Intramolecular General Acid Catalysis in the Hydrolysis of Acetals with Aliphatic Alcohol Leaving Groups

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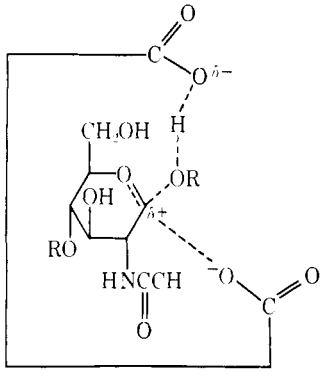
Abstract: The pH-rate constant profile for release of salicylic acid from phthalaldehydic acid methyl salicyl acetal at 15 °C in 50% dioxane-H_2O (v/v) is bell shaped. The salicyl carboxyl group acts as an intramolecular general acid, but electrostatic catalysis by the second carboxyl group does not occur, indicating that the critical transition state is reached before the carbonium ion intermediate is extensively developed. Benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal hydrolyzes with hydronium ion catalysis at the same rate as the corresponding methyl ester and gives a plot of log k_{obsd} vs. pH that shows only a very slight inflection at pH values close to the pK_a of the carboxyl group. Intramolecular general acid catalysis is therefore not a favorable mechanism when the leaving group is an aliphatic alcohol. When there is strong electron withdrawal in the benzaldehyde portion of the molecule, as with the *m*-chloro and *p*-nitro derivatives, then ionization of the cyclohexyl carboxyl group produces large rate enhancements of 100-500-fold. The ρ value for hydronium ion catalyzed hydrolysis of substituted benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal neutral species is −4.15, but in hydrolysis of the corresponding monoanions ρ is −0.95. Thus, the carboxyl group substituent is participating in the reaction but only to a significant extent when the carbonium ion intermediate is destabilized, thereby indicating electrostatic participation. Electrostatic stabilization effects become important only when there is a large amount of bond breaking in the transition state. The pH-rate constant profile for hydrolysis of benzaldehyde di(*cis*-2-carboxycyclohexyl) acetal to benzaldehyde in 50% dioxane-H_2O (v/v) shows hydronium ion catalysis at low pH, but in the pH range 3-7 the profile is bell shaped. The rate enhancement in comparison with the corresponding diethyl ester is 4×10^4. Intramolecular general acid catalysis must be occurring in this system even though the leaving group is an aliphatic alcohol. The requirement for the presence of a second *cis*-2-carboxycyclohexyl group before a large catalysis is observed indicates that the carbonium ion *must* be stabilized electrostatically before intramolecular general acid catalysis is possible when the leaving group is poor. The significance of these results for lysozyme catalysis is discussed.

The complete amino acid sequence of the glycosidic enzyme lysozyme has been determined,[1,2] and the three-dimensional structure of the enzyme has been elucidated by X-ray crystallographic analysis at 2-Å resolution.[3,4] Carboxyl groups from glutamic acid-35 and aspartic acid-52 are located at the active site. A number of mechanisms have been suggested for lysozyme involving general acid catalysis by glutamic acid-35.[5] The mechanism which has received the most attention utilizes general acid catalysis by Glu-35 and electrostatic stabilization of the developing glycosyl carbonium ion by the Asp-52 carboxylate anion (I).[4,5]



General acid catalysis by buffer acids has been observed in the hydrolysis of a number of simple acetals,[6-11] and the structural features in the acetal that will facilitate such catalysis have been determined.[12,13] General acid catalysis is detectable when the leaving group is good (a phenol), basicity of the acetal is low, and a moderately stable carbonium ion is formed as an intermediate.[6,7,11] General acid catalysis will also result when the leaving group is poor (an aliphatic alcohol) if the carbonium ion intermediate is exceedingly stable (an alkoxytropylium ion) or if there is great steric strain in the reactant which is relieved in the transition state.[9,10] In all cases ease of C-O bond breaking is the critical feature.

Intramolecular general acid catalysis by a neighboring carboxyl group will give rise to rate enhancements of 10^5-10^6 in hydrolysis of salicylic acid acetals.[14] Benzaldehyde disalicyl acetal, in which there are two properly positioned carboxyl groups, has a bell-shaped pH-rate constant profile for release of salicylic acid and displays a rate enhancement of 3×10^9 in comparison with hydrolysis of the corresponding dimethyl ester.[15] General acid catalysis by the carboxyl group substituent of phthalaldehydic acid methyl substituted phenyl acetals gives rate enhancements of 10^2-10^3 in comparison with hydrolysis of the respective methyl esters.[16] Intramolecular carboxyl group catalysis has also been suggested in hydrolysis of 2,3-(phenylmethylenedioxy)benzoic acid,[17] 2-carboxyphenyl β-D-glucoside,[18] and 2-methoxymethoxybenzoic acid.[18,19] Thus, intramolecular general acid catalysis by a neighboring carboxyl group has been well established in several systems, but these have been either acetals of salicylic acid or of phthalaldehydic acid where the leaving group is very good. Intramolecular general acid catalysis has never previously been observed in the hydrolysis of acetals or ketals with poor aliphatic alcohol leaving groups even though extensive searches have been made.[20,21] This is a matter of great concern in regard to the mechanism of action of lysozyme because the natural substrates for the enzyme have poor leaving groups. Likewise, it has been unambiguously established that electrostatic stabilization of a developing carbonium ion by a neighboring carboxylate anion is capable of generating significant rate enhancements,[16] but concerted bifunctional catalysis analogous to I has not been conclusively demonstrated. In view of the large effective molarity of a suitably located carboxyl group in acetal hydrolysis,[12-14] intramolecular general acid catalysis might be observable even though the leaving group is poor (an aliphatic alcohol) and the carbonium ion intermediate of moderate stability. In contrast, such a combination of structural features would not permit buffer catalysis in bimolecular reactions. We have therefore studied the hydrolysis reactions of the acetals II-V in the attempt to find (1) intramolecular general acid catalysis with acetals of aliphatic alcohols and (2) concerted intramolecular participation by two suitably placed carboxyl groups. The steric alignment in these *cis*-2-carboxycyclohexanol derivatives is excellent for possible proton

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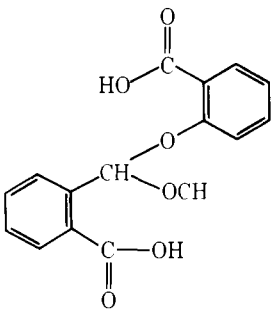
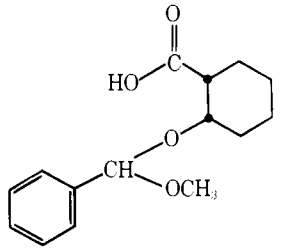


II



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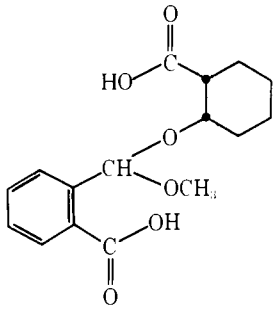

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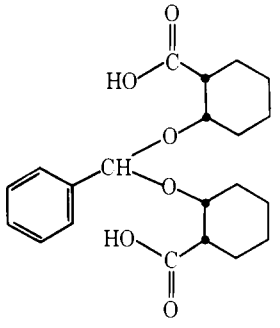
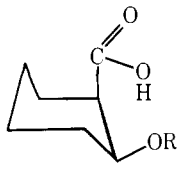


V

transfer to the leaving group oxygen (VI). There is no doubt



VI

that carboxyl group participation is occurring in hydrolysis of V.

