation came later with the metathetical reaction of tris(trifluoromethyl)phosphine and trimethylbismuthine.

**Arsenic.** Unlike phosphorus, mixed haloarsines have not yet been isolated. This is probably due to the faster exchange rates of arsenic. Also unlike phosphorus, exchange reactions of triarylarsones are known as seen in Equations 9, 10, and 11. Triarylarsones generally react with arsenic trichloride to give aryldichloroarsines.

\[
(C_2H_5)_3\text{As} + 1.25 \text{AsBr}_3 \rightarrow (C_2H_5)\text{AsBr}_2 \tag{9}
\]

\[
51\%
\]

\[
(H\text{H})_3\text{As} + 2 \text{AsBr}_3 \rightarrow \text{H}(\text{H})\text{AsBr}_2 \tag{10}
\]

\[
38\%
\]

\[
(CF_3)_3\text{As} + 2 \text{AsCl}_3 \rightarrow (CF_3)\text{AsCl}_2 \tag{11}
\]

\[
50\%
\]
Antimony. The fast rate of exchange for trivalent antimony compounds generally makes isolation of liquid metathesis products difficult. Another difficulty arises from the similar physical properties (boiling and melting points) of the metathesis products. Thus, when trivinylstibine and antimony tribromide were mixed in a 1:2 ratio, the desired dibromo compound could not be obtained. Only the divinyl derivative could be isolated in pure form. However, successful metathetical reactions between various stibines and antimony trihalides have been reported.

Bismuth. Bismuth seems to be the most reactive of the pnictogens in metathetical reactions. Thus, while triarylanthimony, arsenic, and phosphorus compounds require high (ca. 240°C) temperatures, triarylbumuthines react at room temperature in ethereal solvents. These are summarized in Equations 12, 13, and 14.

\[
\begin{align*}
2 (\text{CH}_3\text{C}_{\text{H}}\text{H}_{\text{H}})_3\text{Bi} + \text{BiCl}_3 & \rightarrow (\text{CH}_3\text{C}_{\text{H}}\text{H}_{\text{H}})_2\text{BiCl} & (12) \\
\text{CH}_3\text{C}_{\text{H}}\text{H}_{\text{H}}\text{C}_{\text{H}}\text{H}_{\text{H}}\text{Bi} + 2 \text{BiBr}_3 & \rightarrow \text{CH}_2\text{C}_{\text{H}}\text{H}_{\text{H}}\text{BiBr}_2 & (13) \\
1.4 (\text{C}_{\text{H}}\text{H}_{\text{H}})_3\text{Bi} + \text{BiCl}_3 & \rightarrow (\text{C}_{\text{H}}\text{H}_{\text{H}})_2\text{BiCl} & (14)
\end{align*}
\]

Redox Reactions. Not all trivalent pnictogens undergo metathetical reactions. In some cases, disproportions are observed. Challenger was one of the first to observe this behavior when he mixed triphenylstibine with antimony trichloride as in Equation 15.

\[
\text{C}_{\text{H}}\text{H}_{\text{H}}\text{Sb} + \text{BiCl}_3 \rightarrow \text{C}_{\text{H}}\text{H}_{\text{H}}\text{SbCl}_2 + \text{Bi}_2\text{Cl}_4 (15)
\]

Schmutzler has extensively studied the reactions of chlorophosphines with antimony and arsenic trifluoride which leads to the fluorophosphoranes according to Scheme III. These reactions usually give good yields of the phosphorane (Equation 16), however, phosphines \( R_x P X_{3-x} \), where \( R = R'_f, N R_2, \) or \( O R \) yield only the fluorinated phosphine as previously mentioned.
Sisler has extensively studied the reactions of trialkyl pnictogens with mono-, di-, and trihalo pnictogens. These reactions yield the pentavalent pnictogen and some form of the reduced pnictogen as seen in Equations 17-19. These reactions proceed, in many cases, through an isolable adduct which may be thermally converted to the pentavalent species.

\[
3 (n-C_4H_9)_3P + 2 PCl_3 \rightarrow 3 (n-C_4H_9)_3PCl_2 + 2 P^0 \tag{17}
\]

\[
5 (n-C_4H_9)_3P + 5 \phi PCl_2 \rightarrow 5 (n-C_4H_9)_3PCl_2 + (\phi P)_5 \tag{18}
\]

\[
(n-C_4H_9)_3P + 2 \phi_2PCl \rightarrow (n-C_4H_9)_3PCl_2 + \phi P-\phi_2 \tag{19}
\]

Redox vs. Metathesis. The factors controlling whether two trivalent pnictogens will metathesize or react in a redox manner are difficult to determine. However, certain trends are clear. Most trivalent alkyl phosphines will not metathesize with any pnictogen, but will react to give either an adduct or redox products. Alkylarsines will either metathesize or yield an adduct, but will only rarely pass into the pentavalent state. Antimony generally metathesizes with other antimony compounds if there is at least one good pair of bridging ligands (Cl or Br). Finally, bismuth compounds generally metathesize, however, trivalent bismuth compounds generally oxidize most other pnictogens.

Conclusion. Metathetical reactions provide the synthetic chemist with a large number of substituted trivalent pnictogens. The donor and acceptor properties of these compounds make them quite diverse in their chemical behavior and hence extremely valuable to the synthetic chemist.

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18. Values obtained by $K = K_1 \times K_2$ where $K_1 = \frac{[PA_2B]^2}{[PN_3][PAB]}$ and $K_2 = \frac{[PAB]^2}{[PN_3][PAB]}$.
25. For a review of these compounds see R. Schmutzler, Adv. in Fluorine Chem., 5, 31 (1965).
33. For a summary of these reactions see G. Raiziss, J. Gavson, "Organic Arsenical Compounds", Chemical Catalogue Company, New York, N.Y., 1923.
ORGANOTIN REAGENTS: VERSATILE INTERMEDIATES FOR ORGANIC SYNTHESIS

Reported by John Lloyd
October 6, 1980

Organotin compounds have recently been shown to be versatile and useful reagents for organic synthesis.\(^1\,^2\,^3\) Tin is a member of group IVa and may be expected to share many properties in common with carbon. Although the physical properties of many organotin compounds are very similar to the analogous carbon compounds, the reactivity of the tin-carbon bond is significantly different from that of the carbon-carbon bond.

An examination of some simple atomic properties of tin can give some insight into the reactivity of the tin-carbon bond. Electronegativity predicts the tin-carbon bond to be polarized but much less so than for other organometallic reagents such as organolithiums and Grignard reagents. Tin has a relatively large covalent radius so its reactions show little effect of steric factors. Also tin forms stronger bonds to halogens, oxygen and nitrogen than to carbon. However, caution must be used in predicting the reactivity of tin-carbon bonds from simple atomic properties alone. Other factors such as the polarizability of the tin-carbon bond and the ability to form higher co-ordination complexes lead to results which may have not been predicted on the basis of electronegativity and bond lengths and strengths alone.\(^1\,^2\,^3\)

Organotin compounds can be synthesized by a number of methods, several of which are well adapted for laboratory synthesis. Transmetallation, in which nucleophilic attack by an organometallic on tin effects an exchange of ligands has been used to synthesize tetraorganotins 1, 2, 3, 4, 5, eq. (1).

\[
R_3SnX + R'Li \rightarrow R_3SnR' + LiX
\]

In the reverse sense, a triorganotin anion may react with an electrophile to produce a tetraorganotin, eq. (2).

\[
R_3SnM + R'-X \rightarrow R_3SnR' + MX
\]

\(M=Li, Na, K\)

Reagents such as trimethylstannyllithium will displace a halogen in alkyl and aryl halides,\(^4\,^7\,^8\,^9\) add to the carbonyl of aldehydes and ketones,\(^10\) and add to \(\alpha,\beta\)-unsaturated carbonyl compounds\(^11\,^12\,^13\,^14\,^15\) in both a 1,2 and 1,4 manner that can be controlled by the reaction conditions.\(^16\) In hydrostannation reactions, trialkyltin hydrides add to carbon-carbon multiple bonds to produce the corresponding tetrasubstituted organotin.\(^17\,^18\,^19\) If a leaving group is allylic to the multiple bond the organotin adds highly regiospecifically with allylic rearrangement.\(^20\,^21\,^22\)

Due to the polarization of the tin-carbon bond, organotin compounds usually react with nucleophiles at tin and electrophiles at carbon. Transmetallation has been used extensively for cleavage of the tin-carbon bond and the synthesis of functionalized organolithiums.\(^4\,^9\,^10\,^23\,^24\) A particularly attractive synthesis of functionalized vinylithium reagents can be effected by a sequence of hydrostannation of an acetylene and transmetallation to form the vinylithium reagent.\(^18\,^19\,^25\,^26\)
The reactions of organotin compounds with electrophiles are some of the most interesting and useful reactions of organotins. Most of these reactions involve the reaction of an allyltin reagent at the gamma carbon with an electrophile. Catalysis by Lewis acid is usually employed in additions to carbonyl compounds²⁷ ²⁸ ²⁹ ³⁰ ³¹ or a palladium catalyst in additions to alkyl halides.⁵ ³³ ³⁴ ³⁵ ³⁶ ³⁷ ³⁸ The reaction of an organotin at the alpha carbon with an α,β-unsaturated ketone with titanium tetrachloride catalysis has recently been reported.³² There have also been reports of transfer of organic groups to aryl chlorides.³⁹ ³⁴ ³⁵

Other reactions which further illustrate the versatility of organotin reagents are those of functionalized organotins where the reaction does not involve the cleavage of the tin-carbon bond. Tin has been used as a protecting group for α,β-unsaturated ketones,¹⁵ glycosides⁴² and diols.⁴³ Organotin functionality may be accomodated on Wittig reagents,⁴⁹ ⁴⁵ organolithium reagents,⁶⁶ ⁴⁷ carbenes,⁴⁰ organoboranes⁴⁹ and in Diels-Alder reactions.⁵⁰ The products of these reactions may go on to participate in reactions of the tin-carbon bond as previously discussed.

It can be seen that organotin compounds are versatile reagents for organic synthesis. The key to their versatility lies in the intermediate reactivity of the tin-carbon bond. They undergo synthetically useful transformations involving cleavage of the tin-carbon bond yet the tin-carbon bond is compatible with a wide variety of functionality in the molecule. Organotin compounds are likely to become an even more powerful tool for the organic chemist in the future.

BIBLIOGRAPHY

Reported by Joan Z. Suits          October 9, 1980

Ozonations on Solid Supports

Introduction. Ozone is a versatile chemical reagent which has found much use, both in and out of the laboratory. Naturally occurring ozone in the stratosphere protects life from harmful energy from outer space; ozone has been used in the treatment of wastewater¹ and has been suggested as a possible deterrent to cancer cell growth.² Chemists use ozone to accomplish a variety of synthetic transformations, including cleavage of saturated and unsaturated carbon systems with introduction of an oxygen function and oxidation of functional groups.³ In general, these reactions are performed in solution. Thus, it often happens that a solvent molecule will interfere in the ozonolysis process, resulting in the formation of various by-products.

Recent years have seen a development in the technique of performing reactions on a solid support, such as silica or alumina.⁴ This technique has been applied to a number of reactions, including oxidations, reductions, and aliphatic and aromatic substitutions.⁵ Recently, it has been used in a variety of ozonation reactions.⁶ In general, a substrate is adsorbed onto silica gel and the mixture then cooled to -78°. Ozone is passed over the mixture and then, after removal of unreacted ozone, the mixture warmed to room temperature and the products isolated. This report will review ozonations on solid supports and attempt to illustrate advantages and disadvantages of the technique.

Olefins. The degradation of olefins by ozone to give carbonyl-containing compounds is by far the most familiar ozonolysis reaction. Additionally, it is an extremely complex reaction whose course depends upon solvent, temperature, and substituents on the double bond. The complexities of this reaction have been recently reviewed.⁷

In most systems, ozone adds as a 1,3-dipole to a carbon-carbon double bond, giving an initial moleozonide ¹ which decomposes to the "Criegee intermediate" ², which then forms the ozonide ³ (Scheme I).

\[
\text{Scheme I}
\]

The ozonide ³ can then be treated with water, triphenyl phosphine, pyridine, or some other reducing agent to give the desired products.

Even without direct interference by solvent molecules, formation of ³ does not occur without complication. If the substituents on the olefin are large, 1,3-addition may be blocked, resulting in electrophilic attack by ozone to give a peroxoepoxide which can form an epoxide or rearrange to form a carbonyl compound (Scheme II).
Additionally, the carbonyl oxide of 2 can react with itself to form dimers, or 2 can polymerise to peroxides (Scheme III).

Finally, fragmentation of 1 can occur in either (or both) of two directions. With unsymmetrically substituted olefins, this may result in formation of "crossed ozonides" (Scheme IV).

The formation of crossed ozonides is increased as the polarity of the solvent is increased.

When alkenes are ozonized in aprotic solvents, the products isolated include monomeric ozonides, polymeric peroxides, and polymeric ozonides.5,6 When the reaction is done in participating, protic solvents, yields of crossed ozonides increase and α-oxyalkylhydro peroxides are formed (Scheme V).
An example of problems in solution ozonolysis is given by the reaction of 2-pentene at -70° with ozone, which resulted in formation of both crossed ozonides as well as the normal ozonide, acetaldehyde, propionaldehyde, and peroxides, eq. 1.

\[
\begin{align*}
\text{alkene} & \quad \text{conditions} & \quad \text{product} & \quad \text{yield} \\
\text{pentene} & \quad \text{SiO}_2, \text{anh.} & \quad \text{pentene ozonide} & \quad >80\% \\
\text{cyclopentene} & \quad \text{SiO}_2, 5\% \text{H}_2\text{O} & \quad \text{pentene ozonide CO}_2\text{H} & \quad >80\% \\
\text{cyclpentene} & \quad \text{SiO}_2, 5\% \text{H}_2\text{O} & \quad \text{pentene ozonide CO}_2\text{H} & \quad >80\% \\
\text{cyclohexene} & \quad \text{SiO}_2, 5\% \text{H}_2\text{O} & \quad \text{pentene ozonide CO}_2\text{H} & \quad >80\% \\
\text{pentene} & \quad \text{SiO}_2, \text{anh.} & \quad \text{pentene ozonide} & \quad >90\% \\
\end{align*}
\]

The reactions were performed by adding the alkene (1% by weight) to stirred silica gel at room temperature, cooling the mixture to -78°C, and blowing a stream of 3% O\textsubscript{3}/O\textsubscript{2} over the mixture until it had a pale blue color. After removal of unreacted ozone and warming to room temperature, the product was eluted with methylene chloride.

Under anhydrous conditions, pure ozonides can be isolated, which can then be treated with reducing agents to give desired products. If the reaction is done in hydrated silica gel, the products obtained are those (ideally) expected from an aqueous work-up, without side reactions by solvent.

Presumably, the mechanism for the reaction is the same as in solution. Thus, the problem with bulky substituents on olefins (Scheme IV) might still be expected to cause reactions other than that of 1,3-dipolar addition.
Amines. Ozone has long been used to oxidize amines to the corresponding nitro compounds. The mechanism by which oxidation occurs is initial electrophilic attack by ozone on the amine nitrogen to give a zwitterion intermediate (1), which loses oxygen to give a nitroxide. The nitroxide is then oxidized to the nitroalkane. Other possibilities in the reaction include reversible decomposition of 1 to a zwitterion diradical, and insertion of ozone into the α-CH bond resulting in formation of a ketone. These reactions are shown in Scheme VI.

When amines are ozonized in solution, considerable side reactions can occur. An example is the ozonation of isopropyl amine. The results are illustrated in Table 2.

Table 2. Ozonation of Isopropyl Amine

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>2-nitropropane</th>
<th>Acetone</th>
<th>Isopropylisocyanate</th>
<th>Isopropyl ammonium chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl₃</td>
<td>-65</td>
<td>25-28</td>
<td>4-6</td>
<td>15-18</td>
<td>48-51</td>
</tr>
<tr>
<td>CHCl₂</td>
<td>-30</td>
<td>22-23</td>
<td>10</td>
<td>5</td>
<td>40-47</td>
</tr>
<tr>
<td>CH₃Cl₂</td>
<td>0</td>
<td>14-15</td>
<td>19-22</td>
<td>5</td>
<td>42-46</td>
</tr>
<tr>
<td>CH₄Cl₂</td>
<td>-78</td>
<td>36</td>
<td>12</td>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>Pentane</td>
<td>-78</td>
<td>53</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Acetone is formed by α-insertion. The formation of isopropylammonium chloride and isopropyl isocyanate results from interception of 1 by solvent (Scheme VII).
Similar results are obtained for n-butylamine\textsuperscript{10} and \textepsilon -butylamine.\textsuperscript{11}

In contrast, ozonation of amines on silica gel results primarily in formation of the corresponding nitro product in high yield, with some formation of carbonyl product.\textsuperscript{12} The results are shown in Table 3.

Table 3. Ozonation of Amines on Silica Gel

<table>
<thead>
<tr>
<th>amine</th>
<th>products-% yield</th>
<th>carbonyl derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>[\text{NH}_2]</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>[\text{NH}_2]</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>[\text{NH}_2]</td>
<td>70</td>
<td>none</td>
</tr>
<tr>
<td>[\text{NH}_2]</td>
<td>69</td>
<td>4</td>
</tr>
<tr>
<td>[\text{NH}_2]</td>
<td>66</td>
<td>6</td>
</tr>
</tbody>
</table>

It was found\textsuperscript{12} that the yield of nitro product decreased as the ratio of amine/silica gel, temperature, or water content of the silica gel was increased. The dependence of yield on the amine/silica gel ratio was postulated to be the result of interactions between intermediates in the amine ozonolysis and unreacted amine. Similarly, water in the silica would act as a nucleophilic, protic solvent would act, decreasing yield.

Alkanes. It is thought by some scientists that oxidation of alkanes by ozone contributes to air pollution.\textsuperscript{13} Compared to other organic compounds, alkanes react slowly with ozone, forming alcohols which in some cases are further oxidized to ketones.\textsuperscript{13,14} Generally, a carbon-hydrogen bond is cleaved (the order of reactivity is $3^\circ > 2^\circ > 1^\circ$ with a ratio of 100:10:1) but carbon-carbon bonds have also been cleaved.\textsuperscript{15}

The mechanism by which alkanes are oxidized by ozone in solution is not known. It has been postulated that initial hydrogen abstraction results in formation of an intermediate which has both radical and ionic character.\textsuperscript{16} This intermediate can then decompose via a radical mechanism, resulting in an alcohol with retention or inversion of configuration (Scheme VIII).

Scheme VIII

\[\text{RH} + \text{O}_3 \rightarrow [\text{R}^\cdot, \text{O}_3\text{O}] \rightarrow \text{ROH} + \cdot\text{O}_3 \quad (\text{retention}) \]

\[3\text{O}_2 + \text{R}^\cdot + \text{H}^\ddagger \rightarrow \text{ROH} + \text{HO}^\ddagger \]
It has been found that although solvent polarity does not greatly influence the configuration of alcohols resulting from the ozonation of cis-1,2-dimethylcyclohexane (Table 4), it does influence the extent to which the alcohol formed from cyclohexane are further oxidized to ketones (Table 5).\(^{14a}\)

<table>
<thead>
<tr>
<th>solvent</th>
<th>relative % yields</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-1,2-dimethylcyclohexane (DMC)</td>
<td>85</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>cis-1,2-DMC - acetic acid</td>
<td>85-90</td>
<td>15-10</td>
<td></td>
</tr>
<tr>
<td>cis-1,2-DMC - C(_6)H(_6)</td>
<td>91</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>cis-1,2-DMC - acetone</td>
<td>65</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>cis-1,2-DMC - ethyl acetate</td>
<td>78</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>cis, 1,2-DMC - chloroform</td>
<td>85</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Overall, the reaction proceeds with 60-70% retention of configuration.\(^{14b}\)

<table>
<thead>
<tr>
<th>solvent</th>
<th>relative % yields</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexane</td>
<td>79</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>cyclohexane-acetone</td>
<td>33</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>cyclohexane-ethyl acetate</td>
<td>40</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>cyclohexane-diphenylamine</td>
<td>69</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Other products which have been isolated from cyclohexane ozonation include peroxides and adipic acid, formed by carbon-carbon \(\sigma\) bond cleavage.\(^{15}\) Oxidation of the alcohol to the ketone presumably proceeds via electrophilic ozone attack on oxygen, similar to the attack of ozone on amines.\(^{9}\) In superacid media, the mechanism of the initial attack is presumed to proceed via a protonated ozone insertion into the alkane \(\sigma\) bond, but this does not significantly change the outcome.\(^{16}\)

The technique of dry ozonation was originally developed for use with alkanes.\(^{17}\) It was found that on silica gel at \(-78^\circ\) an almost quantitative conversion of alkane to alcohol, almost exclusively with retained configuration, resulted. Ketones were also observed but this reaction did not occur as readily as in solution. These results are summarized in Table 6.

In contrast to the formation of alcohols in solution, which proceeds with 60-70% stereospecificity,\(^{14}\) formation of alcohols on solid support proceeds with 78-99% stereospecificity.\(^{17}\)

Oxidation by ozone of alkanes can also result in carbon-carbon bond cleavage, especially at higher temperatures.\(^{18}\) As an example, the results from the ozonation of 3-methylpentane are shown in Table 7.

3-Methyl-2-pentanone is formed from the alcohol, which would be expected to oxidize under the reaction conditions. Presumably, both carbon-carbon and carbon-hydrogen cleavage occur via insertion of ozone into the respective \(\sigma\) bonds (Scheme IX).\(^{18}\)
Table 6. Ozonation of Alkanes

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products</th>
<th>% yield(s)</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>65</td>
<td>&gt;99.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79, 0.6</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76, 3.5</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99</td>
<td>&gt;99.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72, 10</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>&gt;99.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95</td>
<td>&gt;99.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76, 5</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 7. Ozonation of 3-Methylpentane

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>OH</th>
<th>O</th>
<th>O</th>
<th>O</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>-45</td>
<td>32</td>
<td>15</td>
<td>20</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>-23</td>
<td>30</td>
<td>15</td>
<td>20</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22</td>
<td>13</td>
<td>20</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>8</td>
<td>10</td>
<td>23</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

Scheme IX

\[ \text{C-H} + \text{O}_3 \rightarrow [\text{C-O-O-O}] \rightarrow \text{C-OH} + \text{O}_3 \]

\[ \text{C-C} + \text{O}_3 \rightarrow [\text{C-O-O-O}] \rightarrow \text{C-O-O-O} \]
The trioxide formed by carbon-carbon insertion decomposes to give products. Such an intermediate has also been postulated in the dry ozonation of bicyclo[n.1.0.]alkanes.\textsuperscript{19}

The selective hydroxylation of aliphatic compounds by means of ozone insertion into the carbon-hydrogen bond has in contrast found much more use, in the syntheses of unusual molecules such as [6]-rotane\textsuperscript{21} and in many natural products syntheses.\textsuperscript{22-27}

\[ \text{[6]-rotane} \]

An example of this is the synthesis of 1-\( \alpha \),25-hydroxy vitamin D\textsubscript{3}(4).\textsuperscript{24a}

\[ \text{4} \]

The key to the synthesis was the regioselective hydroxylation at C-25 of the tetrasubstituted cholestane derivative 5\textsubscript{a}, which was synthesized in five steps from cholesterol (Scheme X).

\[ \text{Scheme X} \]

\[ \text{5} \]

5\textsubscript{a} was adsorbed onto silica gel, cooled to -78°, the mixture saturated with ozone, and then slowly warmed to room temperature. This cooling/saturation/warming procedure was repeated five times and the mixture eluted with ethyl acetate to give 5\textsubscript{b}, which was transformed in three steps to 4 in good overall yield.\textsuperscript{24a} Similar results have been obtained with other steroid derivatives.\textsuperscript{24b}

Recently, similar conversions have been attempted with triterpene derivatives.\textsuperscript{25,26} Thus, friedelane (6) was converted into 18β-19β-epoxy-friedelane (7) in 48% relative yield.\textsuperscript{25}
Other products isolated included 19-oxo- and 16-oxofriedelane and friedelin. The regioselectivity of the triterpene and steroid conversions is postulated to result from preferential adsorption of the A-ring moiety onto the silica gel for steric reasons, leaving the rest of the molecule available for reaction with ozone.

Comparison of Solution and Dry Ozonations—Conclusion. Results so far indicate that ozonations in dry media avoid many of the complications arising from the solvated reactions; most of the side reactions which do occur seem to result from the chemistry of the ozone-substrate reaction itself.

The disadvantages of dry ozonation relative to solution ozonation are that in general it is difficult to monitor the course of the reaction; yields of products, while good, tend to be erratic; and there are technical limitations to the scale which can be used. An interesting method to circumvent these problems has been recently proposed by Beckwith. The problem was regioselective hydroxylation by ozone of the 7-position of 3,7-dimethyl-octanol derivatives, equation 2.

In ethyl acetate solution, the yield of the desired product was less than 35%; on silica gel, the yield was increased to 65%. To further improve the yield, the substrate was first adsorbed onto silica gel and the mixture suspended in Freon-11. Ozone was bubbled into the mixture, and upon workup, over 92% of the desired compound was isolated. This combination of the best of both techniques may well prove to be the most useful technique possible.

BIBLIOGRAPHY

The reaction between Grignard reagents and allyl alcohols in the presence of catalytic amounts of phosphine-ligated nickel dichloride—the Felkin reaction—leads to replacement of the hydroxy group by hydrogen or an alkyl function, depending on the nature of the organometallic reagents. Grignard reagents containing $\beta$ hydrogens lead to hydrogenolysis, while Grignard reagents having no $\beta$ hydrogens yield alkylated or arylated products. Thus, for example, reaction of three butenols with propylmagnesium bromide under the influence of the nickel catalyst yielded the hydrogenated butenes, whereas exposure of the same butenols to methyl and phenylmagnesium bromide afforded substituted olefins (Table 1).

### Table 1. Yields and proportions of olefins obtained from the action of Grignard reagents $RMgBr$ ($R=\text{Me, Ph, Pr}$) upon cis- and trans-2-butenol and $\alpha$-methylallyl alcholhol in the presence of $(\Phi_3P)_2\text{NiCl}_2$

<table>
<thead>
<tr>
<th>Alcholoh</th>
<th>R</th>
<th>% Yield</th>
<th>$=\text{R}$</th>
<th>$=\text{R}$</th>
<th>$=\text{R}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>90</td>
<td>84</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>87</td>
<td>54</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Ph</td>
<td>73</td>
<td>65</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>80</td>
<td>31</td>
<td>39</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>80</td>
<td>7</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Ph</td>
<td>64</td>
<td>7</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>61</td>
<td>53</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>82</td>
<td>29</td>
<td>2</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Ph</td>
<td>31</td>
<td>40</td>
<td>16</td>
<td>44</td>
</tr>
</tbody>
</table>

The latter reactions are outlined in Scheme I. The proposed system involves two stereoisomeric $\pi$-allylnickel intermediates $^4$ and $^6$. Alcohols $^1$ and $^3$ are expected to lead first to the "syn" and "anti" complexes $^4$ and $^6$, respectively. Alcholoh $^2$, however, can lead to both $^4$ and $^6$, which must then afford the same mixture of olefins as are formed from $^1$ and $^3$, respectively. If these reactions occur exclusively via the $\pi$-crotyl intermediates $^4$ and $^6$, then the proportions of olefins formed from $\alpha$-methylallyl alcohol $^2$ must correspond to exactly the same weighted average of the proportions of the same olefins formed from the cis and trans alcohols $^1$ and $^3$, the common weighting factor being the rate ratio $k_s/k_a$. The
proportions of olefins obtained from the three isomeric butenols (1, 2 and 3) and two Grignard reagents (MeMgBr and PhMgBr) are shown in Scheme I, together with the weighting factors \( \frac{k_s}{k_a} \) calculated from them. It is apparent that these weighting factors are indeed identical within experimental error, for all the olefins (7, 8 and 9), which strongly indicates that the reactions take place via \( \pi \)-allylnickel intermediates as shown.\textsuperscript{1c} Catalytic cycles for both nickel-induced substitution and hydrogenation have been proposed.\textsuperscript{1c,d,f}

**Scheme I.**\textsuperscript{1c} Postulated stereoisomeric \( \pi \)-crotylnickel intermediates in the butenol system, with the percentage proportion of olefins (7, 8 and 9, \( R=\text{Me} \) and \( \text{Ph} \)) formed in the reactions of the butenols 1, 2 and 3 with MeMgBr and PhMgBr (catalyzed by \((\text{PPh}_3)_2\text{NiCl}_2\)), and the calculated values of the rate ratio \( \frac{k_s}{k_a} \).

\[ \begin{align*}
\text{Percentage proportion of olefin formed} & \quad \text{from 1} \quad 54.0 \quad 65.5 \quad 46.0 \quad 34.0 \quad 0 \quad 0.5 \\
& \quad \text{from 2} \quad 29.4 \quad 39.7 \quad 68.8 \quad 44.1 \quad 1.8 \quad 16.2 \\
& \quad \text{from 3} \quad 7.4 \quad 6.6 \quad 90.2 \quad 58.6 \quad 2.4 \quad 34.8 \\
\text{k}_s/\text{k}_a \text{ calc.} & \quad 0.90 \quad 1.3 \quad 0.94 \quad 1.4 \quad (-)^{\text{a}} \quad 1.2 
\end{align*} \]
The utility of the Felkin reaction has been extended to the synthesis of structurally complex diterpenes as the following study by Wenkert indicates.\(^6\)

Treatment of 1-vinylcyclohexanol (10a) with methylmagnesium bromide in the presence of the nickel catalyst affords a greater than 3:1 mixture of 1-methyl-1-vinylcyclohexane (11) and \(n\)-propylenecyclohexane (12a).

\[
\begin{align*}
10a, & \quad R=R'=H \\
\text{b,} & \quad R=t-Bu, \quad R'=H \\
\text{c,} & \quad R=H, \quad R'=t-Bu
\end{align*}
\]

As the construction of methylated, vinyl-substituted quaternary carbon sites was of possible importance in terpene synthesis, a determination of the stereochemical consequence of the alkylation reaction was necessary and was made in the following fashion.\(^6\) Exposure of the stereoisomeric alcohols 10b and 10c to methylmagnesium bromide and the nickel catalyst produced the terminal olefins 13 and 14 and the trisubstituted olefin 3b in a 77:4:19 ratio from either alcohol.

\[
\begin{align*}
t-Bu & \quad 13 \\
t-Bu & \quad 14
\end{align*}
\]

The observed high stereoselectivity may result from the equilibrium between \(\pi\)- and \(\sigma\)-allylnickel complexes (15a \(\rightleftharpoons\) 15b \(\rightleftharpoons\) 15c) favoring the least sterically encumbered, quasi-equitorial \(\pi\)-allylnickel intermediate 15c.

\[
\begin{align*}
t-Bu & \quad 15a \\
t-Bu & \quad 15b \\
t-Bu & \quad 15c
\end{align*}
\]

Since vinylcarbinols are easily prepared from aldehydes or ketones and the nickel-induced methylation process shows high preference for quaternization over terminal carbon alkylation, and is furthermore greatly stereoselective, a facile conversion of keto groups into methyl vinyl quaternary chiral centers has become available.

The above two-step conversion was utilized in the partial synthesis of several diterpenes which have methyl vinyl sites as common features, e.g., hibaene (16) and hydrocarbon 17, which interestingly enough, is the only one of the four possible pimaradienes which have not yet been found in nature (Scheme II).\(^6\)
Interestingly, \( \pi \)-allylnickel(0) coupling has also been used in a two-step synthesis of another biologically important natural product, grandisol (18), a component of the sex pheromone of the male boll weevil (Scheme III).

In further investigations, a new reaction was encountered: the direct substitution of alkoxy groups bound to carbon-carbon double bonds by alkyl and aryl functions. Enol ethers are attacked by phenyl and methyl Grignard reagents in the presence of the nickel catalyst to produce olefins, and nickel-mediated arylation of aryl ethers affords biaryls, as can be seen in Tables 2 and 3.

In a mixture of cis and trans-4-methoxy-3-heptene (keto enol ether), substitution by phenylmagnesium bromide occurs such that a predominantly trans mixture is converted to a predominantly cis mixture, a greatly different result than with the cis- and trans-1-methoxy-1-heptene mixture (aldehyde enol ether) (Table 2).

Highly substituted enol ethers, enamines and enolates do not undergo nickel-induced reaction with phenylmagnesium bromide (Scheme IV).
Table 2. The Reactions of Enol Ethers with Phenylmagnesium and Methylmagnesium Bromides

<table>
<thead>
<tr>
<th>Ether</th>
<th>Olefinic Products</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-OMe</td>
<td>o-Ph</td>
<td>71</td>
</tr>
<tr>
<td>Me₃C-Ph</td>
<td>Me₃C-Ph</td>
<td>75</td>
</tr>
<tr>
<td>Me₃C-CH₃Me</td>
<td>Me₃C-CH₃Me</td>
<td>59</td>
</tr>
<tr>
<td>Me₃C-CH₃(CH₂)₃OH</td>
<td>Me₃C-CH₃(CH₂)₃OH</td>
<td>64</td>
</tr>
<tr>
<td>MeO(CH₂)₄Me + MeO(CH₂)₄Me</td>
<td>MeO(CH₂)₄Me + MeO(CH₂)₄Me</td>
<td>79</td>
</tr>
<tr>
<td>MeO(CH₂)₄(CH₂)₂Me + MeO(CH₂)₄(CH₂)₂Me</td>
<td>1.3:1</td>
<td></td>
</tr>
<tr>
<td>Me(CH₂)₂OCH₂(CH₂)₂Me</td>
<td>Me(CH₂)₂OCH₂(CH₂)₂Me</td>
<td>86</td>
</tr>
<tr>
<td>MeO(CH₂)₃CH₂ + MeO(CH₂)₃CH₂</td>
<td>MeO(CH₂)₃CH₂ + MeO(CH₂)₃CH₂</td>
<td>66</td>
</tr>
<tr>
<td>o-OMe</td>
<td>o- Ph</td>
<td>74</td>
</tr>
<tr>
<td>Me₃C-Ph</td>
<td>Me₃C-Ph</td>
<td>75</td>
</tr>
<tr>
<td>Phenyl-CH₂(CH₂)₄OMe</td>
<td>Phenyl-CH₂(CH₂)₄OMe</td>
<td>66</td>
</tr>
<tr>
<td>Phenyl-CH₂(CH₂)₄Me</td>
<td>Phenyl-CH₂(CH₂)₄Me</td>
<td>74</td>
</tr>
<tr>
<td>Phenyl-CH₂(CH₂)₄OMe</td>
<td>Phenyl-CH₂(CH₂)₄OMe</td>
<td>66</td>
</tr>
<tr>
<td>Phenyl-CH₂(CH₂)₄Me</td>
<td>Phenyl-CH₂(CH₂)₄Me</td>
<td>74</td>
</tr>
<tr>
<td>Phenyl-CH₂(CH₂)₄OMe</td>
<td>Phenyl-CH₂(CH₂)₄OMe</td>
<td>66</td>
</tr>
</tbody>
</table>
Scheme IV

$$\text{OMe} \quad \xrightarrow{\text{PhMgBr}} \quad \text{OMgX}$$

$$(\Theta_3 P)_2 \text{NiCl}_2$$

benzene reflux 15-18 hrs

Table 3. The Reactions of Aryl Ethers with Phenylmagnesium Bromide$^a,9$

<table>
<thead>
<tr>
<th>Ether</th>
<th>Products</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-methoxynaphthalene</td>
<td>1-phenynaphthalene</td>
<td>70</td>
</tr>
<tr>
<td>2-methoxynaphthalene</td>
<td>2-phenynaphthalene</td>
<td>77</td>
</tr>
<tr>
<td>2,3-dimethoxynaphthalene</td>
<td>2,3-diphenynaphthalene</td>
<td>45</td>
</tr>
<tr>
<td>m-dimethoxynaphthalene</td>
<td>m-methoxybiphenyl</td>
<td>23 (79)</td>
</tr>
<tr>
<td>p-dimethoxybenzene</td>
<td>p-methoxybiphenyl, p-terphenyl</td>
<td>33 (37)</td>
</tr>
<tr>
<td>p-methoxybiphenyl</td>
<td>p-terphenyl</td>
<td>24 (27)</td>
</tr>
<tr>
<td>m-cresyl methyl ether</td>
<td>m-methylbiphenyl</td>
<td>16 (74)</td>
</tr>
<tr>
<td>p-cresyl methyl ether</td>
<td>p-methylbiphenyl</td>
<td>20 (60)</td>
</tr>
</tbody>
</table>

$^a$Isolated product yields are based upon the initial ether quantity, whereas those in parentheses take into account recovered ether.
In contrast to the inertness of methoxybenzene toward phenylmagnesium bromide, 1- and 2-methoxynaphthalene undergo ready substitution in the presence of the nickel catalyst, and even a vicinal dimethoxynaphthalene undergoes facile interaction with the organometallic reagents, in the face of the inertness of o-dimethoxybenzene and o-cresyl methyl ether under these conditions. Substitution on the naphthalene nucleus occurs even with p-naphthyl p-toluenesulfonate and magnesium p-naphthoxide (Scheme V) in 60% and 16% yield, respectively, in addition to side products.

Scheme V

Recent studies of the reactions of the analogous sulfur compounds have shown that alkenyl sulfides, benzene-thiols and aryl sulfides undergo nickel-mediated conversion to the corresponding substituted olefins (primarily with retention of configuration), toluenes and biphenyls in medium to high yields, as revealed by Tables 4 and 5.

In general, the sulfur compounds undergo the catalyzed Grignard reaction more readily than the corresponding oxy compounds. For example, the facile interaction of aryl sulfides with MeMgBr and the nickel catalyst as well as the ready substitution of aromatic sulfhydryl groups by PhMgBr provide a remarkable contrast to the inertness of anisoles and phenolic hydroxy groups toward these reagents, respectively.

In contrast to the observation of both alkylation and reduction products in the nickel-mediated reaction of organomagnesium reagents having labile β hydrogens with enol ethers, no reduction product resulted from the reaction of the latter reagents with thio enol ethers and aryl sulfides (cf. Table 5).

Selenium compounds are also transformed into substituted olefins and aryls in analogy to the preceding sulfur cases. Thus, the nickel-catalyzed reaction of phenyl vinyl selenide with p-tolylmagnesium bromide yielded p-methylbiphenyl (60%) and p-methylstyrene (25%).

In view of the ease of preparation of enol ethers and alkenyl sulfides from aldehydes and ketones, a facile two-step procedure for the conversion of keto groups into, inter alia, trisubstituted olefins has become available. In addition, keto groups may be converted with high stereoselectivity to methyl vinyl quaternary carbon centers via nickel-induced methylation of the keto-derived vinylcarbinols. Aryl sulfur compounds are remarkably reactive toward nickel-catalyzed substitution; thus, it is observed (vide infra) that aryl sulfides, aryl thiols, aryl sulfoxides, aryl sulfones,
Table 4. The reactions of thioenol ethers and benzenethiol derivatives with methyl, phenyl and p-tolylmagnesium bromides

<table>
<thead>
<tr>
<th>Thio compound</th>
<th>RMgX</th>
<th>Products</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Methylthio-oct-1-ene (4:1)^a</td>
<td>MeMgBr</td>
<td>Non-2-ene (5:1)</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>PhMgBr</td>
<td>1-Phenyloct-1-ene (4:1)</td>
<td>80</td>
</tr>
<tr>
<td>Thiophene</td>
<td>PhMgBr</td>
<td>1,4-Diphenylbuta-1,3-diene</td>
<td>85</td>
</tr>
<tr>
<td>Thianaphthene</td>
<td>MeMgBr</td>
<td>o-Propenyltoluene (1:3)</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>PhMgBr</td>
<td>o-Phenylstilbene (1:1)</td>
<td>61</td>
</tr>
<tr>
<td>Dibenzothiophene</td>
<td>MeMgBr</td>
<td>o,o'-Dimethylbiphenyl</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>PhMgBr</td>
<td>o,o'-Quaterphenyl</td>
<td>52</td>
</tr>
<tr>
<td>Benzenethiol</td>
<td>MeMgBr</td>
<td>Toluene</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>p-toly1MgBr</td>
<td>p-Methylbiphenyl</td>
<td>62</td>
</tr>
<tr>
<td>p-t-Butylbenzenethiol</td>
<td>MeMgBr</td>
<td>p-t-Butyltoluene</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>PhMgBr</td>
<td>p-t-Butylbiphenyl</td>
<td>30</td>
</tr>
<tr>
<td>Thioanisole</td>
<td>MeMgBr</td>
<td>Toluene</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>p-toly1MgBr</td>
<td>p-Methylbiphenyl</td>
<td>74</td>
</tr>
<tr>
<td>p-t-Butylthioanisole</td>
<td>MeMgBr</td>
<td>p-t-Butyltoluene</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>PhMgBr</td>
<td>p-t-Butylbiphenyl</td>
<td>53</td>
</tr>
<tr>
<td>Diphenyl sulfide</td>
<td>MeMgBr</td>
<td>Toluene</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>p-toly1MgBr</td>
<td>p-Methylbiphenyl</td>
<td>74</td>
</tr>
<tr>
<td>p-t-Butylthioanisole oxide</td>
<td>MeMgBr</td>
<td>p-t-Butyltoluene</td>
<td>50</td>
</tr>
<tr>
<td>Diphenyl sulfoxide</td>
<td>MeMgBr</td>
<td>Toluene</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>p-toly1MgBr</td>
<td>p-Methylbiphenyl</td>
<td>57</td>
</tr>
<tr>
<td>Methyl phenyl sulfone</td>
<td>MeMgBr</td>
<td>Toluene</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>p-toly1MgBr</td>
<td>p-Methylbiphenyl</td>
<td>45</td>
</tr>
<tr>
<td>Diphenyl sulfone</td>
<td>MeMgBr</td>
<td>Toluene</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>p-toly1MgBr</td>
<td>p-Methylbiphenyl</td>
<td>53</td>
</tr>
<tr>
<td>Sodium p-toluenesulfinate</td>
<td>p-toly1MgBr</td>
<td>p-Methylbiphenyl</td>
<td>27</td>
</tr>
</tbody>
</table>

^a trans:cis Ratio
<table>
<thead>
<tr>
<th>Sulfide</th>
<th>RMgX</th>
<th>Product</th>
<th>% Yield</th>
<th>trans:cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhS—Ph</td>
<td>PhMgBr</td>
<td>Ph—Ph</td>
<td>97</td>
<td>6:94</td>
</tr>
<tr>
<td></td>
<td>BuMgBr</td>
<td></td>
<td>45</td>
<td>6:94</td>
</tr>
<tr>
<td>MeS—Ph</td>
<td>PhMgBr</td>
<td>Ph—Ph</td>
<td>85</td>
<td>95:5</td>
</tr>
<tr>
<td></td>
<td>BuMgBr</td>
<td></td>
<td>64</td>
<td>95:5</td>
</tr>
<tr>
<td>EtS—Ph</td>
<td>PhMgBr</td>
<td>Ph—Ph</td>
<td>96</td>
<td>5:95</td>
</tr>
<tr>
<td>PhS—Ph</td>
<td>PhMgBr</td>
<td></td>
<td>60</td>
<td>--</td>
</tr>
<tr>
<td>PhS—Ph</td>
<td>PhMgBr</td>
<td>Ph—Ph</td>
<td>64(81)</td>
<td>mixture</td>
</tr>
<tr>
<td>PhSMe</td>
<td>BuMgBr</td>
<td>Ph—Bu</td>
<td>29</td>
<td>--</td>
</tr>
<tr>
<td>MeS—Ph</td>
<td>PhMgBr</td>
<td>Ph—Ph</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>EtS—Ph</td>
<td>PhMgBr</td>
<td>Ph—Ph</td>
<td>56</td>
<td>--</td>
</tr>
</tbody>
</table>

Table 5. The reactions of alkyl and aryl sulfides with phenyl- and butyl-magnesium bromides
aryl sulfinates and aryl sulfonates are converted to the corresponding olefins, tolenes and biphenyls in medium to high yields.

BIBLIOGRAPHY


2. For further mechanistic details, see references 1c, d and f.

3. This must be true whether or not the isomeric π-crotyl complexes 4 and 6 are interconverted (e.g., via the σ-complex 5), and whatever the relative rate of this interconversion (if it occurs); slow (anti→syn) interconversion of π-crotylnickel complexes has been observed by C. A. Tolman, J. Am. Chem. Soc., 92, 6777 (1970).

4. \( k_s / k_a = (X_2 - X_1) / (X_1 - X_2) \) where \( X \) stands for the percentage proportion of any one olefin \( X \) \( (X = 7, 8 \text{ or } 9, R = \text{Me or Ph}) \) formed from the alcohol \( n \) \( (n = 1, 2 \text{ or } 3) \).

5. The proportions of cis-2-pentene \( (9, R = \text{Me}) \) formed are so close together that it is not possible to calculate a significant value of \( k_s / k_a \) for this olefin (see ref. 4).


