The Acid-Catalyzed Hydrolysis of 2-(Substituted phenyl)-1,3-oxathiolanes

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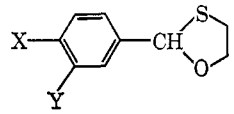
Abstract: The rates of acid-catalyzed hydrolysis of a series of 2-(substituted phenyl)-1,3-oxathiolanes have been measured in H_2O and 50% dioxane–H_2O. A plot of the logarithms of the rate constants *vs.* σ, the Hammett substituent constant, is curved, the point for the *p*-methoxy-substituted compound showing considerable positive deviation from the line established by the use of *meta*-substituted compounds and compounds having electron-withdrawing substituents in the *para* position ($\rho = -2.8$). The *p*-methoxy group produces negative deviation when σ^+ constants are employed and H_2O is the solvent. Reasonable linearity is obtained, however, with σ^+ and the logarithms of rate constants measured in 50% dioxane–H_2O. A plot of log k_{obsd} for hydrolysis of 2-(*p*-nitrophenyl)-1,3-oxathiolane in various aqueous HCl solutions *vs.* $-H_0$ is linear with a slope of 1.23. Thus, the transition state in these hydrolysis reactions must resemble a carbonium ion with the most likely mechanism involving a unimolecular decomposition of a protonated intermediate. The value of k_{D_2O}/k_{H_2O} for hydrolysis of 2-(*p*-methoxyphenyl)-1,3-oxathiolane (1.93) is considerably less than normally observed for hydrolysis of analogous acetals and may indicate that the protonated intermediate has sulfur protonated. The value of ΔS^* for hydrolysis of 2-phenyl-1,3-oxathiolane is −13.2 eu.

Strong electron withdrawal in the leaving group of an acetal, which greatly reduces the basicity of oxygen and at the same time facilitates C–O bond breaking, will change the mechanism of acid-catalyzed hydrolysis from A-1, normally observed with acetals,[1] to one involving partially rate-determining proton transfer.[2] Replacement of an acetal oxygen by sulfur might therefore also give rise to mechanistic differences since sulfur is much less basic than oxygen. An investigation of thioacetal hydrolysis is also of interest since the lysozyme-catalyzed hydrolysis of a thioglycoside unexpectedly proceeds at a rate comparable to that for the corresponding glycoside.[3] An understanding, therefore, of the mechanism of hydrolysis of these compounds might provide a clue to the mechanism of action of the enzyme. As a consequence, a study of the hydrolysis of a series of 2-(substituted phenyl)-1,3-oxathiolanes has been made.[4] The general formula for these compounds is shown in I–VII.



I, X = OCH_3; Y = H
II, X = CH_3; Y = H
III, X = H; Y = H
IV, X = Cl; Y = H
V, X = NO_2; Y = H
VI, X = H; Y = CH_3
VII, X = H; Y = OCH_3

Experimental Section

Materials. The 2-(substituted phenyl)-1,3-oxathiolanes were prepared by treating the appropriately substituted benzaldehyde with β-mercaptoethanol in refluxing benzene in the presence of a trace of *p*-toluenesulfonic acid. Water was continuously removed from the reaction by azeotropic distillation with benzene. After collection of a theoretical amount of water, the mixture was washed with either aqueous $NaHCO_3$ solution or 2% NaOH. This was followed by a thorough wash with water. The aqueous layer was further extracted with ether. The combined benzene–ether extract was dried over anhydrous sodium sulfate. Solvent was evaporated, and the residual material was purified either by recrystallization or distillation through a Nester-Faust spinning-band column.

2-(*p*-Methoxyphenyl)-1,3-oxathiolane had bp 123° (0.8 mm), $n^{24}D$ 1.5824. *Anal.* Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.34; H, 6.18.

2-(*p*-Methylphenyl)-1,3-oxathiolane had bp 100° (0.75 mm), $n^{24}D$ 1.5744. *Anal.* Calcd for $C_{10}H_{12}OS$: C, 66.62; H, 6.71. Found: C, 66.41; H, 6.54.

2-Phenyl-1,3-oxathiolane had bp 83° (2.5 mm), $n^{24}D$ 1.5843; lit.[5] bp 86–87° (5.0 mm).