Experimental Section

Materials. 2-Carbethoxycyclohexanone (K&K) was converted to 2-carbethoxycyclohexanol by reduction in absolute ethanol with platinum oxide as the catalyst according to the procedure of Smissman and Mode.[22] The alcohol distilled at 96–103 °C at 4.0 mm. Employing this method, Smissman and Mode[22] reported an 87% yield of *cis*-2-carbethoxycyclohexanol. The NMR spectrum (Varian EM-360) of the fraction distilling at 96–98 °C (4 mm) was compared to those of the pure cis and trans isomers as reported by Mori et al.[23] Integration of the spectrum revealed that this fraction contained 85–90% cis isomer, while the fraction distilling at 98–103 °C contained approximately 70% cis isomer. Only the lower boiling fraction was used in the synthesis of the mixed acetals. The *cis*-2-carbethoxycyclohexanol was converted to its sodium salt by dissolving a 5% excess of the alcohol and sodium methoxide in methanol and boiling off the methanol at atmospheric pressure. This process not only formed the sodium salt of the alcohol but converted the ethyl ester to a methyl ester. In order to determine whether epimerization occurred during this reaction, a sample of the sodium salt was acidified with 5 M HCl in methanol; the re-formed alcohol distilled at 70 °C (0.8 mm). The NMR spectrum of the 2-carbomethoxyclohexanol was compared with that of the ethyl ester in $CDCl_3$ with Me_4Si as an internal standard (δ 0 ppm). Mori[23] has shown that the resonance of the hydrogen attached to the 1 carbon of 2-carbethoxycyclohexanol occurs at δ 4.1 for the cis isomer and at δ 3.7 for the trans isomer and uses this difference as a means of distinguishing them. The spectrum of the methyl ester alcohol had a proton resonance at δ 4.1 and none at δ 3.7. Since these peaks are not expected to vary as the ester group is changed from ethyl to methyl it is apparent that epimerization does not take place in the reaction with sodium methoxide. USP methyl salicylate (Baker) was used without further purification.

The mixed acetals were prepared by a procedure described previously[16] but with some modifications. The various α-chlorobenzyl methyl ethers were synthesized as before. The freshly distilled chloro ether was quickly placed in a bent addition flask connected to a vacuum line. The air in the flask was evacuated, and the stopcock connecting the flask to the vacuum line was closed. At this point, two more flasks were connected to the vacuum line. One bent addition flask contained *N,N*-dimethylformamide, the reaction solvent. The central receiving flask contained the sodium salt of methyl salicylate or *cis*-2-carbomethoxycyclohexanol. When the two flasks had been pumped on the vacuum line for several minutes to remove traces of alcohol and water vapor, the bent flask containing the DMF was rotated so the solvent flowed into the flask containing the sodium salt. The stopcock connecting the chloro ether to the line was then opened and the flask was rotated until the chloro ether flowed into the reaction mixture. The mixture was allowed to stand for 20 min, and the postreaction procedure was as previously described.[16]

2-Carbomethoxybenzaldehyde 2-carbomethoxyphenyl methyl acetal had bp 130 °C (0.005 mm), n^{25}_D 1.5140. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.38; H, 5.50.

Benzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal had bp 112 °C (0.01 mm), n^{25}_D 1.5040. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.07; H, 7.91. Found: C, 68.89; H, 7.81.

4-Methoxybenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal had bp 127 °C (0.005 mm), n^{24}_D 1.5096. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.23; H, 7.79. Found: C, 65.53; H, 7.61.

3-Chlorobenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal had bp 115 °C (0.02 mm), n^{24}_D 1.5143. Anal. Calcd for $C_{16}H_{21}O_4Cl$: C, 61.44; H, 6.72; Cl, 11.33. Found: C, 61.30; H, 6.60; Cl, 11.30.

4-Nitrobenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal had bp 160 °C (0.05 mm), n^{25}_D 1.5236. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.44; H, 6.50; N, 4.33. Found: C, 59.00; H, 6.70; N, 4.17.

2-Carbomethoxybenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal had bp 133 °C (0.008 mm), n^{24}_D 1.5088. Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.28; H, 7.14. Found: C, 63.78; H, 7.20.

4-Carbomethoxybenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal had bp 145 °C (0.005 mm), n^{24}_D 1.5108. Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.28; H, 7.14. Found: C, 64.23; H, 7.22

The symmetrical dicyclohexyl acetal V was prepared by acetal interchange. A four- or fivefold excess of *cis*-2-carbethoxycyclohexanol was mixed with benzaldehyde dimethyl acetal and a few drops of concentrated HCl. The mixture was heated until the required amount of methanol distilled off and was then purified by vacuum distillation.

Benzaldehyde di(*cis*-2-carbethoxycyclohexyl) acetal had bp 175 °C (0.02 mm), n^{25}_D 1.5058. Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.44; H, 8.33. Found: C, 69.67; H, 8.09.

The acetal esters were converted to their carboxylate salts by hydrolysis in NaOH–EtOH solution. These salts were not isolated but used in situ. In most studies, 0.1 mL of a solution that was $2\text{–}4 \times 10^{-2}$ M in acetal ester in EtOH was mixed with 0.1 mL of 2 M NaOH in 80/20 (v/v) EtOH/H_2O and allowed to stand overnight. With phthalaldehydic acid methyl salicyl acetal, the solution was used after 3 h. The dioxane employed was spectral grade (Mallinckrodt) and was refluxed over sodium borohydride for 3 h and distilled prior to use.

Kinetic Measurements. The rates of hydrolysis of the acetals were measured on a Gilford Model 2000, Beckman Model 25, or Durrum D 110 stopped-flow spectrophotometer. The rate of appearance of aldehyde from the cyclohexyl acetals was monitored at the following wavelengths: 250 (III, III′, and V),[24] 255 (IV′), 255 (*p*-carboxybenzaldehyde acetals), 260 (*p*-nitrobenzaldehyde acetals), 250 (*m*-chlorobenzaldehyde acetals), and 285 nm (*p*-methoxybenzaldehyde acetals). In all cases, the UV spectrum of the product solution was identical with that of the product aldehyde and alcohol at the same concentration and conditions. Reactions of IV did not give aldehyde as a product; consequently, appearance of acylal was followed at 285 nm. Reaction of the salicyl acetal (II) was followed by observing salicylic acid release at 310 nm. In a typical experiment where the reactant half-life was 10 s or greater, 10–20 μL of the acetal ester or acetal acid stock solution was injected into 2–3 mL of reactant solution maintained at the desired temperature.

