

Nucleophilic Displacement Reactions at the Thiol Ester Bond. IV. General Base Catalyzed Hydrolysis of Ethyl Trifluorothiolacetate. Kinetic Evidence for the Formation of a Tetrahedral Intermediate¹

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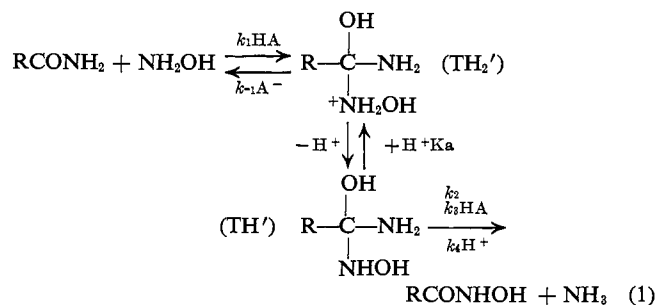
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The hydrolysis of ethyl trifluorothiolacetate in water at 30° ($\mu = 1.0 M$) at zero buffer concentration is kinetically described by $v = [1/(2.31 + 6.6a_H)] + 5.25 \times 10^5 a_{OH^-}$ [ester]. The spontaneous hydrolysis, which is fairly insensitive to μ , is catalyzed by general bases and inhibited by the general acid $NH_3^+OCH_3$ (inhibition by the general acids H_3CCOOH and $HCOOH$ cannot be differentiated from a solvent effect). These experimental data when combined with the determined solvent kinetic isotope effects, Brønsted β -constant, and product analysis are consistent with the mechanism of eq. 18.

Introduction

There are several examples in the literature of addition compounds of carboxylic esters formed in non-aqueous solution.⁴ Thus, Bender⁵ has shown spectroscopically the existence of a tetrahedral addition compound formed from ethyl trifluoroacetate and ethoxide ion in *n*-butyl ether. Until recently, the only evidence of addition compounds of carboxylic esters formed in aqueous solution was supplied by H_2O^{18} exchange studies performed by Bender and his co-workers.⁴ Bruice and Fedor,^{1c} on the basis of an extensive study, have shown kinetically the formation of intermediates in the reaction of alkyl thiol esters with hydroxylamine and methoxylamine and have suggested that these are tetrahedral intermediates in acid-base equilibria. Martin and Henkle⁶ subsequently reported that the hydroxylaminolysis of *n*-butyl thiolacetate at pH 6.12, 5.73, and 5.31 is a simple general base catalyzed reaction, there being no evidence for intermediate formation. However, the three values of the apparent third-order rate constants determined by Martin and Henkle⁶ give an equally poor fit to the kinetic scheme they suggest as well as to the scheme shown by Bruice and Fedor^{1c} to apply to *n*-butyl thiolacetate, isopropyl thiolacetate, *t*-butylthiolacetate, and γ -thiolbutyrolactone over an extended pH range. Martin⁷ and co-workers observed an inverse dependence of hydrogen ion concentration at low pH on the intramolecular

acetyl transfer reaction in S-acetylmercaptoethylamine and have interpreted this result on the basis of the formation of tetrahedral intermediates which are in acid-base equilibrium. The hydrolysis of 4-substituted thiazolines is also inhibited in acidic solution, and the inhibition may be accounted for by a mechanism involving a tetrahedral intermediate.⁸ Jencks and Gilchrist⁹ recently reported kinetic evidence for the existence of tetrahedral intermediates in the hydroxylaminolysis of formamide and acetamide. A mechanism suggested by them which explains the experimental data is shown in expanded form in eq. 1. The mechanism (1) differs slightly from that reported⁹ in that in eq. 1 two intermediates, TH_2' and TH' , are shown to



be in equilibrium.¹⁰

In continuance of our program to help clarify the mechanisms by which thiol esters may undergo solvolysis and nucleophilic attack, we report here the reaction of ethyl trifluorothiolacetate with oxygen and nitrogen nucleophiles. The choice of substrate was dictated by the observations of Bender⁵ with ethyl trifluoroacetate and by the expectation that with this substrate information on the mode of formation of a tetrahedral intermediate in a general base catalyzed reaction might be obtained. Thus, Jencks and Carriuolo¹¹ had shown previously that spontaneous hydrolysis as well as the acetate ion catalysis of hydrolysis of acyl-activated esters most likely are examples of general base catalysis.

(8) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964).

(9) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **86**, 5616 (1964).

(10) The mechanism of Jencks and Gilchrist tends to be misleading since on cursory inspection there appears to be a violation of the principle of microscopic reversibility. Thus the k_1 and k_{-1} paths of their mechanistic scheme appear to be general acid catalyzed steps. Comparison of eq. 1 above with their eq. 1⁹ indicates that these authors have chosen to combine a proton transfer in an equilibrium with a general base rate step, yielding a rate step which appears to be general acid catalyzed.

(11) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961).

(1) For parts I-III of Thiol Esters see: (a) T. C. Bruice, J. J. Bruno, and W. S. Chou, *J. Am. Chem. Soc.*, **85**, 1659 (1963); (b) L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 4117 (1964); (c) T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 4886 (1964); (d) a portion of this paper appeared as communications: L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 5697 (1964).

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(4) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960), and references therein.

(5) M. L. Bender, *J. Am. Chem. Soc.*, **75**, 5986 (1953).

(6) R. B. Martin and L. P. Henkle, *J. Phys. Chem.*, **68**, 3438 (1964).

(7) R. B. Martin and R. I. Hedrick, *J. Am. Chem. Soc.*, **84**, 106 (1962).

Experimental

Materials. Ethyl trifluorothiolacetate was prepared by slowly adding trifluoroacetic anhydride (Eastman, White Label) to a cooled 10% *M* excess of ethyl mercaptan (K & K Laboratories). The mixture was allowed to stand at room temperature for 24 hr. and then distilled three times through a Vigreux column, b.p. 83–84° (733 mm.) (lit.¹² 90.5° at 760 mm.). The infrared spectrum was identical with the published spectrum of Hauptschien, Stokes, and Nodiff¹² and the ultraviolet spectrum showed a single peak at 244 m μ (ethanol) (ϵ 4150). Inorganic salts (Mallinckrodt analytical reagent grade) were oven dried at 110° and stored over P₂O₅ until used. Acetic acid and formic acid (Baker Analyzed reagent) were distilled from glass prior to use. Methoxylamine hydrochloride (Eastman, White Label) was dried and stored over P₂O₅ until used. Imidazole (Eastman, White Label), crystallized from acetone–petroleum ether (b.p. 30–60°), was dried and stored over P₂O₅ until used. Freshly boiled demineralized distilled water was used to prepare solutions. Deuterium oxide, 99.7%, was supplied by the Atomic Energy Commission through Cornell University Stores. Moisture was excluded from experiments involving deuterium solvent kinetic isotope effects with the exception of potassium deuterium hydroxide pellets containing some potassium hydroxide hydrate. The maximum amount of water as contaminant in these experiments was 0.4%. Deuteriochloric acid was prepared from deuterium oxide and hydrogen chloride. Hydrochloric acid was Baker Analyzed reagent.

Apparatus. A Zeiss PMQ II spectrophotometer equipped with a thermostated brass cuvette holder, through which was circulated water of constant temperature, was used for kinetic measurements. All pH measurements were made with a Radiometer Model 22 pH meter with a Model PHA 630 Pa scale expander. The combined glass calomel electrode (Radiometer G.K. 2021C) and electrode cell compartment were thermostated at the reaction temperature, $\pm 0.1^\circ$. Addition and mixing of ester were accomplished as previously described.^{1b,c}

Kinetics. The disappearance of ethyl trifluorothiolacetate with time was followed spectrophotometrically by recording the decrease in thiol ester absorbance at 244 m μ . The nucleophile and its conjugate acid supplied the buffer capacity at all pH values. Free nucleophile concentration was corrected for pH change when pH varied by more than 0.02 pH unit on serial dilution. Solutions were brought to a calculated ionic strength of 1 *M* with potassium chloride. Deaerated water was used to prepare solutions and cuvettes of 2-ml. capacity were filled to the stopper level with solution. A solution in the reference cell identical with the reaction solution (minus ester) was used to compensate for absorbance due to reactants. The concentration of nucleophile was always in excess of the concentration of ester (*ca.* 1×10^{-4} *M*) so that pseudo-first-order kinetics were obtained. Reaction rates were followed to a minimum

of 3 half-lives. The *H_p* of the reaction solution was always determined at the beginning of each run and was periodically checked after some runs to ensure constancy of pH during runs. Pseudo-first-order rate constants were calculated from the slopes of plots of $\log(O.D._0 - O.D._\infty)/(O.D._t - O.D._\infty)$ vs. time. *pK_a'* values were determined by the method of half-neutralization ($\mu = 1$ *M* with KCl) or were obtained from the literature: imidazole, 7.09; methoxylamine, 4.75; acetate, 4.61; formate, 3.61; and phosphate dianion, 6.9.¹³ The *pK_a'* for acetate from 15.4 to 35.8° was found to be invariant within the error of measurement. *pK_a'* values in deuterium oxide were determined by the method of half-neutralization ($\mu = 1$ *M* with KCl): imidazole, 7.58 (lit. 7.54¹⁴); methoxylamine, 5.23; and acetate, 5.08. *pD* was determined from pH by the method of Fife and Bruce.¹⁵ The autoprotolysis constants used for water and deuterium oxide were 1.47×10^{-14} and 2.24×10^{-15} , respectively.^{16,17}

