[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS SCHOOL OF MEDICINE]

The Influence of the Leaving Tendency of the Phenoxy Group on the Ammonolysis and Hydrolysis of Substituted Phenyl Acetates

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The ammonolysis of *p*-nitrophenyl, *m*-nitrophenyl, *p*-chlorophenyl, phenyl and *p*-cresyl acetates in aqueous solution has been found to be subject to general base catalysis by amine but not to specific lyate ion catalysis eliminating amide ion as an intermediate. The importance of general base catalysis decreases with the increased leaving tendency of phenoxide ion and for *m*- and *p*-nitrophenyl acetates ammonolysis proceeded without measurable catalysis. The Hammett ρ constant for the non-catalyzed ammonolysis reaction is three times as large as that for the general base-catalyzed reaction. It is suggested that the mechanism which fits the experimental data best is one in which an NH_3 molecule acts as a concerted acid–base catalyst in removing a proton from the attacking amine and simultaneously protonating the leaving group.

Introduction

Ester aminolysis, in analogy to ester hydrolysis,[1–6] is subject to acid and base catalysis. For the aminolysis reaction considerable controversy surrounds the particular mechanisms of catalysis. Thus, Betts and Hammett,[7] in their study of the ammonolysis of methyl phenyl acetates in anhydrous methanol determined the reaction to be $^3/_2$ order in NH_3 and to be accelerated by MeO^- and retarded by NH_4^+. These workers considered the catalysis to involve proton abstraction from ammonia, either prior to or during formation of the transition state. Mechanisms involving specific base (1) or general base (2) catalysis were suggested as being in accord with the kinetic results.

$$RNH_2 + ROH \rightleftharpoons RO^- + RNH_3^+$$

$$2RNH_2 \rightleftharpoons RNH^- + RNH_3^+$$

$$R''COOR' + RNH_2 \longrightarrow R''CONHR + R'OH \quad (1)$$

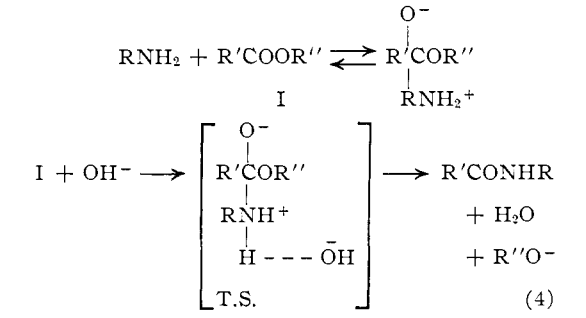
$$R''COOR' + RNH^- \longrightarrow R''CONHR + R'O^-$$

$$2NH_3 + \text{ester} \rightleftharpoons (\text{complex}) \longrightarrow \text{products} \quad (2)$$

In (2) the complex is proposed to be a carrier of the amide anion. Similar kinetic results and mechanistic considerations were presented by Watanabe and DeFonso[8] in their investigations of the reaction of *n*-butylamine with ethyl formate in ethylene glycol and ethanol as solvents. Hawkins and Tarbell found that in the reaction of *n*-butylamine with ethyl thiolacetate and β-acetaminoethyl thiolacetate in aqueous solution the only term pertaining to aminolysis was

$$\text{d amide}/dt = k(NH_3)(OH^-)(\text{ester}) = k'(RNH^-)(\text{ester}) = k''(NH_3)^2(\text{ester})/(NH_4^+) \quad (3)$$

