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Nucleophilic Displacement Reactions at the Thiolester Bond. III.[1] Kinetic Demonstration of Metastable Intermediates in the Hydroxylaminolysis and Methoxylaminolysis of Thiolesters and Thiolactones in Aqueous Solutions

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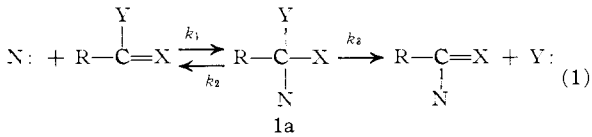
The hydroxylaminolysis and methoxylaminolysis of δ-thiolvalerolactone, γ-thiolbutyrolactone, *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate have been examined in aqueous solution. The reactions do not go through the formation of oximinothiolacetates as shown for the *n*-butyl ester. With the exception of the hydroxylaminolysis of *n*-butyl thiolacetate all of the reactions investigated are kinetically described by the expression $v = k_2'(B)(ester) + k_3'(B)^2(ester)$. For the hydroxylaminolysis of *n*-butyl thiolacetate the terms k_2' could not be detected. Both the apparent second-order rate constants, k_2', and the apparent third-order rate constants, k_3', are functions of acidity. The k_3' constants pertain to termolecular general catalyzed processes as shown by the determined values of $T\Delta S^*$, $k_3'^H/k_3'^D$, and the ratio of $k_3'(a_H = 0)/k_3'(a_H = \infty)$. The kinetics of ester disappearance (and product appearance in the case of the *n*-butyl ester) are explicable on the basis of the formation of tetrahedral intermediates along parallel reaction paths, said intermediates being in acid–base equilibria. The requirements for the acid–base "cross-over" between parallel reactions have been provided and on the basis of these requirements it has been shown that the mechanisms are symmetrical (general catalysis is required in both the formation of tetrahedral intermediates and their partitioning). The rates of hydroxylaminolysis of the alkyl thiolacetates are a function of the nature of the leaving group so that the order of reactivity of these thiolacetates is *n*-butyl > isopropyl > *t*-butyl.

Introduction

Nucleophilic displacement reactions on compounds of general structure R—C(Y)=X have commonly been assumed to proceed *via* the intermediate formation of metastable tetrahedral intermediates 1a. How-



(1)

1a

ever, few examples are available in the literature which provide evidence of the existence of intermediates of type 1a. The classical examples are found in the specific acid and specific base catalyzed hydrolysis of esters and amides as studied by Bender and co-workers.[4] In these studies it was established that exchange reactions occurred between H_2O^{18} and the ester or amide carbonyl oxygen. However, no evidence has been forthcoming establishing such intermediates to exist in aqueous solution when nucleophilic agents other than the lyate species are employed. Bender[5] demonstrated spectroscopically the existence of stable salts in the addition of sodium methoxide and ethoxide to ethyl trifluoroacetate in di-*n*-butyl ether. Evidence exists for the formation of tetrahedral intermediates in a number of reactions involving nucleophilic attack at aromatic sp^2-hybridized carbon.[6,7] Hand and Jencks[8] observed maxima in the pH-rate profiles in the reaction of imido esters with amines to yield amidines. They interpreted their kinetic data to establish that nucleophilic attack to yield a tetrahedral intermediate was rate limiting on the alkaline side of the maxima while conversion of tetrahedral intermediate to product is rate limiting on the acid side of the maxima of the pH-rate profiles. Product isolation on both sides of the pH maxima substantiated the conclusions drawn from their rate studies. Martin and co-workers,[9,10] examining the kinetics of hydrolysis of 2-methyl-Δ^2-thiazoline, based the interpretation of their results on the formation of a tetrahedral precursor, 2-hydroxy-2-methylthiazoline, of the hydrolysis product. Hydroxylamine, semicarbazide, and amines in general rapidly react with aldehydes and ketones at neutral pH to form carbinolamines which undergo rate-limiting dehydration to products.[11–13] Cordes and Jencks[14] have shown imine formation to undergo a transition in rate-determining step from rate-limiting dehydration of carbinolamine at neutral pH to rate-limiting amine attack at acid pH.

We report herein the kinetic results of a study of the reaction of hydroxylamine and methoxylamine with alkylthiolacetates, δ-thiolvalerolactone, and γ-thiolbutyrolactone which we believe establish the first instances of tetrahedral intermediates in displacement reactions on a thiolester bond and the only cases for tetrahedral intermediates in nucleophilic displacement reactions on ester bonds when the nucleophile is other than a water lyate species.[15]

Experimental

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 Radiometer Model PHA 630 Pa scale expander. The combined glass–calomel electrode (Radiometer G.K. 2012 C) and electrode cell compartment were thermostated at the reaction temperature, ±0.1°. Mixing of ester with nucleophile solution was accomplished with a 2-ml. glass hypodermic syringe which was fitted with a polyethylene "needle."

(1) For Parts I and II 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).

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(3) Postdoctoral Fellow of the Department of Chemistry, Cornell University.

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

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

(6) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958).

(7) S. D. Ross, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

(8) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 3505 (1962).

(9) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961).

(10) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *ibid.*, **81**, 5089 (1959).

(11) A. V. Willi, *Helv. Chim. Acta*, **39**, 1193 (1956).

(12) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).

(13) T. C. French and T. C. Bruice, *Biochemistry*, **3**, 1589 (1964).

(14) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).

(15) A portion of the study appeared as Communications to the Editor; T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 738, 739 (1964).

The syringe was thermostated in a brass holder maintained at the temperature of the reaction mixture.

Compounds.—γ-Thiolbutyrolactone, δ-thiolvalerolactone, *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate were prepared for a previous study and stored at 0–5° until used.[3b] Hydroxylamine hydrochloride (Baker and Adamson Reagent) was crystallized from aqueous ethanol, dried, and stored over P_2O_5 in a desiccator. Methoxylamine (Eastman Kodak Co., White Label) was dried and stored over P_2O_5. The ability to obtain experimentally the calculated pH values within 0.02 pH unit served as a check for the purity of these salts. Acetohydroxamic acid, m.p. 90–91°, was prepared by the Wise[16] modification of Blatt's method. O-Acetylhydroxylamine hydrochloride, m.p. 98°, lit. 108°, was prepared from ethyl N-hydroxyacetimidate, b.p. 26–27° (0.6 mm.), lit. 60° (13 mm.),[17] and ethyl N-acetoxyacetimidate, b.p. 55° (2.5 mm.), $n^{23.5}$D 1.4316, lit. 86° (16 mm.), n^{20}D 1.4332,[18] by the method of Zinner. The hydrochloride salt is unstable and gradually decomposes with evolution of hydrogen chloride. Potassium chloride, ferric chloride, potassium hydroxide, and potassium acid phthalate were analytical reagent grade chemicals (Mallinckrodt Chemical Works). *n*-Butyl oximinothiolacetate was prepared in low yield from acetonitrile and *n*-butyl mercaptan by Houben's and Zivadinovich's[19] procedure for the preparation of *n*-butyl oximinothiolformate. The compound is a white, crystalline solid, m.p. 53°, practically insoluble in water and soluble in ether and ligroin. In 1 *M* KCl solution the oximinoester has a λ_{max} of 231 mμ and a molar extinction of 7850. The infrared spectrum (KCl) shows strong absorption at 3.02 and 6.22 μ, consistent with OH and C=N frequencies. *Anal.* Calcd. for $C_6H_{13}NOS$: C, 48.94; H, 8.90; N, 9.51. Found: C, 48.71; H, 8.92; N, 9.35.

Kinetics.—The following wave lengths were used to observe the decrease in thiolester absorbance: γ-thiolbutyrolactone, 237 mμ; δ-thiolvalerolactone, 239.5 mμ; *n*-butyl thiolacetate, 235 mμ; isopropyl thiolacetate, 235 mμ; *t*-butyl thiolacetate, 233 mμ.

The following procedure was used to add the thiolester to the hydroxylamine solution. One drop of thiolester in ether was introduced down the barrel of a 2-ml. glass hypodermic syringe which was thermostated at the reaction temperature, usually 30 ± 0.1°. Hydroxylamine solution was withdrawn from a thermostated cuvette into the syringe and expelled into the cuvette. The process was repeated several times until mixing was judged to be complete. The reaction mixture was allowed to stand for temperature re-equilibration and the decrease in thiolester absorbance was recorded with time. The concentration of thiolester so obtained was *ca.* 2×10^{-4} *M*.

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 unit on serial dilution. All solutions were brought to a calculated ionic strength of 1 *M* with potassium chloride. Deaerated water was used to prepare solutions. The cuvettes were filled to the stopper level with solution and the solution was degassed with nitrogen prior to each run. A solution in the reference cell identical with the reaction solution (minus ester) was used to compensate for absorbance attributed to reactants. The concentration of nucleophile was always in excess of the concentration of ester, so pseudo-first-order kinetics were obtained. Reaction rates were followed to at least three half-lives (Fig. 1) and linear plots were generally obtained to a minimum three half-lives with the single exception of the reaction of δ-thiolvalerolactone with hydroxylamine which gave poor pseudo-first-order kinetics. The pH 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. Pseudo-first-order rate constants were calculated from the slopes of plots of log $O.D._0/O.D._t$, (corrected for the end absorbance of liberated mercaptan) *vs.* time.

The reaction of O-acetylhydroxylamine hydrochloride with hydroxylamine as well as the formation of acetohydroxamic acid from *n*-butyl thiolacetate and hydroxylamine were followed by a modification of Lipmann's and Tuttle's procedure.[20] Each study of the rate of disappearance of *n*-butyl thiolacetate with hydroxylamine, the rate of appearance of acetohydroxamic acid from *n*-butyl thiolacetate and hydroxylamine, and the rate of appearance of acetohydroxamic acid from O-acetylhydroxylamine hydrochloride and hydroxylamine was performed on the same solution to obviate concentration and pH changes. For the latter two reactions the appearance of hydroxamic acid was followed by withdrawing 1-ml. aliquots of the thermostatted reaction mixtures (ester and hydroxylamine) which were pipetted into 1 ml. of 5% ferric chloride–3 *N* hydrochloric acid solution (1:1) contained in 2-ml. cuvettes and determining the hydroxamic acid–ferric ion complex spectrophotometrically at 540 mμ. The reference cells contained the same reagents as the reaction solution (minus ester) to compensate for absorbance of reagents. Pseudo-first-order conditions were maintained and pseudo-first-order rate constants were calculated from slopes of plots of log $O.D._\infty/(O.D._\infty - O.D._t)$ *vs.* time. The spontaneous rate of hydrolysis of O-acetylhydroxylamine hydrochloride at pH 5.4 and pH 7.5, examined with a Radiometer Type TTT 1a titrator at 30°, was found to be negligible compared with its rate of hydroxylaminolysis. Measurable hydrolytic rates of O-acetylhydroxylamine hydrochloride were observed at 68°.

