It would be very improbable to have a linear structure, because in that case the number of associated molecules should be greater than two.

The same kind of calculations was carried out with the data of the *m*-hydroxybenzoic ester, and a value for A_t mon was found to be 2.68. $n = 3.08$ and $K = 1.62 \times 10^5$.

The value of n suggests, therefore, that three molecules form a cyclic compound. By building the model it agrees with this suggestion (Fig. 2).

The free energy of association for the *p*-hydroxy ester is -1.56 kcal. and -6.58 kcal. for the *m*-ester.

The ΔF difference between the *m*- and *p*-esters may be explained as follows: when the *p*-hydroxy ester is arranged in a cyclic dimer, the carbonyl group is not in the same plane as the benzene ring, and some resonance energy is lost. In the *m*-hydroxy ester, three molecules can be arranged in such a way that the three benzene rings and the three carbonyls are in the same plane and, therefore, the resonance energy of the system does not decrease.

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MEXICO 20, D. F.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Kinetics of Alkaline Hydrolysis and *n*-Butylaminolysis of Ethyl *p*-Nitrobenzoate and Ethyl *p*-Nitrothiolbenzoate[1a]

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The kinetics of alkaline hydrolysis of ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate were studied by spectrophotometric analysis at 300 mμ. The rate of alkaline hydrolysis is first order in hydroxide ion concentration in the *p*H range 8 to 12 for the ester and from *p*H 9 to 12 for the thiol ester. The concurrent alkaline hydrolysis and *n*-butylaminolysis of these esters was interpreted in terms of the rate equation $v = k_1[E][OH^-] + k_2[E][RNH_2] + k_3[E][RNH_2]^2 + k_4[E][RNH_2][OH^-] + k_5[E][RNH_2][RNH_3^+] + k_6[E][RNH_3^+]$, where [E] represents the ester or thiol ester concentration. At 25.6° and ionic strength 0.50, in aqueous solution containing 1.7% v/v acetonitrile, ethyl *p*-nitrobenzoate did not undergo any detectable aminolysis; for this ester $k_1 = 0.63$ l./mole sec. Under the same conditions the thiol ester reacted differently, forming principally *N*-*n*-butyl-*p*-nitrobenzamide. The values of the rate constants of its reaction are $k_1 = 0.52$ l./mole sec., $k_2 = 0.015$ l./mole sec., $k_3 = 0.27$ l.^{2}/mole^2 sec., $k_4 = 13.6$ l.^{2}/mole^2 sec., $k_5 = k_6 = 0$. General base catalysis of thiol ester aminolysis, indicated by the k_3 and k_4 terms, probably proceeds *via* proton abstraction by a base from the tetrahedral addition intermediate.

The effects of variations in thiol ester structure upon rates of hydrolysis have been reported for many thiol acetates. Schaefgen[2a] studied the acid and alkaline hydrolysis of ethyl thiolacetate in acetone-water mixtures, and the same solvent was subsequently used by several other authors. Rylander and Tarbell[2b] compared the rates of acid and alkaline hydrolysis, and the respective energies of activation, of methyl, ethyl, isopropyl, isobutyl, and *t*-butyl thiolacetates with those of the corresponding acetates. Allyl, benzyl, and triphenylmethyl thiolacetates and acetates were similarly compared by Morse and Tarbell.[3] The kinetics of hydrolysis of many thiolacetates were investigated in fully aqueous solution by Noda, Kuby, and Lardy.[4] From these and other studies[5] a few generalizations can be made concerning the hydrolytic reactions of thiolesters: (1) The rates of alkaline hydrolysis of the compounds CH_3COSR are fairly sensitive to the nature of the R group. The ratios of the rate constants to the corresponding acid hydrolysis constants can be correlated with the Taft substituent constants.[6] The energies of activation in such a series are variable and tend to increase with increase in electron-donating ability of the R group. The rates of alkaline hydrolysis of the corresponding oxygen esters can be either less or greater than those of the thiol esters, though the difference is seldom large (usually within a factor of two). For the oxygen compounds neither the rate constants nor the activation energies are very sensitive to the structure of the R group. (2) The rates of acid hydrolysis of thiol esters appear to be less sensitive to structure than do the rates of al-

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[1] (a) This research was supported by Grant H-2416 of the National Institutes of Health; (b) National Institutes of Health Postdoctoral Research Fellow; (c) Present address, Department of Chemistry, Northwestern University.

[2] (a) J. R. Schaefgen, *J. Am. Chem. Soc.*, **70**, 1308 (1948); (b) P. N. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3021 (1950).

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kaline hydrolysis. Apparently in all cases the rate for the oxygen ester is greater than that for the thiol ester; thus for the ethyl acetate–ethyl thiolacetate pair the factor is about 30-fold.[2a] The energies of activation for the thiol esters are larger than for ordinary esters.

Although explanations have been offered for many of these observations, the comparative kinetics of ester and thiol ester reactions are not well understood. In particular, the similar rates of alkaline hydrolysis for an ester-thiol ester pair are not expected, since the RS^- group, being a weaker base than the RO^- group by several orders of magnitude, should be a superior leaving group.

