tracted with ether and the dried ether solution evaporated *in vacuo*. The residual product, consisted of a mixture of *cis* and *trans* isomers [glpc: 10% SE-30 on 60–80 Firebrick, 135°; retention time (*cis*) 6.3 min, retention time (*trans*) 8 min; nmr: 5.57 (q, C=CH, J = 2 Hz), 2.13 (d, *trans* C=CCH$_3$, J = 2 Hz), 1.88 (d, *cis* C=CCH$_3$, J = 2 Hz)]. It was used in the next step without additional purification.

3-Methyl-2-nonen-1-ol. To a suspension of lithium aluminum hydride (1.03 g) and aluminum chloride (0.73 g) in absolute ether (75 ml), ethyl 3-methyl-2-nonenoate (2.14 g) in ether (20 ml) was added dropwise at −30°. After being stirred for 15 min at −30°, the mixture was hydrolyzed with wet ether and saturated aqueous ammonium chloride and then extracted with ether. Glpc (10% SE-30 on 60–80 Firebrick, 135°; retention time (*cis*) 6.2 min, retention time (*trans*) 6.5 min) showed a shorter retention time (4 min) impurity (~15%) which was probably the saturated alcohol 3-methylnonan-1-ol, an innocous impurity since it would be unreactive in the next condensation.

2-Methyl-3-(3-methyl-2-nonenyl)-1,4-naphthoquinone (XIX). Using crude 3-methyl-2-nonen-1-ol (above), boron trifluoride etherate, and 2-methyl-1,4-naphthoquinone under standard reaction conditions,[22] the allylic naphthoquinone XIX was prepared. Purification was effected by column chromatography to yield a mobile yellow oil; uv: 325 nm (ϵ 3050), 268 (16,690), 260 (17,000), 248 (17,990), and 243 (17,000); nmr: 7.8 (m, 4, ArH), 4.96 (t, 1, C=CH, J = 7 Hz), 3.27 (d, 2, CH_2CH=, J = 7 Hz), 2.11 (s, 3, ArCH$_3$), and 1.76 (s, 3, C=CCH$_3$); mass spectrum: m/e 310 (M$^+$, 80), 295 (10), 225 (90), 198 (100), and 186 (40).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.3; H, 8.4. Found: C, 81.4; H, 8.4.

Comparative Photolysis of 2-Methyl-3-(3-methyl-2-nonenyl)-1,4-naphthoquinone (XIX) and MK-2 (XVIII). MK-2 (XVIII) (40 mg) and the allylic naphthoquinone XIX (40 mg) were photolyzed together in cyclohexane (100 ml). The solvent was carefully evaporated but not to complete dryness and the residue was diluted to 1 ml with ether. A 10-μl aliquot was assayed by glpc (6 ft × 0.25 in. column of 20% propylene glycol succinate on 60–80 Firebrick) and compared with a standard mixture containing 100 μg each of 2-octanone (retention time 4 min) and 2-methyl-2-hepten-6-one (retention time 5 min). The yields were: 2-octanone, 8.6 mg, 52%; 2-methyl-2-hepten-6-one, 1.9 mg, 12%.

Photostability of 2-Methyl-2-hepten-6-one. Two separate photolysis mixtures were made—one (A) containing MK-2 (40 mg) in 100 ml of cyclohexane and the other (B) containing, in addition, 2-methyl-2-hepten-6-one (25 mg); both were photolyzed for 1 hr after which 2-methyl-2-hepten-6-one (25 mg) was added to A. Both solutions were evaporated and each residue was diluted to 1 ml with ether. Glpc assay (above) showed the same ketone content in both A and B, indicating the ketone to be photostable.

Degradation of Ketone XIV from MK-9 (II-H). A. Reduction of Ketone XIV. The ketone (23 mg) was heated to reflux in absolute ethanol (3 ml) and tosyl hydrazide (11 mg) for 30 min, after which time tlc (solvent: 40% ethyl ether in petroleum ether) indicated the condensation to be complete. Four portions of sodium borohydride (40 mg each) were added while the solution was at reflux. After 1 hr the solution was cooled and acidified with dilute HCl, and the product was extracted into ether. Chromatography (eluent: petroleum ether) gave the colorless alkene XX as an oil (9 mg); mass spectrum: m/e 590 (M$^+$).

B. Ozonolysis of Alkene XX. Alkene XX (1 mg) was dissolved in methylene chloride (0.5 ml) and methanol (0.5 ml). The mixture was cooled in a Dry Ice–acetone bath and a stream of ozone enriched oxygen from a flow-through microozonizer[23] was bubbled into the solution until an excess of ozone was present. The solution was then flushed with nitrogen and trimethyl phosphite (5 mg) was added after which the solution was allowed to warm to room temperature. 2,4-Dinitrophenylhydrazine (7 mg), absolute ethanol (2 ml), and a drop of concentrated HCl were added, and the solution was refluxed for 5 min. The solvent was evaporated and the mixture chromatographed (eluent: 15% ethyl ether in petroleum ether), the 4-methylnonanal 2,4-dinitrophenylhydrazone being the first orange fraction; mass spectrum: m/e 336 (M$^+$, 60), 265 (30), 224 (70), 206 (100), and 83 (50).

(23) M. Beroza and B. A. Bierl, *Anal. Chem.*, **38**, 1976 (1966).

The Hydrolysis of Thioimidate Esters. II.[1] Evidence for the Formation of Three Species of the Tetrahedral Intermediate

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Abstract: The yield of amine formed on hydrolysis of the two thioimidate esters I and II varies with pH in a complex manner which has been interpreted in terms of two alternative mechanisms. The first involves three tetrahedral addition intermediates (cationic, neutral, and anionic) in acid–base equilibrium, each species partitioning to different ratios of amine to amide product. According to the second mechanism, hydrolysis proceeds *via* an anionic intermediate and two intermediates of zero net charge. Interconversion of the latter two species requires diffusion-controlled general acid–base catalysis. Buffer catalysis of amine formation with a tetrahedral intermediate generated from ethyl thioacetimidate (III) occurs with a Brønsted slope β = 0.94. This finding is, within experimental error, consistent with the value of β = 1.00 expected for a diffusion-controlled proton transfer and supports the second mechanism. Quantitative relationships are presented which allow the calculation of predicted rate–pH profiles for aminolysis reactions of esters and thiolesters which proceed *via* cationic, neutral, and anionic intermediates.

In 1959, Martin, *et al.*, showed that an unstable intermediate was formed during the hydrolysis of 2-methyl-Δ^2-thiazoline, and suggested that the same tetrahedral addition intermediate lay on the reaction pathway for the intramolecular aminolysis of the thiol ester S-acetylcysteamine.[2] A kinetic study of the latter reaction also gave evidence for an intermediate, although some features of the aminolysis reaction and of thiazoline hydrolysis could not be accommodated

(1) For a previous study in this series, see: R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Am. Chem. Soc.*, **89**, 6984 (1967).

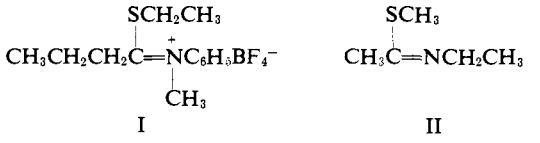
(2) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *ibid.*, **81**, 5089 (1959).

by a single, comprehensive, reaction scheme.[3] Subsequently, the study of the hydrolysis of acyclic thioimidate esters revealed that two species of the tetrahedral intermediate participated in the hydrolysis process.[1] The assumptions that these two forms of the intermediate represented a conjugate acid–base pair and that the same intermediates were necessarily produced during the aminolysis of thiol esters had two major consequences: (a) the aminolysis reaction undergoes a change in rate-determining step with pH, and (b) the nature of the rate-determining step for aminolysis at various pH values may be assigned by examination of the products of thioimidate ester hydrolysis.[1,4] Recently, Barnett and Jencks[5] have shown that the initial products of thiazoline hydrolysis also vary with pH and have advanced an explanation which appears to reconcile the dissonant aspects of thiazoline hydrolysis and intramolecular thiol ester aminolysis.

In our previous work on thioimidate ester hydrolysis, experiments were carried out over a limited range of pH only, owing to inconveniently slow rates of hydrolysis or to the onset of parasitic side reactions.[1] As a result of extending our studies over a wider pH region with each of two thioimidate esters, we are led to new conclusions concerning the structure of the tetrahedral intermediates formed in thioimidate hydrolysis and, probably, in thiol ester aminolysis.