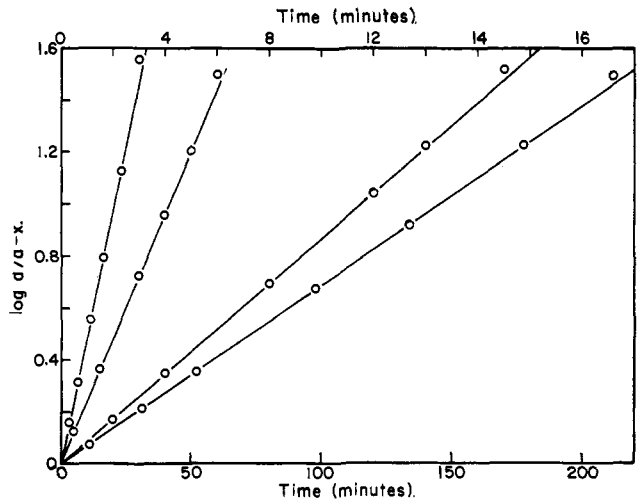


Fig. 1.—Pseudo-first-order rate plots for the hydroxylaminolysis of *n*-butyl thiolacetate at pH 6.03.

The possibility of reaction of *n*-butyl mercaptan with acetohydroxamic acid and with O-acetylhydroxylamine to form *n*-butyl thiolacetate was examined in the following manner. Into 2-ml. cuvettes containing 0.5 *M* (total) hydroxylamine solution (μ = 1 *M* with KCl) at pH 5.42 and *n*-butyl mercaptan of approximately 10^{-4} *M* concentration was added, in separate experiments, sufficient O-acetylhydroxylamine hydrochloride or acetohydroxamic acid to make resultant solutions approximately 10^{-4} *M*. No increase in optical density, measured at 235 mμ, with time was observed. Each experiment was repeated at pH 7.06 with 0.2 *M* (total) hydroxylamine solution (μ = 1 *M* with KCl) and again no increase in optical density with time was observed. Thus, neither O-acetylhydroxylamine nor acetohydroxamic acid undergoes any measurable reaction with *n*-butyl mercaptan under conditions employed in the hydroxylaminolysis of *n*-butyl thiolacetate.

The attempted reaction of *n*-butyl oximinothiolacetate with hydroxylamine was performed at pH 7.03 and 5.40 at 0.2 *M* (total) hydroxylamine concentration. At pH 7.03 an optical density change of 0.005 unit in 24 hr. indicated no reaction of hydroxylamine with the oximinothiolacetate. At pH 5.40 no change in optical density in 1 hr. similarly indicated no reaction of hydroxylamine with the oximinothiolacetate. Further, at 10^{-3} *M* concentrations of *n*-butyl oximinothiolacetate no ferric hydroxamate color could be developed. These results indicate that *n*-butyl oximinothiolacetate is neither an intermediate nor a product in the hydroxylaminolysis of *n*-butyl thiolacetate. The latter conclusion is supported by the fact that at pH 7.03 and 5.4 the conversion of *n*-butyl thiolacetate to acetohydroxamic acid is 100 ± 3% as determined from standard acetohydroxamic acid curves obtained under the conditions of the hydroxylaminolysis reactions.

The hydroxylaminolysis of *n*-butyl thiolacetate at pH 5.42 and at pH 7.05 was performed in aqueous solution at a calculated ionic strength of 0.5 *M* with potassium chloride. The apparent third-order rate constants obtained from plots of k_{obsd} *vs.* $(NH_2OH)^2$ were within 1.6 and 7.5%, respectively, of those constants

(16) W. M. Wise and W. W. Brandt, *J. Am. Chem. Soc.*, **77**, 1058 (1955).
(17) J. Houben and E. Schmidt, *Ber.*, **46**, 3616 (1913).
(18) G. Zinner, *Arch. Pharm.*, **293**, 657 (1960).
(19) J. Houben and R. Zivadinovich, *Ber.*, **69**, 2352 (1936).
(20) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

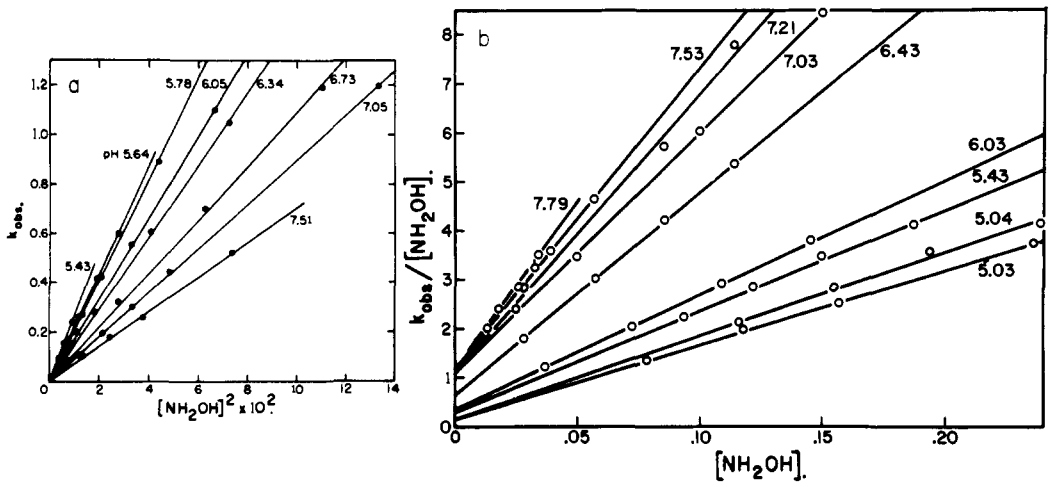


Fig. 2.—(a) Plot of the pseudo-first-order rate constants (min.$^{-1}$) *vs.* the square of the concentration (M) of free hydroxylamine base for the hydroxylaminolysis of *n*-butyl thiolacetate. (b) Plot of the pseudo-first-order rate constants divided by the concentration of free hydroxylamine base *vs.* the concentration of free hydroxylamine base for the hydroxylaminolysis of γ-thiolbutyrolactone. NOTE ADDED IN PROOF.—In Fig. 2b the assignment of pH values has been reversed. pH should decrease with increasing slope as in Fig. 2a.

calculated from reactions examined in aqueous solution at a calculated ionic strength of 1 M with potassium chloride.

The heat of ionization of hydroxylammonium chloride, calculated to be 16.6 kcal. mole^{-1}, was determined from the slope of a plot of log K_a' *vs.* $1/T$. The pK_a' values determined by the method of half-neutralization are: 5.70 at 44.7°, 6.03 at 30°; lit.[21] 6.04, 6.32 at 15°. The pK_a' of methoxylamine was taken to be 4.81.[3a]

The hydroxylaminolysis of *n*-butyl thiolacetate in D_2O was examined at pH 6.08 and 7.93. pD was determined from the pH-meter reading by the correction of Fife and Bruice[22]; the pK_D for hydroxylamine, determined by the method of half-neutralization, was found to be 6.46 (μ = 1.0 with KCl; lit.[3a] 6.49). Deuterium oxide was supplied by the Atomic Energy Commission through Cornell University Stores.

Results[23]

***n*-Butyl Thiolacetate.**—The pseudo-first-order rate constants (k_{obsd}) for the disappearance of *n*-butyl thiolacetate at any constant pH are linearly dependent upon the second power of the hydroxylamine concentration (Fig. 2). At all acidities investigated no measurable rate of ester disappearance was observed in the absence of hydroxylamine.[24] The hydroxylaminolysis reaction, therefore, requires 1 mole of free hydroxylamine base as reactant plus a second mole of either the free base or its conjugate acid as catalyst. At any constant pH where $N_T = {}^+NH_3OH + NH_2OH$

$$-\mathrm{d(ester)}/\mathrm{d}t = k_3'(\mathrm{ester})(NH_2OH)(N_T) \quad (2)$$
$$k_3' = k_{obsd}/(NH_2OH)(N_T)$$

A plot of $k_{obsd}/(NH_2OH)^2$ *vs.* a_H/K_a' is provided in Fig. 3a. In Fig. 3a, when $a_H/K_a' = 0$ then $({}^+NH_3OH) = 0$ and the limiting rate constant for the general base catalyzed hydroxylaminolysis reaction (k_{gb}) is provided by the intercept on the $k_{obsd}/(NH_2OH)^2$ axis. As the

$$-\mathrm{d(ester)}/\mathrm{d}t = k_{gb}(NH_2OH)^2(\mathrm{ester}) \quad (3)$$

value of a_H/K_a' increases from 0 the value of $k_{obsd}/(NH_2OH)^2$ does not increase in a linear fashion as anticipated for a reaction undergoing simultaneous general base and general acid catalysis (*i.e.*, eq. 4; see

$$-\mathrm{d(ester)}/\mathrm{d}t = (k_{gb} + k_{ga}a_H/K_a')(NH_2OH)^2(\mathrm{ester}) \quad (4)$$

dashed line in Fig. 3a). Instead, as the values of a_H/K_a' increase from 0, the value of $k_{obsd}/(NH_2OH)^2$ first increases rapidly and then slowly, becoming a linear function of the acidity only at the higher acid concentrations. Clearly, as the acidity increases the rate changes from one strongly dependent on acidity to one which is less dependent. The points on the plot of Fig. 3a are experimental and the curve theoretical, being derived from eq. 5.

$$\frac{k_{obsd}}{(NH_2OH)^2} = \frac{2.77 \times 10^{-6} + 22.4a_H + (1.35 \times 10^6)a_H^2}{4.8 \times 10^{-7} + a_H} \quad (5)$$
$$= (k_I + a_Hk_{II} + a_H^2k_{III})/(k_{IV} + a_H) \quad (5a)$$

