than the rate constant for collapse of the tetrahedral intermediate. A mechanism of this type would be for all practical purposes concerted and in accord with a previously proposed mechanism.[1a]

Acknowledgment. This work was supported by a grant from the National Institutes of Health. We thank Professor C. A. Bunton for reading and commenting on the preprint of this paper.

Nucleophilic Displacement Reactions at the Thiol Ester Bond. V. Reactions of 2,2,2-Trifluoroethyl Thiolacetate[1]

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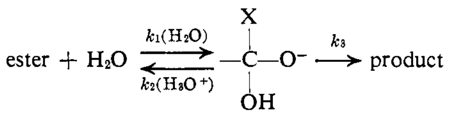
Abstract: The kinetics for the reactions of 16 nucleophiles with 2,2,2-trifluoroethyl thiolacetate have been determined (30°, $\mu = 1.0$ with KCl in water). For hydrazine, morpholine, glycine, ethanolamine, hydroxide ion, carbonate ion, and the anions of pentaerythritol, 2,2,2-trifluoroethanol, and cyanide the reactions were found to be only first order in both the ester and nucleophile (k_n[E][B]). The first authenticated case for a reaction of an amine with an ester which is first order in the ester and first order in the conjugate acid of the base (k_{BH^+}[E][BH$^+$]) has been found for tris(hydroxymethyl)aminomethane. This nucleophile also exhibits a simple nucleophilic term (k_n[B][E]). The base hydroxylamine exhibits the terms (k_n[B][E] + k_{gb}[B]^2[E] + k_{ga}[B][BH$^+$][E]). The value of log k_n for the reaction of 13 nucleophiles exhibiting this constant with the thiol ester and with *p*-nitrophenyl acetate follow quite precisely the equation $\log k_n = \log k_{n_{p\text{-NPA}}} + 0.6$. From the equation and the lack of a significant element effect, it is argued that the rate-determining step for the thiol and nitrophenyl esters is nucleophilic attack of the base species at the carbonyl carbon. For piperidine the rate terms for reaction with the thiol ester are (k_{gb}[B]^2[E] + k_I[OH$^-$][E]) where $k_I = 158 \times k_{OH}$ and k_{OH} is the true second-order rate constant for the reaction of hydroxide with the thiol ester in the absence of piperidine. Consistent with this finding is mechanism 15 (see text) where $k_2[\text{pipH}^+] \gg k_3$ and $k_I = K_a'k_1k_3/k_2K_w$. The reaction of the thiol ester with imidazole is complicated by a reverse reaction.

Kinetic evidence for the formation of tetrahedral intermediates in the reaction of nucleophiles with thiol esters has been obtained from previous studies in this laboratory. The kinetics for the reaction of δ-thiolvalerolactone, γ-thiolbutyrolactone, *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate with methoxylamine and hydroxylamine are explicable on the basis of the formation of tetrahedral intermediates along parallel general base and general acid catalyzed reaction paths, these intermediates being in acid-base equilibria.[1c] Since the acid-base equilibria of tetrahedral intermediates allow crossing over from the reaction pathway of one symmetrical mechanism to another, the term "cross-over" mechanism was offered for this phenomenon. In the hydrolysis of ethyl trifluorothiolacetate the pH-rate profile was interpreted as due to an unsymmetrical mechanism involving general base (by water) catalyzed addition of water to the ester carbonyl group, acid (by $H^{-}{}_3O$) catalyzed collapse of intermediate to starting ester, and spontaneous conversion of the tetrahedral intermediate to products (eq 1).[1d] The proposed mechanism, which requires the presence of a tetrahedral intermediate, has recently been confirmed by Bender using O^{18} exchange techniques.[4] The decrease in k_{obsd} with increasing hydrogen ion concentration has been shown, through experiments with LiCl solutions, not to be due to a decrease in a_{H_2O}.[5] A similar pH-rate profile has recently been obtained for the hydrolysis of benzoyl and *p*-chlorobenzoyl cyanide by Hibbert and Satchell.[6] These investigators have interpreted their results *via* eq 1. In the cross-over mechanism and that of type 1 we have, therefore, evidence for tetrahedral intermediates along the reaction path in both symmetrical and unsymmetrical general catalyzed reactions on thiol esters.



$$\text{ester} + H_2O \underset{k_2(H_3O^+)}{\overset{k_1(H_2O)}{\rightleftarrows}} -\overset{\displaystyle X}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-O^- \xrightarrow{k_3} \text{product} \qquad (1)$$

The present study deals with the reaction of nucleophiles with 2,2,2-trifluoroethyl thiolacetate. In contrast to ethyl trifluorothiolacetate, electron-attracting substituents for this ester are present on the thiol rather than acyl moiety. The objective of this study is to determine something of the nature of the mechanism of nucleophilic displacement on an aliphatic thiol ester with a good leaving group particularly in regard to the formation of tetrahedral intermediates and the nature of the rate-determining step.

Experimental Section

Apparatus. Absorbance measurements were made on a Zeiss PMQ II spectrophotometer or Gilford Model 2000 or 220 recording

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[1] For previous papers in this series 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**, 738, 739, 4886 (1964); (d) L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 5697 (1964); **87**, 4138 (1965).

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[4] M. L. Bender, private communication.

[5] T. C. Bruice and M. J. Gregory, unpublished results.