Reactions having half-lives of 5 s or less were monitored with the stopped-flow spectrophotometer. The acetal acid in approximately 0.002 M NaOH solution was placed in one drive syringe, while the other contained the appropriate buffer solution. Good first-order kinetics were obtained for at least 3 half-lives. Kinetic parameters for these and all the other reactions were evaluated using a nonlinear least-squares computer program.

Significant buffer catalysis was not observed in the hydrolysis of

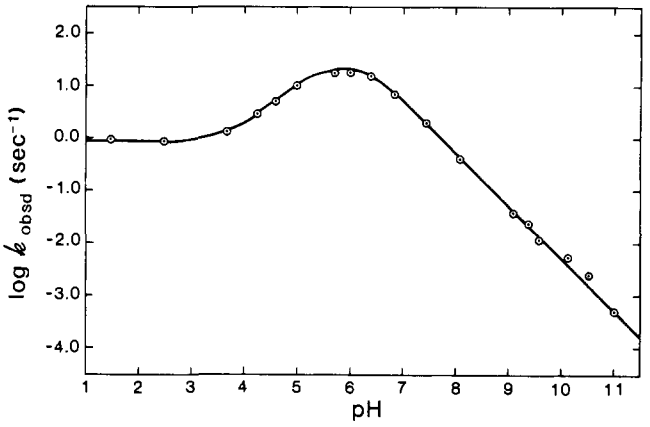


Figure 1. A plot of log k_{obsd} vs. pH for release of salicylic acid from phthalaldehydic acid methyl salicyl acetal (II) in 50% dioxane/H_2O (v/v) at 15 °C (μ = 0.1 with KCl).

Table I. Titrimetrically Determined pK_a Values in 50% Dioxane/H_2O (v/v) at 30 °C (μ = 0.1)

compd	pK_1	pK_2
benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	6.94	
p-methoxybenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	6.82	
m-chlorobenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	6.67	
o-carboxybenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	5.43	6.67
p-carboxybenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	5.38	6.63

any of the acetal acids. Therefore, in rate measurements requiring a buffered solution a 0.02 M concentration of buffer was routinely employed. Reaction solution pH values were measured with a Beckman Model 3500 digital pH meter standardized with Mallinckrodt standard buffer solutions.

Titrimetric Determination of pK_a values. The dissociation constants of the acetal acids were measured at 30 °C, μ = 0.1 M, in 50/50 (v/v) dioxane/water using a Radiometer Type SBR2c/TTT1c titration assembly previously described.[25] Titration curves were evaluated using a nonlinear least-squares computer program. The titrimetrically determined pK_a values are reported in Table I.

Product Characterization. It has previously been shown that the reaction product of phthalaldehydic acid methyl phenyl acetals is 3-methoxyphthalide.[16] In order to determine the hydrolysis product of IV, a 0.9-g sample of this compound was hydrolyzed at 50 °C at pH 6.0 in 50 mL of 50% dioxane/water (v/v). The product solution was extracted with several portions of hexane, and the extracts were dried with sodium sulfate and concentrated on a rotary evaporator. The infrared spectrum of the extract had a strong carbonyl absorption at 5.6 μ (indicative of a lactone) and qualitatively resembled the spectrum of 3-methoxyphthalide. However, there was a second carbonyl absorption at 5.9 μ and a broad hydroxyl peak at 3.0–3.5 μ due to 2-carboxycyclohexanol.

Results

In Figure 1 is shown a plot of log k_{obsd} vs. pH for release of salicylic acid from phthalaldehydic acid methyl salicyl acetal (II) in 50% dioxane/H_2O (v/v) at 15 °C (μ = 0.1). The plot is bell shaped with the data giving a good fit to eq 1 or the equivalent eq 2:

$$k_{obsd} = \frac{k_1K_1a_H^2 + k_2K_2K_1a_H}{a_H^2 + K_1a_H + K_2K_1} \quad (1)$$

$$k_{obsd} = \frac{k_{H_2A}a_H^2 + k_{H_1A}K_1a_H}{a_H^2 + K_1a_H + K_2K_1} \quad (2)$$

k_1 is the second-order rate constant for hydronium ion catalyzed reaction of the monoanionic species, k_2 is the second-order rate constant for hydronium ion catalyzed reaction of the dianionic species, k_{H_2A} and k_{H_1A} are the rate constants for intramolecular general acid catalysis by an un-ionized carboxyl group in the neutral and monoanionic species, respectively, and K_1 and K_2 are the first and second acid dissociation constants. The values of the constants are given in Table II. The second product of the reaction is 3-methoxyphthalide.

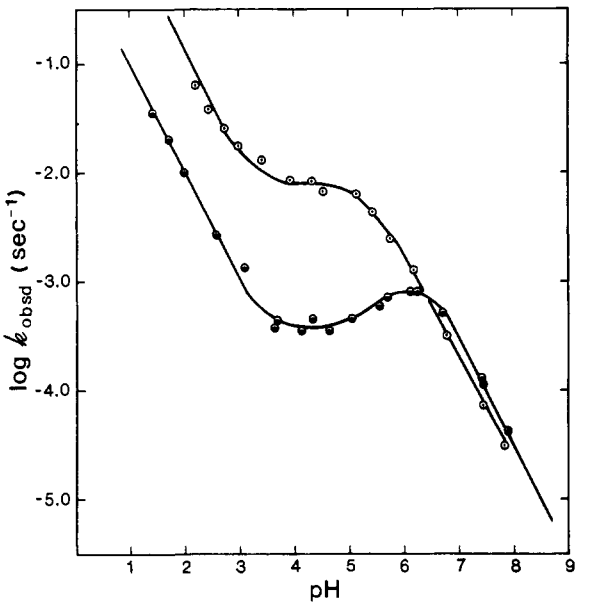


Figure 2. Plots of log k_{obsd} vs. pH for reaction of phthalaldehydic acid *cis*-2-carboxycyclohexyl methyl acetal IV (⊙) and terephthalaldehydic acid *cis*-2-carboxycyclohexyl methyl acetal (◒) in 50% dioxane/H_2O at 50 °C (μ = 0.1 with KCl).

Plots of log k_{obsd} vs. pH for reaction of phthalaldehydic acid *cis*-2-carboxycyclohexyl methyl acetal (IV) and terephthalaldehydic acid *cis*-2-carboxycyclohexyl methyl acetal in 50% dioxane/H_2O at 50 °C are shown in Figure 2. In contrast with II hydronium ion catalysis of the reaction of the neutral species is now observed necessitating an additional term (k_H) in the rate equation (eq 3). The values of k_{obsd} are closely similar for the two compounds at pH values >7.

$$k_{obsd} = \frac{k_Ha_H^3 + k_1K_1a_H^2 + k_2K_2K_1a_H}{a_H^2 + K_1a_H + K_2K_1} \quad (3)$$

