Further Investigation of the Neighboring Carboxyl Group Catalysis of Hydrolysis of Methyl Phenyl Acetals of Formaldehyde. Electrostatic and Solvent Effects

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Abstract: The rate constants for hydrolysis of several methyl phenyl acetals of formaldehyde have been determined (30°) as a function of pH, concentration of added surfactant, and volume per cent of added dioxane. The acetals employed contained carboxyl groups ortho (2 position) to the acetal group as well as other substituents in the 4 and 6 positions. Rate constants have been derived for the apparent specific acid-catalyzed hydrolysis of the species possessing undissociated and dissociated carboxyl groups. A Brønsted α value of *ca.* -1.0 for the dependence of intramolecular general acid catalysis on the pK_a of the neighboring carboxyl group is calculated. This sensitivity to the pK_a of the *o*-carboxyl group has been interpreted in terms of either: (a) an intramoleculr general acid catalysis involving essentially complete proton transfer in the transition state or (b) a mechanistically indistinguishable electrostatically (by *o*-COO^-) assisted A-1 process. The latter is favored since acetal bonds of the type investigated are not subject to (bimolecular) general acid catalysis. The surfactants CTA^+Br^- and Igepal (a neutral surfactant) have a slight depressant effect upon the hydrolytic rate constant above their critical micelle concentration. The negatively charged detergent LS^-Na^+, above its critical micelle concentration, increases the rate constant for specific acid catalyzed hydrolysis of undissociated acetal (*i.e.*, RCOOH) by 45-fold. For the dissociated acetal species (*i.e.*, $RCOO^-$) the detergent has but a twofold effect on the specific acid catalyzed rate constant. This, in combination with previous results, indicates that juxtapositioning of a neighboring negatively charged entity does not appreciably accelerate the A-1 process already assisted by an *o*-carboxyl anion. The addition of dioxane increases the pK_a of the *o*-carboxyl group so that anchimeric participation by this group in acetal hydrolysis is apparent at much higher pH. The general shape of the pH–rate profile for the hydrolysis of the di-*o*-carboxyl-substituted acetal retains the characteristic plateau shape even at a concentration of 80% (v/v) dioxane. The absence of a tendency toward a bell-shaped profile indicates that concerted participation of the carboxyl groups is not kinetically significant. Comparison of the rate constants derived for *o*-carboxyl group participation over a range of dioxane concentration indicates that the rate is only slightly sensitive to change in pK_a induced by solvent change. This, in connection with the large sensitivity of rate to change in pK_a induced by structural variation, is interpreted as indicating an enhancement of either intramolecular proton transfer associated with general acid catalysis or the proposed ion-pair formation associated with *o*-carboxyl anion stabilization of the A-1 process.

It has become evident, from model building based on X-ray studies, that the functional groups available for the bond-making and -breaking processes in the mechanism of lysozyme action are Asp-52 and Glu-35 at the active site and the 2-acetamido group of the natural substrate.[3] Employing these three functional groups a finite set of plausible mechanisms may be conceived.[4] The listed mechanistic possibilities include roles for the functional groups of carboxyl general acid catalysis, carboxyl anion nucleophilic attack, carboxyl anion electrostatic stabilization of insipient oxocarbonium ion, and intramolecular nucleophilic catalysis by the 2-acetamido group. The importance of the various modes of catalysis has been reviewed in the light of the present state of knowledge concerning the enzymology of lysozyme.[5] Physical-organic studies have established that a carboxyl group juxtaposed to an acetal or glycosidic bond may perform a role of general acid catalyst for hydrolysis.[6] The 2-acetamido group of 2-deoxy-2-acetamido-β-D-glucosides have been shown to be effective intramolecular nucleophiles for the spontaneous hydrolysis of derived phenyl glycosides[6c,7] and to assist in the specific acid catalyzed hydrolysis of methyl 2-acetamido-2-deoxy-β-D-glucopyranoside[8] as well as in the intramolecular general acid catalysis of the hydrolysis of *o*-carboxyphenyl 2-acetamido-2-deoxy-β-D-glucopyranoside.[6c] Of the various possible mechanisms for lysozyme,[4] that which receives the most support[5] at present derives from the original suggestion[3] that the carboxyl group of Glu-35 acts as a general acid catalytic moiety and the carboxyl anion of Asp-52 serves to electrostatically stabilize the insipient oxocarbonium ion formed in the transition state for the general catalysis. This possibility has been explored in a physical-organic model (the hydrolysis of the monoanion of 2-methoxymethoxyisophthalic acid, VII).[9] Definitive evidence was presented to show that neighboring carboxyl anion electrostatic facilitation to intramolecular carboxyl group general acid catalysis was not important. The present study extends our investigation of the hydrolysis of methyl phenyl acetals to in-

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(3) 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); D. C. Phillips, *Sci. Amer.*, **215**, 78 (1966).

(4) G. Lowe, *Proc. Roy. Soc., Ser. B*, **167**, 431 (1967).