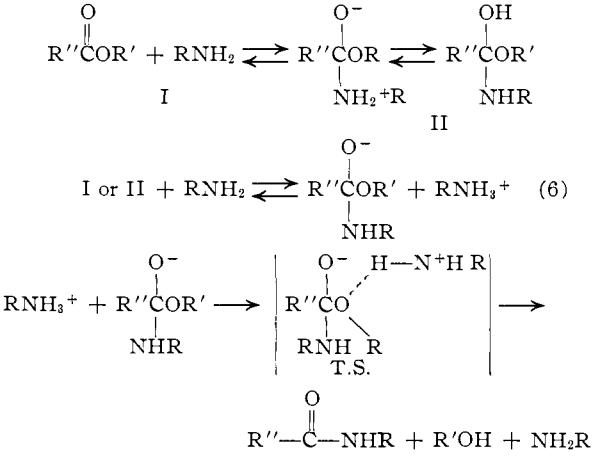
Possibly due to the improbable existence of RNH^- in aqueous solution, mechanism 4—kinetically equivalent to 1—was suggested by the latter workers.[9]



In extending these studies both lyate anion and cation catalysis were found to be of importance in the reaction of *n*-butylamine with α-naphthyl acetate[10] and a series of thiol esters.[11]

$$\text{d amide}/dt = k(RNH_2)(\text{ester})(OH^-) + k'(RNH_2)(\text{ester})(H^+) \quad (5)$$
$$= k''(RNH^-)(\text{ester}) + k'''(RNH_3^+)(\text{ester}) \quad \text{etc.}$$

In a reinvestigation of the reaction of ethyl formate with *n*-butylamine in ethanol, Bunnett and Davis[12] found the catalysis to be of the general base type. This finding eliminates mechanism 1 from being of importance in this system since (1) requires apparent specific lyate ion catalysis. Arguments presented by these workers favored 6 as that for general base catalysis of the aminolysis reaction.



Employing aqueous solutions, Jencks and Carriuolo[13] found the reaction of an assortment of

(1) T. C. Bruice and G. L. Schmir, THIS JOURNAL, **79**, 1663 (1957).
(2) T. C. Bruice and G. L. Schmir, *ibid.*, **80**, 148 (1958).
(3) T. C. Bruice and R. Lapinski, *ibid.*, **80**, 2265 (1958).
(4) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1656 (1957).
(5) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1652 (1957).
(6) E. R. Garrett, *ibid.*, **79**, 3401 (1957).
(7) R. L. Betts and L. P. Hammett, *ibid.*, **59**, 1968 (1937).
(8) W. H. Watanabe and L. R. DeFonso, *ibid.*, **78**, 4542 (1956).
(9) P. J. Hawkins and D. S. Tarbell, *ibid.*, **75**, 2982 (1953). It is difficult to assign a true priority to this type mechanism since its existence has been contemplated for some time (see G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1945, p. 415).
(10) P. J. Hawkins and I. Piscalnikow, THIS JOURNAL, **77**, 2771 (1955).
(11) D. S. Tarbell and D. P. Cameron, *ibid.*, **78**, 2731 (1956).
(12) J. F. Bunnett and G. I. Davis, *ibid.*, **82**, 665 (1960).
(13) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960).

primary and secondary amines with phenyl acetate to be subject to one or another type of acid and base catalysis. Arguments presented by these workers favored mechanisms for general base catalysis in which a proton is removed from either the attacking amine or from an addition compound, by a second molecule of amine, in the transition state. The suggested mechanism would then resemble 4, as applied to specific base catalysis.

The important difference between the transition state for general base catalysis as suggested by Bunnett and Davis[12] on the one hand and by Jencks and Carriuolo[13] on the other is that the former workers prefer protonation of the leaving group by aminium ion while the latter favor proton abstraction by amine. The two mechanisms are, of course, kinetically equivalent. The purpose of this investigation has been to determine the effect of the electronic nature of the leaving group on the mechanism of ammonolysis in order to provide additional data that might be useful in differentiating between these kinetically equivalent mechanisms. For this purpose we have chosen to study the ammonolysis of substituted phenyl acetates. The ammonolysis reactions reported here were carried out in buffered 1% aqueous dioxane (v./v.) at an ionic strength of 1.0 M and a temperature of 30°. In all the kinetic runs the value of A_T (where $A_T = NH_3 + NH_4^+$) exceeded that of the ester (E) to an extent (10^2 to 10^3) which allowed us to consider A_T constant through the reactions. The appearance of P_T (P_T = phenol + phenolate), determined spectrophotometrically was, therefore, always pseudo first order

