Progress in

PHYSICAL
ORGANIC
CHEMISTRY

VOLUME 4

Editors

ANDREW STREITWIESER, JR., Department of Chemistry
University of California, Berkeley, California

ROBERT W. TAFT, Department of Chemistry
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Introduction to the Series

Physical organic chemistry is a relatively modern field with deep roots in chemistry. The subject is concerned with investigations of organic chemistry by quantitative and mathematical methods. The wedding of physical and organic chemistry has provided a remarkable source of inspiration for both of these classical areas of chemical endeavor. Further, the potential for new developments resulting from this union appears to be still greater. A closing of ties with all aspects of molecular structure and spectroscopy is clearly anticipated. The field provides the proving ground for the development of basic tools for investigations in the areas of molecular biology and biophysics. The subject has an inherent association with phenomena in the condensed phase and thereby with the theories of this state of matter.

The chief directions of the field are: (a) the effects of structure and environment on reaction rates and equilibria; (b) mechanism of reactions; and (c) applications of statistical and quantum mechanics to organic compounds and reactions. Taken broadly, of course, much of chemistry lies within these confines. The dominant theme that characterizes this field is the emphasis on interpretation and understanding which permits the effective practice of organic chemistry. The field gains its momentum from the application of basic theories and methods of physical chemistry to the broad areas of knowledge of organic reactions and organic structural theory. The nearly inexhaustible diversity of organic structures permits detailed and systematic investigations which have no peer. The reactions of complex natural products have contributed to the development of theories of physical organic chemistry, and, in turn, these theories have ultimately provided great aid in the elucidation of structures of natural products.

Fundamental advances are offered by the knowledge of energy states and their electronic distributions in organic compounds and the relationship of these to reaction mechanisms. The development, for example, of even an empirical and approximate general scheme
for the estimation of activation energies would indeed be most notable.

The complexity of even the simplest organic compounds in terms of physical theory well endows the field of physical organic chemistry with the frustrations of approximations. The quantitative correlations employed in this field vary from purely empirical operational formulations to the approach of applying physical principles to a workable model. The most common procedures have involved the application of approximate theories to approximate models. Critical assessment of the scope and limitations of these approximate applications of theory leads to further development and understanding.

Although he may wish to be a disclaimer, the physical organic chemist attempts to compensate his lack of physical rigor by the vigor of his efforts. There has indeed been recently a great outpouring of work in this field. We believe that a forum for exchange of views and for critical and authoritative reviews of topics is an essential need of this field. It is our hope that the projected periodical series of volumes under this title will help serve this need. The general organization and character of the scholarly presentations of our series will correspond to that of the several prototypes, e.g., *Advances in Enzymology*, *Advances in Chemical Physics*, and *Progress in Inorganic Chemistry*.

We have encouraged the authors to review topics in a style that is not only somewhat more speculative in character but which is also more detailed than presentations normally found in textbooks. Appropriate to this quantitative aspect of organic chemistry, authors have also been encouraged in the citation of numerical data. It is intended that these volumes will find wide use among graduate students as well as practicing organic chemists who are not necessarily expert in the field of these special topics. Aside from these rather obvious considerations, the emphasis in each chapter is the personal ideas of the author. We wish to express our gratitude to the authors for the excellence of their individual presentations.

We greatly welcome comments and suggestions on any aspect of these volumes.

ANDREW STREITWIESER, JR.
ROBERT W. TAFT

A. Streitwieser and R. W. Taft regret very much that Saul G. Cohen has considered it necessary to withdraw as Co-editor on this and subsequent volumes. We are greatly indebted for his contributions to Volumes 1–3.
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Mechanism and Catalysis for the Hydrolysis of Acetals, Ketals, and Ortho Esters

By E. H. Cordes
Indiana University, Bloomington, Indiana

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I. Introduction

Studies concerned with mechanisms and catalysis for the hydrolysis of acetals, ketals, and ortho esters have been seminal in the development of a general understanding of these topics for reactions in aqueous solution. Indeed, pioneering studies on general acid–base catalysis, solvent deuterium isotope effects, reaction kinetics in strongly acidic media, and structure–reactivity correlations have employed these substances as substrates. Such early studies, together with significant recent developments, have clearly established the principal mechanistic and catalytic features of these hydrolytic processes. These are summarized in this review.

In acidic aqueous solutions, acetals, ketals, and ortho esters hydrolyze according to the overall stoichiometry indicated in eq. (1).
These reactions occur with the rupture of two covalent bonds to carbon and involve at least two proton transfer reactions. Hence the overall reaction must be multistep. Our first concern in this review is the nature of the intermediates formed in such multistep processes; i.e., the reaction pathway. Subsequently, attention is directed to identification of the rate-determining step, to catalytic mechanisms, and, in general, to a precise definition of transition state structures.

