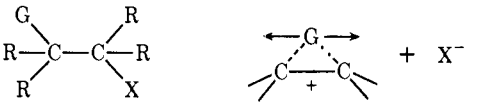
does a vinyl group. The "strain" in both the cyclopropyl and vinyl groups makes the electrons more delocalizable, but these systems need not be "relieved" by nuclear movement in order to afford stabilization or stereochemical control. We therefore see that σ–π conjugation is not simply an excuse for drawing different dotted lines but is phenomenologically very different from either internal displacement or fragmentation.

It is not suggested that the cations which are intermediates in solvolysis reactions are not bridged. The important point of this paper (and our other papers on this subject) is that because all, or nearly all, of the stabilization of cations as measured by solvolysis reactions is also seen in vertical processes, such bridging contributes very little to the stabilization at the transition state. Therefore, if a bridged ion were formed it would have a low vibration frequency for the vibration shown. Prevention of such bridging does not



alter the stabilization.

While we have previously demonstrated the importance of vertical stabilization by both polarized and strained σ bonds, we have not shown that these effects act to the exclusion of bridging except in a few cases.[4a] Having established the expectations and requirements for vertical stabilization we may further probe experimentally for its importance as we do in subsequent papers on this subject.

Acknowledgment. We gratefully acknowledge the support of this work by the Air Force Office of Scientific Research, and the helpful advice from Professors Charles Perrin, Paul D. Bartlett, Edward Kosower, G. Dann Sargent, and Paul v. R. Schleyer.

Electrostatic Catalysis. IV. Intramolecular Carboxyl Group Electrostatic Facilitation of the A-1-Catalyzed Hydrolysis of Alkyl Phenyl Acetals of Formaldehyde. The Influence of Oxocarbonium Ion Stability

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Abstract: The hydrolysis of a series of alkyl phenyl acetals of formaldehyde has been studied (H_2O, 30°, μ = 1.0) as a function of pH. Rate constants are derived for specific acid-catalyzed hydrolysis of compounds with *o*-$COOCH_3$, *o*-COOH, and *o*-COO^- substituents on the phenyl ring. All second-order rate constants are correlated by the Taft $\rho^*\sigma^*$ relationship utilizing the σ^* values of the alkyl substituents. The rates of *o*-COO^--substituted compounds exhibit a 500-fold positive deviation but the ρ^* value for all three series is -3.0 ± 0.05. The identical sensitivity to oxocarbonium ion stability suggests the carboxyl facilitated reaction may best be described as an electrostatically stabilized A-1 reaction. The hydrolysis of a system possessing two bulky ortho groups was investigated in an attempt to observe intermolecular general acid catalysis in the hydrolysis of a formal. The failure to observe either a rate enhancement over a nonhindered system or buffer catalysis is attributed to a decrease in pK_a of the conjugate acid and the instability of the oxocarbonium ion.

Interest in the mechanism of hydrolysis of acetals was greatly stimulated by the elucidation of the tertiary structure of crystalline hen egg white lysozyme.[2,3] In particular, due to the proximity of the protonated carboxylic acid group of glutamic acid **35** at the point of C–O bond cleavage of the substrate, several studies have been directed toward carboxylic acid group facilitation of the hydrolysis of glycosides and acetals.

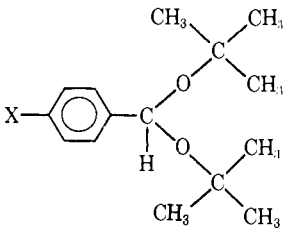
Fife and coworkers[4–7] and Capon and his associates,[8,9] have delineated the structural requirements for the observation of intermolecular general acid catalysis of hydrolysis in a number of systems. Studies from this laboratory,[10–12] from Fife's group,[13] and from Capon's group[14–16] have probed the structural, electronic, and steric origins of facilitated acetal hydrolysis in intramolecular models.

(1) Predoctoral Fellow of the National Institutes of Health, 1968–1971. A portion of the material to be submitted by B. M. D. in partial fulfillment of the requirements for the Ph.D. in Chemistry, University of California at Santa Barbara.
(2) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Nature (London)*, **206**, 757 (1965).
(3) D. C. Phillips, *Sci. Amer.*, **215**, 78 (1966); for a recent review see D. M. Chipman and N. Sharon, *Science*, **165**, 454 (1969).
(4) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).
(5) T. H. Fife and L. H. Brod, *ibid.*, **92**, 1681 (1970).
(6) T. H. Fife and E. Anderson, *J. Org. Chem.*, in press.
(7) E. Anderson and T. H. Fife, *J. Amer. Chem. Soc.*, in press.
(8) B. Capon and M. C. Smith, *J. Chem. Soc. B*, 1031 (1969).
(9) E. Anderson and B. Capon, *ibid.*, 1033 (1969).
(10) D. Piszkiewicz and T. C. Bruice, *J. Amer. Chem. Soc.*, **90**, 2156 (1968).
(11) B. M. Dunn and T. C. Bruice, *ibid.*, **92**, 2410 (1970).
(12) B. M. Dunn and T. C. Bruice, *ibid.*, **92**, 6589 (1970).
(13) T. H. Fife and E. Anderson, personal communication.
(14) B. Capon and M. C. Smith, *Chem. Commun.*, 7, 523 (1965).
(15) B. Capon, *Tetrahedron Lett.*, 911 (1963).
(16) B. Capon, M. C. Smith, E. Anderson, R. H. Dahm, and G. H. Sankey, *J. Chem. Soc. B*, 1038 (1969).