Figure 3 shows a plot of log k_{obsd} vs. pH for hydrolysis of benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal (III) to benzaldehyde in 50% dioxane/H_2O (v/v) at 50 °C with μ = 0.1 (KCl). The rate constants for compound III should follow the equation

$$k_{obsd} = k_Ha_H\left[\frac{a_H}{K_a + a_H}\right] + k_1a_H\left[\frac{K_a}{K_a + a_H}\right] \quad (4)$$

for hydrolysis of an acetal with one carboxyl group substituent where K_a is the dissociation constant for the carboxyl group. The lack of a significant inflection in the profile at pH values near the pK_a shows that k_H and k_1 have similar values. The point at pH 7.46 deviates from the best fit line by 46% indicating a small rate-enhancing effect (less than a factor of 2) of ionization of the carboxyl group. The pH–log rate constant profile for the corresponding *p*-methoxy-substituted compound is also a straight line with a slope of −1.0 at all pH values. Also included in Figure 3 are plots of log k_{obsd} vs. pH for hydrolysis of *m*-chlorobenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal and *p*-nitrobenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal. With these compounds, where there is strong electron withdrawal in the aldehyde portion of the molecule,

Table II. Rate Constants for Reaction of Carboxyl Substituted Acetals in 50% Dioxane/H_2O (v/v), μ = 0.1 (with KCl), and Kinetically Determined pK_a Values

compd	temp, °C	k_H, $M^{-1}s^{-1}$	k_1, $M^{-1}s^{-1}$	k_2, $M^{-1}s^{-1}$	pK_1	pK_2
benzaldehyde methyl salicyl acetal	30		2.94×10^7[a]			
	30		5.55×10^7			
	25		1.2×10^7[a,b]			
o-carboxybenzaldehyde methyl salicyl acetal	30			8.86×10^6[a]		
	30			1.68×10^8		
	15		3.12×10^5	5.44×10^7	5.56	6.08
benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	30	16.6				
	50	99.4	<200			
p-methoxybenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	30	396	396			
	50	1840	1840			
m-chlorobenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	50	2.19	177		6.75	
p-nitrobenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	50	0.063	36.5		6.75[c]	
o-carboxybenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	30	1.00	308	308	5.56	
	50	9.35	2160	2160	5.42	
p-carboxybenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal	50	1.00	78.2	3410	5.83	6.67
benzaldehyde di(*cis*-2-carboxycyclohexyl) acetal	30	50[a]		3.04×10^4[a]		
	50	23.2	1380	3.48×10^5	5.85	7.65

[a] Determined in H_2O. [b] Reference 14. [c] Assumed value to fit the data.

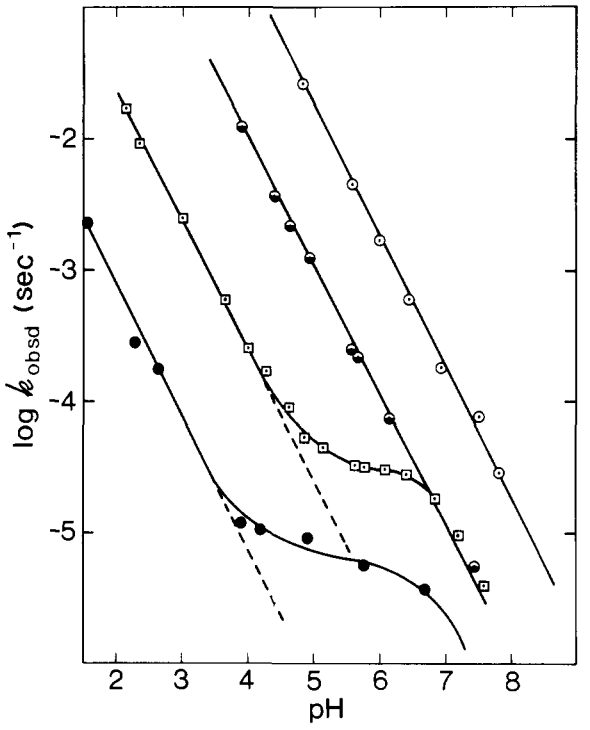


Figure 3. Plots of log k_{obsd} vs. pH for hydrolysis of *p*-methoxybenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal (⊙), benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal III (◒), *m*-chlorobenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal (⊡), and *p*-nitrobenzaldehyde *cis*-2-carboxycyclohexyl methyl acetal (●) in 50% dioxane/H_2O at 50 °C (μ = 0.1 with KCl).

k_1 is much larger than k_H. Plots of log k_H and k_1 for hydrolysis of the substituted benzaldehyde *cis*-2-carboxycyclohexyl acetals at 50 °C vs. σ, the Hammett substituent constant, are

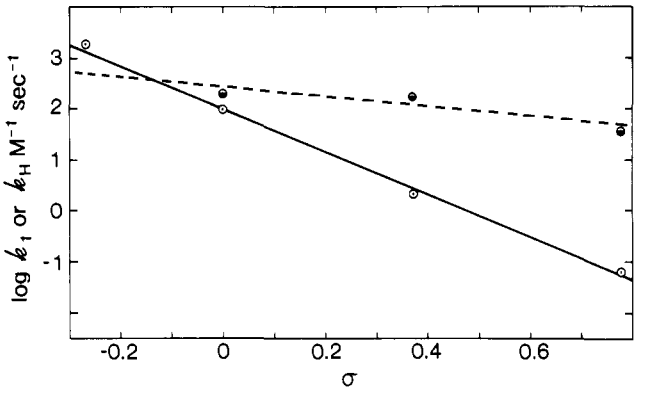


Figure 4. Plots of log k_H and log k_1 for hydrolysis of substituted benzaldehyde *cis*-2-carboxycyclohexyl methyl acetals in 50% dioxane/H_2O at 50 °C (μ = 0.1 with KCl) vs. σ, the Hammett substituent constant. The point for III in the log k_1 plot is an upper limit.

shown in Figure 4. The values of ρ are −4.15 for k_H and −0.95 for k_1. Rate constants for hydrolysis of the carboxyl substituted acetals are given in Table II. The kinetically determined pK_a values in Table II match closely the values in Table I which were obtained titrimetrically.

A plot of log k_{obsd} vs. pH for hydrolysis of benzaldehyde di(*cis*-2-carboxycyclohexyl) acetal (V) to benzaldehyde in 50% dioxane/H_2O (v/v) at 50 °C with μ = 0.1 (KCl) is presented in Figure 5. The profile for hydrolysis of V is bell shaped, the data giving a good fit to eq 3 or the equivalent equation

$$k_{obsd} = \frac{k_H a_H^3 + k_{H_2A} a_H^2 + k_{H_1A} K_1 a_H}{a_H^2 + K_1 a_H + K_2 K_1} \quad (5)$$

for intramolecular general acid catalysis. Note that the following kinetic equivalences hold:

$$k_{H_2A} = k_1 K_1$$
$$k_{H_1A} = k_2 K_2 \quad (6)$$

Table III. Rate Constants for Hydrolysis of Acetal Esters in 50% Dioxane/H_2O (v/v) at 30 °C, μ = 0.1 (with KCl)

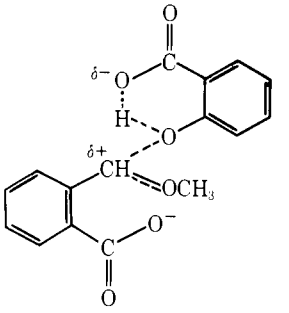
compd	k_H, M^{-1} s^{-1}	$k_0 \times 10^3$, s^{-1}
benzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal	17.1	
p-methoxybenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal	192	
m-chlorobenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal	0.096	
p-nitrobenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal	0.0040	
p-carbomethoxybenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal	0.070	
o-carbomethoxybenzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetal	0.355	
benzaldehyde methyl methyl salicyl acetal	103	1.58
2-carbomethoxybenzaldehyde methyl methyl salicyl acetal	16.2	0.040
benzaldehyde di(*cis*-2-carbethoxy)cyclohexyl acetal	1.17	
	7.6[a]	

[a] 50 °C.

