Mechanism and Catalysis for Hydrolysis of Acetals, Ketals, and Ortho Esters

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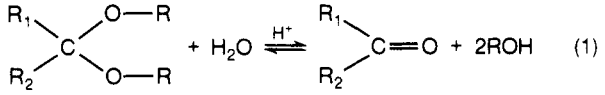
Received June 19, 1973 (Revised Manuscript Received November 12, 1973)

Contents

I. Introduction

Hydrolysis of acetals, ketals, ortho esters, and related substrates is described by the equation



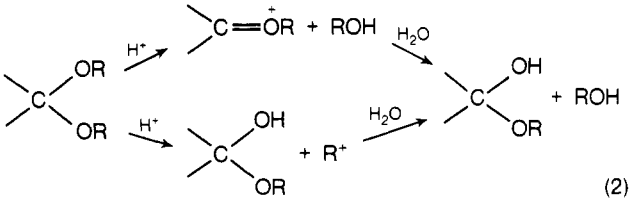
(1)

The complete reaction requires the rupture of two carbon–oxygen bonds, the addition of a molecule of water to the substrate, and several proton-transfer reactions. It follows that the hydrolytic reaction must involve formation of a number of intermediates along the reaction pathway. This simple realization immediately raises a large number of questions concerning reaction mechanisms such as: What is the structure of the intermediates involved? Which step of the reaction sequence is rate determining? Do changes in rate-determining step occur as a function of pH or catalyst concentration? Since the general class of substrates under consideration here includes a variety of individual structures, it is clear that the answers to these and other questions may vary from substrate to substrate. Moreover, superimposed on each of the above questions are those concerned with catalysis. It is well established that hydrolysis of most acetals, ketals, and ortho esters occurs with specific acid catalysis and that hydrolysis of certain of these substrates occurs with general acid catalysis as well. What is the mechanism of such catalysis? What is the role of proton-transfer reactions in determining overall reaction rates? How do these findings relate to the observation of enzymatic catalysis for substrates of related structure? In view of the number of questions involved in specification of mechanism and catalysis for hydrolysis of these simple substrates, it is not surprising that a substantial literature exists dealing with these matters. To present a current summary of this literature is the task of this review.

The hydrolysis of acetals and related substrates has not been reviewed in detail since 1967,[1] although a recent brief review is available.[2] In the succeeding five years, substantial new information, leading to new insights, has been collected. Much of this is in the areas of isotope effects, intramolecular group participation, surfactant catalysis, and enzyme catalysis for these reactions. This review will bring the previous one up to date in those areas previously covered and will develop others that have become important only recently.

Acetals, ketals, and ortho esters are structurally related to a number of other classes of compounds, the hydrolysis of which has received study. Frequently, we shall have the opportunity to refer to these related reactions. The simplest related compounds are formed by replacement of one or more of the oxygen atoms by nitrogen or sulfur; such a substitution yields thioacetals, carbinolamines (important as intermediates in carbonyl addition reactions), oxazolidines, oxathiolanes, and so forth. Also directly related are the glycosides and *N*-glycosides (glycosylamines). The hydrolysis of these substrates has been recently reviewed.[3,4]

Certain aspects of the hydrolysis of acetals, ketals, and ortho esters appear so well established as to not require development here. These aspects may be considered as background to the current review. Important among them is the site of bond cleavage for these reactions. In principle, carbon–oxygen bond cleavage might occur so as to yield either a carboxonium ion or alkyl carbonium ion intermediates (eq. 2). On the basis of the



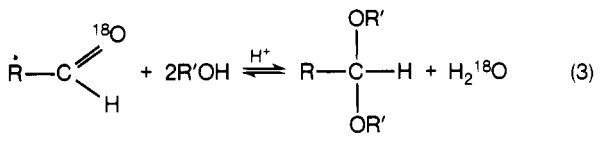
(2)

relative stabilities of the two intermediates, one might expect the reaction to occur with cleavage of that bond leading to formation of the carboxonium ion. This expectation has been fully borne out. 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.[5] This finding excludes formation of the alkyl carbonium ion, in which case substantial or complete racemization of the alcohol would be expected, and an A2 reaction involving nucleophilic attack of solvent on the alcohol 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.[6,7]

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.[8] The parent alcohols chosen for study were (−)-α-phenethyl alcohol, methylvinylcarbinol, and phenylvinylcarbinol. 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 with 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.[9,10] Finally, the possibility that hydrolysis of these substrates occurs *via* nucleophilic attack of solvent at the carbinol carbon atom was explicitly excluded through the observation that methanolysis of a phenethyl alcohol derived acetal yields 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.*, strongly corroborated the above conclusion in an isotope tracer study of acetal formation and hydrolysis.[11] 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 3). In a like fashion, hydrolysis of



(3)

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 3). 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 case 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, hydrindene, and 1-phenylcyclohexane yield the cis diols almost exclusively on hydrolysis, a result consistent only with carbonyl carbon–oxygen bond cleavage.[12-14] These results should not be interpreted to indicate that cleavage of the alcohol carbon–oxygen bond, by either a unimolecular or bimolecular process, never occurs in these reactions. But they do serve to indicate that such a reaction pathway will be restricted to substrates of unusual structure or will contribute in only a minor way to the overall hydrolytic process for substrates of ordinary structure.

A second matter which seems to be generally agreed upon is the noninvolvement of water as a nucleophilic reagent in the transition state for hydrolysis of acetals, ketals, and ortho esters. This point has been explicitly assumed in the formulation of eq 2 which indicates carbonium ion pathways only. Several lines of evidence, including volumes of activation, entropies of activation, structure–reactivity correlations, solvent isotope effects, and the like, suffice to indicate the involvement of carbonium ions in the transition state for hydrolysis of most of the substrates in this class.[1] Again, this is not to suggest that A2 reactions never occur for the hydrolysis of these substrates; in fact, we shall devote some effort to detecting those cases in which such a route may be important. Moreover, we will have the occasion to review much of the information which has led to the conclusion that water is not involved as a nucleophile in the transition state for these reactions. But our discussion will be in the context of the assumption that this is the case. For extensive documentation of the point, the reader may refer to the earlier review.[1]

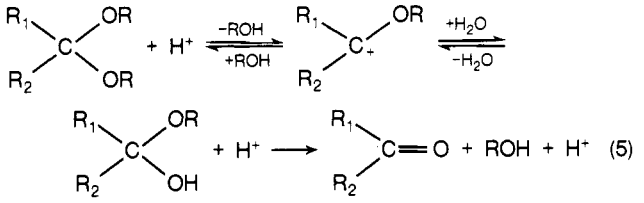
Finally, we may note that a great many investigations have established that the rate law for hydrolysis of most of the substrates under consideration has the form

$$k_{obsd} = k_H(H^+) + \sum_i k_{HA_i}(HA)_i \qquad (4)$$

in which the terms corresponding to general acid catalysis are frequently not important.

II. The Rate-Determining Step

The considerations just cited permit us to formulate the hydrolysis of acetals, ketals, and ortho esters according to the multistep pathway shown in eq 5 in which proton transfer reactions have not been explicitly included.

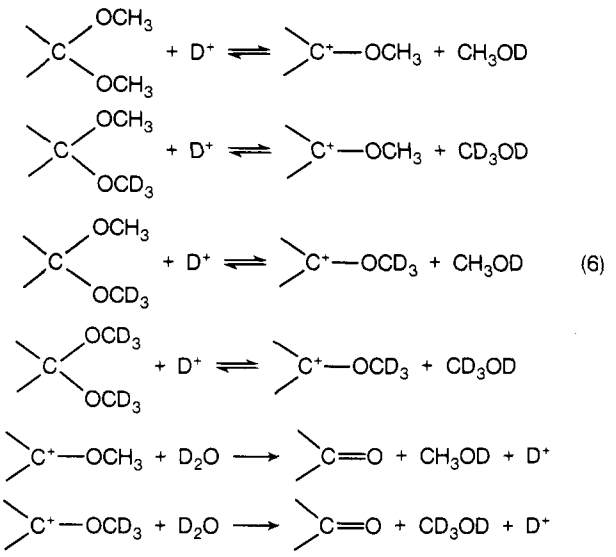


(5)

We will consider the importance of proton transfer reactions for hydrolysis of these substrates below. At the moment, let us consider which of the steps of eq 5 is the best candidate for rate-determining step. In solutions containing little alcohol, rate-determining reaction of the carbonium ion with solvent is extremely unlikely since this requires that alcohol react with the carbonium ion, regenerating starting material, more rapidly than water reacts with the carbonium ion, yielding products. Since the *rate constants* for reaction of alcohol and water are almost certainly about the same, the *rate* for the latter reaction must be greater than that for the former. A similar argument suggests that the tetrahedral intermediate decomposition, the final step, is not rate-determining. Since the overall equilibrium constant for interconversion of substrate and tetrahedral intermediate should be about unity, the latter would be present in much greater concentration than the former were equilibrium established, owing to the high concentration of water relative to alcohol. Since the *rate constants* for decomposition of these species should be about equal, the *rate* for intermediate decomposition should be greater than the corresponding quantity for the substrate. These conclusions are fully corroborated in kinetic studies of ketal and ortho ester hydrolysis conducted in the presence of deuterated alcohols.

A study of the kinetics and product composition for the hydrolysis of methyl ketals and methyl ortho esters in

methanol-d_4–deuterium oxide mixtures (eq 6), employing proton magnetic resonance spectroscopy as an analytical



(6)

tool, has provided a simple and straightforward experimental distinction between several of the possible rate-determining steps for these reactions.[15,16] The experimental quantities determined by this method in the study of, for example, methyl orthobenzoate hydrolysis, include the first-order rate constants for the disappearance of the methoxy protons of the ortho ester, $k_{\text{ortho ester}}$, for the appearance of the methyl protons of methanol, k_{MeOH}, and for the appearance of the methoxy protons of the carboxylic ester, k_{ester}. Since the proton resonance singlets for each of these groups are well separated, the rate constants can be determined simultaneously. In addition, the ratio of integrated proton intensities at infinite time of the products to some internal, time-independent standard provides a quantitative measure of product composition for many substrates.

Both the product composition and the relative magnitudes of the various rate constants are functions of the nature of the rate-determining step. If carbonium ion formation were rapid and reversible (*i.e.*, carbonium ion formation not rate determining), the methoxy groups of the starting material would be rapidly exchanged for deuteriomethoxy groups through reaction of the carbonium ion with solvent deuteriomethanol. The ortho ester would be converted more slowly to carboxylic ester product. Thus, $k_{\text{ortho ester}}$ and k_{MeOH} would be considerably larger than k_{ester}. Furthermore, little or no carboxylic ester product containing methoxy protons would be formed since virtually all of the ortho ester would have been converted into the corresponding deuterated material in the preequilibrium exchange reactions. In contrast, if carbonium ion formation were rate determining, methanol would not be exchanged for deuteriomethanol in a preequilibrium reaction; hence, $k_{\text{ortho ester}}$, k_{MeOH}, and k_{ester} would be nearly identical. In addition, only protio carboxylic ester would be produced as reaction product.

Studies of this type have been performed employing 2,2-dimethoxypropane, 6,6,6-trimethoxyhexanonitrile, methyl orthobenzoate, and methyl orthocarbonate as substrates.[16] The course of the hydrolysis of methyl orthobenzoate as a function of time is indicated in Figure 1. As may be judged qualitatively from this figure, the rate of disappearance of the methoxy protons of the ortho ester is comparable to the rate of appearance of the corresponding protons of methyl benzoate. Furthermore, a rather substantial amount of methyl benzoate, as opposed to deuteriomethyl benzoate, is formed in the reaction as judged from the intensity of the appropriate signal in the infinite time spectrum. These results are just those predicted on the basis of rate-determining carbonium ion formation. A quantitative treatment of the kinetics of reactions of this type reveals that the relative magnitudes of the various rate constants and the product composition patterns are those expected for rate-determining carbonium ion formation provided that deuterium oxide and deuteriomethanol are about equally reactive toward the carbonium ion. The latter conclusion is in accord with the relative reactivities of water and methanol toward, for example, the *tert*-butyl and benzhydryl carbonium ions.[17-20]

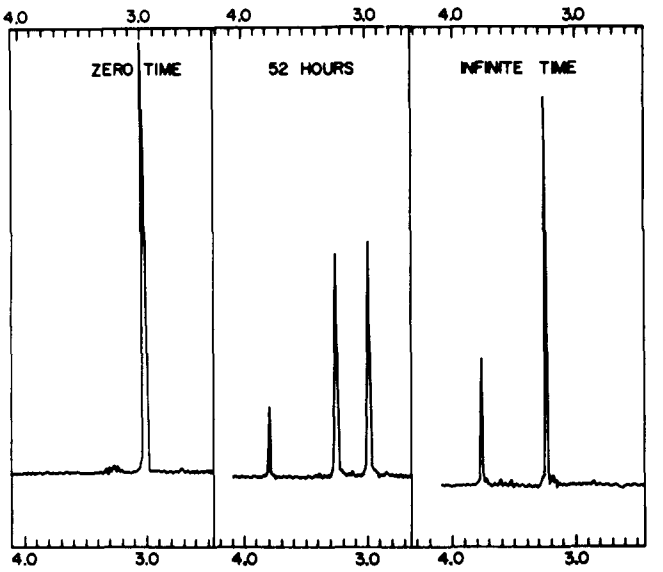
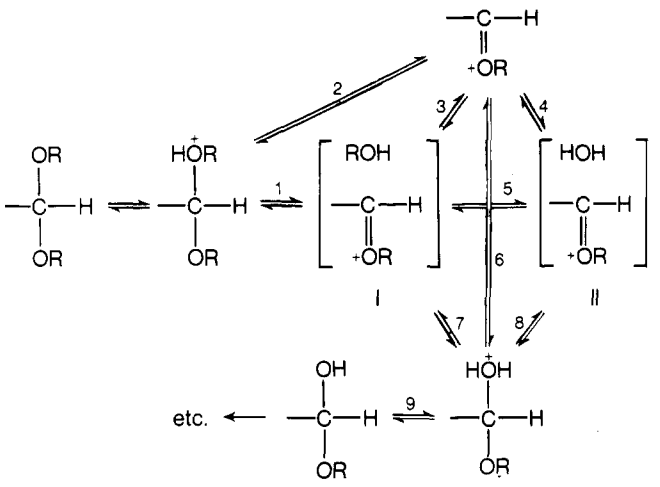


Figure 1. Initial, intermediate, and final proton magnetic resonance spectra for the hydrolysis of methyl orthobenzoate in an equimolar mixture of deuterium oxide and methanol-d_4. Methoxy protons of ortho ester appear at 3.0 ppm, those of methyl benzoate at 3.8 ppm, and those of methanol at 3.25 ppm (from ref 16).

These data suggest that the hydrolysis of acetals, ketals, and ortho esters occurs with rate-determining formation of the carbonium ion derived directly from the substrate (we shall have to modify this conclusion somewhat to account for the importance of proton transfer reactions for hydrolysis of some of these substrates). But the formulation of eq 5 is certainly incomplete in the respect that the possibility of ion–molecule pairs as discrete intermediates has been neglected. What about the possibility that diffusion apart of the carbonium ion–alcohol pairs is the rate-determining step? To examine this possibility, the course of acetal hydrolysis is formulated in detail in Scheme I. Let us consider each of the mechanistically distinct pathways.

The simplest pathway is 2 → 6 → 9; this is symmetrical about the free carbonium ion and does not involve formation of ion–alcohol pairs. If this route is correct, step 2 must be rate determining since carbonium ion formation is irreversible. The reaction pathway 1 → 5 → 8 → 9 is symmetrical about structures I and II, carbonium ion–alcohol pairs. Reaction 5 cannot be rate determining in this sequence since this would require that the α-deuterium isotope effect be maximal for all acetals, contrary to results described below. Reaction 8 cannot be rate determining either since this would require that I and II be in equilibrium with each other, and the latter will certainly exist in higher concentrations than the former (due to high concentration of water relative to alcohol in the reaction medium). It follows that the reverse of reaction

SCHEME I



1 would be slower than reaction 8 in the forward direction, ruling out 8 as the rate-determining step. Reaction 1 is the remaining possibility. The reaction pathway 1 → 3 → 4 → 8 → 9 is similar to that just described except that the free carbonium ion is considered to be an intermediate along the reaction coordinate. The arguments just developed apply to this case with equal force: reaction 1 is the only reasonable rate-determining step. Finally, reaction pathways such as 1 → 7 → 9 or 1 → 3 → 6 → 9 appear to be unlikely on the basis of lack of symmetry with respect to acetal and hemiacetal. That is, it seems unlikely that one would form I as an intermediate without also forming II as an intermediate. In view of these considerations, we are strongly inclined to the view *that either reaction 1 or 2 must be rate determining for* acetal and ketal hydrolysis. Inclusion of a proton transfer process then accounts for the rate-determining step for ortho ester and orthocarbonate hydrolysis.

To this point, we have established that the transition state for hydrolysis of acetals, ketals, and ortho esters involves carbon–oxygen bond cleavage, which may be accompanied by proton transfer, leading to formation of a carbonium ion derived from the carbonyl moiety of the substrate. In an effort to define the transition state structure more precisely, let us review several aspects of these reactions including substrate basicities, structure–reactivity relationships, secondary deuterium isotope effects, and solvent deuterium isotope effects. These considerations will lay the foundation for a consideration of catalytic mechanisms subsequently.