[6] F. Hibbert and D. P. N. Satchell, *Chem. Commun.*, 516 (1966).

spectrophotometer. Kinetic solutions were maintained at 30 ± 0.1° by circulating water at this temperature through the cuvette holder (Zeiss) or through Beckman double thermospacers (Gilford). Reaction rates too fast to follow visually were followed on a stopped-flow apparatus.[7] Hydroxide-catalyzed rates were determined with a Radiometer TTT 1b autotitrator with a PHA 630 scale expander, using a Metrohm EA 115X glass electrode. The titration cell was maintained at 30 ± 0.1° by means of a water jacket, all reactions being carried out under nitrogen. pH measurements were made with a Radiometer Model 22 pH meter with a PHA 630 scale expander, using a combined glass–calomel electrode (Radiometer G.K. 2021C). The electrode was thermostated at the temperature of the kinetic runs.

Materials. 2,2,2-Trifluoroethyl Thiolacetate. To a stirred suspension of lithium hydroxide monohydrate (18.9 g; 0.45 mole) in diglyme (75 ml) was added thiolacetic acid (35.0 g; 0.46 mole) followed by 114 g (0.45 mole) of 2,2,2-trifluoroethyl *p*-toluenesulfonate[8] and the mixture heated to 120°. A mixture of immiscible liquids distilled off. When distillation ceased, water (50 ml) was added and distillation was continued. The lower layer of the distillate was separated and dissolved in ether (200 ml). The aqueous upper layer was extracted with ether (five 20-ml portions), and all ether extracts were combined, washed with water (two 100-ml portions), and dried over magnesium sulfate. Removal of the ether left a yellow oil (32.3 g). Distillation of the oil once through a 6-in. Vigreux column and twice through a 16-in., spinning-band column gave a colorless liquid (15.6 g, 22% theory), bp 115°, $n^{25}\text{D}$ 1.399. *Anal.* Calcd for $C_4H_5F_3OS$: C, 30.35; H, 3.19; F, 36.04; S, 20.27. Found: C, 30.37; H, 3.18; F, 35.82; S, 20.10.

2,2,2-Trifluoroethanethiol. 2,2,2-Trifluoroethyl thiolacetate (1.0 g) was added to a solution of imidazole (1.0 *M*) in 10 ml of 90% aqueous ethanol. The mixture was stirred for 4 hr, and the temperature of the solution was raised. The portion of the distillate boiling below 45° was collected and redistilled to give 2,2,2-trifluoroethanethiol (148 mg), bp 37–40°. The thiol was dissolved in dioxane (10 ml) and stored under nitrogen in a refrigerator.

Methoxylamine (Eastman White Label) and ethanolamine (K and K Laboratories) hydrochlorides were recrystallized from ethanol–ether mixtures. Hydrazine hydrochloride (Matheson Coleman and Bell, practical grade) and ethylenediamine dihydrochloride (Eastman White Label) were recrystallized from ethanol–water mixtures. Hydroxylamine hydrochloride (Baker reagent) was recrystallized from ethanol. Piperidine hydrochloride was prepared by passing dry HCl gas through an alcoholic solution of piperidine (Eastman, practical grade). The precipitated salt was recrystallized from an ethanol–ether mixture. Imidazole (Eastman White Label) was recrystallized twice from acetone–petroleum ether (bp 30–60°) mixtures. Morpholine (Eastman, practical grade) was refluxed over sodium metal for 24 hr and distilled under nitrogen, bp 125–126°. 2,2,2-Trifluoroethanol (Matheson Coleman and Bell) was distilled before use, bp 75–76°. Tris(hydroxymethyl)-aminomethane (Matheson Coleman and Bell), glycine (Fisher reagent), and pentaerythritol (Eastman White Label) were used without further purification.

Determination of the pK_a' of 2,2,2-Trifluoroethanethiol. Aliquots (0.2 ml) of a solution of the thiol (16.3 mg) in water (10 ml) were added to 8-ml aliquots of imidazole or morpholine buffer solutions ($[B_T] = 0.4$ *M*) and the absorbance of the thiol at 235 mμ was measused in each buffer. A plot of absorbance *vs.* pH could be fitted to a theoretical titration curve for an acid of p$K_a' = 7.3$.

Kinetics. The rate of disappearance of 2,2,2-trifluoroethyl thiolacetate in various buffers was followed by measuring the variation in absorbance at 240 mμ. A stock solution of the ester (40–50 mg) in peroxide-free dioxane (10 ml) was prepared. One drop of this solution in 2 ml of buffer gave a solution approximately 10^{-4} *M* in ester. Freshly distilled water was used to prepare buffer solutions. Serial dilutions were made with 1.0 *M* potassium chloride solutions stored under nitrogen. The reactions were carried out in Ŧ cuvettes, filled so that no air space remained when the stopper was fitted. Absorption due to the various buffers was compensated for by using a reference cell containing only the buffer solution. The concentration of buffer was always in large excess over the concentration of ester, resulting in pseudo-first-order kinetics. Reactions were routinely followed to two half-lives or more. Disappearance of thiol ester was followed at 240 mμ (with imidazole at 245 mμ). Pseudo-first-order rates were obtained from the slopes of plots of log ($OD_t - OD_\infty$) or log ($OD_\infty - OD_t$) *vs.* time. The pH of solutions were determined before and after each run. Hydroxide-catalyzed rates were determined by titration. To 25 ml of 1.0 *M* potassium chloride solution was added 0.1 ml of stock ester solution. The solution was titrated with 0.0128 *N* carbonate-free potassium hydroxide solution. The pH-Stat was calibrated at pH 6.97 and 9.90. Pseudo-first-order rates were calculated from plots of log [(milliliters of titrant)$_\infty$ − (milliliters of titrant)$_t$] *vs.* time. The pK_a' values used were those given by Bruice, Bruno, and Chou.[1a]

Results[9]

The kinetic rate expressions for the reactions of 16 nucleophiles with 2,2,2-trifluoroethyl thiolacetate in water at 30°, at a total ionic strength of 1.0, are given in Table I. The methods used to determine these expressions are given below.