Results

Selection of the thioimidate esters I and II for detailed



I II

study was guided by the following considerations. First, neither compound could undergo the base-catalyzed elimination reaction, characteristic of thioimidates unsubstituted on nitrogen, which yields nitrile and mercaptan.[1,6,7] The second objective was to avoid the pronounced decrease in the rate of hydrolysis which occurs near neutral pH with many imines as a result of the decrease in the concentration of the protonated species.[2,8] This aim was achieved in two ways: (a) by using a cationic thioimidate ester (I) incapable of deprotonation;[1,9] (b) by using a thioimidate ester (II) of sufficiently high pK so that the pH-independent rate of hydrolysis at alkaline pH might be expected to be at least as high as the rate of hydrolysis in weakly acidic solution.[9a,10]

The pH–rate profiles for disappearance of I and II in 10% acetonitrile–water at 30° conform to expectation (Figure 1). The rate data for I are extrapolated to zero buffer concentration in those pH ranges where catalytic effects were noted. Buffer concentrations of up to 0.08 M caused increases of no more than 35% over the extrapolated values (acetate and imidazole buffers). With II, most experiments were carried out at the single buffer concentration of 0.02 M and no correction was applied. The profile for I resembles closely that for the hydrolysis of other quaternary thioimidates;[9a,11] the hydrolysis of II is similar to that of the relatively basic thioimidate 2-methyl-5,6-dihydro-1,3-thiazine[9a] and of basic imidate esters.[10b]

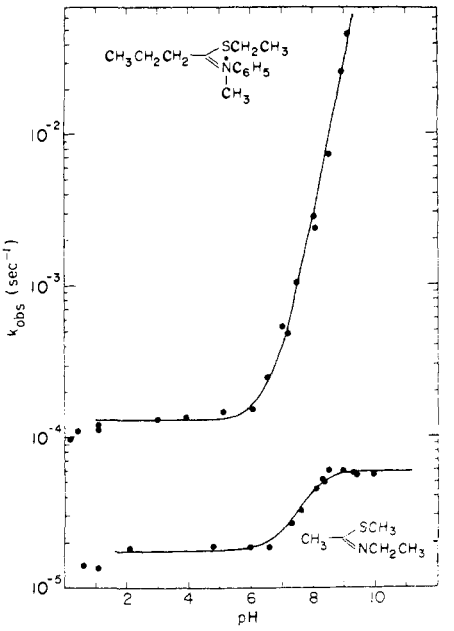


Figure 1. pH–rate profiles for hydrolysis of thioimidate esters I and II in 10% acetonitrile–water, μ = 0.50, 30°. Solid curves are calculated from eq 1 and 2, using constants of Table I.

The data of Figure 1 are again interpreted in terms of the familiar mechanism proposed in many earlier cases.[8,10b,12] For the present purpose, the salient feature of the hydrolysis mechanism at pH 2–10 is the rate-determining attack of water or hydroxide ion on the cationic substrate to give intermediates which rapidly yield the products of hydrolysis. We concern ourselves below with the question of the structure of the reaction intermediates and its relationship to the nature of the hydrolysis products. The small rate decreases noted at pH <2 are equivocal: possibly suggestive of an approaching transition in rate-limiting step,[2] they more likely result from activity coefficient effects seen in media of increasing ionic strength.[13] The solid lines (Figure 1) are calculated from eq 1 or 2, using the constants

$$k_{obsd} = k_5 + k_7[OH^-] \quad (1)$$

$$k_{obsd} = \frac{[H^+](k_5 + k_7[OH^-])}{([H^+] + K_a)} \quad (2)$$

summarized in Table I.[14] The kinetically derived

(3) (a) R. B. Martin and R. I. Hedrick, *J. Am. Chem. Soc.*, **84**, 106 (1962); (b) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964).
(4) G. L. Schmir, *J. Am. Chem. Soc.*, **90**, 3478 (1968).
(5) R. Barnett and W. P. Jencks, *ibid.*, **90**, 4199 (1968).
(6) A. Bernthsen, *Ann. Chem.*, **197**, 341 (1879).
(7) W. Autenrieth and A. Brüning, *Ber.*, **36**, 3464 (1903).
(8) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965), and references cited therein.
(9) For studies of the hydrolysis of quaternary immonium salts, see: (a) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961); (b) K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, **86**, 2413 (1964).
(10) (a) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963); (b) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **90**, 4413 (1968).
(11) G. E. Lienhard and T.-C. Wang, *ibid.*, **90**, 3781 (1968).
(12) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).
(13) G. M. Blackburn and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 2638 (1968).
(14) Equations 1 and 2 are based on the assumption that the rate-determining step for hydrolysis in the pH range of this study is nucleophilic attack on the C=N bond of I or of the conjugate acid of II.

Table I. Rate and Equilibrium Constants for the Hydrolysis of Thioimidate Esters at 30° [a,b]

	I	II
pK_a	[c]	7.75 ± 0.12
$k_5 \times 10^5$, sec^{-1}	13.0	1.77
k_7, M^{-1} sec^{-1}	3000	106
k_7/k_5, M^{-1}	2.3×10^7	6.6×10^6
pK' [d]	1.98	2.7
pK'' [d]	7.22	6.3
P^+ [d]	0.97	0.84
P^0 [d]	0.142	0.065
P^- [d]	0.006	0.001

[a] Constants are defined for the processes shown in Scheme I and eq 1 and 2. [b] In 10% acetonitrile–water, μ = 0.50 M. [c] Not defined. [d] Defined in Table V.

value of pK_a = 7.75 may be compared to those of 6.97 found for ethyl thioacetimidate[1] and of 7.6 for a six-membered cyclic thioimidate ester.[9a] Values of the ratio k_7/k_5 previously encountered with other thioimidate esters have been: 1×10^7 (2-methyl-Δ^2-thiazoline),[15] 1.3×10^7 (2-methyl-Δ^2-thiazine),[9a] 4.8×10^7 (ethyl N,N-dimethylthioacetimidate),[11] and 7.6×10^7 M^{-1} (2,3-dimethylthiazolinium ion).[9a]

The extent of C=N bond cleavage accompanying the hydrolysis of I was determined by colorimetric assay of N-methylaniline. As expected,[1] the amine yield varied with pH, and, at fixed pH, with buffer concentration (Table II). Buffer effects, however, were small, and the yields of amine produced at zero buffer concentration could be accurately estimated by linear extrapolations (Table II, columns 5 and 10). The intercept values obtained in these and additional experiments (Figure 2) do not vary with pH as the titration curve of a monovalent acid, in contrast to previous experience with thioimidate[1] and imidate esters.[8,10b] For the moment, we show that the more complex influence of pH on amine yield can be correlated with the ionization behavior of a hypothetical divalent acid whose three species break down to amine in 97, 14.2, and 0.6% yield, respectively, as pH increases. Transitions from one species to the other occur at pH 1.98

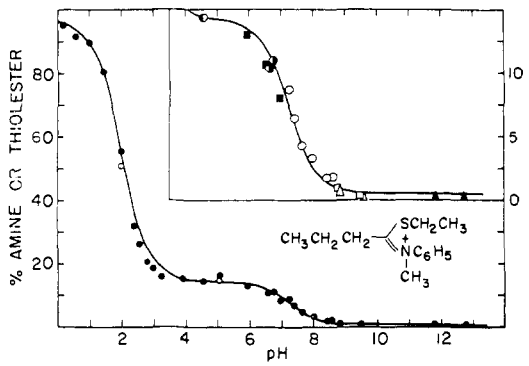


Figure 2. Effect of pH on the yield of N-methylaniline or of ethyl thiolbutyrate obtained on hydrolysis of I. The inset (ordinate, right scale) shows the data at pH 4–13 with an expanded ordinate. Buffers used at pH <4 are HCl and chloroacetate. At pH >4 (see inset): ◐, acetate; ■, maleate; ◑, imidazole; ○, Tris; △, borate; □, carbonate; ▲, NaOH. In the complete profile, the closed circles give the yield of amine and the open circles the yield of thiol ester. The solid lines are calculated from eq 3, using constants of Table I.

