chromator combination was applied. All of the corrections are required at each wavelength involved in excitation and emission. Flourescence quantum yields are summarized in Table I.

Fluorescence Lifetimes. Nanosecond fluorescence lifetimes of solutions corresponding to those used for determining fluorescence quantum yields were measured on a phase shift instrument using a modulated nitrogen source. Argon instead of prepurified nitrogen was used to flush the fluorometric solutions. The lifetimes measured are reported in Table I.

Acknowledgment. We wish to thank the National Science Foundation for a grant which supported this work. We also thank Professors Roswell and Brand for help with the computer program required to obtain corrected fluorescence spectra and E. I. Du Pont de Nemours & Co. for the use of their phase-shift fluorescence lifetime apparatus.

Mechanism of Acid-Catalyzed Thiolactonization. Kinetic Evidence for Tetrahedral Intermediates

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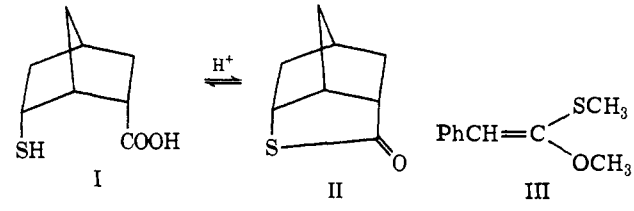
Received March 27, 1972

Abstract: The thiolactonization of the mercapto acid I in the pH range 0–5 (30°) proceeds *via* acid-catalyzed and pH-independent pathways. The reaction kinetics have been interpreted in terms of a mechanism involving a transition in the rate-determining step at pH 2.94; rate-limiting decomposition of cationic and neutral tetrahedral intermediates at pH >3 gives way to rate-limiting formation of the intermediates at lower pH. Both reaction steps appear to be subject to general acid–base catalysis by carboxylate buffers. The nonlinear dependence of the rate of lactonization of I on formate buffer concentration is suggested to result from self-association of buffer components to form catalytically inactive aggregates. The relevance of the present findings to the concept of "orbital steering" is discussed.

The first evidence for the participation of tetrahedral addition intermediates in thiol ester hydrolysis was obtained with thiol esters derived from trifluoroacetic acid.[2-4] Subsequently, it was shown that the pH–rate profile for the acid-catalyzed hydrolysis of methyl thiolformate could be explained by a mechanism which included tetrahedral intermediates in acid–base equilibrium.[5] The pathways of breakdown of the intermediates generated from ethyl trifluorothiolacetate and methyl thiolformate were found to differ significantly, accounting for the observation that hydrolysis of the former ester was inhibited in acid solution, while that of the latter exhibited acid catalysis.

Although the mechanism advanced for the hydrolysis of methyl thiolformate was in accord with the kinetic data provided, the pH–rate profile of the reaction did not unambiguously rule out other possibilities. It appeared desirable to investigate the hydrolysis of additional aliphatic thiol esters, both to place the favored mechanism on firmer grounds and to obtain quantitative information concerning the effect of structural changes on the modes of breakdown of the tetrahedral intermediates involved in these reactions.

The relatively slow rates of the acid-catalyzed hydrolysis of simple (*i.e.*, not bearing strongly electron-attracting substituents) aliphatic thiol esters at ambient temperature[6] prompted us to undertake the study of acid-catalyzed thiolesterification, whose mechanism should consist of the microscopic reverse of acid-catalyzed thiol ester hydrolysis. To ensure the rapid reaction rates which would allow kinetic study over a wide range of pH, we selected for detailed investigation the thiolesterification of the bicyclic mercapto acid I, whose high reported[7] rate of acid-catalyzed lactonization was well suited to our purposes. To our knowledge, no extended study of thiolesterification has been recorded.



I II III

Results

First-order rate constants for the thiolesterification of the sodium salt of I were determined in aqueous solution, 30°, μ = 1.0 (LiCl), by measuring the rate of increase of absorbance at 243 nm (Table I). At pH >2.7, weak catalysis by formate and acetate buffers was noted, similar to that seen in the hydrolysis of ethyl trifluorothiolacetate.[2] For buffer concentrations rang-