The conclusions of these physical organic studies may be briefly summarized as follows. Intermolecular general acid catalysis by buffer species can occur (a) when the energy barrier to protonation (eq 1) is higher than

$$A + H^+ \rightleftharpoons AH^+ \longrightarrow B^+ + COH \qquad (1)$$

the barrier to decomposition of the conjugate acid[6,9] [*i.e.*, with a very stable oxocarbonium ion such as that derived from the tropylium ion or with a system very strained in the ground state such as **1**] or (b) when the



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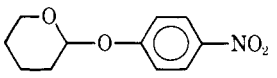
carbonium ion is of sufficient stability and the leaving group is very good[4] (*i.e.*, **2**).



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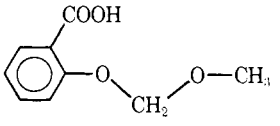
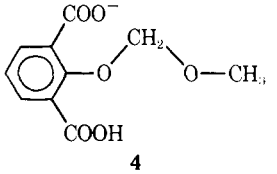
Kinetically apparent intramolecular general acid catalysis may be observed in systems that contain a suitably positioned carboxylic acid group[10,11,16] (*i.e.*, **3**). In the case of **3** neither of the criteria are satisfied for the



3

observation of intermolecular general acid catalysis and, in fact, it has not been observed.[11,12]

The glycosyl carbonium ion derived from the natural substrates for lysozyme is not of great stability and the leaving group is much worse than the phenyl systems that have received much study. The possibility that stabilization of the carbonium ion derives from electrostatic participation by a second carboxyl group (Asp-52 COO^-) has been explored[11] in the hydrolysis of compound **4** and no kinetic evidence was obtained for



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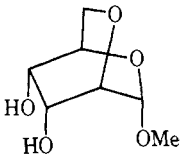
this postulation. The use of substrate distortion by lysozyme to provide a planar conformation in the ground state resembling the oxocarbonium ion transition state has been probed[17] through the study of compound **5** with similar lack of revealing rate enhancement.



5

(17) T. A. Giudici and T. C. Bruice, *Chem. Commun.*, 690 (1970).

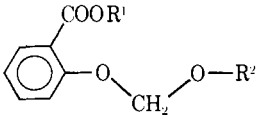
Since the lysozyme–substrate complex resembles compound **3** in its approximation of the carboxylic acid and the ether oxygen and in the relative instability of its carbonium ion, the rapid hydrolysis of **3** may be mechanistically similar to the lysozyme reaction. Further evidence on the mechanism of this facilitation is then desirable.

Based solely on the form of the rate equation, the position of the proton in the critical transition state for hydrolysis of **3** is not determined (*i.e.*, it may be anywhere between the carboxyl group and the oxygen atom of **3**). This study considers the influence of oxocarbonium ion stability on the rate of hydrolysis of compounds related in structure to **3** (*i.e.*, I–V, XI, XIV–XVII) and was undertaken to yield information on the structure of the critical transition state for hydrolysis facilitated by a neighboring carboxyl group. In addition, the hydrolyses of compounds XII and XIII were studied in an attempt to determine if steric strain in the ground state[7] is a sufficient condition to allow the observation of intermolecular general acid catalysis in a case where the oxocarbonium ion is not very stable.

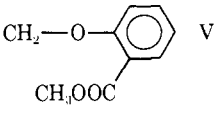
Experimental Section

Synthesis. Compounds I–V were prepared by the condensation of the sodium salt of methyl salicylate with the appropriately substituted α-chloro ether. The preparation of the α-chloro ethers followed, in general, the procedure of Marvel and Porter.[18] However, paraformaldehyde was used in place of a commercial formalin solution. Thirty grams (1.0 mol) of paraformaldehyde and 70 g of water were mixed with 2 ml of concd HCl, and the slurry was stirred with heating until a clear aqueous solution was obtained. Upon cooling, from 0.2 to 1.0 mol of the appropriate alcohol was added. The flask was suspended in an ice water bath and

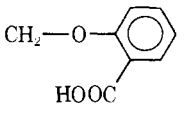
Chart I



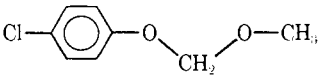
$R^1 = CH_3$		$R^1 = H$	
$R^2 = CH_2CH_3$	I	$R^2 = CH_2CF_3$	XI
CH_3	II	CH_2CH_3	XIV
CH_2CF_3	III	CH_3	XV
$CH_2C_6H_5$	IV	$CH_2C_6H_5$	XVI



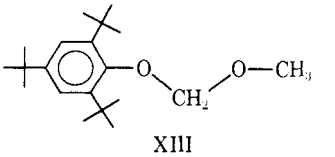
V



XVII



XII



XIII

HCl was bubbled through the solution for 2 hr. In most cases the α-chloro ether separated out as an oil. The oil was collected, filtered through $CaCl_2$ (small pellets), and, if possible, distilled. Chloromethyl ethyl ether (VI) ($CH_3CH_2OCH_2Cl$) was obtained in reasonable purity by distillation. It had bp 80.5° (760 mm) [lit.[19] bp 81–82° (760 mm)]. Chloromethyl methyl ether

(18) C. S. Marvel and P. K. Porter, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 369.

