General Acid Catalysis in the Hydrolysis of 1,3-Dioxolanes and 1,3-Oxathiolanes. The Hydrolysis of Acetals and Thioacetals of *p*-(Dimethylamino)benzaldehyde

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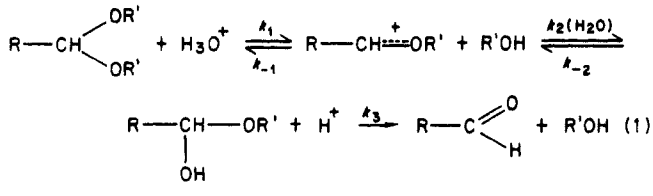
Abstract: Rate constants have been determined for hydrolysis of acetal and *O,S*-thioacetal derivatives of *p*-(dimethylamino)benzaldehyde in H_2O. The plots of log k_{obsd} vs. pH for the di-*n*-propyl acetal, the 1,3-dioxolane, and the 1,3-oxathiolane are pH independent from pH 1 to 4–5 and linear with a slope of −1.0 at pH >5. General acid catalysis was not observed in the hydrolysis of the di-*n*-propyl acetal. Consequently, the rate-determining step must be breakdown of the protonated acetal to an oxocarbonium ion. Apparent general acid catalysis was observed in the hydrolysis of the 1,3-dioxolane and the 1,3-oxathiolane. The plots of k_{obsd} vs. buffer concentration are curved at pH >6 in reactions of the former compound, which indicates that the rate-determining step is changing with increasing buffer concentration to a step with little or no dependence on buffer concentration. The rate-determining step in the reactions of the 1,3-dioxolane and the 1,3-oxathiolane at pH >5 and at low buffer concentrations is attack of a water molecule on the carbonium ion intermediate produced by hydronium ion catalyzed decomposition of the acetal. This must be a consequence of rapid reversal of the ring-opening step. At pH >7.5 attack of OH^- on the carbonium ion intermediate occurs in hydrolysis of the dioxolane, and the rate-determining step changes to ring opening near pH 8. Rapid attack of a β-substituent group on an oxocarbonium ion intermediate was demonstrated in ring closure of the oxocarbonium ion produced by C–S cleavage of *p*-(dimethylamino)benzaldehyde *O*-(β-mercaptoethyl) *S*-(β-hydroxyethyl) thioacetal; the values of k_{obsd} for hydrolysis of that compound are identical with those of 2-(*p*-(dimethylamino)phenyl)-1,3-oxathiolane at pH >4. The rate constants for hydrolysis of the 4,4,5,5-tetramethyl-1,3-dioxolane are relatively small, and there is only a 100-fold difference in the second-order rate constants for hydronium ion catalyzed hydrolysis of the neutral and protonated species in contrast with the difference of at least 10^4 with the dipropyl acetal and the 1,3-dioxolane. Solvent involvement in the rate-determining step with that compound may be occurring by an A-2 mechanism. Thus, in the hydrolysis of the acetals of *p*-(dimethylamino)benzaldehyde changes in structure have led to different mechanisms or rate-determining steps.

The hydronium ion catalyzed hydrolysis of acetals must proceed via the scheme shown in eq 1. Thus, there are three possible



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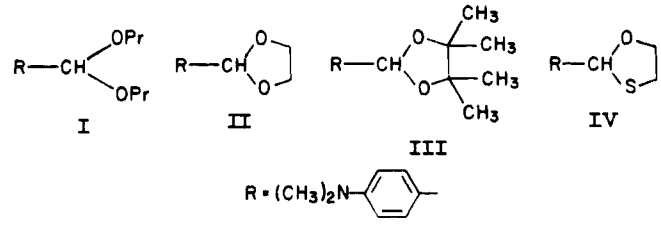
rate-determining steps in the reaction. The breakdown of the protonated acetal to a resonance stabilized oxocarbonium ion is generally the rate-determining step in the hydrolysis of simple acetals.[2,3] However, it has been shown that with substituted benzaldehyde diethyl acetals the rate constants for hemiacetal hydrolysis are only slightly greater than those for initial breakdown of the acetal at pH <5.[4,5] From extrapolation of Hammett σ ρ plots for these reactions it can be ascertained that the second-order rate constants for the hydronium ion catalyzed steps in acetal and hemiacetal breakdown will become equal at σ = −0.5.[5] Nevertheless, with a *p*-dimethylamino substituent group (σ = −0.8) it is doubtful whether hemiacetal breakdown would be rate limiting in the hydrolysis of acyclic acetals since at pH values greater than 5 hemiacetal breakdown becomes pH independent and then OH^- catalyzed and would therefore be fast,[5] and below pH 5 the *p*-dimethylamino group will be protonated, which will greatly slow the breakdown of the protonated acetal. Reversibility should not be significant in the hydrolysis of an acyclic acetal since the concentration of R'OH will be small. However, it has been estimated[6] that the rate constant for attack of H_2O on the *p*-(dimethylamino)phenylethyl 1-methoxy cation is only 5×10^3 M^{-1} s^{-1}. A rate constant of similar magnitude could allow that step to become rate determining in the hydrolysis of the cyclic acetal 2-(*p*-(dimethylamino)phenyl)-1,3-dioxolane where a rapid reversal of ring opening might occur, i.e., k_2 will be rate determining if $k_{-1} > k_2$. It has been suggested that this may indeed be the case generally in the hydrolysis of 1,3-dioxolanes,[7] although there is no compelling evidence. Reversibility has been detected in the ring opening of tropone ethylene ketal with $k_{-1}/k_2 = 4.3$.[8] A study of the hydrolysis of acetal derivatives of *p*-(dimethylamino)-benzaldehyde should allow the determination of the mechanistic feasibility of such a reaction in a system where hemiacetal breakdown is not a complication and would therefore greatly increase understanding not only of the mechanisms by which acetals hydrolyze but also of the mechanism of interaction of water with stabilized carbonium ions. Consequently, we have investigated the mechanisms of hydrolysis of I–IV.



