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Nucleophilic Displacement Reactions at the Thiolester Bond. II. Hydrazinolysis and Morpholinolysis in Aqueous Solution

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The kinetics of hydrazinolysis and morpholinolysis of a series of thiolesters and thiolactones have been determined. The reactions are subject to general-acid- (k_{ga}) and general-base- (k_{gb}) catalyzed attack of the nucleophile. For all the thiolesters and lactones investigated the ratios of k_{gb}/k_{ga} (at 30°) were found to be between 1.00 and 1.82. In the hydrazinolysis of *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate, the rate constants k_{gb} and k_{ga} were found to exhibit almost equal sensitivity to steric hindrance. The sensitivity of these constants to steric hindrance was greater than that exhibited by k_n as anticipated from the presumed greater steric requirement of the transition states associated with the catalytic reactions. As previously found by us, for oxygen esters, the α -effect is of greater importance in the catalyzed reaction. Activation parameters for the general-acid- and general-base-catalyzed hydrazinolysis and morpholinolysis of δ -thiolvalerolactone in water have been determined. The hydrazinolysis reactions are nearly insensitive to temperature change (3–40°) and practically all of the free energy of activation resides in the entropy of activation term. The values of $T\Delta S^*$ are those anticipated of termolecular reactions. For k_{ga} and k_{gb} , deuterium solvent isotope effects are consistent with mechanisms involving proton abstraction in the rate-limiting step. The competitive hydrazinolysis of δ -thiolvalerolactone with ethanolamine is kinetically described by the expression $v = [k_n(\text{H}_t) + k_{gb}(\text{H}_t)^2 + k_{ga}(\text{H}_t)(\text{H}_p) + k_n(\text{EA}_t) + k_{mgb}(\text{EA}_t)(\text{H}_t) + k_{hyd}](\text{lactone})$. The competitive hydrazinolysis of δ -thiolvalerolactone and of butyl thiolacetate with imidazole are kinetically described by the expression $v = [k_n(\text{H}_t) + k_{gb}(\text{H}_t)^2 + k_{ga}(\text{H}_t)(\text{H}_p) + k_n(\text{Im}_t) + k_{mgb}(\text{Im}_t)(\text{H}_t) + k_{mga}(\text{Im}_p)(\text{H}_t)](\text{ester})$. There was no definitive evidence of alterations in values of rate constants determined in competitive catalysis experiments from their values which were separately determined in noncompetitive experiments. Unlike the terms containing only the nucleophile and its conjugate acid or base (*i.e.*, k_{ga} and k_{gb}), the mixed terms (*i.e.*, k_{mga} and k_{mgb}) are not nearly identical. The larger of the two mixed terms is determined by the pK_a' of the catalytic species as anticipated for reactions involving proton abstractions or donation in the transition state.

Introduction

In a previous study the kinetics of the reaction of nineteen nucleophiles with δ -thiolvalerolactone was described.³ The nucleophiles were divided into three kinetic categories: (1) those which reacted with the thiolactone by a simple bimolecular reaction; (2) those which reacted with the thiolactone by general-base assistance; (3) those which reacted with the thiolactone by both general-base and general-acid assistance to nucleophilic attack. No explanation accounted for the fact that nucleophiles of similar type were found in both category (1) and (3). Thus ethanolamine, ethylenediamine, and tris(hydroxymethyl)aminomethane, all primary amines, underwent simple bimolecular reaction with δ -thiolvalerolactone, while glycine, methoxyamine, and hydrazine underwent termolecular general-base- and general-acid-catalyzed reactions with the thiolactone. Also, the thiolactone was found to be equally sensitive to both catalytic processes when the conjugate base or acid of the nucleophile acted as catalyst.

The purpose of this investigation was to examine further reactions of nucleophiles with thiolesters to determine: (1) whether δ -thiolvalerolactone was equally sensitive to general-base- and general-acid-catalyzed assistance to nucleophilic attack over a temperature range or only at a single temperature (30°); (2) whether those nucleophiles which reacted with δ -thiolvalerolactone *via* general-acid and general-base assistance by their own conjugate acids and bases were equally sensitive to general-acid and general-base assistance by other nucleophiles acting as acids and bases; (3) whether deuterium solvent isotope effects supported general-acid and general-base mechanisms

for reactions found to be kinetically termolecular; (4) whether other thiolesters exhibit the same approximate sensitivity to general-acid- and general-base-assisted processes as δ -thiolvalerolactone; (5) whether steric hindrance to the third-order catalytic processes (*i.e.*, general acid and general base) was approximately the same or greater than that for simple unassisted nucleophilic attack; and (6) whether evidence could be obtained from examination of competitive catalysis experiments for the existence of tetrahedral intermediates in general-acid- and general-base-catalyzed nucleophilic displacements on thiolester bonds.

Experimental

Apparatus.—A Zeiss PMQ II spectrophotometer equipped with a thermostated cuvette holder was used. All pH measurements were made with a Radiometer Model 22 pH meter with a Radiometer Model PHA 630 Pa scale expander. The combined glass-calomel electrode (Radiometer GK 2021C) was thermostated at the temperature of the reaction solution which was maintained at $\pm 0.1^\circ$. Reaction rates too rapid to follow visually were recorded on a Direct Brush Oscillograph Model RD 232100.

Materials.— δ -Thiolvalerolactone was prepared from thiolacetic acid (Eastman Kodak Co.) and 4-pentenoic acid, b.p. 183–186° (748 mm.), $n_{27.5D}^{25} 1.4300$,⁴ by the procedure of Korte and Buchel; b.p. 76–78° (1.5 mm.), $n_{25D}^{25} 1.5269$, lit.⁵ value 63–66° (0.6 mm.). γ -Thiolbutyrolactone was prepared from γ -chlorobutyronitrile (Aldrich Chemical Co.) and thiourea (Matheson Coleman and Bell) by the procedure of Truce and Abraham; b.p. 44.5–45° (1.3 mm.), $n_{25D}^{25} 1.5220$; lit.⁶ value 53–54° (3 mm.), $n_{25D}^{25} 1.5200$. Butyl thiolacetate (Eastman Kodak Co.) was distilled before use; b.p. 159–160° (740 mm.), $n_{25D}^{25} 1.4580$; lit.⁷ value, 163.4° (760 mm.), $n_{25D}^{25} 1.4570$. Isopropyl thiolacetate, b.p. 117° (748 mm.), $n_{25D}^{25} 1.4482$ (lit.⁸ value, 126–127° (760 mm.), $n_{23.5D}^{25} 1.4502$), and *t*-butyl thiolacetate, b.p. 120–121° (748 mm.), $n_{25D}^{25} 1.4498$ (lit.⁸ value 38° (14 mm.), $n_{23.5D}^{25} 1.4490$), were prepared by adding dropwise the appropriate mercaptan

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(3) T. C. Bruce, J. J. Bruno, and W. S. Chou, *J. Am. Chem. Soc.*, **85**, 1659 (1963).

