lute sodium hydroxide solution in order to complete formation of 2. Good agreement was obtained when both methods were used.

The value of k_{obsd} for each run was obtained from the slope of $\ln(1/[1 - (A_t - A_0)/(A_\infty - A_0)])$ *vs.* time in seconds, and could be determined either graphically or by a least-squares fit of the data points by computer. The values of k_{obsd} for a series of buffer dilutions, when used to obtain a second order rate constant by plotting *vs.* catalyst concentration, were first corrected for minor differences in hydroxide ion concentration. Choosing the hydroxide ion concentration of the most concentrated buffer as the reference, $[OH^-]_{ref}$, the values of k_{obsd} for series were then corrected according to the expression

$$k_{obsd\ corr} = k_{obsd\ uncorr} + k_{OH}([OH^-]_{ref} - [OH^-]_{obsd})$$

The values listed as k_{obsd} throughout this paper are values of $k_{obsd\ corr}$. Temperature dependence measurements were conducted by use of the constant temperature water circulator at 20, 25, 30, and 35° and plots of $\ln k$ *vs.* $1/T(°K)$ showed good linearity and yielded a slope of $-E_a/R$. The other activation parameters were calculated as indicated in Table V. The values of k_{AB} at each temperature were obtained from the slope of the linear portion of a plot of k_{obsd} *vs.* [CMA][CMAH$^+$]. The value obtained at 25° by this method was identical with that obtained by first subtracting k_B and k_A terms as described in the Results section.

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The Mechanism of the Acid-Catalyzed Hydrolysis of Methyl Thiolformate

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Abstract: The pH–rate profile for the hydrolysis of methyl thiolformate in H_2O (30°) has been determined in the pH range 0–4.6. The dependence of the reaction rate on acidity has been interpreted in terms of a mechanism involving the participation of cationic and neutral tetrahedral addition intermediates, with a change in rate-determining step occurring at pH 1.2. In a parallel study, the hydrolysis of the ketene *O,S*-acetal I has been found to be subject to catalysis by hydronium ion and acetic acid. The products of the reaction vary with pH, the predominant product at acid pH being the thiol ester III, while mainly the oxygen ester IV is formed at pH > 3. The observation that the effect of pH on the rate of the reaction does not parallel its influence on the nature of the reaction products supports the postulation of at least one intermediate on the reaction pathway. The properties of the related intermediates formed in the hydrolyses of methyl thiolformate and of I have been compared and found to be in general agreement.

Kinetic studies of the hydrolysis of thiol esters were reported at least as early as 1948,[2] and continued sporadically for the next decade.[3] The first evidence for the formation of tetrahedral addition intermediates in thiol ester hydrolysis was described by Fedor and Bruice in their important investigation of the hydrolysis of ethyl trifluorothiolacetate;[4] their conclusions, based on kinetic arguments, were later confirmed by oxygen exchange experiments.[5] So far as we are aware, direct evidence for tetrahedral intermediates exists only for thiol esters derived from trifluoroacetic acid.[4–6]

The present investigation of the hydrolysis of methyl thiolformate was undertaken to establish whether tetrahedral intermediates could be shown to be a general feature of thiol ester hydrolysis. If this were the case, we were interested in obtaining information concerning the possible existence of various ionic forms of the intermediates, and in determining the pathways of breakdown of each species.

The generation of the intermediates of acyl transfer reactions by indirect routes which do not lie on the main reaction path for acyl transfer has provided a useful ancillary approach to the study of the properties of these transient intermediates.[7] For instance, the assignment of the nature of the rate-limiting steps under various conditions in the aminolysis of esters and in the alcoholysis of amides was facilitated by parallel studies of the hydrolysis of imidate esters.[8–11] With regard to

(1) Postdoctoral trainee of the National Institutes of Health, 1970–1971.
(2) J. R. Schaefgen, *J. Amer. Chem. Soc.*, **70**, 1308 (1948).
(3) (a) H. Böhme and H. Schran, *Chem. Ber.*, **82**, 453 (1949); (b) P. N. Rylander and D. S. Tarbell, *J. Amer. Chem. Soc.*, **72**, 3021 (1950); (c) B. K. Morse and D. S. Tarbell, *ibid.*, **74**, 416 (1952); (d) L. H. Noda, S. A. Kuby, and H. A. Lardy, *ibid.*, **75**, 913 (1953); (e) E. Heilbronn, *Acta Chem. Scand.*, **12**, 1481 (1958).
(4) L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **87**, 4138 (1965).
(5) M. L. Bender and H. d'A. Heck, *ibid.*, **89**, 1211 (1967).
(6) R. Barnett and W. P. Jencks, *J. Org. Chem.*, **34**, 2777 (1969).
(7) G. L. Schmir, *J. Amer. Chem. Soc.*, **90**, 3478 (1968).
(8) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965).
(9) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

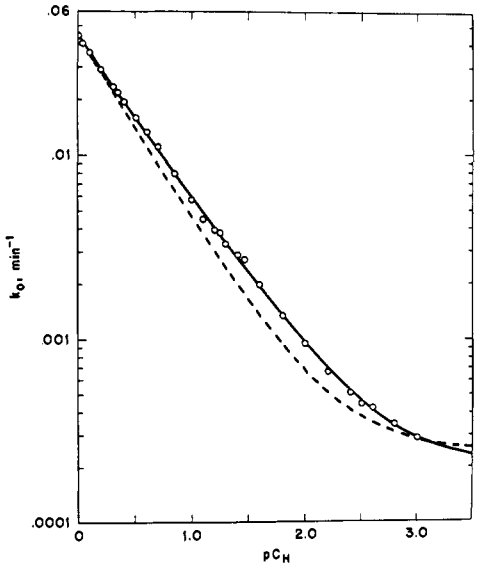
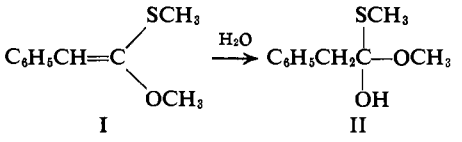


Figure 1. pH–rate profile for the hydrolysis of methyl thiolformate in H_2O, 30°, μ = 0.97. The solid and dashed curves are calculated from eq 3 and 2, respectively, using the constants given in the text.

the putative intermediates of thiol ester hydrolysis, the hydrolysis of the ketene *O,S*-acetal I should proceed *via* the intermediate II, closely related to the intermediates



I II

postulated in thiol ester hydrolysis. For this reason, the results of the study of the hydrolysis of I are also reported in the present paper.

