bases such as morpholine and carbonate were ineffective as catalysts when reactants were of *ca.* 10^{-4} *M* and from the Linweaver–Burk kinetics obtained, it was suggested that a preequilibrium complex of aldimine with imidazole and imidazolium ion occurred followed by an intracomplex general catalysis. It was thus established that *the rate-determining prototropic shift could be catalyzed via general base and/or acid catalyzed mechanisms.* Imidazole catalysis of the prototropic shift in the reaction of glutamic acid and 3-hydroxypyridine-4-aldehyde was subsequently established[1f] to be quite effective. In the absence of imidazole, only a portion of the product arose from the transamination reaction while in the presence of imidazole catalyst not only was the appearance of products accelerated but the reaction was directed quantitatively to transamination (*i.e., general bases catalyze the transamination reaction but not competing side reactions leading to other products*). For the reaction of glutamic acid with 3-hydroxypyridine-4-aldehyde glutamic acid itself was not found to be a catalyst. Catalysis of the quantitative prototropic conversion of the aldimines of alanine and 3-hydroxypyridine-4-aldehyde to its isomeric ketimine has been shown to be catalyzed by alanine itself as well as by water, formate, acetate, phosphate, and imidazole (this study). *Carbanion intermediates have been established,* deuterium isotope effects determined, and *the Brønsted relationship for the general base catalyzed isomerization of each aldimine species established.* Unlike the reaction of α-phenylglycine with pyridoxal, the reactions of glutamic acid[1f] and alanine (ref 1h and this study) with 3-hydroxypyridine-4-aldehyde are dependent on the first power of the catalyst concentration and give no evidence of catalyst–substrate complex formation.[16]

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[16] Note Added in Proof. Studies in progress (J. R. Maley and T. C. Bruice) have established that N-methylpyridine-4-aldehyde undergoes a transamination reaction with alanine in basic media. This shows that the 3-hydroxyl group is not required for transamination if a positive charge can be maintained on the pyridine nitrogen at basic pH. That the observed reaction is transamination and not decarboxylation has been shown by both polarographic product analysis and the lack of reaction of the imine of 2-amino-2-methylpropionic acid.

Aminolysis of Phenyl Acetates in Aqueous Solutions. VII.[1] Observations on the Influence of Salts, Amine Structure, and Base Strength

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Abstract: The rate of aminolysis of phenyl acetate (PA) by various amines can be predicted from $v = [\mathrm{PA}]\cdot[\mathrm{amine}](k_{\mathrm{OH}}\cdot[\mathrm{OH}^-] + k_{\mathrm{n}} + k_{\mathrm{gb}}[\mathrm{amine}] + k_{\mathrm{ga}}[\mathrm{amine{-}H}^+])$. The only reported case for a specific acid term in the aminolysis of an acetylated phenol could not be substantiated. The effect of changing salts at $\mu = 1.0$ for KCl, $(\mathrm{CH_3})_4\mathrm{NCl}$, $(n\text{-}\mathrm{C_3H_7})_4\mathrm{NCl}$, and LiCl has been investigated for a series of amines of varying structure. The effect of salt type on k_{n}, k_{gb}, k_{ga}, and k_{OH} is discussed in terms of preferential salting in or out of ground and transition states. In addition the possibility that $\mathrm{Li(OH_2)_3}^+$ might act as a general acid catalyst for the aminolysis reaction is considered. The values of ρ for the aminolysis of substituted phenyl acetates by aziridine and two azetidines have been determined and shown not to differ appreciably from values of ρ obtained for amines not exhibiting steric acceleration. The aminolysis of PA has been extended to substituted hydrazines and trifluoroethylamine. The reaction of PA with morpholine was reinvestigated. The α effect already observed in the hydrazinolysis of PA decreased with N-methyl substitution and disappeared completely on N,N-dimethyl substitution. A critical evaluation of existing postulations regarding the origin of the α effect is offered. Morpholine appears to be the first secondary amine to exhibit a k_{gb} term in the aminolysis of a phenyl acetate. Brønsted equations for k_{n}, k_{gb}, k_{ga}, and k_{OH} are derived, and the effects of variation of the structure of the amine are discussed. Plausible mechanisms associated with each rate term which are consistent with the observed salt effects, deuterium solvent isotope effects, ρ values, and Brønsted β values are postulated.

Under the experimental conditions in which amine and its conjugate acid are in great excess over substrate, the values of the pseudo-first-order rate constants (k_{obsd}) for ester aminolysis have been found to be correlated by[1,4]

$$k_{\mathrm{obsd}} = k_{\mathrm{n}}[\mathrm{N_f}] + k_{\mathrm{gb}}[\mathrm{N_f}]^2 + k_{\mathrm{ga}}[\mathrm{N_f}][\mathrm{NH^+}] + k_{\mathrm{OH}}[\mathrm{N_f}][\mathrm{OH^-}] \quad (1)$$

where $[\mathrm{N_f}]$ and $[\mathrm{NH^+}]$ represent concentrations of amine and its conjugate acid, respectively, k_{n}, k_{gb}, k_{ga}, and k_{OH} represent rate constants for unassisted

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[1] For previous studies in this series see: (a) T. C. Bruice and M. F. Mayahi, *J. Am. Chem. Soc.*, **82**, 3067 (1960); (b) T. C. Bruice and J. J. Bruno, *ibid.*, **83**, 3494 (1961); (c) T. C. Bruice and S. J. Benkovic, *ibid.*, **85**, 1 (1963); (d) *ibid.*, **86**, 418 (1964); (e) T. C. Bruice and R. G. Willis, *ibid.*, **87**, 531 (1965); (f) L. R. Fedor, T. C. Bruice, K. L. Kirk, and J. Meinwald, *ibid.*, **88**, 108 (1966).

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[4] W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960).

or water-assisted nucleophilic attack, apparent self-assisted general base catalyzed nucleophilic attack, nucleophilic attack assisted by the conjugate acid species, and hydroxide ion catalyzed nucleophilic displacement by amine on the ester bond, respectively. The reaction of tertiary amines with phenyl acetates has not been found to be subject to either general base or hydroxide ion catalysis in agreement with the presumption that these terms are associated with mechanisms involving the breaking of an N–H bond. The importance of the self-assisted general catalytic terms k_{ga} and k_{gb} is greater for esters with poor leaving groups.[1a,d,4] The relative importance of the various terms is dependent upon the temperature[1c,5] and salt employed to maintain constant ionic strength.[5] One must assume that all mechanistically allowable paths are operative in any given aminolysis reaction, but only those which account for experimentally detectable amounts of the product can be determined kinetically. The majority of the studies to date have been carried out at 25–30° at $\mu = 1.0$ with KCl. With phenyl acetate under these conditions, certain amines are subject to general base catalysis, others to general acid catalysis, and still others to both. The k_{OH} term may be generally detectable if reactions are carried out at sufficiently high pH.[1e] The employment of high pH is often not practical with the more reactive amines, and high pH values are not normally encountered in investigations employing amines of moderate pK_a'. Thus, in many cases no attempt has been made to establish the k_{OH} term. Aside from temperature, solvent, and the salt employed to maintain constant ionic strength the numerical values of the terms k_{gb}, k_{ga}, and k_n are a function of (a) the basicity of the amine,[1e,4] (b) steric factors such as the C–N–C bond angle,[1f] and (c) the presence or absence of an unshared pair of electrons α to the nucleophilic nitrogen (the so-called α effect as with hydrazine[1d]). The dependence of the k_{OH} term on factors a and c has not been determined.

The present paper reports on the investigations of several aspects of the aminolysis of phenyl acetates. We have reinvestigated the *n*-butyl aminolysis of α-naphthyl acetate because this reaction is the only reported case of specific acid catalysis (*i.e.*, $k_H a_H[N_f]$) of the aminolysis of an acetylated phenol.[6] In addition, knowledge of the dependence of the various rate terms on the basicity of attacking amine has been extended; the steric effects of alkyl substituents on the enhanced rates of reaction of hydrazine with phenyl acetates has been examined; the influence of the nature of the salt employed to maintain constant ionic strength has been investigated with amines of various types; and the influence of C–N–C bond angle constraint on the sensitivity to electronic effects has been determined. Mechanisms consistent with the present state of knowledge are presented.

Experimental Section

Materials. Methylamine as a 40% aqueous solution (Eastman), anhydrous ethylamine (Eastman), and glycine (Fisher) were used as obtained from the supplier. *n*-Propylamine (Eastman), *n*-butylamine, bp 67° (Eastman), morpholine, bp 125–126°, 85% aqueous hydrazine, technical grade, bp 120° (Matheson Coleman and Bell), and N,N-dimethylhydrazine, bp 61–64° (Aldrich), were redistilled through a 1-ft Vigreux column, and the middle fraction was used. N-Methylhydrazine hydrosulfate (Eastman) and technical grade hydrazine hydrochloride (Matheson Coleman and Bell) were recrystallized from aqueous ethanol one and two times, respectively. They were dried and stored over P_2O_5 *in vacuo*. *n*-Propylhydrazine dihydrochloride was prepared from *n*-propylhydrazine oxalate (K and K) by extraction of an alkaline solution of the oxalate with chloroform and precipitation of the dihydrochloride by bubbling gaseous hydrogen chloride through the solution. The crude product was recrystallized from boiling ethanol (1.7 g/25 ml) which was previously saturated with gaseous hydrogen chloride. *n*-Butylamine hydrochloride and N,N-dimethylhydrazine hydrochloride were prepared by saturating ethereal solutions of the amines with gaseous hydrogen chloride and recrystallizing the precipitate from ether–ethanol mixtures. Solutions of tetramethylammonium chloride (Eastman) were filtered before use. Tetra-*n*-propylammonium chloride solutions were prepared by passing tetra-*n*-propylammonium bromide solutions through a column of Dowex AG1-X8 (200–400 mesh, chloride form). A test for chloride according to the method of Mohr indicated complete conversion.[7] A sample of the resulting solution was titrated with 0.1 *N* silver nitrate and adjusted to 1.0 *M* with water. The precipitated silver chloride was white and dissolved completely in 2 *N* ammonia. Tetramethylammonium hydroxide was prepared in the following manner: 900 ml of 1 *N* aqueous sodium hydroxide was passed through a column packed with 100 ml of Dowex AG1-X8. A chloride test at this point was negative.[7] The column was rinsed until the pH of the effluent was below 9, and 13.2 g (0.12 *M*) of tetramethylammonium chloride dissolved in 100 ml of water was added. Effluent (100 ml) was collected at pH 11. The concentration of the effluent was determined by titration with standardized HCl. A second sample of the effluent was neutralized with nitric acid and the amount of chloride anion present was determined by Mohr's method.[7]