(4) R. Paul, *Ann. Chem.*, **18**, 330 (1932).

(5) F. Korte and K. H. Buchel, *Ber.*, **93**, 1021 (1960).

(6) W. E. Truce and D. J. Abraham, *J. Org. Chem.*, **28**, 964 (1963).

(7) F. W. Wenzell and E. E. Reid, *J. Am. Chem. Soc.*, **59**, 1089 (1937).

(8) P. N. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3021 (1950).

(Eastman Kodak Co.) to a 50% excess of acetyl chloride (Baker and Adamson Reagent) cooled to 0°. The reaction mixture was allowed to stand at room temperature for 1 day and was then heated on a steam bath for 6 hr. Excess acetyl chloride was removed by distillation and the remaining thioester was twice distilled through a vacuum-jacketed Vigreux column, the center fractions of distillate being used for the study. Hydrazine dihydrochloride and imidazole (Eastman Kodak Co., White Label) were stored over P₂O₅ in a desiccator protected from light. Ethanolamine hydrochloride (K and K laboratories, Inc.) was crystallized from methanol and stored over P₂O₅ in a desiccator. Morpholine (Eastman Kodak Co., practical) was purified by distillation after refluxing for 20 hr. over sodium metal; b.p. 125–126° (748 mm.). Deuterium oxide, 99.7%, was supplied by the Atomic Energy Commission through Cornell University stores. Potassium deuterioxide was prepared from potassium hydroxide (Mallinckrodt Chemical Co. Analytical Reagent) and deuterium oxide. Deuteriochloric acid was prepared from hydrogen chloride gas and deuterium oxide. Base solutions were standardized against primary standard potassium acid phthalate (Mallinckrodt Chemical Co.) and acid solutions were standardized with base solutions of determined concentration. Precaution was taken to exclude moisture from solutions in deuterium isotope effect studies. pH readings were converted to pD readings by the correction of Fife and Bruce.⁹ Recently boiled distilled water was used in the preparation of solutions.

Kinetics.—The following wave lengths were used in observing the rate of ester disappearance: δ -thiolvalerolactone, 239.5 m μ ; γ -thiolbutyrolactone, 237 m μ ; butyl thiolacetate, 235 m μ ; isopropyl thiolacetate, 235 m μ ; *t*-butyl thiolacetate, 233 m μ . The reaction of butyl thiolacetate with imidazole, at high imidazole concentrations, was followed at 239 m μ because of the high absorbance of imidazole of 235 m μ . A stock solution of the appropriate ester was prepared in ether. One drop of the ethereal solution was introduced down the barrel of a thermostated 2-ml. glass hypodermic syringe fitted with a polyethylene "needle." The thermostated solution of the nucleophile contained in a 5 cuvette, filled to the stopper level with solution previously degassed with nitrogen, was then drawn into the syringe and expelled back into the cuvette. The process was repeated until mixing was judged to be complete. The concentration of ester so obtained was ca. 2×10^{-4} M. Absorbance due to reagents was compensated for by the use of solutions identical with the reaction solution, minus ester, in the reference cell. pH was determined at the beginning of each run and was periodically checked at the completion of some runs in each study. Buffer capacity of reaction solutions was supplied by the nucleophile and its conjugate acid. The concentration of nucleophile was always in excess of the concentration of ester so that pseudo-first-order kinetics were obtained. Reactions were generally followed to at least three half-lives and were found to be first order. Pseudo-first-order rate constants were obtained from the slope of plots of $\log O.D._t/O.D._\infty$ (corrected for absorption of thiol formed) against time. Potassium chloride was added to bring all solutions to a calculated ionic strength of 1 M. In the temperature dependence studies the heats of ionization of hydrazine and morpholine were taken into account. The following pK'_a values were obtained for morpholine: 5°, 9.28; 13°, 9.10; 20°, 8.96; 30°, 8.70; 44.5°, 8.46. A plot of $\log K'_a$ against $1/T$ is linear and the heat of ionization of morpholine calculated from the slope of the line is 8.36 kcal.mole⁻¹. The heat of ionization of hydrazine was taken as 10.4 kcal.mole⁻¹.¹⁰ The pK'_D for hydrazine at 30° and at 17° was determined by half-neutralization to be 8.69 and 9.08, respectively. The pK'_D for morpholine at 13° is 9.68. The pK'_a values used for imidazole and ethanolamine were 7.14 and 9.72, respectively.³

Results¹¹

The hydrazinolysis of δ -thiolvalerolactone in water was examined in the temperature range 3–39.4°. At

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

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

(11) Abbreviations used in this study are: H_t = concentration of NH₂NH₂; H_p = concentration of NH₂NH₂⁺; Im_t = concentration of free imidazole; Im_p = concentration of imidazolium ion; M_t = concentration of free morpholine; M_p = concentration of morpholinium ion; EA_t = concentration of free ethanolamine; a_H = hydrogen ion activity as determined by the glass electrode; K'_{IM} , K'_{EA} , K'_M , K'_H = apparent dissociation constants determined by the method of half-neutralization for imidazole,

all temperatures studied the reaction was found to proceed by nucleophilic attack of hydrazine on the thiolactone as well as by general-acid-catalyzed and general-base-catalyzed assistance to nucleophilic attack. At constant pH the rate expression for the disappearance of thiolactone is given by eq. 1. The contribution of the hydrolytic rate to k_{obsd} in the acidity range examined was negligible. Plots of $k_{obsd}/(H_t)$ vs. (H_t) are

$$-d(\text{lactone})/dt = k_{obsd}(\text{lactone}) = [k_n(H_t) + k_{ga}(H_t)(H_p) + k_{gb}(H_t)^2] \times (\text{lactone}) \quad (1)$$

linear, having as slope the apparent third-order rate constant k_3' and as intercept the nucleophilic rate constant k_n . For several pH values plots of $k_{obsd}/(H_t)^2$ (i.e., k_3') vs. a_H/K'_H provide a linear relationship of slope k_{ga} and intercept k_{gb} . The Arrhenius activation parameters, Table I, have been obtained for k_{ga} and k_{gb}