Reactions First Order with Respect to Nucleophiles. Plots of k_{obsd} *vs.* $[B_T]$ were linear, of slope $= k_2'$ and intercept $= k_{OH}[OH^-]$, where k_2' is the second-order rate constant at a given pH. Plots of k_2' *vs.* $K_a'/(K_a' + a_H)$ were linear, of slope k_2 and intercept zero, where k_2 is the true second-order rate constant for the expression

$$\frac{-d[E]}{dt} = k_2[E][B] \qquad (2)$$

where $k_2' = k_2K_a'/(K_a' + a_H)$. This shows dependence of the rate of disappearance of ester on the first power of the concentration of basic species [B], the latter acting as a nucleophile or as a general base catalyst to assist the attack of water at the carbonyl carbon. Nucleophiles 1–9 in Table I react with the ester according to expression 2.

For tris(hydroxymethyl)aminomethane (Tris) and ethylenediamine (compounds 11 and 12a,b; Table I) plots of k_{obsd} *vs.* $[B_T]$ were linear, but plots of k_2' *vs.* $K_a'/(K_a' + a_H)$ exhibited upward curvature. For Tris, a plot of $k_2'(K_a' + a_H)$ *vs.* a_H was linear, of slope k_{2_A} and intercept $k_{2_B}K_a'$ (Figure 1). These results are in accord with

$$\frac{-d[E]}{dt} = k_{2_A}[\text{Tris-H}^+][E] + k_{2_B}[\text{Tris}][E] \qquad (3a)$$

or

$$\frac{-d[E]}{dt} = k_{2_A}/K_a'[\text{Tris}][E]a_H + k_{2_B}[\text{Tris}][E] \qquad (3b)$$

which gives $k_2' = (k_{2_A}a_H + k_{2_B}K_a')/(K_a' + a_H)$ for (3a) or $((k_{2_A}a_H/K_a') + k_{2_B})[K_a'/(K_a' + a_H)]$ for (3b).

For ethylenediamine a plot of $k_2'(K'_{a_1}K'_{a_2} + K'_{a_1}a_H + a_H^2)$ *vs.* a_H was linear, of slope $k_{2_{BH}}K'_{a_1}$, and intercept $k_{2_B}K'_{a_1}K'_{a_2}$ (Figure 2), where K'_{a_2} and K'_{a_1} are the dissociation constants for the mono- and dipro-

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(7) T. C. French, S. J. Benkovic, and T. C. Bruice, *Rev. Sci. Instr.*, **36**, 860 (1965).

(8) W. F. Edgall and L. Parts, *J. Am. Chem. Soc.*, 77, 4899 (1955).

(9) Abbreviations employed in this study are: $[B_T] = [B] + [BH^+]$;

$$BH^+ \xrightleftharpoons{K_a'} B + H^+; \quad [B_T] = [BH_2^{2+}] + [BH^+] + [B];$$

$$BH_2^{2+} \underset{+H^+}{\overset{K_{a_1}}{\underset{}{\xrightleftharpoons{-H^+}}}} BH^+ \underset{+H^+}{\overset{K'_{a_2}}{\xrightleftharpoons{-H^+}}} B;$$

k_{obsd}, pseudo-first-order rate constant determined at constant values of pH and $[B_T]$; k_2', apparent second-order rate constants determined at a fixed pH; k_3', apparent third-order rate constants determined at a fixed pH; k_2, pH-independent, second-order rate constants; k_3, pH-independent, third-order rate constants; a_H, hydrogen ion activity as determined by the glass electrode, $[OH^-] = a_H/1.48 \times 10^{-14}$.

Table I. Experimentally Determined Rate Expressions for the Reactions of Nucleophiles with 2,2,2-Trifluoroethyl Thiolacetate (30°, μ = 1.0, in H_2O)

	Nucleophile	Rate expression	Rate constants[a]	pH range	No. of pH's	No. of k_{obsd}	Concn range, M^{-1}
1	Hydrazine	k[E][B]	209	7.35–8.60	4	16	0.20–0.01
2	Morpholine	k[E][B]	5.72	8.21–9.56	4	20	0.50–0.05
3	Glycine	k[E][B]	55.9	7.10–10.61	4	16	0.50–0.1
4	Ethanolamine	k[E][B]	59.0	9.02–10.26	5	25	0.14–0.01
5	Hydroxide	k[E][B]	64.5	9.90–11.04	7	7	
6	Carbonate	k[E][B]	1.82×10^{-1}	9.15–9.96	3	10	0.40–0.06
7	Pentaerythritol	k[E][B]	2.87×10^{3}	9.66–10.13	2	8	0.50–0.10
8	CF_3CH_2OH	k[E][B]	1.31×10^{3}	9.60–9.99	2	8	1.00–0.20
9	Cyanide	k[E][B]	2.95	9.27–9.57	2	8	0.10–0.02
10	Borate	No reaction	. . .	9.43	1	3	0.10–0.05
11	Tris(hydroxymethyl)-aminomethane	(a) k[B][E] (b) $k[BH^+]$[E]	4.2×10^{-2} 1.02×10^{-2}	7.39–8.98	4	16	0.70–0.14
12	Ethylenediamine	(a) $k[BH^+]$[E] (b) k[B][E]	6.0×10^{-1} 182	6.97–9.47	6	30	0.30–0.03
13	Methoxylamine	$k[B][BH^+]$[E]	2.0	3.97–5.31	5	25	1.00–0.1
14	Hydroxylamine	(a) k[B][E] (b) $k[B]^2$[E] (c) $k[B][BH^+]$[E]	33.0 89.0 54.7	5.31–6.52	5	25	0.20–0.02
15	Piperidine	$k[B]^2$[E] $k[OH^-]$[E]	1.04×10^{4} 1.02×10^{4}	10.22–11.69	5	20	0.15–0.04
16	Imidazole	k[B][E]	6.85	5.24–7.80	7	36	0.50–0.15