Experimental Section

Materials. *p*-(Dimethylamino)benzaldehyde di-*n*-propyl acetal (I) was prepared by refluxing the aldehyde, excess *n*-propyl alcohol, and 2 drops of concentrated HCl in benzene. Water was continuously removed by azeotropic distillation employing a Dean-Stark trap. The acid was neutralized with K_2CO_3, and the mixture was allowed to stand over KOH pellets. The mixture was filtered, and the benzene was then removed by rotary evaporation. The compound boiled at 92 °C (0.7 mm), n_D^{26}

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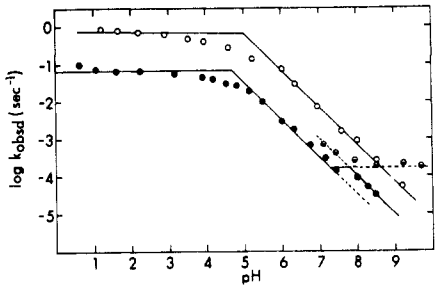

Figure 1. Plots of log k_{obsd} vs. pH for the hydrolysis of *p*-(dimethylamino)benzaldehyde di-*n*-propyl acetal (I) (○) and 2-(*p*-(dimethylamino)phenyl)-1,3-dioxolane (II) (●) in H_2O at 30 °C, μ = 0.5 M with KCl. The points (◒) are for the buffer-independent reactions of II at high buffer concentration.

1.5205. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.71; H, 9.99; N, 5.57. Found: C, 71.93; H, 9.66; N, 5.27.

The 1,3-dioxolane and oxathiolane derivatives were prepared by refluxing equimolar quantities of ethylene glycol or β-mercaptoethanol, *p*-(dimethylamino)benzaldehyde, and 2 drops of concentrated HCl in benzene. Water was continuously removed by azeotropic distillation employing a Dean-Stark trap. After collection of a theoretical amount of water, the mixture was treated as in the synthesis of I. The product was purified by distillation at reduced pressure or recrystallization. 2-(*p*-(Dimethylamino)phenyl)-1,3-dioxolane (II) melted at 58–60 °C after recrystallization from a chloroform–hexane mixture. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.45; H, 7.77; N, 7.25. Found: C, 68.62; H, 8.01; N, 7.15. 2-(*p*-(Dimethylamino)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (III) boiled at 122–125 °C (0.3 mm). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.24; N, 5.62. Found: C, 72.19; H, 8.91; N, 6.03. 2-(*p*-(Dimethylamino)phenyl)-1,3-oxathiolane (IV) melted at 56–57 °C after recrystallization from a chloroform–hexane mixture. Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.15; H, 7.17; N, 6.69. Found: C, 63.48; H, 7.20; N, 6.42. Mass spectral analysis confirmed the mass at 209. The NMR spectrum had peaks (δ) at 6.70, 6.60, 4.97 (C–H), 2.93 (CH_3), 2.83, 2.80, 2.77 and 2.74, 2.71, 2.67, two triplets (CH_2). $(CH_3)_4Si$ (δ 0) was employed as an internal standard. 2-(*p*-Methoxyphenyl)-1,3-dioxolane was the same as previously reported.[9]

When *p*-(dimethylamino)benzaldehyde and mercaptoethanol were mixed and refluxed in benzene, as in the synthesis of IV, but with ommission of the KOH treatment, a solid was obtained which after recrystallization from a chloroform–hexane mixture melted at 86–87 °C. This compound is the mixed acyclic *O,S*-thioacetal *p*-(dimethylamino)-benzaldehyde *O*-(β-mercaptoethyl)-*S*-(β-hydroxyethyl) thioacetal (V). Anal. Calcd for $C_{13}H_{21}NO_2S_2$: C, 54.32; H, 7.37; N, 4.87. Found: C, 53.97; H, 7.19; N, 4.69. Mass spectral analysis confirmed the mass as 287. The first major fragment has a mass of 209. The NMR spectrum had peaks (δ) at 6.70, 6.60, 4.98 (CH), 2.94 (CH_3), 2.83, 2.80, 2.77 and 2.74, 2.70, 2.67, two triplets (CH_2), and 3.68 and 2.00 (OH and SH).

All other chemicals were reagent grade. Amine buffer components were freshly distilled or recrystallized before use.

Kinetic Measurements. The rates of hydrolysis of compounds I–V were measured spectrophotometrically with a Beckman Model 25 or a Pye-Unicam SP8-100 spectrophotometer by following the absorbance increase due to appearance of aldehyde at 360 nm. The ionic molarity of all buffers was maintained constant at 0.5 M with KCl. Stock solutions of substrate were prepared in anhydrous acetonitrile. Kinetic runs were initiated by injecting 15 μL of the substrate stock solution into 3 mL of temperature-equilibrated buffer in the cuvette. Reactions that were too rapid to be monitored with a conventional spectrophotometer were followed with a Durrum Model D-110 stopped-flow spectrophotometer. In rate measurements carried out with the stopped-flow spectrophotometer 150 μL of acetal stock solution was mixed in one syringe with 15 mL of 0.005 M NaOH plus 0.5 M KCl solution. The other syringe contained the appropriate buffer also with μ = 0.5 M. The reactions were pseudo first order for at least 4 half-lives. The values of k_{obsd}, the pseudo-first-order rate constants, were calculated with an IBM-370 computer. Reaction mixture pH values were measured with a Beckman 3500 digital pH meter.