The above observations apply to those reactions which occur with acyl-sulfur fission, which has been demonstrated in the hydrolysis of many thiol esters.[2b,3,5c] In certain compounds alkyl-sulfur cleavage can occur, and this hydrolytic route has been observed in the acid hydrolysis of triphenylmethyl thiolacetate[3] and triphenylmethyl thiolbenzoate.[7]

Most of the investigations of thiol esters have followed the discovery that acylated coenzyme A, an intermediate in many biochemical reactions, is a thiol ester.[8] In some of these studies the reaction between amines and simple thiol esters has been taken as a possible model for certain coenzyme A systems.[9] Thus Tarbell and his co-workers[10] have measured the rates of *n*-butylaminolysis of $CH_3COSC_2H_5$, $CH_3COSCH_2CH_2NHCOCH_3$, and several related thiol esters; these compounds are simple models for acetyl coenzyme A. The modification of the ethyl thiolacetate structure with β- or γ-amido groups caused no important variations in rates of aminolysis. Overbeek and Koningsberger[5b,11] studied the reaction of glycine with ethyl thiolacetate. The aminolysis of the corresponding oxygen esters was not reported in these papers. The reactions of thiol esters with several other nucleophiles have been briefly studied. Hydroxylamine reacts to give the corresponding hydroxamic acid.[4] Other reagents which react with thiol esters are semicarbazide, hydrazine, and substituted hydrazines.[4] Imidazole catalyzes the hydrolysis of ethyl thiolacetate[12] and acetylthiocholine.[13]

The object of the present work was to compare the relative susceptibility of an oxygen ester-thiol ester pair to some simple nucleophiles in order to obtain a better understanding of thiolester reactivity. Ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate were chosen because their reactions can be easily followed spectrophotometrically without interference from the product ethanethiol, which undergoes subsequent oxidation. The kinetics of alkaline hydrolysis and of the reaction with *n*-butylamine are presented in this paper.

EXPERIMENTAL

Materials. Ethyl *p*-nitrobenzoate (Eastman Kodak white label) was recrystallized from 95% ethanol; m.p. 56.5–57°. Ethyl *p*-nitrothiolbenzoate was prepared by warming *p*-nitrobenzoyl chloride and ethanethiol in pyridine solution; the mixture was poured into ice water and the light yellow precipitate was removed by filtration, washed with sodium bicarbonate solution and then with water, and recrystallized from acidified aqueous ethanol; m.p. 69.5–70° (lit.[14] m.p. 67–68°). *p*-Nitrobenzoic acid (Fisher reagent grade) was recrystallized from benzene; m.p. 243.5–244.5°. *N*-*n*-Butyl-*p*-nitrobenzamide was prepared by adding *n*-butylamine to a benzene solution of *p*-nitrobenzoyl chloride, refluxing for 15 min., and washing successively with sodium carbonate solution, dilute hydrochloric acid, and water. The solution was evaporated to dryness and the residue recrystallized from petroleum ether (b.p. 60–80°) and then from xylene; m.p. 104-104.5° (lit.,[15] m.p. 102.5–103°). *n*-Butylamine (Eastman Kodak white label) was distilled at atmospheric pressure (b.p. 77.2–77.4°), and its purity checked by titration with perchloric acid in acetic acid solution, using *p*-naphtholbenzein as a visual indicator. It was sealed under nitrogen in Pyrex ampoules and stored in a refrigerator. Acetonitrile (Eastman Kodak "spectro" grade) was used directly.

Phosphate, carbonate, and borate buffers were prepared from reagent grade materials according to standard formulas.[16] Standard sodium hydroxide solutions were made from a saturated solution of sodium hydroxide and carbonate-free water and were standardized against potassium biphthalate. Hydrochloric acid solution was standardized against borax. Buffers of *n*-butylamine were prepared from accurately weighed samples of *n*-butylamine and known volumes of standard hydrochloric acid solution. The ionic strength of all solutions was brought to a desired value by the addition of reagent grade potassium chloride, when necessary.

Kinetics of alkaline hydrolysis. The rates of alkaline hydrolysis of ethyl *p*-nitrobenzoate and of ethyl *p*-nitrothiolbenzoate were measured in borate, carbonate, and phosphate buffers and in sodium hydroxide solutions at an ionic strength of $0.05M$. A stock solution of the sample compound in acetonitrile was added to the thermostatted solvent and the rate was followed by measuring the change in absorbance at 300 mμ for both esters. The acetonitrile concentration was 2% v/v; variation in acetonitrile concentration from 1.7 to 3.3% caused no significant variations in the observed rates. The initial concentration of the thiolester was about $1 \times 10^{-4}M$ and of the oxygen ester about $2 \times 10^{-4}M$. For solutions of *p*H less than 10.5,

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aliquots were withdrawn at appropriate intervals and the absorbance measured on a Beckman DU spectrophotometer; the temperature of the solutions was 24.7°. Reactions in solutions of higher *p*H were followed by continuous recording of the absorbance with a Beckman DK-2 spectrophotometer fitted with a water-jacketed cell compartment; the temperature in the cell compartment varied from 24.8° to 25.4°. Reactions were usually followed until 75-85% completed and a final (infinity time) reading was taken. *p*H measurements were made with a Radiometer model 3i *p*H meter equipped with a high-alkaline range glass electrode. The estimated uncertainty in *p*H values is ±0.02 unit. For calculations with these results $pK_W = 14.00$ was used.