(1) Postdoctoral Research Fellow of the National Institutes of Health, 1971–1972.
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Table I. Rate Constants for the Thiolactonization of I[a]

pH[b]	Buffer	[M]	$10^3 k_{obsd}$, sec^{-1} [c]	$10^4 k_{B_t}'$, M^{-1} sec^{-1} [d]	$10^3 k_w$, sec^{-1} [d]
−0.21	HCl		61.7		
0.09			29.6		
0.40			16.5		
0.62			11.8		
0.79			7.73		
1.09			4.54		
1.49			2.75		
1.79			2.01		
2.09			1.55		
2.72	Formate	0.0388	1.07		
2.73		0.0582	1.11		
2.72		0.0776	1.16		
2.72		0.097	1.22	23.2	0.975
2.97		0.0388	0.833		
2.97		0.0582	0.875		
2.97		0.0776	0.915		
2.97		0.097	0.946	19.5[e]	0.76[e]
2.97		0.175	1.06		
2.97		0.291	1.22		
2.96		0.466	1.39		
2.97		0.582	1.46		
3.27		0.0388	0.523		
3.27		0.0582	0.552		
3.27		0.0776	0.587		
3.27		0.097	0.606	14.6	0.468
3.78	Acetate	0.0233	0.231		
3.77		0.0388	0.234		
3.77		0.0776	0.264		
3.77		0.155	0.309	6.12	0.214
4.28		0.0388	0.0936		
4.28		0.0582	0.107		
4.28		0.0776	0.117		
4.28		0.097	0.126	5.16	0.0765
4.74		0.0233	0.0450		
4.76		0.0388	0.0600		
4.76		0.0776	0.0697		
4.77		0.155	0.0977	3.67	0.0344
5.28		0.0388	0.0260		
5.28		0.0582	0.0305		
5.28		0.0776	0.0344		
5.28		0.097	0.0380	2.06	0.0183

[a] In H_2O, 30°, μ = 1.0 (LiCl). [b] Measured pH, except for HCl solutions, where pH = − log [HCl] − 0.22 (see Experimental Section). [c] Observed first-order rate constant. [d] k_{B_t}' and k_w are, respectively, the slopes and intercepts of plots of k_{obsd} *vs.* total buffer concentration at constant pH. [e] Data obtained at buffer concentrations below 0.1 *M* were used in the calculation of k_{B_t}' and k_w.

ing up to 0.1 *M*, plots of k_{obsd} *vs.* total buffer concentration at constant pH were approximately linear but deviated significantly from linearity when formate buffers up to 0.6 *M* were used (Figure 1). Increasing concentrations of methanol (up to 3.2%, v/v) had no effect on the rate of cyclization of the thiol acid at pH 2.97, 0.097 *M* formate buffer, the rate constants varying randomly in the range of 9.26–9.60 × 10^{-4} sec^{-1}, with an average value of 9.42 ± 0.11 × 10^{-4} sec^{-1}. The lack of solvent effect is in contrast to the behavior of the thiol esters ethyl trifluorothiolacetate[2] and methyl *S*-trifluoroacetylmercaptoacetate,[8a] where the rate of hydrolysis is significantly reduced by low concentrations of organic solvents.

The pH–rate profile for the thiolactonization reaction (using rate constants extrapolated to zero buffer concentration) exhibits two regions where log k_{obsd} is approximately linearly dependent on pH (slope = −1), with a bridging region of lesser slope (Figure 2). The limiting value of the second-order rate constant ($k_{obsd}/[H^+]$) for acid catalysis in the acidity range of 0.2–1.0 *M* HCl is 3.77 × 10^{-2} M^{-1} sec^{-1}.[8b]

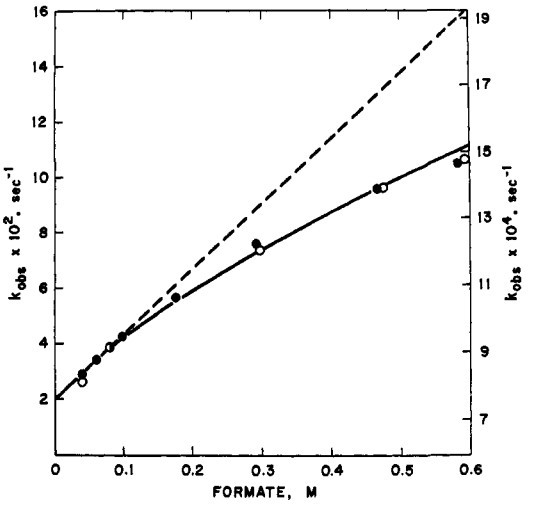


Figure 1. Effect of formate buffer concentration on the rate of lactonization of I (●, right ordinate) and of hydrolysis of the ketene acetal III (○, left ordinate) at pH 2.97, 30°. The solid line is calculated on the assumption that formate buffer dimers are not catalytically active (eq 7 and 8). The dashed line is based on eq 1, with k_w = 0.76 × 10^{-3} sec^{-1} and k_{B_t}' = 1.95 × 10^{-3} M^{-1} sec^{-1}.

