Intramolecular Carboxyl Group Participation in Acetal Hydrolysis

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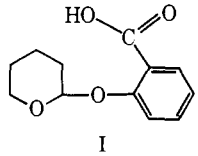
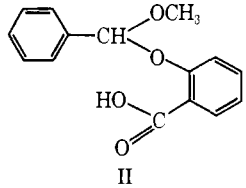
Abstract: The rates of hydrolysis of the ortho carboxyl-substituted acetals, 2-(*o*-carboxyphenoxy)tetrahydropyran, benzaldehyde methyl (*o*-carboxyphenyl) acetal, and benzaldehyde methyl *S*-(*o*-carboxyphenyl) thioacetal have been determined. A pronounced carboxyl group participation is observed in the hydrolysis of the oxygen acetals. In the solvent 50% dioxane–water, 2-(*o*-carboxyphenoxy)tetrahydropyran hydrolyzes 10^5–10^6 times faster than the corresponding compound having a para carboxyl group or the unsubstituted derivative. In water the rate enhancement is 1.4×10^4. In contrast, only a small rate accelerating effect due to the ortho carboxyl group is seen in the hydrolysis of the thioacetal. Intramolecular carboxyl group catalysis is greatly favored over intermolecular buffer acid catalysis in hydrolysis of the tetrahydropyran acetals as indicated by the ratio of the first-order rate constant for intramolecular catalysis and the second-order rate constant for formic acid catalyzed hydrolysis of the unsubstituted derivative. This ratio is 580 *M* even though the intramolecular reaction was studied at 15° while the bimolecular reaction was studied at 50°. Increasing the stability of the intermediate carbonium ion has only a small effect on the maximum differences in rate between ortho and para carboxyl-substituted phenolic acetals.

Intermolecular general acid catalysis by buffer acids has been observed in the hydrolysis of 2-(substituted-phenoxy)tetrahydropyrans,[2,3] benzaldehyde methyl phenyl acetals,[4] and tropone diethyl ketal.[5] Intramolecular catalysis by a neighboring carboxyl group has been observed in the hydrolysis of *o*-carboxyphenyl β-D-glucoside[6] and 2-methoxymethoxybenzoic acid.[6,7] In these cases there is no evidence for buffer acid catalysis in the hydrolysis of corresponding acetals without carboxyl group substitution.[6-8] If the mechanism of the intramolecular reactions involves general acid catalysis, then it is clear that intramolecular general acid catalysis is greatly favored over intermolecular catalysis, but a quantitative assessment of this advantage has not as yet been possible. The study of acetals or ketals having a properly positioned neighboring carboxyl group, in cases where buffer acid catalysis has been observed in the hydrolysis of the unsubstituted compounds, would allow a direct comparison of the relative efficiency of intra- and intermolecular catalysis in these reactions. We have therefore studied the hydrolysis of 2-(*o*-carboxyphenoxy)tetrahydropyran (I) and benzaldehyde methyl (*o*-carboxyphenyl) acetal (II).



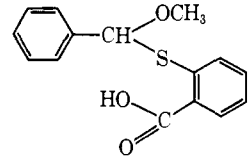
I



II

Since bimolecular general acid catalysis is observed in the hydrolysis of the unsubstituted compounds[2-4] it is reasonable that intramolecular carboxyl group participation would proceed by the same mechanism. Thus, kinetically equivalent possibilities would not complicate mechanistic interpretation of carboxyl group involvement in these reactions to the same extent as in the previous studies of intramolecular catalysis in acetal hydrolysis.[6]

Although general acid catalysis is not observed in the hydrolysis of benzaldehyde methyl *S*-phenyl thioacetals,[9] it might be detected in an intramolecular reaction if indeed intramolecular catalysis is greatly favored over buffer acid catalysis. We have, therefore, also studied the hydrolysis of benzaldehyde methyl *S*-(*o*-carboxyphenyl) thioacetal (III).