Results

The Hydrolysis of Methyl Thiolformate. First-order rate constants for the disappearance of the thiol ester in aqueous solution, 30°, μ = 0.97 (LiCl) are summarized in Table I. At the relatively low concentrations of acetate buffer used (<0.08 *M*), there is no evidence for significant general acid–base catalysis, although weak catalysis was seen in the hydrolysis of ethyl trifluorothiolacetate.[4] An interesting feature of the pH dependence of the rate of hydrolysis of methyl thiolformate is that a plot of log k_{obsd} *vs.* pH in the range of pH 0–2 exhibits acceptable rectilinear behavior, but with a slope of about 0.8 (Figure 1). Some additional rate measurements are recorded in Table II. Substitution of KCl for LiCl has little effect on the reaction rates. An increase in ionic strength from 0.97 to 3.0 *M* (with LiCl) leads to rate increases of 40–60%; it may be noted, however, that the ratios of the rate constants for reactions carried out at pH 0.3 and 2.0 are nearly equal for 0.97 and 3.0 *M* ionic strength (being 25 and 27, respectively). This observation suggests that the pH–rate profiles are similar at both ionic strengths, and consequently, that the nonintegral slope observed at μ = 0.97 is not the result of substitution of LiCl for HCl as pH is increased.

(10) B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 917 (1967).
(11) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

Table I. pH–Rate Profile for the Acid-Catalyzed Hydrolysis of Methyl Thiolformate[a]

pC$_H$[b]	Buffer	$k_0 \times 10^2$, min^{-1} [c]	$k_{calcd} \times 10^2$, min^{-1} [d]
0.013	HCl	4.47 ± 0.08[e]	4.47
0.043		4.06[f]	4.18
0.110		3.70	3.62
0.208		2.88	2.92
0.314		2.36	2.35
0.360		2.19	2.12
0.411		1.94	1.91
0.509		1.59	1.56
0.615		1.34	1.26
0.712		1.12	1.04
0.848		0.791	0.792
1.01		0.569	0.581
1.11		0.476 ± 0.012[e]	0.484
1.20		0.396	0.410
1.26		0.383	0.367
1.30		0.330	0.340
1.41		0.288	0.278
1.47		0.270	0.252
1.61		0.198	0.193
1.81		0.135	0.134
2.01		0.0950	0.0945
2.21		0.0673	0.0684
2.41		0.0513	0.0517
2.51		0.0445	0.0456
2.61		0.0426	0.0406
2.80		0.0326	0.0338
3.01		0.0291	0.0290
3.65	Acetate[g]	0.0216	
3.63		0.0222	
3.63		0.0220	
4.64	Acetate[h]	0.0256	
4.64		0.0265	
4.63		0.0267	

[a] In H_2O, 30°, μ = 0.97 *M* (LiCl), except where indicated. [b] pC$_H$ = −log [HCl], except for experiments in acetate buffer, where measured pH is given. [c] Observed first-order rate constant. [d] First-order rate constants calculated from eq 3, using constants of Table IV. [e] Average of four determinations. [f] μ = 0.93 *M*. [g] Acetate buffer at 0.019, 0.058, and 0.078 *M*, respectively. [h] Acetate buffer at 0.039, 0.058, and 0.078 *M*, respectively.

Table II. Effect of Added Salts on Rates of Hydrolysis of Methyl Thiolformate[a]

pC$_H$[b]	μ, *M*	[KCl], *M*	[LiCl], *M*	$k_0 \times 10^2$,[c] min^{-1}
0.423	0.95	0.57		1.75
0.724	0.95	0.76		0.955
1.025	0.95	0.84		0.566
0.31	3.0		2.51	3.59
1.31	3.0		2.95	0.547
2.01	3.0		2.99	0.134

[a] In H_2O, 30°. [b] pC$_H$ = −log [HCl]. [c] Observed first-order rate constant.

Under comparable aqueous conditions, methyl thiolformate ($t_{1/2}$ 15.5 min at 30°, 1 *N* HCl) is hydrolyzed 53 times more rapidly than isobutyl thiolacetate,[3d] and nearly as rapidly as ethyl trifluorothiolacetate ($t_{1/2}$ 5.8 min),[4] owing, of course, to the onset of acid inhibition with the latter compound at pH < 2. In the pH range for the pH-independent water-catalyzed reaction, the acyl-activated thiol esters ethyl trifluorothiolacetate[4] (30°) and ethyl *S*-trifluoroacetylmercaptoacetate[6] (25°) undergo hydrolysis 2000 and 19,000 times faster, respectively, than methyl thiolformate.

The Hydrolysis of the Ketene *O,S*-Acetal. The substance isolated from the synthesis of I by a published

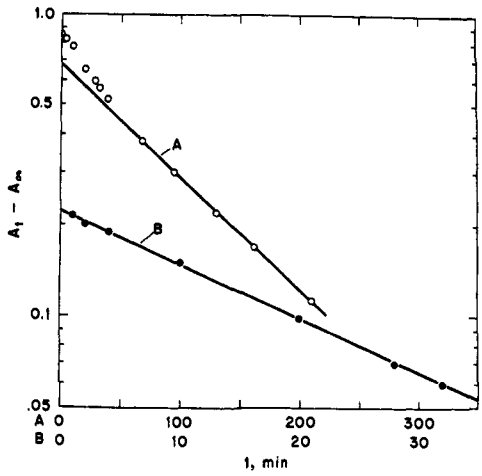
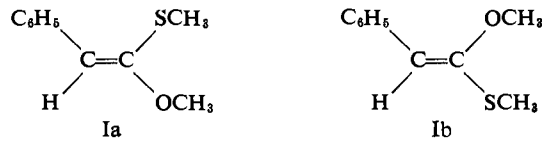


Figure 2. Semilogarithmic plot of absorbance data for the hydrolysis of I (0.018 M acetate buffer, pH 5.57, I at 5.35 $\times$ 10^{-5} M): A, complete reaction (upper abscissa scale); the line drawn through the points obtained in the latter part of the reaction is used to calculate the rate constants for the slow component; B (lower abscissa scale), the line is drawn through the points obtained in the early part of the reaction, after correction for the absorbance contribution by the slow component.

procedure[12a] appears to consist of a mixture of the geometrical isomers Ia and Ib.[12b,d] On the basis of



nmr data (see Experimental Section), the major component (approximately 70% of the mixture) is provisionally assigned the structure Ia. Hydrolysis of I results in the quantitative formation of mixtures of the thiol ester III and of its oxygen counterpart IV.

