reactions[19] in which the preferred course of reaction is *trans* coplanar except in cases where this geometry cannot be achieved. In these cases a coplanar *cis* elimination becomes preferred.

A consideration of the solvolysis of 2,2-diphenylcyclopropyl chloride lends additional support to this alternative approach. Since one phenyl group must rotate inward regardless of the direction of rotation, then the steric compression cannot be avoided. This steric compression may prevent extensive ring opening in the transition state thereby cancelling the expected stabilization from the added phenyl group.

It is difficult to make a clear distinction between the two pathways based on literature examples. Most alkyl-substituted cyclopropyl derivatives seem to behave as predicted,[7] showing large rate effects. However, at least one exception is the apparently anomalous behavior of the *exo*- and *endo*-norcaranyl chlorides[7] and tosylates.[10] Our system, utilizing aromatic substituents, strongly suggests the alternative type of behavior. The large resonance stabilization capabilities and the sensitive steric requirements of the phenyl group in the *cis* position may be sufficient to favor the alternate mode of ring opening over the predicted mode which is sterically less favorable and must necessarily sacrifice some of the resonance stabilization. A decision between the two alternatives should be possible through investigation of additional substituent effects designed to emphasize the stereoselective properties of the ring-opening reaction.

(19) C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *J. Am. Chem. Soc.*, 87, 2421 (1965); J. L. Coke, and M. P. Cooke, Jr., *ibid.*, 89, 2779 (1967).

The Hydrolysis of Thioimidate Esters. Tetrahedral Intermediates and General Acid Catalysis[1]

Rama K. Chaturvedi, Andrew E. MacMahon, and Gaston L. Schmir

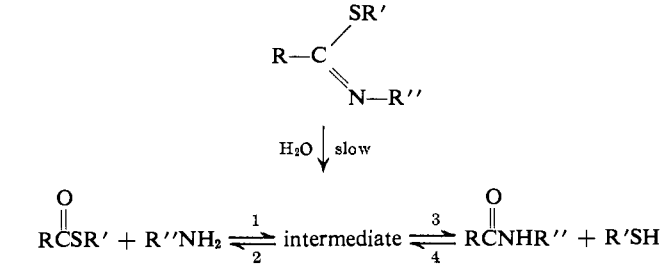
Contribution from the Department of Biochemistry, Yale University, New Haven, Connecticut 06510. *Received August 7, 1967*

Abstract: The hydrolysis of four acyclic thioimidate esters has been investigated in the pH range 0–10 at 30°. The pH–rate profiles exhibit the features characteristic of the hydrolysis of other imines (thiazolines, oxazolines, Schiff bases, iminolactones). The nature of the products of hydrolysis is influenced by pH and by the concentration of buffers. Hydrolysis yields thiol esters and amines at pH <2 and amides (and mercaptans) at higher pH. Increasing buffer concentration at pH 2–6 directs the breakdown of a tetrahedral intermediate from C–S to C–N bond cleavage. Buffer effects on the products are in quantitative agreement with a mechanism involving general acid catalysis of the breakdown of an anionic carbinolamine intermediate. Some conclusions concerning the mechanism of the aminolysis of thiol esters are presented.

The chemistry of the tetrahedral addition intermediates generated in nucleophilic reactions of carboxylic acid derivatives is the subject of continuing investigation.[2] The very existence of such intermediates has been convincingly demonstrated in relatively few instances.[2,3] Questions ancillary to the proof of existence of the intermediate deal with the nature of the rate-determining step, and with the mechanisms available for the catalysis of the several steps of the acyl transfer reaction.

A particularly simple approach to the mechanism of certain acyl transfer reactions consists of the detailed study of the factors influencing the nature of the products of hydrolysis of related imidates. The principle is illustrated in Scheme I. Evidence for the existence

Scheme I



of an intermediate in the hydrolysis of the imidate provides compelling support for the participation of the same intermediate in the acyl transfer reactions leading to interconversion of the products (*via* the sequences 1–3 or 4–2). Determination of the yields of the products formed *via* reactions 2 and 3 upon hydrolysis of the imidate immediately indicates which step is rate determining when the related acyl transfer reaction

(1) (a) This work is taken in part from a dissertation presented by A. E. M. in partial fulfillment of the requirements for the M.D. Degree, Yale University, 1964. (b) Financial support by the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged (Grant No. AM-04288).

(2) (a) M. L. Bender, *Chem. Rev.*, 60, 53 (1960); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.

(3) (a) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, 83, 2267 (1961); (b) M. L. Bender and R. J. Thomas, *ibid.*, 83, 4183, 4189 (1961); (c) R. B. Martin and R. I. Hedrick, *ibid.*, 84, 106 (1962); (d) B. Hansen, *Acta Chem. Scand.*, 17, 1307 (1963); (e) R. B. Martin, A. Parcell, and R. I. Hedrick, *J. Am. Chem. Soc.*, 86, 2406 (1964); (f) T. C. Bruice and L. R. Fedor, *ibid.*, 86, 4886 (1964); (g) W. P. Jencks and M. Gilchrist, *ibid.*, 86, 5616 (1964); (h) G. E. Lienhard and W. P. Jencks, *ibid.*, 87, 3855 (1965); (i) L. R. Fedor and T. C. Bruice, *ibid.*, 87, 4138 (1965); (j) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 20, 1892 (1966); (k) B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.*, 89, 917 (1967).

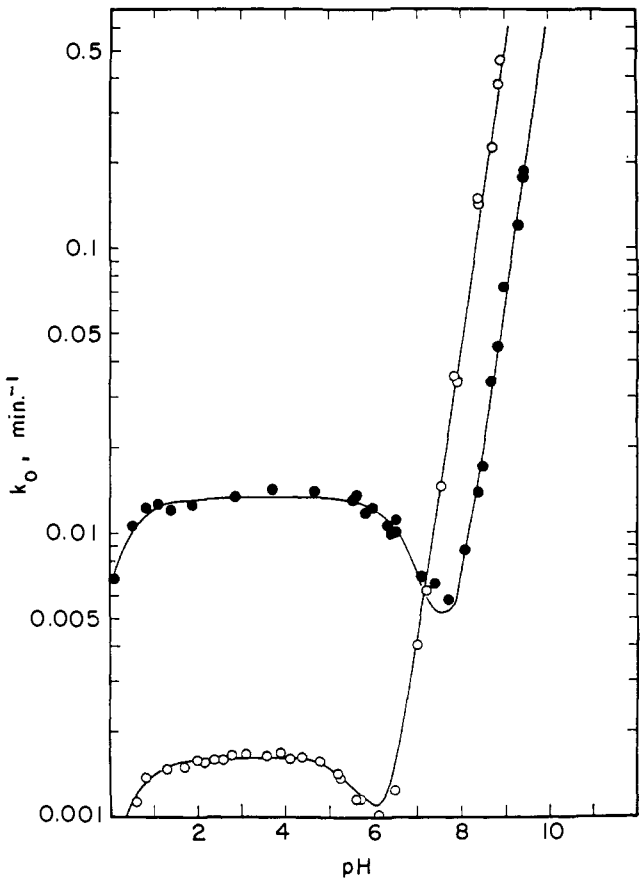


Figure 1. pH–rate profiles for disappearance of thioimidates I and II at 30°: ●, I in 10% acetonitrile–H_2O, μ = 0.45; ○, II in 10% ethanol–water, μ = 0.90. Solid curves are calculated from eq 1 and 3, using constants of Table I.