It is generally recognized[21,25,26] that hydroxylamine may act as either an oxygen or a nitrogen nucleophile to yield as the initial product, from acyl derivatives, either hydroxamic acids or O-acylhydroxylamines. As a means of determining if the nature of the plot of

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

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

(23) Abbreviations used in this study are: N_T = total hydroxylamine concentration; (NH_2OH) = concentration of hydroxylamine as free base; ($^+NH_3OH$) = concentration of hydroxylamonium ion; (CH_3ONH_2) = concentration of free methoxylamine; ($CH_3ON^+H_3$) = concentration of methoxylamonium ion; ($RONH_2$) = concentration of free methoxylamine or hydroxylamine; ($RONH_3^+$) = concentration of methoxylamonium ion or hydroxylamonium ion; a_H = hydrogen ion activity as determined by the glass electrode; K_a' = apparent dissociation constant for hydroxylamine or methoxylamine determined by the method of half-neutralization; $-dE/dt = k_{obsd}(\mathrm{ester})$; k_{obsd} = the pseudo-first-order rate constant given in units of min.$^{-1}$; k_2' = the apparent second-order rate constant; k_n = the second-order rate constant for the reaction of ester with nucleophile; k_3' = the apparent third-order rate constant; k_{ga} = the third-order rate constant for the general acid catalyzed reaction of ester with nucleophile; k_{gb} = the third-order rate constant for the general base catalyzed reaction of ester with nucleophile; concentration terms are given in units of moles l.$^{-1}$.

(24) The second-order rate constant for the acid-catalyzed hydrolysis of a series of alkyl thiolacetates is *ca.* 0.5×10^{-3} l. mole^{-1} min.$^{-1}$; P. N. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3021 (1950).

(25) A. W. Scott and B. L. Wood, *J. Org. Chem.*, **7**, 508 (1942).

(26) W. P. Jencks, *J. Am. Chem. Soc.*, **80**, 4581, 5485 (1958).

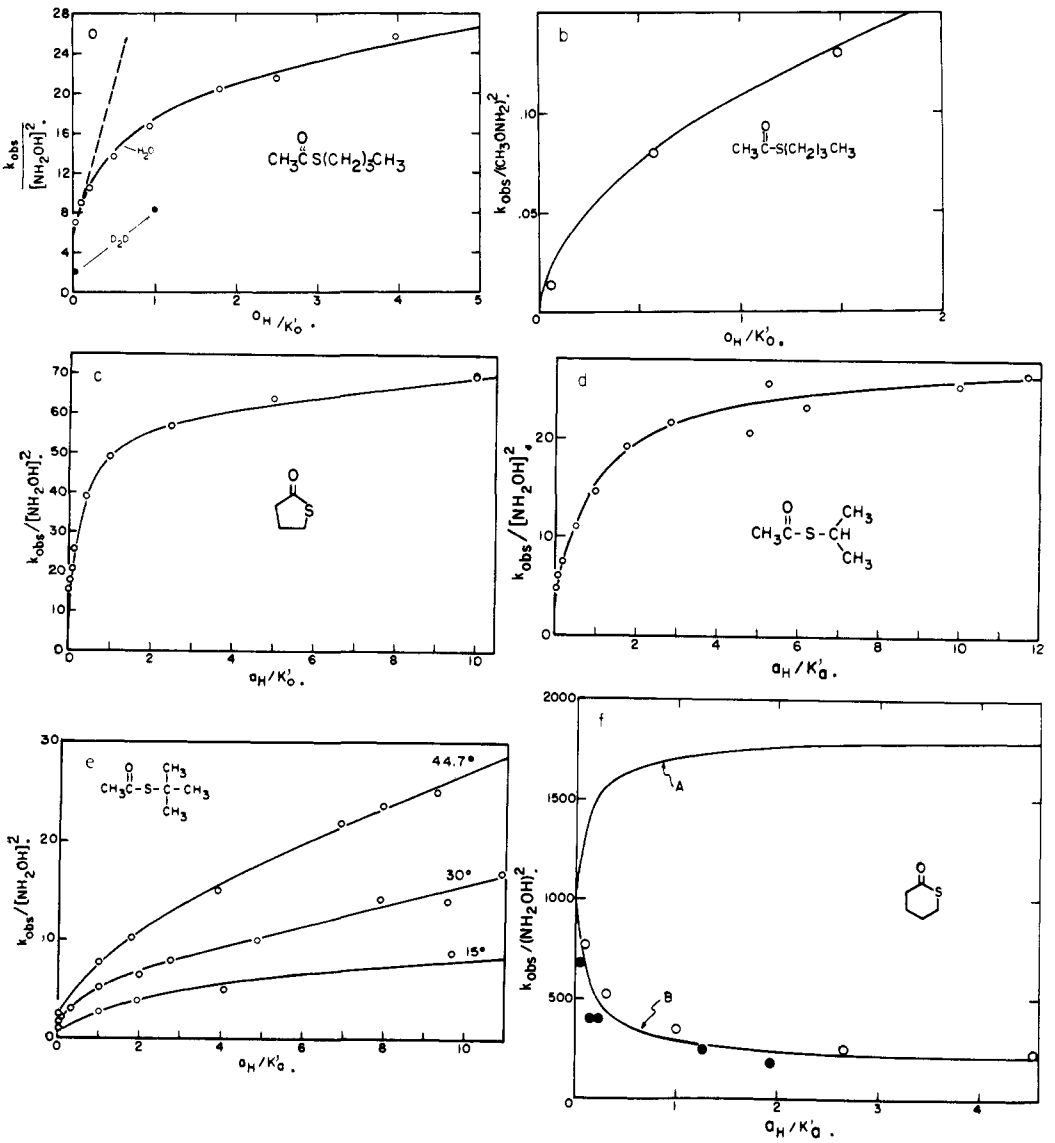
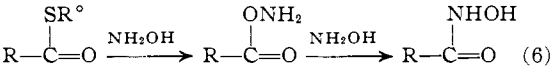


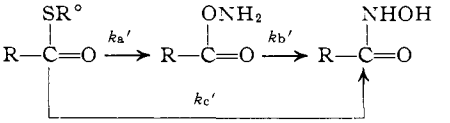
Fig. 3.—Plots of the apparent third-order rate constants, k_3', *vs.* a_H/K_a' for: (a) the hydroxylaminolysis of *n*-butyl thiolacetate; (b) the methoxylaminolysis of *n*-butyl thiolacetate; (c) the hydroxylaminolysis of γ-thiolbutyrolactone; (d) the hydroxylaminolysis of isopropyl thiolacetate; (e) the hydroxylaminolysis of *t*-butyl thiolacetate; (f) the hydroxylaminolysis of δ-thiolvalerolactone.

Fig. 3a is attributed to N or O attack by hydroxylamine, the rate of acetohydroxamic acid formation from thiolester was determined in reactions covering the pH range of 5.4 to 7. In all instances the ester was found to be completely converted to hydroxamic acid, but the rate of hydroxamic acid formation was found to be less than the rate of ester disappearance. This result suggests the intermediate formation of O-acetylhydroxylamine and its conversion, by reaction with additional hydroxylamine, to acetohydroxamic acid (a well known and rapid reaction[26]). Under the pseudo-first-order conditions employed reaction 6



(6)

amounts kinetically to a simple A → B → C problem.[27] Since the concentration of A and C are known, with time the concentration of B is also known. At all the pH values employed B was found to amount to no more than 15% of A_0 at the time of its maximum concentration (Fig. 4). However, by employing the simple integrated equations for the A → B → C problem[27] and solving for the maximum, B should approach 40–70% of A_0 over the pH range studied, based on the calculated constants for the disappearance of A and appearance of C. Therefore, all of C does not arise through B, a fact also shown by the lack of a lag period in the production of C. We must, therefore, postulate that hydroxylamine reacts with the thiolester to produce acetohydroxamic acid directly as well as O-acetylhydroxylamine which is then converted to acetohydroxamic acid *via* reaction with the excess hydroxylamine. For purposes of employing (7) the



(7)

rate constants k_b' were determined by studying the reaction of hydroxylamine with O-acetylhydroxylamine as a function of pH and hydroxylamine concentration. No measurable hydrolysis of O-acetylhydrox-

(27) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 166.

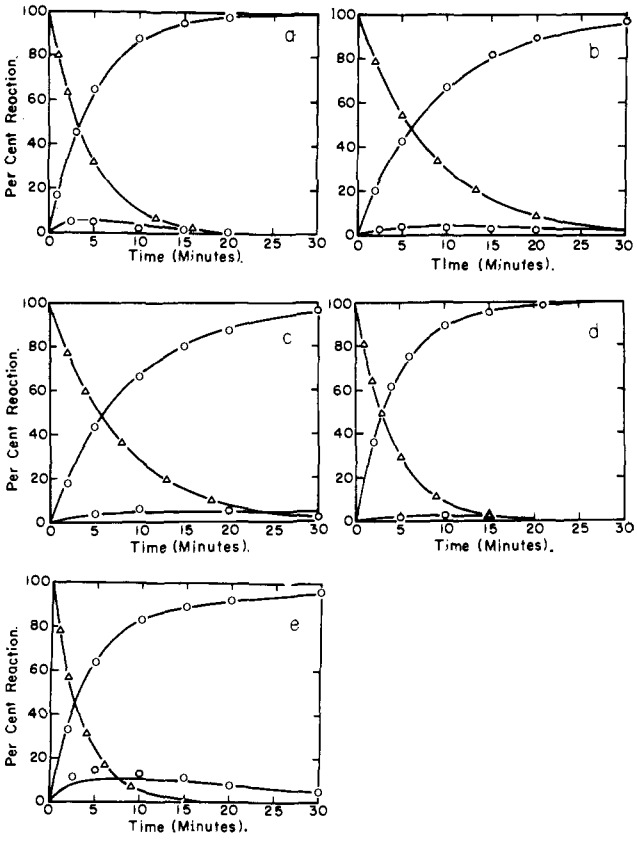


Fig. 4.—Pseudo-first-order plots for the disappearance of *n*-butyl thiolacetate in hydroxylamine solution, the appearance of acetohydroxamic acid from *n*-butyl thiolacetate in hydroxylamine solution, and the appearance and disappearance of O-acetylhydroxylamine from *n*-butyl thiolacetate in hydroxylamine solution with time. Solid lines are obtained from theoretical rate constants and points are experimentally determined values for the following concentrations of total hydroxylamine and pH values: (a) 0.5 *M*, pH 5.42; (b) 0.2 *M*, pH 5.82; (c) 0.16 *M*, pH 6.07; (d) 0.2 *M*, pH 6.36; (e) 0.2 *M*, pH 7.06.

ylamine was observed (employing a pH-stat) in the absence of hydroxylamine. The rate constants for the disappearance of ester equals ($k_a' + k_c'$). Integration of the rate expression for appearance and disappearance of A, B, and C in terms of ($k_a' + k_c'$) is readily accomplished, providing separate solutions to

$$A = A_0 e^{-(k_a' + k_c')t}$$

$$B = \frac{A_0 k_a'}{k_b - (k_a' + k_c')} [e^{-(k_a' + k_c')t} - e^{-(k_b' t)}] \quad (8)$$

$$C = A_0 - A - B$$

k_a', k_b', and k_c' at all acidities. At each pH investigated, values for k_a' were used which provided the best fit of experimental points to the theoretically calculated (C) curve. The determined concentrations of A, B, and C with time are reasonably well provided by the determined values of the rate constant. The curves of Fig. 4 have been constructed from these determined constants.