(VII) (CH_3OCH_2Cl) had bp 59–60° (760 mm) [lit.[18] bp 59.5° (760 mm)]. Chloromethyl trifluoroethyl ether (VIII) ($CF_3CH_2OCH_2Cl$) and chloromethyl benzyl ether (IX) ($C_6H_5CH_2OCH_2Cl$) could not be distilled due to extensive decomposition upon heating above 100°. These oils were dried with $CaCl_2$, gassed with N_2, and heated to 50°. This procedure removes HCl which interferes with the next step of the synthesis. Infrared spectra of both of these oils were consistent with their structure and different from the parent alcohols. In particular, the O–H stretching absorption of the alcohols was absent in the product and the product contained new peaks in the C–O stretching region and the C–Cl stretching region. *sym*-Dichlorodimethyl ether (X) ($ClCH_2OCH_2Cl$) was prepared[20] by mixing 60 g of paraformaldehyde and 80 g of 80% H_2SO_4 in a 1-l. flask. The flask was cooled in ice water while 140 ml of $ClSO_3H$ was added slowly. The product oiled out, and was dried ($CaCl_2$) and subjected to a reduced pressure of 50 mm for 15 min. This removes contaminating HCl. The product had bp 99–100° (760 mm) [lit.[20] 102–105° (760 mm)].

Compounds I–V were prepared in the following manner: methyl salicylate (15.1 g; 0.1 mol) [freshly distilled bp 100° (26 mm)] in 150 ml of benzene was slowly dripped into a 2-l. round-bottomed flask containing 12 g of NaH in 500 ml of dry benzene. The α-chloro ether (0.2 mol) was added rapidly, and the mixture was allowed to stir 24 hr. The mixture was filtered and the benzene removed by rotary evaporation to yield the crude acetals.

Methyl 2-ethoxymethoxybenzoate (I) had bp 106° (0.7 mm); nmr triplet centered at δ 1.10 (3 H), quartet centered at 3.62, and singlet at 3.70 (total 5 H), singlet at 5.11 (2 H), multiplet from 6.65 to 7.65 (4 H) ($DCCl_3$, TMS). *Anal.*[21] Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.72. Found: C, 63.19; H, 6.86.

Methyl 2-methoxymethoxybenzoate (II) was prepared for an earlier study.[11]

Methyl 2-(2′,2′,2′-trifluoroethoxymethoxy)benzoate (III) distilled at approximately 120° at 0.75 mm. However, considerable mineral oil codistilled with the acetal and some separated upon standing. The clear oil was converted to the free acid by saponification with 1.0 *M* KOH. The acid, 2-(2′,2′,2′-trifluoroethoxymethoxy)benzoic acid (XI) was isolated by acidification and extraction with diethyl ether. After three recrystallizations from CCl_4 (white needles), XI had mp 98–100°. *Anal.* Calcd for $C_{10}H_9F_3O_4 \cdot 0.5H_2O$: C, 46.34; H, 3.89; F, 21.99. Found: C, 46.92; H, 4.05; F, 20.53.

Despite the discordant analysis for fluorine, this compound behaved predictably in its hydrolytic reactivity and exhibited tight isosbestic points in repetitive scans during its hydrolysis. The kinetics of its hydrolysis were rigorously pseudo first order and titration of the carboxylic acid group yielded a reproducible spectral change and reasonable calculated pK_a value (see below and Results).

Methyl 2-benzyloxymethoxybenzoate (IV) was distilled at 132–140° at 0.15 mm. The distillate was not pure as evidenced by the appearance of three spots in the tlc on silica gel (ligroin–benzene, 6:4). The compound was purified by chromatography on a silica gel column (2 cm × 58 cm). The product eluted with a 9:1 mixture of benzene and ether: nmr multiplet from δ 6.9 to 7.7, singlet at 5.16 (2 H), singlet at 4.60 (2 H), and singlet at 3.72 (3 H) ($CDCl_3$, TMS). *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.27; H, 6.39.

***sym*-Di(2-carbomethoxyphenoxy) dimethyl ether** (V) was isolated by silica gel chromatography of the crude oil. The product was eluted from the 1.5 × 25 cm column with an 8:2 mixture of benzene–ligroin. This material crystallized upon standing and was further purified by recrystallization from a benzene–ligroin mixture. The flat, colorless plates had mp 53–55°; nmr singlet at δ 3.72, singlet at 5.34 and multiplet from 6.66 to 7.64 ($CDCl_3$, TMS). *Anal.* Calcd for $C_{18}H_{18}O_4 \cdot 0.5H_2O$: C, 60.84; H, 5.39. Found: C, 60.56; H, 5.57.

2-Ethoxymethoxybenzoic acid (XIV), 2-methoxymethoxy benzoic acid (XV), 2-benzyloxymethoxybenzoic acid (XVI), and *sym*-di(2-carboxyphenoxy) dimethyl ether (XVII) were generated from the corresponding methyl esters by saponification in 0.1 *N* KOH. With the exception[11] of XV, these free acids were not isolated. Their formation could be followed by repetitive scanning spectrophotometrically.

Compounds XII and XIII were prepared by the reaction of the appropriate phenolate with VII under similar conditions used for the preparation of I–V.

4-Chloromethoxymethoxybenzene (XII) was prepared[11] for an earlier study.

2,4,6-Tri-*tert*-butylmethoxymethoxybenzene (XIII) was prepared using DMSO as the reaction solvent as both NaH in benzene and *n*-butyllithium in hexane were ineffective in preparing the correct product. The work-up of the reaction in DMSO included pouring the mixture into 1.0 *N* aqueous base and extracting with benzene. The resulting oil distilled at 102° (0.35 mm) and solidified. This solid was twice recrystallized from methanol and sublimated in a zonal sublimation apparatus to yield large, square, colorless crystals which had mp 85–86°; nmr singlet at δ 7.23 (2 H), singlet at 4.87 (2 H), singlet at 3.62 (3 H), singlet at 1.44 (18 H), and singlet at 1.30 (9 H). *Anal.* Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.32; H, 11.18.

