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ORGANIC SEMINAR ABSTRACTS
1970-1971

Semester II

School of Chemical Sciences
Department of Chemistry
University of Illinois
Urbana, Illinois
SEMINAR TOPICS
II Semester 1970-71

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Ronald P. Taylor

New Photoproducts from Pyrimidine Bases
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Polymerization of Cyclic Ethers with Organometallic Catalysts
Jiro Yamamoto
METHYLENE TRANSFER REAGENTS

February 8, 1971

Reported by James Chesquiere

Many synthetic problems involve the addition of a methylene group to form a new moiety. The most common types of methylene transfer reactions are the Wittig reaction, the Simmons-Smith reaction, the homologation of aldehydes and ketones, and the addition of methylene transfer reagents to an electrophilic double bond. This seminar will discuss the formation of a three-membered ring by the transfer of a methylene group to an electrophilic double bond, as generalized in Scheme I. Various sulfur ylides have proven to be the most useful methylene transfer reagents involved in the formation of the new three-membered ring.

Epoxide formation using dimethyloxosulphonium methyldide (1) or the more active dimethylsulphonium methyldide (2) and a saturated carbonyl compound generally proceeds smoothly under mild conditions in good yields (Table 1). Simple alkenes do not react with 1 or 2 to yield cyclopropanes. However, \( \alpha, \beta \)-unsaturated ketones react with 1 to yield cyclopropanes exclusively and with 2 to yield unsaturated oxiranes exclusively (Table 1). Diphenylsulphonium alkylides also add to carbonyl groups to form alkyl substituted oxiranes (Table 1), and add to \( \alpha, \beta \)-unsaturated ketones to yield substituted cyclopropanes.

The transfer of a methylene group under mild conditions from N,N-dimethylaminophenylsulphonium methyldide (3) to a carbonyl group results in the formation of oxiranes in good yields (Table 1). Cyclopropyl compounds are formed by the reaction of 3 with simple alkenes, and with \( \alpha, \beta \)-unsaturated carbonyl compounds (Table 1). Methyl and ethyl substituted cyclopropanes are formed by employing the corresponding ethylides and isopropyldide. Optically active oxiranes and cyclopropanes are synthesized by using optically active N,N-dimethylamino-p-tolyloxosulphonium methyldide (4) (Table 1).

Another new methylene (or substituted methylene) transfer reagent is N-p-toluenesulfonylmethylphenylsulfoximine (5). The reaction of 5 (as its sodium salt) with an electrophilic double bond under mild conditions yields the corresponding three-membered ring in good yields (Table 1). Methylene transfer reagents have also been employed in the formation of spiropentanes (Table 1) and related compounds.
<table>
<thead>
<tr>
<th>Reactant</th>
<th>Methylene Transfer Reagent</th>
<th>Type of Product</th>
<th>Conditions</th>
<th>Yield, Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Ph)₂C=O</td>
<td></td>
<td>oxirane</td>
<td>50°, 1 hr</td>
<td>90, 2</td>
</tr>
<tr>
<td>(Ph)₂C=O</td>
<td></td>
<td>oxirane</td>
<td>0°, 1 hr</td>
<td>84, 2</td>
</tr>
<tr>
<td>PhCCH=CHPh</td>
<td></td>
<td>cyclopropane</td>
<td></td>
<td>95, 3</td>
</tr>
<tr>
<td></td>
<td>(Ph)₂S=C(CH₃)₂</td>
<td>oxirane</td>
<td>-60°, 3 hr</td>
<td>82, 13</td>
</tr>
<tr>
<td></td>
<td>(Ph)₂S=C(CH₃)₂</td>
<td>cyclopropane</td>
<td>-60°, 1½ hr</td>
<td>74, 4</td>
</tr>
<tr>
<td>PhSO₂CH=CH₂</td>
<td></td>
<td>oxirane</td>
<td></td>
<td>84, 8</td>
</tr>
<tr>
<td>PhCH=CHPh</td>
<td></td>
<td>cyclopropane</td>
<td>25°, 20 hr</td>
<td>100, 8</td>
</tr>
<tr>
<td>PhCCH=CHPh</td>
<td>PhS=C(CH₃)₂</td>
<td>oxirane</td>
<td></td>
<td>60, 6</td>
</tr>
<tr>
<td></td>
<td>(CH₃)₂CHSCH(CH₃)₂</td>
<td>cyclopropane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhCH=CHCO₂CH₃</td>
<td></td>
<td>oxirane</td>
<td></td>
<td>60, 7</td>
</tr>
<tr>
<td>PhCH=NPh</td>
<td></td>
<td>aziridine</td>
<td>25°, 20 hr</td>
<td>86, 9</td>
</tr>
<tr>
<td>PhCCH=CHPh</td>
<td>PhS=C(CH₃)₂</td>
<td>spiropentane</td>
<td>25°, 20 hr</td>
<td>80, 10</td>
</tr>
<tr>
<td>PhCH₃</td>
<td></td>
<td>oxirane</td>
<td></td>
<td>68, 9</td>
</tr>
<tr>
<td>PhCH=CHPh</td>
<td>(CH₃)₂CHSCH(CH₃)₂</td>
<td>cyclopropane</td>
<td></td>
<td>86, 9</td>
</tr>
</tbody>
</table>

**BIBLIOGRAPHY**

ACYL DERIVATIVES OF SOME PYRIDONES AND PYRIMIDINONES
Reported by Ronald P. Taylor
March 8, 1971

The substitution of ambifunctional nucleophilic compounds, and the tautomeric equilibria of ambident nitrogen heterocycles have long been intriguing problems. Heterocyclic compounds containing the amide structure have been concluded by comparison of their spectral properties with those of their N- and O-alkylated derivatives, to exist predominantly in the lactam form, rather than in the tautomeric lactim form. Between the alkylated derivatives, the O-alkyl isomer is generally the less stable and, under suitable conditions, will isomerize to the more stable N-alkyl isomer. However, acyl derivatives of these heterocycles have been less extensively studied, and little is known about the relative stabilities of isomeric N-acyl and O-acyl derivatives.

Recent work indicates that acyl derivatives of several six-membered lactams may be more easily prepared than their scarcity in the chemical literature would imply. Acyl derivatives of other heterocycles, e.g., the "azolides" have been used synthetically because of their acylating ability. Since acyl derivatives of lactams function as strong acylating agents, they may also have potential synthetic utility.

N-Acyl and O-acyl derivatives of 2-pyridone, of 4-pyridone (4,5), of 6-phenanthridinone (6,7), and of several pyrimidinones have recently been reported. Experiments have shown that in several cases the O-acyl derivative is the more stable; this contrasts with the results of alkylation studies in which the N-alkyl isomer is generally the more stable.

Uncatalyzed acyl migrations have been observed, both in the solid state at 130° and in solution between -40° and +111°C, for conversion of an initially formed kinetically favored product to a thermodynamically more stable product; several rearrangements produced equilibrium mixtures of the two isomers.

The mechanisms of these acyl migrations have not yet been studied in detail. The mechanistic evidence obtained from studies of acyl migrations in β-aminoalcohols may, however, provide useful analogies for interpreting the results of rearrangements in heterocyclic systems.
BIBLIOGRAPHY

NEW PHOTOPRODUCTS FROM PYRIMIDINE BASES

Reported by Robert L. Cundall

March 11, 1971

The lethal action of ultraviolet irradiation on micro-organisms has been commonly attributed to the formation of cyclobutane "dimers" of the pyrimidine bases. However, evidence now indicates that the formation of other photoproducts from pyrimidine bases may be responsible for a portion of the damage previously attributed to dimers and photoproducts; these photoproducts will be referred to as "adducts" and "spore photoproduct." Thymine photoproducts, but not dimers, have been found in uv irradiated bacterial spores, and irradiation of deoxyribonucleic acid (DNA) has also produced thymine photoproducts distinct from dimers. A report of the formation of two components other than the cis-syn thymine dimer 2 from uv irradiation of aggregated thymine has been followed by structural determinations of these compounds and others of similar nature, including the major adduct derived from DNA and the major spore photoproduct.

Irradiation of DNA produces two major photoproducts, as demonstrated by thin layer and paper chromatography. Photoreversal of what was considered the "dimer" (type 2) constituent by 254 nm light did not completely convert it to monomer; rather, a fraction of the product was a new compound with chromatographic properties similar to thymine dimer. This new compound has also been produced by irradiation of frozen solutions of cytidine and thymidine and of uracil and thymine. The resulting adduct 3a has been envisioned as arising from an azetidine 4a or oxetane 4b intermediate formed by addition of a carbonyl or imine group across the thymine 5-6 double bond. The oxetane of the analogous thymine-thymine compound 4c was found to be stable below -80°C. The thymine-thymine adduct 3b formed from thymine and thymidine and the uracil-uracil adduct 3c from uracil have been characterized. A thymine compound which combines the properties of dimer and adduct has also been characterized as the trimer.

The structure of the major photoproduct isolated from irradiated spores, which has also been isolated from irradiated dry DNA's and from irradiated thymidine, has recently been determined. The spore photoproduct 5 has been postulated to be formed by combination of the radicals A and B.
BIBLIOGRAPHY


SOME APPLICATIONS OF $\Delta V^+$ TO SOLVOLYSIS MECHANISMS

Reported by Arnold R. Miller
March 15, 1971

INTRODUCTION

The common activation parameters arise by virtue of the transition-state theory's treating the activated complex as a thermodynamic entity whose equilibrium concentration (hence the rate) can be specified by its free energy of activation; $\Delta H^+$ and $\Delta S^+$ derive directly from the Gibbs equation. Likewise, any other thermodynamic relation between $\Delta G$ and one or more state variables leads to additional parameters; for example, the relation $\Delta G/\Delta V = V$ furnishes the activation volume. Thus, $\Delta V$ is neither more nor less fundamental than another, and in the final analysis merely offers a different point of view—a complementary approach to the problem of describing the transition state. As expected, the volume of activation can often give information unattainable from the other parameters due to the fact that the former is largely a function of purely spatial variables, rather than, for instance, molecular vibrations or forces.\(^2\) Needless to say, the converse is also true. The text at hand will discuss, besides the general remarks, two recent applications of the activation volume parameter to solvolyses: (1) detection of neighboring-group participation and (2) location of solvolysis reactions along the $S_N^1-S_N^2$ continuum.

GENERAL

In their classical paper of 1935,\(^3\) Evans and Polanyi addressed the question of why the rate of reaction in solution varies with applied hydrostatic pressure, and thereby developed the concept of an activation volume, which will be defined here as the difference between the partial molar volumes of the transition and initial states $\Delta V^* = V^* - V_i$ (1). In addition, they showed that it follows directly from the transition-state theory that $\left(\frac{d\ln k}{dP}\right)_T = -\Delta V^*/RT$ (2) and introduced the symbols $\Delta_1 V^*$ and $\Delta_2 V^*$ to represent, respectively, the contributions to $\Delta V^*$ arising from the change in volume of a molecule itself as it assumes the transition state and the change in volume of the molecule's environment, the solvent, upon activation; that is $\Delta V^* = \Delta_1 V^* + \Delta_2 V^*$ (3).

Factors Affecting $\Delta_1 V^*$. The main contributions here are bond formation or fission, and steric hindrance (vide infra). Virtually from the definition of chemical bonding, it follows that bond formation in an transition state will be attended by a decrease in molecular volume and a $\Delta_1 V^* < 0$, and conversely bond fission gives $\Delta_1 V^* > 0$; typical values are $10 \text{ cm}^3/\text{mole}$.\(^4\)

Factors Affecting $\Delta_2 V^*$,\(^1,6\) When the forces between activated complex and solvent exceed the corresponding forces for the initial state, the occurrence of the former will result in a contraction of the solvent. The preponderant force is solvent electrostriction arising from charge formation (or destruction) in the transition state—an effect sufficiently pronounced that in these processes the $\Delta_2 V^*$ term generally eclipses $\Delta_1 V^*$; for example, $S_N^1$ reactions, despite the fact that bond stretching is occurring in the transition state, are virtually always accompanied by large negative $\Delta V^*$ values, typically around $-20 \text{ cm}^3/\text{mole}$.\(^5\)

The phenomenon of electrostriction, or contraction of the solvent by a charged center, can probably be discussed most easily in terms of the Drude-Nernst equation,\(^4\) $\Delta Ve = -q^2/2\pi \epsilon D^2 \Delta \epsilon/\Delta P$ (4). This long-established model describes the volume change, $\Delta Ve$, of a medium of dielectric constant $D$, resulting from the transfer of an ion of radius $r$ and charge $q$ from a vacuum into the dielectric. Two points regarding this relation are noteworthy in the present context: the medium electrostriction (1) is independent of the sign of $q$, and (2) varies inversely as the radius of the ion.
Although the model as derived applies strictly to univalent spherical ions, valuable qualitative correlations can usually be drawn by its application to organic structures. For example, the solvolyses of EtCl, EtBr, and EtI in methanol have activation volumes of -40, -30, and -25 cm$^3$/mole, respectively, reflecting the dependency of activation volume on the radius of the anionic leaving group.\(^5\)

In the discussion that follows, the relative magnitudes of quantities will be determined by their positions on the number scale, not by their absolute values; e.g., the quantity $x = -6$ is considered to be larger than $x = -9$.

ANCHIMERIC ASSISTANCE

$\sigma$ Participation. The increase in activation volume noted above for increased charge dispersion in a larger anionic leaving group should, according to equation \((4)\), hold for the cation as well. In view of this, le Noble and Yates\(^8\) proposed that a proper examination of the activation volume parameter might serve to clarify the nature of the transition states leading to the postulated and controversial nonclassical carbonium ions. That is, if the incipient carbonium ion arising from, say, exo-2-norbornyl brosylate does indeed possess the charge dispersed upon carbon atoms C-1, C-2, and C-6, then that charge may be considered to be of effectively larger radius $r$ than if it were classically localized; alternatively, the total charge may be considered as being constituted of electrically smaller charges $q$ of invariant radius. From either point of view, it follows from equation \((4)\) that this transition state should have a larger activation volume than would be observed for an incipient classical ion, as in the endo epimer.

Before proceeding farther, it is probably desirable to mention a few words in regard to the reliability of the relevant measurements.\(^8\)-\(^11\) In the later work of le Noble and his collaborators, an activation volume error of $\pm 0.3$ cm$^3$/mole is estimated. The previous work\(^8\)-\(^9\) was somewhat less accurate due primarily to a different monitoring technique, and the corresponding error as claimed, $\pm 1$ cm$^3$/mole, may possibly be too low in an absolute sense; however, because the errors responsible were likely systematic, the differences in $\Delta V_0$ values probably are reliable to the extent claimed.

Brown, et al.,\(^12\) have rightly pointed out from steric considerations that the most appropriate model for the norbornyl system is not the cyclohexyl but the cyclopentyl analog, and the first three entries of Table 1 accordingly allow a comparison of their solvolyses in terms of volumes of activation. It is clear that 3, which undoubtedly solvolyses via a classical transition state, has an activation volume identical within the limits of experimental certainty to that of 2 (the endo epimer), whereas the $\Delta V_0$ value for 1 is significantly more positive, a fact which suggests charge dispersion, as hypothesized. Entries 4 through 8 allow comparison of the solvolysis behavior of a series of cycloalkyl tosylates; the activation volume of the lowest member, cyclobutyl tosylate, is significantly the largest, though by a difference just outside experimental uncertainty. This is in accord with the incipient occurrence of the nonclassical bicyclobutonium ion as first proposed by Roberts and his coworkers;\(^13\) the smallness of the effect is also consistent with the hypothetical species' unsymmetrical, nearly classical nature. Of the last two members in the table, structures 9 and 10, the former can assume a transition state approaching the completely symmetrical, homoaromatic cation conceived by Winstead, Sonnenberg, and DeVries;\(^14\) and in light of the large volume increment found previously for the symmetrical norbornyl cation, it is satisfying that here, too, the volume increment is of comparable magnitude.

As is well known, the school of thought led by H. C. Brown views the
Table 1.9 Solvolysis Activation Volumes for Several Benzenesulfonates

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Temperature</th>
<th>Solvent</th>
<th>% Acetone</th>
<th>$\Delta V_\sigma$ (cm$^3$/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>exo-2-norbornyl brosylate</td>
<td>40.00</td>
<td>94.0</td>
<td>-14.3</td>
<td></td>
</tr>
<tr>
<td>endo-2-norbornyl brosylate</td>
<td>40.00</td>
<td>94.0</td>
<td>-17.8</td>
<td></td>
</tr>
<tr>
<td>cyclopentyl brosylate</td>
<td>40.00</td>
<td>94.0</td>
<td>-17.7</td>
<td></td>
</tr>
<tr>
<td>cyclobutyl tosylate</td>
<td>40.00</td>
<td>70.0</td>
<td>-15.8</td>
<td></td>
</tr>
<tr>
<td>cyclopentyl tosylate</td>
<td>40.00</td>
<td>70.0</td>
<td>-17.0</td>
<td></td>
</tr>
<tr>
<td>cyclohexyl tosylate</td>
<td>40.00</td>
<td>70.0</td>
<td>-17.5</td>
<td></td>
</tr>
<tr>
<td>cycloheptyl tosylate</td>
<td>40.00</td>
<td>70.0</td>
<td>-17.7</td>
<td></td>
</tr>
<tr>
<td>cyclooctyl tosylate</td>
<td>25.00</td>
<td>70.0</td>
<td>-16.5</td>
<td></td>
</tr>
</tbody>
</table>

solvolysis rate ratios of 1 and 2 not as indicating an acceleration of the exo epimer by anchimeric assistance, but as a retardation of the endo. They15 rationalize the latter effect in an appealing way: the transition state of 2 must, as specified by the Hammond postulate, involve at C-2 a nearly fully-formed p orbital partially bonding with the leaving group. From simple geometric considerations, it follows that the leaving group must be pressed laterally into the 5,6-endo hydrogens as the rehybridization process proceeds, a consequence of which would be, in this view, abnormally high activation energy. Since some reactions16,17 involving sterically crowded transition states exhibit somewhat increased negative activation volumes due to the greater transition-state density imparted by interpenetrating groups, it is reasonable to ask if the observed $\Delta V_\sigma$ difference between 1 and 2 might not also be ascribable to steric hindrance.

Examination of Table 2 allows the magnitude attributable to such an effect to be ascertained. It may be noted that 11 and 12 should experience no more steric inhibition of ionization of the kind envisioned by Brown than does the exo norbornyl case since, in both, the leaving group departs in a direction divergent to neighboring groups. However, this is not true of 13 and 14, and because of steric interaction of their leaving groups with the axial hydrogens, these compounds serve as models for the endo norbornyl system; 15 is the endo norbornyl epimer.

The $\Delta V_\sigma$ values of Table 2 are, as a group, more accurate than those reported before, and partially for that reason the absolute values of these volumes are somewhat greater than those of Table 1. The near identity of the five quantities makes the conclusion unmistakable: there is no observable significant correlation in these systems between $\Delta V_\sigma$ and steric hindrance, and the differences noted before appear validly attributable to $\sigma$ participation with non-classical charge dispersion.

$\pi$-Participation. le Noble, Yates, and Scaplehorn9 have reported in addition an observed correlation between $\pi$ participation and activation volume; however, due to the seemingly less clear-cut behavior of that phenomenon, this discussion will refer the interested reader to the original source.
The Effect of Steric Hindrance on $\Delta V^*$

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta V^*$ (cm$^3$/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONs</td>
<td>-20.0 ± 0.3</td>
</tr>
<tr>
<td>ONs</td>
<td>-20.5 ± 0.3</td>
</tr>
<tr>
<td>ONs</td>
<td>-21.6 ± 0.3</td>
</tr>
<tr>
<td>ONs</td>
<td>-20.6 ± 0.3</td>
</tr>
<tr>
<td>ONs</td>
<td>-21.0 ± 0.3</td>
</tr>
</tbody>
</table>

-5.4 ± 1.0 cm$^3$/mole, -1.0 ± 1.0 cm$^3$/mole, and -21.0 ± 1.0 cm$^3$/mole, respectively, for 16-18. Furthermore, 19 shows a normal-solvolysis activation volume, and it has been corroborated by a thorough adjunct study that it solvolyzes without assistance. That it does not show participation is similar to what Winstein, et al., found for the methoxypropyl analog; that it does show a normal activation volume is an additional substantiation of the soundness of the method's premises.

In Summary, le Noble and coworkers have demonstrated that $\sigma$ and $\text{Ar}_1$ participation are accompanied and detectable by an increased volume of activation.

### THE SOLVOLYSIS CONTINUUM

The question regarding the position of certain solvolysis reactions along a mechanistic continuum (and indeed even the question of a continuum itself$^{20}$ has been the subject of much discussion and study, especially in the case of benzyl chloride and its derivatives. Laidler$^{21}$ has suggested the symbolism which will be used here, namely, the designations $S^+(1)$ and $S^-(1)$ for mechanisms lying inside the boundaries located by the conventional $S_N^1$ and $S_N^2$ extremes. The differences encountered in the mechanistic pro-
gression are considered to be due entirely to the role of solvent in the transition state. In the $S_1$ limit, the solvent merely solvates the activated complex without forming bonds of any covalent character; at the $S_2$ boundary, partial covalent bonding is occurring between solvent and transition state. The term "covalency" may be given a more rigorous definition in terms of charge distribution, as is illustrated below for the transition state of a general nucleophilic displacement reaction $X + YZ$, $X^{-} + Y^{-} \rightarrow Z^{-}$, in which $a$ and $b$ are the changes in the effective charges upon $X$ and $Y$ as the latter go from the initial to the transition state. Thus, a pure $S_1$ reaction is defined as one having $a = 0$, an $S_2(1)$ as one having $a \approx 0$, and an $S_2(2)$ as one having $a \gg 0$. It should be noted here that the non-thermodynamic variable, time, is not involved.

Laidler and Martin have recently examined the solvolysis activation volumes for a series of substituted benzyl chlorides in an attempt to clarify the nature of the transition state in these systems; their pertinent data--the substituents, the corresponding activation volumes, and the latter's first derivative, a compressibility measure--are presented in Table 3. The activation volumes in each case were determined from four rate measurements in the pressure range 0.00101 to 1.033 kbar by the quadratic method.²²

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Mole fraction of acetone</th>
<th>$\Delta V_0$ (cm$^3$/mole)</th>
<th>$\frac{\partial \Delta V_0}{\partial P}$ (cm$^3$ mole$^{-1}$ kbar$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$-NO$_2$</td>
<td>.1407</td>
<td>-23.3 ± 0.2</td>
<td>16 ± 6</td>
</tr>
<tr>
<td>$p$-Cl</td>
<td>.1407</td>
<td>-21.8 ± 0.1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>H</td>
<td>.1407</td>
<td>-21.4 ± 0.8</td>
<td>1.5 ± 1.5</td>
</tr>
<tr>
<td>$p$-CH$_3$</td>
<td>.1407</td>
<td>-18.5 ± 0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

The absolute magnitudes of these volumes are not particularly enlightening here, and the results were "interpreted on the view that the mechanisms are $S_2(1)$" with the $p$-NO$_2$ case tending toward $S_2(2)$. Their discussion was that the larger $\Delta V$ for the $p$-CH$_3$ compound is explained by two factors: (1) charge delocalization upon the aromatic ring with subsequent lessened electrostriction (a larger $\Delta V$ term), and (2) longer $C-C$ and $C-C-O$ bonds in the $p$-CH$_3$ case, thus implying less covalent character for the transition state (a larger $\Delta V$ term). The lesser compressibility for $p$-CH$_3$ was used apparently in substantiation of the last-mentioned effect: The shorter bonds in the $S_2(2)$ transition state of the $p$-NO$_2$ case leads to a structure of greater density, hence a larger $\partial \Delta V / \partial P$. The second factor's significance is open to objections which must be, however, precluded here due to lack of space. Nonetheless, the remaining rationale seems insufficient by itself to allow an a priori conclusion regarding any differences in mechanism.

The remainder of this review will treat the work of J. B. Hyne and his collaborators regarding transition-state-solvent interactions which led to certain electrostatic transition-state models and a new measure of the electrical nature of the solvolysis transition state. One of the more commonly-known facts of physical chemistry is that the partial molal volume of a ground state, $V_1$, varies with the composition, $x$, of a binary solvent mixture; that is, $V_1 = f(x)$, and generally passes through some extremum; Hyne and coworkers (and others) in similar regard to the behavior of $\Delta H^+$ and $\Delta S^+$ first showed that $\Delta V_0$ varies in a similar manner. By ascertaining $\Delta V_0$ at a given solvent composition from pressure-rate data,
measuring $\bar{V}_t$ directly for the same composition in a dilatometer, and substituting both into equation (1), the value of $\bar{V}_t$ at that composition can be derived. It is found that $\bar{V}_t$ also varies as a function of $x$, and it is the nature of this variation that can be revealing of the electrical properties of the transition state.

As a basis for understanding the variation of $\bar{V}_t$, Lee and Hyne\textsuperscript{25} made a thorough study of the $\bar{V}_t$ variation in a series of tetraalkylammonium chlorides--tetramethyl through tetra-n-butyl--as possible transition-state models. This analysis was accomplished by dissecting the observed $\bar{V}_t$ variation of the salts into the individual contributions of the constituent anion and cations. The method of Conway and coworkers,\textsuperscript{28} originally proposed for obtaining ionic partial molal volumes of tetraalkylammonium salts with a common anion in water, was adapted here for use in aqueous ethanol mixtures. In this method, the partial molal volume for each of the salts of the series, in a given solvent composition, is plotted versus the molecular weight of its cation. The observed linear dependence is then extrapolated to zero cation weight to give the partial molal volume contribution of chloride. The volumes so obtained are displayed below as Fig. 1; it is noteworthy that the value obtained for $X = 0$ is in agreement with previous determinations\textsuperscript{29} made by other methods. The partial molal volumes of each of the cations could then be determined by subtracting the extrapolated $\bar{V}_{\text{Cl}^-}$ values for each composition from the observed values of the salts. The cation dependencies on $X$ are shown in Figure 2.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{$\bar{V}_0$ vs. $x$ for $\text{Cl}^-$}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{$\bar{V}_0$ vs. $x$ for $R_4N^+$ cations.}
\end{figure}

Clearly when $x = 0.3$, that mole fraction of EtOH offers a special influence upon the partial molal volumes of charged species. One rationale\textsuperscript{25} is that at that composition the solvent has minimum free volume and is nearest to being close-packed; that is, the open structure characteristic of water has been completely filled in and broken down by the organic component. (The latter may be considered a crystal impurity.) Consequently, the binary solvent system is
maximally unstructured and the solvent molecules are relatively the most available for electrostrictive interaction; whereas, beyond \( x = 0.3 \), the solvent availability effect is offset by the increasing proportion of organic component. Further evidence\(^3\)\(^0\) attesting to the correctness of this idea is the fact that the first derivative of viscosity with respect to \( x \) is a minimum at approximately the same composition, thus indicating minimum structure. That electrostriction effects are an essence of the phenomenon is shown by the actual negative partial molal volume for the chloride ion.

Implicit in the above mentioned extrapolation procedure is the fact that \( R_4N^+ \) cations behave as non-electrolytes and effect virtually no hydration.\(^2\)\(^8\) Thus, the maxima in the cation \( \bar{V}_i \) curves are strictly a function of size, were the dissolution mechanism simple expansion of the solvent to accommodate the solute.\(^2\)\(^5\) Therefore, the sums of the two sets of curves (see Fig. 3) reflect a balance between hydrophobic size of the cations and the electrostriction effect of the anion.

Fig. 3 shows the \( \bar{V} \) dependencies for a variety of species--the tetra-alkylammonium salts, the \( \bar{V}_j \) curve for benzyl chloride, and the \( \bar{V}_i \) curve for anilinium chloride as a possible model for the preceding transition state. The question of whether anilinium chloride is a reasonable transition-state electrostatic model (it is a good structural model) for \( S_1 \) solysis of the latter species was considered by the authors to be answerable by reference to this figure. From the \( \bar{V}_i \) behavior, it seems that the transition state must have a somewhat lower surface charge density--hence, lesser electrostriction--than does anilinium chloride.