[a] Given in units of minutes and M^{-1}.

tonated amine, respectively. These results are in accord with

$$\frac{-d[E]}{dt} = [E](k_{2_{BH}}[BH^+] + k_{2_B}[B]) \tag{4}$$

which gives

$$k_2' = \frac{k_{2_B}K'_{a_1}K'_{a_2} + k_{2_{BH}}K'_{a_1}a_H}{K'_{a_1}K'_{a_2} + K'_{a_1}a_H + a_H^2}$$

Reactions Second Order with Respect to Nucleophiles. The apparent third-order rate constants (k_3') were obtained from the slopes of plots of k_{obsd} *vs.* $[B_T]^2$. For methoxylamine a plot of k_3' *vs.* $a_H/(K_a' + a_H)^2$ was linear, of slope k_3K_a' and intercept zero. This shows a rate expression of

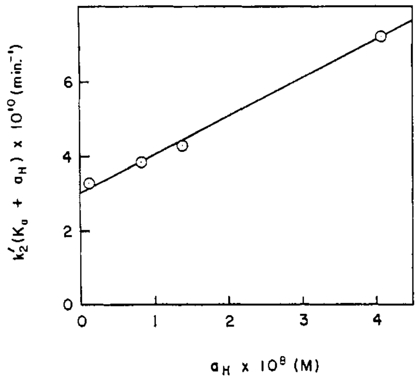


Figure 1. Plot of the product of the apparent second-order rate constant and the sum of the dissociation constant and hydrogen ion activity *vs.* the hydrogen ion activity for the reaction of tris(hydroxymethyl)aminomethane with the thiol ester.

$$\frac{-d[E]}{dt} = k_3[B][BH^+][E] \tag{5}$$

which leads to $k_3' = k_3K_a'a_H/(K_a' + a_H)^2$. For piperidine plots of k_{obsd} *vs.* $[B_T]^2$ were linear, of slope k_3' and with intercepts which did not correspond to $k_{OH}[OH^-]$, although the intercept rates (k_I) followed the equation $-d[E]/dt = k_I[E][OH^-]$. This phenomenon will be discussed later.

A plot of k_3' *vs.* $[K_a'/(K_a' + a_H)]^2$ was linear, of slope k_3 and intercept zero. This shows a rate expression of

$$\frac{-d[E]}{dt} = k_3[B]^2[E] \tag{6}$$

where $k_3' = k_3[K_a'/(K_a' + a_H)]^2$.

Reactions Showing Mixed-Order Kinetics. Only hydroxylamine exhibited kinetics of mixed order. Plots of k_{obsd} *vs.* $[B_T]$ or $[B_T]^2$ were curved. Plots of $k_{obsd}/[B_T]$ *vs.* $[B_T]$ were linear, of slope k_3' and intercept k_2'.

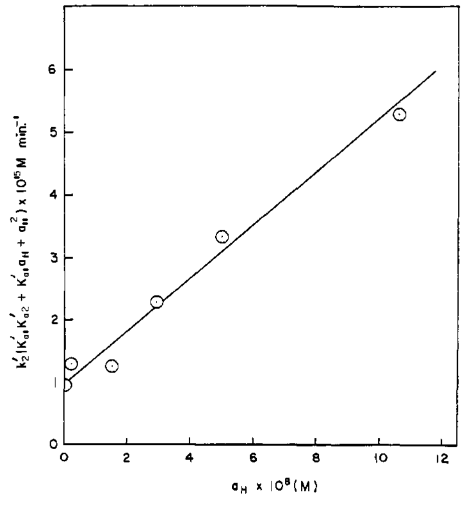


Figure 2. Plot for eq 4 for the reaction of ethylenediamine with the thiol ester, where intercept = $k_{2B}K'_{a1}K'_{a2}$ and the slope = $k_{2BH}k'_{a1}$.

A plot of k_2' *vs.* $K_a'/(K_a' + a_H)$ was linear, of slope k_2 and intercept zero. A plot of k_3' *vs.* $a_H/(K_a' +$

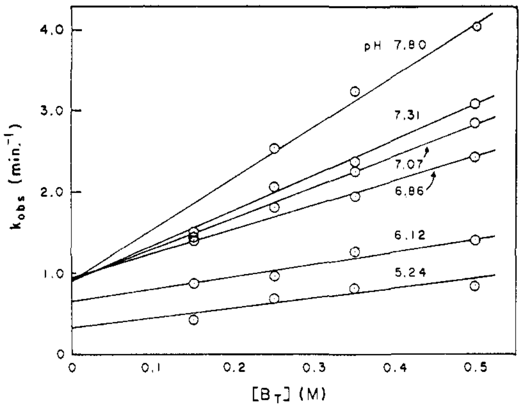
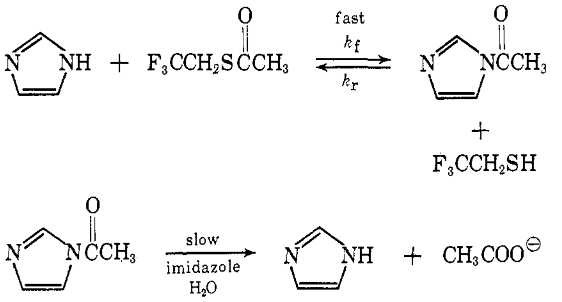


Figure 3. The linear dependence of the pseudo-first-order rate constants for the reaction of imidazole with 2,2,2-trifluoroethyl thiolacetate on the total imidazole concentration.