Kinetics. All hydrolytic reactions were initially studied by repetitive scanning in 1.00 *N* HCl at ambient temperature. In all cases the product spectra were identical with the spectra of the corresponding phenol. No intermediate species could be detected. The kinetic measurements of the rates of hydrolysis of compounds I–V, XI, and XIV–XVII were performed by spectrophotometrically measuring the production of the methyl salicylate or salicylic acid formed. Aqueous buffers at total $\mu = 1.0$ were employed. Buffer dilutions on compounds XIV, XV, and XVI revealed no dependence of k_{obsd} on concentration of buffer from 0.1 to 1.0 *M*. Rates with half-lives of less than 1 day were obtained with automatic recording apparatus. Rates of hydrolysis of the less reactive species (III, V, XI, and XVII) were obtained by aliquoting at appropriate time intervals from a 100-ml buffer solution containing the substrate at *ca.* 10^{-4} *M* and manually reading the OD at several wavelengths. (The calculated k_{obsd}'s at different wavelengths agreed within 2%). These solutions, contained in 100-ml volumetric flasks, were suspended in large rate baths held at 30°. The pH values of all solutions were determined before and at the completion of the reaction and rates were rejected if the pH changed by more than 0.03 pH unit. For the extremely slow hydrolytic rates, points were taken at long time intervals. A typical plot of the kinetic data is shown in Figure 1 for compound XVII at pH 3.49.

Rates of hydrolysis of compounds XII and XIII were performed at 60° in a solution of 50% v/v ethanol–water due to the insolubility of XIII in pure water and the slow rates of hydrolysis. Appearance of substituted phenol was followed spectrophotometrically at the appropriate wavelength. The buffer solutions were gassed with N_2 before reactions were initiated. The pH of these solutions was measured at 30° and an electrode correction applied based on interpolation from the data of Bates, *et al.*[22] This corrected pH value is not directly comparable to pH measured in pure aqueous solution.

In all cases rate constants (k_{obsd}) were obtained by standard methods. In some instances, OD_∞ was obtained by heating a reaction solution to 105° for several days, then cooling to 30° and reading the OD. This process yielded good results only if the phenol was stable at the higher temperature.

pK_a Determinations. Spectrophotometric titrations were performed in the equilibrium titration cell of Maley and Bruice.[23] Compound XI was dissolved in a slightly basic solution at 2.0×10^{-4} *M* and the 25-ml solution was titrated with small additions (10 μl) of various solutions in HCl. Spectra were recorded at each pH value over a 90-mμ range in the uv region. The titrations were reversed by the addition of KOH and the spectra recorded again. Plots of OD *vs.* pH were superimposible for titrations with acid or base indicating the stability of the protonated species during the short time interval necessary for titration. The pK_a was calculated using standard equations and a minimum of 15 OD–pH points within 1 pH unit of the calculated pK_a. The pK_a determined for XI in this manner was 3.50 ± 0.04.

XI

$$ArCOOH \underset{}{\overset{pK_a = 3.50}{\rightleftharpoons}} ArCOO^- + H^+$$

λ_{max} 284 mμ λ_{max} 273 mμ

isosbestic points, 257 and 272 mμ

(19) J. W. Farren, H. R. Fife, F. E. Clark, and C. E. Garland, *J. Amer. Chem. Soc.*, 47, 2419 (1925).

(20) N. N. Vorozhtzov and E. N. Yurigina, *Zh. Obshch. Khim.*, 1, 49 (1931); *Chem. Abstr.*, 25, 4522 (1931).

(21) All analyses performed by Elek Microanalytical Laboratories, Torrance, Calif.

(22) R. G. Bates, M. Paabo, and R. A. Robinson, *J. Phys. Chem.*, 67, 1833 (1963).

(23) J. R. Maley and T. C. Bruice, *Anal. Biochem.*, 34, 275 (1970).

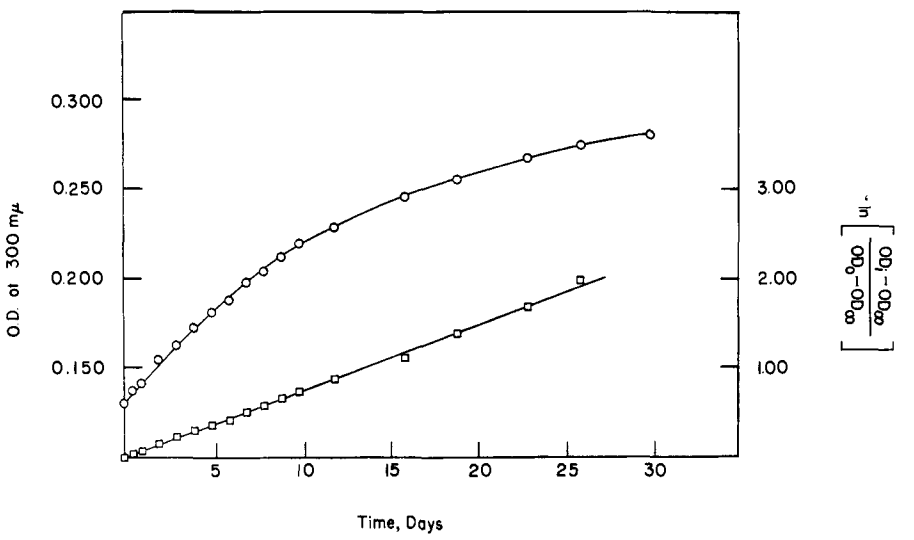


Figure 1. Plot of optical density determined at 300 mμ *vs.* time in days for the hydrolysis of compound XVII at pH 3.49 (○). Also plotted are the calculated values of $\ln[(OD_i - OD_\infty)/(OD_0 - OD_\infty)]$ (□).