Results

The plot of log k_{obsd} vs. pH for hydrolysis of 2-(*p*-methoxyphenyl)-1,3-dioxolane in H_2O at 50 °C (not shown) is linear with a slope of −1.0 at pH values less than 7. The second-order rate

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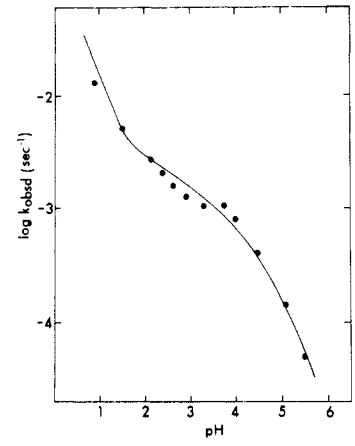


Figure 2. Plot of log k_{obsd} vs. pH for the hydrolysis of 2-(*p*-(dimethylamino)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (III) in H_2O at 70 °C, μ = 0.5 M with KCl.

Table I. Rate Constants for Hydrolysis of Acetal Derivatives of *p*-(Dimethylamino)benzaldehyde in H_2O at μ = 0.5 M (with KCl)

compd	T, °C	k_H', M^{-1} s^{-1}	k_HK_a,[a] s^{-1}	k_H, M^{-1} s^{-1}	pK_{app}
I	30		0.7	7.0×10^4	4.9
II	30		0.072	3.6×10^3 [b]	4.7
	50		0.4	6.8×10^3 [b]	4.3
III	70	0.15		1.5×10^1	4.0
IV	50		0.001	2.8×10^1	4.5
	70		0.0096	2.0×10^2	4.2
V	70		0.0005	2.0×10^2	

[a] The value of k_{obsd} in the pH-independent reaction at pH <4. [b] At pH less than 7.5.

constant for hydronium ion catalyzed hydrolysis (k_H) is 440 M^{-1} s^{-1}. In contrast, with *p*-(dimethylamino)benzaldehyde di-*n*-propyl acetal (I) and 2-(*p*-(dimethylamino)phenyl)-1,3-dioxolane (II), the plots of log k_{obsd} vs. pH in Figure 1 are pH independent at pH values from 1 to 4, and only at pH >4 do the plots have slopes of −1.0. The values of k_{obsd} in the hydrolysis of II are those obtained in HCl solutions or at zero buffer concentration. The equation for k_{obsd} at pH <7 is eq 2, where K_a is the dissociation constant of the conjugate acid (protonated dimethylamino group).

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

The observed reaction is, therefore, a hydronium ion catalyzed reaction of the neutral species. The hydrolysis of II is 2.2-fold faster in D_2O than in H_2O at pD and pH values of 6.60. The rate constants k_H for hydrolysis of I and II were determined as a function of temperature in the range 20 to 60 °C at pH 6.35. The values of ΔH^* and ΔS^* are 11.7 kcal/mol and +2.0 eu and 10.5 kcal/mol and −7.3 eu for I and II, respectively. The plot of log k_{obsd} vs. pH for hydrolysis of 2-(*p*-(dimethylamino)phenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (III) (Figure 2) has two regions with slopes of −1.0. In that case eq 3 is followed. The rate constants for these reactions are given in Table I.

$$k_{obsd} = k_H' a_H \left(\frac{a_H}{K_a + a_H} \right) + k_H a_H \left(\frac{K_a}{K_a + a_H} \right) \quad (3)$$

The plot of log k_{obsd} vs. pH in Figure 3 for hydrolysis of 2-(*p*-(dimethylamino)phenyl)-1,3-oxathiolane (IV) in H_2O at 70 °C shows that the reaction follows eq 2, although the value of k_H is considerably less than that of II (240-fold less at 50 °C). Also included in Figure 3 is the plot of log k_{obsd} vs. pH for hydrolysis of *p*-(dimethylamino)benzaldehyde *O*-(β-mercaptoethyl) *S*-(β-hydroxyethyl) thioacetal (V) at 70 °C. Again k_{obsd} was obtained in HCl solutions or by extrapolation to zero buffer concentration. The values of k_{obsd} for aldehyde formation are pH independent at pH <2 but increase thereafter with increasing pH. At pH >4 the rate constants decline with increasing pH. The

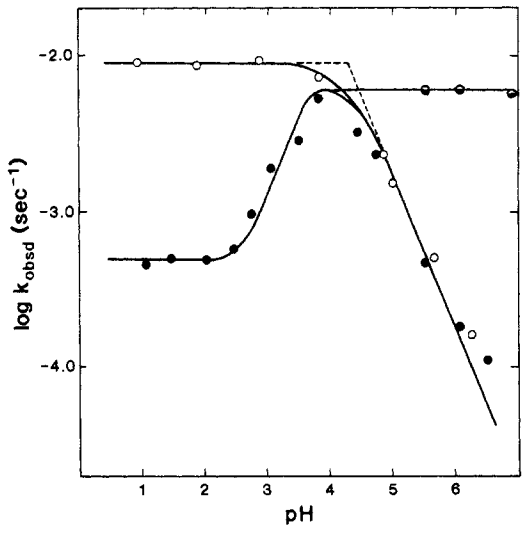


Figure 3. Plots of log k_{obsd} vs. pH for aldehyde formation in the hydrolysis of 2-(*p*-(dimethylamino)phenyl)-1,3-oxathiolane (IV) (○) and *p*-(dimethylamino)benzaldehyde *O*-(β-mercaptoethyl) *S*-(β-hydroxyethyl) thioacetal (V) (●) and for the formation of the intermediate (◒) in H_2O at 70 °C, μ = 0.5 M with KCl.