$$dP_T/dt = k_{obsd}(E) \text{ and } k_1 = k_{obsd} - k_w \qquad (7)$$

where k_1 is the pseudo first-order rate constant for ammonolysis at given value of pH and A_T and k_w is the solvolytic constant for the ester at the same pH. The values of k_w were determined independently. At any fixed value of pH and A_T the apparent second-order rate constant (k_2') for ammonolysis was obtained *via* 8

$$k_2' = \frac{k_{obsd} - k_w}{A_T(K_a/(K_a + a_H))} = \frac{k_1}{NH_3} \qquad (8)$$

where K_a is the dissociation constant for NH_4^+ and a_H is the hydrogen ion activity as determined by the glass electrode. Plots of k_2' *vs.* (NH_3) were found to be linear even when the reactions were studies over a range of 10^2 in the concentration of lyate ions. Therefore, insofar as substituted phenyl acetates are concerned, there appears to be no specific acid or base catalysis in their ammonolysis. The slopes of the plots afforded the catalytic coefficients (k_{NH_3}) and the intercepts at (NH_3) = 0 gave the true second-order rates of ammonolysis (k_2).

Experimental

Hydrolysis rates for the *m*- and *p*-nitrophenyl acetates were obtained titrimetrically at constant pH. The reactions were carried out at 30 ± 0.1° in 1% dioxane–water (v./v.) at an ionic strength of 1.0 M (with KCl) under N_2. To prevent alteration of ionic strength during the course of the reaction the standard base (*ca.* 0.01 N KOH) was prepared in 1 M KCl. The reactions were followed to completion and the first-order solvolysis constants determined by the method of Guggenheim.[14] Only those runs in which the standardization of the pH-stat with buffer before and after the reaction differed by 0.02 pH unit or less were calculated.

For *p*-cresyl, phenyl and *p*-chlorophenyl acetates the solvolysis constants were determined spectrophotometrically in phosphate and borate buffers. Because of absorption by *p*-cresyl acetate and phenyl acetate, continuous variation curves were made for ester and *p*-cresol or phenol at each pH and the extent of reaction determined from these curves. The hydrolytic constants were then determined by employing the conventional form of the first-order rate equation. The catalysis brought about by buffer ions was eliminated by varying the total buffer concentration (0.2–0.05 M) at constant pH and extrapolating to zero buffer. In all runs with buffers the ionic strength was adjusted to a calculated value of 1.0 M with KCl.

Ammonolysis Rates.—Standard taper silica cuvettes of 1-cm. diameter with Thunberg tops were employed as the reaction vessels and rates were followed in a thermostated spectrophotometer (30 ± 0.1°). Into the Thunberg top was weighed the correct quantity of NH_4Cl and onto this was added 0.04 ml. of a dioxane solution of the ester (*ca.* 10^{-4} M in ester). The Thunberg top was then placed onto the cuvette which contained 4 ml. of the buffer or 4 ml. of a standard KOH solution previously equilibrated at 30° and the reactants mixed by shaking. The reactions were followed to completion and the rate constants for platinum release determined by the method of Guggenheim'[14] (*p*-nitrophenyl acetate, 400 mμ; *m*-nitrophenyl acetate, 420 mμ; *p*-chlorophenyl acetate, 285 mμ; phenyl acetate, 275 mμ; *p*-cresyl acetate, 280 mμ). The base concentrations of the solutions in the cuvettes were adjusted so that addition of the NH_4Cl brought about a drop in pH to a value approximated by prior experiments. The actual pH of the run was taken at the termination of the reaction. In the non-buffered runs NH_3 was always present in at least a 50-fold (and usually much higher) excess over the ester so that drifting of the pH in the course of the reaction was prevented. The ionic strength was maintained at 1.0 M by adding sufficient KCl to the base solution in the cuvette so that At + KCl = 1.0 M.