Product Analysis. The reaction solutions of the thiol ester with the nucleophiles reported herein were scanned using a Perkin-Elmer 202 recording spectrophotometer. Only disappearance of the peak at 244 m μ with time was evidenced. The ultraviolet absorption spectra of ethyl trifluorothiolacetate was examined in CHCl₃ and in CHCl₃–acetic acid solutions in order to determine if significant complex formation occurred between the thiol ester and acetic acid. The λ_{max} values for the thiol ester in CHCl₃ and in CHCl₃–12.2% w./v. acetic acid solution are the same within 1 m μ (245 m μ). The optical density of ethyl trifluorothiolacetate in a 6% w./v. solution of acetic acid in CHCl₃ shows a 4% decrease from the optical density value determined in CHCl₃. The absence of any new spectral bands in the region 240–300 m μ and the magnitude of the decrease in absorbance of the thiol ester in 6% acetic acid–CHCl₃ solution suggest that complex formation is of little significance. The infrared spectra of the reaction products of ethyl trifluorothiolacetate, 0.05–0.1 *M*, with various nucleophiles in deuterium oxide were obtained on a Unicam SP. 200 spectrophotometer using a pair of Irtran-2 cells of 0.025-mm. thickness. Only a single band at 1678 cm.⁻¹, measured from the 1603-cm.⁻¹ band of polystyrene, was found in the carbonyl region of the spectra. Trifluoroacetic acid in deuterium oxide shows a single band at 1678 cm.⁻¹. Thus the final carboxylic product of solvolysis of ethyl trifluorothiolacetate in aqueous solution is trifluoroacetic acid or trifluoroacetate ion. Results are given in Table I.

Trifluoroacetic acid and ethyl mercaptan at 4×10^{-4} *M* concentrations in 1 *M* HCl do not undergo reaction to form ethyl trifluorothiolacetate as indicated by an optical density value which is stable with time and which can be accounted for by the added mercaptan alone. Mercaptans do not react appreciably with perfluoroacids to form thiol esters. Thus, Hauptschien and co-workers¹² obtained a 5% yield of

(13) J. T. Edsall and I. Wyman, "Biophysical Chemistry," Vol. I, Academic Press Inc., New York, N. Y., 1958.

(14) T. C. Bruce and J. J. Bruno, *J. Am. Chem. Soc.*, **84**, 2128 (1962).

(15) T. H. Fife and T. C. Bruce, *J. Phys. Chem.*, **65**, 1079 (1961).

(16) T. C. Bruce and J. J. Bruno, *J. Am. Chem. Soc.*, **83**, 3494 (1961).

(17) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd Ed., Butterworth and Co. (Publishers) Ltd., London, 1959.

(12) M. Hauptschien, C. S. Stokes, and E. A. Nodiff, *J. Am. Chem. Soc.*, **74**, 4005 (1952).

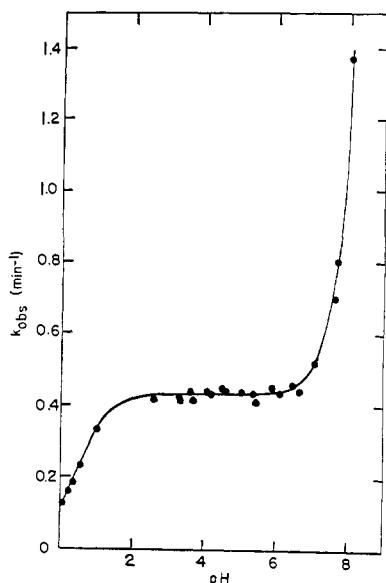


Figure 1. pH-rate profile for the hydrolysis of ethyl trifluorothiolacetate in water at 30° and $\mu = 1 M$.

ethyl heptafluorothiobutylate from ethyl mercaptan and heptafluorobutyric acid by heating these reactants at 100° for 24 hr. These investigators were unable to isolate any diethyl thiol ester from the reaction of a 2:1 M ratio of ethyl mercaptan with perfluoroglutaric anhydride. The acyl-oxygen bond in preference to

Table I. Infrared Spectrophotometric Analysis of the Carboxylic Acid Product Obtained in the Solvolysis of Ethyl Trifluorothiolacetate in Deuterium Oxide

Nucleophile	Concn., M	pH (30°)	Wave no., cm.^{-1}
D ₂ O	50		1677
DCl	0.65		1678
Imidazole	0.50	7.21	1678
Phosphate	0.10	5.98	1678
Methoxylamine	0.50	4.78	1677
Acetate	0.50	4.72	1678
Formate	0.50	3.50	1678

the alkyl-oxygen bond of methyl trifluoroacetate is broken during hydrolysis in acidic, basic, or initially neutral solution.¹⁸ *t*-Butyl thiolacetate undergoes AAC2 scission.¹⁹

Results²⁰

The hydrolysis of ethyl trifluorothiolacetate in water in the pH range 0–8 is kinetically described by eq. 2

(18) C. A. Bunton and T. Hadwick, *J. Chem. Soc.*, 3248 (1958).

(19) T. C. Bruice in "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, p. 425, and references therein.

(20) Abbreviations used in this study are: a_{H} and a_{D} , hydrogen ion activity and deuterium ion activity, respectively, as determined at the glass electrode (the necessary corrections being made to determine a_{D} ; see Experimental); a_{OH} and a_{OD} , hydroxide ion activity and deuteriooxide ion activity, respectively, calculated from $K_{\text{w}}/a_{\text{H}}$ and $K_{\text{D}}/a_{\text{D}}$ where K_{w} and K_{D} are the autoprotolysis constant for water and the autodeuterolysis constant for deuterium oxide, respectively; K_{s}' , the apparent dissociation constant, determined under experimental conditions, for the acidic species of a nucleophile; k_2' , the pH-dependent apparent second-order rate constant; k_2 , the true second-order rate constant in units of $M^{-1} \text{ min.}^{-1}$; k_{obsd} , the pseudo-first-order rate constant for ester disappearance in units of min.^{-1} ; $k_{\text{H}_2\text{O}}$ and $k_{\text{D}_2\text{O}}$, rate constants for spontaneous hydrolysis in units of min.^{-1} , the concentration

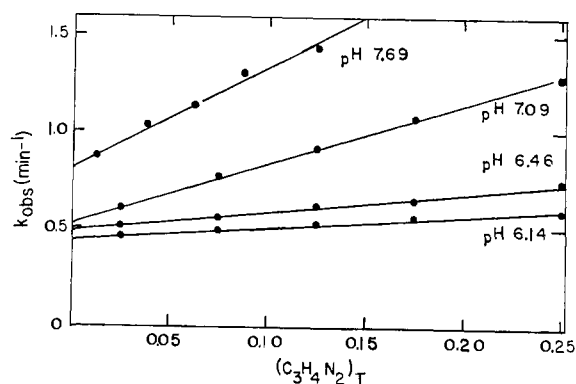


Figure 2. Plots of the pseudo-first-order rate constants vs. total imidazole concentrations at constant pH.