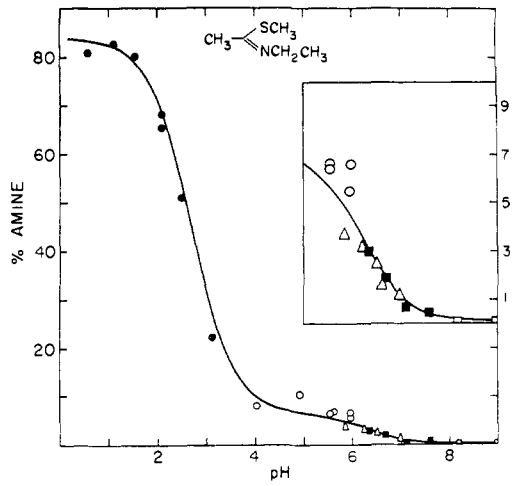
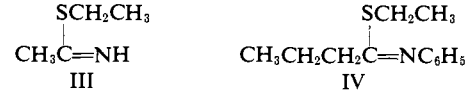


Figure 3. Effect of pH on the yields of ethylamine obtained on hydrolysis of II. The inset (ordinate, right scale) shows the data at pH 5–9 with an expanded ordinate. The following buffers were used: ●, HCl; ○, acetate; △, maleate; ■, tetramethyleneglutaric acid; □, borate. The solid lines are calculated from eq 3, using constants of Table I.

(pK') and 7.22 (pK''). The dependence of amine yield on pH calculated from these assumptions is in good accord with observation (Figure 2). The yields of thiol ester produced at three pH values were measured by reaction with hydroxylamine and agreed well with the yields of N-methylaniline.

Similar, although less precise, observations were made with the aliphatic thioimidate II (Table III and Figure 3). In this case, it proved difficult to correct accurately for buffer catalysis on amine yield at pH 4–6; as experienced earlier,[1] the hydrolysis products of thioimidates derived from aliphatic amines seem to be more sensitive to buffer effects. The solid line of Figure 3 is again calculated on the assumption that products are formed from three species in acid–base equilibrium, giving amine in yields of 84, 6.5, and 0.1%, respectively, with transitions at pH 2.7 and 6.3. Although these values may not be quantitatively correct, it is clear that the amine yields at pH 5–8 are not consistent with any mechanism involving a simple, sigmoid, product transition at about pH 2.7. That the first transition in products takes place at pH 2.7 is in accord with the effects of pH on the hydrolysis of ethyl thioacetimidate (III) (pK' = 2.71).[1] In the aromatic series, the changeover in products occurs at pH 2.89 with ethyl N-phenylthiobutyrimidate (IV);[1] N-methylation (to give I) hinders amine expulsion and shifts pK' to 1.98.

The hydrolysis of III is particularly susceptible to



buffer influences on the yield of thiol ester.[1] For reasons which are given below, data were obtained on the ability of some additional catalysts[16] to promote amine expulsion from III (Table IV). As before, K_{app} is a quantitative measure of catalytic effectiveness and is equal to the concentration of buffer required to give a half-maximal increase in thiol ester yield.

(15) G. L. Schmir, *J. Am. Chem. Soc.*, 87, 2743 (1965).

(16) Earlier data are summarized in Table II of ref 1.

Table II. Effects of Buffers and pH on the Yield of N-Methylaniline Obtained from Hydrolysis of I[a]

pH	Buffer	Concn,[b] M	Amine yield, %	Intercept,[c] %	pH	Buffer	Concn,[b] M	Amine yield, %	Intercept,[c] %
0.17	HCl		95.1		6.78	Imidazole	0.02	11.4	11.0
0.56			91.6		6.78		0.04	11.7	
1.00			89.8		6.80		0.08	12.4	
1.43			80.6		6.90	Maleate	0.02	8.3	8.0
2.00			55.4[d]		6.95		0.04	8.6	
2.41			31.8		6.98		0.08	9.0	
2.80			20.8		7.20	Tris	0.02	9.0	8.6
2.99	Chloroacetate	0.02	19.9	18.5	7.25		0.04	9.1	
2.98		0.04	21.4		7.26		0.08	10.1	
2.95		0.08	23.5		7.94	Tris	0.02	4.7[f]	3.3
3.25	Chloroacetate	0.02	16.6	15.8	7.99		0.04	6.0	
3.23		0.04	17.4		8.02		0.08	8.6	
3.22		0.08	18.9		8.75	Carbonate	0.02	1.1	0.9
3.89	Formate	0.02	16.6	16.1	8.82		0.04	1.3	
3.91		0.04	17.1		8.86		0.08	1.5	
3.92		0.08	18.0		9.49	Borate	0.02	0.4	0.35
5.06	Acetate	0.02	17.7[e]	15.0	9.57		0.04	0.5	
5.06		0.04	19.8		9.61		0.08	0.6	
					11.8	NaOH		0.3	

[a] At 30° in 10% acetonitrile–water, μ = 0.50 *M*. [b] Total concentration of all species of buffer. [c] Yield at zero buffer concentration, obtained by linear extrapolation. [d] Assay for thiol ester gave 50.5%. [e] Assay for thiol ester gave 14.2%. [f] Assay for thiol ester gave 3.0%.

Table III. Effects of Buffers and pH on the Yield of Ethylamine Obtained from Hydrolysis of Methyl N-Ethylthioacetimidate (II)[a]

pH	Buffer	Concn,[b] M	Amine yield, %	Intercept,[c] %	pH	Buffer	Concn,[b] M	Amine, yield, %	Inter-cept,[c] %
0.57	HCl		80.9		6.34	TMG[d]	0.02	3.0	2.95
1.13			82.6		6.34		0.03	2.9	
1.55			80.2		6.71	TMG[d]	0.02	1.8	1.8
2.09			65.5		6.72		0.03	1.8	
2.50			51.0		6.22	Maleate	0.02	3.2	3.2
3.13			22.1		6.22		0.03	3.2	
4.04	Acetate	0.02	18.2	8.0	6.63	Maleate	0.02	1.6	1.6
4.05		0.03	23.4		6.63		0.03	1.6	
5.55	Acetate	0.02	7.9	6.4	8.21	Borate	0.02	0.0	
5.54		0.03	8.7						

[a] At 30° in 10% acetonitrile–water, μ = 0.50 *M*. [b] Total concentration of all species of buffer. [c] Yield at zero buffer concentration, obtained by linear extrapolation. [d] Tetramethyleneglutaric acid (1,1-cyclopentanediacetic acid).

Asymptotically reached yields of thiol ester at high buffer concentration were 90–95% and K_{app} was calculated by computer fitting of the data to the equation for the three-parameter rectangular hyperbola.[1]

Discussion

It appears convincingly established that the hydrolysis of imidate and thioimidate esters proceeds through the formation and decomposition of tetrahedral addition intermediates. Firm support for this conclusion was first obtained by Martin and coworkers from studies of the effect of pH on the rate of hydrolysis of Δ^2-thiazolines and related compounds.[2,3b,9a] Subsequent investigations showed that the rate-determining step and product-forming step were independently affected by variation in pH and in buffer concentration.[1,8,10b,13,17] The latter observations are particularly useful criteria for the detection of intermediate species in those instances where the pH–rate profile for imidate hydrolysis offers no or ambiguous evidence for a transition in rate-determining step.

Assuming that the existence of intermediates in the hydrolysis of imidate esters has been satisfactorily proven, we examine the data of the present study in the light of questions concerning the number, structures, and properties of the intermediates formed from thioimidate esters. We pay principal attention to the effects of pH on product distribution (Figures 2 and 3) and, in the sequel, we develop our earlier conclusions[4]

Table IV. Effect of Carboxylic Acid Buffers on the Yield of Ethyl Thiolacetate Obtained from Hydrolysis of Ethyl Thioacetimidate (III)[a]

pH	Buffer	Concn,[b] M	Thiol ester, %	$K_{app} \times 10^2$,[c] M
3.18	CH_3OCH_2COOH	0.02	52.2	4.7 ± 0.6
3.16		0.03	59.6	
3.13		0.06	70.2	
3.12		0.18	85.1	
3.97	CH_3OCH_2COOH	0.02	27.6	11.8 ± 2.4
3.98		0.04	34.3	
3.98		0.06	42.9	
4.05		0.18	66.4	
4.06		0.36	82.4	
4.16	$ClCH_2CH_2COOH$	0.02	26.4	5.2 ± 1.8
4.20		0.04	40.0	
4.24		0.08	58.0	
4.26		0.30	80.9	
4.38	CH_3COOH	0.02	29.6	4.6 ± 0.6
4.39		0.03	40.7	
4.43		0.08	59.7	
4.44		0.30	80.4	

[a] At 30° in 10% acetonitrile–water, μ = 0.45. [b] Total concentration of all species of buffer. [c] Standard deviation is indicated.

(17) (a) B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.*, **88**, 551 (1966); (b) M. Kandel and E. H. Cordes, *J. Org. Chem.*, 32, 3061 (1967); (c) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 90, 2622 (1968).

regarding the mechanism of the aminolysis of esters and thiol esters.

