pentane was added to the salt solution. After removal of salts and solvent the products were isolated by preparative glpc. **19** and **20** were obtained in a 1:3 ratio, respectively (estimated by nmr). Total yield was about 40%.

Reaction of Deprotonated *O-tert*-Butyldimethylsilylhydroxylamine (6) with Trimethylchlorosilane. To a solution of 0.25 g (1.7 mmol) of **6** dissolved in a 4:1 pentane–THF mixture at −78° was added 1 equiv of *n*-butyllithium. After 10 min 0.2 g (1.8 mmol) of trimethylchlorosilane was added to the solution. The salts and solvent were removed and the products isolated by glpc preparative methods. **19** and **20** were obtained in a 3:1 ratio, respectively (estimated by nmr). Total yield was about 60%.

Cleavage Reactions of 1. Cleavage of the N–O Bond in the Lithium Salt of 1 by *tert*-Butyllithium. To a stirred solution of 10 ml (8.0 g, 45 mmol) of **1** in 35 ml of pentane was added 73 ml (90 mmol) of 1.24 *M tert*-butyllithium over a 30-min period producing a white slurry. After the mixture was stirred at room temperature for 24 hr, the slurry was slowly added to a solution of 15 g (105 mmol) of MeI in 50 ml of pentane at −78°, which dissolved the salt immediately. After the mixture was stirred for 10 min, 10 ml of THF was added causing solid to precipitate. The reaction mixture was warmed slowly to room temperature and stirred overnight. The next day the liquid was removed from the reaction vessel by vacuum distillation and collected in a Dry Ice trap. Glpc analysis of the crude reaction mixture showed one major product. Distillation of the product mixture afforded 6.1 g (77%) of heptamethyldisilazane (**17**).[21] The ir of this compound was superimposable with that of a known sample.

Cleavage of the Si–N Bond in 1 by the Lithium Salt of Pyrrole. A solution of 4.05 g (22.9 mmol) of **1** in THF–pentane was reacted with 1 equiv of *n*-butyllithium at −78°. The salt solution was then treated with 1.5 g (23 mmol) of pyrrole producing an amber colored solution. This reaction mixture was then refluxed for 48 hr. The liquid was removed from the reaction vessel by vacuum distillation and collected in a Dry Ice trap. Glpc analysis of this liquid showed two products. They were isolated by glpc preparative methods. The product with shorter retention time was identified as hexamethyldisiloxane. *N*-Trimethylsilylpyrrole (**18**) was also isolated (1 g, 30%), and its structure was confirmed by comparison of its ir and nmr spectra with that of a sample prepared from the reaction of potassium pyrrole and trimethylchlorosilane.[22] The same products were obtained when equivalent amounts of **1** and pyrrole were refluxed in THF and a catalytic amount of alkyllithium was added.

Anal. Calcd for $C_7H_{13}NSi$: C, 60.37; H, 9.41; N, 10.06; Si, 21.17. Found: C, 60.29; H, 9.45; N, 10.16; Si, 20.34.

Reactions of Deprotonated *O*-Trimethylsilyl-*N*-methylhydroxylamine (7). i. With Methyl Iodide. To a solution of 4.0 g (33 mmol) of **7** dissolved in 20 ml of pentane was added 21 ml (23.6 mmol) of 1.6 *M n*-butyllithium at room temperature. Sufficient heat to reflux pentane was evolved and a clear colorless solution was formed. After the mixture was stirred for 24 hr at room temperature the solution had become slightly cloudy and was added to a pentane–THF solution of excess methyl iodide. Precipitation of a white solid occurred immediately. This reaction mixture was stirred overnight at room temperature. The liquid was removed from the solid by vacuum distillation at 25° and was collected in a Dry Ice trap. The clear colorless solution was distilled at atmospheric pressure and 3.8 g (86%) of **21** was collected at 40–45° (97 Torr). Ir and nmr spectra were consistent with the proposed structure. Analytically pure samples were obtained by preparative gas chromatography.

Anal. Calcd for $C_5H_{15}NSiO$: C, 45.06; H, 11.35; N, 10.51; Si. 21.07. Found: C, 44.94; H, 11.44; N, 10.61; Si, 21.30.

ii. With *tert*-Butyldimethylchlorosilane. To a solution of 1.22 g (10.22 mmol) of **7** in 10 ml of pentane was added 6.5 ml (10.4 mmol) of 1.6 *M n*-butyllithium in pentane–THF. The reaction mixture changed to pale yellow but salt did not precipitate for several hours. Analysis of the reaction mixture by glpc showed one product. The solid was removed by filtration and the product was isolated (1.65 g, 70%) by glpc preparative methods. Ir and nmr spectra were consistent with the proposed structure for **22**.

Anal. Calcd for $C_9H_{25}NSi_2O$: C, 51.44; H, 11.66; N, 6.00; Si, 24.06. Found: C, 51.33; H, 11.71; N, 6.06; Si, 23.87.

Acknowledgment. The authors wish to express their appreciation to Alma Dancer for valuable technical assistance.

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Hydrolysis of Acyl-Activated Thiol Esters. Acid Catalysis and Acid Inhibition[1a]

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Abstract: The hydrolysis of 11 acyl-activated thiol esters RCOSR′ has been studied in the pH range 0–12 at 30°. Strongly acyl-activated thiol esters (R = CF_3, CCl_3, CF_3CF_2) show pronounced acid inhibition of the rate of hydrolysis at pH <2. Weakly acyl-activated thiol esters (R = CH_2Cl, NO_2CH_2) undergo acid-catalyzed hydrolysis. Thiol esters with electron-withdrawing substituents of intermediate strength (R = CHF_2, CH_3SCO, $CHCl_2$) show either modest acid inhibition or inhibition followed by acid catalysis as acidity increases further. A general mechanism which includes anionic, neutral, and cationic tetrahedral intermediates is proposed to account for the observed pH–rate profiles, with the existence of acid inhibition being directly related to the ratio of the rate constants for breakdown of the neutral intermediate to products and reactants.

In weakly acidic solution, the hydrolysis of thiol esters derived from acetic acid,[2] formic acid,[3] and benzoic[4] acid exhibits acid catalysis. In intriguing contrast, the rate of hydrolysis of thiol esters derived from trifluoroacetic acid is inhibited at acid concentra-

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Table I. Rate Constants for the Hydrolysis of Esters ($RCOSCH_3$) of Methanethiol[a]

		10^4k_{obsd}, sec^{-1} [b]					
pH[c]	Buffer, *M*	R = CF_3	CCl_3	CF_3CF_2[d]	CHF_2	$CHCl_2$	CH_3SCO
−0.21	HCl, 1.0	28.2, 28.4	1.86	3.42	4.80, 4.82	0.521, 0.517	0.515
0.09	0.5	32.8	2.36				
0.19	0.4	36.0		3.84	4.28	0.482	0.513
0.39	0.25	44.7, 43.7	3.19				
0.49	0.2			4.30, 4.33	4.34	0.466	0.526
0.60	0.16		3.58				
0.79	0.10	61.1	4.22	4.45	4.74	0.492	0.545
1.09	0.05	72.2	4.93	4.67	5.05	0.478	0.555
1.39	0.025	77.3	5.34				
1.49	0.02				5.28	0.484	0.566
1.60	0.016		5.53				
1.79	0.01	82.7	5.86	4.90	5.36	0.506, 0.507	
2.09	0.005	85.0	5.71	4.92	5.38, 5.35	0.500	0.572
2.39	0.0025		5.85	4.96			
2.49	0.002	84.8					
2.79	0.001		5.84				
2.98	Formate				5.53		0.586
3.28	Formate	87.4			5.52	0.505	
3.76	Acetate		6.04				
4.76	Acetate		5.87				
5.85	Phosphate		5.93				
6.42	Phosphate		5.31			0.71	2.04
7.24	*N*-Ethylmorpholine	117					
7.41	Tris		9.01			2.5	14.4
7.64	Tris		11.2			4.08	25.0
7.78	*N*-Ethylmorpholine	193					
7.94	Tris		15.9			7.34	48.0
8.47	Tris		37.5			23.9	
10.88	NaOH, 0.004		8870	25,000	39,600	6890	63,700
11.18	0.008		19,700				
11.28	0.01		25,200	63,000	89,200	17,200	139,000
11.58	0.02			133,000	199,000	36,300	309,000