2-(*p*-Chlorophenyl)-1,3-oxathiolane had bp 120° (1.7 mm), $n^{23}D$ 1.5916; lit.[6] bp 124° (0.9 mm).

2-(*p*-Nitrophenyl)-1,3-oxathiolane had mp 74°; lit.[6] mp 73–77°.

2-(*m*-Methylphenyl)-1,3-oxathiolane (prepared using toluene as the solvent) had bp 95.5–96° (0.75 mm), $n^{23}D$ 1.5711. *Anal.* Calcd for $C_{10}H_{12}OS$: C, 66.62; H, 6.71. Found: C, 66.68; H, 6.68.

2-(*m*-Methoxyphenyl)-1,3-oxathiolane (prepared using toluene as the solvent) had bp 116° (0.65 mm), $n^{24}D$ 1.5792. *Anal.* Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.09; H, 5.94.

2-Phenyl-2-methyl-1,3-oxathiolane (prepared using toluene as the solvent) had bp 114° (5.5 mm), $n^{24}D$ 1.5664. *Anal.* Calcd for $C_{10}H_{12}OS$: C, 66.62; H, 6.71; S, 17.79. Found: C, 66.81; H, 6.84; S, 17.49.

Dioxane was purified by the method of Fieser,[7] and was stored frozen in brown bottles. Acetonitrile was Eastman Kodak Spectrograde and was further purified by twice distilling it from P_2O_5 and once from K_2CO_3.

Kinetic Measurements. The equipment and procedures were the same as previously employed.[8–10] The rates were measured spectrophotometrically with a Zeiss PMQ 11 spectrophotometer by following the appearance of the aldehyde product. The oxathiolanes were dissolved in acetonitrile, and the rates were initiated by adding one drop of this solution to 3.5 ml of acidic solution in the cuvet with a calibrated dropping pipet and with vigorous stirring. The cuvet was then stoppered tightly with a Teflon stopper. Pseudo-first-order rate constants (k_{obsd}) were calculated from the slopes of plots of log $(OD_\infty - OD_0)/(OD_\infty - OD_t)$ *vs.* time.

(1) E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).
(2) T. H. Fife and L. K. Jao, *J. Am. Chem. Soc.*, **90**, 4081 (1968).
(3) G. Lowe, G. Sheppard, M. L. Sinnott, and A. Williams, *Biochem. J.*, **104**, 893 (1967).
(4) After submission of this paper for publication another paper appeared also dealing with the hydrolysis of these compounds: N. C. De and L. R. Fedor, *J. Am. Chem. Soc.*, **90**, 7266 (1968).
(5) F. Kipnis and J. Ornfelt, *ibid.*, **71**, 3555 (1949).
(6) J. R. Marshall and H. A. Stevenson, *J. Chem. Soc.*, 2360 (1959).
(7) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.
(8) T. H. Fife, *J. Am. Chem. Soc.*, **89**, 3228 (1967).
(9) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(10) T. H. Fife and L. Hagopian, *ibid.*, **31**, 1772 (1966).

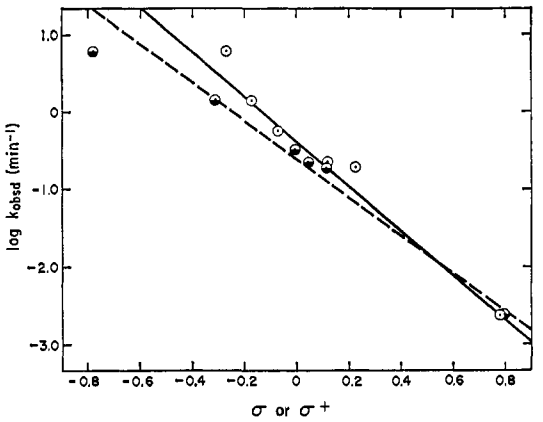


Figure 1. Plot of log k_{obsd} for hydrolysis of 2-(substituted phenyl)-1,3-oxathiolanes in 1.01 M HCl at 30° *vs.* σ or σ^+.