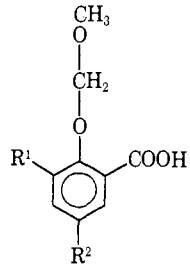
(5) M. A. Raftery and T. Rand-Meir, *Biochemistry*, 7, 3281 (1968).

(6) (a) B. Capon and M. C. Smith, *Chem. Commun.*, 7, 523 (1965); (b) B. Capon, *Tetrahedron Lett.*, 911 (1963); (c) D. Piszkiewicz and T. C. Bruice, *J. Amer. Chem. Soc.*, **90**, 2156 (1967); (d) B. Capon, M. C. Smith, E. Anderson, R. H. Dahm, and G. H. Sankey, *J. Chem. Soc. B*, 1038 (1969).

(7) D. Piszkiewicz and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 6237 (1967).

(8) D. Piszkiewicz and T. C. Bruice, *ibid.*, **90**, 5844 (1968).

(9) B. M. Dunn and T. C. Bruice, *ibid.*, **92**, 2410 (1970).



IV, $R^1 = H$; $R^2 = NO_2$
V, $R^1 = R^2 = H$
VI, $R^1 = CH_3$; $R^2 = H$
VII, $R^1 = COOH$; $R^2 = H$

clude the influence of solvent composition and the presence of micelles. It is known that solvent composition can alter the mechanism of orthoformate and possibly of acetal hydrolysis from specific to general acid catalysis[10] and the specific acid catalyzed hydrolysis of benzaldehyde diethyl acetals has been shown to be facilitated by negatively charged micelles of lauryl sulfate presumably *via* electrostatic stabilization of the transition state.[11]

Experimental Section

Materials. Of the acetals employed in this study, 2-methoxymethoxyisophthalic acid, 2-methoxymethoxybenzoic acid, and 2-methoxymethoxy-3-methylbenzoic acid were prepared for an earlier study.[9] 2-Methoxymethoxy-5-nitrobenzoic acid was prepared by a modification of the procedure provided in ref 9 and is described below. Sodium lauryl sulfate (SLS^-) and hexadecyltrimethylammonium bromide (CTA^+) were obtained from City Chemical Corporation and were purified by the procedure of Duynstee and Grunwald.[12] Igepal RC-760 (Dodecyl phenol condensed with 18 ethylene oxide units) was obtained from General Aniline and Film Corporation and was used without further purification. Dioxane (1–4) was purified by the following procedure. Spectroquality dioxane (Matheson Coleman and Bell) was refluxed over sodium metal for a minimum of 24 hr, then distilled through a4-ft column packed with glass helices. The middle of the constant boiling fraction was retained for kinetics. This fraction gave a negative test with starch–iodide test paper and the vpc on 20% XF 1150 silicon on Chromosorb W 60–80 (oven temperature 68°, injection port 155°, helium flow 45 ml/min) failed to detect any impurities.

2-Methoxymethoxy-5-nitrobenzoic Acid (IV). 5-Nitrosalicylic acid I (25 g) (Eastman Organic) was esterified with diazomethane by the method of Werner[13] to yield methyl 5-nitrosalicylate II which melted at 115–116° after recrystallization from methanol (lit.[14] mp 119°). After generation of the phenolate anion with NaH in benzene, treatment with chloromethyl methyl ether produced the acetal, methyl 2-methoxymethyl-5-nitrobenzoate (III). The reaction mixture was allowed to settle, the benzene solution was filtered and reduced to dryness to yield a light yellow oil which separated into two layers. The upper layer of mineral oil was removed and the lower yellow layer solidified. The solid was twice sublimated (80°, 0.5 mm) to yield white crystals with mp 66–67.5°; nmr singlets at δ 3.5, 3.9, and 5.3, doublet centered at δ 7.2, and a multiplet at δ 8.0–8.45.

Anal.[15] Calcd for $C_{10}H_{11}NO_6$: C, 49.80; H, 4.60; N, 5.81. Found: C, 50.02; H, 4.62; N, 5.85.

2-Methoxymethoxy-5-nitrobenzoic acid (IV) was obtained by mixing 8.5×10^{-5} mol of III in acetonitrile with 6×10^{-5} mol of KOH in water. The resulting solution was used as the stock solution for kinetics. Product analysis is provided below.

Kinetics. All kinetics were performed at 30.0 ± 0.1° using apparatus and methods previously provided.[9] The hydrolysis of IV was followed at wavelengths between 315 and 330 mμ. The pseudo-first-order rate constants (k_{obsd}) were obtained by calculating the slopes of plots of log $(OD_\infty - OD_0)/(OD_\infty - OD_i)$ *vs.* time or by the method of Guggenheim.[16] Constant pH was maintained by HCl–KCl, formate, chloroacetate, or acetate buffers. The pH meter corrections for dioxane solutions were interpolated from the data of Van Uitert and Fernelius[17] and the equation true pH = $B + \Delta$, where B = measured pH and $\Delta = \log U_H^\circ + \log 1/\gamma$.