(*e.g.*, the aminolysis of the thiol ester) is studied under the same conditions. Clearly, this information is important for the understanding of the effects of structural variation and of catalysts on the rate of the aminolysis reaction. Product analysis thus furnishes a simple means of defining the factors which control the breakdown of some tetrahedral intermediates, not amenable to study *via* the oxygen-18 exchange technique introduced by Bender.[4]

Our previous investigation of the hydrolysis of the iminolactone 2-(N-phenylimino)tetrahydrofuran[5] provided an initial test of the validity of the approach described above.[6] The findings that the products of iminolactone hydrolysis were markedly influenced by pH and by the presence of certain buffers led directly to the establishment of bifunctional catalysis in the intramolecular alcoholysis of 4-hydroxybutyranilide.[3k]

The present paper describes the extension of our studies to the hydrolysis of thioimidate esters. Detailed kinetic studies with cyclic thioimidates (Δ^2-thiazolines, dihydrothiazines) had earlier shown that the hydrolyses of these substances involved the formation of tetrahedral addition intermediates.[7] Acyclic

(4) M. L. Bender, *J. Am. Chem. Soc.*, 73, 1626 (1951).
(5) N-(Dihydro-2[3H]-furylidene)aniline.
(6) (a) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, 87, 5692 (1965); (b) B. A. Cunningham and G. L. Schmir, *ibid.*, 88, 551 (1966).
(7) (a) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *ibid.*, 81, 5089 (1959); (b) R. B. Martin and A. Parcell, *ibid.*, 83, 4830 (1961); (c) G. L. Schmir, *ibid.*, 87, 2743 (1965).

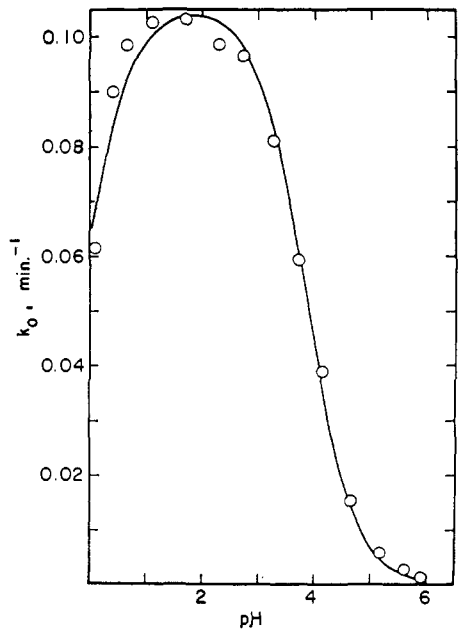
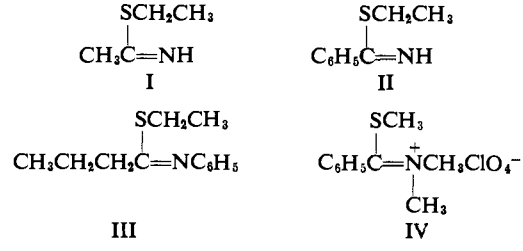


Figure 2. pH–rate profile for hydrolysis of thioimidate III in 10% acetonitrile–water, μ = 0.45, 30°. Solid curve is calculated from eq 1, using constants of Table I.

thioimidate esters have received scant attention.[8] In this work, we report findings bearing on the existence and properties of tetrahedral intermediates in thioimidate hydrolysis, as well as some conclusions concerning the mechanism of aminolysis of thiol esters.

Results

Kinetic Studies. The kinetics and products of hydrolysis of four thioimidate esters (I–IV) were investigated.



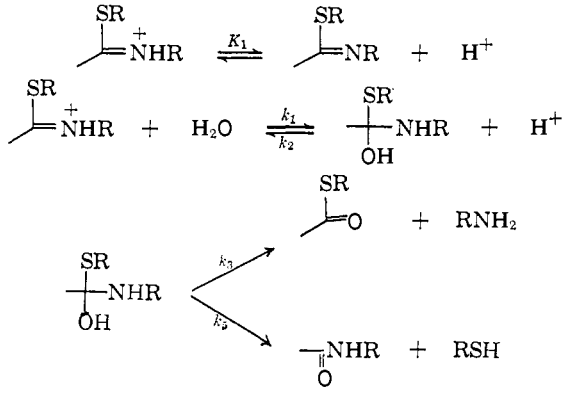
Observed first-order rate constants for the disappearance of I and II in 10% acetonitrile–water (I) or 10% ethanol–water (II) at 30° are presented in Figure 1. Similar data were obtained with III (Figure 2). Increasing buffer concentrations (0.02–0.15 *M*) at fixed pH had nearly no effect on the rate of hydrolysis of III. With I, small rate increases were noted in the presence of phosphate and imidazole buffers; observed rate constants in 0.1 *M* phosphate or imidazole (pH 5.5–6.4) were 10–50% greater than the rate constant extrapolated to zero buffer concentration. In this pH range, the data of Figure 1 are corrected for buffer catalysis. The rate constant for hydrolysis of II at pH 1–5 is about twice as large as that reported[8] for hydrolysis in unbuffered solution at 25°. The rate of disappearance of the cationic thioimidate IV at pH 7.8–10.1 was directly proportional to hydroxide

(8) R. H. Hartigan and J. B. Cloke, *ibid.*, 67, 709 (1945).

ion activity,[9] with a second-order rate constant (k_7) of 2160 M^{-1} min^{-1}.

At pH <7, the pH–rate profiles for I, II, and III are those expected for the hydrolysis of imines. Accordingly, we interpret these results in terms of the common mechanism postulated for the hydrolysis of Schiff bases, thiazolines, dihydrothiazines, oxazolines, and iminolactones (Scheme II).[10] The evidence in

Scheme II



support of this proposal has been extensively discussed and will not be restated here.[11] According to Scheme II, hydrolysis proceeds *via* addition of water to the protonated thioimidate to yield an uncharged tetrahedral intermediate. With decreasing pH, a transition occurs from rate-determining hydration to rate-determining decomposition of the intermediate. Assumption of a steady state in the carbinolamine leads to eq 1 for the dependence of observed first-order rate constants (k_o) for thioimidate disappearance on pH. Least-squares values of the constants K_1, k_1, and (k_3 + k_5)/k_2 were obtained by fitting the data of Figures 1 and 2 to the assumed rate eq 1 by means of an IBM 7094 computer (Table I). The kinetically determined values of pK_1 for I and II are in reasonable agreement with those based on titration data.

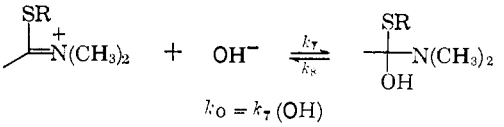
$$k_o = \frac{k_1(\mathrm{H})(k_3 + k_5)/k_2}{((\mathrm{H}) + K_1)((\mathrm{H}) + (k_3 + k_5)/k_2)} \qquad (1)$$

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

	I	II	III	IV
pK_1	7.01,[c] 6.97[d,e]	6.04,[c] 5.86[d,f]	3.84[c]	[g]
$k_1 \times 10^4$, min^{-1}	133	16.1	1050	[h]
$(k_3 + k_5)/k_2$, M	1.0	0.71	1.5	[h]
k_7, M^{-1} min^{-1}	[h]	[h]	[h]	2160
pK'[i]	2.71	[h]	2.89	[h]
k_e, M^{-1} min^{-1}	7×10^3[j]	5×10^4	[g]	[g]

[a] Constants are defined for the processes shown in Figure 5 and eq 1–3. [b] Compounds I, III, and IV in 10% acetonitrile–water, μ = 0.45 M; II in 10% ethanol–water, μ = 0.9 M. [c] Calculated from kinetic data. [d] Determined by spectrophotometric titration in 10% ethanol–water, μ = 0.9 M. [e] pK_1 = 6.9 in H_2O at 25 ± 3°: ref 25. [f] pK_1 = 6.05 in H_2O at 25°: ref 8. [g] Not defined. [h] Not measured. [i] $K' = K_3k_9/(k_3 + k_5)$. [j] k_e = 14–17 × 10^3 M^{-1} min^{-1} in 10% ethanol–water, μ = 0.9 M.