TABLE I
ACTIVATION PARAMETERS FOR THE HYDRAZINOLYSIS AND MORPHOLINOLYSIS OF δ -THIOLVALEROLACTONE^a (25°)

	$-k_{ga}$, kcal. mole ⁻¹	$T\Delta S^*$	$-k_{gb}$, kcal. mole ⁻¹	$T\Delta S^*$
	ΔH^*		ΔH^*	
Hydrazine	0.6	-15.1	-0.4	-15.8
Morpholine	5.3	-15.2	3.7	-16.1

^a The values of E_a were determined from plots of $\log k_{rate}$ vs. $1/T$; $\Delta H^* = E_a - RT$; $\Delta F^* = RT 2.303 \log (KT/k_{rate}h)$; $-T\Delta S^* = \Delta F^* - \Delta H^*$. The standard state used was mole l.⁻¹ and time in sec. Frost and Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 95–97.

by plotting the logarithm of the rate constants as a function of the reciprocal of the absolute temperature (Fig. 1). The unreliability of the second-order rate constant, k_n , made determination of activation parameters for this constant unrealistic. The value for k_n , determined at 30° as an average of eight values, is 9 ± 1 l. mole⁻¹ min.⁻¹ and may be compared with the value for $k_{ga} = 1380$ l.² mole⁻² min.⁻¹, and the value for $k_{gb} = 2000$ l.² mole⁻² min.⁻¹, given in Table II. The deuterium solvent isotope effect, determined at 17°, is 1.73 for the general-base term and 2.12 for the general-acid term (Table II). An isotope effect was obtained for the nucleophilic term, but no significance is attributed to the effect owing to the unreliability of k_n .

The morpholinolysis of δ -thiolvalerolactone in water, examined in the temperature range 5–44.5°, was found to proceed by general-acid-catalyzed and general-base-catalyzed assistance to nucleophilic attack at all temperatures studied.³ At constant pH the disappearance of thiolactone is given by eq. 2. At constant pH, plots of k_{obsd} vs. $(M_t)^2$ are linear with slope k_3' and inter-

$$-d(\text{lactone})/dt = k_{obsd}(\text{lactone}) = [k_{ga}(M_t)(M_p) + k_{gb}(M_t)^2 + k_{hydr}] \times (\text{lactone}) \quad (2)$$

cept k_{hydr} , the apparent hydrolytic constant. For several pH values, plots of k_3' vs. a_H/K'_M provide a linear relationship of slope k_{ga} and intercept k_{gb} . Morpholine is a less effective nucleophile than is hydrazine ethanolamine, morpholine, and hydrazine (second pK'_a), respectively; $-dE/dt = k_{obsd}(E)$; E = concentration of ester or lactone; k_3' = apparent third-order rate constant; k_n = the second-order rate constant for the reaction of ester with nucleophile; k_{ga} and k_{mga} = the third-order rate constant for the general-acid-catalyzed reaction of ester with nucleophile; k_{gb} and k_{mgb} = third-order rate constant for the general-base-catalyzed reaction of ester with nucleophile; k_{hydr} = apparent rate for hydrolysis at any constant acidity.

TABLE II
THE KINETIC EXPRESSIONS AND ASSOCIATED RATE CONSTANTS DETERMINED FOR THE REACTION OF A SERIES OF BASES WITH THIOACTONES AND THIOLESTERS; SOLVENT WATER, TEMPERATURE 30°, IONIC STRENGTH 1.0 M (WITH KCl)

Base	Reaction kinetics ^b	Rate constants ^a	pH range employed	No. of pH values at which k_{obsd} was detd. ^d	No. of k_{obsd} values detd.	Concn. range for base, M	$k_{\text{H}}/k_{\text{D}}$
δ -Thiolvalerolactone							
1	$\text{H}_2\text{NNH}_2^{\text{c},\text{f}}$	$k(\text{BH}^{\oplus})(\text{B})(\text{L})$ $k(\text{B})^2(\text{L})$	1.38×10^3 2.00×10^3	7.03–9.07	8	25	0.005–0.04 2.12/17° 1.73/17° >2/17°
2	Morpholine ^g	$k(\text{B})(\text{L})$ $k(\text{B})(\text{BH}^{\oplus})(\text{L})$ $k(\text{B})^2(\text{L})$	9.0 ± 1 6.0×10^{-1} 10.0×10^{-1}	8.09–8.59	3	12	0.2–1.0 4.4/13° 4.0/13°
3	Hydrazine (B)–imidazole (B') ^e	$k(\text{B})(\text{B}')(\text{L})$ $k(\text{B})(\text{B}'\text{H}^{\oplus})(\text{L})$	620 1980	6.7–8.2	7	28	0.01–0.05(B) .16–.80(B')
4	Hydrazine (B)–ethanolamine (B') ^e	$k(\text{B})(\text{B}')(\text{L})$	3950 ± 200	8.78–9.60	8	32	.008–0.012(B) .04–0.36(B')
γ -Thiolbutyrolactone							
5	Hydrazine	$k(\text{B})^2(\text{L})$ $k(\text{B})(\text{BH}^{\oplus})(\text{L})$	60 60	7.52–8.94	6	25	.06–0.34 1.62/30° 2.25/30°
6	Morpholine	$k(\text{B})^2(\text{L})$ $k(\text{B})(\text{BH}^{\oplus})(\text{L})$	0.100 0.068	8.23–8.73	3	11	.28–0.68
<i>n</i> -Butyl thiolacetate							
7	Hydrazine	$k(\text{B})(\text{E})$ $k(\text{B})^2(\text{E})$ $k(\text{B})(\text{BH}^{\oplus})(\text{E})$	0.13 25.5 14.0	7.62–8.48	3	12	.02–0.30 1.27/30° 1.66/30° 2.12/30°
8	Hydrazine (B)–imidazole (B') ^e	$k(\text{B})(\text{B}')(\text{E})$ $k(\text{B})(\text{B}'\text{H}^{\oplus})(\text{E})$	17.2 48.0	7.59–8.44	3	12	.04–0.18(B) .16–0.20(B')
Isopropyl thiolacetate							
9	Hydrazine	$k(\text{B})(\text{E})$ $k(\text{B})^2(\text{E})$ $k(\text{B})(\text{BH}^{\oplus})(\text{E})$	0.14 14.6 9.1	7.57–8.53	3	12	.05–0.30
<i>t</i> -Butyl thiolacetate							
10	Hydrazine	$k(\text{B})(\text{E})$ $k(\text{B})^2(\text{E})$ $k(\text{B})(\text{BH}^{\oplus})(\text{E})$	0.10 2.05 1.88	7.57–8.53	3	12	0.1–0.5