Besides the obvious and usual questions regarding the accuracy of the \( \bar{V}_i \) curve, at this stage it is relevant to question also the validity of such a comparison, since it is clear that the two types of species--salts and transition states--are by no means electrical congeners. The salts are undoubtedly fully ionized in these media; the transition states are mere dipoles. Hyne and Lee\(^2\)\(^8\) remind the reader in this regard that what is being observed in these studies is not the charge density on single atoms, but the sum of electrostrictive effects of constituent cation and anion of the solute species. "Nothing is implied about the relative charge densities on the individual ions; for example, the degree of charge development in the transition state may well be much less than the full ionic character of \( Et_4N^+Cl^-\), but the charge that has developed in the transition state may be much more accessible to the solvent than is the case in the bulkier tetraethylammonium cation." However, it may seem somewhat precarious to compare directly the two last-mentioned species since they have, besides differing charge densities, also differing hydrophobicities. This last problem can be surmounted by a comparison such as that shown in Fig. 4. The study\(^2\)\(^7\) through which these were derived was designed to ascertain the \( \bar{V}_i \) variation as a function of reaction position along the continuum, and consequently \( t-BuCl \), benzyl chloride, and the latter's \( p-Cl \) derivative were examined. (It was the original intention to use the \( p-OCH_3 \) derivative as the \( S_1 \) example, but due to solubility difficulties, \( t-BuCl \) was employed instead.\)\(^3\)\(^1\) By other evidence, these compounds are thought to solvolyze via \( S_1 \), \( S_2(1) \), and \( S_2(2) \) mechanisms, respectively. Although the three species offer differing hydrophobicities, and thus direct analysis of their \( \bar{V}_i \) curves is spoiled, this difference is manifested in both the \( \bar{V}_i \) and the \( \bar{V}_j \) curves, and it follows that the \( \Delta \bar{V}_i \) dependency reflects a true charge difference stemming primarily from differently-charged transition states. That is, the deeper minimum in the \( \Delta \bar{V}_i \) curve as one progresses toward the \( S_1 \) extreme presumably indicates increasing charge density in the transition state.
In Summary. The employment of activation volumes directly for the purpose of determining a reaction's mechanism along the S,1-S,2 mechanistic scale seems inconclusive; however, a new technique involving examination of $\bar{V}_t$ or $\Delta V^*$ as a function of the mole fraction of a cosolvent in water may be useful.
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29. see e.g. E. Glueckauf, Trans. Faraday Soc., 61, 914 (1965).


Reported by Neil E. Nodelmen

March 18, 1971

The effect of pressure on the rate constant for a chemical reaction is related to the activation volume, \( \Delta V^* \), by equation (1). The activation volume reflects differences in bond lengths, geometry, and solvation between the transition state and reactants. For reactions involving free radicals or nonpolar molecules, solvation effects would be expected to contribute less to the values of \( \Delta V^* \) than for polar reactions. Hence, \( \Delta V^* \) for the former can be assigned mainly to bond length and geometry changes. Earlier reviews of the subject have appeared.\(^1\)\(^2\)

\[
dlnk/dp = -\Delta V^*/RT (1)\]

Radical Reactions. Recent studies of homolytic scission reactions have shown that observed activation volumes are positive and range from less than +1 cc/mole to greater than 10 cc/mole.\(^3\)\(^4\) The initially formed geminate radicals from initiators decomposing via a one-bond scission mechanism can potentially reform starting material \((k_1)\) in a process (cage combination) competitive with separative diffusion \((k_d)\). The observed \( \Delta V^* \) values reflect not only the values for homolytic scission, \( \Delta V^*_i \), but also the pressure dependence of the ratio \( k_1/k_d \) (equation 2).

Free radical initiators decomposing via simultaneous two-bond scission, for which \( k_1 = 0 \), generally give smaller values of \( \Delta V^* \) than do one-bond scission initiators (Table 1). This implies that the ratio \( k_1/k_d \) for one-bond scission initiators increases with pressure. The product distribution from thermal decomposition of \( t \)-butyl phenylperacetate also is consistent with the contention that cage combination increases relative to diffusion with an increase in pressure.\(^5\)\(^6\)

Several two-bond scission initiators give values of \( \Delta V^* \) in the range of 4 to 5 cc/mole and such values may be typical for \( \Delta V^*_i \). The low values for \( t \)-butyl phenylperacetate and the substituted compounds may reflect solvent electrostriction.\(^10\)\(^11\) The contribution for solvent changes, \( \Delta V^*_solv \), may be calculated for the substituted peresters (equation 3). The negative signs of these numbers support a transition state more polar than the reactant; the absolute magnitude of \( \Delta V^*_solv \) increases as the electron donating ability of the substituent increases.

A detailed study of the pressure dependence of the cage effect has been carried out for \( t \)-butyl hyponitrite \( [(CH_3)_3CO-N=N-OC(CH_3)_3] \) decomposition in \( n \)-octane.\(^7\)\(^9\) \( Di-t \)-butyl peroxide and \( t \)-butyl alcohol constitute 95 to 100\% of the decomposition products. The difference in activation volumes for diffusion and cage combination of \( t \)-butoxy radicals \( (\Delta V^*_d - \Delta V^*_c) \) is determined from the pressure dependence of the ratio \( k_d/k_c \), which is equal to \( 2(k_1/k_d)/(k_1 + k_d) \). The magnitude of the variation in \( \Delta V^*_d - \Delta V^*_c \) (+30 to +7 cc/mole) over a 4000-atm pressure range probably arises from an inverse pressure dependence of \( \Delta V^*_c \). If one attributes the pressure dependence of \( k_1 \) to viscosity variation\(^d\) (from the known dependence of solvent viscosity on pressure), a knowledge of the viscosity dependence of \( k_d/k_c \) at atmospheric pressure provides a means for independent calculation of \( \Delta V^* \) and, hence, the activation volume for radical combination. For \( t \)-butoxy radicals \( \Delta V^*_c = -5 \) cc/mole and is observed to be pressure independent.

\[ A-B \xrightarrow[k_1]{} (A- \cdot B) \xrightarrow[k_d]{} A^+ + \cdot B \]

\[
\Delta V^*_solv = \Delta V^*_solv = \Delta V^*_obs - \Delta V^*_i (2)\]

Molecular Reactions. The Diels-Alder additions of various dienes to maleic anhydride have activation volumes (-36.7 cc/mole for the isoprene reaction) which are significantly
more negative than the volume changes on reaction \((-33.7 \, \text{cc/mole})\). Secondary \(\pi\)-electron interactions at nonbonding atoms in the transition state may explain the abnormally small volumes of the transition states for the maleic anhydride reactions. For the reaction of an acetylenic dienophile, in which the positions of the nonbonding atoms do not allow secondary interaction to occur, the transition state is somewhat larger than the products, as expected.

Racemizations. Activation volumes have been determined for a number of racemizations of pyramidal sulfur compounds in order to help discriminate between bond distortion and bond breaking as rate-determining steps. Racemization of diaryl sulfoxides have \(\Delta V^*\) near zero, which suggests racemization by pyramidal inversion. Racemization of benzyl \(p\)-tolyl sulfoxide has \(\Delta V^* = +26 \, \text{cc/mole}\), indicative of a reversible homolysis with loss of optical activity accompanying the recombination process.

Conformational Equilibrium. Internal solvent pressure \((P_i)\) studies, may provide a rapid way to evaluate volumes of activation. Internal pressure is defined as a change in the internal energy with respect to a change in volume at constant temperature, \((dE/dV)_p\). Conformational studies of 4,4-dimethyl-2-silapentane, employing nuclear magnetic resonance, have established that internal solvent pressure increases the population of the "gauche-butane" conformation with respect to the "trans-butane" conformation. A plot of \(\ln k\) vs \(P_i\) yields a difference in molar volumes of -3.7 cc/mole for the trans-gauche equilibrium.

Table 1. Observed Activation Volumes for Decomposition of Free Radical Initiators

<table>
<thead>
<tr>
<th>One-Bond Initiators</th>
<th>Solvent, (^\circ\text{C})</th>
<th>(\Delta V^*)</th>
<th>Two-Bond Initiators</th>
<th>Solvent, (^\circ\text{C})</th>
<th>(\Delta V^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzoyl peroxide</td>
<td>CCl(_4) 60 10</td>
<td></td>
<td>AIRN</td>
<td>toluene 70 4</td>
<td></td>
</tr>
<tr>
<td>t-butyl peroxide</td>
<td>CCl(_4) 120 13</td>
<td></td>
<td>t-butyl hyponitrite</td>
<td>octane 55 4.3</td>
<td></td>
</tr>
<tr>
<td>t-butyl perbenzoate</td>
<td>cumene 80 11</td>
<td></td>
<td>(\mathbf{S})CO(_3)(CH(_3))(_3)</td>
<td>cumene 80 3.9</td>
<td></td>
</tr>
<tr>
<td>pentaphenylethane</td>
<td>toluene 70 13</td>
<td></td>
<td>(\mathbf{t})-butyl phenyl-peracetates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH(_2)CH(_2)CH=</td>
<td>CO(_3)(CH(_3))(_3)</td>
<td></td>
<td>m-Cl</td>
<td>cumene 80 1.6</td>
<td></td>
</tr>
<tr>
<td>CH(_2)CH(_2)CH=</td>
<td>C(_3)H(_7)(n)</td>
<td></td>
<td>m-Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH(_2)CH(_2)CH=</td>
<td>C(_3)H(_7)(n)</td>
<td></td>
<td>p-Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-isomer</td>
<td>cumene 100 9</td>
<td></td>
<td>p-CH(_3)</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>cis-isomer</td>
<td>cumene 100 7</td>
<td></td>
<td>p-CH(_3)</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p-OCH(_3)</td>
<td></td>
<td>6.0</td>
</tr>
</tbody>
</table>

\(\text{Reference 11 and references therein.}\)

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The postulation that hormones play a role in the sexual reproduction of fungi was not experimentally verified until 1920. In 1958, it was found that sirenin, contained in the liquid excreted by the female gametes of the water mold Allomyces, is able to attract the male gametes. Sirenin was later purified via its diester with 4-(4-nitrophenylazo)benzoic acid (bis-NABS-sirenin), and its molecular formula was established to be C_{15}H_{24}O_{2}.\(^3\)

Nutting, Rapoport and Machlis determined the structure of sirenin to be 9-[(E)-4-hydroxy-3-methyl-2-butenyl]-10-hydroxy-2-carene (1).\(^4\)-\(^5\) The structural determination was carried out by comparing spectroscopic data for sirenin and the products formed by mono-ozonolysis of bis-NABS-sirenin -- NABS hydroxyacetone and two aldehydes, by manganese oxidation of sirenin to a dialdehyde and by periodate-permanganate treatment followed by esterification of sirenin to give a cyclopropane triester, whose properties were compared with those of synthetic samples of four possible isomeric structures.

In the same year Ohta and Hirose reported the structure of sesquicarene, a component of the essential oil of the fruits of Schisandra chinensis, to be 9-[3-methyl-2-butenyl]-2-carene (2), which has the same structure as sirenin without the two hydroxyl groups.\(^6\) The absolute configuration was assigned as in 2 because the specific rotations of sesquicarene and its tetrahydro derivative\(^5\) were of opposite signs from those of (+)-2-carene and (-)-cis-carane.\(^7\)

Recognition that the carbon skeletons of sirenin and sesquicarene are the same has spurred much work on the syntheses of both. The key step in forming the bicyclo[4.1.0]heptane ring system is a stereospecific intramolecular carbene addition reaction.\(^8\)-\(^9\) The desired precursors are the diazo ketone 3 (R=H or CH\(_3\)), the diazo compound 4, or the sodium salt of the toluene-p-sulfonylhydrazone 5. A comparison of the synthetic routes described for converting commercially available precursors for sesquicarene is given in Table I, and for sirenin in Table II.

The number of steps and the overall yields show that sesquicarene is easier to make than sirenin since there are no hydroxyl groups to be introduced in preparing sesquicarene. The simplest route for producing sesquicarene is oxidation of redistilled commercial farnesol (using only the cis,trans isomer) to the aldehyde, which is converted to the hydrazone. After oxidation of the hydrazone to the diazo compound, which is cyclized by adding cuprous iodide to give sesquicarene in 25% overall yield.\(^10\) It was later found that when mercuric iodide is used for the cyclization, it isomerizes most of the trans,trans isomer to cis,trans, thereby eliminating the necessity of purifying commercial farnesol.\(^11\)

In the synthesis of sirenin, the \(\alpha\)-ketocarbene from the diazo compound 3 (R=H) is used to generate the bicyclo[4.1.0]heptane. A hydroxymethyl group can be added to the 3-position easily by treatment with basic dimethyl carbonate, followed by reduction to the alcohol.\(^22\)-\(^23\) The \(2\)-keto group is removed by reduction to the alcohol and the hydroxyl by dehydration to give the \(\Delta^2\)-alkene. The hydroxyl group on the isopentenyl side chain can be introduced directly, by oxidation with selenium dioxide to give an \(\alpha,\beta\) unsaturated aldehyde, which is reduced to the alcohol.\(^22\)-\(^23\) It can also be introduced indirectly, by ozone cleavage of the double bond to form an aldehyde, followed by reaction with the sodium salt of methyl 2-diethylphosphonopropionate and reduction of the ester to the alcohol.\(^19\)
Table I. Racemic Sesquicarene Synthesis.

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Number of steps</th>
<th>Approximate overall yield, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geranyl bromide</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Cyclopropyl methyl ketone</td>
<td>8</td>
<td>6</td>
<td>11, 12</td>
</tr>
<tr>
<td>Ethyl 5,5-ethylenedioxy-2-methylbutanoate</td>
<td>11</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Farnesol (via (_3) R=CH(_3))</td>
<td>9</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Farnesol (via (_5))</td>
<td>4</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Farnesol (via (_5), heat cyclization)</td>
<td>4</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Farnesol (via (_5), photolytic cyclization)</td>
<td>4</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Farnesol (only cis, trans)</td>
<td>4</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Farnesol (commercial, trans, trans; cis, trans; 1:5:1)</td>
<td>4</td>
<td>35</td>
<td>17</td>
</tr>
</tbody>
</table>


Table II. Racemic Sirenin Synthesis.

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Number of steps</th>
<th>Approximate overall yield, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopropyl methyl ketone</td>
<td>17</td>
<td>1</td>
<td>12, 18</td>
</tr>
<tr>
<td>Geraniol</td>
<td>12</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Geranyl acetate</td>
<td>12</td>
<td>2</td>
<td>20, 21</td>
</tr>
<tr>
<td>Geraniol</td>
<td>10</td>
<td>2</td>
<td>17, 21</td>
</tr>
<tr>
<td>6-Methyl-5-heptan-2-one</td>
<td>10</td>
<td>6</td>
<td>22, 23</td>
</tr>
</tbody>
</table>

BIBLIOGRAPHY

LANTHANIDE NMR SHIFT REAGENTS

Reported by Ronald J. Converse

March 25, 1971

I. INTRODUCTION

Nuclear magnetic resonance has shown itself to be a remarkably useful analytical tool in organic chemistry, but until recently the similar chemical shifts of various types of protons bonded to carbon have led to resolution difficulties. Several techniques, including use of solvent effect, double resonance, and instruments of higher field, have been developed to improve resolution of normally overlapping resonances. The most powerful of these techniques involves the use of europium and praseodymium tris-β diketone complexes.

In June, 1969, Hinkley reported improved resolution of the nmr spectrum of cholesterol in the presence of the dipyridine adduct of tris-(dipivalomethanato)europium(III) [Eu(DPM)₃], ₁ referred to in subsequent publications as tris-(2,2,6,6-tetramethylheptane-3,5-dionato)europium(III) [Eu(tmdh)₃] or Eu(thd)₃]. To explain the spectrum obtained with ₁, Hinkley postulated a through-space (pseudocontact) interaction of europium and hydrogen nuclei, whereby those protons nearest europium in space should be most strongly affected. Hinkley stated that the europium-induced resonance shifts were concentration dependent, and he concluded that the bonding site of a cholesterol molecule to europium was the hydroxyl group of cholesterol. An almost feverish activity in the area of lanthanide shift reagents is apparent from the chemical literature since Hinkley's first report. This activity has centered around two points: (1) understanding and improvement of the technique, and (2) application of shift reagents to the spectra of relatively complicated organic molecules under conditions reported by Hinkley and later workers.

Much of the theory of pseudocontact nmr shifts existed before Hinkley's first paper.²⁻⁴ Indeed Hinkley stated that his experimental results were merely verification of his own predictions. Contact and pseudocontact shift had been the subjects of numerous papers involving transition and rare earth metals.²,⁵⁻⁹ Most of the work before Hinkley's first report was carried out on relatively homogeneous metal complexes. Before Hinkley's report, it was recognized that the pseudocontact contribution to the chemical shifts of protons in metal-organic complexes should increase in progressing from first row transition metals to the rare earth metals, and that the pseudocontact contribution should dominate the chemical shifts of protons in organic complexes of rare earth metals.² It was recognized that europium (III), as a tris-β-diketone complex in solution, can readily increase its coordination number in the presence of Lewis bases.¹⁰⁻¹² It was also known that β- or 9-coordinate europium complexes showed large contact or pseudocontact nmr shifts.²,⁸ Hinkley's main contribution lies in seeing the potential usefulness of the readily reversible Lewis acid-base interactions in nmr spectra of Lewis bases.

II. WORK ON IMPROVEMENT AND UNDERSTANDING OF THE SHIFT REAGENT TECHNIQUE

Recent work has explored the effects of changes in the central ion¹³,¹⁴ and changes in ligands¹⁵,¹⁶ of the shift reagent. Crump and coworkers compared relative line broadening and shift power of a series of tris-DPM complexes of trivalent praseodymium, samarium, europium, terbium, holmium, and ytterbium with benzyl alcohol, 2,4-t-butylcyclohexanone, dimethyl tetradecanediolate, and n-pentylamine as substrates.¹³ These workers found that ₁ and Pr(DPM)₃, ₂, gave the least line broadening and showed shift powers
of about equal magnitude but of opposite sign. Sanders and Williams have compared three tris-β-diketone complexes of europium (III) as potential shift reagents: the hydrated acetylacetonate, 3, the dibenzoylmethanate, 4, and 1, which were judged generally most useful.\textsuperscript{15} Compound 3 gave only about 7% of the shifts seen with 1. The corresponding anhydrous complex was hygroscopic. Compound 4 was poorly soluble in nonpolar solvents. A brochure claims that 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione (fod) is superior to DPM as a shift reagent ligand, since the fluorocarbon group increases the solubilities and Lewis acidities of the europium and praseodymium tris complexes, 5 and 6, respectively.\textsuperscript{16} More work needs to be done for a thorough understanding of the properties required of the ideal shift reagent ligand.

Relative magnitudes of resonance shift per functional group are the following: -NH\textsubscript{2} > -OH > -CHO > -COR > -OR > -COOR > -CN > -NO\textsubscript{2}.\textsuperscript{15} Polynuclear molecules generally yield complex spectra on use of a shift reagent, but some derivation can simplify such spectra. Crump and coworkers have shown that derivatization of alcohols to trifluoroacetates and of ketones to ethylene thiketals practically erases resonance shifts arising from shift reagent complexation at the underivatized sites.\textsuperscript{17}

\[ \begin{array}{c}
\text{CH}_3 \\
\text{H-C} \\
\text{C-O} \\
\text{CH}_3 \\
\text{H-C} \\
\text{C-O} \\
\text{H}_2\text{O} \\
\text{Eu} \\
\end{array} \]

\[ \begin{array}{c}
\text{CH}_3 \\
\text{H-C} \\
\text{C-O} \\
\text{CH}_3 \\
\text{H-C} \\
\text{C-O} \\
\text{CH}_3 \\
\text{H-C} \\
\text{C-O} \\
\text{H}_2\text{O} \\
\text{Eu} \\
\end{array} \]

\[ \begin{array}{c}
\text{CF}_3\text{CF}_2\text{CF}_2 \\
\text{H-C} \\
\text{C-O} \\
\text{H}_2\text{O} \\
\text{Eu} \\
\end{array} \]

III. APPLICATIONS OF SHIFT REAGENTS

The first and most obvious use of the shift reagents has been resolution improvement. A beautifully simplified spectrum of 1-hexanol has been published by Sanders and Williams.\textsuperscript{16} Normally, proton resonances of all methylene groups except that bearing the hydroxyl group lump together between 1.2 and 1.7 ppm (6). After addition of 1 to the nmr sample, all methylene proton resonances were separately observable, showing the first order splitting pattern for each group. The shifted methylene proton resonances ranged from about 2.2 ppm (for the methylene protons farthest from the hydroxyl group) to about 10.5 ppm (6) (for the protons of the methylene group bearing the hydroxyl group) when 0.29 mole of 1 was added.

Demarco and coworkers have published a first order spectrum obtained from cis-4-t-butylcyclohexanol with 1, showing all nonequivalent proton resonances separately observable with fine structure.\textsuperscript{18} Wahl and Peterson have reported obtaining first order spectra from 1- and 2-adamantanols, 7 and 8, respectively, with 1.\textsuperscript{19} Briggs and coworkers have reported complete resolution of the nmr spectra of borneol,\textsuperscript{21} 9, and 1-pentanol\textsuperscript{22} with 2. Demarco and coworkers have reported obtaining a high degree of resolution of the nmr spectra of a steroid, androstan-2β-ol, 10, and a triterpene, friedelan-3β-ol, 11, by use of 1, spin decoupling, and 100 MHz and 220 MHz spectrometers.\textsuperscript{23}

Liska and coworkers have used the splitting patterns of the first order spectrum obtained from a coumarin derivative, 12, with 1 to choose between two possible structure assignments, 12 and 13.\textsuperscript{24} Hinkley has plotted the
change in chemical shift vs the change in dipyrine adduct concentration to resolve a long-standing dispute over assignment of the three methyl resonances in the nmr spectrum of (+)-camphor. Fraser and Wigfield have illustrated with three examples the use of 1 in assigning configuration to rigid sulfoxides. By using 1 and decoupling experiments, Achmatowicz and coworkers assigned configuration of the carboxyl group of a pentacyclic diterpene, trachyloban-19-oic acid, 17, on the basis of comparison of the spectra of the lithium aluminum hydride reduction products of 15 and of the known kaur-16-enolic acid, 16. Carroll and Blackwell have reported using the splitting pattern in Eu(DPM)2-simplified spectra to confirm an assignment of preferred configuration of cis- and trans-3,5-dimethylvalerolactones, 17 and 18, respectively. Use of 1 has afforded a first order spectrum of endrin, 19, and has allowed determination of configuration of the proton in photodieldrin, 20, which has migrated during photolysis of dieldrin, 21. The configurations of isomeric 3-chloro-5-acetoxynortricyclenes, 22 and 23, have been assigned recently on the basis of the relative changes in chemical shifts of the respective CHCl protons with changes in concentration of 1. Whitesides and Lewis have made an important extension of the shift reagent idea by using an optically active β-diketone as ligand in a shift reagent for determining enantiomeric purity. These workers made tris-[3-(t-butylhydroxymethylene)-(+)camphorato]europium(III), 24, and obtained chemical shift differences ranging from 0.5 to 1.4 ppm for the CHNH2 protons in enantiomeric mixtures of β-phenylethylamine, amphetamine, and 2-aminobutane. Enantiomeric resolutions of 2-octanol, β-phenylethanol, cyclohexymethylcarbinol, and benzyl methyl sulfoxide were too small to be useful under conditions used with the amines. This paper illustrates that perhaps one should be cautious in assigning structures (as in Ref. 30) or preferred conformations on the basis of differences in rate of change of chemical shift with change in shift reagent concentration, because shift reagent complexes with the isomers of interest may have different stability constants.

A pair of recent papers have proposed the use of rare earth metal ions as spectroscopic probes of electrostatic binding sites in enzymes. It was argued that the rare earth metal ions form mainly electrostatic complexes like those of calcium, that a direct relationship exists between ionic size and the strength of binding of metal ions with closed electronic shells to β-methylnaspartase, and that the ionic radii of the rare earth metal ions approximate the ionic radius of calcium(II). Nmr data on the association of a 1:1 europium(III) lysozyme complex with a substrate analog, methyl N-acetyl-β-glucosaminide (Me-β-NAG), show shifts of +1.6 and -2.8 ppm in the resonances of the acetamido and glycosidic methyl groups, respectively, of Me-β-NAG (D2O, 40°, pD 5-6). More work is needed to explain these preliminary results, but it does appear that lanthanide cations can be useful in the elucidation of some enzyme-substrate interactions.
IV. GENERAL AND EXPERIMENTAL INFORMATION

Tris-DPM complexes of 15 trivalent rare earth metal ions were made in about 1965 by Eisentraut and Sievers.\textsuperscript{34} These complexes readily underwent vacuum sublimation without apparent decomposition at temperatures between 100° and 200°, and could be readily separated from each other by glc. Most of these complexes were stable to melting and heating above 300°. Crump and coworkers have reported that the colors of anhydrous, freshly sublimed 1 and 2 are pale yellow and pale green, respectively, and that absorption of atmospheric moisture changes the colors to white and yellow, respectively.\textsuperscript{13} Compounds 1, 2, 5 and 6 slowly absorb moisture from air and thus should be stored over P\textsubscript{2}O\textsubscript{5}.\textsuperscript{16,17}

A shift reagent is generally added a little at a time, so that one may follow the various resonances as they shift. In this way one avoids accidental overlap of differently shifted resonances and finds the shift reagent concentration which affords maximum resonance dispersions.\textsuperscript{17,25,35} Armitage and Hall suggest the use by aliquot of a concentrated carbon tetrachloride stock solution of the shift reagent.\textsuperscript{35} Polar solvents should be avoided, since they compete with the substrate of interest in the formation of a shift reagent complex and thus cause a decrease in resonance shift from that possible in nonpolar solvents.\textsuperscript{17} Shift reagent substrates should therefore be dry in order to produce maximum resonance shifts. Shift reagent substrates may be recovered from the nmr sample by tlc on silica gel.\textsuperscript{18}

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The Chemistry of Insect Defense

Reported by Carl R. Cappel

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Communication between animals by means of chemical stimuli has been an area of recent extensive investigation. Two main classes of communicative interactions have been separated; that between members of the same species, and that between members of different species.

Compounds used between like species, important for the regulation of courtship and other social activities, include sex attractants, alarm substances, aggregation-promoting substances, and territorial and trail markers. These substances are commonly classed as pheromones, and have been adequately reviewed elsewhere. 1, 2

Defensive secretions, set apart from the pheromones but matching them in importance, serve for the transmission of information between members of different species. These compounds, unlike the pheromones, which are usually produced in vanishingly small amounts, are generally odorous and discharged in substantial quantities.

Insects, arachnids, myriapods, and crustaceans compose the group of animals known as arthropods. Of all land-dwelling animals, arthropods probably have the most diverse and best evolved chemical defenses. The secretory cells are often elaborate in structure, and the secretions are commonly stored in sac-like reservoirs. These glands may occur singly, in pairs, or in multiple pairs, and may be found on the head, thorax, or abdomen.

One of three modes of discharge is typically found. The secretion may simply ooze out from the gland onto the animal's own surface, the secretion may be "aired" by evaporation of the entire gland, or the gland contents may be discharged as a spray, sometimes to a distance of several feet. Although usually not fatal, the secretion causes the attacker acute discomfort for some time, usually sufficient for the attacked animal to make its escape. The secretions are usually effective against predatory arthropods, small mammals, some fish and amphibians, birds, and, very importantly, against microorganisms.

Due to difficulties in capturing and maintaining the arthropods, the isolation, purification, and identification of the small amounts of defense substances are a constant problem. If enough animals are available, the defensive glands are often removed, crushed, and extracted. Otherwise, the animals may be induced to excrete their chemicals onto pieces of filter paper, which are then extracted. Separation and purification are usually effected by chromatography, while identification is accomplished by means of spectroscopy. 3

Arthropod defensive chemistry to 1965 was extensively reviewed recently by Weatherston 4 and the present review will concentrate mainly on investigations reported since 1965. Classification of the defensive substances is arbitrary because of the great diversity in the nature of the compounds isolated to date. The following headings will be treated: (a) quinones, (b) terpenes, (c) steroids, (d) acids and derivatives, (e) hydrogen cyanide, (f) heterocycles, and (g) miscellaneous compounds.