[a] In 0.33% $CH_3CN–H_2O$ (except for $CF_3CF_2COSCH_3$), $\mu = 1.0$, 30°. [b] Except for HCl and NaOH solutions, rate constants are extrapolated to zero buffer concentration. [c] Measured pH, except for HCl solutions, where pH = −log [HCl] − 0.21. [d] 2.7% $CH_3CN–H_2O$, $\mu = 0.97$, except for NaOH solutions, where solvent was 4% $CH_3CN–H_2O$, $\mu = 0.96$.

tions greater than 0.01 *M*.[3a,5] The latter behavior has been interpreted in terms of a mechanism involving the formation of neutral and anionic tetrahedral addition intermediates.[3a,5]

It has also been reported that the kinetics of the hydrolysis of methyl thiolformate[3b] and of the lactonization of a bicyclic aliphatic mercapto acid[6] give evidence for the participation of cationic and neutral tetrahedral intermediates in the acid-catalyzed hydrolysis and formation of thiol esters. An important and unexplained difference exists in the pathways of breakdown of the various neutral tetrahedral intermediates formed during thiol ester hydrolysis: while the kinetic and oxygen-18 exchange data for ethyl trifluorothiolacetate require that the neutral intermediate decompose with predominant or exclusive departure of water, the study of the hydrolysis of methyl thiolformate suggested that the corresponding neutral intermediate expels methanethiol about 98% of the time. With the related neutral intermediate formed in the thiolactonization of 6-mercaptobicyclo[2.2.1]heptane-2-carboxylic acid, the rates of expulsion of thiol and water are in a ratio of about 40:1.

The present study was undertaken with the aim of defining the relationship between thiol ester structure and the observation of acid catalysis or inhibition. Ultimately, it was hoped to provide an explanation of the kinetic phenomena in terms of the properties of the intermediates formed in these reactions.

Results

First-order rate constants for the hydrolysis of 11 acyl-activated thiol esters derived from methane- and ethanethiols were determined spectrophotometrically in predominantly aqueous solutions (μ = 1.0, LiCl) at 30°. In the case of dimethyl thioloxalate, the wavelength of measurement was selected so that essentially only the conversion of the dithiol ester to the monothiol ester was followed. At pH >2, where the monothiol ester exists mainly as the anion, its rate of hydrolysis is expected to be very slow.[7]

Small catalytic effects of formate, acetate, phosphate, and *N*-ethylmorpholine buffers were observed, with rate increases in 0.1 *M* buffer varying from 10 to 40% above the rate extrapolated to zero buffer concentration. In contrast, the rates of disappearance of some of the thiol esters were markedly increased by Tris buffer. With all buffers at concentrations up to 0.1 *M*, plots of k_{obsd} *vs.* total buffer concentration were linear, and the slopes and intercepts of these lines were calculated by least squares. In cases where more than one buffer ratio was used, reaction rates were found to depend on the concentration of the conjugate base form of the buffers. The buffer reactions,

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(7) (a) The rates of the water and hydroxide-catalyzed hydrolyses of ethyl *o*-nitrophenyl oxalate are at least 10^3 times faster than those of the anion of *o*-nitrophenyl hydrogen oxalate.[7b] (b) T. C. Bruice and B. Holmquist, *J. Amer. Chem. Soc.*, 89, 4028 (1967).

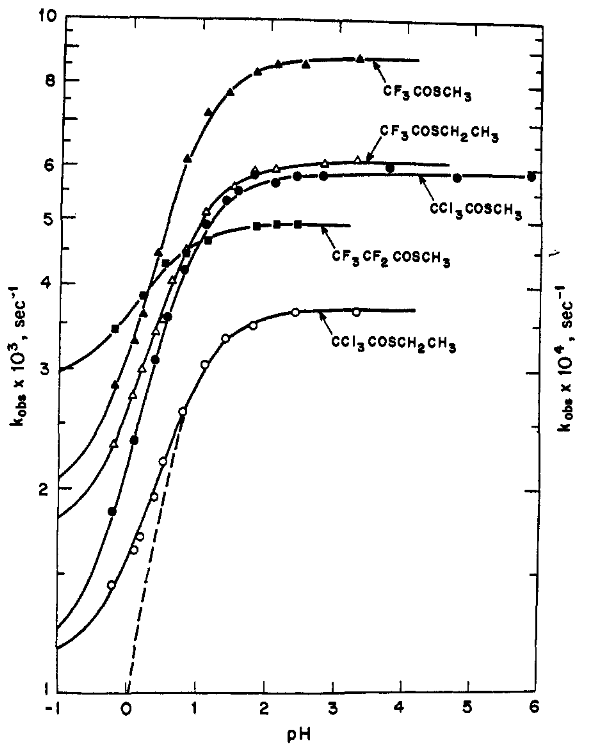

Figure 1. pH–rate profiles for the hydrolysis of acyl-activated thiol esters at 30°, $\mu = 1$: (△, ▲) left ordinate; (○, ●, ■) right ordinate. Solid lines are calculated from eq 4, using constants of Table II. Dashed line is calculated on assumption that only T^- is converted to products.

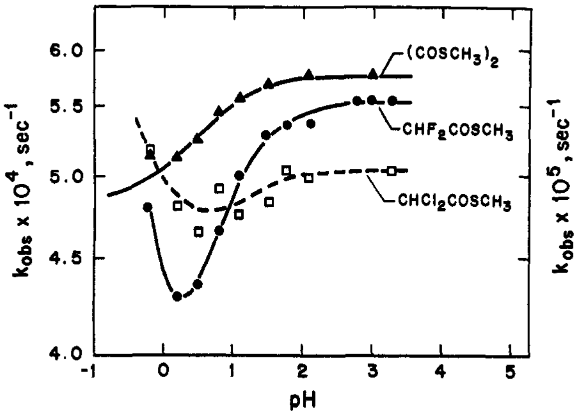

Figure 2. pH–rate profiles for the hydrolysis of acyl-activated thiol esters at 30°, $\mu = 1$: (●) left ordinate; (▲, □) right ordinate. Solid lines are calculated from eq 4 (with addition of k_H term in case of CHF_2COSCH_3). Dashed line is arbitrary representation of data.

which probably represent general base catalysis of hydrolysis[5a,c] (with the exception of Tris, where the high rate suggests a nucleophilic reaction), were not investigated in detail.

Kinetic data over the entire pH range studied (0–12) are presented in Table I for six methyl thiol esters. Rate data obtained at pH <4 for 10 of the 11 substrates investigated are shown in Figures 1–3. With respect to the effect of pH on the rate of hydrolysis, the thiol esters fall into three broad categories, which appear related to the extent of electron withdrawal in the acyl group. Thiol esters with strongly electron-withdrawing substituents (CF_3, CCl_3, CF_3CF_2) exhibit marked acid inhibition at pH <2 (Figure 1). With less electron withdrawal (CHF_2, $CHCl_2$, dimethyl thioloxalate), a modest but real decrease in rate of hydrolysis with increasing acidity is observed, followed, in at least one case, by a rate increase as acidity increases further (Figure 2). The hydrolysis of thiol esters derived from weaker acids ($NO_2CH_2COSCH_3$, $ClCH_2COSCH_3$) is catalyzed by acid, and no region of acid inhibition is discernible (Figure 3).