^a Given in time units of minutes and concentration units of M. ^b The basic species are designated B and the conjugate acids, BH[⊕]. Lactone concentrations are designated L and thiolacetate, E. ^c Part of the data taken from ref. 3 of this paper. ^d k_{obsd} are the pseudo-first-order rate constants determined at constant acidity and under the conditions of (B + BH) \gg (ester or lactone). ^e Only mixed terms are indicated. ^f For the temperature dependence study, the concentration ranges for hydrazine at temperatures other than 30° were comparable to the range for 30°. A total of 30 pH values and 143 k_{obsd} values provided the information for the Arrhenius plot (Fig. 1). ^g For the temperature dependence study, the concentration ranges for morpholine at temperatures other than 30° were comparable to the range for 30°. A total of 15 pH values and 60 k_{obsd} values provided the information for the Arrhenius plot (Fig. 1).

toward the thiolester bond and at 30° the catalytic constants are approximately one two-thousandths for the morpholinolysis reaction than those for the corresponding hydrazinolysis reaction (Table II). The Arrhenius plot is illustrated in Fig. 1 and the activation parameters, evaluated for 25°, are given in Table I. The deuterium solvent isotope effect is 4.0 for the general-acid term and 4.4 for the general-base term (Table II).

The hydrazinolysis of δ -thiolbutyrolactone in water at 30° (pH 7.5–8.9) proceeded more slowly than that of the homologous δ -thiolvalerolactone, as anticipated. Simple nucleophilic attack of hydrazine at the thiolester bond could not be demonstrated. The disappearance of thiolactone is described by the rate expression 3.

$$-d(\text{lactone})/dt = k_{\text{obsd}}(\text{lactone}) = [k_{\text{ga}}(\text{H}_f)(\text{H}_p) + k_{\text{gb}}(\text{H}_f)^2](\text{lactone}) \quad (3)$$

At constant pH, plots of $k_{\text{obsd}}/(\text{H}_f)$ vs. (H_f) are linear with zero intercept and slope k_3' (Fig. 2). When k_3' is plotted as a function of $a_{\text{H}}/K_{\text{H}}'$ a linear relationship is obtained having as slope k_{ga} and as intercept k_{gb}

(Fig. 3). The third-order catalytic constants so obtained each have the value 60 l.² mole⁻² min.⁻² (Table II). The deuterium solvent isotope effects are 1.62 for k_{gb} and 2.25 for k_{ga} (Table II).

Morpholinolysis of γ -thiolbutyrolactone in water at 30° proceeded by general-acid-catalyzed and general-base-catalyzed assistance to nucleophilic attack. Thus the rate expression for thiolactone disappearance at constant pH is given by eq. 2. Plots of the apparent third-order rate constants, k_3' , vs. $a_{\text{H}}/K_{\text{M}}'$, are linear with slope k_{ga} and intercept k_{gb} (Fig. 3). The third-order catalytic constants are smaller by approximately a factor of ten than those for the morpholinolysis of δ -thiolvalerolactone (Table II).

The hydrazinolysis of *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate in water at 30° proceeded by nucleophilic attack as well as by general-acid- and general-base-catalyzed assistance to nucleophilic attack and the rate expression is given by (1). Plots of the apparent third-order rate constants vs. $a_{\text{H}}/K_{\text{H}}'$ are shown in Fig. 4. The values for the constants

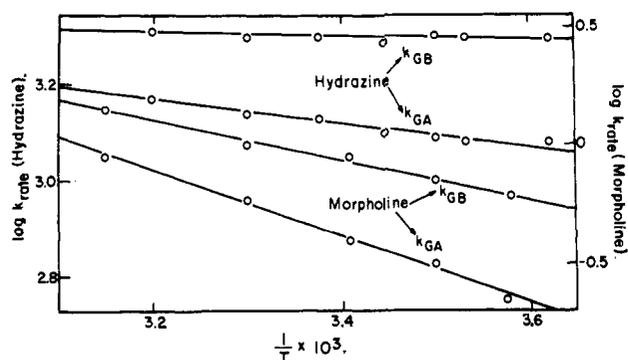


Fig. 1.—Arrhenius plot of the third-order catalytic constants, k_{ga} and k_{gb} , for the hydrazinolysis and morpholinolysis of δ -thiolvalerolactone.

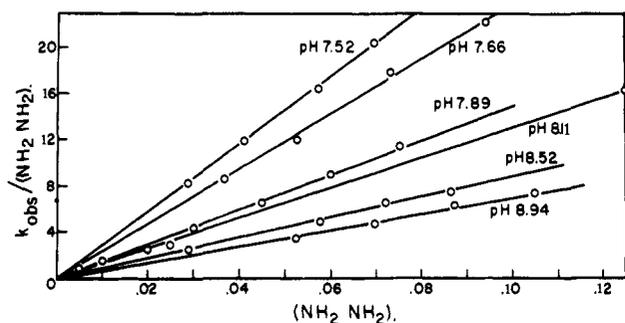


Fig. 2.—Plot of the dependence of the pseudo-first-order rate constants (min^{-1}) divided by the concentration (M) of free hydrazine base vs. the concentration (M) of free hydrazine for the hydrazinolysis of γ -thiolbutyrolactone at constant pH.

are given in Table II. The deuterium solvent isotope effects for n -butyl thiolacetate are: $k_n = 1.27$, $k_{gb} = 1.66$, $k_{ga} = 2.12$ (Table II).