Several mechanisms of thioimidate hydrolysis are consistent with a two-stage variation of amine yield with pH. We select two possibilities for detailed discussion, with emphasis on the implications of each for ester (thiol ester) aminolysis.

Cationic, Neutral, and Anionic Intermediates in Acid–Base Equilibrium

The mechanism pictured in Scheme I is in quantitative agreement with the observed effects of pH on both rates and products of hydrolysis (Figure 1–3). This formulation states that hydrolysis proceeds *via* nucleophilic addition of solvent species to yield one or more species of the tetrahedral intermediate (TH_2^+, TH, and T^-), depending on pH. Each species breaks down to amine and amide, although possibly to different extents which are represented by the partitioning factors P^+, P^0, and P^- (defined in Table V). Throughout the pH range investigated, hydration of the C=N bond of the imidate is rate determining, and the influence of pH on the product distribution is not reflected in the kinetics of imidate disappearance.

Table V. Definitions of Parameters Used in Calculation of pH–Product Profiles for Thioimidate Ester Hydrolysis and pH–Rate Profiles for Thiol Ester Aminolysis[a]

$$K' = (k_2' + k_3')K_1/(k_2 + k_3)$$
$$K'' = (k_2'' + k_3'')K_2/(k_2' + k_3')$$
$$P^+ = k_2/(k_2 + k_3)$$
$$P^0 = k_2'/(k_2' + k_3')$$
$$P^- = k_2''/(k_2'' + k_3'')$$

[a] Rate and equilibrium constants refer to steps of Scheme I.

Use was made of the steady-state approximation to show that the dependence of amine yield on pH is given by eq 3, where pK' and pK'' (see Table V) are the pH values where transition occurs between the product set arising from the intermediates TH_2^+ and TH, and TH and T^-, respectively. The constants K' and K'' are equivalent to the dissociation constants K_1 and K_2 only in cases where the ratios $(k_2' + k_3')/(k_2 + k_3)$ and $(k_2'' + k_3'')/(k_2' + k_3')$ are equal to unity. The solid curves of Figures 2 and 3 are calculated from eq 3 using the values of the constants listed in Table I.

$$\text{amine yield} = \frac{P^+ + \frac{P^0K'}{[H^+]} + \frac{P^-K'K''}{[H^+]^2}}{1 + \frac{K'}{[H^+]} + \frac{K'K''}{[H^+]^2}} \qquad (3)$$

The product transition occurring at low pH may now be assigned to the transition between species TH_2^+ and TH rather than to the TH–T^- transition; the limited data previously obtained[1] did not allow an unambiguous choice to be made between the two alternatives, although the kinetics of thiol ester aminolysis tended to support the present interpretation.[4] Varying degrees of confidence are to be attached to the numerical values selected to give acceptable fits to eq 3. With both I and II, pK' and pK'' seem reasonably accurate, especially with the former substance. On the other hand, it is not possible to specify the degree to which P^+ and P^- differ significantly from 100 and 0%, respectively, except with II, where the deviation of P^+ from 100% seems well beyond experimental error. Since the magnitude of the terms P^+ and P^- determine the extent to which acid- and base-catalyzed pathways are important in the aminolysis of thiol esters (see below), precise knowledge of the partitioning factors is required for the accurate prediction of the aminolysis pH profile.

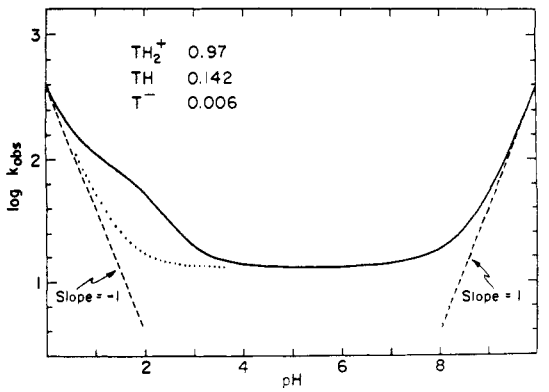


Figure 4. Predicted pH–rate profile for the aminolysis of ethyl thiolbutyrate with N-methylaniline. The solid curve is calculated from eq 10, using the values of the parameters P^+, P^0, P^-, K', and K'' deduced from the hydrolysis of I (see Table V). The dotted line is calculated for a mechanism obeying eq 4. The ordinate is in arbitrary units.

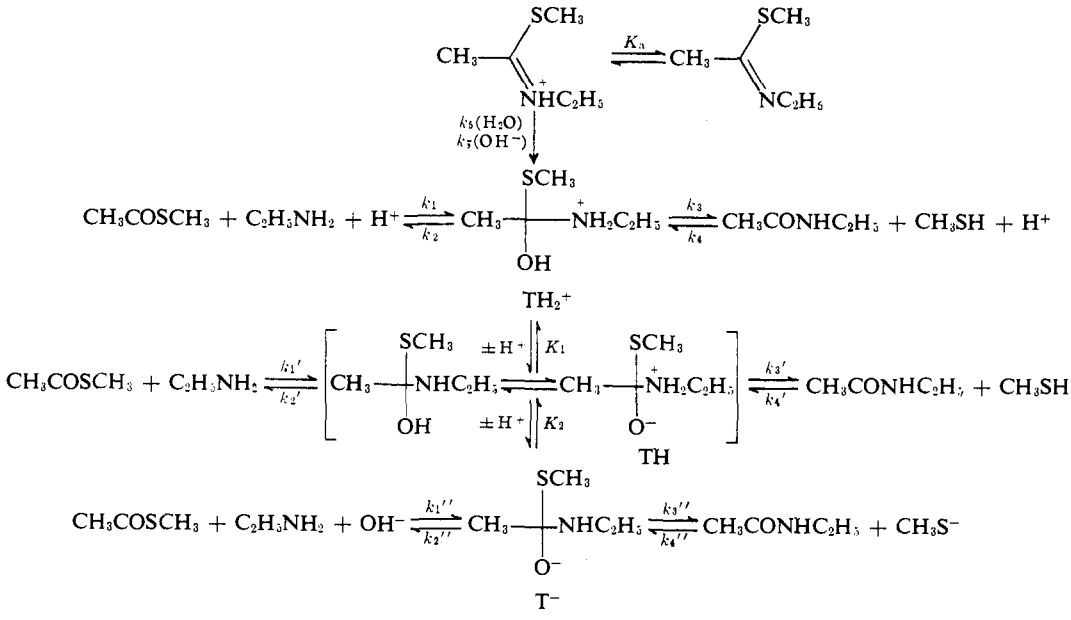
Earlier work with imidate esters derived from aliphatic alcohols has shown that the kinetic transition from TH to T^- takes place in the pH range 6.3–8.4, with TH yielding almost exclusively amine while T^- is converted largely to amide.[8,10b,13] Exceptional behavior is shown by phenyl N-methylacetimidate, whose product–pH profile resembles those of I and II and has been similarly interpreted.[17c] With these three compounds, the predominant expulsion of amine from TH_2^+ presumably results from amine protonation. The lower yield of amine at pH 4–6 may be the consequence of an unfavorable equilibrium between neutral and zwitterionic species of TH, the former expelling mercaptan preferentially. It is clearly of interest to further define the factors which determine the partitioning ratios P^+, P^0, and P^- as well as the relative importance of the intermediates as a function of pH.

If the aminolysis of esters and thiol esters proceeds through tetrahedral intermediates identical with those generated in imidate hydrolysis, and the rate of interconversion of the several intermediate species is fast (*i.e.*, proton transfers are not rate determining), then it is possible to predict the rate–pH profile of the aminolysis reaction from the product–pH profile of the imidate hydrolysis.[4] The predicted rate–pH profile for the reaction of N-methylaniline with ethyl thiolbutyrate was calculated from eq 10 (Appendix), using the parameters of Table I, and is shown in Figure 4 (solid line). In over-all appearance, the calculated pH–rate profile resembles that for the simple rate law of eq 4 but deviates appreciably from the latter in the pH range 0.5–3. The gentle slope of about −0.4 in that region reflects

$$k_{obsd} = k_H[H^+] + k_{H_2O} + k_{OH}[OH^-] \qquad (4)$$

the transition from TH_2^+ to TH at pH 2. The second product transition at pH 7.2 causes an imperceptible rate increase near neutral pH, largely masked by the onset of hydroxide-catalyzed aminolysis at *ca.* pH 8.