Decomposition of the thiol ester was observed to be accelerated by oxygen. Thus at *p*H 10.10, the second-order rate constant was 0.535 l./mole sec. in a nitrogen atmosphere, 0.594 l./mole sec. in air, and 0.744 l./mole sec. in an oxygen atmosphere. At very high *p*H, where the hydrolysis is extremely rapid, this effect is not important. At lower *p*H values solvents were flushed with nitrogen before addition of the sample. For reactions followed with the Beckman DU, aliquots were sealed under nitrogen in Pyrex ampoules, which were immersed in the water bath and removed at intervals for spectral analysis.[17]

The effect of ionic strength upon the rates of hydrolysis was studied in sodium hydroxide solutions containing potassium chloride to give the desired ionic strength. The reactions were followed with the DK-2 spectrophotometer, the cell compartment temperature being 25.6 ± 0.1°. In these solutions the acetonitrile concentration was 1.7%.

Kinetics of aminolysis. The aminolysis of ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate was studied in buffer solutions of *n*-butylamine and *n*-butylammonium chloride at a constant ionic strength of 0.50. All reactions were followed by absorbance measurements at 300 mμ with the Beckman DK-2 spectrophotometer. The temperature was 25.6 ± 0.1° during these measurements and the acetonitrile concentration was 1.7%. Duplicate determinations were performed in most of the kinetic runs; the maximum deviation of any measurement from the mean was 1.7%. *p*H measurements were made with a Radiometer model 4b meter standardized against 0.01*M* trisodium phosphate[18]; the estimated uncertainty is ±0.02 unit.

The compositions of the amine buffers are given in Table IV. Concentrations of free amine, $[RNH_2]$, were found by subtracting the concentration of protonated amine, $[RNH_3^+]$, from the total amine concentration, and $[RNH_3^+]$ was calculated with the relation $[RNH_3^+] = [Cl^-]_{HCl} + [OH^-]$, which represents the principle of electroneutrality in these basic solutions; the quantity $[Cl^-]_{HCl}$ is the concentration of chloride ion added in the form of hydrochloric acid.

In all calculations with data at 25.6° which require the quantity pK_W the value 13.98 was employed.[19] This is probably not the correct value in all solutions, because the measured *p*H will not correspond precisely to hydrogen ion activity and the response of the glass electrode may vary with the salt composition of the sample solutions. Another factor which can affect the experimental *p*H values (and the true value of pK_W) is the modification of the solvent by acetonitrile (1.7%) and free *n*-butylamine (up to 4.5%). Because of these uncertainties the quantity $[OH^-]$ derived from the *p*H measurements may not have any absolute significance, but the values are assumed to be approximately internally consistent.

Analysis of products. Ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate both hydrolyze in alkaline solution to yield *p*-nitrobenzoate anion, and the absorption spectra of completely hydrolyzed solutions were quantitatively accounted for on this basis (except for absorption by ethanethiol, in the thiol ester hydrolysis, at lower wave lengths). The product of ethyl *p*-nitrobenzoate reaction in the presence of *n*-butylamine also was determined to be *p*-nitrobenzoate anion.

The absorption spectrum of completely reacted ethyl *p*-nitrothiolbenzoate in *n*-butylamine buffer solutions resembled that of *N*-*n*-butyl-*p*-nitrobenzamide. A quantitative determination was made of the proportion of amine product by the reaction. Several solutions (similar to those used for the kinetic runs) were prepared with known concentrations of free and protonated amine, and known *p*H; sufficient potassium chloride was added to bring the ionic strength to 0.50. Samples of ethyl *p*-nitrothiolbenzoate in acetonitrile solution were added. After the reactions were complete the amine concentrations of the solutions were brought to a common value and an excess of hydrochloric acid was added. Accurately prepared solutions of *p*-nitrobenzoic acid and *N*-*n*-butyl-*p*-nitrobenzamide, in solvent of the same final amine and hydrochloric acid composition, were also made up, and the absorbances of all solutions at 290 mμ were measured with a Beckman DU spectrophotometer. The molar absorptivities[20] of the standard solutions were: *p*-nitrobenzoic acid, 4.67×10^3; and *N*-*n*-butyl-*p*-nitrobenzamide, 7.96×10^3. From these data and the concentration of thiol ester added the percentage yield of amide was calculated (Table I). The major product is seen to be the amide under these conditions. (For explanation of the last column in Table I see *Results* section.)

TABLE I

PER CENT YIELD OF AMIDE IN THE *n*-BUTYLAMINOLYSIS OF ETHYL *p*-NITROTHIOLBENZOATE

Total Amine Concentration[a]	$[RNH_2]$[a]	*p*H	% Amide Produced	% Amide Calculated
0.1046	0.0524	10.87	79	84
0.4185	0.3033	11.29	95	97
0.1046	0.0324	10.52	73	79

[a] In moles/liter.