$C_6H_5CH_2COSCH_3$ III $C_6H_5CH_2COOCH_3$ IV

A. Kinetic Studies. The rate of hydrolysis of I was measured in 10% CH_3CN–H_2O, 30°, μ = 0.45 (KCl), in the pH range 0.35–5.55. Owing to unequal rates of hydrolysis of the isomers Ia and Ib, first-order plots were not linear (Figure 2A) but could be resolved into the component reactions (see Experimental Section). The resulting rate constants are presented in Table III. At fixed pH, the rate of hydrolysis of I is linearly dependent on the concentration of acetate buffer; rate constants extrapolated to zero buffer concentration are also given in Table III (last column). At zero buffer concentration, the hydrolysis of both Ia and Ib obeys the rate law $k_0 = k_H[H^+]$, with k_H = 700 and 2180 M^{-1} min^{-1} for Ia and Ib, respectively (Figure 3). No water reaction was detected. The conclusion that Ia is the less reactive isomer is based on the observation that, at zero time, the slowly reacting component

(12) (a) R. Raap, *Can. J. Chem.*, **46**, 2251 (1968). For an alternate synthesis, see Y. A. Boiko, B. S. Kupin, and A. A. Petrov, *J. Org. Chem. USSR*, **2**, 1893 (1966). (b) The alkylation of ethyl thionopropionate in alkaline medium gives rise to a mixture of the corresponding *cis*- and *trans*-ketene *O,S*-acetals.[12c] (c) P. J. W. Schuijl and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **87**, 929 (1968). (d) The sample of I used to obtain the published[12a] nmr spectrum was prepared by alkylation with methyl iodide (rather than with dimethyl sulfate). It is possible that the composition of the product with respect to geometrical isomers is dependent on the nature of the methylating agent used (R. Raap, personal communication).

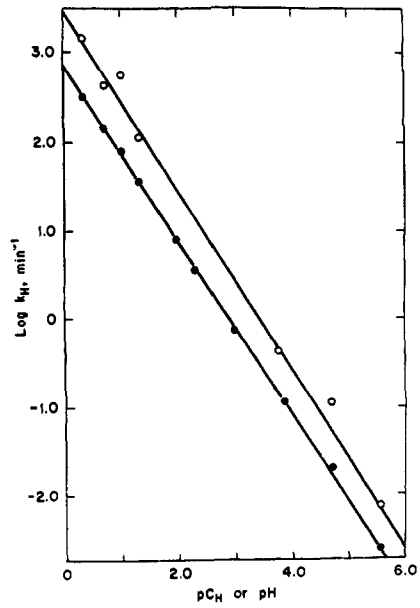


Figure 3. pH dependence of the rate constants for the hydrolysis of the two isomers of I in 10% CH_3CN–H_2O, 30°, μ = 0.45. At pH > 3, the rate constants are those calculated for zero buffer concentration. The lines are drawn with slope = −1.

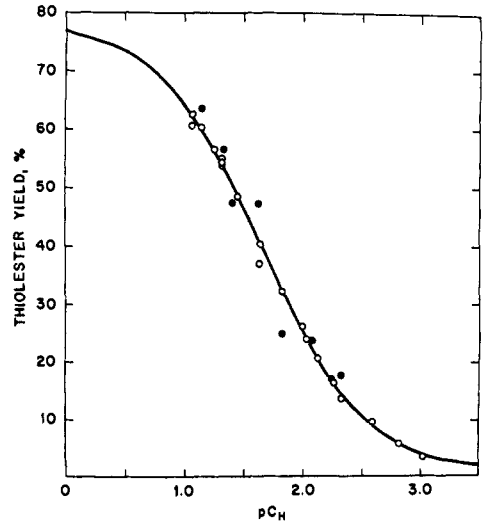


Figure 4. Effect of pH on the yield of thiol ester III formed on the hydrolysis of I: ○, spectrophotometric assay; ●, hydroxylamine assay. The line is the calculated titration curve of an acid of pK' 1.66, with asymptotes at 78.5 and 0.9%.

accounts for about 75% of the total absorbance at 280 nm (Figure 2). Comparable rate differences have been reported for the acid-catalyzed hydrolysis of the geometrical isomers of β-substituted vinyl ethers, the cis isomers reacting two–seven times faster than the trans compounds.[13]

The catalysis by acetate buffer appears to be due solely to acetic acid, with catalytic coefficients of 2.5 ± 0.1 and 14.4 ± 0.4 M^{-1} min^{-1} for the hydrolysis of Ia and Ib, respectively.[14]

B. The Reaction Products. The yield of the thiol ester III produced upon hydrolysis of the ketene *O,S*-acetal I increases with decreasing pH (Figure 4). The

(13) (a) T. Okuyama, T. Fueno, H. Nakatsuji, and J. Furukawa, *J. Amer. Chem. Soc.*, **89**, 5826 (1967); (b) P. Salomaa and P. Nissi, *Acta Chem. Scand.*, **21**, 1386 (1967); (c) T. Okuyama, T. Fueno, and J. Furukawa, *Bull. Chem. Soc. Jap.*, **43**, 3256 (1970).