III. Basicities for Acetals, Ketals, and Ortho Esters

Acetals, ketals, and ortho esters are weak oxygen bases. Since the hydrolysis of these species usually involves acid catalysis, a quantitative understanding of their basic properties is highly desirable for attainment of a better understanding of the mechanism of these reactions. The acid lability of these reactants precludes direct measurement of their extent of protonation as a function of the acidity of the medium, the most straightforward means of measuring base strength. As an alternative for cases of this type, it is possible to employ stretching frequencies in the infrared of O–H or O–D bonds of probe molecules dissolved in the substance of interest as a measure of the basicity of those species to which the probe molecule forms hydrogen bonds.[21] The magnitude of the frequency shift for each of the compounds of interest relative to a suitable nonbasic standard is a measure

TABLE I. Basicities for Acetals, Ketals, and Ortho Esters

Substrate	pK_a[a]	Log k_2[b]	Ref
A. Dialkoxymethanes[c]			
Dimethoxymethane	−4.57		23
Diethoxymethane	−4.13		23
Diisopropoxymethane	−3.70		23
Di-*tert*-butoxymethane	−2.85		23
Di-2-fluoroethoxymethane	−4.99		23
Di-2-chloroethoxymethane	−5.32		23
Di-2,2,2-trifluoroethoxymethane	−8.40		23
Di-2,2,2-trichloroethoxymethane	−7.85	3.38	23
Diphenoxymethane	−6.53		23
B. Other Acetals and Ketals			
2,2-Dimethoxypropane	−5.2		24
Benzaldehyde diethyl acetal[d]	−5.7		24
Acetaldehyde ethyl 2,2,2-trichloroethyl acetal	−7.53	7.16	e
2-Methyl-1,3-dioxolane	−4.60	2.71	f
C. Ortho Esters			
Methyl orthoformate	−5.69	8.00	g
Ethyl orthoformate	−5.18	8.05	g
Isopropyl orthoformate	−4.38	7.62	g
2-Chloroethyl orthoformate	−6.57	7.10	g
Methyl orthoacetate	−6.4		24
Ethyl orthoacetate	−4.72	10.45	g
Methyl orthocarbonate	−8.5		24
Ethyl orthocarbonate	−6.31	9.27	h

[a] For the conjugate acid of the indicated substrates. [b] Logarithms of the calculated first-order rate constants, in sec^{-1}, for the decomposition of the protonated substrates (see text). [c] Values of pK_a for the conjugate acids of a number of unsymmetrical dialkoxymethanes have been measured as well; see ref 23. [d] Values of pK_a for several para-substituted derivatives have also been measured but are not detectably different from that for the parent compound; see ref 24. [e] A. Kankaanpera, *Suomen Kemistilehti B*, **42**, 460 (1969). [f] A. Kankaanpera, *Acta Chem. Scand.*, **23**, 2211 (1969). [g] A. Kankaanpera and M. Lahti, *Suomen Kemistilehti B*, **42**, 427 (1969). [h] A. Kankaanpera and M. Lahti, *Acta Chem. Scand.*, **23**, 2465 (1969).

of the relative basicity of these compounds. In addition, it is possible to calculate approximate values of pK_a by use of a linear relationship which has been established between $\Delta\mu$ and pK_a developed for a series of compounds, the values of pK_a of which may also be measured by conventional means.[21] The most commonly used probe molecule for such studies is deuteriomethanol.

The first measurements of the basicity of acetals, ketals, and ortho esters were obtained using this technique with phenol as the probe molecule.[22] These early studies indicated that the following order of basicity obtains: ethers > ketals > ortho esters > orthocarbonates.[22] The fact that increasing substitution of alkoxy for alkyl functions lowers basicity is the expected result on the basis that the alkoxy function has the greater inductive electron-withdrawing capacity. Subsequently, there have been a number of systematic studies of the basicity of these substrates, notably in the laboratories of Kankannpera. Results of these studies are collected in Table I.

The values of pK_a collected in Table I should be viewed with some reservations since some oxygen bases are known to deviate substantially from the linear $\Delta\mu$ against pK_a plot. Nevertheless, these substances are structurally related, and differences in values of pK_a, within a given study at least, are real and the absolute values may be regarded as reasonable approximations. There are two instances in these data in which indicated differences cannot be as large as indicated: those between methyl and ethyl orthoacetates and between methyl and ethyl orthocarbonates. The large differences ob-

tained in different laboratories cannot be accounted for on the basis of the difference in electron-withdrawing capacity of the methyl and ethyl functions.

Note that a direct comparison between the basicity of acetals and ketals, on the one hand, and ortho esters, on the other, actually requires a statistical correction. The former substrates have two sites for protonation and the latter three (in the case of orthocarbonates, there are four). The result is that ortho esters and orthocarbonates appear to be somewhat more basic compared to acetals and ketals than they really are. The indicated statistical corrections have not been applied to the data in Table I since these corrections may not be larger than the errors in the measurements themselves.

The effects of structure on basicity of acetals, ketals, and ortho esters are accounted for quite nicely on the basis of polar effects of the various substituents involved.[23,24] In fact, for those cases in which comparison is possible, the measured values of pK_a agree quite well with values calculated prior to these measurements on the basis of a linear free-energy relationship and effects of polar substituents.[25] This result strongly suggests that double bond–no bond resonance, which should dramatically reduce the basicity of ortho esters and orthocarbonates relative to acetals and ketals, is not important for these compounds.[26]

Values of pK_a for the conjugate acids of acetals, ketals, and ortho esters may yield direct information concerning the mechanism of hydrolysis of these substances. Let us consider one possible mechanism, that involving rapid reversible protonation of the substrate followed by rate-determining carbonium ion formation (A1).

$$S + H^+ \overset{K_{SH}}{\rightleftharpoons} SH^+ \xrightarrow{k_2} \text{products} \qquad (7)$$

For the mechanism, the first-order rate constant, k_2, for decomposition of the protonated species may be calculated from the measured second-order rate constant for the overall reaction and the dissociation constant for the conjugate acid of the substrate: $k_2 = k_H K_{SH}$. For several of the substances of Table I, logarithms of values of k_2 have been calculated from available data and are included in the table. For many of the substrates, mostly simple acetals and ketals, reasonable values of k_2 are obtained, and a simple A1 mechanism is at least possible in these cases. For other substrates, including ortho esters, orthocarbonates, and very weakly basic acetals, calculated values of k_2 are near or greater than the diffusion-controlled limit. For these substrates, the simple A1 mechanism cannot be correct, and we must consider more complicated alternatives. First, it is possible that protonation of the substrate occurs in a separate step from carbon–oxygen bond cleavage and is partially or completely rate determining. Second, substrate protonation and carbon–oxygen bond cleavage may be concerted processes. Distinction between these two is difficult. We will return to this point later and discuss it in more detail in light of additional data to be reviewed.

IV. Structure–Reactivity Relationships

A great deal of information has been collected relating to structure–reactivity correlations for hydrolysis of acetals, ketals, and ortho esters. These data, together with that for some related reactions, are summarized in Table II. A detailed examination of all of these data would be prohibitive in terms of space, and we focus attention on some salient features.

First, second-order rate constants for specific acid catalyzed hydrolysis of these substrates are quite sensitive to the nature of polar substituents in the carbonyl moiety of the substrate (entries 1–21); without exception, rate constants increase markedly with increasing electron donation from the polar substituent. This is, of course, precisely the expected result on the basis of a transition state which has partial carbonium ion character: the developing carbonium ion will be stabilized relative to the substrate by those substituents which donate electrons. These data argue strongly against reaction mechanisms involving nucleophilic attack by water in the transition state and those involving rate-determining substrate protonation, for which much smaller effects of polar substituents would be expected.

For those substrates bearing polar substituents in an aryl moiety, rate constants for specific acid catalyzed hydrolysis are more frequently correlated by the σ rather than by the σ^+ substituent constants. Only the data for the benzylidene–lincomycin acetals (entry 5) follow the σ^+ constants and those for para-substituted benzaldehyde diethyl acetals in 50% dioxane (entry 12) and for 2-(4-substituted phenyl)-1,3-dioxolanes (entry 9) follow constants intermediate between σ and σ^+.[27]

$$\log (k/k_0) = \rho[\sigma + r(\sigma^+ - \sigma)] \qquad (8)$$

At first glance this is a surprising result, since the σ^+ substituent constants quite frequently successfully correlate data for carbonium ion reactions, for which electron donation by resonance is frequently of special importance.[28] A complete explanation of the mechanism of hydrolysis of these substrates will have to account for the observation that electron donation by resonance is evidently not particularly important; we return to this point later in the discussion in light of insight gained through study of secondary deuterium isotope effects (section VI).

Values of ρ for acid-catalyzed hydrolysis of methyl orthobenzoates increase with increasing methanol content in the solvent (entries 1–3). This result may reflect either a medium effect or a change in rate-determining step or both. It is clear that when the concentration of methanol in the solvent is sufficiently high, the carbonium ion will more often react with methanol, regenerating ortho ester, than with water, yielding products. This has the effect, then, of changing the rate-determining step from carbonium ion formation to trapping of the carbonium ion by water. It is, however, not clear that a change in rate-determining step necessarily requires a change in the value of ρ since the two transition states involved are likely to be quite similar. Moreover, data to be discussed below suggest that values of ρ are not particularly sensitive indicators of changes in transition state structure. The possible importance of medium effects is emphasized by the observation that hydrolysis of methyl orthobenzoates in micelles of sodium dodecyl sulfate also exhibits a more negative value of ρ than the same reaction in water (compare entries 1 and 4). On the other hand, the hydrolysis of benzaldehyde diethyl acetals is about equally sensitive to substituent effects in water and 50% dioxane (entries 10–12), suggesting the medium effects may not greatly influence ρ in this case. However, hydrolysis of these substrates in the presence of micelles of sodium dodecyl sulfate is more sensitive to the nature of polar substituents than is the reaction in water (entry 13).

Hydrolysis of orthobenzoates in water is less sensitive to the nature of polar substituents than is the hydrolysis of acetals of benzaldehyde in the same solvent (compare entry 1 with entries 10 and 14). This observation provides mild support for the idea that the transition state for acetal hydrolysis may have more carbonium ion character

TABLE II. A Summary of Linear Free-Energy Relationships for Hydrolysis of Acetals, Ketals, and Ortho Esters

Substrates	ρ	No. of substituents	Temp, °C	Solvent	Ref	Comments
A. Variable Polar Substituents in Carbonyl Moiety of Substrate						
1. Methyl 4-substituted orthobenzoates	−1.16	7	25	Water	47	
2. Methyl 4-substituted orthobenzoates	−2.02	5	30	70.0% methanol	*a*	
3. Methyl 4-substituted orthobenzoates	−2.3	5	25	98.0% methanol	47	
4. Methyl 4-substituted orthobenzoates	−2.5	5	25	0.03 M SDS[b]	97	
5. 3,4-O-(4-Substituted benzylidene)lincomycin acetals	−1.85[c]	5	70	Water	*d*	r = 0.996
6. 2-(4-Substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes	−2.0	4	30	Water	*e*	
7. 2-Alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes	−2.2[f]	4	30	50.0% dioxane	*g*	
8. 2,2-Di(4-substituted phenyl)-1,3-dioxolanes	−2.3	4	30	20.0% dioxane	64	
9. 2-(4-Substituted phenyl)-1,3-dioxolanes	−3.25[h]	5	30	50.0% dioxane	1, 42	
10. 4-Substituted benzaldehyde diethyl acetals	−3.3	6	25	Water	55	
11. 3-Substituted benzaldehyde diethyl acetals	−3.35	4	30	50.0% dioxane	1, 42	
12. 3,4-Substituted benzaldehyde diethyl acetals	−3.35[h]	8	30	50.0% dioxane	1, 42	
13. 4-Substituted benzaldehyde diethyl acetals	−4.1	6	25	SDS[b]	55	
14. 4-Substituted benzaldehyde di-*tert*-butyl acetals	−3.97	5	25	Water	*i*	
15. 1,1-Dialkyl-1,1-diethoxymethanes	−3.600[j]	20	25	49.6% dioxane	*k*	Error = 0.115
16. 1-Alkyl-1-methyl-1,1-diethoxymethanes	−3.541[f]	9	25	49.6% dioxane	*k*	Error = 0.176
17. 1-Alkyl-1,1-diethoxymethanes	−3.652[f]	15	25	49.6% dioxane	*k*	Error = 0.081
18. 2-Alkyl-1,3-dioxolanes	−3.92[l]	7	25	Water	*m*	Error = 0.49, r = 0.998
19. 2,2-Dialkyl-1,3-dioxolanes	−4.00[j]	5	30	50.0% dioxane	57	
20. 2-(Alkylmethyl)-2-methyl-1,3-dioxolanes	−1.48[f]	8	30	Water	79	
21. 2-(Alkylmethyl-)2,5,5-trimethyl-1,3-dioxanes	−1.33[f]	8	30	Water	79	
B. Variable Polar Substituent in Nondeparting Alkoxy Function						
22. $ROCH_2OC_6H_4$-2-$COOCH_3$	−3.00[f]	4	30	Water	84	Error = 0.05
23. $ROCH_2OC_6H_4$-2-COOH	−3.00[f]	5	30	Water	84	Error = 0.05
24. $ROCH_2OC_6H_4$-2-COO^-	−3.00[f]	5	30	Water	84	Error = 0.05
25. Methyl 2-substituted-2-deoxy-β-D-glucosides	−2.34[f]	4	60	Water	2	
26. CH_3COOCH_2OR	−3.42[f,n]	3	25	Water	*o*	Error = 0.30, r = 0.997
27. $ROCH_2OR$	−4.31[f,n]	7	25	Water	*p*	Error = 0.20, r = 0.993
28. $ROCH_2OCH_3 \rightarrow ROCH_2^+ + CH_3OH$	−4.11[f,n]	6	25	Water	*q*	Error = 0.38, r = 0.976
29. $ROCH_2OR$	−1.96[f,n]	6	25	Water	*q*	Error = 0.29, r = 0.941
30. $ROCH_2OR$	−2.17[f,n]	4	25	Water	*o*	Error = 0.38, r = 0.942
31. $R_3COCH_2OCR_3$	−0.83[f]	12	25	Water	*m*	Error = 0.12, r = 0.984
32. $R_3COCH_2OCR_3$	−0.86[f]	12	25	60.0% dioxane	*m*	Error = 0.08, r = 0.996
33. 5,5-Disubstituted-2,2-dimethyl-1,3-dioxanes	−0.52[f]	7	30	Water	79	
34. $(RO)_2CH$	−1.58[f,n]	5	25	Water	*r*	Error = 0.02, r = 0.999
35. $(RO)_3CH$	−1.89[f,n]	5	25	65.0% dioxane	*r*	Error = 0.18, r = 0.979
C. Variable Polar Substituent in Leaving Alkoxy Function						
36. 3,4-Substituted phenyl-α-D-glucosides	−0.006	10	70	Water	*s*	
37. 2,4-Substituted phenyl-β-D-glucopyranosides	−0.06	6	78.2	Water	80	
38. 4-Substituted phenyl-β-D-glucopyranosiduronic acids	−0.09	3	25	Water	*t*	Error = 0.05
39. Aryl 2-acetamido-2-deoxy-β-D-glucopyranosides	−0.11	5	78.2	Water	80	
40. 3,4-Substituted phenyl-α-maltosides	−0.25	10	60	Water	*u*	
41. 3,4-Substituted phenyl-β-D-glucosides	−0.66	11	60	Water	*v*	
42. 4-Substituted phenyl-β-D-glucopyranosides	−0.48	3	25	Water	*t*	Error = 0.04
43. Formaldehyde methyl 4-substituted phenyl acetals	−0.25	4	56	Water	85	
44. 2-(4-substituted phenoxy)tetrahydropyrans	−0.92	6	30	50.0% dioxane	31	
45. $CH_3OCH_2OR \rightarrow CH_3OCH_2^+ + ROH$	Parabola	6	25	Water	*q*	
46. $RCOOCH_2OCH_3$	0	3	25	Water	32	
47. 2-Alkoxytetrahydrofurans	Parabola	5	25	Water	*w*	
48. 2-Alkoxytetrahydropyrans	Parabola	5	25	Water	*w*	
D. Substituent Effects on General Acid Catalyzed Hydrolysis						
49. 2-(4-Substituted phenoxy)tetrahydropyrans	0.9	3	50	50.0% dioxane	31	k_{HCOOH}
50. Benzaldehyde methyl 3-substituted phenyl acetals	0.89	4	20	Water	30	k_{CH_3COOH}
51. 4-Substituted benzaldehyde di-*tert*-butyl acetals	−2.02	4	25	Water	*i*	k_{CH_3COOH}
52. 2,2-Di(4-substituted phenyl)-1,3-dioxolanes	−2.41	3	30	20.0% dioxane	64	$k_{Cl_2CHCOOH}$ Error = 0.10, r = 0.997