$a_H)^2$ was linear, of slope $k_{3A}K_a'$ and intercept $k_{3B}(K_a')^2$. The complete rate expression is therefore

$$\frac{-\mathrm{d}[\mathrm{E}]}{\mathrm{d}t} = k_2[\mathrm{B}][\mathrm{E}] + k_{3A}[\mathrm{BH}^+][\mathrm{B}][\mathrm{E}] + k_{3B}[\mathrm{B}]^2[\mathrm{E}] \qquad (7)$$

Reaction with Imidazole. Plots of k_{obsd} *vs.* [B_T] at various pH's for the reaction of imidazole with the thiol ester were found to be linear (Figure 3). However, the intercepts on the k_{obsd} axis at [B_T] = 0 did not conform to $k_{OH}[OH^-]$. The reaction of imidazole with the ester was complicated by a number of effects. At the wavelength (245 mμ) used to follow the reaction the measured absorbance is a combination of the absorbances of the thiol ester (λ_{max} 226 mμ), the thiolate anion (λ_{max} 228 mμ), and acetyl imidazole (λ_{max} 245 mμ). Furthermore, study of the reaction is complicated by a reverse reaction and hydrolysis of the acetylimidazole.



(8)

At pH 7.08 and $[IM]_T$ = 0.5 *M*, k_{obsd} for disappearance of ester is 2.85 min^{-1}, while k_{obsd} for hydrolysis of N-acetylimidazole is 4.5 × 10^{-2} min^{-1}.[10] At the completion of the equilibrium associated with k_f (eq 8), the thiol disappears owing to air oxidation with a rate constant of 10^{-2} min^{-1}. Therefore, the hydrolysis of N-acetylimidazole and disappearance of thiol occur at rates much smaller than the reaction of imidazole with the ester and do not complicate the determination of the rate constants for this reaction.

That thiol does react with N-acetylimidazole and an equilibrium is obtained was shown by studying the effect of added thiol on the equilibrium concentration of N-acetylimidazole and on the rate of disappearance of the ester. Addition of an amount of thiol equal to approximately 4.5 times the initial concentration of ester to 0.5 *M* imidazole buffer at pH 6.08 depressed the equilibrium concentration of acetylimidazole by approximately 20%. The use of this pH, which is 1.3 pH units below the pK_a' of the thiol, permits measurement of the absorbance due to acetylimidazole at 245 mμ, without interference from the thiolate anion. It can be shown from this experiment that the equilibrium concentration of ester is about 5% of the initial ester concentration in the absence of added thiol, and under these conditions.

Under pseudo-first-order conditions an equilibrium reaction of this type (eq 10) gives an integrated rate expression of the form[11]

$$\ln (E_0 - EE_e/E_0) - \ln (E - E_e) = k_f(E_0 + E_e)/(E_0 - E_e)t \qquad (9)$$

where E_0 = initial concentration of ester, E = ester concentration, E_e = equilibrium concentration of ester, and t = time. The term ln ($E_0 - EE_e/E_0$) remains essentially constant during the reaction, as illustrated by the lack of upward curvature of plots of log ($E - E_e$) *vs.* *t*. The slopes of these plots are thus related to k_f, the forward rate of the reaction

$$2.303(\text{slope}) = (E_0 + E_e)/(E_0 - E_e)k_f = k_{obsd} \qquad (10)$$

and

$$k_{obsd} = k_f + 2(E_0 - E_e)k_r \qquad (11)$$

The effect of the reverse rate on buffer dilution plots depends on the dependence of the equilibrium on buffer concentration. The intercepts at [B_T] = 0 found here are due to an equilibrium which is pH dependent only, and are equal to $2[E_0 - E_e]k_r$ or 2[acetylimidazole]k_r. No attempt has been made to study the reverse reaction, and the rate constant for the forward reaction was obtained from plotting the slopes of the buffer dilution plots, k_2' *vs.* $K_a'/(K_a' + a_H)$. The second-order rate constant was obtained as the slope of this plot.

Discussion

From Table I it is evident that 2,2,2-trifluoroethyl thiolacetate exhibits its own unique reaction pattern with nucleophiles. The pK_a' values of 2,2,2-trifluoroethanethiol (7.3) and *p*-nitrophenol (7.15) are nearly identical and, therefore, one might anticipate a broad similarity in their reactions with nucleophiles. As we shall see this is so for simple nucleophilic attack (k_n). However, for the nucleophiles investigated *p*-nitrophenyl acetate exhibits susceptibility only to second-order nucleophilic attack except in the case of methoxylamine where general acid catalysis (k_{ga}) is also found.[12] From Table I it can be seen that 2,2,2-trifluoroethyl thiolacetate reacts with methoxylamine only through general acid catalysis. In addition the thiol ester is susceptible to general catalysis of the acid or basic type by hydroxylamine and piperidine. The susceptibility of the thiol ester to general acid and general base catalysis is much less than for δ-thiolvalerolactone.[1a] For this thiolactone, glycine, hydroxylamine, methoxylamine, morpholine, piperidine, and hydrazine

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(10) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).

(11) A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, p 186.

(12) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960).

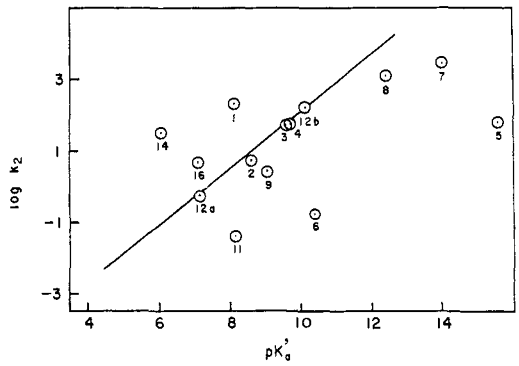

Figure 4. Brønsted plot for the second-order rate constants for reaction of 14 nucleophiles with 2,2,2-trifluoroethyl thiolacetate. The numbers refer to the compounds of Table I.

exhibit k_{ga} and/or k_{gb} terms. The thiolactone thus behaves more like phenyl acetate than p-nitrophenyl acetate, an expectation based on the fact that both possess leaving groups that are stronger bases (essentially identical pK_a' values of 10.0[13] and 9.89, respectively) than the leaving groups for 2,2,2-trifluoroethyl thiolacetate and p-nitrophenyl acetate.