The saponification of compound V at pH 12.15 to yield compound XVII could be followed to completion by repetitive scanning of the solution in the titration cell[23] of the Cary 15. This solution of 10^{-5} *M* could then be spectrophotometrically titrated.

$$\mathbf{V} \xrightarrow[3\text{ hr}]{\text{pH }12.15} \mathbf{XVII}$$

λ_{max} 288 mμ λ_{max} 273 mμ

isosbestic points, 223, 253, and 274 mμ

The OD data taken from spectra changes at both 290 and 233 mμ could be fit to titration curves with a single calculated pK_a of 4.10 ± 0.04. This is not unexpected since the compound is

$$\underset{\lambda_{max}\ 287.5,\ 230}{\mathbf{XVII}\ \ Ar(COOH)_2} \underset{}{\overset{pK_{app} = 4.10}{\rightleftharpoons}} \underset{\lambda_{max}\ 274}{Ar(COO^-)_2} + 2H^+$$

isosbestic points, 222, 256, and 273.5 mμ

a symmetrical dicarboxylic acid with the two carboxyl groups fairly remote from one another. Attempts to separate the pK_a's by potentiometric titration at 10^{-3} *M* were unsuccessful due to the insolubility of the fully protonated species. An approximate neutralization equivalent could be obtained by isolating some of the solid acid (mp 133–135°) and titrating a suspension of this until the sample dissolved and the pH was steady at neutrality. The calculated value of 169 is in reasonable agreement with the theoretical value of 159.15.

Apparatus. Automatic recording of rates was accomplished with a Gilford Model 2000 spectrophotometer. Manual readings were taken on a Zeiss PM QII spectrophotometer. The temperature of the cell compartment during the rates performed at 60° was monitored with a Gilford thermosensor and was constant throughout the reaction.

Infrared spectra were recorded using a Perkin-Elmer 137 sodium chloride spectrophotometer. Ultraviolet spectra and all repetitive scans were recorded on a Perkin-Elmer Model 350 or a Cary 15 recording spectrophotometer, each equipped with a repetitive scan accessory. Nmr spectra were recorded on a Jeolco C6OHL.

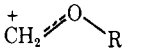
All pH values of kinetic solutions were determined with a Radiometer Model 22 pH meter equipped with a Model 630 scale expander and a combined glass calomel electrode (GK 2302 C).

Results

The rates of hydrolysis of compounds I and III–V obtained in aqueous HCl–KCl buffer at 30° with $\mu = 1.0$ are plotted in Figure 2. Under pseudo-first-order conditions eq 2 is sufficient to describe the observed rate.

$$k_{obsd} = k_H(a_H) \qquad (2)$$

Values of k_H, the second-order rate constant for specific acid-catalyzed hydrolysis, may then be obtained from the rate in 1.00 *M* HCl. The log k_H values are plotted in Figure 3 as a function of the σ^* values[24] for the R substituent in **6**.



6

Similarly, the values of log k_{obsd} for the hydrolyses of compounds XI and XIV–XVII are plotted *vs.* pH in Figure 2. The lines through the points in Figure 2 for compounds XI and XIV–XVII have been calculated from eq 3, where k_H is the second-order rate constant

$$k_{obsd} = k_H a_H\left(\frac{a_H}{K_{app} + a_H}\right) + k' a_H\left(\frac{K_{app}}{K_{app} + a_H}\right) \qquad (3)$$

for specific acid-catalyzed hydrolysis of the undissociated acetal, k' is the second-order rate constant for apparent specific acid-catalyzed hydrolysis of the ionized species, a_H is the hydrogen ion activity as measured by the glass electrode, and K_{app} is the kinetically apparent dissociation constant of the carboxyl group. The values of k_H, k', and K_{app} employed to provide the best fits of the lines to the experimental points are tabulated in Table I. The derived values, log k_H and log k', are also plotted in Figure 3 as a function of the σ^* values of R in **6**.

Table I. Derived Values of Rate Constants and Ionization Constants Utilized to Provide the Calculated Lines of Figure 2

Substrate	k_H, M^{-1} min^{-1}	pK_{app}	k', M^{-1} min^{-1}
XI	1.50×10^{-3}	3.50[b]	0.37
XIV	1.95	3.70	600.0
XV[a]	0.56	3.75	150.0
XVI	0.22	3.80	75.0
XVII	1.88×10^{-3}	4.20[c]	1.00

[a] Data from ref 11. [b] Spectral $pK_a = 3.50$. [c] Spectral $pK_a = 4.10$.

(24) (a) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, 74, 2729 (1952); (b) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 222.