Quinones

Benzoquinones have been the most widely found components of arthropod defensive substances, having been isolated from many species of Arachnida, Diplopoda, and Insecta. Some quinones isolated to date are benzoquinone, toluquinone, 2, 3- and 2, 5-dimethylbenzoquinone, 2, 3, 5-trimethylbenzoquinone, 2-ethylbenzoquinone, 2-methoxybenzoquinone, 2-methoxy-3-methylbenzoquinone, and 2, 3-dimethoxybenzoquinone. 4-8

The bombardier beetle, a brachynid, probably has the most unique defense mechanism in the entire animal kingdom. It stores stabilized hydroquinones in a hydrogen peroxide solution whose concentration is often as high as 28%. A hot toxic gas consisting of benzoquinone, toluquinone, and unreacted hydro-
quinone and hydrogen peroxide is emitted with an audible report produced by oxygen under pressure. The defensive spray mixture has been found to be ejected at a temperature of 100°C.7

Disc electrophoresis, gel filtration, and density gradient centrifugation of the contents from the explosion chambers indicated seven protein fractions. These corresponded to four catalases and three peroxidases. Isolation by micro zone electrophoresis and gel filtration gave one purified catalase (molecular weight 225,000) and one purified peroxidase (molecular weight 60,000). The catalase is employed for the decomposition of hydrogen peroxide into water and oxygen, and the peroxidase is used for the oxidation of hydroquinone.8,9

The quinones have been shown to be biosynthesized via two independent paths. Labeling studies with the beetle Eleodes longicollis suggested that benzoquinone biosynthesis involved the utilization of a preformed aromatic ring of tyrosine or phenylalanine, while 2-methylbenzoquinone and 2-ethylbenzoquinone were built up from acetate units.10

TERPENES

A number of terpenes have been isolated and characterized to date. In order to discuss recent biosynthesis schemes, a few of the terpenes discovered before 1965 will be reviewed. For additional information on terpene defense substances the reader is referred to Weatherston's review.4

In 1955 Cavill and co-workers isolated 2-methyl-2-hepten-6-one and a dicarbonyl compound (C₁₀H₁₆O₂), which they named iridodial, from the ant Iridomyrmex humilis. The colorless, optically active oil readily polymerized to a glassy mass but could be distilled under reduced pressure to give back the monomer. Oxidation with potassium permanganate and sodium bicarbonate in acetone produced two diacids (C₁₀H₁₆O₄), indicating that the original compound was a dialdehyde. The two diacids were identified as nepetalinic acid, 1, and its stereoisomer, 2. The structure of iridodial was thus concluded to be 2. Treatment of 2 with hot aqueous sodium hydroxide yielded isoiridomyrmecin, 4, which has been isolated from the ant Iridomyrmex nitidus.11,12 Iridomyrmecin, 5, has also been isolated from several species of ants. Iridodial has been synthesized from D- (+)-pulegone as shown in scheme 1. The stereoselectivity of the synthesis was confirmed when the product was oxidized to give nepetalinic acid, 1.13-15

\[ \text{Scheme 1} \]
Terpenes \( \text{6} \) has been obtained from Dolichoderus and Iridomyrmex ants and was designated as dolichodial.\(^{10}\) The almost colorless liquid, bp 96\(^\circ\) (2 mm), has been characterized by derivative formation, by ultraviolet and infrared spectroscopy, by its conversion into iridodial, \( \text{3} \) and by its oxidation into the nepetalinic acids \( \text{1} \) and \( \text{2}.^{17} \) It has also been isolated from the walking stick Anisomorpha buprestoides, and was designated as anisomorphal.\(^{18}\) This compound is strongly irritating to the skin and has been known to cause transient but serious injury to the eyes. The walking stick employs a spray mechanism and is the only insect studied thus far which will spray its secretion before any direct attack is made. It can eject its spray with extreme accuracy toward a bird in its vicinity and blue jays have been shown to remain aloof even when presented to the stick insects no more often than every two to three weeks. Nothing is known about the sensory input the insect uses for taking aim. Characterization of anisomorphal by ultraviolet, infrared, and nmr spectroscopy, along with derivative formation, indicated the identical structure \( \text{6} \). Hydrogenation also produced iridodial, \( \text{3}.^{18} \)

A biosynthetic scheme for the terpenes discussed has been proposed by Cavill and Robertson, and is presented in scheme 2.\(^{19} \) Here citral, \( \text{7} \), has been regarded as the basic unit. A stereospecific reduction of citral to (-)-citronellal, \( \text{8} \), followed by a terminal oxidation and Michael addition would yield iridodial \( \text{3} \), from which \( \text{4} \), \( \text{5} \), and \( \text{6} \) could be obtained.\(^{19} \) Isotope labeling studies have indicated that the ant Acanthomyops claviger synthesizes citral and citronellal from acetate and mevalonate.\(^{20} \) It has also been shown that the walking stick synthesizes anisomorphal from labeled acetate and mevalonate.\(^{21} \)

The grasshopper, Romalea microptera, responds to disturbance by emitting a froth from the openings on its thorax. Chromatography on silica gel of the milkings from 1000 animals gave a colorless, crystalline compound, mp 128-128.5\(^\circ\). Infrared, ultraviolet, nmr, and high resolution mass spectroscopy indicated the compound to be a new allene sesquiterpene, \( \text{2} \). This compound is thought to be produced by degradation of closely related carotenoids such as fucoxanthin, \( \text{10} \) or neoxanthin, \( \text{11}.^{22} \)

Finally, the water beetle Stenus bipunctatus excretes a mixture of surface active agents on the surface of the water when disturbed. These compounds act as a motor to propel the beetle toward the shore. Separation of the mixture by gas chromatography yielded three components. The principle component was identified as 1,8-cineole, \( \text{12} \), while isopiperitenol, \( \text{13} \), and 2-methyl-2-hepten-6-one were also present. Identification was effected by comparison with authentic samples.\(^{23} \)
The great diving beetle Acilius sulcatus emits a milky liquid from its prothoracic defensive glands which poisons fish and amphibians. This secretion was found to contain 21-hydroxy-4-pregn-3,20-dione (cortexone), \[ \text{14} \]. A large number of keto steroids have now been isolated from the water beetles Acilius sulcatus, Dytiscus marginalis, Ilybius fenestratus, and Agabus bipustulatus. These include, in addition to cortexone, the steroids \[ \text{15-24} \].

Separation and isolation of the steroids was carried out by thin layer chromatography in all cases. The identifications were effected by infrared, nmr ultraviolet, and mass spectroscopy, and by circular dichroism.
ACIDS AND DERIVATIVES

Arthropods must protect themselves not only against predators but also against microorganisms. Beetles, preferring to live in warm and humid surroundings, would be especially affected by microorganisms. Because bacteria survive in neutral or weakly alkaline media, the simplest way for a beetle to protect itself is to make its surroundings acidic or strongly basic. Carboxylic acids are the most commonly used antiseptics. Formic, methacrylic, and tiglic acids are especially good cytotoxins and are used by many species of beetles.\textsuperscript{23} Nineteen members of the subfamily Carabinae and six members of the subfamily Harpalinae produce a mixture of methacrylic (87-94\%) and tiglic acids (6-13\%).\textsuperscript{34}

The defensive secretions of many arthropods are strongly odorous and usually represent common organic chemicals. Short chain aliphatic acids and aldehydes are commonly isolated from arthropods. These have been discussed by Weatherston.\textsuperscript{4}

Recently, acetic, propionic, isobutyric, and isovaleric acids have been isolated from the ant Myrmicaria natalensis.\textsuperscript{19} The cervical gland of the caterpillar of the swallowtail butterfly Papilio machaon produces iso-butyrlic and 2-methylbutanoic acids.\textsuperscript{35} The pygidial defensive glands of the beetles Asaphidion flavipes and Bembidion quatriguttatum contain p-valeric acid.\textsuperscript{23} The cockroach Eurygotic floridana has been found to secrete almost pure trans-2-hexenal.\textsuperscript{36}

Benzoic acid and its derivatives, as well as phenolic compounds, are common disinfectants used by water beetles. Benzoic acid, p-hydroxybenzoic acid, methyl p-hydroxybenzoate, methyl 3,4-dihydroxybenzoate, ethyl 3,4-dihydroxybenzoate, and p-hydroxybenzaldehyde have been found in the pygidial defensive glands of Dytiscinae, Colymbetinae, and Carabidae.\textsuperscript{23,37,38,39} In one study nine strains of bacteria were tested and none was able to decompose methyl p-hydroxybenzoate. Interestingly, the microorganisms have never built up resistance to this compound despite its use by water beetles for millions of years.\textsuperscript{23}

The cantharid beetle Cnapholathus lecontei, secretes an acetylenic acid as its major defensive compound. The acidic secretion from 1500 beetles was separated with aqueous sodium bicarbonate. Mass spectral and ultraviolet absorption data indicated the molecular formula to be C\textsubscript{16}H\textsubscript{12}O\textsubscript{2}, and indicated a chromophore of type 25. Data from nmr and infrared spectroscopy led to structure 26, 8-decene-1,6-diynoic acid, for this compound. Even though several acetylenic substances are found in plants, this is the first one isolated from animals. Comparison of the acetylenic acidic substance with the naturally occurring methyl ester of 26 has confirmed the structure assignment.\textsuperscript{40}

Massoilactone, 27, has been isolated from two species of formicine ants of the genus Camponotus and claimed to be a defensive secretion. It is a powerful skin irritant and produces systolic standstill in frog heart muscle. Its structure was confirmed by comparison of the naturally occurring plant product with the synthesized racemic mixture. However, this compound was obtained by extraction of the whole ants and not from a certain known defensive gland.\textsuperscript{41}

Another lactone, marginalin, 28, has been isolated from the pygidial defensive glands of the beetle Dytiscus marginalis. Its structure was assigned on the basis of absorption, nmr, and mass spectroscopy, and finally by synthesis.\textsuperscript{42}

Recently, Schildknecht and Koob have discovered that a leaf cutter ant, Atta sexdens, secretes phenylacetic acid, indolylacetic acid, and 3-hydroxydecanoic acid. This mixture kills certain bacteria and fungi but does not affect the fungi on which the ant feeds.\textsuperscript{43}
One of the most interesting components of defensive secretions so far elucidated is the highly toxic compound hydrogen cyanide. An intriguing question is how living cells produce such toxins without poisoning themselves. Since the millipedes producing hydrogen cyanide have a defensive apparatus composed of two glands, the theory is that the cyanide is produced and stored in one gland in a non-toxic form, and cyanogenesis is then carried out in the second gland when needed. Some plants are known to use 8-glucosidases to hydrolyze cyanogenic compounds to give hydrogen cyanide, benzaldehyde, and a carbohydrate. One millipede, Pachydesmus crassicutis, has been found to excrete hydrogen cyanide, benzaldehyde, and a carbohydrate having the same chromatographic behavior as glucose. 44 Five species of polydesmoids produced hydrogen cyanide and one, Apheloria corrugata, also produced benzaldehyde. No sugars were found in the secretion, but mandelonitrile, 22, was shown to be present in the inner chamber of the defensive gland. An enzyme also isolated, whose character is still unknown, would convert the mandelonitrile into hydrogen cyanide and benzaldehyde. 45, 46

HETEROCYCLES

Two separate groups isolated a new mixture of heterocyclic compounds from the millipede Glomeris marginata. 47-49 Preparative thin layer chromatography separated the mixture into two components whose molecular formulas were shown to be C_{11}H_{12}N_{2}O and C_{10}H_{10}N_{2}O by high resolution mass spectra. Nuclear magnetic resonance assigned the structures of glomerin, 30, and homoglomerin, 31. These structures were confirmed by comparison with synthesized samples.

The beetle Illybius fenestratus excretes a toxin from its prothoracic defensive glands which has been shown to cause clonic spasms in mice. Separation of the glandular secretion by gel chromatography produced a yellow solid, whose melting point was 75-76.5°. Ultraviolet, infrared, nmr, and mass spectroscopy indicated the material to have one of the four structures 32-35. Decomposition of the material in tritiated water gave 8-hydroxyquinoline as one of the reaction products, thus indicating structure 33 as correct. Partial synthesis of 33 from 4,8-dihydroxyquinoline-2-carboxylic acid, 36, produced methyl 8-hydroxyquinoline-2-carboxylate (32), whose properties and spectra were identical with those of the natural substance. 51
MISCELLANEOUS COMPOUNDS

In order to protect themselves against microorganisms, three water beetles, Oceoptoma thorica L., Silpha obscura L., and Phosphysa atrata L., secrete a 4.5% ammonia solution over their bodies.\textsuperscript{52} Phenols are also effective cytotoxins and \textit{m}-cresol has been found in a number of water beetles.\textsuperscript{23}

The carboxylic acids and aldehydes occurring in the defensive secretions of arthropods are generally accompanied by an aliphatic hydrocarbon, which aids in the penetration of the active substance. Decane, undecane, and tridecane have been isolated from various species.\textsuperscript{19,23,37,53}

The beetle \textit{Dytiscus marginalis} excretes a paste-like glycoprotein in which is imbedded the active compounds methyl \textit{p}-hydroxybenzoate and benzoic acid. The glycoprotein was found to be of high molecular weight, and contained eighteen different amino acids as well as galactose, mannose, glucose, ribose, and glucuronic acid. The cysteine-cystine content was very high (17.25% of the molecular weight) and the protein appeared to be cross-linked by \textit{p}-hydroxybenzaldehyde and the \textit{\alpha}-amino groups of lysine. Due to the sugar components, the film is removed when the insect enters the water, thus rendering the beetle's surface hydrophobic again.\textsuperscript{54,55}

In 1965 Quilico and co-workers isolated the defensive components pederin, \textsuperscript{27} and pseudopedrin, \textsuperscript{38} from the insect \textit{Paederus fuscipes}. Degradation according to Scheme 3, as well as nmr, infrared, and ultraviolet spectroscopy enabled the structures to be proposed.\textsuperscript{56}

There has always been the question as to whether arthropod defensive chemicals arise by biosynthesis or whether they only represent a concentration of certain toxins from the diet. However, as already discussed, the isolation of certain precursors, as well as some labeling experiments, has supported the biosynthesis of some toxins by the animals themselves. Recently it was shown that eight species of caterpillars from the family Papilionidae secrete isobutyric and \textit{\alpha}-methylbutyric acids when fed on a variety of different diets.\textsuperscript{57} On the other hand, it has been shown that the water beetles must absorb cholesterol or steroids of similar nature with their food to produce the steroid toxins previously discussed.\textsuperscript{23}

Many arthropods may also possess repellent substances in the blood and other parts of the body. Very few of these possibilities have been investigated to date. These efforts may well be worth while, as compounds not only of unusual chemistry, but also of medical significance may be discovered.
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ION KINETIC ENERGY MASS SPECTROMETRY

Reported by David Dieterich  
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INTRODUCTION

Metastable transitions occurring within the mass spectrometer can provide a wealth of information of potential utility to the chemist. The low abundance and diffuse shape of the signal obtained from these transitions has delayed accurate analysis, yet recent intrumental advances employing double-focusing mass spectrometers have afforded the direct observation of metastable transitions at high sensitivity. The most powerful of these techniques is ion kinetic energy mass spectrometry (IKE).

THE INTERPRETATION OF METASTABLE TRANSITIONS

Many ions formed within the source of a mass spectrometer are so highly excited that they undergo a series of unimolecular decomposition reactions within the ionization chamber. Those product ions sufficiently stable to survive traversal of the mass spectrometer will give rise to the conventional mass spectrum. Ions which decompose along their path through the mass spectrometer are referred to as metastable ions. A small fraction of the total number of metastable transitions occurring within the mass spectrometer may be observed in the conventional mass spectrum as diffuse peaks centered at non-integra mass values, but most metastable transitions are not observed due to their low intensity, rarely greater than two percent of the base peak and often much less.

The recent interest generated toward the detection of metastable transitions is a consequence of their potential usefulness.\(^1\)\(^2\) For example, the interpretation of mass spectra is facilitated greatly by consideration of metastable ions and accurate mass determination. McLafferty has proposed that the ratio of abundances of metastable ions from the same precursor ion is independent of energy and characteristic of the structure of the precursor ion and has used this hypothesis to distinguish between isomeric ions.\(^1\)\(^2\) The kinetic energy released in the decomposition of ions supporting multiple charges has been calculated from metastable transitions.\(^1\) Metastable transitions also afford the calculation of thermodynamic properties if certain assumptions are made.\(^1\)\(^5\) Isotopic purity has been determined by analysis of metastable transitions in cases in which analysis of the mass spectrum is difficult due to interferences.\(^6\) Finally, the quasi-equilibrium theory of mass spectra predicts the rate constant of an ion decomposition to be proportional to the excess energy, the internal energy less the activation energy, of the decomposing ion. Since metastable ions decompose at slower rates than those ions constituting the normal mass spectrum, it is proposed that metastable transitions should be more sensitive to subtle structural changes in the decomposing ion.

INSTRUMENTAL CONSIDERATIONS

The high resolution attainable in double-focusing mass spectrometers is the direct result of the combination of direction focusing with velocity focusing.\(^7\) Velocity focusing occurs when a beam of ions of the same mass and initial direction but with varying velocities are focused. Direction focusing occurs when a beam of ions of the same mass and velocity but a narrow distribution in initial direction are focused. A single-focusing mass spectrometer employs only direction focusing, thereby limiting the theoretical resolution attainable in the instrument to the velocity distribution of the ions.

Consider the double-focusing mass spectrometer used by Beynon in IKE studies (Figure 1).\(^8\) The RMH-2 mass spectrometer, built by Hitachi-Perkin Elmer to the specifications of McLafferty, is of modified Nier-Johnson geometry and has extended field-free regions for the study of metastable transitions. The accelerated ions are collimated by the source lens system, pass through the source slit, traverse the field-free region and enter the electrostatic analyzer.
The radius of curvature \( R \) of an ion which has been accelerated through a potential \( V \) and is perpendicularly incident upon a homogeneous electric field \( E \) may be obtained from fundamental considerations: \( R = \frac{2V}{E} \). The radius of curvature of the ion beam is independent of mass and dependent only upon the energy of the beam and the voltage applied to the electric sector; therefore when considering ions of the same charge, the electrostatic analyzer separates ions of varying energies and focuses ions of one energy onto the \( \beta \)-slit.

The focused ion beam from the electrostatic analyzer, after passing through the energy resolving \( \beta \)-slit, is offered to the magnetic analyzer. The common equation characteristic of the Dempster instrument relating the mass to charge ratio of an ion to the radius of curvature \( R \) of the ion beam and the strength of the magnetic field \( H \) may be derived: \( \left( \frac{m}{e} \right) = H^2R^2/2V \). The radius of curvature of the ion is dependent upon the mass to charge ratio: the magnetic analyzer is a mass analyzer.

There are three field-free regions which may be used to study metastable transitions: the first field-free region between the source and the entrance to the electrostatic analyzer, the second field-free region between the electrostatic analyzer and the magnetic analyzer, and the source lens system which constitutes a third field-free region. The resident time of an ion passing through various sections of this double-focusing mass spectrometer is shown in Figure 2. Metastable transitions occurring within the post magnet field-free region will not be discussed in this abstract.

Those ions of normal mass which decompose within \( 10^{-7} \) sec. will decompose within the source. Ions decomposing within the accelerating region will give rise to a continuum and will not be focused. Those ions decomposing within the third field-free region, the source lens system, will have acquired only a fraction of their full energy of acceleration and will be of lower energy than the main ion beam. These ions will not have sufficient energy to pass through the electrostatic analyzer with the main ion beam and will not be observed in the normal mass spectrum.

Consider an ion of mass \( m_1 \) and charge \( q_1 \) which has acquired its full energy of acceleration and undergoes decomposition in the first field-free region to an ion of mass \( m_2 \) and charge \( q_2 \) and a neutral specie. Due to conservation of momentum and energy, the velocity of the parent and daughter ions will be identical if there is no loss of internal energy. The 'metastable ion' will therefore possess a fraction \( \left( \frac{m_1 q_1}{m_2 q_2} \right) E \) of the energy of an identical stable ion in the main ion beam, and will not be passed through the electric sector unless the voltage \( E \) is reset to \( \left( \frac{m_2 q_2}{m_1 q_1} \right) E \). Decompositions occurring within the first and third field-free regions may be distinguished, as the fraction of full acceleration of the ion, which decomposes within the third field-free region, is dependent upon the voltage applied to the source lenses.

Ions decomposing in the second field-free region will give rise to a broad peak in the mass spectrum centered at an apparent mass \( m' \) defined by: \( m' = \frac{m_2^2}{m_1} \). More precise equations defining the position of the metastable transition as a function of the amount of internal energy released have been derived.\(^1\)

The condition necessary to transmit ions through the electric sector of a double-focusing mass spectrometer is that:

\[
\frac{\text{Energy Main Ion Beam}}{\text{Electric Sector Voltage}} = \frac{V}{E} = \text{constant}
\]

Once the mass spectrometer is 'tuned' to allow passage of the main ion beam, those metastable ions decomposing before the electric sector will not pass through the energy resolving \( \beta \)-slit. Those metastable ions in the main ion beam which decompose in the second field-free region will be observed as diffuse, low-intensity peaks in the mass spectrum.

Jennings\(^9\) proposed that by varying the ratio \( V/E \) from that value necessary to transmit the main ion beam, one could 'defocus' the mass spectrometer to afford passage of those ions which had undergone metastable transitions. In such a mode,
the mass spectrometer would act as an energy filter allowing the operator to observe ions of lower energy in the absence of the main ion beam. Barber and Elliott\textsuperscript{10} and Beynon, Saunders and Williams\textsuperscript{11} reported the detection of pure metastable spectra by increasing the accelerating voltage while leaving the voltage across the electrostatic analyzer constant. Although affording the detection of metastable transitions at high sensitivity, this technique suffers from the disadvantage that source tuning conditions, due to ion penetration effects, are changed when the accelerating voltage is altered. This technique does have the advantage that by setting the mass analyzer to transmit a given mass and then scanning the accelerating voltage, only decompositions resulting in a product ion of that mass will be observed. Major\textsuperscript{12} proposed varying the electric sector voltage while keeping the accelerating voltage constant. This technique greatly expands the observable range as the accelerating voltage may be altered only by a factor of five, but suffers from the disadvantage that the mass scale changes when the energy of the ion beam is altered. These metastable defocusing techniques due to their ability to uniquely determine the mass of the parent ion and the daughter ion at high sensitivity have had wide application in the recent literature.

Since the detector is placed after the magnetic analyzer, the analysis of metastable transitions by defocusing techniques may be complicated due to consecutive decompositions. For example, consecutive metastable ion decompositions have been observed for \(3-(2,4,6\text{-trimethoxyphenyl})\text{-butan-2-one}\) and benzofuran-3-carboxylic acid.\textsuperscript{13} Kiser, Sullivan and Lupin have directly observed the consecutive metastable ion decompositions of hexacarbonyl chromium(0) by varying the electric sector voltage and monitoring the signal from the \(\beta\)-ion current electrode.\textsuperscript{14} In this experiment the electric sector voltage was varied until a signal was detected on the \(\beta\)-ion current monitor immediately behind the \(\beta\)-slit. Analysis of the transition signals verified the consecutive loss of carbon monoxide molecules from the molecular ion. The first IKE spectra were reported when Beynon replaced the \(\beta\)-ion current monitor electrode with an electron multiplier.\textsuperscript{15} This detection system afforded analysis of the energy profile at the \(\beta\)-slit at high sensitivity; a signal of intensity \(10^{-2}\) of the base peak in the normal mass spectrum can easily be analyzed.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{RML-2 Mass Spectrometer}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{RML-2 Time Scale}
\end{figure}

To obtain the time in \(\mu\text{scc.}\), multiply by \(\frac{(m/V)^3}{6}\).
APPLICATIONS OF IRE SPECTROSCOPY

I. Characterization of Organic Compounds

An IKE spectrum of a compound is similar to a fragmentation pattern in that it is characteristic of a compound and may be used for purposes of identification. The partial IKE spectrum of N-carbobenzyox-L-alanyl-L-valine is shown in Figure 3 to demonstrate the wealth of information available.

Mass analysis of any of the peaks in an IKE spectrum is afforded by setting the electric sector voltage to correspond to the peak of interest (E1) and subsequently scanning the magnetic field. The mass scale is dependent upon the value of the electric sector voltage so that the true mass to charge ratio of the daughter ion m2/q2 may be calculated from the apparent mass to charge ratio (mθ):

\[ m_2/q_2 = m_θ (E/E_1) \]

Mass analysis of a broad IKE peak may be made at any electric sector voltage (E1) across the peak, the only requirement being that E1 is accurately known. The mass to charge ratio of the parent ion can then be calculated knowing the electric sector voltage corresponding to the center of the peak (Ec):

\[ m_1 = (q_1E/q_2Ec)m_2 \]

Although the technology appears to be available, to date there have been no reports concerning on-line computer analysis of IKE spectra.

II. Ion-Molecule Reactions

Chemical ionization mass spectrometry has found application in the study of molecules which fragment readily under electron bombardment and exhibit a molecular ion of extremely low intensity. Ionization of the compound of interest is effected by ion-molecule reactions between a molecule of the compound and an ionizing collisional gas. Although chemical ionization mass spectrometric studies often employ methane as a collisional gas, the choice of collisional gas is not limited to methane and indeed different spectra result if the ionizing gas is changed. Correct interpretation of the quasi-molecular ion and any unimolecular decompositions of the quasi-molecular ion is fundamentally related to knowledge of the ion-molecule reaction.

Charge-transfer reactions often occur in ion-molecule reactions. In the IKE spectrum of argon gas, peaks were observed at electric sector voltages of 1.5E, 2E, 3E, and 4E corresponding to collision induced charge-transfer reactions of argon atoms supporting multiple charges. Nitrogen was used as the collisional gas in all cases. Transitions occurring at electric sector voltages of 0.67E and 0.50E corresponded to collision induced charge-transfer reactions of charged clusters of argon atoms. The collision induced decompositions of the metastable positive ions of methane have been studied as a function of collisional gas pressure.
The detection of a metastable ion-molecule reaction product has been demonstrated using IKE spectroscopy. Peaks corresponding to [M+H]± and [M+CH₃CO]± have been observed in the normal mass spectrum of n-butyl acetate. A pressure sensitive peak was observed in the IKE spectrum at an electric sector voltage of 0.521E. Subsequent mass analysis showed the mass to charge ratio of the daughter ion to be 61 indicating that the parent ion had a mass of 117, [M+H]

<table>
<thead>
<tr>
<th>Transition</th>
<th>IKE-Electric Sector Voltage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ar⁺⁺⁺ → Ar⁺⁺</td>
<td>1.5E</td>
</tr>
<tr>
<td>Ar⁺⁺ → Ar⁺⁺</td>
<td>2.0E</td>
</tr>
<tr>
<td>Ar⁺⁺⁻ → Ar⁺⁻</td>
<td>3.0E</td>
</tr>
<tr>
<td>Ar⁺⁺⁺⁺ → Ar⁺⁺⁺⁺</td>
<td>4.0E</td>
</tr>
</tbody>
</table>

### III. Unimolecular Decompositions of Ions Supporting a Single Charge

Extensive studies employing ¹³C and deuterium labeling have led to the conclusion that the [C₆H₆]⁺ ion formed from the electron bombardment of toluene does not retain the benzyl structure but rather undergoes ring enlargement to the troprylium ion. The mechanism and kinetics of the loss of H⁺ from the molecular ion of toluene are less well defined. For those ions decomposing within the ionization chamber, three facts are evident: there is a preference for loss of a side chain hydrogen over a ring hydrogen, ring hydrogens are lost with equal probability regardless of their position on the ring, and there is a deuterium isotope effect. These results have been rationalized on the basis of incomplete scrambling in the cycloheptatriene ion or competitive hydrogen loss from a cycloheptatriene ion and the unarranged molecular ion of toluene.

Analysis of the [C₆H₅]⁺ ion's decomposition is based upon the measurement of a preference factor, the ratio of probability of loss of hydrogen from a side chain position to loss of a hydrogen from a ring position, and an isotope factor, the ratio of the probability of loss of a hydrogen to the probability of loss of a deuterium atom in the same position. For those ions decomposing within the ionization chamber, analysis of the normal mass spectrum afforded calculation of the preference factor and the isotope factor to be 1.32 and 1.58, respectively.

The IKE spectrum of toluene affords calculation of the preference factor and isotope factor for those ions with half-lives two orders magnitude larger than those observed in the normal mass spectrum. The preference factor of 1.00 of those ions observed in the IKE spectrum indicates that on the time scale of 10⁻⁵ sec, the hydrogens of the [C₆H₅]⁺ ion have completely equilibrated. The isotope factor was determined to be 3.50. These results are not in contradiction with the earlier data due to the half-lives of the ions in question.

The mechanism of the expulsion of OH* from the [M-C₆H₅]⁺ ion observed in the mass spectrum of ethyl benzoates has been studied using IKE spectroscopy. Earlier information on the molecular ion of benzoic acid was consistent with an ion in which, on the time scale of 10⁻⁵ sec., both oxygen atoms had equilibrated and there was complete scrambling of the acid hydrogen with the ortho hydrogens on the benzene ring. The four possible decompositions of a sample fully labeled with deuterium in the ethyl group and with ¹⁸O in the carbonyl group and the corresponding electric sector voltage for each of the transitions are shown in Table 1, and the observed IKE spectrum is shown in Figure 4.

The total probability, as measured from metastable abundance ratios, of the loss of OH* and ¹⁸OH* to the total probability of losing OD* and ¹⁸OD* is approximate 2:1. But the ratio of the probability of losing OH* to ¹⁸OH* is 4:2 while the ratio of the probability of losing OD* to ¹⁸OD* is 1:2, implying that the two oxygen atoms are not equivalent. Therefore structures in which the deuterium atom cannot readily transfer between the oxygens do not seem to be important. A process suggesting scrambling of the deuterium by exchange with the ortho
hydrogens would require the steps given in Scheme 1. No expulsion of OD• can occur before four rotations of the side chain. Assuming this interpretation to be correct, an estimate of the rate of rotation of the rate of rotation of the side chain in the [M-C2H4]+ ion may be made on statistical grounds.

Subsequent studies using ethyl benzoates-ο, m and p-d1 have shown that the presence of the side chain has entirely suppressed any scrambling of the carbons or hydrogens in the benzene ring. Analysis of a sample of benzoic acid-ο-d1 suggests that equilibration is slightly more complete in the molecular ion than in the [M-C2H4]⁺ ion of the esters. Relative abundances of the [M-OD]⁺ and [M-ΟΗ]⁺ ions from a sample of benzoic acid-ο-d1 as a function of ionizing energy indicates that the [M]+->[M-ΟΗ]⁺ decomposition is the lower energy process.