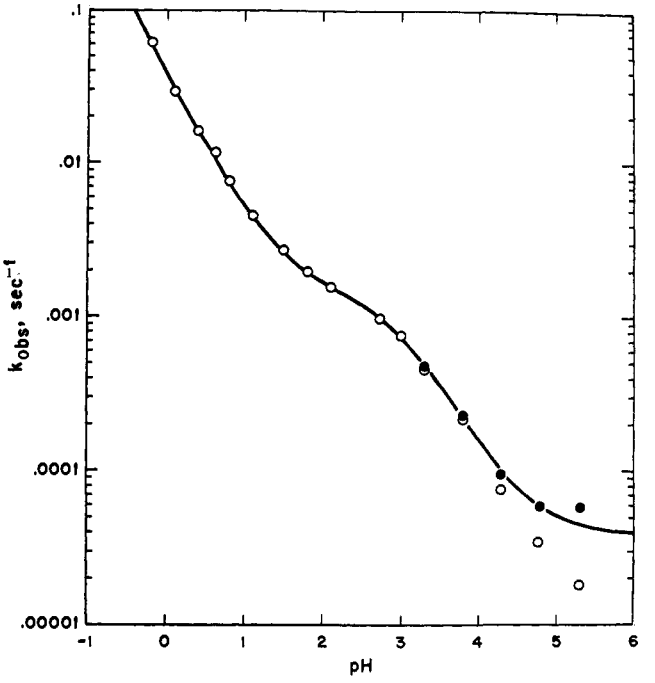
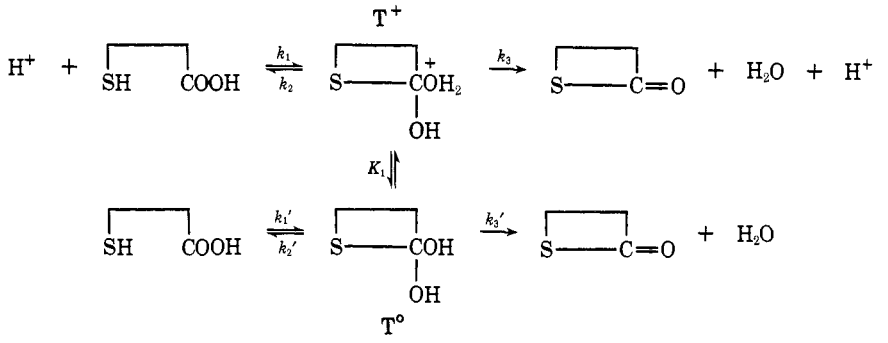


Figure 2. pH–rate profile for the lactionization of I in H_2O, 30°, μ = 1.0. ○, observed first-order rate constants. ●, observed first-order rate constants divided by the mole fraction of substrate in the neutral form. The solid line is calculated from eq 4, using the constants summarized in Table II.

(8) (a) R. J. Zygmunt and R. E. Barnett, *J. Amer. Chem. Soc.*, **94**, 1996 (1972). (b) The value of 3.77 × 10^{-2} M^{-1} sec^{-1} is based on hydronium ion *activity;* the corresponding constant based on hydrogen ion *concentration* is 6.24 × 10^{-2} M^{-1} sec^{-1}. The latter value may be compared to that of 4.38 × 10^{-2} M^{-1} sec^{-1} obtained by Storm and Koshland at 25° (20% ethanol–water, μ = 0.4) in the range of 0.1–0.4 *M* HCl.[7,9]

(9) D. E. Koshland, personal communication.

Scheme I



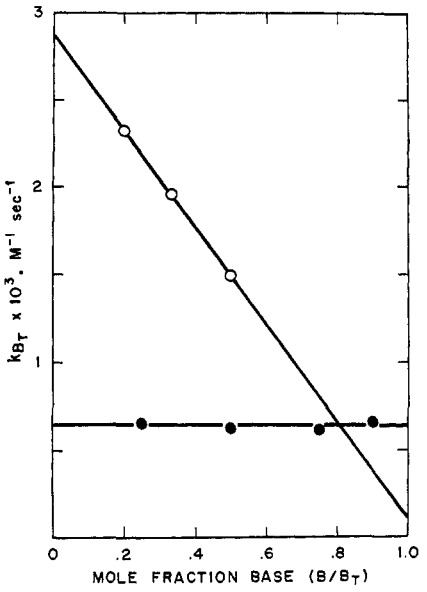


Figure 3. Dependence of the second-order rate constant for catalysis by acetate (●) and formate (○) buffers on the mole fraction of buffer in the conjugate base form.