During the course of this investigation it became necessary to obtain an approximate rate constant for the reaction of n -butyl thiolacetate with imidazole in water. The constant was evaluated at pH 7.7 and has the value of $0.04 \text{ l. mole}^{-1} \text{ min}^{-1}$ at 30° and is reported here as a value determined from the slope of a plot of k_{obsd} vs. (Im_t) at $0.5 M$ and $1.0 M$ total imidazole concentration. Bender and Turnquest¹² reported an approximate value for k_n for the reaction of ethyl thiolacetate with imidazole in water at pH 7.13 and 26.2° of $0.01 \text{ l. mole}^{-1} \text{ min}^{-1}$.

The reaction of δ -thiolvalerolactone with competing nucleophiles in aqueous solution was examined at 30° . The disappearance of lactone was followed in the presence of hydrazine and ethanolamine in the pH range 8.8–9.6. At constant pH the concentration of hydrazine was maintained at a constant value of approximately $0.01 M$ while the concentration of ethanolamine was varied from approximately 0.04 to $0.4 M$. It was assumed that the thiolactone underwent hydroxyethylaminolysis by nucleophilic attack and that it underwent hydrazinolysis by general-acid- and general-base-catalyzed assistance to nucleophilic attack as reported by Bruce, Bruno, and Chou.³ The disappearance of thiolactone at constant pH is kinetically described by eq. 4. Plots of $[k_{\text{obsd}} - (k_n(\text{EA}_t) + k_{\text{OH}}(\text{OH}^-))]/$

$$-d(\text{lactone})/dt = k_{\text{obsd}}(\text{lactone}) = [k_n(\text{H}_t) + k_{ga}(\text{H}_t)(\text{H}_p) + k_{gb}(\text{H}_t)^2 + k_n(\text{EA}_t) + k_{\text{OH}}(\text{OH}^-) + k_{\text{mgb}}(\text{H}_t)(\text{EA}_t)] \times (\text{lactone}) \quad (4)$$

(12) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1658 (1957).

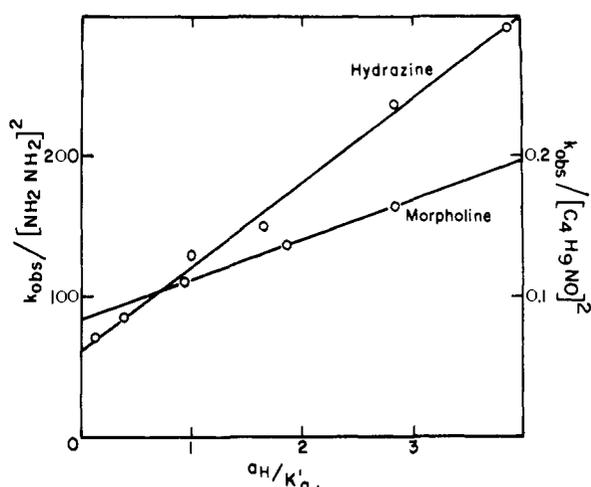


Fig. 3.—Plot of the apparent third-order rate constant ($\text{l.}^2 \text{ mole}^{-2} \text{ min}^{-1}$), as a function of a_{H}/K_a' , for the hydrazinolysis and morpholinolysis of γ -thiolbutyrolactone.

(H_t) vs. (EA_t) are linear at constant pH and have as intercept $[k_n(\text{for hydrazine}) + (\text{H}_t)(k_{ga} a_{\text{H}}/K_{\text{H}'} + k_{gb})]$ and as slope k_{mgb} , the mixed general-base catalytic constant. This constant was pH independent in the acidity range examined and has the value $3950 \pm 200 \text{ l.}^2 \text{ mole}^{-2} \text{ min}^{-1}$ evaluated from eight pH runs (Table II). Evaluation of the intercept data, after k_n (for hydrazine) was subtracted, proved meaningless since the hydrazine general-acid and general-base terms accounted for approximately 7% of k_{obsd} . Good pseudo-first-order kinetics were difficult to obtain at high pH values, in spite of precautions taken, owing to oxidation of the liberated thiol. In order to determine whether ethanolamine was capable of perturbing the pure hydrazine constants, the experiment was altered and thiolactone disappearance was followed in the pH range 7.2–8.5. The concentration of ethanolamine was maintained at a constant value in a given run, approximately 0.04 – $0.2 M$, while the concentration of hydrazine was varied from approximately 0.04 – $0.16 M$. At constant pH the rate expression 4 was assumed to be valid. Plots of $[k_{\text{obsd}} - (k_n(\text{EA}_t) + k_{\text{OH}}(\text{OH}^-))]/(\text{H}_t)$ vs. (H_t) are linear and have for slope $(k_{ga} a_{\text{H}}/K_{\text{H}'} + k_{gb})$ for hydrazine and for intercept $[k_n(\text{for hydrazine}) + k_{\text{mgb}}(\text{EA}_t)]$. For several pH values a plot of the apparent third-order rate constant for hydrazine as a function of $a_{\text{H}}/K_{\text{H}'}$ resulted in a linear relationship of slope k_{ga} for hydrazine and intercept k_{gb} for hydrazine. The values of the third-order rate constants so obtained are $1480 \text{ l.}^2 \text{ mole}^{-2} \text{ min}^{-1}$ for k_{ga} and $2000 \text{ l.}^2 \text{ mole}^{-2} \text{ min}^{-1}$ for k_{gb} . Thus the general-base catalytic constant remains unchanged from what it is at 30° in the absence of ethanolamine and the general-acid catalytic constant is increased approximately 8%. Again, the intercept data (less k_n for hydrazine) was not amenable to further treatment since it represented approximately 5% of the observed rate constant in the concentrations and the acidity range employed.

A similar study was conducted with δ -thiolvalerolactone in the presence of hydrazine and imidazole in aqueous solution in the pH range 6.7–8.2. At constant pH the concentration of hydrazine was maintained at approximately $0.01 M$ and the concentration of imidazole was varied from approximately 0.05 to $0.5 M$.