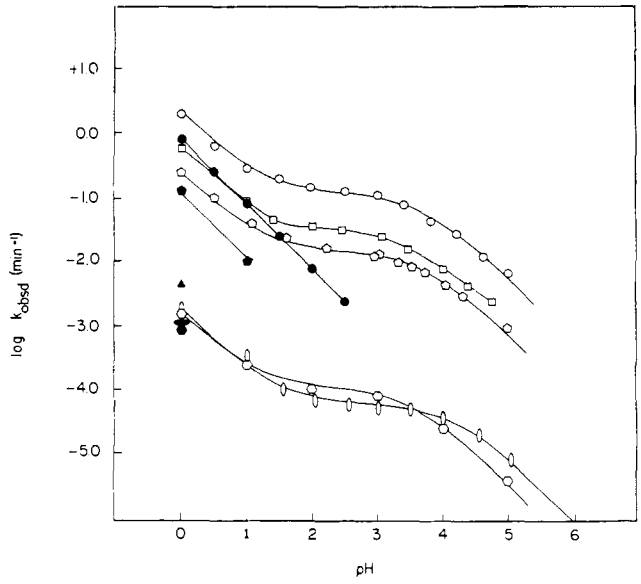


Figure 2. Spectrophotometrically determined pH–log k_{obsd} profiles for the hydrolysis of the following compounds listed in Chart I (H_2O, μ = 1.0, 30°) (I ●) (III ●) (IV ■) (V ▬) (XI ○) (XIV ○) (XV □) (XVI ⬠) (XVII ◊).

With the exception of compounds XI and XVII the ionization constants of the acids could not be directly determined due either to competing hydrolysis or insolubility. For XI the thermodynamic pK_a value of 3.50 has been used to calculate the theoretical line in Figure 2 with excellent agreement with the kinetically apparent constant. For compound XVII the kinetically derived value for pK_a of 4.20 is in fair agreement with the spectral pK_a of 4.10.

The calculated values of k_{obsd} for the hydrolysis of XII and XIII at 60° in solution of 50% v/v EtOH–H_2O are plotted *vs.* pH in Figure 4. Care was taken that the two compounds were hydrolyzed under identical conditions to facilitate comparisons. In both 1.00 *M* HCl and 0.10 *M* HCl the rates for the two compounds were virtually the same. Compound XIII was also hydrolyzed at pH 3.39 in formate buffers at 0.10, 0.50, and 1.00 *M* total formate. No dependence of rate on buffer concentration was detected (the rates at 0.10 and 1.00 *M* differed by 2%).

Discussion

The rate constant in eq 2 pertains to specific acid catalysis of acetal hydrolysis.[25] For eq 3, k_H refers to the same process operating on the acetal species containing a protonated carboxyl group. In Figure 3 it may be seen that these rates are correlated well by σ^* which is an indication of polar or inductive effects.

The value of ρ^* obtained from both the line through the points for $COOCH_3$-substituted compounds (I, III, IV, and V) and the line through the points for COOH-substituted compounds (XI, XIV, XV, XVI, and XVII) is −3.00. This value may be compared to the values of −3.652 for the acid-catalyzed hydrolysis of $RCH(OEt)_2$ in 50% dioxane, −3.541 for the acid-catalyzed hydrolysis of $RC(CH_3)(OEt)_2$ in 50% dioxane, both obtained by Kreevoy and Taft,[26] and −4.173 for the hydrolysis of symmetrical formulas $H_2C(OR)_2$ in water.[27] Thus, the value of ρ^* obtained for our system is in accord with the specific acid process being postulated.

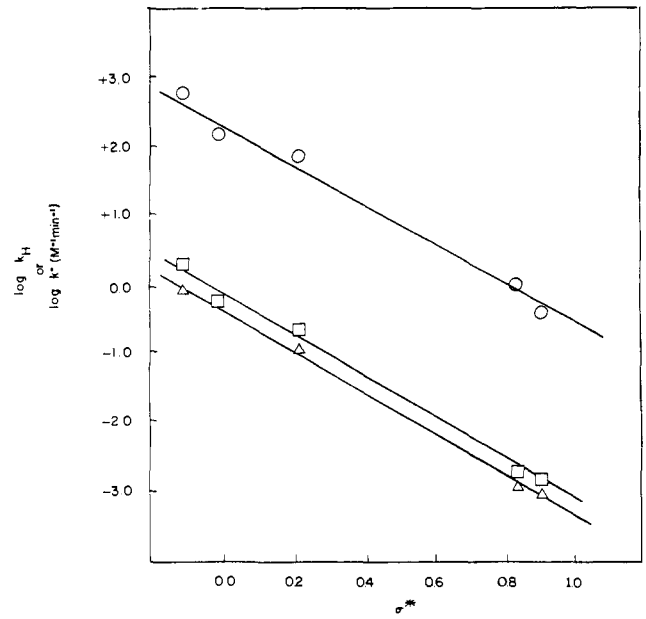


Figure 3. Plot of log k_H or log k' *vs.* the σ^* values of the alkyl substituent. The σ^* values are from ref 24b. The value of σ^* utilized for compounds V and XVII is that given for $CH_2OC_6H_5$: log k_H for $COOCH_3$-substituted compounds (△), log k_H for COOH-substituted compounds (□), and log k' for COO^--substituted compounds (○).

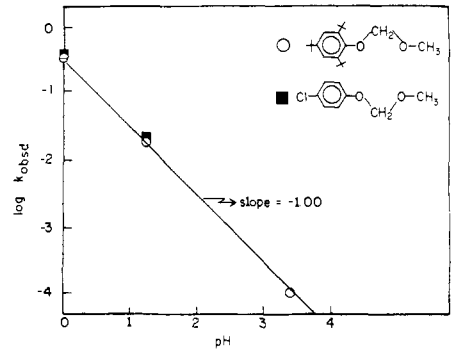
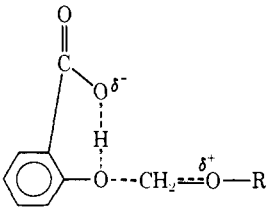


Figure 4. Plot of log k_{obsd} *vs.* pH for the hydrolysis of 2,4,6-tri-*tert*-butylmethoxymethoxybenzene (○) and 4-chloromethoxymethoxybenzene (■) (50% v/v EtOH–H_2O, μ = 1.0, 60°).