Table 1. Potential Decompositions of the [M-C2H4]⁺ ion of Labeled Ethyl Benzoates.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>FE (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C7H5D0180]⁺ → [C7H4D18O]⁺</td>
<td>86.4</td>
</tr>
<tr>
<td>[C7H5D0180]⁺ → [C7H4D18O]⁺</td>
<td>85.6</td>
</tr>
<tr>
<td>[C7H4D0]⁺ → [C7H4D0]⁺</td>
<td>84.8</td>
</tr>
<tr>
<td>[C7H3O]⁺ → [C7H3O]⁺</td>
<td>84.0</td>
</tr>
</tbody>
</table>

Figure 4
IKE Spectrum of Labeled Ethyl Benzoates

Scheme 1

IV Unimolecular Decomposition of Ions Supporting Multiple Charges

Ion kinetic energy mass spectrometry affords the direct observation of the decomposition of ions supporting multiple charges. For example, the high energy IKE spectra of naphthalene is shown in Figure 5. A doubly charged ion (m1) which decomposes to two singly charged ions (m2, m3) will lead to broad peaks in the IKE spectrum at electric sector voltages of (2m2/m1)E and (2m3/m1)E. One peak will occur in the low energy IKE spectrum and suffer possible interference from peaks due to the decomposition of singly charged ions, the other peak will occur in the high energy IKE spectrum and can only suffer interference from peaks due to the decomposition of other ions supporting a multiple charge. Peaks due to the decomposition of ions supporting multiple charges will be broader than peaks due to collision induced charge-transfer reactions due to a release in kinetic energy as a result of charge separation in the transition.

Peaks A, B, and C in the high energy IKE spectrum of naphthalene are collision induced charge-transfer reactions. The intensity of a collision induced reaction is dependent upon the relative abundance of the ion, the collision reaction cross-section with the background gas, and the specie of collisional gas. Peaks D to J are 'dish-topped' peaks resulting from the decomposition of doubly charged ions. The kinetic energy (T) released upon decomposition can be calculated using the equation: T = eVm2/8m3(ΔE/E1)², in which ΔE is the width of the energy peak at maximum intensity. The intercharge distance (r) in the m1²⁺ ion can be estimated from the relationship:

In some cases where overlapping peaks in the IKE spectra prevent accurate measurement of the peak width, it is convenient to alter the experimental conditions slightly. By removing the detector behind the β-slit and setting the magnet to transmit ions of mass m2, the metastable transition may be observed.
by scanning the accelerating voltage. The kinetic energy released may then be calculated from the equation: \( T = eV_1 m_2 / 3m_3 (\Delta V / V_1)^2 \), in which \( V_1 \) is the value of the high voltage and \( \Delta V \) is the voltage spread in the peak. The kinetic energy of separation of daughter ions in the decomposition of doubly charged parent ions has been calculated for several metastable transitions of benzene, toluene, naphthalene, 2-methylnaphthalene, anthracene and biphenyl.

Beynon has determined the charge separation in the \([C_6H_6]^{2+}, [C_6H_4]^{2+}\) ion produced by the electron bombardment of benzene\(^{31,32}\) and in the triply charged molecular ion of biphenyl.\(^33\) The values in the benzene series 5.8\(\AA\), 6.2\(\AA\), and 6.2\(\AA\), respectively, are too large to support a cyclic ion since the diameter of a benzene ring is only 2.9\(\AA\) and leads to the conclusion that these ions must have a linear structure. The analysis of the triply charged molecular ion of biphenyl is more difficult due to the presence of three charges, but it was concluded that the ion contained one singly charged six membered ring attached to a six membered chain which supported two charges.\(^33\)

Figure 5
High Energy IKE Spectrum of Naphthalene

V. Interpretation of Fragmentation Patterns

As all the metastable transitions occurring within the mass spectrometer between the accelerating region and the electric sector may be observed in the IKE spectrum, an IKE spectrum can provide a great deal of information which may be used to relate fragments in the normal mass spectrum. However, analysis of a typical IKE spectrum of one hundred peaks would be a tiresome endeavor without the aid of a computer. It appears that to take full advantage of the technique, an on-line computer system is necessary.

VI. Potential Applications

Since the mass spectrometer in IKE studies is used as an energy filter, those transitions which are observed have a lower excitational energy than similar ions in the normal mass spectrum. Therefore, the IKE spectrum should be more representative of subtle structural changes in the molecule than the normal mass spectrum.\(^{16,18}\) The utility of IKE spectra for the distinction of subtle structural differences in molecules is yet undefined.

CONCLUSION

Ion kinetic energy mass spectrometry is a new technique for the study of ion decompositions occurring within the mass spectrometer. The technique's utility as a tool for distinguishing subtle differences between compounds remains to be explored. The usefulness of IKE mass spectrometry in the interpretation of
fragmentation patterns appears to be related to this technique's compatability with on-line computer analysis. Although some aspects of IRE mass spectrometry are amenable to current on-line computer techniques, total automation may be difficult.\textsuperscript{35}

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RECENT ADVANCES IN NATURAL ABUNDANCE CARBON-13 MAGNETIC RESONANCE

Reported by Brock Siegel
April 29, 1971

GENERAL ASPECTS

Natural abundance carbon-13 nuclear magnetic resonance (cmr) is potentially one of the most powerful tools available for the elucidation of both the chemical and the electronic structures of molecules. Improved instrumentation now allows routine cmr spectra to be recorded from small sample quantities. The advantages of observing carbon resonances are two-fold: 1) most reactions involve the formation or scission of bonds to carbon, and 2) the framework of organic molecules is based on carbon atoms. Hence, cmr enables one to study specifically the atoms of interest -- including quaternary centers. Recent reviews of cmr have dealt with chemical shifts of carbon-13 nuclei, and various applications of carbon-hydrogen coupling. The following discussion surveys the recent technological advances employed in studying carbon-13 magnetic resonance.

In practice, the overall resolution of cmr is better than that of nmr. This is due, in part, to the sharp absorbance lines of carbon signals; half-widths are commonly less than one Hz. The total range of chemical shifts of carbon-13 is approximately 450 ppm, more than an order of magnitude greater than that of hydrogen. Hence, it has been possible to observe resolved signals for each carbon nucleus in macromolecules such as dicyanocobalamin containing 62 different carbon atoms.

Some general characteristics of the hydrogen and carbon-13 nuclei are shown in Table I.

![Figure 1 CMR of dicyanocobalamin.](image_url)

Table I. Nuclear properties of carbon-13 and hydrogen.

<table>
<thead>
<tr>
<th></th>
<th>spin</th>
<th>nmr frequency at 23,487 G</th>
<th>magnetogyric ratio, γ</th>
<th>relative sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H</td>
<td>½</td>
<td>100.00 MHz</td>
<td>26,753 rad sec⁻¹ G⁻¹</td>
<td>1.00</td>
</tr>
<tr>
<td>13C</td>
<td>½</td>
<td>25.14</td>
<td>6,728</td>
<td>1.59 x 10⁻²</td>
</tr>
</tbody>
</table>

SENSITIVITY AND PROTON DECOUPLING TECHNIQUES

The primary drawback in cmr, and the reason for its slow evolution is the poor signal to noise ratio (S/N). This impairment is illustrated by an early cmr of butenone in Figure 2. The low natural abundance and the small magnetogyric ratio combine to make the S/N ratio of carbon-13 only 1/1600 that of hydrogen at the same field strength. This impairment has been partially overcome with time averaging multichannel analyzers. These small computers divide the nmr spectrum into several small frequency domains and store the time averaged signal for each domain; resonance signals add coherently, while random...
noise is averaged to zero. After $M$ complete spectra have been recorded, the S/N ratio is enhanced by the factor $\sqrt{M}$. Clearly, spectrometers must have precise frequency locks and good field stability for the long periods of data acquisition required for carbon-13.

Another factor contributing to the poor S/N ratio in cmr spectra is that most carbon atoms in organic molecules are substituted with hydrogen. The dipolar coupling between adjacent carbon and hydrogen nuclei splits the carbon-13 resonance into a multiplet. This decreases the signal intensity of each carbon resonance and tends to obscure the spectrum. Double resonance techniques have been employed to collapse the multiplet carbon signals into singlet absorptions. For example, in a Zeeman field of 24,000 G, proton resonances occur at 100 MHz, while the carbon resonances are in the 25 MHz region; irradiation of the sample with a noise modulated 100 MHz carrier frequency will simultaneously saturate all of the hydrogen resonances. Recording the carbon-13 spectrum at 25 MHz under these conditions gives sharp singlets for each set of equivalent carbon atoms.

Inherent in the proton noise decoupling experiment (PND) is a nuclear Overhauser enhancement (NOE) of the carbon signals. NOE is a phenomenon which increases the intensity of the resonance signal of a given nucleus if a neighboring nucleus is irradiated with an RF field at its absorption frequency. In cmr spectra, irradiation of all protons increases the area of the resonance signals of those carbons directly bonded to protons. The NOE factor is proportional to $(1/r_{CH}^2)$, where $r_{CH}$ is the distance between the carbon of interest and neighboring protons. For carbon atoms directly bonded to protons, the enhancement factor is approximately three, and rapidly drops to zero for greater than one bond distances. Overall, the intensities of carbon absorptions usually increase an order of magnitude as a result of the NOE factor and PND.

Unfortunately, since the enhancement factor varies with the proximity and number of protons about neighboring carbon nuclei, any quantitative relation between peak area and the number of carbon nuclei is lost. At best, the weakest signals may be ascribed to quaternary carbons. The effect of the NOE factor is illustrated in Figure 3 by the cmr spectrum of pyrene. Note, for example, that the peak area of carbon 2 is more than that of carbon 15.

Two different approaches have been undertaken to remove the variable NOE factor. In one Gutowsky and Natusch claim that the addition of small amounts of paramagnetic metal ions to the sample solution may reduce the NOE factor to zero, without serious line broadening; however, this technique could involve solubility problems in most organic solvents. Allerhand has recently begun developing a second approach in experiments with viscous solvents. Unfortunately, these solvents would introduce new carbon-13 absorptions to the spectra in addition to posing solubility problems. Clearly, more research would be valuable in this area, as a quantitative relationship between peak areas under PND conditions would greatly simplify the interpretation of cmr spectra.

Another proton decoupling technique commonly used is called off-resonance decoupling. The sample is irradiated with either a single frequency (SFOR) or a noise modulated band (NOR) several hundred hertz away from the proton absorption region. This results in only partially decoupling the cmr spectrum; hence, all carbon-13 resonances except those of quaternary centers become buried in the noise. NOR decoupling is illustrated in Figure 4.

If the off-resonance decoupling field is weak (spin-tickling) then the carbon resonances are partially split into multiplets depending on the number of adjacent protons. Hence, identification of methine, methylene, and methyl carbon atoms is greatly facilitated.

![Figure 2 CMR of butenone, CH3=CH·COCH3.](image)
ANALYTICAL TECHNIQUES

Continuous Wave Spectroscopy. The first natural abundance cmr spectra were reported by Lauterbur in 1957. These spectra were recorded in a slow passage experiment with a continuous wave (CW) of irradiation through the carbon-13 absorption region. This is an analogous method to that now used for pmr spectra, and hence suffers from the poor S/N ratios for carbon-13 nuclei. At present, though, this is the most widespread source of cmr data.

Another more sensitive technique for generating CW cmr spectra is based on the internuclear double resonance experiment (INDOR) and the resulting NOE. A low power RF field is positioned on a specific absorption peak in the pmr region, while a second, more powerful RF field sweeps through the carbon-13 absorption frequencies. This second RF field partially saturates the carbon resonances that it traverses. If the carbon directly bonded to the proton is irradiated, the intensity of the pmr signal increases according to the NOE factor. By recording the change in intensity of a specific proton absorption as a function of the carbon frequencies traversed, and exact duplicate of the undecoupled cmr spectra may be obtained for the adjacent carbon atom. An example of this technique is shown in Figure 5.

For information about specific carbon atoms in molecules having well resolved pmr spectra, the INDOOR experiment removes the difficulties inherent in determining which absorption peak corresponds to which carbon in the complete cmr spectrum.
The major limitation of INDOH cmr is that only those carbons directly bonded to protons with well defined absorptions may be studied. Hence, no quaternary, dissubstituted olefinic, or ketonic carbon atoms are detectable.

**Fourier Transform Spectroscopy.** A more sophisticated approach to cmr, known as Fourier Transform Spectroscopy (FTS), employs a pulsing RF field. 

Greatly enhanced sensitivity, shorter data acquisition periods, and smaller sample requirements characterize FTS. In conventional slow passage CW nmr experiments, only a very small portion of the spectrum is observed at any given instant. A more efficient technique is to examine the entire absorption region of interest in the same instant. An obvious solution is to use a large number of transmitters and receivers corresponding to a multitude of frequencies. In 1966, Ernst demonstrated that a series of modulated RF pulses from a single transmitter is an excellent approximation to an infinite number of different frequency transmitters simultaneously irradiating the sample. If the signal generated by the sample under these conditions is recorded against time, the resulting Free Induction Decay (FID) pattern is just the Fourier transform of the high resolution frequency spectrum. The FID pattern of mesitylene is shown in Figure 6. Figure 7 illustrates the cmr frequency spectrum of Vitamin A acetate obtained by FTS.

The normal pulse time of the RF field is between 1 and 100 microseconds. The FID pattern accumulated after each pulse is usually time averaged before being Fourier transformed: computer memory space is the major limitation to data acquisition, as the FID pattern lasts approximately two seconds. The sensitivity improvement of FTS relative to CW cmr is shown by equation (1); \( \Delta \delta \) is the frequency range of the entire spectrum investigated, and \( \Delta \nu \) is the natural line width of an absorption. A FT experiment on carbon-13 at 25 MHz over a 5 MHz range with line widths on the order of 0.5 Hz would be expected to improve the S/N ratio by two orders of magnitude over CW cmr. Commonly, a S/N improvement by an order of magnitude is realized.

In the following description of carbon-13 FTS the direction of the static Zeeman field, \( H_0 \), defines the z axis. When molecules are placed in this homogeneous field, the nuclear magnetic moments are oriented with a Boltzmann distribution favoring allignment parallel to \( H_0 \). The torque placed on the magnetic moments by \( H_0 \) causes them to precess in random phase about the z axis with characteristic Larmor frequencies. This gives rise to a macroscopic magnetization vector, \( M_y \), parallel to \( H_0 \), whose magnitude is determined by the Boltzmann distribution of nuclear moments. This state is illustrated in Figure 8.

Irradiation of the sample by a rapid pulse of a wide-band RF field, \( H_1 \), causes all nuclear moments to precess simultaneously in phase. In a field of 24,000 G, \( H_1 \) is approximately four to five gauss for carbon-13 nuclei. This is just sufficient power to achieve a uniform excitation of all nonequivalent sets of carbon-13 nuclei in a 200 ppm spectral range. The macroscopic magnetization vector is tilted through an angle \( \alpha \) from \( H_0 \), as a result of the in-phase precession. This is shown in Figure 9.

As \( M \) relaxes to its equilibrium position, \( M_0 \), the nuclear moments lose phase coherence. During this period, the FID pattern is generated by the beat frequencies between sets of nonequivalent nuclei rotating at different Larmor frequencies. The FID pattern is time averaged and separated from noise in a multichannel analyzer. The resulting signal may be Fourier transformed with a digital computer to the corresponding high-resolution frequency spectrum. Examples of FT cmr spectra are illustrated in Figures 1 and 7.

The angle of tilt, \( \alpha \), is determined by the period of RF irradiation \( \tau \), as described in equation (2); \( \gamma \) is the magnetogyric ratio of carbon-13 nuclei.

\[
\alpha = \left( \frac{\gamma H_1 \tau}{2} \right)
\]

(2)
Commonly, an angle much less than 90° is used, so that the period between RF pulses is short. The off-pulse period is determined by the length of time required for all carbon-13 nuclei in the sample to re-establish a Boltzmann distribution along the z axis. This period is proportional to the spin lattice relaxation time, $T_1$. Clearly, the application of FTs loses its value if $T_1$ is long. Typical values of the spin lattice relaxation time for carbon-13 nuclei are only a few seconds, but quaternary carbons and ketonic carbons may have values that range into minutes.\(^{21,23,25}\) If a sample with a long $T_1$ were irradiated with an RF pulse before the establishment of a Boltzmann distribution of the nuclear moments, the resulting FID pattern would be severely attenuated.\(^{23}\) Subsequent RF pulses would continue to diminish the signal intensity, as the magnitude of the macroscopic magnetization vector would be considerably less than its relaxed value.

**Partially Relaxed Pulse Spectroscopy.** The development of Partially Relaxed Fourier Transform (PRFT) spectroscopy enables rapid sequencing of multiple pulse RF fields without appreciable loss of intensity of the FID pattern.\(^{21,23,25}\) Two of these techniques will be discussed: Driven Equilibrium (DEFT)\(^{23}\) and Spin Echo (SEFT).\(^{21}\) In each case the direction of the Zeeman field defines the $+z$ axis of a right handed coordinate system, which is in a frame of reference rotating at the Larmor frequency of a given set of nuclear moments. This is illustrated in Figure 10.

The DEFT experiment is initiated by a 90° wide-band RF pulse, $H_1$, along the -x axis. This simultaneously brings all nuclear moments in phase,\(^{23}\) thus rotating $M_0$ onto the $+y$ axis, as shown in Figure 11.

The nuclear moments are rotating in phase about the z axis in the xy plane. At the instant the RF field is removed, the moments begin to lose phase coherence, causing them to spread in the xy plane with some moments precessing faster than the others. If at a time, $\tau^*$, after the 90° degree pulse is removed, a 180° pulse is applied along the -x axis, each moment is rotated about the x axis onto the $-y$ axis. The 180° pulse has effectively reflected each moment through the $xz$ plane such that the faster moments are behind the slower ones. At time $2\tau^*$ all nuclear moments come back into phase. This generates an echo or duplicate of the FID pattern.

If at the peak of the echo, a 90° refocussing pulse is applied along the -x axis, the aggregated moment vector, $M$, is rotated into the original position of $M_0$. The magnitude of $M$ should approximate the $M_0$ value for all nuclei, as the entire sequence of RF pulses requires only a fraction of a second. Hence, DEFT experiments may re-establish the equilibrium magnetization in a considerably shorter period than $T_1$, and thus allow the rapid initiation of another pulse sequence.\(^{23}\)

**DEFT and FT cmr spectra are compared in Figure 12, for acetic acid.**\(^{23}\) The spin lattice relaxation time is approximately 50 seconds at the carboxylic carbon. The FID pattern of the FT experiment arises from a series of 90° pulses with a two second off-pulse period. The DEFT experiment also initiates a pulse train every two seconds. Clearly, DEFT may enhance signals from nuclei with long $T_1$: thus achieving reasonable S/N ratios within minutes, rather than hours.

**DEFT differs from SEFT in that all data for the latter experiment are taken from a series of repetitive echoes, while DEFT utilizes the original FID patterns.**\(^{21,23}\) Accumulation of data from an echo train, rather than the original FID pattern, has the advantage that at $t=0$, the signal is not obscured by an intense RF pulse.\(^{21}\) The uncertainty in the DEFT and FT patterns may cause spurious features in the transformed high-resolution frequency spectra.

A SEFT experiment is also initiated by a 90° pulse directed along the -x axis, which turns $M_0$ into the xy plane.\(^{21}\) After a time $\tau^*$, the sample is
irradiated by a 180° pulse also along the -x axis. An echo is observed at 2τ*, just as in the DEFT experiment. If, however, another 180° pulse is applied at 3τ*, a second echo is observed after 4τ*. Application of subsequent 180° pulses at (n+1)τ* intervals results in echoes at (n+2)τ* intervals. Data have been successfully obtained from a spin echo train of over 60 echoes, although the intensity of subsequent echoes slowly decreases. For mesitylene, a S/N ratio of 28 was obtained from a SEFT cmr in only two minutes; the same sample required over 50 minutes of CW irradiation for a S/N ratio of 16. In theory, DEFT could be superior to SEFT cmr, but to date insufficient data have been reported to make any quantitative arguments.

A potential difficulty common to all pulse techniques would be a rapid decay of the FID pattern and its echoes. The period of efficient data acquisition is determined by the effective spin spin relaxation time, T*, which corresponds to the rate of loss of phase coherence of the nuclear moments. The time T* is composed of both the natural spin spin relaxation time, T**, and that time, T^, due to inhomogeneity in the Zeeman field. For spin ½ nuclei in liquid samples, inhomogeneity usually dominates, causing complete spin randomization in two seconds (0.25 Hz). If, however, T* is short, then the time requirements to attain a given S/N ratio may diminish the usefulness of pulse techniques. Two cases in which a short T* could be realized are: 1) rapid chemical exchange among the nuclei of interest, and 2) coupling of the carbon-13 nuclei to adjacent quadrupolar nuclei undergoing rapid relaxation. The seriousness of this problem may only be recognized after more experimental data have been accumulated.

Figure 5 INDOOR cmr of the isopropyl cation at -20°.

Figure 6 FID pattern of mesitylene carbon-13 nuclei.

Figure 7 FT cmr of Vitamin A acetate in dioxane.
Figure 8  Nuclear moments precessing about $H_0$.

Figure 9  $H_1$ induced in-phase precession of nuclear moments about $H_0$.

Figure 10  Macroscopic magnetization vector in equilibrium with $H_0$.

Figure 11  Macroscopic magnetization vector rotated into xy plane.
Figure 12 DEFT and FT cmr FID patterns for acetic acid.

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SUBSTITUENT EFFECTS IN UNIMOLECULAR ION DECOMPOSITIONS

Reported by Julie Liao

INTRODUCTION

The kinetic approach to mass spectrometry has been described and applied rather extensively recently. From studies of substituent effects and metastable characteristics, one can often gain structural information useful in analytical applications of mass spectrometry, in the evaluation of structure/reactivity relationships, and in the study of mechanisms in electron-impact induced reactions. This report is a review of the basic theories involved in the kinetic approach to mass spectrometric study and their applicability.

HAMMETT EQUATION

Reactions in a mass spectrometer are considered to be sets of competing consecutive unimolecular decompositions, which can be represented by Eq. 1; the mass spectrum recorded is a sampling of the product distribution of these processes. In Eq. 1, A1 and A2 are formed from the molecular ion M+ with rate constants k1 and k2, respectively, and m1 and m2 represent the metastable ion peaks associated with the corresponding reactions.

For a reaction sequence such as that shown in Eq. 2, it is sometimes possible to put mass spectral phenomena on the same sort of quantitative bases that are used in solution chemistry. Thus, by applying the steady state approximation to the concentrations of all the ions in the ion source and assuming that the recorded intensities are proportional to the concentrations of ions in the ion source, one can define a quantity Z, a measure of the relative abundances of ions in the spectrum (Eq. 3). If the total rate of consumption of ion A is independent of the nature of the precursor, then it is possible to relate a Z value and Z0 value for some standard compound to the relative rates of formation of the ion A+ (Eq. 4). A Hammett equation may then be set up in the usual manner (Eq. 5) and the effect of substituents on various fragmentation processes can be examined in the context of this linear free energy relationship.

\[ Z = \frac{[A^+]}{[M^+]} \]  

\[ Z/Z_0 = \frac{k}{k_0} \]  

\[ \log(Z/Z_0) = \rho \sigma \]  

APPLICATIONS OF HAMMETT EQUATION

The data obtained for the decompositions of substituted benzophenones are summarized in Eq. 6. The sign and value of \( \rho \) (1.0) show that electron withdrawing substituents accelerate the breaking of the bond between the carbonyl carbon and the substituted ring. This represents a reduction of the product ion abundance by electron-donating groups and was ascribed to increased stabilization of the decomposing bond. The much smaller value of \( \rho \) (0.0) for breaking the bond on the other side of the carbonyl group, showing a negligible substituent effect, is consistent with the greater distance of the substituent from the reaction site. However, the formation of the YC6H400 ion, which involves the breaking of the same bond, has a \( \rho \) value of

\[ M + e \rightarrow M^+ \rightarrow A^+ \rightarrow \text{fragments} \]  

\[ M + e \rightarrow M^+ \rightarrow A^+ \rightarrow \text{fragments} \]  

\[ Z = [A^+]/[M^+] \]  

\[ Z/Z_0 = k/k_0 \]  

\[ \log(Z/Z_0) = \rho \sigma \]
-0.4. The difference can probably be attributed to stabilization of the product ion by electron-donating substituents. This case (the formation of YC₁₅H₂₄CO⁺) parallels the reduction of ionization and appearance potentials caused by electron-donating substituents⁵ and provides support for the proposal¹⁰ that stabilization of the ion provides an important driving force for such decomposition reactions. The above data suggest, however, that the ability of a substituent to stabilize the charged product (YC₁₅H₂₄CO⁺) is more important than its ability to stabilize the neutral product (YC₁₅H₂₄O). A final observation on this system is that the small positive value of ρ₄(+0.4) suggests that electron-withdrawing substituents cause a more rapid decarbonylation of the benzoyl ion.

Correlations between two sets of compounds which might produce the same series of ions by a set of similar processes also exist.² ⁷ A straight line with a slope of 0.97 was obtained when the log (Z/Z₀) values for benzophenones⁺ were plotted against the log (Z/Z₀) values for acetophenones, where Z = [YC₁₅H₂₄]⁺ / [YC₁₅H₂₄COR⁺]. The same relationship exists between acetophenones and methyl benzoates. This correlation implies that the rate constants involved in the production and consumption of YC₁₅H₂₄ ions are similar for the two sets of compounds. A similar approach has been used to compare the RCO⁻ structures in the spectra of substituted benzophenones (R = C₆H₅) and acetophenones (R = CH₃), and good linear relationships were also found.

The substituent effects have also been applied to the assignment of ion structures and to the elucidation of mechanisms for reactions occurring in a mass spectrometer. The effects of a variety of substituents on the mass spectral behavior of phenyl ethyl ethers¹¹ (Eq. 7), nitrobenzenes¹² (Eq. 8), and anisoles⁷ (Eq. 9) have been studied. Each of the rearrangement reactions (Eq. 7-9) involves the loss of a small molecule from an aryl derivative. The data indicate that the effect of a particular substituent in the meta position is substantially different from its effect in the para position for the reactions described by Eq. 8 and Eq. 9, but loss of ring position identity appears to occur for the reaction in Eq. 7. It was suggested that for Eq. 7 there may be an initial fast hydrogen rearrangement to yield an ion such as [YC₁₅H₂₄OCH₃H₄]⁺ which has sufficient stability to permit isomerization of the ring position.¹² ¹³ The data also show a large difference in the substituent effects for the reactions in Eq. 8 and Eq. 9. For reaction 8, electron-donating groups in the para position accelerate the decomposition of the molecular ion, while for reaction 9 they retard the decomposition. The difference has been explained in terms of different transition states for these reactions. For equation 8, a three-membered ring transition state was suggested, in agreement with the observation that for those substituents having a lone pair of electrons on the atom bonded to the ring there was a ten-fold variation in the relative intensities of the YC₁₅H₂₄O⁺ ion for the para and meta compounds (Eq. 10). For reaction 9, a four-centered rearrangement mechanism has been proposed¹⁴ (Eq. 11). A similar analysis was used to explain the mechanism of the loss of CO₂ from aryl methyl carbonates and aryl phenyl carbonates, and the loss of C₂H₄ from butyrophenones.¹⁵ ¹⁶

\[ \text{Eq. 6} \]

\[ YC₃H₄CO⁺ → YC₃H₅⁺ + CO₂ \]

\[ \rho_3 = -0.4 \]

\[ YC₃H₄ → YC₃H₅⁺ + CH₄ \]

\[ ρ₁ = 1.0 \]

\[ YC₃H₅⁺ → C₂H₄ + CₛH₅⁺ \]

\[ ρ₂ = 0.0 \]

\[ \text{Eq. 7} \]

\[ YC₃H₄NO₂⁺ → YC₃H₄O⁺ + NO \]

\[ \text{Eq. 8} \]

\[ YC₃H₄OCH₃⁺ → YC₃H₅⁺ + CH₃O \]

\[ \text{Eq. 9} \]
ENERGETIC CONSIDERATIONS AND METASTABLE ION CHARACTERISTICS

To characterize an ion fully, one must be able to specify its elemental composition, structure, and internal energy. Because their shapes and relative abundances are characteristic, metastable ion peaks are usually used along with substituent effects on the reaction and appearance potentials of the ions under consideration in comparing ions produced from different precursors. An ion will give rise to a metastable ion peak if it fragments within a narrow specified time interval after leaving the ion source. In a typical magnetic sector mass spectrometer a large fraction of the ions with a decomposition rate constant (k) of approximately $10^5$ sec$^{-1}$ gives rise to metastable ion peaks. Ions with $k > 10^6$ sec$^{-1}$ fragment in the ion source and produce daughter ions. Ions with $k < 10^5$ sec$^{-1}$ are collected as such. The rate constant for a fragmentation is a function of the internal energy ($E$) of the ion undergoing decomposition, the number of effective oscillators (n) in this ion, the frequency factor ($v$) for the reaction, and the activation energy ($E_a$) for the reaction as given by equation 12.

$$ k = v [(E - E_a)/E]^{n-1} $$

Reactions giving relatively intense metastable ion peaks also show a difference between the appearance potentials of the fragment ion and the accompanying metastable ion peak.