wherein concentration terms for water have been omitted.²¹ The pH-rate profile (Figure 1) was constructed from eq. 2 and the points were experimentally

$$-d(\text{ester})/dt = \left[\frac{1}{2.31 + 6.6a_{\text{H}}} + 5.25 \times 10^5 a_{\text{OH}} \right] (\text{ester}) \quad (2)$$

determined. The k_{obsd} values in the acid region of Figure 1 were obtained by following the disappearance of ester at 244 $m\mu$ in dilute hydrochloric acid. The k_{obsd} values between pH 2.5 and 8 in Figure 1 were obtained by extrapolation of linear plots of pseudo-first-order rate constants vs. total buffer concentration to zero buffer concentration employing the buffers acetate, formate, phosphate, and imidazole, each at five concentrations at each constant pH (see Figure 2 for an illustration of the intercept data used). The method used to evaluate the sum of the neutral water rate and hydroxide rate, *i.e.*, $k_{\text{H}_2\text{O}} + k_{\text{OH}}(\text{OH}^-)$, at pH 8.04 constitutes the single exception to the stated method. At this pH the summed rate constant was evaluated by subtracting the contribution of 0.06 M imidazole from the pseudo-first-order rate constant obtained at this single imidazole concentration. The second-order rate constant for the reaction of imidazole with ethyl trifluorothiolacetate was determined previously at four pH values (Figure 2 and Table II). This procedure was necessary because significant pH changes occurred during reaction of the thiol ester with more dilute imidazole solutions at pH 8.04 ($\text{p}K_{\text{a}}$ of trifluoroacetic acid = 0.23 at 25°),²³ and the extrapolated rate constant was valueless. Also, rates of reaction of ester with imidazole at concentrations of imidazole $> 0.06 M$ were too rapid to follow accurately by conventional techniques. The value of the second-order rate constant for the attack of hydroxide ion at the thiol ester

term for water (deuterium oxide) being omitted; k_{OH} and k_{OD} , the second-order rate constant for the attack of hydroxide (deuteriooxide) ion at the ester bond; $(\text{Im})_{\text{T}}$, the total concentration of imidazole equal to the sum of the concentrations of imidazole free base and conjugate acid [(Im) plus (ImH⁺), respectively]; $(\text{P})_{\text{T}}$, the total concentration of phosphate ion equal to $(\text{H}_2\text{PO}_4^-)$ plus (HPO_4^{2-}) .

(21) A small error is incurred in reading pH values between pH 0 and 1.²² Thus the measured pH is greater than the true pH and consequently the true value of a_{H} is slightly greater than measured experimentally. Equation 2 can be expressed in terms of the stoichiometrically determined concentrations of hydrogen ion rather than a_{H} . If this is done the coefficient of (H_3O^+) is 5.4. Correspondingly for eq. 4, a_{D} may be replaced by the stoichiometrically determined concentration of (D_3O^+) , and the coefficient of this concentration term is then 29.5.

(22) R. G. Bates, "Electrometric pH Determinations," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 241.

(23) A. L. Henne and C. J. Fox, *J. Am. Chem. Soc.*, 73, 2323 (1951).

Table II. Tabulation of Rate Constants for the Reaction of Ethyl Trifluorothiolacetate with Various Nucleophiles ($T = 30^\circ$, $\mu_{\text{calc}} = 1.0 M$ with KCl)

Nucleophile	k_{rate}	pH (pD) range	No. of pH (pD) values	No. of k_{obsd}	Concentration range of nucleophile, M	$k_{\text{rate}}^{\text{H}}/k_{\text{rate}}^{\text{D}}$
Water	0.433 min. ^{-1a}	0-8.04	27	27 ^b	ca. 53.4 ^c	3.0±0.3
Hydroxide ion	$5.25 \times 10^6 M^{-1} \text{min.}^{-1}$	0-8.04	22	22 ^b		0.78
Deuterium oxide	0.146 min. ^{-1a}	0.40-8.33	9	6 ^b	ca. 53.6 ^h	
Deuterioxide ion	$6.6 \times 10^6 M^{-1} \text{min.}^{-1}$	0.40-8.33	4	6 ^b		
Phosphate monoanion	$0.5 M^{-1} \text{min.}^{-1}$	5.36-7.64	6	30	0.014-0.44	
Phosphate dianion	$5.6 M^{-1} \text{min.}^{-1}$	5.36-7.64	6	30	0.014-0.44	
Imidazole	$6.3 \pm 0.2 M^{-1} \text{min.}^{-1}$	6.14-7.64	4	21	0.0125-0.25	3.1
Imidazole (D ₂ O)	$2.08 \pm 0.05 M^{-1} \text{min.}^{-1}$	7.59-8.33	3	15	0.025-0.250	
Methoxylamine	$135 \pm 9 M^{-1} \text{min.}^{-1}$	3.79-5.55	4	17	0.005-0.03	4.4
Methoxylamine (D ₂ O)	$30.7 M^{-1} \text{min.}^{-1}$	5.23	1	5	0.005-0.035	
Acetate ion	$0.666 M^{-1} \text{min.}^{-1}$	3.29-5.45	7	38	0.1-1.0	2.1
Formate ion	$0.500 M^{-1} \text{min.}^{-1}$	2.58-4.18	4	20	0.1-1.0	
Acetate buffer	$1.538 M^{-1d}$					
	$0.770 M^{-1} \text{min.}^e$					
Formate buffer	$1.154 M^{-1f}$					
	$0.673 M^{-1} \text{min.}^g$					

^a Concentration term for nucleophile omitted. ^b Number of intercept values obtained by extrapolating plots of pseudo-first-order rate constants vs. concentration of buffer to zero buffer concentration. ^c Approximate molarity of water in 1 M KCl solution, density = 1.04. ^d Coefficient of acetate ion, $k_2'/\text{CH}_3\text{CO}_2^-$, for eq. 11. ^e Coefficient of acetic acid, $k_2'/\text{CH}_3\text{CO}_2\text{H}$, for eq. 11. ^f Coefficient of formate ion, k_2'/HCO_2^- , for eq. 11. ^g Coefficient of formic acid, $k_2'/\text{HCO}_2\text{H}$, for eq. 11. ^h Approximate molarity of deuterium oxide in 1 M KCl solution, density = 1.149.

bond (Table II) was determined from the slope of plots of extrapolated pseudo-first-order rate constants, *vide supra*, vs. K_w/a_H , where the pseudo-first-order rate constant = $k_{\text{H}_2\text{O}} + k_{\text{OH}}(\text{OH}^-)$ (Figure 3). The

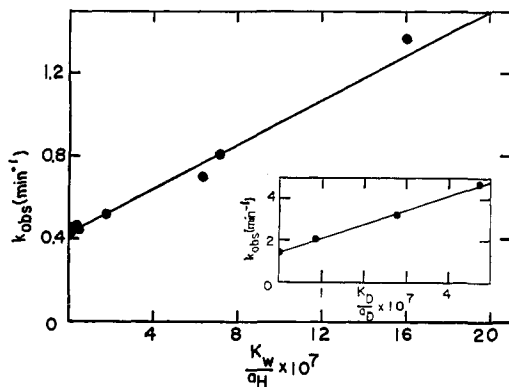


Figure 3. Plot of the sum of the spontaneous and hydroxide rate, $k_{\text{H}_2\text{O}} + k_{\text{OH}}(\text{OH}^-)$, vs. K_w/a_H . Similarly for the reactions in D₂O.

points near the ordinate in Figure 3 represent 18 intercept determinations (18 pH values and 90 k_{obsd} values). The intercept in Figure 3 is the neutral water rate (Table II) in which the concentration term for water is omitted. The relationship of the observed pseudo-first-order rate constant to acidity from pH 0 to 6 is given by eq. 3 which correctly predicts that a plot of $1/k_{\text{obsd}}$ vs. a_H is linear with slope $6.6 M^{-1} \text{min.}$ and

$$k_{\text{obsd}} = 1/(2.31 + 6.6 a_H) \quad (3)$$

intercept 2.31 min. (Figure 4). Thus when a_H becomes quite small, expression 3 reduces to $k_{\text{obsd}} = 0.433 \text{ min.}^{-1}$, which is the value of the neutral water rate constant, the concentration term for water being omitted (Table II).