To determine whether subsequent hydrolysis of the amide would occur during the kinetic observations a sample of *N*-*n*-butyl-*p*-nitrobenzamide was added to an *n*-butylamine buffer solution (total amine concentration 0.1*M*, *p*H 10.6) and the solution was equilibrated at 24.7°. The absorbance at 270 mμ and at 300 mμ was periodically measured with a Beckman DU, and no change in absorbance was noted in 24 hr. Under the conditions of the kinetic experiments reported here, therefore, no hydrolysis of the product amide occurs before the thiol ester reaction is completed.

RESULTS

Alkaline hydrolysis. The concentration of hydroxide ion was maintained essentially constant in kinetic runs by means of buffers or excess sodium hydroxide, and the observed kinetics were first order with respect to the carboxylic acid derivative; examples of the first order plots are shown in Fig. 1. The observed rate constant calculated from the

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(17) Overbeek and Koningsberger (Ref. 5b) have reported that ethyl thiolacetate undergoes decomposition in the presence of oxygen.

(18) R. G. Bates, G. D. Pinching, and E. R. Smith, *J. Research Natl. Bur. Standards*, **45**, 418 (1950).

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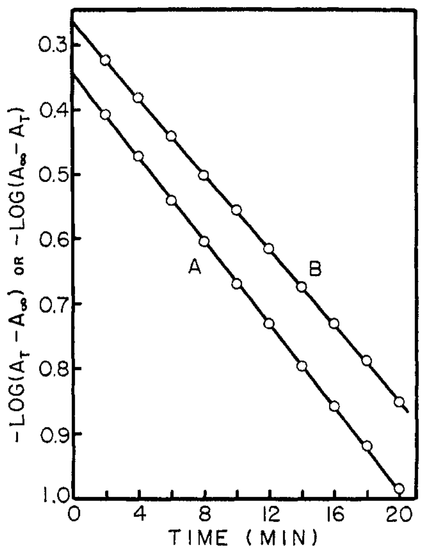

Fig. 1. Alkaline hydrolysis in *p*H 11.38 phosphate buffer. A. Ethyl *p*-nitrobenzoate. B. Ethyl *p*-nitrothiolbenzoate

slopes of plots of log $(A_\infty - A_t)$ [for ethyl *p*-nitrobenzoate] or $\log(A_t - A_\infty)$ [for ethyl *p*-nitrothiolbenzoate] *vs.* time, are listed in Table II with the measured *p*H. The calculated second order constants are seen to be constant over the *p*H range 8 to 12 for the ester and 9 to 12 for the thiol ester. The deviations from constancy at lower *p*H values have not been thoroughly studied since this *p*H region did not figure in subsequent work.

TABLE II

KINETICS OF ALKALINE HYDROLYSIS OF ETHYL *p*-NITROBENZOATE AND OF ETHYL *p*-NITROTHIOLBENZOATE

*p*H	No. Detns.	k_{obs}, Sec.$^{-1a}$	k_{OH}, L./Mole Sec.
		ETHYL *p*-NITROBENZOATE	
12.00	4	$5.38 \pm 0.04 \times 10^{-3}$	0.538
11.38	4	$1.28 \pm 0.03 \times 10^{-3}$	0.531
10.09	2	$6.64 \pm 0.05 \times 10^{-5}$	0.540
9.09	2	$6.64 \pm 0.05 \times 10^{-6}$	0.540
7.99	1	5.33×10^{-7}	0.546
7.14	1	2.56×10^{-7}	1.86
		ETHYL *p*-NITROTHIOLBENZOATE	
12.00	8	$4.48 \pm 0.20 \times 10^{-3}$	0.448
11.38	5	$1.15 \pm 0.05 \times 10^{-3}$	0.478
10.70	2	$2.43 \pm 0.04 \times 10^{-4}$	0.473
10.10	2	$6.75 \pm 0.38 \times 10^{-5}$	0.535
9.09	3	$5.77 \pm 0.21 \times 10^{-6}$	0.469
8.31	1	1.45×10^{-6}	0.711

[a] Precision expressed as mean deviation, where m.d. = $\dfrac{\Sigma|x_i - \bar{x}|}{n - 1}$.

The second order constants for alkaline hydrolysis increase with ionic strength, as shown in Table III. The change is not large and is similar in magnitude for both compounds.