The reactions of nucleophiles 11 and 12 of Table I exhibit the term $k[\mathrm{BH}^+][\mathrm{E}]$ or the kinetically equivalent term $k[\mathrm{B}][\mathrm{E}]a_\mathrm{H}$. This kinetic dependence is expected for ethylenediamine (12), and is regarded as due to nucleophilic attack by the free amino group of the monoprotonated diamine. A term of this nature with Tris (11) is unusual, showing either general acid catalyzed hydrolysis or specific acid catalyzed aminolysis of the thiol ester. This is the first case of this type of reaction encountered in reactions of nucleophiles with esters. An analysis of the products from 1.0 *M* Tris at pH 8.17 by hydroxamate tests using p-nitrophenyl acetate[14] as a standard showed that only 30% of the ester was converted to acetylated Tris. This suggests that the acid-catalysis term is due to general acid catalyzed hydrolysis and the reaction associated with the term $k[\mathrm{B}][\mathrm{E}]$ is acetylation of the Tris. Further work on the products of Tris with esters is planned.

A Brønsted-type plot for nucleophiles showing second-order terms with 2,2,2-trifluoroethyl thiolacetate is shown in Figure 4. Fair correlation between pK_a' and k_n was found for only five amines. Of the remaining nucleophiles, rates for imidazole, hydroxylamine, and hydrazine are above this line and oxyanions, cyanide, and Tris fall below this line. The rates for oxyanions were so scattered as to make any relationship to pK_a' meaningless. As expected, hydroxylamine and hydrazine show an α effect. The present situation with regard to this effect has been reviewed in the previous paper,[15] and it is sufficient to mention here that 70% of the enhanced rate for hydrazine can be explained by using a K_a' for hydrazine of twice that of ammonia.[16] The residual enhancement is small but still significant. Aside from the α effect the scatter in the Brønsted plot is that normally encountered when bases of different types are employed (compare Figure 3 in ref 17 to Figure 1 of ref 18). This scattering of points is related to the nucleophilic atom and its charge type, relative solvation, and steric effects. A means of normalizing these factors is to plot the log of the rate constants for the reactions of nucleophiles with the substrate under consideration *vs.* the log of the corresponding rate constants for the reactions of the same nucleophiles with another substrate. This procedure is a means of comparing the $\Delta F^{\neq}$ for two reactions.

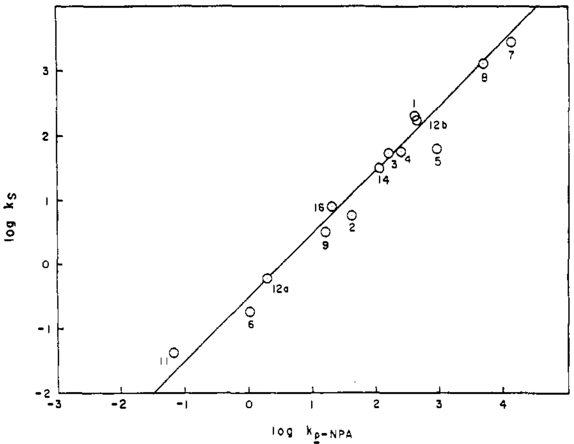

Figure 5. Plot of the log of the second-order rate constants (log k_S) for the reactions of nucleophiles with 2,2,2-trifluoroethyl thiolacetate *vs.* the log of the second-order rate constants ($k_{p\text{-NPA}}$) for the reactions of the same nucleophiles with p-nitrophenyl acetate. The numbers refer to compounds of Table I.

From transition state theory it can be shown that

$$\log k_1 = \log k_2 - \frac{1}{2.303RT}(\Delta F_1^{\neq} - \Delta F_2^{\neq}) \qquad (12)$$

where k_1 and k_2 are rate constants associated with $\Delta F_1^{\neq}$ and $\Delta F_2^{\neq}$. From eq 12

$$\frac{\mathrm{d}\log k_1}{\mathrm{d}\log k_2} = 1 - \frac{1}{2.303RT}\left[\frac{\mathrm{d}(\Delta F_1^{\neq} - \Delta F_2^{\neq})}{\mathrm{d}\log k_2}\right] \qquad (13)$$

In eq 13, k_1 and k_2 now pertain to the rate constants for the reaction of a series of nucleophiles with substrates S_1 and S_2. The values of $(\Delta F_1^{\neq} - \Delta F_2^{\neq})$ pertain to the difference in the free energies of activation for nucleophiles with S_1 and S_2. For cases where plots of log k_1 *vs.* log k_2 are linear and of slope 1.0 it follows from eq 13 that $(\Delta F_1^{\neq} - \Delta F_2^{\neq})$ for each of the nucleophiles reacting with S_1 and S_2 must be a constant equal to (2.303RT)(intercept of the plot). Slopes greater or less than 1.0 are possible if $(\Delta F_1^{\neq} - \Delta F_2^{\neq})$ varies with $\Delta F_2^{\neq}$ in a linear fashion. As $\Delta F_1^{\neq}$ differs for different nucleophiles, a linear variation of $(\Delta F_1^{\neq} - \Delta F_2^{\neq})$ with $\Delta F_2^{\neq}$ implies a linear relationship of $\Delta F_1^{\neq}$ to $\Delta F_2^{\neq}$, a relationship anticipated from the usefulness of other extrathermodynamic relationships.