Trifluoroethylamine hydrochloride was prepared from trifluoroacetamide using a slight modification of the method of Bissell and Finger.[8] The excess of lithium aluminum hydride was destroyed with ethyl acetate. Attempts to decompose it with water as suggested resulted in explosions. 3-Hydroxymethyl-3-phenylazetidine, 3-methyl-3-phenylazetidine hydrochloride, and aziridine were samples from a previous study.[1f] Aziridine, distilled at 56–57° [lit.[9] bp 55–57° (760 mm)], was stored over sodium hydroxide pellets. Phenyl acetate (PA), $n^{27}{}_D$ 1.5018 (lit.[10] n_D 1.5012), was prepared according to a previous method.[10] *p*-Nitro-, *m*-nitro-, *p*-chloro-, *p*-methoxy-, and *p*-methylphenyl acetate were samples used in a previous study.[10] α-Naphthyl acetate was prepared by the method of Chattaway.[11] Recrystallization from aqueous methanol produced white prisms, mp 45° (lit.[11] 48–49°). Unless mentioned otherwise, all the chemicals purchased were the best grade available. All recorded melting points are uncorrected. When advantageous, amines were kept under P_2O_5 *in vacuo* before use.

Apparatus. Kinetic measurements were made with a Gilford Model 2000 or a Zeiss PMQ II spectrophotometer. The Zeiss was equipped with a thermostated brass cuvette holder and the Gilford with dual thermospacers through which water was circulated at 30° for aminolysis and at 25° for reactions with N-substituted hydrazines.

The pH of the kinetic solutions was determined both prior to and at the completion of reactions using a Radiometer Model 22 pH meter equipped with a Radiometer Model PHA 630 Pa scale expander. The electrode was thermostated at the temperature of the kinetic experiments. The rate constants for hydrolysis of phenyl acetate were determined with a Radiometer TTT 1b autotitrator equipped with a PHA scale expander and a thermostated Metrohm microtitration cell as described by Bruice and Bradbury.[12] Potentiometrically determined pK_a' values were obtained by use of the same apparatus.

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[5] W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 104 (1966).

[6] P. J. Hawkins and I. Piscalnikow, *ibid.*, 77, 2771 (1955).

[7] I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Analysis," 3rd ed, The Macmillan Co., New York, N. Y., 1952, p 542.

[8] E. G. Bissell and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959).

[9] H. Wenkes, *J. Am. Chem. Soc.*, 57, 2328 (1935).

[10] T. C. Bruice and G. L. Schmir, *ibid.*, 79, 1663 (1957).

[11] F. D. Chattaway, *J. Chem. Soc.*, 2495 (1939).

[12] T. C. Bruice and W. C. Bradbury, *J. Org. Chem.*, **28**, 3403 (1963).

Table I. pK_a' Values for Amines (H_2O; μ = 1.0 with KCl)

Amine	Temp, °C	pK_a'
Hydrazine	10	8.60
	18	8.40
	25	8.20
	34	7.98
N-Methylhydrazine	11	8.60
	16	8.48
	25	8.20
	35.5	8.00
	40.5	7.88
N,N-Dimethylhydrazine	16	7.70
	25	7.56
	35.5	7.39
	40.5	7.28
Trifluoroethylamine	30	5.63

Table II. pK_a' Values for Primary Aliphatic Amines at 30°

Amine	pH for half-neutralized amine at molarity					
	0.05	0.10	0.30	0.50	0.70	1.00
			μ = 1.0 with KCl			
n-Butylamine	10.64	10.67	...	10.65	...	10.60
Ethylamine	...	10.71	10.71	10.70	10.70	10.69
Methylamine	...	10.69	10.69	10.68	10.69	10.68
Ammonia	...	9.32	9.32	9.33	9.33	9.33
			μ = 1.0 with $(CH_3)_4NCl$			
n-Butylamine	10.59	10.60	...	10.58	...	10.54
n-Propylamine	10.55	10.56	10.56	10.56	10.55	10.54
Ethylamine	10.71	10.68	10.68	10.68	10.68	10.68
Methylamine	...	10.60	10.61	10.61	10.62	10.62
Ammonia	...	9.30	9.31	9.31	9.31	9.32
			μ = 1.0 with $(n\text{-}C_3H_7)_4NCl$			
n-Propylamine	...	10.44	10.44	10.44	10.43	10.41
			μ = 1.0 with LiCl			
Methylamine	10.42	10.41	10.41	10.38	10.33	...

pK_a' Determinations. For the calculation of the pK_a' values determined potentiometrically the method of Albert and Sergeant[13] was employed (Table I). The pK_a' of the amines of Table II were determined by half-neutralization and serial dilution.

Kinetics. In order to maintain a constant pH, the amines were employed as buffer as well as nucleophile. The amine concentration was maintained in large excess over that of ester in order to obtain pseudo-first-order kinetics. Unless otherwise stated, the amine–amine hydrochloride buffers were prepared shortly before use by the addition of calculated amounts of standardized aqueous potassium hydroxide to aqueous solutions of known concentration of the amine hydrochloride or by addition of calculated amounts of standardized hydrochloric acid to aqueous solutions of known concentration of the amine. Ionic strength was maintained constant at 1.0 by addition of potassium chloride, tetramethylammonium chloride, tetra-*n*-propylammonium chloride, or lithium chloride. The water employed was either freshly glass distilled or saturated with nitrogen before use. Dilute solutions of the esters were prepared in pure dioxane and kept frozen in the refrigerator when not used. Solutions were either discarded at the end of each day or refrozen. The presence of peroxides in the stored samples were checked with iodine–starch paper before use. The reactions were initiated by addition of one drop of the ester solution to a cuvette containing the amine solution, which had been thermally equilibrated at the temperature of the experiment. The rate of appearance of phenoxide ions was determined at the following wavelengths: *p*-NO_2, 400 mμ; *m*-NO_2, 350 mμ; *p*-Cl, 285 mμ; *p*-H, 275 mμ; *p*-CH_3, 280 mμ; and *p*-CH_3O, 288 mμ. The rate of appearance of α-naphthoxide was determined at 307 mμ. In the case of trifluoroethyl aminolysis of phenyl acetate 2-ml samples of the amine–amine hydrochloride buffer containing the substrate were sealed in ampoules and shaken at 30° in a water bath. The appearance of the phenol was then determined spectrophotometrically by opening ampoules at periodic time intervals and transferring the contents to a cuvette which was placed in the Zeiss instrument. Optical densities at t_∞ were taken as those obtained by measuring the absorbance of buffer solutions of phenol identical in concentration with that of the ester employed in the kinetic run. Because of instability, aziridine buffers were prepared an average of 4 min before use.[1f] The aziridine was added from a micrometer syringe to a standardized hydrochloric acid solution thermostated at 30°. This technique was necessary in order to avoid decomposition of the aziridine before the pH of the buffers could be adjusted to a desired tolerance of ±0.05 pH unit. The azetidine buffers were prepared by the procedure of Fedor, *et al.*[1f] The rates of hydrolysis of the substituted phenyl acetates (μ = 1.0 with KCl, 30°) were literature values.[1a] Addition of ethylenediaminetetraacetic acid (EDTA 10^{-4} *M*) to kinetic runs employing aziridine and the azetidines did not affect the results. The hydrazinolysis of PA was performed under the same conditions used by Bruice and Benkovic.[1d] EDTA about 10^{-4} *M* was added to reaction mixtures containing hydrazines to prevent possible heavy metal catalyzed decomposition. The pK_a' value for hydrazine (μ = 1.0 with KCl) at 30° (pK_a' = 8.08) was interpolated from values[1c] obtained at different temperatures (see Table I). pK_a' determination by half-neutralization showed that this value is the same in 1 *M* tetramethylammonium chloride. In this solvent, redistilled aqueous hydrazine solution was used to adjust the pH of the buffers to a tolerance of ±0.02 pH unit. For the reaction carried out with methyl- and N,N-dimethylhydrazine the water was distilled and stored under nitrogen. In the cuvettes, the air was also replaced by nitrogen.

The glycinolysis of PA (μ = 1.0 with KCl) was carried out in the same manner as the hydrazinolysis of PA. However, because of the concentration dependence of the pK_a' of glycine, each diluted solution prepared from the initial solution was carefully adjusted to the initial pH. The tolerance was ±0.02 pH unit and no pH drift was observed during the course of the reaction. When a constant ionic strength was maintained with tetramethylammonium chloride, the pH of the glycine buffers was adjusted with tetramethylammonium hydroxide. The serial dilutions were made by the combination of calculated amounts of standard tetramethylammonium chloride and tetramethylammonium hydroxide solutions, each containing identical glycine concentration. The instability of the tetramethylammonium hydroxide solutions forced all kinetic studies to be carried out within 2 days of the preparations of solutions. The drift in pK_a' due to serial dilution of the glycine buffers was taken into account in the calculation of rate constants.