In Fig. 5 the values of $k_a'/(NH_2OH)^2$, $k_b'/(NH_2OH)^2$, and $k_c'/(NH_2OH)^2$ have been plotted *vs.* a_H/K_a'. Inspection of Fig. 5 reveals that the value of $k_c'/(NH_2OH)^2$, as opposed to the values of $k_a'/(NH_2OH)^2$ and $k_b'/(NH_2OH)^2$, exhibits the same dependency on a_H/K_a' as the disappearance of ester (Fig. 3a). Therefore, the mechanism leading directly from ester to

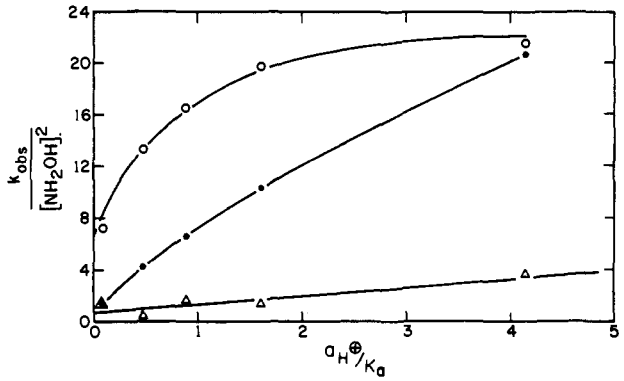


Fig. 5.—Plots of k_a', k_b', and k_c' divided by the square of free hydroxylamine base *vs.* a_H/K_a' for the hydroxylaminolysis of *n*-butyl thiolacetate where $k_{obsd} = k_c'$ (○), $k_{obsd} = k_b'$ (●), and $k_{obsd} = k_a'$ (▲).

acetohydroxamic acid is that which undergoes a change in rate-limiting step with increase in acidity.

In separate experiments the reactions of *n*-butyl mercaptan with acetohydroxamic acid and O-acetylhydroxylamine were investigated. No thiolester was found to be synthesized in either case. The inability to realize these back reactions under the conditions of the hydroxylaminolysis reaction suggests that the dependence of the rate constant on acidity is not attributed to an equilibrium situation. Additional experiments have shown the reactions discussed to be rather insensitive to a twofold change in ionic strength.

The tendency of hydroxylamine to yield oximes on reaction with carbonyl compounds and the rather closer similarity of the thiolester carbonyl group to a keto function[28] suggested that in some manner (not immediately obvious) the intermediate formation of an oximino thiolacetate might account for the pH dependence of the reaction of hydroxylamine with *n*-butyl thiolacetate. *n*-Butyl oximinothiolacetate was

$$n\text{-}C_4H_9\text{—}S\text{—}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}\text{=}O + H_2NOH \longrightarrow n\text{-}C_4H_9\text{—}S\text{—}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}\text{=}NOH + H_2O \quad (9)$$

synthesized and found not to react with hydroxylamine, under the conditions of the ester experiments, to yield acetohydroxamic acid. Further, the compound, at ten times the concentration of thiolester employed in the kinetic experiments (*i.e.*, at 10^{-3} *M*), does not give a color reaction with ferric chloride and, therefore, could not be mistaken for acetohydroxamic acid. Thus, a reaction of type 9 can be of no significance in the hydroxylaminolysis of *n*-butyl thiolacetate.

The reaction of methoxylamine with *n*-butyl thiolacetate at pH 4.64, 5.08, and 6.05 was examined in aqueous solution at 30° (Fig. 3b). Good pseudo-first-order kinetics were obtained. However, no attempt was made to procure a detailed pH-rate profile owing to the fact that the reaction was very slow. The reaction was found to be both first and second order in methoxylamine (10). The apparent second-order rate constant, k_2', varies with acidity and likely obeys the relationship of eq. 11a. The variation of the apparent third-order catalytic constant, k_3', with acidity is accurately described by (5a) if $k_I = 0$. The appro-

(28) D. Cook, *J. Am. Chem. Soc.*, **80**, 49 (1958).

TABLE I

DETERMINED CONSTANTS FOR CATALYTIC ATTACK OF $NH_2OH + NH_2OCH_3$ ON THIOLESTERS AND THIOLACTONES (μ = 1.0 M)

Substrate	Nucleophile[a]	pH range	Temp., °C.	No. of pH values at which k_{obsd} detd.	No. of k_{obsd} values detd.	k_I	k_{II}	k_{III}	k_{IV}	Molar concn. range for nucleophile
$k_{obsd}/(NH_2OR)^2 = (k_I + k_{II}a_H + k_{III}(a_H)^2/(k_{IV} + a_H)$										
γ-Thiolbutyrolactone	H	5.0–7.8	30	10	40	1.85×10^{-6}	60.3	1.14×10^{4}	2.64×10^{-7}	0.05–0.4
n-Butyl thiolacetate	H	5.4–7.5	30	10	40	2.77×10^{-6}	22.4	1.35×10^{6}	4.80×10^{-7}	.05– .8
Isopropyl thiolacetate	H	5–7.5	30	12	48	1.5×10^{-6}	21	8×10^{5}	5×10^{-7}	.04– .4
t-Butyl thiolacetate	H	4.99–7.50	30	10	40	9.60×10^{-7}	6.48	1.1×10^{6}	7.1×10^{-6}	.08– .6
t-Butyl thiolacetate	H	5.71–7.82	15	5	20	1.73×10^{-6}	9.45	1.15×10^{5}	3.26×10^{-6}	.1– .6
t-Butyl thiolacetate	H	4.73–7.11	44.7	7	28	4.13×10^{-6}	16.8	1.61×10^{6}	1.89×10^{-6}	08– .8
n-Butyl thiolacetate	M	4.64–6.05	30	3	12	...	0.082	4.82×10^{4}	1.63×10^{-7}	.4–1.0
δ-Thiolvalerolactone[b]	H	5.37–7.54	30	10	40	1.3×10^{-4}	190	...	1.3×10^{-7}	.01–0.1
δ-Thiolvalerolactone[b]	M	4.29–5.92	30	5	30	1.76×10^{-7}	2	3.64×10^{5}	2.33×10^{-7}	.05– .5
						k		k	k	
$k_{obsd}/(NH_2OR) = (k_V + k_{VI}a_H)/(k_{VII} + a_H)$										
γ-Thiolbutyrolactone	H	5–7.8	30	10	40	1.38×10^{-8}		1.15	1.3×10^{-7}	0.05–0.4
Isopropyl thiolacetate	H	5–7.5	30	12	48	8×10^{-8}		0.26	1×10^{-6}	.04– .4
t-Butyl thiolacetate	H	4.99–7.50	30	10	40	2.9×10^{-8}		.21	5×10^{-7}	.08– .6
t-Butyl thiolacetate	H	5.71–7.82	15	5	20	6×10^{-9}		.153	3.3×10^{-7}	.1– .6
t-Butyl thiolacetate	H	4.73–7.11	44.7	7	28	5×10^{-8}		.395	3.9×10^{-7}	.08– .8
δ-Thiolvalerolactone[b]	M	4.29–5.92	30	5	18	5×10^{-9}		.18	1.3×10^{-7}	.05– .5

[a] H = hydroxylamine, M = methoxylamine. [b] Part of the data was taken from ref. 3a.

priate rate constants k_{II}, k_{III}, and k_{IV} employed to fit the experimentally determined third-order rate con-

$$-d(\text{lactone})/dt = k_2'(\text{lactone})(NH_2OCH_3) + k_3'(\text{lactone})(NH_2OCH_3)^2$$

$$\frac{k_{obsd}}{(NH_2OCH_3)} = k_2' + k_3'(NH_2OCH_3) \quad (10)$$

stants to the plot of Fig. 3b are provided in Table I. The variation in k_3' with acidity could also be described by 5a if k_I/k_{IV} is some finite value so small as to be considered zero.

γ-Thiolbutyrolactone.—The hydroxylaminolysis of γ-thiolbutyrolactone in the pH range 5–7.8 was found to be both first and second order in hydroxylamine (10). Plots of $k_{obsd}/(NH_2OH)$ *vs.* (NH_2OH) are linear and have for slope the apparent third-order rate constant, k_3', and for intercept the apparent second-order rate constant, k_2' (Fig. 2). From Fig. 2 it can be seen that both the apparent second-order and apparent third-order rate constants are functions of acidity. The acidity dependence of the apparent third-order rate constant (Fig. 3c) is given by the same equation (5a) which was employed for the hydroxylaminolysis of *n*-butyl thiolacetate. The values of the constants k_I, k_{II}, k_{III}, and k_{IV} employed to calculate the theoretical curve of Fig. 3c are provided in Table I. The dependence of the apparent second-order rate constants on acidity is given by 11. The points on the plot of Fig. 6 are experimentally determined values

$$k_{obsd}/(NH_2OH) = 1.3 \times 10^{-8} + 1.15a_H/(1.3 \times 10^{-7} + a_H) \quad (11)$$

$$= (k_V + k_{VI}a_H)/(k_{VII} + a_H) \quad (11a)$$

and the curve is theoretically derived from 11. From Fig. 6 it can be seen that the nucleophilic rate constant changes from one independent of acidity at $a_H/K_a' = 0$ to one highly dependent on acidity and finally to one that is again independent of acidity at $a_H/K_a' = \infty$.