III

Experimental Section

Materials. 2-(*o*-Carboethoxyphenoxy)tetrahydropyran was prepared by treating 2-chlorotetrahydropyran with the sodium salt of ethyl salicylate. 2-Chlorotetrahydropyran was prepared by addition of gaseous HCl to dihydropyran at 0° until a theoretical amount had been absorbed. The product was then distilled.

2-(*o*-Carboxyphenoxy)tetrahydropyran dicyclohexylammonium salt was prepared by hydrolyzing the corresponding ethyl ester with the following procedure. Ester (1 g) was accurately weighed in a tared flask. An exactly equivalent amount of standardized barium hydroxide solution (*ca.* 0.4 *N*) was introduced from a buret. The solution was shaken mechanically until clear and neutral. An exactly equivalent amount of 0.1 *M* dicyclohexylammonium sulfate solution was then added from a buret, and the precipitated barium sulfate was removed by centrifuging and decanting. The aqueous solution of the salt was lyophilized, and the residual salt was recrystallized from methanol–ether. *Anal.* Calcd for $C_{24}H_{37}NO_4$: C, 71.43; H, 9.24; N, 3.47. Found: C, 71.22; H, 9.04; N, 3.55.

The above technique is useful for preparation of carboxyl-substituted acetals where the acetal is too unstable to be isolated by acidifying the solution resulting from alkaline hydrolysis.

2-(*p*-Carboxyphenoxy)tetrahydropyran was prepared from the corresponding ethyl ester that had been obtained by addition of ethyl *p*-hydroxybenzoate to dihydropyran (bp 141° (2.5 mm)), by

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(2) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).
(3) T. H. Fife and L. H. Brod, *ibid.*, **92**, 1681 (1970).
(4) E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969).
(5) E. Anderson and T. H. Fife, *J. Amer. Chem. Soc.*, **91**, 7163 (1969).
(6) B. Capon, M. C. Smith, E. Anderson, R. H. Dahm, and G. H. Sankey, *J. Chem. Soc. B*, 1038 (1969).
(7) B. Dunn and T. C. Bruice, *J. Amer. Chem. Soc.*, **92**, 2410 (1970).
(8) D. Piszkiewicz and T. C. Bruice, *ibid.*, **89**, 6237 (1967).
(9) T. H. Fife and E. Anderson, *ibid.*, **92**, 5464 (1970).

shaking 1 g of ester with a twofold excess of 0.2 *M* NaOH until the solution was clear. The solution was diluted threefold and equal volumes of ice and ether were added. The mixture was vigorously stirred and carefully acidified to pH 3 with HCl. The ether layer was dried with $MgSO_4$. The ether solution was then concentrated to about 10 ml, and 50 ml of hexane was added. Upon standing, the material crystallized. The crystals were washed with hexane and when dried, melted at 144–146°. *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.87; H, 6.31. Found: C, 64.82; H, 6.51.

Benzaldehyde methyl *S*-(*o*-carbomethoxyphenyl) thioacetal was prepared by the method of Fife and Anderson[9] from α-chlorobenzyl methyl ether and sodium methyl thiosalicylate. The compound was distilled and boiled at 158° (0.1 mm) giving a viscous oil which crystallized on standing to give a pale yellow solid. This was recrystallized from hexane to give a white powder melting at 58–60°. *Anal.* Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.56; S, 11.11. Found: C, 66.27; H, 5.16; S, 11.05.

Benzaldehyde Methyl *S*-(*o*-Carboxyphenyl) Thioacetal. The methyl ester (1 g) was shaken with a threefold excess of 0.3 *M* NaOH in 25% ethanol–water at 40° until the solution was clear and all the ester had dissolved (2 days). The solution was mixed with a twofold volume of ice and covered with 100 ml of ether. The solution was then vigorously stirred and slowly acidified with 1 *M* HCl to pH 7, and then with 0.1 *M* HCl to pH 2.5. The ethereal layer was separated, dried with $MgSO_4$, and evaporated to dryness at room temperature *in vacuo*. The white residual solid was recrystallized from 25% ether–hexane and melted at 131–132°. *Anal.* Calcd for $C_{15}H_{14}O_3S$: C, 65.69; H, 5.11; S, 11.69. Found: C, 65.70; H, 5.16; S, 11.50.