10. E. Wenkert, unpublished observations.


Hypervalent, or electron-rich bonding, is a term used to describe molecules formed by elements whose formal valence-electron shell contains electrons in excess of the traditional stable octet. Although molecules such as PCl₅ and SeCl₄ were prepared before 1820 by Davy and Berzelius, it has been only recently that the bonding in these molecules has been described.¹

Although the seminar will focus on non-metal species, the majority of geometrical isomerizations which have been studied have been on compounds of the type ML₆, where M is a metal and the ligands are mono- or bidentate.² Isomerization mechanisms which involve no bond rupture at the central atom include the Bailar twist⁴ (rotation about a C₃ axis) and the Ray and Dutt twist⁵ (rotation about a C₂ axis). A dissociative mechanism can occur through tetra- or pentacoordinate intermediates.²

Few geometrical isomers of hexacoordinated non-metal species have been reported. The recently reported³ isomerization of some hexacoordinate phosphorus anions showed the cis isomer to predominate in equilibrium at room temperature. The only chalcogen (S,Se,Te) for which cis and trans isomers of the same composition has been earlier reported is tellurium.⁶

Some cis hexacoordinate sulfur compounds (persulfuranes) are known. With the exception of a cis persulfuran reported by Cady,⁷ all of these are constrained in a cis configuration by incorporation of the sulfur in a ring system.⁸ We have isolated 1 and 2 and studied the acid catalyzed conversion of 1 to the more stable 2. Thermochemical studies of the hydrolysis of 1 and 2 to the common product 3 show 2 to be favored by 2.0 ± 0.5 kcal/mole over 1. The non-dissociative twist mechanisms for the conversion of 1 to 2 have activation barriers greater than 45 kcal/mole. This was determined by heating a solution of 1 in quinoline at 235°C for 18 h without any detectable isomerization.⁹
BIBLIOGRAPHY


2. For reviews on rearrangement of octahedral metal complexes see (a) N. Serpone and D. G. Bickley, Prog. Inorg. Chem., 17, 391 (1972); (b) J. J. Fortmann and R. E. Sievers, Coord. Chem. Rev., 6, 331 (1971).

SYNTHESIS AND UTILITY OF VINYL SILANES IN ORGANIC SYNTHESIS

Reported by Pam Albaugh-Robertson

October 23, 1980

In the past decade a great deal of work has been reported on the use of silicon reagents, particularly in the area of synthetic organic chemistry.¹ The focus of this account is the synthesis and utility of organosilicon reagents in which silicon is ultimately bonded to four carbon atoms with at least one of these carbons possessing unsaturation, that is, vinylsilanes.

Silicon differs electronically from carbon in that it is more electropositive than carbon and has vacant d-orbitals. From these facts several trends are observed:¹ ² ¹) a Si-C bond is more polarized than a corresponding C-C or C-H bond and thus is more susceptible to attack by oxygen or halogen nucleophiles; 2) the electron-releasing capability of silicon allows a Si-C bond to stabilize a β-carbonium ion;³ 3) the electron-withdrawing capability of silicon allows it to stabilize an adjacent carbanion. These aforementioned properties are quite evident in the synthesis and reactions of vinylsilanes.

Vinylsilanes can be prepared from a variety of substrates, depending in part on the substitution needed in the vinylsilane. Typical substrates used include vinyl halides, acetylenes, ketones, and compounds already containing a Si-C bond. Vinyl halides can be coupled with a chlorosilane by treatment with sodium⁵ or the vinyl halide may be metallated prior to reaction with a chlorosilane.⁶ Acetylenes or the 1-silylacetylenes undergo hydrosilation,⁷ hydroboration,⁸ hydroalumination,⁹ reduction,⁰ hydrogenation,¹¹ or reaction with copper reagents,¹² as well as many other reagents,¹³ to yield vinylsilanes. Ketones can be converted to vinylsilanes by reaction with bis- or tris- (trimethylsilyl)-methyllithium¹² or by the reaction of the alkenyllithium derived from an arenesulfonylhydrazone with a chlorosilane.¹³

Vinylsilanes often exhibit high degrees of regio- and stereo-selectivity in reactions. Addition of electrophiles (see Scheme I) usually leads to overall electrophilic substitution via loss of the silyl group.¹² ¹⁴ ¹⁵ ¹⁶ ¹⁷

Scheme I

\[ \text{SiR}_3 \xrightarrow{E^+} \xrightarrow{X^-} \xrightarrow{E} \]

The electrophile becomes bound to the carbon originally bearing the silicon atom, and the reaction may proceed with retention or inversion of geometrical configuration depending on the reaction conditions.

The Si-C bond is stable to free-radical reactions and cycloaddition reactions.¹ The vinylic Si-C bond is generally resistant to nucleophilic cleavage, with the notable exception by fluoride ion when there is a β-hydroxyl in the allylic position.¹⁵ ¹⁶ Certain organometallics can add to vinylsilanes if
there is a leaving group in an allylic position, no substitution on the vinylsilane, or if there is an additional anion-stabilizing group on the \( \sigma \)-carbon.\(^1\) Addition across the double bond,\(^2\)\(^3\)\(^{15}\)\(^{19}\)\(^{23}\) for example, hydroboration,\(^2\) also occurs without cleavage of the C-Si bond.

Epoxidation of vinylsilanes leads to the epoxysilanes which can be transformed to carbonyl compounds or other epoxides.\(^2\) The presence of a halogen on the double bond of a vinylsilane allows for further substitution of the double bond.\(^2\)\(^3\)

Vinylsilanes can be valuable intermediates for stereocontrolled syntheses. But, the employment of vinylsilanes in organic synthesis has only begun. Therefore, the full profitability of vinylsilanes as viable precursors has yet to be realized.

BIBLIOGRAPHY


MECHANISTIC ASPECTS OF THE PHOTOTAUTOMERISM
OF PHENOLS AND AROMATIC KETONES

Reported by Sander G. Mills

The ability of aromatic systems such as 1 and 2 to tautomerize upon irradiation (to 1a and 2a respectively) has been widely studied in the last thirty years. Innumerable examples of these processes have been discovered in this time, and a variety of synthetic and technological applications demonstrated.\(^{1,2}\) However, in most cases the mechanisms remained unclear. Recent work, using very fast kinetics techniques, theoretical models, and substituent effect studies have extended our understanding of these systems.

Phenol Derivatives. The first examples of phototautomerism came in the 1950's, based on the observation of unusually large shifts in fluorescence maxima in salicylic acid derivatives.\(^{3}\) Shortly thereafter, Cohen and coworkers\(^{4}\) reported that photochromic properties of salicyclidine anilines (anils) were also from tautomeric shifts (i.e., \(2 \rightarrow 2a\)).\(^{4}\) These proton transfers could be rationalized qualitatively by noting that the acid-base properties of many functional groups shift strongly in the first excited singlet state.\(^{5}\) Phenols, for instance, become more acidic and carbonyl groups more basic,\(^{10}\) facilitating the proton transfer. It was also shown that the H-bond between the donor and receptor sites was necessary, since the anil of p-hydroxy benzaldehyde was not photochromic.\(^{6}\)

In the anils,\(^{7}\) a further isomerization occurs to give 3, which is assumed to be the photochromic (colored) species.\(^{4,6}\) Subsequent investigations\(^{8,9}\) have established that, contrary to expectation, the vibrationally relaxed excited singlet cis-quinoid 2a does not appear to be the direct kinetic precursor to 3. Spectra of the conformationally more rigid system 4 showed similar behavior.\(^{10}\) On the basis of these results, as well as semi-empirical calculations on the excited state surface of \(2 \rightarrow 2a,\)\(^{11}\) it was suggested that the intermediate that partitioned between the cis and trans form of the quinone displayed a geometry twisted about both the C1-C7 bond and the C7-N bond, which was postulated to occur only in a nonvibrationally relaxed level of the singlet excited state.\(^{11}\) In nano- and picosecond studies of 2 and 4\( (X=\phi),\) Rentzepis and coworkers\(^{12}\) tentatively concluded that a transient observed at 4K (whose lifetime was only 7 psec) was this unrelaxed species, and supported this speculation with the viscosity\(^{12}\) and excitation wavelength dependence of the fluorescence spectra.\(^{11}\)
Aromatic Ketones. The photoreduction of benzophenone to benzapinacol, which proceeds through the \( ^3n,\pi^* \) state, displays a decreased product quantum yield when an ortho alkyl substituent is present.\(^1\) This has been attributed to the transformation \( 1 \rightarrow 1a \), and has been detected via ESR experiments and has been trapped by dienophiles. This process has been observed in other aryl and alkyl aryl ketones as well as \( o \)-alkyl benzaldehydes.\(^{1a,13-18}\)

The results of flash photolysis studies on \( 1 \) have been in dispute.\(^{19-22}\) Uji-Ie and coworkers\(^2\) claimed that two non-interconverting ketone triplets led to the \( cis \) and \( trans \) dienols separately. Das et al.\(^{21,22}\) interpreted the data in terms of a single triplet precursor to both products, supporting the assignment with measurements of the electron transfer properties of the biradical precursor.\(^{22}\) Theoretical studies,\(^{23,24}\) performed on \( cis-2 \)-butenal (a model for the aromatic ketones) have been used to evaluate the energies of excited state structures, but their applicability to aromatic systems is limited by the neglect of steric factors in the larger systems.

In contrast to benzophenone derivatives, 2-alkylphenyl alkyl ketones show two distinct enol triplet precursors,\(^{19,22}\) and these are assigned to the \( syn \) and anti conformers of the ketone triplet. As expected, the \( syn \) isomer has a much shorter lifetime because of the closeness between the oxygen and the labile hydrogen. 2,6-dialkylphenyl ketones, also studied by these authors,\(^{13,22}\) gave complex results. Wagner\(^13\) studied the competition between type II photoelimination and ortho proton abstraction in 5. \( \Phi \) could not rationalize the kinetics, solvent data, and quencher behavior with a simple

\[
\begin{align*}
\text{O} & \quad \text{hv} \rightarrow \quad \text{O} \\
\text{5} & \quad \text{+} \quad \text{OH}
\end{align*}
\]

model, but speculated that it may involve the geometry dependent equilibration between triplet \( n,\pi^* \) and \( \pi,\pi^* \) states lying fairly close in energy.\(^{25}\)

BIBLIOGRAPHY

TWO DIMENSIONAL NUCLEAR MAGNETIC RESONANCE AND SOME APPLICATIONS IN ORGANIC CHEMISTRY

Reported by Tuyen T. Nguyen November 3, 1980

Nuclear Magnetic Resonance (NMR) spectroscopy has been a very useful tool for structural determination of organic molecules. However, with complex molecules it is sometimes not possible to make a complete assignment of the investigated spectrum. The recent development of the two-dimensional (2D) NMR, in which chemical shift and spin coupling in weakly coupled spin systems are separated, provides a new way to analyze the complex spectra of organic molecules such as those of carbohydrates and steroids.

The 2D NMR spectroscopy involves a plot of spectral data where both variables are frequencies. By definition, the stacking of a set of spectra as a function of time in a two dimensional manner is not considered a two-dimensional spectrum. In general, a signal \( s(t_1, t_2) \), which is a function of two time variables \( t_1 \) and \( t_2 \), can be transformed into a signal \( S \), which is a function of two frequencies \( \omega_1 \) and \( \omega_2 \), by a two dimensional Fourier transformation:

\[
S(\omega_1, \omega_2) = \hat{F}_{t_1,t_2}[s(t_1,t_2)]
\]

The 2D NMR spectrum is obtained this way. To introduce the two independent time variables, \( t_1 \) and \( t_2 \), the time axis is divided into three periods: preparatory, evolution and detection periods. In the preparatory period, the system is prepared to give a suitable initial state. The system evolves under the influence of a Hamiltonian \( H_1 \) in the evolution period. At the end of this period the system will have a particular state that depends on \( H_1 \) and the elapsed time \( t_1 \). The time variable \( t_1 \) is the length of the evolution period, and \( t_2 \) is the running time of the detection period. The resulting signal \( s(t_1,t_2) \) is the function of both time variables as presented in Figure 1.

Figure 1. The basic principle of 2 dimensional spectroscopy.

-预备期
-演变期
-检测期
Based on this principle, many kinds of 2D spectra can be generated. In this seminar, we are concerned only with 2D spectroscopy of proton, and proton-coupled carbon-13.

The Carr-Purcell experiment. The Carr-Purcell spin-echo experiment is the basis of 2D spectroscopy. This experiment uses two radiofrequency (rf) pulses that have the magnetic component perpendicular to the macroscopic magnetic moment \( M \) which is the sum of all the magnetic moments \( M \) of nuclei in the sample. In the rotating frame of reference, a coordinate system in which the \( x' \) and \( y' \) axis rotate synchronously with the radiofrequency field around the \( z' \) axis, which is in the direction of the external magnetic field, a 90° rf pulse in the \( x' \) direction will tip \( M \) onto the \( y' \) axis (as shown in Figure 2a). As a result of field inhomogeneity in the external field, some magnetic component \( M \)'s precess faster than \( \omega \) and some precess slower. Therefore, in the rotating frame of reference, magnetic components \( M \) begin to fan out in 2b. After a time \( \tau \), the transverse decaying magnetization is reflected into its mirror image (relative to the \( x'z' \) plane) by a 180° pulse, as shown in 2c. At time \( 2\tau \), all the components will converge (2d) to give an echo (2e), and then they will fan out again (2f). Therefore after the 90°

**Figure 2.** The basis of the Carr-Purcell spin-echoes experiment

(a) Magnetization \( M \) is flipped onto the \( y' \) axis by \( H_1 \).
(b) Its components spread out due to the external field inhomogeneity.
(c) Conversion to the mirror image by \( H_1 \).
(d) Refocussing of \( M \) which gives an echo in (e).
(f) Components spread out afterward.
pulse, 180° pulses at $t$, 3$t$, 5$t$... will produce echoes at 2$t$, 4$t$, 6$t$...

In practice, a 90° or a 180° pulse is produced empirically to give best echoes. A small inaccuracy of the 180° pulse will eventually lead the magnetization out of the x'y' plane. Meiboom and Gill suggested the 180° pulse to be applied along the y' axis. This modification corrects the problem of the Carr-Purcell experiment. It is illustrated in a sequence of figures (3a-3f) analogous to those of 2 except that the 180° pulse is applied above the y' axis.

**Figure 3.** The Meiboom-Gill experiment

(a) A pulse slightly smaller than 180° will focus M above the x'y' plane in (b). The magnetizations spread out above the xy plane in (c). The same pulse puts the magnetization on the x'y' plane(d) which gives an echo in (e). The process continues in (f).

**Echo modulation.** Echo modulation or J modulation occurs when a single spin species A is weakly coupled by J Hz ($2\pi J$ radsec$^{-1}$) to another nucleus of the same species X. The rf pulses affect both nuclei. In the reference frame rotating at the radio frequency, after the initial 90° pulse, the magnetization will split into two components centered about the positions $(\omega + \pi J)t$ and $(\omega - \pi J)t$. When the 180° refocussing pulse is applied (as in the Meiboom-Gill experiment), the mirror image of the two components are formed, but the pulse also simultaneously rotates the magnetization of X so the two components are also interchanged. At time $t=2t$, two discrete com-
ponents are observed. This phenomenon is illustrated in Figure 4.

Figure 4. Effect of homonuclear spin-spin coupling in the Carr-Purcell-Meiboom-Gill experiment

If the 180° pulses are applied in a sequence at time $t$, $3t$, $5t$, ... echoes will form at $2t$, $4t$, ... The amplitude of the echoes will decay gradually due to spin-spin relaxation. Fourier transformation of the echoes that are obtained at $2t$, $4t$, ... will give a $J$ spectrum which shows only the effect of spin coupling. An example of a $J$ spectrum is shown in Figure 5.

Figure 5. The $J$-spectrum of CH$_2$ClCHCl

![J-spectrum of CH$_2$ClCHCl](image)
Homonuclear 2D spectroscopy. The homonuclear ($^1H-^1H$) 2D spectroscopy can be obtained in the following ways. The 90° pulse in the $x'$ direction starts the evolution period ($t_1$). At $\tau(1/2 t_1=\tau)$ seconds later, a 180° refocussing pulse is introduced which will give a spin-echo at $t_1$ or $2\tau$. The free decay of this echo is then sampled. A large number of free decaying echoes are collected with $t_1$ systematically varied. Fourier transformation of this set of data yields a two dimensional spectrum. The amplitudes of the spin-echoes are affected only by spin-spin coupling constants and the relaxation process. Therefore, multiple splitting will be seen in the $\omega_1$ direction while all the resonance absorptions will be contained in the $\omega_2$ direction. The basic scheme for 2D J spectroscopy is illustrated in Figure 6. An example of a proton 2D spectrum is shown in Figure 7.

Figure 6. Basic scheme of proton 2D NMR

Figure 7. A "rough" spectrum of $\text{CH}_3\text{CH}_2\text{OH}$

It should be noted that peaks of every multiple are on a straight line, therefore a projection along a line 45° from the $\omega_2$ axis, in a procedure which is described by Nagayama and Ernst, will give a completely decoupled spectrum. This is basically a way to obtain a proton spectrum with broad band proton
decoupling (Figure 8).

**Figure 8.** Projection of the 2D spectra of CH₂CH₂OH onto the ω₂ axis at 45° angle gives proton-decoupled proton spectrum.

Heteronuclear (¹H-¹³C) 2D J-spectroscopy. There are several ways to obtain proton-coupled ¹³C spectra. Let us consider the method that involves a "proton flip." This method also utilizes two pulses, 90° and 180°, this time at the ¹³C resonance frequency. The detection period, as before, starts at time 2τ. However, the 180° pulse at the carbon resonance frequency will not invert the spin state of proton(s) coupled to the carbon atom. Therefore, no J modulation occurs. To introduce this J modulation, a 180° pulse, which

**Figure 2.** Two basic methods to obtain a 2D spectra of ¹³C NMR. Method (a) gives coupling information in both ω₁ and ω₂ dimensions. Method (b) gives coupling information only in the ω₁ dimension.

(a)
is synchronized with the other 180° pulse, is applied simultaneously into the decoupling channel. This pulse inverts the spin state of the proton, thus J modulation occurs. At the preparation period, all protons are radiated to establish a nuclear Overhauser effect. At the detection period, if the protons are radiated (as in 9b), only chemical shift is contained in the t₂ dimension. In this case, after the Fourier transformation, we have the 2D ¹³C spectrum which has chemical shift in w₂ dimension and ¹H-¹³C coupling in w₁ dimension. If the protons are not decoupled in the detection period (in 9a), a full undecoupled ¹³C spectrum is seen in the w₂ dimension.

Applications. Two dimensional J-spectroscopy has been used to assign chemical shifts and coupling constants of protons in various classes of compounds. These include nucleoside monophosphates, peptides, mono- and disaccharides, and steroids. Usually the assignments are made based on 2D spectra only. However relaxation rates, nuclear Overhauser enhancement differences, and decoupling difference techniques are also used in the more complex molecules. An example of this is the analysis of proton NMR spectrum of 1-dehydrotestosterone. Recent improvement in the shortening of the measuring time enhances the usefulness of 2D J-spectroscopy in solving complicated spectra.

BIBLIOGRAPHY

The homogenous asymmetric hydrogenation of prochiral olefins catalyzed by chiral rhodium(I) complexes is an important synthetic method.\textsuperscript{1} Although simple olefins generally give low optical yields (less than 50\% ee), much better results (optical yields greater than 90\% ee) have been obtained for the reduction of (Z)-$\alpha$-N-Acylamidoacrylic acids and esters, forming amino acid derivatives (Eq. 1).\textsuperscript{1-5} The chiral rhodium(I) catalyst, prior to addition of the prochiral amino acid precursor, is typically of the form $[\text{RhL}_nS_n]^+_X^{-}$, where L is a chiral phosphine ligand and S is a solvent molecule. The optical yields of 80-99\% ee found for the asymmetric reduction of (Z)-$\alpha$-N-Acylamido acrylic acids and esters have led to a number of studies dealing with substrate specificity,\textsuperscript{17} asymmetric induction and finally, determination of the individual steps in the overall mechanism. This review will focus on these studies.

\begin{equation}
\begin{array}{c}
\text{R'}O_2C\text{NHCOR} + H_2 \\
\text{H} \quad \text{THF}
\end{array}
\end{equation}

[\text{RhL}_nS_n]^+_X^{-} \quad \text{R'}O_2C\text{NHCOR}

\text{*chiral center}

The ability of a chiral catalyst to effect high optical yields is thought to be a function of the rigidity of the ligand-metal complex.\textsuperscript{16} Generally low optical yields are obtained when the phosphine is unidentate while bidentate ligands give better results.\textsuperscript{16} Ligands in which the chirality resides on the phosphorus atoms\textsuperscript{3} or the carbon chain\textsuperscript{17} have given equally good results.\textsuperscript{1} Bosnich has recently provided evidence that the success of these chiral bidentate ligands can be traced to the chiral array of quasi-axial and quasi-equatorial substituents on the chelating phosphorus atoms.\textsuperscript{1,6}

It is known that (Z)-$\alpha$-N-Acylamidoacrylic acids and esters give much higher optical yields of reduced products than the corresponding E isomer.\textsuperscript{3} Separate studies by Knowles\textsuperscript{9} and Kagan\textsuperscript{10} have addressed this phenomena, each using deuterium labeling as a method of determining the reaction pathway. Both studies concluded that E to Z isomerization was the cause of decreased optical yield for the E isomer, although each group postulated a different isomerization mechanism.

A detailed reaction mechanism has recently been reported by Halpern based on comparison studies of the hydrogenation of alkyl (Z)-$\alpha$-N-Acetamidocinnamates in methanol, using either the chiral complex [Rh(S,S-Chiraphos)]\textsuperscript{+} or the achiral [Rh(diphos)]\textsuperscript{+} as the homogenous catalyst.\textsuperscript{11-14} Examination of the rate data and identification of several intermediates led to the conclusion that the enantioselectivity of these reactions was determined by the rate of hydrogen addition to the diastereomeric catalyst-substrate adducts and not by the preferred mode of binding of the prochiral olefin to the chiral catalyst.\textsuperscript{15} This interpretation provides an explanation for the inverse dependence of optical yield on the partial pressure of hydrogen observed in similar systems.\textsuperscript{3,14,16}
BIBLIOGRAPHY

NEW 2-SUBSTITUTED ALLYL ANIONS: $\beta^1$ LITHIATION OF $\alpha,\beta$-UNSATURATED SECONDARY AMIDES

Reported by Dale Kempf

November 10, 1980

The synthetic potential of 2-substituted allylic carbanions has only begun to be realized. A number of examples have appeared in the literature including those in which the substituent $Y$ (anion 1) is formally alkyl, phenyl, CN, SiMe$_3$, CONR$_2$, CH$_2$OLi, CO$_2$R, O$,^9$ CH$_2$Li, and most recently, CONLiR.$^{11,12}$ For best synthetic utility, $Y$ should be (a) inert to the conditions used for preparing the anion and (b) easily transformed to other functional groups in later steps. In addition, for some reactions it is preferable for $Y$ to be electron withdrawing.

2-substituted allyl anions have been generated by conrotatory ring opening of cyclopropyl anions$^{13}$ and by metal-halogen or metal-oxygen exchange of allylic halides and ethers. A more general method, however, is through direct deprotonation of 2-substituted propenes, since electron withdrawing groups at the termini are required for ring opening$^{14}$ and more complex precursors are required for the exchange reactions. A few of the anions generated by deprotonation require additional activation at the 1 and 3 positions as well.

The anions thus prepared have often been used with olefins in 1,3-anionic cycloadditions to give cyclopentanes (Eq. 1).$^{2a-c,3,15}$ First noted in the

\[
\begin{align*}
\text{Y} & \quad + \quad \text{M}^+ \\
\text{X} & \quad \text{Z} \\
\text{M}^+ 
\end{align*}
\]  

reactions of allylic Grignards with benzyne,$^{4,16}$ the cycloaddition may be concerted in some instances,$^{3b}$ but has been shown to be stepwise in one case.$^5$ Activated olefins and an electron withdrawing substituent (CN, Ph, CONR$_2$) at the 2-position of the anion are required for the cycloaddition to progress, the latter in order to stabilize the anionic product.

Trapping the allyl anions at one of the termini results in electrophilic substitution at that position (Eq. 2). Reaction with aldehydes and ketones leads to $\alpha$-methylene butyrolactones when $Y$ is of the acid oxidation level.$^{6a,7a,b}$

\[
\begin{align*}
\text{Y} & \quad \text{M}^+ \\
\text{E}^+ \\
\text{Y} & \quad \text{E} \quad \text{E}
\end{align*}
\]  

The anions have also been trapped with alkyl and trialkylsilyl halides to give noncyclized products.$^{1d,2d,6b,7c}$ Several 2-alkyl allyl anions have been employed as isoprenyl anion synthons.$^{1a-d}$

Special examples of 2-substituted allyl anions include $\alpha,\alpha'$ ketone di-anions (2) and the trimethylenemethane dianion (3). Ketone dianions have been
found to be much more nucleophilic than their enolate precursors though somewhat less selective.\(^9\) The trimethylene methane dianion has recently been shown to be synthetically as well as theoretically useful.\(^{10}\)

![Diagram](attachment:image.png)

The 2-substituted allyl anions which appear to be the most promising synthetically are those derived from \(\alpha,\beta\)-unsaturated secondary amides.\(^{11}\) Amides can be readily converted to other functionalities, and initial deprotonation deactivates the carbonyl group toward nucleophilic attack. Most important, the strong directing ability of the secondary amide monoanion\(^{17}\) enables \(\beta\)' proton removal in the presence of potentially acidic \(\beta\) and \(\gamma\) hydrogens.\(^{18}\) As shown in Eq. 3, the dianion formed from \(N\)-methyl-1-cyclohexene-

\[
\begin{align*}
\text{CONHCH}_3 & \quad 2 \text{s-BuLi/TMEDA} \\
-78^\circ, \text{THF} & \quad \xrightarrow{\text{Li}^+} \\
\text{E}^+ & = \text{CH}_3\text{OD, CH}_3(\text{CH}_2)_5\text{Br, CO}_2, (\text{CH}_3)_2\text{CO, Ph}_2\text{CO, (n-Bu)}_3\text{SnCl}
\end{align*}
\]

carboxamide can be trapped with a number of different electrophiles in synthetically useful yields. The deprotonation is also selectively \(\beta\)' in five-membered and acyclic cases.\(^{11,12}\) Reaction with ketones followed by cyclization leads to the corresponding \(\alpha\)-alkylidene butyrolactones.\(^{11,12}\)

The synthetic potential of these amide dianions appears to be quite high due to the selectivity observed in deprotonation. However, regioselectivity in the subsequent reactions with electrophiles can be a problem if the allylic system is unsymmetrically substituted and isomeric mixtures can be formed.\(^{11}\) Furthermore, the reaction conditions appear to be important, since some substituted acryanilides have been shown to serve as Michael acceptors with alkyl and aryllithium bases.\(^{19}\)

**BIBLIOGRAPHY**


THE UGI REACTION

Reported by Jim Gloer

Classical methods for peptide synthesis involve amide bond formation by reaction of an acylating derivative of an N-terminally protected α-amino acid with the α-amino group of a C-terminally protected component. Fragment coupling, the technique of choice for making large peptides, is also achieved in this manner. Although these methods are often adequate, problems are frequently encountered in the areas of side reaction, racemization, yield, and hence purification.

The Ugi Reaction (Four Component Condensation) offers an alternative approach to peptide synthesis and fragment coupling which has already demonstrated potential in dealing with these difficulties. The most important application of the Ugi Reaction to peptide chemistry is in the area of fragment coupling. It has allowed the coupling of two peptide fragments to occur in good yield with essentially no racemization.

This review will examine the Ugi Reaction and its advantages over classical techniques. A discussion of the problems encountered in employing this method as well as their possible solutions will be included. In addition to this, other useful syntheses utilizing the Ugi Reaction will be outlined.

The Reaction. The Ugi Reaction in this context (Scheme I) involves the condensation of four components: a primary amine, an aldehyde, an acid, and an isonitrile, and may be viewed as a cross between a Mannich Reaction and a Passerini Reaction. The mechanism involves initial condensation of the amine with the aldehyde to give the Schiff base, which is protonated in the presence of acid. This species and the carboxylate anion then react with the terminal carbon of the isonitrile via a series of equilibria to give the usually non-isolable intermediate, which rapidly rearranges by a cyclic, first order pathway to afford the stable adduct 2. Depending on the choice of components, the reaction product may then be cleaved at bond A to give a new peptide or at bond B, which results only in the coupling of the acid and the amine.
A closer examination of the route leading to formation of 2 has established that the mechanism is complex, involving a series of four alternative ways to form 1 (Scheme Ia). A further complication is introduced by the fact that the intermediates in each pathway are in dynamic equilibrium with all the other intermediates in the other pathways, so that the kinetics of the reaction are not trivial.

Scheme Ia. Mechanism of the Ugi Reaction

The scope of the Ugi Reaction is by no means limited to peptide chemistry. Some other aspects of this versatile synthetic method are discussed later in this abstract.

Peptide Synthesis. The most widely used methods of peptide synthesis are based on the use of carboxyl group-activated amino acids or the use of coupling reagents, which both function by similar mechanisms. Many of these methods have been used for decades and have proven reliable and useful, but all have their drawbacks. The azide method, for example, (Scheme II), developed by
Curtius in 1902, allows formation of peptide bonds with very little racemization. However, the intermediate hydrazide and the azide itself are susceptible to substantial side reactions, such as amide formation and Curtius rearrangements.\textsuperscript{1} Dicyclohexylcarbodiimide is the most widely used coupling reagent (Scheme III). It gives good yields with minimal side reactions, but racemization is a problem, even in the presence of N-hydroxysuccinimide.\textsuperscript{11,10}

\begin{align*}
\text{Scheme III. Amino Acid Coupling with Dicyclohexylcarbodiimide (DCC)}
\end{align*}

\[
\text{RCOOH} + \text{\text{DCC}} \rightarrow \text{RC-NH-C=O} + \text{Dicyclohexylurea}
\]

All of these methods also involve protection of N- and C-termini as well as many of the common amino acid residues, followed by deprotection to allow reaction with the next protected amino acid to be added onto the chain. Consequently, several steps are required to add each amino acyl residue.

Application of the Ugi Reaction to peptide synthesis (Scheme I) has several advantages over classical techniques. Fewer steps are involved in synthesis by this method. Two new peptide bonds and an extra amino acyl unit are formed in effectively one step, and the only functional groups which require protection are COOH, NH\textsubscript{2}, and SH.\textsuperscript{3} Unusual amino acids which do not occur in nature or are difficult to synthesize (e.g., isotopically labelled, sterically hindered) might be easily incorporated into a peptide by Ugi Reaction via their aldehydes.\textsuperscript{3,7} α-alkyl amino acids are accessible through the appropriate ketones.\textsuperscript{11}

Peptide bond formation by the Ugi Reaction is a unimolecular process, as opposed to classical methods of peptide bond formation which involve bimolecular reactions. The formation of the peptide bonds from the acylating intermediate \textsubscript{1} is much faster than classical bimolecular peptide bond formation. The rearrangement of \textsubscript{1} to give \textsubscript{2} occurs after the rate determining steps\textsuperscript{7} and no products of intermolecular reactions involving \textsubscript{1} have been isolated. Advantages stemming from this include the occurrence of fewer side reactions and less racemization, hence, purification problems are less pronounced than those of classical methods.

Unfortunately, this method introduces new problems which have yet to be completely solved. For the reaction to yield an optically pure product, one must start with an optically pure isonitrile. Stereospecific synthesis of α-isocyanoadic derivatives is troublesome, but has been accomplished in some instances by dehydration of the N-formyl-t-butyl esters\textsuperscript{12} with phosgene at temperatures below -20°C in the presence of N-methylmorpholine (Scheme IV).\textsuperscript{12,13} The isocyanate group is more easily introduced into a fragment in which the carbonyl is that of an amide, because the anionic intermediate leading to racemization is not formed as readily.\textsuperscript{3} In fact, dipeptides and oligopeptides pose little problem in their stereospecific conversion to isonitriles.
A more difficult problem is that of the amine component. Its structure must be such that bond A (Scheme I) is easily severed, but it must also be able to perpetrate asymmetric induction on the new α-carbon if we wish to designate the stereochemistry there. Three classes of amines which have potential to satisfy these conditions have been investigated. Ugi adducts of resonance stabilized vinyl amines (3) easily cleave under mild conditions, but can possess little asymmetric inducing power because any chiral elements would have to be relatively far away from the forming chiral center. β-alanine derivatives (4) demonstrate good stereoselectivity, but cleavage is effected only by strong base, which can damage a peptide and promote racemization. The best solution to the problem so far involves the use of chiral α-ferrocenyl alkylamines (5). The obtained adducts (e.g., 6 and 7) are formed in good yield and are easily cleavable due to facile formation of α-ferrocenylcarbonium ions. The proximity of the chiral center to the site of the forming chiral center allows >90% stereoselectivity to be achieved under proper conditions.

Each of the alternative pathways in Scheme Ia has a different propensity towards stereoselectivity. If the conditions are chosen to favor the most selective pathway, then the stereoselectivity will be optimized. The reaction in Scheme Ia (with S-α-phenylethylamine) was carried out 264 times under various conditions which influence the concentrations of the intermediates in Scheme Ia. It was concluded that maximum amounts of S,S diastereomer were obtained when the reaction was made to proceed through the nitritium ion. Maximum S,R diastereomer was obtained when the reaction proceeded mainly via path X. These trends hold for chiral α-ferrocenylalkylamines and allow the selection of optimum reaction conditions for maximum stereoselectivity. This observed stereoselectivity can be influenced by addition of ammonium salts of the acid component and enhanced by selective acidolysis.

An Ugi Reaction of N-formyl-L-valine with R-1-ferrocenyl-2-methylpropanamine, 2-methylpropanal, and N-(2-isocyanato-3-methylbutanoyl)-L-valine gives products 6 and 7 in the ratio 91.2:8.8. Addition of two equivalents of tetraethylammonium N-formyl-L-valinate increases the ratio to 98.5:1.5. Selective acidolysis (Scheme V) of this mixture for 1.5 hr followed by recovery of unreacted material increases the ratio to >99.98:0.02 with a loss of only 4.2% of 6. 6 can then be cleaved to give essentially optically pure 8 in 73% overall yield.

The chiral α-ferrocenylalkylamines necessary for the reaction are accessible via the synthetic route outlined in Scheme VI. If the Ugi Reaction products are cleaved with thioglycolic acid/TFA, the chiral product 9 and the subsequently regenerated α-ferrocenylalkylamine (Scheme V) both result
from retentive $S_1$ reactions. The reaction is observed experimentally to be first order and the retentive mechanism can be attributed to participation of the ferrocenyl group in the stabilization of the carbonium ion.

**Scheme V.** (Fc=ferrocenyl)

\[
\begin{array}{c}
\text{HC-VAL-N-CH-C-VAL-VAL-OMe} \\
\text{CH(CH}_3)_2 \\
\text{Fc} \\
\text{CH(CH}_3)_2
\end{array}
\xrightarrow{\text{HSCH}_2\text{COOH \ TFA}}
\begin{array}{c}
\text{HC-VAL-N-CH-C-VAL-VAL-OCH}_3 \\
\text{CH(CH}_3)_2 \\
\text{Fc} \\
\text{CH(CH}_3)_2
\end{array}
\]

- $\text{6=S(R)SSS}$
- $\text{7=S(R)RSS}$

\[
\begin{array}{c}
\text{HSCH}_2\text{COOH} \\
\xrightarrow{\text{CF}_3\text{COOH}}
\end{array}
\xrightarrow{\text{To completion}}
\begin{array}{c}
\text{HC-VAL-VAL-VAL-OMe} \\
\text{(R)} \\
\text{Fc} \\
\text{CH(CH}_3)_2
\end{array}
\rightarrow
\begin{array}{c}
\text{SCH}_2\text{COOH} \\
\text{NH}_3\text{Cl}, \text{HgCl}_2, \text{conc. NH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{NH}_2 \\
\text{Fc} \\
\text{CH(CH}_3)_2
\end{array}
\]

- $\text{8}>99.98\%$ opt. pure
- $\text{9}>98\%$ opt. pure
- $\text{10}>99.98\%$ opt. pure

**Scheme VI.** (Fc=ferrocenyl)

\[
\begin{array}{c}
\text{Fc-CHO} \\
\xrightarrow{\text{HNMe}_2/\text{KCN/MeOH}}
\end{array}
\xrightarrow{\text{Et}_2\text{O}}
\begin{array}{c}
\text{Fc-CH-NMe}_2 \\
\text{CN} \\
\text{96%}
\end{array}
\rightarrow
\begin{array}{c}
\text{Fc-CH-} \\
\text{i-pr-MgBr} \\
\text{95%}
\end{array}
\]

- Racemate
- Resolution w/ D-Tartaric Acid

\[
\begin{array}{c}
\text{HSCH}_2\text{COOH} \\
\xrightarrow{\text{HCOOH, TFA}}
\end{array}
\rightarrow
\begin{array}{c}
\text{Fc-CH} \\
\text{i-pr} \\
\text{80%}
\end{array}
\rightarrow
\begin{array}{c}
\text{NH}_3\text{Cl}, \text{HgCl}_2, \text{conc. NH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{Fc-} \\
\text{i-pr} \\
\text{56%}
\end{array}
\]

- $\text{10}$

Experimentation with this method has focussed on the synthesis of small model compounds, but some small peptides have been made. The synthesis of optically pure glutathione and the tetravaline derivative (vide supra) are noteworthy examples. Also of interest is the use of formaldehyde as the aldehyde component. The new amino acyl unit in this case is glycyl, which requires no asymmetric influence. This ploy has been used in the synthesis of melanocyte inhibiting factor analogs.

**Fragment Coupling.** An alternative for the synthesis of large peptides and proteins involves the synthesis of smaller fragments followed by the splic-
ing together of these pieces. This technique was employed in the first synthesis of a protein over 100 residues in length and will undoubtedly be the method of choice in the future in synthesis of such compounds.

Large fragment coupling by classical methods is hindered primarily by the requirement that the reaction be second order. Collisions between the sites of reaction are very infrequent due to fragment size and low concentrations. Side reactions, particularly racemization (Scheme VII), which are often first order (or pseudo first order), compete very effectively with the desired reaction. Racemization of the acylating peptide fragment can occur either by direct proton loss from the α-carbon (path I) or, more likely, via azlactone enolate formation (path II).

Scheme VII

Application of the Ugi Reaction to fragment coupling (cleavage at bond B, Scheme I) seems capable of surmounting these obstacles. Intramolecular, rapid formation of the peptide bond is the main reason for the potential superiority of the Ugi Reaction over conventional methods. Racemization cannot occur until the intermediate 1 (Scheme I) is formed. Once 1 is formed, the proximity of the reacting groups assists very rapid rearrangement to 2, which cannot racemize. Thus minimized racemization (and side reactions) can be attributed to the fleeting existence of 1, in contrast to the relatively lengthy time that the c-terminally activated fragment exists in conventional syntheses. An additional boon of this method is the solubility of the adduct 2 and the cleavage by-products in organic solvents, facilitating isolation of the final peptide derivative.

The only barrier to successful application of the reaction to fragment coupling is the necessity for mild, facile removal of the aldehyde-isonitrile moiety. Several approaches to this dilemma have been investigated via simple model reactions. The isonitrile is usually important only in solubility considerations, but such couplings utilizing cyclohexylisocyanide proceed as much as ten times faster than couplings using t-butylisocyanide. No study has been published which gives a definitive reason for this. Cleavability of 2 depends only on the choice of the aldehyde component. Products of nearly 100% optical purity were commonly obtained from model reactions such as those shown in Table 1. 2-Nitro-benzaldehyde gives acceptable yields (65-70%) and allows cleavage by photolysis at 350 nm (60-80%). Electron donating counterparts, such as 2,4-dimethoxybenzaldehyde give poor yields for both the reaction and subsequent cleavage with anhydrous acid. 4-Pyridinecarboxaldehyde used in the synthesis of a dipeptide gave a 60% yield in the condensation step and quantitative cleavage under controlled potential. Further studies on this method are in order. Some other aldehydes were investigated, but the most promising of all so far is 1-BOC-3-formylindole (11). The H-bond adduct of TFA and 12 has a high tendency towards fragmentation due to the stability of the resulting carbonium ion. Using TFA for this cleavage is sometimes desirable, since TFA is often the reagent of choice for deprotection as well. Ugi Reactions with this alde-
hyde (Scheme VIII) give yields 260% and the adduct is cleaved mildly with cold TFA in trifluoroethanol (70-75%).

\[ \text{Scheme VIII.} \quad (\text{BOC} = \text{O} \text{C(CH}_3)_3) \]

\[
\begin{align*}
\text{BOC-gly-ala-OH} + \text{CHO} + \text{VAL-OC}_2\text{H} &\xrightarrow{\text{MeOH}} \text{gly-ala-val-OC}_2\text{H} \\
\text{BOC-gly-ala-NCH}_2\text{C-OC}_2\text{H} &\xrightarrow{\text{CF}_3\text{COOH}} \text{gly-ala-val-OC}_2\text{H} > 99\% \text{ optically pure}
\end{align*}
\]

**Table 1**

<table>
<thead>
<tr>
<th>acid</th>
<th>amine</th>
<th>aldehyde</th>
<th>% yield</th>
<th>% cleavage</th>
<th>overall % yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>pht-gly-OH</td>
<td>H-gly-Otbu</td>
<td>0-nitrobenzaldehyde</td>
<td>67</td>
<td>61(hv)</td>
<td>41</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>2,4-dimethoxybenzaldehyde</td>
<td>34</td>
<td>38(HF)</td>
<td>13</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>4-pyridinecarboxaldehyde</td>
<td>60</td>
<td>100 (electrolysis)</td>
<td>60</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>3-formylindole</td>
<td>45</td>
<td>81(TFA)</td>
<td>36</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>3-formylindole</td>
<td>35</td>
<td>79(TFA)</td>
<td>28</td>
</tr>
<tr>
<td>ph-CH$_2$COOH</td>
<td>ph-CH$_2$NH$_2$</td>
<td>2,4-dimethoxybenzenaldehyde</td>
<td>75</td>
<td>38(TFA)</td>
<td>28</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>3-formylindole</td>
<td>62</td>
<td>70(TFA)</td>
<td>43</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>Ferrocenecarboxaldehyde</td>
<td>77</td>
<td>49(TFA)</td>
<td>38</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>N-methyl-2-pyrrolocarboxaldehyde</td>
<td>68</td>
<td>53(TFA)</td>
<td>36</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>0-nitrobenzaldehyde</td>
<td>72</td>
<td>65(hv)</td>
<td>47</td>
</tr>
<tr>
<td>Z-gly-ala-OH</td>
<td>H-leu-gly-Ot-bu</td>
<td>0-nitrobenzaldehyde</td>
<td>71</td>
<td>78(hv)</td>
<td>55</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>2,4-dimethoxybenzaldehyde</td>
<td>75</td>
<td>10(TFA)</td>
<td>8</td>
</tr>
</tbody>
</table>
Tables 1 and 2 summarize the results of some model reactions of this type with respect to yield and optical purity of the products.

### Table 2

<table>
<thead>
<tr>
<th>product</th>
<th>mode of synthesis</th>
<th>aldehyde</th>
<th>% racemization*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCHCH₃ B-NH-CH-CO-leu-OMe</td>
<td>DCCD-HOSU</td>
<td>------</td>
<td>10-11%</td>
</tr>
<tr>
<td>&quot;</td>
<td>mixed anhydride</td>
<td>------</td>
<td>96-100%</td>
</tr>
<tr>
<td>&quot;</td>
<td>4CC</td>
<td>4CC</td>
<td>12%</td>
</tr>
<tr>
<td>N-TFA-VAL-gly-OEt</td>
<td>4CC</td>
<td>Cl₃CH=CH-CHO</td>
<td>0.25%</td>
</tr>
<tr>
<td>N-TFA-phe-gly-OEt</td>
<td>4CC</td>
<td>3-formylindole</td>
<td>0-1%</td>
</tr>
<tr>
<td>N-formyl-VAL-gly-OEt</td>
<td>4CC</td>
<td>&quot;</td>
<td>0-1%</td>
</tr>
</tbody>
</table>

* of aa unit that must normally be activated.

Recently, Ugi and coworkers have developed a new class of aldehydes that may prove even more efficient.²⁶,²⁷ 8-Halogenated butenals, such as 13, form adducts that are easily cleaved by supernucleophiles such as Co₁-phthalocyanine anion. Syntheses with model compounds have shown that good yields are obtained with practically no racemization. 13 is obtained via Wittig reaction of chloral with 2-oxoethylidenetriphenylphosphorane.²⁶ This class of aldehydes should give better overall yields and allow cleavage of the adduct without effect on other protecting groups.