(14) Calculated using the value of pK_a = 4.76 for acetic acid under these conditions.[8]

Table III. Rate Constants for the Hydrolysis of the Two Isomers of 1-Methoxy-1-methylthio-2-phenylethylene[a]

pH[b]	Buffer	[Buffer], M	k_0, min^{-1} [c]	Slope, M^{-1} min^{-1} [d]	Intercept, min^{-1} [d]
		Slow Component			
0.35	HCl	0.45	319		
0.70		0.20	141		
1.00		0.10	69		
1.30		0.05	35.4		
1.97		0.0101	7.98		
2.27		0.0536	3.61		
3.00		0.001	0.732		
3.83	Acetate	0.009	0.146		
3.87		0.045	0.228		
3.84		0.09	0.315		
3.81		0.18	0.511	2.12	0.128
4.73		0.009	0.0305		
4.71		0.045	0.081		
4.70		0.09	0.144		
4.71		0.18	0.227	1.40	0.0180
5.57		0.018	0.00834		
5.56		0.045	0.0125		
5.56		0.09	0.0332		
5.57		0.18	0.0606	0.325	0.0023
		Fast Component			
0.35	HCl	0.45	1430		
0.70		0.20	423		
1.00		0.10	606		
1.30		0.050	114		
3.83	Acetate	0.009	0.534		
3.87		0.045	0.955		
3.84		0.09	1.62		
3.81		0.18	2.64	12.3	0.432
4.73		0.009	0.161		
4.71		0.045	0.336		
4.70		0.09	0.876		
4.71		0.18	1.31	6.90	0.119
5.57		0.009	0.0407		
5.56		0.045	0.0851		
5.56		0.09	0.189		
5.57		0.18	0.376	2.06	0.0072

[a] At 30° in 10% acetonitrile–water, μ = 0.45 M. [b] In HCl solution, "pH" is defined as −log [HCl]. [c] Observed first-order rate constant. [d] Slopes and intercepts of plots of k_0 *vs.* total buffer concentration.

results of the hydroxylamine assay were in general accord with the more precise direct spectrophotometric measurements. The transition from the formation of the ester IV (and methanethiol) to that of the thiol ester (and methanol) is accurately described by the sigmoid curve characteristic of the dissociation of an acid of pK = 1.66 ± 0.03, with asymptotes at 78.3% (at low pH) and at 0.9% (at high pH).[15] Although reliable measurements of the yield of thiol ester could not be obtained at pH < 1.05, where the observed yield is only 80% of the calculated asymptotic value, the good fit of the spectrophotometric data to the calculated sigmoid curve strongly supports the conclusion that the yield of thiol ester in acid solution is significantly lower than 100%. While it would have been desirable to determine the products of hydrolysis of each of the isomers of I separately, it is probable that, for both compounds, the effect of pH on the nature of the hydrolysis products is independent of the effect of pH on the rate-limiting step of the hydrolytic reaction.

Discussion

It is well known that the hydrolysis of thiol esters[2,3a,d,e,6,17] and of thiol acids[18] is subject to acid catalysis. On the basis of limited data, it has been variously concluded that the rate of hydrolysis is directly proportional to the concentration of hydrogen ion,[2,3d] that a water-catalyzed reaction occurs concurrently with acid catalysis,[6,17] and that the rate-determining step is the uncatalyzed or acid-catalyzed attack of water on the thiol ester.[3d,e,6] With the exception of the hydrolysis of phenyl thiolformate,[6] insufficient data were reported in these studies to allow a critical appraisal of various mechanistic possibilities. Curiously, the only thiol esters whose hydrolysis in acid solution is known to proceed *via* tetrahedral intermediates suffer acid inhibition rather than acid catalysis of the rate of hydrolysis.[4-6] In what follows, we consider the proposition that tetrahedral addition compounds are generally transient intermediates in the acid-catalyzed hydrolysis of thiol esters.

The Mechanism of Hydrolysis of the Ketene *O,S*-Acetal. Although ketene *O,S*-acetals have been available at least since 1960,[12a,c,19] no study of the mechanism of their hydrolysis seems to have been carried out. The principal experimental findings of the present work are: (1) the rate-determining step of the overall reaction is catalyzed by hydronium ion and by general acids (acetic acid); (2) the dependence of the product-

(15) The best values of the three parameters were obtained with the use of the computer program HYPREPLT.[16]

(16) R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 6984 (1967).

(17) D. P. N. Satchell and I. I. Secemski, *J. Chem. Soc. B*, 1306 (1970).

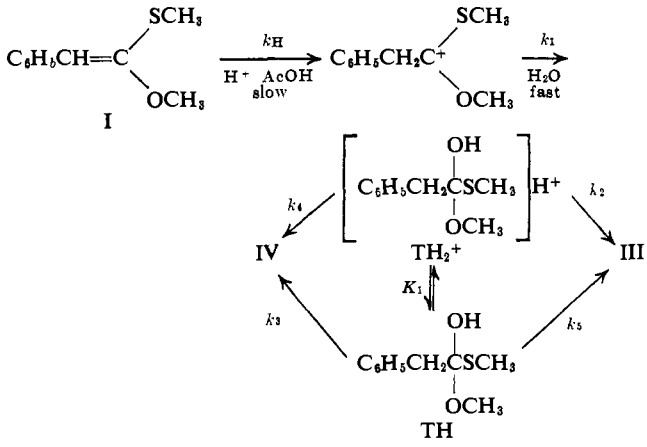
(18) J. Hipkin and D. P. N. Satchell, *Tetrahedron*, **21**, 835 (1965).

(19) (a) H. J. Alkema and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **79**, 1257 (1960); (b) W. E. Truce and R. J. Steltenkamp, *J. Org. Chem.*, **27**, 2816 (1962); (c) G. Strickmann and G. Barnikow, *Z. Chem.*, **10**, 223 (1970).

determining step on pH is not related to the effect of pH on the rate-determining step; this observation requires that the rate-limiting step be the formation of an intermediate, whose breakdown to products occurs *via* one or more fast reactions.

The main features of the tentative mechanism (Scheme I) offered for the hydrolysis of I are: (1) a rate-deter-

Scheme I

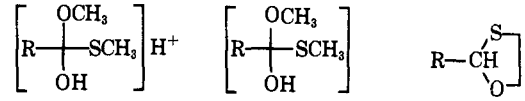


mining proton transfer converts the ketene *O,S*-acetal to a resonance-stabilized carbonium ion which undergoes rapid hydration to a cationic carbinol (TH_2^+); (2) the latter breaks down to a mixture of the thiol ester III and the ester IV, containing about 78% of thiol ester; (3) at higher pH, the cationic carbinol exists in equilibrium with its conjugate base, TH, which is converted almost exclusively (>97%) to the ester IV. Implicit in Scheme I is the expectation that both isomers of I will give the same product, *i.e.*, that rotation about the C_1–C_2 bond in the carbonium ion or the carbinols will be faster than subsequent covalent changes. The proposed rate-determining proton transfer is analogous to the well-established initial step of the hydrolysis of ketene *O,O*-acetals[20] and enol ethers,[13,21] and is supported by the observed general acid catalysis. Product formation *via* two intermediates in acid–base equilibrium accounts for the sigmoid dependence of the yield of thiol ester on pH; assumption of a steady state in carbonium ion and in both carbinols leads to eq 1 for