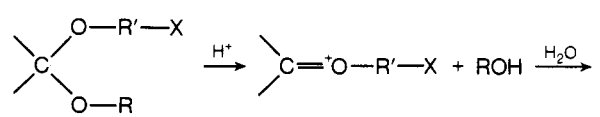
TABLE II. *(Continued)*

Substrates	ρ	No. of substituents	Temp, °C	Solvent	Ref	Comments
53. Methyl 4-substituted orthobenzoates	Hyperbola	5	30	70.0% methanol	*a*	k_{ClCH_2COOH}
54. $(RO)_2CH$	−2.11[f,n]	2	25	Water	*x*	$k_{H_3AsO_4}$
55. $(RO)_3CH$	−1.52[f,n]	2	25	Water	*x*	$k_{H_2PO_4^-}$
E. Substituent Effects on pH-Independent Hydrolysis						
56. *cis*-2-Alkyl-5-methyldioxolones-(4)	−3.65[f]	3	25	Water	33	Estimate
57. $RCOOCH_2OCH_3$	1.41[f,n]	3	35	Water	32	Error = 0.04, r = 0.999
F. Substituent Effects on Substrate Protonation						
58. $ROCH_2OR$	3.90[f,n]	9	25		*y*	Error = 0.30, r = 0.975
59. $(RO)_3CH$	4.73[f,n]	7	25		*z*	Error = 0.61, r = 0.946
G. Substituent Effects on Related Hydrolytic Reactions						
60. Alkyl vinyl ethers	−2.22[f,n]		25	Water	*aa*	
61. $ROCH_2Cl$	−2.77[f,n]	4	25	53.3% ethanol 46.7% dioxane	*o*	k_0, error = 0.40, r = 0.960
62. 2-(4-Substituted phenyl)-1,3-oxathiolanes	−1.66	5	30	Water	*bb*	Error = 0.07, r = 0.975
63. 2-(4-Substituted phenyl)-1,3-oxathiolanes	−2.05	5	30	Water	*bb*	$k_{Hg^{2+}}$, error = 0.05, r = 0.983
64. 2-(3,4-Substituted phenyl)-1,3-oxathiolanes	−2.11[c]	7	30	50.0% dioxane	*cc*	r = 0.995
65. Aryl β-D-thioglucosides	−0.9				2	
66. Benzaldehyde methyl *S*-(substituted phenyl) thioacetals	−1.0				65	
H. Substituent Effects on Base-Catalyzed Hydrolysis						
67. 3,4-Substituted phenyl-α-D-glucosides	2.8	8	70	Water	*s*	
68. Aryl 2-acetamido-2-deoxy-β-D-glucopyranosides	2.6[l]	3	78.2	Water	80	k_0
69. 3,4-Substituted phenyl-β-D-glucosides	2.48	11	60	Water	*v*	
70. 3,4-Substituted phenyl-α-maltosides	2.51	10	60	Water	*u*	
I. Substituent Effects on Enzyme-Catalyzed Hydrolysis						
71. β-(2,4-Substituted phenyl)-di-*N*-acetylchitobiosides	1.23	4	35	Lysozyme	34	k_{cat}, error = 0.17
72. Aryl β-D-glucosides	−1	11	30	Emulsin	*v*	k_2/k_1
73. Aryl β-D-glucosides	1	11	30	Emulsin	*v*	k_3
74. Aryl α-maltosides	−0.45	10	37	Taka-amylase A	*u*	K_m
75. Aryl α-maltosides	2.00	10	37	Taka-amylase A	*u*	$k_{overall}$

[a] H. Kwart and M. B. Price, *J. Amer. Chem. Soc.*, **82,** 5123 (1960). [b] SDS is sodium dodecyl sulfate; the value of ρ refers to the hydrolysis of these substrates when incorporated into the micellar pseudophase formed from this surfactant. [c] The linear free energy relation obeyed is log $(k/k_0) = \sigma^+\rho^+$. [d] M. J. Taraszka and W. Morozowich, *J. Org. Chem.*, **33,** 2349 (1968). [e] T. H. Fife, *J. Amer. Chem. Soc.*, **89,** 3228 (1967). [f] The linear free relation obeyed is log $(k/k_0) = (\Sigma\sigma^*)\rho^*$. [g] T. H. Fife and L. H. Brod, *J. Org. Chem.*, **33,** 4136 (1968). [h] The linear free energy relation obeyed is log $(k/k_0) = \rho[\sigma + r(\sigma^+ - \sigma)]$ in which $r = 0.5$. [i] E. Anderson and T. H. Fife, *J. Amer. Chem. Soc.*, **93,** 1701 (1971). [j] The linear free energy relation obeyed is log $(k/k_0) = (\Sigma\sigma^*)\rho^* - h(\Delta h)$; [k] M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77,** 5590 (1955). [l] The linear free energy relation obeyed is log $(k/k_0) = \sigma^-\rho^-$. [m] F. Aftalion, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1497 (1965). [n] Least-square values, calculated by the author. Values for σ and σ^* were taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23,** 420 (1958), and R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, respectively. [o] P. Salomaa, *Suomen Kemistilehti B,* **33,** 11 (1960). [p] A. Skrabal and H. H. Eger, *Z. Phys. Chem.*, **122,** 349 (1926). [q] P. Salomaa, *Ann. Acad. Sci. Fenn., Ser. A2,* No. 103, 1 (1961). [r] A. Kankaanpera and M. Lahti, *Suomen Kemistilehti B,* **43,** 75 (1970). [s] A. N. Hall, S. Hollingshead, and H. N. Rydon, *J. Chem. Soc.*, 4290 (1961). [t] L. K. Semke, N. S. Thompson, and D. G. Williams, *J. Org. Chem.*, **29,** 1041 (1964). [u] S. Matsubara, *J. Biochem. (Tokyo),* **49,** 232 (1961). [v] R. L. Nath and H. N. Rydon, *Biochem. J.*, **57,** 1 (1954). [w] A. Kankaanpera and K. Miikki, *Suomen Kemistilehti B,* **41,** 42 (1968). [x] A. Kankaanpera and M. Lahti, *ibid.*, **43,** 105 (1970). [y] A. Kankaanpera, *Acta Chem. Scand.*, **23,** 1723 (1969). [z] A. Kankaanpera and M. Lahti, *ibid.*, **42,** 427 (1969). [aa] P. Salomaa, A. Kankaanpera, and M. Lajunen, *Acta Chem. Scand.*, **20,** 1790 (1966). [bb] N. C. De and L. R. Fedor, *J. Amer. Chem. Soc.*, **90,** 7266 (1968). [cc] T. H. Fife and L. K. Jao, *ibid.*, **91,** 4217 (1969).

than that for ortho ester hydrolysis, a point to which we return later.

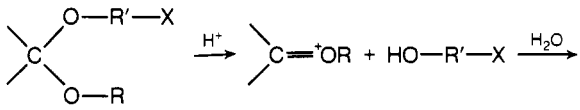
Second, rate constants for hydrolysis of acetals, ketals, and ortho esters increase with increasing electron donation from polar substituents located in that alkoxy function which does not leave in the rate-determining step (entries 22–35).



products (9)

Without exception values of ρ^* are negative and most such values are large. This is the expected result based on carbonium ion formation in the transition state; as in the case of polar substituents in the carbonyl moiety, electron donation will stabilize a developing carbonium ion in the transition state relative to the ground state. In those cases in which comparison is possible, medium effects on values of ρ^* are not large (compare entries 31 and 32, 34 and 35). For modest structural changes, values of ρ^* are independent of the nature of the leaving group (compare entries 22–24).

Third, for hydrolysis of glycosides and acetals, rate constants are not markedly sensitive to the nature of polar substituents in the leaving group (eq 10) (no. 36–48). In most cases, small negative values of ρ are obtained. This is reasonably interpreted to reflect the opposing effects of polar substituents on substrate protonation and



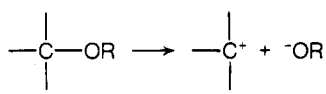
products (10)

carbon–oxygen bond cleavage. Electron donation from a polar substituent, for example, would tend to increase the extent of protonation but retard the rate of decomposition of the protonated substrate. The observation of negative values of ρ suggests that the former effect is somewhat the more important of the two. Alternatively, the effects of polar substituents can be viewed simply as stabilization of the departing leaving group, which bears a partial positive charge in the transition state, relative to the uncharged ground state by electron donation.

Fourth, linear free energy relationships for *general acid catalyzed* hydrolysis of acetals, ketals, and ortho esters have been investigated in a few cases (entries 49–55). For polar substituents in the carbonyl moiety of the substrate, entries 51 and 52, negative values of ρ are obtained, as expected. In the case of hydrolysis of benzaldehyde di-*tert*-butyl acetals, the specific acid catalyzed reaction is substantially more sensitive to the nature of polar substituents than is the acetic acid catalyzed reaction (compare entries 14 and 51). In contrast, the specific and general acid catalyzed hydrolyses of 2,2-di(4-substituted phenyl)-1,3-dioxolanes are about equally sensitive to this parameter (compare entries 8 and 52). The hydrolysis of ortho esters bearing polar substituents in the alkoxy moiety is about equally sensitive to the nature of polar substituents for the specific and general acid catalyzed reactions (compare entry 34 with 54 and 55).

Of considerable interest is the observation that general acid catalyzed hydrolysis of 2-(4-substituted phenoxy)tetrahydropyrans and benzaldehyde methyl 3-substituted phenyl acetals is characterized by *positive* values of ρ (entries 49 and 50) even though the specific acid catalyzed hydrolysis of the former compounds at least has a negative value of ρ (entry 44). This result has been interpreted to suggest that carbon–oxygen bond cleavage is particularly important relative to substrate protonation for the general acid catalyzed reactions.[29,30]

Fifth, in a few cases, hydrolysis of acetals and related substrates has been shown to occur *via* pH-independent, as well as acid-catalyzed, pathways.[31-33] pH-independent reactions are ordinarily important only in those cases in which the leaving group forms a particularly stable anion, such as a carboxylate or phenolate ion. In two cases, entries 56 and 57, linear free-energy relationships have been established for pH-independent hydrolyses of these substrates. Electron-donating substituents in the carbonyl moiety (entry 56) and electron-withdrawing substituents in the leaving group (entry 57) increase the rate constants for the pH-independent hydrolyses, suggesting that this reaction involves the simple unimolecular decomposition of the substrate.[31-33]



(11)

Sixth, in two cases, substituent effects on the basicity of acetals and ortho esters have been measured (entries 58 and 59); basicities were measured as described in section III. The large positive values of ρ^* indicate that the *dissociation* constants for the conjugate acids of these substrates increase with increasing electron-withdrawing power of the polar substituent, as expected.

Finally, among those enzymatic reactions involving glycosides as substrates for which linear free energy relationships have been established (entries 71–75), that involving lysozyme is particularly interesting.[34] Note that the effect of polar substituents in the leaving group is such that increasing electron withdrawal leads to increasing reactivity. This is the result found for the general acid catalyzed hydrolysis of related substrates but is contrary to that observed for specific acid catalyzed hydrolysis (see above and Table II). This observation lends support to the suggestion that general acid catalysis is involved in the catalytic process of lysozyme.[35]

All of the data collected in Table II refer to correlations of structure with reactivity within a group of closely related substrates. As noted in the discussion above, these data lend strong support to the general aspects of the mechanism of hydrolysis of acetals, ketals, and ortho esters as developed in sections I and II. However, correlations of structure with reactivity which extend beyond these bounds pose an interesting and important question with which we must concern ourselves; specifically, the replacement of methyl groups with methoxy groups in the series $RC(CH_3)_2OCH_3$, $RC(CH_3)(OCH_3)_2$, $RC(OCH_3)_3$, $C(OCH_3)_4$. The transition from ether to ketal is accompanied by an enormous increase in reactivity; in contrast, those from ketal to ortho ester and ortho ester to orthocarbonate are accompanied by decreases in reactivity.[25] That is, increasing stability of the carbonium ion intermediate does not uniformly result in increasing reactivity of the substrate. This is a surprising result since one would have expected that those factors which stabilize the carbonium ion intermediate relative to the ground state would stabilize the developing carbonium ion in the transition state as well. The resolution of this problem has come out of secondary deuterium isotope effects for these reactions, and we will return to a consideration of this topic in section VI.

Quite aside from apparent surprises in structure–reactivity correlations, we have discovered a number of differences in the sensitivity of rates to polar substituents as a function of substrate structure. For example, it has been pointed out that the hydrolysis of ortho esters is generally less affected by a change in polar substituent than is hydrolysis of acetals (Table II). Findings of this type must be accounted for in terms of details of transition state structure not thus far specified. Until this point, hydrolysis of the entire spectrum of substrates has been considered to proceed through carboxonium ion intermediates, the formation of which is irreversible. The structure–reactivity correlations just described indicate that the individual reactions may differ in two important respects: timing of proton transfer relative to cleavage of carbon–oxygen bonds (specific acid *vs.* general acid catalysis) and extent of cleavage of carbon–oxygen bonds in the transition state. That these factors differ from substrate to substrate is also attested to by solvent deuterium isotope effects, to which we now turn.

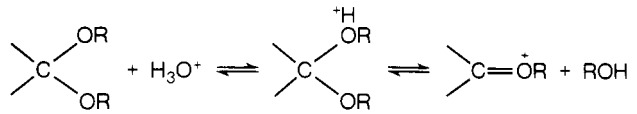
V. Kinetic Solvent Deuterium Isotope Effects

Measurement of relative rate constants for organic reactions in light and heavy water has long been employed in efforts to probe transition state structures; several excellent reviews are available.[36] Significant developments in interpretation of deuterium isotope effects through vibrational analysis of models of transition state structures have been achieved in recent years.[37-39] In addition, a very useful and computationally quite simple theory for interpretation of solvent deuterium isotope effects has been formulated by Schowen.[36] In what fol-

lows, we shall employ certain results derived by this method.

Since hydrolysis of those substrates of interest here does not involve solvent as nucleophilic reagent, solvent deuterium isotope effects arise from two basic sources[36]: (i) the function of lyonium ion as a proton-transfer agent in the transition state (regardless of whether the proton transfer is complete or not) and (ii) qualitative and/or quantitative changes in solute–solvent interactions as one moves from ground to transition state.[40,41] Both factors will probably be important for the bulk of the reactions under consideration.

The calculations of Schowen, in agreement with conclusions of others, strongly suggest that solvent deuterium isotope effects for acetal or ortho ester hydrolysis will not serve to distinguish between mechanisms which do and do not involve water as a nucleophile.[36] However, since the former possibility has already been largely eliminated, attention may be focused on the question of what these isotope effects may reveal concerning details of transition state structures leading to formation of carboxonium ions. For those reactions occurring with preequilibrium protonation of substrate followed by rate-determining carbon–oxygen cleavage (Scheme I, step 7), calculations suggest that the observed solvent–deuterium isotope effect, k_{D_2O}/k_{H_2O}, should vary between 2.3 and 3.4 as the extent of carbon–oxygen bond cleavage in the transition state increases.[36]



k_{D_2O}/k_{H_2O} = 2.3 k_{D_2O}/k_{H_2O} = 3.4 (12)

Consequently, for those substrates hydrolyzing by this mechanism, semiquantitative information concerning this parameter should be extractable from measurements of this isotope effect. For those substrates whose hydrolysis occurs with carbon–oxygen bond cleavage and protonation concerted in some sense, deuterium solvent isotope effects are expected to be less than 2.3. Hence, these measurements may aid in distinguishing between the A1 and A-SE2 mechanisms whether or not general acid catalysis is experimentally observable.

Kinetic solvent deuterium isotope effects for hydrolysis of acetals, ketals, and ortho esters, together with information for some related reactions, are collected in Table III. The care with which these data have been measured has occasionally left something to be desired: note that several independent determinations for the hydrolysis of the same substrate sometimes yield inconsistent values. Despite uncertainties of this type, the data collected in Table III do permit a series of conclusions to be drawn.

First, solvent deuterium isotope effects for hydrolysis of acetals and ketals of simple structure, which are believed to hydrolyze by the simple A1 mechanism, fall into the range 2.5–3.3 (entries A: 20–23, 26–39, 42–46). This is expected on the basis of the calculations of Schowen,[36] as noted above, corroborating the assignment of the A1 mechanism and strongly suggesting that significant carbon–oxygen bond cleavage has occurred in the transition state for hydrolysis of these substrates.

Second, for a series of structurally related 2-(substituted phenyl)-1,3-dioxolanes (entries A: 27–30), the solvent isotope effects exhibit a general trend toward increasing values with increasing electron-withdrawing capacity of the polar substituent.[42] This observation suggests that the extent of carbon–oxygen bond cleavage increases with decreasing stability of the intermediate carboxonium ion, as expected on the basis of the considerations of Hammond and Thornton.[43,44] In contrast, the solvent isotope effect for the hydrolysis of *p*-nitrobenzaldehyde diethyl acetal is slightly less than is that for hydrolysis of the corresponding *p*-chloro compound (entries A: 42 and 43).[42] However, the difference may lie within the error of the experimental measurements; a careful restudy of these isotope effects appears warranted.