Product Study. The reactions of III were followed by repetitive scanning utilizing the equilibrium cell of Bruice and Maley.[18] A 5.0×10^{-5} *M* solution of III at pH 11.2 was scanned at 2-min intervals from 350 to 220 mμ. The spectra show a decrease in absorbance below 309 mμ and an increase in absorbance above 309 mμ with the time indicating basic hydrolysis of the ester group to produce IV. The pH of the solution was rapidly adjusted to 3.60 by dropwise addition of 2 *M* HCl. Scans run from 350 to 220 mμ at 3-min intervals show an increase in absorbance above 304 mμ and a decrease in absorbance between 304 and 261 mμ with isosbestic points at 304, 261, 246, and 232 mμ consistent with release of substituted phenol. The absorption spectra of the product of the reaction is identical with a genuine sample of 5-nitrosalicylic acid I at the same pH. Addition of concentrated HCl lowered the pH to 0.80. The solution was then titrated with base from pH 0.80 to 4.00 which yielded a spectral change (350 to 220 mμ) with an isosbestic point at 316 mμ corresponding to ionization of the carboxyl group. Titration from pH 4.00 to 7.20 produced no spectral change. On titration from pH 7.20 to 12.5 the spectra (490 to 290 mμ) show the build-up of a peak at 408 mμ with an isosbestic point at 353 mμ. Spectral data obtained at sixteen pH's between 8.50 and 10.90 have been used to calculate a pK_a of 9.83 for the ionization of the phenol of 5-nitrosalicyclic acid. This value is in agreement with that obtained for a genuine sample of 5-nitrosalicylic acid I.

Results

The hydrolysis of compound IV was studied in the pH region 0.0–4.65 (H_2O, μ = 1.0, 30°). The values of log k_{obsd} are plotted as a function of pH in Figure 1. Included in Figure 1 is the profile for the hydrolysis of 2-methoxymethoxybenzoic acid V using the data of our earlier study.[9] The points of Figure 1 are experimental and the curves theoretical, having been generated by eq 1 and the values of the constants provided in Table I.

$$k_{obsd} = (k_H a_H + k' K_{app}) a_H / (K_{app} + a_H) \quad (1)$$

In eq 1, K_{app} is the kinetically apparent acid dissociation constant of the carboxyl group and a_H is the hydrogen ion activity as measured by the glass electrode.

Table I. Derived Values of the Rate Constants and Apparent pK_a's for the Hydrolysis of Acetals IV, V, VI, and VII

Acetal	Added reagent	Concn or %	k_H, M^{-1} min^{-1}	k', M^{-1} min^{-1}	pK_{app}, M
IV			0.50	180	2.70[a]
V			0.56	150	3.75[b]
VI	SLS^-	0.03 *M*	31.0	700	3.90[a]
VI			0.70	420	3.50[a]
VII			5.00	6,000	2.80[b]
VII	Dioxane	50%	5.00	200,000	5.20[a]
VII	Dioxane	80%	1,000	60,000,000	8.75[a]
IV	Dioxane	50%	0.1	6,000	5.00[a]
V	Dioxane	50%	0.1585	2,000	6.20[a]

[a] This study. [b] Reference 9.

(10) (a) R. H. DeWolfe and R. M. Roberts, *J. Amer. Chem. Soc.*, 76, 4379 (1954); (b) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, 77, 3146 (1955).
(11) R. B. Dunlap, G. A. Ghanim, and E. H. Cordes, *J. Phys. Chem.*, 73, 1898 (1969).
(12) E. F. J. Duynstee and E. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540 (1959).
(13) E. Werner, *J. Chem. Soc.*, **115**, 1096 (1919).
(14) A. N. Meldrum and N. W. Hirve, *J. Indian Chem. Soc.*, **5**, 95 (1928).
(15) Analysis performed by Edward Sutcliffe, Santa Barbara, Calif.
(16) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).
(17) L. G. Van Uitert and W. C. Fernelius, *J. Amer. Chem. Soc.*, **76**, 5887 (1954).
(18) T. C. Bruice and J. R. Maley, *Anal. Biochem.*, **34**, 275 (1970).