$$\%\ \text{thiol ester} = \frac{\left(\frac{k_2}{k_2+k_4}\right)[H^+] + \left(\frac{k_5K_1}{k_2+k_4}\right)}{[H^+] + K_1\left(\frac{k_3+k_5}{k_2+k_4}\right)} = \frac{\left(\frac{k_2}{k_2+k_4}\right)[H^+] + \left(\frac{k_5}{k_3+k_5}\right)K'}{[H^+] + K'} = \frac{P^+[H^+] + P^0K'}{[H^+] + K'} \quad (1)$$

the dependence of thiol ester yield on pH. P^+ and P^0 represent the partitioning ratios of the cationic and neutral carbinols (0.785 and ≤ 0.03, respectively), while pK' is the pH (1.66 ± 0.03) where both carbinols contribute equally to product formation. Since the effect of pH on carbinol breakdown occurs after the rate-limiting protonation, it is not reflected in the rate of the overall reaction. A similar analysis was applied to the separate influences of pH variation on the rates and products of the hydrolysis of imidate[7–9] and thioimidate[16,22] esters. As was pointed out earlier,[8,16] the sigmoid dependence of product yield on pH requires only the postulation of a conjugate pair of intermediates; a mechanism involving neutral and anionic carbinols would account equally well for the data of Figure 4. The observation of acid catalysis in the hydrolysis of methyl thiolformate (see below) suggests that the reaction pathway including cationic and neutral intermediates is the more likely one.

Consideration of the data of Figure 4 in terms of Scheme I leads to the conclusion that, in the decomposition of cationic carbinols of type V, the expulsion of methanol is slightly favored over that of methanethiol (relative rates being 3.6:1 for R = benzyl). This ratio is perhaps unexpectedly low, in view of the apparently greater basicity of ethers compared to thioethers,[23] and of comparisons of the relative rates of the acid-catalyzed



V VI VII

breakdown of the hydrate and ethyl hemithioacetal of acetaldehyde.[24a] The acid-catalyzed hydrolysis of 1,3-oxathiolanes (VII) might provide useful information concerning the relative leaving abilities of geminal alcohols and alkyl mercaptans, although very different processes will be involved in the stabilization of the incipient carbonium ions formed from VII and V. At present, it is uncertain whether the acid-catalyzed hydrolysis of 1,3-oxathiolanes and benzaldehyde monothioacetals proceeds with initial C–O[25] or C–S[26] bond cleavage. A proton magnetic resonance study of the protonation of 1,3-oxathiolanes in strongly acidic medium has been interpreted in favor of the reversible formation of the carbonium ion derived from C–O bond fission,[27] but this behavior may reflect thermodynamic stability rather than kinetic factors.

The limiting yield of thiol ester produced on hydrolysis of I at pH > 3 is no more than 3% and possibly much less. Thus, a lower limit of 30 (in favor of RSH) is set on the relative rates of expulsion of CH_3SH and CH_3OH from the neutral carbinol VI (R = benzyl). It is noteworthy that the related neutral tetrahedral species formed in the hydrolysis of ethyl trifluorothiol-

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(21) A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Amer. Chem. Soc.*, **93**, 413 (1971); G. E. Lienhard and T. C. Wang, *ibid.*, **91**, 1146 (1969). Both papers contain numerous references to earlier studies of enol ether hydrolysis.

(22) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969).

(23) pK_a for dimethyl ether has been reported as −3.83 [E. M. Arnett and C. Y. Wu, *ibid.*, **82**, 4999 (1960)], while that of dimethyl sulfide is given as −5.3 [E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 388 (1963)]. It should be noted, however, that widely varying pK_a values for ethers have been obtained by different experimental methods [S. Searles and M. Tamres in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, p 260].

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(25) N. C. De and L. R. Fedor, *J. Amer. Chem. Soc.*, **90**, 7266 (1968).

(26) (a) T. H. Fife and L. K. Jao, *ibid.*, **91**, 4217 (1969); (b) T. H. Fife and E. Anderson, *ibid.*, **92**, 5464 (1970).

(27) F. Guinot, G. Lamaty, and H. Munsch, *Bull. Soc. Chim. Fr.*, 541 (1971).

acetate is believed to expel H_2O much more easily than ethanethiol.[4-6] If the low rate of hydrolysis of $CF_3COSC_2H_5$ in strong acid is taken[24b] as evidence for the existence of a neutral pathway for the expulsion of RSH, it may be calculated[7] that the relative rates of expulsion of H_2O and ethanethiol from the neutral intermediate are in the ratio of 8:1.

If it is assumed that the tetrahedral adducts V and VI constitute adequate models for the (potential) intermediates of thiol ester hydrolysis in acidic solution, the mechanism of thiol ester hydrolysis should include: (1) rate-limiting water-catalyzed and acid-catalyzed attack of water on thiol ester at pH > 2, and (2) a partial or complete transition occurring at pH 1–2 to rate-determining breakdown of neutral and cationic intermediates; the extent to which formation or breakdown of intermediates would be rate limiting at lowest pH would depend on the relative rates of breakdown of the cationic intermediate to RSH and ROH, respectively.

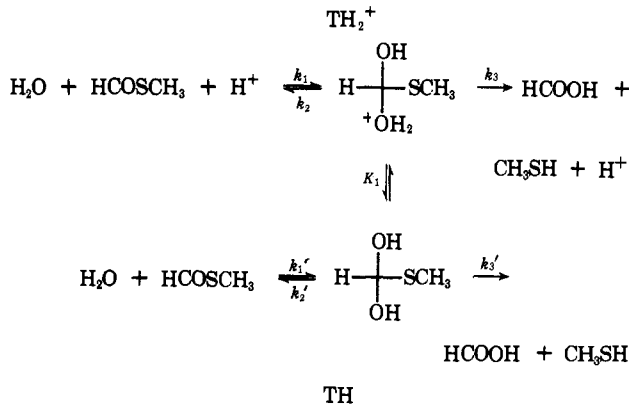
Thiol Ester Hydrolysis. The simplest mechanism which will be examined for its ability to account for the pH–rate profile for the hydrolysis of methyl thiolformate (Figure 1) is one consisting solely of the summation of acid-catalyzed (k_H) and spontaneous (k_w) hydrolysis steps throughout the pH range 0–3 (eq 2).

$$k_0 = k_H[H^+] + k_w \qquad (2)$$

The dashed line in Figure 1 is calculated using $k_H = 4.49 \times 10^{-2}\ M^{-1}\ min^{-1}$ and $k_w = 2.46 \times 10^{-4}\ min^{-1}$, values selected so that the calculated curve coincides with the measured rate constants at pH 0 and 3. The deviations of the calculated curve from the observed rates are not large, hardly exceeding 40% at their maxima at pH 1.5–2. However, the observed rate constants are *all* too high. Attempts to reduce the average deviations by increasing the value of k_H would result in a calculated curve which would intersect the line defined by the observed values, so that all points below a certain pH would fall below the curve, while all points above that pH would lie on or above the theoretical curve.