TABLE III

EFFECT OF IONIC STRENGTH ON RATES OF ALKALINE HYDROLYSIS

Ionic Strength	k_{OH}, l./mole sec.
ETHYL *p*-NITROBENZOATE	
0.006	0.53
0.20	0.64
0.36	0.59
0.49	0.63
0.60	0.65
ETHYL *p*-NITROTHIOLBENZOATE	
0.006	0.45
0.20	0.53
0.36	0.48
0.49	0.51
0.60	0.53

Concurrent hydrolysis and aminolysis. The design of the aminolysis experiments was based upon rate Equation 1.[21]

$$-d[\mathrm{E}]/dt = k_1[\mathrm{E}][\mathrm{OH}^-] + k_2[\mathrm{E}][\mathrm{RNH_2}] + k_3[\mathrm{E}][\mathrm{RNH_2}]^2 + k_4[\mathrm{E}][\mathrm{RNH_2}][\mathrm{OH}^-] + k_5[\mathrm{E}][\mathrm{RNH_2}][\mathrm{RNH_3}^+] + k_6[\mathrm{E}][\mathrm{RNH_3}^+] \quad (1)$$

[E] represents the ester or thiol ester concentration, $[\mathrm{RNH_2}]$ is the concentration of free *n*-butylamine, and $[\mathrm{RNH_3}^+]$ is the concentration of protonated amine. The experimental rate was observed to be first order with respect to [E] in buffers containing excess amine; that is,

$$-d[\mathrm{E}]/dt = k_{obs}[\mathrm{E}] \quad (2)$$

The dissociation constant of the protonated amine is written $\mathrm{K_a} = [\mathrm{H}^+][\mathrm{RNH_2}]/[\mathrm{RNH_3}^+]$; this expression can be combined with Equations (1) and (2) to give (4),

$$\frac{(k_{obs} - k_1[\mathrm{OH}^-])}{[\mathrm{RNH_2}]} = (k_3 + k_5[\mathrm{H}^+]/\mathrm{K_a})[\mathrm{RNH_2}] + (k_2 + k_4[\mathrm{OH}^-] + k_6[\mathrm{H}^+]/\mathrm{K_a}) \quad (4)$$

which indicates that, if the *p*H is maintained constant and the amine concentration is varied, a plot of $(k_{obs} - k_1[\mathrm{OH}^-])/[\mathrm{RNH_2}]$ *vs.* $[\mathrm{RNH_2}]$ should yield a straight line. From such plots at several values of *p*H the constants k_3 and k_5 may be evaluated from the variation of the slope with $[\mathrm{H}^+]$. The intercept is a quadratic function of $[\mathrm{H}^+]$, but simplifies if either k_4 or k_6 is equal to zero; if both k_4 and k_6 are greater than zero a simple linear extrapolation cannot be made, though the constants can be found analytically.

The rate of reaction of ethyl *p*-nitrobenzoate did not appear to be affected by *n*-butylamine. The kinetics were studied in *n*-butylamine buffers (total

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(21) Similar rate equations have previously been suggested to account for aminolysis of esters and thiol esters, though in no single system have all six terms been required to explain the data. (a) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960); W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960); Ref. 10, 11.

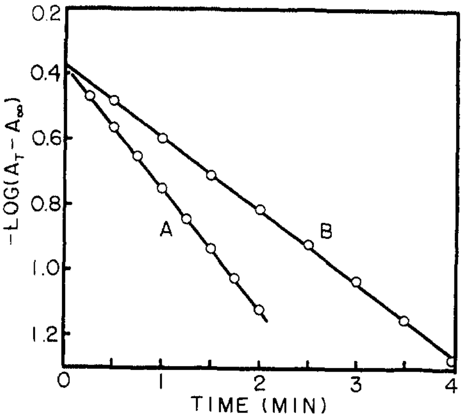


Fig. 2. Typical kinetic runs in the n-butylaminolysis of ethyl p-nitrothiolbenzoate. A. $(RNH_2] = 0.1483$, $[RNH_3^+] = 0.0595$ mole/l.; pH = 11.27. B. $[RNH_2] = 0.1521$, $[RNH_3^+] = 0.3703$ mole/l.; pH = 10.44

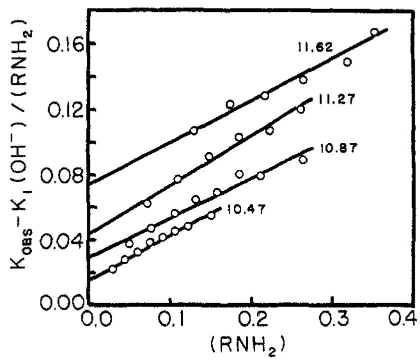


Fig. 3. Plot of Equation (4) for the n-butylaminolysis of ethyl p-nitrothiolbenzoate. Numbers denote pH

amine 0.1–0.5M) at three pH values. The quantity $(k_{obs} - k_1[OH^-])/[RHN_2]$ was a positive or negative number of the order 10^{-4}; in the calculation of this quantity k_1 was taken as 0.63 l./mole sec. It is concluded that the constants k_2, k_3, k_4, k_5, and k_6 are not significantly different from zero under the conditions of the experiments.

The reaction rate of ethyl p-nitrothiolbenzoate was significantly accelerated by n-butylamine. Typical first order plots are shown in Fig. 2. The data are listed in Table IV and the plots of $(k_{obs} - k_1[OH^-])/[RNH_2]$ *vs.* $[RNH_2]$ are given in Fig. 3. The lines are reasonably straight, though a slight curvature may be present in some of them. Variations in pH may be responsible for some of the deviations. It may be significant that curvature seems to occur at lower values of $[RNH_2]$ when the pH is lowered; that is, curvature may be associated with high concentrations of amine salt. This slight trend of points away from linearity was neglected in the construction of lines, which was done by the least-squares method. The equations of the lines are given in Table V.