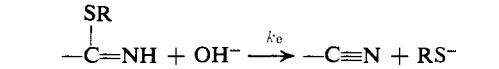
To account for the kinetic behavior of IV, we suggest that hydroxide ion attacks the cationic substrate (eq 2), a reaction for which there is ample precedent.[10,11]



$$k_o = k_7(\mathrm{OH}) \qquad (2)$$

We point out at the outset that the kinetic data described here are consistent with the mechanism advanced in Scheme II and eq 2 but do not constitute unequivocal evidence for it. The essential feature of the mechanism is the existence of an addition intermediate whose neutral form leads to product and whose cationic form reverts solely to imine, with a consequent change in rate-limiting step at low pH. The experimental support for this proposal rests on the decreased rate of hydrolysis at low pH. The magnitude of this decrease is meager by comparison to that observed with thiazolines[7] and Schiff bases[11] and is susceptible to other interpretation. Later in this paper, we present additional findings which convincingly support the existence of tetrahedral intermediates in thioimidate hydrolysis.

An unusual feature of the pH–rate profiles for I and II (Figure 1) is the rapid rate of disappearance of thioimidate at alkaline pH. The mechanism of eq 2 does not explain this observation, since the parallel decrease in protonated thioimidate and increase in hydroxide ion concentration should result in a constant rate of hydrolysis.[10,11] A kinetically plausible mechanism involving nucleophilic attack of hydroxide ion on neutral thioimidate is unlikely; a rare example of such a reaction involves *p*-chlorobenzilidene aniline at pH >12.[12] It is probable that the hydroxide ion catalyzed reaction represents elimination to nitrile and mercaptan (eq 3), in analogy to previous observations with imi-



$$k_o = k_eK_1(\mathrm{OH})/(K_1 + (\mathrm{H})) \qquad (3)$$

dates[13] and thioimidates.[8,14] Calculated values of k_e are included in Table I.[9]

The curves presented in Figures 1 and 2 are computed from eq 1 (for III) and from eq 1 and 3 (for I and II), using the constants summarized in Table I.

The Reaction Products. The nature of the products of thioimidate hydrolysis depends on pH and, at fixed pH, on the identity and concentration of the buffer used. These phenomena were studied extensively with the unsubstituted thioimidate I, which proved particularly sensitive to buffer effects. Typical experiments are shown in Figure 3 and data from a number of additional cases are summarized in Table II.

Most experiments at fixed pH were carried out with increasing amounts of one buffer only. In some cases (experiments 3–5), a low concentration (0.018 M) of maleate buffer was employed to maintain constant pH, so that the concentration of some other species (*e.g.*,

(9) Hydroxide ion activity calculated from the observed pH and pK_w = 14.
(10) References 6a and 7c and earlier work cited therein.
(11) W. P. Jencks, *Progr. Phys. Org. Chem.*, 2, 63 (1964).
(12) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 832 (1962).
(13) (a) H. I. Schlesinger, *Am. Chem. J.*, 39, 719 (1908); (b) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 3505 (1962).
(14) (a) A. Bernthsen, *Ann. Chem.*, 197, 341 (1879); (b) W. Autenrieth and A. Brüning, *Ber.*, 36, 3464 (1903).

Table II. Effect of Buffers on the Yield of Ethyl Thiolacetate Obtained from Hydrolysis of Ethyl Thioacetimidate (I)[a]

Expt	pH	Buffer, *M*	Thiol ester, %	Intercept,[b,c] %	Maximum yield, %	$K_{app} \times 10^3$, *M*[c]
			a. Phosphate			
1	5.44	0.018	33.3	4.8 ± 1.9	89	3.5 ± 0.3
	5.47	0.027	40.1			
	5.48	0.054	55.8			
	5.47	0.108	68.9			
	5.45	0.216	77.9			
2	6.19	0.009	21.6	7.6 ± 2.6	88	4.3 ± 0.6
	6.20	0.027	37.6			
	6.22	0.054	52.5			
	6.20	0.216	77.1			
3[d]	6.17	0.0	6.6	6.6[e]	(79)[f]	4.9 ± 0.5
	6.25	0.018	26.9			
	6.31	0.054	43.4			
	6.33	0.108	55.3			
			b. Imidazole			
4[d]	5.40	0.0	8.7	8.7[e]	86	2.9 ± 0.5
	5.46	0.009	24.8			
	5.45	0.036	52.4			
	5.46	0.072	64.6			
	5.49	0.144	70.6			
5[d]	6.15	0.0	6.8	6.8[e]	85	3.1 ± 0.3
	6.24	0.0072	21.1			
	6.25	0.036	48.9			
	6.26	0.108	69.4			
			c. Acetate			
6	4.29	0.018	25.1	11.2 ± 2.9	91	7.5 ± 1.3
	4.29	0.036	39.2			
	4.30	0.090	55.2			
	4.32	0.216	72.9			
	4.32	0.360	76.8			
7	4.97	0.018	16.5	(5)[f]	96	15 ± 2
	4.97	0.036	23.4			
	4.98	0.090	39.2			
	4.98	0.144	47.6			
	4.99	0.288	64.0			
8	5.50	0.036	14.8	(5)[f]	(83)[f]	22 ± 5
	5.52	0.090	25.0			
	5.53	0.144	32.9			
	5.55	0.288	45.3			
			d. Cyanoacetate			
9	2.79	0.018	51.5	43.0 ± 1.2	85	8.2 ± 1.3
	2.75	0.090	65.6			
	2.74	0.216	72.5			
	2.73	0.360	78.9			
10	3.09	0.018	37.9	32.0 ± 1.4	80	11.2 ± 1.7
	3.06	0.090	52.4			
	3.05	0.288	66.2			
			e. Maleate			
11	5.39	0.017	6.8	4.6		
	5.40	0.033	8.9			
	5.44	0.049	10.7			
12	6.11	0.017	5.8	4.6		
	6.16	0.033	7.0			
	6.18	0.049	7.8			
13	6.85	0.017	3.9	3.7		
	6.86	0.033	4.9			
	6.90	0.049	4.6			
			f. HCl			
14	1.46		83.8			
	1.84		81.3			
	2.15		75.0			
	2.44		64.0			

[a] At 30° in 10% acetonitrile–water, μ = 0.45 *M*. [b] Extrapolated, except where stated. [c] Standard deviation is indicated. [d] In 0.018 *M* maleate buffer. [e] Measured directly. [f] Approximate.

imidazole) could be varied over a wide range; small amounts of maleate buffer do not appreciably increase the yield of thiol ester produced. Some significant features of these results are: (a) At lowest buffer concentrations, the yields of thiol ester increase with decreasing pH. (b) Imidazole and phosphate buffers possess rather similar abilities to increase thiol ester yield (compare experiments 1 and 4 or 3 and 5), an

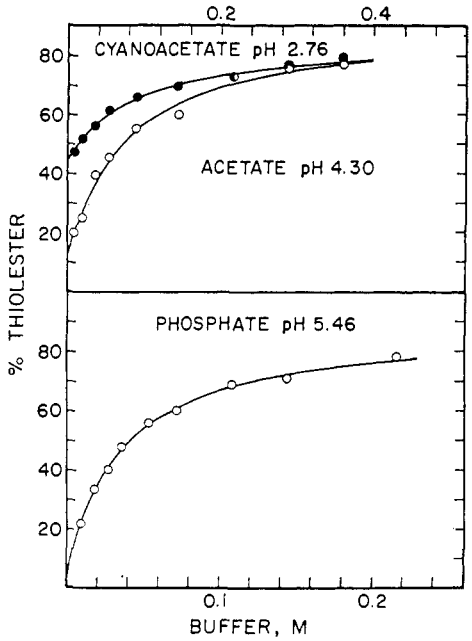


Figure 3. Effect of buffer concentration on yield of ethyl thiolacetate resulting from hydrolysis of thioimidate I. Solid curves are calculated from parameters given in Table II, as discussed in the Results section: cyanoacetate and acetate, upper abscissa; phosphate, lower abscissa.