The second mechanism to be considered (Scheme II) involves acid-catalyzed and spontaneous addition of

Scheme II



water to the thiol ester to yield, respectively, cationic (T_2H^+) and neutral (TH) intermediates. Both intermediates can break down either to thiol ester (and water) or to acid (and mercaptan), to extents defined by their partitioning ratios $P^+ [= k_2/(k_2 + k_3)]$ and $P^0 [= k_2'/(k_2' + k_3')]$. The pH value where the transition in rate-limiting step will occur, if $P^+ \neq P^0$, is given by $H^+ = K' = (k_2' + k_3')K_1/(k_2 + k_3)$. This general type of mechanism has previously been discussed in detail[7,22] and, in the extreme case where $P^+ \simeq 1$ ($k_2 \gg k_3$) and $P^0 \simeq 0$ ($k_3' \gg k_2'$), is expected to give rise to characteristic pH–rate profiles with two regions of slope zero and two regions of slope −1. If the limiting conditions do not apply, the regions of slope 0 and −1 begin to merge and the evaluation of the three parameters K', P^+, and P^0 becomes more difficult. Application of the steady-state assumption to Scheme II gives rise to several equivalent formulations for the dependence of k_0 on pH, one of which is given in eq 3,

$$k_0 = \frac{k_1[(1 - P^+)[H^+] + K'(1 - P^0)][[H^+] + K'P^0/P^+)}{[H^+] + K'} \qquad (3)$$

which has been derived earlier.[22] The solid line in Figure 1 represents the curve calculated from eq 3, using the values for k_1, P^+, P^0, and pK' given in Table IV (last column). The limiting values of $k_0/[H^+]$ and

Table IV. A Comparison of the Values of the Parameters Used in the Calculation of the Product–pH Profile for the Hydrolysis of I and of the pH–Rate Profile for the Hydrolysis of Methyl Thiolformate

	I[a]	Thiol ester[b]
P^+	0.785	0.48
P^0	0.009[c]	0.021
pK'	1.66 ± 0.03	1.23
k_1		$8.46 \times 10^{-2}\ M^{-1}\ min^{-1}$
k_1'		$2.18 \times 10^{-4}\ min^{-1}$ [d]

[a] Parameters refer to Scheme I and eq 1. [b] Parameters refer to Scheme II and eq 3. [c] Approximate value, possibly an upper limit. [d] The values of P^+, P^0, K', k_1 and k_1' are mutually related so that selection of values for four of the parameters determines the value of the fifth.

k_0 at low and high pH (eq 4 and 5, respectively) are

$$\text{low pH} \qquad k_0/[H^+] = k_1(1 - P^+) \qquad (4)$$

$$\text{high pH} \qquad k_0 = k_1(1 - P^0)(K'\ P^0/P^+) \qquad (5)$$

$4.4 \times 10^{-2}\ M^{-1}\ min^{-1}$ and $2.13 \times 10^{-4}\ min^{-1}$. Also, owing to the equilibrium relationship of eq 6, another expression for k_0 at high pH (eq 7) leads to the value

$$k_1/k_2 = k_1'/k_2'K_1 \qquad (6)$$

$$\text{high pH} \qquad k_0 = k_1'(1 - P^0) \qquad (7)$$

$k_1' = 2.18 \times 10^{-4}\ min^{-1}$. A comparison of observed and calculated rate constants for the hydrolysis of methyl thiolformate is presented in Table I. The average per cent deviation of calculated from observed k_0 values is 2.5%, only three points out of 27 values of k_0 deviating by more than 4%. In terms of Scheme II, the rate-determining step in the hydrolysis reaction is the water- and acid-catalyzed formation of the intermediates at pH > 2. At pH 1.23, there occurs a transition to a situation where formation and breakdown of the intermediates are equally rate determining.

The mechanism of Scheme II receives support through the quantitative comparison of the pathways of break-

down of the intermediates generated from I and from $HCOSCH_3$ (Table IV). In both reactions, the cationic carbinols expel ROH and RSH about equally well (compare values of P^+), while the neutral intermediates decompose with predominant expulsion of RSH (*cf.* P^0). The product transition in the hydrolysis of I takes place at pH 1.66, while the corresponding transition in rate-limiting step for thiol ester hydrolysis occurs at pH 1.23. Given the differences in the structure of the intermediates of Schemes I and II, the agreement in the values of P^+, P^0, and K' is probably as good as could be expected, and suggests that Scheme II may represent the mechanism of the acid-catalyzed hydrolysis of methyl thiolformate, and indeed, of thiol esters in general, with the exception of those derived from strongly acyl-activated acids.

It would be expected that the acid-catalyzed alcoholysis of thiol esters should also involve the participation of tetrahedral intermediates. In the only such study of which we are aware,[28a] no evidence for intermediates was obtained, the reaction rate remaining directly proportional to $[H^+]$ in the range 0.02–3 *M* HCl.

The question of the nature of the rate-determining step in acid-catalyzed thiolactonization reactions has been raised by Capon[28b] in a recent evaluation of the concept of "orbital steering."[28c] Applying the principle of microscopic reversibility to Scheme II, we conclude that, at pH > 2, the rate-limiting step in thiolactonization will be the breakdown of tetrahedral intermediates; at lower pH, formation of the intermediates will become partly or mainly rate determining. Clearly the complication introduced by this change in rate-limiting step must be explicitly considered when mechanistic conclusions are based on comparisons of relative rates of acid-catalyzed lactonization and thiolactonization.