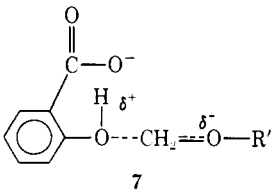
The constant k' in eq 3 pertains to the kinetically equivalent mechanisms of intramolecular general acid-catalyzed hydrolysis of the undissociated species and specific acid-catalyzed hydrolysis of the ionized species. The sole distinction between these mechanisms involves the extent of proton transfer in the transition state for carbon–oxygen bond cleavage **7**.

Incursion of a general acid-catalyzed pathway would be expected to shift the transition state for hydrolysis away from the oxocarbonium ion intermediate. It would then be anticipated that the dependence of the reaction rate on oxocarbonium stability, as reflected in ρ^*, would be lessened.[28] However, as is seen in Figure

(25) E. H. Cordes, *Advan. Phys. Org. Chem.*, 4, 1 (1967).
(26) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, 77, 5590 (1955).
(27) (a) A. Skrabal and H. H. Eger, *Z. Physik. Chem.*, 122, 349 (1926); (b) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman Ed., Wiley, New York, N. Y., 1956, Chapter 13.
(28) A search of the literature for verification of this expectation provided the following information. Substitution in the glycon portion



a, intramolecular general acid

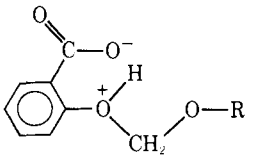


7

b, specific acid carboxylate

3, the ρ^* obtained from correlation of log k' with σ^* is identical within experimental error with the ρ^* value for specific acid catalysis of hydrolysis of the protonated form of the same substrates and for specific acid catalysis of the $COOCH_3$-substituted substrates.

Since the sensitivity to oxocarbonium stability is identical for the two processes, one may conclude that the transition state for each is equally close to the oxocarbonium intermediate. It follows that the reaction mechanism may best be described as involving total proton transfer to the oxygen atom similar to the specific acid-catalyzed mechanism. The rate enhancement of nearly 1000-fold may be attributed to a stabilization of the protonated ether oxygen by a zwitterion structure such as **8**.



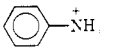
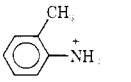
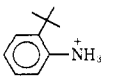
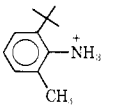
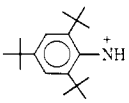
8

Other evidence in accord with this conclusion (total proton transfer) is the Brønsted α value of *ca.* -1.0 calculated assuming intramolecular general acid catalysis for 2-methoxymethoxybenzoic acid *vs.* 2-methoxymethoxy-5-nitrobenzoic acid,[12] and a comparison of the log k_{ga} values associated with intramolecular general acid catalysis for the two carboxyl groups of **4**.[11]

A possible analogy to the proposed structure **8** is the 45-fold rate enhancement of the specific acid-catalyzed hydrolysis of 2-methoxymethoxy-3-methylbenzoic acid provided by a 0.03 *M* solution of sodium lauryl sulfate, a negatively charged micelle-forming agent.[12] Cordes and coworkers have also observed catalysis of acetal hydrolysis by solutions of sodium lauryl sulfate.[29] They attributed this catalysis to electrostatic stabilization of the positively charged transition state by the negatively charged micelle surface.

In a recent publication, Fife and Anderson have reported[7] that the di-*tert*-butyl acetals of substituted benzaldehydes **1** are subject to general acid catalysis by buffer species whereas the diethyl acetals are not. They attribute this to the relief of the strain in the ground state upon reaching the transition state. This makes the bond-breaking processes easier and thus subject to buffer catalysis. We have attempted to achieve the same effect in our system through the hydrolysis of XIII. The rate of hydrolysis of XIII is, however, no greater than that of XII,[30] and at pH 3.39 there is no observable buffer catalysis of hydrolysis. The lack of enhanced reactivity even in specific acid catalysis is surprising since our earlier results[11] demonstrated that two bulky groups (*i.e.*, $COOCH_3$ and NO_2) ortho to the acetal group would provide a rate enhancement of about 17-fold. The observed lack of enhanced reactivity for XIII is reasonable, however, if steric inhibition of preequilibrium protonation is invoked. Data relevant to this point are provided by pK_a values of anilines (Table II). This steric inhibition to protonation would be expected to reduce the pK_a of the phenolic ether oxygen of XIII. Hence, any increase in rate due to relief of steric strain would be compensated for by a decrease in the amount of the protonated species in solution. The lack of general acid catalysis in this system must be due to the instability of the carbonium ion relative to the benzylic carbonium ion in Fife's study and the difficulty of protonation as evidenced by the specific acid rate.

Table II[a]

Compd	pK_a
	4.58
	4.38
	3.78
	3.31
	<2.0

[a] H. C. Brown, D. H. McDaniel, and O. Hafliger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, p 611.