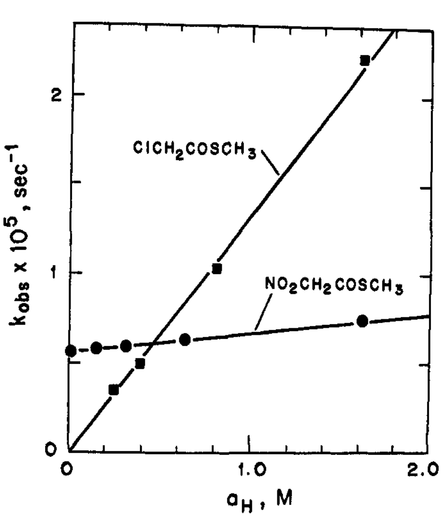

Figure 3. Dependence of rate of hydrolysis of thiol esters on hydrogen ion activity, 30°, $\mu = 1$.

At pH >2, the pH–rate profiles for the hydrolysis of the thiol esters showed a broad pH-independent region which gave way to a base-catalyzed reaction at pH values above neutrality (eq 1). The rates of

$$k_{obsd} = k_{H_2O} + k_{OH}[OH^-] \tag{1}$$

the hydroxide dependent reactions were, for the most part, determined by stopped-flow spectrophotometry, using NaOH solutions. In some cases, rate measurements made in Tris buffer were also used to calculate k_{OH}. Values of k_{obsd} obtained at constant pH were plotted *vs.* Tris buffer concentration to yield pH-dependent intercepts (eq 2), from which k_{OH} was obtained.

$$k_{obsd} = k_{H_2O} + k_{OH}[OH^-] + k_B[Tris] \tag{2}$$

Values of k_{OH} determined in this manner varied by as much as 20% from those derived from the stopped-flow studies, and are considered less reliable, owing to the steep dependence of k_{obsd} on Tris concentration. The high reactivity of thiol esters of trifluoroacetic acid in neutral solution precluded the use of the stopped-flow technique; k_{OH} was calculated from experiments in *N*-ethylmorpholine buffer at two different buffer ratios.

The rate constants for hydrolysis of $CH_2ClCOSCH_3$ and $NO_2CH_2COSCH_3$ were fitted to eq 3, from which

$$k_{obsd} = k_H[H^+] + k_{H_2O} \tag{3}$$

k_H was obtained as the slope of plots of k_{obsd} *vs.* $[H^+]$. With $CH_2ClCOSCH_3$, the intercept was indistinguishable from zero (Figure 3), and no value of k_{H_2O} was obtained for this unreactive substrate. No change in the ultraviolet spectrum of $NO_2CH_2COSCH_3$ was noted after 2 hr at pH 12, suggesting

Table II. Rate Constants for Hydrolysis of Thiol Esters[a]

Thiol ester	pK_a[b]	$k_{H_2O} = k_1'$[c] $\times 10^4$, sec^{-1}	$k_{OH} = k_1''$[d] $\times 10^{-3}$, $M^{-1}\ sec^{-1}$	$10^5 k_H$,[e] $M^{-1}\ sec^{-1}$	P^0[f]	$10^3 P^-$[f]	pK''[f]
CF_3COSCH_3	−0.78[g]	87.5	11.8		0.78	6.7	0.64
$CF_3COSC_2H_5$		61.7	6.7		0.72	4.6	0.61
CCl_3COSCH_3	−0.5[h]	5.93	0.85,[i] 0.80[j]		0.81	6.0	0.54
$CCl_3COSC_2H_5$		3.73	1.53		0.69	20.7	0.70
$C_2F_5COSCH_3$	−0.4[k]	4.94	2.32		0.44	4.4	0.16
CHF_2COSCH_3	1.24[l]	5.48	3.37	11.2	0.55	14.2	0.45
$CHCl_2COSCH_3$	1.29[l]	0.51	0.62,[i] 0.55[j]				
$CHCl_2COSC_2H_5$		0.30	0.45				
$CH_3SCOCOSCH_3$	1.04[k]	0.58	5.41,[i] 3.7[j]		0.15	95	0.66
$NO_2CH_2COSCH_3$	1.68[l]	0.0056		0.11			
$CH_2ClCOSCH_3$	2.86[l]			1.25			
$HCOSCH_3$[m]	3.77[l]	0.036	0.08–0.16[n]		0.021		

[a] At 30°; for solvent, see Table I and Experimental Section. [b] pK_a of acid from which thiol ester is derived. [c] See eq 1 and 5. [d] See eq 1 and 6. Rate constants are based on activity of hydroxide ion. [e] Equation 3; for CHF_2COSCH_3, see Discussion. Rate constants are based on activity of hydronium ion. [f] $P^0 = k_2'/(k_2' + k_3')$; $P^- = k_2''/(k_2'' + k_3'')$; $K'' = (k_2'' + k_3'')K_2/(k_2' + k_3')$; see Scheme I. [g] References 30 and 32. [h] References 31 and 32. [i] Stopped-flow. [j] Tris buffer. [k] See Experimental Section. [l] Reference 8a, p J-154. [m] Reference 3b. [n] D. J. Shire, Ph.D. Thesis, University of Sheffield, 1969; 30°, μ = 1.0 (KCl).

that the carbanion expected[8a] to be formed by ionization at the α carbon is fairly stable and that the E1cb mechanism of ester hydrolysis[8b,c] does not occur with this thiol ester.[8d,e]

Rate constants for the pH-independent (k_{H_2O}), the hydroxide dependent (k_{OH}), and the acid-catalyzed (k_H) reactions are summarized in Table II. Good agreement was obtained with the values of these constants reported[5a] for $CF_3COSC_2H_5$.[8f]

The effect of increasing the ionic strength from 1.0 to 4.0 M (LiCl) in acid solution was examined with several thiol esters (Figure 4 and Table III). Thiol esters which undergo hydrolysis *via* a neutral transition state show a decrease in rate of about 70%. In the pH region of acid inhibition (anionic transition state), a lesser rate decrease of 40–50% is observed (*e.g.*, CCl_3COSCH_3 at 1.0 M HCl; CHF_2COSCH_3 at 0.4 M HCl). Rate decreases have been reported for both pH regions with $CF_3COSC_2H_5$.[5a] In contrast, thiol esters which react mainly *via* an acid-catalyzed reaction ($CH_2ClCOSCH_2$, $HCOSCH_3$) show an increase in rate of about 60% when ionic strength is increased from 1.0 to 4.0 M. The rate of hydrolysis of CHF_2COSCH_3 increases steadily in the range of 0.1–4 M HCl (μ = 4.0), and the shape of the pH-rate profile

Table III. Effect of Ionic Strength on Thiol Ester Hydrolysis[a]

Thiol ester	[HCl], M	$10^4 k_{obsd}$, sec^{-1} μ = 1.0	$10^4 k_{obsd}$, sec^{-1} μ = 4.0
CCl_3COSCH_3	0.002	5.35	1.73
	0.1	4.22	1.02
	1.0	1.86	1.10
CHF_2COSCH_3	0.005	5.36	1.77[b]
	0.4	4.28	1.97
$CHCl_2COSCH_3$	0.01	0.506	0.154
	1.0	0.519	0.276
$CH_2ClCOSCH_3$	1.0	2.29	3.70
$HCOSCH_3$[c]	0.05	0.34	0.547
	0.5	2.36	3.59

[a] In 0.33% CH_3CN–H_2O, 30°; ionic strength maintained with LiCl. [b] 0.004 M HCl. [c] Reference 3b.