Benzaldehyde methyl (*o*-carbomethoxyphenyl) acetal was prepared by the same procedure as that used for the corresponding thioacetal except methyl salicylate was substituted for methyl thiosalicylate, and the product was purified by distillation, boiling at 132° (0.05 mm). *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.59; H, 5.92. Found: C, 70.80; H, 6.15.

In view of the very large hydrolytic rate constant, no attempt was made to isolate the free acid or its salts. Instead, a stock solution of the sodium salt of the acid was made by the following procedure. To 5 ml of an approximately 0.1 *M* solution of KOH in 85% aqueous ethanol was added 25 μl of the methyl ester. This would give an approximately 2×10^{-2} *M* solution. After about 5 min a tlc of the solution was run and no methyl ester was detectable either by iodine staining, spraying with Brady's reagent (2-4-DNP), or by fluorescent techniques on fluorescent silica. After hydrolysis of the acetal under the experimental conditions for the rate measurements, the final ultraviolet spectrum was that of an equimolar mixture of salicylic acid and benzaldehyde.

Dioxane was purified by the method of Fieser[10] and was stored frozen in brown bottles.

Kinetic Measurements. The rate constants for hydrolysis of the acetals were determined spectrophotometrically with a Cary 15 spectrophotometer. The appearance of the appropriate phenol or phenolate ion was measured, except in the case of the thioacetal (III) and benzaldehyde methyl (*o*-carbomethoxyphenyl) acetal with which hydrolysis was followed by measuring the appearance of benzaldehyde. Stock solutions of the acetals were prepared in either methanol or aqueous acetonitrile. To initiate the reactions 10 μl of stock solution was added to 1.4 ml of buffer in the cuvette. The reactions were followed to completion, and pseudo-first-order rate constants (k_{obsd}) were calculated by a rigorous least-squares procedure with an IBM 360-40 computer. Temperature was maintained constant (±0.05°) by circulating water from a Precision Scientific Temptrol 154 water bath around a Thelma thermostated cell.

The pH of each solution was measured with a Model 22 Radiometer pH meter standardized with aqueous buffers. The glass electrode gives the correct pH reading in concentrated dioxane–H_2O mixtures.[11]

Results

In Figure 1 is shown a plot of k_{obsd} for hydrolysis of 2-(*o*-carboxyphenoxy)tetrahydropyran in 50% dioxane–H_2O at 15° and μ = 0.1 (with KCl) *vs.* pH. The plateau in the profile at pH values approaching the pK_a of the carboxyl group represents either general acid catalysis by the un-ionized carboxyl group or a transition from hydronium ion catalyzed hydrolysis of the un-ionized species to a faster hydronium ion catalyzed hydrolysis of the ionized species. These possibilities are kinetically equivalent, and either eq 1 or eq 2 fits the

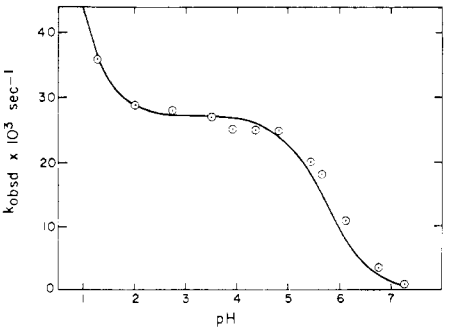


Figure 1. Plot of k_{obsd} for hydrolysis of 2-(*o*-carboxyphenoxy)-tetrahydropyran in 50% dioxane–H_2O at 15° *vs.* pH.