TABLE IV

KINETIC DATA FOR ETHYL p-NITROTHIOLBENZOATE IN n-BUTYLAMINE BUFFERS

Total Amine Concentration[a]	$[RNH_2]$[a]	$k_{obs} \times 10^2$, sec.$^{-1}$	$(k_{obs} - k_1[OH^-])/[RNH_2]$[b]
	pH = 10.47 ± 0.02		
0.1045	0.0302	0.0826	0.0217
0.1567	0.0454	0.137	0.0267
0.2089	0.0606	0.212	0.0322
0.2612	0.0759	0.306	0.0381
0.3134	0.0911	0.388	0.0408
0.3657	0.1064	0.493	0.0448
0.4179	0.1216	0.596	0.0477
0.5224	0.1521	0.852	0.0550
	pH = 10.87 ± 0.01		
0.1046	0.0524	0.236	0.0370
0.1569	0.0780	0.408	0.0471
0.2092	0.1056	0.634	0.0563
0.2614	0.1321	0.883	0.0637
0.3139	0.1587	1.14	0.0693
0.3660	0.1853	1.53	0.0804
0.4183	0.2120	1.73	0.0794
0.5229	0.2651	2.41	0.0894
	pH = 11.27 ± 0.01		
0.1039	0.0733	0.550	0.0621
0.1558	0.1107	0.949	0.0766
0.2078	0.1483	1.45	0.0910
0.2597	0.1857	2.03	0.103
0.3116	0.2234	2.49	0.107
0.3636	0.2609	3.24	0.120
0.4155	0.2986	3.50	0.114[c]
0.5194	0.3735	4.90	0.129[c]
	pH = 11.62 ± 0.02		
0.1042	0.0863	0.966	0.0907[d]
0.1563	0.1303	1.61	0.107
0.2085	0.1756	2.37	0.123
0.2606	0.2182	3.03	0.128
0.3127	0.2652	3.89	0.138
0.3648	0.3098	4.86	0.149
0.4169	0.3548	6.20	0.168
0.2512	0.4448	7.28	0.159[c]

[a] In mole/liter. [b] $k_1 = 0.52$ l./mole sec. [c] Rejected. [d] Rejected because pH (11.53) differed widely from the mean.

TABLE V

EQUATIONS OF LINES ACCORDING TO EQUATION (4) FOR THE n-BUTYLAMINOLYSIS OF ETHYL p-NITROTHIOLBENZOATE

pH	$[OH^-]$, Mole/l.	Equation[a]
10.47	3.09×10^{-4}	$y = 0.273x + 0.015$
10.87	7.76×10^{-4}	$y = 0.244x + 0.029$
11.27	1.95×10^{-3}	$y = 0.302x + 0.043$
11.62	$4.37 + 10^{-3}$	$y = 0.257x + 0.074$

[a] $y = (k_{obs} - k_1[OH^-])/[RNH_2]$; $x = [RNH_2]$.

The slopes of the lines do not appear to vary with pH, hence k_5 is taken equal to zero. The mean of the slopes is 0.269 ± 0.025 l.^{2}/mole^2 sec. A plot of the intercepts against $[H^+]$ produces a curve, while the plot of intercept *vs.* $[OH^-]$ yields a reasonably straight line (Fig. 4). The least-squares equation of this line is

$$\text{Intercept} = 13.6[OH^-] + 0.015.$$

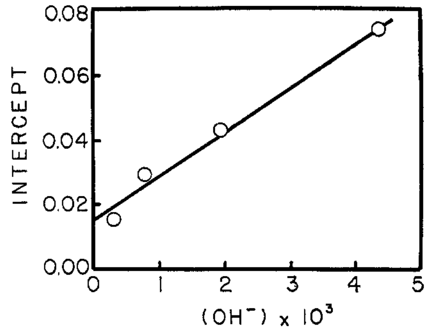


Fig. 4. Plot of the intercepts from Fig. 3 *versus* hydroxide ion concentration

The rate constants for the aminolysis are therefore k_2 = 0.015 l./mole sec., k_3 = 0.27 l.^{2}/mole^2 sec., k_4 = 13.6 l.^{2}/mole^2 sec., and $k_5 = k_6 = 0$.

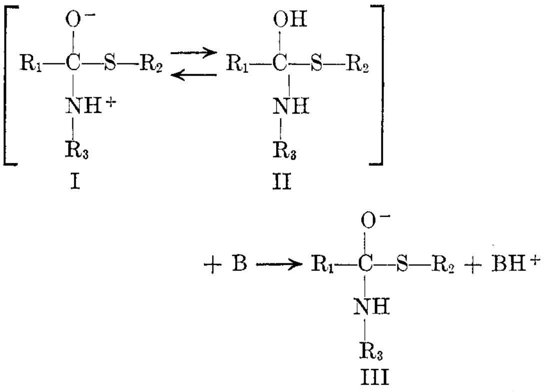
These constants can be used to calculate the expected first order rate constant at any amine concentration and pH; the observed values can be reproduced to better than 10%. In a similar calculation the percentage yields of amide to be expected under the conditions given in Table I are listed in the last column of that table. The agreement with experiment is satisfactory.