The aliphatic amines *n*-butyl-, *n*-propyl-, ethyl-, methylamine, and ammonia were handled according to their volatility. The three former were used as anhydrous reagents, the two latter as about 2 *N* standardized solutions in water. All solutions were kept under nitrogen in tightly closed containers. All the operations of solution preparation and dilutions were made under nitrogen atmosphere, exposing the amine to the air or evaporation for a minimum period of time. A weighed amount of anhydrous amine was added from

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(13) A. Albert and E. P. Sergeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

a buret into a volumetric flask on a torsion balance. The required amount of standardized hydrochloric acid was added at once, followed by the necessary amount of salt [*i.e.*, KCl, LiCl, $(CH_3)_4NCl$, $(n\text{-}C_3H_7)_4NCl$] for a final ionic strength of 1.0, and the solution was brought to the required volume with water. After mixing, the solution was introduced into a 50-ml buret, and the serial dilutions were prepared quickly. The upper part of the solution in the buret was discarded. The serial dilutions of amine so prepared were thermostated and kinetic studies initiated immediately so that all dilutions were studied as soon as practicable (usually within 1 hr). Because of the slowness of reaction of ammonia with PA, a time period in excess of 1 hr was necessary before kinetic studies could be initiated on all serial dilutions, but frequent checking was applied so that the influence of decomposed tetramethylammonium chloride was within the experimental errors. The pH of each amine solution was adjusted within 0.03 pH unit. A finer adjustment did not improve the results, owing to the evaporation of the solutions and contamination by carbon dioxide. The maximum pH drift (ΔpH) during the reaction for the most diluted solution was *n*-butylamine, 0.04; *n*-propylamine, 0.04; ethylamine, 0.03; methylamine, 0.06, and ammonia, 0.02.

The pseudo-first-order rate constants were calculated by the method of Guggenheim[14] and from the slopes of plots of log $[(OD_\infty - OD_0)/(OD_\infty - OD_t)]$ *vs.* time.

The second-order rate constants for the hydroxide ion catalyzed hydrolysis (k_w) of PA were determined autotitrimetrically without buffer or spectrophotometrically (275 mμ) using serially diluted carbonate buffers. For the latter method the values of k_w were obtained by extrapolation to zero buffer concentration (Table III).

Table III. Second-Order Rate Constants (k_w) for OH^--Catalyzed Hydrolysis of PA (μ = 1.0, 30°)

Salt, 1 *M*	No. of pH values	No. of buffer dilutions	k_w, M^{-1} min^{-1}	Slope of the log k_{obsd} *vs.* pH plot
LiCl[a]	5	...	317	1.02
KCl[a]	3	...	223[c]	1.0
$(CH_3)_4NCl$[a]	4	...	105.8	0.91
$(CH_3)_4NCl$[b]	4	3	108	1.0
$(n\text{-}C_3H_7)_4NCl$[b]	4	5	63.6	0.98

[a] Autotitrator. [b] Spectrophotometer. [c] See ref 1a.

Results and Discussion[15]

All reactions reported in this paper were studied in water under the conditions in which $[N_T] >> [\text{ester}]$[15] so that pseudo-first-order conditions were followed. In addition, ionic strength was maintained at a constant value of 1.0 and except where noted a temperature of 30 ± 0.1° was employed.

Influence of the Cation Employed to Hold Constant Ionic Strength. The inability to substantiate a reported[4] k_{gb} term in the *n*-butyl and *n*-propyl aminolysis of phenyl acetate[1e] has led to an extension of studies of aminolysis of this ester by *n*-alkylamines.[5] In the latter study both potassium chloride and tetramethylammonium chloride were employed to maintain constant ionic strength. On the basis that the reaction of hydrazine and imidazole with phenyl acetates showed general catalytic terms which are favored at low temperatures,[1d] a temperature of 5° was employed rather than the conventional 25–30° range. Under these conditions and at a constant ionic strength of 1.0 it was reported that the aminolysis of phenyl acetate by all the primary amines investigated followed eq 2.

$$(k_{obsd} - k_w[OH^-])/[N_f] = (k_n + k_{OH}[OH^-]) + k_{gb}[N_f] \quad (2)$$

In practice, eq 2 was assumed, and sufficient kinetic data were gathered to furnish the value of the slopes and intercepts of plots of $(k_{obsd} - k_w[OH^-])/[N_f]$ *vs.* $[N_f]$ at a single pH (see Table I of ref 5). The intercept was assigned the value $(k_n + k_{OH})$ and the slope that of k_{gb}. The values of k_n and k_{OH} were then separated by determining the effect of pH on $(k_{obsd} - k_w[OH^-])$ at a single concentration of buffer. This treatment suffers in that it explicitly assumes that all dependence of the rate of the aminolysis reaction on the second power of the total buffer concentration is a dependence on the second power of the base form of the buffer and ignores the possible involvement of its conjugate acid. In short, k_{ga} terms are considered unimportant, which is highly speculative in the light of the large k_{ga} terms in the hydrazinolysis,[1d] hydroxyl aminolysis,[4] and methoxyl aminolysis[4] of phenyl acetate. In addition the reactions of ethyl-, *n*-propyl- and *n*-butylamine were not investigated at constant ionic strength at 25 or 30° and it was felt that a comparison of salt effects under the same temperature conditions was warranted. For these reasons and since theoretical arguments proposed for a salt effect on a k_{gb} term that might consist in part of a k_{ga} term might not be valid, we have reinvestigated the effect of KCl and $(CH_3)_4NCl$ as ionic atmospheres in the aminolysis reaction. For this purpose the reactions of NH_3, CH_3NH_2, $C_2H_5NH_2$, $n\text{-}C_3H_7NH_2$, $n\text{-}C_4H_{10}NH_2$, glycine, and NH_2NH_2 with phenyl acetate at 1.0 μ with KCl and $(CH_3)_4NCl$ have been studied at 30°.

From eq 1 it follows that plots of $(k_{obsd} - k_w[OH^-])/[N_f]$ *vs.* $[N_f]$ should provide as slope (*S*) the sum $(k_{gb} + k_{ga}a_H/K_a')$ and as intercept (*I*) the sum $(k_n + k_{OH}K_w/a_H)$. Plots of *S* *vs.* a_H/K_a' provide k_{gb} as intercept and k_{ga} as slope. Plots of *I* *vs.* K_w/a_H provide k_n as intercept and and k_{OH} as slope. The graphical data for methylamine in $(CH_3)_4NCl$ are provided in Figures 1, 2, and 3; a tabulation of concentration, pH, and number of experimentally determined k_{obsd} values for all the amines may be found in Table IV and a summary of rate constants in Table V.

For the aminolysis reactions the amine buffer concentrations (Table IV) ranged from 0.1 to 1.0 *M* (glycine to 2.2 *M*). This means that the reactions are subject to a considerable change in ionic atmosphere upon dilution. The predominant cation present on the acid side of the amine pK'_{a1} at 1.0 *M* amine is the NH^+ species, but on the basic side it is replaced by the cation employed to maintain constant ionic strength. This cation also replaces NH^+ during a serial dilution at any given pH. The reported values for k_n, k_{OH}, k_{ga}, and k_{gb} are therefore composite values which are effected by the change of ions over the entire concentration and

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

(15) Abbreviations employed are: PA, phenyl acetate; k_n, second-order rate constant for nucleophilic displacement of phenol from PA by amine; k_{gb}, third-order rate constant, first order in ester and second order in amine, for amine-catalyzed nucleophilic displacement of phenol from PA by amine; k_{ga}, third-order rate constant for nucleophilic displacement of phenol from PA by amine as catalyzed by the conjugate acid of the amine; k_{OH}, hydroxide ion catalyzed nucleophilic displacement of phenol from PA by amine; k_{hyd}, first-order rate constant for hydrolysis of PA at a constant pH; $k_w[OH^-] = k_{hyd}$; k_{obsd}, the pseudo-first-order rate constant for disappearance of PA (all rate constants are reported in time units of minutes and concentration units of moles liter^{-1}); $[N_f]$, concentration of amine; $[NH^+]$, concentration of conjugate acid of amine, etc.; $[N_T] = [NH^+] + [N_f] + [N^-]$; a_H, hydrogen ion activity as determined by the glass electrode, and

$$[NH^+] \overset{K'_{a1}}{\rightleftharpoons} [N_f] \overset{K'_{a2}}{\rightleftharpoons} [N^-]$$

Table IV. Experiments for the Aminolysis of Phenyl Acetate at 30°

Amine	Concentration range, M	KCl pH range	KCl No. of pH values	KCl No. of k_{obsd}	$(CH_3)_4NCl$ pH range	$(CH_3)_4NCl$ No. of pH values	$(CH_3)_4NCl$ No. of k_{obsd}
NH_2NH_2	1.0–0.1	7.67–8.21	2	12	7.65–8.42	6	31
Glycine	2.2–0.1	9.78–10.17	2	10	9.48–10.28	3	16
n-Butylamine	1.0–0.05	10.07–10.98	4	23	10.10–11.11	14	72
n-Propylamine	1.0–0.1	. . .	*a*	. .	10.00–10.94	6	31
Ethylamine	1.0–0.1	10.23–11.01	4	20	9.77–11.15	10	51
Methylamine	1.0–0.05	9.98–10.99	6	38	10.15–11.12	6	40
Ammonia	1.0–0.1	8.87–9.94	8	30	8.80–9.69	6	44

[a] The values of Bruice and Willis[1e] have been taken for the comparison.

pH range investigated. The constants are, nevertheless, comparable for experiments in which the counter cations differ since the same experimental regime was employed in all cases for their determination.