Scheme I

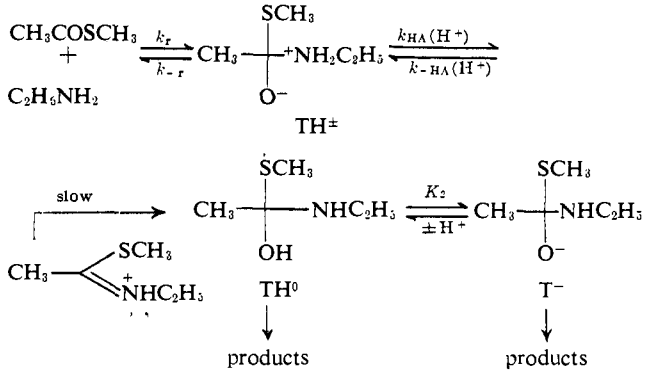


It is important to note that the pH values at which specific acid and base catalysis set in are directly dependent on the partitioning factors P^+ and P^-. Since these terms are of low accuracy in this work, the pH–rate profile is not well defined at the extremes of pH. Finally, it should be emphasized that hydroxide ion catalysis at pH >8 represents catalysis of the nucleophilic attack of amine on thiol ester; on the other hand, the acid-catalyzed reaction seen at pH <1 reflects the increasing concentration of the cationic species TH_2^+ whose breakdown is rate limiting. Thus, despite the superficial resemblance of the calculated profile to that predicted for simple catalysis of a nucleophilic attack step which is rate determining throughout the entire pH range (eq 4), pH dependencies such as that seen in Figure 4 may conceal complex mechanistic events.

A mechanism including only rate-determining formation or breaking of bonds to carbon (Scheme I) is in agreement with presently available data on the hydrolysis of acyclic thioimidate esters. With 2-methyl-Δ^2-thiazoline, the effect of pH on the hydrolysis products is not consistent with the kinetics of acetyl transfer in S-acetylcysteamine. To resolve this problem, Barnett and Jencks have proposed an ingenious mechanism involving, at some pH values, a rate-determining proton transfer between two species of the tetrahedral intermediate.[5] We now consider the relevance of this hypothesis to the hydrolysis of I and II.

The Conversion of Neutral to Zwitterionic Intermediates by Diffusion-Controlled Proton Transfers. The essential features of the mechanism of Scheme II are: (a) rate-determining hydration of the thioimidate ester yields two species of the tetrahedral intermediate (TH^0 and T^-), with partitioning factors P^0 and P^-; (b) the zwitterionic intermediate $TH^\pm$ breaks down exclusively to amine; conversion of the uncharged species of zero net charge (TH°) to its zwitterionic counterpart ($TH^\pm$)

Scheme II



requires acid catalysis. Although the proton transfer step (k_{-HA}) is probably never rate limiting in imidate hydrolysis, the reverse step k_{HA} may become rate limiting in the aminolysis of the thiol ester.

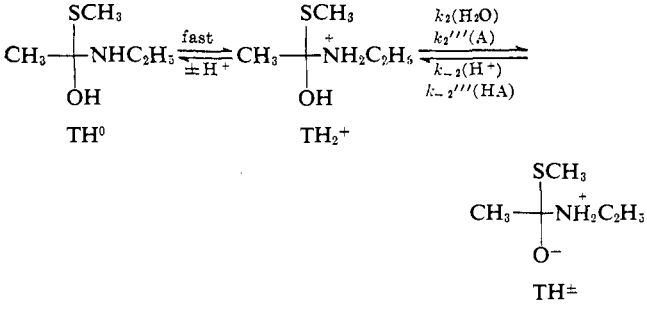
The mechanism of Scheme II predicts that the dependence of amine yield on pH will obey a relationship analogous to eq 3, and thus be described by curves such as those of Figures 2 and 3. This conclusion necessarily follows from the fact that acid catalysis is required to interconvert species $TH^\pm$ and T^0, although both possess zero net charge. Put another way, product analysis does not distinguish between a mechanism involving a neutral and cationic intermediate in rapid equilibrium, or a mechanism involving the (relatively) slow, acid-catalyzed, conversion of a neutral intermediate (TH^0) to another neutral species ($TH^\pm$).

The rate–pH profiles and product–pH profiles for I and II can be equally well accommodated by Schemes I and II. In the case of 2-methyl-Δ^2-thiazoline, two criteria were used to rule out a mechanism analogous to that of Scheme I: (a) although the kinetics of

thiol ester aminolysis demand that, at some pH values, a cationic transition state be on the reaction pathway, the hydrolysis of the thiazoline is inhibited at acid pH;[2,3] (b) the observed pH–rate profile for the aminolysis reaction deviates markedly from that predicted from the effect of pH on the products of thiazoline hydrolysis, assuming that intermediates are in rapid equilibrium.[4,5] With I and II, neither criterion can be applied since (a) the meager rate decreases at low pH probably reflect changes in the activity of water, and (b) no data are available concerning the kinetics of the corresponding thiol ester aminolysis.

The acid-mediated isomerization of TH^0 to $TH^{\pm}$ postulated by Barnett and Jencks[5] proceeds in two steps (Scheme III), a rapid proton transfer to nitrogen,

Scheme III



followed by a relatively slow, base-catalyzed, proton abstraction from oxygen (A and HA are buffer components). Studying the reverse reaction, Barnett and Jencks observed that the Brønsted slope α for the general acid catalyzed step k_{-2}''' was 0.03, providing strong support for a diffusion-controlled, proton-transfer reaction.

The influence of general acid–base catalysts in thioimidate ester hydrolysis manifests itself mainly on the product distribution, and has been interpreted either in terms of the interaction of general base catalysts with the conjugate acid of an intermediate pair (in this case, A and TH_2^+) or in terms of its kinetic counterpart (HA and TH^0).[1] Using the former mechanism, the abilities of basic catalysts (relative to water) to promote the expulsion of amine from TH_2^+ is given by eq 5,[1,4,17a] where k_2 and k_2''' refer to catalysis by water and general bases, K_a' is the acid dissociation constant of the catalyst, and pK' is the pH where transition occurs between the two sets of products. It is not possible to measure k_2''' directly since the rate-limiting step of thioimidate hydrolysis is the formation of the intermediates; however, by determining the *relative* catalytic efficiencies of a series of general bases in increasing amine yield in the hydrolysis of III, data are obtained which allow the construction of a Brønsted plot for step k_2''', if indeed the mechanism of Scheme III is generally applicable to acyclic thioimidate esters (Table VI).

The Brønsted plot (Figure 5) which relates k_2''' to pK_a has a slope β of 0.94 (least squares), with catalyst basicity varying over 4.5 pK units. A value of β = 1.00 is expected[18] for a diffusion-controlled proton transfer in the thermodynamically unfavorable direction. The present finding suggests that the mechanism of hydrolysis of 2-methyl-Δ^2-thiazoline[5] may apply to acyclic thioimidate esters as well.

Table VI. General Base Catalysis of Amine Expulsion from a Cationic Tetrahedral Intermediate Formed in the Hydrolysis of III[a]

Catalyst	pK_a'	k_2'''/k_2, M^{-1} [b]
$CNCH_2COO^-$	2.42[a,c]	38
$CH_3OCH_2COO^-$	3.55[a,c]	270
$ClCH_2CH_2COO^-$	4.09[a,c]	1000
CH_3COO^-	4.76[a,c]	2800
HPO_4^{2-}	6.77[d]	340,000
Imidazole	7.02[d]	750,000

[a] At 30° in 10% acetonitrile–water, μ = 0.45. [b] Calculated from eq 5. Values of K_{app} are taken from Table IV of this paper and Table II of ref 1; pK' = 2.71. [c] Determined by titration of the sodium salts (0.05 M) with 0.5 N HCl; the titration data were analyzed by the method of Reed and Berkson (W. M. Clark, "Oxidation–Reduction Potentials of Organic Systems," Williams and Wilkins Co., Baltimore, Md., 1960, p 149). [d] At 30° in 10% acetonitrile–water, μ = 0.50.[8]

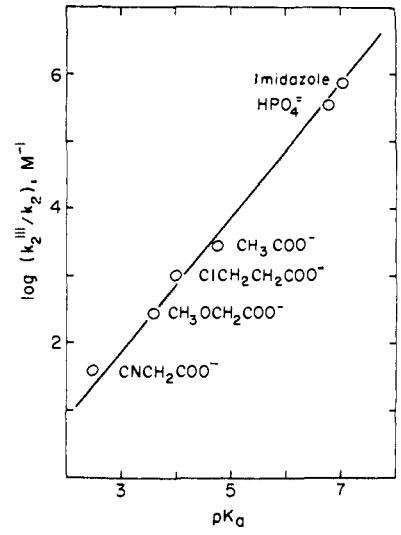


Figure 5. Brønsted plot for catalysis of amine expulsion from the tetrahedral intermediates formed from III.

$$K_{app} = \frac{(k_2'/k_2''')([H^+] + K')([H^+] + K_a')}{[H^+]K_a'} \quad (5)$$

In summary, both Schemes I and II are compatible with the available information on the hydrolysis of thioimidates I, II, and III, although the buffer catalysis experiments tend to favor Scheme II. It is not yet known to what extent proton transfer reactions must be explicitly considered in other imidate and acyl transfer systems.