At low buffer concentrations, the rate of lactonization increases linearly with total buffer and obeys eq 1, where k_w is the rate constant for cyclization in the

$$k_{obsd} = k_w + k_{B_t}'[B_t] \quad (1)$$

absence of buffer species. To evaluate the separate contributions of the acidic (k_{BH}) and basic (k_B) components of the buffers, the slopes (k_{B_t}') obtained from plots of eq 1 were first divided by the mole fraction of the substrate thiol acid in the neutral form (pK_a 4.94) to yield corrected second-order rate constants k_{B_t}. The dependence of the latter on the mole fraction of buffer in the conjugate base form (eq 2 and 3, and Figure

$$k_{B_t}[B_t] = k_B[B] + k_{BH}[BH] \quad (2)$$

$$k_{B_t} = k_{BH} + ([B]/[B_t])(k_B - k_{BH}) \quad (3)$$

3) indicates that both the basic and acidic species of acetate buffer catalyze the thiolactonization of the neutral mercapto acid I to about equal extents (k_{CH_3COOH} = 6.45 × 10^{-4} M^{-1} sec^{-1}, $k_{CH_3COO^-}$ = 6.34 × 10^{-4} M^{-1} sec^{-1}). In formate buffers, catalysis is predominantly by formic acid (k_{HCOOH} = 2.88 × 10^{-3} M^{-1} sec^{-1}); there appears to be a small but probably real catalysis by formate ion (k_{HCOO^-} = 1.1 × 10^{-4} M^{-1} sec^{-1}).

For reasons discussed below, the effect of formate buffers on the rate of hydrolysis of the ketene *O,S*-acetal III was studied at pH 2.97. As previously reported,[5] carboxylic acids catalyze the hydrolysis of the ketene acetal, but the dependence of rate on buffer concentration is not linear when formate buffers up to 0.6 *M* are used, and rates at high buffer concentrations fall below those expected from the rate increases caused by low concentrations of buffer (Figure 1).

Discussion

Mechanism of Thiolactonization. When expressed in terms of neutral substrate, the pH–rate profile for the lactonization of I exhibits the complex appearance which suggests the occurrence of a multistep process (Figure 2). The existence of two regions of zero slope and of two regions of negative unit slope in the plot of log *k* *vs.* pH is expected for an acyl-transfer reaction involving the participation of cationic and neutral intermediates in acid–base equilibrium;[10] this idealized pH–rate profile will seldom be observed, the more usual situation resembling that of Figure 2, with the particular values of the kinetic constants determining the precise shape of the pH–rate profile.

According to Scheme I, the thiolactonization reaction proceeds *via* cationic (T^+) and neutral (T^0) tetrahedral addition intermediates, each of which may be converted to thiolactone. The steady-state rate expression (eq 4)[11a] based on Scheme I is similar to that previously given to account for the hydrolysis of methyl thiolformate.[5,11b] Its principal features are the explicit inclusion of terms (P^+ and P^0) for the partitioning of the tetrahedral intermediates between reactants and products, as well as a composite constant (K') whose value indicates the pH at which a transition in the rate-determining step will occur if $P^+ \neq P^0$ (see Table II for definitions of these terms). Appropriate selection of values (Table II) for the parameters k_1, P^+, P^0 and K' of eq 4 generates a calculated curve

$$\frac{k_{obsd}}{f} = \frac{k_1([H^+]P^+ + K'P^0)([H^+] + K'(1 - P^0)/(1 - P^+))}{[H^+] + K'} \quad (4)$$

which is in satisfactory accord with the experimental observations (Figure 2). Implicit in Scheme I and the selected values of the rate constant ratios is the

(10) G. L. Schmir, *J. Amer. Chem. Soc.*, 90, 3478 (1968).

(11) (a) f = mole fraction of substrate in the neutral form; (b) the differences between eq 4 of this paper and eq 3 of ref 5 result from the different definitions of P^+ and P^0 in terms of the rate constants involved. In both studies, the partitioning ratios P^+ and P^0 were defined to denote the extent to which H_2O is expelled from the corresponding intermediates.