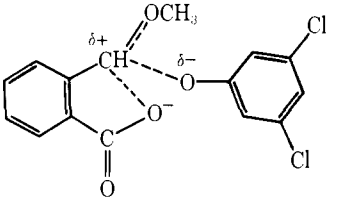
In Table III are presented the second-order rate constants k_H for hydronium ion catalyzed hydrolysis at 30 °C in 50% dioxane/H_2O of the acetal esters. A pH-independent reaction was also observed with benzaldehyde methyl methyl salicyl acetal and *o*-carbomethoxybenzaldehyde methyl methyl salicyl acetal for which rate constants (k_0) are given. A plot of log k_H for hydrolysis of the substituted benzaldehyde *cis*-2-carbomethoxycyclohexyl methyl acetals vs. σ was linear with a slope ρ of −4.6.

Discussion

The pH–rate constant profile for release of salicylic acid from phthalaldehydic acid methyl salicyl acetal (II) is bell shaped (Figure 1) similar to that for benzaldehyde disalicyl acetal.[15] In view of the magnitude of the rate constants (Table II) there is little doubt that the salicyl carboxyl is participating in the reaction as an intramolecular general acid (VII) analogous to the other salicyl acetals that have been investigated where such participation has been well established.[14,15] The enhancement in k_{obsd} is 4×10^5 in comparison with the corresponding dimethyl ester and 10^4 in comparison with benzaldehyde methyl methyl salicyl acetal. The product of the reaction is 3-methoxyphthalide, but that conveys no mechanistic information; an acylal could result from nucleophilic carboxyl group attack in the rate-determining step or from carbonium ion capture after the rate-determining step. The magnitude of the rate constant k_2 (10^8 M^{-1} s^{-1}) is within a factor of 3 of k_1 for hydrolysis of benzaldehyde methyl salicyl acetal.[14] Since the electronic effect of an ortho carboxylate ion should be small ($\sigma \sim 0$ to −0.1), it is apparent that the phthalaldehydic acid carboxyl group is not participating. It has been shown that a neighboring phthalaldehydic acid carboxylate anion can enhance the rate of acetal hydrolysis by electrostatically stabilizing the developing carbonium ion (VIII),[16] but such an effect was found only in the pH-independent unimolecular decomposition where extensive bond breaking is required to attain the transition state and, as a consequence, the carbonium ion is well developed in the transition state.



VII

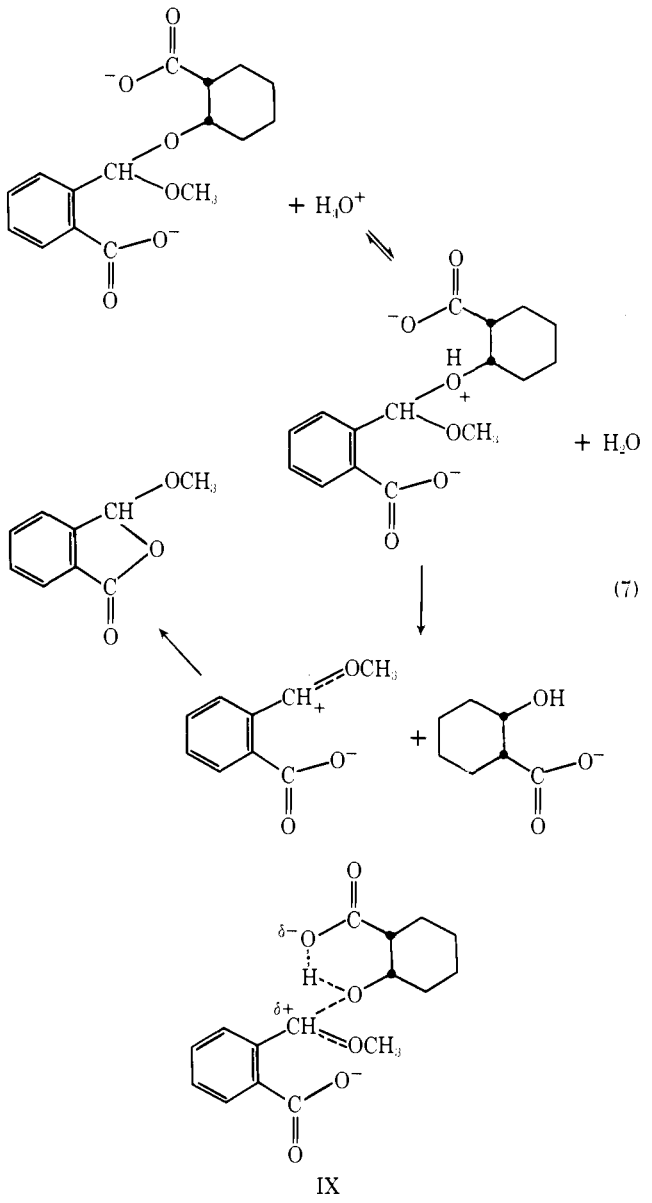


VIII

The lack of participation by the phthalaldehydic acid carboxyl group in reaction of II is very likely due to the critical transition state being reached before the carbonium ion is sufficiently developed for electrostatic stabilization to be effective, This illustrates the central problem with bifunctional mechanisms such as I for the lysozyme reaction, which is that the structural features that will promote general acid catalysis and electrostatic stabilization are in opposition. The occurrence of intramolecular general acid catalysis is dependent upon an easily broken C–O bond, resulting in a transition state with little bond breaking. However, for electrostatic stabilization effects to be significant the C–O bond must be appreciably broken. Thus, for both mechanistic features to occur simultaneously, there must be a precise balancing of effects which is reflected in the amount of bond breaking in the transition state.