Cl₃C-CH=CH-CHO

13

Little exploration of this technique beyond the realm of simple model reactions has been reported, a notable exception being the recent synthesis of some cyclic peptide derivatives by Immer, et al.²⁵

Other Applications of the Ugi Reaction. Many other acids and amines can be used in the condensation.²⁶,²⁷ Acids such as HNCO, HNCS, HN₃, H₂S₂O₃, H₂Se, and H₂O give intermediates which rearrange in a variety of ways. In the cases of H₂O, H₂Se, and H₂S₂O₃, the intermediate initial adduct tautomerizes to give the amide, selenamide, or thioamide product. HN₃ causes cyclization of the initial adduct to give a tetrazole. These reactions take place regardless of whether a primary or secondary amine is used. HNCO and HNCS provide novel routes to some interesting heterocyclic compounds when condensed with primary amines.¹⁶ Hydroxylamines and hydrazines have been employed with some success as amine
components in Ugi Reactions. The first preparation of N-aminopeptides was achieved by the use of hydrazines as the amino components in Ugi Reactions. β-lactams are accessible through intramolecular Ugi Reactions.

Conclusions. Moderate success has been achieved in dealing with the problems inherent in this approach to peptide chemistry. Progress is continuing, but competitiveness with other methods of peptide synthesis has not attained a level of superiority necessary to bring the Ugi Reaction into common usage in this area. Nevertheless, these studies have already paid dividends in the fields of isonitrile chemistry, ferrocene chemistry, supernucleophiles, and asymmetric synthesis, which would seem to justify further investigations.

BIBLIOGRAPHY

SOLID STATE ORGANIC PHOTOCYCLIZATIONS

Reported by Barbara Murray

November 17, 1980

Major advances have been made recently in solid state chemistry enabling chemists to offer explanations for experimental observations previously unexplainable.\(^1\),\(^2\) Using this knowledge, attempts at "crystal engineering" are being made, with hopes of forcing molecules into space groups conductive to a specific reactivity.\(^3\)

Two important concepts in solid state chemistry are topotaxy and topochemical control. Topotaxy means that the product has a definite orientation with respect to the starting material,\(^4\) while topochemical control means that reactions in crystals proceed with a minimum of atomic and molecular movement.\(^5\) In the solid state the intrinsic reactivity of a molecule can be of secondary importance to topochemical considerations such as space group or the distance between molecules.\(^6\) Solid state reactions may proceed either by a "homogenous" mechanism in which there is a solid solution formed, or by a "heterogeneous" mechanism in which there is no mixing of product and starting material.\(^7\)

One type of solid state reaction that has proved useful both synthetically and mechanistically is photocyclizations such as \([2+2]\) and \([4+4]\) dimerizations.\(^8\)-\(^13\) The crystal structure of the monomer is crucial: The double bonds involved must be between 3.6 and 4.1 Å apart\(^14\) and parallel in order for the reaction to occur. The stereochemistry of the photodimer is determined by the geometry of the overlapped molecules.\(^5\) Recently Jones and Thomas have studied the photoreactivity of 2-benzyl-5-benzylidenecyclopentanones\(^3\) (1). They have tried to determine factors needed for crystal engineering and have monitored a single-crystal \(\rightarrow\) single-crystal photodimerization.\(^15\)

Using solid state chemistry it is possible to achieve absolute asymmetric syntheses, making chiral products from achiral precursors\(^6\) because molecules that are achiral in solution can crystallize in chiral crystals.\(^16\) Several optically active photo-dimers have been synthesized in the solid state from achiral monomers.\(^17\)-\(^22\) Addadi and Lahav have used the monomer (2) in the first solid state asymmetric synthesis with quantitative diastereomeric yield.\(^20\)
It is possible to do photopolymerizations in the solid state which
do not occur in solution and which often yield crystalline polymers
of extended chains. Although solution polymerizations are often
amorphous, single-crystal polymerizations are possible
in the solid state. An example of a solid state photopolymerization
is shown in Eq. 1.

\[
\text{Ph-CH=CH-N} \rightarrow \text{Ph} \quad \text{hv} \\
\text{Ph-CH=CH-N} \rightarrow \text{Ph}
\]

As more of the factors involved in solid state reactions become
known, it should be possible to control the conditions to achieve a
particular reaction result. In fact, solid state reactions which do
away with solvent complications may soon become standard techniques for
organic chemists.

BIBLIOGRAPHY

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INTERFERONS; STRUCTURES AND TECHNOLOGIES

Reported by Gary Harbour November 20, 1980

**Introduction.** The primary structures of interferon (IFN) proteins determined so far are not unusual. They are straight chain proteins with no modifications at the amino or carboxyl termini, some may be glycoproteins. IFNs are an interesting study in structure determinations because of their unique circumstances. Their low cellular concentrations and difficulty of purification assures minute sample sizes. Media attention as "an ideal cancer drug"¹ and money (§150 million by pharmaceutical companies, §9 million by the National Cancer Institute and §3.8 million by the American Cancer Society)¹ have kept IFN at the frontier of technology. This seminar will examine IFN structural work and some of its associated technologies.

In 1957 Isaacs and Lindenmann² reported the discovery of a substance responsible for the phenomenon known as viral interference. They found that when heat-inactivated virus was incubated with a cell culture, the culture exhibited a resistance to a challenge virus. Furthermore, when the medium was filtered free of virus and cells and then used to culture new cells, they too were protected.

There are currently three classes of IFNs recognized based upon their antigenic specificities (α, β, γ).³ The nomenclature defines the species (IFNs are species specific) and the class of IFN (e.g., Hu IFN-α1 would be an IFN from a human source belonging to the α class). In addition, the cell type is sometimes given.

The largest source of IFN is from induction of cell cultures, the form of IFN produced being dependent on cell type and inducer type.⁴ Recombinant genetics has produced several lines of E. coli, producing both Hu IFN-α⁵ and Hu IFN-β,⁶ and will soon be a major supplier of IFNs.

The most common assay for IFN is based upon the cytopathic effect and relies upon the adsorption of a cellular dye by living cells.⁷ A unit of IFN is the dilution required to inhibit cell destruction by one-half in the assay.

A wide variety of purification schemes have been utilized with IFNs. Each class of IFN is amenable to different purification schemes. Some of the techniques employed include high pressure liquid chromatography,⁸ molecular size exclusion chromatography,⁹ electrophoresis,¹⁰ antibody affinity chromatography,¹¹ polynucleotide chromatography,¹² zinc chelate affinity chromatography,¹³ lectin and hydrophobic chromatography.¹⁴ Most overall yields range from five to fifteen percent with activities of 10⁶ to 10⁷ units/mg.

**IFNs as Glycoproteins.** IFNs were recognized early as being or containing protein, from their destruction by proteolytic, but not other enzymes.¹⁵ Studies also showed it to be of heterogeneous charge by electrophoresis, isoelectric focusing and ion exchange chromatography.¹⁶ This kind of heterogeneity is often observed with glycoproteins, which contain variable amounts of terminal (sialic acid → galactose →) moieties. Each sialic acid adds a negative charge and hence its presence or absence contributes to the heterogeneity. Schonne et al.,¹⁷ showed that neuraminidase decreased the heterogeneity of crude rabbit IFN on isoelectric focusing, without destroying its activity. Dorner et al.¹⁸
showed that the heterogeneity returned upon reincorporation of CMP-sialic acid.

The production of IFNs in the presence of inhibitors of glycosidation has been investigated. Fujigawa et al. induced Mu IFN production in the presence of tunicamycin, $^{33}$S-methionine, and $^3$H-glucosamine. He found that the IFN shifted to a lower molecular weight and had a higher $^3$S/$^3$H ratio than controls.

The only indications of specific sugars in purified IFN samples were observed by Tan et al. who found evidence of galactosamine or mannosamine in Hu IFN-β and by Cabrer et al. who identified glucosamine in Mu IFN-α and β. Both findings were the result of amino acid analysis.

IFN Proteins. Amino acid analysis of IFN's has revealed similar compositions, for IFN-αs and IFN-βs and some differences. Table 1 compares the various amino acid compositions determined and inferred from various studies. Rubinstein et al. were the first to report an amino acid analysis (Table 1) on a highly purified interferon (2-4 x $10^8$ units/mg). They found Hu IFN-α from leukocytes to be rich in leucine, lysine, glutamic acid/glutamine and aspartic acid/aspargain. This has since been found to be a property of all IFNs. It also contained very little tryptophan. Based upon a minimum cystine content, the protein was calculated to have a molecular weight of 18,000 daltons. Zoon et al. reported an amino acid analysis of Hu IFN-α from lymphoblasts with a molecular weight of 18,500 daltons and an activity of 2.5 x 10^8 units/mg, based upon the amino acid analysis (Table 1). Attempts to identify the amino terminus by dansylation failed, due to contaminating peptides.

Tan et al. were the first to purify Hu IFN-β (5 x 10^8 units/mg) with respect to both size (20,000 daltons) and charge. The results are similar to those for Hu IFN-α but with some discrepancies. They incorrectly found the peptide to be void of methionine (resistant to cyanogen bromide) and tryptophan (hydrolysis in 4 N methane sulfonic acid, 18 h, 25°C). Knight et al. have also published an amino acid analysis for Hu IFN-β (2-8 x 10^8 units/mg).

Cabrera et al. isolated a Mu IFN-α (20,000 daltons) and two Mu IFN-βs (33,000 daltons and 26,000 daltons) from murine Ehrlich ascites tumor cells. Two dimensional thin layer chromatography of the tryptic digest of the proteins revealed the similar nature of the Mu IFN-βs and distinct differences in the Mu IFN-α. Amino acid analysis also showed the Mu IFN-βs to be similar while Mu IFN-α was slightly different (Table 1). A mixture of the Mu IFN-βs gave only dansylisoleucine, while Mu IFN-α gave a mixture of dansylisoleucine and bis-dansyllysine upon dansylation. When a mixture of the Mu IFN-βs was subjected to dansyl-Edman degradation, the second and third amino acids were determined as lysine and tyrosine, respectively. Treatment of the mixture with carboxypeptidase A followed by ¹⁴C-dansylation revealed phenylalanine, leucine, and lesser amounts of lysine, indicating the partial sequence Ile-Lys-Tyr—[Lys, Phe, Leu].

Automated amino acid sequencing was first successfully used on IFNs by Hunkapiller and Hood. The very limited amounts of IFN available made sequencing by conventional methods impossible.
Hunkapiller and Hood have developed sequencing techniques 10,000 times as sensitive as Edman and Begg's original sequenator.\(^2^2\) They have sequenced the amino terminal of five different IFNs: Hu IFN-α (Zoon \textit{et al.}\(^2^3\)), Hu IFN-β (Knight \textit{et al.}\(^2^0\)), Mu IFN-α and two Mu IFN-βs (Taira \textit{et al.}\(^2^4\)).

The major component of Hu IFN-α from lymphoblasts produced and purified by Zoon \textit{et al.} was subjected to six sequencings at 20-500 pico moles per run. The sequence of the first 20 amino terminal amino acids was established and later expanded to 35 amino acids (Figure 2).

Hu IFN-β produced and purified by Knight \textit{et al.} was sequenced in three runs, 0.4 to 2 μg samples, to give 13 amino terminal amino acids (Figure 2). A high yield in the first cycle of Met-PTH (60-100%) and the lack of unblocked minor peptide sequences (< 5%) confirmed the homogeneity of the sample. Repetitive cycle yields were 92-95%. There were no similarities in the Hu IFN-α and Hu IFN-β amino terminal sequences.

When the three mouse IFNs produced and purified by Taira \textit{et al.} were sequenced, the two Mu IFN-βs gave identical sequences for the first 24 amino terminal amino acids with the exception of residue 17, which was not identified (Figure 2). The first 20 amino terminal residues revealed by protein sequencing of Mu IFN-α showed little homogeneity with Mu IFN-βs. It was however noted that Mu IFN-βs have three of thirteen amino terminal amino acids in common with Hu IFN-β. Mu IFN-α shows correlation with 13 out of 20 of the amino terminal amino acids of Hu IFN-α.

**Nucleotide Sequencing.** Recently the entire amino acid sequence of several IFNs has been implied by sequencing of various genes coding for IFN proteins.

There are two main schemes for sequencing DNA. They are the chain terminating\(^2^5\) and the Maxam-Gilbert\(^2^6\) methods. Both rely on incorporation of \(^3^2\)P into all possible fragments of the DNA containing the 5' end and a specific 3' terminal nucleotide, followed by resolution of these fragments by size on denaturing acrylamide gel. Therefore, three specific terminators or three specific cleavages are needed. As a check, most work is done with four terminators or four cleavages.

The chain-terminating method relies upon incorporation of the 2',3'-dideoxytriphosphate analogs of the four nucleotides into the growing nucleotide sequence along with a \(^3^2\)P-nucleotide.

The Maxam-Gilbert method relies upon chemical cleavage of terminally labeled DNA at a specific nucleotide. The purine-specific reaction is methylation with dimethylsulfate producing 7-methylguanine and 3-methyladenine\(^2^7\) in a 5:1 ratio.\(^2^8\) The glycosidic linkage of a methylated purine is unstable upon heating at pH 7, the rate of liberation of 3-methyladenine being greater than 7-methylguanine.\(^2^7\) The resulting nick in the DNA can be hydrolysed with 0.1 M NaOH at 90°C.\(^2^6\) Because guanine methylates five times faster than adenine complete hydrolysis of the bases followed by hydrolysis of the sugars from the phosphates in alkali gives a dark band for guanine and a light one for adenine. However, gentle treatment of the methylated DNA in dilute acid to preferentially remove the
3-methyladenines, followed by cleavage with alkali, gives dark bands for adenine and light bands for guanine.

Pyrimidine bases are attacked by hydrazine which cleaves the base and leaves ribosylhydrazone.\textsuperscript{29} The DNA is then cleaved by displacement of the products of the hydrazine reaction from the sugar by piperidine, which also catalyzes the \(5\)-elimination of phosphates. This gives rise to bands from cytosine and thymine of similar intensity. The reaction of hydrazine with thymine can be preferentially suppressed by 2 M sodium chloride, giving rise to bands only from cytosine.

Mantei et al.\textsuperscript{30,32} combined the cDNA coding for Hu IFN-\(\alpha\) from reverse transcription of isolated Hu IFN-\(\alpha\) mRNA with the pBR322 plasmid. They have cloned it in \textit{E. coli} and sequenced the 910 base pair (bp) insert.

The plasmid was cleaved at the Pst I site and elongated with dG residues. The dC elongated Hu IFN-\(\alpha\) cDNA was hybridized with the plasmid and patched with DNA polymerase, then sealed with DNA ligase. A restriction site map of the insert was generated (Figure 1) by the Smith-Birnstiel method,\textsuperscript{31} which is similar to the Maxam-Gilbert method except that partial digestion by various restriction enzymes replaces specific base cleavages. As an example, complete cleavage of the

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure1.png}
\caption{Strategy for the determination of the nucleotide sequence of Hu IFN-\(\alpha\) DNA. The filled circles represent labeled 5' termini, the solid arrows indicate the sequences read off the fragments. The dashed lines represent regions not read off a particular fragment. Upper map: numbers indicate bp; black segment, interferon coding sequences; hatched segment, putative signal sequence; white segment, non-coding region; straight lines, next to rectangle, homopolymeric dG:dC flanking regions; wavy lines, pBR322.}
\end{figure}

plasmid with Pst I, labeling the fragments with \(^{32}\text{P}\) and separating them by electrophoresis gives the 910 bp insert. Cleavage with a second restriction enzyme with only one site, Bgl II, results in isolation of two double-strand fragments with one labeled 5' end. These are partially digested separately by a variety of restriction enzymes and resolved by electrophoresis. The sequential restriction sites along the fragment are then read off the gel.
Each fragment (Figure 1) was isolated and sequenced, thus giving pieces small enough to sequence, overlap to establish continuity, and by sequencing both strands, an internal check.

A typical isolation (fragments A and B) involves cleavage of the plasmid with Bsp I and isolation of the fragments by electrophoresis (a 232 bp section for A and a 949 bp section for B). These are labeled at the 5' ends and cleaved with Pst I, giving upon separation a 5' labeled Bsp I - Pst I 83 bp section for A and a 5' labeled Bsp I - Pst I 827 bp section for B.

The nucleotide sequence has 23 dG residues in the homopolymeric flanking region. An ATG initiation codon at -69 bp codes for a 23 residue signal peptide, or a second in-phase ATG triplet at -45 bp codes for a 15 residue signal peptide. The mature IFN protein was predicted by comparison to Zoon's amino terminal sequence. The mature protein is 166 residues long and transcription terminates with a TAA codon. The untranslated 3' end is 242 nucleotides long and has a high A + T content. The AATAAAA sequence appears 21 bps upstream from the poly A tail. The mature IFN protein coded for has a calculated molecular weight of 19,388 daltons compared to 25,000 to 21,000 for glycosylated Hu IFN-α and 21,800 to 15,000 for nonglycosylated Hu IFN-α by electrophoresis.

In the first 35 amino terminal amino acids there are nine differences from Zoon's Hu IFN-α. Each one could arise from a single base change. The magnitude of these differences suggests that these are not multiple alleles but are different genes. Mantei looked through his clones for further evidence of this and found a clone with a different restriction pattern. The structure of this gene was presented by Streuli et al. 32 (Figure 2). They proposed the existence of at least three Hu IFN-α genes. This was based on the fact that Mantei's Hu IFN-α (Hu IFN-α1) differs from Zoon's Hu IFN-α (Hu IFN-α3) in nine of thirty-five amino terminal amino acids and the newly sequenced Hu IFN-α (Hu IFN-α2) in 20% of the nucleotides (10% in the coding region) and 17% of the amino acid residues. Hu IFN-α2 differs from Hu IFN-α3 in five of the first thirty-five residues. Hu IFN-α2 is only 165 amino acids long compared to 166 for Hu IFN-α1. Hu IFN-α1 is 10 to 20 times as active on bovine as on human cells while Hu IFN-α2 is twice as active on human as on bovine cells.

Coeddel et al. 5b independently proposed the same structure for Hu IFN-α2 except for one base at position 68 which changes an AGA codon for arginine to an AAA codon for lysine.

More recently, Nagata et al. 5c have reported the existence of at least eight distinct chromosomal genes for Hu IFN-α. It is hoped that the genes may code for specific activity and the effects so far ascribed to Hu IFN-α may be due to a mixture of different effects of all the Hu IFN-αs.

Allen and Fantes, using Hu IFN-α produced on a large scale (4 mg for this study alone compared to 2.4 mg total for three amino terminal sequences by Hood and Hunkapiller 21), separated it into two fractions on sephadex G-75 (A, B). Two dimensional chromatography of the tryptic digest of the performic acid oxidized fractions showed A to be almost homogeneous, in contrast to B. The proteins and some of
Table 1. Amino Acid Compositions Residues/166 Residues

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>IFN-αs</th>
<th></th>
<th>IFN-βs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Asx</td>
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<tr>
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</tr>
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</tr>
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</tr>
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<tr>
<td>Lys</td>
<td>12.0</td>
<td>10.5</td>
<td>17.4</td>
<td>8</td>
</tr>
<tr>
<td>Arg</td>
<td>7.5</td>
<td>9.7</td>
<td>10.5</td>
<td>12</td>
</tr>
<tr>
<td>Trp</td>
<td>0.7</td>
<td>0.6</td>
<td>ND</td>
<td>2</td>
</tr>
</tbody>
</table>

A, Rubinstein et al., leukocyte Hu IFN-α; B, Zoon et al., lymphoblast, Hu IFN-α; C, Cabrer et al., Mu IFN-α; D, Mantei et al., Hu IFN-α; E, Tan et al., fibroblast Hu IFN-β; F, Knight et al., fibroblast Hu IFN-β; G, Cabrer et al., Mu IFN-β; H, Taniguchi et al., Hu IFN-β; ND, not determined.

The peptides resulting from tryptic and chymotryptic cleavages have been sequenced by the dansyl-Edman method (Figure 2). Some of the cycles in A were found to consist of two amino acids indicating two very similar homologs, while some fragments from B could be separated into at least three homologous series.

Because of gaps in the sequences and because of the lack of overlap in many of the cleavages, little ordering of the peptides could be made. However, the inferred protein sequence derived for other Hu IFN-αs could be used as a pattern to piece together the fragments. From this it was clear that A probably is or contains Hu IFN-α2 differing only in positions 83 (Asp/Lys) and 87 (Pro/Glu), while B resembles Hu IFN-α1 differing in positions 60 (Met/Leu) and 64 (Thr/Ile). Other than Zoon's amino terminal sequence, Allen's fragments give the first direct evidence supporting the DNA inferred Hu IFN-α amino acid sequences. Especially important is the C-terminal region which shows no modifications.
Figure 2.\(^a\)

### Amino Acid Sequences

<table>
<thead>
<tr>
<th>Amino Acid Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>E</td>
</tr>
<tr>
<td>F</td>
</tr>
</tbody>
</table>

**Com:**

1. **A**
   - KRES PALLHVLYVLYSECCSCLG
   - GLFET
2. **B**
   - KRES PALLHVLYVLYSECCSCLG
   - GLFET
3. **C**
   - KRES PALLHVLYVLYSECCSCLG
   - GLFET
4. **D**
   - KRES PALLHVLYVLYSECCSCLG
   - GLFET
5. **E**
   - KRES PALLHVLYVLYSECCSCLG
   - GLFET
6. **F**
   - KRES PALLHVLYVLYSECCSCLG
   - GLFET

---

A Hu IFN-\(\beta\) gene has been sequenced by Taniguchi et al.\(^{34,68,c}\) (Figure 2) who recombined cDNA synthesized in vitro by reverse transcription of fibroblast Hu IFN-\(\beta\) mRNA. The plasmid cDNA was isolated and fragments containing the cDNA mapped. The fragments were sequenced by the Maxam-Gilbert method. There are at least six codons before the first in-phase AUG codon. By comparison to Knight's\(^{50}\) first amino terminal sequence, the first amino acid of the mature protein was identified and it was preceded by a 21-residue signal peptide. The mature protein was 166 residues long and translation terminated by a TGA codon. The molecular weight calculated for the peptide would be 20,040 daltons compared to 26,000 to 20,000 daltons for glycosylated and 16,000 daltons for nonglycosylated Hu IFN-\(\beta\) by electrophoresis.

Dermeyck et al.\(^{6b}\) independently determined the identical nucleotide sequence from an E. coli clone in which they had implanted the Hu IFN-\(\beta\) gene. They also noted that N-glycosidic linkage is possible at the -Asp-Glu-Thr- sequence (position 80).

---

\(^{a}\)Comparison of IFN proteins: A, Hu IFN-\(\alpha\) (Mantei et al.); B, Hu IFN-\(\alpha\)-\(\beta\) (Allen et al.); C, Hu IFN-\(\alpha\) (Streuli et al.); D, Hu IFN-\(\alpha\)A (Allen et al.); E, Hu IFN-\(\alpha\)-3 (Zoon et al.); F, Mu IFN-\(\alpha\) (Taira et al.); Com, Common amino acids in all IFN-\(\alpha\); a, Hu IFN-\(\beta\) (Knight et al.); b, Hu IFN-\(\beta\) (Taniguchi et al.); Mu IFN-\(\beta\) (Taira et al.); and common amino acids in all IFN-\(\beta\). The sequences are written in one letter nomenclature. According to the IUPAC-IUB Commission on Biochemistry Nomenclature: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine; Z, Glx; B, Asx.
Conclusion. The two types of IFN genes sequenced to date (Hu IFN-αs and Hu IFN-βs) code for proteins with many differences: They are neutralized by different antibodies, their target cell specificities differ and their amino acid sequences differ.\textsuperscript{32} However, a comparison of the nucleotide sequences of the coding regions shows an average homology of 45%. Rather than being random, specific regions of the DNA seem to account for the homology. On this basis and the degree of homology of human β-globin, α-globin and myoglobin (24% homology) and their calculated divergence of 500 to 1,000 million years (vertebrates develop) Taniguchi et al.\textsuperscript{35} predict that all vertebrates will possess IFN-αs and -βs. This is evident in the case of Hu IFN-α, which has more in common with Mu IFN-β than Hu IFN-β, which in turn has more in common with Mu IFN-β than Hu IFN-α.

BIBLIOGRAPHY

THE INHIBITION OF THYMIDYLATE SYNTHETASE BY 5-SUBSTITUTED URIDINES

Reported by Marc d'Alarcao

November 24, 1980

Introduction. The ability to selectively inhibit the growth of rapidly proliferating cells has been the goal of medical researchers for many years. It is clear that such an ability would have profound consequences in the treatment of neoplastic disease as well as certain bacterial and viral infections. One approach to this problem has been to try to block the ability of a cell to manufacture normal DNA. In this way those cells which are dividing rapidly, and consequently producing relatively large amounts of DNA, will be selectively damaged.

During the biosynthesis of DNA, ample supplies of the four DNA nucleotides must be maintained within the cell. Of these only 2'-deoxythymidine monophosphate (dTMP) is synthesized de novo for this process. The other three are readily available via enzymatic interconversions. The blocking of dTMP synthesis in vivo, therefore, will uniquely end normal DNA synthesis and result in "thymineless death.""1

dTMP is synthesized in the cell by the enzyme thymidylate synthetase (TS) from 2'-deoxyuridine monophosphate (dUMP) by methyl transfer from a cofactor, N\(^5\),N\(^10\)-methylene tetrahydrofolic acid (CH\(_2\)-THF). During the course of this reaction the cofactor not only undergoes a demethylation, but also an oxidation to dihydrofolic acid (DHF) and, therefore, must be regenerated by a two enzyme process before it can be reused in the thymidylate synthetase reaction. The overall scheme is illustrated in Figure 1.

**Figure 1**

![Diagram of thymidylate synthetase reaction]

- dUMP → TS → dTMP
- CH\(_2\)-THF → serine hydroxymethyl transferase → tetrahydrofolate acid (THF)
- DHF → dihydrofolate reductase
An extensive research effort has been undertaken aimed at the inhibition of these enzymatic processes. For example, amethopterin\(^2\) (methotrexate) and trimethoprim\(^5\)\(^,\)\(^6\) are potent competitive inhibitors of dihydrofolate reductase and are currently finding clinical use as antileukemic and antibacterial agents, respectively. It is the purpose of this report to describe some recent approaches to the inhibition of thymidylate synthetase by dUMP analogues substituted in the 5-position, as well as to present highlights of the historical progress in the field.

**Catalytic Mechanism.** Several excellent discussions of the mechanism of catalysis for thymidylate synthetase have appeared.\(^4\)\(^-\)\(^7\) Following is a description of the most widely accepted pathway (Fig. 2) from reactants to products, and some of the more persuasive arguments in support of this pathway.

There is little doubt that in productive catalysis the enzyme exhibits cooperative binding; TS binds CH\(_2\)-THF first (step 1, Fig. 2), then this binary, non-covalent complex accepts dUMP to form (step 2, Fig. 2) a ternary, non-covalent complex.\(^8\) Step 3 in the sequence, however, has been subject to some debate. To support their hypothesis that attack by some TS nucleophile on the 6-position of the dUMP ring is necessary to activate the 5-position toward electrophiles, Santi and Brewer\(^9\) performed an interesting model study. These workers subjected a series of uridines varying in the number and position of hydroxyl groups on their sugar moieties to sodium methoxide in deuterated methanol and monitored the incorporation of deuterium at the 5-position of the pyrimidine. They found that incorporation only occurred in those compounds which have a hydroxy group in a spacial disposition allowing them to add nucleophilically to the 5,6 double bond (Fig. 3). The conclusion which was drawn was that nucleophilic attack is an essential prerequisite to electrophilic substitution at the 5-position of these systems.

The most convincing evidence to date that nucleophilic addition to the 6-position of dUMP occurs in the TS reaction has come from studies with 5-fluoro-2'-deoxyuridine monophosphate (F-dUMP). This analogue when incubated with TS and CH\(_2\)-THF forms what is believed to be a covalent adduct with the enzyme.\(^10\) If radiolabeled analogue ([6\(^-\)\(^3\)H]-F-dUMP) and cofactor ([\(^14\)C]-CH\(_2\)-THF) are employed and the resulting complex is subjected to degradation by trypsin, both radioisotopes are found to remain bound to the same peptide fragment.\(^11\) Additionally, slow dissociation of the complex is found to be first order and temperature dependence studies of the rate constant yield an activation barrier of \(E = 29.0\) Kcal/mol.\(^12\) These data are consistent with the formation of a covalent, ternary complex such as [A] in Fig. 2. It is believed the F-dUMP enters the catalytic cycle in the same way as the natural substrate, proceeding through steps 1, 2, and 3 (Fig. 2), but cannot undergo step 4 due to lack of an abstractable proton at the 5-position. It is therefore trapped as the fluoro analogue of intermediate [A].

To further investigate this hypothesis, a mixture of [2\(^-\)\(^14\)C]-F-dUMP and [6\(^-\)\(^3\)H]-F-dUMP was incorporated into a complex with CH\(_2\)-THF and TS. The rate constants for dissociation of each radiolabeled species were obtained showing an isotope effect \(k_1/k_{\text{D}} = 1.23.\)\(^12\) This is equivalent to a \(k_1/k_{\text{D}} = 1.15.\)\(^13\) This secondary kinetic isotope effect is consistent with the decrease in coordination expected upon dissociation of intermediate [A].

The \(^19\)F NMR spectrum has been observed for the F-dUMP-TS-(CH\(_2\)-THF) complex. A doublet of triplets is seen, believed to arise from coupling with the 6-proton as well as the two methylene bridge protons between F-dUMP and THF.\(^14\)
Figure 2

\[ \text{dUMP} + \text{TS} + \text{CH}_2\text{-THF} \xrightarrow{\text{Step 1}} \text{dUMP} + \text{TS}-(\text{CH}_2\text{-THF}) \]

\[ \text{dUMP-TS}-(\text{CH}_2\text{-THF}) \]

\[ \text{Step 2} \]

\[ \text{Step 3} \]

\[ \text{Step 4} \]

\[ \text{Step 5} \]

\[ \text{Step 6} \]

\[ \text{dTMP} + \text{TS} + \text{DHF} \xrightarrow{\text{Step 6}} \text{dTMP} + \text{TS-DHF} \]
The possibility remains that in intermediate [A] the methylene bridge is bonded to N¹⁰ of THF rather than N⁵ as depicted in Fig. 2. Though this possibility cannot at present be ruled out, Sommer and Santi¹⁵ contend that the ultraviolet and fluorescence spectra of the complex (with F-dUMP) resemble those of 5-methyl tetrahydrofolic acid more than the 10-methyl derivative.

The question of which active site nucleophile is involved in the formation of intermediate [A] has also been answered by study of the F-dUMP covalent complex. When treated with Raney Nickel the complex rapidly releases both F-dUMP and cofactor.¹¹ This suggests the possibility of a sulfur nucleophile. Subsequent sequencing studies on the peptides derived from this complex strongly suggest that it is the -SH function of a cysteine residue in the active site which is the nucleophile.¹⁶,¹⁷

Unfortunately F-dUMP cannot be used to help elucidate the mechanism of steps after step 3 (Fig. 2), since it never reaches them. For this reason there is considerably more debate regarding these subsequent steps. For example, it has been suggested that step 4 may not actually involve a proton abstraction but first a 1,3 hydride shift from C-6 of THF to the bridge methylene (Fig. 4).¹³ Pogolotti and Santi¹⁸ favor the scheme illustrated in Fig. 2 on the basis of kinetic studies which they performed on the hydrolysis of 5-p-nitrophenoxyuracils in which there is strong evidence for [B]-type intermediates. Conclusions from this indirect evidence on the mechanism of TS catalysis is, of course, highly speculative.
That a hydrogen is transferred from C-6 of THF to the methyl group of dTMP at some point seems certain. If [6-^3H] labeled CH₂-THF is used as co-factor in the reaction, the resulting dTMP has exactly one ^3H and two ^1H in the methyl group. An attempt has been made to measure an isotope effect in this case and preliminary results indicate that the magnitude of kᵢ/kᵣ is about of the order of a primary kinetic isotope effect in the rate determining step.¹⁹

The mechanism illustrated in Fig. 2, therefore, is consistent with all the available data. For this reason analysis of inhibition shall be based on that scheme.

Inhibition. One can envision three general modes of inhibition based on the mechanism illustrated in Fig. 2. These will be considered separately.

i) reversible, noncovalent inhibition

In this case the inhibitor competes with dUMP for the binding site on the enzyme. The degree of inhibition is based solely on the relative affinity of TS toward the two competing compounds. Santi has sought to establish some quantitative structure-activity relationships among 5-substituted pyrimidines and he proposes the following minimal requirements on the dUMP analogue for efficient binding to TS:²¹ a) 5'-phospho-2'-deoxyribosyl moiety, b) 2-keto function, c) 3-NH function, and d) a 4-substituent which doesn't tautomERICally remove the 3-proton. Fortunately the 5-position substituent may vary considerably without precluding binding.

A number of workers have synthesized and tested pyrimidines on this basis.²⁰⁻²⁸ A brief list of such compounds and their inhibitor constants is presented in Table 1. It should be noted that dTMP is a weak competitive inhibitor of TS.

ii) reversible, covalent inhibition

Inhibitors of this type initially compete for the active site of the enzyme as in the previous case, but once bound they are subject to nucleophilic substitution at the C-6 position resulting in a relatively stable covalent complex. This complex can slowly dissociate to release unchanged inhibitor and enzyme.

F-dUMP is an inhibitor of this kind, and as mentioned earlier, the ternary F-dUMP-TS-(CH₂-THF) complex has been isolated.¹⁰⁻¹⁷

5-nitro-2' deoxyuridine monophosphate (NO₂-dUMP) also exhibits this kind of inhibition. Initially it binds competitively with a Kᵢ=0.029μM (L. Casei TS).²⁹ Upon incubation, however, NO₂-dUMP forms a covalent adduct which can slowly dissociate.³⁰ It is interesting that, unlike F-dUMP, this compound does
Table 1. Inhibitor constants for some 5-substituted dUMP's with thymidylate synthetase from L. Casei

<table>
<thead>
<tr>
<th>5-substituent</th>
<th>Ki (uM)</th>
<th>reference</th>
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<tbody>
<tr>
<td>-CN</td>
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<td>25</td>
</tr>
<tr>
<td>-SH</td>
<td>0.04</td>
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<tr>
<td>-CH₂–S–CH₃</td>
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<td>-CH₂–S–CH₃</td>
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</tr>
<tr>
<td>-CH₂OH</td>
<td>8.30</td>
<td>20</td>
</tr>
<tr>
<td>-CH₃ (dTMP)</td>
<td>15.50</td>
<td>20</td>
</tr>
<tr>
<td>-CH=N–OH (isomer mixture)</td>
<td>2.10</td>
<td>28</td>
</tr>
<tr>
<td>-</td>
<td>0.67</td>
<td>28</td>
</tr>
</tbody>
</table>

not require the presence of CH₂–THF to form a stable covalent complex. This is interpreted\textsuperscript{21} as resulting from the great stability of the anion which is formed upon nucleophilic addition to position 6 of the pyrimidine (Fig. 5).

![Figure 5](image)

Studies on the position of equilibrium of 1,3-dimethyl-5-nitouracil and various nucleophiles support this hypothesis.\textsuperscript{31}

An interesting case of this type of interaction occurs among the larger halogenated dUMP's. Both 5-bromo- and 5-iodo-2'-deoxyuridine monophosphate actually act as substrates in the TS reaction in marked contrast to the fluoro and chloro analogues.\textsuperscript{32} This is difficult to rationalize unless one assumes that the larger, more polarizable halogens can be abstracted by a nucleophile in the active site as illustrated in Fig. 6. In this case dTMP would be produced in the normal way.\textsuperscript{32} If the halogenated enzyme can be somehow regenerated then the catalytic cycle can continue. Clearly further study is needed to confirm (or rule out) this hypothesis.
iii) irreversible covalent modification

Inhibitors of this type compete with the natural substrate for the binding site on TS; but once bound are able to form a covalent bond via a reaction off of the normal enzymatic pathway. In this way the enzyme is bound to the inhibitor in an unnatural covalent way preventing binding of natural substrate. With judicious choice of latent functionality on the inhibitor, this modification can be made effectively irreversible.

The earliest attempt to inactivate TS in this way utilized 5-trifluoromethyl-2'-deoxyuridine monophosphate\(^3\) (CF\(_3\)-dUMP). This compound competed favorably with dUMP for the TS active site (Ki=0.039\(\mu\)M)\(^2\) and once bound inactivated the enzyme. This inactivated enzyme cannot be regenerated by dialysis\(^3\) (in contrast to F-dUMP). Santi\(^21,3\) suggests that upon nucleophilic addition to C-6, fluoride anion is displaced from the CF\(_3\) group forming the reactive difluoro alkene which can alkylate, irreversibly, some active site nucleophile (Fig. 7). Release of fluoride has been observed upon incubation of CF\(_3\)-dUMP with TS.\(^21\)

A clever extension of this principle utilizes vinylogues of (CF\(_3\)-dUMP) which maintain the same reactivity pattern as the parent compound but now can extend the range of the reactive function to "find" more distant nucleophiles. The first member of this series (CF\(_3\)-(CH=CH)-dUMP) where \(n=1\) has been prepared and is also an irreversible inactivator of TS.\(^3\)
A distinct type of inactivation may be in effect in the case of 5-formyl-2'-deoxyuridine monophosphate. Although little work has been done to elucidate the mechanism involved here, it has been suggested that after initial competitive binding \((K_i=0.017\mu M)\), a Schiff base is formed at the active site resulting in the observed inactivation.\(^{36}\)

Compounds with more remote functionality have also been prepared. 5-\(\alpha\)-bromoacetyl-2'-deoxyuridine monophosphate, for example, has been reported to irreversibly inactivate TS after binding \((K_i=4\mu M)\).\(^{37}\) Again this is attributed to alkylation of some internal nucleophile. A similar compound, 5-(iodoacetamidomethyl)-2'-deoxyuridine represents a very important advance in this type of inhibition.\(^{38}\) When this compound is incubated with TS isolated from calf thymus, only competitive inhibition is observed \((K_i=27\mu M)\). However, when the same experiment is done substituting TS from Ehrlich ascites tumor cells, irreversible modification occurs. This represents the first time that this kind of inhibition selectivity has been seen for any TS inhibitor.

Conclusion. Though many questions remain unanswered in the mechanism and inhibition of TS, much of the work described herein has resulted in important clinical advances in the treatment of various disorders. F-dUMP, for example, has enjoyed wide clinical use in breast cancer, colon cancer, and leukemia patients, both alone and in concert with other agents such as methotrexate. T-dUMP, on the other hand, has proven to be a very effective antiviral compound. These and other tangible successes serve to illustrate the fruitful nature of research in the area of thymidylate synthetase inhibition.

BIBLIOGRAPHY

THE CHEMISTRY OF TETRACYANOETHYLENE

Reported by A. Bashir-Hashemi

December 1, 1980

Tetracyanoethylene (TCNE) is a versatile compound of exceptional reactivity.\(^1\) For the purposes of this abstract, emphasis has been given to recent developments in the chemistry of TCNE, e.g., heterocyclic formation, cycloaddition and ene reactions.

Tetracyanoethylene \(^1\) has been prepared from malononitrile \(^2\) by four different methods.\(^1\) The original preparation consisted of the interaction of malononitrile with sulfur monochloride, in boiling 50/50 chloroform-tetrachloroethylene. A second method involves the vapor phase chlorination-dehydrochlorination of malononitrile at 450°C. The preparation of TCNE has also been accomplished by the condensation of malononitrile with 1,3-bis(acetoxyimino)-2-propanone, followed by pyrolysis of the adduct \(^3\). However, the preferred synthetic preparation of TCNE (62% yield) is the debromination of the KBr complex of dibromomalononitrile \(^4\) with copper powder in boiling benzene. The reaction is believed to involve an intermediate dicyanocarbene, which dimerizes to tetracyanoethylene.\(^1\) TCNE is a colorless crystalline solid and melts at 198-200°C. TCNE slowly evolves hydrogen cyanide when exposed to moist air at room temperature.\(^2\)

Formation of Heterocyclic Compounds. TCNE is a useful starting material for the syntheses of five or six-membered heterocycles, with one or two heteroatoms.\(^1\) Thiophenes, pyrroles, isoxazoles, pyrazoles, pyrimidines and pyridines may all be synthesized from TCNE. For example, addition of hydrogen sulfide to TCNE in the presence of a base gives a cyclized product, 2,5-diamino-3,4-dicyanothiophene \(^5\), which can be rearranged to a mercaptopyrrole \(^6\) under the influence of alkali.

Some of the unique reactions of TCNE are given in Scheme I.\(^1\)

Diels-Alder Cycloaddition Reactions. TCNE is a reactive dienophile and undergoes a \(4\pi + 2\pi\) cycloaddition reaction with conjugated dienes such as butadiene and anthracene. Thus when butadiene is added to TCNE in THF at 0°C, the solution first takes on the bright yellow color of the \(\pi\)-complex, and then gives way to the colorless cycloadduct. Tetracyanohexene \(^13\) begins to separate in nearly quantitative yield.\(^3\)
TCNE will react with dienes such as 2-vinyl naphthalene. This unusual cycloaddition occurs spontaneously and rapidly without added catalyst or application of heat.

\[
\text{Geometry Effect on Diels-Alder Reactions. In addition to the frontier orbital factors, geometry plays an important role in the novel (14\pi + 2\pi) cycloaddition of TCNE and heptafulvalene } 14 \text{ to give the adduct } 15. \quad \text{The HOMO coefficients for heptafulvalene are highest at the central bond, but any }
\]
Reaction at this site would have to be, as a result of the orbital symmetry, antrafacial on one of the components, and this is geometrically unreasonable under modest reaction conditions. A Diels–Alder reaction across the 1,4 positions would be another possibility, but this evidently does not occur, probably because the carbon atoms are held too far apart. The only reasonable pathway for cycloaddition which remains is the addition of TCNE to the carbons adjacent to the central double bond (1,1') in 15. By orbital symmetry this reaction must also proceed antrafacially with respect to one of the π-systems, however, the heptafulvalene can easily assume the appropriate geometry.

Sesquifulvalene 16 presents another case where frontier orbital control does not govern regioselectivity. The sesquifulvalene 17 does give the adduct

18 with TCNE, as expected from the coefficients of the HOMO of the unsubstituted system. However, the sesquifulvalene 19 gives a [12π + 2π] adduct 20 instead, while the sesquifulvalene 21 gives a [4π + 2π] adduct 22.

---

0.426
-0.284
-0.098
0.183
-0.64
0.531
228
228
16 HOMO

---
Another interesting cycloaddition is the reaction of TCNE with allene tetramer (1,3,5,7-tetramethylene cyclooctane 23). Here, TCNE undergoes a 1,7-addition to give the tricyclic compound, 24, formed by a \((\pi_2^S + \pi_2^S + \pi_2^S)\) trans annular cyclization. Studies of 23 with molecular models indicated that the conformation, 23-a, places opposite pairs of double bonds parallel to one another at a distance of about 2.7 Å. It appeared that at this distance there is appreciable \(\pi\)-orbital interaction of the double bonds in each pair and thus the compound might exhibit enhanced reactivity of a kind normally associated with conjugated systems.

Reaction of TCNE with bicyclo [2,2,n] alkadienes has been investigated. TCNE reacts with bicycl. [2,2,n] alkadienes (n=1,2) in \(\text{CH}_2\text{Cl}_2\) in a \([\pi_2^S + \pi_2^S + \pi_2^S]\) HOMO-Diels-Alder fashion. For (n=3,4) no addition has been observed.

\(2\pi + 2\pi\) Cycloaddition. Thermal \((2 + 2)\) cycloaddition leading to four-membered rings are less frequently encountered than \(4\pi + 2\pi\) cycloaddition reactions. The suprafacial combination of two \(\pi\)-bonded systems, \(\pi_2^S + \pi_2^S\), is not expected to be energetically favorable due to orbital symmetry. These reactions are usually restricted to allenes, ketenes, polyhaloethylenes, conjugated dienes, and strained hydrocarbons. It is generally assumed that the concerted \((2 + 2)\) cycloaddition is by-passed and the two new \(\sigma\) bonds are formed in a stepwise fashion. The reverse type of process, the rupture of a four-membered ring to form two alkene molecules, should also occur in a nonconcerted
fashion.\textsuperscript{12,13}

Two different pathways have been proposed for thermal (2 + 2) cycloaddition reactions, a singlet biradical (I) or a zwitterionic tetramethylene derivative (II).\textsuperscript{13}

![Diagram of pathways](image)

Bartlett's masterful investigation of cyclobutane formation from 1,1-dichloro-2,2-difluoro ethylene and from the cis, trans isomeric hexa-2,4-dienes demonstrated the biradical course to be operate.\textsuperscript{12}

Cyclobutane formation by reaction of TCNE with enole ethers proceeds, according to R. Huisgen's investigations, via a zwitterion type intermediate, 24.\textsuperscript{13}

\[
\text{H}_2\text{C} = \text{CH} - \text{OCH}_3 + (\text{CN})_2\text{C} = \text{C}(\text{CN})_2 \\
\xrightarrow{25^\circ\mathrm{C}} \\
24 \quad 90\% \text{ yield}
\]

The fact that simple alkenes and the double bond of acrylic esters are inert to TCNE does not support a biradical intermediate of Type (I), but lends support to the zwitterion (II). Structure 24 illustrates the efficient charge stabilization of the presumed intermediate from methyl vinyl ether and TCNE.