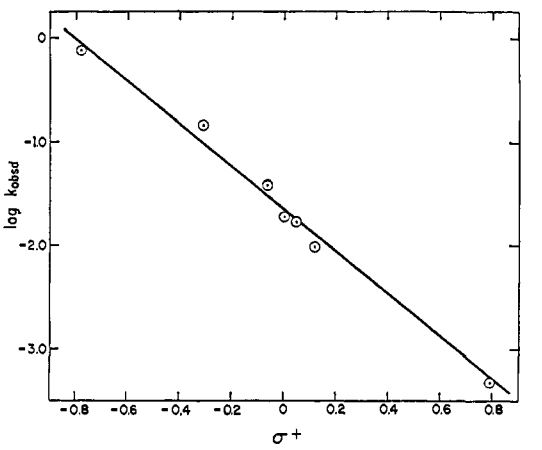


Figure 2. Plot of log k_{obsd} for hydrolysis of 2-(substituted phenyl)-1,3-oxathiolanes in 50% dioxane–H_2O (HCl catalyst) at 30° *vs.* σ^+.

Results

In Table I, rate constants are given for hydrolysis of 2-(substituted phenyl)-1,3-oxathiolanes at 30° in aqueous HCl and 50% dioxane–H_2O (v/v) with HCl as the catalyst. Also reported in Table I are values of the rate constants in cases where D_2O was the solvent. The logarithms of the first-order rate constants obtained in 1.01 M HCl are plotted in Figure 1 *vs.* σ, the Hammett substituent constant.[11] The point for the *p*-methoxy-substituted compound deviates positively. Employing *meta*-substituted compounds and compounds having electron-withdrawing substituents in the *para* position, a straight line relationship is obtained with a slope, ρ, of -2.8. In Figure 2 is shown a plot of log k_{obsd} *vs.* σ^+,[12] for the data obtained in 50% dioxane–H_2O with 1.01 M HCl as the catalyst. A reasonably straight-line relationship is obtained with a ρ^+ of -2.11 (r = 0.995), but a plot *vs.* σ was curved. The better correlation with σ^+ in the mixed solvent very likely indicates that the transition state more closely resembles a carbonium ion in 50% dioxane–H_2O than in water.[13]

In Table II, rate constants for hydrolysis of 2-(*p*-nitrophenyl)-1,3-oxathiolane at 30° and at various HCl concentrations are presented. In Figure 3 is shown a plot of log k_{obsd} *vs.* $-H_0$, the Hammett acidity function.[14] It can be seen that there is direct proportionality. The slope of the plot is 1.23. A plot of (log k_{obsd} + H_0) *vs.* the logarithms of the activity of water[15] in the HCl solutions (not shown) was curved.

Table I. Rate Constants for Hydrolysis of 2-(Substituted phenyl)-1,3-oxathiolanes at 30° in Water and in 50% Dioxane–H_2O

Compd	Substituent	Solvent	Catalyst, M	k_{obsd}, min^{-1}
I	*p*-OCH_3	H_2O	HCl, 1.01	6.09
I	*p*-OCH_3	H_2O	HCl, 0.1	0.310
I	*p*-OCH_3	D_2O	DCl, 0.1	0.600
II	*p*-CH_3	H_2O	HCl, 1.01	1.42
III	*p*-H	H_2O	HCl, 1.01	0.351
IV	*p*-Cl	H_2O	HCl, 1.01	0.196
V	*p*-NO_2	H_2O	HCl, 1.01	0.00238
VI	*m*-CH_3	H_2O	HCl, 1.01	0.562
VII	*m*-OCH_3	H_2O	HCl, 1.01	0.218
2-Phenyl-2-methyl-1,3-oxathiolane		H_2O	HCl, 1.01	0.701
I	*p*-OCH_3	50% dioxane–H_2O	HCl, 1.01	0.778
II	*p*-CH_3	50% dioxane–H_2O	HCl, 1.01	0.146
III	*p*-H	50% dioxane–H_2O	HCl, 1.01	0.0194
IV	*p*-Cl	50% dioxane–H_2O	HCl, 1.01	0.00978
V	*p*-NO_2	50% dioxane–H_2O	HCl, 1.01	0.00048
VI	*m*-CH_3	50% dioxane–H_2O	HCl, 1.01	0.0394
VII	*m*-OCH_3	50% dioxane–H_2O	HCl, 1.01	0.0173
II	*p*-CH_3	50% dioxane–D_2O	DCl, 1.0	0.324