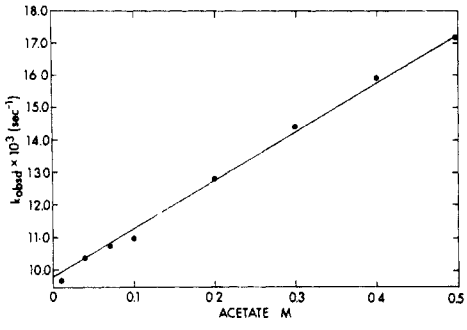


Figure 4. Plot of k_{obsd} vs. the total concentration of acetate buffer in the hydrolysis of 2-(*p*-(dimethylamino)phenyl)-1,3-dioxolane in H_2O at pH 5.51 and 30 °C, μ = 0.5 M with KCl.

slope of the plot of log k_{obsd} vs. pH is then −1.0, and the rate constants are nearly identical with those of IV. At pH values greater than 5, a rapid decline in absorbance occurs at 270 nm prior to the appearance of aldehyde. This reaction is first order and pH independent to at least pH 10 ($k_0 = 6.3 \times 10^{-3}$ s^{-1}). Thus, an intermediate is being produced that releases aldehyde slowly. In the reaction the spectrum changes rapidly from that of V to that of IV and then relatively slowly to the spectrum of the aldehyde.

Buffer catalysis was not observed in the hydrolysis of I at pH 6.21 in cacodylate buffer, at pH 6.41 in 2,6-lutidine buffer, at pH 7.10 in Tris buffer, or at pH 7.55 and 8.10 in *N*-ethylmorpholine buffer. The buffer concentrations in these reactions were varied from 0.05 to 0.5 M. Likewise, buffer catalysis was not detected in the hydrolysis of III at pH 4.72 in acetate buffers ranging in concentration from 0.01 to 1.0 M. As seen in Figure 4 weak buffer catalysis was detected in the hydrolysis of II in acetate buffer (k_{HA} = 0.1 M^{-1} s^{-1}). Cacodylate buffers at pH 6.05, 6.48, and 6.62 gave increased curvature at low buffer concentrations followed by a reasonably linear relationship between k_{obsd} and buffer concentration between 0.1 and 0.5 M. However, the catalytic effect in that buffer concentration range (0.1–0.5 M) was quite small, only 51% at pH 6.05 ($k_{HA} = 8.0 \times 10^{-3}$ M^{-1} s^{-1}). With weaker buffer acids (imidazole, *N*-ethylmorpholine, morpholine, and carbonate conjugate acids) the catalysis increases, and curvature in the plots of k_{obsd} vs. buffer concentration at constant pH becomes more pronounced, as shown in Figure 5. With imidazole and *N*-ethylmorpholine buffers in the pH range 6.5 to 7.5, k_{obsd} becomes nearly independent of buffer at high concentration (0.5 M). Curvature was quite pronounced in morpholine, *N*-ethylmorpholine, and carbonate buffers at pH >8.

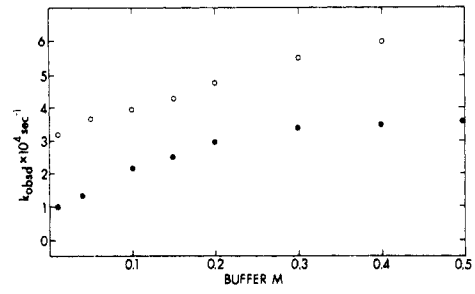


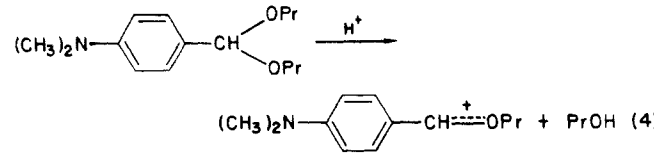
Figure 5. Plots of k_{obsd} vs. the total concentration of imidazole (○) at pH 7.10 and *N*-ethylmorpholine (●) at pH 8.0 in the hydrolysis of 2-(*p*-(dimethylamino)phenyl)-1,3-dioxolane in H_2O at 30 °C, μ = 0.5 M with KCl.

With these buffers, k_{obsd} was essentially independent of buffer concentration at concentrations greater than 0.4 M. The values of k_{obsd} in the buffer-independent reactions (pH >8) at higher buffer concentration were reasonably constant at 2×10^{-4} s^{-1}. For example, in carbonate buffer the value was 1.7×10^{-4} s^{-1} at pH 9.65. In NaOH solutions (unbuffered) the reactions were much too slow to be accurately measured.

Buffer catalysis was also observed in the hydrolysis of the oxathiolane IV at 70 °C with cacodylate buffers at pH 6.12 and 5.45, and the plots of k_{obsd} vs. total buffer concentration were linear at concentrations between 0.01 and 0.5 M. The catalysis was 3.5-fold in this concentration range at pH 6.12. The second-order rate constant for cacodylic acid catalysis k_{HA} at 70 °C was 1.85×10^{-3} M^{-1} s^{-1}. Buffer dilution plots were identical in the reactions of IV and V at pH >4.

Discussion

The plots of log k_{obsd} vs. pH for hydrolysis of I–IV at pH >5 are linear with slopes of −1.0. This shows clearly that breakdown of a hemiacetal intermediate cannot be rate determining in that pH range. Hemiacetal hydrolysis is water catalyzed at pH 5–6 and is OH^- catalyzed at pH >6;[5] log k_{obsd} at pH >5 would therefore be either pH independent or a linear function of pH with a slope of +1.0 (I) if that step were rate limiting. The rate constants for hydrolysis of the neutral species of *p*-(dimethylamino)benzaldehyde ethyl hemiacetal at 30 °C, estimated by extrapolation of Hammett $\sigma\rho$ plots[5] to σ = −0.8, are the following: $k_H = 4 \times 10^4$ M^{-1} s^{-1}, $k_0 = 10^{-2}$ s^{-1}, and $k_{OH} = 4 \times 10^6$ M^{-1} s^{-1}. The plot of log k_{obsd} vs. pH for hemiacetal hydrolysis will then have lines of slope −1.0 and 1.0 intersecting at about pH 6. Thus, only in the pH range below 6 could hemiacetal breakdown influence the observed rate constants for the hydrolysis of *p*-(dimethylamino)benzaldehyde di-*n*-propyl acetal (I).[10] General base catalysis might be expected in the attack of H_2O on the oxocarbonium ion intermediate. However, there is no detectable buffer catalysis in the hydrolysis of I. Furthermore, the k_H value for I fits reasonably well on the Hammett $\sigma\rho$ plot for hydrolysis of substituted benzaldehyde diethyl acetals in H_2O at 30 °C.[5] The *n*-propyl alcohol leaving group should not greatly alter the rate constant in comparison with ethanol. Therefore, the rate-determining step in the hydrolysis of I must be the acid-catalyzed breakdown of the acetal to an oxocarbonium ion (eq 4). This reaction could involve protonation of the acetal followed by