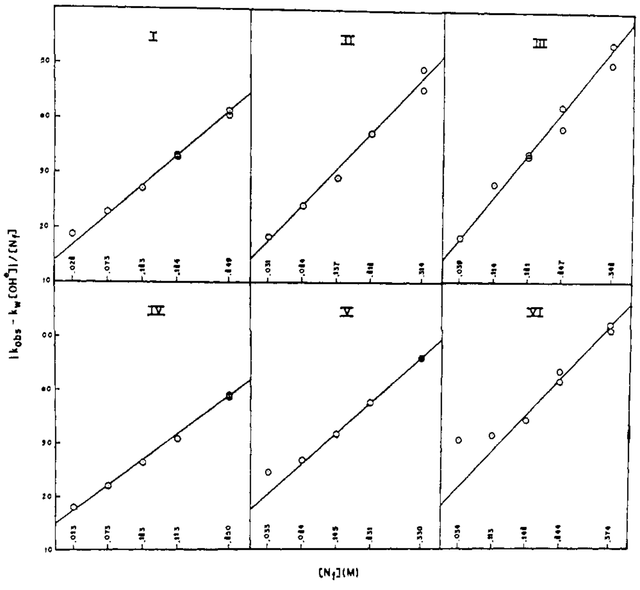

Figure 1. Plots of $(k_{obsd} - k_w[OH^-])/[N_f]$ *vs.* $[N_f]$ for the reaction of PA with methylamine [30°, μ = 1.0 with $(CH_3)_4NCl$]: I, pH 10.15, $[B_T]$ = 0.1–1.0 M; II, pH 10.19, $[B_T]$ = 0.1–1.0 M; III, pH 10.42, $[B_T]$ = 0.1–1.0 M; IV, pH 10.63, $[B_T]$ = 0.05–0.5 M; V, pH 10.92, $[B_T]$ = 0.05–0.5 M; VI, pH 11.12, $[B_T]$ = 0.05–0.5 M.

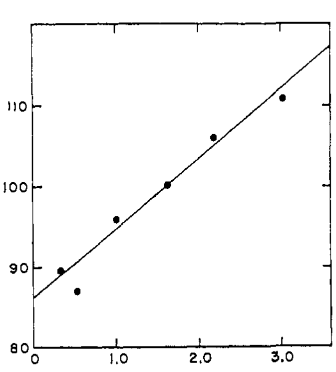

Figure 2. Plot of the slopes (S) of Figure 1 *vs.* a_H/K_a' providing k_{gb} as intercept and k_{ga} as slope.

The per cent of amide arising through the mechanisms of aminolysis associated with the various rate constants is dependent on the pH, the concentration of amine, and the value of the rate constant. The extreme ratios of k_{gb}/k_{ga} are found in the methyl aminolysis in KCl and the *n*-propyl aminolysis in $(CH_3)_4NCl$. At 1.0 pH unit above and below pK'_{a_1} and at B_T = 1.0 M, the percentage contribution to the aminolysis reaction may be calculated as in Table VI. Both the contribution of k_{ga} and k_{gb} can be seen to be important in the vicinity of the pK'_{a_1} of the amine under consideration. Thus, although the ratio of k_{gb}/k_{ga} is greatest for methyl aminolysis (KCl), at the lower pH the por-

Table V. Rate Constants for the Ammonolysis and *n*-Alkylaminolysis of Phenyl Acetate in H_2O [30°; μ = 1.0 with KCl and $(CH_3)_4NCl$]

Amine	k_n, l. mole^{-1} min^{-1}	l.^{2} mole^{-2} min^{-1} k_{OH}	k_{gb}	k_{ga}
		In K^+Cl^-		
Glycine	0.51	. . .	1.13	. . .
NH_2NH_2	0.60	. . .	~18.0	2.3
NH_3	0.15	*a*	0.90	0.055
CH_3NH_2	16.45	6.75 × 10^3	103.6	5.16
$C_2H_5NH_2$	5.9	2.72 × 10^3	8.17	*b*
n-$C_3H_7NH_2$	4.15	3.48 × 10^3	*b*	*b*
n-$C_4H_{10}NH_2$	6.70	1.06 × 10^3	*b*	*b*
		In $N^+(CH_3)_4Cl^-$		
Glycine	0.43	. . .	0.955	. . .
NH_2NH_2	0.39	. . .	14.0	3.2
NH_3	0.125	*a*	0.65	0.134
CH_3NH_2	13.35	2.77 × 10^3	86.2	8.65
$C_2H_5NH_2$	4.64	1.15 × 10^3	5.9	2.26
n-$C_3H_7NH_2$	3.24	1.41 × 10^3	2.6	1.97
n-$C_4H_{10}NH_2$	4.12	0.675 × 10^3	3.15	(0.341?)[c]

[a] Not a great enough pH range was employed to determine this constant. [b] Experimentally not detectable. [c] An uncertain constant. If the k_{ga} term contributes, it amounts to only a small per cent of product in the concentration range of amine employed.

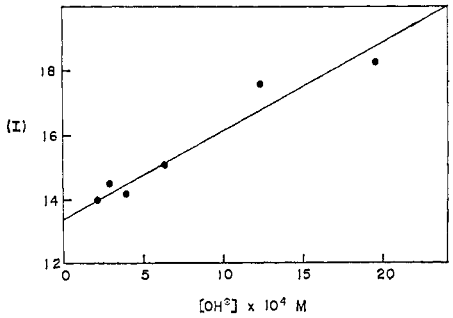

Figure 3. Plot of the intercepts (I) of Figure 1 *vs.* k_w/a_H providing k_n as intercept and k_{OH} as slope.

Table VI. Product Ratios in the Aminolysis of Phenyl Acetate

For CH_3NH_2 in KCl	pH 9.68	pH 11.68
k_n, %	53.0	10.3
k_{OH}, %	1.5	30.1
k_{gb}, %	30.4	59.3
k_{ga}, %	15.1	0.3
For $n\text{-}C_3H_7NH_2$ in $(CH_3)_4NCl$	pH 9.54	pH 11.54
k_n, %	60.7	24.9
k_{OH}, %	1.4	55.5
k_{gb}, %	4.4	18.2
k_{ga}, %	33.5	1.4

tion of product arising *via* k_{ga} is 50% that *via* k_{gb}. For *n*-propyl aminolysis where the ratio of $k_{gb}/k_{ga} = 1.3$, the k_{gb} term can be seen to be of little importance at the lower pH.

The following discussion of our results is not meant to be quantitative but to supply a qualitative rationale to the data. The perturbations of ground and transition states by dissolved salts must involve not only the alterations of the solvent structure but interactions of the cationic and anionic species with the ground and transition states.[16,17] Potassium ion is disruptive to the structure of water while tetraalkylammonium ions increase the organization of water.[18-20] Indeed, tetramethylammonium chloride is mildly surface active and tetrapropylammonium halide decidedly so.[21] Neutral organic compounds such as phenyl acetate are salted in by tetraalkylammonium ions and salted out by potassium ion.[16,17,22] The same is apparently true for amines. Thus, potassium ion salts out trimethylamine, aniline, benzylamine, ammonia, and piperidine[16,19] while tetraalkylammonium salts salt in benzylamine.[20] Glycine does not behave as an ordinary amine being salted in by both potassium and tetraalkylammonium salts.[23]

From the Brønsted rate equation it follows that an increase in activity of the ground state should result in an increase in rate while an increase in the activity of the transition state would have an opposite effect. For all the amines in Table V $k_n{}^{K^+}/k_n{}^{N^+(CH_3)_4} = 1.33 \pm 0.14$ (disregarding hydrazine and *n*-butylamine the ratio is 1.23 ± 0.03). This similar salt effect holds over a 100-fold change in k_n. For the five amines exhibiting k_{gb} terms the ratio $k_{gb}{}^{K^+}/k_{gb}{}^{N^+(CH_3)_4} = 1.28 \pm 0.08$. Thus, for these amines k_n and k_{gb} are favored in KCl solutions over $(CH_3)_4NCl$ solutions to the same extent. These results do not support the contention that the general means of determining k_{gb} employing K^+ to hold constant μ provide smaller values for k_{gb} than when $N^+(CH_3)_4$ is employed for this purpose.[5] A common feature of the mechanism associated with both k_n and k_{gb} terms is the reaction of neutral amino groups and neutral ester through what must be $(+\delta) - (-\delta)$ charged transition states. A reasonable assumption is that the ground states are preferentially more salted out than the transition states by K^+ as compared to $N^+(CH_3)_4$. A reasonable explanation for the lack of general acid and base terms with *n*-propyl- and *n*-butylamines in KCl is that as the nonpolar lyophobic alkyl group increases in size a point is reached when the transition state becomes more salted out than does the ground state. This factor would not be expected to come into play in $(CH_3)_4NCl$ solutions since nonpolar organic compounds are salted in by this salt.

For k_{ga} the rate constants for all amines studied are smaller in the presence of K^+ than $N^+(CH_3)_4$ (for the three numerically comparable cases $k_{ga}{}^{K^+}/k_{ga}{}^{N^+(CH_3)_4} = 0.56 \pm 0.11$). In the general acid catalyzed aminolysis, assuming general acid catalysis in the attack of amine on ester, a formally positively charged ground state must yield to a charge dispersed transition state. The same reasoning that was applied to k_n and k_{gb} suggests greater salting out of the transition state as compared to the ground state for K^+ compared to $N^+(CH_3)_4$.

The values of k_{OH} are more affected by the change of salt, the ratios of $k_{OH}{}^{K^+}/k_{OH}{}^{N^+(CH_3)_4}$ being 3.3, 2.4, 2.5, and 1.57 (going from methylamine to *n*-butylamine). The calculated values of k_{OH} are dependent on the value of a_{H_2O} which is scarcely dependent on the salt concentration and type[24] in the concentration range employed. Since a_H is known (glass-electrode value) and $K_w/a_H = a_{OH}/a_{H_2O}$, it follows that calculated values of a_{OH} are not significantly altered by change in salt type; the increase in k_{OH} by K^+ as compared to $N^+(CH_3)_4$ is, therefore, to be found in a preferential salting out of amine and ester as compared to the transition state by K^+.