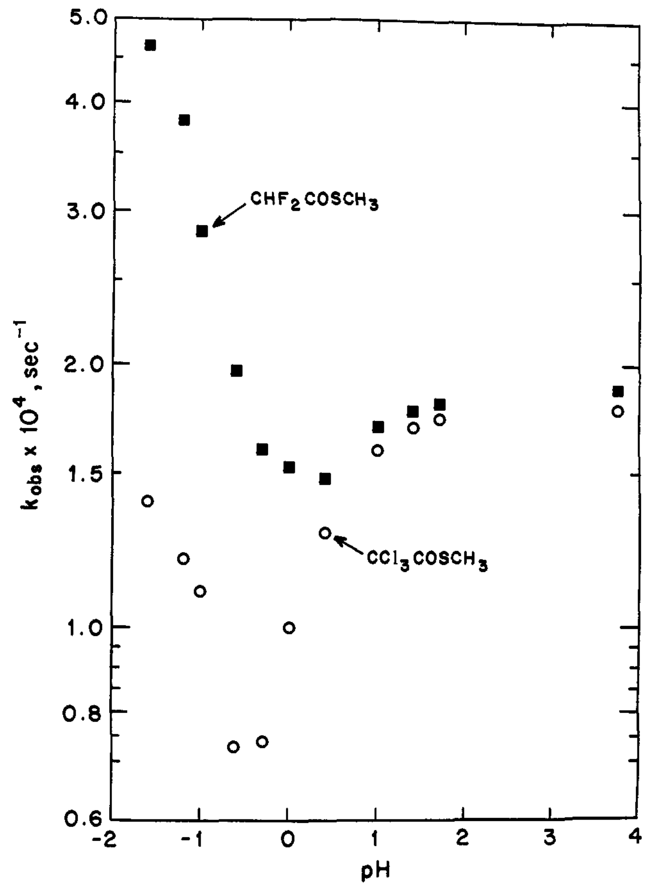

Figure 4. pH-rate profile for thiol ester hydrolysis, 30°, μ = 4. For calibration of pH scale, see Experimental Section.

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(8) (a) pK_a for $NO_2CH_2CO_2C_2H_5$ is 5.87: W. P. Jencks and J. Regenstein in "Handbook of Biochemistry," The Chemical Rubber Co., Cleveland, Ohio, 1968, p J-187; (b) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2993, 3003 (1969); (c) R. F. Pratt and T. C. Bruice, *ibid.*, **92**, 5956 (1970). (d) From the rate of water-catalyzed hydrolysis (k_{H_2O}) of $NO_2CH_2COSCH_3$ and the linear relationship between k_{H_2O} and k_{OH} (see Discussion), k_{OH} for the neutral thiol ester is estimated as 500 $M^{-1}\ sec^{-1}$. Assuming a stable carbanion and a pK_a of 6 for its conjugate acid, a pH-independent rate constant of $5 \times 10^{-6}\ sec^{-1}$ is predicted for hydrolysis in the pH region where the substrate has been completely converted to its carbanion. (e) It appears uncertain whether a thiol ester derived from the acidic thiol 2,2,2-trifluoroethanethiol is hydrolyzed *via* the E1cb pathway;[8c] with its much poorer leaving group, $NO_2CH_2COSCH_3$ would be even less likely to give rise to a reactive carbanion. (f) Fedor and Bruice[5a] report $k_{H_2O} = 7.21 \times 10^{-3}\ sec^{-1}$ and $k_{OH} = 8.75 \times 10^3\ M^{-1}\ sec^{-1}$ at 30°, μ = 1.0 (KCl). The small differences between these values and those of Table II may be due to the use of LiCl in the present study.

is similar to that observed at $\mu = 1.0$ (Figures 2 and 4). A less pronounced rate increase occurs with CCl_3COSCH_3 in 1.0–4.0 *M* HCl ($\mu = 4.0$).

Discussion

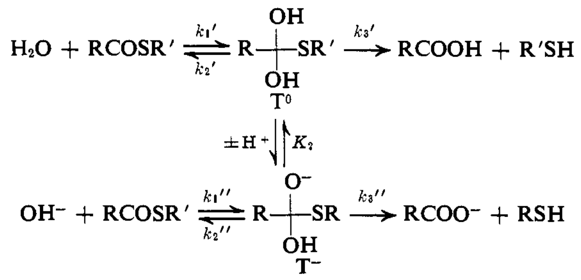
The observation of acid inhibition in the hydrolysis of ethyl trifluorothiolacetate, first made by Fedor and Bruice,[5a] constituted a significant contribution to the understanding of the mechanism of nucleophilic reaction at the thiol ester carbonyl function, particularly with regard to the chemistry of the unstable tetrahedral intermediate for which it provided the first evidence in thiol ester hydrolysis. Later investigations extended this finding to other thiol esters of trifluoroacetic acid[3a,5b,c] and led to the proposal that, at least in the case of the more reactive methyl *S*-trifluoroacetylmercaptoacetate, there occurred a diffusion-controlled, rate-determining, proton-transfer step.[5c] It appears, from the present study, that the phenomenon of marked acid inhibition is common to strongly acyl-activated thiol esters (RCOSR′, where R = CF_3, CCl_3, CF_3CF_2), is weaker but still experimentally detectable with somewhat less electron-withdrawing acyl groups (R = CHF_2, $CHCl_2$(?)), and disappears when the pK_a of the acid component of the thiol ester exceeds about 1.5.

On the other hand, acid catalysis of thiol ester hydrolysis is clearly detectable at $[H^+] \leq 1$ *M* with thiol esters derived from fairly basic carboxylic acids (acetic,[2] benzoic,[4] formic,[3] chloroacetic acids) of pK_a ranging between 4.8 and 2.8, and becomes less important relative to the rate of the water catalyzed reaction with $NO_2CH_2COSCH_3$ (pK_a of RCOOH = 1.7).

Does acid catalysis occur with thiol esters of stronger acids? As with the hydrolysis of, *e.g.*, succinic[9a] and glutaric[9b] anhydrides, the rate-diminishing effect of increasing ionic strength requires the use of media of constant ionic strength to detect the possible existence of weak acid catalysis. With CHF_2COSCH_3 (Figure 4), the increase in rate of hydrolysis at [HCl] = 0.1–4 *M* ($\mu = 4.0$, LiCl) is approximately proportional to $[H^+]$, with the exception of the point at 4 *M* HCl. A less pronounced and nonlinear rate increase is seen with CCl_3COSCH_3. We conclude that acid catalysis probably takes place at $[H^+] \geq 1$ *M* with the difluoro thiol ester (pK_a of RCOOH = 1.2) but is in doubt in the case of the trichloro thiol ester. Frequent use has been made of concentrated LiCl solutions to detect catalytic effects of hydronium ion, on the assumption that Li^+ and H^+ have similar influences on the activity of water.[7b,10] A number of instances are known, however, where the substitution of H^+ for Li^+ at constant ionic strength results in either a small increase[7b,11] or decrease[12] in rate, presumably owing to unequal effects of these cations on the activities of substrates or transition states. For this reason, it does not seem possible to make a convincing choice between acid catalysis and activity effects in the case of methyl trichlorothiolacetate.

Reaction Mechanism. For the hydrolysis of thiol esters which exhibit acid inhibition, we propose to consider in detail the mechanism of Scheme I, which is in essence that suggested by Fedor and Bruice[5a] and others.[3a,13] Its main features are the inclusion of neutral and anionic tetrahedral intermediates, and the provision of a change in rate-determining step at low pH. In one aspect, the mechanism of Scheme I differs from its predecessors in that it includes explicitly a pathway to products from the neutral tetrahedral intermediate (T^0) rather than solely from the anionic intermediate (T^-). If the only pathway to products (*i.e.*, for expulsion of mercaptan) were from an anionic intermediate, then it would be expected that the rate of thiol ester hydrolysis at low pH would approach zero, and the plot of log k_{obsd} *vs.* pH would approach a limiting slope of 1. With all the compounds showing well-defined acid inhibition (Figure 1), positive deviations from a limiting line of slope 1 were observed, *i.e.*, the reaction rates fell less rapidly than expected if only T^- contributed to products (see, for example, Figure 1, dashed line) and appeared to reach low, but nonzero, limiting values. The simplest way to accommodate these findings is to include a (minor) pathway to products from the neutral intermediate T^0. The necessity for the additional pathway had already been pointed out[13] on the basis of the published data[5a] for $CF_3COSC_2H_5$ in 2 *N* and 6 *N* HCl. In that case, it was not possible, however, to assess quantitatively the importance of this additional path since the high acidity data were obtained at ionic strengths higher than that (1.0 *M*) used for the rate measurements at pH >0.