Isopropyl Thiolacetate.—In the pH range 5–7.5 the hydroxylaminolysis of isopropyl thiolacetate was found to be both first and second order in hydroxylamine (10). Plots of $k_{obsd}/(NH_2OH)$ *vs.* (NH_2OH) are linear with slope k_3' and intercept k_2'. The apparent second- and

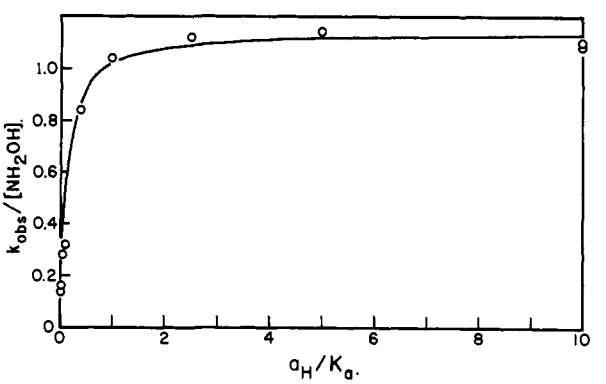


Fig. 6.—Plot of the apparent second-order rate constants, k_2', *vs.* a_H/K_a' for the hydroxylaminolysis of γ-thiolbutyrolactone.

third-order rate constants exhibited the same dependence on acidity as the corresponding constants for γ-thiolbutyrolactone. Thus, the over-all hydroxylaminolysis of isopropyl thiolacetate is kinetically described by 5a and 11a. The variation in the apparent third-order rate constant with acidity is shown in Fig. 3d; the points are experimentally determined values and the curve is theoretically derived from 5a employing the constants provided in Table I. The variation in the apparent second-order rate constant with acidity (11a, figure not shown) is provided by the appropriate rate constants of Table I.

***t*-Butyl Thiolacetate.**—The hydroxylaminolysis of *t*-butyl thiolacetate was studied at 15, 30, and 44.7°. The reaction was found to be both first and second order in hydroxylamine at all three temperatures (10). In Fig. 3e the apparent third-order rate constants have been plotted as a function of acidity. The points are experimentally determined values and the curves are

theoretically derived from eq. 5a employing the appropriate constants of Table I. The variations in the apparent second-order rate constants with acidity follow the predicted form of eq. 11a when the appropriate rate constants of Table I are employed.

δ-Thiolvalerolactone.—The reaction of δ-thiolvalerolactone with both hydroxylamine and methoxylamine has been previously examined by Bruice, Bruno, and Chou.[1] In the previous study it was reported that the hydroxylaminolysis reaction followed the anticipated kinetic equation for an aminolysis reaction which was subject to general base catalysis (*i.e.*, $k_{gb}\cdot(NH_2OH)^2$(lactone)), while the methoxylaminolysis reaction was found to follow the prescribed kinetic equation for an aminolysis reaction subject to both general base and general acid catalysis ($k_{gb}(NH_2OCH_3)^2$(lactone) + $k_{ga}(^+NH_2OCH_3)(^+NH_3OCH_3)$(lactone)). Since the hydroxylaminolysis and methoxylaminolysis of all the thiolesters employed in this study exhibited an unusual dependence on acidity not prescribed by the simple equations for general base or general base plus general acid catalysis, a re-examination as well as an extension of the kinetic results of the previous study was carried out.

For the hydroxylaminolysis of δ-thiolvalerolactone the pseudo-first-order kinetics are not reliable and log $a/(a - x)$ *vs.* time plots show downward curvature. The reaction is characterized by an initial rapid reaction followed by a slow reaction, suggestive of the formation of a highly absorbing intermediate which is itself attacked by hydroxylamine to yield product. Employing initial rates (one to two half-lives) and eq. 10, it is found that the calculated apparent third-order catalytic constant decreases with increasing acidity until at high acidity the constant becomes insensitive to pH. Thus, plots of k_3' *vs.* a_H/K_a' exhibit downward curvature and gradually plateau (Fig. 3f). The curve of Fig. 3f is theoretical, being derived from eq. 12 employing the constants provided in Table I, and the points are experimentally determined values.

$$k_{obsd}/(NH_2OH)^2 = (K_I + K_{II}a_H)/(K_{IV} + a_H) \quad (12)$$

The rate data for the methoxylaminolysis of δ-thiolvalerolactone are described by 10. The variation of the apparent second-order rate constant with acidity is described by 11a and the best fit of the experimental values to the theoretical curve is given by the constants provided in Table I. The variation of the apparent third-order constant with acidity is kinetically described by 5a and the best fit of the experimental values to the theoretical curve is provided by the appropriate constants of Table I (figures for the methoxylaminolysis of δ-thiolvalerolactone not provided).

Discussion

The hydroxylaminolysis and methoxylaminolysis of a series of thiolesters and thiolactones have been investigated. The reactions have been found to be kinetically both first and second order in the amine. For the substrates γ-thiolbutyrolactone, *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate, terms second order in hydroxylamine were obtained. In addition, with the exception of *n*-butyl thiolacetate, terms first order in hydroxylamine were also obtained. Failure to observe a second-order term for *n*-butyl thiolacetate is probably attributed to the relatively small contribution of a noncatalyzed nucleophilic attack compared to the contribution of the catalytic processes to the over-all reaction rate. A similar phenomenon was observed in the hydrazinolysis of γ-thiolbutyrolactone, kinetically third order over-all, and the hydrazinolysis of δ-thiolvalerolactone, *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate which were both second order and third order over-all.[3b]

The hydroxylaminolysis of *n*-butyl thiolacetate has been shown to occur *via* nucleophilic attack by the nitrogen function of hydroxylamine. In subsequent discussions it will be assumed that reactions of hydroxylamine with the other thiolesters and lactones occur in a similar manner (methoxylamine must operate as a nitrogen nucleophile). To test the possibility that *n*-butyl oximinothiolacetate (9) is an intermediate or product in the hydroxylaminolysis reaction it was itself subjected to the hydroxylaminolysis reaction and found not to yield acetohydroxamic acid (or to give a color with $FeCl_3$ in dilute HCl). It is, therefore, not an intermediate or product. For the fraction of the products appearing *via* reactions kinetically first order in nucleophile and first order in substrate, the rate expression (in the pH range investigated) is found to alter with the hydrogen ion concentration

$$v = [k_V/k_{VII}](NH_2OR)(\text{substrate}) \text{ at } a_H = 0 \quad (13)$$

$$v = \frac{[k_V + k_{VI}a_H]}{[k_{VII} + a_H]}(NH_2OR)(\text{substrate}) \text{ at intermediate } a_H$$

$$v = k_{VI}(NH_2OR)(\text{substrate}) \text{ at very high values of } a_H$$

R = H, CH_3

A somewhat similar variation of the rate equation is obtained for the fraction of the products arising *via* reactions kinetically second order in the nitrogen nucleophile and first order in the ester, *viz.*

$$v = [k_I/k_{IV}](NH_2OR)^2(\text{substrate}) \text{ at } a_H = 0 \quad (14)$$

$$v = \frac{[k_I + a_Hk_{II} + a_H{}^2k_{III}]}{[k_{IV} + a_H]}(NH_2OR)^2(\text{substrate}) \text{ at intermediate } a_H$$

$$v = [k_{III}K_a'](NH_2OR)(^+NH_3OR)(\text{substrate}) \text{ at high } a_H$$

In 13 the reaction changes from one of simple nucleophilic attack at the thiolester bond at low acidity to one unconventionally dependent upon hydrogen ion concentration at intermediate pH to one of simple nucleophilic attack at the thiolester bond at high acidity. The rate constants for the over-all bimolecular nucleophilic reaction at low and high acidities are, however, not equal. In 14 the kinetic expression at very low hydrogen ion concentration is that anticipated for a general base catalyzed reaction; at intermediate pH values the rate expression is unique representing neither classical general base nor general acid catalysis while at high acidity the rate expression is that for general acid catalysis. In summary, the limiting cases (very high and very low acidities) for both the

terms first and second order in nitrogen base are conventional, but at intermediate acidities the rate expressions represent neither simple nucleophilic, general base catalyzed nucleophilic, nor general acid catalyzed nucleophilic processes, nor any simple summation of these processes. Clearly, at intermediate pH values complex, and as yet unrecognized, mechanisms must be in operation and these must involve acid–base equilibria. The change in mechanism with acidity is convincing evidence for the existence of intermediates which must be in acid–base equilibria and whose formation and partitioning are of kinetic significance.