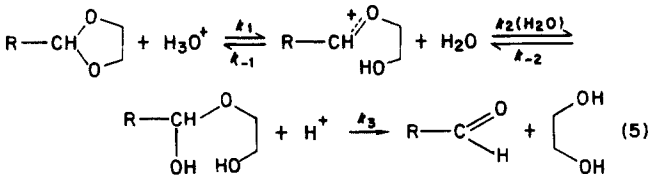


(10) Hemiacetal breakdown will become pH independent at the pK_a of the dimethylamino group conjugate acid as does acetal breakdown, and that reaction might be competitive at pH <5. However, a hydronium ion catalyzed reaction of the protonated hemiacetal should occur at a higher pH (1–2) than in the case of the acetal because of the difference in Hammett ρ values, −1.9 and −3.25, respectively.[5] It will be noted in Figure 1 that the pH-independent reactions give no indication of a change in rate-determining step below pH 5.

rate-determining decomposition of the conjugate acid to an oxocarbonium ion (A-1 mechanism), or it might proceed with concerted proton transfer and C–O bond breaking. However, the lack of detectable general acid catalysis by buffer acids renders the latter possibility unlikely.

The apparent pK_a of 4.9 observed in the hydrolysis of I is in the range expected for a phenyl-substituted dimethylamino group conjugate acid. A neutral dimethylamino group in the para position will greatly stabilize the developing oxocarbonium ion in the transition state as the C–O bond breaks. Protonation of that group is then responsible for the large plateau in the log k_{obsd}–pH profiles in Figure 1, i.e., the pH-independent region represents a transition between a hydronium ion catalyzed breakdown of the conjugate acid (protonated dimethylamino group) and a faster hydronium ion catalyzed reaction of the neutral species. The former reaction is not observed even at pH values below 1. Consequently, there is a difference of at least 10^4 in the rate constants for the two reactions. Protonation of the dimethylamino substituent will change σ from −0.8 to approximately +0.82 (the σ value for $(CH_3)_3N^+$); therefore in view of the ρ value of −3.25 for hydrolysis of substituted benzaldehyde diethyl acetals in H_2O at 30 °C,[5] there should be a difference of 10^5 in the second-order rate constants for hydronium ion catalyzed hydrolysis of the neutral and protonated species. Thus, the pH-independent region represents hydronium ion catalyzed hydrolysis of the neutral species under conditions of pH where the conjugate acid is the predominant species. A protonated dimethylamino group would not only prevent resonance stabilization of the oxocarbonium ion but would also exert an electron-withdrawing inductive effect that would lower basicity and destabilize the developing oxocarbonium ion. It should be noted that the log k_{obsd} vs. pH profile for hydrolysis of 2-(*p*-methoxyphenyl)-1,3-dioxolane, which lacks the dimethylamino substituent, is completely linear with a slope of −1.0 between pH 3 and 7.

In the initial ring-cleavage step of the hydronium ion catalyzed hydrolysis of 1,3-dioxolanes the leaving group does not break away from the molecule. Therefore, the possibility exists for reversibility of the reaction via intramolecular attack of the alcohol hydroxyl group on the oxocarbonium ion intermediate (eq 5). If reversibility is sufficiently facile, then subsequent steps in the reaction could become rate determining. Equation 6 will then be applicable.



(5)

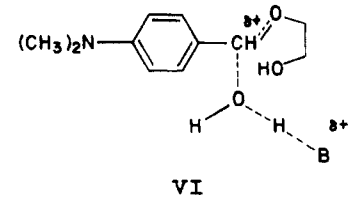
$$k_{obsd} = \frac{k_1 k_2 (H_2O) a_H}{k_{-1}(H_2O) + k_2(H_2O)} \quad (6)$$

If $k_2 > k_{-1}$ then $k_{obsd} = k_1 a_H$, assuming, of course, that hemiacetal breakdown is rapid. However, if $k_{-1} > k_2$, then eq 7 holds and k_2 will be rate determining if k_3 (OH^- or H_2O) is large.

$$k_{obsd} = \frac{k_1 k_2 a_H}{k_{-1}} \quad (7)$$

The ΔS^* for hydrolysis of 1,3-dioxolane derivatives of substituted benzaldehydes is 8–10 eu more negative than in the case of analogous diethyl acetals.[9] This might be taken as evidence for the general involvement of solvent in dioxolane hydrolysis[7,11] although other interpretations are possible.[9,12-15] Negative ΔS^* values in the hydrolysis of cyclic acetals could also result from restriction of rotation about the breaking bond in the transition state or from lower basicity of the cyclic acetal than analogous open chain derivatives.[9] Solvent involvement in the rate-determining step is in fact unlikely in the hydrolysis of 2-(substituted phenyl)-1,3-dioxolanes with electron-withdrawing substituents in view of the D_2O solvent isotope effects and substituent effects which are identical with those in hydrolysis of analogous diethyl acetals ($\rho = -3.35$).[9,16] As shown, the conditions for rate-determining attack of H_2O on a discrete oxocarbonium ion intermediate are quite stringent, i.e., $k_{-1} > k_2$ and $k_3(OH^-$ or $H_2O) > k_{-2}a_H$. The critical question, of course, is whether the reverse reaction (k_{-1}) can compete effectively with attack of 55.5 M H_2O on the oxocarbonium ion (k_2).