Experimental Section[19]

Methyl[α-(ethylthio)butylidene]phenylammonium Tetrafluoroborate (I). A. N-Methylbutyranilide. To a solution of 21.4 g (0.2 mol) of freshly distilled N-methylaniline in 40 ml of benzene was added dropwise 31.6 g (0.2 mol) of butyric anhydride, and the mixture was refluxed for 45 min. After removal of the solvent *in*

(18) (a) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964); (b) M. Eigen, *Discussions Faraday Soc.*, **39**, 7 (1965).

(19) All melting points are uncorrected. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

vacuo, the residue was dissolved in 100 ml of ether and extracted with five 100-ml portions of 5% aqueous $NaHCO_3$, followed by washing with dilute aqueous HCl and saturated aqueous NaCl solution. The ethereal phase was dried with $MgSO_4$; most of the solvent was removed *in vacuo* and the residue distilled. The main fraction (70% yield) was a colorless liquid, bp 99° (1.4 mm), $n^{25}D$ 1.5189 (lit.[20] bp 143° (17 mm), $n^{25}D$ 1.5183); the ultraviolet spectrum (CH_3CN) showed: λ_{max} 232 mμ (ε 5000); infrared spectrum (thin film): 6.01 and 6.24 μ.

B. N-Methylthionbutyranilide. The general method of Hahn, *et al.*,[21] to convert amides to thionamides was used. To a solution of 11.1 g (0.063 mol) of N-methylbutyranilide in 50 ml of pyridine (dried over NaOH and distilled) was added, in small portions over a period of 30 min, 14 g (0.063 mol) of P_2S_5. The mixture was maintained at reflux temperature for 45 min; the hot supernatant liquid was separated from a copious tarry sediment by decantation into 250 ml of water at 60°. After cooling, the resulting aqueous suspension was extracted with six 50-ml portions of ether. The ethereal phase was then washed successively with several 30-ml portions of 3 *N* HCl (until the aqueous wash remained acidic) and with saturated aqueous NaCl solution. After drying over $MgSO_4$, the ether was evaporated *in vacuo* and the residue distilled. The product, obtained in 50% yield, was a golden liquid, bp 122–123° (1.3 mm); $n^{25}D$ 1.5861 (*Anal.* Calcd for $C_{11}H_{15}NS$ (193.30): C, 68.33; H, 7.82; N, 7.25; S, 16.58. Found: C, 68.35; H, 8.04; N, 7.06; S, 16.45); ultraviolet spectrum (CH_3CN): λ_{max} 276 mμ (ε 17,000); infrared spectrum (thin film): 6.24 μ (aromatic C=C), no absorption in the region 5–6 μ.

C. The preparation of I was accomplished by dropwise addition of a solution of 2.05 g (0.011 mol) of N-methylthionbutyranilide in 2.5 ml of CH_2Cl_2 to an ice-cold solution of 2 g (0.011 mol) of triethyloxonium tetrafluoroborate[22] in an equal volume of CH_2Cl_2. The reaction mixture was kept 1 hr at 0° and an equal period at room temperature. On addition of 20 ml of sodium-dried ether, the product was obtained as colorless crystals (2.9 g, 88% yield). Recrystallization of 2.4 g of crude I from 20 ml of CH_2Cl_2 and 50 ml of ether gave 1.91 g of I, mp 86–88° (*Anal.* Calcd for $C_{13}H_{20}NSBF_4$ (309.18): C, 50.48; H, 6.52; N, 4.53; S, 10.37. Found: C, 50.52, H, 6.57; N, 4.48; S, 10.55); ultraviolet spectrum (CH_3CN): λ_{max} 263 mμ (ε 12,000); infrared (Nujol): 6.38 μ, with a shoulder at 6.26 μ.

In preliminary work, a solution of N-methylthionbutyranilide in dry acetone was heated at reflux temperature for 2.5 hr with a small excess of ethyl iodide to form the iodide salt corresponding to I (35% yield, mp *ca.* 134°).[23] Treatment of the iodide in acetonitrile solution with 1 equiv of anhydrous $AgClO_4$ yielded the corresponding perchlorate salt, mp 121–122°, which could be recrystallized from acetonitrile–ether and had an ultraviolet spectrum closely similar to that of I. The difficulty of separating the perchlorate salt from contaminating $AgClO_4$ led to the abandonment of this approach in favor of the use of triethyloxonium tetrafluoroborate as alkylating agent.

Methyl N-Ethylthioacetimidate (II). A. N-Ethylthionacetamide was prepared in 38% yield from N-ethylacetamide by the method described above for N-methylthionbutyranilide. The product had bp 82° (0.9 mm);[24] $n^{25}D$ 1.5562 (lit.[25] bp 140° (20 mm); $n^{20}D$ 1.5590[26]); ultraviolet spectrum (CH_3CN): λ_{max} 265 mμ (ε 12,100).[27]

B. Conversion of N-ethylthionacetamide to II was accomplished by the method described[29] for the analogous N-methyl compound. Ice-cold methyl iodide (2.8 g, 0.02 mol) was added dropwise (slowly enough to avoid an exothermic reaction) to 1 g (0.01 mol) of N-ethylthionacetamide maintained at 0°. The yellow crystals which separated during the next 2 hr at 0° were washed with ether, then agitated with a mixture of aqueous K_2CO_3 (5.6 g in 10 ml of H_2O) and ether. The ethereal phase was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and distilled. The product was a colorless liquid, bp 49–50° (25 mm); $n^{25}D$ 1.4844 (lit.[26] bp 44–48° (12 mm); $n^{20}D$ 1.4893) (*Anal.* Calcd for $C_5H_{11}NS$ (117.21): C, 51.23; H, 9.46; N, 11.95. Found: C, 51.01; H, 9.48; N, 11.72); ultraviolet spectrum: λ_{max} 231 mμ (ε 5900) in ethanol; λ_{max} 264 mμ (ε 9900) in 98% aqueous ethanol containing 0.1 *N* HCl;[30] infrared spectrum (thin film): 6.13 μ (C=N).

Ethyl thioacetimidate hydrochloride (III) and **ethyl thiolacetate** were samples used previously.[1] **N-Methylaniline hydrochloride,** prepared by passing gaseous HCl into the ethereal solution of the amine, was recrystallized twice from ethanol–ether and had mp 125° (lit.[31] 125°). **Ethylamine hydrochloride** (Eastman) had mp 112–114° (lit.[32] 110°) after two recrystallizations from ethanol–ether.

Kinetic Measurements. Acetonitrile and imidazole were purified as previously described.[8] 1,1-Cyclopentanediacetic acid (Aldrich Chemical Co.) was recrystallized from hot water. Other buffers and inorganic salts were of reagent grade and were used without further purification. Glass-distilled water was employed throughout and was boiled prior to use in experiments at pH >7.

The medium used for the kinetic studies was 10% acetonitrile–water (v/v), at ionic strength 0.50, adjusted with added KCl (except in acidic solution of pH <0.3, where the concentration of HCl exceeded 0.5 *M*). Constant pH was maintained with HCl, chloroacetate, formate, acetate, imidazole, Tris, and borate buffers in the appropriate ranges. With I, buffer concentration at fixed pH varied in the range 0.02–0.08 *M*. The hydrolysis of II was investigated at buffer concentrations of 0.02 *M*.

Rates of hydrolysis were determined spectrophotometrically by following the decrease in absorbance at 266 mμ (I, concentration *ca.* 6×10^{-5} *M*) and, with II, at 245 mμ (pH <8) or 230 mμ (pH >8), the concentration of II varying in the range $0.7–1.2 \times 10^{-4}$ *M*. The apparatus used has been described previously, and first-order rate constants were calculated as usual.[1]

In one experiment, the rate of hydrolysis of I (1.9×10^{-3} *M*) was measured by hydroxamic acid assay[1] of the thiol ester produced. Although the yield of thiol ester is only about 20% at pH 5.12 (0.05 *M* acetate buffer), in the present assay the molar extinction coefficients of the products of reaction of hydroxylamine with ethyl thiolbutyrate and I are 3000 and 200, respectively. The consequent increase in absorbance at 540 mμ allowed the calculation of a rate constant of 1.74×10^{-4} sec^{-1}, in good agreement with that of 1.69×10^{-4} sec^{-1} obtained from the disappearance of I.