### II. Reaction Pathways

The first step in acetal, ketal, or ortho ester hydrolysis in which the making or breaking of covalent bonds to carbon is involved may be visualized as occurring via one of the four transition states shown in structures 1-4. Each of these transition states is pictured, for the sake of clarity, as having arisen from the conjugate acid of the substrate. Kinetic studies indicate the presence of a proton or the kinetic equivalent in the transition state but leave uncertain the question of timing of proton transfer relative to cleavage of the C—O bond. We return to this point below. Transition states 1 and 2 picture these hydrolyses as occurring via unimolecular decomposition of the conjugate acids of the substrates with cleavage of the carbonyl carbon–oxygen and alcohol carbon–oxygen bonds, respectively (A-1 reactions). The corresponding carbonium ions are the immediate
products. Transition states 3 and 4 include the participation of water as nucleophilic reagent with carbon-oxygen bond cleavage at the sites indicated (A-2 reactions). The immediate products are identical to those formed from addition of one molecule of water to the carbonium ions generated from transition states 1 and 2. Distinction between these transition states involves (a) localization of the site of C—O bond cleavage and (b) identification of the immediate product of C—O cleavage as a carbonium ion or its hydrate. We consider these topics in sequence.

A. THE SITE OF CARBON-OXYGEN BOND CLEAVAGE

Several lines of evidence conclusively establish that, for most cases at least, the hydrolysis of acetals proceeds with cleavage of the carbonyl carbon-oxygen bond. The earliest convincing evidence for this point of view is the important work of Lucas and his associates on the hydrolysis of acetals derived from optically active alcohols. For example, hydrolysis of the D(+)-2-octanol acetal of acetaldehyde in dilute aqueous phosphoric acid yields 2-octanol having the same optical rotation as the original alcohol from which the acetal was synthesized (1). This finding excludes formation of the alkyl carbonium ion (transition state 2), in which case substantial or complete racemization of the alcohol would be expected, and an A-2 reaction involving nucleophilic attack of solvent on the alcohol (transition state 4), in which case optical inversion of the alcohol would be expected. Similarly, the formal, acetal, and carbonate derived from D(-)-2,3-butanediol and the acetal derived from D(+)-2-butanol undergo acid-catalyzed hydrolysis with complete retention of configuration at the carbinol carbon of the alcohol (2,3).

Drumheller and Andrews have investigated the possibility that certain acetals, prepared from alcohols capable of forming relatively stable carbonium ions, might hydrolyze by the alkyl carbonium ion pathway (transition state 2) (4). The parent alcohols chosen for study were (-)α-phenethyl alcohol, methylvinyl carbinol, and phenylvinyl carbinol. Derivatives of each of these alcohols are well known to readily undergo SN1-type displacement reactions. Hydrolysis of the acetal prepared from (-)α-phenethyl alcohol (in dilute sulfuric acid solution) produced alcohol with optical properties identical to those of the original alcohol, as in the cases described above. Similarly, hydrolysis of the methylvinylcarbinyl acetal yielded only
methylvinylcarbinol, and hydrolysis of the phenylvinylcarbinol acetal yielded phenylvinylcarbinol as the immediate reaction product. Thus, the latter two hydrolyses proceed without the allylic rearrangements (yielding crotyl alcohol and cinnamyl alcohol) characteristic of the corresponding carbonium ions (5,6). Finally, the possibility that hydrolysis of these substrates occurred via transition state 4 (nucleophilic attack of solvent at the carbinol carbon atom) was explicitly excluded through the observation that methanolation of a phenethyl alcohol-derived acetal yielded phenethyl alcohol and not the corresponding methyl ether. Thus, it is safe to conclude that even in these cases, deliberately chosen to accentuate the possibility of alcohol carbon-oxygen bond cleavage, acetal hydrolysis occurs with carbonyl carbon-oxygen bond cleavage.

Bourns et al. have strongly corroborated the above conclusion in an isotope tracer study of acetal formation and hydrolysis (7). The condensation of benzaldehyde and n-butyraldehyde, enriched in \(^{18}O\), with n-butyl and allyl alcohols yielded acetals of normal isotopic abundance and \(^{18}O\)-enriched water [eq. (2)]. In a like fashion, hydrolysis of benzaldehyde di-n-butyl acetal and n-butyraldehyde di-n-butyl acetal in \(^{18}O\)-enriched water yielded alcohols of normal isotopic content [the reverse of eq. (2)]. Thus, these reactions clearly proceed with carbonyl carbon-oxygen bond cleavage (or formation).