The rate data for the ammonolysis of the various substituted phenyl acetates are presented in Table I.

Product analyses were carried out in the case of the *p*-nitro and *p*-methyl esters. For this purpose reactions of ester with NH_3 were carried out under conditions identical to those employed for the kinetic experiments. The reactions were allowed to go to completion and acetamide formed was determined by conversion to acetyl hydroxamic acid ferric ion complex by the method of Katz, Lieberman and Barker.[15] The absorbance of the complex was determined spectrophotometrically at 540 mμ and the concentration of acetamide determined from a standard curve prepared from standard solutions of acetamide. In the pH range employed the appearance of acetamide accounted for between 93 and 107% of ester employed.

Apparatus and Materials.—The esters were prepared and purified by previously published procedures.[1] Ammonium chloride (J. T. Baker analyzed) was weighed to ±0.01 mg. The determination of pH was carried out with a model 22 Radiometer pH meter. All spectrophotometric studies were made with a model PMQII Zeiss spectrophotometer thermostated by a Precision constant temperature circulating water-bath. The pH-stat assembly was based on the Radiometer TIIIa autotitrator and has been described previously.[16,17]

Results

Solvolysis rates for the substituted phenyl acetates when plotted in the form of log k_w *vs.* pH yield straight lines of slope 1.0 (Fig. 1). Therefore, in the pH range employed, the solvolysis of these esters may be considered to be solely (OH^-) catalyzed. This observation agrees with the results of Tommilla and Hinshelwood,[18] who found that for a

(14) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(15) J. Katz, I. Lieberman and H. A. Barker, *J. Biol. Chem.*, **200**, 417 (1953).

(16) T. C. Bruice and J. M. Sturtevant, THIS JOURNAL, **81**, 2860 (1959).

(17) T. C. Bruice, *ibid.*, **81**, 5444 (1959).

(18) E. Tommilla and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1953).

series of substituted phenyl acetates in 60% aqueous acetone (30°) the rate constants for OH^- catalysis exceeded those for H_3O^+ catalysis by 10^4 to 10^5. The value of the k_{OH^-} constants for hydrolysis calculated from Fig. 1 are presented in Table II. A conventional Hammett plot (not shown) of these values affords a ρ of 1.1 which is comparable to the ρ-value (1.0) for the alkaline hydrolysis of substituted phenyl acetates in 60% acetone–water (30°) and in 28.5% ethanol–water (ρ 1.15) containing 0.2 M phosphate buffer (30°).[1] Thus, though the absolute rates of alkaline hydrolysis for substituted phenyl acetates in the various solvents are solvent dependent, the substituent effects on ΔF^* appear to be identical.