Papain. The mechanism of the papain-catalyzed hydrolysis of esters and amides is believed to involve participation of an acyl enzyme intermediate formed by acylation of the sulfhydryl group in the active site of the enzyme.[29] For anilide substrates, it has been suggested[29a] that the rate-determining step in the acylation reaction is the breakdown of an anionic tetrahedral intermediate, with general acid catalysis by a neighboring imidazolium ion. From studies of the hydrolysis of thioimidate esters[16,22] and of the aminolysis of thiol esters,[30] it is known that, at pH > 2, intermediates of types VIII and IX break down with predominant formation of mercaptan and amide. Catalysis by hydronium ion or by general acids enhances the rate of expulsion of amine to form thiol ester, and provides support for a similar mechanism in the papain-catalyzed hydrolysis of amides.

The results of the present study suggest that, at least for alkyl ester substrates, the rate-determining step in the acylation of papain may also be the breakdown of a tetrahedral intermediate, owing to the greater leaving ability of mercaptan from the corresponding neutral and anionic intermediates. General acid catalysis by an appropriately situated group would be expected to increase the rate of acyl-enzyme formation by assisting the departure of the alkoxy substituent, a process which normally requires a relatively high concentration of hydronium ion (pH < 2). Also, it is possible that the geometrical constraints imposed by the catalytic system of the enzyme are sufficient to direct general acid catalysis exclusively to the departing alkoxy group, unlike the effect of external hydronium ion, which appears to enhance the leaving ability of both alkythio and alkoxy substituents to similar extents. With regard to aryl ester substrates, the pathways of breakdown of the putative tetrahedral intermediates are not certain; it is anticipated that the aryloxy function will be a more effective leaving group than the alkoxy substituent, and may, in fact, compete favorably with the alkythio group over a large range of pH values.

Experimental Section[31]

1-Methoxy-1-methylthio-2-phenylethylene (I) was prepared from 4-phenyl-1,2,3-thiadiazole[32] according to the method of Raap,[12a] using a fresh solution of sodium methoxide in anhydrous methanol. After addition of dimethyl sulfate, the solution was stirred for 20 min, and then extracted with five 200-ml portions of ether. The ether extracts were pooled, washed with saturated NaCl solution, and dried over Na_2CO_3. After evaporation of the ether at reduced pressure, fractional distillation yielded I as a colorless liquid: bp 78° (0.35 mm) [lit.[12a] bp 81–82° (0.2 mm)]; uv (CH_3CN) λ_{max} 281 nm (ϵ 17,800); the infrared spectrum (thin film) showed no carbonyl absorption in the range 5–6 μ; nmr δ ($CDCl_3$) 7.1–7.6 (5 H, multiplet), 5.9 (1 H, singlet), 3.71 (3 H, 2 singlets), 2.22 (3 H, 2 singlets) [lit.[12a] δ (CCl_4) 7.1–7.6 (5 H, multiplet), 5.86 (1 H, singlet), 3.73 (3 H, singlet), 2.24 (3 H, singlet)]. Both at δ 3.71 and 2.22, the two singlets, of unequal size, are separated by approximately 1 Hz, the smaller peaks being upfield of the large peak at δ 3.71 and downfield of the large peak at δ 2.22. Estimation of the relative areas of the two CH_3S and the two CH_3O singlets suggests that I consists of a mixture of the isomers Ia and Ib, approximately in the ratio of 2:1, respectively. The tentative structural assignment is based on the spectral data reported for *cis*-and *trans*-β-methylthiostyrene.[33] The formation of both geometrical isomers of I was not reported in the previous description of its synthesis.[12a,d] I could not be stored at room temperature for more than a day, but was stable for months as a dilute solution in dry acetonitrile containing *ca.* 0.001 *M* triethylamine.

Methyl thiolformate was prepared by adding 100 g (2.1 mol) of methyl mercaptan to 300 ml of formic–acetic anhydride reagent[34] at 5–10°. After stirring for 3 hr at room temperature, the solution was distilled. The fraction boiling at 74–88° was neutralized with saturated K_2CO_3 solution and extracted with ether, and the ether extract was redistilled through a Vigreux column. A center fraction of material boiling at 81° (lit.[35] bp 88°) was retained for kinetic

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(31) All boiling points are uncorrected. Ultraviolet spectra were determined by means of a Perkin-Elmer Model 350 recording spectrophotometer. Nmr spectra were obtained with a Varian Model A-60 spectrometer with tetramethylsilane as internal standard.

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(33) A. A. Oswald, K. Griesbaum, B. E. Hudson, Jr., and J. M. Bregman, *J. Amer. Chem. Soc.*, 86, 2877 (1964), report signals at δ 2.02 and 2.04 for the SCH_3 groups of *cis*- and *trans*-β-methylthiostyrene, respectively.

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(35) H. Böhme and J. Roehr, *Justus Liebigs Ann. Chem.*, **648**, 21 (1961).

measurements: uv (H_2O) λ_{max} 233 nm (ϵ 5100) (lit.[36] λ_{max} 233.5 nm (ϵ_{233} 4540)); ir 3.54 (CH) and 5.98 μ (C=O) (lit.[36] 5.98 μ); nmr (neat) δ 2.36 (3 H, singlet), 10.2 (1 H, singlet) [lit.[35] 2.33 (3 H, singlet), 10.09 (1H, singlet)].

Methyl phenylthiolacetate[37] (III) was purified by distillation on a Nester-Faust spinning band column: bp 103–105° (5.5 mm); $n^{25}D$ 1.5603 (lit.[37] bp 126° (11 mm), $n^{20}D$ 1.5611); uv λ_{max} 235 nm (ϵ_{max} 5220) (10% CH_3CN–0.01 *M* HCl); nmr (neat) δ 2.05 (3 H, singlet), 3.66 (2 H, singlet), 7.17 (5 H, singlet); ir 5.90 μ (C=O).

Methyl phenylacetate (IV) was prepared in 80% yield by the dropwise addition of 20 g of phenylacetyl chloride to 200 ml of methanol at 0–5°, followed by distillation at atmospheric pressure: bp 216°; $n^{25}D$ 1.5057 (lit.[38] bp 57–60° (0.5 mm)); $n^{20}D$ 1.5050); nmr (neat) δ 3.45 (5 H, 2 peaks), 7.16 (5 H, singlet).