The facile reaction of TCNE with ethyl cis-1-alkenyl ether, 25 produced quantitatively two cyclobutane derivatives.\textsuperscript{14} The configuration of the alkenyl ether is retained in the major product, 28, while the NMR chemical shifts of the minor product leave no doubt that it has the trans structure, 29. In terms of the zwitterion mechanism, rotation about the marked bond of 26 begins to compete with cyclization.

The amount of stereochemical integrity lost increases with solvent polarity.\textsuperscript{16} Thus, starting from R=C\textsubscript{2}H\textsubscript{5}, one obtains 2\% of the trans product in benzene, 7\% in dichloromethane, 10\% in ethyl acetate, and 18\% in acetonitrile. A longer lifetime for intermediates 26 and 27 in a more polar solvent due to better solvation and diminished coulomb attraction of the charge centers, appears to be responsible for this outcome.
The rate of TCNE cycloadditions is immensely dependent on solvent polarity;¹⁵ $K_{\text{acetonitrile}}/K_{\text{cyclohexane}}$ amounts to 63,000 for 4-methoxy-styrene, 29,000 for anethole and 2600 for butyl vinyl ether. Such large dependencies appear to be unique among cycloadditions, and this fits one's expectation for a zwitterion intermediate formation.

**Ene Reactions.** Although the Alder-ene reaction is quite common with simple alkenes,¹⁶ it occurs relatively infrequently with conjugated dienes because most good enophiles are also effective Diels-Alder dienophiles.

Ene reactions are seen with constrained dienes which cannot achieve the syn arrangement required for the Diels-Alder reaction.¹⁷, ¹⁸, ¹⁹ Although the ene reaction also appears to be subject to steric influence, probably due to the preferred orbital geometry for the concerted hydrogen transfer.²⁰ While TCNE reacts with cyclopentadiene in a $(4\pi + 2\pi)$ cycloaddition manner, it reacts with 1,3-cyclohexadienes 31²³ and 1,4-cyclohexadiene²² through the ene reaction.

The aromatization of cyclohexadienes with TCNE is a very mild reaction that has seen occasional synthetic use.¹⁹,²¹ Equimolar amounts of 1,4-cyclohexadiene and TCNE in boiling dioxane give benzene in 98% yield.²¹ B. M. Jacobson has investigated the aromatization of 1,4-cyclohexadiene with TCNE.²² The aromatization is actually initiated via an ene reaction to give 5-(1,1,2,2-tetracyanoethyl)-1,3-cyclohexadiene, 30. The elimination of tetracyanoethane from 30 produces the aromatized product.
In both THF and acetonitrile-d₃, the disappearance of 1,4-cyclohexadiene is a second-order reaction, first order in 1,4-cyclohexadiene and first order in TCNE. The rate constants at 35°C are 5.3 x 10⁻³ LM⁻¹min⁻¹ and 6.4 x 10⁻² LM⁻¹min⁻¹, respectively. The conversion of the intermediate 30 into benzene follows first-order kinetics with rate constants 3.87 x 10⁻⁷min⁻¹ in THF and 1.62 x 10⁻⁵min⁻¹ in acetonitrile-d₃.

As to the further mechanistic details of the formation and decomposition of 30, it should be noted that there is a modest color change upon mixing the TCNE and 1,4-cyclohexadiene presumably from a charge-transfer complex being formed. The tenfold increase in the rate constant for formation of 30 on going from THF to CD₃CN might be considered support for a rather more polar transition state than usual in the ene reaction. The merely fourfold increase in the decomposition rate of 30 would seem small if the reaction proceeds through dissociation to cyclohexadienyl cation, but a preliminary run in a 65:35 acetone-water mixture showed a further large rate increase.²²

In the case of 1,3-cyclohexadienes, 31, three mechanisms have been formulated for the elimination step,²³ an isoretero-ene reaction(σ² + π² + σ²) (Eq. 2), a simple homolytic one (Eq. 3), and a heterolytic reaction (Eq. 4).
As it was tempting to suspect concerted decomposition as in Eq. 2, compound \(31b\) was prepared for comparison. In the latter, the trans arrangement of the tetracyanoethyl group and the departing hydrogen preclude a concerted intramolecular elimination. However \(31a\) and \(31b\) were found to decompose at comparable rates (see Table 1). Further, the rate constant was strongly dependent on solvent, with marked enhancement in both protic and aprotic polar solvents.

**Table 1. Variation in Decomposition Rates of 31a and 31b with Solvent Polarity at 35°C**

<table>
<thead>
<tr>
<th>adduct</th>
<th>solvent</th>
<th>rate constant (\times 10^6 \text{s}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>31a</td>
<td>ether</td>
<td>1.5</td>
</tr>
<tr>
<td>31a</td>
<td>acetone</td>
<td>41</td>
</tr>
<tr>
<td>31a</td>
<td>ethanol</td>
<td>170</td>
</tr>
<tr>
<td>31a</td>
<td>acetone/D_2O 75:25 v/v</td>
<td>270</td>
</tr>
<tr>
<td>31b</td>
<td>acetone</td>
<td>36</td>
</tr>
<tr>
<td>31b</td>
<td>dimethylformamide</td>
<td>210</td>
</tr>
<tr>
<td>31b</td>
<td>acetone/D_2O 75:25</td>
<td>460</td>
</tr>
</tbody>
</table>

These results suggest the heterolytic path to be in effect.

**Uses of TCNE.** The uses of TCNE include inhibition of polymerization, the aromatization of certain nonconjugated cycloalkadienes and increasing the photosensitivity of some organic dyestuffs. It has also been used in the determination of aliphatic, alicyclic, aromatic 1,3-dienes, phenols, and aryl ethers, analogous to the broad utility of metal-EDTA chelates in inorganic analysis. TCNE, like EDTA, is a fairly general complexing agent and reacts rapidly under mild conditions.

**BIBLIOGRAPHY**


REMOTE FUNCTIONALIZATION REACTIONS

Reported by Venkatesalu Bakthavachalam          December 4, 1980

Enzymic reactions bring about highly selective transformations at extraordinarily high rates. The most intriguing feature of enzyme catalyzed reactions is their remarkable regioselectivity, especially those involving transformations at centers which are not activated in the usual chemical sense. A typical example for this kind of transformation is the selective dehydrogenation of stearic acid to oleic acid (Eq. 1). Selectivity of this nature is believed to be the result of geometrical restrictions imposed in the enzyme-substrate complex which fits only certain substrates and where only certain points in the substrate molecule can be attacked. In contrast, chemical reactions almost always occur at sites which are dictated by an already present functional group. As an attempt to mimic the selectivity of enzymic reactions, there have been interesting investigations of functionalization at non-activated centres or reactions at positions remote from the functional group.¹

A number of intramolecular free radical reactions have been observed which involve the formation of a reactive hetero atom radical in a molecule, which then abstracts a hydrogen atom attached to a δ-carbon atom, thus initiating functionalization at a non-activated site (Eq. 2).² The Barton reaction,³

\[
\begin{align*}
\text{H} & \quad \text{Y} \quad \text{X} \\
& \xrightarrow{-X^*} \\
& \quad \text{H} \quad \text{Y}^* \\
& \quad \quad \quad \text{\^{\_}} \text{YH} \quad \text{+X'}^* \\
& \quad \quad \quad \quad \quad \text{X'}^\text{YH} \\
\end{align*}
\]

\[
\text{Y}=0, \text{N}; \text{X}=\text{halogen, NO, OH, Pb(OOCCH}_3)_3
\]

which involves the photolysis of alkyl nitrites, belongs to this category. The mechanism of this reaction has been investigated⁴ and the procedure has been employed in many useful transformations in steroids,⁵ terpenes,⁶ and other natural products.⁷ In a related reaction Cekovic reported the formation of remote olefinic bonds by a metal catalyzed decomposition of hydroperoxides and alkyl nitrites.⁸

A new photochemical reaction reported by Watts and coworkers has the advantage of reiterative functionalization; a parent functional group migrates down the backbone of the substrate regioselectively and leaves behind a daughter functional group (Scheme I).⁹ This reaction has been applied to functionalize

\[\text{Scheme I}\]

![Diagram of Scheme I]
non-activated methyl groups in steroids.¹⁰

Money and coworkers investigated the remote oxidation of terpenes,¹¹ fatty acid esters,¹² and macrocyclic acetates and macrolides¹³ with chromium trioxide. Their approach is based on the notion that certain molecules are intrinsically susceptible to oxidation at centres which are generally considered to be unreactive. Lactones and cyclic ketones were formed by the remote oxidation of carboxylic acids by peroxodisulfuryldifluoride¹⁴ and by direct anodic oxidation.¹⁵ Ferrous ion has been found to induce stereo-specific hydroxylation in cyclohexanol¹⁶ and remote oxidation in the decomposition of a rigid epidioxide.¹⁷

Certain phthalimides (2) with terminal sulfide functions bearing N-alkyl side chains undergo regioselective photocyclization to give azathiacyclols (3).¹⁸ This reaction has been utilized in a facile synthesis of medium to large size ring systems including analogs of cyclic peptides, lactones and crown ethers.¹⁹

Breslow and coworkers have devised a series of remote functionalization reactions.²⁰ The principle behind this study is the directed functionalization of the substrate at a remote site, the selectivity being determined by the geometry of an associated reagent, catalyst, or template. Photolysis of attached or complexed benzophenone groups has been employed in the remote oxidation of long-chain alcohols²¹ and steroids.²² Selective halogenation of steroids has been achieved by using attached aryl iodide templates.²³ Few related remote functionalization reactions were reported by other workers.²⁴ Template directed remote epoxidation of olefins²⁵ and the selective epoxidation of arachidonic acid has also been observed.²⁶

Remote functionalization reactions serve as conformational probes for flexible alkyl chains,²⁷ micelles,²⁸ and for model membrane systems.²⁹ Win-nik has developed a computer simulation program for predicting the sites of attack in the remote oxidation reactions of fatty acid esters and long chain alcohols.³⁰

As we have seen, remote functionalization reactions add a new dimension to organic synthesis. Even though the methods listed so far may not be generally applicable, continued interest in this area will certainly enhance our ability to perform chemical transformations which mimic both the style and selective results of biochemistry.

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2. For reviews, see (a) K. Heusler and J. Kalvoda, Angew. Chem. Int. Ed., 3, 525 (1964); (b) M. L. Mihailovic and Z. Cekovic, Synthesis, 209 (1970);


HYPERVALENT HYDROGEN

Reported by Charles Perkins December 11, 1980

The significance of the chemistry of hydrogen is obvious. What is less obvious is that much of this chemistry can be viewed as a consequence of a hydrogen centered, three center, four electron (3c,4e) hypervalent bond. Many aspects of the chemistry of sulfuranes, phosphoranes, numerous other types of hypervalent compounds, as well as bimolecular substitution reactions on carbon, are effectively explained in terms of 3c,4e bonding. Various features of hydrogen chemistry are also made more tractable when the central role of this ubiquitous bonding arrangement is recognized.

An early recognition of the applicability of the 3c,4e bonding description to hydrogen chemistry is exemplified by Pimentel's"M. O. description of the bifluoride ion (HF$_2^-$). In this description the four bonding electrons fill the two lowest energy orbitals ($\psi_1$ and $\psi_2$) formed by the combination of two 2p orbitals (one on each fluorine) and the 1s orbital of hydrogen (Figure 1).

Figure 1. An approximate M.O. scheme for hypervalent hydrogen

\[
\begin{align*}
\psi_3 & \quad (P_A - P_B)^-S_H \\
\psi_2 & \quad (P_A + P_B)
\end{align*}
\]

\[
\begin{align*}
\psi_1 & \quad (P_A - P_B)^+S_H \\
\psi_2 & \quad (P_A + P_B)
\end{align*}
\]

When interpreting hydrogen chemistry in terms of a hypervalent bonding structure, there are a number of interesting features that it would be well to remember.

1) Since only one orbital is bonding, $\psi_3$, the overall bonding order of each single bond will be less than a normal covalent bond, while the bonding distances are expected to be longer; 2) A continuum of degrees of hydrogen bonding can be described simply by varying the coefficients in the manner shown in Figure 2. As $b$ coefficients decrease from unity to zero the atom "B" is moved away from the symmetry position; 3) An accompanying attribute of electronegativity is the degree to which an atom or group of atoms may accommodate electron density with a minimum increase in energy. Since
the orbitals comprising \( \psi_2 \) concentrate virtually all of the electron density on the outer two atoms, the more electronegative are A and B, the more stable will be this bonding structure; 4) Since the 1s orbital of the central hydrogen is employed, rather than a p orbital (which is what is utilized in the linear hypervalent bonding with other central atoms) the hypervalent hydrogen bond may deviate from linearity to a large degree without a concomitant loss of stability. A large departure from linearity, which in other systems would significantly reduce overlap with the central p orbital, is not seen in the otherwise equivalent hypervalent bonds of the trihalides; 5) A similar overall bonding order would be expected if only three electrons occupied \( \psi_1 \) and \( \psi_2 \).

A three electron system centered on sulfur has been postulated to exist for sulfuranyl radicals. It is a tantalizing model to apply to hydrogen atom abstraction; 6) Placing two electrons in this system describes the now familiar hypovalent bonding in boranes.

**Bifluoride.** Stable, isolable hypervalent hydrogen species are known under the guise of "strong" hydrogen bonds. Given the stabilizing effect of electronegativity on the outer atoms in the hypervalent bond, it is not surprising that bifluoride, (HF)\(^-\), is among the most stable hypervalent hydrogens. The unusual strength of this hydrogen bond was first implied by the results of an x-ray study as early as 1923. This evidence for the strength of this hypervalent bond, the short R(F...F) distance of 225 pm for potassium difluoride, has since been further confirmed by data from the various studies used to detect strong hydrogen bonds. Outright measurement of bond strengths have provided a variety of values ranging from 152 kJ/mole (36.3 kcal/mole) to 243 kJ/mole (58.1 kcal/mole). Theoretical calculations have varied from 167 kJ/mole (39.9 kcal/mole) to 234 kJ/mole (55.9 kcal/mole). These values fall in the range of covalent bond strength.

**Ligands.** Comparisons between hypervalent systems can be fruitful. One interesting parallel is between apicophilicity and hypervalent hydrogen bond strengthening character. Although all of the factors that determine the apicophilicity of ligands in \( \psi\)-TBP structures are not present in strong hydrogen bonded molecules, there is a striking resemblance between the kinds of chemical species that form strong hydrogen bonds and those that preferentially occupy apical positions. Of the five brominanes extant (Table 1) the first four of them have apical ligands which are among those species that form the strongest of hydrogen bonds (Table 2). Phosphorane apicophilicity

<table>
<thead>
<tr>
<th>Brominane</th>
<th>Apical ligand</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrF(_3)</td>
<td>F</td>
<td>5a</td>
</tr>
<tr>
<td>Br(ONO(_2))(_3)</td>
<td>ONO(_2)(^-)</td>
<td>5b</td>
</tr>
<tr>
<td>Br(FSO(_3))(_3)</td>
<td>(FSO(_3))(^-)</td>
<td>5c</td>
</tr>
<tr>
<td>CF(_3)BrCF(_3)</td>
<td>CF(_3)O(^-)CF(_3)</td>
<td>5d</td>
</tr>
<tr>
<td>B(FSeO(_3))(_3)</td>
<td>(FSeO(_3))(^-)</td>
<td>5e</td>
</tr>
</tbody>
</table>
and sulfurane apicophilicity\textsuperscript{7b,8} parallel hypervalent hydrogen bond strength-

<table>
<thead>
<tr>
<th>Strong H Bond</th>
<th>R(X...X)</th>
<th>Detection Method</th>
<th>\textless \text{Van der Waal's R}</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cs(C\textsubscript{3}F\textsubscript{3}C\textsubscript{0})\textsubscript{2}H</td>
<td>238 pm</td>
<td>x-ray</td>
<td>62</td>
<td>9a</td>
</tr>
<tr>
<td>K(C\textsubscript{3}F\textsubscript{3}C\textsubscript{0})\textsubscript{2}H</td>
<td>243.7 pm</td>
<td>x-ray neutron</td>
<td>57</td>
<td>9b</td>
</tr>
<tr>
<td>K(C\textsubscript{4}H\textsubscript{3}C\textsubscript{0})\textsubscript{2}H</td>
<td>247.6 pm</td>
<td>x-ray</td>
<td>53</td>
<td>9c</td>
</tr>
<tr>
<td>K(\textsubscript{2}H\textsubscript{2}C\textsubscript{2}C\textsubscript{0})\textsubscript{2}H</td>
<td>244.4 pm</td>
<td>x-ray</td>
<td>56</td>
<td>9d</td>
</tr>
<tr>
<td>K(F-H-F)\textsubscript{2}H</td>
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<td>neutron x-ray</td>
<td>63</td>
<td>9e</td>
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<tr>
<td>Cs(Cl-H-Cl)\textsubscript{2}1/3 H\textsubscript{3}O\textsuperscript{+}</td>
<td>314 pm</td>
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<td>9f</td>
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<td>Cs(Br-H-Br)\textsubscript{2}1/2 H\textsubscript{3}O\textsuperscript{+}</td>
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<td>9g</td>
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<tr>
<td>Cs(NO\textsubscript{3}-H-NO\textsubscript{3})</td>
<td>246.8 pm</td>
<td>x-ray neutron</td>
<td>55</td>
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<td>244 pm</td>
<td>x-ray</td>
<td>56</td>
<td>9i</td>
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<tr>
<td>Br\textsuperscript{-}H\textsuperscript{+}CO-H\textsubscript{2}C\textsubscript{0}-H\textsuperscript{-}</td>
<td>240 pm</td>
<td>neutron</td>
<td>60</td>
<td>9j</td>
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<tr>
<td>K(Cl\textsubscript{2}H\textsuperscript{2}C\textsubscript{0})\textsubscript{2}H</td>
<td>237 pm</td>
<td></td>
<td>63</td>
<td>9a</td>
</tr>
<tr>
<td>K(pClC\textsubscript{3}H\textsubscript{2}O\textsubscript{2})HPO\textsubscript{3}H\textsubscript{3}Cs(\textsubscript{3}C\textsubscript{0})\textsubscript{2}</td>
<td>258.2 pm</td>
<td>x-ray</td>
<td>41</td>
<td>9k</td>
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<td>NaH(SO\textsubscript{3})\textsubscript{2}</td>
<td>243.4 pm</td>
<td></td>
<td>56</td>
<td>9l</td>
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</tbody>
</table>

Cyclic structures. Inclusion of the hypervalent atom in a five-membered ring linking an apical and an equatorial position has been shown to be a stabilizing influence in hypervalent compounds.\textsuperscript{7a,b} This effect may be subsummed under the general category of ring strain effects. In the context of ring stabilization, however, the hydrogen case differs from other cyclic systems because in hydrogen cyclic systems the ring must include two apical positions. The flexibility of the hydrogen hypervalent bond and the shorter distances involved allow this structural idiosyncrasy to exist. There are a number of very stable molecules with hydrogen included in a cyclic system. Besides the three representatives below, \textsubscript{1}, \textsubscript{2}, \textsubscript{3},\textsuperscript{11} numerous oximato complexes, \textsubscript{4}, have very short R(O...O).\textsuperscript{4} It is worth noting that the neutral zwitterion
has the shortest \( R(0-0) \). One of the best suited ligands for stabilizing sulfuranes, brominanes, iodonanes, siliconates, phosphorinanes, and more highly oxidized analogues of some of these compounds, is the hexafluoronated cyclic alkoxy ligand shown in 5, 6, and 7. The low \( \text{pK}_a \) of perfluoropinacol is attributable to formation of the stable five membered ring, 8, that bears an obvious resemblance to the compounds containing two "magic" ligands. To put this low \( \text{pK}_a \) in perspective, it may be compared to the \( \text{pK}_a \) of perfluorot-butyl alcohol (9.52).

Polarization. Structures of compounds containing unsymmetrical, presumably polarized hypervalent bonds have been determined by x-ray crystallography. A study of carbonyl stretching frequencies in variously substituted sulfuranes further attests to the polarized nature of some hypervalent bonds. There are numerous examples of polarized hypervalent hydrogen bonds, but there is a unique feature about the polarizability of hydrogen bonds. Protons are thought to exist in four different types of potential wells.

**Figure 3.** Potential wells for hydrogen containing bonds
When the proton is in certain kinds of 3a, b, or c type potential energy wells, however, it may (unlike other atoms) easily oscillate over a "large" distance. For proton environments that can be characterized by 3b or 3c, the motion, energy levels, transition probabilities and lingering times in each well have been investigated.\(^{16}\) In this molecular environment the possibility of displacement of a proton causes a polarizability 1-2 orders of magnitude greater than the polarizability due to electronic displacements alone. An important contribution to the unusual mobility of the proton in the hydrogen bond is its tunneling through the energy barrier in the double minimum type of potential.

Another aspect of the polarization of hypervalent bonds is the relative length of each bond in the two bond system. In a hydrogen bond complex the substituent that is the most basic is the one expected to be closest to the hydrogen. The longer bond is the bond that, when broken, results in the smaller loss of energy. This is simply a consequence of the meaning of "stronger" and "weaker" base. The phenomenon of hypervalent bonds being skewed in such a way that the longer of the two bonds is the most energetically favorable to break, has been documented in sulfurane chemistry.\(^{14B}\) It may be that both phenomena are a consequence of the ligands' ability to accommodate a negative charge. This electron distribution can be translated into a hypervalent M.O. description by mixing in a larger coefficient of the \(\text{P}_B\) orbital into \(\psi_2\), the non-bonding orbital. This is analogous to a resonance theory description that includes a larger contribution of the appropriate unbonded form (Figure 4).

**Figure 4.** Resonance description of polarized hypervalent sulfur and hydrogen bonds

\[
\begin{align*}
\text{Y}^- & \leftrightarrow \text{Y} \leftrightarrow \text{Y}^- \\
\text{S}^+ & \leftrightarrow \text{S} \leftrightarrow \text{S}^+ \\
\text{H} & \leftrightarrow \text{H} \\
\text{X}^- & \leftrightarrow \text{X} \\
\text{Y}^- & \leftrightarrow \text{Y}^{-} \\
\text{X}^- & \leftrightarrow \text{X}^{-} \\
\end{align*}
\]

Unsymmetrically substituted hypervalent bonds sometimes appear to be stronger than either of the symmetric analogs. \textit{Ab initio} calculations\(^{17}\) of the fluoride-formic acid system, diforate, and difluoride, indicate that the fluoride-formic acid complex is the most stable of the three.

More evidence for the added strength of the asymmetric bond is provided by dissociation studies of Jasinski.\(^{18}\) For a series of substituted carboxylic acids with a given reference anion (e.g., acetate or nitrobenzoate) the value of the \(K_{\text{AHB}} = \frac{[\text{AH}^-][\text{B}^-]}{[\text{AH}][\text{B}]}\) increases with acid strength. Noteworthy in this context is that the trifluoro, dichloro, and other substituted acetic acid-acetate combinations have a greater \(K_{\text{AHB}}\) than the acetic acid-acetate \(K_{\text{AHA}}\). This is another example of a correct prediction based on the hypervalent model. It is not what one would expect from electrostatic considerations alone. There also appear to be some sulfur centered asymmetric hypervalent bonds stronger than their symmetric siblings.\(^{19}\)
Proton Transfer. During the course of proton transfers, intermediates and/or transition states that include hypervalent hydrogen may occur. Considering the potential wells 3b and 3c may shed some light on the discreet steps of this process. As the abstracting moiety approaches, well 3b (with the depth of the minima possibly reversed) will describe an intermediate hydrogen bonded complex. The proton's energy will exceed the barrier (or the proton may tunnel through it) forming a proton-transfer complex. The complex may dissociate to leave products. Figure 5 illustrates a possible hypervalent M.O. description of this process. By carefully adjusting the pka of the donors and acceptors, evidence of the intermediates is observed in IR spectra.\textsuperscript{20} The results of such a study are given in Table 3. The alcohols

Table 3. Effect of hydrogen bonding on the NH\textsb{2} vibrations of n-propyl amine

<table>
<thead>
<tr>
<th>Donor</th>
<th>Solvent</th>
<th>(\nu(O-H, N))\textsuperscript{a} cm\textsuperscript{-1}</th>
<th>(\nu(N^+H...O))\textsuperscript{b} cm\textsuperscript{-1}</th>
<th>pka</th>
<th>Asym. free (\nu(NH_2)) cm\textsuperscript{-1}</th>
<th>Asym. Assoc. (\nu(NH_2)) cm\textsuperscript{-1}</th>
<th>Asym. (\Delta\nu(NH_2)) cm\textsuperscript{-1}</th>
<th>Sym. free cm\textsuperscript{-1}</th>
<th>Sym. Assoc. (\nu(NH_2)) cm\textsuperscript{-1}</th>
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</thead>
<tbody>
<tr>
<td>2,6-dinitrophenol</td>
<td>benzene</td>
<td>2760,2500</td>
<td>3.76</td>
<td>3390</td>
<td>3390</td>
<td>3360</td>
<td>30</td>
<td>3324</td>
<td>3299</td>
</tr>
<tr>
<td>p-nitrophenol</td>
<td>benzene</td>
<td>2760,2500</td>
<td>7.15</td>
<td>3390</td>
<td>3390</td>
<td>3360</td>
<td>30</td>
<td>3324</td>
<td>3300</td>
</tr>
<tr>
<td>m-nitrophenol</td>
<td>benzene</td>
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<td>3390</td>
<td>3390</td>
<td>3362</td>
<td>28</td>
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<td>3300</td>
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<tr>
<td>p-chlorophenol</td>
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<td>3040</td>
<td>9.38</td>
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<td>3390</td>
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<td>phenol</td>
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<td>3390</td>
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<tr>
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<td>10.19</td>
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<td>3390</td>
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<td>3390</td>
<td>3390</td>
<td>3382</td>
<td>8</td>
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<tr>
<td>t-butanol</td>
<td>CCl\textsubscript{4}</td>
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<td>17.62</td>
<td>3390</td>
<td>--c</td>
<td>--</td>
<td>--</td>
<td>3324</td>
<td>--c</td>
</tr>
</tbody>
</table>

\(\textsuperscript{a})\) Shift in O-H bond due to H-bond  
\(\textsuperscript{b})\) The NH\textsb{2} stretching vibration.  
\(\textsuperscript{c})\) Obscured by the broad (O-H... N) bond

are arranged in the order of increasing acidities. The trend in the \(\nu(O-H...N)\) column indicates increasing hydrogen bonding as do the N-H shifts. Two new bonds appear in the series at p-cresol, which are attributable to the proton transfer complex. For the next three alcohols in this series a tautomeric equilibrium appears between the H-bonded and proton transfer complexes. For the rest, of lower pka (58.28) the \(\nu(O-H...N)\) band doesn't exist. The equilibrium is shifted almost entirely to the proton-transfer complex. Observe the transition from one type of potential energy function to another as the pka was varied. At high pka there was a type 3c function that was replaced by another type 3c function with the second minimum lower than the first. Both complexes may be described by the hypervalent M.O. description using the appropriate coefficients in a manner suggested by Figure 4.
If the two minima in these potential energy functions are separated by a large barrier the proton transfer rate is expected to be slow. The height of this barrier will reflect the stability of the hypervalent transition state. The maximum in potential energy becomes greater (shown in Figure 6) as those features that stabilize hypervalent hydrogen are reduced. The height of the maximum in a proton transfer between two carbons would be expected to reflect the lesser electronegativity of carbon vs. nitrogen or oxygen. Consequently the rate of transfer between two carbons is substantially slower. A characteristic rate for each is given in Table 4.

Table 4. Proton Transfer Rates

<table>
<thead>
<tr>
<th>acid</th>
<th>base</th>
<th>solvent</th>
<th>K_P</th>
<th>K_r</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃OH</td>
<td>CH₃O⁻</td>
<td>Methanol</td>
<td>1.8 x 10⁻⁰</td>
<td>1.8 x 10⁻⁰</td>
<td>22a</td>
</tr>
<tr>
<td>(PhCH₂)₂CH₃NH</td>
<td>(PhCH₂)₂CH₃N</td>
<td>DMSO</td>
<td>6 x 10⁶</td>
<td>6 x 10⁶</td>
<td>22b</td>
</tr>
<tr>
<td>CH₃SOCH₃</td>
<td>CHSCOCH₂⁻</td>
<td>DMSO</td>
<td>10</td>
<td>10</td>
<td>22c</td>
</tr>
</tbody>
</table>

Figure 6. Potential energy function for proton transfer between carbon and oxygen

One can imagine hydrogen atom transfer going through a similar process involving 3c, 3e hypervalent hydrogen bond. Such a bond would be expected to have a bond order the same as the 3c, 4e bond. One would therefore predict that a one electron oxidation of bichloride [Cl-H-Cl⁻] and dibromide [Br-H-Br⁻] would have a small effect on the bond order. Force constants for both the anions and the neutral molecules have been measured and are quite similar.²³ [HCl₂]⁻ and HCl₂ have (16 and 14 mdyne/pm). [HBr₂]⁻ and HBr₂ have (13 and 14 mdyne/pm). These results would clearly imply Pimentel's description and are not, in any obvious way, predictable from considerations based on either an electrostatic or a charge transfer model.

Bifurcated hydrogen bonds. When hydrogen is bonded to more than two atoms it is said to be in a bifurcated hydrogen bond. A number of crystals (glycine, Tultons salts, 1,3,5-triamino-2,4,6-trinitrobenzene, to name a few) contain bifurcated hydrogen bonding.²⁴ Few of these unusual structures have been observed in solution. An interesting rarity is the dioxane alcohol 8.²⁵ The coupling constant ³J₇HCOH for a dilute solution of 8 is compared to two groups of similar systems in which the dihedral HOCH angles are constrained to be either 180° or 150°. When the angle is 180° the coupling constants are in the range of 12.0 Hz to 12.5 Hz. When the angle is on 150° a value of ³J₇HCOH =9.8 is reported.²⁶ The coupling of a 0.005M sample of 8 was 12.1 Hz. In creased concentration resulted in a decrease in coupling constants. This is ascribed to an increase in intermolecular hydrogen bonding perturbing the
180° dihedral angle. Further comparisons of coupling constants with unsubstituted dioxanes show a difference in values attributable to the expected conformational alterations.

A possible bonding scheme for the electrons about hydrogen is described in Figure 7.

![Figure 7. M.O.'s of a symmetric bifurcated hydrogen](image)

The many parallels in structure and reactivity between hydrogen chemistry and the chemistry of other systems known to involve hypervalent systems are strong evidence for the existence and in many cases the central role of hypervalent hydrogen.

BIBLIOGRAPHY


21. The effect on the intermediates (the minima) is comparatively small.


ORGANIC SEMINAR ABSTRACTS

Summer, 1981

University of Illinois

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SEMINARY TOPICS

Summer Session, 1981

The Didemmins: Antiviral, Antitumor Depsipeptides
from a Caribbean Tunicate........................................................................238
James B. Gloer

Selectivity Studies of Alkyl Radicals............................................................241
Timothy D. Krizan

The Synthesis and Chemistry of "Nonclassical" Condensed Thiophenes.........250
M. A. Rossman

Studies on the Kinetics and Mechanisms of the Reactions
of Ketones and Esters with sec-Butyllithium.............................................264
Munther Al-Aseer

Intramolecular N-acyliminium Ion Cyclizations..........................................267
Bruce C. Hamper

Synthetic Approaches to the Isocomene and Modhephene Sesquiterpenes.....276
Steve Ashburn
The Didemnins: Antiviral, Antitumor Depsipeptides from a Caribbean Tunicate

Reported by James B. Gloer

June 15, 1983

In recent years, the sea has emerged as a potential source of new drugs and many bioactive compounds have been isolated from marine organisms. Investigations of some such organisms have produced the isolation of numerous polypeptide toxins and venoms. Several novel amino acids and small peptides have also been discovered.

The didemnins5-7 (1 - 3) are a new class of bioactive depsipeptides which were isolated from a Caribbean tunicate (Trididemnum sp.) and which show great promise as antiviral and antitumor agents. This account will focus on the isolation, structure elucidation, and bioactivity of the didemnins.

Isolation. The didemnins were isolated from tunicates, or sea squirts, which were collected at several locations by Rinehart and coworkers during the Alpha Helix Caribbean Expedition in 1978. Briefly, the compounds were obtained by extracting the animals with 3:1 methanol:toluene, partitioning the supernatant solution with 1 N sodium nitrate, separating the resulting layers, and extracting the aqueous phase with chloroform. The chloroform fraction was chromatographed on silica gel to afford crude mixtures of didemnins which were separable by HPLC.

Structures. Didemnin A (MW 942, C49H78N5O12), the major component, is also the simplest. The compound was hydrolyzed and the resulting amino acids derivatized to form their N-TFA-O-n-butyl esters. GC/MS of this mixture demonstrated the presence of one mole each of leucine (Leu), threonine (Thr), proline (Pro), N-methylleucine (MeLeu), N,0-dimethyltyrosine (Me2Tyr), and statine9,10 (Sta: 4-amino-3-hydroxy-6-methyl-heptanoic acid), which was confirmed by coinjection with standards. These residues account for all
but C₈H₁₂O₃ of the molecular formula of didemnin A. This unit was identified by examination of the ¹H NMR spectrum of didemnin A as an hydroxyisovalerylpropionyl (Hip) residue. The configurations of Leu, Pro, MeLeu, and Thr were all assigned as L by GC of their N-pentafluoropropionyl-0-n-butyl esters on chiral substrate RSV-007¹¹ and comparison of retention times with standard DL mixtures.

The sequence of didemnin A was ascertained by examination of partial acidic and basic hydrolysates. The fragments obtained were assigned structures by HRPDMS, supplemented by HREIMS of didemnin A itself, and overlapping permitted assignment of the structure as 1.

Didemnin B (MW 1111; C₅₇H₈₉N₇O₁₅) showed a high degree of homology with 1. The El mass spectra are nearly identical up to m/z 942. The ¹H NMR spectra are also quite similar, but the downfield shift of the N-methyl group of MeLeu relative to its position in 1 showed that didemnin B differs from didemnin A by acylation of the free N-methyl group with a C₈H₁₁NO₃ unit. Hydrolysis, followed by derivatization and GC analysis, showed the presence of an additional mole of proline and the lactyl moiety was established by examination of the ¹H NMR spectrum of didemnin B. These and other data allowed assignment of the structure as 2.

Didemnin C (MW 1014; C₅₂H₈₂N₆O₁₄) was found only in trace amounts. Hydrolysis, derivatization, and GC analysis gave the same trace as did didemnin A. The ¹H NMR and El mass spectrum show similarity with those of 1 and 2 and the remaining C₃H₅O₂ is accounted for by tentative assignment of the structure as 3.

**Activity.**⁷,¹² Didemnin A inhibits a broad spectrum of both RNA and DNA viruses in vitro, including Herpes simplex virus. ID₅₀ vs L1210 leukemic cells is 0.031 µg/ml. In vivo studies have shown significant protection of mice from genital HSV-2 infection, T/C vs P₃₈₈ leukemia up to 161, and T/C vs B₁₆ melanoma up to 148.

Didemnin B is more active than didemnin A in most cases, but is also more toxic. It is more active in in vitro antiviral testing and has ID₅₀ vs L1210 cells of 0.0011 µg/ml. In vivo testing in mice has shown better protection at lower concentrations from genital HSV-2 than didemnin A, T/C vs P₃₈₈ leukemia up to 199 and T/C vs B₁₆ melanoma up to 160.

These compounds already show promise as drugs, but their potential value may lie in studies of derivatives or analogs.

**BIBLIOGRAPHY**

12. All antiviral and antitumor testing other than on shipboard was performed by The Upjohn Company, Kalamazoo, Michigan.
Every time a chemist carries out a reaction, a selectivity principle is invoked, usually in an implicit manner. More explicit forms of selectivity principles have been known for several years. After briefly examining the reactivity-selectivity principle (RSP), this seminar will focus upon recent applications of it and the readily derivable isoselective relationship (ISR) to the chemistry of alkyl radicals.

The Reactivity-Selectivity Principle. The selectivity, $\chi$, can be defined as follows. If initial compound, $I$, can react with either $R_1$ or $R_2$ with respective rate constants $k_1$ and $k_2$ (Eq. 1), $\chi$ will be equal to the ratio of $k_1$ and $k_2$. For slow reactions, $\chi$

$$\chi = \frac{k_1}{k_2}$$

(1)

can be calculated from the rate constants of the individual reactions. Some reactions, however, such as free radical and carbene additions, occur too rapidly to allow direct, accurate measurement. In these cases, the ratio of rate constants can be determined by allowing $I$ to react competitively with a mixture of $R_1$ and $R_2$. The selectivity can then be calculated from the product ratio (Eq. 2).

$$\chi = \frac{k_1}{k_2} = \frac{[P_1][R_2]}{[P_2][R_1]}$$

(2)

A qualitative statement of the RSP is that as reactivity for a certain molecule increases, the selectivity decreases proportionally. A reaction coordinate diagram (Fig. 1) can be used to illustrate this statement. The more reactive starting material, $I_1$, by application of the Hammond postulate, will have an earlier transition state with less interaction with $R$ than $I_2$. In the later transition state of $I_2$, the difference in activation energies between $I$ and $R_1$, and $I$ and $R_2$ will be greater than for $I_1$. Therefore, since selectivity is a

Figure 1. Reaction of $I_1$ and less reactive $I_2$ with $R_1$ and $R_2$
measure of rate constant ratios, I$_2$ will be the more selective starting material.

For the RSP to be valid for a series of reactions, a straight line with negative slope must result when \( \ln \chi \) is plotted against \( \ln k \) of the reference reaction. This relationship is not always observed. In the reactions of substituted arylsulfonyl chlorides with the competitive system aniline/3-chloroaniline, a straight line with positive slope resulted when \( \ln \chi \) was plotted against \( \ln k \).\(^3\) This means that the most reactive arylsulfonyl chloride is also the most selective. This and other examples have led some researchers to conclude that the entire RSP is invalid.\(^4\) Even though, in most cases, it has been possible to rationalize the breakdown of the RSP\(^1,5\), extreme care should be used in application of it to an unknown system. The remainder of this seminar will deal with other cases where the RSP does not hold.

The Isoselective Relationship. The isokinetic relationship for a set of reactions relates the activation parameters of the individual reactions. When a continuity of mechanism exists, a plot of \( \Delta H^\circ \) against \( \Delta S^\circ \) for a set of reactions should yield a straight line with slope \( \beta \). In theory, \( \beta \) is the isokinetic temperature, the temperature at which the rates of all reactions in the set will be the same. The values for \( \beta \) for many sets of reactions are too high to be achieved experimentally. Some \( \beta \) values have been reported that are theoretically accessible, but these low values resulted from incorrect statistical treatment.\(^6\)

The ISR, formally similar to the isokinetic relationship, can be easily derived. Combination of the Eyring equations for two reactions yields Equation 3.\(^2\) At a temperature where the selectivities coincide, T$_{18}$, \( \delta \ln \chi = 0 \). Equation 3 can then be converted to Equation 4.\(^7\)

\[
\ln \chi = \ln \frac{k_1}{k_2} = \frac{\Delta H^\circ_2 - \Delta H^\circ_1}{RT} - \frac{\Delta S^\circ_2 - \Delta S^\circ_1}{R} \tag{3}
\]

\[
\delta(\Delta H^\circ_2 - \Delta H^\circ_1) = T_{18} \delta(\Delta S^\circ_2 - \Delta S^\circ_1) \tag{4}
\]

For a set of reactions with identical mechanism, plotting \( \Delta H^\circ_2 - \Delta H^\circ_1 \) against \( \Delta S^\circ_2 - \Delta S^\circ_1 \) should result in a straight line with slope T$_{18}$.

Use of the RSP to elucidate reaction mechanisms has been criticized\(^4\), but Giese circumvented most of the complaints by proposing that plots of activation parameters be used instead of \( \ln \chi \) vs. \( \ln k \). Giese used a plot of \( \Delta \Delta H^\circ \) vs. \( \Delta \Delta S^\circ \) to support his previous conclusion that addition of halogens to alkyl substituted norbornene-5,6-diesters (1) gave an intermediate proposed as 2 while addition of PhSCl to 1 gave an intermediate proposed as 3, with a different type of bonding.\(^8\) The relative ratios of structural isomers were converted into activation parameter differences. The resulting plot gave two, almost perpendicular, lines indicating that the intermediates were indeed different.
The isoselective temperature is of theoretical interest. The selectivities for each reaction in a series will be equal at $T_{Is}$. Above $T_{Is}$, as reactivity increases, selectivity should increase also, constituting a violation of the RSP. By plotting $\ln X$ against $T^{-1}$, the selectivities should coincide at $T_{Is}$, if $T_{Is}$ is experimentally achievable and if it has any actual, physical significance.

The selectivities of dihalocarbene addition to olefins have been studied. At 25°C, CF$_2$, the least reactive carbene studied, was the most selective. At 110°C, CBr$_2$, the most reactive carbene studied, was the most selective. When $\ln X$ was plotted against $T^{-1}$ for all the carbones studied, the lines intersected at $T$=90°C. In the case of dihalocarbenes, the ISR proves to be more than just a theoretical curiosity.

**Selectivities of Alkyl Radicals.** Giese decided to apply the ISR to the chemistry of alkyl radicals. The usual method to form these radicals is to thermolyze peresters or azo compounds, often at temperatures in excess of 100°C. Recently, it was found that alkyl radicals could be quantitatively generated by NaBH$_4$ reduction of alkyl mercuric halides, even at temperatures well below 0°C. With a wide temperature range in which the radicals could be generated, Giese hoped to obtain fairly accurate differences in activation parameters as well as observe $T_{Is}$ for common radical processes.

Giese formed various alkyl and aryl radicals in the competitive system BrCCl$_3$/CCl$_4$, measuring their selectivities from $T$=0°C to $T$=130°C. The graph of $\ln X$ against $T^{-1}$ for all of the radicals generated shows two distinct sets of lines (Fig. 2). One set of these lines corresponds...
to the $\sigma$ radicals, where the unpaired electron is in an

Figure 2. Plot of $\ln X$ against $T^{-1}$ for alkyl and aryl radicals.

sp$^2$ orbital. The other set of lines corresponds to the planar $\pi$ radicals, where the unpaired electron is in a $p$ orbital. Statistical analysis$^6$ of these lines show that $T_{1S}$ is about 70°C for the $\pi$ radicals and about 40°C for the $\sigma$ radicals.$^{12}$ A plot of $\Delta S^\text{Cl}_0 - \Delta S^\text{Br}_0$ against $\Delta H^\text{Cl}_0 - \Delta H^\text{Br}_0$ yields two straight lines (Fig. 3). The slopes of the lines show that $T_{1S} = 50 \pm 30°C$ for $\pi$ radicals and $T_{1S} = 40 \pm 20°C$ for $\sigma$ radicals. These values are in agreement with the experimentally observed $T_{1S}$ values.
Figure 3. Activation parameter difference plot for the reaction of alkyl and aryl radicals with BrCCl₃/CCl₄.

At 0°C, CH₃ is the least selective π radical measured and C₂H₃ is the least selective σ radical measured. At 130°C, above Tₛ for both types of radicals, CH₃ and C₂H₃ are the most selective π and σ radicals measured.

**Steric Studies.** Giese noticed that as the shielding of the radical increased, the value of ΔH°₃Cl - ΔH°₃Br increased and below Tₛ, the selectivity increased. To see if the selectivity in radical abstraction of halogens from BrCCl₃/CCl₄ was sterically determined, he plotted lnX of π radicals against Eₛ parameters at various temperatures. In the Taft-Hancock equation, the Eₛ values are steric substituent constants which measure the effect of an alkyl substituent upon the rate of a reaction as compared to the rate of a reference reaction. For each temperature, a straight line was obtained. From this evidence, Giese was satisfied that only steric effects were important in the transition state.

Beckhaus pointed out that since Eₛ values were defined in terms of rate comparisons to reference reactions, they are not totally free from non-steric factors which may affect the relative reactivities. He designed a new parameter, Sₚ, designed to reflect only the front strain, or steric effect of either the attacking or leaving group of a molecule in a reaction (Eq. 5).

\[
Sₚ = ΔH_P^0 (R - C[CH₃]₃) - ΔH_P^0 (R - CH₃) + 88.7 \text{kJ/mole}
\]
Giese plotted $\Delta H^\#_{\text{Cl}} - \Delta H^\#_{\text{Br}}$ against $S_F$ for $\sigma$ and $\pi$ radicals, obtaining a straight line for each type of radical. As expected, the planar $\pi$ radicals have a greater $S_F$ than the pyramidal $\sigma$ radicals, due to a greater steric interaction between the substituents in a planar geometry.