By selecting systems in which the molecular ion $M^+$ and the daughter ion $A^+$ comprise the major portion of the total ionization at all electron energies and comparing only the rates for this major reaction of m- and p-Y isomeric substrates, factors such as different bond strengths of all bonds formed or cleaved in the reaction, competitive reactions in the molecular ions, secondary decompositions of the daughter ions under consideration, frequency factor differences, and degree of freedom differences are reduced to a minimum. If molecular ions of identical ionization potentials and energy distributions of m- and p-Y isomers each rearrange to some common ion prior to decomposition in the ion source, then these common ions will behave identically, and $Z_P/Z_M$ will be a good measure of the relative similarities and differences between them. For each pair of m- and p-Y isomers with the same substituent Y undergoing the reaction in Eq. 2, four possible extreme energetic situations can be summarized as the following. Case A, the ionization potentials of m- and p-Y isomers are different ($IP_m \neq IP_p$), but the appearance potentials of $A^+$ are the same for the two isomers ($AP_m = AP_p$); therefore, the activation energies for the reactions of m- and p-Y isomers are different ($E_m \neq E_p$). Case B: $IP_m = IP_p$, but $AP_m \neq AP_p$; therefore, $E_m \neq E_p$. Case C: $IP_m = IP_p$, and
APm = APp; therefore Em = Ep. Case D: IPm ≠ IPp, and APm ≠ APp, but the difference between IPm and IPp is the same as that between APm and APp; therefore Em = Ep. By examining \( \frac{Zp}{Zm} \) as a function of electron energy over a wide range, one can distinguish between the above energy situations. Thus in the simplest possible case, different rates for m- and p-Y isomer pairs of compounds at 70 eV will result in the same Zp/Zm ratio as the threshold (lowest energy at which particular ion peak can be observed) is approached for case A but variation of Zp/Zm will be observed as the threshold is approached for case B, because the reaction with the higher appearance potential (m- or p-Y) is discriminated against preferentially. Similarly, Zp/Zm = 1.0 for case C and this value will be found over the whole electron energy range. Finally, variation of Zp/Zm is expected for case D as the electron energy is changed.

A further probe into molecular ion energy and structure is provided by metastable ion relative abundances.\(^{17}\) It has been pointed out\(^ {17} \) that ions \( M^+ \) identical in structure and energy will give identical \( \frac{[m^*]}{[M^+] to [M^{-}]} \) (Eq. 2) ratios. Of the four cases cited above, only case C would be expected to give identical \( \frac{[m^*]}{[M^+] or [m^*]}{[A^+] ratios for m- and p-Y isomers over the electron energy range from 70 eV to threshold. The metastable ion peaks accompanied with further fragmentation of \( A^+ \) can be used to aid the elucidation of the structure and energy of ions \( A^+ \). Again, only case C would be expected to give identical \( \frac{[ma]}{[A^+] \) ratios for each m- and p-Y isomer pair over the whole electron energy range. Identical \( \frac{[ma]}{[M^+]} \) ratios have been used\(^ {24} \) as evidence for common, rearranged molecular ions of the same energy. It was, therefore, proposed\(^ {4} \) that observation of \( \frac{Zp}{Zm} \) and \( m^* \), \( m^* \), \( m^* \), \( m^* \) relative abundances, over the electron energy range 70 eV to threshold for the one major reaction (Eq. 2) of m- and p-Y isomer pairs of compounds should provide information as to the equality or difference in energy of the relevant isomeric ions and their activated complexes. Among the systems studied are meta- and para-substituted benzyx phenyl ethers,\(^ {25} \) toluenes,\(^ {25} \) and chloro-benzenes.\(^ {27} \)

For the reaction in equation E13, \( \frac{Zp}{Zm} \) was found to vary with electron energy in the range of 70 eV to 9 eV for each substituent Y, which indicates a difference in transition state energies for each isomer pair of compounds. Metastable ion characteristics indicate decomposing molecular ions of different energy and/or structure for each m- and p-Y pair, as \( \frac{[m^*]}{[M^+] } \) ratios are different over the energy range 70 eV to 15 eV. Similar relative metastable ion peak abundances \( \frac{[ma]}{[M^+] \) for further decomposition of \( YC_2H_5CH_3^+ \) ions over the same electron energy range suggest decomposing species of common structure and energy for each m- and p-Y isomer pair, except where \( Y = CH_3 \) and \( NO_2 \). Based on these data, the author\(^ {4} \) suggested that for the reaction in equation E13, rearranged molecular ions, tropylium-like transition state and substituted tropylium ions as the immediate cleavage product might be involved for substituents \( Y = CH_3, \ F, \ Cl, \ Br, \ and \ CF_3; \) and unarranged molecular ions and benzylic transition states were present when \( Y = CH_3 \) and \( NO_2 \).

Mass spectral data for the reaction given in equation E14 showed that over the electron energy range 70 eV to 10 eV, \( \frac{Zp}{Zm} \) when \( Y = CH_3, \ F, \) and \( CN, \) consistent with case C above, and with identical transition state energies for isomeric pairs of compounds. When \( Y = Cl \) and \( Br, \frac{Zp}{Zm} \) but the ratio \( \frac{Zp}{Zm} \) is constant, consistent with case A above, then the transition state energies for m- and p-Y pair of isomers would be identical. When \( Y = CH_3, \frac{Zp}{Zm} \) and the ratio \( \frac{Zp}{Zm} \) varies with electron energy, consistent with different transition state energies for the m- and p-CH_3 isomers. Similar studies have been done with meta and para substituted chlorobenzenes\(^ {27} \) and the evidence obtained is consistent with rearrangement prior to cleavage in the molecular ions to lose Cl.
For the reaction described by equation 1, the metastable ion peak \((m^*_1)\) for the first process \((M^* \xrightarrow{k_1} A^+_1)\) is derived from ions with internal energy between \(E\) and \(\delta E\). The fractional abundance of this metastable ion peak is given by equation 15, where \(f(E)\) is the fraction of ions having internal energy \(E\) to \(E + \delta E\), \(\delta E\) is a small increase in \(E\), \(k_1\) and \(k_2\) are the rate constants of the reaction at an energy \(E\), and \(t_1\) and \(t_2\) are the times required to enter and leave the field-free region, respectively.

Using equation 12 and equation 15, one can derive the following relationships: When \(v_1 = v_2\), then \(k_1/k_2 = [(E-Ea_1)/(E-Ea_2)]^{n-1}\), and \([m^*_1]_E/[m^*_2]_E\) is independent of the value of the frequency factors. If \(Ea_1 = Ea_2\), then \([m^*_1]/[m^*_2] = v_1/v_2\).

For a hypothetical compound with the parameters given in Table 1, the \([m^*_1]_E/[m^*_2]_E\) ratio is calculated as a function of the internal energy \(E\) (Figure 1, curve a).

From Figure 1, three qualitative generalizations can be made: (1) \([m^*_1]_E/[m^*_2]_E\) approaches \(v_1/v_2\) at high values of \(E\); (2) At low values of \(E\), a slight increase in activation energies results in a large increase in \([m^*_1]_E/[m^*_2]_E\) ratio; (3) For reactions with high frequency factors, the ratio \([m^*_1]_E/[m^*_2]_E\) is large even if there are only slightly different activation energies for the reactions. All these generalizations can be applied to the total metastable ion peak abundance ratios \([m^*_1]/[m^*_2]\) since \([m^*_1]_E\) can be expressed by equation 16, where \(E_{\text{max}}\) is the maximum internal energy of the ions.

Data obtained for the competitive rearrangement and cleavage reactions for anisole, butyrophenone, \(n\)-butylbenzene and 2-phenylethanol are summarized in Table 2.

From Table 2 it is clear that the approximate activative energy (AP-IP) is larger for the cleavage reactions than for the apparently competitive rearrangement processes. In addition, the metastable ion peak for rearrangement \((m^*_R)\) is considerably more intense than that for the parallel cleavage \((m^*_C)\), as has been proposed by McLafferty 30 and others. 31

\[
[m^*_1]_E = f(E) \cdot \frac{k_1}{k_1 + k_2} \cdot \frac{e^{-(k_1 + k_2)t_1} - e^{-(k_1 + k_2)t_2}}{e^{-(k_1 + k_2)t_2} - e^{-(k_1 + k_2)t_2}} \cdot \delta E \quad \text{Eq. 15}
\]

\[
[m^*_1] = \int_{Ea_1}^{E_{\text{max}}} f(E) \cdot \frac{k_1}{k_1 + k_2} \cdot [e^{-(k_1 + k_2)t_1} - e^{-(k_1 + k_2)t_2}] dE \quad \text{Eq. 16}
\]
Table 1. Parameters Used for Calculation of Metastable Ion Peak Abundance Ratios Shown in Figure 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (number of atoms in the molecule)</td>
<td>20</td>
</tr>
<tr>
<td>M (number of decomposition pathways of M⁺)</td>
<td>2</td>
</tr>
<tr>
<td>IP (IP of the compound)</td>
<td>10 eV</td>
</tr>
<tr>
<td>t₁ (time estimated for a molecular ion of m/e 120 to reach the second field-free region of the mass spectrometer)</td>
<td>9.8 sec</td>
</tr>
<tr>
<td>t₂ (time estimated for a molecular ion of m/e 120 to leave the second field-free region of the mass spectrometer)</td>
<td>14.5 sec</td>
</tr>
<tr>
<td>Eₐ₁ (activation energy of the first reaction)</td>
<td>2.0 eV</td>
</tr>
<tr>
<td>Eₐ₂ (activation energy of the second reaction)</td>
<td>2.2 eV</td>
</tr>
<tr>
<td>ν₁ (frequency factor of the first reaction)</td>
<td>(1 \times 10^{13} \text{ sec}^{-1})</td>
</tr>
<tr>
<td>ν₂ (frequency factor of the second reaction)</td>
<td>(1 \times 10^{13} \text{ sec}^{-1})</td>
</tr>
</tbody>
</table>

Figure 1. The variation of metastable ion peak abundance ratio \([m_{1}^{*}]_{E} / [m_{2}^{*}]_{E}\) as a function of internal energy \(E\) of the ions generating the metastable ion peaks.

\[
\frac{[m_{1}^{*}]_{E}}{[m_{2}^{*}]_{E}}
\]

---

a. parameters in Table 1.  
b. the same parameters as in a except \(ν₂ = 10ν₁\).  
c. the same parameters as in a except \(E_{a₂} = 2.4 \text{ eV}\).
Table 2. Measured Quantities for Competitive Rearrangement and Cleavage Reactions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction</th>
<th>$A^+<em>{a}$ - $IP</em>{b}$</th>
<th>$m^*/m_C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) anisole</td>
<td>M-CH₃</td>
<td>3.51</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>M-CH₂O</td>
<td>2.91</td>
<td></td>
</tr>
<tr>
<td>(II) 2-phenylethanol</td>
<td>M-CH₂OH</td>
<td>2.64</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>M-CH₂O</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>(III) butyrophenone</td>
<td>M-C₃H₇</td>
<td>1.46</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>M-C₃H₄</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>(IV) n-butylbenzene</td>
<td>M-C₃H₇</td>
<td>2.57</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>M-C₃H₈</td>
<td>1.39</td>
<td></td>
</tr>
</tbody>
</table>

a. $A^+$ is the appearance potential for the particular fragment ion in the reaction
b. $IP$ is the ionization potential of the molecule

SUMMARY

The factors influencing relative metastable ion abundances at the collector of ions $A^+$ and $m^+$ and the corresponding metastable ion peaks for the electron-impact induced reaction $M^+_r \rightarrow A^+$ can be summarized as to be potentially a function of the following factors upon varying a substituent group:

1. The distribution of the internal energy values of the precursor ion. Since there is little probability that an ion, once formed, will gain or lose energy before it undergoes decomposition, the rate of its decomposition by a particular path depends on the internal energy acquired when it is formed, which in turn depends on the energy of the bombarding electrons and the structure of the molecule. If the only effect of adding a substituent to a molecule is to shift the internal energy of the molecular ion to lower value, then the $Z$ value should be lowered. In addition, this factor can be used to explain the nearly identical substituent effects for certain substituted phenetoles. It is also possible to change the shape of the ion-energy curve without changing the ionization potential appreciably. This has been used as a basis for the partial explanation for the degree-of-freedom effect on the relative abundance of metastable ion peaks.

2. The substituent effect on the activation energy, the stability of the production, and the bond strengths of all bonds cleaved or formed in the reaction have to be considered.

3. The fraction of the activated complexes which lead to the reaction under consideration may change. This is because the total number of quantum states increases as the substituent becomes more electron-donating, thus lowering the ionization potential.

4. Competitive reactions may become important when certain substituents are introduced. This lowers considerably the fraction of ions in the ion source having the energy to undergo the reaction being studied.

5. The secondary decompositions of a product ion must be considered regardless of whether or not the product ion retains the substituent. This effect can be reduced by using low voltage electrons.
In summary, gaseous ion structures are virtually impossible to prove at the present, but some correlations can be made by designing critical experiments to distinguish among all chemically reasonable alternative structures. One must always be prepared, however, for complex situations which might arise in any electron-impact reaction. Actual determination of the structures and energy distributions of ions produced in the mass spectrometer remains a formidable task.

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EXPLANATIONS OF THE ORTHO EFFECT

Reported by Brad Glorvigen May 6, 1971

INTRODUCTION

The classical Hammett \( \alpha - \beta \) approach is of great use in correlating rate and equilibrium data for meta and para-substituted benzene derivatives.\(^1\) The failure of the Hammett equation to correlate such data when applied to ortho-substituted compounds is a well-known phenomenon to the physical organic chemist.\(^2\) This deviation from normal behavior is termed an ortho effect and is usually rationalized by recognizing that, in addition to the usual electrical effects influencing the reaction center of substituted benzenes, proximity effects are operative in the ortho-substituted systems. Some of the more important proximity effects are 1) intramolecular hydrogen bonding between substituent and reaction site, 2) intramolecular van der Waals or London forces; i.e., steric interaction due to non-bonded repulsion between substituent and reaction site in the ground or transition state (primary steric effect), 3) steric inhibition of resonance due to alteration of geometric requirements, either between the reaction site and the ring or between the substituent and the ring or both, (secondary steric effect), 4) steric inhibition of solvation, 5) steric inhibition to attack of the reagent.

Traditionally the ortho effect has been attributed entirely to steric effects, which are present for an ortho but not a para substituent. The implicit assumption was that ortho and para electrical effects are very similar. To be sure, in many cases steric effects are large and overwhelm electrical effects. Meyer's early observation of the ortho effect in acid-catalyzed esterification of benzoic acids illustrates this point.\(^3\) He found a marked decrease in rate when an ortho methyl, nitro or halo group was present, and double ortho substitution so severely retarded the rate that essentially no reaction occurred under conditions normally leading to very high yields.

Recently, however, increased emphasis on electrical effects has been proposed by some workers to explain ortho effects in systems where steric effects may not be of overwhelming importance. The majority of this seminar will deal with a few types of reactions in such systems and attempt to examine critically the nature of the ortho effect.

QUANTITATIVE DESCRIPTION OF ORTHO SUBSTITUENT EFFECTS

In 1927 Kindler was the first to make a crude quantitative estimate of the effect of an ortho substituent.\(^4\) He empirically observed that the alkaline hydrolysis rates of corresponding \( m \) - and \( p \)-substituted ethyl cinnamates and benzoates followed the relation \( (k/k_0)^{1/2} \) benzoate = \( (k/k_0) \) cinnamate. According to Kindler failure of \( \sigma \)-substituted esters to fit the equation was due to an ortho effect in benzoate hydrolysis. By taking a ratio of the expected ortho rate constants to those observed, a measure of the ortho effect was obtained. Ratios found were: \( F=1, C1=2, Br=5; I=7.5, \) and \( NO_2=11. \) The order corresponded qualitatively to one of increasing group size.

The major quantitative separation of steric and polar effects for ortho substituents is the well-known method of Taft using rate data from acidic and basic ester hydrolysis, which allows evaluation of the polar effect from \( \sigma \) constants given by the equation \( \sigma_{o} = 1/2.48 [\log (k/k_0) \beta \log (k/k_0)] \), where \( k_0 \) represents the rate of the standard \( \sigma \)-methyl benzoate, \( k \) is the rate for the substituent of interest, and \( A \) and \( B \) refer to acid and base.\(^5\) As a result of assumptions made in the analysis \( \log (k/k_0) \) measures the steric effect of the ortho substituent. Although often criticized, Taft's work has prompted important work by other researchers. To date 32 different sets of \( \sigma \) constants have been defined for such varied reactions as ionizations,\(^6\) ester hydrolysis, ester pyrolysis,\(^7\) acid esterification with diazodiphenylmethane,\(^8\) electrophilic aromatic substitution, and ir,\(^9\) nmr,\(^10\) and polarography data.\(^11\)

No one set of constants has been generally successful in describing the reactivities of ortho-substituted compounds, although all are supposed to
represent only electrical effects. Charton, by use of the extended Hamnett equation \( \alpha = \alpha_I + \beta \sigma_R + h \), where \( \alpha \) is the quantity correlated, \( h \) is the intercept (usually the value for hydrogen) \( \alpha \) and \( \beta \) are proportionality coefficients, and \( \sigma_I \) and \( \sigma_R \) are inductive and resonance parameters, has shown that these sigma constants can indeed be accounted for solely by electrical parameters, but also that \( \varepsilon = \beta / \alpha \) varies considerably with the reaction (usually 0.5-1.0) and that no one or even a few sets of \( \sigma_R \) values is sufficient to correlate all the data.\(^{12}\) These results indicate that accounting for many types of ortho effect is not a simple task.

UNIMPORTANT OF STERIC EFFECTS \(^{13}\)

The most recent controversial position on the nature of the ortho effect has been taken by Charton in a series of papers attempting to show that for many reactions showing an ortho effect, steric effects are unimportant and that the effects of ortho substituents may be accounted for solely in terms of electrical effects. His method involves correlating large amounts of literature data with the extended Hamnett equation above including, initially, a term \( \pi \rho \) representing a steric factor. Multiple linear regression analysis with "t-tests" are used and the significance of the coefficients determined. In all cases studied he concludes \( \pi \) is insignificant and then proceeds with correlations using the reduced equation(s). For electrophilic aromatic substitution good correlations are obtained using both \( \sigma_I \) and \( \sigma_R \), with the result that \( \alpha_R \) and \( \alpha_I \) are equal.\(^{13}\) Consideration of the transition state seems to indicate this may actually be the case.

Acid-catalyzed ester hydrolysis and acid esterification rates correlate with the equation \( \alpha = \alpha_R + h \).\(^{14}\) The importance of a resonance effect is not unreasonable when considering the important steps in the reaction:

\[
\begin{align*}
(1) \quad & \text{\text{ArC}_{OR}} + \text{H} + \text{Keq} \quad \text{\text{ArC}_{OR}} \quad \text{\text{OH}} \\
& \text{\text{ArC}_{OR}} \quad \text{\text{OH}} \\
(2) \quad & \text{\text{ArC}_{OR}} + \text{H}_{2}\text{O} \quad \text{\text{ArC}_{OR}} \quad \text{\text{OH}} \quad \text{\text{OH}}_{2} \\
& \text{\text{ArC}_{OR}} \quad \text{\text{OH}} \quad \text{\text{OH}}_{2} \\
\end{align*}
\]

The rate observed, \( k \), will equal \( k_{\text{Keq}} \) and a resonance effect could be observed.

Basic ester hydrolysis correlates well with the equation \( \alpha = \alpha_R + h \) for substituted methyl and ethyl benzoates.\(^{15}\) Such a result is also not unreasonable because resonance should not be important in the transition state. Combination of the results for acidic and basic ester hydrolysis implies that Taft's separation of steric and polar effects is quite faulty. \( \sigma_R \) would measure a difference in inductive and resonance effects on ester hydrolyses, and \( E = \log \left( k / k_k \right) \) would mainly measure the resonance effect of an ortho substituent. Charton reached this conclusion earlier by examining the Taft steric parameters directly; although aliphatic \( E_s \) values depended only on the van der Waals radius, \( E_s \) did not depend on it at all, but rather was accounted for in terms of \( \sigma_I \) and \( \sigma_R \).\(^{16}\)

Although correlations do have value, it is often not wise to use them as guides for theoretical reasoning. Several faults are present in Charton's work. Almost universal exclusion of t-butyl and nitro substituents from correlations tacitly concedes that steric effects are not unimportant, and the use of small ranges of sigma values represented by alkyl and halogen substituents limits testing of the linear relation severely. The wide difference in \( \alpha \) and \( \beta \) values indicates that it is hard to correlate one reaction with another, a task that should be made easier if steric effects are not involved. Charton's as well as others' use of nmr and polarography data is also of limited value.\(^{17,18}\)
One reason is that spectral and reactivity data do not necessarily correlate. In polarography, for example, the steric requirements of the electron are so small that steric effects should not be significant. Furthermore this type of data only yields information about one state of a molecule, whereas reactivity depends on both ground and transition states.

IONIZATION OF ACIDS

The acid-strengthening effect of ortho compared with para substituents in benzoic acid has traditionally been explained as a secondary steric effect. X-ray values of the interplanar angle between phenyl and carboxyl in $\text{\(^\circ\)}$-substituted benzoic acids indicate distortion from coplanarity (for example, $\text{H}=^0$, $\text{F}=1.3$, $\text{Cl}=13.7$, $\text{Br}=18.3$, $\text{I}=28$, $\text{Me}=2.0$, and $\text{Me}=\text{Et}=11$). Estimates usually indicate that conjugation with the ring is about 1 kcal more important in the free acid than in the anion. The clearest case in support of this explanation is for alkyl substituents. An ortho effect is often easiest to observe for these substituents because of their relatively small polar effects, and in acid ionization steric and polar effects work in opposite directions. The following sample of $\text{pK}_a$'s for benzoic acids illustrates the point ($\text{H}_2\text{O}$, 25°C): Unsubstituted, 4.20; $\text{O}$-, $\text{m}$-, and $\text{p}$-methyl, 3.91, 4.27, and 4.37 respectively; 2,6-dimethyl, 3.25; $\text{O}$- and $\text{p}$-t-butyl, 3.53, 4.40.

Nevertheless, care is needed in interpreting even these simple data. The differences in $\text{pK}_a$'s between ortho and para substituted acids are solvent dependent. In 50% ethanol the $\text{pK}_a$ for benzoic acid is 5.76 and the values for the $\text{O}$- and $\text{p}$-Me acids are 5.78 and 6.00; in aqueous DMSO at concentrations above 65% there is no measurable difference and in benzene the $\text{p}$-isomer is the stronger acid. Charton has suggested that solvent variation affects the value of $\beta$. A plot of $\text{pK}_a$ vs. $\text{E}_s$ (aliphatic) for $\text{O}$-alkyl benzoic acids shows methyl, ethyl, and isopropyl in a straight line, but the $\text{pK}_a$ for t-butyl is considerably higher than expected, indicating possible steric inhibition of solvation for the anion. More definite statements about acid ionization can be made after discussing esterification of acids with diazodiphenylmethane and comparing these two related reactions.

ESTERIFICATION OF ACIDS WITH DIAZODIPHENYL METHANE

The currently accepted mechanism of the reaction of carboxylic acids with diazodiphenylmethane (DDM) to form benzhydryl esters is shown below. Included in the scheme is the competing reaction of an alcohol (the usual solvent) with DDM, catalyzed by the acid to form benzhydryl ethers.

$$\text{ArCO}_2\text{OH} + \text{Ph}_2\text{C}=\text{N}=\text{N} \xrightarrow{\text{slow}} [\text{ArCO}_2^- + \text{Ph}_2\text{C}=\text{N}=\text{N}] \xrightarrow{\text{fast}} [\text{ArCO}_2^- + \text{CH}_2\text{Ph}_2]$$

Since the rate-determining step is the proton transfer from the acid to DDM, acid strength is an important factor. The kinetics of this reaction for substituted benzoic acids have been studied in detail by Chapman in dioxane, ethyl acetate, 2-methoxyethanol, ethanol, DMP, and DMSO. The importance of polar factors is indicated by a substantial decrease in rate for methyl compared to hydrogen ortho substitution, but the regular increase in rate as the series methyl through t-butyl is traversed also indicates the importance of a secondary steric effect. In general the rate increases with increasing solvent polarity, but in DMSO and DMP large reductions in rates are observed. The effect is due to extremely strong solvation of the acidic
proton, and is so great that a secondary steric effect is no longer evident. A plot of \( \log k \) vs. \( E_g \) gives four parallel lines in solvents excluding DMF and DMSO indicating that the secondary steric effect here is not solvent dependent. An expected lack of solvation in the ortho cavity (the space between the two ortho substituents) explains this. Extrapolation of the solvent curves to \( E_g = 0 \) and calculation of the value \( \log k(E_g = 0) - \log k_H \) gives a measure of the polar effect; although such as effect is present for alkyl groups it differs little from one group to another.

Conversely, the effects of ortho halogen substituents provide evidence for the dominance of a polar effect considerably stronger from the ortho than the para position. An estimate of the possible steric effect of a halogen on \( \log k \), \( \Delta \log k \), may be taken from \( \log k \) vs. \( E_g \) (results were averaged using aliphatic and aromatic values) for alkyls and is shown below. The value of \( (\log k_F/k_F - \Delta \log k) / \log k_F/k_F \) should then give a relative polar effect of halogens for \( \alpha \)- and \( \rho \)-positions. It appears that Cl, Br, and I are 3 times more strongly electron withdrawing from the \( \alpha \)- than from the \( \rho \)-position.

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>Cl</th>
<th>Br</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \log k )</td>
<td>+0.03</td>
<td>+0.04</td>
<td>+0.05</td>
<td>+0.09</td>
</tr>
<tr>
<td>polar effect</td>
<td>5.23</td>
<td>2.86</td>
<td>3.21</td>
<td>3.34</td>
</tr>
</tbody>
</table>

This phenomenon is attributed to an increased direct field effect for the \( \alpha \)-substituent. Relative polar effects for Cl of 3.2 and 3.8 for the reactions of chloro-substituted benzyol chlorides with aniline and chloro-substituted anilines with benzyol chloride in benzene support the above data.\(^{29}\) Ionization of phenols and anilinium ions, for which secondary steric effects are thought to be unimportant, give similar ratios of \( \log k_F/k_F / \log k_F/k_F \) for halogens.\(^{30}\)

The solvent effect on the ortho effect was investigated by studying the reaction of phenylacetic acids, a system not subject to secondary steric effects, with DDM in ethyl, methyl, propyl, isopropyl, \( t \)-butyl and \( t \)-amyl alcohol.\(^{31,32}\) The overall ortho effects are considerably less than in benzoic acid. All four \( \alpha \)-alkyl acids are less reactive than phenylacetic acid, and all four \( \alpha \)-halo and \( \alpha \)-nitro acids react more quickly, but only in the more polar alcohols are they more reactive than the \( \rho \)-isomers. The most discernible effect for \( \rho \)-alkyl groups is seen in \( \Delta \log k_F \) values (\( \log k_F/k_F \)): the magnitude of a retardation effect becomes greater as the solvent polarity decreases (bulkiness increases); comparable effects are observed for methyl, ethyl, and isopropyl, presumably due to adoption of conformations minimizing interaction, but the effect of \( t \)-butyl is progressively enhanced, indicating possible steric inhibition of solvation. Using results from the alkyls enables a separation of steric and polar effects for halogens and nitro to be performed. A detailed procedure with several quantitative assumptions yields instructive results; \( \Delta \log k_F \) is separated into steric and polar terms, \( \Delta \log k_F^S \) and \( \Delta \log k_F^P \) and the ratio \( \log k_F^P/\log k_F^P \) indicating the ratio of \( \alpha \)- and \( \rho \)-polar effects is evaluated. For the more polar alcohols \( P \) is about 1.4–1.5, but becomes close to 1.0 in tertiary alcohols. The essence of the explanatory treatment lies in considering the differential action of the solvent on the positive and negative poles of the \( \alpha \), \( \rho \), and \( \rho \)-substituents.

**COMPARISON OF ACID IONIZATION AND REACTION WITH DIAZODIPHENYL METHANE**

A good linear relationship in each of the six solvents mentioned earlier (ethanol, dioxane, etc.) for plots of \( \log k \) for reaction of \( \alpha \)-substituted benzoic acids with DDM at \( 30^\circ\) vs. \( p_k^\alpha \) for ionization implies a relation between the factors governing each reaction. The main factor varying through the series (methyl and halogens) is the polar effect. Since the secondary steric effects for halogens in the DDM reaction were shown to be small, the graph approximates a Hammett plot and \( \rho_o \) and \( \sigma_o \) may be estimated. Although \( \rho_o \) differs from \( \rho \), the important fact is that \( \rho_o \) is relatively insensitive to solvent change, again indicating that for ortho substituents the solvent does little to transmit polar effects since it can not fit in the ortho cavity. Similar lack of solvent
dependence has been found by Charton. Bowden has compared the two reactions in trans-cinnamic, phenoxycetic, 3-phenylpropionic and cis and trans-α-phenyl-cinnamic acids for methyl, fluoro, chloro, bromo, nitro, and methoxy substituents and has explained the results in terms of an enhanced direct field effect from the ortho position. In the study of the cumulative ortho effect in disubstituted benzoic acids and 2-substituted 5-amino benzoic acids, Hojo has likewise explained the results in terms of a direct field effect.