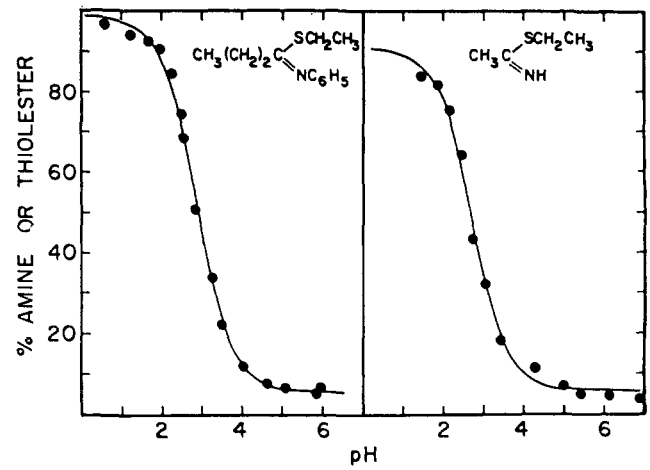


Figure 4. Effect of pH on the yields of aniline and ethyl thiolacetate obtained on hydrolysis of thioimidates III and I, respectively. Solid lines are calculated titration curves for monovalent acids of $pK' = 2.89$ and 2.71, respectively.

observation in marked contrast to those made with the iminolactone system.[6b] (c) Under conditions (pH 5.5) where the rate of hydrolysis of I increases by 25%, the yield of thiol ester produced varies from 5% (at zero phosphate buffer concentration) to 69% (at 0.11 *M* phosphate buffer).

To evaluate quantitatively the ability of a buffer to alter the yield of thiol ester produced on hydrolysis of I, the treatment used with the iminolactone system was applied to the present data.[6b] A_B is the thiol ester yield at a given buffer concentration. A_0 is the thiol ester yield in the absence of (reactive) buffer; $\Delta A = A_B - A_0$, $\Delta A_{max} = \Delta A$ at infinite buffer concentration. Equation 4 describes the dependence of the increase in thiol ester yield on total buffer concentration. If A_0 is known for a given pH, the constants

$$\Delta A/\Delta A_{max} = [\text{buffer}]/([\text{buffer}] + K_{app}) \qquad (4)$$

ΔA_{max} and K_{app} may be evaluated from data such as those of Figure 3 by using double reciprocal plots of $1/\Delta A$ *vs.* 1/[buffer].[6b] The absence of noncatalytic buffers throughout most of the pH range of this investigation prevented the direct determination of A_0. Computer fitting of the data to the equations for two- or three-parameter rectangular hyperbolas (see Experimental Section) yielded, for each experiment, values of the three desired constants: A_0, the thiol ester yield at zero buffer concentration; A_{max} ($= A_0 + \Delta A_{max}$), the maximum yield of thiol ester, reached asymptotically at infinite buffer concentration; K_{app}, the concentration of buffer required to produce a half-maximal increase in thiol ester yield.

The yields of thiol ester at zero buffer concentration (Table II, column 5) are plotted as a function of pH in Figure 4. The gradual transition from the appearance of ethyl thiolacetate and ammonia to that of acetamide and ethyl mercaptan is described by the sigmoid curve characteristic of a univalent acid of $pK = 2.71$, with asymptotes at 91% (low pH) and 6% (high pH). It is also seen that the maximum yields of thiol ester obtainable at constant pH are significantly lower than 100%, ranging from 85 to 90% for the most reliable experiments (Table II, column 6). Some uncertainty is attached to these extrapolated maximum values, since the highest *observed* yield in buffered solution never exceeded 80%. It is noteworthy, however, that the calculated maximum yield at acid pH is 91%.

The last column of Table II gives quantitative measure of the catalytic effectiveness of various buffers at several pH values. At present, it is sufficient to note that imidazole and phosphate buffers are rather more efficient catalysts than are carboxylate buffers; all are far less effective than the catalysts encountered in iminolactone hydrolysis.[6b] The curves shown in Figure 3 are calculated from eq 4, using the values of the intercept yield (A_0), the maximum yield (A_{max}), and K_{app} given in Table II for the appropriate experiments.

The hydrolysis of the N-substituted thioimidate III is far less susceptible to buffer effects on the nature of the products (Table III). At each pH, the yield of aniline produced in the absence of buffer catalysis could be obtained simply by linear extrapolation of data collected at low buffer concentration. The variation of these intercept values (Table III, last column) with pH is presented in Figure 4; as with I, the extent of C–N bond cleavage decreases with increasing pH; data are well correlated by a sigmoid curve of apparent $pK = 2.89$ and asymptotes of 98.5% (low pH) and 5% (high pH).

Limited study of two other thioimidates lends additional support to the notion that the products of hydrolysis of acyclic thioimidates stem largely from C–N bond cleavage at acid pH and from C–S fission at neutral or alkaline pH, transition occurring at about pH 3. Hydrolysis of II at pH 2.1 (HCl), 3.1, and 4.3 (0.02 *M* cyanoacetate or acetate buffer) gave approximate yields of ethyl thiolbenzoate of 90, 47, and 36%, respectively, without correction for buffer effects. Exposure of IV to alkaline pH (pH 8.6–12.3) resulted in the appearance of <2% dimethylamine. Ultra-

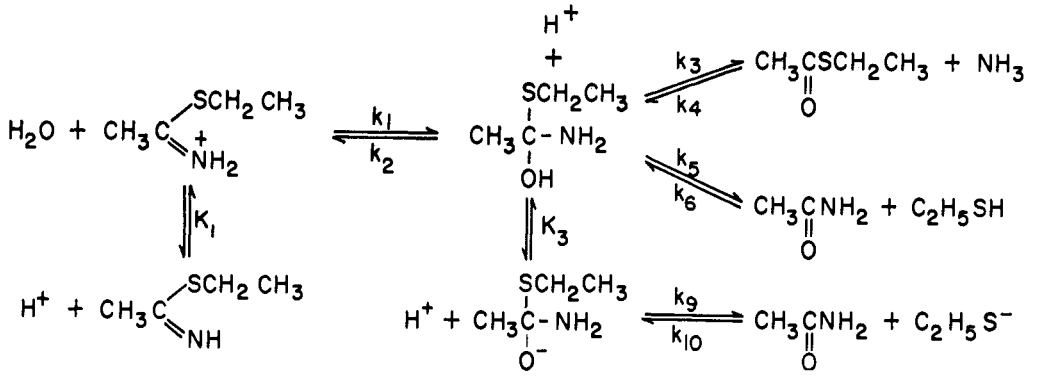


Figure 5. Mechanism of hydrolysis of thioimidate esters.

violet spectra of reaction mixtures at pH 9.0 indicated quantitative formation of N,N-dimethylbenzamide.

Table III. Effects of Buffers on the Yield of Aniline Obtained from Hydrolysis of Ethyl N-Phenylthiobutyrimidate (III)[a]

Expt	pH	Buffer	Concn, *M*	Aniline, %	Intercept,[b] %
1	5.86	Imidazole	0.02	5.4	5.1
	5.84		0.05	6.0	
	5.83		0.10	6.6	
2	5.93	Phosphate	0.02	8.8	7.1
	5.91		0.05	11.2	
	5.89		0.20	18.8	
3	6.00	Maleate	0.01	7.1	6.6
	5.99		0.02	7.5	
	5.98		0.03	8.0	
4	4.07	Acetate	0.02	13.9	11.8
	4.07		0.03	15.4	
	4.06		0.05	17.2	
	4.03		0.20	28.2	
5	4.64	Acetate	0.01	8.5	7.6
	4.67		0.02	9.6	
	4.65		0.03	10.1	
	4.68		0.20	20.7	
6	5.09	Acetate	0.01	6.7	6.4
	5.10		0.02	7.0	
	5.10		0.03	7.3	
	5.11		0.20	11.8	
7	2.58	Cyanoacetate	0.02	71.0	68.5
	2.57		0.03	72.1	
	2.54		0.04	73.5	
	2.52		0.20	81.3	
8	2.86	Cyanoacetate	0.02	56.1	50.7
	2.84		0.03	59.6	
	2.82		0.04	61.9	
	2.81		0.20	72.3	
9	3.30	Cyanoacetate	0.02	36.5	33.7
	3.29		0.03	38.2	
	3.27		0.04	39.2	
	3.25		0.20	50.3	
10	3.50	Cyanoacetate	0.02	27.5	22.0
	3.49		0.03	30.5	
	3.48		0.04	32.3	
	3.44		0.20	37.5	
11	2.51	HCl		74.5	
	2.27			84.5	
	1.97			90.6	
	1.67			92.6	
	1.25			94.1	
	0.60			96.1	

[a] At 30° in 10% acetonitrile–water, μ = 0.45 *M*. [b] From linear extrapolation to zero buffer concentration.