As a means of gaining possible further insight into the specific salt effects on the aminolysis reaction, the *n*-propyl aminolysis of PA, in $\mu = 1.0$ tetra-*n*-propylammonium chloride, and the methyl aminolysis of PA in lithium chloride solutions were investigated. Like the tetraalkylammonium salts lithium salts are, for completely different reasons, structure forming in water (unlike K^+).[25,26] In addition Li^+ salts salt out amines less than K^+ salts, and indeed, whereas K^+ salts out ammonia, Li^+ salts it in.[27] The properties of the tetra-*n*-propylammonium ion accentuate those of the tetramethylammonium ion.

The reaction of *n*-propylamine with PA at $\mu = 1.0$ with tetra-*n*-propylammonium chloride was subjected to the same kinetic analysis described previously. The reaction proceeded with good first-order kinetics. Results are provided in Table VII. Comparison of the results of Tables V and VII reveals that k_n and k_{OH} continually decrease and k_{ga} increases on going from K^+ to $N^+(CH_3)_4$ to $N^+(n\text{-}C_3H_7)_4$. The anomalous effect is found in k_{gb} which is decreased by a factor of 2 in going from $N^+(CH_3)_4$ to $N^+(n\text{-}C_3H_7)_4$.

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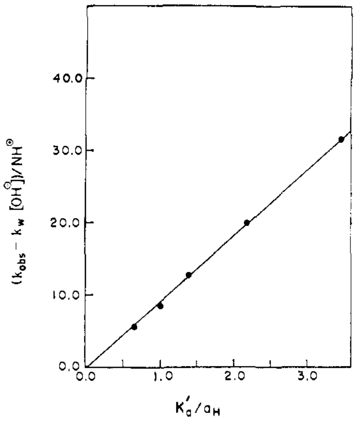


Figure 4. Plot of $(k_{obsd} - k_w[OH^-])/[NH]$ *vs.* k_a'/a_H for the reaction of α-naphthol acetate with *n*-butylamine [H_2O, 30°, μ = 1.0 with $(CH_3)_4NCl$] providing k_n as the slope.

The study of the reaction of methylamine with PA in LiCl at 1.0 μ proved to be complicated owing to the apparent dependence of pK_{app} on Li^+ concentration. Rate constants calculated from experiments in which the pH was adjusted to constant values and pK_a' taken as that at 0.5 *M* in N_T differed significantly from those calculated on the basis of the amount of HCl added to partially neutralize the amine. The values of the various rate constants calculated by these two methods are presented in Table VIII. Owing to the uncertainty in the values of k_n and k_{gb}, we can only say that these rate constants are in the range determined when K^+ or $N^+(CH_3)_4$ is employed to hold constant μ. No k_{ga} constant could be detected. However, the ratio of k_{gb}/k_{ga} is particularly great for CH_3NH_2. Of interest is the dependence of k_{OH} on the cation employed to maintain constant μ (*i.e.*, $N^+(CH_3)_4$:K^+:Li^+ = 1:3.4:7.8–11.6). The ratio of values for the hydroxide-catalyzed hydrolysis of PA in 1 *M* salt solutions is $(n\text{-}C_3H_7)_4NCl$:$(CH_3)_4NCl$:KCl:LiCl $\cong$ 0.63:1:2.4:2.9 (see Experimental Section). Comparison of these ratios indicate that Li^+ has a particularly large effect on k_{OH}. Taken in combination with the much greater effects of both K^+ and Li^+ on k_{OH} as compared to k_n and k_{gb} suggests that interaction of the metal ion with the transition state is important in the mechanism associated with k_{OH} possibly as shown in i. Lithium ion has been proposed to owe much of its characteristics in aqueous solution to the association with the oxygens of water which make the protons more acidic.[16,17] In i the hydrated lithium is acting as a general acid catalyst.

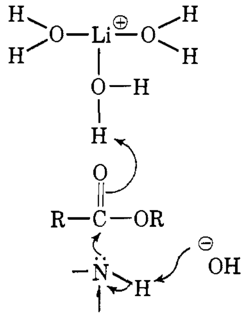
Table VII. Kinetic Results for the Reaction of *n*-Propylamine with PA at μ = 1.0 with Tetra *n*-propylammonium Chloride (30°)

pH range	11.15–10.09
No. of pH values	6
No. of k_{obsd} values determined	30
k_n = 1.62 l. mole^{-1} min^{-1}	
k_{OH} = 430 l.^{2} mole^{-2} min^{-1}	
k_{gb} = 1.50 l.^{2} mole^{-2} min^{-1}	
k_{ga} = 3.40 l.^{2} mole^{-2} min^{-1}	

Table VIII. Calculated Rate Constants for the Reaction of CH_3NH_2 with PA at μ = 1.0 with LiCl

pH range	10.66–9.98
No. of pH values	5
No. of k_{obsd} values determined	33
k_n = 11.8^a–16.0^b l. mole^{-1} min^{-1}	
k_{OH} = 2.34 × 10$^{4\,a}$ – 1.59 × 10^4 l.^{2} mole^{-2} min^{-1}	
k_{gb} = 114^a – 100^b l.^{2} mole^{-2} min^{-1}	

[a] From measured pH values. [b] From calculated pH values.



i

It should be noted that where comparisons can be made, the values of the determined rate constants of Table V are not too unlike those determined by Jencks and Gilchrist[5] and by Bruice and Mayahi.[1a]

***n*-Butylaminolysis of α-Naphthyl Acetate.** The *n*-butylaminolysis of α-naphthyl acetate was studied with both KCl and $(CH_3)_4NCl$ to maintain constant ionic strength. The reactions employing KCl were studied between pH 10.32 and 11.17. Below pH 9.9 difficulties were experienced in measuring the concentration of α-naphthol spectrophotometrically because it was slowly precipitated from the reaction mixture. This could be verified by the observation that α-naphthol absorbance decreases with time in buffers below pH 9.9. At the pH values employed and with total amine concentration greatly exceeding ester, plots of log $[(OD_\infty - OD_0)/(OD_\infty - OD_t)]$ *vs.* *t* were linear up to three half-lives. The same rate law pertained when appearance of α-napthol (307 mμ) or disappearance of α-naphthyl acetate (273 mμ) was followed.

$$(k_{obsd} - k_w[OH^-]) = (k_n + k_{OH}[OH^-])[N_f] \quad (3)$$

Plots of $[N]_T$ *vs.* k_{obsd} at all pH values were linear indicating no kinetic terms second-order in butylamine or its conjugate acid.

The *n*-butyl aminolysis of α-naphthyl acetate at 1.0 μ with $(CH_3)_4NCl$ exhibits no hydroxide-dependent term nor a term second order in amine species. Thus, plots of $(k_{obsd} - k_w[OH^-])/[NH^+]$ *vs.* K_a'/a_H are linear with zero intercept and provide as slope k_n (Figure 4).

A summary of kinetic data for the *n*-butyl aminolysis of α-naphthyl acetate is provided in Table IX. Our results in both KCl and $(CH_3)_4NCl$ do not agree with those of Hawkins and Piscalnikow[6] who reported specific acid catalyzed *n*-butyl aminolysis of α-naphthyl acetate. Thus, no aminolysis of an oxygen ester has been established to occur with specific acid catalysis though a possible case for a thiol ester may be found in the following paper. The salt effect on k_n and k_{OH} is similar to that found for PA being, however, much more pronounced for k_{OH}.

Trifluoroethyl Aminolysis of Phenyl Acetate. The appearance of phenol from phenyl acetate in the pres-

Table IX. n-Butyl Aminolysis of α-Naphthyl Acetate at 30° in Aqueous Solution, $\mu = 1.0$

pH range	No. of k_{obsd} determined	k_n, l. mole^{-1} min^{-1}	l.^{2} mole^{-2} min^{-1} k_{OH}	k_w
KCl to maintain constant μ				
9.9–11.17	41	10.5	229	120
$(CH_3)_4NCl$ to maintain constant μ				
10.40–11.11	25	9.11	...	157

ence of trifluoroethylamine was followed at pH 6.15 and 5.18 ($\mu = 1.0$ with KCl). The volatility of trifluoroethylamine and its slow reaction with phenyl acetate made it necessary to conduct the reaction in ampoules so that spectrophotometric readings could be taken at intervals of 1–7 days. Possibly for this reason, results with this amine were far less satisfactory than desired. The reactions were followed to 0.3–2 half-lives. Plots of log $[(OD_\infty - OD_0)/(OD_\infty - OD_t)]$ *vs.* time were linear but plots of k_{obsd} *vs.* total amine concentration curve upward indicating a second-order dependence of the reaction on the amine. Equation 4

$$dP/dt = (k_n[N_f] + k_{gb}[N_f]^2 + k_{ga}[N_f][NH^+])[\text{ester}] \quad (4)$$

$$k_{obsd}/[N_f] = k_n + [N_f][k_{gb} + k_{ga}(a_H/K'_{a1})]$$

predicts the ten determined k_{obsd} values with an average deviation of 20%. Plots of $k_{obsd}/[N_f]$ *vs.* free amine at each pH were linear[28] affording k_n as the ordinate intercept and $[k_{gb} + k_{ga}(a_H/K_a)]$ as the slope. A two-point plot of the slopes *vs.* a_H/K_a afforded an approximate k_{gb} as ordinate intercept and k_{ga} as slope. Attempts to calculate the data with an equation involving only nucleophilic and general base catalyzed terms lead to an average deviation of 70% in the calculated and found k_{obsd} values. The inclusion of the general acid term in eq 4 is thereby justified. The determined rate constants were: $k_n = 9.6 \times 10^{-5}$ l. mole^{-1} min^{-1}, $k_{gb} = 4.9 \times 10^{-4}$ l.^{2} mole^{-2} min^{-1}, and $k_{ga} = 6.7 \times 10^{-4}$ l.^{2} mole^{-2} min^{-1}. These constants are to be considered only as approximations. They do serve, however, to provide additional data for the construction of Brønsted plots (see Mechanism section).