One controversy that has raged in the literature deals with the structure of the tert-butyl radical. Studies using PES$^{17a}$ and ESR$^{17b,c}$ have indicated a tetrahedral structure. A later ESR study, however, indicated that the matrix may distort the radical from the planar equilibrium conformation.$^{17d}$ A further PES study by Beauchamp indicated that although the radical is undergoing complex geometry changes, the changes may be due to very low barriers for both out-of-plane bending and internal rotation.$^{17e}$ Beauchamp concluded that PES data do not justify the statement that the radical is planar.

In his initial studies of alkyl radicals, Giese generated the tert-butyl radical. In both the plots of $\Delta S^\#_{\text{Cl}} - \Delta S^\#_{\text{Br}}$ against $\Delta H^\#_{\text{Cl}} - \Delta H^\#_{\text{Br}}$ and $\Delta H^\#_{\text{Cl}} - \Delta H^\#_{\text{Br}}$ against $S_F$, the point for the tert-butyl radical fell squarely upon the lines for $\pi$ radicals, suggesting that the radical is indeed planar. Giese decided that no data exist to justify the conclusion that radicals change from planar to pyramidal structure with increasing alkylation.

From the same plots, Giese found that the 7-norbornyl radical (4) was pyramidal in structure, agreeing with the ESR studies of Kochi.$^{18}$

![Pyramidal Structure](image)

From their linear relationship, it appears that the change in activation enthalpy difference is determined by the steric change. The bulkier radicals, with a greater $\Delta H^\#_{\text{Cl}} - \Delta H^\#_{\text{Br}}$, are, however, the less reactive radicals. Giese points out that the slower reactions, with a later transition state, would be expected to reflect the C-Cl and C-Br bond energy difference to a greater extent than the faster reactions with an earlier transition state.$^{11,19}$

The $\Delta S^\#_{\text{Cl}} - \Delta S^\#_{\text{Br}}$ values also increase as radical size increases, with $\Delta S^\#_{\text{Cl}} - \Delta S^\#_{\text{Br}}$ for the methyl radical equal to $79$e.u. and $\Delta S^\#_{\text{Cl}} - \Delta S^\#_{\text{Br}}$ for the tert-undecyl radical equal to $+9$e.u.$^{11}$ Giese suggested that in a later transition state, the steric hindrance of the larger Br atom causes Br abstraction to be increasingly unfavored. An incomplete selectivity study on other alkyl radicals has indicated that the activation entropy difference is almost zero for Cl abstraction from $\text{CCl}_4$, so the increase of $\Delta S^\#_{\text{Cl}} - \Delta S^\#_{\text{Br}}$ may be due to the Br atom only.$^{20}$

Bridgehead Radicals. In studies with the BrCCl$_3$/CCl$_4$ competitive system, Rüchardt found that the selectivities of bridgehead radicals were an order of magnitude less than those of other non-planar carbon radicals.$^{21}$ Stock compared the selectivities of bridgehead radicals at $80^\circ$C and found that the cubyl radicals was more than twice as selective as the 1-adamantyl radical, the most sterically hindered of the bridgehead radicals studied.$^{22}$ From the RSP, the 1-adamantyl radical would be expected to be the most selective of the radicals studied. Stock was surprised by the actual selectivity order and could not offer a reasonable explanation for it.
Giese studied the selectivities of the same bridgehead radicals from 50°C to 140°C. The resulting plot of lnX against T⁻¹ leads to an intersection of the lines at T = -60°C. The order of selectivities observed by Stock is therefore easily explained by noting that the selectivities were measured well above Tis.

Polar Effects. Giese did some studies on polar effects in the addition of free radicals to alkenes. Using a competition system of styrene with various ring-substituted styrenes, he measured the temperature dependence of Hammett ρ values for various alkyl radicals. The ρ values, which function as measures of selectivity, coincide at T = 70°C, at a value of about +0.5. This positive ρ value indicates a partial negative charge on the benzylic carbon in the transition state (5). Below 70°C, as expected, the tertiary radicals have the highest ρ values.

Giese also studied why electrophilic radicals chose to add to the least substituted carbon in additions to alkenes, believing that there were two major possibilities for the reason. The least substituted carbon is chosen either as a result of product stabilization, with the adduct radical most stable at the most substituted carbon, or because of a stabilizing polar effect in the transition state. To distinguish between the two effects, Giese added nucleophilic alkyl radicals to a competitive system of maleic anhydride and methyl maleic anhydride. With this system, the polar effect and product stabilization effect will oppose each other. The results show that the radicals overwhelmingly preferred to attack the unsubstituted maleic anhydride, with the tertiary radicals unsurprisingly showing the most selectivity at room temperature. Giese concluded that the radical stabilization effect is minor in comparison to the polar effect in these additions, ignoring the possible steric retardation of the methyl group. There were no experiments run, however, to prove that the steric effect of the methyl group was negligible.
Using perturbation molecular orbital theory, Giese constructed Figure 4 to describe alkyl radical addition to olefins. Any substituents on either the radical or the olefin that would lower the difference in energy between the radical SOMO and the olefin LUMO ought to increase both the reactivity and the selectivity, due to better orbital interaction. To lower the olefin LUMO, electron withdrawing groups must be added. To raise the radical SOMO, electron donating groups must be added. Giese studied the selectivities and reactivities of the cyclohexyl radical with various alkene pairs at 20°C. As the substituents on the olefins increase in electron-withdrawing ability, both reactivity and selectivity increase (Table 1).

Table 1. Relative reactivities and selectivities of olefin pairs in the reaction with the cyclohexyl radical at 20°C.

<table>
<thead>
<tr>
<th>Competing olefins</th>
<th>relative $k_H$</th>
<th>$k_H/k_{CH_3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>styrene/a-methylstyrene</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>methylacrylate/methyl methacrylate</td>
<td>6.7</td>
<td>1.3</td>
</tr>
<tr>
<td>acrylonitrile/methyl acrylonitrile</td>
<td>24</td>
<td>1.8</td>
</tr>
<tr>
<td>fumarodinitrile/methyl fumarodinitrile</td>
<td>310</td>
<td>4.4</td>
</tr>
<tr>
<td>maleic anhydride/methyl maleic anhydride</td>
<td>730</td>
<td>5.0</td>
</tr>
</tbody>
</table>

In conjunction with the molecular orbital argument, it is possible to draw a polar transition state (6) which would be stabilized by both electron
donating alkyl groups on the radical and electron withdrawing groups on the olefin.\(^{26}\)

In these molecular orbital arguments, steric effects are not taken into account. In the cases where steric effects are important, the predicted selectivity order may not match the experimental selectivity order. In the radical addition to diethyl fumarate and methyl acrylate, the tert-butyl radical is the least selective of the radicals studied at 20°.\(^{26}\) Giese claimed that the steric interference of the second ester group on the fumarate made it more difficult for the tertiary radical to approach the more reactive olefin, thus decreasing the selectivity.

**Conclusion.** Though the RSP is not valid in all cases, it is still possible to gain a great deal of information from selectivity studies. From the studies of the selectivities of alkyl radicals, information has been obtained in the areas of radical structure, intermediates in reaction mechanisms, steric effects, and polar effects. The ISR, which invalidates many previous selectivity studies, will be a useful tool in the future in the further study of the above areas, as well as many others.

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1. For recent reviews of the reactivity-selectivity principle, see:

The Synthesis and Chemistry of "Nonclassical" Condensed Thiophenes

Reported by M. A. Rossman  
June 22, 1981

Introduction

A "nonclassical" thiophene is one for which no uncharged singlet structure can be written other than one containing a tetracovalent sulfur as part of the thiophene ring. This review will provide an historical account of the synthesis and chemistry of "nonclassical" condensed thiophenes.¹

There are a great number of classes of compounds that contain a tetracovalent sulfur. In acyclic systems, tetracovalent sulfur is in sulfur dioxide,² sulfanylamines,³ sulfur dialdimes,⁴ sulfines,⁵ thiocarbonyl imines,⁶ and thiocarbonyl ylides.⁷ Several examples of heterocycles containing tetracovalent sulfur have been reported. The best known examples of this type are the thia-benzene derivatives,⁸ thiathiophene derivatives,⁹ thiopyran derivatives,¹⁰ and meso-ionic compounds.¹¹

Valence Shell Expansion of Sulfur¹¹

The fact that furan and pyrrole are less aromatic than thiophene has puzzled scientists for many years.¹² Pauling was the first person to examine this problem when he applied molecular orbital theory to thiophene in 1935.¹³ At that time it was assumed that the electronic structure of thiophene was analogous to furan. In 1939, Pauling compared bond lengths, resonance energy values, and dipole moments for thiophene, pyrrole, and furan.¹⁴ On the basis of that evidence, Pauling proposed that an expansion of the sulfur valence shell to include d-orbitals could be a factor in accounting for the increased stabilization of the thiophene molecule. Therefore, in a valence bond description of thiophene, the structures (la → c) were important contributors to the resonance hybrid of thiophene.

In 1949, Longuet-Higginson further developed this concept in molecular orbital terms.¹⁵ He demonstrated that the 3pz orbital and the 3dxz and 3dyz orbitals of sulfur could be mixed to give three hybrid orbitals, two of which are mutually non-orthogonal and have the proper energy and symmetry characteristics required for entering into conjugation with the 2pz orbitals of the neighboring ring carbon atom. The third pd² orbital, which is orthogonal to the other two is mainly 3d in character and is of too high in energy to be occupied in the ground state. Longuet-Higginson concluded that by invoking the pd² hybrid orbitals, the pronounced stability of thiophene was readily explained. Various Hückel-type calculations using the Longuet-Higginson model have been carried out on thiophene and other heterocyclic sulfur compounds.¹⁶ Critics of this model contend that there is no reason to suppose on the basis of stability alone that d-orbital participation is significant.¹⁷ Kreevoy performed LCAO-MO calculations on thiophene and neglected participation by the sulfur d-orbitals. He obtained results in fairly good agreement with the experimental data.¹⁸
Zaull has argued that sulfur hybrid pd$^2$-orbitals would be of too high energy and produce too much angle strain to participate effectively.\textsuperscript{19} Numerous other molecular orbital calculations have been carried out on thiophene Sulfur d-orbital participation was explicitly considered by Pitts and Bielefield using the SCF-PPP method and concluded that the inclusion or deletion of sulfur d-orbitals has little effect on the calculated total energy.\textsuperscript{20} The sophisticated Pople-Segal CNDO method of Clark\textsuperscript{21} and that of Dewar and Trinajstic\textsuperscript{22} have led to the conclusion that sulfur d-orbital participation is insignificant in the thiophene ground state but may strongly influence the excited state. However, the actual extent of sulfur d-orbital participation in thiophene remains a matter of controversy.

**Thieno[3,4-c] thiophene**

In an attempt to resolve the dilemma raised by the question of d-orbital participation in thiophene, Cava initiated a study of the unknown heterocycle, thieno[3,4-c] thiophene 2.

![Thieno[3,4-c] thiophene diagram]

Such a system forced the sulfur atom into using the pd-hybrid orbitals. Thieno[3,4-c] thiophene 2 may be considered as "nonclassical" in that the only uncharged resonance contributors are structures containing a tetracovalent sulfur atom (2a → c). The molecular symmetry of 2 allows both sulfur atoms to have partial tetracovalent character to favor sulfur d-orbital participation. Without d-orbital participation, the molecule must be either a thiocarbonylylide (2d → e) or a diradical 3.

This is in contrast to the other isomers which are classical and are known stable structures.\textsuperscript{23}

Early theoretical studies using the SCF-MO method by Dewar\textsuperscript{22} and Clark\textsuperscript{21} predicted that 2 would be a highly reactive antiaromatic compound with a triplet ground state. These calculations neglected any contribution from the sulfur 3d-orbitals. However, Cava re-examined this compound with the inclusion of the 3d-orbital and predicted singlet ground states with major resonance contribution from 2a.\textsuperscript{24} The thieno[3,4-c] thiophenes are members of 10 π-electron
condensed systems called heteropentalenes.\textsuperscript{25}

Cava reported evidence for the existence of a derivative of 2 in 1967.\textsuperscript{26} A mixture of the sulfoxide 4 and neutral alumina was heated under a vacuum at 140-150°C in a sublimer. A small amount of a bright yellow fluorescent solid was condensed on the dry ice cold finger but it decomposed upon warming to room temperature. No product was isolated when n-phenylmaleimide (NPM) was added in an attempt to trap the intermediate 5. Next, sulfoxide 4, was dehydrated in refluxing acetic anhydride in the presence of n-phenylmaleimide to afford 6 and 7 in 24 and 10\% yield, respectively. In a later experiment, oxygen was excluded and the yield of 6 and 7 rose to 49 and 18\% respectively.\textsuperscript{27} As expected, the addition of the dienophile occurs at the ring of highest electron density. Similar treatment of sulfoxide 8 afforded a mixture of exo- and endo adducts 9 and 10 in 54 and 13\% yield, respectively.\textsuperscript{27}

\[
\begin{align*}
\text{EXO} & : \quad R = \text{CH}_3 \\
\text{ENDO} & : \quad R = \text{CO}_2\text{CH}_3 \\
\text{cis} & : \quad R = \text{CO}_2\text{CH}_3
\end{align*}
\]

However, such a dehydration and addition might easily follow a concerted scheme which does not require an intermediate involving d-orbitals or a triplet ground state.

In 1969, tetraphenylthieno[3,4-c] thiophene 12 was the first reported example of an isolable "nonclassical" condensed thiophene.\textsuperscript{28} In the first synthesis, tetrabenzoylethane 13 was allowed to react with P\textsubscript{2}S\textsubscript{5} in hot xylene to afford a mixture of cis- and trans-dihydrosulfide 14 and 15 in 34 and 6\% yield respectively. The cis-sulfur 14 was oxidized to the sulfoxide 16 with sodium periodate. Pummer-like dehydration of sulfoxide 16 in refluxing
acetic anhydride afforded 12 in 87% yield.

\[
\begin{align*}
13 & \xrightarrow{\text{P}_2\text{S}_5 / \text{xylene}} 14 + 15 \\
& \xrightarrow{\text{NaIO}_4} 16 \\
& \xrightarrow{\text{Ac}_2\text{O}} 12
\end{align*}
\]

In a second synthesis, \(\text{P}_2\text{S}_5\) was allowed to react with the diketone 17 to yield 12 in 83% yield.\(^{29,30}\)

\[
\begin{align*}
17 & \xrightarrow{\text{P}_2\text{S}_5} 12
\end{align*}
\]

Later, Potts synthesized 12 utilizing a meso-ionic heterocycle 18.\(^{31a,b}\)

\[
\begin{align*}
18 & \xrightarrow{\phi-\text{C}-\phi} 17 \\
& \xrightarrow{\phi-\text{C}-\phi} 12
\end{align*}
\]

In 1976, Cava reported the synthesis of 12 by a base-catalyzed sulfoxide dehydration.\(^{32}\) Due to their instability in \(\text{H}_2\text{O}\), the cis- and trans sulfoxides of 14 and 15 were subjected to base dehydration in benzene solution with vigorous exclusion of oxygen to yield 12. If oxygen is present, the resulting product is the diketone 17.

Physical Evidence for Tetraphenylthieno[3,4-\(\phi\)]thiophene (12)\(^{29}\)

The tetraphenylthieno[3,4-\(\phi\)]thiophene 12 forms a high melting (mp. 257–258°)
purple crystals that are stable indefinitely at room temperature. It is nonpolar in that it can be recrystallized from hexane and elutes from a basic alumina column with hydrocarbon solvents. The $^1$H-NMR spectrum consists of one sharp singlet at 67.12. No ESR signal is observed from benzene solutions of 12 which indicates a singlet ground state. A single crystal x-ray analysis of 12 shows that the thienothiophene nucleus is planar. The phenyl substituents at C-1 and C-4 are rotated out of the plane by 39.6°, the phenyls at C-3 and C-6 are 58.4° out of the plane. In addition, the C-phenyl bond (1.48 Å) corresponds to $sp^2$-$sp^2$ single bonds. The C-5 bonds are shorter than the corresponding bonds in thiophene and the $C_\alpha-C_\beta$ and $C_\beta-C_\beta$ bonds are relatively long.

The reason for the enhanced stability of the tetraphenylthieno[3,4-\(c\)]-thiophene (12) is not very clear. Because the phenyls are rotated out of the thiophene plane, which results in partial orbital overlap, complete resonance stabilization is impossible. Another reason for this stability might be steric hindrance to reaction. Muller carried out additional calculations in a photoelectron spectral study of 12.33 The conclusion was that d-orbitals played no important role in the singlet ground state and that some thienothiophenes could not be isolated due to their high reactivity and not their instability. Therefore, 12 was stable due to steric hindrance to reaction. However, in 1976 Potts reported to have generated 19 and 20 but found that they were unstable and unisolable.34

Other physical studies have been performed on 12. For example, the radical cation and the radical anion of 12 have been studied by ESR and ENDOR spectroscopy.35 Trinajstic calculated the topological resonance energy for 12 and found that it should be less stable than its positional isomers.36
Chemistry of Thieno[3,4-c]thiophene 12

Numerous reactions have been carried out on 12 and all involve addition of reagents across the C-1 and C-3 positions of the thieno[3,4-c]-thiophene system. These reactions include oxidations, reductions, and additions.

Although 12 is stable indefinitely in the solid phase, 12 undergoes oxidation when irradiated in the presence of oxygen. It is believed that 12 is in an excited state and sensitizes the formation of singlet oxygen which adds to the C-1 and C-3 positions of ground state 12 to form a peroxide intermediate 21. This intermediate is unstable and decomposes to give a variety of products.

\[
12 \xrightarrow{hv, O_2} \left[ \begin{array}{c}
\text{S} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \right] \xrightarrow{} \text{21} + 17
\]

Thienothiophene 12 is oxidized to 17 with peracetic acid or m-chloroperbenzoic acid. The reaction of 12 with chromic acid in refluxing acetic acid produced 17 in 60% yield. When 12 is subjected to catalytic hydrogenation in benzene solution with palladium on carbon, the cis-sulfide 16 was obtained in 80% yield.

Several addition reactions have been reported for thienothiophene 12. Methanol added across the 1,3-positions of 12 with a trace amount of H_2SO_4 to afford a methoxy sulfide which is unstable and reverts to 12 upon heating. However, methanol did not add to 12 under basic conditions. N-phenylmaleimide (NPM) added to 12 to give a mixture of exo- and endo-adducts 22 and 23.

\[
12 + \text{NPM} \xrightarrow{} \text{EXO} - 22 + \text{ENDO} - 23
\]
Dimethyl acetylene dicarboxylate (DMAD) added to 12 to produce adduct 24 which underwent spontaneous aromatization by the loss of sulfur to afford benzo[c]thiophene 25 in 80% yield.\textsuperscript{29}

\[
12 + \text{DMAD} \rightarrow 24 \rightarrow 25
\]

**Thieno[3,4-c]pyrrole**

The introduction of a nitrogen atom into the second ring of a fused "nonclassical" thiophene system creates a system represented by only one uncharged structure 26a.

\[
\begin{align*}
26a & \leftrightarrow 26b \\
& \leftrightarrow 26c
\end{align*}
\]

It is likely that the charged resonance forms (26b + c) contribute more to the total structure than 2a due to the greater basicity of nitrogen relative to sulfur. The first example of a thieno[3,4-c]pyrrole was reported by Cava in 1972.\textsuperscript{38} Treatment of the diketone 27 with P\textsubscript{2}S\textsubscript{5} in refluxing toluene afforded a brown solid believed to be a P\textsubscript{2}S\textsubscript{5} adduct 28. The treatment of 28 with hot 10% NaOH afforded heterocycle 29.

\[
\begin{align*}
27 & \xrightarrow{P_2S_5} 28 \\
& \xrightarrow{10\% \text{ NaOH}} 29
\end{align*}
\]
Potts employed a meso-ionic compound 30 to prepare 27 which was converted to 29. However, reaction of 33 with P2S5 produced only 35 arising from the demethylation of 34.

Physical Properties of Thienopyrroles

Thienopyrrole 29 forms bright red high melting crystals. All attempts to recrystallize 29 failed due to its extreme sensitivity to light and air. However, thienopyrrole 31 was stable and could be recrystallized from acetic anhydride. Compounds 29 and 31 exhibited no ESR signal in solution which demonstrated singlet ground states. These findings contradicted earlier studies that thienopyrroles would be unstable and have triplet ground states.

Chemistry of Thienopyrroles

The thienopyrroles 29 and 31 contain the equivalents of both azomethine
and thiocarbonyl ylides, thus offering dipolarphiles, both olefinic and acetylenic, two reactive centers. For the reactions with olefins, it appeared that addition across the pyrrole ring was kinetically favored while addition across the thiophene ring was thermodynamically favored.\textsuperscript{31b}

Thienopyrrole 29 was treated with fumaronitrile in benzene at 80°C for one hour and the fumaronitrile added across the azomethine ylide to afford adduct 36. However, at 110°C for 12 hours, adduct 37 was isolated in 67% yield. When the temperature of the reaction was increased to 140°C, thermal elimination of H\textsubscript{2}S occurred to yield the isoindole 38.

![Adducts 36, 37, and 38](image)

Similar results were obtained by the reaction of thienopyrrole 29 with n-phenylmaleimide (NPM), acrylonitrile, and ethyl acrylate. However, dimethyl acetylene dicarboxylate (DMAD) added across the pyrrole ring of 29 to give adduct 39.

![Adducts 39 and 40](image)

Thienopyrroles 29 and 31 were decomposed by acid but were stable to alkali.\textsuperscript{24} Thienopyrrole 29 underwent catalytic hydrogenation with palladium on carbon to afford the cis-thiophene 40. Thienopyrrole 31 underwent oxidation with peracetic acid to afford a mixture of diketone 17 and its mono-n-phenylimine 41.

\[
\begin{align*}
29 + \text{CH}_3\text{CO}_3\text{H} &\rightarrow 17 + \text{41} \\
\end{align*}
\]

Other Systems

Over the past five years, many other heterocycles containing a "nonclassical" thiophene nucleus have been synthesized. They are listed in the following table for easy reference.
<table>
<thead>
<tr>
<th>Condensed Thiophene</th>
<th>Starting Material</th>
<th>RXN Conditions</th>
<th>Product Stable</th>
<th>Adducts Formed</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Condensed Thiophene 1" /></td>
<td><img src="image2" alt="Starting Material 1" /></td>
<td>$\text{Ac}_2\text{O}, \Delta$</td>
<td>No</td>
<td>DMAD</td>
<td>24</td>
</tr>
<tr>
<td><img src="image3" alt="Condensed Thiophene 2" /></td>
<td><img src="image4" alt="Starting Material 2" /></td>
<td>$\text{P}_2\text{S}_5, \text{Pyr}, \Delta$</td>
<td>Yes</td>
<td>DMAD, Dimethylmalate</td>
<td>42</td>
</tr>
<tr>
<td><img src="image5" alt="Condensed Thiophene 3" /></td>
<td><img src="image6" alt="Starting Material 3" /></td>
<td>$\text{P}_2\text{S}_5, \text{Pyr}, \Delta$</td>
<td>Yes</td>
<td>DMAD, NPM</td>
<td>43, 44</td>
</tr>
<tr>
<td><img src="image7" alt="Condensed Thiophene 4" /></td>
<td><img src="image8" alt="Starting Material 4" /></td>
<td>$\text{P}_2\text{S}_5, \Delta$</td>
<td>Yes</td>
<td>NPM</td>
<td>45</td>
</tr>
<tr>
<td><img src="image9" alt="Condensed Thiophene 5" /></td>
<td><img src="image10" alt="Starting Material 5" /></td>
<td>$\text{Ac}_2\text{O}, \Delta$</td>
<td>No</td>
<td>NPM, DMAD</td>
<td>46</td>
</tr>
<tr>
<td><img src="image11" alt="Condensed Thiophene 6" /></td>
<td><img src="image12" alt="Starting Material 6" /></td>
<td>$\text{Ac}_2\text{O}, \Delta$</td>
<td>Yes</td>
<td>DMAD, NPM</td>
<td>47, 48</td>
</tr>
</tbody>
</table>

*R=\emptyset, R_1=H or R=\text{CH}_3, R_1=H or R=\emptyset, R_1=\text{Me}
<table>
<thead>
<tr>
<th>Condensed Thiophene</th>
<th>Starting Material</th>
<th>RXN Conditions</th>
<th>Product Stable</th>
<th>Adducts Formed</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Condensed Thiophene" /></td>
<td><img src="image2" alt="Starting Material" /></td>
<td>Ac₂O, Δ</td>
<td>No</td>
<td>NPM, DMAD</td>
<td>49</td>
</tr>
<tr>
<td><img src="image3" alt="Condensed Thiophene" /></td>
<td><img src="image4" alt="Starting Material" /></td>
<td>S₂Cl₂, DMF</td>
<td>Yes</td>
<td>---</td>
<td>50</td>
</tr>
<tr>
<td><img src="image5" alt="Condensed Thiophene" /></td>
<td><img src="image6" alt="Starting Material" /></td>
<td>S₂Cl₂, DMF</td>
<td>Yes</td>
<td>---</td>
<td>51</td>
</tr>
<tr>
<td><img src="image7" alt="Condensed Thiophene" /></td>
<td><img src="image8" alt="Starting Material" /></td>
<td>S₂Cl₂, DMF</td>
<td>Yes</td>
<td>---</td>
<td>52</td>
</tr>
<tr>
<td><img src="image9" alt="Condensed Thiophene" /></td>
<td><img src="image10" alt="Starting Material" /></td>
<td>P₂S₅, Pyr, Δ</td>
<td>Yes</td>
<td>NPM, Fumaronitrile</td>
<td>28,29</td>
</tr>
<tr>
<td><img src="image11" alt="Condensed Thiophene" /></td>
<td><img src="image12" alt="Starting Material" /></td>
<td>P₂S₅, Pyr, Δ</td>
<td>Yes</td>
<td>NPM</td>
<td>44</td>
</tr>
<tr>
<td><img src="image13" alt="Condensed Thiophene" /></td>
<td><img src="image14" alt="Starting Material" /></td>
<td>P₂S₅, Pyr, Δ</td>
<td>No</td>
<td>Dimer</td>
<td>44</td>
</tr>
<tr>
<td><img src="image15" alt="Condensed Thiophene" /></td>
<td><img src="image16" alt="Starting Material" /></td>
<td>Ac₂O, Δ</td>
<td>No</td>
<td>NPM</td>
<td>41</td>
</tr>
</tbody>
</table>

R = CH₃ or CO₂Me
### Conclusion

The synthesis and chemistry of "nonclassical" condensed thiophenes has greatly contributed to the understanding of tetracovalent sulfur heterocycles.

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Studies on the Kinetics and Mechanism of the Reactions of Ketones and Esters with sec-Butyllithium

Reported by Munther Al-Aseer

June 25, 1981

The addition reactions of organolithium reagents\(^1\) to carbonyl compounds (aldehydes,\(^2\) ketones,\(^2\) esters,\(^3\) carboxylic acids\(^4\)) have found wide synthetic utility in the recent past due primarily to the greater versatility of such reagents relative to the corresponding Grignard reagents.\(^5\) Reactions of lithium reagents with hindered ketones and esters usually give high yields of the tertiary alcohols at the expense of reduction and enolization by-products so troublesome in comparable Grignard preparations.\(^3\)

Until recently little research had been carried out on the kinetics and mechanisms of the reactions of ketones and esters with organolithium reagents. In an early study, Swain\(^6\) found that the reaction of phenyllithium with Michler’s ketone in ether-toluene solvent is nearly first order in phenyllithium. Smith and coworkers\(^7\) employed UV and IR stopped-flow spectrophotometric techniques\(^8\) to investigate the reaction of ketones and esters with methyl-lithium in diethyl ether. They reported that the reaction was one-fourth order in alkyl lithium and first order with respect to ketone. The data were said to be consistent with a mechanism involving predominant reaction through monomeric methyl lithium which is in equilibrium with tetrameric methyl lithium.

\[
\text{Scheme I}
\]

\[
(CH_3Li)_4 \xrightleftharpoons[\text{K}]{\text{4CH}_3\text{Li}} \text{Substrate} + \text{CH}_3\text{Li} \xrightarrow{k} \text{Product}
\]

\[
\text{Rate} = kK[(CH_3Li)_4]^{1/4}[\text{Substrate}]
\]

Many of the reactions of organolithium reagents with organic compounds in aromatic and ethereal solvents are thought to occur through monomeric organolithium in equilibrium with higher aggregates.\(^9\) In contrast, the direct attack of aggregated lithium reagent on substrate (in addition to attack by monomer) is thought to be the basis for the first order dependence on reagent found for many reactions in aliphatic solvents.\(^10\) Allison and Smith\(^7c\) observed shifts in the UV maximum and IR carbonyl stretching frequency of ketones and esters to longer wavelengths upon mixing with cyclopentyl lithium in cyclohexane. They attributed these shifts to complex formation between the carbonyl compound and lithium reagent aggregates. The rates of disappearance of esters and ketones were found to be either independent or inversely dependent on reagent concentration. A mechanism in which ketone complex or ester complex can rearrange to products and free ketone or free ester can react with monomeric cyclopentyl lithium to give products was proposed.

In the present study, infrared stopped-flow spectrophotometry has been employed to examine the kinetics of the reactions of a series of substituted aromatic ketones 1 and esters 2 with sec-butyllithium in cyclohexane at 25°C.
Infrared scans of reacting solutions of all compounds indicated formation of substrate-sec-BuLi tetramer complexes. Esters exhibited larger IR shifts (20-35 cm⁻¹) than did ketones (10-20 cm⁻¹) upon mixing with sec-BuLi. The magnitude of the shift for ketones and esters increased as the ring substituent became more electron-donating. The observed first order rate constant, under conditions of excess reagent, was found to vary in its dependence on sec-BuLi concentration with the electronic nature of the substituent. Electron-withdrawing substituents led to the common behavior of increasing pseudo-first order rate constants with increasing reagent concentration. Electron-donating substituents gave rise to a maximum rate constant followed by a decrease in rate constant with larger reagent concentrations. The experimental rate data for ketones are accommodated by a previously proposed mechanism⁷c for the reactions of ketones with organolithiums in which monomeric and aggregated reagent species participate in a competitive fashion.

Scheme II

\[
\begin{align*}
\text{(sec-BuLi)}_4 & \xrightarrow{\text{fast}} 4 \text{ sec-BuLi} \\
\text{(sec-BuLi)}_4 + \text{ketone} & \iff \text{sec-BuLi}_4 \cdot \text{ketone} \iff \text{Product}
\end{align*}
\]

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Intramolecular N-acyliminium ion cyclizations

Reported by Bruce C. Hamper
June 29, 1981

Iminium ions have the potential of initiating intramolecular cyclizations in the construction of alkaloids and other nitrogen heterocycles. An iminium ion intermediate, once generated, can undergo electrophilic addition to an activated aryl substituent or an active methylene group. (Fig. 1) Such methodology is limited by difficulties in the preparation of the necessary iminium ion precursor, poor regio- and stereoselectivity and low reactivity of the iminium ion. These problems have been circumvented in specific cases by the formation of the more reactive N-acyliminium ion. Notable examples include the synthesis of erythrina, lycopodine, aspidosperma and eserine alkaloids.

Following the observation by Speckamp in 1971 that the reduction of succinimides leads to an amidecarbinol, a useful precursor of N-acyliminium ions, the importance of these intermediates in cationic initiated cyclizations increased steadily. (Eq. 1) The ability to

\[
\begin{align*}
\text{R} & \quad \text{NaBH}_4, \text{pH}=8 \\
\text{R} & \quad \text{HCOOH} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

generate N-acyliminium ions regiospecifically from imides is important for the formation of azabicyclics and 1-azaspirans -- two techniques to be discussed which have been employed with success in the stereocontrolled synthesis of natural products.

The well-known biomimetic cyclizations of carbocations with olefins need not be restricted to the carbocyclic field. Cyclic N-acyliminium intermediates have been shown to initiate cyclizations with unactivated olefins or acetylenes to afford bridgehead nitrogen heterocycles in excellent yields. The substituted imide may be prepared by the classical method of the condensation of the appropriate primary amine with a dicarboxylic acid or anhydride or by the more recent oxidation-reduction procedure of Mitsunobu. (Eq. 2)
Formation of the N-substituted imide, 1,

![Chemical structure](image)

takes place at room temperature in high yields. Reduction of the imide with NaBH₄/H⁺ in ethanol affords the ethoxylactam, 9 2, which on treatment with formic acid at room temperature yields the bicyclic product, 3. (Scheme 1, Table 1). 10, 11

![Scheme I](image)

Alternatively the hydroxylactam can be generated by the addition of an alkyl Grignard to the carbonyl functionality (Scheme II) to form a quaternary bridgehead carbon atom in the cyclic product.

![Scheme II](image)

These cyclizations typically show a high degree of stereoselectivity which has been rationalized in terms of a concerted, six-member transition state as shown in Figure 2. Concerted anti-addition across the double bond accounts for the retention of the olefin geometry. The possibility of nearly synchronous bond formation is supported by the observed stereoselectivity in the majority of the cases studied. However, if R₁ is a methyl group a 1:1 mixture of the two possible epimers is obtained. Clearly, attachment of an alkyl group at the vinylic carbon developing positive charge will stabilize an intermediate carbocation which can lead to a loss of stereochemistry.
Table 1
N-acyliminium ion cyclizations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imide</th>
<th>Product</th>
<th>Scheme I (R=H) Yield</th>
<th>Scheme II (R=CH₃) Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Imide 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>90%</td>
<td>71%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Imide 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Imide 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>78%</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Imide 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

1:1 mixture
Subsequently it was found that imides containing both an aryl substituent and an olefinic substituent can give rise to tetracyclic products in a stereospecific manner and excellent yields.\textsuperscript{11,12} (Table 2) All of the imides investigated led to products retaining the olefinic geometry of their precursors. This is especially surprising in the case of entry 3 in which only one epimer is formed. In the analogous olefin cyclization (see entry 4, Table 1) the olefinic geometry was lost. Evidently the aryl substituent, which serves as an internal nucleophile, affords greater selectivity than the corresponding olefin cyclizations.

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imide</th>
<th>Product</th>
<th>Scheme I (R=H)</th>
<th>Scheme II (R=CH\textsubscript{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>&gt;95%</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>&gt;95%</td>
<td>41%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>89%\textsuperscript{b}</td>
<td>93%\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} all cyclizations were performed with HCOOH, except as noted
\textsuperscript{b} 10\% CF\textsubscript{3}CO\textsubscript{2}H/CH\textsubscript{2}Cl\textsubscript{2}
\textsuperscript{c} CHCl\textsubscript{2}COOH
\textsuperscript{d} not optimized

The cyclization of N-acyl iminium ions containing an acetylene moiety can potentially give rise to two different ring size bicyclic products corresponding to a formal x-endo-dig or (x-1)-exo-dig ring closure.\textsuperscript{13} (Fig. 3) For the case of a terminal acetylene, R=H, the x-endo-dig cyclization product is obtained. The authors rationalize this behavior in terms of the comparative
energies of a primary vs. secondary vinyl cation.\textsuperscript{14} The formation of products 6a and 6b are considered to arise via cationic transition states 5a and 5b respectively. Transition state intermediate 5a, which is formally a primary vinyl cation (R=H), would be expected to be of higher energy than secondary vinyl cation 5b.\textsuperscript{14b} Therefore the formation of 6-endo-dig product 6b from 4 will have a lower energy of activation, favoring this cyclization mode.

Methyl acetylenes (R=CH\textsubscript{3}) are electronically unbiased since both 5a and 5b are secondary vinyl cations and consequently may be expected to give rise to both products. However

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure3}
\caption{Figure 3}
\end{figure}

(x-1)-exo-dig cyclization predominates in all instances except for the formation of the most strained azabicyclo [5.5.0] product (see Entry 3, Table

\begin{table}
\centering
\caption{N-acyliminium-acetylene cyclizations}
\begin{tabular}{cccc}
\hline
Imide & (x-1)exo-dig, 3a & x-endo-dig, 3b & Entry & n & R & yield & 3a/3b \\
\hline
 & & & & 1 & H & 97\% & 0:100 \\
 & & & & 2 & H & 88\% & 0:100 \\
 & & & & 3 & CH\textsubscript{3} & 91\% & 10:90 \\
 & & & & 4 & CH\textsubscript{3} & 92\% & 85:15 \\
 & & & & 5 & H & 92\% & 0:100 \\
 & & & & 6 & H & 86\% & 0:100 \\
 & & & & 7 & CH\textsubscript{3} & 90\% & 100:0 \\
 & & & & 8 & CH\textsubscript{3} & 90\% & 100:0 \\
\hline
\end{tabular}
\end{table}
For methyl acetylenes both transition states 5a and 5b are secondary vinyl cations and therefore the preferred cyclization mode would be determined by the difference in activation energies to form the bent or linear vinyl cation. According to ab initio calculations, vinyl cations prefer a linear geometry as in 5a over bent structure 5b.\textsuperscript{16} Although this rationale is supported by the observed results, analogous studies of carbocyclic systems have led to alternative proposed transition state models to account for the cyclized products.\textsuperscript{17}

The synthetic utility of the acetylene cyclization has recently been demonstrated in the short total synthesis of mesembrine, epi-dihydromaritidine and dihydromaritidine.\textsuperscript{18} Synthesis depends on two key steps; the regioselective reduction of the disubstituted succinimide and stereoselective ring closure affording the desired bicyclic ketalactam. Earlier studies of succinimides revealed the general principle that reduction occurs at the carbonyl group adjacent to the more substituted α-carbon.\textsuperscript{19} A 1:4 mixture of the mesembrine precursors 8 and 9 respectively was obtained by NaBH\textsubscript{4} reduction. Ring closure lead to the desired bicyclic amide-ketone, 10 in 85% yield. (Fig. 4)

1-Azaspirans have been obtained from the addition of the appropriate Grignard reagent to an imide followed by formolysis.\textsuperscript{20} As observed previously in the addition of methyl Grignard to imides, only fair yields of the addition products were obtained. In the case of glutarimides further complications arise from the facile ring opening of the addition product to an open chain amide-ketone. Despite these drawbacks two groups simultaneously reported the formal synthesis of perhydrohistrionicotoxin, 13, using the Grignard addition-cyclization approach outlined, in part, in Figure 5.\textsuperscript{21}
Although both groups report similar yields of the spiroamide 11, their observations of the product composition differ. Two different cyclization pathways can be envisaged leading to either the 6,6-spiro amide 11, or 6,5-spiroamide 12. Previously it was observed that 6-endo-trig cyclization occurred for unbiased olefins. Consequently it comes as no surprise that Schoemaker observed a 30% yield of 11 with less than 0.5% of either of the epimers of 12.21a Evans, in his analogous study reports a 40% and 30% yield of 11 and 12 respectively.21b To further complicate matters, if 3,5-morpholinedione 14 is substituted for glutarimide in the Grignard-addition-cyclization only the stereoselective 5-exo-trig ring closure is observed.22 Apparently, small changes in either the experimental conditions or the substrate can have a profound influence on the product composition.

Gephyrotoxins, a class of alkaloids derived from poison-dart frogs have recently received attention as synthetic targets due to their unusual neurological properties.23 Total synthesis of depentylerperhydrogephyrotoxin, 16, has been achieved utilizing N-acyliminium ion cyclizations.24 (Fig. 6)
The tricyclic lactam 18 is formed stereospecifically from 17 in 85% yield. Cyclization can proceed through six-member chain transition state 19 or 20 (Fig. 7) to form 18 and 21 respectively, however only 18 is observed as the product. The activation energy is less for the cyclization of 19 to 18 due to unfavorable development of A₁,₃ strain between the cyclohexane ring and the carbonyl group in the formation of 21. Consequently a high yield of the desired tricyclic lactam 18 is obtained.

In conclusion, N-acyliminium ions have been shown to afford intramolecular cyclization with unactivated olefins and acetylenes in a stereo-selective manner. Model studies have shown these cyclizations to possess a high degree of predictability in the formation of two or more chiral centers. N-acyliminium ions will doubtless continue to play an important role in the synthesis of alkaloids and other nitrogen heterocycles.

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Synthetic Approaches to the Isocomene and Modhephene Sesquiterpenes

Reported by Steve Ashburn
July 2, 1981

Recently two novel classes of carbocyclic sesquiterpenes have been isolated, 1-14 of which (-)-isocomene (1) and (-)-modhephene (2) are examples. As can be seen in the latter cases, these molecules possess triquinane and propellane skeletons, respectively, which heretofore have been unencountered in natural products. A biogenetic scheme has been proposed for isocomene, modhephene and others from β-caryophyllene (3).1d

These unusual hydrocarbons recently have attracted considerable synthetic interest. (1)-Isocomene has been synthesized by Oppolzer,15 Pirrung,16 Paquette,17 Dauben,18 and Wender19 in that order. (2)-Modhephene has been synthesized by Smith20 and Paquette.21 Thus is the extent of synthetic work among these rapidly expanding classes of sesquiterpenes. Three of the above syntheses, however, are of proven general use in the construction of the triquinane and propellane skeletons, as well as short, elegant and high-yielding. The work of Smith and Pirrung involves the Cargill rearrangement22 and its carbocationic equivalent, respectively, as the key step. Thus, a simple two-step sequence of photochemical [2+2] cycloaddition to an enone followed by acid-catalyzed rearrangement affords stereoselectively the modhephene skeleton in the first case and stereospecifically in the latter example. The recent work of Wender on arene-olefin cycloadditions19,23 provides yet another elegant two-step cycloaddition-rearrangement sequence to the isocomene skeleton (eq. 1). This intramolecular version24 of

\[
\text{[\text{arene-olefin cycloaddition}] \quad \text{hv} \quad \text{[\text{1:1}} \quad \text{240°}} \quad \text{(1)}
\]

the arene-olefin cycloaddition reaction23 provides stereospecifically SIX chiral centers at once! Thermolysis of the resulting mixture produces dehydroisocomene which is hydrogenated to isocomene (1). Wender has also used this reaction in a short synthesis of α-cedrene.23

The intramolecular photochemical cycloaddition reaction is rare in natural products synthesis; other than the aforementioned work of Pirrung16 and Wender19,23 and an attempted synthesis of cedrene,26 it has appeared only recently in Oppolzer's longifolene synthesis27 and his studies on the tricyclo[6.2.1.0^1^5\]undecane skeleton (e.g., the gibberellins and zizaanes).28

It appears that the intramolecular [2+2] photochemical cycloaddition reaction of enones followed by acid-catalyzed rearrangement as well as arene-olefin photocycloaddition reactions followed by thermal rearrangement provide short, high-yielding and stereoselective routes to the isocomene and modhephene skeletons and other carbocyclic terpenoids having bridged structural features.
The latter reactions are especially elegant in that six chiral centers are stereospecifically generated in a manner adaptable to many of the title compounds as well as other terpenoids of novel and interesting structure.

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ORGANIC SEMINAR ABSTRACTS

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SEMINAR TOPICS
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The Synthesis and Biological Activity of Tricyclic Nucleosides
   Related to Tubercidin, Toyocamycin, and Sangivamycin........1
   M. A. Rossman

Electrochemical Fluorinations........................................3
   Dale Kiesewetter

Recent Synthetic Approaches to the Ansamycin Antibiotic
   Maytansine.............................................................5
   Doug Phillipson

The Use of Carbohydrates for the Synthesis of Natural Products.....14
   Marietjie Potgieter

Synthetic Approaches to the Prelog-Djerassi Lactone..............23
   Michael S. Dappen

Synthesis of Chiral Secondary Alcohols from Aldehydes and
   Ketones Using Chiral Ligands......................................32
   Raju Mohan

Ketene Dithioacetals in Organic Synthesis............................41
   Mike Hermata

Bifunctional DNA Intercalators as Potential Biological Probes
   and Medicinal Agents..................................................50
   Scott Daniels

Mechanistic Aspects of Polymer Supported Catalysis in Triphase
   Systems..........................................................................58
   David R. Hay

N-Glycosylation of N-Heterocycles....................................67
   Tom Stevenson

Tetronic Acids and Tetramic Acids.....................................69
   Srinivasan Nagarajan

Chemical Applications of Ultrasound..................................71
   Charles Little
THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF TRICYCLIC NUCLEOSIDES
RELATED TO TUBERCIDIN, TOYOCAMYCIN, AND SANGIVAMYCIN

Reported by M. A. Rossman

September 10, 1981

The synthesis of tricyclic nucleosides is a relatively new area of nucleoside research. Interest in this field was generated by the isolation and structure determination of the nucleoside Wybutosine (1). Wybutosine was determined to reside at the 3' end of the anticodon of yeast tRNA^Phe.

The unique tricyclic structure of 1 generated considerable interest in the design and synthesis of other closely related tricyclic nucleosides. The preparation of some tricyclic nucleosides has been accomplished by chemical modification of natural purine ribosides. Leonard and coworkers have treated adenosine and guanosine with chloroacetaldehyde to afford 1,N^6-etheno-adenosine and 1,N^2-etheno-guanosine. The addition of chloroacetaldehyde occurred across the 1- and N^6-positions of adenosine and the 1- and N^2-positions of guanosine to afford the etheno-purine ribosides. Other interesting tricyclic nucleosides were afforded by treating guanosine with malondialdehyde and methyImalondialdehyde in which addition occurred across the 1- and N^2-positions of guanosine. Most of these tricyclic nucleosides have possessed characteristic fluorescent properties which have made them useful in biochemical studies.