Table II. Definitions and Values of the Parameters Used in the Calculation of the pH–Rate Profile for the Lactonization of I[a,b]

P^+	$k_3/(k_2 + k_3)$	0.972
P^0	$k_3'/(k_2' + k_3')$	0.025
K'	$K_1(k_2' + k_3')/(k_2 + k_3)$	1.15×10^{-3} M ($pK' = 2.94$)
k_1		3.88×10^{-2} M^{-1} sec^{-1}
k_1'		1.55×10^{-3} sec^{-1}

[a] Parameters refer to Scheme I and eq 4. [b] The values of P^+, P^0, K', k_1, and k_1' are related by the equilibrium relation $k_1/k_2 = k_1'/k_2'K_1$, so that selection of values for four of the parameters determines the value of the fifth.

following description of the reaction mechanism. At pH >3, the rate-determining step of the lactonization reaction is the water- and acid-catalyzed breakdown of a neutral addition intermediate (T^0); at pH 2.94 (pK'), there occurs a transition in the rate-limiting step to water and acid-catalyzed formation of the intermediates.

The limiting value of $k_{obsd}/[H^+]$ at lowest pH (eq 5) is 3.77×10^{-2} M^{-1} sec^{-1}, and that for k_{obsd}/f at

$$\text{low pH} \quad k_{obsd}/[H^+] = k_1P^+ \tag{5}$$

high pH (eq 6) is 3.88×10^{-5} sec^{-1}, which leads to a

$$\text{high pH} \quad k_{obsd}/f = k_1P^0K'[(1 - P^0)/(1 - P^+)] = k_1'P^0 \tag{6}$$

value of 1.55×10^{-3} sec^{-1} for k_1'.

The dependence of the rate of lactonization of I on pH (Figure 2) is difficult to explain by any mechanism not involving a change in the rate-determining step and, hence, appears to require the postulation of intermediates on the reaction pathway. On the basis of the kinetics alone, however, it is not possible to assign the nature of the rate-limiting steps at high and low pH. A calculated curve identical with that of Figure 2 can be obtained from eq 4, using the values $P^+ = 0.028$, $P^0 = 0.975$, $K' = 1.15 \times 10^{-3}$ M, and $k_1 = 1.35$ M^{-1} sec^{-1}. Selection of these alternate values for the partitioning ratios P^+ and P^0 simply reverses the assignment of the rate-limiting steps, with formation of the intermediates being rate determining at pH >2.94 and their breakdown rate determining at lower pH.

In the case of the hydrolysis of methyl thiolformate, the assignment of the rate-limiting steps was based on a study of the effect of pH on the products of hydrolysis of the ketene acetal III.[5] Using the observation that intermediates related in structure to T^+ and T^0 broke down with predominant expulsion of CH_3OH at low pH and of CH_3SH at higher pH, it was concluded that the rate-limiting steps in thiol ester hydrolysis were mainly rate-determining formation of intermediates at high pH and their breakdown at low pH. Applying the principle of microscopic reversibility, we now suggest that, for thiolactonization, formation of intermediates is rate limiting at pH <3; at higher pH, the expulsion of water from the intermediates is rate determining, in accord with the parameters summarized in Table II. Similar reasoning was previously employed to define the nature of the rate-limiting steps in the alcoholysis of amides and the aminolysis of esters.[10,12,13]

With methyl thiolformate hydrolysis, the values of P^+, P^0, and pK' were 0.48, 0.021, and 1.23, respectively. The differences in the pathways of breakdown of the cationic species T^+ formed from methyl thiolformate and I are noteworthy. In the former case, H_2O and CH_3SH are expelled equally well, while with I, expulsion of H_2O is 35 times more rapid than that of the mercaptan. Although it is not presently possible to predict the effects of structural change on the values of the three constants, and hence on the pH–rate profile, there may exist a correlation between pK' and the pK_a of the acyl portion of the substrate, with the more acidic compounds undergoing the change in rate-limiting steps at lower pH.

Buffer Catalysis. The lactonization of I is subject to concurrent general-acid, general-base catalysis by carboxylic acid buffers (Figure 3), precedent for which exists in the lactonization of phenolic acids.[14] It is likely (see below) that both steps of the reaction are susceptible to catalysis; owing to the weak catalysis observed, and to complications at higher buffer concentrations, no attempt has been made to evaluate the separate influences of general acid–base catalysts on the formation and decomposition of the tetrahedral intermediates.