Product Analysis. Use was made of colorimetric methods for the determination of N-methylaniline and ethylamine produced in the hydrolysis of I and II, respectively. In some cases, the concurrent formation of ethyl thiolbutyrate (from I) was measured. Reactions were allowed to proceed to completion under conditions identical with those employed in the kinetic experiments except that substrate concentrations were higher in pH regions where the yield of amine was low. In the case of III, previously determined kinetic data were used.[1] Solutions of N-methylaniline, ethylamine, and ethyl thiolacetate were maintained under conditions identical with those used in the hydrolysis experiments and were assayed in the same way as the latter. To calculate the yield of ethyl thiolbutyrate formed from I, ethyl thiolacetate was employed as colorimetric standard.

A. N-Methylaniline was assayed colorimetrically by means of a modification of the procedure of Sawicki, *et al.*[33] To 1-ml aliquots of reaction mixtures were added successively 3 ml of 2 *M* chloroacetic acid buffer (pH 2.34, 25% free base), 1 ml of H_2O, and 0.5 ml of a (previously filtered) 0.35% aqueous solution of 3-methyl-2-benzothiazolone hydrazone hydrochloride (Aldrich Chemical Co.). Ten minutes later was added 1 ml of 0.6% $FeCl_3 \cdot 6H_2O$ in 0.01 *N* HCl and the mixture kept at 30° for 30 min, with occasional shaking to remove slowly evolving gas bubbles. The ab-

(20) S. I. Gertler and A. P. Yerington, U. S. Department of Agriculture, Agricultural Research Service, Entomology Research Branch ARS-33-31, 1956; *Chem. Abstr.*, 50, 17297 (1956).

(21) V. Hahn, Z. Stojanac, O. Scedrov, N. Pravdic-Sladovic, S. Tomasic, and D. Emer, *Croat. Chem. Acta*, **29**, 319 (1957).

(22) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(23) The method used is similar to that described by B. Böttcher and F. Bauer, *Ann. Chem.*, **568**, 218 (1950).

(24) The boiling point reported herein is consistent with that found by Colebourne, *et al.*,[26] but not with that of 63–66° (0.02 mm) reported by Moore and Saville.[26]

(25) N. Colebourne, R. G. Foster, and E. Robson, *J. Chem. Soc., C*, 685 (1967).

(26) C. G. Moore and R. W. Saville, *ibid.*, 2082 (1954).

(27) The reported[26] value of ϵ_{max} 1260 at λ_{max} 264 mμ (solvent unspecified) seems inconsistent with the present finding. By comparison, the ultraviolet spectrum of N,N-dimethylthionacetamide (CH_3CN) shows λ_{max} 270 mμ (ε 15,400) and has been recorded[28] in ethanol with λ_{max} 269 mμ (ε 15,000).

(28) M. J. Janssen, *Rec. Trav. Chim.*, **79**, 454 (1960).

(29) I. L. Knunyants and L. V. Razvadovskaya, *J. Gen. Chem. USSR*, **9**, 557 (1939).

(30) The bathochromic shift observed on protonation of II is characteristic of thioimidates.[15]

(31) A. Key and P. K. Dutt, *J. Chem. Soc.*, 2035 (1928).

(32) G. W. Watt and J. B. Otto, *J. Am. Chem. Soc.*, **69**, 836 (1947).

(33) E. Sawicki, T. W. Stanley, T. R. Hansen, W. Elbert, and J. L. Noe, *Anal. Chem.*, **33**, 722 (1961).

sorbance of the deep blue solution at 570 mμ was compared to that of standard solutions of N-methylaniline hydrochloride. Aliquots (1-ml) of the latter containing amine at 1×10^{-4} *M* had an absorbance of about 0.7 under these conditions (1-cm light path), and the color appeared stable for at least 5 hr. Phosphate buffer was the only buffer encountered which interfered with the assay, owing to the precipitation of ferric phosphate.

The concentration of I varied in the range $1\text{–}20 \times 10^{-4}$ *M*, depending on the expected yield of N-methylaniline. At alkaline pH, where amine yield was low and the major products are amide and mercaptan, the developed color was deep green, rather than blue. This was found to result from reaction of ethanethiol in the assay to form a yellow product. Control experiments showed that the yellow chromophore had no absorption at 570 mμ and that ethanethiol at 1.2×10^{-3} *M* caused no increase or diminution of the absorbance at 570 mμ of amine solutions at $0.2\text{–}0.8 \times 10^{-4}$ *M*. When N-methylaniline at 0.8×10^{-4} *M* was mixed with a 23-fold excess of I undergoing hydrolysis at pH 8.8 (0.04 *M* borate buffer), the resulting absorbance at 570 mμ could be precisely accounted for by the sum of the contributions of the added amine and that resulting from breakdown of I. Incubation of N-methylbutyranilide at pH 0.2 for a period equal to the hydrolysis reaction time at that pH led to the appearance of <0.5% N-methylaniline.

B. Ethylamine was determined by means of a modification[1] of the method of Dahlgren.[34] A 1-ml aliquot containing amine at 1×10^{-4} *M* gives an absorbance of about 0.45 (1-cm light path). Concentrations of II varied from 1 to 13×10^{-4} *M*, depending on the expected yield of amine, and quartz cells of 5-cm light path were used to measure the absorbance at 540 mμ for reactions where the amine yield was <10%. N-Ethylacetamide at 10^{-3} *M* gives negligible absorption at 540 mμ.

C. Ethyl Thiolacetate. The yield of thiol ester formed on hydrolysis of III was measured by direct spectrophotometric assay at 240 mμ.[1] Eight different buffer concentrations were usually employed at each pH, and K_{app} was calculated by computer fitting of the data to the three-parameter hyperbola.[1]

D. Ethyl thiolbutyrate was estimated by hydroxamic acid assay using ethyl thiolacetate as standard. The concentration of I varied from 3 to 19×10^{-4} *M*, depending on pH.

E. Spectral Analysis. Ultraviolet spectra were recorded in the range of 220–400 mμ after hydrolysis of I at pH 1.57 (HCl), 5.05 (0.02 *M* acetate buffer), 7.48 (0.02 *M* Tris buffer), and 9.54 (0.02 *M* carbonate buffer). Yields of N-methylaniline were 95, 18, 7, and 0.4%, respectively. These spectra were compared to those of synthetic mixtures whose composition was based on the measured amine yield, and which contained ethyl thiolacetate and ethanethiol instead of the corresponding butyl derivatives. The major contribution to the spectrum of the reaction mixture at pH 1.37 was that of the thiol ester (λ_{max} 233 mμ) while, at alkaline pH, the spectra were influenced mainly by the presence of N-methylbutyranilide (no λ_{max} at >220 mμ; ϵ_{225} *ca.* 6000 in 10% acetonitrile–water). In all cases, the final spectrum of the reaction mixture agreed closely with that of the reconstituted product mixture. No evidence was found for the formation of N-methylthionbutyranilide at any pH (λ_{max} 272 mμ (ϵ 15,600) in 10% acetonitrile–water).

Acknowledgment. Support of this work by the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged (Grant No. AM-04288). We wish to thank Mrs. Madeline F. Baer for excellent assistance.

Appendix

The following discussion refers, in part, to previously elaborated relationships between the product–pH profiles of imidate ester hydrolysis and the rate–pH profile for the corresponding ester aminolysis.[4] In sections A and B, below, we reformulate previously derived equations to explicitely show that knowledge of partitioning factors for intermediates and of pH values for the product transitions uniquely and completely determine the shape of the aminolysis rate–pH profile. In section C, we give the relevant equations for the three-intermediate system which had not been previously treated.

(34) G. Dahlgren, *Anal. Chem.*, **36**, 596 (1964).