Less experimental work on the site of carbon-oxygen bond cleavage has been reported for the cases of ketal and ortho ester hydrolysis. One would expect that these substrates behave in a fashion similar to that of acetals. Some very early work on hydrolysis of ketals tends to bear out this supposition. The acetone ketals of the cis 1,2-diols of tetrahydronaphthalene, hydridene, and 1-phenyl cyclohexane yield the cis diols almost exclusively on hydrolysis; a result consistent only with carbonyl carbon-oxygen bond cleavage (8–10). Recently, Taft has studied the hydrolysis of methyl orthocarbonate in \(\text{H}_2\text{H}^{18}\text{O}\). While most of the \(^{18}O\) does appear in the carbonyl group of dimethyl carbonate as expected, there is appreciable formation of \(\text{CH}_3\text{H}^{18}\text{OH}\) and \(\text{CH}_3\text{O}—\text{O—CH}_3\), i.e., methylation of the nucleophiles water and methanol either by the orthocarbonate or the corresponding car-
bonium ion (11). These products almost certainly arise in bimolecular reactions involving alcohol carbon–oxygen bond cleavage (transition state 4 or a variant thereof).

The early suggestion of Hammett, based on the relative rates of hydrolysis of several formals (12), that acetal hydrolysis occurs via formation of the alcohol-derived carbonium ion must be abandoned in light of the above considerations (13). The data available to Hammett is also consistent with formation of the carbonium ion according to transition state 1. A sizable amount of subsequent work on structure-reactivity correlations for acetal and ketal hydrolysis provides strong support for the latter alternative (14).

In summary, the data indicated above and reasonable extrapolations thereof strongly suggest that, in the preponderant majority of cases, acid-catalyzed hydrolysis of acetals, ketals, and ortho esters occurs with cleavage of the carbonyl carbon–oxygen bond. We now turn to a consideration of the distinction between the two transition states, 1 and 3, which involve bond cleavage of this type.

B. THE QUESTION OF SOLVENT PARTICIPATION AS NUCLEOPHILIC REAGENT

Several independent lines of evidence strongly suggest that the acid-catalyzed hydrolysis of acetals, ketals, and ortho esters proceeds by a reaction pathway not involving solvent as nucleophilic reagent, i.e., that 1 describes the transition state for the initial reaction in which covalent bonds to carbon are broken [eq. (3)]. These lines of evidence derive from studies on (1) the reaction kinetics, (2) structure-reactivity correlations, (3) entropies of activation, (4) volumes of activation, (5) isotope effects, (6) correlation of rates with acidity functions, (7) rate and product studies in the presence of added nucleophilic reagents, and (8) solvent effects. We consider the results of these studies sequentially.
1. Reaction Kinetics

The hydrolysis of the substrates in question is almost invariably dependent upon acid catalysis. That is, the rate laws for reactions in dilute aqueous solution have the form

\[ k_{\text{obs}} = k_{i=1}(\text{H}^+) + \sum k_{i=1}(\text{HA})_i \]

(4)

in which the terms in the summation on the right-hand side of the equation are frequently negligible (see p. 32). The complete dependence of these reactions on acid catalysis suggests that water does not participate as a nucleophilic reagent. If water were able to expel alcohol from the protonated substrates in nucleophilic reactions, then one might expect that hydroxide ion (or other nucleophilic reagent) would expel alkoxide ion from the corresponding free bases. Since the latter reactions are not observed, one suspects that the former reactions do not occur either. This is, of course, a naive argument and provides only weak evidence against nucleophilic participation by water.

The hydrolyses of 2-phenyl-1,3-dioxanes possessing o- or p-phenolic substituents do exhibit pH-independent, as well as acid-catalyzed, reactions (44). However, solvent deuterium isotope effects suggest that the pH-independent reaction is, in fact, the hydronium ion-catalyzed hydrolysis of the phenolic form of the substrates. This is, of course, a kinetically indistinguishable alternative to a formulation involving an uncatalyzed (or solvent-catalyzed) reaction pathway.

In some instances of acetal hydrolysis, nucleophilic reaction paths do seem to be important. In each of these cases, the nucleophilic reaction is intramolecular, not intermolecular. The cleavage of certain glycosides, such as phenyl-\(\beta\)-d-glucoside, is subject to catalysis by hydroxide ion (116). These reactions are not properly regarded as hydrolyses, however, since the oxygen at C-2 participates in the expulsion of phenoxyde ion with formation of the 1,6-anhydro sugar. Similar comments apply to the recent conclusion of Capon and Thacker that acid-catalyzed ring closure (not hydrolysis) of dimethyl acetals of glucose and galactose involves nucleophilic attack synchronous with rupture of the acetal bond [eq. (5)] (15). This conclusion is based on the observations (1) that the configuration at carbon 4 of the sugar moiety influences the rate of furanoside formation and (2) that the rate of these ring closures is 30 to 340 times more rapid than that predicted from data on related substrates.
More directly pertinent to the question at hand is the recent suggestion of Speck et al. that the acid-catalyzed hydrolysis of methylthioacetaldehyde diethyl acetal occurs with neighboring group participation of the methylthio function [eq. (6)] (117).