TABLE I

KINETIC DATA FOR THE AMMONOLYSIS OF SUBSTITUTED PHENYL ACETATES

pH	A_T	NH_3[a] mole/l.	k_w min.$^{-1}$ × 10^{-2}	k_{obs}	k_2 l. mole^{-1} min.$^{-1}$
		p-$CH_3C_6H_4OCOCH_3$			
8.38	0.805	0.058	0.0273	0.922	0.154
8.70	.8	.101	.065	2.17	.192
8.74	.6	.0885	.0708	1.50	.1616
9.05	.6	.1519	.158	3.33	.199
9.31	.6	.234	.298	6.35	.259
9.45	.8	.376	.422	12.67	.326
9.71	.6	.369	.794	11.98	.303
9.8	.8	0.532	1.00	21.5	.385
		$C_6H_5OCOCH_3$			
6.90	0.8	0.002	0.0030	0.0491	0.245
6.91	1.0	.00255	.0030	.0653	.2481
6.92	0.5	.00131	.0031	.0384	.269
7.35	.8	.00526	.005	.1241	.226
7.58	.5	.006	.012	.1252	.189
7.82	1.0	.0212	.0138	.538	.247
8.02	0.5	.016	.024	.411	.2409
8.02	1.0	.032	.024	1.006	.307
8.35	0.8	.054	.0501	1.542	.276
8.64	0.5	.06	.10	1.842	.29
8.68	0.8	.106	.110	3.33	.304
8.68	1.0	.133	.110	5.46	.305
9.12	0.5	.147	.302	5.63	.361
9.27	1.0	.37	.417	20.81	.552
9.43	0.8	.344	.603	18.44	.518
9.67	1.0	.595	1.318	41.68	.678
9.77	0.5	.325	1.394	16.17	.455
		p-$ClC_6H_4OCOCH_3$			
7.52	0.9	0.00924	0.01	0.99	1.06
8.00	.4	.0122	.033	1.236	0.986
8.08	.9	.0338	.04	3.45	1.011
8.30	.7	.042	.066	4.53	1.061
8.61	.4	.045	.138	4.395	0.946
8.65	.7	.0861	.151	9.68	1.106
9.05	.9	.238	.380	30.4	1.26
9.05	.7	.186	.380	21.5	1.14
9.24	.4	.142	.603	15.2	1.03
9.40	.7	.312	.912	38.8	1.22
9.69	.9	.544	1.74	83.25	1.52
9.74	.7	.444	1.905	57.6	1.25
9.75	.4	.256	1.995	31.5	1.15
		m-$NO_2C_6H_4OCOCH_3$			
8.75	0.1	0.0151	0.447	16.47	10.6
8.97	.3	.069	.741	75.4	10.8
9.07	.1	.027	.933	29.5	10.6
9.27	.3	.111	1.479	113.5	10.1
9.42	.1	.0455	2.089	49.8	10.49
		p-$NO_2C_6H_4OCOCH_3$			
7.94	.15	.0004125	0.126	13.55	32.3
8.10	.0419	.00163	.174	5.7	33.85
8.24	.10	.00525	.251	16.06	30.1
8.3	.15	.009	.275	28.85	31.75
8.52	.041	.00389	.457	11.9	29.3
8.6	.10	.01125	.549	33.4	29.1
8.74	.15	.0221	.759	61.5	27.45
8.75	.041	.00615	.794	18.08	28.1
8.90	.0403	.00816	1.096	25.8	29.4
9.00	.10	.0239	1.38	71.7	29.4
9.00	.15	.0356	1.38	106.5	29.4
9.15	.041	.0127	1.995	39.4	30.2
9.55	.041	.0216	4.266	63.8	27.5
9.68	.10	.0605	6.607	175	27.8
9.72	.10	.062	7.24	169	26.1

[a] Calculated from A_T employing a pK_a' for ammonia of 9.5 determined by the method of half neutralization and serial dilution (see ref. 2).

Ammonolysis.—In Fig. 2 there are presented plots of k_2' *vs.* (NH_3) for p-cresyl, phenyl and p-chlorophenyl acetates. In Table II the determined rate constants are recorded. No general base catalysis terms could be detected with the p-nitro and m-nitro esters, the values of k_2' for these compounds being invariant with NH_3 and lyate ion concentration (Table I).