The solvolysis of ethyl trifluorothiolacetate in deuterium oxide in the pD range 0.40 to 8.33 is kinetically described by eq. 4. The numerical values of eq. 4

$$-d(\text{ester})/dt = [1/(6.85 + 33.88a_D)] + 6.6 \times 10^6 a_{\text{OD}}(\text{ester}) \quad (4)$$

were obtained for the reaction in deuterium oxide by methods described for the rates in water. However,

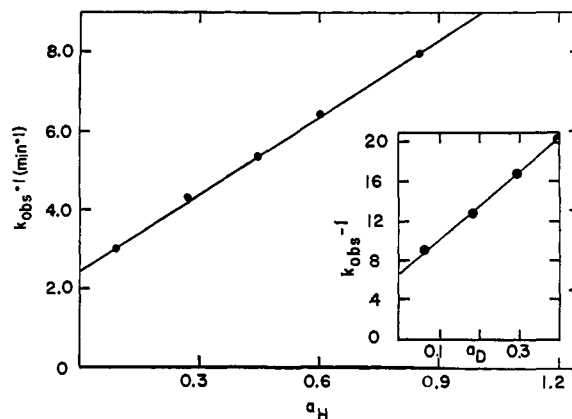


Figure 4. Plot of the reciprocal of the pseudo-first-order rate constant vs. a_H or a_D for the hydrolysis of ethyl trifluorothiolacetate in moderately strongly acidic solution.

only rates in imidazole buffer (five imidazole concentrations at each of three pD values: 7.59, 8.10, 8.33) were used to evaluate the sum of the neutral deuterium oxide rate and deuterioxide rate, $k_{\text{D}_2\text{O}} + k_{\text{OD}}[\text{OD}^-]$ (concentration term for deuterium oxide omitted from $k_{\text{D}_2\text{O}}$). The neutral deuterium oxide rate was separately determined as the reciprocal of the intercept value of a linear plot of $1/k_{\text{obsd}}$ vs. a_D for four values of a_D for solvolysis experiments run in deuteriochloric acid in deuterium oxide (eq. 5) (Figure 4, Table II).

$$k_{\text{obsd}} = 1/(6.85 + 33.88a_D) \quad (5)$$

The effect of changing salt concentration on the rate of ester hydrolysis was determined at pH 4.58 in 0.1 *M* potassium acetate solutions. To 1 ml. of 1.0 *M* potassium acetate solution ($\mu = 1$ *M* with KCl) in each of six 10-ml. volumetric flasks was added known volumes of 1 *M* KCl solution. The final volumes were brought to 10 ml. by addition of distilled water to the mark. The data are given in Table III.

Table III. Variation of the Pseudo-First-Order Rate Constant with Changing Potassium Chloride Concentration^a

Calcd. ionic strength, <i>M</i>	Pseudo-first-order rate const., min. ⁻¹
0.1 (reference acetate solution)	0.512
0.2	0.511
0.4	0.492
0.6	0.481
0.8	0.467
1.0	0.449

^a For the reaction of ethyl trifluorothiolacetate with 0.1 *M* potassium acetate solution (pH = 4.58, *T* = 30°).

The sensitivity of the neutral water rate, $k_{\text{H}_2\text{O}}$, to ionic strength was examined by following the rate of ester disappearance in acetate buffer at pH 3.77 and calculated ionic strength (KCl) of 0.12 *M*. The results are given in Table IV. A plot of k_{obsd} vs. total acetate concentration is linear and has as intercept the neutral water rate, $k_{\text{H}_2\text{O}} = 0.475$ min.⁻¹. Thus, increasing the calculated ionic strength from 0.12 to 1 *M* depresses the value of the neutral water rate constant *ca.* 9%.

Table IV. Hydrolysis of Ethyl Trifluorothiolacetate^a

Acetate buffer concn., <i>M</i>	k_{obsd} , min. ⁻¹
0.1	0.475
0.3	0.460
0.5	0.453
0.7	0.447
1.0	0.431

^a In acetate buffer at pH 3.77 and $\mu_{\text{calcd}} = 0.12$, *T* = 30°.

The effect of changing ionic strength on the rate of thiolester solvolysis was also examined in 0.3 *M* HCl solution. The pseudo-first-order rate constant for ester solvolysis in 0.3 *M* HCl solution, $\mu = 1$ *M* with KCl, is 0.227 ± 0.005 min.⁻¹ for three determinations. The pseudo-first-order rate constant for ester solvolysis in 0.3 *M* HCl solution, no added KCl, is 0.239 min.⁻¹. Thus there is a 5.3% increase in rate on decreasing the calculated ionic strength from 1 to 0.3 *M*.

The temperature dependence of the neutral water rate was examined in the temperature range 15.4 to 35.8°. The rate of thiolester disappearance was determined at five temperatures in half-neutralized acetate buffer ($\mu_{\text{calcd}} = 1$ *M* with KCl). For each temperature a plot of five k_{obsd} values vs. five corresponding buffer concentrations (0.1–1 *M*) was linear and gave as intercept the neutral water rate, $k_{\text{H}_2\text{O}}$, in units of min.⁻¹. The hydroxide rate at pH 4.61 is negligible. The data are summarized in Table V. A plot of $\log k_{\text{H}_2\text{O}}$

Table V. Temperature Dependence of the Neutral Water Rate^a

Temp., °C.	$k_{\text{H}_2\text{O}}$, min. ⁻¹
15.4	0.164
20.2	0.230
25.2	0.318
30.0	0.433
35.8	0.660

^a For the hydrolysis of ethyl trifluorothiolacetate ($\mu = 1.00$ *M* with KCl).

vs. $1/T$ is linear and from the slope of the line the Arrhenius activation energy, 11.7 kcal. mole⁻¹, may be calculated. The Arrhenius activation enthalpy, evaluated for 25°, is 11.1 kcal. mole⁻¹. The value of $T\Delta S^*$ for the neutral water rate, $k_{\text{H}_2\text{O}}$, is, of course, dependent on the water concentration term introduced into the rate constant. Using as standard state time in units of seconds and concentration in units of moles at 25°, the calculated activation entropy, $T\Delta S^*$, is -11.6 or -14.1 kcal. mole⁻¹ depending on whether the spontaneous rate is divided by 53.7 *M*, the molarity of water in 1 *M* potassium chloride solution of density 1.04, or $(53.7 \text{ } M)^2$, *i.e.*, $(\text{H}_2\text{O})^2$. The activation entropy of -11.6 kcal. mole⁻¹ would then be associated with the nucleophilic attack of water at the ester bond and the activation entropy of -14.1 kcal. mole⁻¹ would be associated with a general base assisted attack of water at the ester bond. Bruice and Benkovic²⁴ and Fedor and Bruice^{1b} have found that catalytically assisted nucleophilic reactions at oxygen ester and thiol ester bonds are accompanied by $T\Delta S^*$ values of -12 to -15 kcal. mole⁻¹.

The imidazole-catalyzed hydrolysis of ethyl trifluorothiolacetate from pH 6.14 to 8.04 is kinetically described by eq. 6. Plots of k_{obsd} vs. total imidazole concentration are linear, at constant pH, with slope $-d(\text{ester})/dt = [k_2'(\text{Im})_{\text{T}} + k_{\text{H}_2\text{O}} + k_{\text{OH}}(\text{OH}^-)](\text{ester})$ (6)

k_2' , the pH-dependent apparent second-order rate constant, and intercept $k_{\text{H}_2\text{O}} + k_{\text{OH}}(\text{OH}^-)$ (Figure 2). The second-order rate constant, k_2 (Table II), was evaluated by dividing k_2' by the mole fraction of free imidazole [$K_a'/(a_{\text{H}} + K_a')$]. The value of k_2 determined in deuterium oxide is given in Table II.

The phosphate-catalyzed hydrolysis of ethyl trifluorothiolacetate in the pH range 5.36–7.64 is kinetically described by eq. 7. At constant pH, plots of $-d(\text{ester})/dt = [k_2'(\text{P})_{\text{T}} + k_{\text{H}_2\text{O}} + k_{\text{OH}}(\text{OH}^-)](\text{ester})$ (7)

k_{obsd} vs. total phosphate concentration are linear with slope k_2' and intercept $k_{\text{H}_2\text{O}} + k_{\text{OH}}(\text{OH}^-)$. Plots of k_2' vs. pH give a typical sigmoid titration curve from which the second-order rate constants for the reaction of ester with phosphate monoanion and phosphate dianion may be evaluated (Figure 5). The curve of Figure 5 is derived theoretically from eq. 8 wherein $k_{\text{H}_2\text{PO}_4^-}$ and $k_{\text{HPO}_4^{2-}}$ represent the second-order rate constants for catalyzed hydrolysis by phosphate

$$k_2' = \frac{k_{\text{H}_2\text{PO}_4^-}}{(a_{\text{H}} + K_a)/a_{\text{H}}} + \frac{k_{\text{HPO}_4^{2-}}}{(a_{\text{H}} + K_a)/K_a} \quad (8)$$

(24) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, **86**, 418 (1964).