Discussion

The acid-catalyzed hydrolysis of thioimidate esters to thiol esters is a well-established reaction.[8,15] It has not been widely recognized that amides may result from thioimidate hydrolysis, although there exist scattered reports in the literature of the isolation of amides after exposure of thioimidates to alkaline or weakly acid media.[16] The results of the present work suggest that the latter reaction is a general one.

The Mechanism of Hydrolysis. The mechanism depicted in Figure 5 is proposed to account for the following features of thioimidate hydrolysis: a pH–rate profile including acid inhibition, and decreasing rates with decreasing extent of substrate protonation; transition from (mainly) C–N bond cleavage at acid pH to C–S bond cleavage at higher pH. We have earlier expressed reluctance to find support in the kinetic data for the existence of the tetrahedral intermediate(s); the observation that the products of hydrolysis may be profoundly altered by catalysts which affect the hydrolysis rate little or not at all constitutes more convincing evidence for this conclusion.

The suggested mechanisms for the hydrolyses of thiazolines,[7] aliphatic Schiff bases,[11] and iminolactones[6] all include the provision that the initially formed cationic carbinolamine must divest itself of a proton prior to conversion to products. We have retained this feature, and added a further ionization step (neutral intermediate $\rightleftharpoons$ anionic intermediate) to explain the effect of pH on the nature of the hydrolysis products (Figure 4). This modification does not alter the interpretation of the kinetic data, since ionizations occurring after rate-limiting hydration (step k_1) would not be reflected in the pH–rate profile. The sigmoid curve relating extent of C–N bond cleavage to pH is predicted for this type of mechanism,[6b] and the apparent dissociation constant $K' = K_3k_9/(k_3 + k_5)$.

Accurate knowledge of the yields of thiol ester (or amine) at extremes of pH is important since it provides information concerning the modes of breakdown of carbinolamines in various ionization states. Unfortunately, our results are inadequate for definitive interpretation: while it is clear that the neutral intermediate derived from III undergoes (almost) exclusively C–N cleavage (98.5% yield), it is not certain whether I

(15) (a) O. Wallach, *Ber.*, **11**, 1590 (1878); (b) O. Wallach and H. Bleibtreu, *ibid.*, **12**, 1061 (1879); (c) W. Steinkopf and S. Müller, *ibid.*, **56**, 1930 (1923); (d) R. J. Kaufmann and R. Adams, *J. Am. Chem. Soc.*, **45**, 1744 (1923); (e) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948); (f) P. Chabrier, S.-H. Renard, and K. Smarzewska, *Bull. Soc. Chim. France*, 1167 (1950).

(16) (a) S. Gabriel and P. Heymann, *Ber.*, **24**, 783 (1891); (b) B. Holmberg, *Arkiv Kemi, Mineral. Geol.*, **24A**, No. 3 (1947); (c) G. Ehrensvärd and B. Davidsson, *ibid.*, **24A**, No. 6 (1947); (d) B. Böttcher and F. Bauer, *Ann. Chem.*, **568**, 218 (1950).

Table IV. Comparison of Relative Values of K_{app} Observed and Calculated for Two Possible Mechanisms of Buffer Catalysis

Buffer	pK	pH[a]	Relative values of K_{app}: Calcd, Mechanism A[b]	Calcd, Mechanism B[c]	Found
Phosphate	6.77[d]	6.28 ± 0.04	8.33	1.27	1.40
		6.21 ± 0.03	6.85	1.22	1.23
		5.46 ± 0.02	1.00	1.00	1.00
Imidazole	7.02[d]	6.24 ± 0.03	6.8	1.13	1.07
		5.46 ± 0.02	1.00	1.00	1.00
Acetate	4.76[d]	5.52 ± 0.02	82.0	4.91	2.94
		4.98 ± 0.01	9.2	1.93	2.00
		4.30 ± 0.01	1.00	1.00	1.00
Cyanoacetate	2.47[e]	3.06 ± 0.01	2.54	1.27	1.37
		2.76 ± 0.02	1.00	1.00	1.00

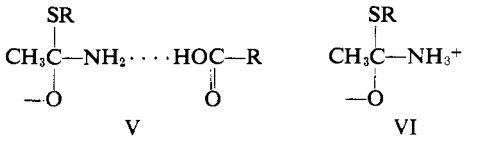
[a] Arithmetic average of pH values for experiments such as listed in Table II. [b] Calculated from ref 6b, eq 6, for reaction of conjugate acid of buffer with neutral tetrahedral intermediate. [c] Calculated from ref 6b, eq 7, for reaction of conjugate acid of buffer with anionic tetrahedral intermediate. [d] Reference 6b. [e] In H_2O at 25°: G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth & Co. (Publishers) Ltd., London, 1961, p 294.

behaves similarly. Both the extrapolated thiol ester yield at acidic pH (91%) and the maximum thiol ester yields in the presence of catalyzing buffers (85–90%) lead to the conclusion that k_3/k_5 = *ca.* 10, *i.e.*, that significant C–S bond cleavage may occur with the neutral carbinolamine derived from I. This finding would not be unprecedented, since it is reported that analogous neutral intermediates obtained from thiazolines may undergo predominant C–N fission,[7b] predominant C–S fission,[17] or exhibit intermediate behavior.[7a]

The observed yields of aniline or thiolester at pH 6 were 5–6% (Figure 4), suggesting that the anionic carbinolamines may suffer partial C–N cleavage. The accuracy of these results is not high since, for instance, III is contaminated with small amounts of impurities of unknown structure. We view these data with reserve and consider the pathways of breakdown of the anionic intermediates not to be firmly established.

It should be stressed that the results of the present study primarily provide evidence for the contention that, in thioimidate hydrolysis, there exist reaction intermediates linked by acid–base equilibria. The conjugate acid of this pair of intermediates yields mainly thiol ester (and amine) while the conjugate base collapses with expulsion of mercaptan. The choice of neutral and anionic structures for the conjugate pair of carbinolamines is made largely on the basis of analogy to other imine hydrolyses.[10,11] The possible intervention of a cationic intermediate has not been rigorously ruled out, and alternative mechanisms involving a cationic and neutral intermediate as the conjugate pair giving rise to different products are not excluded.

General Acid Catalysis and the Breakdown of Tetrahedral Intermediates. To account for the ability of buffers to influence the nature of the hydrolysis products without sensibly affecting the rate of the over-all reaction, it is proposed that buffers interact with and thereby control the mode of breakdown of the tetrahedral intermediate. The dependence of K_{app} on pH (Table II) allows selection between two possible situations: (a) interaction between the conjugate acid of the buffer and the neutral tetrahedral intermediate (mechanism A), (b) interaction between the conjugate acid of the buffer and the anionic intermediate, or its kinetically indistinguishable counterpart including the basic species of the buffer and the neutral intermediate (mechanism B). Relative values of K_{app} at several pH values may be computed for each mechanism, using the expressions developed earlier[6b] (Table IV, columns 4 and 5); these are compared, for several buffers, to experimentally observed relative values of K_{app}. Although agreement is not perfect, it may be concluded that the predominant mechanism of buffer catalysis involves the conjugate acid of the buffer and the anionic carbinolamine (or some kinetic equivalent). A possible formulation is shown as V; the essential feature is the general acid catalyzed conversion of the anionic carbinolamine to a species resembling the neutral



(zwitterionic) intermediate VI presumably required for amine expulsion. In accord with the postulate of general acid catalysis is the observation that imidazole and phosphate buffer produce nearly the same effect.

The present findings stand in marked contrast to those made in the iminolactone system.[6] In that case, the breakdown of the addition intermediate was extraordinarily sensitive to bifunctional catalysts; monofunctional buffers of the same pK had little influence on product distribution. Clearly, the curious differences between the catalytic phenomena observed in the two systems thus far studied merit detailed investigation.