$$k_{obsd} = (k_0 + k_1 a_H)\left(\frac{a_H}{K_a + a_H}\right) \quad (1)$$

$$k_{obsd} = k_1 a_H\left(\frac{a_H}{K_a + a_H}\right) + k_2 a_H\left(\frac{K_a}{K_a + a_H}\right) \quad (2)$$

observed data, where k_0 is a rate constant for intramolecular general acid catalysis, k_1 is the second-order rate constant for hydronium ion catalyzed hydrolysis of the un-ionized acetal, k_2 is the second-order rate constant for hydronium ion catalyzed hydrolysis of the acetal in which the carboxyl group is ionized, and K_a is the dissociation constant of the carboxyl group. The line in Figure 1 is theoretical and can be calculated from either eq 1 or eq 2 using the values of the rate constants in Table I and $K_a = 1.91 \times 10^{-6}$. Buffer catalysis was not observed with acetate buffers (1.0–0.1 *M* total) at pH 5.93 in 50% dioxane–H_2O at 15° and μ = 0.5, or in phosphate buffers (0.5–0.082 *M* total) at pH 6.52 in H_2O at 25° and μ = 1.0. The value of k_2 in H_2O at 15° was 3.404×10^3 M^{-1} sec^{-1}.

The hydrolysis of the ethyl ester of I and 2-(*p*-carboxyphenoxy)tetrahydropyran was also studied at 15° with 50% dioxane–H_2O as the solvent. At pH 1.28, k_{obsd} for hydrolysis of the ester was 1.22×10^{-3} sec^{-1}, from which a second-order rate constant, $k_H = 2.32 \times 10^{-2}$ M^{-1} sec^{-1}, can be calculated. Thus, if eq 2 describes the hydrolysis of I, k_2 is 6.1×10^5 greater than k_H for the ester. This is the maximum difference in k_{obsd} for hydrolysis of these compounds at any pH. In comparison with hydrolysis of the unsubstituted derivative 2-phenoxytetrahydropyran,[2] in 50% dioxane–H_2O at 15°, k_2 is 3.8×10^5 greater than k_H. These differences are much larger than would be expected on the basis of differences in inductive effects.

A more exact comparison can be obtained with the para carboxyl-substituted derivative, 2-(*p*-carboxyphenoxy)tetrahydropyran, where electronic effects are closely similar but where the carboxyl group cannot participate in the reaction. The rate of hydrolysis was too slow to measure accurately at relatively high pH; consequently, k_2 could not be directly measured. However, for that compound k_{obsd} in 50% dioxane–H_2O at 15° and pH 1.28 is 4.84×10^{-4} sec^{-1}, from which k_1 can

(10) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1955, p 284.

(11) H. P. Marshall and E. Grunwald, *J. Chem. Phys.*, 21, 2143 1953).

Table I. Rate Constants for Hydrolysis of Carboxyl-Substituted Acetals

Compound	k_1, M^{-1} sec^{-1}	k_2, M^{-1} sec^{-1}	k_0, sec^{-1}
2-(*o*-Carboxyphenoxy)tetrahydropyran[a]	1.67×10^{-1}	1.42×10^{4}	2.71×10^{-2}
2-(*p*-Carboxyphenoxy)tetrahydropyran[a]	9.20×10^{-3}		
Benzaldehyde methyl (*o*-carboxyphenyl) acetal[b]		1.21×10^{7}	
Benzaldehyde methyl *S*-(*o*-carboxyphenyl) thioacetal[c]	2.91×10^{-1}	9.32	3.16×10^{-3}

[a] In 50% dioxane–H_2O (v/v) at 15° and μ = 0.1. [b] In H_2O at 25° and μ = 0.1. [c] In H_2O at 30° and μ = 0.1.

be calculated to be 9.20×10^{-3} M^{-1} sec^{-1}. From the ρ of −0.9 for hydronium ion catalyzed hydrolysis of 2-(4-substituted phenoxy)tetrahydropyrans[2] and the σ values for COOH and COO^- (0.45 and 0), taking these values to be the same in 50% dioxane–H_2O as in H_2O, it can be calculated that k_2 (para) should be 2.5 times larger than k_1 (para). Thus, k_2 (para) would then be only 1.6×10^{-6} times as large as k_2, calculated for the ortho carboxyl-substituted acetal. This method has previously been used to estimate the difference in rate of hydrolysis of the ortho and para isomers of the carboxyphenyl β-D-glucosides.[6] It is evident that the neighboring carboxyl group in I is greatly enhancing the rate of the reaction. In H_2O at 15° at pH 1.10 (0.1 M HCl) k_{obsd} was 7.76×10^{-3} sec^{-1}. Thus, k_1 (para) in H_2O is 9.77×10^{-2} M^{-1} sec^{-1}. The 18.1-fold difference between k_1 (ortho) and k_1 (para) in 50% dioxane–H_2O is probably due in part to steric acceleration by the ortho substituent. It has been shown previously that ortho substituents will give rise to a small enhancement of the rate of hydronium ion catalyzed hydrolysis of methyl phenyl acetals of formaldehyde[7] and phenyl glycosides.[12]