Scheme I



Reaction mechanisms such as that of Scheme I, which include two intermediates of different net charge, offer an opportunity to observe a change in rate-limiting step as a function of pH. The sole requirement for a change in rate-limiting step to occur is that the partitioning of T^0 and T^- be different, *i.e.*, that $k_3'/k_2' \neq k_3''/k_2''$. In that sense, the partitioning is "unsymmetrical,"[5a] but it is not essential that there exist only one pathway to product (*e.g.*, *via* T^-) and only one pathway between reactants and intermediates (*e.g.*, step $k_1' - k_2'$). If the partitioning ratios of T^0 and T^- are very different (*e.g.*, $k_2'/k_3' \gg 1$; $k_2''/k_3'' \ll 1$), the pH–rate profile will consist of four well-separated regions,[14] two of slope 0 and two of slope 1. The extent of "acid inhibition" is a measure of the extent

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[9] (a) C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *J. Chem. Soc.*, 5361 (1963); (b) C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *ibid.*, 6174 (1965).

[10] (a) R. A. Robinson and R. H. Stokes, "Electrolytic Solutions," Butterworths, London, 1969, p 483; (b) F. A. Long, F. B. McDevit, and F. B. Dunkle, *J. Phys. Chem.*, **55**, 813 (1951); (c) C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, **31**, 3764 (1966); (d) G. J. Kasperek, T. C. Bruice, H. Yagi, N. Kaubisch, and D. M. Jerina, *J. Amer. Chem. Soc.*, **94**, 7876 (1972).

[11] S. Marburg and W. P. Jencks, *ibid.*, **84**, 232 (1962).

[12] T. H. Fife and D. M. McMahon, *J. Org. Chem.*, **35**, 3699 (1970).

[13] W. P. Jencks in "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 518–523.

[14] G. L. Schmir, *J. Amer. Chem. Soc.*, **90**, 3478 (1968).

to which the two regions of slope 0 are separated from each other, which depends on the partitioning ratios of T^0 and T^-.

In terms of the mechanism of Scheme I, when will acid inhibition such as that of Figure 1 be experimentally detectable? This depends, of course, on the precision of the experimental observations, *i.e.*, on the minimum separation of two regions of zero slope which could be observed. Assuming that $k_3'' \gg k_2''$ (*i.e.*, that T^- expels almost exclusively mercaptan),[5] and that a rate decrease of 20% would not be missed, it may be shown from the steady-state rate equation for Scheme I (see below) that a maximum value of 4 for k_3'/k_2' would lead to detectable acid inhibition. The smaller the value of k_3'/k_2', *i.e.*, the greater the difference in the pathways of breakdown of T^0 and T^-, the greater the degree of acid inhibition. In the limit, if $k_3' = 0$, the reaction rate would approach zero at high acidity.

The steady-state rate equation for Scheme I (eq 4)

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

contains terms for the partitioning of the two intermediates P^0 $(= k_2'/(k_2' + k_3'))$ and P^- $(= k_2''/(k_2'' + k_3''))$ as well as a constant K'' $(= (k_2'' + k_3'')K_2/(k_2' + k_3'))$, which indicates the pH value at which the change in rate-limiting step takes place.[14,15] The curves shown in Figure 1 and that for dimethyl thioloxalate (Figure 2) are calculated from eq 4 using the values of P^0, P^-, K'' and k_1' summarized in Table II. For methyl difluorothiolacetate (Figure 2), a term k_{H} was added to eq 4 to account for the observed rate increase at lowest pH. In view of the scatter in the data for methyl dichlorothiolacetate, no information could be obtained concerning the partitioning ratio of the intermediates presumably formed with this substance also. Similarly, the kinetic data for $\mathrm{NO_2CH_2COSCH_3}$ and $\mathrm{CH_2ClCOSCH_3}$ (Figure 3) show no change in rate-determining step over the pH range studied, and hence yield no information concerning any intermediates which may be formed. As previously noted,[14] the extent of acid inhibition is directly related to the magnitude of the partitioning ratio P^0 for the neutral intermediate; likewise, the distance along the pH axis between the pH where the change in rate-limiting step takes place (pK'') and the higher pH where base-catalyzed hydrolysis begins is a direct measure of the partitioning ratio P^- for the anionic intermediate (the larger the distance, the smaller the value of P^-). Put another way, if the anionic intermediate exclusively breaks down to mercaptan ($k_2'' = 0$), then k_1'' must also be zero (by microscopic reversibility) and no specific base-catalyzed pathway would be seen at high pH.

The following relationships exist between the empirical constants for the water catalyzed ($k_{\mathrm{H_2O}}$) and hydroxide catalyzed (k_{OH}) reactions (eq 1) and the constants of Scheme I (eq 5 and 6). In agreement

$$k_{\mathrm{H_2O}} = k_1'k_3''/(k_2'' + k_3'') = k_1'(1 - P^-) \tag{5}$$

$$k_{\mathrm{OH}} = k_1''k_3''/(k_2'' + k_3'') = k_1''(1 - P^-) \tag{6}$$

with previous formulations,[5] we suggest that at pH >2, the rate-determining steps for the hydrolysis of strongly acyl-activated thiol esters consist of the formation of neutral or anionic intermediates. A partial, but not complete, change in rate-determining step takes place at pH 0.5–0.7, approaching a situation where the breakdown of T^0 is mainly rate limiting. In fact, in the most favorable cases ($\mathrm{CF_3COSCH_3}$, $\mathrm{CCl_3COSCH_3}$) where $P^0 \simeq 0.8$, $k_2'/k_3' \simeq 4$, so that even here the formation step k_1' is partly rate limiting. With $\mathrm{CCl_3COSC_2H_5}$, $P^0 = 0.69$, so that $k_2'/k_3' = 2.2$, and both formation and decomposition of the neutral intermediate T^0 would contribute substantially to the rate-determining step in the limiting, pH-independent, rate region at high acidity.

When acid inhibition is visibly less, as with dimethyl thioloxalate, the value of the partitioning ratio P^0 required to fit the rate data is small (*ca.* 0.15), indicating that $k_3'/k_2' = 5$–6, *i.e.*, that even when the pathway to product formation is that proceeding *via* the neutral intermediate T^0, expulsion of mercaptan is preferred over that of water. In this case, no real change in rate-determining step (in the usual sense of the expression) has taken place as a result of the transition from T^- to T^0 as the main product-forming route. Nevertheless, T^0 is slightly less suitable as a reaction intermediate for hydrolysis than is T^- since the former breaks down about 20% of the time to expel water, and this property of T^0 is reflected in the small decrease of about 20% in the rate of hydrolysis of dimethyl thioloxalate.[16a]

In summary, the following may be said concerning the nature of the rate-determining steps in thiol ester hydrolysis, in cases where proton transfer steps themselves are not rate limiting.[16b] Strongly acyl-activated thiol esters undergo hydrolysis at pH >2 with rate-determining formation of intermediates. At lower pH, the rate-limiting step is the breakdown of an anionic or neutral intermediate. With less electron withdrawal in the acyl group, the transition at pH *ca.* 1 is only partial, *i.e.*, below pH 1 both formation and decomposition of intermediates are partially rate-determining. With thiol esters of more basic acids ($\mathrm{HCOSCH_3}$), the kinetic data indicate that P^0 is even smaller (0.021), *i.e.*, T^0 expels predominantly mercaptan, and the

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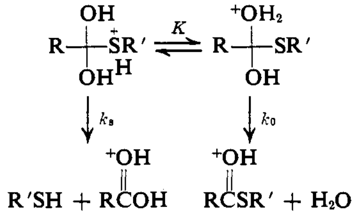
(15) R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, **91**, 737 (1969).