Cyanoacetic acid is not a better catalyst than acetic acid (Table II), although a considerably stronger acid. This observation receives a natural explanation when the proposed mechanism of buffer catalysis is considered. The effectiveness of any catalyst will be determined by two factors: (a) the slope of the Brønsted plot relating intrinsic catalytic constant to pK of the catalyst; (b) the pH at which the experimental measurement is made—this factor determines both the fraction of total buffer in the active form and the (apparent) fraction of total carbinolamine in the anionic form. Since the reaction partners are affected in the opposite sense by pH variation, it is expected that *observed* catalytic efficiency (in terms of K_{app}) will vary with pH as a bell-shaped curve.[3a] The relevant expressions

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

are eq 5 and 6, where E = intrinsic catalytic constant, E_0 = observed catalytic contant, K_1 and K_2 are apparent

$$E_0 = EK_2(H)/((H) + K_1)((H) + K_2) \quad (5)$$

$$E = GK_1^{\alpha} \quad (6)$$

dissociation constants for buffer and carbinolamine, respectively (the latter constant being equivalent to $K' = K_3k_9/(k_3 + k_5)$ of Figure 5, and not to K_3). Equation 6 is simply the Brønsted relationship. With the assumptions that $E = 100$ for a catalyst of $pK_1 = 5$, $pK_2 = 3$, and the Brønsted slope $\alpha = 0.3$, observed catalytic efficiencies were calculated for buffers of pK_1 2, 3, 4, and 5 as a function of pH (Figure 6). It is evident that the relative effectiveness of a catalyst is strongly dependent on the experimental pH. For measurement at fixed pH, and with a given Brønsted coefficient α, the best catalyst will possess a dissociation constant $K_1 = \alpha H/(1 - \alpha)$.

The Aminolysis of Thiol Esters. The results of the present work provide indirect but substantial evidence for the participation of tetrahedral addition intermediates in the aminolysis of thiol esters. Two additional predictions may be made: (a) At pH >4, the rate-determining step of the aminolysis of acyclic thiol esters by ammonia, dimethylamine, and aniline is nucleophilic addition to the carbonyl group; at pH <2, rate-determining decomposition of the addition intermediate prevails. (b) Buffer catalysis (phosphate, imidazole, carboxylate buffer) occurs on the first step of the aminolysis reaction, and this catalysis leads to a transition from rate-limiting formation to rate-limiting breakdown of the intermediate, at least at pH 2–6, and probably at higher pH also; the conversion of intermediate to amide and mercaptan is either uncatalyzed or nearly so.

Kinetic studies of the aminolysis of thiol esters have led earlier investigators to implicate addition intermediates in these reactions.[3c,f] In one instance, the nonlinear dependence of aminolysis rate on buffer concentration has been interpreted in terms of a change in rate-limiting step.[17] From extended studies of the relative rates of reaction of nucleophiles with thiol and oxygen esters, Bruice and co-workers have suggested that the aminolysis of trifluoroethyl thiolacetate proceeds with rate-limiting attack of the nucleophile,[18] while with δ-thiolvalerolactone, partitioning of the intermediate may be of significance, at least with some amines.[19]

We conclude with some brief comments on the intriguing question of the differences in the rates of aminolysis of oxygen and thiol esters. Connors and Bender[20] reported that the alkaline hydrolysis of ethyl *p*-nitrobenzoate and of ethyl *p*-nitrothiolbenzoate proceeded at approximately equal rates; reaction with *n*-butylamine could be studied with the thiol ester but was undetectable with the oxygen ester. To account for the aminolysis behavior, the plausible suggestion was made that while aminolysis of the thiol ester occurred with rate-determining nucleophilic addition of the amine, the reaction with the oxygen ester was retarded by unfavorable partitioning of the intermediate, *i.e.*, in the latter reaction, conversion of intermediate to products was rate limiting.

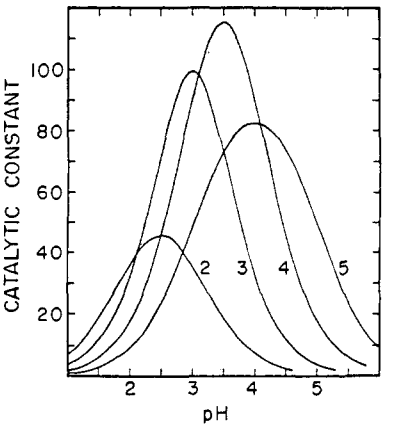


Figure 6. Effect of pH on relative catalytic efficiency of general acid catalysts interacting with the conjugate base of the tetrahedral intermediate. Numbers denote the pK of the general acid catalyst.

The present investigation supports the conclusion that the aminolysis of ethyl *p*-nitrothiolbenzoate involves rate-limiting addition to the carbonyl group. From our studies of iminolactone hydrolysis,[6] and employing the reasoning stated in the introductory section, we suggest that at pH >10, the reaction of aniline with γ-butyrolactone likewise takes place with rate-limiting attack of the nucleophile. Additional data based on current work in this laboratory are in agreement with the hypothesis that at pH >10, the reaction of aliphatic and aromatic amines with alkyl acetates also occurs with rate-limiting formation of tetrahedral intermediates. If these conclusions may be extended to the reaction of *n*-butylamine with ethyl *p*-nitrobenzoate, it would appear that the differences in the response of oxygen and thiol esters to aminolysis must be sought in the subtle factors which control nucleophilic attack on carbonyl groups and not in explanations involving partitioning of tetrahedral intermediates.

Experimental Section[21]

Ethyl thioacetimidate hydrochloride[22] (I) had mp 138–140° (lit.[23] mp 143°). *Anal.* Calcd for $C_4H_{10}ClNS$ (139.66): N, 10.03, S, 22.91. Found: N, 10.00; S, 22.74. Spectral analysis gave λ_{max} 244 mμ [ϵ_{max} 9600 (CH_3CN), ϵ_{243} (0.01 *M* HCl) 9600[24] (lit.[25] ε 9950)].

Ethyl thiobenzimidate hydrochloride[14a] **(II)** had mp 185–187° after recrystallization from glacial acetic acid–ether (lit.[14a] mp 188°); λ_{max} 264 mμ [ε 11,300 (CH_3CN)].

Ethyl N-phenylthiobutyrimidate (III) was purchased from Aldrich Chemical Co. Since the preparation of this compound does not seem to have been recorded in the chemical literature, evidence in support of the assigned structure and some of the properties of this substance are summarized here. *Anal.* Calcd for $C_{12}H_{17}NS$ (207.33): C, 69.51; H, 8.27; N, 6.76; S, 15.46. Found: C, 69.43; H, 8.24; N, 6.74; S, 14.90; bp 100–103° (1.5 mm); $n^{25}D$ 1.5538. The ultraviolet spectrum (CH_3CN) showed: λ_{max}

(18) M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, **89**, 2121 (1967).
(19) T. C. Bruice, J. J. Bruno, and W.-S. Chou, *ibid.*, **85**, 1659 (1963).
(20) K. A. Connors and M. L. Bender, *J. Org. Chem.*, **26**, 2498 (1961).
(21) All melting points are uncorrected. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Ultraviolet spectra were determined by means of a Perkin-Elmer Model 350 recording spectrophotometer.
(22) E. Schmidt, *Ber.*, **47**, 2545 (1914).
(23) A. Hantzsch, *ibid.*, **64**, 661 (1931).
(24) Extrapolated to zero time.
(25) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **87**, 3863 (1965).

239 mμ (ε 13,500); infrared spectrum (thin film): 6.15 and 6.27 μ. The homologous compound ethyl N-phenylthioacetimidate[15a] showed the following spectral characteristics: ultraviolet, λ_{max} 237 mμ [ε 13,100 (CH_3CN)]; infrared (thin film) 6.13 and 6.25 μ. Vapor phase chromatography of distilled samples of III using columns of 20% silicone gum rubber SE-30 on Anakrom ABS (90–100 mesh) showed that the thioimidate (retention time *ca.* 40 min at 145°) was contaminated with several minor impurities amounting to 3–5% of the total material. No aniline, however, could be detected (retention time 2.6 min under identical conditions).