Table II. Rate Constants for Hydrolysis of 2-(*p*-Nitrophenyl)-1,3-oxathiolane at Various HCl Concentrations at 30°

HCl, M	k_{obsd}, min^{-1}	HCl, M	k_{obsd}, min^{-1}
1.0	0.00238	4.80	0.2315
2.03	0.010	5.29	0.303
3.53	0.0694	5.90	0.557

Table III. Rate Constants for Hydrolysis of 2-Phenyl-1,3-oxathiolane at Various Temperatures in 1.0 M HCl

Temp, °C	k_{obsd}, min^{-1}	Temp, °C	k_{obsd}, min^{-1}
20	0.100	40	0.643
30	0.351	50	1.80

The rate constants for hydrolysis of 2-phenyl-1,3-oxathiolane in 1.0 M HCl at 20, 30, 40, and 50 ± 0.1° are given in Table III. In Figure 4 is shown the plot of log k_{obsd} *vs.* $1/T$°K. The value of ΔH^* is 16.8 ± 0.4 kcal/mol, and ΔS^* has the value -13.2 ± 1.2 eu. The uncertainties in ΔH^* and ΔS^* were calculated from the standard error of the plot of ln k_{obsd} *vs.* $1/T$.

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(12) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957).

(13) This could result if solvation of the carbonium ion by water is an important stabilizing influence. In 50% dioxane–H_2O such solvation would be more difficult than in water and, as a consequence, the intermediate carbonium ion would be less stable. Accordingly, the transition state should more closely resemble a carbonium ion in the mixed solvent.

(14) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).

(15) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4978 (1961).

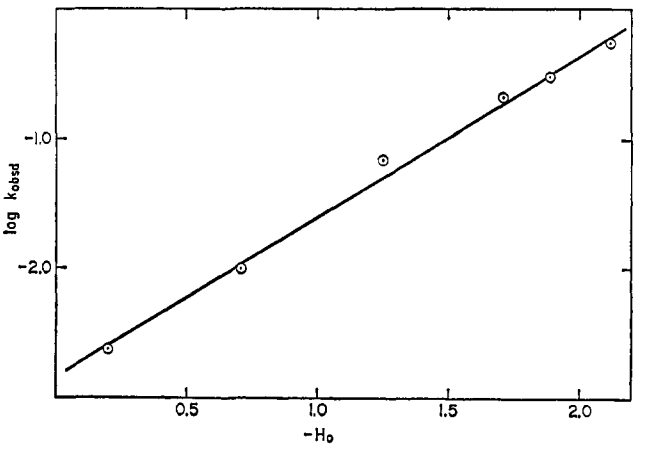


Figure 3. Plot of log k_{obsd} for hydrolysis of 2-(*p*-nitrophenyl)-1,3-oxathiolane in various aqueous HCl solutions at 30° *vs.* $-H_0$.

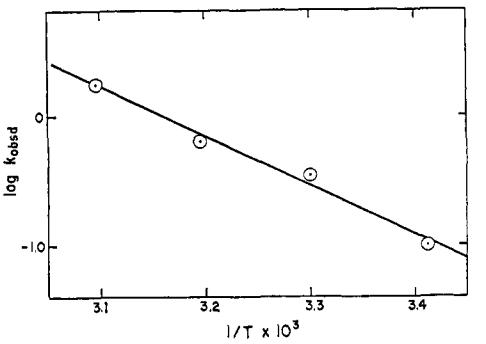


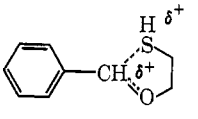
Figure 4. Plot of log k_{obsd} for hydrolysis of 2-phenyl-1,3-oxathiolane in aqueous 1.0 *M* HCl *vs.* $1/T$°K.