The plot of log k_{obsd} vs. pH for the hydrolysis of 2-(*p*-(dimethylamino)phenyl)-1,3-dioxolane (II) at zero buffer concentration is very similar to that of I at pH <8, and k_H is only 19-fold less than the k_H value of I. However, the D_2O solvent isotope effect (k_D/k_H) is only 2.2 in contrast with values greater than 2.75 in acetal hydrolysis proceeding by an A-1 mechanism.[2,3,9] The value of ΔS^* is 9.3 eu more negative with II than with I, and buffer catalysis is detectable in the hydrolysis of II, whereas such catalysis is absent in the hydrolysis of I. As should be the case,[18] the magnitude of the apparent general acid catalysis increases as the buffer acid becomes weaker, but curvature in the plots of k_{obsd} vs. buffer concentration becomes markedly apparent. The curved plots show that the rate-determining step is changing as the buffer concentration is increased to one with little or no dependence on buffer concentration. The rate-determining step at pH >5 cannot be hemiacetal breakdown at either low or high concentrations of buffer in view of the shape of the log k_{obsd} vs. pH profiles. Furthermore, the k_H value of II (at zero buffer concentration) is only 15-fold larger than that of the corresponding *p*-methoxy-substituted compound, which is approximately fourfold less than expected on the basis of the difference in σ constants for the substituent groups and the ρ value of −3.35. This indicates that the rate-determining step is also changing with the changing substituent group.[19] Thus, the rate-determining step at zero buffer concentration in the hydrolysis of II can most reasonably be ascribed to attack of a water molecule on the oxocarbonium ion intermediate produced in ring opening (k_2). This reaction then is general base catalyzed (VI). As the rate of the reaction is



VI

increased by increasing the buffer concentration, the rate-determining step changes to ring opening, which is only weakly catalyzed or uncatalyzed by buffers of low pK_a analogous to the uncatalyzed reaction of I. It is clear that in the hydrolysis of II, k_2 and k_{-1} cannot differ greatly since a fourfold change in k_{obsd} is sufficient to change the rate-determining step (see Figure 5). The estimated ratio of k_{-1}/k_2 from the k_{obsd} values of the nearly buffer independent reaction and the intercept ($k_{ind}/k_{int} = (k_{-1}/k_2) + 1$) is reasonably constant (1–2) in the pH range 6–7.5 in imidazole and *N*-ethylmorpholine buffers as demanded by mechanism VI. General base catalysis might also be expected in the ring-closure step. However, that would then require general acid catalysis in the ring-opening reaction ($\alpha < 1.0$). If, on the other

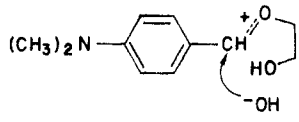
(11) Capon, B.; Thacker, D. *J. Chem. Soc. B* **1967**, 185.
(12) Fife, T. H.; Hagopian, L. *J. Org. Chem.* **1966**, *31*, 1772.
(13) Fife, T. H. *J. Am. Chem. Soc.* **1967**, *89*, 3228.
(14) Fife, T. H.; Brod, L. H. *J. Org. Chem.* **1968**, *33*, 4136.
(15) The smaller second-order rate constant for the hydronium ion catalyzed hydrolysis of tropone ethylene ketal in comparison with tropone diethyl ketal is due primarily to difficulty of ring opening.[8]

(16) It can, of course, be argued that the overall ρ value for equilibrium ring opening and subsequent attack of a water molecule in dioxolane hydrolysis might coincidentally be the same as the ρ value in hydrolysis of diethyl acetals, but note that ρ^+ is 1.6 for attack of H_2O on substituted phenylethyl-1-methoxy cations.[17]
(17) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238.
(18) Fife, T. H.; Anderson, E. *J. Org. Chem.* **1971**, *36*, 2357.
(19) The point for a *p*-dimethylamino substituent has a small negative deviation (~0.4 log units) on the plot of log k_H vs. σ for hydrolysis of substituted benzaldehyde 1,3-dioxolanes in water at 30 °C.

hand, ring opening occurs via the conjugate acid, then in ring closure the transition state must also be reached without proton transfer. The plots of k_{obsd} vs. buffer concentration at pH >8 show that indeed the ring-opening reaction is general acid catalyzed by very weak buffer acids.

The alternative to VI is a mechanism in which the ring-opening reaction of II at low buffer concentration is rate determining and general acid catalyzed. As buffer concentration is increased the rate of the k_{-1} step would then increase due to general base catalysis so that k_2 would eventually become rate limiting if that step is not significantly buffer catalyzed. However, the value of k_H at 30 °C for II is 2-fold greater than that of the correspondingly substituted 2-(*p*-(dimethylamino)styryl)-1,3-dioxolane.[20] If ring opening was rate-determining in the hydrolysis of these dioxolanes, the *p*-(dimethylamino)cinnamaldehyde derivative should hydrolyze more rapidly than II because of increased stabilization of the developing oxocarbonium ion, e.g., 2-styryl-1,3-dioxolane hydrolyzes 18 times faster in H_2O at 30 °C than 2-phenyl-1,3-dioxolane.[20] Increased oxocarbonium ion stability would, of course, reduce the ease of nucleophillic attack by water. Consequently, mechanism VI must be considered most likely for the reaction at low buffer concentration and pH <7. This mechanism is supported strongly by the kinetic data of pH >8.