Dimethyl[α-(methylthio)benzylidene]ammonium perchlorate (IV) was prepared by treating a methanolic solution of the corresponding iodide[16d] with the equivalent amount of anhydrous silver perchlorate dissolved in methanol.[26] Silver iodide was removed by filtration, the solution was concentrated *in vacuo* to a small volume, and the residue was diluted with ether. The crystalline product had mp 128–129°. *Anal.* Calcd for $C_{10}H_{14}ClNO_4S$ (279.74): C, 42.93; H, 5.04; N, 5.01; S, 11.46. Found: C, 42.57; H, 5.07; N, 4.79; S, 11.55. Spectral analysis gave λ_{max} 258 mμ [ϵ_{max} 12,000 (CH_3CN)].

Ethyl thiolacetate was prepared from ethanethiol and acetyl chloride by the general procedure of Fedor and Bruice,[28] and was distilled twice. The ultraviolet spectrum in methanol yielded: λ_{max} 232 mμ (ε 4400) [lit.[29] λ_{max} 232 mμ (ε 4170)];[30] in 10% acetonitrile–water, λ_{max} 233 mμ (ε 4800).

Methyl thiolbenzoate[31] had bp 89–90° (3 mm) [lit.[31] bp 134° (25 mm)]. The ultraviolet spectrum in acetonitrile showed: λ_{max} 265 mμ (ε 7000) and 236 mμ (ε 9600).

Dimethylamine hydrochloride was recrystallized twice from ethanol–ether.

Kinetic Measurements. Acetonitrile and imidazole were purified as previously described.[6a] Buffers and inorganic salts were of reagent grade and were used without further purification.

With the exception of rate measurements performed during the hydrolysis of II, the medium used for the kinetic studies was 10% acetonitrile–water (v/v), at ionic strength 0.45, adjusted with added KCl. The hydrolysis of II was studied in 10% ethanol–water, μ = 0.9. Constant pH was maintained with HCl, chloroacetate, formate, acetate, phosphate, imidazole, Tris, and borate buffers in the appropriate ranges. Concentrations of buffers used for the hydrolysis of I and II were 0.02–0.06 *M*, except from phosphate and imidazole buffers at pH 5.5–6.5, which varied from 0.02 to 0.15 *M* (in the case of I). With III, rate measurements were limited to the range of pH 0–6, owing to the low reaction rate at higher pH, and buffer concentrations varied in the range 0.04–0.15 *M*. The hydrolysis of IV was investigated at pH 7.8–10.1 (0.04 *M* phosphate or borate buffers), rates becoming inconveniently small at lower pH. Measurements of pH were generally performed with a Radiometer PHM 4d pH meter.

The rates of hydrolysis of all the thioimidates were determined spectrophotometrically. Reactions were generally carried out in a Teflon-stoppered cuvette kept in the water-jacketed cell holder of a Zeiss PMQ II spectrophotometer. Reaction was initiated by the addition of a small volume of an acetonitrile solution of thioimidate. With II, reaction mixtures were placed in stoppered volumetric flasks immersed in a constant temperature bath at 30°. Aliquots were withdrawn and the optical density change recorded using a Beckman Model DU spectrophotometer.

Wavelengths employed and concentration ranges for the thioimidate esters of this study were: I, 260 mμ at pH <7, 250 mμ at pH 7–10 (2–3 × 10^{-4} *M*); II, 290 mμ at pH <7, 270 mμ at pH 7–9 (1 × 10^{-4} *M*); III, 280 mμ (1.5–1.7 × 10^{-4} *M*); IV, 260 mμ (1 × 10^{-4} *M*). In all cases, absorbance decreased with time. Reactions were followed for at least two half-lives; final optical densities were obtained generally after six to ten half-lives of reaction and the observed rate constants were calculated using the integrated form of the first-order rate equation.

Product Analysis. The extent of C–N bond cleavage occurring on hydrolysis of the thioimidates I–IV was determined either by colorimetric assay of the amine produced (with III and IV) or by measurement of the yield of thiol ester concurrently formed (with I and II). Reactions were allowed to proceed to completion (six to ten half-lives) under conditions identical with those employed in the kinetic experiments, except that, when necessary, substrate concentrations differed slightly from those of the kinetic runs.

For the hydrolyses of I, III, and IV, solutions of ethyl thiolacetate, aniline, or dimethylamine, respectively, were maintained under conditions identical with those used for the hydrolysis experiments and were assayed in the same manner as the latter. Calculation of the yield of ethyl thiolbenzoate produced on hydrolysis of II was based on the use of methyl thiolbenzoate as spectrophotometric standard.

A. Aniline was determined colorimetrically by means of a modification of the Bratton–Marshall procedure.[6] Depending on the expected yield of aniline, the concentration of III varied from 1 to 3 × 10^{-4} *M*. Control experiments with butyranilide in 0.25 *N* HCl or at pH 5.9 (0.2 *M* phosphate buffer) excluded the possibility that aniline was derived from the hydrolysis of initially formed butyranilide. Incubation of aniline with ethyl thiolacetate in 0.25 *N* HCl or at pH 5.9 (phosphate or imidazole buffer) led to no disappearance of aniline, indicating that the aminolysis reaction leading to interconversion of products was negligible.

B. Ethyl thiolacetate was determined either by reaction with hydroxylamine (for hydrolyses carried out in the presence of maleate buffer) or by direct spectrophotometric assay of reaction mixtures.

1. Hydroxamic Acid Formation. A modification of the method of Lipmann and Tuttle was employed.[32] A 3-ml aliquot containing thiol ester at 1 × 10^{-4} *M* gave an optical density of *ca.* 0.3 under these assay conditions. Generally, the concentration of I was 3 × 10^{-4} *M*, except for experiments carried out in maleate buffer alone (Table II, experiments 11–13). In the latter case, substrate concentration was 1.2 × 10^{-3} *M*, since the extent of conversion of thioimidate to thiol ester is low. To achieve this final concentration of substrate in the reaction mixture, it was not possible to use the customary procedure of initiating reaction by adding to an aqueous buffer solution a small volume of (concentrated) stock solution of thioimidate in acetonitrile owing to the limited solubility of I in this solvent. Instead, the substrate was dissolved in maleate buffer, to which were rapidly added the other reaction components.

2. Spectrophotometric Assay. For reactions carried out in the absence of maleate buffers, ethyl thiolacetate was determined from its absorbance at 233 mμ (phosphate buffers) or 240 mμ (acetate and cyanoacetate buffers). Neither acetamide nor ethanethiol absorb appreciably at these wavelengths.[33] The concentration of I was 1.8–2.1 × 10^{-4} *M*.

Control experiments at pH >1.5 showed that hydrolysis of the thiol ester was negligible under the conditions of hydrolysis of I. At lower pH, however, acid-catalyzed disappearance of the thiol ester was noted, in accord with expectation.[34] Product determination was therefore not performed at pH <1.5.

C. Dimethylamine. The yield of dimethylamine formed on hydrolysis of the thioimidate IV (5 × 10^{-4} *M*) was determined with a modification of the procedure of Dahlgren.[36] To 1-ml aliquots of reaction mixture were added in rapid succession 3.5 ml of 1 *M* $NaHCO_3$ and 0.5 ml of aqueous NaOCl solution (*ca.* 0.05%).[37] After 1 min, excess hypochlorite was destroyed by the addition of 0.5 ml of 0.25% aqueous sodium nitrite. One minute later, 0.5 ml of starch–potassium iodide reagent[36] was added; after 5 min, absorbance at 540 mμ was measured using cells of 1- or 5-cm path length. A 1-ml aliquot containing dimethylamine at 1 × 10^{-4} *M* gives an absorbance of about 0.4 under these assay conditions (1-cm light path). Potassium chloride, acetonitrile, and phosphate

(26) The starting material, N-methylthiobenzamide, was obtained from N-methylbenzamide by the general method of Hahn, *et al.*[27]

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

(28) L. R. Fedor and T. C. Bruice, *J. Am. Chem. Soc.*, 86, 4117 (1964).