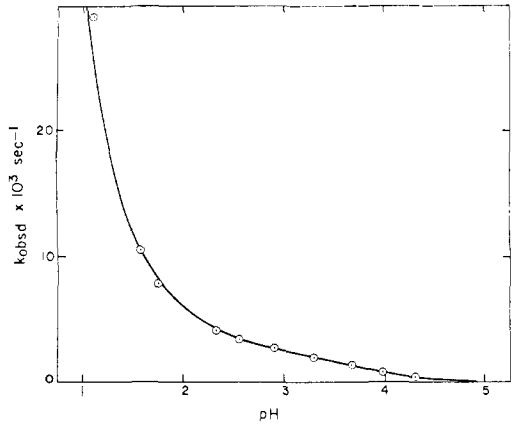


Figure 2. Plot of k_{obsd} for hydrolysis of benzaldehyde methyl *S*-(*o*-carboxyphenyl) thioacetal in H_2O (μ = 0.1) at 30° *vs.* pH.

The hydrolysis of benzaldehyde methyl (*o*-carboxyphenyl) acetal could only be studied at relatively high pH due to its rapid hydrolysis at lower pH. As a consequence, a complete pH–rate constant profile could not be obtained. However, the value of k_2 was determined to be 1.21×10^{7} M^{-1} sec^{-1} at 25° in H_2O and μ = 0.1, by obtaining k_{obsd} at several pH values where the carboxyl group is almost completely ionized (pH 8.70–10.15). In that pH region a plot of log k_{obsd} *vs.* pH was linear with a slope of −1.0. Buffer catalysis was not observed with ethylethanolamine buffers (0.066–0.70 M) in H_2O at pH 10.15 or in 50% dioxane (0.08–0.40 M) at pH 9.75.

(12) R. L. Nath and H. N. Rydon, *Biochem. J.*, **57**, 1 (1954).

Table II. Rate Constants for Hydrolysis of Benzaldehyde Methyl (*o*-Carbomethoxyphenyl) Acetal in H_2O at 25° with μ = 1.0 M, Maintained Constant with KCl

Acid	pH	k_{HA},[a] M^{-1} sec^{-1}	k_{int},[b] sec^{-1}	k_H,[c] M^{-1} sec^{-1}
H_3O^+	2.81		0.102	65.0
Formic	3.98	0.216	0.0080	63.4[d]
Acetic	4.55	0.07	0.00288	
Cacodylic	5.64		0.00187	
Cacodylic	6.06	0.0094	0.00143	

[a] Second-order rate constant for general acid catalysis. [b] Intercept value in plots of k_{obsd} *vs.* acid concentration. [c] Second-order rate constant for hydronium ion catalysis. [d] Value calculated from eq 3 with k_0 = 0.00138 sec^{-1}.

The rate of hydrolysis of the methyl ester of II was measured as a function of buffer concentration in formic, acetic, and cacodylic acid buffers in H_2O at 25° with μ = 1.0 maintained constant with KCl, and catalysis was observable. The values of the rate constants are given in Table II. Spontaneous hydrolysis was found to follow eq 3, involving hydronium ion catalysis

$$k_{obsd} = k_H a_H + k_0 \quad (3)$$

(k_H = 63 M^{-1} sec^{-1}) and a pH-independent reaction (k_0 = 0.00138 sec^{-1}). Thus, the value of k_2 for II is 1.9×10^{5}-fold greater than k_H for the methyl ester. This comparison does not take into account the difference in ionic strength which will reduce the rate difference slightly.