Table VI. A Comparison of the Observed Pseudo-First-Order Rate Constants^a

a_H	$[HA_e]$	$[A_e]$	$k_{\text{obsd, calcd.}}$	$k_{\text{obsd, exptl.}}$
4.73×10^{-4}	9.5×10^{-2}	5.00×10^{-3}	0.423	0.403
5.13×10^{-4}	2.86×10^{-1}	1.40×10^{-2}	0.404	0.396
5.19×10^{-4}	4.77×10^{-1}	2.30×10^{-2}	0.387	0.368
5.31×10^{-4}	6.69×10^{-1}	3.10×10^{-2}	0.371	0.362
5.37×10^{-4}	9.56×10^{-1}	4.40×10^{-2}	0.351	0.324
3.89×10^{-4}	9.40×10^{-2}	6.00×10^{-3}	0.424	0.419
4.07×10^{-4}	2.83×10^{-1}	1.70×10^{-2}	0.406	0.403
4.17×10^{-4}	4.72×10^{-1}	2.80×10^{-2}	0.391	0.385
4.17×10^{-4}	6.61×10^{-1}	3.90×10^{-2}	0.376	0.368
4.27×10^{-4}	9.46×10^{-1}	5.40×10^{-2}	0.357	0.345
2.69×10^{-4}	9.20×10^{-2}	1.00×10^{-3}	0.426	0.424
2.82×10^{-4}	2.75×10^{-1}	2.50×10^{-2}	0.412	0.419
2.82×10^{-4}	4.59×10^{-1}	4.10×10^{-2}	0.400	0.410
2.82×10^{-4}	6.43×10^{-1}	5.70×10^{-2}	0.388	0.392
2.82×10^{-4}	9.18×10^{-1}	8.20×10^{-2}	0.374	0.375
2.09×10^{-4}	8.90×10^{-2}	1.10×10^{-2}	0.428	0.405
2.09×10^{-4}	2.68×10^{-1}	3.20×10^{-2}	0.417	0.410
2.11×10^{-4}	4.48×10^{-1}	5.20×10^{-2}	0.407	0.403
2.14×10^{-4}	6.28×10^{-1}	7.20×10^{-2}	0.398	0.398
2.14×10^{-4}	8.97×10^{-1}	1.03×10^{-2}	0.386	0.394
8.51×10^{-5}	7.80×10^{-2}	2.20×10^{-2}	0.437	0.455
8.51×10^{-5}	2.33×10^{-1}	6.70×10^{-2}	0.444	0.449
8.32×10^{-5}	3.86×10^{-1}	1.14×10^{-1}	0.451	0.461
8.32×10^{-5}	5.40×10^{-1}	1.60×10^{-1}	0.458	0.477
8.04×10^{-5}	7.66×10^{-1}	2.34×10^{-1}	0.469	0.468
2.63×10^{-5}	5.20×10^{-2}	4.80×10^{-2}	0.457	0.461
2.57×10^{-5}	1.53×10^{-1}	1.47×10^{-1}	0.506	0.518
2.46×10^{-5}	2.50×10^{-1}	2.50×10^{-1}	0.554	0.541
2.46×10^{-5}	3.50×10^{-1}	3.50×10^{-1}	0.597	0.587
2.19×10^{-5}	4.71×10^{-1}	5.29×10^{-1}	0.679	0.682
1.05×10^{-5}	3.00×10^{-2}	7.00×10^{-2}	0.475	0.484
9.77×10^{-6}	8.60×10^{-2}	2.14×10^{-1}	0.560	0.569
9.12×10^{-6}	1.35×10^{-1}	3.65×10^{-1}	0.648	0.661
8.32×10^{-6}	1.78×10^{-1}	5.22×10^{-1}	0.738	0.742
7.43×10^{-6}	2.33×10^{-1}	7.67×10^{-1}	0.877	0.868
3.85×10^{-6}	1.40×10^{-2}	8.60×10^{-2}	0.488	0.468
3.55×10^{-6}	3.80×10^{-2}	2.62×10^{-1}	0.600	0.587
3.24×10^{-6}	5.80×10^{-2}	4.42×10^{-1}	0.714	0.705

^a With those calculated from eq. 11 for the solvolysis of ethyl trifluorothiolacetate in acetate buffer ($\mu = 1 M$ with KCl, $T = 30^\circ$).

mono- and dianion and the points are experimentally determined values. To further test the reality of catalysis by phosphate monoanion eq. 8 was arranged into the linear form of eq. 9. A plot of $k_2'(a_H + K_a)$ vs. a_H is linear with slope $k_{H_2PO_4^-}$ and intercept $k_{HPO_4^{2-}}K_a$. The values for the rate constants obtained

$$k_2'(a_H + K_a) = K_{H_2PO_4^-}a_H + k_{HPO_4^{2-}}K_a \quad (9)$$

by either method are in very good agreement and are given in Table II. In eq. 9 K_a is the second dissociation constant for phosphoric acid.

The reaction of methoxylamine with ethyl trifluorothiolacetate (pH 3.79–5.55) is kinetically described by eq. 10. At constant pH plots of k_{obsd} vs. free methoxyl-

$$-d(\text{ester})/dt = [k_2(\text{CH}_3\text{ONH}_2) + k_{H_2O}](\text{ester}) \quad (10)$$

amine concentration are linear with slope k_2 and intercept k_{H_2O} (Table II). The contribution of the hydroxide rate to k_{obsd} is negligible in the pH range examined. The deuterium solvent kinetic isotope effect for k_2 (Table II) is 4.4.

Hydrolysis of ethyl trifluorothiolacetate in acetate buffer (pH 3.29–5.45) is kinetically described by eq. 11 wherein $k_2'_{\text{RCO}_2^-}$ and $k_2'_{\text{RCO}_2\text{H}}$ have the values given in Table II and $R = \text{CH}_3$. Experimentally, plots of

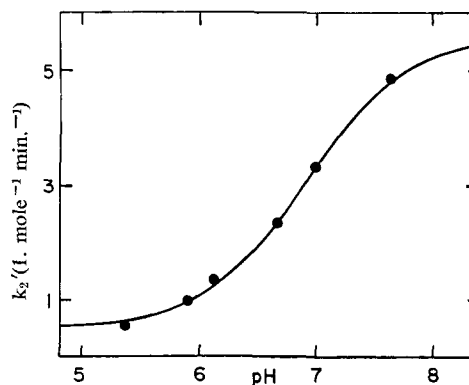


Figure 5. Plot of the apparent second-order rate constant, k_2' , vs. pH for the reaction of ethyl trifluorothiolacetate in phosphate buffer solution.

k_{obsd} vs. acetate ion, acetic acid, or total acetate concentration are linear at any pH. It is not apparent from

$$-d(\text{ester})/dt = \left[\frac{1 + k_2'_{\text{RCO}_2^-}(\text{RCO}_2^-)}{2.31 + 6.6a_H + k_2'_{\text{RCO}_2\text{H}}(\text{RCO}_2\text{H})} \right](\text{ester}) \quad (11)$$

eq. 11 that this should be so. However, the deviation from linearity of plots of k_{obsd} derived theoretically from eq. 11 vs. a function of acetate concentration (0.1–1 M) is practically imperceptible. At concentrations of total acetate $>1.0 M$, eq. 11 predicts a non-linear dependence of k_{obsd} on concentration. The apparent second-order rate constant derived from slopes of plots of k_{obsd} vs. acetate buffer concentration decreases with increasing acidity, assuming negative values at high acidity where the depression of the neutral water rate becomes quite apparent. When the concentration of acetate ion and acetic acid is zero, expression 11 reduces to eq. 3. Since in the pH region investigated the a_H term is negligible, the rate is simply the spontaneous rate, $k_{H_2O} = 0.433 \text{ min.}^{-1}$. The constants 1, 2.31, and 6.6 of eq. 11 were evaluated from rate data obtained at high acidity (eq. 3, Figure 4). The rate coefficients for acetate ion and acetic acid, $k_2'_{\text{RCO}_2^-}$ and $k_2'_{\text{RCO}_2\text{H}}$ were determined on a Control Data 1604 computer, using the Fortran programming method, as those values which provided calculated constants closest to experimentally determined rate constants. Using the constants of Table II to calculate 38 k_{obsd} values it is found that 29 k_{obsd} (calculated) are within 2.5% of the experimentally observed values, five k_{obsd} (calculated) are within 2.5–5% of the experimentally observed values, three k_{obsd} (calculated) are within 5–7.5% of the experimentally observed values, and one k_{obsd} (calculated) is less than 8.4% of the experimentally observed values. The sum of the squares of the deviations is 0.005, and the rate data are given in Table VI. As an additional test of the validity of eq. 11, the rate of ester disappearance in 0.4 M acetic acid ($\mu = 1 M$ with KCl) at pH 2.47 was $0.375 \pm 0.002 \text{ min.}^{-1}$ for three runs. The calculated value of k_{obsd} from eq. 11 is 0.378 min.^{-1} . In 1 M acetic acid solution ($\mu = 1 M$ with KCl) at pH 2.26, k_{obsd} is 0.313 min.^{-1} , and the calculated value of k_{obsd} from eq. 11 is 0.321 min.^{-1} . It is worth noting that most of the discrepancy between k_{obsd} values experimentally determined and k_{obsd} values calculated from

eq. 11 is resolvable if allowance be made for the fact that the spontaneous rate is an averaged experimentally determined intercept value obtained from plots of k_{obsd} vs. a function of acetate concentration and is thus subject to error. Equation 11 makes no allowance for this fact and requires the neutral water rate to be 0.433 min^{-1} under conditions of zero acetate ion and acetic acid concentration. For hydrolysis of ethyl trifluorothiolacetate in acetate buffer, the deuterium solvent kinetic isotope effect for the spontaneous rate, $k_{\text{H}_2\text{O}}$, was determined to be 2.74 and for the acetate-catalyzed reaction at half-neutralization, 2.1 (Table II).