The evidence favoring this reaction pathway consists of the observation that the methylthio compound hydrolyzes about two orders of magnitude more rapidly than the corresponding methoxy compound, methoxyacetaldehyde dimethyl acetal. Since the polar substituent constants for methylthio and methoxy functions are similar, this finding suggests a rate-augmenting effect not attributable to a difference in inductive effects. If eq. (6) does, in fact, correctly describe the reaction pathway for methylthioacetaldehyde diethyl acetal, then formation of the cyclic sulfonium ion must be rate-determining since both molecules of ethanol liberated in the reaction appear simultaneously.
**TABLE I. A Summary of Linear Free Energy Correlations for Acetal, Ketal, and Ortho Ester Hydrolysis**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>No. of substituents</th>
<th>Solvent</th>
<th>Temp., °C.</th>
<th>Correlation obeyed</th>
<th>ρ</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (\text{RIR}_2\text{C}(\text{OC}_2\text{H}_5))</td>
<td>4</td>
<td>50% aqueous dioxane</td>
<td>30</td>
<td>(\log (k/k_0) = \sigma \rho)</td>
<td>(\rho = -3.35)</td>
<td>16</td>
</tr>
<tr>
<td>2. (\text{RIR}_2\text{C}(\text{OC}_2\text{H}_5))</td>
<td>8</td>
<td>50% aqueous dioxane</td>
<td>30</td>
<td>(\log (k/k_0) = \rho[\sigma + r(\sigma^+ - \sigma)])</td>
<td>(\rho = -3.35) (r = 0.5)</td>
<td>16,21</td>
</tr>
<tr>
<td>3. (\text{RIR}_2\text{C}(\text{OC}_2\text{H}_5))</td>
<td>5</td>
<td>50% aqueous dioxane</td>
<td>30</td>
<td>(\log (k/k_0) = \rho[\sigma + r(\sigma^+ - \sigma)])</td>
<td>(\rho = -3.25) (r = 0.5)</td>
<td>16,21</td>
</tr>
<tr>
<td>4. (\text{R}_1\text{R}_2\text{C}(\text{OC}_2\text{H}_5)_2)</td>
<td>23</td>
<td>49.6% aqueous dioxane</td>
<td>25</td>
<td>(\log (k/k_0) = (\Sigma \sigma^<em>) \rho^</em> + 0.54(\Delta \eta))</td>
<td>(\rho^* = -3.60)</td>
<td>18</td>
</tr>
<tr>
<td>5. (\text{H}_2\text{C}((\text{OR})_2))</td>
<td>7</td>
<td>Water</td>
<td>25</td>
<td>(\log (k/k_0) = \sigma^* \rho^*)</td>
<td>(\rho^* = -8.3)</td>
<td>12,19</td>
</tr>
<tr>
<td>6. (\text{H}_2\text{C}((\text{OR})_2))</td>
<td>6</td>
<td>Water</td>
<td>25</td>
<td>(\log (k/k_0) = \sigma \rho)</td>
<td>(\rho = -3.35)</td>
<td>12,20</td>
</tr>
<tr>
<td>7. (\text{RIR}_2\text{C}(\text{OC}_2\text{H}_5))</td>
<td>5</td>
<td>70% aqueous methanol</td>
<td>30</td>
<td>(\log (k/k_0) = \sigma \rho)</td>
<td>(\rho = -2.0)</td>
<td>17</td>
</tr>
</tbody>
</table>

\(a\) \(\text{R}_1\text{R}_2\) chosen so as to preclude direct pi conjugation with the reaction center.
2. Structure–Reactivity Correlations

At this point, attention is directed to those structure–reactivity correlations which exist within individual reaction series (i.e., relative hydrolysis rates for methyl acetals or alkyl aldehydes). Interseries comparisons are deferred for the moment (cf. p. 29).

In several instances, second-order rate constants for reactions of interest here are correlated by one or more linear free-energy relation-

![Diagram](image)

Fig. 1. Plots of the logarithms of second-order rate constants for hydrolysis of (O) substituted benzaldehyde diethyl acetals and (●) 2-(substituted phenyl)-1,3-dioxolanes against $\sigma + 0.5(\sigma^+ - \sigma)$. The values on the left ordinate refer to the benzaldehyde acetals and those on the right to the dioxolanes. Constructed from data of Fife and Jao (16).
ships. These cases are collected in Table I. Second-order rate constants for acetal and ketal hydrolysis are very sensitive to structural alterations in both the aldehyde and alcohol moieties. Such rate constants for hydrolysis of a series of \( m \)-substituted diethyl acetals of benzaldehyde are correlated by the Hammett \( \sigma \) constants and a \( \rho \) value of \(-3.35\) (16). This \( \rho \) value is consistent with and support for rate-determining carbonium ion formation since, in this case, electron donation from a polar substituent will both favor preequilibrium substrate protonation and stabilize the carbonium ion developing in the transition state. For compounds substituted in the \( \text{para} \) position with groups capable of electron donation by resonance, second-order rate constants fall somewhat above the line established by the \( m \)-substituted compounds when plotted against the \( \sigma \) constants and somewhat below a corresponding line when plotted against the \( \sigma^* \) constants. Data of this type may be treated according to the considerations of Yukawa and Tsuno, who have suggested a linear free-energy correlation of the form (21).