(29) F. Korte and K.-H. Löhmer, *Ber.*, 91, 1397 (1958).

(30) For a series of alkyl thioacetates derived from straight-chain and branched alkyl mercaptans, the ultraviolet spectrum in methanol shows λ_{max} 231 mμ (ε 4300–4500): L. H. Noda, S. A. Kuby, and H. A. Lardy, *J. Am. Chem. Soc.*, 75, 913 (1953).

(31) L. S. Pratt and E. E. Reid, *ibid.*, 37, 1937 (1915).

(32) M. L. Ernst and G. L. Schmir, *J. Am. Chem. Soc.*, 88, 5001 (1966). The concentration of the ferric chloride reagent used was 40% and not 50% as stated in the reference.

(33) The molar extinction coefficients of N-acetylcysteamine and of *n*-butylmercaptan have been reported to be about 100–200 at 230 mμ in H_2O,[7a,30] *i.e.*, less than 5% of that of ethyl thiolacetate.

(34) The hydrolysis of ethyl thiolacetate in 0.1 *N* HCl (24.6% acetone, 30°) occurs with a half-life of 240 hr[35] while that of isobutyl thiolacetate in 1 *N* HCl (H_2O, 30°) requires 13.7 hr.[30]

(35) J. R. Schaefgen, *J. Am. Chem. Soc.*, 70, 1308 (1948).

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

(37) Commercially available sodium hypochlorite solution (4–6%) was diluted 1:100 with water. The product sold under the trade name of Clorox was also satisfactory.

or borate buffers do not interfere with color development. At concentrations equivalent to that of the substrate, neither N,N-dimethylbenzamide nor a mercaptan (thioglycolic acid) contribute to or reduce the absorbance at 540 mμ.

D. Ethyl Thiolbenzoate. On completion of the hydrolysis of II (65 hr), calculation of the yield of thiol ester was made from the absorbance of reaction mixtures at 270 mμ, using molar extinction coefficients of 7700 (for methyl thiolbenzoate) and 560 (for benzamide).

E. Spectral Analysis. Complete ultraviolet spectra of reaction mixtures were taken on completion of the hydrolysis of each thioimidate under a variety of conditions. These spectra were compared to those of synthetic mixtures whose composition was based on the results of the above-described analyses for amine or thioester product. In general, only products expected to contribute significantly to the ultraviolet spectrum were included in the synthetic mixture. In all cases, the final spectrum of the reaction mixture agreed closely with that of the reconstituted product mixture. Some examples are (a) hydrolysis of I at pH 2.5 (HCl) and 6.2 (three different concentrations of phosphate buffer) and comparison with mixtures of ethyl thiolacetate and acetamide; (b) hydrolysis of II at pH 2.3 and 4 and comparison with mixtures of methyl thiolbenzoate and benzamide (after reaction of II at pH 9.0, the spectrum of the products was nearly identical with that of benzonitrile); (c) hydrolysis of III at pH 4.1 and comparison with a mixture of butyranilide and ethyl thiolacetate; (d) hydrolysis of IV at pH 10.0, followed by acidification to pH 3. The final spectrum was superimposable on that of N,N-dimethylbenzamide [no maximum at >220 mμ; (ϵ_{225} 8000)].

Determination of Constants by Computer Analysis. A. Kinetic Measurements. The best values of the constants k_1, $(k_3 + k_5)/k_2$, and K_1 for the hydrolyses of I, II, and III were obtained by a least-squares fit of the observed rate constants (corrected for hydroxide-catalyzed reactions) to eq 1 using an IBM 7094 computer. The program used (DBELL) is based on the iterative procedures discussed by Cleland.[38]

B. Product Analysis. Plots of the yield of amine (or thiol ester) as a function of buffer concentration (Figure 3) are rectangular hyperbolas characterized by three constants: the yield at zero buffer concentration (intercept on the y axis), the yield at infinite buffer concentration, and K_{app} (the concentration of buffer required to achieve half of the maximum possible increase in yield). Least-squares values of these constants were obtained by two procedures. The first made use of a fit to the two-parameter hyperbola with zero intercepts, according to Bliss and James.[39] If a buffer is available which does not affect product yield, then the influence of other catalysts may be studied in the presence of the unreactive buffer. In that event, product yield in presence of the unreactive buffer may be taken as the yield at zero catalyst concentration. This situation was approached in a few experiments only (Table II, experiments 3–5) since most buffers had significant effects on the product distribution. When the Y intercept was not known, the best value of the yield at zero catalyst concentration was taken as that (assumed) value which gave the best fit of the data to a rectangular hyperbola.

The second procedure employed a program written for the three-parameter hyperbola (program HYPREPLT).[38] Least-squares values of the three desired constants were obtained directly and agreed closely with those determined by the first method.

The theoretical curves of Figure 4 were also calculated by use of program HYPREPLT which yielded the apparent pK of the sigmoid curves as well as the yields of product approached asymptotically at high and low pH.

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(38) W. W. Cleland, *Nature*, **198**, 463 (1963). We are grateful to Professor Cleland, of the University of Wisconsin, for providing us with this program.

(39) C. I. Bliss and A. T. James, *Biometrics*, **22**, 573 (1966). We are indebted to Dr. K. R. Hansen, of the Connecticut Agricultural Experiment Station, for the use of this program.

Unsaturated Neopentyl Compounds. Homoallenyl Participation in the Acetolysis of 2,2-Dimethyl-3,4-pentadienyl *p*-Bromobenzenesulfonate[1a]

Robert S. Bly,[1b] A. R. Ballentine,[1c] and Soon U. Koock[1b]

Contribution from the Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208. *Received April 12, 1967*

Abstract: The acetolysis of 2,2-dimethyl-3,4-pentadienyl *p*-bromobenzenesulfonate is about 1200 times as rapid at 75° as that of 2,2-dimethylpentyl *p*-bromobenzenesulfonate and yields a mixture containing ~12% 2-methyl-1,4,5-hexatriene, ~11% 2-methyl-2,4,5-hexatriene, and 77% 2-methyl-4,5-hexadien-2-yl acetate. Similarly, the solvolysis of the unsaturated brosylate in 95% ethanol at 75° is about 1500 times as rapid as that of the saturated brosylate and yields a mixture comprised of 5% hydrocarbons and 95% 2-methyl-4,5-hexadien-2-yl ethyl ether. A Taft–Streitwieser treatment is used to estimate that participation of the homoallenyl group enhances the acetolysis rate of the unsaturated brosylate by a factor of 8300–58,000 times at 75°. The increased participation of homoallenyl compared to homoallyl is attributed largely to the decreased stability of its ground state. The failure of solvolyzing 2,2-dimethyl-3,4-pentadienyl *p*-bromobenzenesulfonate to produce cyclic products probably results from the effect of the *gem*-dimethyls which stabilize the acylic cation, dimethyl-2,3-butadienylcarbonium ion, with respect to the cyclic α-(2,2-dimethylcyclopropyl)vinyl cation.

Although the chemical literature is replete with examples of participation by isolated olefinic double bonds in both the rate- and product-determining steps of solvolytic displacement reactions,[2] there appear

(1) (a) Portions of this work have been presented before the Southeast–Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Dec 2–4, 1965, Abstracts, p 46; at the 39th Annual Meeting of the South Carolina Academy of Science, Clinton, S. C., April 22–23, 1966 [*Bull. S. Carolina Acad. Sci.*, **28**, 45 (1966)], and at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 11–16, 1966, Abstract S042; (b) to whom all correspondence should be addressed at the Department of Chemistry, the University of South Carolina; (c) Summer Research Participant at the University of South Carolina from the Department of Chemistry, The Citadel.

(2) For recent reviews, see (a) P. D. Bartlett, *Ann.*, **653**, 45 (1962); (b) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 192 ff; (c) B. Capon, *Quart. Rev.* (London), **18**, 45 (1964); (d) M. J. S. Dewar and A. P. Marchand, *Ann. Rev. Phys. Chem.*, **16**, 321 (1965).