Hydrolysis of ethyl trifluorothiolacetate in formate buffer in the pH range 2.58–4.18 is kinetically described by eq. 11, $R = \text{H}$, and the behavior of thiol ester toward formate buffer is qualitatively the same as its behavior toward acetate buffer. Values of the coefficients of formate ion, $k_2'_{\text{RCO}_2^-}$, and formic acid, $k_2'_{\text{RCO}_2\text{H}}$ (Table II) were determined on a Control Data 1604 computer using the Fortran programming method (data not shown). Seventeen of 20 calculated k_{obsd} values were within 2.5% of the experimentally determined values and the remaining three calculated k_{obsd} values were between 2.5 and 5% of the experimentally determined values. The sum of the squares of the deviations is 0.002.

Discussion

The pH–rate profile for the hydrolysis of ethyl trifluorothiolacetate may be divided into three portions (eq. 2 and Figure 1). Between pH 0 and 2.5, k_{obsd} is proportional to the activity (concentration) of hydroxide ion or inversely proportional to the hydrogen ion activity (concentration). Between pH 2.5 and 6, hydrolysis must be due to spontaneous reaction of ester with water since k_{obsd} is insensitive to changes in a_{OH^-} or a_{H^+} . At pH values greater than 6, the rate of hydrolysis becomes dependent on the first power of the hydroxide ion concentration. The spontaneous solvolysis and hydroxide ion catalyzed hydrolysis are as anticipated from previous studies of acyl-activated esters.¹¹ Attention is directed to the unusual pH dependence of the hydrolysis at pH values below 2.5.

The rate of hydrolysis of ethyl trifluoroacetate in 0.05 M hydrochloric acid at 0° is approximately twice as rapid as the neutral water rate at the same temperature,²⁵ suggesting that the pseudo-first-order rate constant in acidic and neutral solutions is expressed by eq. 12. In contrast to the hydrolytic behavior of ethyl

$$k_{\text{obsd}} = k_{\text{H}_2\text{O}} + k_{\text{HCl}}[\text{HCl}] \quad (12)$$

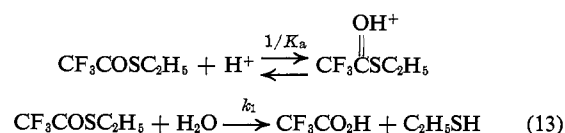
trifluoroacetate, the hydrolysis of ethyl trifluorothiolacetate is retarded by acid (eq. 2), and the pseudo-first-order rate constant is reciprocally related to the hydrogen ion activity. The depression of the spontaneous hydrolytic rate of the thiol ester is apparent at acidities beyond the pH scale range. Thus the pseudo-first-order rate constants for thiol ester solvolysis in 2 M HCl and in *ca.* 6 M HCl are 0.076 and 0.043 min^{-1} , respectively.

Several mechanisms can be suggested which give kinetic solutions possessing the necessary form of eq.

(25) G. Gorin, O. R. Pierce, and E. T. McBee, *J. Am. Chem. Soc.*, **75**, 5622 (1953).

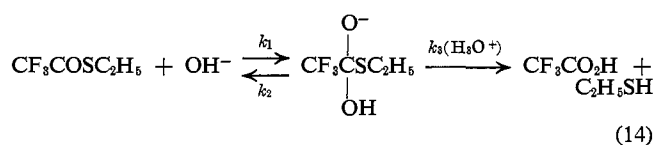
1: (A) pre-equilibrium formation of an unreactive protonated thiol ester with concomitant attack by water on the nonprotonated thiol ester; (B) attack of hydroxide ion at the thiol ester bond to form a tetrahedral intermediate which decomposes spontaneously to starting ester and which is converted to products by hydronium ion catalysis; (C) nucleophilic attack of water at the thiol ester bond to form a tetrahedral intermediate which can revert to starting ester or which can ionize and then collapse spontaneously to products; (D) nucleophilic attack of water at the thiol ester bond assisted by a molecule of water acting as general base catalyst to form a tetrahedral intermediate which by microscopic reversibility reverts to starting ester *via* general acid catalysis by hydronium ion or decomposes spontaneously to products.

Considering mechanism A (eq. 13), a nonreactive



protonated ester in a mechanistic scheme for ester hydrolysis is unreasonable in view of presently accepted theory of ester hydrolysis in acidic media.²⁶ Further, assuming a $\text{p}K_a$ of -7.2 for the thiol ester, it can be shown that at $10^{-4} M$ ester at $\text{pH} = 0$ and $\text{pH} = 1$ the concentration of protonated ester is *ca.* 10^{-12} and *ca.* 10^{-13} , respectively. Thus the mole fraction of protonated ester would be infinitesimal and of no kinetic significance. The assumption that $\text{p}K_a = -7.2$ is based on the comparable activating influence on α -hydrogen atoms by thiol ester and ketone groups¹⁹ and the $\text{p}K_a$ of 2-butanone (-7.2).²⁷

Mechanism B involving attack of hydroxide ion at the ester bond to form a tetrahedral intermediate which decomposes spontaneously to starting ester and which is converted to products by hydronium ion catalysis (eq. 14) gives a steady-state derivation (eq. 15) which has the form of eq. 3. However, it can be shown from



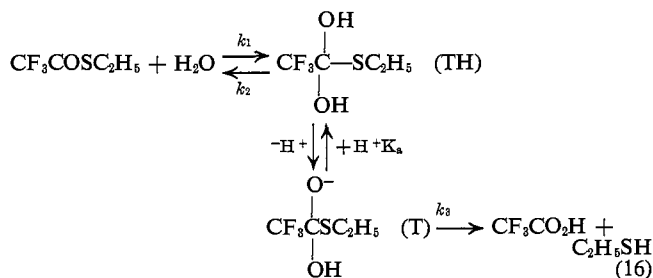
$$\text{rate}/(\text{ester})(\text{H}_2\text{O}) = k_{\text{obsd}} = 1/[(k_2/k_1k_3K_w) + (1/k_1K_w)a_{\text{H}^+}] \quad (15)$$

eq. 15 and 3 that the second-order rate constant for hydroxide attack would be *ca.* $10^{13} \text{ l. mole}^{-1} \text{ min}^{-1}$, a value greater than the rate constant for a diffusion-controlled process. Mechanism B is, therefore, also untenable.

Mechanism C is shown schematically in eq. 16 and its steady-state derivation, which has the form of eq. 3, is provided by eq. 17. The deuterium solvent isotope effect of *ca.* 3 for the k_1 step (see Table II) is inconsistent with the postulate of unassisted nucleophilic attack by water at the ester bond.

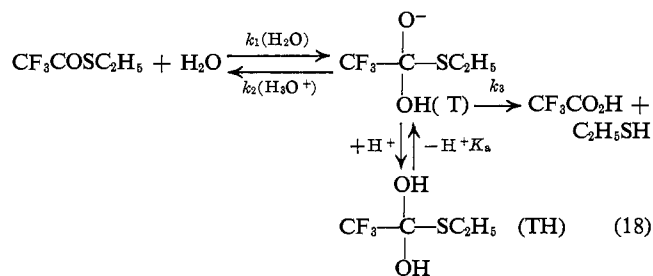
(26) (a) J. H. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941); (b) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(27) H. J. Edward and J. T. Campbell, *Can. J. Chem.*, **38**, 2109 (1960).



$$\text{rate}/(\text{ester})(\text{H}_2\text{O}) = k_{\text{obsd}} = 1/[1/k_1 + (k_2/k_1k_3K_a)a_{\text{H}}] \quad (17)$$