Townsend and coworkers have synthesized several tricyclic nucleosides by modification of the aglycone moiety of Tubercidin (2a), Toyocamycin (2b), and Sangivamycin (2c). This review will provide an analysis of the synthetic strategy used for the chemical modification of these nucleoside antibiotics to afford new tricyclic nucleosides (3,4,5,6,7).

Townsend utilized three synthetic approaches in the syntheses of the tricyclic nucleosides 3-7. First, heteroannulation across the 5- and 6-positions of 2a, 2b, and 2c afforded nucleosides 3,10a,b,6,11 and 2d.12 In the second approach, heteroannulation across the 1- and 4-positions of 2a, 2b, and 2c afforded nucleosides 5a-c.13 Several other tricyclic nucleosides containing fused tetrazole and triazole rings have been prepared in this manner.14,15,16,17 Finally heteroannulation across the 4- and 5-positions of 2a afforded the nucleoside 4.18

Several of these nucleosides showed moderate in vitro cytotoxicity against L-1210 mouse leukemia cells.10b,13,18
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ELECTROCHEMICAL FLUORINATIONS

Reported by Dale O. Kiesewetter  September 28, 1981

Organofluorine chemistry has been of significant interest due to the chemical, thermal, and electrical stability of perfluoro compounds in industrial applications$^1$ and to the altered chemical reactivity$^2$ and biological function$^{2a,3}$ for compounds in which fluorine replaces hydrogen.

The synthesis of organofluorine compounds has been more difficult than the synthesis of other organic halides due to the low nucleophilicity but high basicity of fluoride and to the limited availability of electrophilic fluoride sources. Electrochemical fluorination allows substitution of hydrogen and halogens by fluorine and addition of fluorine to functional groups. Proper control of reaction conditions allows for high selectivity. Electrochemical fluorination will be compared to other methods and proposed mechanisms will be discussed.

Perfluorinated molecules have been prepared electrochemically$^4$ and by high valency metal fluorides at elevated temperatures.$^5$ Hydrocarbons or any functionalized molecule can serve as the substrate; however, simpler substrates generally give higher yields with retention of carbon skeleton. Functional groups are generally cleaved, though chloride is partially retained in both methods and acid and sulfonyl halides are retained in electrolysis as the fluoride. Perfluoro cyclic ethers are formed from alcohols and acids which contain a chain of four or more carbons.$^{4b,6}$ These methods are utilized in industry.$^1$

Selective fluorination of suitably functionalized molecules with reagents providing fluoride or with the electrophilic reagents CF$_3$OF and FCIO$_3$ have been the subject of reviews.$^{2a,2b,7}$ Selective electrochemical fluorination has been achieved with aromatic compounds utilizing fluoride salts in acetonitrile$^8$ and with simple alkyl bromides in HF.$^9$

Fluorination of aromatic compounds in acetonitrile at potentials below that required for fluoride oxidation is believed to proceed by a direct mechanism which involves initial formation of the radical cation followed by fluoride trapping.$^8a$ The variable reactivity of radical cations toward substitution with different nucleophiles led to a debate between Eberson$^{10}$ and Rozhkov$^{8a,11}$ as to the allowedness of fluoride attack on an aromatic radical cation. King has explained this variable reactivity as competition between frontier orbital control and charge density control.$^8d$

Fluorinations in HF are also explained by the direct mechanism due to the formation of rearrangement products from electrolysis of alkyl bromides$^9$ and alkyl fluorides.$^{12}$ A similar ionic mechanism has been proposed for a controlled potential fluorination of propane.$^{13}$
However, indirect mechanisms, which involve participation of the metal electrodes via high valence states, complex formation, or adsorption phenomenon and radical fluorine, are proposed at potential above that required for fluorine evolution. Indirect mechanisms are supported by an induction period characterized by anode corrosion, fluorine evolution, and lack of organic incorporation of fluorine. Studies of fluorine evolution, anode material, and anode corrosion have not yielded definitive conclusions.

The most encouraging aspect of the method is the ability to selectively oxidize the functional group of lowest oxidation potential by control of the anode potential. High yields of desired product are dependent on the stability of the intermediate and the nucleophilicity of fluorine. Deficiency of both factors has been observed which will limit the synthetic utility of the electrochemical method.

BIBLIOGRAPHY

RECENT SYNTHETIC APPROACHES TO THE ANSAMYCIN ANTIBIOTIC MAYTANSINE

Reported by Doug Phillipson

October 8, 1981

Maytansine, 1, the first of a number of related ansamycin antibiotics, was isolated by M. S. Kupchan et al. and Wani et al. and its structure was determined by an X-ray analysis of the 9-O-(3-bromo)-N-propyl ether in 1972. Maytansine possesses significant anti-leukemic activity toward P-388 mouse leukemias at the microgram per kilogram level and has in vivo tumor inhibitory activity as well. Clinical trials in humans which began in 1976, provided considerable stimulus for the development of a synthetic route to 1. Although more recent developments, including the microbial production of a precursor and disappointing clinical trials, have alleviated the need for an efficient preparation of 1, the intellectual and experimental challenge of this synthesis has drawn the attention of a number of groups accomplished at total synthesis. The synthesis of maytansine requires control of stereochemistry at seven chiral centers and maintenance of the integrity of sensitive functional groups along with the construction of a nineteen-membered macrocyclic ring.

The initial efforts of six different groups directed toward the solution of these problems were reviewed by Bartlett. Subsequently and recently, Meyers and Corey completed syntheses of racemic and natural maytansine respectively. The work of these groups is representative of the most efficient approaches to maytansine to date, therefore this work has been chosen for detailed examination. Recent work of Isobe, which involves a retrosynthetic approach quite different from Meyers' or Corey's, will also be discussed.

A retrosynthetic analysis of the successful synthesis of racemic maytansine by Meyers is given in Scheme I. The ansa ring of maytansinol, 2, can be formally opened to give an acyl anion, ester 3, with protecting groups in place of the carbanolamide ring. Disconnection of 3 leads to an aromatic

Scheme I
vinyl anion \(4\) and an aldehyde \(5\). The aromatic portion of \(4\) can be disconnected from the diene segment to give a phenyl anion \(6\) and a diene bromide \(7\). The aldehyde \(5\) can be disconnected to the less complex aldehyde \(9\) and a protected formyl dithio ketal synthon \(8\).

For comparison, a retrosynthetic analysis of Corey's approach is given in Scheme II. Disconnection of the N-methyl-N-acetyl-(1)-alanine residue

**Scheme II**

from carbon 3 of maytansine, and functional group interconversions to remove the epoxy oxygen and to replace the carbinolamide hydroxyl with a methoxyl group, give the macrocyclic alcohol \(10\). Ring opening at the amide bond and additional interconversions to protect the hydroxyl and carbinolamide functions give the amine, ester \(11\). Disjunction of \(11\) yields the \(\alpha,\beta\) unsaturated aldehyde \(12\) and the chiral sulfone anion \(13\). Aldehyde \(12\) is disconnected to give aldehyde \(14\) which in turn is disconnected to the diene aldehyde \(15\) and the anion of the dithane \(16\). The dithiane, \(16\), is obtained from tri-O-acetyl-D-glucal, \(17\), as the ultimate source of carbons six and seven in \(1\).

A third retrosynthetic approach has been offered by Isobe in a paper which described some exploratory work on the synthesis of potential maytansine intermediates. A retrosynthetic analysis which deals with most of the asymmetric centers is reproduced in Scheme III. Disconnection of \(1\) between

**Scheme III**
the epoxide carbons and the olefinic bond closest to the methoxyl group gives a synthon, \( \lambda_8 \). After a number of interconversions, \( \lambda_8 \) could be simplified to the reagent \( \lambda_9 \). Retrosynthetic ring closure affords the acetal, \( \lambda_19 \) which can be seen as originating from D-mannose, \( \lambda_21 \). The analyses presented above all differ in the actual disconnections made to obtain simpler structures, but in each approach, maytansine is disconnected to yield parts which contain the aromatic and associated achiral functionality and a chiral component which contains the correct stereochemistry at carbons corresponding to C6 and C7 of \( \lambda_1 \).

Analysis of Corey's synthesis suggests a deliberate plan to introduce chiral centers one reaction at a time using asymmetric induction techniques to minimize epimer formation. In Meyer's approach there are also some reactions in which stereochemical control might be achieved but others where any asymmetric induction appears unlikely. In a practical synthesis of maytansine it would be desirable to introduce as many of the asymmetric carbons as possible in one unit and Isobe's analysis appears to do this well. One might expect the ring opening disconnections to cause problems in the synthetic direction. High dilution techniques proved sufficient to provide acceptable yields of the cyclized products in each case.

The syntheses of maytansine by Meyers and Corey contain a number of interesting reactions which solved the problems encountered en route to the final product. The key reactions from these syntheses will be discussed in this review.

The coupling proposed by Meyers between the vinyl anion \( \lambda_4 \) and the epoxy aldehyde \( \lambda_5 \) necessitated the synthesis of the diene bromide, \( \lambda_24 \), as shown in Scheme IV. The replacement of a phenolic hydroxyl by chloride using oxalyl chloride to form \( \lambda_23 \) from \( \lambda_22 \) is of interest. The reaction, which probably proceeds by an SN\(_2\)Ar mechanism, fails for phenols without electron withdrawing groups.\(^{10}\) The second reaction worthy of note is the modified Hunsdiecker replacement of an aryl carboxyl group by bromine in the conversion of \( \lambda_24 \) to \( \lambda_25 \). Meyers was able to obtain an acceptable yield of the aryl bromide \( \lambda_25 \) whereas most benzoic acid derivatives give vanishingly small yields using this procedure.\(^{12}\)
In Scheme V is outlined the coupling of \( \text{27} \) and \( \text{5} \) followed by elaboration of the coupling product to maytansinol, \( \text{28} \). The synthesis of racemic \( \text{5} \) was initially accomplished in 15 steps from methallyl alcohol in an overall yield of 3-6%. More recently a very efficient synthesis of optically active \( \text{5} \) has been accomplished and that sequence will be discussed at the conclusion of the description of Meyers synthesis of racemic maytansinol. The coupled product, \( \text{28} \) was desilylated to the corresponding amine alcohol which was treated with tert-butoxymagnesiumbromide and 1-L'- (azodicarboxyldipiperidine according to the method of Narasaka et. al. to give the aldehyde \( \text{29} \). Ring closure of \( \text{30} \) was effected in reasonable yield using a Claisen condensation run at high dilution. In the final elaboration of \( \text{31} \) to \( \text{32} \) it was found to be important to remove the dithioketal before hydrolysis of the ethoxymethyl protecting group. The keto function which resulted from the thiketol was shown to stabilize the allylic methoxyl group toward the aqueous acid. Addition of phenyl chloroformate to the deprotected hydroxyl of \( \text{31} \) followed by treatment of the carbonate with excess ammonia yielded the carbinolamide, \( \text{32} \) with correct relative stereochemistry. It was known from Kupchan's derivatization reactions that the carbon bound to nitrogen in the carbinolamide function did not epimerize. Reduction of \( \text{32} \) afforded \( \pm \) maytansinol which was separated from a mixture of C3 and C10 epimers.

After synthesizing racemic maytansinol, Meyers turned his efforts toward an efficient synthesis of the natural compound. To that end, optically active \( \text{5} \) was recently synthesized as shown in Scheme VI. The ultimate starting
material, 3-hydroxy-2-(S)-methyl propionic acid, was transformed to the aldehyde 33 in five steps. The aldehyde 33 was treated with the lithium anion of N-cyclohexylpropylimine in a directed aldol reaction to give, after

oxalic acid hydrolysis, the α,β unsaturated (E) aldehyde 34 which was reduced to the allylic alcohol 35. Reaction of 35 with t-butyl hydroperoxide in the presence of L-(+)-diethyltartrate and titanium tetraisopropoxide gave the epoxide 36 with >99% ee. Epoxidation of the opposite face of the double bond in 35 could have been achieved by substitution of the enantiomeric tartrate ester in the reaction mixture. A mechanism which accounts for the observed asymmetric induction, which Sharpless has demonstrated to be general for allylic alcohols, was not given. Stereochemical control was also observed in the addition of lithium dithioacetate to the aldehyde 37. The isomer predicted by Cram's rule predominated, giving a 10:1 mixture of 38 and the epimeric alcohol. Past experience with this reaction indicated that lower temperatures were effective in increasing the enantiomeric excess of the product ratio. After protection of the hydroxyl of 38, thiophilic attack at the carbonyl sulfur by ethyl grignard reagent gave an intermediate dithioketal anion which was formylated in situ with 2-(N-formyl-N-methyl) aminopyridine to give (+) 39 as a mixture of diastereomers due to the chiral center of the ethoxyethyl group. The elegance of this sequence is more apparent when one considers that the only chromatographic purification employed to separate diastereomers in the sequence was a separation of 38 from its epimer.

Corey's synthesis of optically active maytansine made use of the sugar derivative tri-O-acetyl-D-glucal as the chiral precursor for the dithiane 40. The glucal was transformed into the dihydroxy acetal, 39 in three unremarkable steps. Treatment of diol 39 with sodium hydride followed by triisopropyl benzene sulfonylimidazole gave the epoxide 40. Corey's procedure is a modifi-
cation of an epoxidation of a similar system carried out by Hicks and Fraser-Reid who employed tosylimadizole to achieve similar stereoselectivity in their epoxidation of methyl 4,6-O-benzylidene-α-D-glucopyranoside. They isolated the intermediate tosylate and found that only one of the vicinal hydroxyls was sulfonylated. However, when Corey allowed to react with tosylimadizole, he obtained a 50:50 mixture of α and β epoxides. These results suggest that the stereoselectivity observed in the formation of is a result of selective sulfonilation followed by displacement of the leaving group by the vicinal alkoxy ion. The synthesis of 16 was completed using a dimethyl cuprate addition to the epoxide 14, giving the diaxial product 15. Ring opening of the acetal in the presence of propane-1,3-dithiol followed by protection of the hydroxyl groups yielded 16 as shown in Scheme VII.

The diene aldehyde 15, previously prepared by Corey, Meyers and Bernauer, reacts with the dithiane anion of 16 to provide 42 as a 1:1 mixture of diastereomers. After chromatographic separation of the diastereomers, epimerization of 42 was achieved through an oxidation reduction sequence to give 42 in 85% overall yield. The aldehyde, 14 obtained as outlined in Scheme VIII, was homologated to the enol 12 using a modified directed aldol reagent devised by Corey for this application. The final two carbons of the anza bridge were introduced using a slight modification of Mioskowski and Solladie's chiral sulfoxide controlled aldol condensation. This reagent converted 12 into the 3-(S) epimer of 42 in 94% e.e. as determined by HPLC of the diastereomers. After protection of the hydroxyl and conversion of the ester of 42 to its corresponding tetra n-butylammonium salt, the ring was closed by addition of the dry salt 44 to a dilute solution of mesitylene sulfonyl chloride. Apparently the mixed anhydride was formed, followed by displacement of the mesitylene sulfonate to give the macrolactam. The (methoxyethyl) methyl protecting group was then cleaved using a two step procedure in which the oxygens of the MEM group were complexed with boron trifluoride. The BF₃ MEM complex was replaced by isopropyl thiol to give an intermediate oxy-thio acetal. Treatment of this intermediate with silver nitrate provided the free hydroxyl which was converted to the carbamate 46. Treatment of as shown in Scheme VIII gave the allylic alcohol 47 which was stereoselectively epoxidized (99% e.e.) using the vanadium catalyzed reaction with tert-butylhydroperoxide. The same selectivity was observed with meta-chloroperbenzoic acid although the overall yield was diminished due to side reactions with the diene moiety. The reaction provides an example in which Corey predicted the transition state for the epoxidation in solution on the basis of a conformational preference evident in the solid state. Acylation of the hydroxyl group of 46 followed by hydrolysis of the carbinolamide methoxyl yielded 1.

Isobe's synthesis of a fragment corresponding to synthon 18, is distinctly different from the above approaches in that D-mannose is converted in twelve high yield steps to a fragment which contains all of the requisite stereochemistry and functionality for use as carbons 5 thru 11 of maytansine. The key step in this sequence is the stereoselective addition of methyl-lithium to the olefin 49 as shown in Scheme IX. The product is reported to be entirely the three isomer formed in 99% yield.

Scheme IX
Isobe rationalized the results by suggesting that the methyl group is delivered to a configuration which has the lithium atom complexed with the ring and carbon 1 oxygens of $\delta^0$ and a conformational preference for the double bond which minimizes steric repulsion. Initial studies with model compounds evaluated by Isobe indicated that a MEM group at carbon 1 provided complete enantiomeric excess, whereas a methoxyl group at carbon 1 gave only approximately 60% e.e. In contrast to these results $\delta^0$, which contains a methoxyl at carbon 1 was reported to give only one product. These contradictions leave the results or the rationale open to question.

The completed syntheses of maytansine provide examples of different approaches to a difficult problem. Some of the strong and weak points of these syntheses are contrasted below. When key reactions failed, Meyers' route shows flexibility in design whereas Corey's route demonstrates his facility with exploring alternate conditions and/or reagents to make a given reaction work. Corey's synthesis was more successful in controlling relative stereochemistry, but Meyers' synthesis required fewer total steps. The macrocyclic ring closure was facile in both syntheses. Both syntheses appear to contain reactions which in hindsight could be simplified. For example, Corey's removal of the MEM group was reportedly designed to protect the labile allylic methoxyl group in $\delta^0$. Faced with a similar situation, Meyers found that prior removal of the lithioketal function provided enough stability to allow for removal of the ethoxyethyl protecting group with 1N HCl.

The synthetic challenge of maytansine has been met, but recall that the initial interest in the compound was on account of its promise as an anti-cancer agent. Much work is still needed in altering the structure of maytansine to decrease the toxicity while maintaining the potency of this very interesting compound.

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THE USE OF CARBOHYDRATES FOR THE SYNTHESIS OF NATURAL PRODUCTS

Reported by Marietjie Potgieter

October 22, 1981

The concept of asymmetric synthesis was first described in 1894 when Emil Fischer outlined its potential based upon the cyanohydrin reaction in the sugar series.\(^1\) Since then, the study of asymmetric synthesis, or "the process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products result",\(^2\) has shown considerable progress.\(^3\) It is still true, however, that the control of absolute stereochemistry and the regiospecific introduction of functionality remain as crucial problems in the construction of chiral compounds. Synthetic schemes which avoid optical resolutions are both efficient and desirable. This report will review the use of carbohydrates to produce optically active intermediates, or "chiral templates",\(^4\) for the synthesis of natural products, and will emphasize recent developments in the total syntheses of macrolide and ionophore antibiotics.

Carbohydrates are a readily available source of a rich variety of chiral compounds that can be easily transformed to chiral acyclic, carbocyclic, and heterocyclic intermediates. The combination of natural chirality, conformational bias, and the inherent topology of a cyclic sugar derivative provide a high degree of regio- and stereo-control for the systematic functionalization of predetermined sites in the molecule.\(^5\,^6\) Despite the similar functionality at all the chiral carbons of a sugar molecule, careful planning of a sequence of protection and deprotection steps will enable the blocking of all positions except the site at which manipulation is desired. Thus functional groups and chiral centers can be introduced in a controlled manner so that the features of the target molecule are established in the chiral template at the outset of the synthesis. This approach to total synthesis requires the recognition of elements of symmetry which can be transposed onto the product from the carbon framework of a suitable sugar derivative. Syntheses utilizing sugar-based chiral templates can be divided into those in which the sugar portion is apparent and those in which it is hidden in the target molecule.

**Compounds in Which the Sugar Portion is Apparent.** This group includes a large number of compounds that contain chiral tetrahydrofuran and tetrahydropyran rings. These include polyether antibiotics, C-nucleosides and C-glycosides, prostaglandin-related compounds, pheromones and insect poisons, natural products of marine origin, and terpenes. The bold lines in Figure 1 show the carbon atoms from the original sugar precursor used to form the chiral template. Further elaboration of the chiral template could be carried out stereoselectively in most cases to give the target molecules shown.

**Compounds in Which the Sugar Portion is Not Apparent.** This group is more difficult to classify because the recognition of the possibility to utilize carbohydrates is dependent mainly on the ingenuity and prejudices of the chemist. It is possible, however, to identify certain structural units within a target molecule that have been previously synthesized from carbohydrates. For example, sugars have been used to form the numerous cyclopentane and cyclopentene chiral
precursors with appropriate functionality for the synthesis of prostaglandins. It was used to synthesize aliphatic cis or trans epoxides suitable for incorporation into leukotrienes, the trichothecene sesquiterpenes, and cerulenin chiral acyclic molecules. A small number of amino acids and alkaloids has also been made. This group will undoubtedly expand to include various other structural types as carbohydrates become a more established source of chiral starting materials. Compounds representative of this group are shown in Figure 2 with bold lines indicating which carbon atoms originate from the sugar precursor.
Figure 2

Macrocycles. The use of carbohydrate precursors in total synthesis has been successfully applied to the challenging problem of macrolide synthesis. The macrolide antibiotics are a group of glycosidically-bound 12-, 14-, and 16-membered macrocyclic lactones obtained from various actinomycetes, many of which are produced commercially as pharmaceuticals. The similar pattern of substituents and chirality that is found at most of the chiral centers in all the "polyoxo" macrocycles led to the development of Celmer's stereochemical model, which correlates their stereochemistry. Structural comparisons between Celmer's model, in Scheme I and pikromycin (2) or erythromycin (3) demonstrate that, despite differences in the level of oxidation or in the substituent at a given carbon, a general pattern of functionality remains. This suggests that the development of a synthetic fragment containing chiral segments of the model would provide an intermediate with applications to the total synthesis of most macrocles. In this case the use of sugar starting materials is particularly efficient.
The Celmer model can also be applied to the aliphatic chains of rifamycin (4), streptovaricin and maytansine (5), although it is less successful with other members of the ansamycin family of antibiotics. One chiral center of 4 and three centers of 5 designated by asterisks have stereochemistry that is opposite to that of the corresponding carbons in the model. The chiral templates developed for maytansine can therefore not be used in the syntheses of the "polyoxo" macrolides, but can find limited application in the syntheses of related maytansinoids.
The synthesis of macrolides presents two major challenges: first, the construction of a sizable lactone ring and, secondly, the stereocontrolled introduction of the numerous chiral centers of the aglycone. A considerable amount of work has been devoted to the first problem resulting in very efficient ring closure procedures. To meet the second challenge a number of workers have successfully pursued the use of commonly available monosaccharides to generate chiral intermediates. In Scheme I, the major disconnections in the synthetic routes to \( \alpha^2 \) are summarized. The numbering of the carbons on the carbohydrate-derived synthons corresponds to numbering the parent aglycone with the carboxyl carbon as C-1.

The two units, 6 and 7, of erythromycin A (2), C-1 - C-6 and C-9 - C-15, respectively, have been prepared through a sequence of high-yield steps which, for the most part, required no chromatographic separation. Inspection of the precursors 8 and 9 shows that the substitution and stereochemistry at C-2 and C-3 of 6 correspond to C-10 and C-11 of 7 and that C-5 in 6 and C-13 in 7 are both hydroxylated, but epimeric. In the retrosynthetic analysis of precursors 8 and 9 a common intermediate 14, shown in Scheme II, was envisioned. This branch point was chosen because further elaboration of the C-5 side chain would give 9, while oxidation of C-6 and subsequent dehydration would give 15, which was expected to be selectively hydrogenated to give 8. Control over the stereochemistry at C-4 and C-5 of 8 was secured by the original choice of the \( \alpha \)-anomeric substitution of 14. Since there is little or no precedence in the carbohydrate series for the direct introduction of equatorial methyl groups such as the C-2 and C-10 substituents, these features were established by base-catalyzed epimerization of ketone 14 in nearly quantitative yields. Similarly, C-3 of 14 was epimerized to give the desired stereochemistry of compound 15. Chain extension and coupling of the two units were also achieved with remarkable selectivity.
Stereospecific aldol condensations\textsuperscript{35} or acylations relying on the stereocontrolled generation of cyclic intermediates have attracted much attention as alternate approaches to the stereocontrolled introduction of the numerous chiral centers of macrolides. These powerful tools have been applied successfully to the synthesis of macrolides and to other areas of synthetic chemistry. However, the carbohydrate-derived "chiral template" approach is the method of choice in a number of cases, due to the high stereoselectivity obtained in the generation of the template and the high enantiomeric excess obtained during further modifications leading to the desired target molecule.

Control of side-chain stereochemistry. The accessibility of unusual branched-chain sugars\textsuperscript{35} can be very useful not only in the synthesis of macrolides, but also in the generation of chiral tetrahydrofuran and tetrahydropyran rings as found in ionophores and a number of other groups of natural products. A common feature of the polyether ionophoric antibiotics is the considerable number of tetrahydrofuran and pyran moieties attached to the macrocycle exclusively at the carbon bound to the ring oxygen.\textsuperscript{37} The control of stereochemistry at this \( \alpha \)-position of the furan and pyran rings is essential during the synthesis of ionophores. A very convenient method of intramolecular transfer of asymmetry via an enolate Claisen rearrangement involving carbohydrate precursors has been developed by Ireland\textsuperscript{38} and was used successfully by his group in the syntheses of the Prelog-Djerassi lactone \textsuperscript{17,29} the nonactic acids \textsuperscript{18 and 19,39} tirandamycinic acid \textsuperscript{20,40} and lasalocid A \textsuperscript{21,41} The circled atoms in Figure 3 indicate the chiral exocyclic atom generated during the rearrangement. This approach is outlined in Scheme III. A heterocyclic

![Figure 3](image)
allylic alcohol is converted to either the aliphatic ester \(^{22}\) or the \(\alpha\)-alkoxy ester \(^{25}\), which ultimately leads to the ethers \(^{23}\) and \(^{26}\), respectively, by \([3,3]\)-sigmatropic rearrangement of the silyl enolates \(^{22}\) and \(^{23}\). Model studies indicated\(^{38}\) that the relative proportions of the two isomeric ketene acetals \(^{23}\) and \(^{25}\) depend on the solvent used during deprotonation. It was also shown that when deprotonation is effected by lithium diisopropyl amide (LDA) in a 23 volume % mixture of hexamethyl phosphoric triamide (HMPA) in tetrahydrofuran (THF), the \(Z\)-enolate anion \(^{28}\) is preferentially formed and silylated. The use of LDA in the absence of HMPA allows the \(E\)-enolate anion \(^{29}\) to predominate. The enolization was determined to be kinetically controlled in both cases\(^{38a}\).

**Scheme III**

\[ \text{i or ii} \]

\[ \text{iii} \]

\[ \text{iv or v, vi, vii} \]

\[ \text{viii, ix} \]

\[ \text{X = Me}_3\text{Si or t-BuMe}_2\text{Si} \]

\[ n = 1, 2 \]

\[ i = \text{RCOCl, pyr. or RCH}_2\text{COCl, n-BuLi; ii} = (\text{RCO})_2\text{O, pyr.}; \text{iii} = \text{Me}_3\text{Si}, \text{pyr.; iv} = \text{pure THF; } \]

\[ v = 23\% \text{HMPA-THF; vi} = \text{LDA or n-BuLi, HMDS; vii} = \text{TMSCl or TBSCl; viii} = \text{room temperature or refluxing benzene; ix} = \text{H}_2\text{O, OH}^-, \text{CH}_3\text{N}_2. \]

and the selectivity obtained was rationalized in terms of the steric requirements of the solvent-dependent transition states.
In the absence of unusual steric constraints and in accordance with experimental observations, \(^{38a}\) these enolate Claisen rearrangements are considered to occur via a chair-like transition state. When the substrate contains a substituted aldehyde and the enol oxygen bears a large silyl group, however, the conformational mobility of the ketene acetal is restricted so that the rearrangement may occur via a boat-like transition state. Since the absolute chemistry of the target molecule is known, definitive stereochemistry can be assigned to the products of the rearrangement and the conformations of the respective transition states can be defined.

The synthetic methods developed to control the side-chain stereochemistry of various furanoid and pyranoid rings should prove to be very valuable in light of the ubiquitous occurrence of such moieties among the abundant acetogenous metabolites and ionophores.

**Conclusion.** It is clear that carbohydrates can be readily elaborated to form chiral templates for asymmetric syntheses. The use of carbohydrates thus provides an interesting approach, which in some cases may prove to be superior in elegance and efficiency in the construction of a variety of multifunctional chiral structures.

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SYNTHETIC APPROACHES TO THE PRELOG-DJERASSI LACTONE

Reported by Michael S. Dappen

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The Prelog-Djerassi lactone 1 has earned a special place in the area of macrolide antibiotics because it is a pivotal compound for both the structure determinations and syntheses of this class of compounds.

The lactone 1 was isolated independently by C. Djerassi1 and V. Prelog2 and their co-workers in 1956 as an oxidative degradation product of the macrolide antibiotics methymycin 2 and narbomycin. Later it was isolated as a degradation product of pikromycin 3 and neomethymycin.5

The lactonacid 1 retains the absolute configuration of four of the chiral centers present in virtually all "polyoxo" macrolide antibiotics as recognized by Celmer in his unifying model for the absolute configuration of this class of compounds.6,7 Thus, the Prelog-Djerassi lactone was essential for the elucidation of the absolute configuration of these chiral centers.5b,8,9 More recently, the lactone has been seen as being of particular value as a synthetic intermediate in syntheses leading to these macrolidic antibiotics, compounds which currently are of synthetic interest.11b,14,17c To date 14 syntheses of this compound have been reported.10-22,27

Each new synthesis has its own merit and, in perspective, the approaches provide an encapsulated history of the advances in synthetic technology from the 1970's to the present. Likewise, syntheses of 1 have provided a useful test for new synthetic methodology.

This abstract will briefly discuss the elucidation of the stereochemistry of the lactone 1. The major portion of this abstract will deal with the many synthetic approaches to the Prelog-Djerassi lactone.

Stereochemical Studies of the Prelog-Djerassi Lactone

The four chiral centers of the lactonic acid 1 correspond to the centers C-4, C-5, C-6, C-8 of the Celmer model.7 Both Prelog and Djerassi originally determined the structure and some of the relative stereochemistry by classical degradation methods. Potassium permanganate oxidation of both methymycin and narbomycin lead to 1. Kuhn-Roth degradation showed the presence of three methyl groups. Pyrolysis of the lactone 1 lead to an α-β unsaturated diacid

\[ \text{R} = \text{Desoaminyl} \]
which was subjected to ozonolysis to provide pyruvic acid and meso-2,4-dimethylglutaric acid as shown in Scheme I. Djerassi later determined the stereochemistry of the 4S center by degradation of neomethylmycin to α-methyl levulinic acid and (-)-methylsuccinic acid. This information, along with the degradation product meso-2,4-dimethylglutaric acid provided the absolute stereochemistry at the C-6 position as R. Rickards and Smith identified the remaining chiral centers as 2R and 3S by NMR and chemical methods using natural material. The major stereochemical points were settled by the J₃,₄ coupling constant of 1 and reduction of 1 to a triol which could be reacted with acetone and acid to give a 6-membered ketal which had couplings consistent with the Karplus dihedral angle relationships. With the stereochemistry of 1 proven, the stereochemistry of all related antibiotics were shown to agree with Celmer's model.

**Synthetic Approaches**

Chronologically, the many syntheses of the lactonic acid 1 illustrate the advances in the control of stereochemistry in organic synthesis. The early trial and error approaches of the 1960's gave way to manipulations of carbocyclic systems during the 1970's, while more recently the use of chiral enolates in aldol condensations and enolate-Claisen rearrangements have been applied to the efficient synthesis of 1.

**Early Synthesis**

In 1963 Bergelson and Batrakov synthesized all four racemic diastereomers related to 1 which had a cis-disposition of the methyl groups in the 4 and 6 position. In their approach the monoester, monoacid chloride of meso-2,4-dimethylglutaric acid was condensed with the magnesium salt of mono-ethyl 2-methylmalonic acid as shown in Scheme II to give the keto-diester 4. Empirical use of various reducing agents, i.e. hydrogenation over Raney nickel, lithium aluminum...
hydride (−68°), and lithium triethylaluminoxydride for the reduction of the carbonyl gave all four possible diastereomers after separation. Hydrolysis of the esters and lactonization provided four lactonic acids. Bergel'son and Batrakov assigned one of these compounds to the racemic Prelog-Djerassi lactone based solely on the IR spectrum. Use of this compound, along with its diastereomers, led to their incorrect assignment of the absolute stereochemistry as 2S, 3R. While their method was sound, as shown subsequently in the correct assignment, the compound chosen by Bergel'son and Batrakov was apparently a diastereomer of the Prelog-Djerassi lactone.

**Syntheses Involving Control of Stereochemistry via Carbocyclic Intermediates.** By the 1970's synthetic methodology had progressed to the point that control of the stereochemistry of a reaction by the use of conformationally rigid carbocyclic systems was widely used. This methodology has been used in the synthesis of 1.

Four years after Rickards and Smith determined the stereochemistry of 1, another synthesis appeared. In this case the lactone 2 was prepared by S. Masamune and co-workers and used as a subunit from which the corresponding seco-acid of methymycin and, subsequently, methymycin, was synthesized.

Retrosynthetic analysis reveals that the two acid functionalities of 1 come from a Lemieux-Rudloff oxidation of a functionalized cycloheptene as shown in Scheme III. However, the main point is that the cis-disposed methyl groups

![Scheme III](image)

on the ring originate from reduction of two carboxylic acids which, in turn, come from oxidative fragmentation of one bridge in a 4.2.1 bicyclo system, thus ensuring the cis-disposition needed.
In the actual synthesis, shown in Scheme IV, bicyclo [4.2.1] nona-2,4,7-triene was hydroborated and oxidized to the exo-hydroxyl compound 5 which was oxidized to the ketone and formylated to form 6. Oxidative cleavage to the cis-dicarboxylic acid was accomplished with sodium metaperiodate. Reaction with m-chloroperbenzoic acid gave a 7:3 mixture of epoxides which were cis and trans with respect to the carboxyl groups. Esterification and ring-opening of the epoxide with lithium dimethylcuprate yielded the lactone ester 7. Lithium aluminum hydride provided the triol with which the two primary alcohol groups were converted to the tosylates and the secondary hydroxyl group was protected with a trimethylsilyl group. Lithium dihydrocuprate cleanly removed the tosyl functionalities to give the desired methyl groups. Oxidation and cleavage of the olefin with KMnO4-NaIO4 led to isolation of the racemic Prelog-Djerassi lactone 1 in 12% overall yield. Using this and another easily-attained segment Masamune and co-workers constructed methymycin.

Stork and White and co-workers published syntheses of 1 in early 1979 which also used cyclic systems to control stereochemistry and which were similar in that they both involved formation of dicarboxylic acids via ozonolytic cleavage of almost identical cycloheptylsilyl enol-ethers. However, each investigator's route is sufficiently different to be worth attention.

White formed a seven-membered ring early in his synthesis via a cycloaddition of a formal oxo-allyl cation with the ketal of 2-acetylfuran as shown in Scheme V. Hydrogenation and then a four-step removal of the resulting ketone was required as normal methods did not work due to the failure of the carbonyl to yield derivatives for reduction to the methylene group.


8, was subjected to a Baeyer-Villiger oxidation to introduce an ester functionality which on hydrolysis reveals a carbonyl and an alcohol, 9. This compound has the opposite stereochemistry of the alcohol required for the Prelog-Djerassi lactone and inversion was achieved in three steps, followed by protection of the alcohol as a tert-butyldimethylsilyl group. The enone functionality was introduced by the usual methods from the ketone to give 10. The remaining methyl group was added with lithium dimethylcuprate and the resulting enolate was trapped with trimethylsilyl chloride to provide 11. The silyl enol-ether was subjected to ozonolysis with a reductive workup to give a compound which, after deprotection of the hydroxyl group, was lactonized and oxidized to the racemic lactone 1.

Stork's synthesis involved the elaboration of a cyclohexane ring via well-known techniques leading to an enol-ether 12 as shown in Scheme VI. The key step of the synthesis is the ring expansion of 12 to give an intermediate similar to that which White had prepared. Thus, cyclopropanation of 12 with dichlorocarbene
yielded \( \text{1}^3 \) which, via a solvolysis reaction, underwent ring expansion to give the chloroenone \( \text{1}^4 \). The remaining methyl group was added with lithium dimethylaprate and the chloride was removed by reductive dehalogenation with chromous perchlorate. Kinetic enolate formation and trapping with trimethylsilyl chloride led to a similar intermediate as White. Ozonolysis with an oxidative workup led directly to the racemic lactone \( \text{1}^6 \).

The first synthesis adaptable to a chiral synthesis and carried out as both a racemic and chiral synthesis was performed by Grieco, et. al. as shown in Scheme VII. A racemic product prepared by this route was carried on to methymycin.\(^{14}\) The highlight of the synthesis is the second and third steps in which a 3.2.1 bicyclic system is created and rearranged to a 3.3.0 system via an allylic cation. The remaining transformations are well-precedented and occur without difficulty. An extra epimerization step was needed as the methylation gave a 1:1 ratio of \( \text{1}^5 \) and its' C-6 epimer.

![Scheme VII](image)

Syntheses Involving Other Synthetic Methods. All the above syntheses, with the exception of the earliest, have involved the use of carbocyclic intermediates to control the stereochemistry. However, recently new methods have been used to this end and each of the next three syntheses present a different technique.

Bartlett and Adams\(^{15}\) employed a cyclization to the six-membered ring in a manner which stereospecifically defines the chiral centers at C-2 and C-3. Thus, starting with compound \( \text{1}^6 \), they envisioned a cyclization as shown in Scheme VIII which would give the correct stereochemistry at C-3 since other transition states appear to be sterically congested. The reagent which effected the cycli-

![Scheme VIII](image)
zation proved to be Hg(OAc)$_2$. Unfortunately, the acid 16 did not cyclize to the lactone upon reaction with mercuric acetate or trifluoroacetate in a variety of solvents. Bartlett and Adams attributed this to the deactivated double bond and a weakly nucleophilic carboxyl group. However, the hemiacetal of the aldehyde-acid did cyclize and that product could be oxidized to the lactone. Thus, the synthesis could have been completed by demercuration with retention of configuration. The reagent reported to demercurate with retention, $^{24}$ H$_2$S and aqueous NaOH, resulted in a 55:45 diastereomeric ratio of isomer at C-2 and the one thought to give no stereoselection $^{24}$, NaBH$_4$, gave only the wrong isomer, i.e. net inversion of configuration at C-2. Bartlett and Adams found that a new reagent postulated by them, Na$_2$CS$_3$, provided the required isomer with 78% retention of configuration. Their synthesis of the Prelog-Djerassi lactone is summarized in Scheme IX. The synthesis is part of Bartlett's general work which demonstrates control of stereochemistry in cyclization reactions.

Ireland and Daub $^{16}$ utilized the enolate-Claisen rearrangement to control the stereochemistry of the Prelog-Djerassi lactone. Inspection of the carbohydrate literature provided a starting compound with the appropriate stereochemistry and functionality for their transformations. Thus, 4,6-O-benzidene-D-allal 17, was first converted to its' propionate ester and by use of lithium hexamethyldisilazide the resulting enolate was trapped with t-Butylidimethylsilyl chloride to give 18, a predominately (Z)-silyl ketene acetal. Dissolution in refluxing benzene effected the enolate-Claisen rearrangement as illustrated in Scheme X. Assuming the Z-ketene acetal was formed, the rearrangement takes place via a boat-like transition state. Hydrolysis of the ketal, protection of the primary alcohol and oxidation of the secondary alcohol yielded 19. The rest of the stereospecific transformations involve use of the carbocyclic framework. Thus, compound 19 was reacted with lithium dimethyl cuprate to add a methyl group and the ketone was subjected to Wittig methylenation which was hydrogenated to give the other methyl group. The protected alcohol was converted to the exo-
methylene compound 20 in four steps. Compound 20 was subjected to ozonolysis and hydrolysis from which the optically active \( \text{II} \) was isolated. Compound 20 is envisioned by Ireland and Daub as a dienophile for hetero-Diels-Alder condensations in synthesis of ionophore antibiotics.\(^{25}\)

Finally, Masamune et. al. have utilized their stereospecific aldol condensation to synthesize the Prelog-Djerassi lactone. In this case \( \text{I} \) serves as an intermediate in their synthesis of 6-deoxyerythronolide B.\(^{17c}\) This synthesis is by far the most efficient to date and represents the most recent in a series of improved syntheses of the Prelog-Djerassi lactone by this group.\(^{17a-c}\) The latest synthesis, which has a 40:1 diastereoselectivity ratio, involves the condensation of the (-) aldehyde of monomethyl-1,3-dimethylglutaric acid with the \( \text{Z} \)-Boronic enolate of the chiral S-reagent derived from mandelic acid as shown in Scheme XI. This synthesis involves only three steps and is accomplished in 85% yield.

\[\text{Scheme XI}\]

**Summary.** This abstract has discussed the many ways that the control of stereochemistry has been used to synthesize the Prelog-Djerassi lactone. The lactone \( \text{I} \) has been seen as an example of how the methodology used to control stereochemistry has progressed over the last two decades. The knowledge gained from synthesis of \( \text{I} \) has been used in a limited way in the synthesis of macroclide antibiotics. With many highly-efficient methods of synthesis of \( \text{I} \) available, synthesis of more macrolide antibiotics and related compounds should seem possible.
BIBLIOGRAPHY

SYNTHESIS OF CHIRAL SECONDARY ALCOHOLS FROM ALDEHYDES AND KETONES USING CHIRAL LIGANDS

Reported by Raju Mohan

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Asymmetric syntheses involve reactions in which a prochiral substrate is converted into a chiral product. Since the substrates are prochiral, asymmetric induction must involve a chiral ligand either in the solvent sphere or as a chiral modifier for a reagent. The ligands provide for a diastereomeric differentiation in the transition states such that a preponderance of either the R or S configuration is favored for the newly formed chiral center. In general, asymmetric synthesis reactions have energies of activation which are well above the normal rotational energy barriers encountered in flexible molecules. Thus the Curtin-Hammett principle applies, namely that the product ratio depends solely upon the free energy differences, \( \Delta \Delta G^\# \), between the competing transition states and not upon the population of various ground state conformations of the reactants.

The extent of asymmetric induction can vary from experimentally non-detectable to essentially quantitative, depending on the energies of the different transition states involved. Experience has shown that the extent of asymmetric induction in both the configuration of the product and the enantiomeric excess can vary with solvent, temperature and structural variations in the substrate. A great deal of empirical work has been done with these variables. In terms of understanding these reactions, the problem is one of defining quantitatively the relative energy levels of the competing transition states leading to the stereochemically different products. This is a complex problem and the general approach has been, with the aid of various simplifying assumptions, to reduce the many transition states to a few, often two, crucial ones which seem to embody the most important interactions. These interactions can then be dealt with intuitively or semiquantitatively. The latter can be achieved by calculation of enantiomeric excess from a free energy relationship derived by Ugi. The free energy difference of diastereomeric transition states, \( \Delta \Delta G^\# \), is related to the ratio of the enantiomeric products which itself is related to the rate constants for their formation \( (k_R, k_S) \).

\[
\Delta \Delta G^\# = -RT \ln \left( \frac{k_R}{k_S} \right)
\] (1)

From the free energy relationship (eq 1) we can calculate the difference in free energies between the diastereomeric transition states using the enantiomeric excess values. Such a relationship is plotted in Figure 1, where the free energy difference in transition states at -78° and 25°C is shown relative to the stereoselectivity.

This review will focus on the use of chiral ligands in the formation of secondary alcohols by addition of organometallic reagents to the prochiral carbonyl group of aldehydes and by the hydride reduction of ketones. An effort will be made to evaluate the ability of these ligands to induce
chirality and their usefulness in stereochemical control of synthetic processes. The reliability of these ligands in postulating transition state models for prediction of configuration will also be discussed.

The preparation of optically active secondary alcohols by the asymmetric addition of organometallic reagents to aldehydes has been less successful than the asymmetric reduction of ketones. Nonetheless we will consider the reaction of aldehydes first since it involves, significantly, C-C bond formation with the simultaneous creation of a new chiral center. Moreover in many cases the aldehydes are more accessible than the corresponding ketones.

Interest in this area of asymmetric synthesis was brought into focus by the work of Nozaki and co-workers who reported in 1968, the use of the alkaloid (-)-Sparteine as a ligand for addition reactions of organometallic reagents to carbonyl compounds. It was found that 1,2 additions of organolithium or organomagnesium reagents to both aldehydes and ketones proceeded dissymmetrically in presence of (-)-Sparteine to give products in which enantiomeric excesses varied from 6-22%. From eq 1, using the enantiomeric excess values of Nozaki and co-workers, we find that the energy difference between the transition states corresponds to about 0.2 kcal/mole. Even with 99% enantiomeric excess, the free energy difference in the diastereomeric transition states corresponds to only about 1.9 kcals/mole and hence data which have low enantiomeric excesses should be interpreted with caution since relatively small energy differences will be involved. Throughout the review, these relationships will serve as a guide for structural and stereochemical understanding of the reactions.
Seebach and co-workers have prepared a number of chiral amino ethers derived from tartaric acid and used them as chiral ligands in addition reactions of aldehydes. Of the two most effective ligands, one was (S,S)-2,3-dimethoxy-N,N,N',N'-tetramethyl-1,4-butane-diamine \( \alpha \) and the other a structurally similar ligand \( \beta \) which contains more hetero atoms.