At pH 7.5 there is a pH-independent region in the plot of log k_{obsd} at zero buffer vs. pH for hydrolysis of II that extends for approximately 0.5 pH units. This undoubtedly reflects rate-determining OH^- attack on the carbonium ion intermediate (VII)



VII

following the H_3O^+-catalyzed ring opening. When the rate of this reaction exceeds that of ring closure, the rate-determining step will change to ring opening (k_1). The plot of Figure 1 again bends downward above pH 8. At pH values greater than 8 the curved plots of k_{obsd} vs. buffer concentration reach a plateau at high buffer with rate constants near 2×10^{-4} s^{-1} in all cases; the reaction at higher buffer concentration is pH independent to at least pH 10 (carbonate buffer). Thus, eq 8 is being followed where k_{OH} is the second-order rate constant for attack of OH^- on the

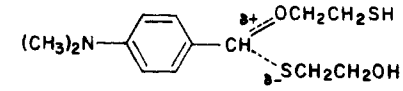
$$k_{obsd} = \frac{k_1 k_{OH} K_w}{k_{-1}} = 2 \times 10^{-4}\ s^{-1} \qquad (8)$$

oxocarbonium ion. The formation of aldehyde will then be pH independent and uncatalyzed by buffer. Since ring opening is rate determining at pH >8 at low buffer concentrations, it is clear that this reaction is general acid catalyzed, although such catalysis is conclusively detected only with very weak buffer acids (*N*-ethylmorpholine, morpholine, and carbonate conjugate acids). The rate-determining step must change in this pH range at high buffer concentration because of general base catalysis in the ring-closure step.

That ring closure via attack of a β-substituent group on the oxocarbonium ion intermediate is an important feature of these reactions is clearly seen in Figure 3. The acyclic thioacetal V hydrolyzes at low pH (<2) in a pH-independent reaction, but the rate constants then increase with increasing pH. The reaction at pH >2 is hydrolysis of the neutral species or a kinetic equivalent. The kinetic equation for the reaction of V is given in eq 9. The kinetics of the reaction as well as the structural information

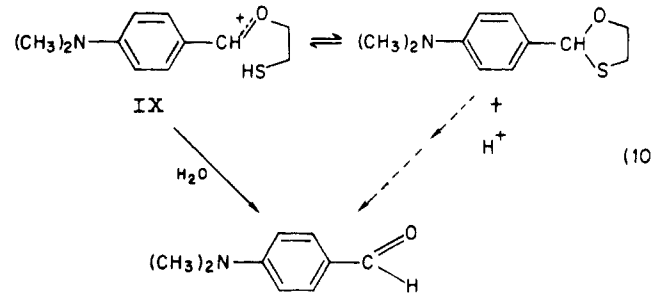
$$k_{obsd} = \frac{k_H K_a a_H + k_0 K_a}{K_a + a_H} \qquad (9)$$

presented in the Experimental Section show conclusively that the compound is an *O,S*-thioacetal. The compound hydrolyzes much more rapidly than would be expected of an *S,S*-thioacetal,[21,22] and the shape of the plot of log k_{obsd} vs. pH shows that it cannot be an *O,O* acetal. It is probable that unimolecular decomposition is occurring, as in VIII, with C–S bond breaking in the transition



VIII

state, analogous to the similar neutral species reaction of *p*-(dimethylamino)benzaldehyde *O*-ethyl *S*-(methyl mercaptoacetate) thioacetal.[22] Unimolecular decomposition reactions have been observed previously in the hydrolysis of acetals[23-25] and thioacetals[22,26,27] having phenolic or thiophenolic leaving groups. A unimolecular breakdown is brought about in those cases by the good leaving groups and the moderately stable oxocarbonium ion intermediates. Such a reaction is also observed at pH >8 in the hydrolysis of tropone diethyl ketal[28] with which the leaving group is an aliphatic alcohol, but the oxocarbonium ion intermediate is then exceedingly stable. The unimolecular reactions of phenolic acetals are quite sensitive to the pK_a of the leaving group.[23,29] Thus, in the neutral species reaction of V the leaving group must be that of lowest pK_a, i.e., sulfur as in VIII. Unimolecular cleavage of the C–O bond would be highly unlikely at low pH. The hydrolysis of *p*-(dimethylamino)benzaldehyde *O*-ethyl *S*-(methyl mercaptoacetate)[22] is pH independent from pH 5 to 13. An intermediate is formed in the hydrolysis of V in a similar rapid pH-independent reaction at pH >5 prior to appearance of aldehyde. At pH >4 a downward bend occurs in the plot of Figure 3 for aldehyde formation in the hydrolysis of V; the values of k_{obsd} for aldehyde formation are then nearly identical with those of the oxathiolane IV. Therefore, ring closure is occurring via the oxocarbonium ion IX produced in the unimolecular breakdown of V (eq 10), i.e., IV is an intermediate in the hydrolysis of V. Clearly, ring closure occurs more rapidly than reaction of the oxocarbonium ion with H_2O.



IX (10)

In view of the apparent general acid catalysis in the hydrolysis of the oxathiolane IV and the rapid ring closure of IX, the rate-determining step in the hydrolysis of IV at pH >4 is very likely attack of water on the carbonium ion intermediate. Carbon–sulfur bond breaking cannot be rate determining because of the rapid reversibility, and C–O bond breaking should not be significantly catalyzed by general acids of low pK_a since the carbonium ion intermediate would be considerably less stable than that derived from I and II. Carbonium ion stabilization is a key factor in allowing general acid catalysis in acetal hydrolysis when the leaving group is an aliphatic alcohol.[2,18] The hydronium ion catalyzed hydrolysis reactions of 2-(substituted phenyl)-1,3-oxathiolanes have been extensively studied.[30,31] The large Hammett

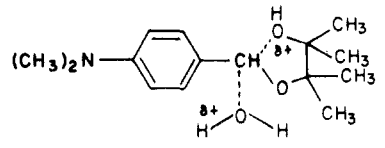
(20) Fife, T. H.; Shen, C. C., unpublished data.

(21) The second-order rate constant for hydronium ion catalyzed hydrolysis of 2-(*p*-(dimethylamino)styryl)-1,3-dithiolane is only 0.28 M^{-1} s^{-1} at 90 °C.[20]

(22) Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476.
(23) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 4081.
(24) Fife, T. H.; Brod, L. H. *J. Am. Chem. Soc.* **1970**, *92*, 1681.
(25) Fife, T. H. Przystas, T. J. *J. Am. Chem. Soc.* **1977**, *99*, 6693.
(26) Fife, T. H.; Anderson, E. *J. Am. Chem. Soc.* **1970**, *92*, 5464.
(27) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 292.
(28) Anderson, E.; Fife, T. H. *J. Am. Chem. Soc.* **1969**, *91*, 7163.
(29) Craze, G. A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 354.
(30) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1969**, *91*, 4217.
(31) De, N. C.; Fedor, L. R. *J. Am. Chem. Soc.* **1968**, *90*, 7266.