Mechanism D is illustrated in eq. 18. Depending on whether one assumes steady state in T and TH or pre-equilibrium formation of T and TH, the rate expres-



sions 19 or 20, respectively, can be derived. Both expressions have the form of eq. 3. The steady-state derivation leading to eq. 19 is preferred to the assumption of the pre-equilibrium formation of T and TH leading to eq. 20. The preference is based on $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 3$ for the spontaneous rate which corresponds to k_1 in eq. 19 or k_3 in eq. 20. It is unlikely that a deuterium solvent isotope effect is associated with collapse of T, although an isotope effect might be associated with general acidic catalysis of the collapse of T by a

$$\text{rate}/[\text{ester}][\text{H}_2\text{O}] = k_{\text{obsd}} = \frac{k_1k_3}{k_3 + k_2a_{\text{H}}} [1/k_1 + (k_2/k_1k_3)a_{\text{H}}]^{-1} \quad (19)$$

$$\text{rate}/[\text{ester}][\text{H}_2\text{O}] = k_{\text{obsd}} = \frac{k_3k_1K_a}{k_1K_a + (k_2K_a + k_1)a_{\text{H}}} [1/k_3 + (k_2/k_1k_3 + 1/k_3K_a)a_{\text{H}}]^{-1} \quad (20)$$

neutral water molecule, such catalysis not being kinetically observable. The Arrhenius activation energy of 11.7 kcal. mole⁻¹, determined for k_1 in eq. 19 or k_3 in eq. 20 (*cf.* eq. 3 wherein $6.6a_{\text{H}}$ is effectively zero at pH 4.61), is more consistent with the general base catalyzed attack of a water molecule at the ester bond than the collapse of a metastable intermediate. From eq. 3 and 19 $k_1 = 0.433 \text{ min.}^{-1}$ and $k_2/k_3 = 2.86$. From eq. 5 and 19, k_1 in $\text{D}_2\text{O} = 0.146$ and k_2/k_3 in $\text{D}_2\text{O} = 4.95$. The deuterium solvent isotope effect associated with k_1 is consistent with the postulate of general base assisted attack of water by another water molecule to give products. The increase in k_2/k_3 in D_2O is consistent with H_3O^+ catalysis in a one-step slow proton removal.²⁸ Thus, no deuterium solvent isotope effect is anticipated for k_3 so that the deuterium solvent isotope effect for k_2 is ~ 0.6 [*i.e.*, $(k_2^{\text{H}}/k_3^{\text{H}}) \cdot (k_3^{\text{D}}/k_2^{\text{D}}) = 2.86/4.95 \cong 0.6$].

(28) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

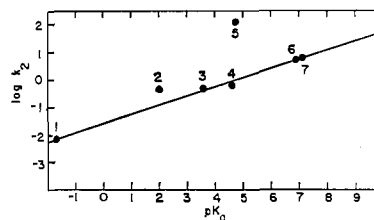


Figure 6. Brønsted plot for the reaction of ethyl trifluorothiolacetate with (1) H_2O , (2) H_2PO_4^- , (3) HCO_2^- , (4) $\text{C}_2\text{H}_3\text{O}_2^-$, (5) CH_3ONH_2 , (6) HPO_4^- , and (7) $\text{C}_3\text{H}_4\text{N}_2$. No statistical corrections have been made. The value of β is 0.33.

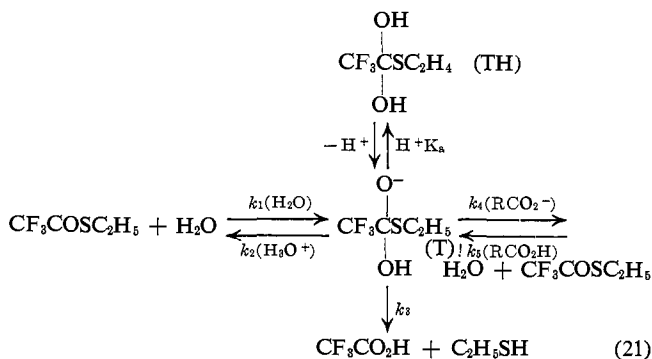
Jencks and Carriuolo¹¹ have suggested a general base-water reaction is operative in the hydrolysis of ethyl difluoroacetate and ethyl dichloroacetate and have supported their conclusion with deuterium solvent kinetic isotope effects and product analysis as well as the fact that the rate constant for the spontaneous rate falls on the same Brønsted plot, $\beta = 0.47$, as do other general bases. For the reactions of ethyl trifluorothiolacetate with nucleophiles reported in Table II, water, formate ion, acetate ion, phosphate dianion, and imidazole form a good Brønsted plot with $\beta = 0.33$ (Figure 6). Phosphate monoanion and methoxylamine show positive deviations, the latter compound possessing a second-order rate constant one hundred times greater than predicted from its basicity and the Brønsted plot. Diethyl ketoxime exhibits a positive logarithmic deviation of 2.1 on a Brønsted plot for the dehydration of acetaldehyde hydrate,²⁹ a reaction which is presumably general base catalyzed. The deuterium solvent kinetic isotope effect of 4.4 for the methoxylaminolysis reaction, which was found to be strictly first order in methoxylamine, and the fact that product analysis shows only the formation of trifluoroacetic acid suggest that methoxylamine is not acting as a nucleophile. Finally, the value of the activation entropy, $T\Delta S^\ddagger$, is consistent with a termolecular process (see Experimental).

The reaction of ethyl trifluorothiolacetate with hydroxide ion is likely a simple bimolecular process and not a general base catalyzed process. Thus $k_{\text{OD}}/k_{\text{OH}} = 1.28$ (Table II) is practically within the 1.4–2.0 range predicted by Long²⁸ for specific hydroxide attack.

The reactions of ethyl trifluorothiolacetate with acetate buffer and with formate buffer are kinetically described by eq. 11 and likely proceed by the same mechanism. Any mechanism consistent with eq. 11 must involve the neutral water reaction as well as the reaction with carboxylate buffer. Since both the neutral water reaction and the acetate buffer reaction exhibit large deuterium solvent kinetic isotope effects (Table II) and since the catalytic constants for the water, formate, and acetate reactions fall on the same Brønsted plot, it is reasonable to assume that these reactions involve general base catalysis of hydrolysis of the thiol ester. Inhibition of ester hydrolysis by acetic and formic acids is not due to complex formation since no complex formation could be detected in chloroform solution and the complexing constant in water would have to be unreasonably large ($K_c \cong 0.33$). Mechanism E which is schematically shown in eq. 21 in-

(29) R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).

volves two general base catalyzed reactions, the one reaction involving two water molecules and the other a



water molecule and carboxylate ion. Any steady-state derivation must postulate a common intermediate for the water reaction and the carboxylate buffer reaction. Otherwise the rate expression for ester disappearance will contain a sum of terms, the neutral water rate term and the carboxylate buffer term. No combination of these terms as a sum can account for a depression of the water rate by carboxylate buffer at high $\text{RCO}_2\text{H}/\text{RCO}_2^-$ (Table VI). Assuming steady state in T and TH, the rate of ester disappearance is given by eq. 22 which has the form of eq. 11. From eq. 11, 22, and

$$\text{rate} = \frac{[k_1k_3(\text{H}_2\text{O})^2 + k_3k_4(\text{H}_2\text{O})(\text{RCO}_2^-)]\text{[ester]}}{k_3 + k_2a_{\text{H}} + k_5(\text{RCO}_2\text{H})}$$

$$k_{\text{obsd}} = \frac{1 + (k_4/k_1)(\text{RCO}_2^-)}{1/k_1 + (k_2/k_1k_3)a_{\text{H}} + (k_5/k_1k_3)(\text{RCO}_2\text{H})} \quad (22)$$

Table II the values for the composite constants were determined, and their values are given in Table VII. A deuterium solvent isotope effect of 2.1 was found for the acetate buffer reaction.

Table VII. Values of Rate Constants Obtained from Eq. 22^a

Catalyst	k_1 , min. ⁻¹ ^b	k_2/k_3 , M ⁻¹	k_4 , M ⁻¹ min. ⁻¹ ^b	k_5/k_3 , M ⁻¹
Water	0.433	2.86		
Deuterium oxide	0.146	4.95		
Acetate ion			0.666	0.375
Formate ion			0.500	0.291

^a For the hydrolysis of ethyl trifluorothiolacetate in formate and acetate buffers ($T = 30^\circ$, $\mu = 1 M$ with KCl). ^b Concentration term for nucleophile omitted.