Third, solvent deuterium isotope effects for hydrolysis of ortho esters are generally smaller than those for hydrolysis of acetals and ketals (entries A: 1–19). As detailed below, ortho esters are usually considered to hydrolyze by the A-SE2 mechanism, involving proton transfer concerted in some sense with carbon–oxygen bond cleavage. The magnitude of the observed isotope effects corroborates and strengthens this conclusion. Within the class of ortho ester hydrolyses, two trends may be observed. First, as the stability of the derived carbonium ion increases, the magnitude of the solvent deuterium isotope effect decreases; compare the values for ethyl orthocarbonate, ethyl orthobenzoate, and ethyl orthoformate. This observation suggests, in accord with expectations,[43,44] earlier transition states for those substrates yielding more stable intermediates. Second, as the basicity of the leaving alcohol decreases, isotope effects also decrease; compare the data for 2-methoxy- and 2-chloroethyl orthoformates and for phenyl orthoformate with that for ethyl orthoformate. This finding is in accord with increasing importance of proton transfer to the leaving group in the transition states for hydrolysis of those substrates possessing very weakly basic leaving groups.

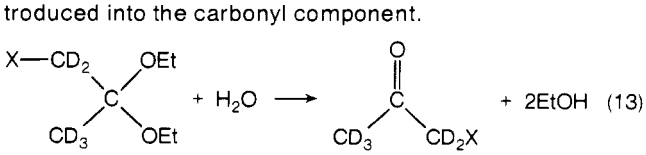
Fourth, hydrolysis of those acetals and ketals of abnormally low basicity occurs with relatively small solvent isotope effects (note entries A: 24, 25, 47–53). This is consistent with the behavior of ortho esters which ordinarily have basicities substantially less than those for simple acetals (Table I). It is not surprising that introduction of polar substituents having the effect of lowering acetal basicity leads to behavior reminiscent of that of ortho esters. Within the class of acetals of abnormally low basicity, a trend toward lower isotope effects with decreasing basicity of the leaving group is observed for hydrolysis of 2-(substituted phenoxy)tetrahydropyrans[31] (entries A: 47–51), consistent with related findings noted above.

Fifth, pH-independent hydrolysis of acetals (entries B: 1–5) occurs with a very small solvent deuterium isotope effect, consistent with the calculations of Schowen.[36]

Finally, solvent deuterium isotope effects for general acid catalyzed reactions are generally smaller than for the corresponding kinetically specific acid catalyzed processes for the same substrates; compare entry A.1 with C.1, entry A.51 with C.3, and entry A.60 with C.5.

VI. Secondary Deuterium Isotope Effects for Hydrolysis of Acetals, Ketals, and Ortho Esters

Both α and β secondary deuterium isotope effects have been measured for the hydrolysis of acetals, ketals, and ortho esters. Effects in the latter category were determined by Shiner and Cross for hydrolysis of the diethyl ketals of acetone, methyl ethyl ketone, methyl isopropyl ketone, and phenoxyacetone in which deuterium was introduced into the carbonyl component.



(13)

k_H/k_D = 1.1–1.25

TABLE III. Kinetic Solvent Deuterium Isotope Effects for Hydrolysis of Acetals, Ketals, and Ortho Esters

Substrate	k_{D_2O}/k_{H_2O}	Temp, °C	Solvent	Ref	Comments
		A. Specific Acid Catalyzed Reactions			
1. Ethyl orthocarbonate	1.40			a	
2. Ethyl orthoacetate	1.87	25	Water	54	
3. Ethyl orthobenzoate	2.30	25	Water	b	
4. Methyl orthobenzoate	2.22	25	Water	c	
5. Isopropyl orthoformate	2.81	25	Water	d	
6. Ethyl orthoformate	2.98	25	Water	d	
7. Ethyl orthoformate	2.88	25	65.0% dioxane	d	
8. Ethyl orthoformate	2.70	15	Water	e	
9. Ethyl orthoformate	2.35	25	Water	f	
10. Ethyl orthoformate	2.31	35	Water	e	
11. Ethyl orthoformate	2.05		Water	g	
12. Methyl orthoformate	2.50	25	Water	d	
13. Methyl orthoformate	2.98	25	65.0% dioxane	d	
14. 2-Methoxyethyl orthoformate	2.07	25	Water	d	
15. 2-Methoxyethyl orthoformate	2.37	25	65.0% dioxane	d	
16. 2-Chloroethyl orthoformate	1.97	25	Water	d	
17. 2-Chloroethyl orthoformate	2.13	25	65.0% dioxane	d	
18. Phenyl orthoformate	0.97	25	40.0% dioxane	h	Error = 0.08
19. Phenyl orthoformate	1.33	25	65.0% dioxane	d	
20. Acetaldehyde dimethyl acetal	2.70	25	Water	i	
21. Acetaldehyde diethyl acetal	2.64	15	Water	j	
22. Acetaldehyde diethyl acetal	2.66		Water	g	
23. Acetaldehyde diethyl acetal	3.08	25	50.0% dioxane	61	Error = 0.03
24. Acetaldehyde ethyl 2,2,2-trichloroethyl acetal	2.05	25	65.0% dioxane	k	
25. Acetone di-2,2,2-trichloroethyl ketal	1.80	25	65.0% dioxane	l	
26. 2-Methyl-1,3-dioxolane	2.78	25	Water	i	
27. 2-Phenyl-1,3-dioxolane	2.76	30	50.0% dioxane	42	
28. 2-(4-Methylphenyl)-1,3-dioxolane	2.82	30	50.0% dioxane	42	
29. 2-(4-Chlorophenyl)-1,3-dioxolane	2.88	30	50.0% dioxane	42	
30. 2-(4-Nitrophenyl)-1,3-dioxolane	3.27	30	50.0% dioxane	42	
31. 2-Phenyl-2-methyl-1,3-dioxolane	2.95	30	50.0% dioxane	57	
32. 2-Phenyl-2-ethyl-1,3-dioxolane	3.01	30	50.0% dioxane	57	
33. 1,3-Dioxane	2.78	25	Water	m	
34. 2-Phenyl-1,3-dioxane	3.12	25	10% acetonitrile	n	
35. 4,4-Dimethyl-1,3-dioxane	2.94	25	Water	m	
36. 2-Phenyl-4,4-5,5-tetramethyl-1,3-dioxolane	2.44	30	Water	o	
37. 2-(2-Methoxyphenyl)-1,3-dioxane	2.94	25	10% acetonitrile	n	
38. 2-(4-Hydroxyphenyl)-1,3-dioxane	2.56	25	10% acetonitrile	n	
39. 2-(2-Hydroxyphenyl)-1,3-dioxane	2.50	25	10% acetonitrile	n	
40. 2-(2-Hydroxy-5-nitrophenyl)-1,3-dioxane	2.38	25	10% acetonitrile	n	
41. 2,2-Diphenyl-1,3-dioxolane	2.63	30	Water	64	
42. 4-Chlorobenzaldehyde diethyl acetal	2.99	30	50.0% dioxane	42	
43. 4-Nitrobenzaldehyde diethyl acetal	2.72	30	50.0% dioxane	42	
44. 2-Methoxytetrahydrofuran	2.94	25	Water	p	
45. 2-Methoxytetrahydropyran	2.94	25	Water	p	
46. 2-Ethoxytetrahydropyran	2.82	30	50.0% dioxane	31	
47. 2-Phenoxytetrahydropyran	2.29	30	50.0% dioxane	31	
48. 2-(4-Methoxyphenoxy)tetrahydropyran	2.48	30	50.0% dioxane	31	
49. 2-(4-Methylphenoxy)tetrahydropyran	2.39	30	50.0% dioxane	31	
50. 2-(4-Chlorophenoxy)tetrahydropyran	2.01	30	50.0% dioxane	31	
51. 2-(4-Nitrophenoxy)tetrahydropyran	1.33	30	50.0% dioxane	31	
52. 2-(2,2,2-Trichloroethoxy)tetrahydropyran	1.59	25	Water	q	
53. 2-(2,2,2-Trifluoroethoxy)tetrahydropyran	1.28	25	Water	q	
54. Sucrose	1.76	25	Water	r	$k_{inversion}$
55. Sucrose	2.10			s	$k_{inversion}$
56. Cane sugar	2.05	25	Water	t	$k_{inversion}$
57. Methyl α-D-glucopyranoside	1.94	59	Water	u	
58. Methyl α-D-xylofuranoside	2.54	25	Water	v	
59. Methyl α-2-deoxy-D-glucopyranoside	2.50	45	Water	w	
60. Benzaldehyde methyl phenyl acetal	0.99	20	Water	30	Error = 0.03
61. Methoxymethyl acetate	2.23	25	Water	32	
62. 4-Ethoxy-4-butyrolactone	2.37	30	Water	x	
63. 2,5,5-Trimethyl-1,3-dioxolone-(4)	1.68	25	Water	y	
		B. pH-Independent Reactions			
1. 2,5,5-Trimethyl-1,3-dioxolone-(4)	0.82	25	Water	y	
2. 4-Ethoxy-4-butyrolactone	0.76	30	Water	x	

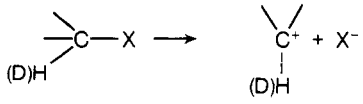
TABLE III. *(Continued)*

Substrate	k_{D_2O}/k_{H_2O}	Temp, °C	Solvent	Ref	Comments
3. 2-(4-Nitrophenoxy)tetrahydropyran	0.90	50	Water	29	
4. 2-(4-Nitrophenoxy)tetrahydropyran	1.10	50	50.0% dioxane	29	
5. Tropone diethyl ketal	0.86	15	Water	65	
C. General Acid Catalyzed Reactions					
1. Ethyl orthocarbonate	0.71			*a*	k_{CH_3COOH}
2. 2-(4-Nitrophenoxy)tetrahydropyran	0.29	50	Water	29	k_{HCOOH}
3. 2-(4-Nitrophenoxy)tetrahydropyran	0.38	50	50.0% dioxane	2	k_{HCOOH}
4. Tropone diethyl ketal	0.67	15	Water	65	$k_{Tris-HCl}$
5. Benzaldehyde methyl phenyl acetal	0.47	20	Water	30	k_{CH_3COOH}, error = 0.007
D. Related Reactions					
1. 2-Phenyl-1,3-oxathiolane	2.15	30	Water	*z*	k_{H^+}
2. 2-(4-Methylphenyl)-1,3-oxathiolane	2.24	30	50.0% dioxane	*aa*	k_{H^+}
3. 2-(4-Methoxyphenyl)-1,3-oxathiolane	1.93	30	Water	*aa*	k_{H^+}
4. Benzaldehyde methyl S-(2,3-dinitrophenyl)-thioacetal	0.90			65	k_0
5. 4-Nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside	0.74	78	Water	*bb*	k_0
6. 2-Nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside	0.94	78	Water	*bb*	k_0
7. 2-Nitrophenyl β-D-glucopyranoside	1.21	78	Water	*bb*	k_0
8. 2-Chloroethyl vinyl ether	0.41	25	Water	*cc*	k_{H^+}
9. Ethyl vinyl ether	0.34[dd]	27	Water	*ee*	k_{H^+}
10. Ethyl vinyl ether	0.15[ff]	27	Water	*ee*	k_{HCOOH}
11. Ketene diethyl acetal	0.16[ff]	10	Water	*gg*	k_0

[a] W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **34**, 245 (1938). [b] R. H. DeWolfe and J. L. Jensen, *J. Amer. Chem. Soc.*, **85**, 3264 (1963). [c] J. G. Fullington and E. H. Cordes, *J. Org. Chem.*, **29**, 970 (1964). [d] M. Lahti and A. Kankaanpera, *Suomen Kemistilehti B*, **43**, 101 (1970). [e] F. Brescia and V. K. La Mer, *J. Amer. Chem. Soc.*, **62**, 612 (1940). [f] F. Brescia and V. K. La Mer, *ibid.*, **60**, 1962 (1938). [g] J. C. Hornel and J. A. V. Butler, *J. Chem. Soc.*, 1361 (1936). [h] M. Price, J. Adams, C. Lagenaur, and E. H. Cordes, *J Org. Chem.*, **34**, 22 (1969). [i] M. Kilpatrick, *J. Amer. Chem. Soc.*, **85**, 1036 (1963). [j] W. J. C. Orr and J. A. V. Butler, *J. Chem. Soc.*, 330 (1937). [k] A. Kankaanpera and M. Lahti, *Acta Chem. Scand.* **23**, 3266 (1969). [l] A. Kankaanpera and M. Lahti, *ibid.*, **23**, 2465 (1969). [m] F. Aftalion, D. Lumbroso, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1950 (1965). [n] M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, **85**, 3006 (1963). [o] T. H. Fife, *ibid.*, **89**, 3228 (1967). [p] A. Kankaanpera and M. Miikki, *Suomen Kemistilehti B*, **41**, 42 (1968). [q] A. Kankaanpera, *Suomen Kemistilehti B*, **42**, 460 (1969). [r] E. A. Moelwyn-Hughes, *Z. Physik. Chem.*, *26B*, 272 (1934). [s] W. H. Hamill and V. K. La Mer, *J. Chem. Phys.*, **4**, 294 (1936). [t] P. Gross, H. Steiner, and H. Suess, *Trans. Faraday Soc.*, **32**, 883 (1936). [u] W. G. Overend, C. W. Rees, and J. S. Sequeira, *J. Chem. Soc.*, 3429 (1962). [v] B. Capon and D. Thacker, *J. Chem. Soc. B*, 185 (1967). [w] C. Armour, C. A. Bunton, S. Patai, L. H. Selman, and C. A. Vernon, *J. Chem. Soc.*, 412 (1961). [x] T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 271 (1965). [y] P. Salomaa, *Acta Chem. Scand.*, **20**, 1263 (1966). [z] N. C. De and L. R. Fedor, *J. Amer. Chem. Soc.*, **90**, 7266 (1968). [aa] T. H. Fife and L. K. Jao, *ibid.*, **91**, 4217 (1969). [bb] D. Piszkiewicz and T. C. Bruice, *ibid.*, **89**, 6237 (1967). [cc] P. Salomaa, A. Kankaanpera, and M. Lahti, *Suomen Kemistilehti B*, **42**, 427 (1969). [dd] Isotopic $\alpha = 0.52$. [ee] A. J. Kresge and Y. Chiang, *J. Chem.Soc. B*, 58 (1967). [ff] Brønsted $\alpha = 0.45$. [gg] A. Kankaanpera and H. Tuominen, *Suomen Kemistilehti B*, **40**, 271 (1967).

For the fully deuterated substrates, values of k_H/k_D of 1.1 to 1.25 were obtained.[45,46] The results substantiate our earlier observations (section IV) that electron donation accelerates the rate of ketal hydrolysis, the expected results in terms of significant carbonium ion character for the transition state.

More recently α-deuterium isotope effects for the hydrolysis of acetals and orthoformates have been probed.[47,48] Isotope effects of this type have been developed into relatively reliable indicators of transition state structure for a variety of reactions.[49] For reactions in which hybridization at carbon changes from sp^3 to sp^2, k_H/k_D is a measure of the net change between the initial and transition state of the bending force constants for



(14)

CHX. Since this bending mode is lost to a variable degree depending on hybridization at carbon in the transition state, isotope effects will vary from unity to a maximal value, near 1.23 when X = ^-OR,[50,51] with increasing cleavage of the C–X bond in the transition state. Thus, for those reactions in which the transition state is substrate-like, values of k_H/k_D near unity will be obtained, and for those having carbonium ion-like transition states, values near 1.23 will be observed. Interpolation between these extremes will provide information concerning transition state structure for intermediate cases.

TABLE IV. Secondary Deuterium Isotope Effects for the Rates of Hydrolysis of Benzaldehyde Diethyl Acetals, Propionaldehyde Diethyl Acetal, and Ethyl Orthoformate[a]

Substrate	$k_H/k_{\alpha D}$
p-Nitrobenzaldehyde diethyl acetal	1.15 ± 0.01
Benzaldehyde diethyl acetal	1.09 ± 0.01
p-Methoxybenzaldehyde diethyl acetal	1.04 ± 0.01
Propionaldehyde diethyl acetal	1.17 ± 0.01
Ethyl orthoformate	1.05 ± 0.01

[a] Modified from ref 47.

α-Deuterium isotope effects for the hydrolysis of propionaldehyde diethyl acetal, three substituted benzaldehyde diethyl acetals, and ethyl orthoformate are collected in Table IV.[47]

The secondary deuterium isotope effect for the hydrolysis of substituted benzaldehyde diethyl acetals increases with increasing electron-withdrawing power of the polar substituent. These data indicate that the extent of C–O bond cleavage in the transition state increases markedly as the stability of the intermediate carbonium ion dimin-

TABLE V. Secondary Deuterium Isotope Effects for the Rate of Hydrolysis of 2-(Substituted phenoxy)tetrahydropyrans in 50% Aqueous Dioxane at 25°[a]

Substrate	$k_H/k_{\alpha D}$
2-(p-Methoxyphenoxy)tetrahydropyran	1.106 ± 0.008
2-(p-Chlorophenoxy)tetrahydropyran	1.095 ± 0.007
2-(p-Nitrophenoxy)tetrahydropyran	1.063 ± 0.005

[a] Modified from ref 47.