\[
\log \frac{k}{k_0} = \rho \left( \sigma + \gamma (\sigma^* - \sigma) \right)
\]

(7)

The second-order rate constants for hydrolysis of \( p \)- and \( m \)-substituted benzaldehyde diethyl acetals are well correlated by eq. (7) and values of \( \rho \) and \( \gamma \) of \(-3.35\) and 0.5, respectively, as illustrated in Figure 1. A very similar situation exists for hydrolysis of 2-(\( p \)-substituted phenyl)-1,3-dioxolanes (Table I and Fig. 1) (16). The fact that these reaction rates are correlated by a set of substituent constants intermediate between \( \sigma \) and \( \sigma^* \) is fully consistent with rate-determining carbonium ion formation.

Kreevoy and Taft have found that second-order rate constants for the hydrolysis of 24 diethyl acetals and ketals of nonconjugated aldehydes and ketones are well correlated, with one exception, by the linear free-energy relationship

\[
\log \left( \frac{k}{k_0} \right) = (\Sigma \sigma^*) \rho^* + (\Delta n) h
\]

(8)
in which \( \sigma^* \) is the sum of the appropriate polar substituent constants (19), \( \Delta n \) is the difference in the total number of \( \alpha \)-hydrogen atoms in the carbonyl moiety and the six in the standard of comparison, diethyl acetal, and \( h \) is an empirical constant measuring the facilitating effect of a single hydrogen on the rate (18). This structure-reactivity correlation is illustrated in Figure 2 for the case \( h = 0.54 \). Both the
ACETALS, KETALS, AND ORTHO ESTERS

Fig. 2. Plot of \(\log(k/k_0) - 0.54(\Delta n)\) against \(\Sigma \sigma^*\). (○) Acetals \(\text{RCH}-(\text{OC}_2\text{H}_5)_2\); (O) ketals \(\text{R(C}_2\text{H}_5)\text{C(OC}_2\text{H}_5)_2\). \(R\) is given with each point. Constructed from data of Kreevoy and Taft (18).

The magnitude of the value of \(\rho^*\), \(-3.60\), and the necessity of including a hyperconjugation term suggest rate-determining carbonium ion formation, not rate-determining solvent attack. The abnormal reactivity of the methyl neopentyl ketal (Fig. 2), the exception noted above, may be accounted for in terms of relief of steric strain as the tetrahedral carbon atom approaches the trigonal configuration in the transition state. The latter point has been further pursued by Kreevoy et al. in a study of hydrolysis rates for bulky and cyclic ketals (22). In all cases, the observed rate constants are consistent with the hypothesis that the transition state has made considerable prog-
The marked effects of substituents on rates for acetal and ketal hydrolysis are not reflected in the overall equilibrium constants for their formation. Hartung and Adkins observed only modest effects on the equilibrium constant for a series of saturated R groups of similar steric requirements (23).

$$RCHO + 2C_2H_5OH \rightleftharpoons RCH(OCC_2H_5)_2 + H_2O \quad (9)$$

The early studies of Skrabal and Eger on the acidic hydrolysis of symmetrical formals have revealed a marked sensitivity of the rates to changes in substituents (Table I, entries 5 and 6) (12,19,20). This

**TABLE II**
Comparison of Substituent Effects on the Relative Rates of Hydrolysis of Acetals and Ketals to Those on the Relative Rates of Hydrolysis of Ortho Esters (modified from ref. 25)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative hydrolysis rate</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetals and ketals$^a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_4$(OC$_2$H$_5$)$_2$</td>
<td>1.00$^b$</td>
<td>18</td>
</tr>
<tr>
<td>CH$_3$CH(OC$_2$H$_5$)$_2$</td>
<td>$6.0 \times 10^3$</td>
<td>18</td>
</tr>
<tr>
<td>C$_6$H$_5$CH(OC$_2$H$_5$)$_2$</td>
<td>$1.7 \times 10^2$</td>
<td>18</td>
</tr>
<tr>
<td>(CH$_3$)$_2$C(OC$_2$H$_5$)$_2$</td>
<td>$1.8 \times 10^3$</td>
<td>18</td>
</tr>
<tr>
<td>Ortho esters$^c$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H—C(OC$_2$H$_5$)$_3$</td>
<td>1.00$^d$</td>
<td>26</td>
</tr>
<tr>
<td>CH$_3$—C(OC$_2$H$_5$)$_3$</td>
<td>38.5</td>
<td>26</td>
</tr>
<tr>
<td>C$_2$H$_5$—C(OC$_2$H$_5$)$_3$</td>
<td>24.3</td>
<td>26</td>
</tr>
<tr>
<td>C$_6$H$_5$—C(OC$_2$H$_5$)$_3$</td>
<td>0.62</td>
<td>27</td>
</tr>
<tr>
<td>C$_2$H$_5$O—C(OC$_2$H$_5$)$_3$</td>
<td>0.17</td>
<td>26</td>
</tr>
</tbody>
</table>

$^a$ Reactions in 49.6% aqueous dioxane at 25°C.