Reactions of Aziridines and Azetidines with Substituted Phenyl Acetates. In a previous study[1f] azetidines and aziridines were shown to have hypernucleophilicity toward phenyl acetate (see Brønsted plot of Figure 6). This feature was ascribed to C–N–C bond angle constraint resulting in less crowding in the transition states associated with the nucleophilic attack of these small ring aliphatic amines at the ester carbonyl group. It was reasoned that, since a steric effect of this type might influence the position of the transition state along the reaction coordinate, the sensitivity of the rate constants for aminolysis reactions with these amines to electronic effects might be different from that noted with other amines. In order to examine this possibility the reactions of 3-hydroxymethyl-3-phenylazetidine, 3-methyl-3-phenylazetidine,[29] and aziridine with *meta-* and *para-*substituted phenyl acetates were studied (30°, $\mu = 1.0$ with KCl). All the reactions were found to be first order in the concentration of unprotonated amine and to follow the rate expression of eq 3. The value of k_n was determined as the slope from plots of $(k_{obsd} - k_w[OH^-])$ *vs.* $[N_f]$. Generally, the reactions were studied at two pH values, one above and one below the pK'_{a1} of the amine, with from five to eight serially diluted solutions of amine at each pH. A summary of the rate data is provided in Table X, and in Figure 5 Hammett $\rho\sigma$ plots for k_n are provided.

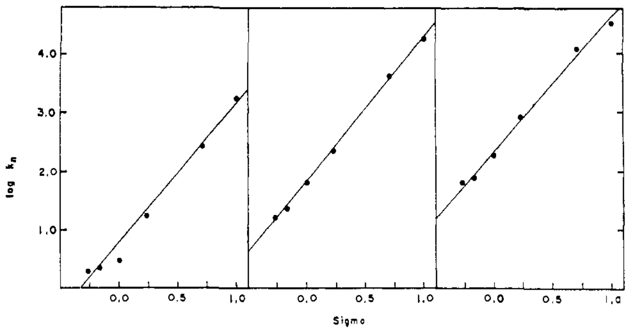


Figure 5. Hammett $\rho\sigma$ plots for the reaction of aziridine (III), 3-hydroxymethyl-3-phenylazetidine (I), and 3-methyl-3-phenylazetidine (II) with *meta-* and *para-*substituted phenyl acetates [H_2O, 30°, $\mu = 1.0$ with KCl]; σ value of +1.0 for p-NO_2 group employed.

Table X. Reaction of 3-Hydroxymethyl-3-phenylazetidine (I), 3-Methyl-3-phenylazetidine (II), and Aziridine (III) with Substituted PA[a]

	I		II		III
Substituent	k_n[b]	$k_{OH} \times 10^{-5}$	k_n	$k_{OH} \times 10^{-5}$	k_n
p-CH_3O	16.3	0.804	64.7	0.66	1.97
p-CH_3	22.9	0.774	75.9	0.64	2.29
H	63[c]	2.39[c]	184[c]	5.48[c]	3 ± 0.5[c]
p-Cl	227	4.27	820	...	17.4
m-NO_2	4,050	...	12,060	5.82	267
p-NO_2	17,900	...	32,400	46.5	1720

[a] The value of k_0 has been determined by Fedor, *et al.*[1f] [b] The units given in minutes and M. [c] From a previous study.[1f]

The values of ρ determined from the plots of Figure 5 are 2.37 for aziridine, 2.41 for 3-hydroxymethyl-3-phenylazetidine, and 2.30 for 3-methyl-3-phenylazetidine. These values may be compared with those previously determined for other amine bases with the same series of esters: 1.8 for imidazole, 2.1 for ammonia, 2.6 for trimethylamine, and 2.9 for hydrazine.[1c] Comparison of the ρ values for aziridine, the azetidines, imidazole, and trimethylamine establishes that the value of ρ could not be directly related to steric factors, pK_a of the base, or the value of k_n with phenyl acetate.

Reactions of Hydrazines with Phenyl Acetate and the Nature of the α Effect. Under the conditions of [nucleophile] ≫ [ester] the reactions of hydrazines with phenyl acetate were found to be pseudo first order over at least the first three half-lives for all the concentrations and acidities investigated. The reactions with hydrazine were studied at six pH values and those with the substituted hydrazines at three pH values employing in each case five dilutions of the appropriate hydrazine buffer. The general equation (4) was em-

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(28) The point corresponding to the largest amine concentration was above the line at each pH investigated. The deviation at the high pH was 30% and at the low pH was 60%.

(29) These samples were from a previous study having been synthesized by Professor J. Meinwald and Dr. K. L. Kirk, Department of Chemistry, Cornell University.

ployed to correlate the k_{obsd} values. The values of k_n were obtained as intercepts of plots of $k_{obsd}/[N_f]$ *vs.* $[N_f]$ at constant pH. The slopes of these plots equal $(k_{ga}a_H/K_a' + k_{gb})$. For N-methyl- and N,N-dimethylhydrazine the value of the slope was found to be independent of a_H so that the k_{ga} terms were not detectable. The results are given in Table XI. From the temperature dependence of pK'_{a_1} (16–40.5°) the enthalpies (ΔH_i) and entropies (ΔS_i) of ionization of the conjugate acids of the hydrazines were determined (Table XII). Attempts to study the kinetics of the reaction of N-(*n*-propyl)hydrazine with phenyl acetate were unsuccessful owing to the decomposition of the basic species in water and the production of absorbing side products.

Table XI. Reaction of Phenyl Acetate with Substituted Hydrazines at 25° (μ = 1.0)

	k_n, l. mole^{-1} min^{-1}	l.^{2} mole^{-2} min^{-1} k_{gb}	k_{ga}
NH_2NH_2	0.4[a]	10.75[a]	2.4[a]
CH_3NHNH_2	0.14	1.25	...
$(CH_3)_2NNH_2$	0.0039	0.00084	...

[a] See ref 1c.

Table XII. Thermodynamic Data at 25° for the Protonation of Hydrazines (μ = 1.0, H_2O)

	pK_a'	ΔH_i, kcal/mole	ΔS_i, eu
NH_2NH_2	8.26	10.5	−2.0
CH_3NHNH_2	8.20	10.0	−3.8
$(CH_3)_2NNH_2$	7.56	7.2	−10.1

The enhanced nucleophilicity observed for a base possessing a pair of unshared electrons α to the nucleophilic atom (as hydrazine) has been termed the α effect.[30] Though in the present studies enhanced nucleophilicity due to the α effect is determined from the extent of positive deviation of log k_{rate} from the Brønsted plot, enhanced nucleophilicity is possibly also encountered in reactions that are not as dependent on pK_a' (as in nucleophilic displacements on benzyl bromide[31,32] and on oxygen[33]). A number of rationales have been provided for the α effect: (a) in displacement reactions on esters, etc., hydrogen bonding to the carbonyl group by hydrogen on the α atom in the transition state;[34,35] (b) intramolecular general base catalysis;[35] (c) stabilization of the transition state owing to overlap of the orbitals of the lone pair of electrons in the α position analogous to the stabilization of the incipient carbonium ion in α-halo ether solvolysis;[30] (d) diminished solvation, *e.g.*, of HOO^- as compared to HO^-;[36] (e) destabilization of the ground state[33] because of repulsions of the nonbonding electron pair, this repulsion being relieved on covalent bond formation by one electron pair. Explanation e is quite similar to that proposed by Ingold[37] who suggests for adjacent nonbonding orbitals that one be in a high energy state resulting in destabilization of the ground state. No single explanation for the α effect appears completely satisfactory as seen from the following observations. Neither hydrogen bonding (as postulated in a) nor intramolecular general base catalysis (as in b) serve to explain the α effect as noted with reagents devoid of hydrogen atoms such as O^-–Cl.[34,38,39] Enhanced solvation of HO^- as compared to HOO^- does serve to explain a portion of the greater nucleophilicity of HOO^- as compared to HO^-. However, this probably does not concern the α effect since the solvation of HO^- makes it a poorer nucleophile than alkoxide ions of similar basicity which are still poorer nucleophiles than HOO^-.[40] In addition, solvation would not appear to be a reasonable explanation for the greater reactivity of hydrazine as compared to ammonia. The change of the solvation of hydrazines on methyl substitution is reflected in the entropies of ionization (ΔS_i) of the conjugate acid species (see Table XII). The determined changes of ΔS_i on methyl substitution are as anticipated from like determination of the values of ΔS_i for ammonia and methyl- and dimethylamine.[41] The large change in ΔS_i from −2.0 eu for hydrazine to −10 eu for N,N-dimethylhydrazine shows that there are large differences in the solvation of these two species. However, ammonia and dimethylamine which also possess large differences in their values of ΔS_i (*i.e.*, −6 eu for ammonia, −9.5 eu for dimethylamine[42]) fall onto the Brønsted plots for nucleophilic and general base assisted attack on phenyl acetate (Figures 6 and 7).

Oximate ion has been reported to be more effective as a general base than anticipated from Brønsted plots in the decompositions of nitramide[43] and the hydration of *sym*-dichloroacetone.[44] Methoxylamine has an enhanced catalytic ability for the general base catalyzed hydrolysis of ethyl trifluorothiolacetate.[45] In addition, the α affect is of greater importance in k_{gb} as compared to k_n in the aminolysis of thiol[46] and phenyl esters (Figures 6 and 7, see also ref 1d). Stabilization of the transition state c owing to overlap of the nonbonding pair of electrons α to the nucleophilic center may serve as a rationale for the α effect in nucleophilic displacement reactions on carboxylic acid esters and amides and alkyl halides but not

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(31) R. G. Pearson and D. N. Edgington, *ibid.*, **84**, 4607 (1962).