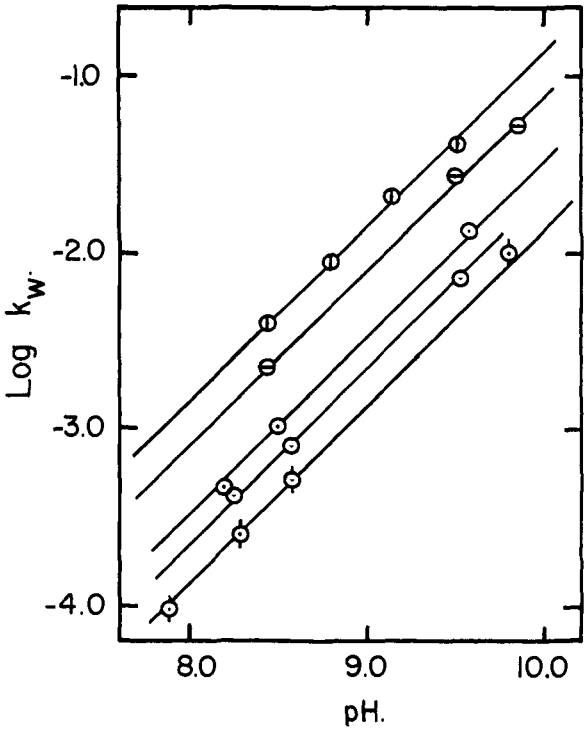


Fig. 1.—Plots of k_w *vs.* pH for substituted phenyl acetates in 1% (v./v.) dioxane–water at 30°; μ = 1.0 M. The linear plots (reading from top to bottom) are for p-nitrophenyl, m-nitrophenyl, p-chlorophenyl, phenyl and p-cresyl acetates.

In Fig. 3 the Hammett plots for k_2 and k_{NH_3} are given and in Table III the calculated ρ-constants for ammonolysis are recorded along with some com-

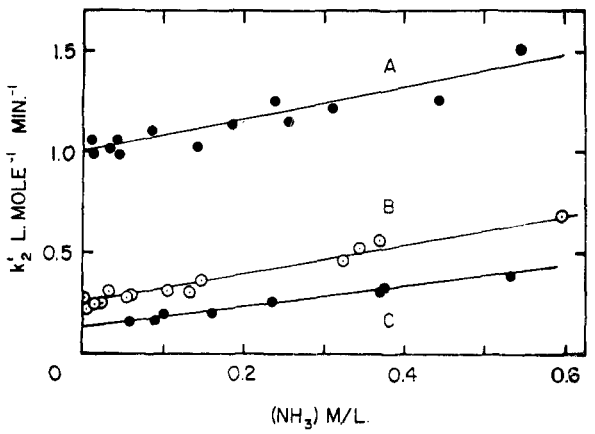


Fig. 2.—Plots of experimental values of k_2' *vs.* (NH_3) for: A, *p*-chlorophenyl acetate; B, phenyl acetate; and C, *p*-cresyl acetate. The *p*H range employed is given in Table I.

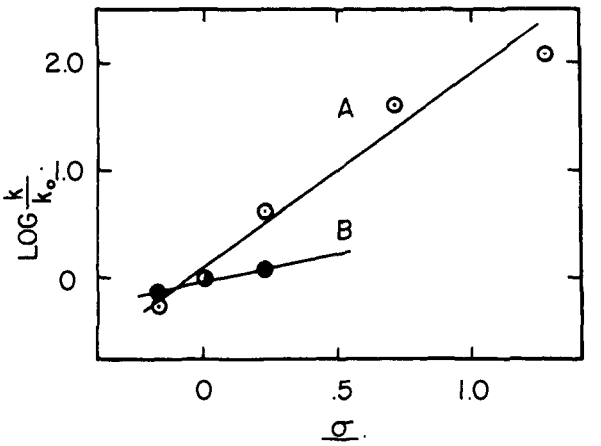


Fig. 3.—Hammett $\rho\sigma$ plots of k_2 (A) and k_{NH_3} (B).

parative ρ-constants for the catalysis of hydrolysis of this same series of esters by H_3O^+, OH^- and imidazole.

TABLE II

THE KINETIC CONSTANTS FOR THE AMMONOLYSIS AND HYDROLYSIS OF *m*- AND *p*-SUBSTITUTED PHENYL ACETATES
$T = 30°$, $\mu = 1.0$ *M*, solvent water

Substituent	σ[a]	k_2, l. mole^{-1} min.$^{-1}$	k_{NH_3}, l.^{2} mole^{-2} min.$^{-1}$	k_{OH^-},[b] l. mole^{-1} min.$^{-1}$
p-NO_2	1.27	29.2	...	1410
m-NO_2	0.71	10.5	...	683
p-Cl	.23	1.03	0.800	417
H	.00	0.245	.722	223
p-CH_3	− .17	0.130	.510	135

[a] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 188. [b] Rate constants for alkaline hydrolysis.