$^b$ $k_3 = 4.13 \times 10^{-4}M^{-1}\text{sec.}^{-1}$.

$^c$ Reactions in water at 25°C.

$^d$ $k_3 = 5.38 \times 10^3M^{-1}\text{sec.}^{-1}$.

sensitivity is presumably the primary consequence of polar effects on the preequilibrium protonation of the substrates. These findings are fully corroborated by a recent and extensive study of formal hydroly-
sis by Salomaa (24). In addition, this worker has developed methods for sorting out the relative contributions of the two C—O fission reactions which occur in the hydrolysis of unsymmetrical acetals and ketals.

Substituent effects on rates of ortho ester hydrolysis are much smaller than the corresponding effects on acetal and ketal hydrolysis (25). Furthermore, the rate constants for ortho ester hydrolysis do not increase uniformly with increasing electron-donating power of the substituent. A quantitative comparison of substituent effects in the two reaction series is presented in Table II. The detailed interpretation of these substituent effects is deferred to a later section. Suffice it to say at this point that these effects are consistent with the intermediacy of carbonium ions in ortho ester hydrolysis. The systematic study of substituent effects in benzaldehyde ortho ester hydrolysis (17) (Table I, entry 7) is badly clouded by an unfortunate choice of solvent (see discussion below), and the value of $\rho$ obtained cannot be firmly relied upon.

3. Entropies of Activation

The use of entropies of activation as a criterion of mechanism for acid-catalyzed reactions in aqueous solution has been reviewed by Schaleger and Long (38). Briefly stated, experience indicates that reactions proceeding with unimolecular decomposition of the protonated substrate (A-1) usually exhibit entropies of activation near zero or somewhat positive while, in contrast, those proceeding with nucleophilic attack of solvent on the protonated substrate (A-2) usually exhibit corresponding values which are large and negative. That bimolecular reactions should exhibit more negative entropies of activation than unimolecular reactions is reasonable in view of the loss of rotational and translational freedom of the water molecule in the transition state. However, variability in the $\Delta S$ accompanying the protonation reaction may cloud the picture, and differences in entropies of activation are not always large enough to permit unambiguous conclusions. A compilation of data relevant to the substrates under consideration is presented in Table III. This data, in light of the above generalization, lends additional support to the concept of carbonium ion intermediates for acetal, ketal, and ortho ester hydrolysis.
TABLE III
Entropies of Activation for Hydrolysis of Acetals, Ketals, and Ortho Esters

<table>
<thead>
<tr>
<th>Compound</th>
<th>ΔS</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetals and ketals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Dimethoxyethane</td>
<td>+6.8</td>
<td>28</td>
</tr>
<tr>
<td>2. Diethoxyethane</td>
<td>+7.0</td>
<td>28,29</td>
</tr>
<tr>
<td>3. Dimethoxyethane</td>
<td>+13</td>
<td>28</td>
</tr>
<tr>
<td>4. 1,3-Dioxolane</td>
<td>-0.6</td>
<td>30</td>
</tr>
<tr>
<td>5. 2,2-Dimethyl-1,3-dioxolane</td>
<td>+7.0</td>
<td>30</td>
</tr>
<tr>
<td>6. 2,4,4,5,5-Pentamethyl-1,3-dioxolane</td>
<td>-3.8</td>
<td>30</td>
</tr>
<tr>
<td>7. Benzaldehyde diethyl acetals</td>
<td>+7.0 to +2.0</td>
<td>16</td>
</tr>
<tr>
<td>8. 2-(Substituted phenyl)-1,3-dioxolanes</td>
<td>-6.9 to -9.6</td>
<td>16</td>
</tr>
<tr>
<td><strong>Ortho esters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Ethyl orthoformate</td>
<td>+6   to +8</td>
<td>28,31</td>
</tr>
<tr>
<td>10. Methyl orthobenzoate</td>
<td>+8.4</td>
<td>32</td>
</tr>
<tr>
<td>11. Ethyl orthobenzoate</td>
<td>-0.3</td>
<td>27</td>
</tr>
<tr>
<td>12. Ethyl orthoacetate</td>
<td>+5.5 (40% dioxane)</td>
<td>27,37</td>
</tr>
<tr>
<td><strong>Some related reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Glucopyranosides hydrolysis</td>
<td>+13 to +17</td>
<td>33</td>
</tr>
<tr>
<td>14. Trioxane depolymerization</td>
<td>+4</td>
<td>34</td>
</tr>
<tr>
<td>15. Methoxymethyl acetate hydrolysis</td>
<td>+3.7</td>
<td>35</td>
</tr>
<tr>
<td>16. Methoxymethyl formate hydrolysis</td>
<td>+2.7</td>
<td>35</td>
</tr>
<tr>
<td>17. γ-Ethoxy-γ-butyrolactone hydrolysis</td>
<td>-6.9</td>
<td>36</td>
</tr>
</tbody>
</table>