In Figure 2 is shown a plot of k_{obsd} *vs.* pH for hydrolysis of benzaldehyde methyl *S*-(*o*-carboxyphenyl) thioacetal in H_2O at 30° and μ = 0.1. Only a small enhancement by the ortho carboxyl group is observed in the hydrolysis of this compound. The values of the rate constants are given in Table I, and the apparent pK_a is 3.47. Formic acid catalysis of the hydrolysis of III could not be detected when formic acid concentration was varied from 0.04 to 0.40 M at pH 3.54.

Discussion

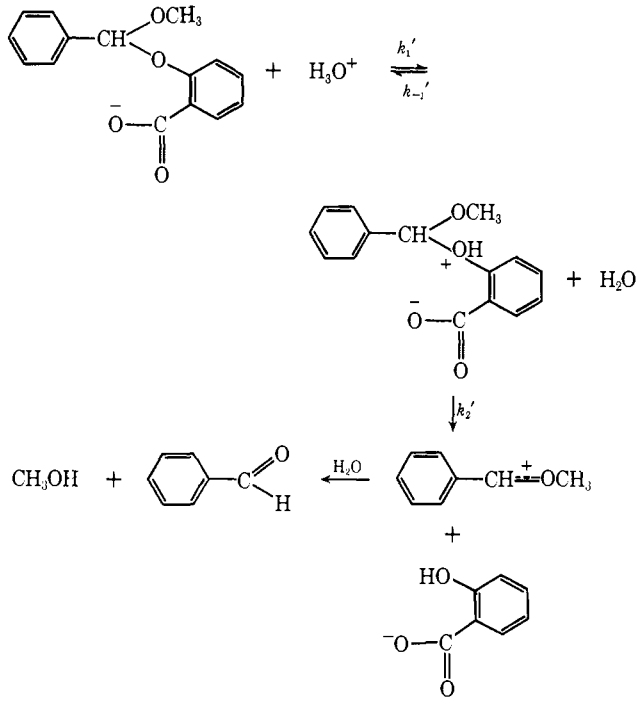
Electrostatic stabilization of a developing carbonium ion can be excluded in the case of benzaldehyde methyl (*o*-carboxyphenyl) acetal. Assuming the observed reaction at high pH to be hydronium ion catalyzed hydrolysis of the anionic species, as in Scheme I, and employing the experimental value of k_2 of 1.21×10^{7} M^{-1} sec^{-1}, then k_2' will be (1.21×10^{7} M^{-1} sec^{-1} × K_{SH^+}) where K_{SH^+} is the dissociation constant of the conjugate acid.

$$k_{obsd} = \left(\frac{k_2'}{K_{SH^+}}\right) a_H \quad (4)$$

The measured dissociation constant of benzaldehyde diethyl acetal[13] is $10^{5.7}$. Considering that aryl ethers are less basic than alkyl ethers[14] by a factor of 10^3 this

(13) T. Pletcher and E. H. Cordes, *J. Org. Chem.*, **32**, 2294 (1967).

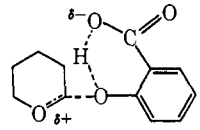
Scheme I



gives a value of k_2' of approximately 10^{16} sec^{-1}. In an A-1 mechanism $k_{-1}'(H_2O)$ must be considerably greater than k_2' since $k_{obsd} = [(k_1' k_2')/(k_{-1}'(H_2O) + k_2')]a_H$. The rate constant k_{-1}' would then necessarily be larger than that for a diffusion-controlled reaction. Therefore, the reaction cannot involve preequilibrium protonation by hydronium ion, assuming normal basicity. A reaction involving proton transfer from hydronium ion in concert with C–O bond breaking is unlikely since buffer acid catalysis would then be expected. It is of interest to note that if the hydrolysis of benzaldehyde methyl (*o*-carboxyphenyl) acetal was to be considered a bimolecular reaction, then it would represent the fastest known acid-catalyzed acetal hydrolysis reaction. The second-order rate constant, k_2, is considerably greater than even that for tropone diethyl ketal[5] despite the large difference in stabilities of the alkoxybenzyl and alkoxytropylium carbonium ions.