The nonlinear dependence of the rate of lactonization on formate buffer concentration (Figure 1) deserves comment. Similar observations have frequently been used as evidence for a change in rate-determining step with increasing buffer concentration.[12,13,15] If one step only of a two-step reaction is susceptible to catalysis, the rate of the reaction will vary with catalyst concentration as a rectangular hyperbola,[10] with the limiting rate at high buffer concentration being equal to that of the step not subject to catalysis. The data of Figure 1 can be fitted reasonably well to a rectangular hyperbola (by means of a double reciprocal plot), with a calculated maximum rate of 2.49×10^{-3} sec^{-1}. The expected rate of lactonization at pH 2.97 if formation of the intermediate had become entirely rate-determining is 1.55×10^{-3} sec^{-1}; if intermediate breakdown was completely rate limiting, the maximum rate would be 1.40×10^{-3} sec^{-1}.[16] It is probable that both reaction steps are catalyzed by buffer species. Effective catalysis is observed at pH 5.28 where breakdown of intermediates is rate determining. At pH 2.97, where both steps are about equally rate limiting, the rate of lactonization (1.46×10^{-3} sec^{-1}) has not yet become independent of buffer concentration at the highest concentration used; it is almost certain that, in the limit, the observed rate would exceed that pre-

(12) B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 917 (1967).
(13) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).
(14) S. Milstein and L. A. Cohen, *ibid.*, **92**, 4377 (1970).
(15) (a) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962); (b) R. B. Martin, A. Parcell, and R. I. Hedrick, *ibid.*, **86**, 2406 (1964); (c) W. P. Jencks and M. Gilchrist, *ibid.*, 86, 5616 (1964); (d) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964); (e) G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, 87, 3855 (1965); (f) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, **20**, 1892 (1966); (g) D. R. Robinson and W. P. Jencks, *J. Amer. Chem. Soc.*, **89**, 7098 (1967); (h) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 477.
(16) It may be shown[10] from eq 4 that, in the region of the pH-independent, rate-limiting formation of T^0, $k_{obsd}/f = P^+k_1'$. At pH 2.94, there would also be a small contribution of the acid-catalyzed formation of the intermediates. The limiting value of k_{obsd}/f in the region of acid-catalyzed breakdown of intermediates is equal to $P^+k_1' \cdot [H^+]/K'$.

dicted for uncatalyzed, rate-determining formation of the intermediate (1.55×10^{-3} sec^{-1}). The apparent fit of the data to a hyperbola is thus fortuitous and probably does not represent the approaching transition from a catalyzed to an uncatalyzed reaction step.

The nonlinear dependence of rate on buffer concentration at pH 2.97 most likely results from self-association of buffer components to form catalytically inactive species. A similar explanation was offered by Gold and coworkers to account for nonlinear catalysis of the hydrolysis of ketene *O,O*-acetals by acetate buffers.[17] Association constants of 0.4 and 1.6 M^{-1} were estimated for the formation of acetic acid and acetic acid–acetate ion dimers, respectively. Using the model of Gold, *et al.*, but without explicit consideration of the ionic species involved in dimer formation, the solid curve of Figure 1 was calculated from eq 7 and 8, where B_f = monomeric buffer, $k_{B_1} = 1.95 \times 10^{-3}$ M^{-1} sec^{-1}, $k_w = 0.76 \times 10^{-3}$ sec^{-1}, and $K = 0.77$ M^{-1}. While this calculation should not be taken too seriously, the required association constant is of reasonable magnitude, and the proposed model may prove to be correct. That the addition of up to 3.2% methanol does not affect the rate of lactonization suggests that the deviation from linearity at high buffer is not the result of a solvent effect by the formic acid component of the buffer, although the rate of hydrolysis of acyl-activated thiol esters is appreciably decreased by small amounts of organic solvents.[2,8a]

$$2B_f \underset{}{\overset{K}{\rightleftharpoons}} \text{dimer} \quad (7)$$

$$k_{obsd} = k_w + k_{B_f}[B_f] \quad (8)$$

Strong support for the present hypothesis comes from the similar nonlinear effects of increasing formate buffer concentration on the rate of hydrolysis of the ketene acetal III (Figure 1). The kinetic data for III have been normalized with respect to those for I by adjusting the ordinate scales so that the intercepts (at zero buffer concentration) and the observed rates at the highest buffer concentration (0.46 *M*) coincide. Clearly, formate buffer affects the hydrolysis of III in a manner precisely parallel to its effect on the lactonization reaction. Regardless of the validity of the dimerization model, it seems that the nonlinear behavior summarized in Figure 1 represents a property of the formate buffer used and is not intrinsic to the reactions studied. In general, it would not have been expected that the hydrolysis of III, proceeding *via* rate-determining protonation at the olefinic carbon,[5,17] would exhibit a change in the rate-limiting step with increasing buffer concentration, although a case of such behavior has recently been reported for vinyl ether hydrolysis.[18]