4. Volumes of Activation

Volumes of activation, like entropies of activation, may be employed as an empirical criterion of reaction molecularity. Typical values of ΔV for acid-catalyzed reactions considered to be unimolecular are in the range of −2 to +6 cm³/mole while those for reactions considered to be bimolecular (with nucleophilic participation of solvent) are in the range −6 to −10 cm³/mole (39). This result is intuitively reasonable since, in the unimolecular case, some loosening of a covalent bond will have occurred in the transition state with an attendant overall increase in volume of the reacting species, while in the bimolecular case, the partial formation of a covalent bond between the substrate and water in the transition state may result in an overall decrease in volume of the reacting species. Volumes of activation are probably a more reliable guide to mechanism than the corresponding entropies in that the volumes changes accompanying
the preequilibrium protonation seem less susceptible to variation than do the entropy changes. In Table IV, volumes of activation for several reactions of interest are recorded. In each case, the value falls into the range typical of reactions involving unimolecular decomposition of the protonated species.

5. Isotope Effects

Solvent deuterium isotope effects on the rate of hydrolysis of certain acetals and ortho esters are collected in Table V. Most of these values fall in the range $k_{\text{D}_2\text{O}}+/k_{\text{H}_2\text{O}}+ = 2$ to $3$. Such solvent deuterium isotope effects probably primarily reflect the isotope effect on the preequilibrium protonation reaction (47). Rate increases of two- to threefold in $\text{D}_2\text{O}$ compared to $\text{H}_2\text{O}$ are typical of acid-catalyzed reactions considered to be unimolecular (A-1) and are similar to those predicted theoretically. For example, Bunton and Shiner have calculated a deuterium solvent isotope effect for acetal hydrolysis of $2.5$ (48). Of particular note are the isotope effects on the hydrolysis of ethyl orthocarbonate. With the hydrated proton as catalyst, the isotope effect is small, and with acetic acid as catalyst, the isotope effect is actually less than unity. These results suggest the involvement of proton transfer in the transition state (cf. discussion, p. 33).

Kilpatrick has carried out a very careful study of the effect of temperature on the solvent deuterium isotope effect for 1,1-dimethoxyethane and 2-methyl-1,3-dioxolane hydrolysis in the temperature range 0 to 40° (45). In both cases, the isotope effect was observed to decrease with increasing temperature. The temperature dependence of the isotope effect is given by $k_{\text{D}_2\text{O}}+/k_{\text{H}_2\text{O}}+ = 1.166$.
TABLE V
Kinetic Solvent Deuterium Isotope Effects for Acid-Catalyzed Acetal,
Ketal, and Ortho Ester Hydrolysis

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>$T$, °C</th>
<th>$k_{\text{D}^+}/k_{\text{H}^+}$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 1,1-Dimethoxyethane</td>
<td>Water</td>
<td>25</td>
<td>2.70</td>
<td>45</td>
</tr>
<tr>
<td>2. 1,1-Diethoxyethane</td>
<td>Water</td>
<td>25</td>
<td>2.66</td>
<td>42</td>
</tr>
<tr>
<td>3. 1,1-Diethoxyethane</td>
<td>50% dioxane</td>
<td>25</td>
<td>3.1</td>
<td>51</td>
</tr>
<tr>
<td>4. 1,1-Diethoxyethane</td>
<td>Water</td>
<td>15</td>
<td>2.61</td>
<td>52</td>
</tr>
<tr>
<td>5. 2-Methyl-1,3-dioxolane</td>
<td>Water</td>
<td>25</td>
<td>2.70</td>
<td>45</td>
</tr>
<tr>
<td>6. 2-Phenyl-1,3-dioxane</td>
<td>10% acetonitrile</td>
<td>25</td>
<td>3.1</td>
<td>44</td>
</tr>
<tr>
<td>7. Ethyl orthoformate</td>
<td>Water</td>
<td>25</td>
<td>2.05</td>
<td>42</td>
</tr>
<tr>
<td>8. Ethyl orthoformate</td>
<td>Water</td>
<td>25</td>
<td>2.35</td>
<td>43</td>
</tr>
<tr>
<td>9. Ethyl orthoformate</td>
<td>Water</td>
<td>15</td>
<td>2.70</td>
<td>31</td>
</tr>
<tr>
<td>10. Ethyl orthoformate</td>
<td>Water</td>
<td>35</td>
<td>2.31</td>
<td>31</td>
</tr>
<tr>
<td>11. Ethyl orthobenzoate</td>
<td>Water</td>
<td>25</td>
<td>2.3</td>
<td>27</td>
</tr>
<tr>
<td>12. Methyl orthobenzoate</td>
<td>Water</td>
<td>25</td>
<td>2.2</td>
<td>32</td>
</tr>
<tr>
<td>13. Ethyl orthocarbonate</td>
<td>Water</td>
<td></td>
<td>1.4</td>
<td>46</td>
</tr>
<tr>
<td>14. Ethyl orthocarbonate</td>
<td>Water</td>
<td></td>
<td>0.7</td>
<td>46</td>
</tr>
</tbody>
</table>

* Catalyst used with substrates 1 through 13 was $\text{H}_3\text{D}_3\text{O}^+$; catalyst used with substrate 14 was $\text{CH}_3\text{COOH(D)}_2$. 

exp ($521/RT$) in the former case and by $k_{\text{D}^+}/k_{\text{H}^+} = 1.191 \exp (501/RT)$ in the latter.