TABLE VI. Relative Reactivities of Certain Acetals, Ketals, and Ortho Esters[a]

Substrate	Rel reactivity
$CH_3CH(OEt)_2$	1
$(CH_3)_2C(OEt)_2$	2,200
$HC(OEt)_3$	680
$CH_3C(OEt)_3$	19,000
$C(OEt)_4$	66

[a] Modified from ref 25.

ishes. Thus, the transition state for hydrolysis of the *p*-methoxy derivative has little carbonium ion character while that for hydrolysis of the *p*-nitro derivative has a good deal of such character. The observed changes cannot be accounted for in terms of increasing nucleophilic participation by solvent since just such a case has been previously identified, and the changes, as expected, are in the opposite direction.[52] The change in transition state structure as a function of substrate reactivity for hydrolysis of the benzaldehyde acetals is perhaps the largest yet observed among carbonium ion processes; the tendency of the transition state to increasingly resemble the product carbonium ion as substrate reactivity decreases (corresponding to a decrease in carbonium ion stability) is in qualitative agreement with the predictions of Leffler,[53] Hammond,[43] and Thornton.[44]

Comparison of the isotope effects for the hydrolysis of ethyl orthoformate and propionaldehyde diethyl acetal with those for hydrolysis of the benzaldehyde acetals reveals, in light of the above discussion, that the transition state for the former substrate has little, and that for the latter substrate has much, carbonium ion character. These conclusions accord with our expectations in light of the transition state structure–carbonium ion stability correlation developed above.

Generalizing, it seems fair to conclude that hydrolysis of orthocarbonates and ortho esters is characterized by reactant-like transition states while hydrolysis of acetals and ketals derived from aliphatic substrates is characterized by carbonium-ion-like transition states. Acetals and ketals derived from aromatic substrates may be expected, as is the case directly studied here, to occupy either of the above categories, or an intermediate one, depending on the nature of the polar substituents (one may note that, for example, *p*-methoxybenzaldehyde diethyl acetal is a "phenyligous" orthoformate). Note that these considerations are fully consistent with conclusions based on structure–reactivity correlations and solvent deuterium isotope effects (sections IV and V). Specifically, hydrolysis of acetals and ketals is generally more sensitive to the nature of polar substituents than is that for ortho esters (Table II). Thus, the extent of C–O bond cleavage deduced on the basis of isotope effects parallels the susceptibility of these reactions to effects of polar substituents. Moreover, rate constants for those substrates considered to hydrolyze by reactant-like transition states are correlated by the σ, not the σ^+, substituent constants. In other cases, such as that of the substituted benzaldehyde acetal hydrolysis in water, for which the transition state structure changes as a function of the nature of the polar substituent (see above), the correlation of rate constants with σ also receives a natural explanation: for those substituents capable of strong electron donation by resonance, the transition states possess little carbonium ion character so that such electron donation is not particularly important. Those substrates hydrolyzing through carbonium ion-like transition states do not possess substituents capable of strong electron donation through resonance.

Finally, we note that the extent of C–O bond cleavage in the transition state also is correlated with solvent deuterium isotope effects: the less covalent bond cleavage, the smaller the solvent isotope effect (Table III). Taken together, these three lines of evidence provide a rather persuasive case for the transition state structures as noted above. Moreover, studies of salt effects on the kinetics of hydrolysis of these substrates has yielded results corroborating this conclusion.[54]

Measurement of the α-deuterium isotope effects for acetal hydrolysis has also been extended to a series of 2-(substituted phenoxy)tetrahydropyrans.[47] In this case attention is focused on the influence of the nature of the leaving group, rather than the carbonyl moiety, on the transition state structure. Results are collected in Table V. These data reveal a change in transition state structure as a function of the basicity of the leaving group. The difference in isotope effect between the *p*-methoxy and *p*-chloro substrates may not be significant, but that between these two species and the *p*-nitro one certainly is real. In all cases, the isotope effects indicate that the transition states have only modest carbonium ion character. The extent of carbonium ion formation increases with increasing substrate reactivity, *i.e.*, with increasing electron-donating power of the polar substituent, but decreases with increasing reactivity of the protonated substrate. This finding is in accord with the Hammond postulate,[43] the rule of Thornton,[44] and previous experimental observations including (i) the susceptibility of the *p*-nitro substrate, but not the others, to general acid catalysis and (ii) the existence of a marked pH-independent reaction for hydrolysis of the *p*-nitro substrate only. On the basis of these observations, Fife and coworkers have concluded that the transition state is reached sooner along the reaction coordinate with increasing electron withdrawal in the polar substituent,[29,31] a conclusion fully corroborated in the present studies.

VII. Relative Reactivities of Acetals, Ketals, and Ortho Esters

Near the conclusion of the discussion of structure–reactivity correlations (section IV), it was noted, without explanation, that substrate reactivities do not always parallel the stabilities of the corresponding carbonium ions. A sample of the data supporting this conclusion is collected in Table VI.[25] Note that the substrate expected to generate the most stable carbonium ion, ethyl orthocarbonate, is the least reactive member of the series. Moreover, triethyl orthoformate is less reactive than 2,2-diethoxypropane, and triethyl orthoacetate is only slightly more reactive than this ketal. Additional examples might be cited; for example, benzaldehyde diethyl acetals substituted with electron-donating polar substituents are more reactive than the corresponding ethyl orthobenzoates.[47,55]

Evidence that, other factors being equal, trialkoxymethyl carbonium ions are more stable than dialkoxyalkylmethyl carbonium ions and so forth derives from the

well-known capacity of the alkoxy function to stabilize carbonium ions through electron donation by resonance and from the direct observation of the conditions required to produce these carbonium ions in strongly acidic media.[56] Of course, in certain instances, naive conclusions may prove inadequate neglecting, for example, steric factors which may be important in determining carbonium ion stabilities. It has been clearly established that steric factors are important in determining reactivities of acetals, ketals, and ortho esters,[33,57-60] and such factors may be important in both substrate and the derived carbonium ion. But the central fact remains that, for several cases at least, carbonium ion stabilities are not reflected in substrate reactivities. The relative unreactivity of orthocarbonates provides the most dramatic example.

Several suggestions have been provided in efforts to account for the unexpectedly low reactivities of ortho esters and orthocarbonates. These include (i) stabilization of substrates through double bond–no bond resonance;[26] no firm evidence for stabilization of this type exists and substrate basicities are nicely accounted for by assuming that it is unimportant.[24] (ii) It has been suggested that the transition state for hydrolysis of these substances occurs so early along the reaction coordinate that only inductive, and not resonance, effects are important in influencing transition state stabilities.[61] Data already presented indicate that this cannot be an accurate explanation, although, as we shall see, it does contain a partial solution to the problem. (iii) As is developed in detail below, the mechanism for hydrolysis of acetals and ketals, on one hand, and ortho esters, on the other, may differ in terms of timing of proton transfer relative to carbon–oxygen bond cleavage. This distinction may account partially for the observed differences.

However, the principal key to the understanding of the relative reactivities of, for example, the compounds collected in Table VI comes from information concerning transition state structures derived on the basis of measurement of α-deuterium isotope effects and corroborated by findings in studies of structure–reactivity correlations, solvent deuterium isotope effects, and salt effects (*vida supra*[54]). That is, the transition state for ortho ester hydrolysis occurs with less carbon–oxygen bond cleavage than does that for hydrolysis of simple acetals and ketals.[47]

This generalization suffices to account for relative reactivities of acetals, ketals, ortho esters, and orthocarbonates. In this series of substrates, hydrogen atoms or alkyl groups are successively replaced by alkoxy groups. The latter are both more electron withdrawing inductively and more electron donating through resonance than the former. Hence, the net effect of replacement of an alkyl group by an alkoxy one on stability of the transition state will depend on the degree of carbonium ion formation in that transition state: alkoxy groups will stabilize a transition state possessing marked carbonium ion character but destabilize one possessing little such character relative to alkyl groups. It follows that ketals are generally more reactive than ortho esters derived from them by replacement of an alkyl group by an alkoxy one since this replacement is accompanied by a transformation from a carbonium-like transition state to a reactant-like one. Thus, the relative energies of the transition states for ketal and ortho ester hydrolysis cannot be rationalized on the basis of comparative ground-state and intermediate-state energies. It also follows, then, that orthocarbonates should be even less reactive than ortho esters, which accords with experimental observation. This is a particularly complicated example in which rate constants and equilibrium constants exhibit divergent behavior with a simple structural change in the substrate.

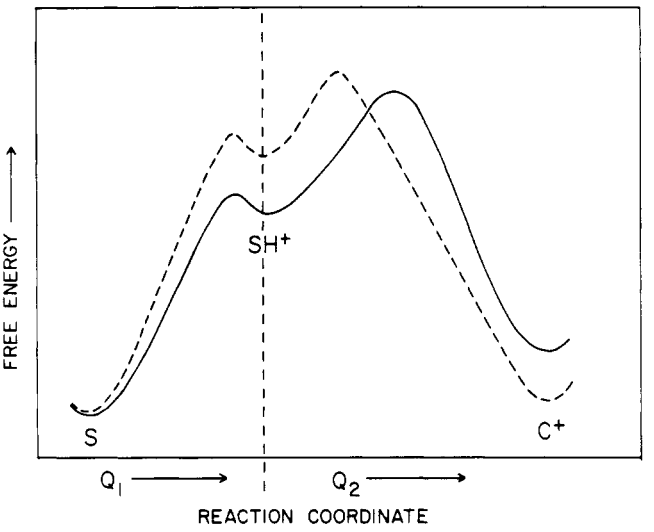


Figure 2. Diagrammatic free energy profiles for acid-catalyzed hydrolysis of a model ketal (solid line) and ortho ester (broken line). The reaction coordinate is broken into two parts: Q_1 refers to formation of the protonated substrate, SH^+, and Q_2 refers to cleavage of the carbon–oxygen bond of SH^+ to yield a carbonium ion, C^+. Note that the ortho ester is less basic than the ketal and is less reactive than the ketal. The degree of covalent bond cleavage in the transition state is greater for decomposition of the conjugate acid of the ketal than for that of the ortho ester.

Assuming that the hydrolytic reactions occur *via* rapid substrate protonation followed by rate-determining carbon–oxygen bond cleavage, these considerations may be summarized in the free energy diagram provided in Figure 2. Substrate protonation and C–O bond cleavage are considered as separate reaction coordinates, Q_1 and Q_2, and the diagram takes into account relative basicities of ketals and ortho esters (section III). For those ortho esters hydrolyzing by a general acid catalyzed route, the corresponding profile would have to be modified so as to avoid the formation of an intermediate. It is to this topic that attention is now directed.

VIII. General Acid Catalysis for Acetal, Ketal, and Ortho Ester Hydrolyses

General acid–base catalysis is experimentally detected as increasing reaction rate with increasing buffer concentration at constant pH. Since the activities of the hydrated proton and hydroxide ion are maintained constant, the increased rates must reflect catalysis by one or both of the buffer components. Mechanistically, general acid–base catalysis is usually considered to provide evidence for proton transfer, which may or may not be concerted with covalent bond formation or breakage, in the transition state.

General acid catalysis for ortho ester hydrolysis was first detected by Brønsted and Wynne-Jones in 1929.[62] Since that time, such catalysis has been searched for with a wide variety of acetals, ketals, and ortho esters and has been observed in several such cases. Work in this area has been recently reviewed in some detail.[2]

Attention here is focused on ascertaining those factors which cause hydrolysis of these substrates to become subject to general acid catalysis and to defining the mechanism of this catalysis. These are matters of great general interest in physical organic chemistry. Jencks has recently formulated a rule (the "libido rule") which attempts to identify those cases in which proton transfer

TABLE VII. General Acid Catalysis for Hydrolysis of Acetals, Ketals, and Ortho Esters

Substrate	Brønsted α	No.	Temp, °C	Solvent	Ref	Comments
1. Ethyl orthocarbonate	0.69	2	30	Water	*a*	
2. Ethyl orthocarbonate	0.60	4	20	Water	*b*, 62	
3. Ethyl orthocarbonate	0.68	2	20	Water	*a*, 62	
4. Methyl orthobenzoate	0.74	7	30	70.0% methanol	*c*	
5. 2-(4-Nitrophenoxy)tetrahydropyran	0.69	5	50	50.0% dioxane	29	
6. 2-(4-Nitrophenoxy)tetrahydropyran	0.50	4	50	Water	29	
7. Benzaldehyde di-*tert*-butyl acetal	0.62	4	25	Water	*d*	
8. Benzaldehyde methyl phenyl acetal	0.60	3	20	Water	30	Error = 0.066
9. 2-Methoxyethyl orthoformate	0.93	5	25	Water	*e*	Error = 0.09
10. 2-Chloroethylformate	0.37	2	25	Water	*e*	
11. Methyl orthoformate	0.58	2	25	Water	*e*	
12. Ethyl orthoformate	0.77	2	35	Water	*f*	
13. Ethyl orthoformate	1.00	2	30	60.4% dioxane	*g*	
14. Ethyl orthoacetate	0.99	2	10	60.4% dioxane	*g*	
15. Ethyl orthoacetate	0.65	4	20	Water	62	Error = 0.03
16. Ethyl orthopropionate	0.65	3	20	Water	62	Error = 0.007
17. 2-Phenoxytetrahydropyran	0.79	2	50	50.0% dioxane	29	
18. 2-(4-Chlorophenoxy)tetrahydropyran			50	50.0% dioxane	29	
19. 2,2-Di(2,2,2-trichloroethoxy)propane	0.53	2	25	65.0% dioxane	*h*	
20. Methyl 4-methoxyorthobenzoate			30	70.0% methanol	*c*	
21. Methyl 4-methylorthobenzoate			30	70.0% methanol	*c*	
22. Methyl 4-chloroorthobenzoate			30	70.0% methanol	*c*	
23. Methyl 4-nitroorthobenzoate			30	70.0% methanol	*c*	
24. Acetaldehyde ethyl 2,2,2-trichloroethyl acetal	0.53	2	25	65.0% dioxane	*i*	
25. 4-Methoxybenzaldehyde di-*tert*-butyl acetal	0.65	2	25	Water	*d*	
26. 4-Methylbenzaldehyde di-*tert*-butyl acetal	0.64	2	25	Water	*d*	
27. 4-Chlorobenzaldehyde di-*tert*-butyl acetal	0.50	2	25	Water	*d*	
28. Benzaldehyde methyl 3-methylphenyl acetal			20	Water	30	
29. Benzaldehyde methyl 3-fluorophenyl acetal			20	Water	30	
30. Benzaldehyde methyl 3-nitrophenyl acetal			20	Water	30	
31. 2,2-Di(4-methoxyphenyl)-1,3-dioxolane	0.56	2	30	20.0% dioxane	64	
32. 2,2-Di(4-methylphenyl)-1,3-dioxolane	0.46	2	30	20.0% dioxane	64	
33. 2,2-Diphenyl-1,3-dioxolane	0.53	2	30	20.0% dioxane	64	
34. Benzophenone diethyl ketal	0.78	3	30	50.0% dioxane	64	Error = 0.11
35. Tropone diethyl ketal	0.75	3	14	Water	65	Error = 0.03
36. Sucrose			25	Water	*j,k*	
37. 2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane	0.68	2	40	Water	*l*	
38. Diethyl phenyl orthoformate	0.47	7	25	50.0% dioxane	*m*	
Catalysis by General Acids Not Observed						
1. Ethyl orthoformate			25	Water	*e*	
2. Ethyl orthoformate			20	Water	62	
3. Ethyl orthoformate			25	65.0% dioxane	*n*	μ = 2.00 M
4. 2-Methylethyl orthoformate			25	Water	*e*	
5. Isopropyl orthoformate			25	Water	*e*	
6. Methyl 4-methoxyorthobenzoate			25	Water	47	Or 70.0% dioxane
7. Methyl 4-methylorthobenzoate			25	Water	47	Or 70.0% dioxane
8. Methyl 4-nitroorthobenzoate			25	Water	47	Or 70.0% dioxane
9. Methyl 4-chloroorthobenzoate			25	Water	47	
10. Methyl orthobenzoate			25	Water	47	Or 70.0% dioxane
11. 2-(4-Methoxyphenoxy)tetrahydropyran			50	50.0% dioxane	31	
12. 2,2-Di(4-chlorophenyl)-1,3-dioxolane			30	20.0% dioxane	64	
13. 2,2-Di(4-methoxyphenyl)-1,3-dioxolane					65	
14. Benzophenone diethyl ketal					65	
15. Benzophenone diethyl ketal			60	50.0% dioxane	66	
16. Benzaldehyde diethyl acetal			65	60.0% dioxane	66	
17. Benzaldehyde diethyl acetal			25	Water	*o*	
18. 2,2-Dimethoxypropane			25	Water	*o*	
19. Acetophenone diethyl ketal					*l*	
20. Acetaldehyde diethyl acetal			20	Water	62	
21. Acetaldehyde diethyl acetal			25	49.6% dioxane	61	
22. Acetaldehyde dimethyl acetal			20	Water	*p*	
23. Ethyl orthobenzoate			20	Water	*g*	Or 20.5% dioxane
24. 2,5-Anhydro-α-L-arabinofuranoside			46	Water	66	
25. 2-Methyl-1,3-dioxolane			20	Water	*p*	
26. Formaldehyde methyl 2,4,6-tri-*tert*-butylphenyl acetal					84	

TABLE VII *(Continued)*

Substrate	Brønsted α	No.	Temp, °C	Solvent	Ref	Comments
27. Ferrocenecarboxaldehyde dimethyl acetal					65	
28. 2,3-Diphenylcyclopropenone diethyl ketal					65	

[a] A. J. Kresge and R. J. Preto, *J. Amer. Chem. Soc.*, **87,** 4593 (1965). [b] W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **34,** 245 (1938). [c] H. Kwart and M. B. Price, *J. Amer. Chem. Soc.*, **82,** 5123 (1960). [d] E. Anderson and T. H. Fife, *ibid.*, **93,** 1701 (1971). [e] A. Kankaanpera and M. Lahti, *Suomen Kemistilehti, B,* **43,** 105 (1970). [f] R. H. DeWolfe and R. M. Roberts, *J. Amer. Chem. Soc.*, **76,** 4379 (1954). [g] R. H. DeWolfe and J. L. Jensen. *ibid.*, **85,** 3264 (1963). [h] A. Kankaanpera and M. Lahti, *Acta Chem. Scand.*, **23,** 2465 (1969). [i] A. Kankannpera and M. Lahti, *ibid.*, **23,** 3266 (1969). [j] J. P. Hammett and M. A. Paul, *J. Amer. Chem. Soc.*, **56,** 830 (1934). [k] A. Hantzsch and A. Weissberger, *Z. Phys. Chem.*, **125,** 251 (1927). [l] T. H. Fife, *J. Amer. Chem. Soc.*, **89,** 3228 (1967). [m] E. Anderson and T. H. Fife, *J. Org. Chem.*, **37,** 1993 (1972). [n] M. Lahti and A. Kankaanpera, *Acta Chem. Scand.*, **24,** 706 (1970). [o] K. Koehler, Ph.D. Thesis, Indiana University, 1968. [p] J. N. Brønsted and C. Grove, *J. Amer. Chem. Soc.*, **52,** 1394 (1930).

is concerted with making or breaking of covalent bonds[63]: "Concerted general acid–base catalysis of complex reactions in aqueous solution can occur only (a) at sites that undergo a large change in pK in the course of the reaction, and (b) when this change in pK converts an unfavorable to a favorable proton transfer with respect to the catalyst; *i.e.*, the pK of the catalyst is intermediate between the initial and final pK values of the substrate site."