TABLE III

HAMMETT ρ CONSTANTS FOR THE SCISSION OF THE O
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—C—O— BOND OF SUBSTITUTED PHENYL ACETATES AT 30°

Reaction	ρ	Solvent
Catalyzed hydrol. by	1.01[a]	60% acetone-H_2O
OH^-	1.1[b]	H_2O, μ 1.0
$H_3{}^+O$	−0.22[a]	60% acetone-H_2O
Imidazole	1.90[a]	28.5% EtOH-H_2O
Ammonolysis terms		
k_2	1.81[a]	H_2O, μ 1.0
k_{NH_3}	0.56[b]	H_2O, μ 1.0

[a] Ref. 1 of this paper. [b] This study.

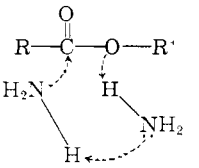
Discussion

The finding that the ammonolysis of substituted phenyl acetates is not subject to specific base catalysis rules out the involvement of amide ion as an intermediate. This observation is in accord with that of Jencks and Carriuolo in the ammonolysis of phenyl acetate.[13] The inability to observe general base catalysis in the case of the *m*- and *p*-nitro esters undoubtedly is due to the magnitude of the uncatalyzed ammonolysis terms and the relative values of ρ for k_2 and k_{NH_3}. Thus, if general base catalysis were operative with these esters its contribution would be expected to be within the experimental error of measuring k_{obsd}. From inspection of the ρ-values for the catalyzed and non-catalyzed reaction it is obvious that as the basicity of the leaving group becomes greater there should be a point at which only the catalyzed term should be kinetically evident, just as in the opposite sense the non-catalyzed term becomes solely predominant with the nitro esters in this study. It is not surprising, therefore, that esters of aliphatic alcohols undergo ammonolysis only through general base catalysis.[7,8,12]

In comparing the ρ-values for k_2 and k_{NH_3} it is found that electronic factors weigh little in the catalyzed reaction while their importance in the non-catalyzed reaction is similar to that previously noted in the nucleophilic displacement of phenoxide from the same series of esters by imidazole (also a neutral nitrogenous base; Table III). In the mechanism proposed by Bunnett and Davis[6] the formation of the intermediate tetrahedral compound would be favored by electron-withdrawing groups in the phenoxide radical, but the protonation of the leaving group would not be so favored. The latter factor should predominate and the over-all result would be expected to be a near cancellation of electronic effects and a resultant small positive ρ. Indeed, Bunnett and Davis have predicted that a lessened sensitivity to the electronic character of the leaving group might be expected for general base catalysis *via* their mechanism. However, a mechanism in which a proton is removed from the attacking amine, as applied by Tarbell[9] for OH^- catalysis[4] and by Jencks for amine catalysis,[13] might also be expected to be characterized by a ρ value smaller than that of the uncatalyzed reaction. This expected decrease in ρ by the proton abstraction mechanism would be related to the fact that a nucleophile stronger than ammonia would be generated in the transition state involving either the initial nucleophilic attack or the partitioning of the tetrahedral intermediate. Thus, the ρ for nucleophilic displacement of phenoxide from phenyl acetates by OH^- is half that for displacement by the weaker nucleophiles, *viz.*, by NH_3 and imidazole. However, it should be noted that the ρ associated with k_{NH_3} is much smaller than that for the attack of OH^-. In specific acid catalysis of the attack of