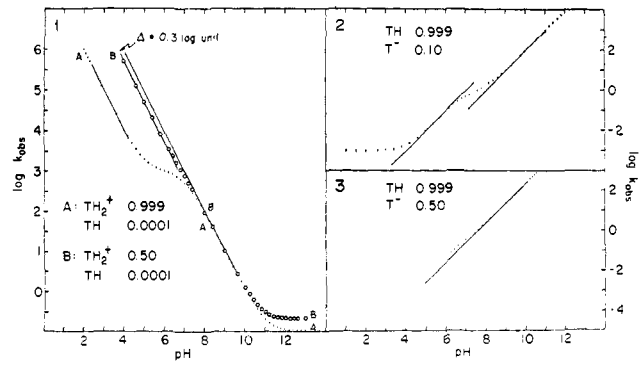


Figure 6. Predicted pH–rate profiles for aminolysis reactions proceeding *via* tetrahedral intermediates in acid–base equilibrium. Partitioning factors for the various ionic species of the intermediate are indicated on the figure. All straight lines are drawn with slope = +1 or −1. (1) Aminolysis through cationic (TH_2^+) and neutral (TH) intermediates. (2 and 3) Aminolysis through neutral (TH) and anionic (T^-) intermediates. The ordinates are in arbitrary units. The curves are calculated from eq 6 (for 2 and 3), and from eq 7 (for 1), using $pK' = pK'' = 7$.

The predicted rate–pH profiles for aminolysis according to one or another mechanism depend completely on the validity of the assumption that intermediates are in rapid equilibrium with each other, regardless of their origin. Indeed, it is precisely when deviations from predicted behavior are noted that additional features must be introduced into the mechanisms.[5]

A. Imidate Hydrolysis and Ester Aminolysis Proceed through Neutral (TH) and Anionic (T^-) Intermediates. Referring to Scheme I of ref 4, we define partitioning factors P^0 and P^- for TH and T^-, respectively; pK'' is the pH at which transition occurs between the two sets of products (see Table V). Using the equilibrium constraints of this system (eq 3 of ref 4), the previously derived expression for the rate of aminolysis (eq 2 of ref 4) becomes eq 6. The term k_1' is the rate constant for attack of free amine on the ester, and is essentially a scale factor whose value does not affect the shape of the rate–pH profile. The appearance of the latter is solely

$$\frac{k_{obsd}}{[\text{free amine}]} = \frac{k_1'((1 - P^0)[H^+] + K''(1 - P^-))(1 + K''P^-/P^0[H^+])}{[H^+] + K''} \quad (6)$$

determined by the three terms P^0, P^-, and K''. The use of eq 6 is illustrated in Figure 6 (parts 2 and 3), where two rate–pH profiles have been calculated using the indicated values of P^0 and P^-. The upper figure is reminiscent of the pH profile for acetyl transfer in O-acetylethanolamine.[4,35] A marked alteration in profile occurs when P^- is varied from 0.10 to 0.50 (lower figure). The only evidence for the transition from one intermediate to another is the small deviation of the calculated curve from linear dependence on hydroxide ion in the region of pH 5 to 8.

B. Imidate Hydrolysis and Ester Aminolysis Proceed through Cationic (TH^{2+}) and Neutral (TH) Intermediates. Similarly, we refer to Scheme II of ref 4, and

(35) B. Hansen, *Acta. Chem. Scand.*, 17, 1307 (1963).

define partitioning factors P^+ and P^0 for TH_2^+ and TH, respectively; pK' is the pH where product transition takes place (see Table V). Using the equilibrium constraints (eq 8 of ref 4), the equation for the pH dependence of aminolysis (eq 7 of ref 4) becomes eq 7 (this paper). As in section A, the shape of the pH profile is

$$\frac{k_{obsd}}{[\text{free amine}]} = \frac{k_1((1 - P^+)[H^+] + K'(1 - P^0))([H^+] + K'P^0/P^+)}{[H^+] + K'} \quad (7)$$

uniquely a function of the three parameters P^+, P^0, and K'. Two examples of calculated pH dependences are given in Figure 6, where P^+ is varied while P^0 and K' remain constant. We draw attention to the shape of curve B, calculated using a partitioning ratio for TH_2^+ similar to that known for 2-methylthiazoline, which gives about 50% amine yield in acid solution.[2,5] It is precisely the fact that the rate–pH profile for the intramolecular aminolysis of S-acetylcysteamine *did not* possess the predicted appearance which led Barnett and Jencks to postulate a novel mechanism.[5]

C. Imidate Hydrolysis and Ester Aminolysis Proceed through Three Intermediates. This is the situation described by Scheme I of the present paper. We define partitioning factors P^+ P^0, and P^-, and transition pH values pK' and pK'', as in Table V. The steady-state treatment leads to eq 3 for the dependence of amine yield on pH. The second-order rate constant for ester aminolysis (in terms of free amine) obeys eq 8; use of

$$\frac{k_{obsd}}{[\text{free amine}]} = \frac{\left[\left(\frac{k_3}{k_2 + k_3}\right)[H^+]^2 + \left(\frac{k_3'}{k_2' + k_3'}\right)K'[H^+] + \left(\frac{k_3''}{k_2'' + k_3''}\right)K'K''\right][k_1[H^+] + k_1' + k_1''[OH^-]]}{[H^+]^2 + K'[H^+] + K'K''} \quad (8)$$

the equilibrium condition (eq 9) and the definitions of

$$k_1[H^+]/k_2 = k_1'[H^+]/k_2'K_1 = k_1''K_w[H^+]/k_2''K_1K_2 \quad (9)$$

P^+, P^0, P^-, K', and K'' converts eq 8 to 10. As before, the shape of the aminolysis pH profile is completely determined by the five parameters which describe the pH dependence of the products of imidate ester hydrolysis; the rate constant k_1 is a scale factor. Assumption of appropriate values for the partitioning factors and for K' and K'' allows the generation of families of product–pH curves and of the corresponding rate–pH profiles (see, for example, Figures 2 and 4). Detailed discussion of such curves is profitably deferred until relevant experimental situations are encountered.

$$\frac{k_{obsd}}{\text{free amine}] = \frac{k_1([H^+]^2(1 - P^+) + K'[H^+](1 - P^0) + K'K''(1 - P^-))([H^+] + K'P^0/P^+ + K'K''P^-/P^+[H]^+)}{[H^+]^2 + K'[H^+] + K'K''} \quad (10)$$

Communications to the Editor

Chemically Induced Dynamic Nuclear Polarization Evidence for One-Electron Transfers during Some Halogen–Metal Exchange Reactions

Sir:

We offer evidence for the formation of free radicals during the exchange reaction between alkyllithium compounds and both alkyl and aromatic iodides. Our approach to the problem has been the search for, and the observation of, chemically induced dynamic nuclear polarization (CIDNP) in the protons of the organohalide formed during the exchange.[1] CIDNP has been shown to result when protons in reacting molecules become dynamically coupled to an unpaired electron while traversing the path from reactants to products.[2] Specifically, if an intermediate free radical is formed and then reacts rapidly in a sample whose nmr spectrum is being taken, polarization of proton spins in the diamagnetic products can often be observed. Since both positive and negative polarization can occur, both nmr emission and enhanced absorption are possible. We propose that the simultaneous observation of both effects in an nmr spectrum under normal high-resolution operating conditions indicates that the protons giving rise to these signals spend some time in residence on an intermediate free radical.[3]

A spectrum[4] taken of a reacting solution of ethyllithium and ethyl iodide in benzene at 40° is shown in Figure 1. The anomalous intensities exhibited by these lines are characteristic of CIDNP. The related ex-

(1) Similar results have been obtained by A. R. Lepley and R. L. Landau, *J. Amer. Chem. Soc.*, 91, 748, 749 (1969).

(2) (a) H. R. Ward and R. G. Lawler, *ibid.*, 89, 5518 (1967); (b) R. G. Lawler, *ibid.*, 89, 5519 (1967); (c) J. Bargon and H. Fischer, *Z. Naturforsch.*, 22a, 1551, 1556 (1967); (d) A. R. Lepley, *J. Amer. Chem. Soc.*, 90, 2710 (1968).

(3) Intermolecular interactions between free radicals and nonreacting molecules also may give rise to polarization effects (see, for example, K. H. Hausser and D. Stehlik, *Advan. Magnetic Resonance*, 3, 79 (1968)). However, strong positive polarization of protons is without precedent in such electromagnetically pumped dynamic nuclear polarization experiments on solutions of neutral free radicals. Furthermore, signal enhancement or dehancement from protons in molecules other than those known to be reactants or products has not been observed in the present system; *e.g.*, ethers which would be expected to be complexed strongly by the alkyllithium and held in the vicinity of the reaction site do not show polarization.

(4) Spectra were taken on a Varian A-60A spectrometer, which was purchased with funds supplied by the National Science Foundation.