Discussion

The acid-catalyzed hydrolysis of 1,3-dioxolanes most likely proceeds by an A-1 mechanism involving pre-equilibrium protonation of the acetal followed by a unimolecular rate-determining cleavage of the protonated acetal to a resonance-stabilized carbonium ion.[9,10] The hydrolysis of the analogous 1,3-oxathiolanes, where an oxygen has been replaced by sulfur, would also appear to involve an A-1 mechanism. Thus, the marked enhancement of the rate by the *p*-methoxy substituent is undoubtedly due to resonance stabilization of an incipient carbonium ion in the transition state. The highly negative value of ρ indicates that the transition state has considerable carbonium ion character.[16] The linearity and slope (1.23) of the plot of log k_{obsd} *vs.* $-H_0$ also can be taken as evidence for an A-1 mechanism. Determination of whether the observed rate constants are proportional to the stoichiometric acid concentration or to h_0 has been a classic method for distinguishing between A-1 and A-2 mechanisms,[14] although criticisms have been made of this method and possible exceptions have been found.[17] Finally, the much faster rates of hydrolysis in D_2O than H_2O indicate that the protonation step is a preequilibrium process. Previous work on the acid-catalyzed hydrolysis of thioglycosides has also been interpreted in terms of an A-1 mechanism.[18]

There are, however, certain striking differences in the hydrolytic behavior of 1,3-dioxolanes and 1,3-oxathiolanes. Replacement of oxygen by sulfur produces a very large rate retardation. For example, in H_2O at 30°, 2-(*p*-methoxyphenyl)-1,3-dioxolane hydrolyzes 1330 times faster than 2-(*p*-methoxyphenyl)-1,3-oxathiolane, and *p*-methoxybenzaldehyde diethyl acetal hydrolyzes approximately 52,000 times faster.[19] The transition state for oxathiolane hydrolysis would appear to have more carbonium ion character than that for hydrolysis of 1,3-dioxolanes when 50% dioxane–H_2O is the solvent as evidenced by the linear $\rho^+\sigma^+$ plot. The *p*-methoxy substituent also greatly enhances the rate of hydrolysis of 2-(*p*-methoxyphenyl)-1,3-dioxolane in 50% dioxane–H_2O so that curvature is obtained in a Hammett[11] plot for hydrolysis of substituted benzaldehyde derivatives, but there is not sufficient carbonium ion character to give a good fit with the σ^+ constants, a pronounced downward curvature being obtained.[9] However, the value of ρ was found to be -3.35 for the 1,3-dioxolanes.

The D_2O solvent isotope effect ($k_{D_2O}/k_{H_2O} = 1.93$) is considerably less than normally found for A-1 acetal hydrolysis which usually gives ratios from 2.7 to 3.0.[9,10] The smaller isotope effect may be indicating that it is sulfur that is protonated in the kinetically important protonated intermediate. Preequilibrium protonation of sulfur might lead to a reduced solvent isotope effect compared to oxygen analogs because of differences in stretching and bending frequencies of –SH as compared to –OH bonds.[20] If this is indeed the explanation for the smaller solvent isotope effect, then the C–S bond must be breaking in the critical transition state as in VIII. This is a reasonable formulation since oxygen



VIII

would stabilize the intermediate carbonium ion much better than would sulfur,[21] and ring-opening reactions of this type generally proceed to give the most stable carbonium ion when two different heterocyclic atoms are in the ring.[22,23] The great carbonium ion character in the transition state could then be due to great

(16) De and Fedor[4] suggested that the hydrolysis of 1,3-oxathiolanes proceeds by an A-2 mechanism. In making this interpretation, emphasis was placed on the magnitude of ρ for hydrolysis in water. The ρ which they reported was considerably more positive than that found in the present study. However, upon correction of their rate constant for the *p*-nitro derivative, they obtain a ρ value in reasonable agreement with that reported in this work; L. R. Fedor, personal communication.

(17) R. W. Taft, Jr., N. C. Deno, and P. S. Skell, *Ann. Rev. Phys. Chem.*, **9**, 306 (1958); E. Whalley, *Trans. Faraday Soc.*, **55**, 798 (1959); J. Koskikallio and E. Whalley, *ibid.*, **55**, 815 (1959); H. Kwart and A. L. Goodman, *J. Am. Chem. Soc.*, **82**, 1947 (1960); A. J. Kresge and Y. Chiang, *ibid.*, **81**, 5509 (1959); R. H. Boyd, R. W. Taft, Jr., A. P. Wolfe, and D. R. Christman, *ibid.*, **82**, 4729 (1960).