The rate of hydrolysis of benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal (III) is nearly identical with that of the corresponding methyl ester. Furthermore, a significant inflection is not observed in the pH–rate constant profile at pH values close to the pK_a of the carboxyl group. Therefore, the carboxyl group of III is not participating in the hydrolysis reaction. This shows that the cyclohexanol leaving group is not sufficiently good for intramolecular general acid catalysis to occur in spite of the facts that (1) the intermediate carbonium ion is reasonably well stabilized, (2) the steric situation is quite favorable for proton transfer from the carboxyl group to the leaving group, and (3) from previous studies of intramolecular general acid catalysis of acetal hydrolysis it has been established that the effective molarity of a neighboring carboxyl group can be 10^4 M or greater.[12-15]

The values of k_{obsd} at high pH are comparable for III and phthalaldehydic acid *cis*-2-carboxycyclohexyl methyl acetal (IV) as seen in Figures 2 and 3. Furthermore, the magnitude of k_2 for IV is similar to that for the para-carboxyl substituted compound. It can be concluded that the aromatic carboxylate anion of IV is not facilitating the rate of the reaction. Thus, the reaction at high pH may involve hydronium ion catalyzed hydrolysis of the dianionic species (eq 7). Intramolecular general acid catalysis in the monoanion reaction which is unassisted by the ortho carboxyl group (IX) is unlikely in view of the lack of carboxyl group participation in hydrolysis of III. The principal product of the reaction is 3-methoxyphthalide

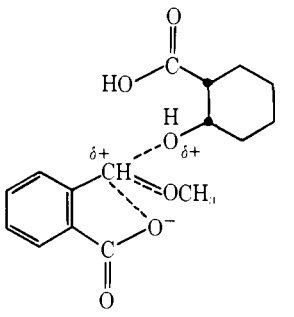


(7)

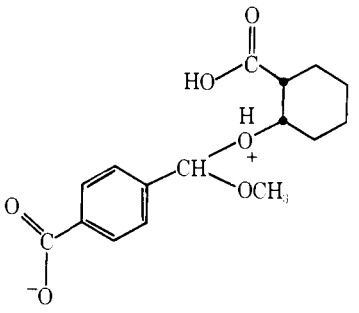
IX

as indicated by the IR and UV spectra of the isolated product, and this must result from carbonium ion capture by the neighboring carboxyl after the rate-determining step.

At lower pH (3–6) IV reacts 10–30 times faster than the para derivative. The hydronium ion catalyzed reaction of the neutral species of IV at low pH is also tenfold faster, which may be due to favorable steric factors. Ortho substituents have previously been found to exert a small steric acceleration on the rates of hydrolysis of substituted phenyl glycosides[26] and methyl phenyl acetals of formaldehyde.[19] However, at high pH steric effects by the ortho carboxylate anion are absent in reaction of IV. Therefore, the moderate rate facilitation by the ortho substituent of IV in the pH range 3–6 could indicate weak carboxyl group participation (X) in the neutral species reaction. Such a reaction involving electrostatic stabilization effects by the aromatic carboxyl is not possible in the case of the para-substituted compound. A less favored neutral species reaction (hydronium ion catalyzed hydrolysis of the monoanion) for the para-substituted compound would lead to the observed bell-shaped pH–rate constant profile. The bell-shaped profile of the para derivative in the pH range 4–7 could also partially represent a rate-retarding effect of solvent (50% dioxane/H_2O) on the neutral species reaction, since the reaction must involve hydronium ion catalysis of the hydrolysis of a monoanionic species, i.e., a zwitterion such as XI must be



X



XI

formed. A zwitterion would be poorly solvated in a solvent of low dielectric constant.[27] The profile for reaction of IV shows a plateau at pH 3–6 which therefore may result from a neutral species reaction such as X in which the transition state would be better solvated than a zwitterion intermediate.

The lack of significant intramolecular general acid catalysis in the reactions of III and IV must be a consequence of the aliphatic alcohol leaving group. With such a poor leaving group the bond-breaking process must be of such difficulty that complete transfer of a proton to the leaving group is required before the transition state can be attained. However, the oxocarbonium ion intermediate is moderately well stabilized, and with a fully protonated leaving group the amount of bond breaking at the transition state will not be extensive. Therefore, electrostatic stabilization of the developing carbonium ion is also not an effective mechanism. Mechanisms for acetal hydrolysis involving carboxyl group participation show great sensitivity to carbonium ion stabilization effects and the nature of the leaving group.[12,13,16] This sensitivity is illustrated nicely by the fact that the structural features of IV do not permit a large enhancement of the rate of the reaction by either carboxyl group.

Strong electron withdrawal in substituted benzaldehyde *cis*-2-carboxycyclohexyl methyl acetals leads to a large enhancement of the rate of hydrolysis at pH values where the carboxyl group is ionizing. This is reflected in the Hammett $\sigma\rho$ plots of Figure 4. The ρ value for the reaction governed by k_H is -4.15, which is close to the value of -3.35 found for hydronium ion catalyzed hydrolysis of substituted benzaldehyde diethyl acetals.[28] A similar large influence of electron withdrawal in the aldehyde is observed in the hydronium ion catalyzed hydrolysis of the methyl esters of the substituted benzaldehyde *cis*-2-carboxycyclohexyl methyl acetals ($\rho = -4.6$). However, the ρ associated with k_1 (-0.95) is much more positive, and in fact the plot shows upward curvature possibly signifying a change in mechanism. In the case of the *p*-nitro derivative k_1 is 580-fold greater than k_H, whereas with the *p*-methoxy substituted acetal k_1 and k_H are identical. An electron-withdrawing group in the meta or para position will reduce the rate by (1) destabilizing the carbonium ion intermediate, (2) decreasing the ease of C–O bond breaking, and (3) reducing basicity. Thus, one or more of the above effects must be overcome in the reaction governed by k_1 at high pH

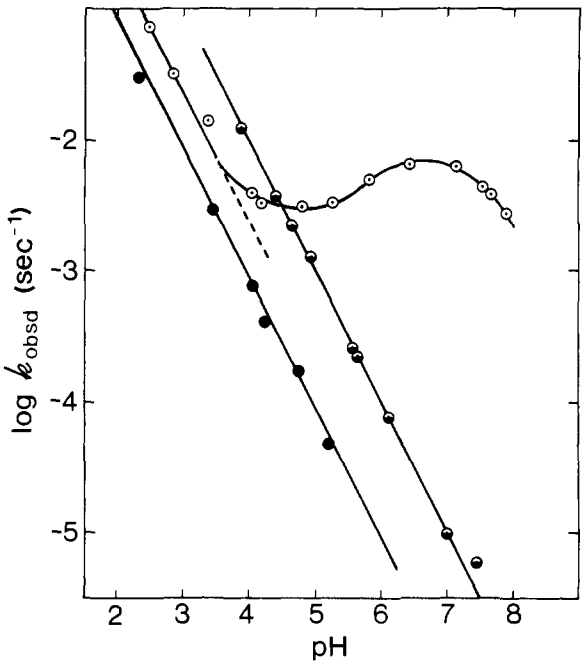
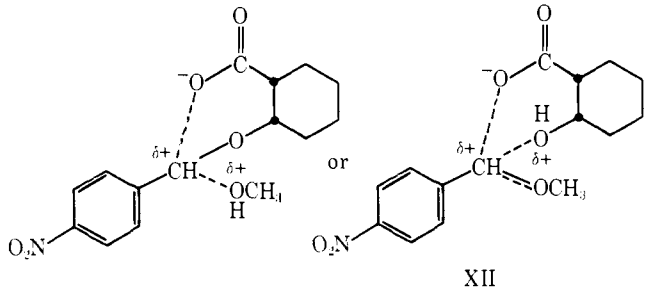


Figure 5. Plot of log k_{obsd} vs. pH for hydrolysis of benzaldehyde di(*cis*-2-carboxycyclohexyl) acetal (⊙) in 50% dioxane/H_2O at 50 °C (μ = 0.1 with KCl). Also included for comparison purposes are plots of log k_{obsd} vs. pH for hydrolysis of III (◒) and benzaldehyde di(*cis*-2-carbethoxycyclohexyl) acetal (●) under the same reaction conditions.