neutral water at the ester carbonyl group of phenyl acetates ρ is essentially zero due to a cancellation of electronic factors. The very small ρ for k_{NH_3} suggests the involvement of an acid-catalyzed mechanism. If the Bunnett mechanism were operative it might be anticipated that other nucleophilic displacements on the ester carbonyl group would be sensitive to general base catalysis. However, the reaction of tertiary amines with phenyl acetate is not subject to general base catalysis.[1,4,13] For these cases the amine cannot lose a proton upon nucleophilic attack but it should be able to partake in the Bunnett mechanism. Also, tertiary amines[4,5] are known to be unable to displace alkoxide ion from aliphatic esters (except in the instance of the more efficient intramolecular process and then only slowly[16]) which would be in accord with the inability to increase nucleophilicity *via* loss of a proton. The argument presented by Bunnett that the proton abstraction mechanism is improbable because general base catalysis is not observed in the nucleophilic displacement of Cl^- from 2,4-dinitrochlorobenzene by amines may be tenuous since the observance of general base catalysis depends on the magnitude of the non-catalyzed rate (as with the nitro esters of this study). On the other hand, the citation by Bunnett of the surprisingly low reactivity of carboxylic acid esters with alkali metal amides in liquid ammonia, due to the lack of suitable general acids in this medium, is compelling evidence for the need for protonation of the leaving group.

A mechanism which would appear to be in accord with all experimental results is that of (9).



(9)

In (9) the attack of NH_3 is assisted by proton abstraction while departure of $-OR'$ is assisted by proton transfer from the incipient ammonium ion. The value of ρ for this mechanism would certainly be quite small since electron attraction would affect the importance of the proton abstraction and donation in opposite sense. Also, the inability to observe general base catalysis in the reaction of tertiary amines with phenyl acetate is accommodated by (9) as is the observed low activity of esters toward amide ion in ammonia.

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BALTIMORE 5, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Derivatives of Sulfenic Acids. XXXVI. The Ionic Scission of the Sulfur–Sulfur Bond.[1] Part 1

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The cleavage of the S–S bond of nitro-substituted aromatic disulfides, R'SSR, by bases, *via* a nucleophilic displacement of mercaptide ion from divalent sulfur is reported. The reactions are equilibria, with the positions of equilibria determined by the nucleophilicity toward sulfur of the displaced mercaptides and displacing nucleophiles. The cleavage is controlled thermodynamically by the comparative nucleophilicities of the entering group, Y^-, and of the leaving mercaptide group, with the bond-breaking step, rather than the bond-making one, being the critical factor. The susceptibility to cleavage of disulfides becomes greater with increasing electron withdrawal by substituents. A spectroscopic method was used to estimate the rates of scission of selected disulfides by a series of nucleophiles. This indicated an order of S-nucleophilicity[4]: $CH_3CH_2S^- > C_6H_5S^- > CN^- > SO_3^= > OH^- > N_3^- > SCN^-, I^-$.

Introduction.—The literature on ionic scissions of sulfur–sulfur bonds has been reviewed recently in some detail.[3,4] Of particular interest are the bimolecular scissions of disulfides by nucleophiles, which with unsymmetrical disulfides R'–SS–R may occur as shown in (a) or as in (b).

$$R'S_aS_bR + Y^- \rightleftharpoons R'S_aY + RS_b^- \quad (a)$$

$$R'S_aS_bR + Y^- \rightleftharpoons R'S_a^- + RS_bY \quad (b)$$

The aim of the present study was to determine which sulfur—in selected unsymmetrical disulfides—serves as the electropositive center for attack by Y^-, and which sulfur is displaced as mercaptide (reactions a or b above). Incidentally, it was desired to obtain information as to the relative susceptibilities to nucleophilic cleavage when selected unsymmetrical disulfides were treated with a series of nucleophiles.

Earlier studies[5,6] have shown, for a few cases, that in unsymmetrical disulfides, R'SSR, where large differences exist in the electronegativities of R' and R, *electrophilic* attack occurs at the sulfur further from the more electronegative group. Thus, in R'S–SR, where R' is very strongly electron withdrawing and R is not, both peracid oxida-

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