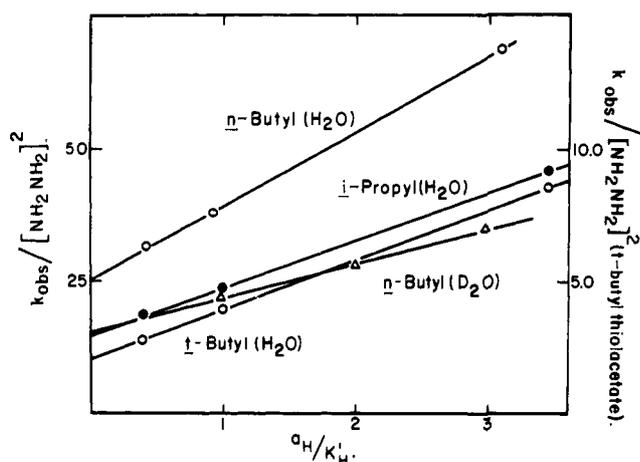


Fig. 4.—Plots of the apparent third-order constants ($l.^2 \text{ mole}^{-2} \text{ min.}^{-1}$) as a function of a_H/K_H' for the hydrazinolysis of *n*-butyl thiolacetate in water, O, and in deuterium oxide, Δ ; isopropyl thiolacetate in water, \bullet , and *t*-butyl thiolacetate in water, \circ .

The rate of ester disappearance is described by eq. 5.

$$-d(\text{lactone})/dt = k_{obsd}(\text{lactone}) = (K_n(\text{Im}_f) + k_n(\text{H}_f) + k_{ga}(\text{H}_f)(\text{H}_p) + k_{gb}(\text{H}_f)^2 + k_{mgb}(\text{H}_f)(\text{Im}_f) + k_{mga}(\text{H}_f)(\text{Im}_p))(\text{lactone}) \quad (5)$$

At constant pH plots of $[k_{obsd} - k_n(\text{Im}_f)]/(\text{H}_f)$ vs. (Im_f) are linear with slope $(k_{mga}a_H/K_{IM}' + k_{mgb})$ and with intercept $[k_n(\text{for hydrazine}) + (\text{H}_f)(k_{ga}a_H/K_2' + k_{gb})]$. For several pH values plots of the apparent third-order rate constants for the mixed terms $(k_{mga}a_H/K_{IM}' + k_{mgb})$ vs. a_H/K_{IM}' provide a linear relationship in which the intercept k_{mgb} is the mixed general-base catalytic constant and in which the slope is the mixed general-acid catalytic constant (Fig. 5). The constants have the values 620 and 1980 $l.^2 \text{ mole}^{-2} \text{ min.}^{-1}$, respectively, and are recorded in Table II. For convenience let the intercept $[k_n(\text{for hydrazine}) + (\text{H}_f)(k_{ga}a_H/K_H' + k_{gb})]$ equal k_I' . For several pH values plots of $[k_I' - k_n(\text{for hydrazine})]/(\text{H}_f)$ vs. a_H/K_H' are linear with slope k_{ga} for hydrazine and intercept k_{gb} for hydrazine. The general-base constant so obtained has a value of approximately 2000 $l.^2 \text{ mole}^{-2} \text{ min.}^{-1}$, its usual value at 30° , and the general-acid constant has a value of approximately 8400 $l.^2 \text{ mole}^{-2} \text{ min.}^{-1}$, about six times its usual value at 30° . The intercept data, k_I' , accounts for some 35% of the observed rate constant.

The reaction of *n*-butyl thiolacetate with the same hydrazine-imidazole mixed system was examined in water at 30° . At constant pH the concentration of imidazole was maintained at approximately 0.2 *M* while the concentration of hydrazine was varied from 0.02 to 0.18 *M* in the pH range 7.5–8.4. The disappearance of thiolester is kinetically described by 5 and at constant pH plots of $(k_{obsd} - k_n(\text{Im}_f))/(\text{H}_f)$ vs. (H_f) are linear and have as slope the apparent third-order rate constant $(k_{ga}a_H/K_H' + k_{gb})$ and as intercept $[k_n(\text{for hydrazine}) + k_{mga}(\text{Im}_p) + k_{mgb}(\text{Im}_f)]$. Plots of $(k_{ga}a_H/K_H' + k_{gb})$ vs. a_H/K_H' follow a linear relationship in which the intercept is the general-base constant for hydrazine and the slope is the general-acid constant for hydrazine. The values so obtained are within experimental error the same as the values determined for hydrazine in the absence of imidazole. For conve-

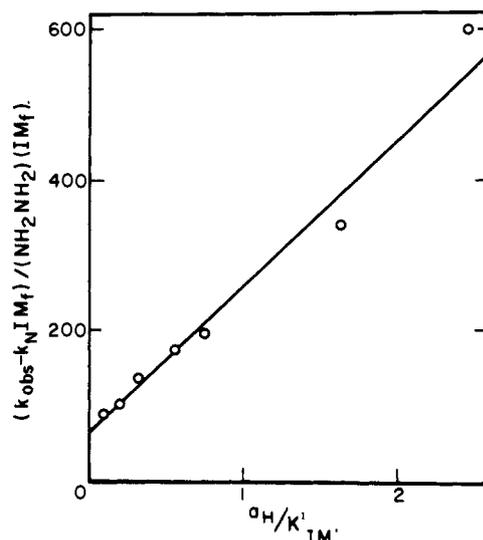


Fig. 5.—Plot of the mixed apparent third-order rate constants ($l.^2 \text{ mole}^{-2} \text{ min.}^{-1}$) as a function of a_H/K_{IM}' for the reaction of imidazole-hydrazine with δ -thiolvalerolactone.

nience let the intercept which contains the mixed general-acid and mixed general-base constants, $[k_n(\text{for hydrazine}) + k_{mga}(\text{Im}_p) + k_{mgb}(\text{Im}_f)]$, equals k_{II}' . Plots of $(k_{II}' - k_n(\text{for hydrazine})/(\text{Im}_f))$ vs. a_H/K_{IM}' are linear having as slope the mixed general-acid constant, and as intercept the mixed general-base constant, k_{mgb} . The values for the constants are given in Table II. Pseudo-first-order kinetics for this system were not too reliable, especially at high pH values. At the conclusion of a *pseudo*-first order reaction an infinity optical density value was obtained which proved to be stable for minutes only. The optical density then increased very slowly.