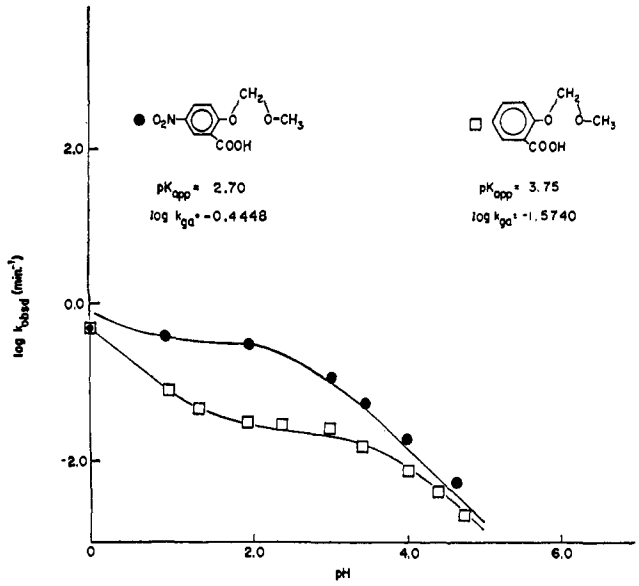


Figure 1. Spectrophotometrically determined pH–log k_{obsd} profiles for the hydrolysis of 2-methoxymethoxy-5-nitrobenzoic acid (IV) and 2-methoxymethoxybenzoic acid (V) (solvent H_2O, μ = 1.0, 30°). Points are experimental and the curves theoretical.

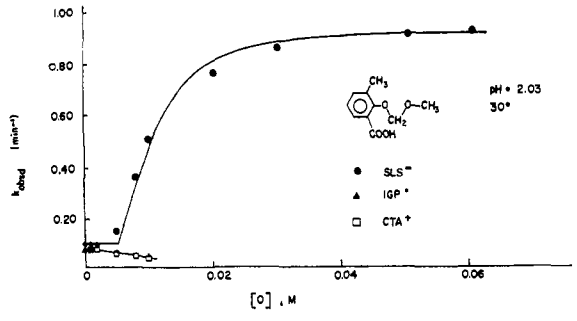


Figure 2. Plots of k_{obsd} for the hydrolysis of 2-methoxymethoxy-3-methylbenzoic acid (VI) *vs.* the concentration of the detergents SLS^-, CTA^+, and Igepal. The curve passing through the points for SLS^- solutions was calculated from eq 2 and the values of the constants provided in the Results.

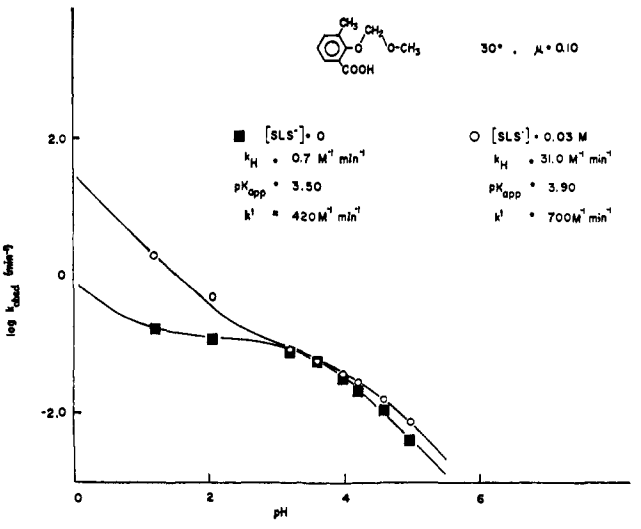


Figure 3. Plots of log k_{obsd} *vs.* pH for the hydrolysis of 2-methoxymethoxy-3-methylbenzoic acid (VI) (water) and in 0.03 *M* SLS^-. Points are experimental and the curves theoretical.

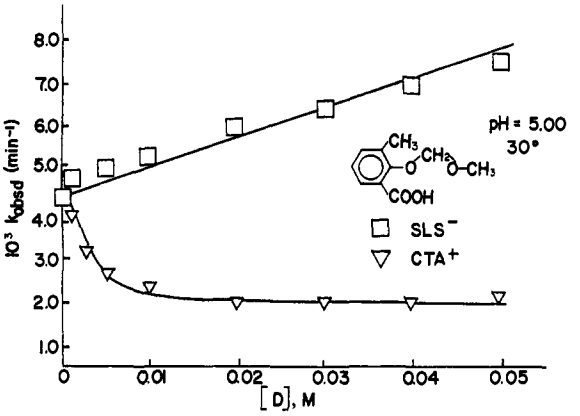


Figure 4. Plots of k_{obsd} for the hydrolysis of 2-methoxymethoxy-3-methylbenzoic acid (VI) *vs.* the concentration of the detergents SLS^- and CTA^+. Points are experimental and the curves were calculated from eq 3 for SLS^- solutions and eq 2 for CTA^+ solutions utilizing the constants provided in the Results.

Interpretation of the constants of eq 1 is provided in the Discussion.

2-Methoxymethoxy-3-methylbenzoic acid VI was hydrolyzed in solutions of varying concentration of micelle-forming agents (sodium lauryl sulfate, SLS^-; cetyltrimethylammonium bromide, CTA^+; and the neutral detergent, Igepal). In Figure 2 a plot is provided of k_{obsd} *vs.* concentration of detergent at pH 2.03 for SLS^-, CTA^+, and Igepal. For all surfactants rates were obtained above and below the critical micelle concentration (cmc). The curve passing through the points for the SLS^- solutions was calculated from eq 2.

$$k_{obsd} = k_0C + k_m(M_T - \text{cmc})^2/[C + (M_T - \text{cmc})^2] \quad (2)$$

The values of the constants used to generate the line are: $k_0 = 0.10$ min^{-1}, $k_m = 0.94$ min^{-1}, $C = 4.0 \times 10^{-5}$, and cmc $= 4.0 \times 10^{-3}$. Interpretation of the parameters of this equation will be found in the Discussion.