(18) C. Bamford, B. Capon, and W. G. Overend, *J. Chem. Soc.*, 5138 (1962); R. L. Whistler and T. Van Es, *J. Org. Chem.*, **28**, 2303 (1963).

(19) The rate constants for hydrolysis of a number of substituted benzaldehyde acetals in H_2O are given in T. H. Fife and L. Brod, *ibid.*, **33**, 4136 (1968).

(20) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966).

(21) For example, chloromethyl ethyl ether hydrolyzes 1600 times faster than chloromethyl ethyl sulfide in aqueous dioxane: H. Böhme, H. Fischer, and R. Frank, *Ann.*, **563**, 54 (1949); H. Böhme, *Chem. Ber.*, **74**, 248 (1941).

(22) T. H. Fife and L. Hagopian, *J. Am. Chem. Soc.*, **90**, 1007 (1968).

(23) For example, 2-(substituted phenyl)-1,3-thiazolidines in acidic solution ring open to give a Schiff base (C–S bond cleavage) even though the predominant species at equilibrium must have nitrogen protonated; T. H. Fife and L. H. Brod, unpublished data.

C–S bond breaking being necessary to reach the transition state. The alternate explanation which cannot be conclusively eliminated is that C–O bond breaking occurs with the oxathiolanes to give a carbonium ion which is not as highly resonance stabilized by the adjoining sulfur as in the case of an adjoining oxygen. Both explanations are in accord with the slow rates of oxathiolane hydrolysis, but the former is preferred in view of the D_2O solvent isotope effect.

The ΔS^* value of -13.2 eu for hydrolysis of 2-phenyl-1,3-oxathiolane in 1.0 *M* HCl is more negative than would be expected for an A-1 reaction,[24] and could indicate some solvent involvement in the critical transition state. However, an A-2 mechanism involving attack of water on the protonated acetal can be ruled out since substitution of a methyl group at the reaction center in 2-phenyl-2-methyl-1,3-oxathiolane accelerates the reaction by a factor of 2, whereas a large retardation in rate would have been expected if solvent attack was taking place at that position.[25] It seems clear that with the 1,3-oxathiolanes bond breaking is of decidedly greater importance in the transition state than bond making with solvent.

Partially rate-determining protonation is less likely in view of the much faster rates in D_2O than H_2O and the high degree of carbonium ion character in the transition state as evidenced by the $\rho\sigma$ plots. Both pieces of evidence indicate that proton transfer is essentially complete. However, there is probably no sharp line of demarcation between these categories of mechanisms in terms of extent of proton transfer from hydronium ion.[2] 1,3-Dioxolanes also exhibit slightly negative ΔS^* values in their hydrolysis reactions. These negative ΔS^* values are very likely due to the cyclic nature of the compounds, and several explanations have been previously suggested.[9,19] The ΔS^* value for 2-phenyl-1,3-oxathiolane then need not be interpreted as indicating a departure from the mechanism supported by the other data.

The mechanism for oxathiolane hydrolysis in which proton transfer is nearly complete shows that a simple reduction in basicity of the substrate is not sufficient to change the mechanism to one *clearly* involving partially rate-determining protonation. It is probably also necessary that the bond-breaking process be made relatively easy as in the hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran.[2] Carbon–sulfur bond breaking, however, might be expected to be more difficult than breaking of the analogous C–O bond.[26]

An enzyme could enhance the bond-breaking process by distorting the substrate, thereby facilitating an ensuing general acid catalyzed reaction. It is possibly this factor that is leading to the faster rates of lysozyme-catalyzed hydrolysis of thioglycosides than would be expected on the basis of the chemical data since in the enzymatic reaction the glycosidic residue undergoing cleavage might be forced to assume a half-chair conformation.[3]

Acknowledgment. This work was supported by National Institutes of Health research grant GM-10613.

(24) F. A. Long, J. G. Pritchard, and F. A. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).

(25) The A-1 hydrolysis of acetophenone diethyl ketal is 33 times faster than benzaldehyde diethyl acetal.[10] However, in contrast, the A-2 hydrolysis of the tetramethylethylene glycol ketal of acetophenone is 540 times slower than that of the corresponding benzaldehyde derivative.[19]

(26) For example, hemithioacetals generally form more readily and are much more stable than the corresponding hemiacetals: E. Campaigne in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 134.