Reactions of n-butyllithium with benzaldehyde in pentane with \( \alpha \) as co-solvent showed that the enantiomeric excess of the alcohols depended on the ratio of ligand to butyllithium and on the temperature. Enantio-meric excesses of up to 38% of the corresponding (R)-alcohol was obtained with lower temperatures and ratio of ligand to butyllithium up to 10:1. At the lowest reaction temperature of \(-130^\circ\)C, this corresponds to \( \Delta \Delta C^\theta = 0.23 \) kcal/mole. The methoxyamine \( \alpha \) was also used as a co-solvent in the 1,2 addition of other Li-, Mg-, Zn- and Cu-organic compounds to aldehydes. With methylolithium and phenyllithium precipitates are formed with \( \alpha \) and the addition occurs from the si face of the aldehyde. (The si and re nomenclature follows the generally accepted system of Hanson.) With butyllithium and isopropyllithium homogeneous solutions are obtained with \( \alpha \) and preferential addition from the re face is observed. With \( R_2CuLi \) and \( R_3ZnLi \) (\( R = C_6H_{13} \)) the additions occurred preferentially from the re face. With Grignard and dialkylmagnesium reagents, the addition is preferentially from the si face.

The temperature effects can be somewhat better understood than the stereochemical course of these reactions. Assuming a negligible entropy difference between the competing transition states eq 1 shows that there should be significant change in stereoselectivity with temperature and higher isomer ratios are expected at lower temperatures. The reversal in stereochemistry with different organometallics and with homogeneous vs heterogeneous adducts is less well understood especially since there is paucity of information regarding structures of the organometallic reagents.

Some of the highest enantiomeric excesses were obtained in reactions of n-butyllithium with benzaldehyde in pentane at \(-78^\circ\)C using \( \beta \) as co-solvent. In this case enantiomeric excesses up to 52% of the (S)-alcohol were obtained when the ratio of ligand to butyllithium was only 2:1. The ligand \( \beta \) was also applied to additions of other organolithiums to different aldehydes and was found to give higher enantiomeric excesses of corresponding alcohols than \( \alpha \). The optimum temperature for the reactions is \(-80^\circ\)C. Qualitatively \( \beta \) directs attack preferentially from the si face for all organolithiums reported. Seebach and co-workers have proposed a structure for the transition state responsible for the enantio- selectivity observed. An alternative transition state is also shown.
Although the difference in the two transition states is only about 0.45 kcal/mole, the transition state leading to the (S)-alcohol would be lower in energy due to less steric interactions as compared to the one leading to the (R)-alcohol. Although Seebach and co-workers observe consistent qualitative results in terms of enantioface differentiation it must be stressed that such small energy differences in the transition state must be interpreted with caution.

Mukaiyama and co-workers have reported high enantiomeric excesses of secondary alcohols in the reactions of organometallic reagents with aldehydes using ligands derived from the amino acid (S)-proline.\(^\text{11}\)

In addition reactions of n-butyllithium to benzaldehyde in dimethoxy-methane (DMM) at \(-78^\circ\)C with 4a as co-solvent, 72% enantiomeric excess of the (S)-alcohol was obtained. At \(-123^\circ\)C in 1:1 DMM-diethylether, an enantiomeric excess of 95% of the (S)-alcohol was obtained. The lithium salt of 10a was used as a chiral ligand for additions of dialkylmagnesium,\(^\text{13}\) alkylcopper,\(^\text{11,12}\) or dialkylzinc\(^\text{13}\) to benzaldehyde. Dialkylmagnesium reagents added the most enantioselectively from the re face in all cases to give enantiomeric excess of (R)-alcohols. Higher stereoselectivity was obtained at lower temperatures and toluene was found to be better than ether solvents in contrast with the solvent effects observed using alkyl lithium.\(^\text{12}\) In analogous alkyl lithium reactions, the stereoselectivity depends on the size of the alkylolithium. It is observed that (S)-alcohols are preferred for n-propyl- or n-butyllithium while (R)-alcohols are preferred for ethyl- or methyl lithium. It does appear certain, though, that two pyrrolidine ligands and the lithiated hydroxymethyl group are essential for asymmetric induction. The ligands 2-hydroxymethyl-1-methyl-pyrrolidine 5 and (2S,2'S)-2-methoxymethyl-1-[(1-methylpyrrolidin-2-yl)-methyl]-pyrrolidine 4b are not effective in asymmetric induction. Two possible diastereomeric transition states are proposed for the reaction of alkyl lithium reagents with benzaldehyde.

**COURSE A:** attack from re face

**COURSE B:** attack from si face
The rigid structures are formed by the coordination of two nitrogen and oxygen atoms to lithium ion of the alkyllithium. Coordination of the oxygen atom of the aldehyde to the lithiated hydroxymethyl group may limit the approach of the aldehyde to either course A or course B. The size of the alkyllithium seems to determine the preferred course. With methylolithium the $\Delta \Delta G^\# = 0.15 \text{ kcal/mole}$ while with ethyllithium $\Delta \Delta G^\# = 0.25 \text{ kcal/mole}$. Even though the stereoselectivity is reversed for n-propyl- and n-butyllithium, a similar increase in $\Delta \Delta G^\#$ values is observed for increasing steric bulk.

A synthetic application of the use of a Mukaiyama ligand $\Delta$ is the asymmetric addition of acetylides to aliphatic aldehydes to yield optically active alcohols. These alcohols are precursors to furanones which themselves are useful intermediates in the synthesis of natural products. An example of such a reaction sequence to product (R)-5-octyl-2-(5H)-furanone is shown in Scheme I.

![Scheme I](image)

The model for the diastereomeric transition states proposed by Mukaiyama and co-workers is consistent with attack preferentially from the $\text{re}$ face of the aldehyde as experimentally observed: with the less bulky acetylide, course A would be preferred leading to the (R)-alcohol.

Most recently, Cram and co-workers have reported two new efficient ligands for asymmetric induction. The binaphthyldiamines $\mathcal{L}$ and $\mathcal{R}$ were chosen based on the well known activation of alkyllithium reagents by $N,N,N',N'$-tetramethylethlenediamine.

![Ligands](image)

Reactions of methyl-, ethyl-, propyl- and butyllithium with benzaldehyde in presence of chiral ligands $\mathcal{L}$ and $\mathcal{R}$ all afforded enantiomeric excesses of the corresponding (R)-alcohols. This suggests that in all cases, the preferred mode of attack is from the $\text{re}$ face of the aldehyde. As with the pyrrolidine ligands, enantiomeric excess values up to 92% were obtained as the solvent composition was changed from pentane to DMM-ether and the reaction cooled to low temperatures.

Cram and co-workers have proposed a transition state for chiral recognition in which the polyspirane structure restricts the degree of freedom regarding orientations of the carbonyl.
This transition state appears less sterically constrained than the other diastereomeric model where the position of the H and R' groups are interchanged. The difference in free energies between the diastereomeric transition states, 1.3 kcaIs/mole, depends on these steric effects and seems responsible for the high chiral recognition of the catalyst.

With respect to clearly defined transition states, the work of Cram and co-workers seems most consistent with qualitative explanations of stereoselectivity in additions of alkyllithiums to aldehydes.

Another route for the preparation of optically active secondary alcohols is through the asymmetric reduction of ketones. There are a variety of methods to accomplish stereoselective reduction of ketones. These involve use of chiral organoboranes, reduction by hydrosilylation or hydrogenation or the use of hydride reagents. More recently, a number of ligands have been used as chiral modifiers of lithium aluminum hydride (LiAlH₄) for asymmetric reduction of ketones to secondary alcohols. The ligands are usually carbinolamines with 2° or 3° carbinol groups in a 1,2 or 1,3 relationship to the 3° amine. It appears that the structural and stereochemical features of these modifiers are better understood than the chiral ligands used for reactions of aldehydes with organometallic reagents.

Seebach and co-workers have used derivatives of tartaric acid to prepare chiral aminodiols. One such modifier is the dimethylamino carbinol which reacts with LiAlH₄ to give the complex. In reactions of acetophenone with the (S)-alcohol was produced in 37% enantiomeric excess.

Addition occurred preferentially from the re face of the ketone as was shown by the reaction of other ketones with the complex. The enantiomeric excess values seemed to decrease with the effect of substitution. From these effects and the sense of chirality of the predominantly formed enantiomers, Seebach and co-workers have discussed some models as possible mechanisms of asymmetric induction.
For the reduction of acetophenone using 10, the free energy difference in transition states is 0.3 kcal/mole. With increased substitution on the ketones, it is likely that the stereoselectivity would decrease since bulky groups would lower the preference for one transition state relative to the other.

Much higher enantioselective reduction of ketones has been achieved using the Mosher-Yamaguchi LiAlH₄-Darvon alcohol (11) complex. These complexes have primarily been used in the synthesis of acetylenic carbinols to be used in crucial transformations to various natural products. Brinkmeyer and co-workers reported enantiomeric excess values of the carbinols up to 91% using the complex 12 in reductions of acetylenic ketones to propargylic alcohols.

Cohen and co-workers have also used the same complex 12 to study the structural factors required in the ligand for achieving high stereoselectivity. They found that all reductions using this complex led to products in which the hydride addition was from the si face and (R)-carbinols were formed preferentially. When complexes of LiAlH₄ were prepared with Darvon alcohol analogs without the methyl group, the asymmetric induction when applied to α,β-acetylenic ketones or acetophenone had a preponderance of carbinol chirality opposite to that using 11. From this observation it appears that the chiral secondary methyl center in 11, although relatively distant from the site of complexation with aluminium, is alone capable of exerting a substantial effect on the asymmetric induction.

In order to understand the stereochemical consequences of the diastereomeric transition states, Morrison and co-workers have investigated some new carbinol modifiers. Some interesting results are observed. With chiral centers only on the carbinols, 13, (R)-alcohols were produced in the reduction of acetophenone in 44% enantiomeric excess. With no carbinol chirality but an (R)-α-methylbenzyl group next to nitrogen, 14, (S)-alcohols in 10% enantiomeric excess were formed. When both chiral directing centers were incorporated as in 15 and 16 the stereoselectivity was increased. With 15, the R-directing influence of S,S-carbinol centers is stronger than the opposing (S)-directing (R)-α-methyl benzyl unit and hence (R)-alcohols are produced in 35% enantiomeric excess. When both centers correlate to induce the (R)-directing effect as in 16, (R)-alcohols are formed in 82% enantiomeric excess. The carbinolamines function as chiral bridges with Li⁺ coordinated to N and the alkoxy groups to the Al thus defining the stereochemistry around the carbonyl group while activating it for hydride acceptance.
Chiral ligands can provide stereospecific asymmetric induction of the carbinol center in the synthesis of chiral secondary alcohols from aldehydes or ketones. From the high stereospecificity of the chiral hydride reagents, synthesis of optically active secondary alcohols by this route provides higher enantiomeric excesses of the corresponding alcohols than that obtained via the addition of organometallic reagents to aldehydes. It is possible that in the case of hydride reagents the steric bulk of the ligand can contribute to the stereoselectivity and quantitative definitions of preferred configurations for the favored transition states are more predictable than in case of ligands used with aldehydes. With respect to addition of organometallic reagents to aldehydes, there appear to be common features between the ligands for high stereoselectivity. Bidentate ligands seem to be the most effective and the more sterically confining a ligand, the greater the chiral recognition.

It appears from the review of literature that the investigation of synthetic utility of ligands has been useful but that considerations regarding the transition states and precise structures of the species involved need to be more fully studied. There appears to be considerable data on structural modifications of the ligand, variations in solvent and temperature conditions and substrate changes but for most cases reliable prediction has still not been generally achieved.

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KETENE DITHIOACETALS IN ORGANIC SYNTHESIS

Reported by Mike Harmata

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Introduction. A major impetus for research in synthetic organic chemistry has been the discovery and development of new processes for the formation of carbon-carbon bonds. Classically, this has meant the synthesis of molecules by reactions between carbon centers which are nucleophilic or electrophilic in character. Such reactions are classical in the sense that the products they form bear consonant or matched charge affinity patterns between functional groups. Within the last decade, however, the development of the use of latent functionality and reagent or reaction umpolung or charge affinity inversion has grown to provide new strategies for the synthesis of compounds which have dissonant or unmatched charge affinity relationships.1

Ketene dithioacetals and related derivatives are an interesting class of synthetically useful compounds which are capable of normal and umpolung carbonyl group reactivity.2 Sulfur's ability to stabilize adjacent anionic, cationic and radical centers makes this diverse reactivity available.

This seminar will illustrate the use of ketene dithioacetals in organic synthesis and point out their advantages and disadvantages. The coverage is selective and emphasizes recent work.

Synthesis – from Ketones and Aldehydes. Ketene dithioacetals are synthesized by a number of practical and interesting routes. Yields are generally in the range of 70 to 90%.

As might be expected, formation of ketene dithioacetals from ketones and aldehydes involves typical carbonyl olefination procedures in which nucleophilic addition to the carbonyl group is followed by elimination of the carbonyl oxygen and some neighboring group to give a double bond.

The use of 2-lithio-2-trimethylsilyl-1,3-dithiane (4) as a reagent for ketene dithioacetal formation via the Peterson olefination process has been reported by Carey and Court,3a Seebach,3b and Lappert.3c Seebach's procedure uses 4 at lower temperatures and consistently gives higher yields of product. With this approach formamides derived from secondary amines give good yields of adducts, and 1,3,5-trithiane and bis(methylthio and phenylthio)ketene dithioacetals are also available.3c

Phosphorous based reagents such as 1,3-dithiolan-2-yltriphenylphosphonium tetrafluoroborate (2),a trimethyl phosphite ylide 3b and 1,3-dithianyltriphenylphosphonium ylides3c have been found to undergo a Wittig reaction only with aldehydes to give high yields of the corresponding ketene dithioacetals. This is valuable in that it provides for selective functionalization of an aldehyde in the presence of a ketone. Phosphonates react with both aldehydes and ketones in high yield under a variety of experimental conditions including phase transfer catalysis, although this is only useful for aromatic aldehydes.4d,e
Recently, bis(phenylthio)methane boronic esters \(^4\) have been introduced as sources of ketene dithioacetals by Mendoza and Matteson.\(^5\) In this reaction an alpha-boro carbanion functions as a Wittig type reagent.

From Esters and Lactones. The general approach for the preparation of ketene dithioacetals from esters and lactones is Lewis acid catalyzed replacement by sulfur nucleophiles of the oxygens of the ester function. Thus, Corey and coworkers\(^6a,b \) have shown that bis(dimethylaluminum)-1,2-ethanediololate and 1,3-propanediololate react in 50-98% yield with esters and lactones to form the corresponding ketene dithioacetals. Similarly, Cohen\(^5c \) has reported that aluminum thiophenoxide converts saturated or \(\alpha,\beta\)-unsaturated esters or acids into ketene dithioacetals or 1,1,3-tris(phenylthio)1-alkenes, respectively.

From Dithianes. The oxidative conversion of a dithiane to a ketene dithioacetal has been investigated. Fujita and coworkers\(^7a \) have reported the use of 2,2′-dipyridal disulfide as an electrophile for 2-alkyl-2-lithio dithianes to give adducts which fragment in high yield to ketene dithioacetals. Oxidation of dithianes with chloramine T followed by treatment with base also produces ketene dithioacetals.\(^7b \)

Lottenbach and Graf\(^7d \) have reported a specific approach to ketene dithioacetals by the lead (IV) acetate cleavage of \(\alpha\)-hydroxy thioacetals. The reaction works well with a number of compounds. For instance, the bicyclic compound \(^8\) gives the cyclohexanecarboxaldehyde derivative \(^9\) in 92% isolated yield. For the most part, however, the oxidation sequence leads to products of further oxidation of the ketene dithioacetals.

From Dithio Acids and Esters. Ketene dithioacetals can also be prepared from dithio esters. Proton abstraction alpha to the dithio acid or ester and S-alkylation give the ketene dithioacetal. Since dithio esters can be readily prepared from carbanions and carbon disulfide, the synthesis is very broad in scope. Grignard reagents,\(^7e \) triphenylphosphonium ylides,\(^7f \) and compounds such as ketones\(^18a-h \) give fair to high yields of ketene dithioacetals with this methodology.

From Thioamides. A mild conversion of thioamides to ketene dithioacetals by a sequence of carbonyl activation by S-methylation and reaction of the resulting salt with 1,3-propanedithiol in refluxing t-butanol or dichloromethane has been reported by Yoshida and coworkers.\(^7g \)

Nucleophilic Addition to Ketene Dithioacetals. The ability of sulfur to stabilize adjacent negative charge\(^8a,b \) is the basis of many of the roles this element plays in organic chemistry. The facile metalation of 1,3-dithianes and the wide utility of the resulting 2-lithio-1,3-dithianes provide one example.\(^2a \) Similar species can be made by nucleophilic attack on ketene dithioacetals.

The \(\beta\) addition of certain 2-alkylidene 1,3-dithianes with alkyl lithiums, except for methyl lithium and less reactive species like ketone enolates, to produce intermediate 2-lithio-1,3-dithianes which can be trapped with electrophiles and hydrolyzed to the corresponding...
Inverse reactivity \( i \). If the ketene dithioacetal bears a gamma hydrogen, proton abstraction to form the useful allylic anion \( g \) predominates. Nucleophilic additions to ketene dithioacetals act as a synthon for ketenes with carbonyl compounds has been reported by Seebach and coworkers. \( ^{2a,9a-c} \) In this sequence ketene dithioacetals act as a synthon for ketenes with

Vinylogously extended ketene dithioacetals, dienes such as \( 9 \), have also been found to add alkyl lithis at C-4 to produce intermediate allylic anions which can be electrophilically trapped. Interestingly, proton abstraction from allylic positions does not appear to be competitive with addition in these systems. \( ^{9c,d} \) Such a metalation, however, does appear to explain side products \( 10 \) and \( 11 \) observed in the synthesis of the insect pheromone \( \text{manicone} \).

The configuration of \( 12 \) is typical of products obtained in this sequence. The reactivity of these reagents constitutes a synthon of the type shown in \( 13 \).

Conjugate addition to ketene dithioacetals has found other applications in synthesis. The terpenoids lanceol and lavandulol have been prepared by this route. \( ^{11} \) Addition of alkyl lithiums to 1,1-bis(ethylthio)-2,2-difluoroethene followed by hydrolysis provides a route to the biologically interesting \( \alpha \)-fluoro carboxylic acids or esters. \( ^{12} \) The addition of
α-phenylthio carbanions to 1,1-bis(phenylthio)ethene with subsequent intramolecular displacement of thiophenoxide to form substituted cyclopropanone phenylthioketals has recently been reported by Cohen and coworkers. Even 1,3-bis(phenylthio)allyl anions can be used in this sequence. The product phenylthioketals can be reductively cleaved to α-phenylthio cyclopropyl carbanions 15. The parent compound of this series has received much attention as an annulating agent. Similar applications of the substituted compounds remain to be developed.

Although in general Grignard reagents do not undergo nucleophilic addition to ketene dithioacetals, Andersen and coworkers have found that the intramolecular reaction does proceed in low to moderate yields. Addition of Grignard reagents to an acyclic 2-chloro ketene dithioacetal and a 2,2-difluoro ketene dithioacetal have also been carried out.

Reduction of ketene dithioacetals by hydride reagents is generally not viable. However, Wong and Gray have developed a very interesting stereoselective synthesis of 2-deoxy pentoses based on the lithium aluminum hydride reduction of a ketene dithioacetal. The sequence is shown in Scheme I. Deuterium labelling indicated that incorporation of hydride from the reducing agent occurs at C-2 with water providing the proton at C-1. Reduction with lithium aluminum deuteride of or gave a single diastereomer or respectively. Further investigation revealed the necessity of the C-3 hydroxyl function in the reduction of the ketene dithioacetal. Based on these observations, the reaction was interpreted as proceeding through an alkoxy aluminum hydride salt with hydride delivery to the double bond occurring in a transition state with the s-trans configuration about the C-2, C-3 bond. The alternative transition state is disfavored due to steric crowding between an ethylthio group and the C-4, C-5 acetonide.

The limited scope of nucleophilic additions to ketene dithioacetals has been nicely circumvented by the development by Schlessinger and coworkers of ketene dithioacetal monosulfoxides. These compounds, easily available from the corresponding thioacetals by oxidation with m-chloroperbenzoic acid or sodium periodate, exhibit Michael reactivity with a much wider range of nucleophiles than ketene.
dithioacetals. Enamines, metalloenamines, ester, \( \alpha-\beta \)-unsaturated ester, \( \beta \)-dicarbonyl, amide and ketone enolates react in high yield to give thioacetal monosulfoxides which are easily hydrolyzable to the corresponding carbonyl compounds.\(^{16a-b,9c,17e}\) The anion resulting from nucleophilic addition to a ketene dithioacetal monosulfoxide can be thermodynamically more stable than the attacking anion. This obtains in the case of ester enolates, for example, and makes possible the trapping of the sulfur stabilized anion with an electrophile. Should the reaction be thermodynamically unfavorable, as in the case of the addition of a sodium malonate, it is possible for the equilibrium to be driven to the right by a second proton transfer from the malonyl function to form a different salt capable of being trapped by electrophilic agents. Yields in these sequences are quite high and reactants are used in a 1:1 molar ratio. Apparently, no example of Michael addition to vinylogously extended ketene dithioacetal monosulfoxides is known.

Several examples of the utility of these compounds can be found in the literature. Schlessinger and coworkers\(^{17a,b}\) have reported the use of ketene dithioacetal monosulfoxides in the preparation of 2-substituted 4-hydroxycyclopentenones by the sequence shown in Scheme II. Michael addition of a substituted \( \alpha \)-methylthio ketone enolate on an appropriate ketene dithioacetal monosulfoxide receptor

![Scheme II](diagram)

gave adduct \(^{22}\) in quantitative crude yield. Hydrolysis of crude \(^{22}\) and cyclization of the resulting keto aldehyde gave good yields of hydroxycyclopentenones \(^{23}\). Untch\(^{17c}\) has used the parent dithioacetal monosulfoxide (\( R_1 = R_2 = H \)) in a convergent total synthesis of (\( \pm \))-prostaglandin F\(_{20}\). The final pieces of the alkaloid (\( \pm \)-1-acetylaspidoalbidine were constructed in a similar fashion.\(^{17d}\) Some 3,4-disubstituted furans and other cyclopentanoids have also been synthesized using a sequence of Michael addition, hydrolysis and acid-or base-catalyzed cyclization.\(^{17e}\) Ketene dithioacetal monosulfoxides are good enolate traps and function well as aldehyde enolate cation equivalents.

Nucleophilic addition to ketene dithioacetals takes place in a classical sense if the acetal is substituted at C-2 with an electron-withdrawing group. Most often this is a carbonyl function.\(^{16}\) Michael addition at the carbon-bearing sulfur and subsequent elimination of none, one or both of the alkyl thio groups leads to novel substituted ethenes or, less frequently, carbonyl compounds with tertiary alpha substituents.
Compounds of this type, so-called α-oxoketene dithioacetals, have been used extensively in the synthesis of heterocyclic compounds. Two examples are shown in the synthesis of pyrrole and pyrimidine.

Carbon nucleophiles add to α-oxoketene dithioacetals as well. Potts and coworkers recently reported the addition of ketone enolates to α-oxoketene dithioacetals to form unsaturated 1,5-diketones which are easily converted to pyridines with ammonium acetate. Corey’s procedure for the introduction of sec-alkylidene or t-alkyl groups alpha to a keto function is a well-known example of this addition elimination process. The conjugate reduction of α-oxoketene dithioacetals with retention or loss of a single alkylthio group has also been reported.

Anions from Ketene Dithioacetals. As noted above, the gamma hydrogens of ketene dithioacetals are acidic, and the resulting anions are synthetically useful.

Facile gamma hydrogen abstraction from ketene dithioacetals occurs with n-butyllithium or lithium diisopropylamide in the presence of HMPA. Electrophilic trapping of the resulting allylic anion followed by hydrolytic removal of the sulfur groups gives carbonyl products. Depending on the regiochemistry of trapping, the allyl anion can function as α-β-unsaturated acyl anion equivalent to give 27 or β-lithio propionate equivalent to give 26. In most cases, trapping at the carbon-bearing sulfur is observed. As in the case of monophenyllithio allylic anions, gamma reactivity predominates with carbonyl electrophiles.

Studies have been conducted which examine steric, solvent, and counter-ion and electrophile effects on the regiochemistry of substitution. It was found that α-alkylation increases with electrophile hardness. Ziegler and Tam found that in alkylations of (R₁ = R₂ = H), increasing steric bulk of the alkylthio groups and presence of a copper (I) counterion increased gamma reactivity greatly. Addition of B to α,β-unsaturated ketones, with respect to regiochemistry on both reactants, has been examined as well. In tetrahydrofuran, B (R₁ = R₂ = H) showed regioselectivity for 1,4-γ-substitution. The addition of HMPA or copper (I) changed the preference to 1,4-α-substitution.
The anions derived from ketene dithioacetals have found application in synthesis. Though regiochemically ambiguous they do trap alkyl halides and protons predominantly or exclusively at C-1. A conversion such as that of a methyl ester to ketene dithioacetal to α-β-unsaturated ketone or aldehyde via the allylic anions provides a viable and useful synthetic transformation. The anions have been used by Kozikowski and Chen in an approach to γ lactones. Also, Ziegler and coworkers have used allyl anions of this type in the synthesis of the pseudo-guanolide sesquiterpenes, aromatin, and confertin.

Under the proper conditions, vinylogously extended ketene dithioacetals can be deprotonated to the corresponding pentadienyl anions. These react with electrophiles at C-1 in 60-90% yields and are synthons for structure 30. Vinyl anions have recently been made accessible by a reductive lithiation procedure developed by Cohen and coworkers. The intermediate anions are acyl anion equivalents formed from electrophilic attack and are synthetically useful.

Marino has studied deprotonation in certain α-oxoketene dithioacetals and has generated, among others, the anion, a vinylogous "dipole-stabilized" carbanion. This is not trapped but cyclizes intramolecularly to form 2-methylthio-3,4-disubstituted thiophenes in low to moderate yields.

Reactions of Ketene Dithioacetals with Electrophiles. Attack of electrophiles on the π system of ketene dithioacetals followed by nucleophilic trapping of the resultant bis-sulfur stabilized cation provides for some useful transformations of these compounds. Thus, dithioorthoesters, thioesters, aldehydes, carboxylic acids, and esters, and α-halo and α,α-dihalo esters are available by protic or Lewis acid mediated reactions.

Andersen and more recently Brinkmeyer reported the use of ketene dithioacetals as initiators in one ring and two ring forming cationic cyclizations, respectively.

The oxidation of 1,3-dithianyl dithioacetals in moderate yields to 1,4-dithiocycloheptan-2-ones has been reported by Hiroi and Sato. Trost and coworkers have shown that these compounds can be converted to esters and ketones and their α,β-unsaturated analogues.
Summary. Methods for the synthesis of ketene dithioacetals are well developed and these compounds are thus easily accessible. They have contributed to carbonyl umpolung technology by providing synthons \( \frac{1}{2}, 13, 28, \) and \( 29. \) Their classical reactions have also added to synthetic methodology. Ketene dithioacetals have found their place in the synthesis of natural products and will probably continue to play a role in this area. It is clear, however, that work expanding the synthetic potential of this functional group would be valuable.

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DNA is the only macromolecular constituent of cells whose detailed structure and conformation are known. Many synthetic compounds and natural products have been identified which interact with DNA, some of which are useful as drugs in the treatment of malignant and infectious disease. Therefore, the study of the binding of these compounds to DNA could lead to a detailed model of this drug-receptor interaction process and provide a basis for the rational design of chemotherapeutic agents.

A major class of these drugs are called intercalators as they function by insertion between the base pairs of DNA as shown in Figure 1.

All known intercalators contain planar unsaturated ring systems, some examples of which are acridine, ethidium, and actinomycin. To allow space for the insertion of these compounds there must be a conformational change in the DNA structure. It has been proposed that, in solution, DNA oscillates due to solvent collisions. At some critical oscillation amplitude, the furanose rings of the backbone sugars can change their pucker with concomitant partial unstacking of the base pairs. The crystal structures of DNA-intercalator complexes show that there is a change from the normal C(2')-endo puckering of the furanose rings to a mixed C(2')- and C(3')-endo conformation around the intercalation site accompanied by unwinding and lengthening of the helical structure as shown in Figures 1 and 2. The conformational change introduces a gap between the base pairs of 3.4 Å, which will precisely accommodate the π system of an intercalator.
In general, as the affinity of an intercalator for DNA increases, so does its biological effect. Accordingly, many of the strongest binding intercalators are of current interest for use as chemotherapeutic agents. In an effort to increase the affinity of intercalative compounds for DNA, and perhaps increase their chemotherapeutic effect, dimers of well-known intercalators have been synthesized and their binding parameters evaluated. In addition, the naturally occurring quinoxaline antibiotics, which have two potential intercalative functions, have been investigated. The rationale for the increased affinity of these bifunctional compounds for DNA is that once one of the functionalities is intercalated, the other is brought in close proximity to another intercalation site. These compounds could also impart a much greater degree of selectivity in their binding to DNA than their monofunctional analogs since whatever constraints apply to the binding site of one chromophore would apply to the other. Therefore, a bifunctional intercalator would require two similar binding sites in close proximity, which would limit the number of locations along the DNA sequence for drug interaction. Recognition sites on DNA for repressors, restriction enzymes, and transcriptional factors are thought to contain repeating base pair sequences. Therefore, site-specific intercalators could provide a handle for controlling different DNA-protein interactions.

The first compound to be identified which bound bifunctionally to DNA was the quinoxaline antibiotic, echinomycin. Echinomycin is produced by a variety of streptomycetes and has been found to be an extremely potent inhibitor of DNA-directed RNA synthesis. Echinomycin is characterized by a cross-bridged cyclic octapeptide containing both D- and L-amino acids to which are attached two quinoxaline-2-carboxilic acid chromophores as shown in Figure 3. Evidence for the bifunctionality of the interaction of echinomycin with DNA has been demonstrated by several experimental methods.

Supercoiled circular PM2 DNA is unwound by intercalating agents with a concurrent change in the sedimentation coefficient from which the unwinding angle can be calculated. Echinomycin produces an unwinding angle approximately twice that of the mono-intercalating agent, ethidium bromide. In addition, sonicated rod-like DNA is lengthened almost twice as much by echinomycin as by monofunctional intercalators as measured by capillary viscometry. Apparently, both quinoxaline chromophores of echinomycin are intercalated into the DNA helix in a bifunctional manner. By similar
methods other quinoxaline antibiotics and their derivatives were found to act as bifunctional intercalators as shown in Table I. \(^{11-13}\)

\[\text{Figure 3}\]

<table>
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<tr>
<th>Compound</th>
<th>Base Pair Preference</th>
<th>(\Delta L_{\text{ethidium}})</th>
<th>(\Delta H_{\text{ethidium}})</th>
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<tr>
<td>TANDEM</td>
<td>A-T</td>
<td>*</td>
<td>1.75 ± 0.23</td>
</tr>
</tbody>
</table>

*no data

The affinity of echinomycin for DNA is about 1000 times greater than that of the monofunctional antibiotic, actinomycin. \(^{11,14}\) The strength of binding of echinomycin to DNA depends, to a large extent, on the presence and integrity of the cross-bridged octapeptide. Quinoxaline-2-carboxamide, which is essentially the intercalative chromophore of echinomycin, shows no detectable interaction with DNA even at high concentrations. \(^{15}\) In addition, when the lactone ring or the cross-bridge was cleaved, there was little or no binding to DNA. \(^{15}\) These facts indicate that a certain degree of conformational rigidity is needed for echinomycin to interact with DNA.

The association constants for the interaction of the quinoxaline antibiotics with a variety of natural and synthetic DNA polymers were determined by partitioning methods. \(^{9-13}\) It was found that some quinoxaline antibiotics showed a preference in binding to DNA rich in adenine-thymine (A-T) base pairs while others bound preferentially to DNA rich in guanine-cytosine (G-C) base pairs as seen in Table I. This selectivity seems to
be due to the nature of the intercalating chromophore and the octapeptide cross-bridge. The echinomycin derivative, 2QN, which has both of the quinoxaline-2-carboxylic acid moieties replaced by quinoline-2-carboxylic acid, shows a preference for A-T base pairs while echinomycin binds stronger to DNA rich in G-C base pairs. The basis of this specificity is unknown but must be due to some differential interaction between these chromophores and the base pairs. Triotsin A, which differs from echinomycin only in the nature and length of its cross-bridge, preferentially binds to A-T rich DNA. The difference in selectivity between Triotsin A and echinomycin is presumably due to a conformational difference between the peptide portions of these molecules.

The exact nature of the interaction of the quinoxaline antibiotics with DNA which results in this base pair specificity cannot be formulated until crystal structures can be assigned. However, conformational studies may provide a clue as to the stereochemical relationship between bound antibiotic and the DNA receptor. The most favorable conformations for echinomycin in solution were determined by $^1$H and $^{13}$C magnetic resonance spectroscopic data, potential energy calculations, and model building. The most stable conformation was selected by optimizing the potential energy with respect to the constraints imposed by ring closure geometry, hydrogen bonding, and the spectroscopic data. This process led to a structure of echinomycin in which all the peptide bonds are trans and the quinoxaline rings and alanine carbonyl oxygens protrude from the same face of the molecule as shown in Figure 4.

Recently, the crystal structure of a synthetic derivative of Triotsin A, des-N-tetramethyl Triotsin A (TANDEM), has been obtained and is shown in Figure 5. TANDEM exhibits bifunctional characteristics and shows a preference for DNA rich in A-T base pairs. Like the model for echinomycin, all peptide bonds are trans and the quinoxaline rings and alanine carbonyl oxygens protrude from the same side of the octapeptide ring system. In addition, it was found that the peptide ring is held in a relatively rigid conformation by hydrogen bonding between the amino hydrogens of the L-valines and the carbonyl oxygens of the L-alanines. TANDEM also displays a helical twist in the same direction as DNA and possesses a two-fold axis of symmetry. Models of the possible intercalation complexes of TANDEM with DNA show that the amino hydrogens of L-alanine can only form hydrogen bonds with the O-2 atoms of thymine, which may
explain the preference of TANDEM for A-T rich DNA. In the models formulated for the binding of echinomycin and TANDEM with DNA, the lipophilic groups point inward toward the base pairs while the majority of the hydrophilic groups face outward for hydrogen bonding with the solvent. These models also indicate that the distance between the quinoxaline rings is 10 to 12 Å which is ideal for sandwiching two base pairs between the quinoxaline chromophores. This mode of binding reinforces the concept of the neighbor exclusion principle which states that intercalators cannot occupy adjacent sites in the DNA helix.\(^{20,21}\) This theory is valid for monofunctional intercalators but studies of the binding of echinomycin to DNA indicate that in some cases the site size for the antibiotic is only three base pairs.\(^6,15\) This implies that echinomycin can form a one base pair sandwich which is in violation of the neighbor exclusion principle.

To investigate the minimum separation between chromophores needed for bifunctional intercalation, a series of unsubstituted acridine dimers, connected at the 9-9' positions by a homologous series of \(\alpha,\omega\)-polyamines were synthesized.

\[
\text{C}_n: \quad n = 2, 4, 5, 6, 8, 10, 12, 14
\]

The ability of these compounds to interact bifunctionally with DNA was determined experimentally by the measurement of the unwinding angle of supercoiled PM2 DNA,\(^{22-24}\) the lengthening of sonicated rod-like DNA,\(^{23,24}\) and the extension of circular DNA by electron microscopy.\(^30\) It was found, in all cases, that the transition from mono- to bifunctional intercalation occurred when \(n = 6,22-24,30\) The maximum distance between the acridine rings in \(C_6\) is 8.1 Å which limits its mode of binding to a one base pair sandwich model. This indicates that the neighbor exclusion principle does not apply to these compounds and its validity needs to be reexamined.\(^22\) The diacridine, \(C_5\), shows transitory behavior - acting as a monofunctional intercalator at low concentrations and a bifunctional intercalator at higher concentrations.\(^23\)

The binding affinity of these diacridines for DNA increases from \(10^5 M^{-1}\) for \(C_2\) and \(C_4\), which is typical for monointercalators, to greater than \(10^9\) to \(10^{10} M^{-1}\) for \(C_6\) and \(C_8\), which bind bifunctionally. The diacridine \(C_6\) shows the maximum binding to DNA as evidenced by the increase in the melting of DNA\(^{28,31}\) as well as partition experiments.\(^28\)

It has been shown that \(C_8\) is taken up by P-388 leukemia cells to a remarkable extent. The concentration of \(C_8\) in the cell and nucleus is 2,000 and 10,000 times greater, respectively, than in the medium.\(^{28,32}\) Short chain diacridines (\(n < 6\)) behave in much the same manner as their mono-intercalating analog, 9-amino acridine, and are accumulated largely in the cytoplasm.\(^28\) The increase in uptake with \(C_6\) and \(C_8\) may be due to the increase in their lipophilicity but the decrease in uptake of the longer chain diacridines indicates that this is not the sole effect and there are other factors to consider.
Agglutination studies with S-180 cells, which give an indication of membrane related interactions, show a maximum effect for C₆ and C₈ diacridines.³³ These studies correlate well with the percent increase in life span (% ILS) of mice bearing P-388 leukemia tumors, which again is largest with the C₆ and C₈ diacridines. These facts indicate that the antitumor effectiveness may be associated with very specific membrane sites that could be characteristic of tumor cells.

Once within the cell, the biological effect of these compounds is most likely related to the inhibition of RNA synthesis by blocking the promoter sites on DNA for RNA polymerase.²⁹,³⁴,³⁵ The bifunctional intercalators have binding constants comparable with RNA polymerase, so will not be easily displaced. Actinomycin, which has a 10,000-fold lower binding constant than RNA polymerase, cannot block the initiation of synthesis but interferes in the elongation process.³⁴

Substituents on the acridine ring could prevent intercalation by steric or electronic effects. They might also increase the affinity of the intercalator for DNA by favorable interactions with the base pairs or phosphate diester backbone. Substituents can therefore determine the specificity and strength of binding. Much less is known about the effect of substituents on the acridine ring than the effect of the connecting chain but a few generalizations can be made which correlate with the binding affinity, % ILS, and toxicity.²⁴,³² Substituents in the 2, 3, or 6 positions of the acridine ring restrict bifunctional intercalation to compounds which have large enough aromatic ring spacing to obey the neighbor exclusion principle but unsubstituted or 4-ethyl diacridines can bifunctionally intercalate with significantly shorter chain lengths. Alkoxy substituents in the 3- or 4-positions of the aromatic ring system give highest % ILS but tend to enhance the toxicity as their size is increased. A 6-nitro substituent generally lowers the toxicity of the substituted diacridines whereas a 2-alkoxy substituent increases the toxicity. Unfortunately these substituent effects cannot be correlated to specific interactions with the DNA molecule since their crystal structures have not as yet been determined.

Other compounds which have been synthesized and exhibit bifunctional behavior include dichloroquine derivatives,³⁶ bis(quinidine) derivatives,³⁷ ethidium and ethidium-acridine dimers,³⁸-⁴⁰ bis(methidium) spermine,⁴¹ and ellipticine dimers.⁴²

The efficiency and specificity of drug action is of the utmost importance in the field of chemotherapy. It has been shown that bifunctional intercalators have as much as 10⁴-fold higher affinity for DNA than their monofunctional analogs. Perhaps the greatest problem with high affinity drugs is their toxicity. However, substituents on the aromatic rings of the bifunctional acridine dimers have produced high affinity, low toxicity compounds and further studies will undoubtedly lead to even less toxic analogs. In addition, trimeric or polymeric intercalative complexes might have even higher affinities for DNA. It has also been seen that the quinoxaline antibiotics show some base pair selectivity. By altering the intercalative moieties and the octapeptide ring system, different base pair selectivity can be achieved. This has led to derivatives which have preference for different types of naturally occurring DNA or certain regions of the DNA sequence. This could allow great flexibility in manipulating the biological processes in which DNA is involved.
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MECHANISTIC ASPECTS OF POLYMER SUPPORTED CATALYSIS IN TRIPHASE SYSTEMS

Reported by David R. Hay

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Insoluble functionalized polymer supports have been used as reagents, substrates and catalysts.\(^1\)\(^2\) These polymers offer the well-known advantages of easy separation from reaction mixtures, simple regeneration for reuse, and compatibility with automation and flow systems often used with large scale packed and fluidized bed reactors. There are also disadvantages in the use of functionalized polymer supports. Their activity is generally less than that of their soluble, unbound counterparts and their physical properties may interfere with their intended use. For example, highly cross-linked macroporous resins often reduce the access of a substrate molecule in reaching a catalytic site and thereby reduce the reaction rate. Also, the most commonly used support, polystyrene cross-linked with 2% divinylbenzene (DVB), can be too gelatinous in certain swelling solvents for use in flow systems and filtrations.\(^3\)\(^4\)

In attempts to overcome these limitations and to better understand the mechanism of polymer-supported catalysis, various workers have studied the mechanism of phase transfer catalysis in aqueous-organic biphasic reactions and their ability to accelerate such processes. When such soluble catalysts are bound to a solid support and used in a so-called triphase system, reaction rates have been found to depend on mixing, catalyst particle size, degree of cross-linking, solvent and temperature.\(^5\)

Phase transfer catalysts include amines, quaternary ammonium salts, quaternary phosphonium salts, crown ethers, cryptands, and linear polyethers. The mechanism is presently thought to involve the catalyst as an agent which transfers one reactant across an interface into another phase so reaction can proceed. Transfer can proceed whether the catalyst is mobile or immobile.

A different and interesting use of a polymer supported triphase system to gain mechanistic information has been used by Rebek in which separate reactants are on different supports.\(^2\) These reagents would therefore be inaccessible to one another but a catalyst in solution would have access to both species. Thus reaction of the catalyst with one reactant would produce a soluble intermediate which could subsequently diffuse and react with the other reactant. Mechanistically, this requires the existence of a polymer-free intermediate. As such this system can be used to detect the presence of reactive intermediates. As an example, imidazole was used as an acyl transfer agent between a polymer bound acetate and a polymer bound amine. In Figure 1, imidazole dissolved in dioxane/H\(_2\)O can react with the acetate yielding an acyl-imidazole intermediate as in step 1. This can be

\[
\begin{align*}
\text{P1} & \xrightarrow{\cdot} \text{CH}_2 - \text{C}=\text{O} - \text{CH}_3 \\
\text{P2} & \xrightarrow{\cdot} \text{CH}_2 - \text{C}=\text{O} - \text{CH}_3
\end{align*}
\]

Figure 1. Triphase Reaction of Imidazole with Polymer-bound Acetate and Polymer-bound Amine.

trapped by the amine in step 1\(^2\) to give the polymer-bound amide product. While the existence of the intermediate is proven unambiguously, only inferences can be drawn about its structure.
Most phase transfer catalysis systems involve reactants which are in separate, immiscible liquids. Kinetic studies of these systems show first-order behavior in substrate concentration and also indicated the rate determining step takes place in the organic phase rather than in the aqueous phase, at the interface, or in micelles. For example, in the reaction of an alkyl halide, RX, in an organic solvent with an aqueous alkali metal M⁺Y⁻ to form RY, an anion salt catalyst Q⁺X⁻ can undergo ion exchange in the water layer to yield a new ion pair Q⁺Y⁻ as shown in step 1 of Figure II. This can dissolve in the organic layer due to the lipophilic nature of Q⁺. Hence Y⁻ is effectively "ferried" across the phase boundary as in step 2. In the organic layer, Q⁺Y⁻ can displace halide from RX giving the product RY and the original ion pair Q⁺X⁻ as in step 3. Finally, X⁻ is "ferried" back into the aqueous layer as Q⁺X⁻ in step 4 where the cycle can be repeated.⁵

A major disadvantage of phase transfer catalysts is that after reaction, they must be removed from the solution. In the particular case of crown ethers, cryptands, or chiral onium salts, the expense warrants as complete a recovery as possible. Attachment of these catalysts to insoluble, cross-linked polymer supports is an attractive solution which allows isolation by simple filtration and quantitative recovery.