The opportunity to observe kinetic evidence for self-association of carboxylate buffers may well depend on the precise experimental conditions of pH, temperature, and ionic strength employed. In a number of studies of acyl transfer, reaction rates have been reported to increase linearly with formate buffer, at concentrations sometimes exceeding 1 *M*.[2,14,19]

Lactonization Reactions and "Orbital Steering." Recent studies suggest that the lactonization of substituted coumarinic acids involves transient intermediates.[20] At least for coumarinic acid itself, the kinetic data[20a] strongly support a mechanism analogous to that of Scheme I, with a transition in the rate-determining step at about pH 3. It is probable that rate-limiting breakdown of intermediates in weakly acidic solution gives way to rate-limiting cyclization at lower pH, *i.e.*, that the expulsion of water from a cationic intermediate is faster than that of phenolic oxygen, although no direct experimental data are available on this point. Possibly, transitions in the rate-determining step with pH will be observed in other cases of lactonization of phenolic acids, as well as in the hydrolysis of phenyl esters. It should be noted, however, that careful scrutiny of the published data for the lactonization of some substituted coumarinic acids[20b] indicates little or no evidence for intermediates; it appears that minor structural changes may significantly alter the behavior of closely related compounds.

The recent introduction[7] of the concept of "orbital steering" to explain certain aspects of rapid intramolecular reactions has engendered much interest and controversy.[21] Regardless of the relative merits of the various points of view, it seems to us that a quantitative evaluation of this proposal requires a detailed understanding of the mechanisms of the reactions used as the experimental basis for this concept. The present study clearly shows that, in the pH range employed (0.1–0.4 *M* HCl),[7,9] the lactonization of I[7] occurs with rate-limiting formation of a cationic tetrahedral intermediate. In the absence of additional data, it is not certain that the same step was rate determining with the other[7] thiolactonizations investigated. The situation with regard to the mechanism of the lactonization of the various aliphatic hydroxy acids studied[7] is much less clear. From studies of oxygen-18 exchange, it is known that the acid-catalyzed hydrolysis of ethyl benzoate[22] and ethyl acetate[23] proceeds with predominant (but not exclusive) rate-limiting formation of an addition intermediate. If these findings are applicable to acid-catalyzed lactonization, it would seem that the rate-determining step in these reactions consists mainly of the acid-catalyzed decomposition of an intermediate. Conclusions based on a comparison of reactions proceeding *via* different rate-limiting steps must be viewed with reserve, if the possible impact of these differences has not been explicitly considered.

Experimental Section[24]

6-*endo*-Mercaptobicyclo[2.2.1]heptane-2-*endo*-carboxylic acid thiolactone (II) was synthesized by a modification of the method of

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Storm and Koshland.[7,9] Cyclopentadiene [bp 45° (lit.[25] 38–46°)], freshly distilled from dicyclopentadiene[25] (Eastman), was condensed with acrylic acid to give a mixture of *endo*- and *exo*-5-norbornene-2-carboxylic acid,[26] bp 99° (1.4 mm) [lit.[27] 118.5–120.5° (5.7 mm)]. The acid (28.2 g, 0.2 mol), 27 g (0.25 mol) of $SOCl_2$, and 3 g of Mg turnings were refluxed in 50 ml of benzene for 1 hr. After cooling, filtration, and removal of excess $SOCl_2$ and benzene, vacuum distillation afforded 25 g (81%) of the acid chloride, bp 57–58° (1.4 mm) [lit.[7,9] 135–140° (10 mm)].