(32) Whether an α effect is exhibited in nucleophilic displacements on the sp^3 carbon is possibly still open to question. Indeed, Jencks [W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960)] has reported that the hydroxylamine oxygen does not exhibit abnormal nucleophilicity toward methyl iodide.

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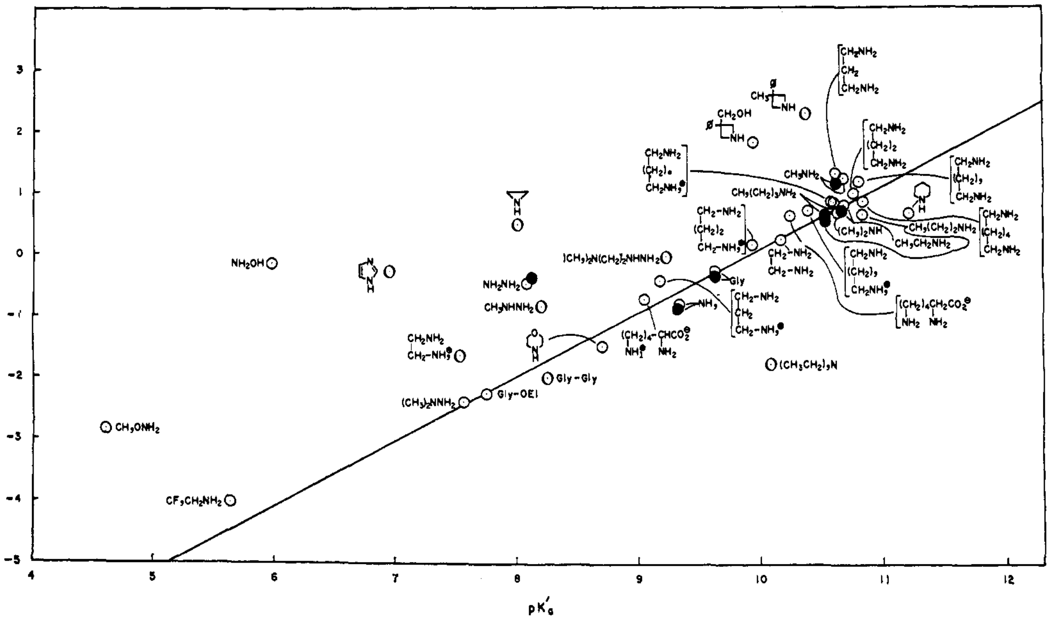

Figure 6. Brønsted plot of log k_n vs. pK_a' for the aminolysis of PA. Values of k_n obtained from this study as well as from ref 1 and 4. Lysine data unpublished (R. W. Huffman, A. Donzel, and T. C. Bruice); μ = 1.0 with $(CH_3)_4NCl$ shaded points, with KCl open points.

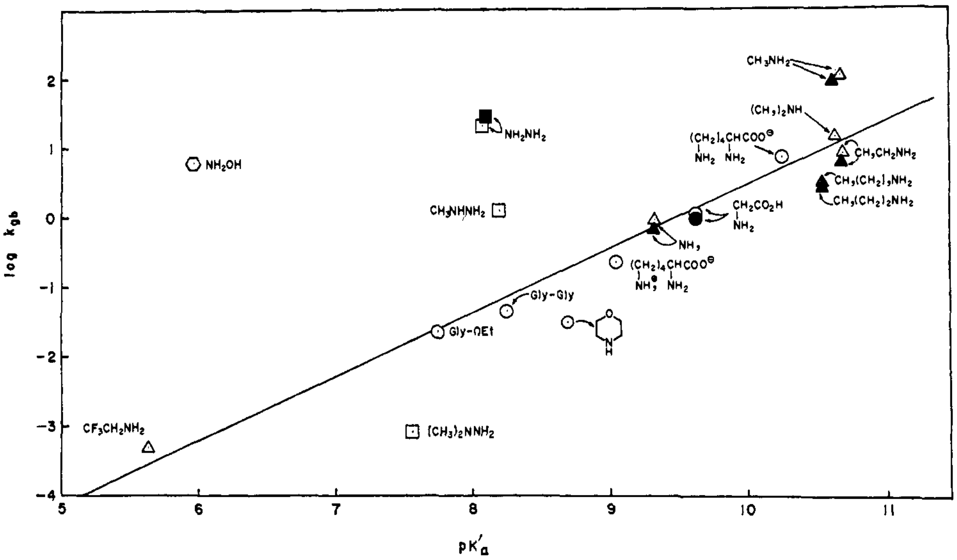

Figure 7. Brønsted plot of log k_{gb} vs. pK_a' for the aminolysis of PA. Values of k_{gb} obtained from this study as well as from ref 1 and 4. Data on lysine unpublished (R. W. Huffman, A. Donzel, and T. C. Bruice). In each case the same amine is the nucleophilic and catalytic species and pK_a' is that for its conjugate acid; μ = 1.0 with $(CH_3)_4NCl$ shaded points, with KCl open points.

when the reagent is acting as a general base. For the latter, the α effect manifests itself as a large positive deviation from a plot of log k_{rate} vs. pK_a'. Overlap of the unshared pair of electrons with an adjacent positively charged center should both lower the transition state and increase the value of pK_a'. These two opposing effects should tend to cancel any positive deviation from a Brønsted plot for general base catalysis. This factor has been suggested[30] not to be of great significance in nucleophilic displacements since the unshared pair of electrons is more completely removed in the transition state than when perturbed by a proton.

One might invoke polarizability as a means of allowing both unshared pairs of electrons to participate in the formation of some transition states. Hydroxylamine and hydrazine, however, possess molar refractions which agree well with the sum of atomic refractions calculated from molecules which do not display abnormal reactivity.[32] Thus, there would be no reason to anticipate unusual polarizability for these reagents. Also, this factor should be unimportant for general base catalysis.

Interpretations of the α effect based on unfavorable interactions between adjacent nonbonding orbitals which raise the ground-state energy of the nucleophile suffer in that not only should log k_{rate} be increased but pK_a' should also be increased. The parallel increase of both log k_{rate} and pK_a' should result in little or no positive deviation from the Brønsted plot. The specific suggestion that the ground state is raised owing to repulsion of nonbonded electron pairs e must, in the case of hydrazine, be considered in the light of the proposed conformation of hydrazine. Raman and infrared spectra have been interpreted[47] as showing

Table XIII. Confidence Level for Brønsted Equations for Rate Constants in the Aminolysis of Phenyl Acetate ($\log k_{\text{rate}} = \beta \text{p}K_a' + C$)

	β Confidence level				$(-)\,C$ Confidence level			
	70%		90%		70%		90%	
	Max	Min	Max	Min	Max	Min	Max	Min
k_n	1.09	1.0	1.17	0.92	10.4	10.3	10.5	10.2
k_{gb}	0.92	0.90	0.93	0.89	8.7	8.5	8.9	8.4
k_{ga}	0.86	0.64	1.20	0.30	7.9	7.5	8.1	7.1
k_{OH}	*ca.* 0				*ca.* −3.0			

hydrazine to exist in a conformation in which the two $-NH_2$ groups are rotated 60° from a *cis* configuration. The nonbonding orbitals are thus *gauche.* Severe electrostatic repulsion might be anticipated to result in a *trans* conformation and especially so, if as is suggested[48] a solvated electron pair is comparable in size to the covalently bonded proton.

From a comparison of the equilibrium constants for the formation of compounds AcOR from acetic acid plus ROH with the $\text{p}K_a'$ of ROH, it can be shown that those esters formed from compounds ROH exhibiting the α effect are thermodynamically more stable.[49] From the carbon basicity (*t*-butyl basicity) of the hydroperoxide anion and the *t*-butyl hydroperoxide anion, Hine[50] suggests that the α effect shows up also as a thermodynamic effect in the attack of nucleophiles on saturated carbon. From these results one might infer that the factors which stabilize the transition state also stabilize the product.

Examination of Figure 6 reveals that the value of $\log k_n$ decreases appreciably on methyl substitution of hydrazine. N,N-Dimethylhydrazine exhibits no enhanced reactivity and the value of $\log k_n$ fits nicely onto a Brønsted plot for the reaction of 1 and 2° amines with phenyl acetate [though with *p*-nitrophenyl acetate (plot not shown) the value of $\log k_n$ exhibits a marked negative deviation]. N-Methylhydrazine does exhibit enhanced nucleophilicity but less than that of hydrazine. For the k_{gb} term hydrazine and N-methylhydrazine exhibit positive deviations from the Brønsted plot which are greater than in the case of the k_n term. The value of $\log k_{gb}$ for N,N-dimethylhydrazine exhibits a marked negative deviation. This must be due to steric factors. That the general catalytic terms exhibit greater sensitivity to steric factors is shown by the inability to detect the k_{ga} term for either N,N-dimethyl- or N-methylhydrazine. In the hydrazinolysis of *n*-butylthiol acetate, isopropylthiol acetate, and *t*-butylthiol acetate, the rate constants k_{gb} and k_{ga} were found to exhibit almost equal sensitivity to steric hindrance.[46] As in the present study the sensitivity of these constants to steric hindrance was greater than that exhibited by k_n. As in the reaction of primary amines with PA the effect of steric hindrance in decreasing rate constants follows the order $k_{ga} > k_{gb} > k_n$ (Table V). For the alkyl-substituted hydrazines it is likely that the position of protonation is at the nitrogen bearing the greater number of alkyl groups,[51] though this may not be the position of acylation; therefore, quantitative correlations of steric effects based on deviations from Brønsted plots for unsymmetrical alkylhydrazines would be questionable.