**Triphase Systems.** The feasibility of such a system in the reaction of aqueous sodium cyanide with 1-bromo- and 1-chlorooctane in benzene to give 1-cyanoctane when catalyzed by polymer supported quaternary ammonium chloride was demonstrated by Regen. The presence of the solid polymer floating on the aqueous-organic interface as shown in Figure III has brought about the term 'triphase' catalysis in which the bound catalyst is regarded as a distinct third phase.⁶,⁷,⁸ Typical yields for these reactions are 73-76% at 90°C over a 3-16 hour period. Control experiments were performed in the absence of the catalyst resin and in the presence of unfunctionalized chloromethylpolystyrene. No reaction was observed indicating the onium salt was indeed the active agent. In addition, other experiments indicated none of the catalyst dissolved or decomposed to yield an active, unbound species.⁵

In an attempt to determine the dependent parameters, the type of polystyrene support material was varied as were the degree of cross-linking, percent ring substitution, and the alkyl groups attached to the nitrogen atom. The results are presented in Table I.
The rate constants are listed in molar quantities where $k^m = k_{obs} / \text{moles of catalyst used for the purpose of comparison.}$

It can be observed from entries 1 and 2 that both microporous and popcorn functionalized resins afforded similar rate constants of 2.2 and 2.5 sec\(^{-1}\) respectively. The macroporous supported catalyst however, which contained 8% DVB, exhibited a decrease in rate by a factor of ten as seen by entry 3. This result suggests the rate is diffusion controlled such that the higher degree of cross-linking forms smaller intraparticle pores and thereby decreases the number of substrate molecules that can reach an active site per unit time. In view of the poor swelling ability of a macroporous resin, the catalytic sites may not be well solvated and this could also limit the diffusion rate.

Larger alkyl groups in the quaternary ammonium group were found to increase the rate somewhat although generally by less than a factor of two as shown in entry 4. This has been interpreted as allowing better solvation of the organic phase and hence a greater concentration of alkyl halide. When the structure of the quaternary ammonium species was changed to include a more hydrophilic -CH\(_2\)CH\(_2\)OH group as shown in entry 5, a slight decrease in rate was observed suggesting a reduction in its ability to dissolve in the organic phase. The seemingly anomalous result in entry 6 indicates changing the alkyl group to a smaller methyl group yields a higher rate constant of 3.0. Although the solvating ability of the cation would be expected to decrease the rate, the reduced steric crowding of the anion apparently more than overcomes this problem.

It was further noticed that changing the extent of loading to 1% and 21% in entries 7 and 8 respectively caused no significant rate change. An interesting result was observed however, in entries 9 and 10 when the percent ring substitution was increased above 45%. In these cases, the rates dropped by more than a factor of one hundred. Accompanying this loss in activity was a substantial change in the swelling properties of the resin. The amount of organic solvent imbibed decreased while the amount of imbibed water increased. Thus resins which were more compatible with the organic phase than with the aqueous phase exhibited greater catalytic activity. The origin of this effect is not known.

From this work it was concluded that at 8-10% ring substitution and low cross-link density, the structure of the quaternary ammonium group and the type of support material used are not of major importance in determining the catalysts activity. At higher degrees of cross-linking, the rate is limited by diffusion and solvation effects.
In further work, it was shown that when the ammonium salt was exchanged for a phosphonium salt, greater activity was observed. Moreover, all triphase reactions proceeded slower that comparable transformations carried out with unbound phase transfer catalysts.

In another systematic study, the length of the pendant chain or "side arm" used to attach the catalyst to polystyrene was varied to examine its influence on the activity of the resulting resin. It was postulated that if the mechanism for bound catalysts was similar to the one for the unsubd phase, one must assume the existence of an aqueous-organic phase boundary at the catalytic site. The transportation of anions across the boundary would then involve motion of the polymer backbone and the functionalized side chain. If this scheme is correct, it would predict improved efficiency of catalysis by lengthening the side chain thus allowing for greater motion. Experiments performed with the resin gave significant improvement in the reaction rates as n was increased from 0 to 3. At longer chain lengths, the catalytic activity approached that of unbound phase transfer catalysts. While this data is consistent with the theory, other effects such as greater solvation or diffusion might also be involved.

Measurements of the reaction rates were determined to establish the components in the rate-determining step. The kinetic studies carried out indicated the displacement reaction was first-order in 1-bromooctane. Examination of the dependency of the rate constant on the amount of cyanide present in the reaction mixture revealed that a tenfold increase in the amount of sodium cyanide employed caused no significant change in the rate of reaction. Furthermore, a plot of $k_{obs}$ as a function of the amount of polymer supported catalyst used, demonstrated that the rate is linearly dependent on the amount of catalyst present.

A kinetic description consistent with the above data and with the data presented in Table I was proposed by Regen. If $P_{CN}$ and $P_{CN}$ represent single quaternary ammonium chloride and quaternary ammonium cyanide groups bound to polystyrene respectively, they are related by the equilibrium constant K. The rate determining step may likewise involve the polymer supported ammonium cyanide reacting with the alkyl bromide related by a rate constant $k_{1}^{m}$. The scheme is then as follows:

\[
\begin{array}{c}
\text{Scheme I. Proposed Mechanism for the Displacement of} \\
\text{Bromide by Polymer Supported Ammonium Cyanide.} \\
\end{array}
\]

\[
P_{CN} + RBr \xrightarrow{k_{obs}} P_{Br} + RCN
\]

Expressing the terms for the polymer supported cyanide and chloride as molar quantities $P_{CN}^{m}$ and $P_{CN}^{m}$, the total molar quantity of ionic groups is $P_{CN}^{m} + P_{Cl}^{m}$. Thus the equilibrium equation may be derived as follows:

\[
K = \frac{(P_{CN}^{m}(CN^{-}))}{(P_{CN}^{m})(Cl^{-})} = \frac{(P_{CN}^{m}(CN^{-}))}{(P_{CN}^{m})(CI^{-})}
\]

and rearranged to

\[
\frac{(P_{CN}^{m}(CN^{-}))}{(CN^{-})K + (Cl^{-})}
\]
This equilibrium equation can be further simplified by assuming K(CN⁻) >> (Cl⁻) since the data show formation of the ammonium cyanide is favored. This yields the following equation:

\[ P_{CN}^n = \frac{(P_{CN}^n K)_{CN}}{(CN^-)K} = P_t^m \]

This suggests the polymer catalyst is almost exclusively in the cyanide form. The rate equation for the disappearance of 1-bromoocctane can then be derived as follows:

\[ \frac{-d(1\text{-bromoocctane})}{dt} = k_1^m P_{CN}^n(1\text{-bromoocctane}) \\
\frac{-d(1\text{-bromoocctane})}{dt} = k_2^m P_t^m(1\text{-bromoocctane}) \\
\frac{-d(1\text{-bromoocctane})}{dt} = k_{obs}^m(1\text{-bromoocctane}) \]

The equality \( k_{obs}^m = k_1^m P_t^m \) can be made since the total quantity of ionic groups bound to the support is constant. Further evidence supporting this mechanism was obtained by isolating and washing the catalyst after only 1/2 hour of reaction time. Analysis revealed that all of the chloride ions had been replaced by cyanide ions indicating the equation \( P_t^m = P_{CN}^n \) is indeed valid.

Thus the proposed mechanism predicts a simple first order dependency on the concentration of 1-bromoocctane which was confirmed by experiment. Similar kinetic behavior was observed when the cyanide form of the resin was placed in the organic 1-bromoocctane solution without any aqueous layer. Also, when water was added as the aqueous layer, first order kinetics were still observed.

From this work, it was concluded that the chemical reaction was rate limiting rather than a physical factor such as diffusion. If this is indeed the case, the reaction should be characterized by the following five points: a first order dependence on alkyl halide concentration would be observed; the rate would be directly proportional to the amount of catalyst used; the rate would be independent of stirring speed; a significant activation energy of more than 10 kcal mol⁻¹ would be required; the rate would be independent of catalyst particle size.

In the system studied by Regen, an increase in stirring speed from 0 to 750 rpm resulted in only a slight rate increase of 20%. Increasing the surface area of the resin by grinding it to a powder actually caused a slight decrease in catalyst activity. The apparent activation energy was measured as 19.9 ± 1.6 kcal mol⁻¹. These data were interpreted in favor of a rate limiting chemical reaction mechanism although the decrease in activity due to reduced particle size could not be explained.

In contrast, a process in which diffusion was rate limiting would be expected to show a dependence of the rate on stirring and particle size. Also, the activation energy would be lower than in the case where chemical reaction is rate limiting. A diffusion controlled process however, would be expected to proceed at a rate which has a first-order dependence on alkyl halide concentration and is directly proportional to the amount of catalyst used as did the chemically controlled reaction.

In another study of the system employed by Regen, a simple ion-exchange model was used by Ford and Tomoi to investigate the importance of diffusion and mass transfer. The basic kinetic steps in ion-exchange have been known
for some time. They are as follows: (1) mass transfer of the reactant from the bulk liquid to the catalyst surface; (2) diffusion of the reactant through the polymer matrix to the active sites; (3) intrinsic reaction at the active sites to yield the product; (4) diffusion of the product out of the matrix into the bulk liquid. The reaction of cyanide with 1-bromooctane to give the expected 1-cyanooctane product differs from ion-exchange only in the presence of two liquid phases rather than one.

This ion exchange model was further elaborated as shown in Figure IV. These diagrams represent the alkyl halide concentration as a function of distance from the particle center for fast and slow mixing.

![Diagram](image)

The initial step shown in both diagrams involves mass transfer of the alkyl bromide from the bulk liquid to the so-called quiet film. This is the layer at the surface of the resin which experiences essentially no turbulent flow since the flow rate increases with distance from the particle surface. This phenomenon is most familiar to chemists as the "Nernst Layer" around the electrode in electrochemistry or the "wall effect" in liquid flow through a pipe. The thickness of this layer depends upon the stirring. The faster the liquid flow, the thinner the quiet film will be as illustrated in Figure IV A.

Diffusion of the substrate across the film constitutes a second step. The rate of this process depends not only upon the thickness of the layer but also upon the diffusion coefficient of the reactant. Whenever mass transfer limits the observed reaction rate, there is a gradient of decreasing concentration of reactant from the bulk liquid across the quiet film to the catalyst surface as shown in Figure IV B.

When the reactant reaches the particle surface, the reaction rate will depend upon the activity of the catalyst, the number of active sites on the polymer surface and intraparticle diffusion throughout the polymer matrix. If the intrinsic reactivity is slow relative to intraparticle diffusion due to low catalyst activity, there will be no concentration gradient from the surface to the center of the particle as shown by pathway (1) in Figure IV. If intrinsic reactivity at an active site is high or intraparticle diffusion is slow, the reaction occurs only on the resin surface as in pathway (2). If both matrix diffusion and chemical reaction proceed at similar rates, there will be an exponential decrease in reactant concentration from the surface to the center of the particle as in pathway (3).

Using this model, the contributions of mass transfer, intraparticle diffusion, and intrinsic reactivity in controlling the observed rates were studied. Experiments were performed to determine the effects on stirring speed, particle size, solvent, degree of cross-linking and temperature on the reaction rate. These effects were then correlated with the appropriate mechanistic steps.

Reaction mixtures were stirred by mechanical stirring, vibromixing, and ultrasonic mixing. Plots of pseudo first-order rate constant vs. stirring speed
show a four-fold rate increase in the case of a 2% DVB resin when the stirring speed was increased from 100 to 650 rpm. Above 650 rpm, the rate becomes independent of stirring. Turbulent vibromixing or ultrasonic mixing gave no additional increase in the reaction rate. This phenomenon occurs with all catalyst particle sizes and all degrees of cross-linking. The dependence of the rate constant on stirring speed decreased as the degree of cross-linking increased and as particle size decreased.

These data were explained by Ford and Tomoi using the models in Figure IV. The only kinetic process limited by mixing is mass transfer. The rate of mass transfer can be described by Fick's first law

$$\text{rate} = -D \frac{\partial C}{\partial x} = -D \left( \frac{C_{\text{bulk}}}{C_{\text{surface}}} \right)$$

where D is the diffusion coefficient, \( \delta \) is the quiet film thickness and C represents the concentration of the reactant.\(^{10} \) The negative sign indicates that the mass flow is in the direction of lower concentration. In the limiting case where the catalyst activity is high, \( C_{\text{surface}} \) will be zero and the rate of mass transfer will be large and proportional to the concentration of the reactant in the bulk liquid. So in all experiments carried out at stirring speeds below that needed to reach a maximum \( k_{\text{obs}} \), a concentration gradient will be established as in Figure IV B and mass transfer will be rate limiting. When stirring speeds are sufficient to give the maximum value of \( k_{\text{obs}} \), Figure IV A applies and mass transfer is not rate limiting.

These results would seem to be in contrast to the data obtained by Regen. His experiments indicated a rate increase of only 20% when the stirring speed was changed from 0 to 750 rpm. This discrepancy might be the result of the different amounts of catalyst employed by each of the workers. Regen typically used 10-15mg of catalyst while Ford and Tomoi used 200-400mg. Since the rate of mass transfer is related to the amount of catalyst, a larger quantity would presumably create a larger concentration gradient between the bulk liquid and the catalyst surface as in Figure IV B. Therefore, mixing would be expected to alter the rate of mass transfer to a greater degree when more catalyst is employed.

The particle size of a heterogeneous catalyst was investigated to determine its effect on reaction rates. It was found that rate constants increased as particle size decreased to a limiting value of \( 1/r=1000 \text{cm}^{-1} \). Below this radius, the rate appears to be independent of particle size. This maximum rate is attained at a particle diameter of 20\( \mu \text{m} \) near the lower limit of particle sizes that can be prepared by suspension polymerization and also near the lower limit of particle sizes that can be separated by simple filtration.

Both intraparticle diffusion and mass transfer limitations on observed rates depend on particle size. If only mass transfer limited the rate, \( k_{\text{obs}} \) would be proportional to the surface area of the catalyst and therefore to \( 1/r \) where \( r \) is the particle radius. Under conditions where mass transfer contributions are negligible, intraparticle diffusion and intrinsic reactivity are rate limiting. As \( 1/r \) increases or rather particle size decreases, the rate depends less on particle size suggesting intraparticle diffusion is becoming less influential while intrinsic reactivity is becoming more influential on the rate. In the case where intrinsic reactivity is rate controlling, there would be no dependence on particle size whatsoever. Thus the dependence on particle size can range from 0 to \( 1/r \).

Once again, the results of Ford and Tomoi conflict with Regen's data. While the former workers observed an increase in reaction rates with decreasing particle size, Regen actually found a slight decrease in the rate. This can probably be explained by the different methods of preparing the polymers. Regen made his smaller
particles by grinding larger ones with a mortar and pestle while Ford and Tomoi used suspension polymerization and sieving to separate various fractions according to size. Therefore, by grinding the resins, Regen may have crushed the polymer matrix and thereby decreased the access of the halide to the catalyst. In addition, the lower quantity of catalyst used by Regen would favor chemical reaction as being rate limiting.

The effect of solvent on the observed rate constant was found to decrease in the order chlorobenzene > toluene > decane over a wide range of particle sizes and percent cross-linking. The ability of the solvent to swell the catalyst resins decreases in the same order as does the solvent dielectric constant. This would imply the more swollen polymer matrix allows for faster intraparticle diffusion and thus faster reaction. It was further observed that a solvent effect was present even when reaction rates approach their maximum value with decreasing particle size, where the observed rate constants are due only to intrinsic reactivity. Solvent effects on intrinsic reactivity must be due to different environments at the active site. This phenomenon is thought to be due to an alteration in the degree of hydration of the cyanide ion or the increased polarity of the organic solvent may cause a more rapid reaction at the aqueous/organic interface at the ion exchange site. Rates of conventional phase transfer catalyzed displacement reactions increase as the dielectric constant of the solvent increases, probably because the solubility of the quaternary onium cyanide in the organic phase increases with increasing solvent polarity.

Another parameter found to affect the rate was the degree of cross-linking. Increasing the level of cross-linking in the support decreases the observed rate constant. This also decreases the extent of swelling of the polymer. The reaction rate can then be controlled by either the amount of cross-linker or the swelling power of the solvent. These data are probably the result of slower intraparticle diffusion due to the smaller pores or channels in the polymer matrix. The structure would also be more rigid so swelling would be expected to decrease.

This explanation was tested by changing the cross-linker for DVB to some longer, more flexible bismethacrylates. This was expected to increase the observed rate since the intraparticle pores would be larger allowing for faster matrix diffusion. However, when 5.3 mole % of this cross-linker was compared to 5.3 mole % DVB, little effect was noticed. This result was interpreted in terms of a rate limited more by intrinsic reactivity than by intraparticle diffusion.

Rates were also measured as a function of temperature. They were found to decrease with decreasing temperature. Activation energies shown in Table II were calculated from Arrhenius plots of kinetic data measured at 50°, 70°, and 90°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Active Site</th>
<th>Particle Size</th>
<th>% DVB</th>
<th>$E_a$ kcal mol⁻¹</th>
<th>$\Delta S^\parallel$ cal deg⁻¹mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\beta^+$</td>
<td>-100+200</td>
<td>2</td>
<td>11.7</td>
<td>-43.4</td>
</tr>
<tr>
<td>2</td>
<td>$\beta^+$</td>
<td>-100+200</td>
<td>10</td>
<td>11.7</td>
<td>-43.0</td>
</tr>
<tr>
<td>3</td>
<td>$\beta^+$</td>
<td>-400</td>
<td>2</td>
<td>13.5</td>
<td>-37.0</td>
</tr>
<tr>
<td>4</td>
<td>$\beta^+$</td>
<td>-60+100</td>
<td>2</td>
<td>21.1</td>
<td>-22.6</td>
</tr>
</tbody>
</table>

The degree of cross-linking appeared to have no measurable effect as shown in entries 1 and 2. The smaller particle size used in entry 3 resulted in an increase in the activation energy and $\Delta S^\parallel$ indicating a slower rate of reaction. This was interpreted in terms of a reaction limited by intrinsic reactivity. It was further observed in entry 4 that use of an ammonium catalyst caused a large increase in the activation energy and $\Delta S^\parallel$ due to its lower degree of activity relative to phosphorus.

When the rate is limited by both intraparticle diffusion and intrinsic reactivity, the apparent activation energy, $E_a$ app, may range from a diffusion limited case
to a reaction limited case as in the equation below where $E_{\text{diff}}$ is the Arrhenius energy for intraparticle diffusion and $E_{\text{react}}$ is the Arrhenius energy for intrinsic reactivity. In Table II, the phosphonium catalyst rates depend on both parameters. The data for the ammonium ion catalyst are strictly under intrinsic reactivity control. From the data, it appears $E_{\text{react}} > E_{\text{diff}}$ and the entropy of diffusion is more negative than $\Delta S^\#$ for intrinsic reaction rates with the phosphonium catalysts. The Arrhenius energy for intrinsic reactivity was then estimated at $E_{\text{react}} \approx 13.5$ kcal mol$^{-1}$ with $E_{\text{diff}} \approx 9-10$ kcal mol$^{-1}$. This estimate of $E_{\text{diff}}$ is similar to observations of $E_{\text{diff}} = 5-10$ kcal mol$^{-1}$ for intraparticle diffusion in aqueous anion-exchange resins.

In summary, the reaction of aqueous sodium cyanide with 1-bromoctane in benzene catalyzed by polymer bound phase transfer onium catalysts has been studied. While the initial results suggested a mechanism in which chemical reaction was rate limiting, a more recent model indicates the system is more complex. In this model, Ford and Tomoi found mixing, catalyst particle size, degree of cross-linking, solvent, and temperature all affect rates of reaction. The experimental conditions that lead to the greatest mass transfer control of observed rates are large particles, slow stirring, and fast intrinsic chemical reaction at the catalyst site. Proper optimization of these parameters can reduce the reaction to the point where intrinsic reactivity is rate controlling but this necessitates small particles and low degrees of cross-linking which could make the polymer too soluble or gelatinous to be of any advantage.

**BIBLIOGRAPHY**

N-GLYCOSYLATION OF N-HETEROCYCLIC

Reported by Tom Stevenson  November 30, 1981

Nucleosides and related compounds comprise a large class of biologically important compounds including RNA and DNA. The search for a better understanding of the function of nucleosides has resulted in the synthesis of many different nucleoside analogues. These compounds have made important contributions in medicine and biochemistry.  

Natural nucleosides consist of a purine or pyrimidine base bonded at the anomeric carbon to a ribose or deoxy ribose sugar. Although many nucleoside analogues have been synthesized by direct alteration of nucleosides, the vast majority are synthesized by coupling of a sugar and heterocyclic base. Coupling procedures for N-glycosylation of heterocycles can lead to products in either α or β configurations. Most natural nucleosides exist as the β anomer but synthetic procedures often lead to mixtures or to the undesired α anomer. The determination of anomeric configuration has therefore required considerable research effort. Methods which take advantage of the difference in NMR coupling constants between anomers have been developed, however no completely general method has yet been reported. Direct N-glycosylation also can lead to polyglycosylation and glycosylation at undesired positions of heterocycles.  

Over the past two decades nucleoside synthesis has been carried out using either the Koening-Knorr technique or the fusion procedure. These procedures have been made largely obsolete by the Hilbert-Johnson technique. Originally conceived as a method for glycosylation of alkoxy heterocycles this approach has been extended with great success to a variety of silylated heterocycles. The reaction of fully silylated heterocycles with peracylated sugars in the presence of Friedel-Crafts catalysts in a variety of solvents leads to high yields of β nucleosides. Most recently less active and therefore more selective catalysts such as trimethylsilyltriflate have been used to further improve this method.  

The course of the silyl Hilbert-Johnson and other methods has been presumed to involve the formation of a reactive sugar cation. In the presence of a 2' acyl protecting group neighboring group assistance can lead to the formation of a delocalized 1,2 acyloxonium ion which allows nucleophilic
attack from only one side, thus leading to only one of the two possible anomers. $^{13}$C NMR studies have indicated that the heterocyclic base and the catalyst exist as a $\sigma$ complex that is in equilibrium with the free components. Since only the free heterocycle can react, the extent of the equilibrium has a profound effect upon nucleoside synthesis. The reversibility of the anomeric bond formation has been shown by the equilibration of mixtures of isomers to the more thermodynamically stable natural isomers in the presence of Friedel-Crafts catalysts.

This reversibility has formed the basis for transglycosylation, a process in which a sugar is transferred from one silylated heterocycle to another. The most successful examples involve the use of pyrimidine bases as glycosyl donors and purine bases as glycosyl acceptors.

The application of phase transfer chemistry to N-glycosylations has shown promising results. Although the reaction of heterocycles with halo sugars in 50% NaOH/CH$_2$Cl$_2$ with phase transfer catalysts results in anomeric mixtures, the ratio of anomers is dependent upon the catalyst.

Nucleoside synthesis can also be accomplished using enzymatic means. The most commonly employed enzyme, purine nucleoside phosphorylase, has the ability to utilize a wide variety of sugars and bases. More importantly even sugars that lead to $\alpha$ anomers via synthetic methods form only $\beta$ nucleosides. Enzymatic transglycosylation can be achieved on a preparative scale employing bacterial cell paste, but reaction conditions must be carefully controlled in order to avoid other enzymatic reactions.

The synthesis of nucleosides and their analogues can be achieved chemically in a number of ways, but in most cases the silyl Hilbert-Johnson method gives the best results. Enzymatic and phase transfer methods also have important functions in the syntheses of certain nucleosides.

BIBLIOGRAPHY

TETRONIC ACIDS AND TETRAMIC ACIDS

Reported by Srinivasan Nagarajan

December 3, 1981

Tetronic acids and tetramic acids are derivatives of the parent acids $\text{1}$ and $\text{2}$ respectively. Spectral data show that tetronic acids exist in the enol form. $\text{1}$

Tetronic acids are produced by fungi$\text{2}$ and also are found in lichens. $\text{3}$ Ascorbic acid, a $\gamma$-substituted-$\alpha$-hydroxyacid, is the most important tetronic acid. $\text{5}$ Except for ascorbic acid no other tetronic acid seems to show any major biological activity. However, different types of activities (antibacterial, herbicidal, etc.) have been reported for many tetronic acids. $\text{5}$ Tetramic acid derivatives are produced by fungi and bacteria$\text{6}$ and are also found in a marine sponge. $\text{7}$ Many of these tetramic acids are antibiotics and other important biological activities have also been recorded. $\text{8}$ This abstract will provide a brief review on the syntheses and reactions of these acids.

Several methods are known for the synthesis of tetronic acids. These include the cyclization of $\gamma$-halogen, $\gamma$-acetoxy-acetoacetic ester derivatives$\text{9}$ (a), hydration of $\alpha,\beta$-acetylenic-$\gamma$-hydroxy acids$\text{10}$ (b), and internal Claisen cyclization of $\alpha$-acyloxy esters$\text{11}$ (c). Tetronic acids have been made from the condensation of a variety of amino acid esters or their derivatives with diketene,$\text{12}$ malonic acid monoesters$\text{13}$ and dienoyl acetyl esters$\text{14}$ followed by cyclization.

Tetronic acids and tetramic acids readily undergo reactions at the $\alpha$-position of the enol. These acids also undergo anhydromerization quite readily.$\text{15}$ Alkylation, acylation, halogenation and nitration reactions are also possible.$\text{16}$ Acylation reactions of tetramic acids were studied since many of the acyltetramic acids are antibiotics.$\text{17}$

The biosynthesis of acyl tetramic acids has been shown to involve two or more acetate and/or propionate units and an appropriate amino acid.$\text{18}$
CHEMICAL APPLICATIONS OF ULTRASOUND

Reported by Charles Little

December 10, 1981

Introduction. Of all sources of radiation used by chemists to transfer energy to chemical reactants, ultrasound and laser light are the two most powerful. Both are capable of supplying power densities of more than $10^6$ watts/cm$^3$, a value which is many orders of magnitude higher than can be supplied from any other source.\textsuperscript{1} Ultrasound can be delivered more conveniently, more safely and less expensively than laser light, so it is not surprising that this source of energy is beginning to be used widely in many areas of scientific research, including chemistry. The purpose of this abstract is to provide a general description of the origins of sonochemical effects as they are currently understood, and to illustrate the utility of ultrasound in current chemical research.

The Origins of Sonochemical Effects. It has been known since 1927 that ultrasound can affect chemical reactions in solution only when the sound wave can induce cavitation—the rapid growth and collapse of bubbles within the liquid.\textsuperscript{2} In non-degassed liquids, microscopic bubbles exist which can act as cavitation nuclei. In the rarefaction half-phase of a sound wave, a cavitation nucleus undergoes nearly isothermal expansion, during which time gases diffuse into the cavity from the bulk liquid. In the compression half-phase, the bubble is then quickly and nearly adiabatically compressed.\textsuperscript{1,3} Under the proper conditions, this compression will lead to intense local pressure and temperature increases,\textsuperscript{1,4} as well as electrical discharges due to the development of non-uniformly distributed, uncompensated electrical charges on the bubble's surface.\textsuperscript{5,6,7} Pressures of hundreds of atmospheres, temperatures of thousands of degrees and electric fields of hundreds of volts/cm are theoretically possible.\textsuperscript{1,4,7}

The extreme conditions that develop in a collapsing cavity make possible the formation of very reactive species—ions, free radicals and thermally excited molecules—which are responsible for the observed sonochemical effects. Exactly how these reactive species are formed is still a matter of debate. There is experimental evidence, however, that pressure, temperature and electric discharge may all contribute to sonochemical effects, with temperature being the dominant factor.

In order to observe sonochemical effects, one must achieve both efficient bubble collapse and a high concentration of collapsing bubbles. Many independent factors have been shown experimentally to affect the efficiency of collapse and the concentration of bubbles.\textsuperscript{1,3} The most important of these are discussed below:

1. Solvent and Solute Vapor Pressure.\textsuperscript{8} For the extreme case of reversible adiabatic collapse, the final temperature reached in a collapsing cavity is given by

$$T_{\text{final}} = T_{\text{initial}} \left( \frac{P_{\text{final}}}{P_{\text{initial}}} \right)^{\frac{\gamma-1}{\gamma}}$$

where $P$ is the pressure inside the cavity and $\gamma$ is the ratio $C_p/C_v$ for the cavity's gaseous interior.\textsuperscript{8} At high solvent or high solute vapor pressures, $P_{\text{final}}/P_{\text{initial}}$ will be small because $P_{\text{initial}}$ will be large. In most cases this will cause $T_{\text{final}}$ to be low and thermal effects to be minimal.

2. $C_p/C_v$ of the Gaseous Cavity. According to the above equation, a large value of $C_p/C_v$, or $\gamma$, will make the factor $(P_{\text{final}}/P_{\text{initial}})^{\frac{\gamma-1}{\gamma}}$ large and $T_{\text{final}}$ high. For example, $T_{\text{final}}$ will be higher if Argon ($\gamma=1.66$) is dissolved in the liquid than it will if Neon 114 ($\gamma=1.09$) is dissolved in the liquid.
3. Bulk Temperature. Since the composition of the gaseous interior of the cavity and the solvent vapor pressure depend on the temperature of the bulk solution, so do $\gamma$ and $P_{initial}$. For every solvent and solute system examined there is a characteristic temperature at which cavitation is most intense. Air saturated water, for example, cavitates most efficiently at 35°C while the optimum temperature for air saturated tetraline is 55°C.

4. Thermal Conductivity. Since the highest temperatures and pressures are achieved in adiabatic collapse, in general those liquids and dissolved gases of lowest thermal conductivity will produce the most efficient cavitation.

5. Surface Tension and Solvent Viscosity. These factors largely affect the radius to which cavitation nuclei grow and the rate of coalescence of bubbles. If bubbles do not grow to some minimum radius during the rarefaction half-phase, they will collapse more slowly and less adiabatically during the compression half-phase. If bubbles grow larger than some maximum radius, they can float to the surface and escape, coalesce and reduce the number of bubbles, fragment into many smaller unproductive bubbles on collapse, or pulsate for many periods without complete collapse. A high surface tension will reduce loss of bubbles by fragmentation and will make it difficult for bubbles to grow too large. A high viscosity will lower the rate of bubble coalescence and thus maintain a high concentration of bubbles.

6. Frequency of Ultrasound. The Rayleigh equation predicts the minimum time necessary for a bubble of radius $R_{max}$ to collapse completely:

$$T_{min} = 0.915 \frac{R_{max}}{p}$$

where $P_1$ is the density of the liquid and $P$ is the sound pressure. If $T_{min}$ is long compared to the duration of the compression half phase, then the bubble cannot collapse completely and the highest temperatures and pressures theoretically possible will not be attained. This places a practical upper limit on the frequency of ultrasound that can induce sonochemical reactions. Yet, higher frequencies produce higher concentration of bubbles, so there is experimentally determined optimum frequency for each solvent and solute system.

7. Acoustic Intensity. Over a broad range of frequencies most systems show a direct, linear relation between sonochemical activity and acoustic intensity. Many systems, however, show much more complicated behavior: in some cases sonochemical activity increases as some fractional power of acoustic intensity, while in other cases it reaches a maximum at some characteristic acoustic intensity. The origins of this non-linear dependence are not known. In all systems, cavitation only occurs above a characteristic threshold intensity which depends upon the tensile strength of the liquid. This threshold intensity in water, for example, is about 0.5 to 1.0 watts/cm².

8. Shape of Reaction Vessel and Volume of Liquid. In cylindrical vessels with flat bottoms, cavitation intensity is very sensitive to the volume of liquid used. If the height of the liquid in the cylinder is a multiple of the half-wavelength of the ultrasound employed, standing waves will be set up due to the reflection off the top surface and cavitation intensity will be at a maximum. This is illustrated in Figure 1 for ultrasound of wavelength 32mm.
In round bottom vessels this dependence on the volume of liquid is greatly attenuated since the establishment of standing waves is virtually impossible.

Most common organic liquids will cavitate if experimental conditions are carefully chosen with the eight factors discussed above in mind. Under almost all experimental conditions ever investigated, however, water cavitates far more efficiently than any other liquid; it is largely for this reason that aqueous systems have been used almost exclusively in sonochemical studies. Yet no synthetically useful application has been found in purely aqueous systems, while many have recently been found in non-aqueous or mixed solvents. It is therefore convenient to discuss aqueous and non-aqueous systems separately. The coverage of aqueous sonochemistry is selective; the coverage of non-aqueous sonochemistry is more complete and emphasizes recent synthetic applications.

Ultrasonic Effects in Aqueous Media. Most sonochemical reactions observed in aqueous media are actually secondary reactions induced by the thermolytic or electronic breakdown of H\textsubscript{2}O. While the early literature stressed the involvement of the primary products, H\textsuperscript{+} and ·OH, in initiating free radical reactions, it is now clear that some solutes are directly affected by the extreme conditions inside a collapsing cavity or near its gas-liquid interface.

Evidence that electric discharge, and not thermolysis, may be the dominant effect when heteroatoms are present may be found in a series of papers by L. A. Spurlock and co-workers\textsuperscript{13-15}. Spurlock noted that he could vary the rate of H\textsubscript{2}O\textsubscript{2} formation in pure water over a wide range by saturating the water with different gases\textsuperscript{13}. Furthermore, the rate of H\textsubscript{2}O\textsubscript{2}formation was found to be almost perfectly correlated with the inverse of the ionization potential of the dissolved gas. This was interpreted to suggest that ionization of the gas by electric discharge, and not thermolysis of H\textsubscript{2}O, is the initial and rate-limiting step in H\textsubscript{2}O\textsubscript{2} formation.

Since H\textsubscript{2}O\textsubscript{2} is the major chemical oxidant formed in sonicated water\textsuperscript{13} one might expect the rate of oxidation of (Bu)\textsubscript{2}S to be sensitive to the rate of formation of H\textsubscript{2}O\textsubscript{2}. In fact, Spurlock found that the rate of oxidation of (Bu)\textsubscript{2}S did not correlate with the rate of H\textsubscript{2}O\textsubscript{2} formation\textsuperscript{13}. Furthermore, hypochlorous acid formation was five times faster than H\textsubscript{2}O\textsubscript{2} formation when CCl\textsubscript{4} was added to the water, yet the rate of oxidation of (Bu)\textsubscript{2}S was only slightly enhanced when CCl\textsubscript{4} was present. These results, and the mixture of products obtained, were explained by a mechanism that required direct ionization of the sulfide as the initial and rate limiting step. Spurlock obtained similar results in a study of several aliphatic amines\textsuperscript{16} and likewise concluded that direct ionization of the amines was the initial step. However, these results are more difficult to interpret due to the great variety of products formed from the amines and the more complicated scheme required to explain their appearance.
Although ionization of solution by electric discharge may be a more general effect than is now recognized, secondary reactions of solutes with species derived from water still satisfactorily explain most experimental results. By homolysis or electron capture water is capable of producing H·, \cdotOH, H\(_2\), OH\(_{-}\), HO\(_2\), O\(_2\)\(_{\cdot}\), H\(_2\)O\(_2\), O\(_3\), and e (aq).\(^4,16,17\) If molecular nitrogen is present, nitrogen fixation occurs, yielding NH\(_3\), HNO\(_2\), HNO\(_3\), and NH\(_2\)OH.\(^4,18\) If carbon monoxide or methane is present, then sonication leads to the formation of HCHO.\(^4,19\) And if carbon monoxide or methane or formaldehyde is present together with nitrogen, then amino acids are formed.\(^1,18,19\)

Sokol'skaya reported that sonication of a nitrogen saturated solution of 2.5% aqueous HCHO (850 kHz, 10 watts/cm\(^2\), 25°C) for 12 hours leads to glycine as the major product, along with trace amounts of alanine, lysine and glutamic acid.\(^19\) Reactions (1)-(5) account for the formation of the major product.\(^16,19\)

1. \(\text{H}_2\text{O} \rightarrow \text{H}^\cdot, \cdot\text{OH}, \text{H}^+\) etc.
2. \(\text{N}_2\) (aq) \(\rightarrow\) NH\(_2\)OH, NH\(_3\)
3. \(\text{NH}_2\text{OH(aq)} + \text{HCHO(aq)} \rightarrow \text{HCN}\)
4. \(\text{HCHO(aq)} + \text{NH}_3\) (aq) + HCN (aq) \(\rightarrow\) NH\(_2\)CH\(_2\)CN
5. \(\text{NH}_2\text{CH}_2\text{CN(aq)} \rightarrow \text{H}^+\) \(\rightarrow\) NH\(_2\)CH\(_2\)COOH

Reactions (4) and (5) represent the Strecker synthesis, which also occurs in the absence of ultrasound.\(^20\) It should be emphasized that the formation of amino acid precursors in equations (2) and (3) is thought to occur by free radical processes. There is no firm experimental evidence for this claim beyond the observation that the known gas phase syntheses of the same precursors are most likely free radical processes. Although Sokol'skaya could explain the appearance of glycine, he could not explain the appearance of the three other amino acids as minor products. Other workers, however, have ruled out one obvious possibility, viz., that they are derived from the ultrasonic degradation of glycine either in the presence or the absence of added formaldehyde.\(^21\)

These results certainly make plausible the notion that prebiotic synthesis could have occurred in underwater explosions, volcanic eruptions or fast moving bodies of water, all of which are capable of sustaining cavitation in water.\(^22\)

The effect of ultrasound on biologically important molecules is of great interest because of the rapidly growing number of applications of ultrasound in medicine and surgery. The ultrasonic degradation of nucleic acid bases has been of particular interest to many workers.\(^12,23-25\)

When 0.1 mM aerated, aqueous solutions of thymine, uracil, cytosine, guanine and adenine were sonicated at 1 MHz at an intensity of 5 watts/cm\(^2\), all five bases were found to decompose at appreciable rates.\(^25\) For example, 80% of the thymine and 45% of the uracil were consumed after 50 minutes of sonication. The kinetic order of the reactions and the effect of radical scavengers on the rates suggested that the degradations were initiated by rate-limiting attack of hydroxyl radical on the bases. Other kinetic studies,\(^12\) as well as very detailed product studies\(^24\) support this mechanistic interpretation, but the gross mechanism of degradation is still not well understood.

The effect of ultrasound on nucleic acid bases suggests that ultrasound may have profoundly deleterious effects on living systems at the molecular level. The same conclusion may be drawn from a study of the sonolytic decomposition of amino acids. Spurlock\(^21\) irradiated 6 mM solutions of glycine, alanine, glutamic acid, glutamine, phenylalanine, histidine, methionine, cystine
and cysteine for 6 hours at 0.8 MHz. The extent of reaction ranges from 8% for glycine to 61% for cysteine. The major reaction of cysteine was oxidation to the disulfide, cystine; for all others, the major reactions were deamination and decarboxylation, presumably by attack of free radicals on the α-carbons. An interesting observation was that the amide functionality in glutamine survived sonication.21 Because of the implications this has for the stability of the primary structure of proteins under sonication, it is unfortunate that the sonochemistry of di- and tri-peptides has not yet been investigated.

**Ultrasonic Effects in Non-aqueous and Mixed Media.** Synthetically useful applications of ultrasound have been found in both homogeneous and heterogeneous systems. In general, faster reactions and higher yields are achieved under milder and more convenient conditions when ultrasound is applied. In homogeneous systems there is experimental evidence that the primary effects of cavitation are responsible for rate and yield increases. On the other hand, the utility of ultrasound in heterogeneous systems has been attributed to the secondary effects of cavitation, such as efficient mixing, emulsification or ultrasonic cleaning of metal surfaces. However, little work has been done specifically to clarify the role of ultrasound in heterogeneous reactions, so mechanistic interpretations should be viewed as speculative for the present.

A good example of a single-phase reaction that can be affected by ultrasound is the alkaline hydrolysis of nitrophenyl esters, reaction (6). Kristol and co-workers26 studied the effect of 20 kHz ultrasound on reaction (6) in THAM

\[
\text{R-CO} - \text{O-NO}_2 + \text{OH}^- \xrightarrow{\text{THAM}} \text{R-CO}^- + \text{H}_2\text{O} + \text{O-N}_2 \text{O}
\]

\[\text{Ja, R=methyl; Jb, R=ethyl; Jc, R=isopropyl; Jd, R=t-butyl}\]

(tris hydroxymethyl amino methane) buffered acetonitrile at pH 8 for compounds \(\text{Ja} - \text{Jd}\). They found that rates were enhanced uniformly for these compounds, as shown in Table 1. Since the rate constants for unsonicated hydrolysis vary almost 20-fold for these 4 compounds, and since Ea's range from 11.9 kcal/mole for \(\text{Ja}\) to 13.7 kcal/mol for \(\text{Jd}\), Kristol was able to rule out thermal effects as the source of the rate enhancements. He concluded that localized pressure increases in the collapsing cavities produced the faster reactions.

Another procedure for alkaline ester hydrolysis under ultrasonic irradiation has recently been reported for a two-phase system.27 The mild conditions and short reaction times make it an attractive alternative to other recently developed methods, such as phase transfer catalysis. For example, sonication of methyl-2,4-dimethylbenzoate in 20% NaOH for 10 minutes at ambient temperature affected the same conversion, 15%, as did 90 minutes of refluxing; after 60 minutes of sonication, the conversion was virtually quantitative. However, this procedure appears to offer no advantage over other methods when the ester is very sterically hindered.27
Thioanides are ordinarily prepared from amides and P4S10 by refluxing in high-boiling solvents for prolonged periods. These compounds can now be made in high yield (77-97%) under milder conditions (less than 2 hours, 30-40°C) by sonicating the amide and 1.0 to 1.5 equivalents of P4S10 in dry THF.28 The developers of this procedure note that it could prove useful for the preparation of thioamides in the presence of other functionalities that would not survive the more stringent conditions required in the absence of sonication.

Several heterogeneous reactions involving active metals have been found to proceed faster under ultrasonic irradiation. Two such reactions that are still rather limited in scope are the coupling of silanes to give disilanes, and the oligomerization of dichlorosilanes to give cyclopolsilanes.29 Both reactions require the presence of lithium, but neither will proceed at ambient temperature unless ultrasound is applied. This procedure could prove to be useful in the synthesis of new silicon compounds for use as silylating agents and as sources of novel silylenes—silicon analogues of carbenes.30

Ultrasound has been shown to have a dramatic effect on the Barbier reaction, which was long ago superseded by the Grignard reaction for the condensation of halides with carbonyl compounds. Luche and Damiano31 found that sonicating mixtures of bromides and carbonyls in technical grade THF with lithium wire gave condensation products in greater than 90% yield in 11 of 14 combinations tried in as little as 10 minutes. Electron transfer agents that were required in the absence of sonication32 were found to be unnecessary. Vinyl, allyl and t-butyl bromides gave excellent yields; even benzyl bromide condensed with acetophenone in 95% yield under sonication, while bibenzyl was the major product of this reaction in the absence of ultrasound.32 So far this procedure has only been used to condense organic bromides with ketones and aldehydes. It remains to be seen whether the scope of this reaction can be expanded to include other organic halides and other carbonyl compounds.

Perhaps the most synthetically useful application of ultrasound that has been reported to date is in the reaction of nucleophiles with α,α′-dibromo-ketones in ultrasonically dispersed mercury.33–38 The versatility of this procedure is illustrated in Scheme I. When the nucleophile is a carboxylic acid or an alcohol, the α-oxo substituted ketones 2 and 4 result. These α-substituted ketones can be made in other ways, but this ultrasonic procedure offers the advantage that more sterically hindered ketones can be used, and that only one nucleophilic group is introduced regardless of the degree of steric hindrance.
When the nucleophile is a ketonic solvent, the 1,3-dioxolans $\delta$ are isolated in good yield, thus providing a convenient one-step synthesis of these heterocycles.$^{39}$

This reaction presumably involves nucleophilic attack on an oxyallyl cation $\gamma$ as shown in Scheme II.$^{33,38}$ In the absence of ultrasound this reaction does not proceed if all substituents $R_1$-$R_4$ in the dibromoketone are alkyls.$^{33,40}$ Fry believes that reduction of the dibromoketone to form the organometallic $\delta$ is merely kinetically unfavorable and can be made to occur at a conveniently fast rate by ultrasonically dispersing the mercury.$^{33}$

Finally, Suslick and co-workers$^{41}$ have recently discovered that ultrasound can increase the catalytic activity of iron carbonyls toward olefin isomerizations by as much as 100,000 times. When they sonicated 1-pentene in the presence of either Fe(CO)$_5$, Fe$_2$(CO)$_5$, or Fe$_3$(CO)$_{12}$ in hydrocarbon solvents, they observed that isomerization of 1-pentene to 2-pentene occurred at much faster rates than in the absence of ultrasound. Fe(CO)$_5$ showed the largest rate enhancements, and Fe$_3$(CO)$_{12}$ the smallest.

Sonolysis of the iron carbonyls alone gave products that were consistent with the direct generation of the transient species, Fe(CO)$_3$, by simultaneous loss of 2 CO's from Fe(CO)$_5$. Suslick proposed that this unsaturated iron carbonyl was the active catalyst responsible for the enhanced rate of olefin isomerization.

Furthermore, Suslick showed that the degree of ligand dissociation from Fe(CO)$_5$ could be controlled by adjusting the vapor pressure of his solvent mixtures so as to affect the efficiency of cavitation.

**Summary.** Ultrasound has been used to effect a wide variety of chemical reactions, although its synthetic utility has only recently begun to be explored. As this report has shown, the origins of sonochemical effects are sufficiently well understood to allow chemists to use ultrasound rationally. It is clear, however, that a better understanding of these effects is desirable in order to make sonochemical reactions more predictable.
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