If the large second-order rate constant in comparison to the methyl ester was due to a decrease in K_{SH^+} because of stabilization of the conjugate acid by the carboxylate anion, then it would be required that K_{SH^+} would have to be reduced by a factor of nearly 10^5. In the case of 2-(*o*-carboxyphenoxy)tetrahydropyran in 50% dioxane–H_2O, a reduction in K_{SH^+} of nearly 10^6 would be required to explain the maximum difference in rate of hydrolysis between the ortho and para carboxyl-substituted compounds. A mechanism involving carboxyl group stabilization of a completely transferred proton on the acetal oxygen is favored by Dunn and Bruice[7,15] as an explanation for neighboring carboxyl group enhancement of the rate of hydrolysis of *o*-methoxymethoxybenzoic acids. These authors point out that such a mechanism is reasonable in view of the lack of buffer catalysis in the hydrolysis of those compounds, since it is likely that structural features allowing intramolecular general acid catalysis to take place would also give rise to buffer acid catalysis with the unsubstituted derivatives.

The employment of D_2O as the solvent, the usual method for distinguishing general acid catalysis from mechanisms in which slow proton transfer does not take place, would give ambiguous results with the present compounds.[16] It is very likely, however, that the mechanism does involve intramolecular general acid catalysis as in IV since general acid catalysis



IV

by buffer acids is observed in the hydrolysis of 2-phenoxytetrahydropyrans[2,3] and benzaldehyde methyl phenyl acetals.[4] It would reasonably be expected that the intramolecular reaction would proceed by the same mechanism. In contrast with the corresponding unsubstituted acetals, buffer acid catalysis cannot be detected with I or II in either 50% dioxane–H_2O or in H_2O. Buffer acid catalysis should not compete effectively with facile intramolecular general acid catalysis, but participation by the carboxylate anion as a nucleophile or by an electrostatic effect would not necessarily compete with, and might actually enhance, catalysis by buffer acids.

The efficiency of intramolecular general acid catalysis in comparison with intermolecular catalysis can be estimated in the reactions by dividing k_0 for I in 50% dioxane–H_2O by the second-order rate constant for formic acid catalyzed hydrolysis of 2-phenoxytetrahydropyran.[2] A ratio of 580 *M* is obtained. This is the concentration of HCOOH in the intermolecular reaction necessary to give a pseudo-first-order rate constant comparable to that determined in the intramolecular reaction. The rate constant for the bimolecular reaction was obtained at 50°, so a comparison at the same temperature would increase the ratio severalfold. Furthermore, formic acid in 50% dioxane–H_2O has a pK_a approximately one unit lower than I. Thus, intramolecular catalysis is greatly favored over bimolecular buffer acid catalysis, and the efficiency of the intramolecular reaction must be due to factors other than an increase in local concentration of the carboxylic acid catalyst.

The rate enhancement in H_2O due to carboxyl group participation is not greatly different for compounds I and II (1.4×10^4 for I and 1.9×10^5 for II) in comparison with suitable derivatives in which participation cannot take place. With carboxyphenyl β-D-glucosides[6] the ortho derivative hydrolyzes 1.4×10^4 times faster than the para carboxyl-substituted compound at pH 4.5. With these compounds, the intermediate carbonium ions are of widely varying stability, the benzylcarbonium ion of II being of greatest and the glucosylcarbonium ion of least stability. An indication of relative stabilities is provided by the greatly different rates of hydrolysis of these compounds. It has been estimated that 2-methoxytetrahydropyran hydrolyzes 3.1×10^7 times faster than methyl α-D-glucopyranoside.[17] Thus, while carbonium ion stability is of

(14) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, **82**, 4999, 5660 (1960).

(15) B. Dunn and T. C. Bruice, *ibid.*, **93**, 5725 (1971).