All the evidence accumulated thus far points to the lack of general acid catalysis in these mixed acetals of formaldehyde. Even the apparent intramolecular general acid catalysis can best be described as carboxylate anion stabilization of an A-1 reaction. This reaction (*i.e.*, compound XV) has been suggested to involve general acid catalysis and has been held as a model for other reactions that show similar kinetic pH dependence.[16] One point used in defense of this choice of mechanism was the finding of buffer catalysis for benzaldehyde methyl phenyl acetals, but this can have no bearing on the hydrolysis of acetals of formaldehyde since the difference in stability of the oxocarbonium ions derived from these species is substantial.

of benzaldehyde di-*tert*-butyl acetals yields a ρ value for hydronium ion catalyzed hydrolysis of -3.97 while the ρ value associated with intermolecular general acid catalysis for the same substrate is -2.02.[7] Also, substitution in the aglycon portion of substituted phenoxytetrahydropyrans yields a ρ value for hydronium ion catalysis of -0.9 while the ρ for intermolecular general acid catalysis is $+0.9$.[5] Though these ρ values are as anticipated, these data do not provide strong support for our argument since for both cases the second-order rate constant for hydronium ion catalysis falls on the Brønsted plot with weak acids. Thus, for these cases, proton transfer from the hydronium ion is partially rate determining.

(29) (a) R. B. Dunlap, G. A. Ghanim, and E. H. Cordes, *J. Phys. Chem.*, 73, 1898 (1969); (b) E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, 2, 329 (1969).

(30) Since our earlier work indicated the absence of electronic effects in these reactions,[11] XII represents a series of acetals lacking the two bulky groups at positions ortho to the acetal linkage.

It is our conclusion that the process we observe with acetals derived from formaldehyde is not classical general acid catalysis, due to the instability of the derived oxocarbonium ion. We suggest that any reaction not subject to intermolecular general acid catalysis could not be subject to intramolecular general acid catalysis, since the major determinant for observation of this mechanism is a relatively stable oxocarbonium ion.

Finally, it should be pointed out that the carboxylate-stabilized A-1 process favored in our system does provide substantial rate enhancements and could be a plausible mechanism for the enzymatic hydrolysis of glycosides, particularly if conducted in a hydrophobic environment.

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Dielectrocyclic Reactions

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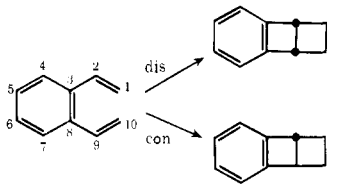
Contribution from the Chemistry Department, University of Calgary, Calgary, Alberta, Canada. *Received June 6, 1970*

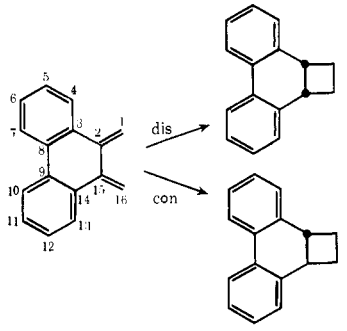
Abstract: Using the cyclizations of *o*-divinylbenzene and 2,2′-divinylbiphenyl to yield cyclobutane containing structures to illustrate the method, a "dielectrocyclic" classification of these reactions is carried out. The conclusions are compared to the Woodward–Hoffmann cycloaddition classification and the, *in principle*, advantages of the present approach are examined. The change in the predicted products due to heteroatom substitution is also investigated.

The orbital symmetry[1] method as developed by Woodward and Hoffmann[2,3] has had considerable application in the treatment of cycloaddition and electrocyclic reactions. The concern of this paper is the treatment of a type of reaction of which the cyclizations indicated in Schemes I and II are illustrative. At

Scheme I. Dielectrocyclic Reaction I



Scheme II. Dielectrocyclic Reaction II



first glance it might appear that these reactions would be best treated as cycloaddition reactions (*i.e.*, 2 + 2 cis/cis or supra,supra[3]). However, the bonding of the ethylenic fragments to the ring rather restricts the orientation of each ethylenic π system and the reaction might better be considered as a type of electrocyclic reaction. One might classify the reactions as "dielectrocyclic reactions," *i.e.*, reactions in which electrons in *two* π orbitals transform by a rotation of part of the orbitals into electrons in *two* σ bonds. Such a treatment would of course preclude consideration of say the antara,antara[3] (trans/trans) and the antara,supra[3] (trans/cis) modes normally included in cycloaddition reactions. However, in view of what is clearly a very restricted motion,[4] particularly in reaction I, and in view of the experimental results for reaction II[5] (see also section I-2 to follow) the contribution of these modes is unlikely.

An advantage of the dielectrocyclic classification is that, in contrast to the cycloaddition approach, one would be able to separately consider the possibility of the trans- and cis-fused products of the supra,supra mode since under the electrocyclic classification these products correspond to, respectively, the conrotatory and disrotatory modes. Further, the consideration of these reactions as proceeding from rotation of π orbitals about a semirigid σ skeleton allows one to comment on the degree of overlap and hence the relative stability of the cyclized products. A final and most important advantage over a simple 2 + 2 cycloaddition classification is that one can readily include the perturbation of the ring system on the course of the reaction.

In proceeding with a dielectrocyclic classification it should be recognized that since four electrons are involved (in contrast to the two electrons in a simple electrocyclic reaction), the symmetry restrictions will be determined by the *product* of two or more spatially different orbitals and consequently the use of state cor-

(1) L. J. Oosterhoff quoted by E. Havinga and J. L. M. A. Schlatmann, *Tetrahedron*, **16**, 151 (1961).

(2) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395, 2046 (1965); *Accounts Chem. Res.*, **1**, 17 (1968).

(3) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Springer-Verlag, West Berlin and Heidelberg, 1970.

(4) The orientations necessary for the supra,antara, etc., modes are illustrated in ref 3, pp 67–69. These modes could only be accommodated at the expense of considerable steric strain and/or a "free" rotation of the termini of the ethylenic fragments.

(5) D. F. Tavares and W. H. Ploder, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, No. P216.