In previous studies Bruice, Bruno, and Chou[1a] and Fedor and Bruice[1b] have shown that thiolesters and thiolactones which are subject to general catalysis of nucleophilic attack by primary and secondary amines usually are as sensitive to general acid catalyzed attack as to general base catalyzed attack if the catalytic species are the conjugate base and conjugate acid forms of the nucleophile.

$$-\mathrm{d(substrate)}/\mathrm{d}t = [k_{ga}(R_2NH)(R_2N^+H_2) + k_{gb}(R_2NH)^2](\mathrm{substrate}) \quad (15)$$

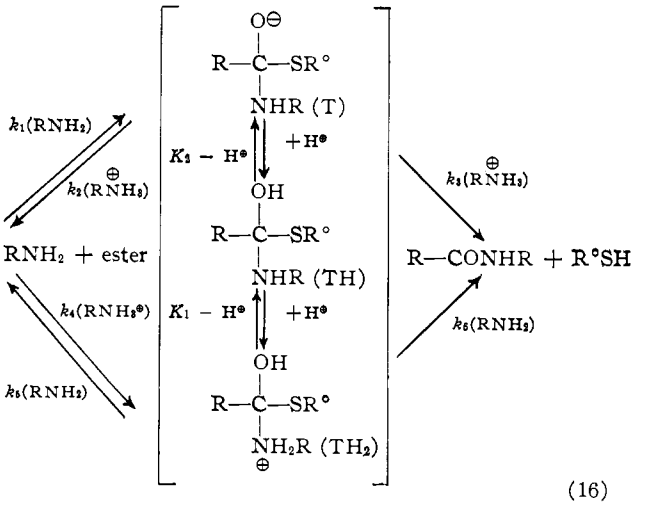
where k_{gb}/k_{ga} = 1.0 to 1.8

For the hydroxylaminolysis reactions of this study the ratios of the values of the rate constants calculated at infinitely low and infinitely high acidity fall between 1.3 and 4.6. Thus, the ratio $(k_I/k_{IV})/k_{III}K_a'$ for the hydroxylaminolysis of *n*-butyl thiolacetate is 4.6; for isopropyl thiolacetate the ratio is 4.0, while for *t*-butyl thiolacetate a ratio of 1.3 is obtained.[29] This suggests that $k_I/k_{IV} = k_{gb}$, that $k_{III}K_a' = k_{ga}$, and that hydroxamic acid is formed from thiolester and thiolactone *via* parallel general base and general acid assisted nucleophilic attack of hydroxylamine on these substrates. This conclusion is supported by the determined deuterium solvent kinetic isotope effects and entropies of activation. For the hydroxylaminolysis of *n*-butyl thiolacetate the ratios of $k_3'^H/k_3'^D$ were determined to be 2.84 and 2.14 at pD = pH values of 8.30 and 6.46, respectively (see Fig. 3a). Values of k^H/k^D of this magnitude indicate proton abstraction or donation in the transition state in agreement with the involvement of general catalytic processes. The Arrhenius activation parameters for the limiting values of k_I/k_{IV} and $k_{III}K_a'$ calculated at $a_H = 0$ and $a_H = \infty$, respectively, for *t*-butyl thiolacetate at three temperatures covering a 30° spread were calculated from slopes of plots of log k_{rate} *vs.* $1/T$. The three-point Arrhenius plots so obtained are not too reliable since the deviation of the points from linearity is appreciable. However, an approximate $T\Delta S^*$ of 12 kcal. mole^{-1} and approximate ΔH^* of 8 kcal. mole^{-1} for each limiting catalytic process were obtained. Bruice and Benkovic[30] and Fedor and Bruice[1a] have found the values of $T\Delta S^*$ for a number of third-order general acid or general base assisted nucleophilic displacement reactions at ester and at thiolester bonds to be *ca.* 12–16 kcal. mole^{-1}. Thus, the approximate value of $T\Delta S^*$ reported herein for the hydroxylaminolysis of *t*-butyl thiolacetate is a reasonable value for $T\Delta S^*$ for catalytically assisted termolecular processes.

In summary, the following observations support parallel mechanisms of general acid and general base catalysis involving acid–base equilibrium of metastable intermediates: (1) The ratio of the limiting rate constants at $a_H = \infty$ and $a_H = 0$ are of the magnitude previously found for simple general acid and general base catalyzed reactions. (2) The deuterium solvent kinetic isotope effects of 2.1 to 2.8 support mechanisms involving proton abstraction in the transition state. (3) The values of $T\Delta S^*$ are in accord with termolecular reactions. (4) At the limiting conditions of $a_H = 0$ and $a_H = \infty$ the forms of the rate equation are those anticipated for general base and general acid catalysis, respectively. (5) At intermediate acidities (see following discussion) the form of the rate equation is that anticipated from acid–base equilibria of metastable intermediates formed in parallel paths of general acid and general base catalysis.

The Crossover Mechanisms.—In the ensuing discussion it is assumed that the phenomena of this study may be explained *via* a bridge of acid–base equilibria between parallel reaction paths. This bridge is suggested to arise under very restricted conditions and allows the crossing over of metastable intermediates between the parallel paths. The various possible *crossover* mechanisms will be discussed along with the appropriate experimental examples applicable to each case.

Case I.—Crossover in parallel general base and general acid catalyzed nucleophilic attack. Assuming steady state in the intermediates T, TH, and TH_2 for mechanism 16 the kinetic expression of 17 can



(16)

be derived. The general form of 17 is more meaningfully expressed as in 18 since it is quite impossible to separate the various constants and it is seen that 18

(29) Although the ratios for the rate constants calculated from the limiting cases for *n*-butyl thiolacetate and isopropyl thiolacetate exceed 1.8, the ratios are of the correct predicted magnitude. The relative uncertainty associated with the limiting general-acid rate constants ($k_{III}K_a'$) compared to the limiting general-base constants (k_I/k_{IV}) introduces an uncertainty into the values of k_{gb}/k_{ga}. Possibly better values of $k_{III}K_a'$ can be obtained by replotting the experimental data according to the expression: $k_{obsd}/(NH_2OH)(^+NH_3OH) = k_{ga} + k_{gb}K_a'/a_H$. Thus, plots of $k_{obsd}/(NH_2OH)(^+NH_3OH)$, *i.e.*, k_3', *vs.* K_a'/a_H are nonlinear, but k_3' values determined at high acidity fall into a small region near the juncture of the k_3, K_a'/a_H axes and visually the scatter in k_3' is lessened, facilitating curve fitting to the experimental points. Also, k_{ga} may be determined as an intercept value rather than as a slope value. When k_{ga} is so determined, the ratio k_{gb}/k_{ga} is 3.8, 1.6, and 1.7 for *n*-butyl, isopropyl, and *t*-butyl thiolacetates.

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

$$\frac{k_{obsd}}{(RNH_2)^2} = \frac{\frac{k_1k_3K_1K_2}{K_a'} + a_H\left[k_1k_6 + \frac{k_3k_4K_1K_2}{K_a'^2}\right] + a_H^2\frac{k_4k_6}{K_a'}}{\frac{K_1K_2}{K_a'}[k_3 + k_2] + a_H[k_6 + k_5]} \quad (17)$$

$$\frac{k_{obsd}}{(RNH_2)^2} = \frac{k_I + k_{II}a_H + k_{III}a_H^2}{k_{IV} + a_H} \quad (18)$$

possesses the same mathematical form as 5a. The rate expression derived from 17 under the limiting conditions of $a_H = 0$ and $a_H = \infty$ are provided by 19a and 19b, respectively, which are expressions for general base and general acid catalyzed nucleophilic reactions. Reactions whose kinetics are in accord

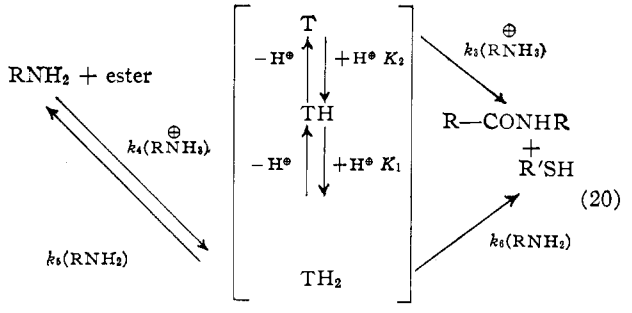
$$\frac{k_{obsd}}{(RNH_2)^2} = \frac{k_1k_3}{k_3 + k_2} \quad (19a)$$

$$\frac{k_{obsd}}{(RNH_2)^2} = \frac{a_Hk_4k_6}{K_a'(k_6 + k_5)} \text{ or}$$

$$\frac{k_{obsd}}{(RNH_2)(RNH_3^{\oplus})} = \frac{k_4k_6}{k_6 + k_5} \quad (19b)$$

with the mechanism of 18 are the over-all third-order hydrolyaminolysis of γ-thiolbutyrolactone, isopropyl thiolacetate, *t*-butyl thiolacetate, and *n*-butyl thiolacetate as well as the over-all third-order methoxylaminolysis of δ-thiolvalerolactone.

Case II.—Crossover in general acid catalyzed nucleophilic attack. For the over-all third-order methoxylaminolysis of *n*-butyl thiolacetate a good fit of the experimental values of $k_{obsd}/(CH_3ONH_2)^2$ to a plot of this function *vs.* a_H/K_a' is obtained if k_1 in 5a is assumed to be negligibly small. The form of the kinetic equation is that of 21 which is obtainable from 20 by assuming steady state in T, TH, and TH_2. Equation



(20)

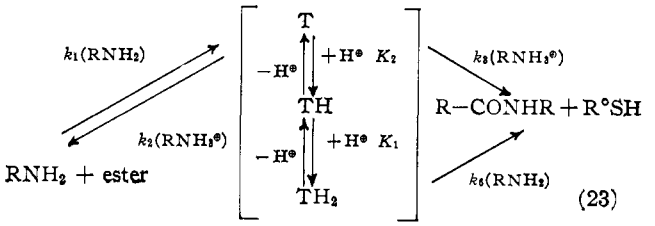
$$\frac{k_{obsd}}{(RNH_2)^2} = \frac{\left[\frac{k_3k_4K_1K_2}{(k_5 + k_6)K_a'^2}\right]a_H + \left[\frac{k_4k_6}{(k_5 + k_6)K_a'}\right]a_H^2}{\frac{K_1K_2k_3}{(k_5 + k_6)K_a'} + a_H} \quad (21)$$

21 has the simplified form of 22. Under the limiting

$$k_{obsd}/(RNH_2)^2 = (k_{II}a_H + k_{III}a_H^2)/(k_{IV} + a_H) \quad (22)$$

conditions of $a_H = 0$, the limiting general base catalytic constant is zero; under the limiting conditions of $a_H = \infty$, the limiting general acid catalytic constant is given by $k_{III}a_H$ (Fig. 3b).