Discussion

Temperature Dependence of Reaction Rate.—Bruce, Bruno, and Chou³ reported the reaction of δ -thiolvalerolactone with hydrazine and with morpholine to proceed *via* general-acid and general-base catalyzed assistance to nucleophilic attack. Further, the rate constants at 30° are equal, or nearly so, demonstrating the equal susceptibility of the thiolester to both forms of catalytic attack. In order to determine if this phenomenon is general over a temperature range or if it applies only at the single temperature, 30° , we examined the dependence of reaction rate on temperature. Inspection of the Arrhenius plots for the hydrazinolysis and morpholinolysis of δ -thiolvalerolactone, Fig. 1, shows that only at the temperature where the plots intersect will k_{ga} be equal to k_{gb} , and for these systems, this temperature is considerably above 30° . However, the two constants are nearly equal at all temperatures studied.

The hydrazinolysis of δ -thiolvalerolactone proceeds much more rapidly than the morpholinolysis of the same thiolester. On the basis of a Brønsted plot, Bruce, Bruno, and Chou³ have shown that hydrazine is a more effective nucleophile in thiolester lysis *via* general-acid and general-base processes than morpholine by $10^{4.5}$. This was attributed to the α -effect¹³ exhibited by nucleophiles such as hydrazine which possess an unshared electron pair on the atom α to the nucleo-

(13) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16, 3233 (1962).

philic center. Comparison of the activation parameters (Table I) shows that the free energy of activation for the catalytic processes for the hydrazinolysis reaction is approximately 4.5 kcal. mole⁻¹ more favorable than for the corresponding processes in the morpholinolysis reaction. The portion of the hydrazinolysis reaction which proceeds through the termolecular terms is practically temperature independent over nearly 40° and essentially all of the free energy of activation resides in the entropy of activation terms.

The simple nucleophilic constant for hydrazinolysis of δ -thiolvalerolactone determined in this study is comparable to the rate constant for nucleophilic attack by the monoacid form of ethylenediamine determined by Bruce, Bruno, and Chou.³ Either the α -effect is not important in the nucleophilic term for hydrazine or ethylenediamine possesses enhanced nucleophilicity. In a recent study Bruce and Benkovic¹⁰ found the α -effect to be approximately ten times as important in the k_{gb} term as in the k_n term in the hydrazinolysis of phenyl acetate and *p*-cresol acetate. In the present study no deuterium kinetic solvent isotope effect was noted for the reaction of ethylenediamine monoacid form with δ -thiolvalerolactone.

Bruce and Benkovic¹⁰ have determined the activation parameters for eleven different nucleophilic reactions on phenyl ester bonds. Empirically it was shown that the product of kinetic order and the factor 4-6 kcal. mole⁻¹ gave the experimentally determined average $T\Delta S^*$. For the hydrazinolysis and morpholinolysis of δ -thiolvalerolactone the same general phenomenon applies and for the catalytically assisted displacement reactions a loss of approximately 5 kcal. mole⁻¹ in activation entropy attends the localization of ester with each reactant and catalytic species to form the transition state.

Sensitivity of Other Thioesters to Hydrazinolysis and Morpholinolysis.—The reactions of hydrazine and of morpholine with δ -thiolbutyrolactone were investigated to determine if another thiolactone would show the same approximate sensitivity to general-acid- and general-base-assisted nucleophilic attack. The hydrazinolysis reaction proceeded by general-acid- and general-base-catalyzed mechanisms at a rate slower than that for δ -thiolvalerolactone. Further, the rate constants have the same value, or nearly so (Table II), showing the thioester to be equally sensitive to both forms of catalysis with hydrazine at 30°. No nucleophilic term was detectable. The catalytic constants are approximately one-thirtieth the corresponding constants for δ -thiolvalerolactone. The reaction of γ -thiolbutyrolactone with morpholine as with δ -thiolvalerolactone exhibited only general-acid and general-base catalysis of nucleophilic attack. The rate constants are approximately one-tenth the constants for the thiolvalerolactone system (Table II) and k_{ga} is approximately two-thirds the value of k_{gb} as was also found for the morpholinolysis of δ -thiolvalerolactone. The *trans*-thiolacetates are less reactive toward hydrazine than the *cis*-thiolactones. Also the hydrazinolysis of *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate are subject to steric effects so that the order of reactivity of these thiolacetates is *n*-butyl > isopropyl > *t*-butyl. The effect of structure on rate is most noticeable in the catalytic terms and in fact the

nucleophilic terms appear to be insensitive to the nature of the alkyl moiety. This suggests that the effect of alkyl substituents on the rate of hydrazinolysis is largely steric rather than polar, since the transition states from the assisted reactions should be more bulky than for the unassisted reaction. An attempt to correlate the catalytic constants with Taft's steric substituent constants, E_s ,¹⁴ was unsuccessful. Thus plots of $\log k_{rate}$ vs. E_s exhibited upward curvature. Similar treatment of the rate constants for acid-catalyzed hydrolysis of thiolacetates, determined by Rylander and Tarbell⁸ at 30°, also resulted in a nonlinear steric energy relationship, the plots exhibiting upward curvature. It is anticipated that for the specific acid-catalyzed hydrolysis polar effects are of little importance and, therefore, that the Taft E_s constants do not apply to thioesters. It has been well established that the sensitivity of k_{gb} and k_{ga} to polar effects is much less than in the case of k_n (see tabulation of ρ constants in ref. 9). Since k_n exhibits the lessened sensitivity toward branching at the α -carbon of the leaving group in the thioesters investigated, we may conclude that the effect on k_{ga} and k_{gb} is almost entirely steric.

In seven nucleophilic displacement reactions at the thioester bond, the ratio of the general-base to the general-acid catalytic constant varied from 1 to 1.8 with a mean value of 1.5. Thus it appears general for the reactions investigated that the catalytic constants k_{ga} and k_{gb} are equal or nearly equal, suggesting the same sensitivity of both terms to steric and polar effects.