(16) (a) The actual value of P^0 for dimethyl thioloxalate may be somewhat higher than given in Table II. No account has been taken of the possible incursion of weak acid catalysis at lowest pH, such as is seen with $\mathrm{CHF_2COSCH_3}$ and possibly also with $\mathrm{CHCl_2COSCH_3}$. The effect of some acid catalysis would be to diminish the acid inhibition and to yield a value of P^0 smaller than the true one. In other words, there may be a somewhat greater difference between the modes of partitioning of T^0 and T^- than is suggested by the constants given for the oxalate in Table II. (b) The assumption has been made throughout this discussion that proton transfer steps not concerted with the formation or breakage of bonds to carbon are not in themselves rate determining. This assumption is supported by the fact that rate-determining, diffusion-controlled, proton transfer seems to occur only with a thiol ester more reactive than $\mathrm{CF_3COSC_2H_5}$ and not with the latter compound.[5c] If the mechanism of Scheme I is modified to consider the proton transfer step between T^0 and T^- as a rate step, it may be shown from the steady-state rate law for the new reaction scheme that the separation of the two rate regions of slope 1 still is directly and only determined by the partitioning ratio P^- of the anionic intermediate. On the other hand, the true value of the partitioning ratio P^0 of the neutral intermediate is *greater* than that calculated from the separation of the two regions of slope zero (*i.e.*, from the acid inhibition) in the pH profile. (c) M. Eigen and L. de Maeyer in "Technique of Organic Chemistry," Vol. VIIIb, A. Weissberger, Ed., Interscience, New York, N. Y., 1963, p 1047.

rate-limiting step remains the formation of intermediates, regardless of whether T^- or T^0 is the species through which product is formed.[3b] In this case, however, a (partial) change in rate-limiting step occurs on conversion of the intermediate to a cationic species T^+, since the latter expels H_2O at least as well as RSH, so that breakdown becomes at least partially rate limiting.

Since P^0 becomes steadily smaller with electron donation in the acyl group, it seems reasonable to suggest that, for the monochloro or nitroacetyl thiol esters, P^0 is in the range 0.02–0.1, *i.e.*, that pH-independent reactions occur with mainly rate-determining formation of intermediates and no acid inhibition is expected. It is not certain whether the onset of acid catalysis with these compounds will lead eventually to a change in the nature of the rate-determining step. Data obtained with $HCOSCH_3$,[3b] a ketene *O*,*S*-acetal,[3b] and a bicyclic thiolactone[6] suggest that the partitioning ratio (expressed as the fraction of the time that water is expelled) of the cationic intermediate may decrease appreciably with electron withdrawing in the acyl function. Thus, it is possible that with $CH_2ClCOSCH_3$ and $NO_2CH_2COSCH_3$ the transition from a neutral to a cationic intermediate would have little effect on the tendency of the intermediate to expel water, *i.e.*, that both neutral and cationic intermediates would yield mainly RSH. If this were true, formation of intermediates would remain rate limiting throughout the entire pH range, for these compounds.

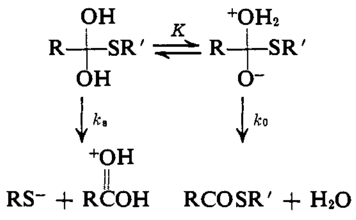
The following scheme (eq 7) is offered to explain



(7)

the increasing tendency of the cationic intermediate to expel mercaptan rather than water as electron withdrawal in the acyl group increases. Assuming that the equilibrium constant K is independent of R, the relative rates of steps k_s and k_0 may depend on the degree of stabilization of the resulting incipient carbonium ion formed on cleavage of the C–O or C–S bond. Destabilization by electron withdrawal in R would favor cleavage of the C–S bond (k_s), owing to the greater degree of stabilization offered by the two remaining hydroxyl groups.

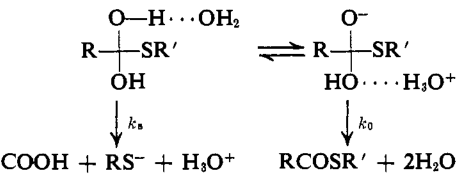
Similar reasoning may explain the observation that electron withdrawal in the acyl group favors the expulsion of water from the neutral species T^0 (eq 8).



(8)

Assuming again that the equilibrium constant K is unaffected by the nature of R, it appears reasonable to suggest that k_s would decrease with electron withdrawal in R, owing to destabilization of the carbonium ion formed on cleavage of the C–S bond. The process k_0 would probably be very fast and limited by the rate of separation of the products. As a result, strong acyl activation would favor the expulsion of water.

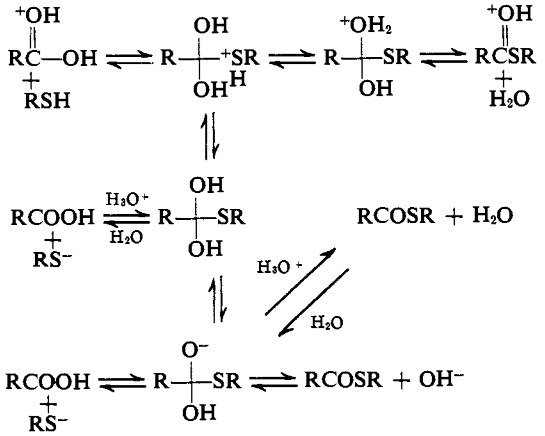
Although eq 8 seems to account for the influence of R on P^0, other considerations require modification of this scheme. First, the observed[5a] solvent deuterium isotope effect and general base catalysis for the reverse of step k_0 suggest that this step is better formulated as the general acid catalyzed (by hydronium ion) decomposition of an anionic species (eq 9). Second, the microscopic reverse reaction of step k_s is the reaction of thiol anion with the protonated carboxylic acid. From a previous study[6] of thiolactonization, and assuming reasonable pK values for the protonation of thiol anion and of the carboxyl group, it may be shown that a first-order rate constant in excess of 10^{12} sec^{-1} would be required to account for the observed rate of thiolactonization *via* this mechanism. Such a high rate constant is improbable,[16c] and, by extension, would seem to rule out this pathway (and its reverse) in the decomposition of the neutral intermediate T^0. A pathway involving the hydroxide-catalyzed attack of thiol on the protonated carboxyl group may also be excluded by the required rate constant which would far exceed the rate of diffusion of the reactants.



(9)

We conclude that a likely mechanism for step k_s is the general base catalyzed (by water) decomposition of the neutral intermediate, with a transition state involving little O–H bond breaking and extensive breaking of the C–S bond (eq 9). In the reverse reaction, the mechanism of thiol ester formation *via* a neutral transition state would involve general acid catalyzed attack of thiol anion. With the assumption that the formation and hydrolysis of diverse thiol esters may be represented by a general mechanism, the preceding discussion is summarized in Scheme II.

Scheme II



Variation of thiol ester structure does not seem to have a systematic effect on the partitioning (P^-) of the anionic intermediate (Table II). In all cases, the ratio k_3''/k_2'' is very large, ranging from 5×10^6 to 3×10^7, and reflects the much greater leaving ability of mercaptan anion relative to that of hydroxide ion.[17] The values of k_3''/k_2'' directly determined in this study may be compared with the estimate of 2000 based on the relative rates of the base-catalyzed decompositions of a hemithioacetal and the hydrate of acetaldehyde.[18] The corresponding partitioning ratio of the anionic tetrahedral intermediate formed during intramolecular acetyl transfer in *S*-acetylmercaptoethanol was estimated as 10^{10}, although some of the assumed rate constant ratios underlying this calculation are open to question.[19]

The pH range at which the transition from T^- to T^0 as the major intermediate takes place is given by pK'' and is nearly constant throughout the series of compounds for which this constant could be evaluated.