Thus, for substituents of moderate bulk the ortho effect has been proposed to be due to the efficient transmission of the polar field effect across a small distance combined with a common displacement for all substituents. The displacement effect is illustrated in the plot below. It seems that introduction of any ω-substituent causes about 0.4 pKₐ decrease. Related studies of cis- and trans- 3-substituted acrylic acids (analogous structurally to α-benzoic acids) give a plot similar to that shown in which the cis-acids correspond to ortho benzoic acids and trans- correspond to meta and para. Since rates for cis- and trans- acids are the same, no secondary steric effect is present, and the cis- acids show a decrease of 0.3 in pKₐ solely because of the position of the substituent and independent of its polar nature.

Relation between pKₐ for water at 25° and log k for reaction with diazodiphenylmethane in ethanol at 30° for a series of substituted benzoic acids.

Substituents: 1, ω-Me. 2, ω-Et. 3, ω-Pr1. 4, ω-F. 5, ω-But. 6, ω-Cl. 7, ω-Br. 8, ω-I. 9, ω-Me 10, ω-Pr1. 11, ω-Me. 12, H. 13, ω-F 14, ω-Cl. 15, ω-I. 16, ω-Cl.

The ω values shown below indicate the similarity of the cis- trans- and ortho systems; also the transmission of polar effects from the ortho position is about twice as efficient as from the meta or para position.

Table 1

<table>
<thead>
<tr>
<th>Reaction constants of Benzoic and acrylic acids</th>
<th>Cpd.</th>
<th>DDM</th>
<th>pKₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans</td>
<td>1.62</td>
<td>2.19</td>
<td></td>
</tr>
<tr>
<td>cis</td>
<td>1.77</td>
<td>2.45</td>
<td></td>
</tr>
<tr>
<td>ω</td>
<td>1.89</td>
<td>2.59</td>
<td></td>
</tr>
<tr>
<td>m, p</td>
<td>0.99</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Chapman has suggested that since secondary steric effects cannot account for an equal decrement in pKₐ for benzoic acids upon ω-substitution another factor may be operative. Solvation (of the "ring" type) of benzoic acid may include solvation by water bridges, thus encouraging the molecule to adopt a planar configuration to increase such stabilization. Ortho substitution will destroy such solvation and facilitate dissociation.
ACID-CATALYZED ESTER HYDROLYSIS AND ESTERIFICATION OF ACIDS

Using studies of the p-toluenesulfonic acid-catalyzed hydrolysis of methyl benzoates in 80% methanol and data from basic hydrolysis in the same solvent Chapman carried out a Taft analysis. The presence of serious discrepancies in the calculated $\sigma^*$ and $E_S$ values and the result that $E_S > E_S^*$ for halogens raised the question as to whether steric effects are really equivalent in acidic and basic hydrolysis. Since the transition states differ by 2 charge units it is unlikely that solvation patterns will be the same. Evidence from Bowden's study of esterification of 3-substituted cis- and trans- acrylic acids and the basic hydrolysis supports the above conjectures. Not only are steric effects not equivalent for the two reactions, but the factor $p_{o-} - p_a$ is considerably larger than 2.48 in this system and for o-substituted benzoates.

Rate data at several temperatures have been measured for the acid-catalyzed esterification of o-benzoic acids with methanol and Arrhenius and activation parameters have been calculated for alkyl and halogen substituents. The steady decrease in $\Delta H^+$ with increasing group size was explained by a primary steric effect. The effects on $\Delta H^+$ are a bit more complex, however. Electron releasers should decrease $\Delta H^+$, while steric inhibition of solvation and a primary steric effect should increase it. The only increase is shown by t-butyl, all other o-substituents produce a decrease, which increases with bulk of the substituent regardless of its polar nature. This evidence might indicate operation of a secondary steric effect, but results from the m- and p-isomers indicate that another factor may be responsible. All substituents regardless of their polar nature or the position of substitution decrease $E_S$ relative to the unsubstituted compound, and a secondary steric effect is not possible in the m- and p-isomers; the explanation of this effect will also be a factor for the o-isomers. Conjugation of the carboxyl should result in an orientation of stabilizing solvent molecules around the ring; introduction of a substituent will interfere with solvation increasing the energy relative to benzoic acid. Decrease in $\Delta S^+$ can also be explained by this effect. A quantitative dissection of effects for o-substituents is not possible because the ring solvation for o- and p-substituents is not the same due to the proximity of the carboxyl group. There is no observation of a similar effect in basic hydrolysis probably because polar effects are much more important. Furthermore, the misbehavior of m- Me in the Hammett plot for this reaction suggests that ring solvation may be responsible since methyl has a weak electrical effect and this explanation would account for the generally poor correlations of this reaction with the Hammett equation.

Comparison of esterification results for phenylacetic acids with benzoic acids indicates that o-substituents still have considerable retarding effects. The greater reactivity of phenylacetic acids can be ascribed to ground state stabilization in benzoic acids through conjugation, attenuation of the phenyl's electron withdrawing effect by the methylene group, and a greater primary steric effect in the transition state for benzoic acids. Similarity of alkyl $E_S$ values in the two systems could be due to lack of a facilitating secondary steric effect in phenylacetic acids, but the greater $E_S$ values in this system for halogens is surprising. The difference is most pronounced for fluorine and decreases progressively to iodine. Polar facilitation of solvation by halogens should be more important in phenylacetic than benzoic acids since the ortho cavity is larger; this increased solvation causes the halogens to behave as if they were larger and so $E_S$ decreases.
BASIC HYDROLYSIS OF ESTERS

Activation parameters have been calculated for the basic hydrolysis of substituted methyl benzoates in 80% methanol. The lack of any clear order in $\Delta S^\ddagger$ values for $\sigma$-substituents indicates that opposing steric effects may be responsible (the hydrolysis of the $m$- and $p$-substituted isomers is isoen trope). A primary steric effect will make $\Delta S^\ddagger$ more negative, and steric inhibition of solvation of the transition state relative to the ground state will make it more positive. A close balance of the two effects is observed for methyl and t-butyl in methanol, but in 60% dioxane, where increased solvation by water probably occurs, the predominance of the inhibition of solvation shows up for t-butyl.

The importance of solvation is again illustrated by polar facilitation of solvation by halogens, causing them to exert a larger bulk effect than alkyl groups of the same size, making $\Delta S^\ddagger$ more negative. For example, in methanol, methyl (van der Waals' radius 1.95 Å) has no effect on $\Delta S^\ddagger$ whereas bromine (1.90 Å) lowers it by 4 e.u.

The variety of effects on $\Delta H^\ddagger$ is too great to attempt a dissection here. Polar effects seem to satisfactorily explain the effect of halogens, and a large primary steric effect is demonstrated by t-butyl.

Similar results obtained for ethyl benzoates in 85% ethanol and 56% acetone show that low rates were due to low values of the pre-exponential factor $A$, values of $E_a$ being comparable for $\sigma$-substituents (the reverse holds for $m$- and $p$-substituents).

The disappearance of the ortho effect when the reaction site is removed from the substituent is often used as evidence indicating the steric nature of the effect. Charton has thus correlated data for 14 reaction series of $\sigma$-substituted benzenes with $\sigma_D$, indicating a proportionality of $\sigma$- and $\rho$-polar effects when the reaction site is separated from the ring by at least two atoms.

Thus phenylacetate hydrolysis will represent an intermediate case.

Hydrolysis rates for substituted ethyl phenylacetates have been measured in 85% ethanol and 56% acetone. All $\sigma$-substituents retard the reaction, even nitro, for which $k_p/k_\text{H} = 8$. Comparison of the results with those obtained for ethyl benzoates is instructive. That the ortho effects operative in benzoate and phenylacetate hydrolysis differ may be indicated by the following facts: 1) o-fluoro increases the rate for benzoates relative to hydrogen and $p$-fluoro, whereas it is a retarding substituent for phenylacetates, 2) ethoxy exerts a weaker retarding effect from the $o$- than the $p$-position in phenylacetates, whereas methoxy has the reverse effect in benzoates, and 3) for phenylacetates hydrolysis is isoen trope (constant A) and slow rates are associated with high $E_a$'s, but the reverse was true for benzoates, i.e., constant $E_a$ and low A's for $\sigma$-substituents.

Consideration of the effects responsible would attribute more importance to primary steric effects in the benzoates and little weight to a secondary steric effect in either. It would appear that a direct field effect cannot predominate for phenylacetates since both halogen and alkyl groups cause retardation, but it or a greater inductive effect from the $o$- than the $p$-position must be important for benzoates to explain halogen and ethoxy effects. Solvation effects must be more important for phenylacetates. To illustrate the effect, log$k_p/k_\text{H}$ values in 56, 60, 70, and 80% acetone were plotted against those in 85% ethanol. Considerable scatter of points even for $m$- and $p$-substituents shows that substituent effects are not equally affected by solvent change. The universal deviation of $\sigma$-substituents, increasing with increasing substituent size and water content of the solvent, coupled with constant A for different solvents and the fact that increasing water content lowers $E_a$ implies that steric inhibition of solvation of the transition state is partly responsible for
this ortho effect. A similar solvent plot for benzoates shows a linear relation with no deviation from o-, m-, or p- substituents. When the solvent was varied from 3-85% ethanol $k_o/k_p$ remained constant even though $k_o/k_p = 50$. Hydrolysis in DMSO gave $k_o/k_p = 300$ and $k_o/k_p = 1.6 \times 10^4$; $p$ varied from 3.1 for 95% DMSO to 1.3 in 3% ethanol, and still $k_o/k_p$ remained constant.\textsuperscript{48}

Russian results on the basic hydrolysis of substituted phenyl esters of p-toluenesulfonic acid indicate that a direct field effect may explain the ortho effect in this system.\textsuperscript{47}

CONCLUSION

Although the various interactions of ortho substituents have long been known to chemists, to date no linear free energy correlations have been generally successful in accurately describing the reactivities of o-substituted compounds. The inherent difficulty in solving such a problem in many systems is that the proximity effects themselves are likely to be variable for a given o-substituent, depending on the nature of the reaction site, the type of reaction, and the reaction conditions. This was true even in the closely related cases examined in this paper. Solvation effects seem to be of particular importance, but also quite variable from one system to another.

Furthermore, before quantitatively assessing steric effects it is necessary to know exactly the electrical effects and whether they are constant from system to system, and if not, how they vary. The systematic investigation of ortho effects (whereas up to now only piecemeal kinetic data are available) is mandatory for a good quantitative understanding of their nature in systems where one effect does not dominate all others.

BIBLIOGRAPHY

INTRODUCTION

In 1844 Mitscherlich reported\(^1\) that sodium ammonium tartrates and paratartrates (i.e., racemic tartrates) had identical interfacial angles and optical axes. However, the tartrates were optically active and the paratartrates were not. Pasteur was startled by this result, since the tartrates he had been studying were hemihedral and the paratartrates were not.\(^2\) When Pasteur examined the crystals of sodium ammonium tartrates and paratartrates he indeed found both hemihedral. He then made an important observation that had apparently escaped Mitscherlich. The faces of the tartrate crystals were all oriented in the same way, while those of the paratartrate were oriented sometimes to the left and sometimes to the right. The resolution was then carried out by separation of the left- and right-handed forms. This account of the first resolution is also the first account of the phenomenon later known as spontaneous resolution.\(^3\)

Although methods of resolution by crystallization have been reviewed,\(^4\) the subclass of resolutions of racemic modifications by spontaneous crystallization without the use of seed crystals has not been dealt with extensively. In the chemical literature the spontaneous separate crystallization of (+)- and (-)-forms in the same vessel has been called spontaneous resolution, though this is not strictly a resolution until the crystals have been separated by hand. This paper will deal with the above situation and those in which resolution takes place by virtue of racemization in solution or melt.

CHARACTERISTICS OF THE SYSTEM

The behavior of optical isomers as studied by the phase rule was first reported by Roozeboom.\(^5\) Although many types of behavior are possible, optical isomers generally exhibit three basic modes of crystallization—formation of separate (+)- and (-)-crystals, racemic compound formation, and solid solution formation.

When one enantiomer has more affinity for itself than its mirror image, molecules of the same configuration pack together in the crystal. The racemic modification consists of a gross mixture of (+)- and (-)-crystals which have the same solid state physical properties as the enantiomers. As with any simple mixture, eutectic behavior is indicated by the melting point diagram. Pinene exhibits this type of behavior, as shown in Fig. 1.\(^6\)

A more common occurrence is the formation of a racemic compound. In this case the enantiomer has a greater affinity for its mirror image than itself and the crystal is built up with equal numbers of (+)- and (-)-molecules. The physical properties are distinctly different from the pure enantiomers. The melting point diagram shows either a maximum or minimum melting point at the racemic composition, as indicated by the diagram for methyl mandelate in Fig. 2.\(^7\)

When enantiomers form solid solutions, they show almost ideal behavior in the solid state in that the homogeneous distribution of enantiomers is random. The physical properties of the solid solution are usually similar to those of the pure enantiomers. In the melting point diagrams ideality, negative deviation, and positive deviation are noted as shown in Figures 3, 4, and 5 for camphene, camphoric anhydride, and camphor, respectively.\(^6\)
RECOGNITION OF SPONTANEOUS RESOLUTION

The event of spontaneous resolution may be detected in four ways—observation of hemihedral faces, determination of melting point diagrams, direct polarimetric examination, and space group determination. The following examples from the chemical literature will illustrate the methods of recognition.

The detection of hemihedral faces is rarely a practical way of determining that a crystallization of separate (+)- and (-)-forms has taken place. Although enantiomers always show hemihedrism in their crystalline forms, the faces are only infrequently well developed.

The initial investigation of gulonic acid lactone (1) indicated that a racemic compound was formed when racemic solutions were evaporated. However, Fischer and Curtiss came to a different conclusion after observing that large single crystals of the lactone had hemihedral faces. Although all the crystals had the same melting point, some rotated polarized light to the left and others to the right, confirming the formation of (+)- and (-)-crystals. No specific data on the optical rotations were given.

One of the first semi-quantitative studies was made on the sodium ammonium tartrates previously mentioned. Kipping and Pope obtained large single crystals by slow evaporation of racemic solutions. In the initial experiment ten crystals were examined, of which five were dextro, four levo,
and one inactive. In an additional experiment nineteen crystals were examined, of which eleven were dextro and eight levo. The crystals were separated on the basis of hemihedral faces with subsequent verification polarimetrically.

In the course of a study of isohydrobenzoin (2), the observation of hemihedral faces indicated that racemic solutions deposited a mixture of (+)- and (-)-crystals. When ethyl acetate solutions of racemic isohydrobenzoin were allowed to evaporate, nine dextro- and four levo-crystals were grown. The separation of the dextro- and levo-forms on the basis of hemihedral faces was confirmed by optical rotation measurements. Specific rotations as high as +92.0, +90.1, and -89.0 degrees were obtained. The specific rotation of the optically pure sample is 92°.

Although crystals grown from chloroform exhibited no hemihedrism, it was noted that some of the crystals had a tendency to develop curved faces on the right side and others on the left. Using this criterion, the crystals were separated and tested with the same results as before.

A much more reliable method of recognizing spontaneous resolution is observation of the melting point diagram. From examination of melting point diagrams, Matell found that the methyl ester of β-phenyl-β-hydroxypivalic acid (2) was a mixture of (+)- and (-)-crystals. When a racemic modification exhibits eutectic melting at the racemic composition, it is an indication that the racemic modification is a mixture of (+)- and (-)-crystals. The same behavior has been reported for β-benzoylhydratropic acid (4) and 3-(3-nitro-4-toluidinomethylene)camphor (5).

Spontaneous resolutions can also be detected by measurement of the optical rotation of solutions made with single crystals. A spontaneous resolution of dilactylamide (6) was detected in this way. Above 35° slow evaporation of racemic solutions of (6) produced large single crystals without hemihedral faces. Individual crystals were then tested and found to have specific rotations as high as +75°. The optically pure compound has a specific rotation of 90.22°.

Most of the cases of spontaneous resolution have been discovered by means of X-ray diffraction studies. The symmetry requirements of the space group of a dissymmetric molecule indicate whether only one form is allowed in the crystal or both. A prime example is the discovery made by R. B. Corey and coworkers. When the authors recrystallized samples of D,L- and L-threonine (7), single crystals from each batch gave identical Laue photographs. An examination of the systematic absences indicated that the space group was P2₁2₁2₁. The symmetry requirements of this space group dictate that only molecules of the same configuration may be found in the crystal. Thus, the inactive sample must have been a mixture of (+)- and (-)-crystals.

In a similar case encountered during the study of the synthesis of certain ketoses, the X-ray powder photographs of samples of racemic and (+)-mannohexulose (8) were identical. Once again the racemic modification was a mixture of separate (+)- and (-)-crystals.

During a routine X-ray examination of heptahelicine, the space group was determined as P2₁. Since molecules of only the same chirality may be found in individual crystals due to symmetry requirements, the authors decided to attempt a resolution by a manual separation of the (+)- and (-)-crystals. The large single crystals obtained from benzene gave specific rotations of + and - 6200°.

In the X-ray structure determination of 1,2,5a,7b-tetrahydro-5aβ,5bα-dimethoxy-5b-h-cyclobuta[1,4]cyclobuta[1,2,5-gh]pyrrolizin-4(5H)-one (2), the space group was P2₁2₁2₁. Once again, this is an indication that the racemic modification was a mixture of (+)- and (-)-crystals.
Another X-ray investigation reveals the sensitivity of crystal formation to small structural changes in the molecule. Both the hydrochloride and hydrobromide of 3-benzylamine-4-hydroxypent-2-enolic acid lactone (10) were recrystallized and their single crystals used for the X-ray examination. The hydrochloride crystallized in P2₁/c, but the hydrobromide was found in P2₁. The symmetry requirements of the respective space groups indicate that the hydrochloride is a racemic compound while the hydrobromide is a gross mixture of (+)- and (-)-crystals. In order to verify this, six of the largest crystals of the hydrobromide were separated and their solutions checked for optical activity. Although no specific values were given, the authors reported that four crystals gave dextrorotatory solutions and two levorotatory.

In another routine X-ray structure determination, 3-chloro-2-decalone (11) formed separate (+)- and (-)-crystals when allowed to crystallize by slow evaporation of solvent. The authors came to this conclusion when crystals grown from a racemic solution were found to fall in P2₁2₁2₁. The observation was verified by melting point data.

X-ray examinations have enabled workers to detect a class of compounds that are not optically active outside of the solid state but exhibit a resolution of dissymmetric forms when they crystallize. One such compound is xylitol (12), which is inactive in solution by virtue of a meso configuration. However, an X-ray examination has revealed that xylitol crystallizes in P2₁2₁2₁. In fact, only molecules of one hand may be found in the crystal. Thus, a resolution of the dissymmetric conformers takes place on crystallization.

Methanesulfinic acid (13) is, of course, inactive in solution. However, when an X-ray examination was carried out, the compound was found in P2₁2₁2₁. As seen above, this is an indication that methanesulfinic acid is dissymmetric in the solid state. The crystal structure determination indicated that a resolution of left- and right-handed spirals had taken place during the crystallization.

A very similar example has been reported recently. Once again a crystal structure revealed that the (+)- and (-)-forms consisted of left- and right-
handed spirals about the α-axis of the crystals of acetophenone. Again, the
space group was reported as \( \text{P} \overline{2} \_1 \text{2} \_1 \).

Since Groth reported in 1919 that benzil (14) crystallizes as dextro-
rotatory and levorotatory crystals, it has been studied extensively. Later,
X-ray examination verified what was already known by specifying the space
group as \( \text{P} \overline{2} \_1 \text{2} \_1 \), which requires that only molecules of one chirality inhabit
the unit cell. The benzil crystals consist of left- and right-handed spirals
along the three-fold screw axis.

When it is known that a compound
is capable of spontaneous resolution,
a procedure can be adopted in which
resolution is nearly complete. The
most common technique is multiple
recrystallization. Anderson and Hill used this technique to resolve atropine
sulfate (15). Several racemic samples were recrystallized and all the levo-
rotatory products combined. After six additional recrystallizations, a con-
stant specific rotation of \(-20.5^0\) was obtained. The process was repeated
with the dextrorotatory products with a resultant specific rotation of \(+20.12^0\).
This amounted to a 77% resolution of the (+)-isomer and a 79% resolution of
the (-)-isomer.

In the course of studying the optical activity of (+)-N-acetyl-α-phenyl-
ethylamine (16), Nerdel and Liebig reported a resolution by multiple re-
crystallization from a benzene-petroleum ether solvent system. The
authors reported that an 80 to 90% yield of completely resolved material was
isolated in this way.

Multiple recrystallizations were used to resolve 1,5-di-(p-chlorophenyl)-1,5-di-(t-butyl)pentatetraene (17). When attempts at obtaining optically
pure cumulene by asymmetric dehydration of the racemic glycol (18) failed,
the authors resorted to multiple recrystallizations. When racemic material
was recrystallized, two levorotatory crops were obtained. These were re-
combined and recrystallized to a constant specific rotation of \(-467^0\). The
moter liquor from the recrystallizations was concentrated and crystals ob-
tained from it. This material was then recrystallized to a constant specific
rotation of \(+447^0\).

One case of a resolution of a solid solution by multiple recrystallization
has been well documented. Synthetic 2,4-dioxo-3,3-diethyl-5-methyl-
piperidine (19) exhibited a finite optical rotation after one recrystallization.
In order to solidify this observation a 10 g sample of the racemic piperidine
was recrystallized. After this single recrystallization 4.6 g of material
was recovered with a specific rotation of \(-6.2^0\). The mother liquor yielded
solid material with a specific rotation of \(+4.1^0\). Then in a marvelous dis-
play of repetition, 20 kg of the racemic piperidine was recrystallized 400
times to a constant rotation. The 3 g isolated after the recrystallizations
had a specific rotation of \(+124^0\). By going through the same procedure with
another sample, 2 g of material was isolated with a specific rotation of \(-118^0\).

The first of two intriguing cases involving the use of pyridine was
reported by R. C. Ferreira in 1953. Racemic narcotine was dissolved in
dilute hydrochloric acid and pyridine was slowly added to the solution,
causing the alkaloid to precipitate. The precipitate was reported to be
from 1.0 to 2.5% resolved. Laudanosine was also resolved in this way.

The report of the second case of this type was stimulated by Ferreira's publication. E. Darmois described an experiment carried out in 1927 in which the resolution of adrenaline was effected in exactly the same way as Ferreira with one important exception: The precipitates were collected and resubjected to the treatment in a kind of multiple fractionation procedure. After five treatments, a constant rotation of +56.4° was obtained.

Another technique that has been used is the formation of inclusion compounds that crystallize as separate (+)- and (-)-forms. Since urea inclusion compounds were first reported in detail, they have been studied extensively. Schlenk was the first to study the inclusion compounds of urea and thiourea. The important fact to be considered here, however, is that both urea and thiourea form crystalline adducts which resolve spontaneously into (+) and (-)-crystals. These adducts with organic compounds belong to the D₅ symmetry class and, thus, consist of chiral spirals with the included molecule on the inside. When an experiment with racemic 2-chloro-octane, it was predicted that a type of diastereomeric influence would produce an adduct of which one combination would have a lower solubility than the other. This prediction was borne out when the complex was decomposed, leaving 2-chloro-octane 95.6% resolved.

Other inclusion compounds that have been studied extensively are those of tri-α-thymotide adducts. When tri-α-thymotide (20) crystallizes from methanol, no adduct is formed. The disymmetric molecules crystallize as a racemate, as indicated by the space group P2₁.

When tri-α-thymotide is crystallized from a solution, a variety of solvent molecules are included into the (+)- and (-)-clathrate crystals. Two major crystal structures have been proposed for the addition compounds—cavity and channel types. The type of inclusion compound formed is dependent on the length of the solvent molecule.

The cavity types are formed by crystallization from small solvent molecules such as ethanol. All cavity types crystallize in P₃₁₂₁, which dictates that only chiral crystals may be formed. The guest molecules fit into the short cavities in the tri-α-thymotide skeleton.

When longer solvent molecules are used such as pentanol, the adduct crystallizes in the channel type configuration. The space groups of the channel adducts vary with the length of the included molecule. However, all exhibit a spiral channel in which the tri-α-thymotide molecules necessarily have the same chirality.

In both types of adduct the tri-α-thymotide molecules are in the configuration of left- and right-handed propellers as indicated by an nmr study. Single crystals of the benzene adduct have shown specific rotations of +63 and -77 degrees.

A recent study used three techniques to carry out the resolution of 1,1'-binaphthyl (21). Resolution occurred when melted samples were allowed to resolidify. Ten samples gave specific rotations after crystallization of -128, -17, +5, -76, -170, -146, -114, -115, +94, and -97 degrees.

A second procedure utilized the polymorphic nature of the compound to effect the resolution. Samples containing the low melting form were heated to 150°. At this temperature the low melting form melts and recrystallization of the high melting form produces a resolution. One application of the procedure resulted in material with a specific rotation of +120°.

The third procedure involves a resolution in the solid state. Solid neat samples of slightly optically active material of the low melting form were heated at 105° for 12 days, yielding a high melting sample with a specific rotation of +220°. Resolutions in this manner have produced material with specific rotations as high as 245°. The best resolution by diastereomeric methods has yielded material with a specific rotation of 190°.

An additional technique that has been used is the direct formation of
optically active material. Havinga\textsuperscript{51},\textsuperscript{52} reported the spontaneous resolution of methylethylallylanilinium iodide. Saturated solutions of the compound were filtered carefully through glass and sealed in glass tubes. The samples were left at zero degrees until crystallization occurred. The samples stood for one year until crystallization was induced by strong cooling. Out of seven samples, three were inactive, two dextrorotatory, and two levorotatory. An attempted resolution by the formation of diastereomers produced a molecular rotation of 16°.\textsuperscript{53} However, molecular rotations of 63° were obtained in the Havinga study.

An explanation of the previous results has been made. Once the crystal nucleus is formed, one enantiomer is rapidly added to it. In the solution, the deficiency of the enantiomer crystallizing is compensated for by racemization of the other isomer. In this way, crystallization may continue until all of the material has been converted to one enantiomer in the crystal.

\[ \text{CONCLUSION} \]

Although a variety of compounds spontaneously resolve, it is not possible to predict when this type of behavior will be exhibited. This is due to a lack of an understanding of the crystallization process and the structure of crystals. However, the phenomenon is much more common than is generally expected and its understanding may be a key to the understanding of the crystallization process.

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ELECTROXIDATION OF AROMATIC HYDROCARBONS AND AMINES

Reported by Edmund F. Perozzi

May 13, 1971

Electrode oxidations and reductions of organic substrates have received increased attention in recent years. Anodic oxidations of many classes of organic compounds have been well reviewed for the years prior to 1968. This seminar will survey subsequent work on mechanisms of electroxidation of aromatic hydrocarbons and amines.

TECHNIQUES

An important technique for the qualitative elucidation of organic electroxidation mechanisms is cyclic voltammetry. A triangular wave is applied to a solid working electrode. Oxidation of a substrate at the working electrode is followed by reduction of the oxidized substances at the same electrode. The entire process may be repeated in a cyclic manner. Other methods such as chronopotentiometry and chronooamperometry are useful for quantitative determinations. These and other techniques have been reviewed by Adams. 5

AROMATIC HYDROCARBONS

Anthracene in acetonitrile-acetic acid (3:1) solution has been shown to undergo an initial one-electron oxidation to form a cation-radical in a step followed by reaction with acetic acid to give 2. The intermediate 2 may then be oxidized to 9-acetoxyanthracene (3). Since 3 is easier to oxidize than the parent anthracene, oxidation continues, with production of blanthrone (4). The initial three steps constitute and "ECE" mechanism, i.e., electrical, then chemical, and finally electrical steps. A similar mechanism is involved in the electroxidation of 9-phenylantracene 7 and 9,10-diphenylantracene. 8,9 With the former substrate, oxidation in acetonitrile-acetic acid (3:1) containing sodium acetate gave products 5 and 6. Oxidation of 9,10-diphenylantracene was also shown by means of a rotating disk electrode to proceed by an ECE mechanism. Here the chemical step may be "outrun" by rotating the electrode fast enough. In a separate study 9,10-diphenylantracene and 9,10-dimethylantracene have been used to establish nucleophilicity in anode processes. 10 The difference in steric hindrance offered by the lutidine isomers was used as a probe for the reaction mechanism.