From the data of Table IV the apparent dissociation constant of n-butylammonium ion can be calculated. (Actually the experimental pH values, rather than the average values given in the table, were used.) The results show no consistent trend with amine concentration. pK'_a is 10.87 ± 0.01 at ionic strength 0.50 and total amine concentration 0.1–0.5M. (The thermodynamic pK_a is 10.597 at 25°.)[22]

DISCUSSION

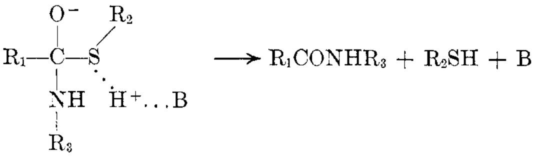
Ethyl p-nitrothiolbenzoate is considerably more reactive toward hydroxide ion than are most thiolacetates.[2b,4,23] Ethyl p-nitrobenzoate is also quite reactive, its second order alkaline hydrolysis rate constant being about one half that of phenyl acetate.[21b] However, while the susceptibility of the thiol ester to aminolysis is consistent with the behavior observed with other thiol esters[10,11a] and with phenyl acetate,[21b] the absence of detectable aminolysis of ethyl p-nitrobenzoate is unexpected. That is, $CH_3CH_2S^-$ and $CH_3CH_2O^-$ appear to be equally good leaving groups with respect to hydroxide ion, but $CH_3CH_2S^-$ is a relatively far better leaving group than $CH_3CH_2O^-$ with respect to n-butylamine. The similar reactivities of ethyl p-nitrobenzoate and ethyl p-nitrothiolbenzoate (and of nearly all ester-thiol ester pairs) toward hydroxide ion may perhaps be the result of a difference in solvent participation for the two compounds. The precise nature and extent of such involvement are unknown for either type of compound. Schaefgen[2a] suggested that attack by hydroxide ion on the carbonyl of an ester may be aided by hydrogen-bonding of a water molecule to the ether oxygen, while this interaction would be absent or of less importance for the thiolester.

Several mechanisms have been proposed to account for the observation of general basic catalysis of aminolysis of esters and thiol esters.[10a,21a,b] One of these involves removal of a proton from the attacking amine by a general base during the transition state of the formation of the tetrahedral addition intermediate. This mechanism is similar to another (Equation 5) in which a proton is removed from the tetrahedral addition intermediate (I or II), and there may be no clear distinction between the two descriptions. The proton abstraction is followed by decomposition of III to



$$\left[\underset{\text{I}}{R_1-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\underset{\displaystyle R_3}{|}}{\underset{\displaystyle NH^+}{|}}}{C}}-S-R_2} \rightleftharpoons \underset{\text{II}}{R_1-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\underset{\displaystyle R_3}{|}}{\underset{\displaystyle NH}{|}}}{C}}-S-R_2}\right] + B \longrightarrow \underset{\text{III}}{R_1-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\underset{\displaystyle R_3}{|}}{\underset{\displaystyle NH}{|}}}{C}}-S-R_2} + BH^+ \quad (5)$$

the amide and the thiol anion. The mechanism shown by reaction (6) involves general acid catalyzed breakdown of III as the slow step; in this



$$R_1-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\underset{\displaystyle R_3}{|}}{\underset{\displaystyle NH}{|}}}{C}}-\overset{\displaystyle R_2}{S}\cdots H^+\cdots B \longrightarrow R_1CONHR_3 + R_2SH + B \quad (6)$$

scheme the formation of III from I or II is regarded as a fast reversible reaction.[21a] This mechanism leads to observed general base catalysis if the base B which is responsible for proton removal from I or II is the conjugate base of the general acid BH^+ involved in reaction (6); this may not generally be the case. Bunnett and Davis[21a] have pointed out that the better the leaving group the less is the likelihood that mechanism (6) will be important. In fact, in the pH range employed in the present work the product thiol was largely ionized (the

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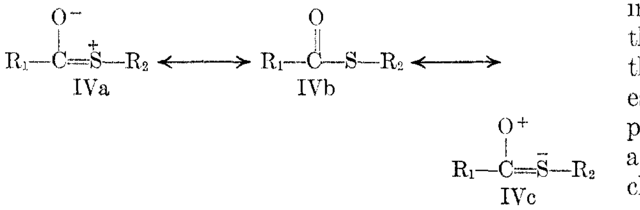
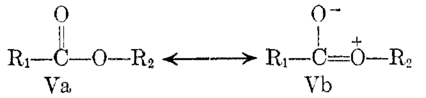
[22] A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, **47**, 34 (1951).