The hydrolyses of VI in 0.03 *M* SLS^- at μ = 0.1 (NaCl) and with no detergent at μ = 0.1 are represented by the pH–rate profiles of Figure 3. The points of Figure 3 are experimental and the curves theoretical having been generated from eq 1 and the constants of Table I.

In Figure 4 a plot is provided of k_{obsd} *vs.* detergent concentration at pH 5.00 for SLS^- and CTA^+. The line through the points for SLS^- solutions has been calculated from eq 3 and the following constants: $k_0 = 4.7$

$$k_{obsd} = k_0C + (M_T - \text{cmc})/[C + (M_T - \text{cmc})] \quad (3)$$

$\times 10^{-3}$ min^{-1}, $k_m = 2.0 \times 10^{-2}$, $C = 0.2$, and cmc $= 4.0 \times 10^{-3}$. The curve passing through the points for CTA^+ solutions was generated by eq 2 and the following parameters: $k_0 = 4.4 \times 10^{-3}$, $k_m = 2.0 \times 10^{-3}$, $C = 8.0 \times 10^{-6}$, and cmc $= 1.0 \times 10^{-4}$.

The hydrolysis of 2-methoxymethoxyisophthalic acid VII was performed in solutions containing 50% (v/v) dioxane–water and 80% (v/v) dioxane–water. Compounds IV and V were also hydrolyzed in 50% v/v dioxane–water. The pH–rate profiles are provided in Figure 5. The points are experimental and the curves were generated from eq 1 utilizing the constants tabulated in Table I.

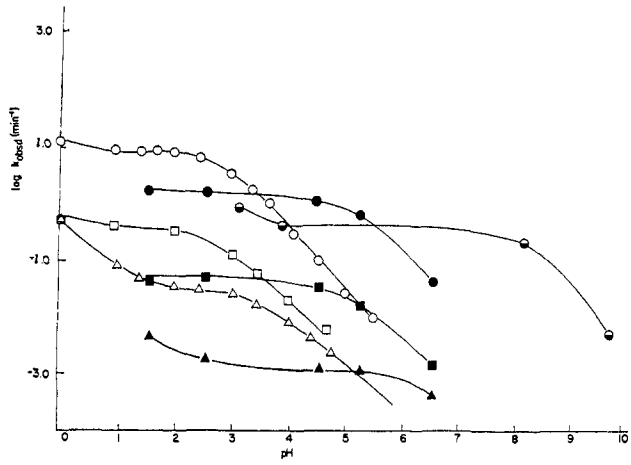


Figure 5. Plots of log k_{obsd} *vs.* pH: for the hydrolysis of 2-methoxymethoxyisophthalic acid (VII) in water (○), in 50% (v/v) dioxane–water (●), and in 80% (v/v) dioxane–water (◒) at 30°; for the hydrolysis of 2-methoxymethoxy-5-nitrobenzoic acid (IV) in water (□) and in 50% (v/v) dioxane–water (■) at 30°; and for the hydrolysis of 2-methoxymethoxybenzoic acid (V) in water (△) and in 50% (v/v) dioxane–water (▲) at 30°. Curves are calculated from eq 1 and the values of the constants recorded in Table I.

Discussion

In eq 1 the constant k_H pertains to specific acid catalyzed hydrolysis of the undissociated form of the acetals IV, V, VI, and VII. The constant k' is calculated assuming specific acid catalyzed hydrolysis of the ionized form of the acetals and is related to the kinetically equivalent constant for intramolecular general acid catalyzed hydrolysis, k_{ga}, by eq 4.

$$k_{ga} = k'K_{app} \quad (4)$$

In the preceding paper on this topic[9] it was suggested that the transition state for the reaction involving intramolecular carboxyl group participation may be viewed as involving a species in which a proton is almost completely transferred from the carboxyl group to the phenolic ether oxygen. This was supported by the ratio of k_{ga} rate constants derived for the participation of the two undissociated carboxyl groups of VII and a reasonable approximation of pK_{app_1} and pK_{app_2}. Unfortunately a Brønsted correlation of the k_{ga} terms and pK_{app} values for the series of compounds possessing a carboxyl group next to the acetal linkage was precluded by the steric acceleration of the substituent in the 3 position upon the catalytic rate derived from the carboxyl group in the 1 position. This problem is circumvented by the comparison of compounds IV and V since the steric parameters around the acetal will be identical. From the data in Table I a direct comparison of the rate constants for IV and V may be made yielding a Brønsted α value for the intramolecular general acid catalyzed reaction of *ca.* −1.0. This indicates essentially total transfer of the proton in the transition state.