Hydrolysis of the compounds under consideration here certainly meets these criteria, for example, general acid catalysis of ortho ester hydrolysis involving proton transfer from the hydrated proton, $pK_a = -1.74$, to a site having an initial pK near −8 and a final one near 17. The rule suggests that we might expect the probability of observing general acid catalysis to increase with decreasing substrate basicity, which has the effect of increasing the difference between the basicities of the site at which catalysis occurs between the initial and final states. Moreover, we might anticipate that general acid catalysis would be increasingly easy to observe with increasing stability of the carboxonium ion intermediate, on the basis of the considerations of Hammond[43] and Leffler.[53] Both of these expectations are in fact borne out.

In Table VII are collected the available data for general acid catalysis for hydrolysis of acetals, ketals, and ortho esters. Note that the table is divided into two sections, the first for those substrates whose hydrolysis does exhibit general acid catalysis and the second for those substrates for which such catalysis has been sought but not observed. Where possible, values of the Brønsted exponent for general acid catalyzed reactions are included.

Data in Table VII should be taken with two substantial reservations. First, considerable disagreement exists in the literature concerning which reactions are actually subject to general acid catalysis. Note that certain substrates are listed in both parts of Table VII; that is, in certain laboratories the hydrolysis of these has been found to be subject to general acid catalysis and in others not. A typical case is provided by benzophenone diethyl ketals which were reported subject to general acid catalysis;[64] however, extensive efforts to confirm this observation have led to the opposite conclusion.[65,66] It is the opinion of the present authors that hydrolysis of this substrate is not subject to general acid catalysis. Difficulties in ascertaining the sensitivity of these substrates to general acid-catalyzed hydrolysis stem from the fact that rate constants frequently increase very slightly with increasing buffer concentration. One has then the twin problems of deciding whether the observed increase is beyond experimental error and, if it is, whether it reflects general acid catalysis or a medium effect. The latter problem is rendered more compelling by the fact that mixed solvents were employed in many efforts to detect general acid catalysis. Dangers inherent in such searches have been elegantly revealed by the studies of Salomaa, *et al.*,[67] who have demonstrated that the hydrolysis of ethyl orthobenzoate in 67% dioxane–33% water (w/w) in the presence of chloroacetate buffers shows either catalysis or inhibition depending on the nature of the salt employed to maintain constant ionic strength. This finding throws many observations of general acid catalysis for ortho ester hydrolysis into doubt.

Second, Brønsted α values for entries 10–37 in Table VII were calculated by us from very few data points, usually the catalytic constants for the hydrated proton and one weak acid. These values, hence, should be regarded as crude estimates, nothing more.

In view of these reservations, what can one conclude concerning general acid catalysis for these substrates? The following statements appear reliable. First, hydrolysis of ortho esters derived from aliphatic alcohols is subject to general acid catalysis; the corresponding Brønsted α values are large, 0.8–1.0. Second, hydrolysis of diethyl phenyl orthoformate, an ortho ester with a phenolic leaving group, is subject to general acid catalysis with a Brønsted exponent near 0.5. Third, hydrolysis of acetals and ketals derived from ordinary carbonyl compounds and aliphatic alcohols is not subject to general acid catalysis. Fourth, hydrolysis of acetals and ketals which have a phenolic or other very weakly basic leaving group or which form particularly stable carbonium ions is subject to general acid catalysis. Values of the Brønsted exponent vary from 0.75 to 0.50. Fifth, hydrolysis of benzaldehyde *tert*-butyl acetals is subject to general acid catalysis.

In attempting to rationalize these observations, the reaction-coordinate contour diagrams first employed by More O'Ferrall and applied by Jencks to related reactions[63] will prove useful. In Figure 3, a two-dimensional representation of the three-dimensional reaction surface for specific acid-catalyzed hydrolysis of an acetal or related substrate is provided. The progress of proton transfer is shown along the vertical axis and progress of C–O bond cleavage along the horizontal axis. As this contour diagram is constructed, the preferred pathway involves protonation of the substrate followed by cleavage of the C–O bond, *i.e.*, the classical A1 mechanism. Note that a variety of additional mechanisms for acetal hydrolysis can be visualized through making simple changes in this diagram. For example, if we suppose that the substrate is less basic, making formation of the conjugate acid less favorable, and the carbonium ion more stable, we could arrive at a mechanism in which C–O bond cleavage occurs prior to protonation. In Figure 3, this would involve moving first along the horizontal axis and then vertically, rather than *vice versa*. Kinetically, this would correspond to a pH-independent hydrolysis reaction. Note that several such cases have been identified (Table III); these all involve either very weakly basic substrates or formation of particularly favorable carbonium ions or both, as we anticipated.

One can imagine an intermediate case between the two extremes thus far considered; it is shown diagram-

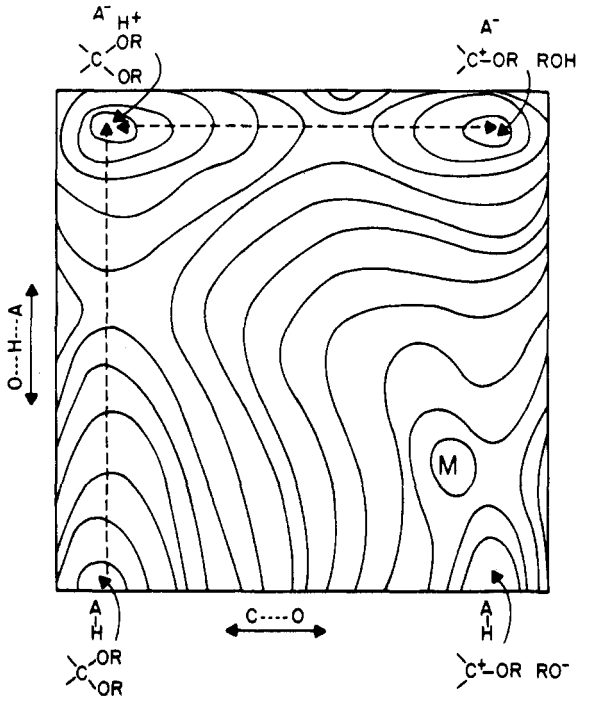


Figure 3. Contour diagram illustrating the pathway for specific acid catalyzed hydrolysis of an acetal or related substrate. M denotes an energy maximum (modified from ref 63).

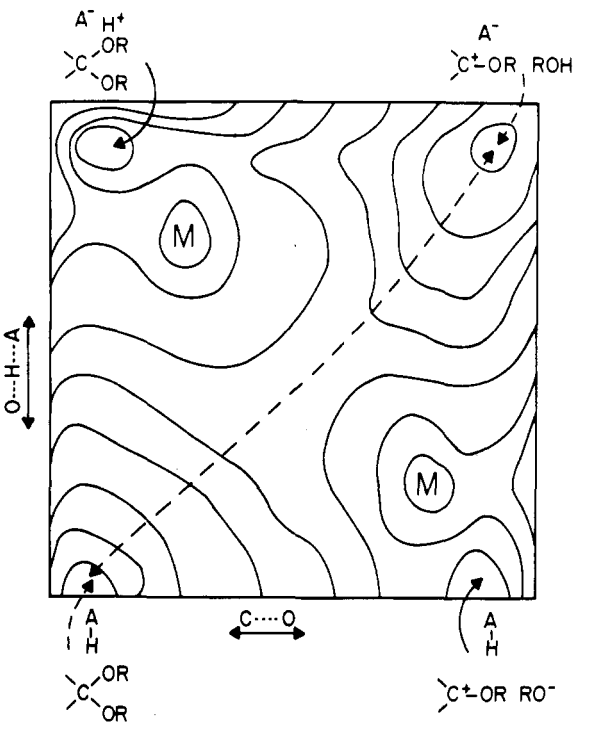


Figure 4. Contour diagram for general acid catalyzed hydrolysis of an acetal or related substrate involving concerted substrate protonation and carbon-oxygen bond cleavage. M denotes an energy maximum (modified from ref 63).

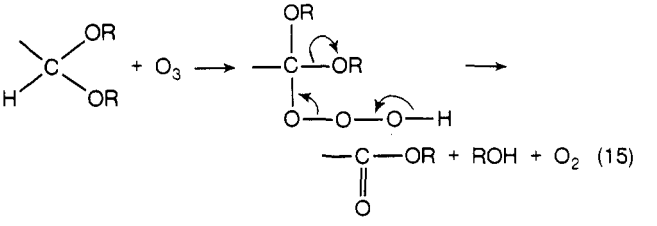
matically in Figure 4. As the substrate becomes less basic and the carboxonium ion more stable, one forms a lowest energy pathway in which proton transfer and covalent bond cleavage are concerted. Again, these are precisely the conditions under which general acid catalysis is observed for acetal, ketal, and ortho ester hydrolysis (Table VII).

In the preceding pages, the word "concerted" or the phrase "concerted in some sense" have been repeatedly used to describe the temporal relationship of proton transfer and heavy atom reorganization for hydrolysis of those substances exhibiting the phenomenon of general acid catalysis. However, "concerted" has different meanings to different scientists. At one extreme, Bauer has defined a concerted reaction as one in which no intermediates with lifetimes of at least one molecular vibration occur along the reaction path between reactants and products.[68] Other chemists have suggested that "concerted" should be interpreted more liberally to include complex reactions in which more than one diffusion-controlled encounter may be involved.[69] In addition, there remains uncertainty concerning whether, according to the definition of Bauer, proton transfer is ever truly concerted with heavy atom reorganization. It has been argued that proton transfers to electronegative atoms do not accompany heavy atom reorganization and that the proton remains in a stable potential in the transition state.[70] It has also been argued that proton transfer occurs in the transition state but that the proton remains in a stable potential throughout the process.[1] These arguments have been considered in detail recently.[36] It is our belief that evidence is not yet in hand to decide unequivocally among the various possibilities for general acid catalysis of hydrolysis of acetals, ketals, and ortho esters.

Regardless of the exact relationship between timing of proton transfer and heavy atom reorganization, it is pertinent to point out that values of secondary deuterium isotope effects and Brønsted exponents give rather different pictures of transition state structure. Specifically, for those substrates which hydrolyze *via* general acid catalyzed pathways, α-deuterium isotope effects suggest that rather little C–O bond cleavage occurs at the transition state;[47] in contrast, values of α are usually large (Table VII), suggesting considerable proton transfer at the transition state. At the minimum, this result requires caution in the interpretation of Brønsted exponents in terms of extent of heavy atom reorganization in the transition state.

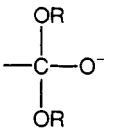
IX. Stereoelectronic Theory for Hydrolysis of Ortho Esters

Deslongchamps and coworkers have made a series of interesting observations concerning conformation requirements for ozonolysis of acetals[71,72]; these appear to have important consequences for hydrolysis of ortho esters as well. Specifically, one can write six gauche conformations for an acetal (Figure 5). Only those conformations having an electron pair orbital on each acetal oxygen oriented antiperiplanar to the C–H bond (A, C, and F in Figure 5) are reactive toward ozone. The relationship between this observation and the hydrolysis of ortho esters derives from the mechanism of the ozonolysis reaction, considered to occur with insertion of ozone into the C–H bond followed by decomposition[71,72] (eq 15). Note



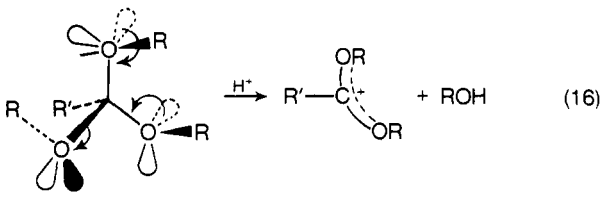
that the hydrotrioxide intermediate is structurally related to ortho esters and to tetrahedral intermediates believed to occur in hydrolysis and alcoholysis of carboxylic esters. In fact, Deslongchamps, *et al.*, have extended their observations on acetal ozonolysis to a theoretical analy-

sis of the modes of decomposition of such tetrahedral intermediates.[73] If orbital orientation is important in determining routes of decomposition of tetrahedral intermediates of the structure



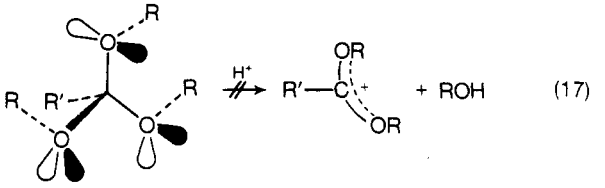
it follows that such orientation should be important for hydrolysis of ortho esters as well.

The considerations of Deslongchamps suggest that only those conformations of ortho esters should decompose in which electron pair orbitals on each of the nonleaving alkoxy function are antiperiplanar with respect to the C–O bond to be cleaved. Since there are 18 gauche conformations for an ortho ester, it is awkward to consider them all. Suffice it to note that eq 16 is an acceptable



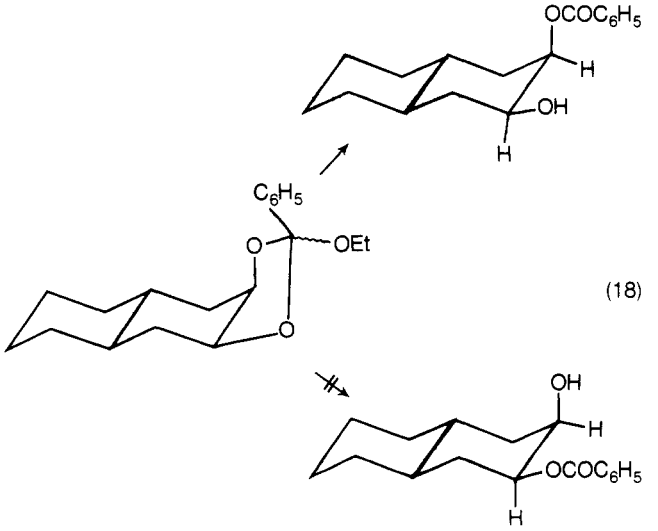
(16)

pathway but that eq 17 is not. There is some evidence to



(17)

suggest that these considerations are correct. For example, it has been reported that hydrolysis of an ortho ester fused to a six-membered ring yields predominantly the axial ester–equatorial alcohol rather than the axial alcohol–equatorial ester[74] (eq 18).