Shiner and Cross have measured the secondary deuterium isotope effect resulting from $\alpha$-deuteration in the carbonyl component on the rates of hydrolysis of the diethyl ketal of acetone, methyl ethyl ketone, methyl isopropyl ketone, and phenoxyacetone (49). For the fully $\alpha$-deuterated substrates, a value of $k_{\text{H}}/k_{\text{D}}$ of 1.1 to 1.25 was obtained in each case. These results may be attributed to either the greater relative inductive electron donating power of H compared to D or to the greater relative hyperconjugative electron-donating power of H compared to D or to both (50). Regardless of the precise explanation, these results substantiate the earlier conclusion that electron donation accelerates ketal hydrolysis, as expected in terms of rate-determining carbonium ion formation.

6. Correlations of Rates with Acidity Functions

The hydrolysis of dimethoxymethane (53), diethoxymethane (29), and 1,1-dimethoxy-2-chloroethane (51) in moderately concentrated solutions of mineral acids is characterized by rate constants which are
correlated by the Hammett acidity function, $h_0$, and not by the molar concentration of acid. This finding, according to the Zucker-Hammett hypothesis, suggests a unimolecular reaction path (54,55). So many exceptions to this hypothesis have been recognized the correlations of rate constants with $h_0$ cannot be relied upon as an indication of mechanism (56,57). Nevertheless, the above findings are consistent with and limited support for a unimolecular reaction path for the hydrolysis of acetals at least. Kreevoy has extended these observations to 50% aqueous dioxane solutions, a medium in which $h_0$ is not strictly defined, for the hydrolysis of four ketals and acetals (58). With varying concentrations of perchloric acid in this solvent, the rates of hydrolysis are correlated with the proton-donating power of the solvent as measured by the extent of protonation of 2-nitro-4-chloroaniline.

A related criterion of mechanism developed by Bunnett is considerably more rigorous and is based on the correlation ($w$ values) of rate constants with the activity of water for reactions run in moderately or strongly acidic media (59). Correlation of rate constants with water activity for acetal hydrolysis yields values of $w$ which are characteristic of reactions thought to occur by unimolecular reaction paths (59).

7. Experiments with Added Nucleophilic Reagents

Each of the criteria indicated above provides support for the thesis that the initial step involving carbon-oxygen bond cleavage for the hydrolysis of acetals, ketals, and ortho esters involves unimolecular decomposition of the protonated substrates rather than a bimolecular reaction involving solvent as the nucleophilic reagent. Taken together, these criteria constitute a strong case for this conclusion. Considerable further support is provided by studies of the hydrolysis of methyl orthobenzoate and ethyl orthocarbonate in the presence of added nucleophilic reagents.

The first-order rate constants for the decomposition of methyl orthobenzoate in slightly acidic aqueous solution are independent of the concentration of added hydroxylamine and semicarbazide under conditions in which an appreciable fraction of the ortho ester yields amine addition products rather than methyl benzoate (32). This result is illustrated in Figure 3. For example, in the presence of 0.9M hydroxylamine at pH 5.45, approximately 85% of the methyl
orthobenzoate yields a hydroxylamine addition product, probably \( N \)-hydroxymethyl benzimidate, yet the first-order rate constant \((0.00038 \text{ sec}^{-1})\) is not appreciably different from that measured in the absence of hydroxylamine \((0.00035 \text{ sec}^{-1})\). Methyl benzoate does not react with hydroxylamine under the conditions of these reactions at an appreciable rate. Furthermore, the fraction of methyl orthobenzoate yielding methyl benzoate as the product may be accurately calculated, assuming that the conjugate acid of the ortho ester undergoes a unimolecular decomposition yielding an intermediate carbonium ion which is then rapidly partitioned between water, yielding methyl benzoate, and amine, yielding amine addition product. On this basis, the free base of hydroxylamine is calculated to be 2000-fold and the free base form of semicarbazide 275-fold more reactive toward the carbonium ion than water. These results strongly suggest that solvent does not participate as a nucleophilic reagent in the rate-determining step of acid-catalyzed methyl orthobenzoate hydrolysis. The above experiments are closely related to the rate-product criterion originally employed by Ingold and his co-workers for the identification of unimolecular solvolysis reactions (60).