Two interrelated questions arise concerning the mechanism of neighboring carboxyl group participation. The first concerns the exact role of the carboxyl group and the second concerns the relative extent of carbonium ion character of the transition state for this reaction and for the lysozyme-catalyzed reaction. With an α value of near −1.0 the catalysis may be viewed as carboxylate anion stabilization of an A-1 reaction or as concerted proton transfer and C–O bond fission with the transition state reached very late along the reaction coordinate. In either event the transition state will occur *no earlier* than the corresponding transition state for an A-1 reaction. By determination of the secondary deuterium kinetic isotope effects[19] Raftery, *et al.*, have demonstrated that the lysozyme-catalyzed hydrolysis of phenyl-β-D-glucopyranosides involves a transition state with no more oxocarbonium character than the transition state for an A-1 hydrolytic reaction on the same substrate. Since their results were also obtained using phenolic leaving groups, we may conclude from the arguments above that our reaction is proceeding with no less oxocarbonium ion character in the transition state than a similar reaction catalyzed by lysozyme.

Of possible relevance to the mechansim of intramolecular carboxyl group catalysis in our system is the study of Benkovic and Dunikoski[20] in which similar intramolecular catalysis is noted for sulfate and phosphate ester hydrolyses. They have rationalized participation of the neighboring general acid type on the basis of stabilization through hydrogen bonding in the products. They find a linear correlation between the rate enhancement observed for a given pair of substrates of a particular reaction series and the difference in hydrogen bonding in the products as derived from the phenolic pK_a's. A comparison of the rates k_H and k' for compound V gives a rate ratio that falls very near the line constructed by Benkovic and Dunikoski. The fact that such seemingly diverse reactions as sulfate ester hydrolysis, phosphate ester hydrolysis, and acetal hydrolysis should yield a reasonable linear free energy relationship is because only the *rate accelerations* brought about by neighboring group participation in one of a pair of compounds of similar electronic nature of the reaction site are being compared. Benkovic and Dunikoski point out that the correlation of rates with product stability is in accord with a transition state reached late along the reaction coordinate.

In a series of recent publications,[21] Capon and coworkers have discussed the requirements for the observation of intermolecular general acid catalysis in acetal hydrolysis. Two factors seem important: (1) the basicity of the oxygen of the leaving group must be low enough so that protonation is difficult; and (2) the carbonium ion formed must be stabilized relative to a simple alkoxonium ion (Alk—O⁺=CH_2). Based on these arguments and the lack of buffer catalysis in all our reactions, it would seem that our compounds fall in that class that are not subject to general acid catalysis. Mechanistically, it then seems reasonable to infer that these compounds are not subject to intramolecular general acid catalysis. It follows that perhaps the best description of the neighboring carboxyl facilitation in the hydrolysis of methyl phenyl acetals of formaldehyde is electrostatic or hydrogen-bonding stabilization of an A-1 reaction. For such a mechanism the concentration of preequilibrium protonated acetal would be increased by the electrostatic effect of the neighboring carboxyl anion. It should be pointed out, however,

(19) F. W. Dahlquist, T. Rand-Meir, and M. A. Raftery, *Proc. Nat. Acad. Sci. U. S.*, **61**, 1194 (1968).

(20) S. J. Benkovic and L. K. Dunikoski, Jr., *Biochemistry*, **9**, 1390 (1970).

(21) (a) B. Capon and M. C. Smith, *J. Chem. Soc. B*, 1031 (1969); (b) E. Anderson and B. Capon, *ibid.*, 1033 (1969); (c) B. Capon, M. C. Smith, E. Anderson, R. H. Dahm, and G. H. Sankey, *ibid.*, 1038 (1969).

that the structure of the critical transition state for such a process would be quite similar if not identical with one for intramolecular general acid catalysis.

Cordes and coworkers have studied[11] the influence of SLS^- on the specific acid catalyzed hydrolysis of para-substituted benzaldehyde diethyl acetals and have attributed the rate increases noted to electrostatic stabilization of the transition state. It seemed of interest, then, to ascertain whether catalysis could be observed in the hydrolysis of acetals of our series. Accordingly we have examined the reaction of compound VI in solution containing increasing concentrations of positively charged (CTA^+), negatively charged (SLS^-), and neutral (Igepal) micelle-forming agents with the results displayed in Figures 2, 3, and 4. In Figure 2 (pH 2.03) only a small inhibition is observed in solutions of CTA^+ or Igepal. With increasing SLS^- concentration, however, the rate is first unaffected, then increases sharply, and finally reaches a maximum. This behavior may be explained by a partitioning of the substrate between the bulk aqueous phase (A_{H_2O}) and the micelle phase (A_m), with no micelles present below the cmc of 0.004 M. A partition coefficient C' may be defined by eq 5.[22] The volume of the bulk phase may be consid-