(18)

Clearly these considerations may affect both the rate and course of ortho ester hydrolysis, particularly in those cases in which one or more of the alkoxy functions is incorporated into a ring system. Perhaps the point can be seen most clearly by extending our considerations from ortho esters to acetals. In the latter case, it is reasonable to assume that decomposition of the protonated substrate will require that an electron pair orbital on the nonleaving

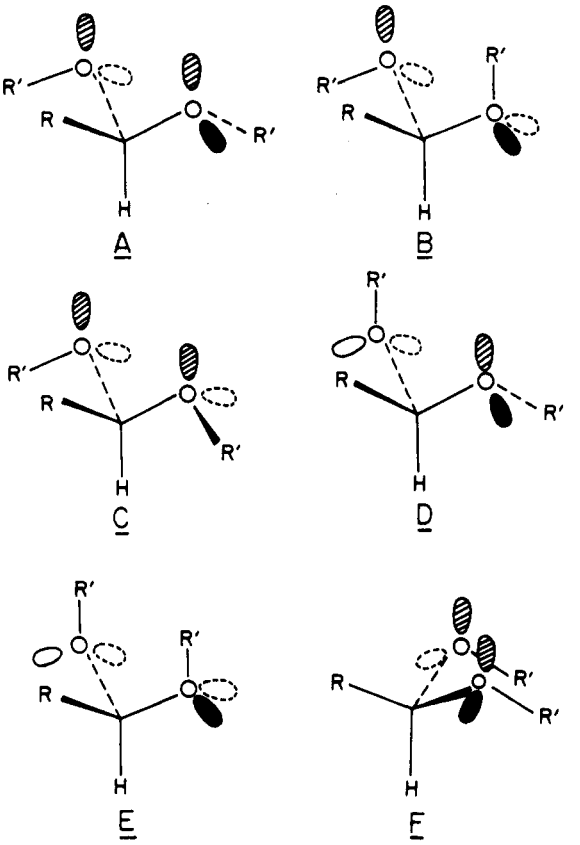


Figure 5. The six gauche conformers of a symmetrical acetal. Those electron pair orbitals on oxygen which are antiperiplanar to the C–H bond are cross-hatched (ref 73).

alkoxy function be antiperiplanar with respect to the C–O bond to be cleaved. Referring to the conformations of acetals shown in Figure 5, this rule suggests that A and B can decompose in only one manner, C cannot decompose at all, and the D, E, and F can decompose with loss of either alkoxy function.

A full appreciation of the influence of these considerations for the rate and course of hydrolysis of acetals, ketals, and ortho esters must await further investigations.

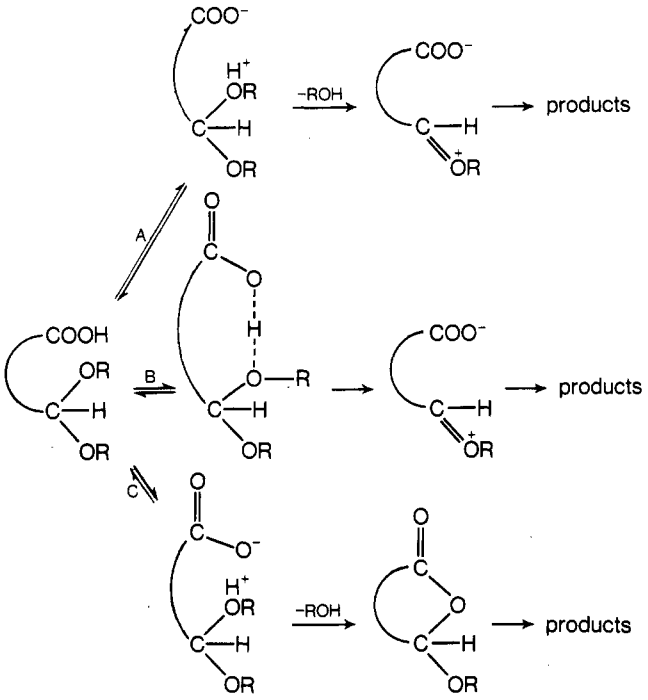
X. Intramolecular Facilitation of Acetal Hydrolysis

The complete tertiary structure of hen egg white lysozyme reveals that two carboxyl groups, Asp 52 and Glu 35, are located in the immediate vicinity of the glycosidic C–O bond cleaved in the course of the catalytic process.[35,75-77] This observation has generated considerable speculation concerning the possible role of these groups in the enzymatic reaction. Asp 52 is frequently believed to participate either as a nucleophilic reagent or to electrostatically stabilize a developing carbonium ion in the transition state, and Glu 35 has been tentatively assigned a role as general acid catalyst aiding the departure of the leaving group.[35,77] The mechanism of lysozyme-catalyzed reactions and its relationship to mechanisms for acetal hydrolysis have been reviewed in detail.[78] Since bond-changing reactions in enzymatic processes occur within a substrate–enzyme complex, these considerations have focused attention on intramolecular facilitation of the hydrolysis of glycosides and acetals, particularly those in which one or more carboxyl functions are positioned so as to permit participation in the reaction.

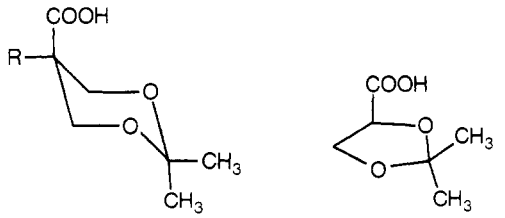
At the outset, we may note that pH-independent hydrolysis of an acetal or related compound bearing a car-

boxyl group may reflect three kinetically indistinguishable mechanisms: specific acid catalyzed hydrolysis of the carboxylate form of the substrate (which may or may not involve facilitation through electrostatic stabilization of the developing carbonium ion); intramolecular general acid catalysis by the carboxylic acid group; and nucleophilic attack by the carboxylate on the protonated substrate. These possibilities are depicted in Scheme II. Since kinetics will not serve to distinguish these possibilities, alternative methods must be employed for those cases in which evidence for intramolecular participation is observed.

SCHEME II



In 1967, Bruice and Piszkiewicz carefully reviewed previous claims for intramolecular participation in glycoside and acetal hydrolysis and found little firm evidence establishing such participation.[79] Moreover, these workers carefully examined the kinetics of hydrolysis of 1,3-dioxanes and 1,3-dioxolanes substituted with carboxyl functions (**1** and **2**) and found no evidence for intramo-

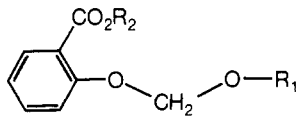


1 2

lecular facilitation in either case.[79] A subsequent investigation by the same workers failed to reveal evidence for such facilitation for glycoside hydrolysis.[80]

Subsequently, Capon and coworkers did observe abnormally rapid hydrolysis for 2-carboxyphenyl-β-D-glucoside and *o*-carboxyphenyl methyl acetals, indicating some form of participation.[81-83] On the basis of the solvent isotope effect, these workers suggested that facilitation involved general acid catalysis by the carboxylic acid function (pathway B, Scheme II).

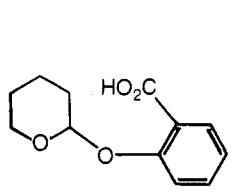
Dunn and Bruice, in an extensive series of investigations, have confirmed the intramolecular participation of the carboxyl group in hydrolysis of *o*-carboxyphenyl alkyl acetals.[84-86] However, these workers attribute the facilitated hydrolysis to electrostatic stabilization by the carboxylate ion (pathway A, Scheme II) rather than to general acid catalysis. Rate increases of 350- to 1000-fold have been observed. This conclusion is based on the observation that the sensitivity of hydrolysis rates to polar substituents in the alkyl moiety (R_1)



3

is independent of the nature of the group in the ortho position: carboxymethyl, carboxyl, or carboxylate ($\rho^* = -3.0$).[84] It is argued that were the catalysis of the general acid type to obtain, one would have expected a diminished value of ρ^* for the reactions of those substrates bearing the carboxylic acid group in the ortho position. This contention is supported by the observations cited above concerning structure reactivity correlations (IV, Table II). Although one cannot be certain concerning the interpretation of these results, the arguments favoring electrostatic stabilization appear stronger than those for general acid catalysis. Note that electrostatic stabilization for hydrolysis of these substrates may be independently observed (section XI) and that general acid catalysis for compounds for this type is not observed in intermolecular reactions (section VIII).

An alternative approach to study of intramolecular carboxyl group participation in acetal hydrolysis has been taken by Fife and Anderson who have elected to search for such participation in substrates for which intermolecular general acid catalysis has been observed for the unsubstituted compounds. Hydrolysis of 2-(*o*-carboxyphenoxy)tetrahydropyran (**4**) and benzaldehyde methyl (*o*-carboxyphenyl) acetal (**5**) proceeds with pronounced car-



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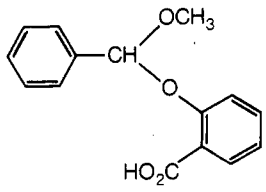
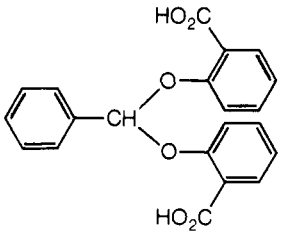


5

boxyl group participation.[87] Rate increases over the corresponding unsubstituted compounds in the range of 10^4–10^6, depending on substrate structure and solvent, are observed. In contrast to cases previously discussed, it is reasonable to attribute these rate increases to intramolecular general acid catalysis since the unsubstituted compounds exhibit intermolecular general acid catalysis (Table VII). Moreover, the magnitude of calculated rate constants and the magnitude of the observed facilitation appear too large to be accounted for in terms of electrostatic facilitation (ref 87 and section XI). Note that a concentration of at least 580 *M* formic acid would be required to achieve a rate of hydrolysis of unsubstituted tetrahydropyran phenol acetal equal to that observed for the *o*-carboxyl-substituted one.[87] Clearly, intramolecular general acid catalysis must involve some reaction facilitation that does not derive solely from approximation of substrate with acid catalyst.

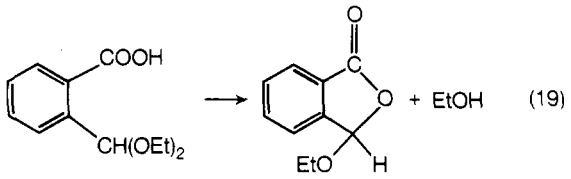
A particularly striking rate increase for acetal hydrolysis deriving from intramolecular carboxyl group participation is provided by benzaldehyde disalicyl acetal (**6**). Hy-



6

drolysis of this compound exhibits a bell-shaped dependence of rate on pH, as does the hydrolysis of glycosides by lysozyme, with a rate maximum near pH 6 in 50% dioxane.[88] At the rate maximum, this compound is 2.7 $\times$ 10^9 times more reactive than the corresponding dimethyl ester, which may reflect both intramolecular general acid catalysis and electrostatic facilitation by a carboxylate function.[88]

Anderson and Capon have searched carefully for nucleophilic participation in reactions of acetals.[89] In several cases including the hydrolysis of 4-aminobutyraldehyde diethyl acetal, 2-pyridylmethylaminoacetaldehyde diethyl acetal, and succinaldehyde acid dimethyl acetal, no evidence for such participation could be found. On the other hand, in 82% aqueous dioxane at an apparent pH of 9.46, the rate of cyclization of 2-carboxybenzaldehyde diethyl acetal is 3000 times that for hydrolysis of terephthalaldehydic acid diethyl acetal, providing strong evidence for carboxyl group participation.[89] It should be specifical-



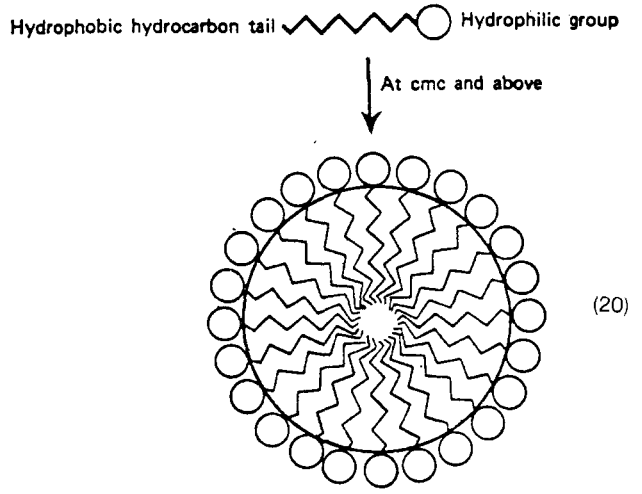
(19)

ly noted that the combination of rate enhancement and appearance of the cyclized product do not demand that the carboxylate group participate as a nucleophilic agent in the transition state. It is also possible to account for the results by assuming that the rate enhancement results from electrostatic stabilization of a developing carbonium ion in the transition state followed by cyclization in a step subsequent to the rate-determining one.

Overall, these studies offer modest support for the concept of general acid catalysis or nucleophilic catalysis in lysozyme-catalyzed reactions. Electrostatic facilitation of acetal, ketal, and glycoside hydrolysis appears on firmer ground. Such catalysis has been probed for these reactions in detail for systems containing ionic surfactants. We close this review with a consideration of this topic.

XI. Surfactant Catalysis for Hydrolysis of Acetals, Ketals, and Ortho Esters

During the last 15 years it has been firmly established that a number of organic reactions are subject to catalysis by micelle-forming surfactants. This field has been reviewed in detail.[90-92] In the great majority of cases, surfactant catalysis is the consequence of micelle formation (eq 20). That is, typically 50–100 individual surfactant molecules aggregate above a certain concentration, the critical micelle concentration (cmc), to form a structure in which the polar headgroups, typically charged in these studies, are exposed to the aqueous environment. Muller has recently considered several aspects of micellar structure and formation in detail.[93] For our purposes, it



(20)

will suffice to note that the micellar surface is amphipathic; that is, it possesses simultaneously both hydrophobic and hydrophilic properties.[92] Consequently, reactions in which one substrate is an organic molecule and the other an ion can and do occur on the micellar surface, frequently at a rate substantially altered from that for simple aqueous solution. Among those reactions known to be subject to surfactant catalysis, hydrolysis of acetals, ketals, and ortho esters has been studied particularly extensively. Results of these efforts have recently been summarized in detail.[94]

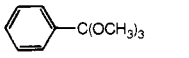
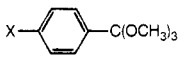
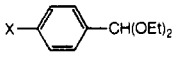
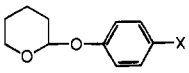
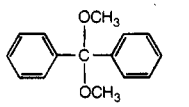
As has been developed in the previous section of this review, hydrolysis of the substrates of interest here should be subject to electrostatic facilitation by anionic groups, reflecting the cationic character of the transition states involved. Thus, micelles formed from anionic surfactants, such as sodium dodecyl sulfate, bear a substantial negative charge at the micellar surface. The resulting electrostatic field is expected to stabilize the cationic transition state relative to the ground state, the substrate on the micellar surface and the hydrated proton in the bulk phase. The converse is also true: micelles formed from cationic surfactants should tend to inhibit hydrolysis of substrates having cationic transition states. These expectations are fully borne out in experimental studies; pertinent data are collected in Table VIII. In each case studied, despite wide variation in substrate and surfactant structure, anionic surfactants catalyze and cationic ones inhibit the hydrolysis of acetals, ketals, and ortho esters. Nonionic and zwitterionic surfactants tend to inhibit these reactions, perhaps reflecting the lower polarity at the micellar surface compared to the bulk phase.

Fluorine-19 nmr measurements on appropriately labeled acetals and ortho esters strongly suggest that these compounds are incorporated onto the micellar surface rather than into the micellar interior.[95] This is the expected result in terms of the behavior of other organic molecules[90]; those with appreciable polar character tend to occupy the micellar surface, not the interior.

Turning attention from the qualitative information of Table VIII, let us consider some details of hydrolysis of acetals, ketals, and ortho esters in the presence of micelle-forming surfactants.

One of the fundamental characteristics of micelle catalysis for organic reactions is the nature of the dependence of reaction rate on surfactant concentration. A typical example, for the SDS-catalyzed hydrolysis of methyl orthobenzoate, is shown in Figure 6.[96] The concentration profile is multiphase; below the cmc for the surfactant, the rate constants are independent of the surfactant con-

TABLE VIII. Summary of Qualitative Effects of Several Surfactants on the Rate of Hydrolysis of Acetals, Ketals, and Ortho Esters (from Ref 94)

Substrate	Surfactants	Effect	Ref
 Methyl orthobenzoate	Sodium alkyl sulfates Isomeric hexadecyl sulfates Substituted oxyethylene sulfates Sodium 2-dodecylbenzenesulfonate Disodium sulfoalkyl sulfates Alkyl disulfonates Sulfoalkylcarboxylates α-Sulfoalkyl esters	Catalysis	97, 55, 96
	Dodecyldimethylphosphine oxide Dodecyldimethylammonium propanesulfonate Dodecyldimethylammonium acetate Cetyltrimethylammonium bromide	Inhibition	
 *p*-Substituted methyl orthobenzoates X = OMe, Me, H, F, Cl, NO_2	Sodium dodecyl sulfate	Catalysis	97
 *p*-Substituted benzaldehyde diethyl acetals X = OMe, Me, H, F, Cl	Sodium dodecyl sulfate Sodium decylsulfonate	Catalysis	55
 2-(*p*-Substituted phenoxy)-tetrahydropyrans X = OMe, Me, H, Cl, NO_2	Sodium dodecyl sulfate Sodium 2-hexadecyloxyethyl sulfate Sodium 2-hexadecyloxy-1-methyl sulfate	Catalysis	*a*
	Dodecyldimethylammonium propanesulfonate Dodecyldimethylphosphine oxide	Inhibition	
 Benzophenone dimethyl ketal	Sodium dodecyl sulfate	Catalysis	*b*
	Octadecyldimethylammonium bromide	Inhibition	

[a] A. Armas, H. Clemente, J. Coronel, F. Creazzola, A. Cuenca, J. Francis, A. Malpica, D. Quintero, R. Romero, J. Salazar, N. Sanchez, R. Von Bergen, J. Baumrucker, M. Calzadilla, and E. H. Cordes, *J. Org. Chem.*, **37**, 875 (1972). [b] A. Alam, Trabajo Especial de Grado, Escuela de Quimica, Facultad Ciencias, Universidad Central de Venezuela, 1972.

centration. Above the cmc, the rate constants rise rapidly with increasing surfactant concentration, level off, and finally decrease with increasing concentration of this surfactant. At the optimal surfactant concentration, a rate augmentation of 85-fold at 25° is observed for this reaction. Profiles of this type can be rationalized on the basis of (1) the necessity of micelles for catalysis, (2) adsorption of a progressively greater fraction of the substrate into the micellar phase until that fraction approaches unity with increasing surfactant concentration, and (3) inhibition of the micellar reaction by the counterions of the surfactant itself. In the case of methyl orthobenzoate hydrolysis in the presence of sodium dodecyl sulfate, it has been shown that this interpretation must be substantially correct.[96] The equilibrium constant for the association of substrate with surfactant is 73 M^{-1}. This value accounts quantitatively for the increase in rate constant with increasing surfactant concentration. That is, when the substrate is predicted to be 50% associated with the micellar phase on the basis of the equilibrium constant, about 50% of the maximum catalysis is experienced and so on. Furthermore, when the total concentration of sodium ion is maintained constant by the addition of the necessary quantities of inorganic salts, the inhibition of the reaction at high surfactant concentrations disappears.