Chemiluminescence is a phenomenon which has been shown to occur during several electrode reactions. It was noticed in the reaction of 9,10-diphenylantracene cation with sodium methoxide, and also with the same cation and the anion of 9,10-diphenylantracene. The latter effect is explained as an annihilation of a cation and an anion, producing an excited singlet which may emit a photon upon relaxation to the ground state. In the case of rubrene, the solvent dimethylformamide became the electron donor, forming solvent radicals. 12

AROMATIC AMINES

Aromatic amines appear to undergo a wider scope of electrochemical reactions. Diphenylamine systems (e.g., 7) were examined and were found to lose two electrons in an apparent one-step oxidation, followed by a chemical step to produce benzoquinone and various substituted anilines (e.g., 8) in an EC process. 13 N,N-Dimethylaniline, however, goes through a very complex mechanism to produce crystal violet (9). 14

In an experiment with optically transparent electrodes, Kuwana and Strojek were able to determine spectrophotometrically that the oxidation of o-toluidine (10) goes through a charge transfer intermediate by an EE process. 15

A typical ECE process was shown by electrolysis of carbazole. The coupling products of the electroxidation (e.g., 11) were correlated with HMO calculations.
REARRANGEMENTS IN ORGANO SILICON COMPOUNDS: RECENT MECHANISTIC STUDIES

Reported by Donald S. Mueller    May 17, 1971

Organo silicon compounds, like carbon compounds, rearrange via cationic, anionic, radical, and concerted pathways, depending upon the conditions employed. Participation by silicon's 3d orbitals, which permit electron delocalization and orbital overlap unavailable to carbon, 1 is the explanation given for most deviant rearrangements (as compared to carbon systems) observed in organosilicon compounds.

Cationic mechanisms are proposed for rearrangements which occur in the presence of Lewis acids. 2-5 These acids initiate the formation of siliconium ions (R₃Si⁺) or other positively-charged intermediates (the formal existence of siliconium ions is disputed) 6-8 and then quench the rearrangement. For example:

\[
\begin{align*}
\text{CH}_3 - \text{Si}-\text{CH}_2\text{Cl} + \text{AlCl}_3 & \rightarrow \text{CH}_3 - \text{Si}-\text{CH}_2\text{Cl}^+ + \text{AlCl}_4^- \rightarrow \text{CH}_3 - \text{Si}-\text{CH}_2\text{Cl} + \text{AlCl}_4^- \\
\text{C(CH}_3)_3 & \rightarrow \text{C(CH}_3)_3 & \rightarrow \text{C(CH}_3)_3
\end{align*}
\]

Silyl anions, unlike carbanions, are pentacovalent species. They are most often proposed in bimolecular reactions 6 rather than in rearrangements. This seminar will deal solely with rearrangements in which anion formation occurs on an atom attached to the silicon atom.

Intramolecular organosilyl migrations from N→N (1,2); 1,2; 1,4; 10; and 1,5; and (1,2) from C→N 11, C→O 12, and C→Cl 13 have been shown to proceed very rapidly under basic conditions. For example:

\[
\begin{align*}
\text{Ph} & \rightarrow \text{Ph} \rightarrow \text{Ph} \\
\text{N-SiMe}_3 & \rightarrow \text{N-SiMe}_3 & \rightarrow \text{N-SiMe}_3
\end{align*}
\]

Radical rearrangements are proposed in the thermolysis of silanes at elevated temperatures and in peroxide-induced rearrangements. Intramolecular (1,2) migrations of organosilyl groups from Si→Si 14-16 and Si→Si 19 and of phenyl groups from C→Si 1,5; 1,4; and 1,5 22-24, and Si→O (1,2) 25 via radical pathways have now been reported. For example:

\[
\begin{align*}
\text{C(CH}_2\text{)}_3\text{SiMe}_2 + \text{DTBP} & \rightarrow \text{C(CH}_2\text{)}_3\text{SiMe}_2 \\
\text{Me} & \rightarrow \text{Me} & \rightarrow \text{Si(CH}_2\text{)}_3\text{Me}
\end{align*}
\]

- 220 -
Concerted mechanisms, most likely involving [1,5] sigmatropic shifts of silyl groups, in cyclopentadienyl and indenyl systems also were recently reported. For example:

\[
\begin{array}{c}
\text{SiMe}_3 \\
\text{H}
\end{array} \quad \Rightarrow \quad \begin{array}{c}
\text{H} \\
\text{SiMe}_3
\end{array} \quad \Rightarrow \quad \begin{array}{c}
\text{SiMe}_3
\end{array}
\]

BIBLIOGRAPHY

THE PHOTOCHEMICAL AND THERMAL DECOMPOSITION OF METAL CARBOXYLATES

Reported by Donald J. Hart
May 20, 1971

INTRODUCTION

The oxidation of olefins and aromatic hydrocarbons by various higher valent metal acetates, e.g., M(OAc)$_n$ [M = Hg(II),$^{1-3}$ Pb(II),$^{4-6}$ Tl(III),$^{1,3,7,8}$ Pb(IV)$^{1,6,9}$], via formation of an oxymetallation adduct, $^1$, has been well studied.

$$\begin{align*}
\text{H}_2\text{C} &= \text{C} + M\text{(OAc)}_n & \text{H}_2\text{C} &= \text{C} \\
\quad & \quad + \quad & \quad + \\
\quad & \quad M\text{(OAc)}_n & \quad & \quad \text{M(OAc)}_{n-1}
\end{align*}$$

Oxidations of this type occur at or near room temperature (< 40°C) and yield mostly diacettes and allylic acetates. More recently, considerable attention has been given to the study of the photochemical and thermal decomposition of metal carboxylates using such metals as Pb(IV), Co(III), Tl(III), Ce(IV), and Mn(III). In the presence of carboxylic acids, these salts decompose to alkanes, alkenes, esters, and other decomposition products. Reactions with olefins and aromatic hydrocarbons lead to products derived from formation of free radicals. It is the purpose of this seminar to cover the work done in this area.

MECHANISTIC PATHWAYS

Metal carboxylates decompose by either a decarboxylative pathway, equation (1), or a nondecarboxylative pathway, equation (2).$^*$ The resulting radicals can then further react to give products derivable from them.

$$\begin{align*}
\text{M(O}_2\text{CCHR}_1\text{R}_2) & \rightarrow [\cdot \text{O}_2\text{CCHR}_1\text{R}_2] \rightarrow \text{CO}_2 + \cdot \text{CHR}_1\text{R}_2 & \text{(1)} \\
\text{M(O}_2\text{CCHR}_1\text{R}_2) & \rightarrow \text{HOOCCHR}_1\text{R}_2 & \text{(2)}
\end{align*}$$

DECOMPOSITION OF METAL CARBOXYLATES IN THE PRESENCE OF CARBOXYLIC ACIDS

The study of the decomposition of lead(IV) carboxylates has accounted for the majority of work done in metal carboxylate decomposition studies. Although it was originally assumed that lead(IV) underwent a direct two-equivalent transformation to lead(II) with concomitant formation of carbonium or other cationic species, Kochi$^{10}$ was able to show that the thermal and photochemical decompositions of lead(IV) carboxylates proceed via pathway (1). Scheme I shows the mechanism proposed.$^{10,11}$ Combination or disproportionation products arise from $S^*$ (step 3), where HS is usually the solvent. Equation (3) is assumed to be rapid. Analogous mechanisms exist for the thermal decomposition of cobalt(III)$^{13-16}$ and cerium(IV)$^{17,19}$carboxylates and for the photochemical decompositions of thallium(III)$^{18}$ and cerium(IV)$^{17,19}$carboxylates.

Manganic(III) acetate decomposes thermally via pathway (2).$^{20}$ The formation of carboxyalkyl radicals, 2, occurs via a reaction such as shown in equation (11). The decarboxylative pathway, equation (1), for the decomposition of manganic(III) carboxylates was shown to exist, however, when acetate was not used as the ligand.$^{21,22}$ When $R_1 = R_2 = H$, pathway (2) is predominant (97-99.3%)$^{21,22}$; when $R_1$ or $R_2 = \text{alkyl}$, pathway (1) is followed to some extent (6% when manganic propionate is used)$^{22}$; when $R_1$ or $R_2 = \text{benzyl}$, pathway (1) is the predominant route of decomposition.$^{21}$

Tertiary carboxylates give 100% pathway (1) as no $\alpha$-hydrogen atoms are available for abstraction.$^{22}$ These results are probably due to a steric effect.

The photochemical decomposition of manganic(III) and cobaltic(III) carboxylates and the thermal decomposition of thallium(III) carboxylates have not been studied to date.

---

$^*$ Equations (1) and (2), as well as many of the other equations in this abstract, are not balanced.
Scheme I

\[
Pb^{IV}(OAc)_4 + n \text{RCOOH} \rightleftharpoons Pb^{IV}(OAc)_{4-n}(O_2CR)_n + n \text{HOAc} \quad (3)
\]

Initiation:

\[
Pb^{IV}(O_2CR)_4 \rightarrow Pb^{III}(O_2CR)_3 + R^* + \text{CO}_2 \quad (4)
\]

Propagation:

\[
Pb^{III}(O_2CR)_3 \rightarrow Pb^{II}(O_2CR)_2 + R^* + \text{CO}_2 \quad (5)
\]

\[
R^* + Pb^{IV}(O_2CR)_4 \rightarrow Pb^{III}(O_2CR)_3 + R^+ + \text{RCO}_2^\ominus \quad (6)
\]

Termination:

\[
R^* + Pb^{III}(O_2CR)_3 \rightarrow Pb^{II}(O_2CR)_2 + R^+ + \text{RCO}_2^\ominus \quad (7)
\]

\[
R^* + \text{HS} \rightarrow RH + S^* \quad \text{(HS= hydrogen donor)} \quad (8)
\]

\[
R^+ + O_2CR \rightarrow \text{RO}_2CR \quad (9)
\]

\[
R^+ + \text{O}_2CR \rightarrow \text{RO}_2CR \quad (10)
\]

\[
R_1R_2\text{CHCOO} + \text{Mn(OAc)}_2 \rightarrow \text{R}_1\text{R}_2\text{CHCOOH} + \text{Mn(OAc)}_2 \quad (11)
\]

PRODUCTS OF DECOMPOSITION OF ACIDS

It was found\textsuperscript{17} that straight chain acids decarboxylated photochemically in the presence of cerium (IV) acetate primarily to alkanes. \(\alpha\)-Branched acids gave a mixture of alkanes and oxidation products (alkenes, esters, and other products derived from carboxonium ion intermediates). \(\alpha\)-Dibranched acids, however, yielded oxidation products exclusively. This is in accord with the gas-phase ionization potentials for these radicals (see Table I).\textsuperscript{23} As an example of these generalizations,\textsuperscript{17} acetic acid gave 77\% methane and only 3\% methyl acetate. \(n\)-Butyric acid formed 95\% propane and only 2\% propylene. Approximately 0.1\% \(n\)-propyl butyrate and isopropyl acetate and butyrate were also formed. Isobutyric acid gave 64\% propane, 14\% propylene, 3\% isopropyl isobutyrate, and 1\% isopropyl acetate. In contrast, pivalic acid gave 72\% isobutylene, 4\% t-butyl acetate, 4\% t-butyl pivalate, and only 0.1\% isobutane. These decarboxylations apply to such acids as cyclobutanecarboxylic acid as well.\textsuperscript{24} The slower oxidation (eq. 6) of primary radicals and competition from other facile radical reactions (eq. 8) lead primarily to non-oxidative products.

Similar products were obtained in the photochemical decarboxylation of acids in the presence of lead tetraacetate (LTA)\textsuperscript{19,25,26} and in the thermal decarboxylation of acids with lead(IV)\textsuperscript{10,12} and cobaltic\textsuperscript{16} acetate. It was assumed that the alkanes were formed by direct reactions of radicals, whereas the oxidation products (alkenes and esters) were formed from carboxonium ions.\textsuperscript{10,12}

A free radical process for the decarboxylation of acids is supported by the fact that oxygen inhibits the reaction and gives products derivable from radical-oxygen reactions.\textsuperscript{11} Alkyl and alkyldi(proxy) radicals have also been detected by esr.\textsuperscript{12} Chloroform, being a good hydrogen donor, gave significant quantities of isobutane from the photochemical reaction of pivalic acid and ceric acetate, although large amounts of isobutylene remained.\textsuperscript{17} Butyl radicals derived from valeric acid were also effectively trapped by 1,3-butadiene to give a mixture of allylic acetates.\textsuperscript{11}
In contrast to the other metal carboxylates, thallium(III) carboxylates gave slightly different products. The photochemical decomposition of thallium(III) carboxylates was studied at 2537 Å and 3500 Å. Valeric acid gave large quantities of alkanes and dimers as shown in Table 2. A number of other primary acids gave a similar distribution of products. Secondary acids gave a higher yield of alkenes and esters at the expense of alkanes and dimers at both wavelengths. Tertiary acids gave predominantly alkenes with low amounts of dimers at both wavelengths.

To account for these results the mechanism shown in scheme II was postulated. At 2537 Å, enough energy is present to leave the initially formed (eq. 12) metastable thallium(II) species in an excited state which quickly decomposes (eq. 13) leaving two radicals very close to each other which can then form dimers. However, at 3500 Å the metastable thallium(II) species is in a less energetic state and fragments (eq. 13) slowly to reduce the incidence of binolecular radical interactions; hence, lower amounts of dimers are produced.

Manganic acetate in refluxing acetic acid gave 20% acetoxyacetic acid, HOOCH₂OAc, and minor amounts of succinic acid, methylene diacetate, and methyl acetate. Only 2% methane was formed. Scheme III shows the mechanism proposed. Step (16) is just the exchange of ligands on manganese(III), which is analogous to the exchange of ligands on lead(IV) (equation 3). Manganic propionate in benzene gave greater than 5% ethylbenzene. Similar results in chlorobenzene suggest that some decarboxylation occurs to form ethyl radicals.

To determine the relative rates of decarboxylation of primary, secondary, and tertiary acids, the competitive photochemical decarboxylation of pivalic and isobutyric acids by LTA were studied at 30°. The relative rates were determined to be 5:0:1. When pivalic and n-butyric acids were used, the relative rates averaged 90:1. A similar study using pivalic, 2-methylbutyric, and isovaleric acids gave relative rates of 80:5:1 at 80° in benzene. Triphenylacetic and dimethylphenylacetic acids were even faster. The relative rates of decarboxylation of pivalic, isobutyric, and n-butyric acids were 90:7:1 in the presence of ceric carboxylates.

### Table 1. Ionization Potentials of Radicals

<table>
<thead>
<tr>
<th>Radical</th>
<th>I.P. (eV)</th>
<th>Example</th>
<th>I.P. (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>8.3 - 8.7</td>
<td>neopentyl</td>
<td>8.33</td>
</tr>
<tr>
<td>Secondary</td>
<td>7.7 - 7.9</td>
<td>3-pentyl</td>
<td>7.86</td>
</tr>
<tr>
<td>Tertiary</td>
<td>7.1 - 7.4</td>
<td>t-pentyl</td>
<td>7.12</td>
</tr>
</tbody>
</table>

### Table 2. Products of Tl(OAc)₃ and Valeric Acid

<table>
<thead>
<tr>
<th>λ (Å)</th>
<th>n-C₄H₁₀</th>
<th>n-C₆H₁₃</th>
<th>l-C₄H₆</th>
</tr>
</thead>
<tbody>
<tr>
<td>2537</td>
<td>31</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>3500</td>
<td>69</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

\[ (\text{RCO}_2)_3\text{Tl}^{\text{III}} \xrightarrow{h\nu} (\text{RCO}_2)_2\text{Tl}^{\text{II}} + R + \text{CO}_2 \] (12)

\[ (\text{RCO}_2)_2\text{Tl}^{\text{II}} \xrightarrow{\text{fast}} (\text{RCO}_2)\text{Tl}^{\text{I}} + R + \text{CO}_2 \] (13)
This V+ (20) > (l5) .

Pyridine Cu(l) .

Mn(OAc)2 + HOAc —————> HOAc + Mn(OAc)2 + CH3COOH (11)

HOOCC6H4 + Mn(OAc)3 —————> HOOCC6H4OAc + Mn(OAc)2 (14)

2 HOOCC6H4 —————> HOOCC6H4COOH (15)

HOOCH2COO + Mn(OAc)3 —————> AcOCH2COO-Mn(OAc)2 + HOAc (16)

AcOCH2COO-Mn(OAc)2 —————> AcOCH2 + CO2 + Mn(OAc)2 (17)

AcOCH2 + Mn(OAc)3 —————> AcOCH2OAc + Mn(OAc)2 (18)

**CATALYTIC EFFECTS**

It was found that pyridine had an accelerating effect on the rate of decomposition of acids in the presence of LTA.10,11 This can be explained as follows.11 Pyridine complexes with lead(IV) carboxylates, 3, to form the pyridine adduct, 4. Species such as 3 are relatively stable and undergo homolysis rather slowly. However, the formation of pyridine complexes such as 4 can weaken the bonds to the carboxylato ligands so that decarboxylation occurs more readily.

\[
\text{Pb}^{IV}(O_2\text{CR})_4 + m \text{Py} \rightarrow \text{Pb}^{IV}(O_2\text{CR})_4(\text{Py})_m, \quad \text{where Py = pyridine} \quad (19)
\]

Formation of pyridine complexes such as 4 suggests that other species similar to 4 can be formed and general catalysis by nucleophiles should be observed. Indeed, acetate, halides, cyanide, and thiocyanate initiate rapid decomposition of lead(IV) carboxylates.11 Alkyl halides are formed from lead(IV) esters and halides11,27-30 while alkyl cyanides result when cyanide is the nucleophile.11

This nucleophilic reaction with halides has good synthetic value29,31,32 and is applicable to secondary, tertiary, and benzylic acids as well as primary acids. For example, cyclobutyl and neopentyl groups are converted to the corresponding chlorides without rearrangement.31

The addition of a catalytic amount of cupric acetate has an enormous accelerating effect on the rate of decomposition of the metal carboxylates in addition to changing the distribution of products.10,11 Equations (20) and (21), which were shown to occur at rates close to diffusion controlled,10,33 account for the accelerating effect in the presence of LTA. Equations (20) and (21) replace equation (6) (scheme I) in the presence of cupric salts. The almost quantitative yield of 1-butene observed in the decarboxylation of valeric acid in the presence of cupric acetate is expected in view of the fact that the oxidation of butyl radicals by cupric acetate leads cleanly to \( \beta \)-elimination of a hydrogen atom with no rearrangement of the carbon skeleton.34 Similar catalysis was obtained with cupric salts in the presence of the other metal carboxylates.10,17,21

The effect of copper(II) salts on the decarboxylation of acids is to cause the exclusive production of alkenes, whether the acid is primary, secondary, or tertiary. The greatest effect is on primary acids12-25 and the least effect is on tertiary acids.

Alkenes and esters are the major products from carboxylic acids (tertiary, secondary, primary, and even acetic) in the presence of such silver(II) salts as silver(II) picolinate, 5,35 Small amounts of alkanes are obtained as well, but silver(II) must be similar in oxidative power to copper(II).

Strong acids increase the rate of decomposition of ceric carboxylates while increasing the yields of alkenes and esters and decreasing the yields of alkanes.17 A cationic species, 6, is proposed which is assumed to oxidize the resulting radicals at a faster rate than the neutral species.17 This increase of rate with strong acid is general with Pb(IV), Mn(III), Co(III), and Tl(III).

\[
R^+ + \text{Cu(II)} \xrightarrow{\text{fast}} R^\Delta + \text{Cu(I)} \quad (20)
\]

\[
\text{Cu(I)} + \text{Pb(IV)} \xrightarrow{\text{fast}} \text{Cu(II)} + \text{Pb(III)} \quad (21)
\]
REATIONS OF METAL CARBOXYLATES WITH OLEFINS

Metal carboxylates decompose in the presence of olefins to give mixtures of \(\gamma\)-lactones and esters (equation 23). Lead(IV) salts give large amounts of \(\delta\), \(9\), \(3,37\) and only small amounts of \(\zeta\), \(9\), \(37\) In contrast, the decomposition of manganic acetate in the presence of olefins affords a good synthetic route to \(\gamma\)-lactones, \(36\), \(4,43\) giving good yields with most olefins. The high yields of lactones and lack of observed methyl acetate adducts suggest that \(\cdot\text{CH}_2\text{COOH}\) adds to olefins much faster than it is oxidized by manganic acetate. \(35\) LTA, in contrast, gives only minor amounts of lactones because \(\cdot\text{CH}_2\text{COOH}\) radicals are not directly produced in its decomposition. The mechanism in scheme IV accounts for these products. Analogous mechanisms exist when other carboxylic acids are present. Ceric carboxylates also give high yields of \(\zeta\), while giving very little \(\delta\), \(1,19\). This result indicates that cerium carboxylates decompose thermally by pathway (2) in the presence of olefins. In the photochemical reaction of cerium (IV) carboxylates with olefins, large amounts of \(\delta\) were obtained with only small amounts of \(\zeta\), \(1,19\) indicating that pathway (1) is the predominant pathway for photochemical decompositions of ceric carboxylates. The decomposition of other metal carboxylates has not been studied in the presence of olefins.
The reaction of styrene and LTA in acetic acid was studied as a function of temperature. Four products were obtained in significant yield, none of them being lactones. Table 3 shows the distribution of products with

\[
\begin{align*}
\text{PhCH}=\text{CH}_2 & \xrightarrow{\text{LTA} + \text{HOAc}} \text{PhCH}=\text{CH}_2\text{CH}_3 + \text{PhCH}=\text{CH}_2\text{OAc} + \text{PhCH}=\text{CH(OAc)}_2 + \text{PhCHO} \\
& \text{Temp}(\degree \text{C}) & 8 & 2 & 10 & 11 \\
80 & 0.75 & 49 & 3 & 10 & 2 \\
60 & 4 & 29 & 7 & 21 & 2 \\
40 & 15 & 1 & 5 & 45 & 3
\end{align*}
\]

Table 3. Effect of Temperature on Reaction Products of LTA and Styrene

This temperature dependence on the distribution of products is consistent with the observed products derived from the oxymetallation adduct (1) at lower temperature and the observed products derived from decarboxylation at higher temperature.

**REACTIONS OF METAL CARBOXYLATES WITH AROMATIC HYDROCARBONS**

The decomposition of LTA in benzene and toluene was reported prior to 1965. Recently, other metal carboxylate decompositions have also been studied in the presence of aromatic hydrocarbons. Products obtained from the reaction of metal acetates and toluene are shown in equation (26). Table 4 shows the distribution of products in typical reactions. The proposed mechanism to account for these products is shown in scheme V. Ortho and meta isomers are also obtained. For LTA, pathway (2) does not occur. Applying a steady-state treatment to scheme V for LTA leads to equations (27) and (28). A plot of \([12]/[14]\) vs. \([\text{HOAc}]/[\text{PhCH}_3]\) gives a straight line with an intercept \((k_1/k_u)\) of 2.9, indicating that methyl radicals abstract \(\alpha\)-hydrogen atoms from toluene about three times as fast as they add to the aromatic ring. A plot of \([12]/[13 + 15]\) vs. \([\text{PhCH}_3]/[\text{HOAc}]\) gives an intercept \((k_3/k_u)\) of 0.27. Thus, \(\text{CH}_2\text{COOH}\) adds to toluene faster than it abstracts a benzylic hydrogen atom. This is probably due to the greater stability and electronegativity of \(\cdot\text{CH}_2\text{COOH}\).

Although manganic acetate gave the same products with toluene (except for \(14\)) as did LTA, the ratio of \([12]/[13 + 15]\) was constant and independent of the \([\text{PhCH}_3]/[\text{HOAc}]\) ratio used. This indicated that \(\cdot\text{CH}_2\text{COOH}\) radicals form directly from manganic acetate. The reaction of toluene with ceric acetate also gave a constant \([12]/[13 + 15]\) ratio, again indicating that in the presence of radical traps such as olefins and aromatic hydrocarbons, ceric carboxylates decompose via pathway (2).

When the reaction between toluene and ceric acetate was run in a mixture of acetic anhydride and acetic acid, only 12 and 15 were formed. These modified reaction conditions were found to be ideally suited for the simple one-step preparation of arylacetic acids from aromatic hydrocarbons.

Addition of cupric acetate to the reaction of toluene and manganic
acetate decreased the yields of 12, 13, and 15 by more than 90% due to the rapid oxidation of the \( \cdot \text{CH}_2\text{COOH} \) radical by copper(II).\textsuperscript{21}

The reaction of \( \text{p-methoxytoluene} \) with manganic acetate gave \( \text{p-methoxybenzyl acetate} \) and isomeric \( \cdot \text{CH}_2\text{OAc} \) adducts in a 20:1 ratio.\textsuperscript{21,50} This large ratio is inconsistent with the reactivity of the \( \cdot \text{CH}_2\text{COOH} \) radical which would predict a much smaller ratio (see Table 4).\textsuperscript{21,48} These data indicate the existence of a second competing pathway which leads exclusively to \( \text{p-methoxybenzyl acetate} \). Scheme VI shows the mechanism proposed by Dewar and co-workers.\textsuperscript{55} Similar results were obtained using \( \alpha- \) and \( \beta-\text{methoxy-naphthalenes.} \textsuperscript{21,51} \) When potassium bromide was used as a catalyst, similarly large ratios of benzyl acetates were formed from a series of substituted toluenes.\textsuperscript{52}

Finkbeiner and Bush\textsuperscript{38} have argued that the \( \cdot \text{CH}_2\text{COOH} \) radical is not the attacking species in the decomposition of manganic acetate. Their argument was based on the distribution of isomers from chlorobenzene and manganic acetate,\textsuperscript{38,53,54} lack of polystyrene formation,\textsuperscript{38,55} and inertness of methyl benzoate to the reaction.\textsuperscript{56,56} They suggested that the attacking species is a 2-electron oxidant, 16. However, arguments against Finkbeiner's and Bush's objections to \( \cdot \text{CH}_2\text{COOH} \) have been given.\textsuperscript{49}

The decomposition of cobaltic acetate in the presence of toluene led predominantly to benzyl acetate and benzaldehyde.\textsuperscript{57} The very small amount of \( \cdot \text{CH}_2\text{OAc} \) adducts, as opposed to the large amounts of these adducts with manganic acetate and LTA, and the negligible effect copper(II) had on the reaction, indicated a mechanism like that represented in scheme VI.

A possible reaction of the radical cation intermediate, 17, formed as in scheme VI (equation 29), is the attack of a nucleophile on the aromatic nucleus. This was found to be the case in the presence of high chloride ion concentrations.\textsuperscript{57}

**SUMMARY**

Metal carboxylates decompose thermally or photochemically via either a decarboxylative pathway (eq. 1) or a nondecarboxylative pathway (eq. 2) to yield products derived from free radicals. In the presence of carboxylic acids, these salts decompose to alkanes, alkenes, esters, and other decomposition products. The addition of copper(II) salts increase the decomposition rates and affords a good synthetic route to olefins. Alkyl halides are produced in the presence of halides. Lactones are produced in good yields from the reaction of olefins and manganic or ceric carboxylates. Arylacetic acids are obtained in the presence of aromatic hydrocarbons, acetic anhydride, end ceric acetate.

\[
\begin{align*}
\text{CH}_3 & \text{N(OAc)}_n \text{HOAc} \\
\text{CH}_3 & \text{CH}_2\text{OAc} \\
\text{CH}_3 & \text{CH}_2\text{OAc} \\
\text{CH}_3 & \text{CH}_2\text{OAc} \\
\text{CH}_3 & \text{CH}_2\text{OAc} \\
\end{align*}
\]

\text{12} \quad \text{13} \quad \text{14} \quad \text{15} \quad \text{(26)}

**Table 4. Product Distribution in Reactions of Toluene and Metal Acetates**

<table>
<thead>
<tr>
<th>Metal</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb(IV)</td>
<td>32</td>
<td>23</td>
<td>9</td>
<td>5</td>
<td>48\textsuperscript{a}</td>
</tr>
<tr>
<td>Mn(III)</td>
<td>13</td>
<td>33</td>
<td>0</td>
<td>27</td>
<td>21,49</td>
</tr>
<tr>
<td>Ce(IV)</td>
<td>12</td>
<td>26</td>
<td>0</td>
<td>18</td>
<td>19</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Product distribution varies with \([\text{PhCH}_3]/[\text{HOAc}]\) ratio.
Scheme V

\[
\frac{d[12]}{d[14]} = \frac{k_2}{k_5} \left( \frac{\alpha}{\alpha+1} \right) \frac{[M(OAc)]}{[PhCH_3]} + \frac{k_4}{k_5} \tag{27}
\]

\[
\frac{d[12]}{d[15][15]} = \frac{k_3}{k_2} \left( \frac{\alpha}{\alpha+1} \right) \frac{[PhCH_3]}{[M(OAc)]} + \alpha \tag{28}
\]

where \(\alpha = \frac{k_3}{k_4}\).