[23] Preliminary studies of the alkaline hydrolysis of phenyl thiolbenzoate have shown that this too is a fairly reactive thiol ester, with k_{OH} = 0.4 l./mole sec. The reaction was studied at 25° in pH 10 carbonate buffer and in sodium hydroxide solutions, the decrease in thiol ester concentration being followed by absorbance measurements at 240 mμ.

pK_a of ethanethiol is about 10.5)[24] and it seems that general acid assistance would be unlikely. The mechanism according to Equation (5) seems more probable, where B is H_2O, RNH_2, or OH^-, giving rise to terms in k_2, k_3, and k_4, respectively. The rate constant k_2 then would include the concentration of water.

Pertinent to the problem of thiol ester reactivity is the recent infrared study of Baker and Harris,[25] who suggested that the thiol ester structure includes the resonance form IVc, in which the sulfur *d*-orbital is utilized. Oxygen esters, on the other hand, are generally represented by the structures Va and Vb. As a result the carbonyl group of a thiol ester may be considerable less basic than that of the corresponding ester.[25] Proton attack at the carbonyl oxygen should be more important with the ester than with the thiol ester, therefore, and this is consistent with the greater rate of acid hydrolysis always observed for esters. The mode of attack of hydroxide ion upon a structure like IV is not known. Three mechanisms have been proposed for attack by a nucleophile on a carboxylic acid derivative.[26] One of these involves an approach from the rear with respect to the leaving group, another represents the attack as rearward approach with respect to the carbonyl oxygen, and the third pictures the approach as an attack perpendicular to the plane of the carbonyl group. This last approach permits maximum overlap of the π-orbital of the carboxyl group with the orbital of the incoming nucleophile. In a structure such as IV the carbonyl electron distribution is sufficiently altered by hybridization with the sulfur *d*-orbitals so that the approach of the nucleophile may not be controlled simply by the carbonyl group alone, and predictions about rates of alkaline hydrolysis based upon structure IV cannot be made.


IVa IVb IVc


Va Vb

The similarity of alkaline hydrolysis rates for an oxygen ester–thiol ester pair may be explicable in terms of the partition ratio k_2/k_3, where k_2 is the rate constant for return to reactants from the tetrahedral intermediate and k_3 is the rate constant for passage to products.[27] For oxygen esters, values of k_2/k_3 range from essentially zero to about 0.8.[27] It seems reasonable that the constant k_3 for a thiol ester may be considerably larger than that for the corresponding ester, because of the much lower basicity of the thiolate group, and that k_2/k_3 may therefore be even smaller for the thiol ester than for the ester. Because the hydrolytic rate constant may be expressed as $k_h = k_1/(k_2/k_3 + 1)$, where k_1 is the rate constant for the formation of the intermediate, the magnitude of k_h is determined by that of k_1, since k_2/k_3 seems usually to be smaller than one. Thus if the k_1 constants for a thiol ester-ester pair are similar in magnitude it is not surprising that the alkaline hydrolytic constants also are similar. A study of the kinetics of oxygen exchange[27] of ethyl *p*-nitrobenzoate and ethyl *p*-nitrothiolbenzoate has been initiated to obtain evidence bearing on this problem.

The same consideration may be applied to the aminolysis reaction. If the assumption is made that the intermediate corresponding to I and II actually is formed in the oxygen ester–amine system, then the absence of observed reaction may be accounted for by a large value of k_2/k_3 (much greater that one) for this intermediate.

In Table VI reasonable values of k_2/k_3 are shown for the alkaline hydrolysis and aminolysis of both esters. It will be noted that the ratio $(k_2/k_3)_o/(k_2/k_3)_s$ is the same in both systems; this seems to be a reasonable limit to impose upon the possible values of the partition ratio. In the final column of the table are listed the rate constants which would be observed with these assigned ratios. If the values of k_o and k_s (in each system) are comparable, it is seen that the oxygen and thiol esters are of similar reactivity with respect to hydroxide ion, while the thiol ester is much more reactive than the ester with respect to the amine.

TABLE VI

HYPOTHETICAL RATE CONSTANTS FOR HYDROLYSIS AND AMINOLYSIS OF ESTERS AND THIOL ESTERS

	k_1	k_2/k_3	k_{obs}^a
	ALKALINE HYDROLYSIS		
Ester	k_1^o	0.25	$0.8k_1^o$
Thiol ester	k_1^S	0.001	k_1^S
	AMINOLYSIS		
Ester	k_1^o	25	$0.038k_1$
Thiol ester	k_1^S	0.1	$0.91k_1^S$

[a] Calculated with the equation $k_{obs} = k_1/(k_2/k_3 + 1)$.

CHICAGO, ILL.

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[24] D. L. Yabroff, *Ind. Eng. Chem.*, **32**, 257 (1940); J. P. Danehy and C. J. Noel, *J. Am. Chem. Soc.*, **82**, 2511 (1960).

[25] A. W. Baker and G. H. Harris, *J. Am. Chem. Soc.*, **82**, 1923 (1960).

[26] M. L. Bender, *Chem. Revs.*, **60**, 60 (1960).

[27] M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951); M. L. Bender, R. D. Ginger, and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044 (1957).