(16) T. C. Bruice and D. Piszkiewicz, *ibid.*, **89**, 3568 (1967).

crucial importance in allowing general acid catalysis to be detectable, by facilitating C–O bond breaking, it is not of great importance in regard to the magnitude of the rate enhancement produced by intramolecular carboxyl group catalysis. This is undoubtedly due in part to the fact that as the stability of the intermediate carbonium ion increases, the rate of hydronium ion catalyzed hydrolysis of the reference compounds increases as well as the rate constant for intramolecular general acid catalysis. The magnitude of the rate enhancement will then depend on the pK_a of the carboxyl group, the Brønsted coefficient for intramolecular catalysis, and perhaps of greatest importance, the stereochemical situation. The carboxyl group must be oriented correctly in relation to the acetal oxygen for intramolecular proton transfer to occur readily.

In 50% dioxane–H_2O the maximum rate facilitation, k_2(ortho)/k_2(para), is nearly 10^6 in the case of I. Thus, intramolecular catalysis is much more favorable in the less polar solvent than in H_2O where this ratio is 1.4×10^4. Rate constants for hydronium ion catalyzed acetal hydrolysis are normally less in 50% dioxane–H_2O than in H_2O.[3] The k_1 values for the para derivative show this effect of solvent, but the value of k_2 for I is greater in 50% dioxane–H_2O than in H_2O. This may be due to the higher pK_a of the carboxyl group in 50% dioxane–H_2O, since $k_2 = k_0/K_a$. As discussed previously, the magnitude of general acid catalysis in comparison with hydronium ion catalysis will increase as the catalyst acid becomes weaker.[18]

Carboxyl group participation is quite weak in the case of benzaldehyde methyl *S*-(*o*-carboxyphenyl) thioacetal. The difference of 30 between k_1 and k_2 is more than would be calculated from the ρ value of -1.0 for hydronium ion catalyzed hydrolysis of benzaldehyde methyl *S*-(substituted phenyl) thioacetals[9] and the σ values for COO^- and COOH, a factor of about 3 being expected, but the additional difference could be due to a steric or electrostatic effect exerted by the ortho carboxyl group on the hydronium ion catalyzed reaction. Thus, just as buffer acid catalysis cannot be detected with these thioacetals,[9] in contrast to the large buffer catalysis seen in hydrolysis of the corresponding oxygen compounds, there is no conclusive evidence for intramolecular catalysis with III, even though sulfur is of relatively low basicity. This possibly results from the greater difficulty of C–S bond breaking in comparison with the corresponding C–O bond after protonation. Thus, the same structural features are probably important in leading to general acid catalysis in both inter- and intramolecular reactions. Also, of course, because of the presence of sulfur the orientation of the carboxyl group relative to the atom to which proton transfer is occurring will be different.

Several mechanisms have been suggested for the glycosidic enzyme lysozyme involving aspartic acid 52 and glutamic acid 35 in the active site of the enzyme.[19,20] These mechanisms involve glutamic acid 35 acting as a general acid. From models based on X-ray crystallographic data, the oxygen of glutamic acid 35 has been suggested to be 3 Å from the glycosidic oxygen in the substrate at the site of cleavage.[21] Thus, a proton transfer step might proceed readily. The enhancement in rate obtained in lysozyme catalysis in comparison with hydronium ion or hydroxide ion catalysis of glycoside hydrolysis would appear to be 10^5–10^6 for substrates with phenolic leaving groups,[22] although the possibility of nonproductive binding with the compounds studied could be a complication in assessing this difference.[20] Considering the rate enhancement from intramolecular carboxyl group participation found in this study for I in 50% dioxane–H_2O where the pK_a of the carboxyl group is relatively high, it is clear that the efficiency of the enzyme might be explained in terms of intracomplex general acid catalysis. The natural substrates for lysozyme have poor leaving groups. Therefore, the enzyme might necessarily have to facilitate C–O bond breaking for general acid catalysis to occur. It is possible that this could be achieved by electrostatic stabilization of an intermediate carbonium ion or by strain introduced into the substrate by the binding process which would be relieved in the hydrolytic reaction.[19,20] In a simple chemical system, the hydrolysis of benzaldehyde di-*tert*-butyl acetals, it has been shown that relief of ground-state strain in the transition state can give rise to general acid catalysis.[23]

Acknowledgment. This work was supported by research grants from the National Institutes of Health and the National Science Foundation.

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