Scheme VI

\[
\text{ArCH}_3 + Mn(OAc)_3 \xrightleftharpoons[K]{k'} (\text{ArCH}_3^+ \text{OAc}^-) + Mn(OAc)_2 \tag{29}
\]

\[
(\text{ArCH}_3^+ \text{OAc}^-) \xrightarrow{k'_1} \text{ArCH}_2^+ + \text{AcOH} \tag{30}
\]

\[
\text{ArCH}_2^+ + Mn(III) \xrightarrow{\text{fast}} \text{ArCH}_3^+ + Mn(II) \tag{31}
\]

\[
\text{ArCH}_2^+ + \text{AcOH} \xrightarrow{\text{fast}} \text{ArCH}_2\text{OAc} + H^+ \tag{32}
\]

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BIBLIOGRAPHY

54. Reference 55, p. 46.
AUTODICATION OF TRIALKYLBORANES

Reported by Robert J. Hauri
May 24, 1971

The autoxidation of trialkylboranes (the reaction of \( R_3B \) with molecular oxygen) has long been known but the mechanism has not been elucidated. It was originally thought that the autoxidation was a polar process involving 1,3-nucleophilic rearrangement to form organoperoxyboranes, \( 1 \), as shown in equation (1).\(^1\)\(^2\)\(^3\) A more familiar reaction, treatment of boranes with alkaline hydrogen peroxide, results in production of alcohols and is more useful from a synthetic viewpoint.\(^4\) A radical pathway for autoxidation was rejected for several reasons,\(^5\) the primary one being that certain inhibitors had no effects on reaction rates. Shortly thereafter, evidence was accumulated indicating the earlier assumptions were incorrect and that the autoxidations proceed via free radicals.\(^6\)\(^7\)

The syntheses of trialkylboranes used in the mechanistic studies has been adequately summarized.\(^4\) The most common methods involve catalytic addition of borohydrides to olefins, addition of diborane, \( R_2B_2 \), to olefins, and treatment of alkyl Grignard reagents with either boron trifluoride etherate or trimethyl borate.

Davies and Roberts\(^8\)\(^9\) determined that a homolytic mechanism was operative in boron-carbon bond cleavage. Optically active 1-phenylethylboronic acid, when treated with oxygen followed by hydrolysis, yielded 1-phenylethyl hydroperoxide \( 2 \), which had lost all optical activity. By use of powerful radical scavengers,

\[
\begin{align*}
\text{Ph} & \quad \text{CHOOH} \\
\text{Me} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{B} - \text{CH} \\
& \quad \text{C}_2\text{H}_5
\end{align*}
\]

it was determined that the autoxidation must proceed through a free radical intermediate, with 99% racemization. Davies and Roberts\(^10\) have studied the autoxidation of three mixtures of the epimeric trinorborn-2-ylboranes and concluded that a homolytic chain mechanism involving a common norbornyl radical is involved. Similar loss of asymmetry in the sec-butyl group had been reported by Allies and Brindley\(^11\) in the autoxidation of diisopinocampheyl-sec-butylborane, \( 2 \).

Allies and Brindley\(^12\) followed the autoxidation rates of n-butyl, sec-butyl, and isobutyl boranes in benzene and found that the absorption of the first molecule of oxygen to form \( \text{RO}_2\text{BR} \), a peroxyborinic ester, is rapid, \( t_{1/2} < 2 \) sec, while absorption of the second molecule of oxygen to form \( \text{(RO}_2\text{)}_2\text{BR} \), a peroxyboronic ester, is considerably slower. At \(-40^\circ\text{C}\), the absorption of the second oxygen molecule was effectively stopped but even at \(-70^\circ\text{C}\), the uptake of the first molecule of oxygen by borane is fast indicating a very low activation energy for this process. Other authors\(^13\) were able to find \( \text{(CH}_3\text{)}_2\text{B(OCH}_3\text{)}_2 \) as the first detectable species in the autoxidation of trimethylborane at \(-196^\circ\text{C}\).
Recently, it was found that iodine added to THF solutions of trialkylboranes can inhibit uptake of oxygen for several days. The authors concluded that this experimental evidence was compatible with a slow rate of radical initiation followed by very fast chain propagation. Equation (2) was found to be dependent on the steric requirements of the borane and the rate of initiation was determined for this process.

A free radical mechanism consistent with the observable facts is shown in equations (2)-(5). The instability of the peroxide makes its isolation difficult

\[
\text{Initiation: } R_3B + O_2 \rightarrow R'. \\
R' + O_2 \rightarrow RO_2'. \\
RO_2'. + R_3B \rightarrow [RO_2BR_3'] \rightarrow RO_2BR_2 + R'. \\
RO_2BR_2 + RO_2' \rightarrow [(RO_2)_2BR_2'] \rightarrow (RO_2)_2BR + R'.
\]

and intermolecular redox reactions, (5), are significant. Radical scavengers, differing from those used in earlier work, proved useful in attempts to trap alkyl radicals produced in the initiation step, giving information about the rate of equation (2).

\[
RO_2BR_2 + R_3B \rightarrow 2ROBR_2
\]

Synthetic aspects of autoxidation were investigated by Brown and co-workers. The slow, controlled autoxidation of various trialkylboranes, followed by base-catalyzed hydrolysis of the intermediate per oxyborinic ester, gave alcohols in high yield with some loss of stereoselectivity. By autoxidation of trialkylboranes in the presence of alkyl iodides, equations (6)-(8), a chain transfer reaction is possible in which the alkyl group on boron is converted to the iodide before reaction with oxygen can take place. The synthetic utility of this reaction is that it provides a facile means of coupling benzylic and allylic iodides in high yields, equation (8), where R = Et and R' = benzyl, \( p \)-nitrobenzyl, allyl, or 2-methylallyl.

\[
R_3B + O_2 \rightarrow R_2BO_2'. + R'. \\
R' + R'I \rightarrow RI + R'. \\
2R'. \rightarrow R' - R'.
\]

BIBLIOGRAPHY

POLYMERIZATION OF CYCLIC ETHERS WITH ORGANOMETALLIC CATALYSTS

Reported by Jiro Yamamoto      May 27, 1971

Polymers derived from cyclic ethers have considerable industrial importance. For example, polypropylene glycol of low molecular weight, a viscous liquid obtained from the polymerization of propylene oxide, is used in the manufacture of urethane elastomers and poly-3,3-bis(chloromethyl)oxacyclobutane (trade name, Pentone) is a useful plastic. Accordingly, many catalysts have been investigated for the polymerization of cyclic ethers.

In this seminar we shall be interested mainly in the mechanistic aspects of ionic polymerization of epoxides, oxetanes (oxacyclobutanes), and tetrahydrofuran catalyzed by organometallics involving mainly organo-aluminum and -zinc compounds. Typical monomers included are propylene oxide (PO), epichlorohydrin (ECH), 3,3-bis(chloromethyl)oxetane (BCMO), and tetrahydrofuran (THF).

Ionic polymerization of cyclic ethers may involve cationic, anionic, and coordinate anionic mechanisms; explanations of these mechanisms will be given in the following sections.

OXETANES

Oxetanes and tetrahydrofurans (THF) can be polymerized only by cationic catalysts. Oxetanes and tetrahydrofurans (THF) can be polymerized only by cationic catalysts. Oxetanes and tetrahydrofurans (THF) can be polymerized only by cationic catalysts.

Initiation of cationic polymerization of cyclic ethers involves coordination of a monomer to an acidic (or cationic) catalyst, followed by monomer attack on the α-carbon of the coordinated monomer to form the propagating species, trialkyloxonium ion (equation 1). Carbonium ion intermediates are absent in cationic polymerization, as was evidenced by the absence of rearrangement in the polymerization of 3-methyl-1-epoxybutane catalyzed by boron trifluoride and of THF with triethylxonium tetrafluoroborate catalyst. Oxonium ion intermediate is assumed also in polymerization of oxetanes. It is well known that the acid-catalyzed ring opening of epoxides proceeds by a border-line SN2 mechanism with inversion of configuration at the ring opening carbon.

Of various oxetane polymerizations that of 3,3-bis(chloromethyl)oxacyclobutane (BCMO) has been studied most extensively. The common catalyst for oxetane polymerization is boron trifluoride. An alkylaluminum compound alone can induce the polymerization of BCMO at relatively high temperature (80-220°C). In contrast, boron trifluoride catalyzes the polymerization of BCMO even at -50°C.

Treatment of triethylaluminum (AlEt3, Et = C2H5) with a small amount of water increases the Lewis acidity and an AlEt3-H2O catalyst ([H2O]/[AlEt3] = 0-1.5) induces a facile polymerization of BCMO at 0°C, with a maximum rate at [H2O]/[AlEt3] = 1.10 It was further found that addition of a small amount of a "promoter", such as propylene oxide (PO) or epichlorohydrin (ECH), and a "co-catalyst", such as acetyl chloride, to the polymerization mixture of BCMO and triethylaluminum or AlEt3-H2O catalyst remarkably enhanced the polymerization. The AlEt3-H2O-ECH (1:1:1) catalyst system was particularly powerful and polymerized BCMO with high conversion even at -78°C.

The reaction of water with aluminum alkyls was studied by several workers. In the usual region of water concentration employed, 0<[H2O]/[AlR2] ≤1 (R = alkyl) the catalytic species is believed to be the "oxyaluminum" compound, R2Al-O-(AlR2)n-AlR2 (n = 0,1,2, etc.). The role of a "promoter" such as epichlorohydrin is to facilitate the initiation reaction through its rapid cationic cleavage to form the propagating species the trialkyloxonium ion.
Mechanistic studies of the polymerization of BCMO with organoaluminum catalysts have been reported by Penczek, et al.\textsuperscript{18-21} 3,3'-Bis(chloromethyl)oxacyclobutane polymerizes with i-Bu\textsubscript{3}Al (i-Bu = isobutyl)\textsuperscript{18} as well as i-Bu\textsubscript{3}Al-H\textsubscript{2}O catalyst.\textsuperscript{20,21} by a living-type mechanism, i.e., without termination or chain transfer. The molecular weight of the polymer increased linearly with conversion\textsuperscript{18,20} and the molecular weight distribution of the polymer was quite narrow.\textsuperscript{20} These indicated that the active species for polymerization are long-lived and quite stable.\textsuperscript{19-21} At higher conversion, a slow degradative chain transfer occurred.\textsuperscript{21} The polymerization proceeds by a cationic mechanism, as was evidenced by the chain transfer reactions on adding low molecular weight ethers.\textsuperscript{15} In the case of i-Bu\textsubscript{3}Al-H\textsubscript{2}O catalyst, about ten water molecules were suggested to participate in the formation of one active center.\textsuperscript{21} To account for the stability of the counter ion, the catalytic site was proposed to involve a cyclic structure 2.\textsuperscript{21}

Not many other organometallic compounds are acidic enough to polymerize BCMO.\textsuperscript{8} However, Tsuchiya and Tsuruta reported that diethylzinc modified with water (0<\textsubscript{H2O}/[ZnEt\textsubscript{2}]<1.0) in the presence of epichlorohydrin as promoter induced the polymerization of BCMO at 0°C.\textsuperscript{22}

In contrast to the AlR\textsubscript{3}-H\textsubscript{2}O (R = alkyl) catalyst, where visible precipitation was observed when \textsubscript{H2O}/[AlR\textsubscript{3}]\textless 1.5,\textsuperscript{23} the ZnEt\textsubscript{2}H\textsubscript{2}O system is heterogeneous even when \textsubscript{H2O}/[ZnEt\textsubscript{2}]<1. Only the soluble species in benzene or hexane, which have the general structure Et(ZnO)\textsubscript{n}ZnEt (n = 0, 1, 2, etc.),\textsuperscript{24-26} are active catalysts for polymerization of propylene oxide.\textsuperscript{26,28} As was the case in the AlEt\textsubscript{3}-H\textsubscript{2}O system,\textsuperscript{8,9} addition of a controlled amount of water to diethylzinc results in stronger Lewis acidity, the order being ZnEt\textsubscript{2}<Et(ZnO)\textsubscript{n}ZnEt<AlEt\textsubscript{3}.\textsuperscript{26} The precipitate in the reaction of diethylzinc and water contains hydroxyl end groups, i.e., HO(ZnO)\textsubscript{n}R,\textsuperscript{25,28} which is non-acidic\textsuperscript{28} and inactive toward polymerization of propylene oxide.\textsuperscript{28}

TETRAHYDROFURANS

As might be expected from the stability of five- and six-membered cyclic compounds, the six-membered cyclic ether tetrahydrofuran has never been polymerized.\textsuperscript{28,30} However, the five-membered cyclic ether tetrahydrofuran (THF) polymerizes with a small heat of polymerization (- 3.5 kcal/mole).\textsuperscript{28,30} Polymerization of THF is a reversible process and the equilibrium shifts completely to the monomer side at 85 ± 2°C (the so-called ceiling temperature).\textsuperscript{28}
Substitution of a heterocyclic compound invariably decreases its polymerizability and it has long been thought that substituted tetrahydrofurans (except the highly strained 7-oxabicyclo[2,2,1]heptanes) do not polymerize. Recently, however, Dreyfuss and Rhodes reported that 3-methyltetrahydrofuran could be polymerized with such catalysts as boron trifluoride and phosphorous pentafluoride; 2-methyltetrahydrofuran did not polymerize.\textsuperscript{31}

Catalysts for THF polymerization include Lewis acids, oxonium salts, carbonium ions, and strong Brønsted acids.\textsuperscript{1, 35, 29} Organometallic catalysts such as triethylaluminium,\textsuperscript{11} AlEt\textsubscript{3}-H\textsubscript{2}O (usually, 0<<H\textsubscript{2}O/[AlEt\textsubscript{3}]=1.0),\textsuperscript{11} and ZnEt\textsubscript{2}-H\textsubscript{2}O (<<H\textsubscript{2}O/[ZnEt\textsubscript{2}]=1.2)\textsuperscript{22} are effective only in the presence of the promoters or co-catalysts. Inhibition of the polymerization of THF with AlEt\textsubscript{3}-H\textsubscript{2}O(1:1)-ECH catalyst by addition of a small amount of pyridine confirmed the cationic nature of this polymerization.\textsuperscript{8} The role of a promoter, as mentioned previously, is to facilitate the initiation reaction to form the propagating species I (equation 2)\textsuperscript{16}, One line of evidence for this is that when the reaction of THF with AlEt\textsubscript{3}-H\textsubscript{2}O-ECH (2:1:0.2) at 0°C was stopped after two minutes with sodium methoxide, the only low molecular weight alcohol obtained was HOCH(CH\textsubscript{2}Cl)CH\textsubscript{2}O(CH\textsubscript{2})\textsubscript{4}OCH\textsubscript{3}, expected from equation (2).\textsuperscript{17} If formation of the propagating species involved initial coordination of THF to the catalyst, then an alcohol HO(CH\textsubscript{2})\textsubscript{4}O(CH\textsubscript{2})\textsubscript{4}OCH\textsubscript{3} should have been obtained.\textsuperscript{17} Another argument comes from the measurement of the concentration of the propagating species, [P\textsuperscript{+}], by the phenoxyl "end-capping" method,\textsuperscript{32} which involves termination of the propagation with sodium phenoxide, followed by determination of the number of phenyl groups in the polymer by ultraviolet spectroscopy. The results indicate that the propagation rate constant, k\textsubscript{p}, does not depend on the nature of the promoter\textsuperscript{33} but [P\textsuperscript{+}] very much does,\textsuperscript{33, 34} indicating that the promoter is responsible for the initiation reaction.

The phenoxyl end-capping method revealed several aspects of THF polymerization. The propagation rate constant, k\textsubscript{p}, is not very much dependent on the nature of the initiators, indicating that k\textsubscript{p} is almost independent of the counter ions.\textsuperscript{34, 35} The latter mainly affect the termination reaction.\textsuperscript{33, 35, 36}

The detailed mechanism of the initiation reaction is not known. Several workers have suggested the mechanism of equation (2).\textsuperscript{16, 17} Dreyfuss and Dreyfuss suggested a mechanism which involves two organoalumium molecules for the initiation of THF polymerization by AlR\textsubscript{3}(R = alkyl)-ECH catalyst (equation 4).\textsuperscript{29, 29}

![Diagram](image)

This may not be unreasonable; the mechanism proposed for the reaction of trimethylaluminium and benzophenone\textsuperscript{37} or the reaction of triethylaluminium with propylene oxide\textsuperscript{7} involves two molecules of aluminium alkyl per molecule of substrate. However, the polymerization of propylene oxide with trimethylaluminium catalyst follows first-order kinetics in the concentration of the catalyst.\textsuperscript{14} Also, the rate of polymerization of THF with AlEt\textsubscript{3}-H\textsubscript{2}O (2:1) -ECH system is first-order in [AlEt\textsubscript{3}-H\textsubscript{2}O].\textsuperscript{38} These facts argue against equation (4), where one might expect a kinetic expression involving complex terms of [AlR\textsubscript{3}]. No kinetic study is available on THF polymerization with AlEt\textsubscript{3}-ECH catalyst. In the case of AlEt\textsubscript{3}-H\textsubscript{2}O-ECH catalyzed polymerization of THF, the counter ion may involve more than one aluminium atom, contrary to equation (2). Saegusa, et al., reported the effect of water concentration on the catalyst efficiency, [P\textsuperscript{+}]/[AlEt\textsubscript{3}].\textsuperscript{9} The plot of [H\textsubscript{2}O]/[P\textsuperscript{+}] against [H\textsubscript{2}O]/[AlEt\textsubscript{3}] shows the intercept at [H\textsubscript{2}O]/[P\textsuperscript{+}]=22, indicating\textsuperscript{20, 31} that one catalyst site involves about 22 oxygen atoms. Thus, the initiation step may be similar to that shown in equation (5).
The degree of conversion and molecular weight are determined by the stability of the counter ions. Polymerization of THF with AlEt₂-OCH₃ catalyst is remarkable in forming a polymer of high molecular weight. Addition of BCMO to the polymerization mixture after a few months resulted in THF-BCM0 copolymer formation. Thus, the counter ion is quite stable and the active center is "living". Polymerization of THF with AlEt₃-H₂O (2:1) -ECH system was suggested to proceed by a "living" mechanism, without termination or chain transfer. Supporting this proposal, the concentration of ethyl groups bonded to aluminum remained constant during the polymerization, and [Fe⁺], after initial increase, remained constant. The molecular weight distribution was quite narrow.

EPOXIDES

Polymers of rather low molecular weight are obtained with cationic and anionic catalysts. Coordination catalysts produce a high molecular weight polymer. Polymerization of epoxides with simple organometallic compounds is not effective at room temperature but modification of organometallics with active hydrogen compounds such as alcohol, water, and acetylacetone (acac) greatly enhances the catalytic activity.

(1) Organoa aluminum-Water Catalysts. As discussed in the previous sections, the increased Lewis acidity of organometallic compounds treated with water is primarily responsible for the facile cationic polymerization of oxetanes and THF. However, polymerization of epoxides with the same catalyst is a little complicated. Presumably because the basicities of epoxides are low, the alkyl group bonded to aluminum may attack the epoxide monomer coordinated to aluminum or the growing chain end. The result is termination of a cationic polymerization to form an alkoxide linkage which may induce coordinate anionic polymerization of epoxides.

A coordinate anionic mechanism was suggested, for example, in polymerization of propylene oxide with ferric chloride, FeCl₃, where a high molecular weight polymer was obtained in contrast to the results with cationic and anionic catalysts. The catalytic species in this polymerization is believed to be ClFe[OCH₂CH(CH₃)Cl]. The polymerization proceeded with retention of configuration at the secondary carbon of propylene oxide. Price and Osgan proposed a mechanism which involved coordination of a PO monomer to iron, which was then attacked by the alkoxo fragment bound to metal (hence the name coordinate anionic) at the secondary carbon from the front side, in order to account for the retention of configuration (equation 5). Subsequent studies, however, have shown that polymerization of epoxides with any catalyst proceeds with inversion of configuration at the ring-opening carbon and thus, the mechanism shown in equation (5) was rejected.
The ternary catalyst \( \text{Et}_3\text{Al}-\text{H}_2\text{O}-\text{acac}(1:0.5:0.5) \) (acac = acetylacetone) was suggested to be of a coordination type; the structure of the catalytic species was proposed to be \( \mathcal{J} \) from its infrared and ultraviolet spectra.\(^{41}\) To account for the inversion of configuration at the ring-opening carbon, the catalyst site was proposed to involve more than two 

aluminum \( \text{(4)} \) with the ring-opening of propylene oxide preferentially occurring at the primary carbon,\(^{41}\) as might be expected for the anionic ring opening of epoxides.\(^{6}\) The detailed structure of the catalyst site \( \text{(4)} \) is not known.\(^{41}\) In the polymerization of propylene oxide with ferric chloride or \( \text{Et}_2\text{AlCl} \) as catalyst, some amorphous polymer was obtained, in addition to a crystalline polymer, indicating a significant contribution of ring-opening at the secondary carbon, which might arise from cationic polymerization.\(^{41,43}\) This dual mechanism of polymerization is not well understood.\(^{41,43}\)

In the polymerization of epoxides with organoaluminum catalysts observations were frequently made which indicated the presence of more than one polymerization mechanism or catalytic site.\(^14\)\(^{46}\) For example, both THF-epichlorohydrin (ECH) copolymer and crystalline ECH homopolymer was obtained in the copolymerization of THF and ECH with triethylaluminum and \( \text{AlEt}_3-\text{H}_2\text{O} \) \( (1:1) \) catalyst system;\(^{46a}\) addition of pyridine to this system decreased the total polymer yield but the relative amount of ECH homopolymer was much increased.\(^{46b}\) Based on several lines of evidence, Saegusa and co-workers proposed a mechanism for the polymerization of ECH or copolymerization of THF and ECH with triethylaluminum and \( \text{AlEt}_3-\text{H}_2\text{O} \) catalyst, which involves both cationic and coordinate anionic polymerization (Scheme I).\(^{46b}\)

In Scheme I the monomer coordinated to catalyst \( \mathcal{J} \) may be attacked either by THF or ECH monomer to produce an oxonium ion \( \mathcal{6} \) or by an ethyl group to produce an alkoxide \( \mathcal{7}; \mathcal{6} \) will lead to cationic polymerization, forming a THF-ECH copolymer or amorphous ECH polymer, while \( \mathcal{7} \) will induce coordinate anionic polymerization to produce crystalline ECH homopolymer.\(^{46b}\) Supporting Scheme I, Saegusa, et al., found that about 25\% of the ethyl groups bonded to aluminum were lost within an hour during the polymerization of ECH with \( \text{AlEt}_3-\text{H}_2\text{O} \) \( (1:0.5) \) catalyst at \( \text{0\degree C} \).\(^{39}\) One may note in Scheme I, that transfer of an ethyl group should resemble equation \( \mathcal{5} \), which was rejected.

(2) Organoaluminum-Acetylacetone Complex. Ternary catalyst \( \text{AlEt}_3-\text{H}_2\text{O}-\text{acac} \) \( (1:0.5:0.5) \) \( \mathcal{3} \) was mentioned in the previous section. Polymerization of propylene oxide with \( \mathcal{8}\)\(^{47}\) as catalyst was reported by Kuntz and Kroll.\(^{48}\) The compound \( \mathcal{8} \) showed only a low catalytic activity, which was much improved by adding small amount of water \( \text{(0.5 mole per mole of \( \mathcal{8} \))} \). The catalytic species was proposed, without any physical evidence, to be \( \text{i-Bu(acac)}\text{Al}-\text{O-Al(acac)(i-Bu)} \).\(^{48}\) It was also found that a ternary catalyst system, \( \text{Et}_2\text{O-\text{AlEt}_3} \) \( (1:0.5:1) \) shows higher catalytic activity; diethylzinc was even better as the third component.\(^{48}\)

The proposed mechanism for the latter catalyst system involves diethylzinc coordinated to the oxygen atom between the two aluminum atoms \( \mathcal{9} \) with the zinc atom primarily involved in epoxide coordination and aluminum in propagation.\(^{48}\) If diethylzinc coordinates to oxygen as suggested in \( \mathcal{9} \), then the NMR spectrum might show a considerable change in the chemical shift of the ethyl group bonded to zinc. This point, however, was not studied. No polymerization occurred.
when the alkyl groups bonded to aluminum were substituted with chlorine atoms; it was suggested that the initiation step involved the reaction of the alkyl group bonded to aluminum with an epoxide to form the first OR fragment.\(^{48}\)

(5) Organozinc-Water Catalyst. The catalytic activity of dialkylzinc compounds toward epoxide polymerization was much improved by addition of oxygen, alcohol, and water.\(^{25}\) The catalyst systems diethylzinc-oxygen and diethylzinc-alcohol involve zinc alkoxide,\(^{49}\) which will not be treated here.

In contrast to the polymerization of BCMO and THF with \(\text{AlEt}_3\cdot\text{H}_2\text{O}\) catalyst in the presence of epichlorohydrin as a promoter, where polymerization did not occur when the molar ratio \([\text{H}_2\text{O}]/[\text{ZnEt}_2]\) exceeded one,\(^{22}\) the optimum yield in the polymerization of propylene oxide was obtained when \([\text{H}_2\text{O}]/[\text{ZnEt}_2] = 1\) and no polymerization occurred when \([\text{H}_2\text{O}]/[\text{ZnEt}_2] = 2.\(^{22}\)\(^{25},^{37}\) This indicated that there is a cationic species in the \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) catalyst when \([\text{H}_2\text{O}]/[\text{ZnEt}_2] < 1.\(^{22}\) When \([\text{H}_2\text{O}]/[\text{ZnEt}_2] = 1\), there is mainly a coordination-type catalyst because the polymerization of \(\text{D}(+)\)-propylene oxide with \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) (1:1) catalyst produced a polymer with the same optical rotation as that obtained with potassium hydroxide catalyst, thus indicating an anionic ring-opening of propylene oxide.\(^{22}\) When \(0<[\text{H}_2\text{O}]/[\text{ZnEt}_2]<1.\) (1:1) however, there seems to be two mechanisms operative in the polymerization of propylene oxide. In the polymerization of propylene oxide with \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) (1:0.5) catalyst, rapid formation of cyclic tetramer was observed, in addition to a slow formation of a crystalline polymer.\(^{37}\) This is very similar to the polymerization of propylene oxide with \(\text{AlMe}_2\cdot\text{H}_2\text{O}\) catalyst (Me = CH\(_2\))\(^{14}\) and is indicative of the presence of more than one polymerization mechanism. Chu and Price obtained, in the polymerization of \(\text{L}(-)\)-propylene oxide, amorphous and crystalline fractions; the former had a very low optical rotation in contrast to the high optical rotation of the latter.\(^{50}\)

This might suggest the presence of cationic and coordinate anionic mechanisms. Tsuchiya and Tsuruta obtained, in the polymerization of \(\text{D}(+)\)-propylene oxide with \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) (1:0.5) catalyst, a polymer which showed a substantially lower optical rotation than that obtained with \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) (1:1) catalyst, indicating a contribution of cationic polymerization.\(^{22}\) Thus, Tsuruta and co-workers proposed a mechanism similar to Scheme I, involving both cationic and coordinate anionic polymerization.\(^{21},^{25}\) However, it is not well known why the cationic mechanism becomes inoperative when the molar ratio \([\text{H}_2\text{O}]/[\text{ZnEt}_2]\) exceeds one.\(^{22},^{25},^{26}\) If acidity of the catalyst were the most important factor, then the cationic polymerization should occur even when \([\text{H}_2\text{O}]/[\text{ZnEt}_2] = 1\), since \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) (1:1) showed higher acidity\(^{26}\) than \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) (1:0.5 or 1:0.3). One possible answer is the contribution of excess diethylzinc in the \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) catalyst. Furukawa and co-workers found by NMR spectroscopy that the catalyst system \(\text{ZnEt}_2\cdot\text{H}_2\text{O}\) (1:1) contained some unreacted diethylzinc.\(^{25}\) Polymerization of propylene oxide with this catalyst produced low molecular weight oligomers (liquid polymers) in addition to high polymer but no oligomer was formed when excess diethylzinc was removed from the catalyst before the polymerization.\(^{25}\) This suggested that the
presence of excess diethylzinc was responsible for the oligomer formation. If it could be assumed that the low molecular weight oligomers were formed by a cationic mechanism, then the presence of excess diethylzinc should be responsible for the cationic polymerization. Because diethylzinc itself is inactive toward polymerization of propylene oxide, BCMO, and THF, diethylzinc coordinated to such species as EtZn(OEt)nOEt may induce the cationic polymerization. However, this argument cannot explain the fact that BCMO and THF were not polymerized with ZnEt2H2O(1:1)-ECH catalyst system despite the presence of excess diethylzinc.

A recent report by Furukawa and co-workers that the (+)-bis(2-methylbutyl)-zinc-water(1:1) system polymerized stereoselectively racemic propylene oxide shows the importance of the zinc-alkyl group in the catalytic site. Even though no mechanism was suggested, the foregoing discussion strongly suggests a coordinate anionic mechanism for this polymerization. A catalytic site similar to 4, where one alkyl group is retained by one zinc atom, may be suggested, in order to account for the inversion of configuration in the epoxide polymerization and the effect of the asymmetric alkyl group bonded to zinc on the stereoselective polymerization.

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