The acid chloride (25 g, 0.16 mol) was immediately added dropwise to a stirred solution of 22.4 g (0.4 mol) of KOH in 90 ml of 90% ethanol which had been saturated with H_2S.[28] After stirring for 3 hr, the reaction mixture was filtered and the solvent removed under vacuum. The remaining solid was dissolved in 75 ml of H_2O, acidified to pH 1 with concentrated HCl, and extracted with ether. The ether layer was washed repeatedly with aqueous sodium bicarbonate solution until an infrared spectrum of an aliquot drawn from the ether layer showed that no carboxylic acid remained. The ether phase was then dried over anhydrous calcium sulfate and the ether distilled *in vacuo*. The residual oil was sublimed at reduced pressure (1–3 mm) and 100°, giving 1.6 g of II which was recrystallized from ethanol–H_2O: mp 120.5–122°; ir (Nujol) 1695 cm^{-1} (C=O); uv max (95% ethanol) 240 nm (ϵ 3380), (3% CH_3CN–H_2O) 243 nm (ϵ 3600); nmr (CCl_4) δ 3.70 (m, 1, γ hydrogen), 3.15 (m, 1, α hydrogen); mass spectrum *m/e* (rel intensity) 154 (42) (molecular ion), 79 (75), 78 (24), 66 (100), 39 (32).[29]

Anal. Calcd for $C_8H_{10}OS$ (154.24): C, 62.30; H, 6.54; S, 20.79. Found: C, 61.99; H, 6.68; S, 20.12.

For kinetic studies the monosodium salt of I was prepared from the thiolactone by stirring a suspension of 2 mmol of II in a mixture of 40 ml of H_2O and 2 ml of ethanol, containing 2 mmol of NaOH, at 50–60° for 1 hr, followed by lyophilization.

Since small amounts of a by-product (probably the disulfide) produced by this method of hydrolysis interfered with attempts to determine the dissociation constant of the sodium salt of I by potentiometric titration, the following procedure was used to prepare samples for this purpose. A solution of 35.8 mg (0.23 mmol) of II in 1 ml of 95% ethanol was added to 9.25 ml of a rapidly stirred solution of 0.108 *M* NaOH (μ = 1.0) through which nitrogen was bubbled. After 6 min, 0.79 ml of 1 *M* HCl was added to bring the pH to neutrality and a 5-ml aliquot of the solution was immediately titrated with 0.5 *M* HCl. The resulting pK_a was 4.94 (8.3% ethanol–H_2O, μ = 0.925, 30°).

Kinetic Methods. Acetonitrile was purified as previously described.[30] Buffers and inorganic salts were of reagent grade and were used without further purification. Glass-distilled water was employed in the preparation of all solutions.

The thiolactonization of I was studied at 30° in aqueous solution, μ = 1.0, adjusted with added LiCl. Constant pH was maintained with HCl at pH $\leq$2.5; at higher pH, formate or acetate buffers were used at concentrations generally between 0.02 and 0.10 *M*. In 0.005–0.01 *M* HCl solutions (μ = 1.0, LiCl) the equation pH = $-\log$ [HCl] $-$ 0.22 is obeyed and was used in the calculation of pH below pH 2.10. At other pH values, a Radiometer PHM 4d meter was employed to measure pH at the end of each reaction. All pH measurements were made at 30°. pK_a values for formic and acetic acid were found to be 3.28 and 4.28, respectively, by determining the pH of at least three different buffer ratios of each acid under the conditions of the kinetic measurements.

Rates of thiolactonization of the sodium salt of I were determined spectrophotometrically by following the increase in absorbance at 243 nm. Reactions were carried out in the water-jacketed cell holder of a Cary Model 15 spectrophotometer thermostated at 30.0 $\pm$ 0.2° and were initiated by the addition of 0.01 ml of a stock solution of the Na salt of I in H_2O to 3 ml of aqueous buffer solution containing *ca.* 10^{-4} *M* Versene. The final concentration of substrate was about 2×10^{-4} *M*. Reactions were followed for at least 3 half-lives and generally to greater than 6. Rate constants were calculated using the integrated form of the first-order rate equation.

At all pH values in the range 0–5.3, final absorbance values were generally 85–90% of those expected on the basis of the known absorbance of the pure thiolactone. Since the final absorbances did not decrease measurably at pH values where the carboxyl group of I is extensively ionized, it is probable that the apparently incomplete lactonization does not represent the establishment of a detectable equilibrium between mercapto acid and thiolactone. The most likely explanation of the low infinity values is the presence of a nonlactonizable contaminant, such as the disulfide of I.

The hydrolysis of 1-methoxy-1-methylthio-2-phenylethylene (III) was studied in 3% CH_3CN–H_2O, μ = 0.97, 30°. Rate constants were determined spectrophotometrically (ketene acetal at *ca.* 1×10^{-4} *M*) as previously described,[5] except that only data taken after the first half-life were plotted in order to avoid interference from reaction of the more reactive isomer.

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