Kinetic Measurements. Acetonitrile was purified as previously described.[8] 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 hydrolysis of methyl thiolformate was studied in aqueous solution, μ = 0.97, adjusted with added LiCl. Constant pC_H ($pC_H = -\log [HCl]$) was maintained with HCl below pC_H 3.0 and with 0.02–0.08 *M* acetate buffers at higher pH. Between pC_H 2.5 and 3.0, a Radiometer PHM 4d pH meter was used to check the constancy of pH at the beginning and end of the reaction.

Rates of hydrolysis were determined spectrophotometrically by following the decrease in absorbance at 233 nm (thiol ester at *ca.* 1.5×10^{-4} *M*) using a Gilford Model 240 spectrophotometer. Above pC_H 3.0, buffered solutions of thiol ester were pipetted into ampoules which were sealed and placed into a constant temperature bath. Ampoules were withdrawn at intervals and their optical density read with a Zeiss PMQII spectrophotometer. Reactions were followed for at least 2 half-lives. Rate constants were calculated using the integrated form of the first-order rate equation.

The medium used for kinetic studies on I was 10% acetonitrile–water (v/v), at ionic strength 0.45, adjusted with added KCl. Acetate buffers were used to maintain constant pH in solutions of pH > 3.0. Hydrolysis rates were determined spectrophotometrically by following the absorbance decrease at 280 nm (ketene acetal at *ca.* 5×10^{-5} *M*). At pH $\geq$ 2, the reactions were carried out in the water-jacketed cell holder of the Zeiss spectrophotometer, and were initiated by the addition of 0.3 ml of the stock solution of I in acetonitrile (containing triethylamine at 10^{-3} *M*) to 2.7 ml of aqueous buffer solution. Faster reaction rates (at pH < 2) were determined with the use of a stopped-flow spectrophotometer essentially identical with that described by Sturtevant,[39] except for the addition of a Tektronik Model 564 storage oscilloscope. Temperature was maintained at 30.0 ± 0.2° by circulating water through a brass block containing the driving syringes of the stopped-flow apparatus, and through thermospacers lining the spectrophotometer cell compartment which houses the mixing and observation chambers of the apparatus. Except for the polyethylene gaskets, the glass syringes, and the 2-mm pathlength quartz observation chamber, the fluid handling system is constructed of Teflon. Reactions were carried out by filling one drive syringe with a solution of HCl in 10% CH_3CN–H_2O (μ = 0.45 *M*), and the other with a solution of the ketene acetal dissolved in a 0.001 *M* Tris buffer of pH 8.2 (10% CH_3CN–H_2O, μ = 0.45). All kinetic determinations were made by mixing volumes of 0.4 ml from each syringe and at least six measurements were made for each HCl concentration. Rate constants were calculated from photographs of oscilloscope traces of transmittance changes which were read with a microcomparator under tenfold magnification. When converted to optical densities, the average total change was 0.21 absorbance unit.

First-order plots were invariably biphasic (Figure 2, open circles), suggesting that the two isomers of I underwent hydrolysis at different rates. Rate constants for hydrolysis of the less reactive isomer were obtained directly from the latter part of the reaction (Figure 2A). To determine the rate constants for the more reactive component, the absorbance data were treated by the standard procedure for parallel first-order reactions.[40] The resulting plots were generally linear (Figure 2B), although the smaller absorbance changes for the rapid reaction led occasionally to some scatter in the semilogarithmic plots. Assuming equal molar extinction coefficients at 280 nm for the two isomers of I, the ratio of the more reactive to the less reactive isomer is 1:3, which may be compared to the isomer ratio of 1:2 estimated from the nmr data.

Product Analysis. The products of hydrolysis of I were determined to be III and IV by two methods. First, I was hydrolyzed in 0.01 and 0.05 *M* HCl (10% CH_3CN–H_2O, μ = 0.45, 30°) and ultraviolet spectra of the product mixtures were scanned. These spectra were, respectively, essentially identical with spectra of mixtures of III and IV consisting of 29% III and 71% IV (for 0.01 *M* HCl) and 58.5% III and 41% IV (for 0.05 *M* HCl).

Secondly, 0.1 ml of a *ca.* 1 *M* DCl solution in D_2O was mixed with 1.0 ml of a 12.4 *M* solution of I in dimethyl-d_6 sulfoxide. The nmr spectrum of the resultant solution [δ 7.35 (5 H, singlet), 3.9 (0.7 H, singlet), 3.26 (2.5 H, singlet), 2.24 (2.3 H, singlet), 2.03 (0.9 H, singlet)] could be quantitatively accounted for by a mixture composed of 68% III and 32% IV, with methanol and methyl mercaptan present in the same ratio, when compared to the appropriate mixture of III, IV, and methanol in dimethyl-d_6 sulfoxide.

In order to determine the yield of III over a range of acid concentrations, I was hydrolyzed under the same conditions as those employed in kinetic experiments, except that 0.3 ml of a stock solution of I in acetonitrile was added to 2.7 ml of buffer at 30° in a test tube which was immediately stoppered and rapidly mixed by vibration using a Vortex mixer. After 6–10 half-lives of reaction, the concentration of III was determined directly by measurement of the absorbance of the reaction mixture at 235 nm using molar extinction coefficients of 5220 for III and 120 for IV. The concentrations of I varied between 1 and 5×10^{-4} *M*. Alternatively, the thiol ester III was determined by reaction with hydroxylamine, using a procedure previously described for ethyl thiolacetate.[16] A 3-ml aliquot containing III at 3×10^{-4} *M* gave an optical density of *ca.* 0.9 with this assay. The concentration of I was 5.35×10^{-4} *M*.

Control experiments with IV showed that the ester (at 6.70×10^{-4} *M*) did not react appreciably with hydroxylamine under these conditions (absorbance at 540 nm < 0.04). The half-life for hydrolysis of III in 1.0 *M* HCl (30°) was found to be *ca.* 74 hr, indicating that no loss of thiol ester occurred during the time required for complete hydrolysis of I and for subsequent product determination.

At $pC_H > 1$, product yields determined by the direct spectrophotometric method were reproducible within 2–3%; at higher acidity, absorbance data were generally lower than expected on the basis of the experiments at higher pH, and were not reproducible, probably as a result of incomplete mixing for these fast reactions. Attempts were made to use the stopped flow apparatus simply as a rapid mixing device for product determination on reactions performed at $pC_H < 1$. Although satisfactory kinetic data were obtained with this apparatus, the results of product determination showed scatter beyond acceptable limits, for reasons which could not be ascertained.

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