(hydronium ion catalyzed hydrolysis of the monoanionic species or a kinetic equivalent). Electron withdrawal will destabilize the carbonium ion intermediate and will therefore make general acid catalysis less likely,[12,13] On the other hand, destabilization of the carbonium ion intermediate will necessitate a transition state with relatively more bond breaking and, as a consequence, a better opportunity for a suitably placed carboxyl group to function as an electrostatic catalyst. Thus, the neighboring carboxyl group must be participating electrostatically as depicted in XII. Since the aldehyde is the

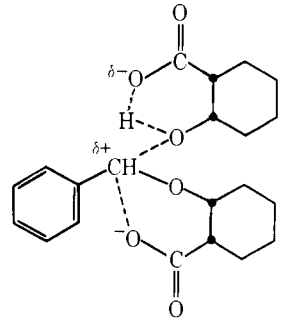


XII

product, if an acylal intermediate is formed it must be unstable under the reaction conditions. If the hydrolysis of 3-*O*-β-D-glucopyranosyl-L-gulonic acid and alginate[21] provides examples of intramolecular catalysis, then the mechanism probably also involves carboxylate ion electrostatic stabilization effects. Glycosides have strongly electron-withdrawing groups in the aldehyde portion of the molecule and are therefore analogous in that respect to the *m*-Cl and *p*-NO_2 derivatives of III.

Benzaldehyde Di(*cis*-2-carboxycyclohexyl) Acetal. The symmetrical dicarboxyl substituted acetal (V) hydrolyzes to benzaldehyde with hydronium ion catalysis at low pH and has a bell-shaped pH–rate constant profile in the pH range 4–7 showing the monoanionic species to be maximally reactive. The rate enhancement in comparison with the diethyl ester is 4 × 10^4, which demonstrates convincingly that carboxyl group participation is occurring. In Figure 5 it can be seen that at pH 7.5 k_{obsd} for hydrolysis of V is 10^3 greater than that for III. The comparison of V with the diethyl ester is, of course, not exact since electronic effects of carbethoxy and carboxyl will be slightly different. However, electronic effects in the leaving group are small in acetal hydrolysis with ρ values from −0.5 to −0.9.[6,16,26] Note that III and its methyl ester III′ hydrolyze at nearly the same rate. The value of k_2 for hydrolysis of V is also ~10^3 larger than k_H for hydrolysis of benzaldehyde dicyclohexyl acetal.[29] Thus, carboxyl group participation takes place in hydrolysis of V, and both carboxyl groups must contribute to the rate constant of the monoanion species.

General acid catalysis by buffer acids is not observed in the hydrolysis of benzaldehyde diethyl acetal;[28] therefore the Brønsted coefficient α must be greater than 0.9[30] and is probably close to 1.0 even though the ethoxybenzyl carbonium ion intermediate is moderately well stabilized. As discussed above, the lack of intramolecular general acid catalysis in the hydrolysis of benzaldehyde *cis*-2-carboxycyclohexyl methyl acetal (III) must reflect the difficulty of the bond-breaking process with an aliphatic alcohol leaving group. The neighboring carboxyl group participation that is found in hydrolysis of benzaldehyde di(*cis*-2-carboxycyclohexyl) acetal must then be a consequence of the presence of the second carboxyl group. Electrostatic stabilization of the intermediate carbonium ion would enhance the ease of C–O bond breaking and thereby lower the Brønsted α sufficiently for intramolecular general acid catalysis to occur (XIII). Steric strain in the reactant



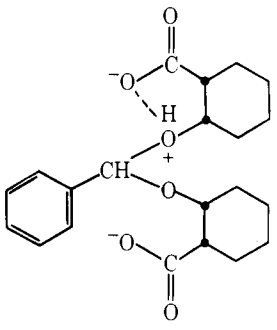
XIII

might also lead to intramolecular general acid catalysis. A Stuart-Briegleb model shows that such strain cannot be pronounced, but it will be noted that benzaldehyde dicyclohexyl acetal hydrolyzes with a second-order rate constant k_H tenfold greater than that for hydrolysis of the corresponding dimethyl acetal.[29] The amount of bond breaking required in the transition state of a general-acid-catalyzed reaction will be greater than in the corresponding hydronium ion catalyzed reaction, and accordingly electrostatic effects can then be relatively more important, The electrostatic stabilization effects in the reactions of *m*-Cl and *p*-NO_2 substituted benzaldehyde *cis*-2-carboxycyclohexyl acetals show the feasibility of that feature in mechanism XIII. There must be a precise balancing of effects influencing the amount of bond breaking required to attain the transition state XIII, and it would be expected that examples of such a mechanism will be rare. Resonance stabilization of the carbonium ion intermediate differs considerably with IV and V, thereby explaining the lack of carboxyl group participation in reactions of IV. Neither carboxyl group of IV participates significantly, but with V it is probable that intramolecular general acid catalysis by one carboxyl group is made possible by the electrostatic stabilization effects of the other.

In comparison with hydrolysis of the respective diethyl ester the rate enhancement in hydrolysis of V is a factor of 4 × 10^4 In contrast, the rate enhancement in the case of benzaldehyde

disalicyl acetal[15] is 3×10^9. In both cases the steric situation is quite favorable for internal proton transfer. Thus, the rate enhancement is highly dependent upon the nature of the leaving group. When the leaving group is an aliphatic alcohol and C–O bond breaking is relatively difficult, proton transfer must be nearly complete in the transition state. Thus, even in a case where the carbonium ion is electrostatically stabilized by a second functional group, the rate enhancement in comparison with hydronium ion catalyzed hydrolysis of the reference acetal should be considerably smaller than when the leaving group is phenolic, i.e., the Brønsted α for general acid catalysis will be larger when the leaving group is poorer.

Mechanism XIII has been shown as a concerted process in which C–O bond breaking and proton transfer occur simultaneously. Bimolecular general acid catalysis in acetal hydrolysis proceeds by a concerted process in view of Brønsted coefficients in the range 0.5–0.7.[7,9,11,31] It is reasonable that this is also the case in intramolecular reactions. In the hydrolysis of benzaldehyde methyl salicyl acetal[14] and *o*-carboxybenzaldehyde methyl salicyl acetal (II) proton transfer is only partial in the transition state since any mechanism involving a conjugate acid intermediate (A-1) can be ruled out. Complete proton transfer to the leaving group would demand that the rate constant for transfer of a proton from the conjugate acid to H_2O would necessarily be much greater than a rate constant for a diffusion-controlled reaction, i.e., $>10^{10}$ M^{-1} s^{-1}. However, in reactions of V formation of a conjugate acid intermediate cannot be rigorously excluded if the dissociation constant of the conjugate acid is less than 10^6 M. Catalysis could then conceivably result from carboxylate ion stabilization of a proton on the leaving group (XIV), thereby lowering the



XIV

dissociation constant of the conjugate acid. Such a mechanism was suggested by Dunn and Bruice[19] to explain the rate enhancements (less than 10^3) found in hydrolysis of methoxymethoxybenzoic acid[18] where the intermediate carbonium ion is quite unstable. However, if mechanism XIV were occurring then it would be expected that marked carboxyl group participation would also occur with III and IV, but that is contrary to the experimental evidence. Therefore, it is preferable to regard the mechanism as concerted, although proton transfer must be well advanced in the transition state.