There can be little doubt about the establishment of general base catalysis for the hydrolysis of the thiol ester (see Figure 6 and Table II) or for hydronium ion inhibition. However, establishment of general acid catalysis of the inhibition of hydrolysis must be considered tenuous. The Brønsted β for general base catalysis is but 0.33 and since the reverse general acid step must proceed through the same transition state it is anticipated that the Brønsted α -constant should be large, approaching that for specific acid catalysis. The inhibition by acetic acid cannot be differentiated from a solvent effect.³⁰ Inhibition of the spontaneous

(30) At pH 2.86, $k_{\text{obsd}} = 0.414 \text{ min.}^{-1}$ for ester solvolysis in 0.1 M acetic acid solution ($\mu = 1.0$) and 0.403 min.^{-1} for ester solvolysis in 0.1 M ethyl acetate solution ($\mu = 1.0$); at pH 2.47, $k_{\text{obsd}} = 0.375 \text{ min.}^{-1}$ for ester solvolysis in 0.4 M acetic acid solution ($\mu = 1.0$) and 0.383 min.^{-1} for ester solvolysis in 0.4 M ethyl acetate solution ($\mu = 1.0$). Thus, the

rate by phosphate buffer, pH 5.36–7.64, was not evidenced. This is anticipated since phosphate mono- and dianions are both ampholytes, and are capable of acting as catalysts as well as inhibitors of the spontaneous rate (Table II). Imidazolium ion was found not to inhibit the rate of ester hydrolysis. Thus in 1 M imidazole solution ($\mu = 1 M$) at pH 3.55, k_{obsd} for ester disappearance is 0.412 min.^{-1} , a value insignificantly different from the spontaneous rate $k_{\text{H}_2\text{O}}$ (Table II). This result is reasonable in view of the fact that imidazolium ion ($\text{p}K_a' = 7.09$) is a poor general acid. Methoxylammonium ion, $\text{p}K_a' = 4.75$, should be as effective a general acid catalyst as acetic acid, $\text{p}K_a' = 4.61$, and if the retarding influence of acetic and formic acids are due to their acting as general acid catalysts then methoxylamine should catalyze the collapse of T to ester (eq. 21). The pseudo-first-order rate constant for the solvolysis of ethyl trifluorothiolacetate at pH 2.56 in 0.5 M methoxylamine solution ($\mu = 1 M$ with KCl) is 0.530 min.^{-1} . From eq. 10 and 3 and Table II the calculated value for k_{obsd} is 0.863 min.^{-1} . Thus methoxylammonium ion is an inhibitor of the neutral water reaction. Many neutral salts "salt in" esters, *i.e.*, salts decrease their activity coefficients.^{31,32} It is possible that methoxylammonium ion at 0.5 M concentrations "salts in" ethyl trifluorothiolacetate with the result that the rate depression in 0.5 M methoxylamine at pH 2.56 is not a kinetic result of added methoxylammonium ion but an effect of this ion on the activity coefficient of the ester. However, from the value of the pseudo-first-order rate constant for ester disappearance in 1 M imidazolium chloride solution, *vide supra*, it may be concluded that substitution of KCl by imidazolium chloride has a negligible effect on the rate of ester solvolysis (the reaction itself is not sensitive to ionic strength (Table III). Extending this conclusion as an approximation to methoxylammonium ion, the difference between the experimentally determined pseudo-first-order rate constant in 0.5 M methoxylamine solution, pH 2.56, and the value calculated from eq. 10, and 13 and the contribution of 0.0032 M free methoxylamine to the rate constant, a difference of 0.333 min.^{-1} , is indeed due to a depression of the spontaneous rate by methoxylammonium ion as indicated in eq. 21. In eq. 21, methoxylammonium ion replaces carboxylic acid. If eq. 21 is correct, it would appear that any general acid of sufficient acidity should inhibit the neutral water rate.

Many kinetic schemes were tested in order to arrive at a reasonable mechanism which satisfied experimental observations. The scheme chosen (eq. 21) has simplicity as well as adherence to the principle of microscopic reversibility to recommend it. Also, the mechanism of eq. 21 is in accord with the experimentally observed deuterium solvent isotope effects. It is evident from eq. 18 and 21 that partitioning of the tetrahedral intermediate is unsymmetrical, *i.e.*, general acid catalysis does not occur in both the conversion of T to ester and products, a finding in contrast to observations of Bruice and Fedor^{1c} who reported mechanisms for the hydroxylaminolysis and methoxyl-

solvolysis rates of thioester in acetic acid and ethyl acetate solutions of equal concentrations at the same pH values are approximately the same.

(31) G. M. Waind, *J. Chem. Soc.*, 2879 (1954).

(32) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 86, 837 (1964).

aminolysis of alkyl thiolacetates and thiolactones involving symmetrical partitioning of intermediates. Symmetrical partitioning of T in eq. 18 would destroy the dependence on acidity of the neutral water rate, $k_{\text{H}_2\text{O}}$. Thus, k_{obsd} would be equal to $k_1k_3/(k_3 + k_2)$, an expression which does not predict inhibition of ester solvolysis at high acidity. Catalysis of the collapse of T to products by carboxylic acid (eq. 21) would yield a rate expression containing square carboxylate terms in the numerator of the rate expression. The mechanism suggested by Jencks and Gilchrist⁹ for the hydroxylaminolysis of formamide and acetamide also involves unsymmetrical partitioning of intermediates (see eq. 1). Our failure to observe thiol ester formation from ethyl mercaptan and trifluoroacetic acid in 1 M HCl solution demonstrates that inhibition

of spontaneous solvolysis in acid solution is not due to an equilibrium situation between ester and products.

A kinetic analysis of experimental data cannot be said to prove a mechanism but can be employed to disprove mechanisms. An attempt has been made to consider kinetically all reasonable mechanisms for the hydrolytic behavior of ethyl trifluorothiolacetate. The favored interpretations are consonant with the experimental data in H₂O and D₂O.

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Preparation and Chemistry of α -Chloroalkyllithium Compounds. Their Role as Carbenoid Intermediates¹

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*The reaction of polychloromethanes with *n*-butyllithium in tetrahydrofuran at low temperatures (-100°) via α -metalation or halogen-metal interconversion has been used to prepare a new class of organolithium reagents, the α -chloroalkyllithium compounds I-IV. The procedure was based on our observation of the remarkable stabilizing influence of tetrahydrofuran on α -chloroalkyllithium structures. At low temperatures, these compounds behave as typical organolithium structures and have been characterized by hydrolysis, deuterolysis, and direct carbonation to the corresponding acids (or derivatives). They react (couple) readily with the more reactive alkyl halides, presumably via nucleophilic displacements of the chloro carbanion on carbon. While these compounds were indefinitely stable at -100° , they decomposed spectacularly above -65° , suggestive of carbene formation via elimination of LiCl. If olefins were present during this decomposition (they were added without evidence of reaction at -100°), good yields of the corresponding cyclopropanes were obtained from α,α -dichlorobenzylithium and trichloromethylithium. In contraindication of a free carbene mechanism in the formation of the cyclopropanes, however, the stability of α -chloroalkyllithium compounds appears influenced by the more nucleophilic olefins, suggestive of a direct reaction of the olefin with the organolithium compound (or its structural equivalent), the reactivity (nucleophilic olefin sequence) and specificity in qualitative accord with results previously thought indicative of a free carbene intermediate. Several mechanisms are considered in the light of these results.*

(1) Paper II in the series Chemistry of α -Halocarbanion Intermediates; presented before the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

α -Haloalkyllithium compounds have been suggested to have transient existence in the proposed carbene-forming reactions of alkyl halides (via α -dehydrohalogenation) and polyhalomethanes (via α -dehalogenation) with organolithium compounds, leading, in the presence of olefins, to cyclopropane ring systems.² The apparent high instability of these compounds, however, had, for the most part, prevented their isolation to date, and even their detection via diverting reactions as carbonation, hydrolysis, and deuterolysis had had but limited success.^{3,4} Distinguishing between the α -haloalkyllithium compounds existing as high energy intermediates in their own right or simply transition states in concerted α -eliminations leading to the free carbene had, therefore, been difficult.

More recently, Miller and Whalen reported the detection of trichloromethylithium as a distinct structural entity, possessing limited stability, in the reaction of bromotrichloromethane with *n*-butyllithium in ethyl ether at -115° .⁵ Moreover, of great significance with respect to the evidence of free carbenes in reactions of this type, they reported its direct rapid reaction at -100° with cyclohexene to yield dichloronorcarane.

Several years ago, an extraordinary and apparently unique stabilizing influence of tetrahydrofuran on α -chloroalkyllithium structures was discovered in this laboratory which led to a broad study of their behavior

(2) For a recent review of the subject of carbene chemistry, see J. Hine, "Divalent Carbon," The Ronald Press Co., New York, N. Y., 1964, and W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964.

(3) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **81**, 4996 (1959).

(4) W. T. Miller and C. S. Y. Kim, *ibid.*, **81**, 5008 (1959).

(5) W. T. Miller and D. M. Whalen, *ibid.*, **86**, 2089 (1964).