Deuterium Solvent Isotope Effects.—The most significant deuterium solvent isotope effects obtained in this study (Table II) were found for the morpholinolysis of δ -thiolvalerolactone. The k_H/k_D of 4.4 and 4.0 for the general-base and general-acid reactions, respectively, supports mechanisms involving proton transfer in the rate-limiting step. The isotope effect for the general-acid constants in the hydrazinolysis reactions of thioesters is also clear and again is suggestive of proton transfer in the rate-limiting step in these reactions. Isotope effects of approximately 1.7 were obtained for the general-base catalytic constants for the hydrazinolysis of δ -thiolvalerolactone, γ -thiolbutyrolactone, and *n*-butyl thiolacetate and, while a deuterium solvent isotope effect of this magnitude is not convincing evidence of proton abstraction in a rate-limiting step¹⁵ it is strongly suggestive. Generally, deuterium solvent isotope effects for general-base-catalyzed aminolysis reactions are small, notable exception being the general-base-catalyzed reaction of imidazole with *p*-cresol acetate ($k_H/k_D = 2.2$)¹⁰ and the hydroxylaminolysis of phenyl acetate ($k_H/k_D = 2.2$).¹⁶

Competitive Catalysis.—The hydrazinolysis of δ -thiolvalerolactone in the presence of imidazole, kinetically described by (5), proceeds in part through a mixed general-acid and a mixed general-base term involving both hydrazine and imidazole: $k_{mga}(H_f)(Im_p)$ and $k_{mgb}(H_f)(Im_f)$. The relative magnitudes of the mixed constants are reversed from what the constants are for the hydrazine general-acid and general-base terms (*i.e.*, $k_{ga}(H_f)(H_p)$ and $k_{gb}(H_f)^2$ (Table II)). The reversal in magnitude of the mixed catalytic terms is explicable

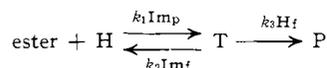
(14) R. W. Taft, Jr., and M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., Chapter 13.

(15) F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

(16) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960).

on the basis of the nucleophilicity and pK_a' of the bases used. As a nucleophilic pair imidazole-hydrazine is less effective than hydrazine-hydrazine. This is anticipated since imidazole (pK_{Im}' 7.14) should be a less effective Brønsted base than hydrazine (pK_H' 8.11) in the general-base-catalyzed assistance to nucleophilic attack by hydrazine. Conversely, imidazolium ion is a better proton donor and is more effective in assisting the nucleophilic attack of hydrazine on the thiolester bond than is hydrazinium ion. Thus, it is anticipated that k_{mga} would be greater than k_{mgb} and further that k_{mga} would be greater than k_{ga} and that k_{gb} would be greater than k_{mgb} . It is assumed that hydrazine, by virtue of its greater nucleophilicity (pK_a' and α -effect), is the attacking reagent at the thiol-ester bond.

It was hoped that kinetic evidence for the existence of an intermediate might be obtained by application of the concept of competitive catalysis. The principle can be illustrated with one of several possible kinetic schemes. Assume the attack of hydrazine on the thiolester to occur by the scheme below and further assume steady state in T.



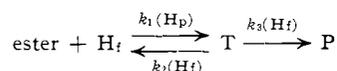
$$dP/dt = k_3(\text{H}_f)(\text{T}) = \frac{k_1k_3(\text{H}_f)^2(\text{Im}_p)(\text{ester})}{k_3(\text{H}_f) + k_2(\text{Im}_f)} \quad (6)$$

assume $k_2(\text{Im}_f) \gg k_3(\text{H}_f)$

$$dP/dt = K_H' \frac{k_1k_3(\text{H}_f)(\text{H}_p)(\text{ester})}{k_2K_{Im}'}$$

where $k_{ga} = K_H' k_1 k_3 / k_2 K_{Im}'$.

For the reaction of hydrazine with the thiolactone one could also write



$$dP/dt = \frac{k_1k_3}{k_2 + k_3} (\text{H}_f)(\text{H}_p)(\text{ester}) \quad (7)$$

where $k_{ga} = k_1k_3/(k_2 + k_3)$.

Kinetically both (6) and (7) are identical; however, if it can be established that k_{ga} for hydrazine has a very different value, in the presence and absence of a weakly nucleophilic base as imidazole, then the conclusion is that the values of k_1 , k_2 , and k_3 are actually different for the two systems and that in fact k_1 , k_2 , and k_3 actually exist and, hence, T exists.

Appropriate treatment of the data for the hydrazinolysis of δ -thiolvalerolactone (*cf.* Results), representative of approximately 35% of the observed rate of reaction, yields general-acid and general-base catalytic constants which are not too accurately determinable. However, the general-acid catalytic constant for hydrazine is greater, by a factor of six, in the presence of imidazole than it is in the absence of imidazole. The error involved in the treatment of the rate data as well as the assumption that the nucleophilic constant for hydrazine attack at the thiolester bond is unperturbed by imidazole require that the alteration in the value of the general-acid constant not be taken as definitive evidence for the existence of an intermediate in thiolester lysis.

Complications in the above system, namely the possibility of internal return of the thiol moiety, suggested that *n*-butyl thiolacetate would be a more acceptable model to study in competitive catalysis. Accordingly, this thiolester was examined with the same nucleophilic pair under conditions wherein the concentration of imidazole was held constant and the concentration of hydrazine was varied at constant pH. The kinetics for the system are described by 5 and, as with δ -thiolvalerolactone, *n*-butyl thiolacetate is sensitive to the same mixed catalytic assistance to nucleophilic attack. The sensitivity of the thiolactone to mixed catalysis is approximately forty times greater than that of the *trans*-ester (Table II). The pure hydrazine general-acid and general-base constants for this system were within experimental error of the constants obtained in noncompetitive experiments and no evidence for intermediate formation was obtained.

The kinetics of the reaction of δ -thiolvalerolactone with hydrazine and ethanolamine is described kinetically by (4). No mixed general-acid term was detectable and this is reasonable on the strength of the ability of hydrazine to act more effectively as a proton donor (pK_a' 8.11) and as a nucleophile (α -effect) toward the thiolester bond than ethanolamine. In concert, hydrazine-ethanolamine are a more effective general-base pair than hydrazine-hydrazine (pK_a' and α -effect). No significant alteration in the values of hydrazine general-acid and general-base constants were observed.

Investigation of nucleophilic displacement reactions at the thiolester bond are being continued.

Acknowledgment.—We should like to thank Mrs. Patricia Benkovic for assistance in the determination of the pseudo-first-order rate constants. This work was supported by a grant from The National Science Foundation.