Phenolic acetals have very low basicity ($pK_a \sim -9$), but this does not appear to be an important factor in the concerted general-acid-catalyzed reactions of unsymmetrical phenolic acetals.[12,13,32] With acetals having a good leaving group and generating a moderately stable carbonium ion it is possible that a conjugate acid intermediate cannot exist. This would be the case if the rate constant for breakdown of such a species were $>10^{13}$ s^{-1}. The C–O bond would then begin to break before proton transfer is complete. Acetals of aliphatic alcohols have considerably greater basicity than phenolic acetals (the pK_a values should be at least 3 pK_a units more positive),[33] and the classical A-1 mechanism for hydrolysis of such acetals involves rate-determining breakdown of a conjugate acid intermediate.[6] With a symmetrical aliphatic acetal reduced basicity of the alcohol will result in a relatively better leaving group, but the second alkoxy group will not stabilize the carbonium ion as well as a group of higher basicity. Effects of basicity of the alcohol on ease of bond breaking will then tend to cancel. The principal effect of basicity will therefore be on the stability of the conjugate acid. The lower this stability the more likely will be a reaction in which bond breaking and proton transfer are concerted. The proposal put forth by Jencks[34] to explain concertedness might then be applicable since basicity of the reactant and product would be widely separated with basicity of the transition state of a concerted reaction intermediate between these extremes. Thus, an unfavorable proton transfer to the reactant would be converted to a favorable proton transfer in the transition state. While basicity is not an important factor in leading to the concerted reactions of unsymmetrical phenolic acetals because of the great ease of bond breaking, it could be of considerable importance in reactions of symmetrical aliphatic acetals. Nevertheless, carbonium ion stabilization from the aldehyde portion of the molecule and electrostatic effects by a neighboring carboxyl group must be of critical significance.

Lysozyme. General acid catalysis only occurs in the hydrolysis of simple acetals when the bond-breaking process is very facile.[12,13] However, in reactions catalyzed by lysozyme, the natural substrates possess poor leaving groups and give rise to carbonium ion intermediates that are quite unstable. As a consequence, for Glu-35 to function as an intracomplex general acid, the enzyme must in some manner make bond breaking easier. This could occur through electrostatic stabilization of the developing carbonium ion by Asp-52 as in I, and by relief of strain in the hexose residue bound in subsite **D**. Carboxylate ion stabilization of a developing carbonium ion is capable of giving rise to rate enhancements of 100–500-fold in favorable situations where extensive bond breaking must occur to attain the transition state. Significant carboxyl group participation does not occur in hydrolysis of III, but the additional carbonium ion stabilization provided by the second carboxyl group of V will allow intramolecular general acid catalysis when the leaving group is poor. However, the rate enhancement in comparison with hydrolysis of the diethyl ester is only 10^4. Thus, in order to obtain a *large* rate enhancement (of the magnitude obtained in enzymatic reactions) in intramolecular reactions of acetals or glycosides with poor leaving groups and which give rise to unstable carbonium ions, an additional factor such as relief of reactant strain appears to be a necessity. Distortion of the substrate in subsite D into a half-chair conformation during the binding process has been postulated, but not proved, as a feature of lysozyme catalysis and could lead to a facilitation in the rate of 10^4.[13] When these factors are added together, i.e., intracomplex general acid catalysis (10^3–10^5), relief of reactant strain (10^4), and electrostatic catalysis (10^2 or greater), rate enhancements would be observed of the magnitude obtained in the enzymatic reactions (10^{10}–10^{11}) even with acetals having the structural features of enzyme substrates. It is highly probable that these three mechanistic features are employed in lysozyme catalysis.

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The Configuration Symmetry Group and Its Application to Stereoisomer Generation, Specification, and Enumeration[1a]

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Abstract: The configuration symmetry group, a novel specification of the symmetry of an organic chemical structure of defined constitution, is formulated. The symmetry operations in this group are represented in part by their effects on the configurations of the stereocenters in the structure. A description follows of how this group is used: (a) to construct for the first time an algorithm that generates all the distinct stereoisomers of a chemical structure of defined constitution, (b) to specify the configuration of the stereocenters of a stereoisomer independent of geometry, and (c) to provide a general counting equation for the number of stereoisomers of a chemical structure that solves a problem dating back to van't Hoff. Several examples are provided.

I. Introduction

A number of ways exist for specifying the symmetry of a chemical structure, each suitable for different purposes. For most applications the familiar geometric point group is chosen.[2a] In some spectroscopic applications it is necessary to take internal motion into account and specify a nonrigid symmetry group.[2b] For applications in dynamic stereochemistry it is necessary to consider the group of all permutations of identical atoms and often several subgroups.[3] Symmetry groups that include the point group and operations that invert chiral centers are useful both in constructing chirality functions[4] and in specifying the pseudochirality of a structure.[5] An extension of the latter concept leads to a novel symmetry group for a chemical structure that includes, in part, features of all these cases. The purpose here is to describe the formulation of this group, which we term the "configuration symmetry group".

This symmetry group is the key construction that leads to three interesting and important results: (a) an algorithm that exhaustively and irredundantly generates the possible distinct stereoisomers of a chemical structure of specified constitution, a result for which no satisfactory solution has been available; (b) a specification of the configuration of a stereoisomer of an organic molecule of specified constitution that is independent of any geometrical property and that is needed for computer-assisted structure elucidation; (c) a general equation for counting these stereoisomers, which represents the solution to this problem dating back to van't Hoff.[6]

This paper and the following one[7] describe the current effort to provide the CONGEN (for *con*strained structure *gen*eration) program with stereochemical capabilities.[8] This paper is primarily concerned with the chemical and mathematical theory necessary to this effort. The following paper is concerned primarily with novel algorithms and the computer implementation.[7] A third paper considers the theory in greater mathematical detail with some extensions to other topics.[9]

II. Chemical Graphs and Symmetry

Throughout this paper, chemical structures are considered as the graphs[10a] defined by their constitution.[10b-d] Thus, atoms correspond to nodes of the graph and bonds correspond to edges. Each node is numbered and each edge is labeled as in Figure 1. The numbering of the nodes is arbitrary but must be retained throughout the procedure.[9] Only atoms that are at most tetravalent are considered at present, Hydrogens are not explicitly considered and are given the number 0. This suppression of hydrogens is a convenient space-saving feature used throughout the CONGEN program,[8] but is not necessary to the algorithm. This suppression will simplify the presentation here without affecting the results in any way.

There are two standard groups[10a] that are used to describe

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