Another basic aspect of reactions in micellar systems is the dependence of rate on surfactant structure. This matter has been dealt with in a qualitative way in Table VIII.

Quite aside from changes in surfactant structure which involve alterations in charge type, there are two general areas of surfactant variability: the nature and position of the head group and the size of the hydrophobic chain. Both factors are important for the micellar catalysis of hydrolysis of acetals and ortho esters.

In Figure 7 are plotted rate constants for hydrolysis of methyl orthobenzoate as a function of the concentration of several sodium hexadecyl sulfates.[97] Note that catalytic efficiency is markedly dependent on the position of the head group; as it is moved further from the terminus of the chain, the catalytic efficiency decreases, both in terms of the maximal catalysis achieved and in terms of the concentration of surfactant necessary to achieve it.

Clearly, the degree of catalysis depends in a sensitive way on details of surfactant structure. Additional examples to support this conclusion are available.[97]

Finally, let us focus attention on the role of surfactant hydrophobicity in determination of catalytic efficiency. It is quite generally true that the more hydrophobic the surfactant, the better catalyst it is. In Table IX, some rate increases for methyl orthobenzoate hydrolysis elicited by several sodium alkyl sulfates are collected. Note that both the maximal catalysis observed and the surfactant concentration required to elicit maximal catalysis are sensitive functions of the length of the alkyl chain.[96] This behavior may reflect the partitioning of substrate between micellar and bulk phases or the precise localization of substrate with respect to the micellar surface which may lead to a direct contribution of hydrophobic forces to the activation energy for the reactions. It is not possible to

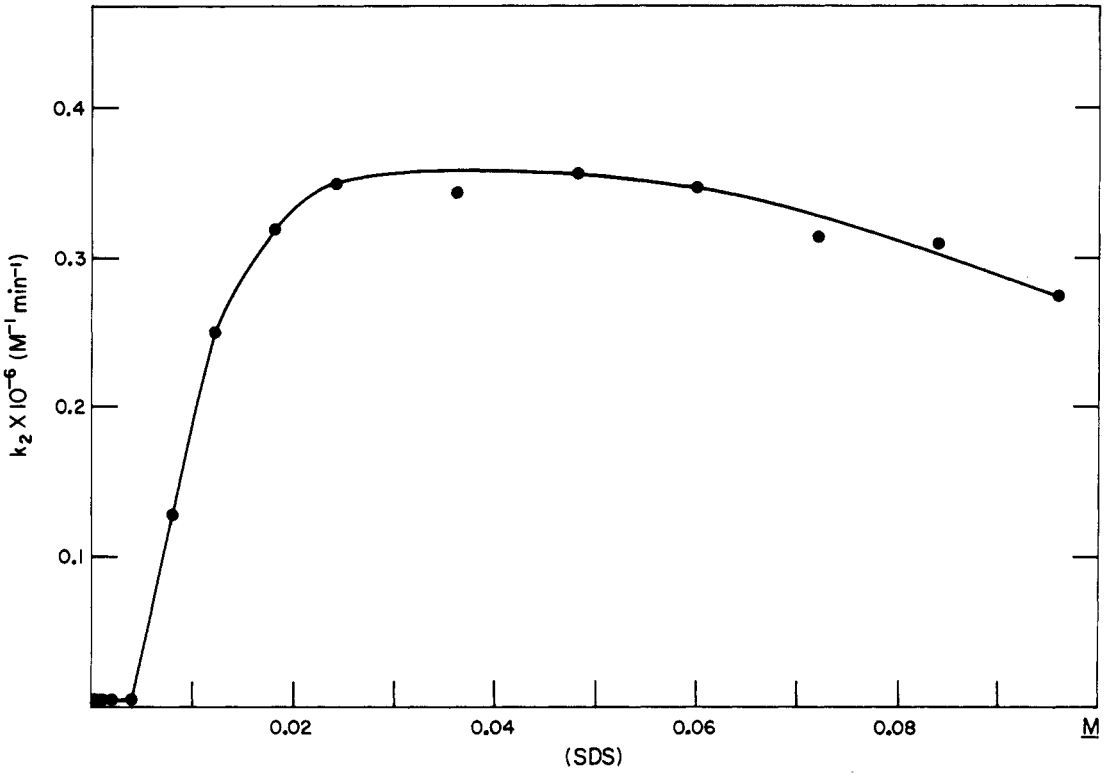


Figure 6. Second-order rate constants for the hydrolysis of methyl orthobenzoate in aqueous solution at 25° plotted as a function of the concentration of sodium dodecyl sulfate. Values of pH were maintained through the addition of 0.01 *M* acetate buffers (from ref 96).

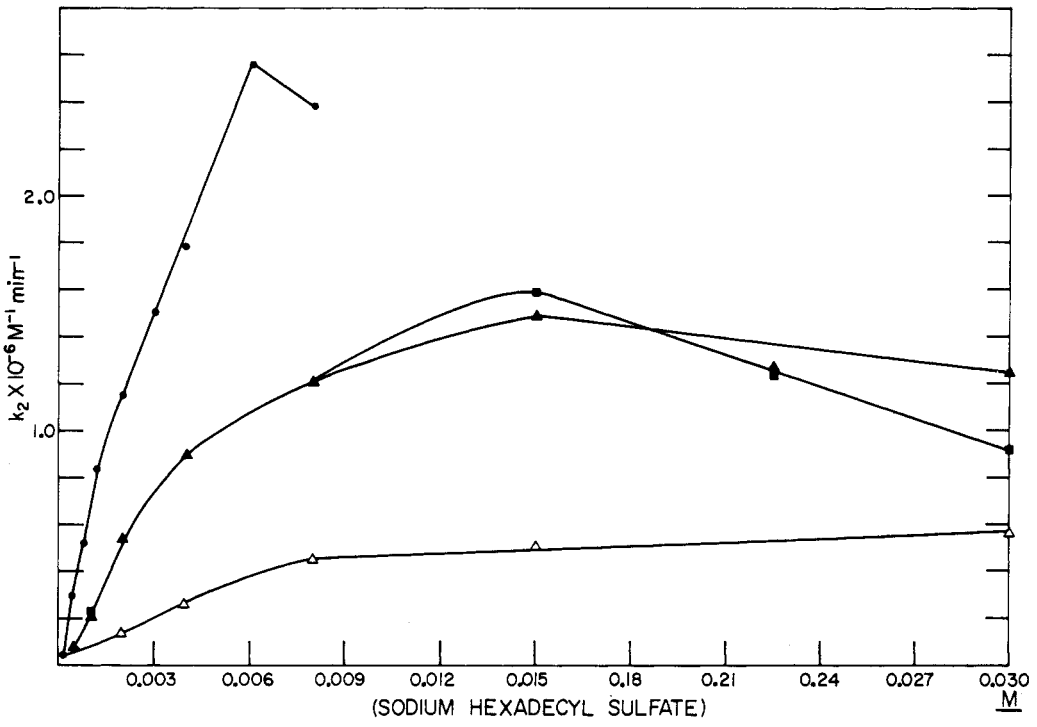


Figure 7. Second-order rate constants for hydrolysis of methyl orthobenzoate plotted against the concentration of 1-hexadecyl (●), 2-hexadecyl (■), 3-hexadecyl (▲), and 5-hexadecyl (△) sodium sulfate.

assess the relative contribution of each of these factors to the observed rate effects at this time.

A third fundamental aspect of reactions in micellar systems is the sensitivity of rates to details of substrate structure. In this regard, there are two aspects of substrate structure that have proved interesting in terms of reaction kinetics in micellar systems: substrate hydrophobicity and polar substituents. Generally, increasing the hydrophobic character of the substrate increases the influence of the micellar phase on the velocity of the reaction, just as increasing the hydrophobicity of the surfactant tends to accentuate these effects. This is true for hydrolysis of acetals and ortho esters. For example, hydrolysis of methyl orthobenzoate and methyl orthovalerate are subject to catalysis by SDS, but hydrolysis of methyl orthoacetate is not.[98] These results most likely reflect the partitioning of substrate between the micellar and bulk phases. For other reactions, however, it seems

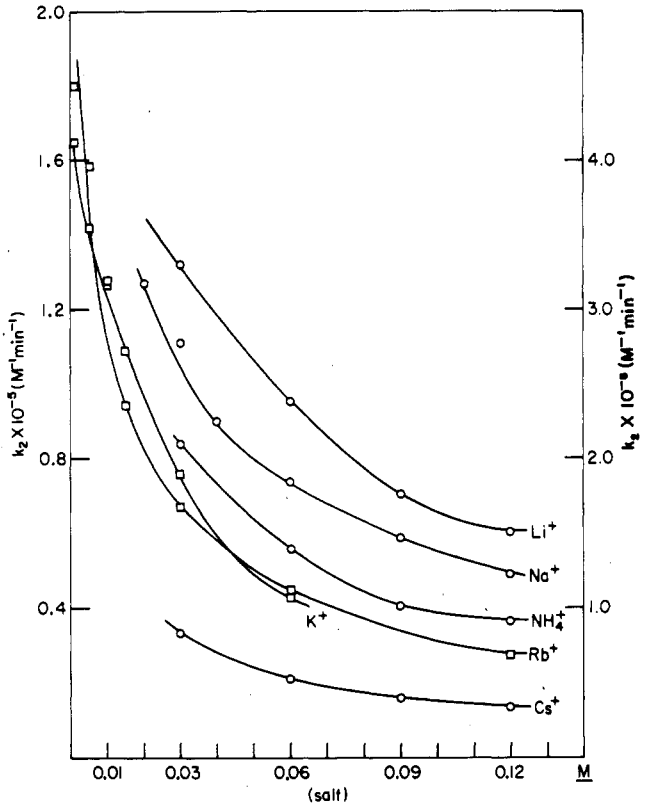


Figure 8. Second-order rate constants for the hydrolysis of methyl orthobenzoate in the presence of 0.01 *M* sodium dodecyl sulfate plotted against the concentrations of several alkali metal ions and ammonium ion.

TABLE IX. Maximal Rate Increases Elicited by a Series of Sodium Alkyl Sulfates for Methyl Orthobenzoate Hydrolysis (from Ref 96)

Sodium alkyl sulfate	Temp, °C	$k_2^0 \times 10^{-6}$,[a] M^{-1} min^{-1}	$k_2 \times 10^{-6}$,[b] M^{-1} min^{-1}	Max rate increase
Octyl	25.0	0.00502	0.0351 at 0.20 *M*	7.0
Decyl	25.0	0.00452	0.121 at 0.075 *M*	26.8
Dodecyl	25.0	0.00452	0.357 at 0.048 *M*	79.0
Tetradecyl	30.0	0.00864	0.793 at 0.020 *M*	91.8

[a] Second-order rate constants in the absence of surfactant. [b] Second-order rate constants for the reaction in the presence of the indicated concentrations of surfactants at which values maximum catalysis occurs.

TABLE X. Effects of Polar Substituents on the Hydrolysis of Acetals and Ortho Esters in Water and in the Presence of Anionic Surfactants[a]

Substrates	Surfactant	$\rho_{micellar}$	$\rho_{aqueous}$	Ref
Methyl orthobenzoates	Sodium dodecyl sulfate	−2.5	−1.2	47, 97
Benzaldehyde diethyl acetals	Sodium dodecyl sulfate	−4.1	−3.3	55
Benzaldehyde diethyl acetals	Sodium dodecyl sulfonate	−4.3	−3.2	*b*

[a] Taken from ref 94. [b] J. Baumrucker and M. Calzadilla, unpublished results.

likely that hydrophobic interactions may contribute to activation energies.[99]

The effects of polar substituents on the rates of organic reactions in micellar phases appear to differ substantially from such effects in aqueous solution. Some pertinent data for hydrolysis of acetals and ortho esters are collected in Table X. Note that, in each case, the reaction in the micellar phase is more sensitive to the nature of polar substituents than the same reaction in water. These data may reflect either medium effects or changes in transition state structure. No firm basis exists for distinguishing between these alternatives at this time.

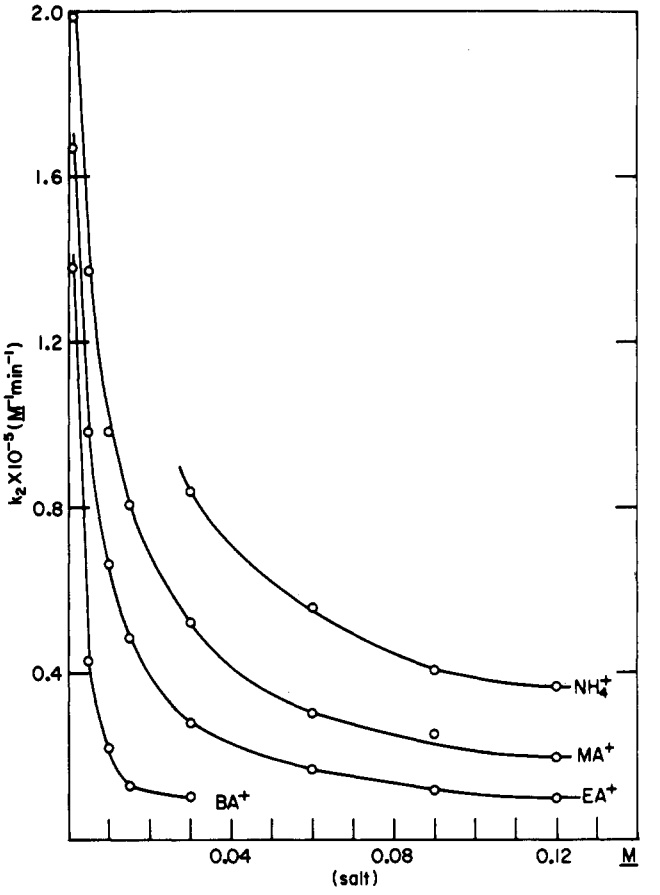


Figure 9. Second-order rate constants for hydrolysis of methyl orthobenzoate plotted as a function of the concentration of several ammonium ions; MA, methyl-; EA, ethyl-; and BA, butylammonium ion.

One of the striking aspects of the kinetics of organic reactions in micellar systems is their sensitivity to salt effects. Changes in the nature or concentration of electrolyte that would lead to barely detectable differences in rates of reactions in purely aqueous systems frequently cause differences of an order of magnitude or more for the same reactions in the presence of ionic surfactants. As an example, we have already noted the inhibition of surfactant-dependent reactions due to the counterion of the surfactant itself.

More systematic studies have been performed: the results of two such studies are shown in Figures 8 and 9. Here second-order rate constants for hydrolysis of methyl orthobenzoate in the presence of sodium dodecyl sulfate are plotted as a function of the concentration of several cations. All are markedly inhibitory. Note that for both series of ions the inhibition increases as the hydrophobic character of the salt increases. These observations can be readily understood in terms of increasing the extent of charge neutralization of the micellar surface. To the extent that catalysis is dependent on electrostatic stabilization of the transition state with respect to the ground state, such charge neutralization must reduce the catalytic effect. In other cases, the salt inhibition may derive principally from the displacement of one reactant from the micellar surface by the electrolyte.

XII. Conclusion

From the considerations developed above, it is clear that understanding of the various aspects of mechanism and catalysis for hydrolysis of acetals, ketals, and ortho esters has improved considerably in the past few years. It is equally clear that a number of questions remain unanswered or partially answered, particularly with respect to relative timing of proton transfer and covalent bond-changing reactions. Nevertheless, it may be fair to claim that the essential features of hydrolysis of acetals and related substrates are now well in hand. Although future studies will doubtlessly add new and useful information to that already known, it is likely that major breakthroughs will come in the related areas of hydrolysis of glycosides and glycosylamines, particularly for the enzyme-promoted processes.

XIII. References

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