Case III.—Crossover in general base-catalyzed nucleophilic attack. Assuming steady state in the intermediates T, TH, and TH_2 for the mechanism 23, the kinetic expression 24 can be derived which has the



(23)

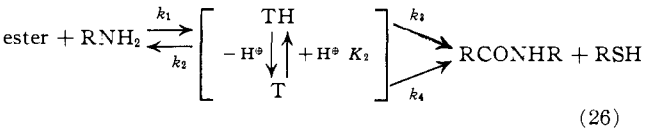
$$\frac{k_{obsd}}{(RNH_2)^2} = \frac{\frac{k_1k_3K_1K_2}{k_6K_a'} + k_1a_H}{\frac{(k_2 + k_3)K_1K_2}{k_6K_a'} + a_H} \quad (24)$$

simplified form 25. Under the limiting conditions of

$$k_{obsd}/(RNH_2)^2 = (k_I + k_{II}a_H)/(k_{IV} + a_H) \quad (25)$$

$a_H/K_a' = 0$, the limiting general base catalytic constant is given by k_I/k_{IV}. Under the limiting conditions of $a_H/K_a' = \infty$, two situations are possible. When $k_I/k_{IV} < k_{II}$ the variation in the apparent third order catalytic constant, k_3', with acidity is illustrated by curve A in Fig. 3f. When $k_I/k_{IV} > k_{II}$ the variation in the apparent third-order rate constant with acidity is illustrated by curve B in Fig. 3f. A possible example of case III wherein $k_I/k_{IV} > k_{II}$ is found in the hydroxylaminolysis of δ-thiolvalerolactone (Fig. 3f-B).

Case IV.—Nucleophilic displacement involving kinetically important acid–base equilibria of tetrahedral



(26)

intermediates. From the steady-state assumption in TH and T one obtains

$$\frac{k_{obsd}}{(RNH_2)} = \frac{\frac{k_1k_4K_2}{(k_2 + k_3)} + \frac{k_1k_3}{(k_2 + k_3)}a_H}{\frac{k_4K_2}{(k_2 + k_3)} + a_H} \quad (27)$$

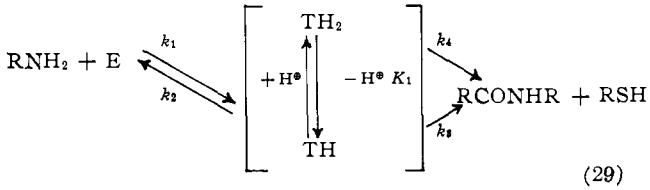
which is of the same mathematical form as 11a. From 27 the rate expressions under the limiting conditions of acidity are provided by 28a and 28b.

$$\frac{k_{obsd}}{(RNH_2)} = k_1 \text{ at } a_H = 0 \quad (28a)$$

$$\frac{k_{obsd}}{(RNH_2)} = \frac{k_1k_3}{(k_2 + k_3)} \text{ at } a_H = \infty \quad (28b)$$

Although 27 is of the correct mathematical form to account for the kinetics of a number of the reactions reported herein, it is theoretically incorrect. By substitution of the limiting values of k_{obsd}/RNH_2 (Table I) into 28a and 28b the impossible result is obtained that $k_3 = n(k_2 + k_3)$, where $n = 3.5$ to 11.5 for the four nucleophilic reactions of Table I that follow this kinetic pattern.

An alternate mechanism is 29 from which 30 may be



(29)

derived by assuming steady state in TH and TH_2.

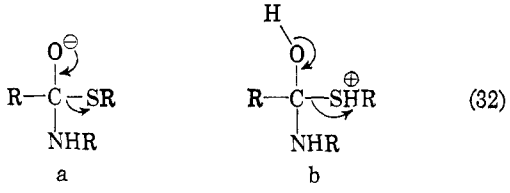
$$\frac{k_{obsd}}{(RNH_2)} = \frac{k_1k_3K_1/k_4 + k_1a_H}{\frac{K_1(k_2 + k_3)}{k_4} + a_H} \qquad (30)$$

It may be seen that 30 is of the same mathematical form as 11a and 27. Under limiting conditions of acidity

$$k_{obsd}/(RNH_2) = k_1k_3/(k_2 + k_3) \text{ at } a_H = 0 \quad (31a)$$

$$k_{obsd}/(RNH_2) = k_1 \text{ at } a_H = \infty \qquad (31b)$$

The difference in 26 and 30 is that in the former the elimination is of an anion from a negatively charged tetrahedral intermediate 32a while in the latter 32b a neutral species is eliminated from a positively charged tetrahedral intermediate. In 32a the driving force



(32)

for elimination is greater than in 32b but in 32b the leaving group is better than in 32a. It might, therefore, be argued that 32a and b are reasonable formal structures for unstable intermediates. Scheme 29 may be pictured as a crossover mechanism involving tetrahedral intermediates formed by simple nucleophilic attack and by $H_3O^{\oplus}$-catalyzed nucleophilic attack wherein the free energy barrier for the latter is too great for the direct conversion of E to TH_2. Hydroxylaminolysis reactions whose second-order rate constants follow 11a and might find explanation through 29 include the hydroxylaminolysis of γ-thiolbutyrolactone, isopropyl thiolacetate, and *t*-butyl thiolacetate. The methoxylaminolysis of δ-thiolvalerolactone and *n*-butyl thiolacetate may be additional examples.

Plots of the log of the second-order rate constants for the reactions of nucleophiles with δ-thiolvalerolactone *vs.* the log of the second-order rate constants for the reaction of the same nucleophiles with *p*-nitrophenyl acetate are presented in Fig. 7 (data from ref. 1a and 1b). The points on the upper line represent displacement reactions whose rate constants are identical for the reaction of a nucleophile with either substrate (slope = 1.0 and intercept = 0). For these reactions it is suggested that the rate-determining step for both substrates is the nucleophilic attack at the ester bonds [*i.e.*, $k_{rate} = k_1k_3/(k_2 + k_3)$ and $k_3 >> k_2$ so that $k_{rate} = k_1$ for both esters] and, therefore, k_1(lactone) = k_1(phenyl ester).[31] That the rate-limiting

(31) Evidence obtained by Taft and co-workers (R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963); R. G. Pew and R. W. Taft, unpublished) on the fluorine nuclear magnetic resonance shielding in *p*-substituted fluorobenzenes indicates that *p*-SMe and *p*-$OC_6H_4NO_2$ substituents possess almost identical shielding parameters (f_H^{p-X} +4.5 and +4.3, respectively, as compared to +7.3 for *p*-OC_6H_5). It can be argued, therefore, that the carbonyl groups of *p*-nitrophenyl acetate and δ-thiolvalerolactone might be electronically very similar and equally susceptible to nucleophilic attack.

(32) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

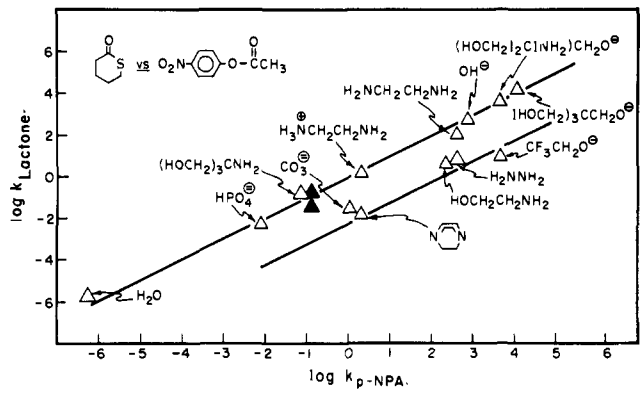


Fig. 7.—Plot of the logarithm of the second-order rate constants, k_n, for δ-thiolvalerolactone *vs.* the logarithm of the second-order rate constants, k_n, for *p*-nitrophenyl acetate for fourteen nucleophiles.

step is the attack on the carbonyl group of *p*-nitrophenyl acetate is supported by the fact that hydrolysis of phenyl esters is not associated with O^{18} exchange of the ester carbonyl group[32] and both $OH^{\ominus}$ and H_2O fall in the upper line of Fig. 7. The lower line of Fig. 7 is drawn for those reactions which are 100 times faster with *p*-nitrophenyl acetate than with δ-thiolvalerolactone. For those reactions it is suggested that $k_{rate} = k_1$ for *p*-nitrophenyl acetate but that $k_{rate} = k_1k_3/(k_2 + k_3)$ for δ-thiolvalerolactone. By substitution of the limiting values at $a_H = 0$ and $a_H = \infty$ (Table I) for the methoxylaminolysis of δ-thiolvalerolactone into 31a,b it can be calculated that $k_1 = 0.18$ and $k_2/k_3 = \alpha = 3.76$. The equations of the plots of Fig. 7 are of the form

$$\log k_{rp\text{-NPA}} = \beta \log k_{rlactone} + C \qquad (33)$$

From the assumption k_1(lactone) = k_1(phenyl ester)

$$\log (\alpha + 1) = C \qquad (34)$$

Substituting the determined value of α for methoxylamine reacting with δ-thiolvalerolactone into 34 and solving provides $C = 0.68$. The shaded triangles of Fig. 7 represent the values for k_1 and $k_1k_2/(k_2 + k_3)$ calculated from the limiting conditions of acidity from eq. 31. The top triangle represents the point for k_1 calculated at $a_H = \infty$. Its fit to this line is as predicted for rate-limiting nucleophilic attack. The bottom triangle, calculated at $a_H = 0$, represents $k_1k_3/(k_2 + k_3)$. It is seen that a line of $\beta = 1.0$ drawn through this point passes through the intercept in the log *k* (lactone) ordinate at $C = 0.6$. This value of *C* may be compared to that value calculated by substituting into (34) the calculated value of α ($C = 0.68$). Thus, the theoretical predictions of the mechanism of the reaction are in harmony with the previously suggested rational for the data of Fig. 7. It should be noted that not only those cases wherein $k_{rate} = k_1$ for thiolactone and *p*-nitrophenyl acetate will fit the upper line of Fig. 7 but also those cases in which α is close to 1.0 for displacements in the thiolactone will provide a fit to

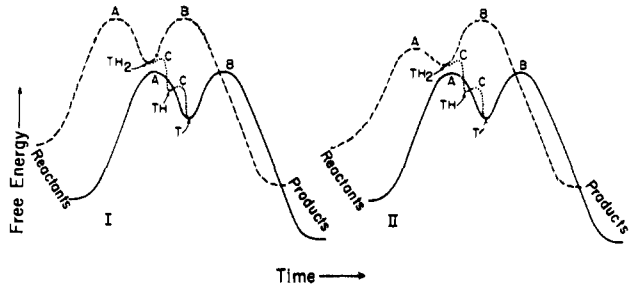


Fig. 8.—Hypothetical reaction coordinate–energy diagrams for cross-over between parallel paths at the tetrahedral intermediates: (a) barriers to tetrahedral intermediate formation comparable; (b) barriers to tetrahedral intermediate formation dissimilar.

the upper line of Fig. 7. Further extensions of the comparison of rate constants for reaction of nucleophiles with *p*-nitrophenyl acetate and δ-thiolvalerolactone are in progress and will be reported shortly.