The close similarity of the k_n terms for the thiol ester and those of p-nitrophenyl acetate is illustrated in Figure 5 which shows a linear relationship of the log of the second-order rate constants for the reaction of a series of nucleophiles with p-nitrophenyl acetate (log $k_{p\text{-NPA}}$) and thiol ester (log k_S). The slope of 1.0 shows

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[13] T. C. Bruice and J. J. Bruno, *J. Am. Chem. Soc.*, **84**, 2128 (1962).

[14] T. C. Bruice and J. L. York, *ibid.*, **83**, 1382 (1961).

[15] T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967).

[16] T. C. Brucie and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 80.

[17] T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, **80**, 2265 (1958).

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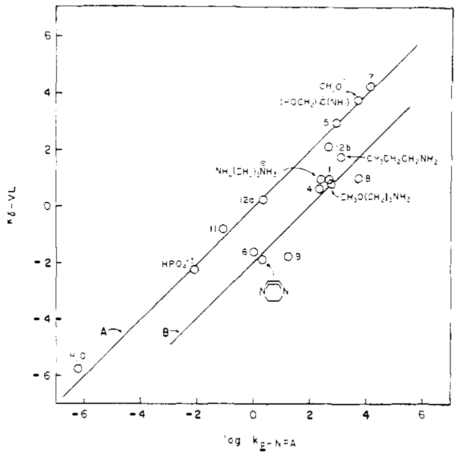

Figure 6. Plot of the log of the second-order rate constants (log $k_{\delta\text{-VL}}$) for the reactions of nucleophiles with δ-thiolvalerolactone *vs.* the log of the second-order rate constants ($k_{p\text{-NPA}}$) for the reactions of the same nucleophiles with *p*-nitrophenyl acetate. The numbers refer to compounds of Table I.

that the Brønsted slope β for any given type of nucleophile is the same for both esters, and the intercept of -0.6 shows that the Brønsted intercept constant for the thiol ester is one-half that for the phenyl ester, for reaction with a given type of nucleophile, and that the difference in free energy of activation for reactions of any nucleophile with the two esters is only 0.83 kcal/mole. In the present case, it may be said that the factors causing deviations in the Brønsted-type relationships for reactions of these two esters apply equally to both, and that the changes in rate constants brought about by a change in pK_a' of the conjugate acid of the nucleophile are identical. This treatment suggests that the difference in free energy of activation for reactions of the thiol ester and *p*-nitrophenyl acetate with the same nucleophile is independent of the nucleophiles used.

The comparison of log k_n values for *p*-nitrophenyl acetate (and therefore, 2,2,2-trifluoroethyl thiolacetate) and δ-thiolvalerolactone has previously been made.[1a,c] This comparison may now be extended by the inclusion of the second-order rate constants for the reaction of CN^-, $NH_2CH_2CH_2CH_2NH_3^+$, $CH_3OCH_2CH_2CH_2NH_2$, and $CH_3CH_2CH_2NH_2$ with both esters.[19] A plot of log $k_{p\text{-NPA}}$ *vs.* log $k_{\delta\text{-VL}}$ is shown in Figure 6. Inspection of this figure reveals that the rate constants are mainly grouped around lines A and B, both of slope 1.0, but of intercepts 0.0 and -1.96, respectively. For the nucleophiles of line A the Brønsted equations are identical for δ-thiolvalerolactone and *p*-nitrophenyl acetate and differ from that for 2,2,2-trifluoroethyl thiolacetate only slightly in the intercept. That the rate-determining step for these reactions is formation of a tetrahedral intermediate is supported by the following facts. For the two acetates there is no element effect on the leaving group, and for OH^- and other oxyanions of high pK_a' there is not expected to be back incorporation of O^{18}[20] as partitioning of intermediates formed from oxyanions of high pK_a' is unlikely. As the effect of partitioning is to lower the over-all rate, these oxyanions would show enhanced rates relative to other nucleophiles for which partitioning is important. Such an effect is not noticed with *p*-nitrophenyl acetate or the two thiol esters, but with phenyl acetate both pentaerythritol and Tris oxyanions show an extremely high reactivity.[14] This lends support to the contention that reactions of amines with *p*-nitrophenyl acetate and 2,2,2-trifluoroethyl thiolacetate do not involve partitioning of the intermediates.

The suggestion that for the reactions of nucleophiles on plot B of Figure 6 partitioning is of importance[1c] is in accordance with the expected decrease in over-all rate for reactions of this type. If this contention is correct then the rate expression most likely to give a simple relationship between rates, such as the one found, is eq 14. This can be derived for a reaction in-

$$\frac{-d[E]}{dt} = (k_1k_3/k_2)[E][N] \tag{14}$$

volving preequilibrium addition of the nucleophile to the ester, followed by a slow reaction to products. If this is so, one would predict a slope of greater or less than 1.0 for the reaction. The slope of 1.0 found here is of dubious value as it is drawn for two groups of rates, and there is not a sufficient spread of data to get a reliable estimate of the slope.

Although many of the amines which give third-order rate expressions with δ-thiolvalerolactone give second-order expressions with 2,2,2-trifluoroethyl thiolacetate, no differentiation between the general base catalyzed addition of an amine to the carbonyl group of the ester and a two-step mechanism involving acid-base equilibria can be made from this. A survey of the possible reaction mechanisms leading to third-order aminolysis terms has been made recently[15] and the present study contributes little to the current knowledge of these reactions.