ρ value (−2.8), established with electron withdrawing meta and para substituents, the proportionality of log k_{obsd} for the *p*-nitro-substituted compound with $-H_0$, and the rate-enhancing effect of methyl group substitution at the reaction center all pointed to an A-1 mechanism (rate-determining ring opening of the protonated species) in the hydrolysis of those compounds.[30] There has been, however, little evidence for the type of initial bond breaking in the hydrolysis of the oxathiolanes, i.e., C–S or C–O.[32] The D_2O solvent isotope effect in these reactions ($k_D/k_H = 1.9$)[30,31] is much less than in the A-1 hydrolysis reactions of *O,O*-acetals and may indicate protonation of sulfur; the solvent isotope effect is similar to that in the hydrolysis of benzaldehyde *O*-methyl *S*-substituted phenyl thioacetals ($k_D/k_H = 1.5$) with which it was shown conclusively that thiophenol is the initial leaving group.[26] It should be noted that if ring closure occurs as in eq 10 at pH <6, then by the principle of microscopic reversibility a hydronium ion catalyzed ring-opening step must take place through the reverse pathway with C–S bond cleavage. Since in the hydrolysis of IV the ring-opening reaction is quite probably a preequilibrium process, then the product would, of course, be formed from reaction of water with the equilibrium mixture of the possible carbonium ions. An A-1 mechanism in the hydrolysis of the 2-(substituted phenyl)-1,3-oxathiolanes and the corresponding 1,3-dioxolanes with electron-withdrawing substituent groups, in contrast with the rate-determining attack of a water molecule on the oxocarbonium ion in the case of the *p*-dimethylamino substituted compounds, would require a smaller sensitivity of ring closure than water attack to the substituent groups.

There is no detectable buffer catalysis in the hydrolysis of the 4,4,5,5-tetramethyl-1,3-dioxolane (III), even though reversibility of ring opening should be greatly enhanced by the geminal methyl group substitution. Proton transfer is therefore not part of the rate-determining step. The rate of hydrolysis of III has been greatly retarded by the methyl group substitution as with other 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes.[13,14] The value of k_H for III is 450-fold less at 70 °C than that of II at 50 °C, and it is 4700-fold less than k_H for I at 30 °C. There is a much smaller difference in k_H and k_H' in the case of III than with I, II, and IV. The reaction of III governed by k_H' is detectable at pH >3, whereas it is not detectable with I, II, and IV even at pH values near 1. Resonance stabilization of the oxocarbonium ion by the neutral *p*-dimethylamino group will be of greatest importance in those reactions in which there is the greatest amount of oxocarbonium ion character in the transition state. Protonation of the *p*-dimethylamino group will have a correspondingly large effect on such reactions, which will be reflected in the difference between k_H and k_H'. Thus, there must be less carbonium ion character in the transition state with III than with I, II, and IV. This implies solvent involvement in an A-2 process (X). Such a mechanism might result if reclosure of the ring is so facile that



X

the reaction cannot readily go forward to products via an oxocarbonium ion intermediate. An A-2 reaction would avoid such an intermediate and allow the reaction to go forward, although at a reduced rate in comparison to analogous acetals with which the reversibility of ring opening is not as favorable.

An A-1 mechanism in the hydrolysis of III would require an early transition state in comparison with I. However, any difficulty in resonance stabilization of the developing oxocarbonium ion or increased steric interactions in an A-1 transition state brought about by the methyl group substitution, which would explain the relatively slow rates, should not lead to a transition state with less oxocarbonium ion character. These factors could, however, contribute to a change in mechanism.[13] It is clear that an A-1 mechanism cannot simply explain both the smaller rate constants[33] and the reduced effect of protonation of the *p*-dimethylamino group in comparison with I and II. Evidence for solvent involvement in the hydrolysis of 4,4,5,5-tetramethyl-1,3-dioxolanes has been presented previously.[13,14] The lack of buffer catalysis in the hydrolysis of III and the relatively small difference in k_H and k_H' is also not in accord with rate-determining attack of H_2O on the oxocarbonium ion; there would appear to be no reason for such a marked difference in the transition state in comparison with II and IV if the rate-determining steps were indeed the same. As a consequence, mechanism X must be considered most probable. Mechanisms VI and X differ mainly in that C–O bond breaking is not complete in X as it is in VI. The absence of buffer catalysis in X must indicate that bond making with water has not progressed to a great extent in the transition state, and accordingly, proton transfer from water is not appreciable. Thus, in the reactions of the *p*-(dimethylamino)benzaldehyde derivatives I–IV changes in structure have led to different mechanisms or rate-determining steps.

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

Registry No. I, 99376-86-0; II, 66929-08-6; III, 99376-87-1; IV, 84350-65-2; V, 99376-88-2.

(32) Mixed acyclic O,S thioacetals of aliphatic alcohols and thiols break down primarily with initial C–O bond breaking.[22] That is, of course, not necessarily the case with cyclic 1,3-oxathiolanes.

(33) Steric hindrance to solvation of the conjugate acid or increased strain in the conjugate acid would reduce basicity and could thereby slow the hydrolysis reaction. However, the ΔS^* values for hydrolysis of 4,4,5,5-tetramethyl-1,3-dioxolanes are considerably more negative than with the analogous 1,3-dioxolanes or diethyl acetals,[14] which argues against hindered solvation being a factor of major importance. Increased strain in the conjugate acid would also, of course, facilitate its decomposition to an oxocarbonium ion.