In agreement with the predictions of mechanism 29, it is found that the limiting constants for the reaction of hydroxylamine with isopropyl thiolacetate and *t*-butyl thiolacetate are very nearly equal. Thus, at $a_H = 0$ the limiting k_2' values are 0.08 and 0.06 l. mole^{-1} min.$^{-1}$ and that at $a_H = \infty$ the limiting k_2' values are 0.26 and 0.21 l. mole^{-1} min.$^{-1}$ for isopropyl thiolacetate and *t*-butyl thiolacetate, respectively. For the hydrazinolysis of *n*-butyl, isopropyl, and *t*-butyl thiolacetates the nucleophilic constants were found to be approximately equal.[3b]

Case V and VI.—General acid, general base, and simple nucleophilic displacement reactions involving kinetically unimportant acid–base equilibria of tetrahedral intermediates. In this class would fall all displacement reactions in which the tetrahedral intermediates were at steady state and in acid-base equilibria but in which the equilibria do not occur along the main reaction path. These cases are kinetically equivalent to addition–elimination reactions not involving acid–base equilibria of metastable intermediates or to direct nucleophilic or catalyzed nucleophilic displacements not involving metastable intermediates. Kinetically, all previously reported aminolyses of esters fall in these categories.

The mechanisms of Cases I to III are, *a priori*, reasonable. Assuming that they are correct, the unique properties required to observe a mechanism involving a crossover between reaction paths are (see Fig. 8): (1) Metastable intermediates (T, TH, TH_2) must be formed. (2) The transition states for the partitioning of the metastable intermediate (A and B) to both products and reactants must be of comparable free energy content. (3) The height of the energy barrier for the transition states for partitioning of the tetrahedral intermediates (A and B) above that of the intermediates must be greater than the energy barriers for proton transfer (*C*) in the acid–base equilibria involving the intermediates T, TH, and TH_2. In addition, to detect experimentally a crossover mechanism the pK_1 and pK_2 values (*i.e.*, $TH_2 \overset{K_1}{\rightleftarrows} TH \overset{K_2}{\rightleftarrows} T$) must be in the vicinity of the pK_a' of the conjugate acid of the nucleophile. In Fig. 8a the energy barriers to the formation of tetrahedral intermediates (A) are comparable while in Fig. 8b one path has a lower energy barrier for intermediate formation. The diagram of 8a serves qualitatively to describe Case I whereas 8b serves to describe Cases II and III. In 8a, reactants proceed to products *via* parallel paths for which barriers A and B are of kinetic significance while in 8b tetrahedral intermediate is formed along one reaction path feeding into the second reaction path to proceed to products along parallel paths. The importance of having tetrahedral intermediates of sufficient stability to allow their acid–base equilibria is of obvious importance. In the O^{18} exchange studies accompaning the hydrolysis of alkyl benzoates Bender and Thomas have argued cogently for the kinetic importance of the proton transfers in the acid–base equilibria of tetrahedral intermediates.[33] The special requirements of the kinetic importance of partitioning of the tetrahedral intermediates in two parallel paths, the stability of the tetrahedral intermediate, and the pK_a's of the tetrahedral intermediates being close to that of the nucleophile are not likely to be met by many reactions. It would be very difficult, *a priori*, to predict which displacement reactions would exhibit crossover phenomena. However, the thiolesters would appear to be good candidates as substrates for the phenomenon since it is known that the addition products of thiols and carbonyl compounds are more stable than the corresponding hemiacetals and acetals[34] and, therefore, likely that tetrahedral intermediates of thiolesters are more stable than those of oxygen esters. In addition, the generally greater reactivity of nitrogen nucleophiles, compared to oxygen nucleophiles, with thiolesters would suggest that the most stable tetrahedral intermediates would be obtained with amines. Of the amines investigated to date possibly only in the case of methoxylamine and hydroxylamine are the pK_a's of the tetrahedral intermediates sufficiently close to the pK_a' of the nucleophiles to detect the crossover mechanism.

The Role of General Catalysis in Nucleophilic Attack and Departure of the Leaving Group.—If our assumptions of crossover mechanisms are correct then, as previously stated, the transition states for nucleophilic attack and for departure of the leaving group must both be of kinetic significance. With this in mind we may write several kinetic expressions for general base (ignoring crossover) catalyzed nucleophilic attack of hydroxylamine (Table II). An analogous set of expressions may be written for general acid catalyzed nucleophilic attack. In Table II, A represents general catalysis in both the nucleophilic attack and departure of the leaving group from the tetrahedral intermediate. For A the reaction is general base catalyzed from starting material to tetrahedral intermediate (k_1) and from the principle of microscopic reversibility general acid catalyzed in the reverse direction (k_2). For symmetry the partitioning of the tetrahedral intermediate is considered to be general acid catalyzed in both forward and reverse directions (k_2 and k_3). In B and C only the steps associated with nucleophilic attack or departure of the leaving group are considered to be general-catalyzed phenomena. Inspection of the rate expressions associated with A to C of Table II reveals that only A provides a rate constant which is not a reciprocal func-

(33) M. L. Bender and R. J. Thomas, *J. Am. Chem. Soc.*, **83**, 4189 (1961).
(34) E. Campaigne, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, Chapter 14.

TABLE II

KINETIC EXPRESSIONS FOR GENERAL BASE CATALYZED HYDROXYLAMINOLYSIS ASSUMING k_1/k_2 AND k_3 STEPS ARE KINETICALLY IMPORTANT

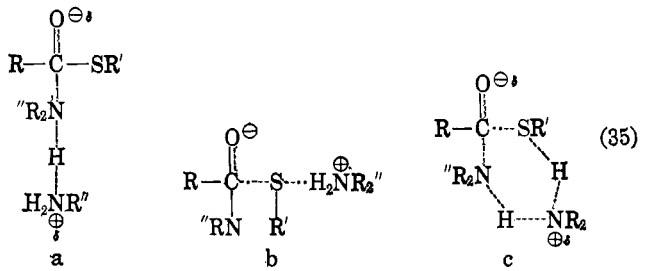
(A) $NH_2OH + E \underset{k_2(NH_3^+OH)}{\overset{k_1(NH_2OH)}{\rightleftharpoons}} T \xrightarrow{k_3(NH_3^+OH)}$ prod.; $v = \left(\frac{k_1k_3}{k_2 + k_3}\right)(NH_2OH)^2(\text{ester})$

(B) $NH_2OH + E \underset{k_2(NH_3^+OH)}{\overset{k_1(NH_2OH)}{\rightleftharpoons}} T \xrightarrow{k_3}$ prod.; $v = \left[\frac{k_1k_3}{k_2(NH_3^+OH) + k_3}\right](NH_2OH)^2(\text{ester})$

(C) $NH_2OH + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} T \xrightarrow{k_3(NH_2OH)}$ prod.; $v = \left[\frac{k_1k_3}{k_2 + k_3(NH_2OH)}\right](NH_2OH)^2(\text{ester})$

tion of catalyst concentration. In B and C the values of $k_{obsd}/(NH_2OH)^2 = k_3'$ would decrease with increasing concentration of the total hydroxylamine concentration. In the experiments reported herein, which involved the determination of well over 500 values of k_{obsd} as a function of total hydroxylamine and methoxylamine concentration, no case was encountered in which k_3' decreased with increasing reagent. If the cross-over mechanism is credible, and therefore both nucleophilic attack and departure of the leaving group are of kinetic significance, then only mechanism A can be correct. Similar arguments may of course be advanced to support catalysis in all steps in general acid-catalyzed reactions of the type reported herein.

The observation of the cross-over mechanism provides, then, a unique opportunity to establish, in at least a few cases, the fact that catalysis occurs in all steps. The question arises as to whether catalysis in all steps is a general phenomena of the aminolysis reaction. The answer must await further experimentation. For reactions exhibiting catalysis in all steps the following comments pertain. If $k_3 >> k_2$, then catalysis would be of importance only in the nucleophilic attack (35a), and if $k_2 >> k_3$ then catalysis would be of importance in the departure of the leaving



a b c (35)

group (35b). If the tetrahedral intermediate were so unstable that diffusion of the catalyst did not occur prior to partitioning, then catalysis would be in both steps and for practical purposes the catalysis would be concerted (35b). One or the other of these mechanisms have been previously suggested.[35-37] The question of symmetry in the chymotryptic catalysis of ester hydrolysis has received consideration[38,39] and the present study lends support in its favor.

The hydroxylaminolysis of a series of thiolacetates in dilute aqueous solution was reported by Noda, Kuby, and Lardy[40] to be kinetically first order in hydroxylamine concentration. However, no detailed study was reported and k_{obsd} values were generally determined at a single hydroxylamine concentration and at one pH. Only in the case of the hydroxylaminolysis of acetylthioglycolic acid was k_{obsd} determined at two pH values with the result that the observed rate constants at one concentration of hydroxylamine and at pH 5.4 and 5.9 were practically identical (*i.e.*, 6.0 and 6.2 l. mole^{-1} min.$^{-1}$, respectively). The somewhat greater lability of acetylthioglycolic acid to hydroxylaminolysis compared to alkyl thiolacetates may be related to the greater leaving tendency of the more acidic thioglycolate anion or even to intramolecular catalysis of the hydroxylaminolysis reaction by the neighboring carboxyl anion (pK_a of carboxyl group of thioglycolic acid 3.68[41]).

Acknowledgment.—This work was supported by the National Institutes of Health and the National Science Foundation. We express our appreciation to Mrs. Stephen Benkovic for assistance in the determination of the rate data.

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(36) W. P. Jencks and J. Carrioulo, *ibid.*, **82**, 675 (1960).
(37) T. C. Bruice and M. F. Mayahi, *ibid.*, **82**, 3067 (1960).
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(39) M. L. Bender, *J. Am. Chem. Soc.*, **84**, 2582 (1962).
(40) L. H. Noda, S. A. Kuby, and H. A. Lardy, *ibid.*, **75**, 913 (1953).
(41) E. Larsson, *Z. anorg. Chem.*, **172**, 375 (1928).