The hydrolysis of thiono esters proceeds *via* addition intermediates closely related to those of thiol ester hydrolysis.[20] In neutral solution, the intermediate(s) decompose exclusively with C–S bond cleavage, while at pH >12 there occurs significant expulsion of alcohol, presumably *via* a dianionic species.[21] Limited data[20a,b] at pH <2 suggest that C–O bond cleavage may begin to take place in acid solution also, possibly *via* a cationic intermediate, whose behavior might be expected to resemble that seen with methyl thiolformate.

The relative sensitivities of acyl-activated thiol esters to nucleophilic attack by water and hydroxide ion are shown in Figure 5. The slope of 1.46 (calculated by least squares, omitting the point for the oxalate) indicates that the water reaction is more sensitive to the nature of the acyl group than is the hydroxide reaction. This effect is similar to that observed with acyl-activated methyl and ethyl esters[22] (slope = 1.4) and *o*-nitrophenyl esters[23] (slope = 1.19). No ready explanation is apparent for the deviation of the point for methyl trichlorothiolacetate, for which the rate of alkaline hydrolysis (but not of the water reaction) is smaller than that of its ethyl analog. This curious behavior is in contrast to that of the two trifluoro and dichloroacetyl thiol esters, and of oxygen esters,[23,24] where the rates of the water and hydroxide reactions are invariably greater for the methyl than for the ethyl esters. The rate constant for the reaction of the oxalate thiol ester with hydroxide ion appears abnormally high. In the hydrolysis of *o*-nitrophenyl esters, the oxalyl and dichloroacetyl derivatives react at about the same rate with either water or hydroxide ion.[7b,23,25]

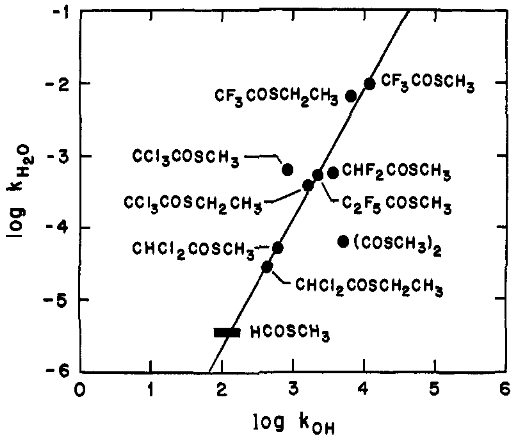


Figure 5. Relationship between rates of water and hydroxide catalyzed hydrolysis of thiol esters. Rate constants are given in Table II.

In the thiol ester series, the relative reactivity to water of dimethyl thioloxalate and methyl dichlorothiolacetate is 0.57 (after a statistical correction of 2 for the oxalate), but the corresponding ratio for the hydroxide reaction is 4.4.

Experimental Section[26]

Methyl trichlorothiolacetate was prepared by the dropwise addition of *ca.* 25 g (0.6 mol) of methyl mercaptan to 54 g (0.3 mol) of trichloroacetyl chloride at 0°. The solution was allowed to stand at room temperature for 24 hr, then was fractionally distilled at atmospheric pressure. The fraction boiling at 165–180° was redistilled and a central cut of material boiling at 175–177° was retained.

This procedure was employed in the synthesis of ethyl trichlorothiolacetate, ethyl and methyl dichlorothiolacetate, dimethyl thioloxalate, and methyl chlorothiolacetate using the appropriate commercially available acid chloride and mercaptan. In the case of the oxalate, no distillation was necessary. The solid residue was recrystallized directly from acetone–water.

Methyl trifluorothiolacetate was prepared by the dropwise addition of 4.9 g (0.024 mol) of trifluoroacetic anhydride to 4.8 g (0.1 mol) of methyl mercaptan, cooled with powdered Dry Ice. After standing at room temperature overnight, the solution was distilled. The fraction distilling at 65–75° was swirled with CaH_2, decanted, and redistilled to yield 3 g (86%) of methyl trifluorothiolacetate.

Methyl difluorothiolacetate was prepared by refluxing 5 g (0.05 mol) of difluoroacetic acid and 23 g (0.15 mol) of benzoyl chloride in 100 ml of benzene. The top of the reflux condenser was connected to a trap and the solution was cooled with Dry Ice–methanol, into which 13 g (0.3 mol) of methyl mercaptan had been introduced. After 20 hr at reflux, the contents of the trap were distilled at atmospheric pressure to give 3.3 g of the thiol ester contaminated with *ca.* 5% benzene as determined from the nmr spectrum.

Methyl pentafluorothiolpropionate was prepared by the same procedure from pentafluoropropionic acid (Matheson Coleman and Bell). Analysis of the product by vapor phase chromatography showed that it contained 2–5% benzene.

Methyl nitrothiolacetate was synthesized from nitroacetyl chloride.[27] A mixture of 10 ml of concentrated H_2SO_4 and 10 ml of 90% aqueous HNO_3 was added dropwise to 62.5 g (0.37 mol) of 1,1-dichloroethylene (Borden Monomer-Polymer Division) at 0°. After 2 hr, the mixture was stirred at room temperature for 1 hr, and the top layer was removed and distilled at 5 mm. The fractions (bp 24–60°, 11 g) whose ir spectrum showed a carbonyl band at 5.6 μ (acid chloride) were pooled and reacted with methyl mercaptan (13 g, 0.3 mol) by the standard procedure.

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[17] The lower value of $k_3''/k_2'' = 10^6$ for the oxalate is not considered reliable, owing to the fact that P^0 and pK'' are not very well defined for this compound.

[18] Reference 13, p 501.

[19] R. B. Martin and R. I. Hedrick, *J. Amer. Chem. Soc.*, **84**, 106 (1962).

[20] (a) S. G. Smith and M. O'Leary, *J. Org. Chem.*, 28, 2825 (1963); (b) S. G. Smith and R. J. Feldt, *ibid.*, 33, 1022 (1968); (c) P. Y. Bruice and H. G. Mautner, *J. Amer. Chem. Soc.*, 95, 1582 (1973).

[21] In the calculation of the relative rates of sulfide expulsion from the monoanionic and dianionic intermediates, it was assumed[20b] that the pH at which the product transition occurred was equal to the pK_a for the monoanion $\rightleftharpoons$ dianion equilibrium. This reasoning is incorrect. The pK_a of the intermediate will be given by the midpoint of the product transition only when the rates of product formation from monoanion and dianion are equal.

[22] J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, 86, 837 (1964).

[23] B. Holmquist and T. C. Bruice, *ibid.*, **91**, 2982 (1969).

[24] E. K. Euranto and A.-L. Moisio, *Suom. Kemistilehti B*, 37, 92 (1964).

[25] The ratio of the rates of the water reactions of ethyl *o*-nitrophenyl oxalate and *o*-nitrophenyl dichloroacetate is 0.45. The corresponding ratio for the hydroxide ion reaction is 1.01.

[26] All boiling points are uncorrected. Ultraviolet spectra were determined by means of a Cary 15 spectrophotometer. Nmr spectra were obtained with a Varian Model A-60 spectrometer with tetramethylsilane as internal standard. An A.E.I. MS-9 mass spectrometer operating at an ionizing potential of 70 eV was used for mass spectra.

[27] I. V. Martynov, Z. I. Khromova, and Y. L. Kruglyak, *Probl. Org. Sin.*, 60 (1965); *Chem. Abstr.*, 64, 8023 (1966).