$$\frac{[A_m][\text{vol bulk phase}]}{[A_{H_2O}][\text{vol micelle phase}]} = C' \qquad (5)$$

ered a constant and the volume of the micellar phase a function of some power of the concentration of micelle-forming agents yielding eq 6, where M_T =

$$\frac{(A_{H_2O})(M_T - \text{cmc})^n}{[A_m]} = C \qquad (6)$$

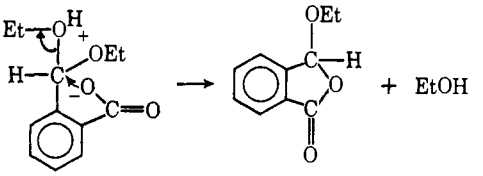
total concentration of surfactant. At constant pH the hydrolysis of acetal is pseudo-first-order in the aqueous phase and in the micellar phase with rate constants k_0 and k_m, respectively, so that the constants k_0 and k_m may be estimated from the extreme portion of Fig-

$$k_{obsd} = k_0C + k_m(M_T - \text{cmc})^n/[C + (M_T - \text{cmc})^n] \qquad (7)$$

ure 2 and the cmc is taken from the point where the increase in rate began. Curve fitting was then accomplished by varying the parameters C and n. It was found that no values of C would give a reasonable fit for values of $n = 1$ or $n = 3$. When $n = 2$ the curve of Figure 2 was calculated with $C = 4.0 \times 10^{-5}$. The maximum rate enhancement at this pH (2.03) is seen to be about tenfold.

In an attempt to separate the effects of SLS^- on the specific acid catalyzed reaction and the intramolecular catalyzed reaction, the pH–rate profiles of Figure 3 were determined. The increase in the specific acid catalyzed rate constant, k_H, of 45-fold is similar to that observed by Cordes, *et al.*, for benzaldehyde diethyl acetals and can probably be explained by the same reasoning that they employ, namely, that the negatively charged micelle electrostatically stabilizes the positively charged transition state with more stabilization occurring at the point where the positive charge is localized to the highest degree. The lack of significant rate enhancement above *ca.* pH 3.2 could have two explanations: (1) the intramolecularly catalyzed reaction (which predominates at these pH's) is not affected by the presence of SLS^-, and/or (2) the binding of the substrate has changed in orientation or degree. That both effects are probably operative is shown by the data of Figure 4 for SLS^- at pH 5.00. Both the parameter C, which is an index of the efficiency of binding, and the form of the equation used to compute the line have changed from pH 2.0 to 5.0. The fraction of the substrate partitioned into the micelle is appoximately 5000 times greater at pH 2.0 than at pH 5.0. Also the rate increase on going from pure aqueous solution to 0.03 M SLS^- solution at pH 5.00 is only 1.7-fold. This may be due to the fact that the transition state at this pH is, on the whole, neutral. In contrast to the poor binding of the ionized substrate to SLS^-, the substract binds very well at pH 5.00 to the cationic micelle, CTA^+ ($C = 8.0 \times 10^{-6}$). Only a small inhibition of the rate (twofold) is detected, however.

In his extensive review[23] of the reactions of carbohydrates and related systems, Capon has reported that phthaladehydic acid diethyl acetal reacted, in aqueous dioxane but not in water, to give the cyclic acylal VIII.



VIII

In order to ascertain what effect change in the dielectric of the media might have on intramolecular carboxyl participation in acetal hydrolysis, the hydrolyses of compounds IV, V, and VII were examined in aqueous dioxane solution. The log k_{obsd} *vs.* pH rate profiles are presented in Figure 5 and the derived constants in Table I. As the concentration of dioxane is increased the pK_{app} values also increase, as anticipated for the ionization of a carboxylic acid.[24] The resultant of this increase in pK_{app} is to extend the plateau rate associated with k_{ga} to higher pH. The lack of any tendency toward a "bell-shaped" log k_{rate} *vs.* pH profile for VII again establishes that there is no evidence for concerted participation of the –COOH and $-COO^-$ groups. Also, since repetitive scans of the reaction of VII at pH's 3.15 and 6.55 do not indicate the production of any species but 2-hydroxyisophthalic acid, it must be concluded that nucleophilic participation of the carboxyl group does not occur. The dependence of log k_{ga} upon pK_{app} for a single compound is linear and of slope −0.33. The decrease in rate with increase in pK_a, due to solvent change, is rather moderate though greater than that noted for intramolecular nucleophilic participation of the carboxyl anion in the hydrolysis of monophenyl phthalate ion.[25] At constant solvent composition the ratio of k_{ga} constants for compounds IV and V remains the same so that the Brnøsted coefficient ($\alpha \approx -1.0$) is not solvent dependent. This invariance of α with solvent composition together with the small sensitivity of k_{ga} to change in pK_{app} by solvent

(22) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Amer. Chem. Soc.*, **90**, 1333 (1968).

(23) B. Capon, *Chem. Rev.*, **69**, 407 (1969).