Tetrahedral Intermediates. Of the nucleophiles shown in Table I only piperidine shows any kinetic evidence for tetrahedral intermediate formation in its reaction with 2,2,2-trifluoroethyl thiolacetate. In this case the significance of tetrahedral intermediate formation was shown by the difference in k_{obsd} extrapolated to zero $[B_T]$ in plots of k_{obsd} *vs.* $[B_T]^2$ and the value of $k_{OH}[OH^-]$ determined independently (titrimetric) at $[B_T] = 0$. The intercept rate (k_I) varied linearly with $[OH^-]$, to give the relationship: $k_I = 1.02 \times 10^4[OH^-]$. The titrimetric rate constant for hydroxide catalysis is 64.5 M^{-1} min^{-1}. Therefore, the rate constant k_I is *ca.* 160 times greater than the true k_{OH} value and must be due to piperidine catalysis, the rate of which is independent of the concentration of piperidine under these conditions. The simplest rationale for this phenomenon is that piperidine acts as a general base on water, to give an intermediate in which partitioning back to reactants is most significant (eq 15).

$$H_2O + \text{ester} \underset{(\text{pipH}^+)k_2}{\overset{(\text{pip})k_1}{\rightleftharpoons}} T \xrightarrow{k_3} \text{products} \tag{15}$$

From this

$$\frac{-d[E]}{dt} = \frac{k_1k_3[E][\text{pip}][H_2O]}{k_2[\text{pipH}^+] + k_3} \tag{16}$$

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[19] The rate constants were determined by Dr. A. R. Butler in this laboratory.

[20] Phenyl benzoate [C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956)] and δ-butyrolactone [M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *J. Am. Chem. Soc.*, **83**, 4193 (1961)] do not exhibit back incorporation of O^{16} into the $C{=}O^{18}$ group during their hydrolysis.

where $k_2[\text{pipH}^+] \gg k_3$

$$\frac{-\text{d}[\text{E}]}{\text{d}t} = \frac{k_1k_3[\text{E}][\text{pip}][\text{H}_2\text{O}]}{k_2[\text{pipH}^+]} = \frac{K_a'k_1k_3[\text{E}][\text{OH}^-][\text{H}_2\text{O}]}{k_2K_w}$$

Thus, $(K_a'k_1k_3[\text{H}_2\text{O}]/K_wk_2) = 1.02 \times 10^4\ M^{-1}\ \text{min}^{-1}$ and $(k_1k_3/k_2)[\text{H}_2\text{O}] = 193.6\ M^{-1}\ \text{min}^{-1}$. The similarity of the unsymmetrical mechanisms of 15 and 1 is obvious. We have previously asserted that for nucleophilic attack only addition to carbonyl is rate determining. Hence it is necessary here to postulate that the rate of addition of water to the ester is so enhanced by general base catalysis that it far exceeds the rate of breakdown of the intermediate (T) to products.

No deviation from third-order kinetics was found for the k_{gb} term for piperidine.

Acknowledgment. This research was supported by a grant from the National Institutes of Health.

Synthesis and Structures of the 2,3-Bis(N-fluorimino)butanes[1]

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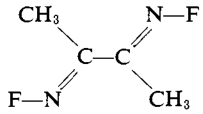
Received October 19, 1966

Abstract: The three 2,3-bis(N-fluorimino)butanes (*syn,syn; syn,anti; anti,anti*) have been prepared, isolated, and characterized. The configurations of these geometric isomers have been determined from combined nmr and mass spectral data. The planarity of the isomers is discussed.

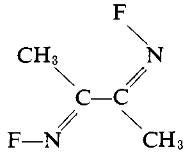
There are relatively few unequivocal examples in which imines have been separated into all possible geometric isomers of known configuration.[2,3] Structural assignments generally have been based upon dipole moments, products from stereospecific reactions, and ultraviolet, infrared, and nmr spectral data. Nmr has been employed extensively in the structural determinations of imines, particularly of isomeric mixtures.[4] These structural assignments have been dependent on the coupling constants and chemical shifts of various groups adjacent to the imine function. Mass spectrometry has not been used to study the geometry of imines.

With the exception of the perfluoro analogs,[5] N-fluorimines have been prepared only recently.[6] Logothetis and Sausen[6b] have reported the only example in which a N-fluorimine (1-cyano-N-fluoroformimidoyl fluoride) has been separated into all geometric isomers. Using fluoroolefins as model compounds, the stereochemistry of these isomers has been assigned by nmr. In a similar manner, structures have also been assigned to isomeric mixtures of other N-fluorimines.[6b]

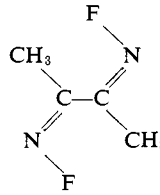
We now wish to report the preparation, isolation, and characterization of the three 2,3-bis(N-fluorimino)-butanes, I (*syn,syn; syn,anti; anti,anti;* the *syn* and *anti* assignments refer to the fluorine and methyl group on the carbon-nitrogen double bond). The configurations of these geometric isomers have been determined from combined nmr and mass spectral data. The symmetrical compounds (*syn,syn* and *anti,anti*) have been differentiated from the unsymmetrical compound (*syn,anti*) by means of their nmr spectra. Specific structures have then been assigned to the symmetrical isomers by means of their mass spectra.



syn,syn
Ia



syn,anti
Ib



anti,anti
Ic

Experimental Section

Elemental analyses were performed by the microanalytical laboratory, Stanford University. Ultraviolet spectra were determined with a Cary 14 recording spectrophotometer. Infrared spectra were recorded with a Perkin-Elmer 237-B grating spectrophotometer.

2,3-Bis(N,N-difluoramino)butane. This compound was prepared by the gas-phase addition of tetrafluorohydrazine to 2-butene.[7]

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[1] This work was supported by the Office of Naval Research, Contract Nonr 3760(00).

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