Table IV. Physical and Spectral Data for Thiol Esters

Thiol ester	Bp,[a] °C	Lit. bp, °C	Ir (cm^{-1})[b]	Uv$_{max}$ (ϵ)[c]	Nmr (δ)
CF_3COSCH_3	62.5–64		1710		2.48[d]
CCl_3COSCH_3	175–177	70 (17 mm)[e]	1700	251.5 (4020)	2.48[f]
$CCl_3COSC_2H_5$	200–205	44 (3 mm)[g]	1700		3.06 (q), 1.38 (t)[d]
$C_2F_5COSCH_3$	73–76		1690	244	2.46[d]
CHF_2COSCH_3	98–100		1700	241 (3920)	2.46 (3 H. s), 5.85 (1 H. s)[d]
$CHCl_2COSCH_3$	183.5–184	81 (23 mm)[e]	1690	246 (3770)	
$CHCl_2COSC_2H_5$	193	177–178[h]	1690	249 (4520)[i]	
$(COSCH_3)_2$	85–86[j]	82.5–83.5[k]	1670[l]	278 (5660)	2.39[f]
$CH_2NO_2COSCH_3$	65–67 (0.35 mm)		1690		2.44 (3 H, s), 5.32 (2 H. s)[d]
$CH_2ClCOSCH_3$	94–96	60 (16 mm)[e]	1690	230 (2400)	2.40 (3 H), 2.33 (2 H)[f]

[a] At atmospheric pressure, unless otherwise indicated. [b] Carbonyl stretching vibration. [c] In acetonitrile. [d] In CCl_4. [e] R. Mayer, S. Scheithauer, and D. Kunz, *Chem. Ber.*, 99, 1393 (1966). [f] In $CDCl_3$. [g] A. C. Pierce and M. M. Joullie, *J. Org. Chem.*, **28**, 658 (1963). [h] P. J. Meyer, *Ber.*, **14**, 1507 (1881). [i] In 10% CH_3CN-H_2O. [j] Melting point. [k] H. O. Jones and H. S. Tasker, *J. Chem. Soc.*, **95**, 1904 (1909). [l] Nujol mull.

Ethyl trifluorothiolacetate was obtained from Eastman Chemicals.

Physical and spectral data for all the thiol esters synthesized for this study are listed in Table IV. The mass spectrum of all new compounds showed the appropriate molecular ion.

Kinetic Measurements. Acetonitrile was purified as previously described.[28] Buffers and inorganic salts were of reagent grade and were used without further purification. Glass distilled water was used in the preparation of all solutions. The hydrolysis of all thiol esters except that of pentafluoropropionic acid was studied at 30° in aqueous solution containing 0.33% acetonitrile, $\mu = 1.0$, adjusted with added LiCl. Constant pH was maintained with HCl at pH ≤ 2.5; at higher pH, formate, acetate, phosphate, Tris, *N*-ethylmorpholine, or dilute sodium hydroxide was used at concentrations generally between 0.02 and 0.10 *M*. In 0.005–0.01 *M* HCl solutions (30°, $\mu = 1.0$, LiCl) the equation pH = $-\log$ [HCl] $-$ 0.21 is obeyed and was used in the calculation of pH below pH 2.10. Similarly, at $\mu = 4.0$ (LiCl), the equation pH = $-\log$ [HCl] $-$ 1.0 was experimentally determined. At pH >2, a Radiometer PHM 4d or Radiometer TTTlc meter equipped with scale expander was employed to measure pH at the end of each reaction. In dilute NaOH solution (0.002–0.02*M*, 30°, $\mu = 1.0$) the measured pH obeyed the equation pH = 13.28 + log [OH], and the activity of hydroxide ion was calculated assuming $K_w = 1.47 \times 10^{-14}$.

Rates of hydrolysis of all thiol esters were determined spectrophotometrically at their respective absorbance maxima (except for methyl thioloxalate which was followed at 310 μm). Reactions were initiated by the addition of 0.01 ml of a stock solution of thiol ester in acetonitrile to 3 ml of aqueous buffer solutions equilibrated at 30° in the cell compartment of a Cary 15 spectrophotometer. In order to obviate volatility and solubility problems encountered in the hydrolysis of methyl pentafluorothiolpropionate, air space in the cuvette was minimized by adding 0.10 ml of stock solution to 3.6 ml of buffer and tightly stoppering the cuvette with a Teflon stopper. Reactions were followed for at least 3 half-lives and generally to greater than 6. For reactions too slow to conveniently obtain an infinity reading, and for reactions of dimethyl thioloxalate in which the slower secondary reactions of the monothiol ester had a small effect on the final absorbance, a modified Guggenheim treatment of the data[29] was used to calculate the infinity value. Rate constants were then calculated using the integrated form of the first-order rate equation and were generally reproducible to better than 3%. A Durrum-Gibson stopped-flow spectrophotometer was used to follow reactions in dilute hydroxide solutions. For reactions at pH >8, a wavelength 10 nm above λ_{max} was used for all the thiol esters, except for the oxalate which was followed at 295 nm. This was necessary in order to avoid interference from mercaptide ion absorption.

pK_a Determinations. The pK_a of pentafluoropropionic acid was determined at ambient temperature by means of a Bruker 60-MHz nmr spectrometer equipped with an ^{19}F probe. The chemical shift difference between the fluorine atoms on the α and β carbons was measured for solutions of the acid (0.06–1.0 *M*) in water, and also in 4.63 *M* $HClO_4$ and 1.3 *M* NaOH, using trifluoroacetic acid as an external standard (Table V). The limiting slope of a plot of the degree of ionization α, *vs.* acid concentration, *c*, yielded an estimate of $K_a = 2.60$ (p$K_a = -0.41$).[30-32] The estimated pK_a based on a plot of pK_a *vs.* σ^* for acyl-activated carboxylic acids is -0.42, using an estimated σ^* of 2.63 for the CF_3CF_2 group.[33]

Table V. Degree of Ionization of Solutions of CF_3CF_2COOH Based on ^{19}F Nmr Measurements

[$C_2F_5CO_2H$], *M*	Δ(Hz)[a]	α[b]
0.33[c]	2354.6	0
0.33[d]	2257.4	1
1.0	2275.7	0.819
0.10	2260.4	0.969
0.080	2259.3	0.980
0.060	2258.6	0.988

[a] Difference between chemical shift in hertz of α and β fluorine atoms. [b] Degree of ionization of pentafluoropropionic acid. [c] In 4.63 *M* $HClO_4$. [d] In 1.33 *M* NaOH.

The pK_a of $CH_3SCOCOOH$ was determined by spectrophotometeric titration ($\mu = 1.0$, 30°) at 290 nm. This compound was obtained by the following procedure. Dimethyl thioloxalate (1.93 g) was dissolved in 100 ml of 50% CH_3CN-H_2O, and a total of 7 ml of a 2 *M* NaOH solution was added in 2-ml aliquots, the pH being allowed to fall after each addition. After *ca.* 10 min. the solution was acidified and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous $MgSO_4$ and the solvent evaporated to yield a yellow oil which was used in the titration. The monomethyl thioloxalate had λ_{max} at 270 nm (1 *M* HCl) while λ_{max} in aqueous phosphate buffer (pH 6.4) was 261.5 nm. The resulting titration data were analyzed by the method of Reed and Berkson,[34] yielding pK_a' = 0.54. Since the pK_a of formic or acetic acid is about 0.5 unit lower in 1.0 *M* LiCl than the thermodynamic value, the thermodynamic pK_a of $CH_3SCOCOOH$ is approximately 1.04.

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(32) It should be noted that the values of the dissociation constants for CF_3COOH and CCl_3COOH, determined by spectroscopic methods and reported in ref 30 and 31, seem more reliable and are considerably larger (pK_a is lower) than those found in the earlier literature.

(33) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 222. The σ^* value for CF_3CF_2 was calculated from the expression

$$\sigma^*_{C_2F_5} = \sigma^*_{CF_3CH_2} + \sigma^*_{CHF_2} + [\sigma^*_{CCl_3} - (\sigma^*_{CHCl_2} + \sigma^*_{CH_2Cl})]$$

(34) W. M. Clark, "Oxidation-Reduction Potentials of Organic Systems," Williams and Wilkins, Baltimore, Md., 1960, p 154. Equation 38 should be corrected to read pK' $-$ p[L]$_r$ = log *C*.