(24) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids, and Peptides," Reinhold, New York, N. Y., 1943, Chapter 4.

(25) T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, **92**, 3422 (1970).

change for a single compound suggests intramolecular carboxyl group catalysis to be enhanced by a decrease in the dielectric constant of the media (*i.e.*, decrease in k_{ga} due to weakening of the acidity of the general acid catalyst is somewhat compensated for by an increase). This suggests that the proton transfer between the carboxyl group of Glu-35 and the substrate in the ES complex of lysozyme may be facilitated by the non-polar nature[26] of the environment of the enzyme surface in this region. An ion-pair formation between a carboxyl anion and a proton would be anticipated to be enhanced by a decrease in the dielectric of the media.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

(26) J. B. Howard and A. N. Slayer, *J. Biol. Chem.*, **244**, 1399 (1969).

Preparation and Synthetic Applications of (Dimethylamino)phenyloxosulfonium Methylide[1]

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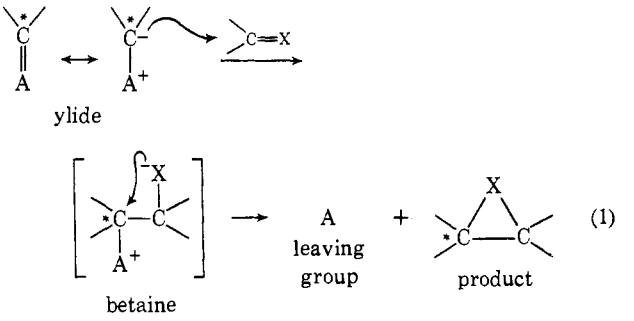
Abstract: The preparations of *N,S*-dimethyl *S*-phenyl sulfoximine and its N-methylated salt—(dimethylamino)-methylphenyloxosulfonium fluoroborate—are described. These materials represent classes of compounds not previously reported. Treatment of the above salt with sodium hydride in a variety of solvents generated the title ylide. The ylide has been shown to react with aldehydes and ketones to produce oxiranes, with electrophilic olefins to yield cyclopropanes, with benzalaniline to produce 1,2-diphenylaziridine, and with benzoyl chloride and phenyl isocyanate to produce carbonyl-stabilized ylides. In the nucleophilic methylene transfer reactions the by-product is *N,N*-dimethylbenzenesulfinamide.

Sulfonium ylides have been extensively utilized as reagents for organic syntheses.[2] The most typical applications of sulfonium ylides involve stepwise methylene insertions across the double bond of a carbonyl or electrophilic olefin to yield an oxirane or cyclopropane, respectively.

Of the sulfonium ylides that have been examined to date, perhaps the most useful is dimethyloxosulfonium methylide (**1**).[3] This ylide is quite reactive, yet moderately stable. Furthermore, the precursor, trimethyloxosulfonium iodide, is easily available by the S methylation of dimethyl sulfoxide. Unfortunately, S alkylation of sulfoxides is not a general reaction and, with trivial exceptions, it is not possible to obtain other salts in the trialkyloxosulfonium series. This limits ylides in the series to the methylide.

We have now achieved the preparation of a new type of oxosulfonium salt—(dialkylamino)oxosulfonium salts.[4] Such salts are derived from sulfoximines and can be prepared with extensive structural variation. The stability and reactivity of the ylides derived by deprotonation of these new salts closely parallel those of dimethyloxosulfonium methylide. In this paper we report the preparation and reactions of the model compound in this series—(dimethylamino)methylphenyloxosulfonium fluoroborate (**3**). This study has provided the foundation for future work which we believe will significantly increase the scope of synthetic applications of sulfonium ylides.[5]

In the design of a new ylide reagent for the stepwise addition of methylene across an electrophilic double bond the following factors need be considered: (1) the nucleophilicity of the carbanionic center, (2) the ability of the onium group to stabilize the anionic site, and, subsequently (3) to act as a leaving group. A generalized ylide reaction is shown in eq 1.



(1)

Very stable ylides (such as those containing additional electronegative substituents on the carbanionic carbon) may lack sufficient nucleophilicity for successful addition to an electrophilic double bond. With very unstable ylides, α elimination to carbenoid species may be a problem.

Dimethyloxosulfonium methylide (**1**) is an ylide reagent with a convenient balance between reactivity and stability. With this ylide the leaving group is dimethyl sulfoxide. This investigation originated with the idea that ylides of similar characteristics might be available

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(1) Part XXVI in the series "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 8648).

(2) For a review of sulfonium ylide chemistry see A. W. Johnson, "Ylide Chemistry," Academic Press, New York, N. Y., 1966.

(3) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(4) For preliminary reports of this work see C. R. Johnson, E. R. Janiga, and M. Haake, *ibid.*, **90**, 3090 (1968).

(5) For example, asymmetric syntheses employing optically active ylides in this series; C. R. Johnson and C. S. Schroeck, *ibid.*, **90**, 6852 (1968).