Dependence of Rate Constants on the Basicity of Amine. In Figures 6 and 7 are presented Brønsted plots of k_n and k_{gb} for all aminolysis reactions studied to date in water at $\mu = 1.0$ (with KCl and $(CH_3)_4NCl$ at 25–30°). The slopes and intercepts of the plots of $\log k_{\text{rate}}$ *vs.* $\text{p}K'_{a_1}$ are the best least-square values obtained for rate constants with primary amines by use of a general least-squares program written by Dr. D. S. Auld for the IBM 1620 computer. The Brønsted equations follow.

$$\log k_n = 1.05\text{p}K_a' - 10.4 \tag{5a}$$

$$\log k_{gb} = 0.91\text{p}K_a' - 8.63 \tag{5b}$$

$$\log k_{ga} = 0.75\text{p}K_a' - 7.6 \tag{5c}$$

Inspection of the maximum and minimum values at 70 and 90% confidence levels (Table XIII) establishes the fact that the sensitivity of k_{ga} to $\text{p}K_a'$ cannot be ascertained with fair certainty and the dependence of k_{OH} (plot not shown) cannot be determined at all. The k_n term is exhibited by all amines examined and for this reason sufficient data have been obtained to determine the Brønsted β and C constants with some degree of certainty. The uncertainty in determining the Brønsted constants for k_{gb}, k_{ga}, and k_{OH} is due to the fact that fewer amines exhibit these terms than exhibit k_n terms. This difficulty is particularly compounded by the fact that many of the amines exhibit deviations from the Brønsted plots due to α or steric effects. A means of normalizing such deviations and determining the Brønsted constants for the catalytic terms is had from plots of $\log k_n$ *vs.* $\log k_{OH}$ (Figure 8), $\log k_{gb}$ (Figure 9), and $\log k_{ga}$ (Figure 10). From these plots the relationships of eq 6 are obtained.

$$\log k_n = 0.59 \log k_{OH} + 1.1 \tag{6a}$$

$$\log k_n = 0.97 \log k_{gb} - 0.76 \tag{6b}$$

$$\log k_n = 1.45 \log k_{ga} - 0.34 \tag{6c}$$

Combining eq 5a with eq 6a, b, and c provides eq 7,

$$\log k_{OH} = 1.78\text{p}K'_{a_1} - 19.5 \tag{7a}$$

$$\log k_{gb} = 1.08\text{p}K'_{a_1} - 9.94 \tag{7b}$$

$$\log k_{ga} = 0.738\text{p}K'_{a_1} - 7.06 \tag{7c}$$

which may be favorably compared to 5b and c and should be considered as being of greater certainty since the former are derived from a larger sample of experimental data.

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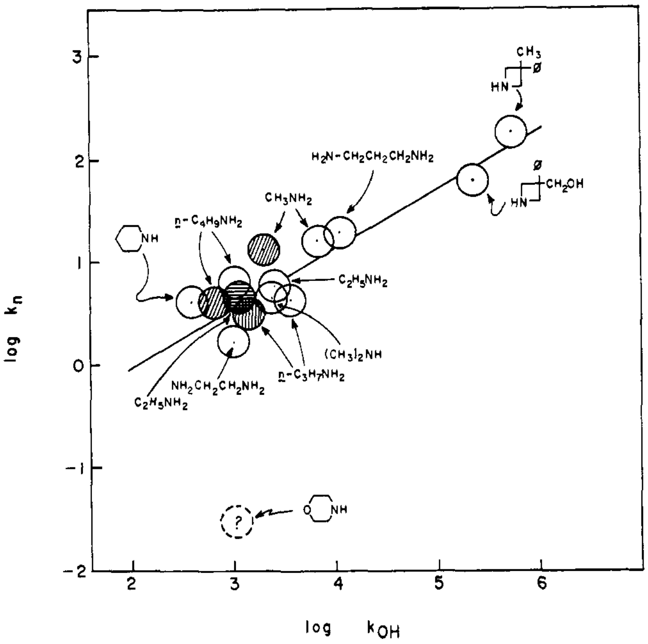


Figure 8. Plot of log k_n *vs.* log k_{OH} for the aminolysis of PA; μ = 1.0 with $(CH_3)_4NCl$ shaded points, with KCl open points.

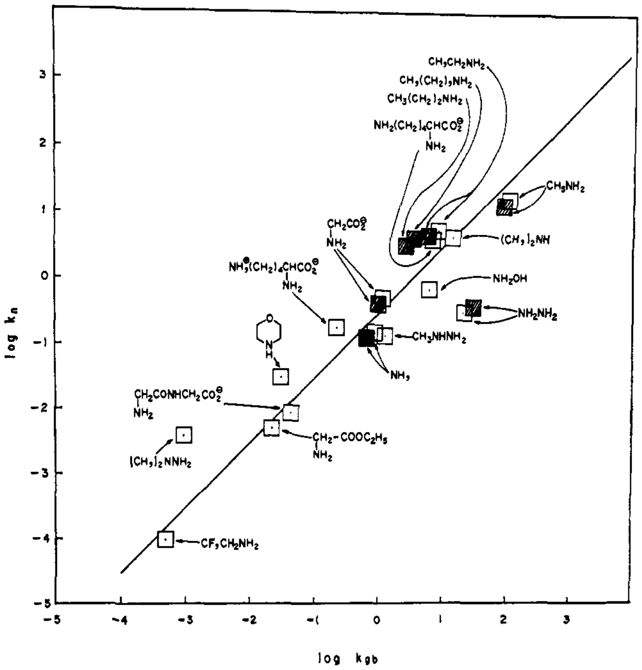


Figure 9. Plot of log k_n *vs.* log k_{gb} for the aminolysis of PA; μ = 1.0 with $(CH_3)_4NCl$ shaded points, with KCl open points.

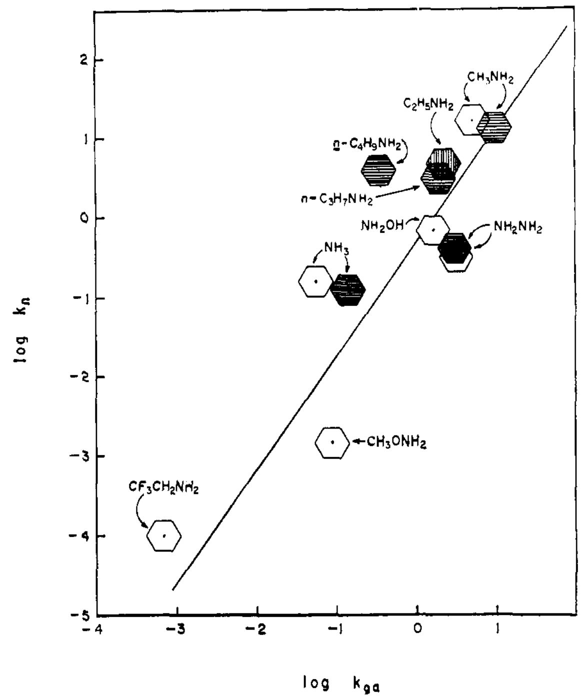


Figure 10. Plot of log k_n *vs.* log k_{ga} for the aminolysis of PA; μ = 1.0 with $(CH_3)_4NCl$ shaded points, with KCl open points.

The greatest deviation in the plot of log k_{OH} *vs.* k_n was found for morpholine[4] (dotted circle in Figure 8). The reaction of this amine with phenyl acetate was, therefore, reinvestigated. The reaction of morpholine with PA was studied at pH values of 9.72, 9.08, 8.70, 8.29, and 7.72 employing five dilutions of the morpholine-morpholine hydrochloride buffer solution between 0.1 and 1.0 *M*. Ionic strength was maintained at 1.0 with KCl (30°). Good first-order kinetics were obtained at all but the two highest pH values. In order to obtain k_{obsd} at these values of pH, OD_∞ values lower than those experimentally determined had to be employed. The best value was chosen by means of a general rate constant computation program written for the IBM 1620 by D. W. Tanner. Plots of $(k_{obsd} - k_w[OH^-])$ *vs.* $[N_T]$ were found to possess an upward curvature indicating the morpholinolysis reaction to be greater than first order in buffer. The curvature increased with increasing pH suggesting a k_{gb} term. No k_{OH} term could be detected. Thus, at a constant $[N_f]$ = 0.5 *M* and at pH values of 9.72, 9.08, and 8.70 the value of $(k_{obsd} - k_w[OH^-])$ is $2.34 \pm 0.05 \times 10^{-2}$ min^{-1}. The values of k_n and k_{gb} (see eq 1) were determined as intercept and slope, respectively, of plots of $(k_{obsd} - k_w[OH^-])/[N_f]$ *vs.* $[N_f]$ (see Figure 11). The values so determined are k_n = 0.0245 l. mole^{-1} min^{-1} and k_{gb} = 0.032 l.^{2} mole^{-2} min^{-1}. Inspection of Figures 6 and 9 reveals that these rate constant values provide a satisfactory fit on the best line drawn for the other amines. General base catalysis in the morpholinolysis reaction provides the first instance of this pathway in the reaction of a secondary amine with PA though this catalytic pathway has been seen in the morpholinolysis and piperidinolysis of thiol esters.[35] Mechanistic suggestions based on the inability to detect k_{gb} terms in the reaction of secondary amines with PA are, therefore, suspect.

Mechanism. The relative importance of the various catalytic terms should be predictable from the Brønsted eq 5a and 7. From these it would be anticipated that all 1 and 2° amines should exhibit k_{gb} terms provided suitable concentrations of amine buffer are employed in kinetic studies. In addition all amines of moderate pK'_{a_1} would be anticipated to exhibit k_{ga} terms in reactions with PA. Values for k_{OH} have generally only been seen for the more basic amines but this may be fortuitous since at pH values near the pK'_{a_1} of many amines the concentration of $[OH^-]$ is very small. Considering only k_n, k_{gb}, and k_{ga} we find: only k_n terms (μ = 1.0 with KCl), (1) most cyclic secondary amines (aziridines, azetidines, piperidine), (2) all α,ω-diaminoalkanes and their monoprotonated forms, (3) 3° amines,

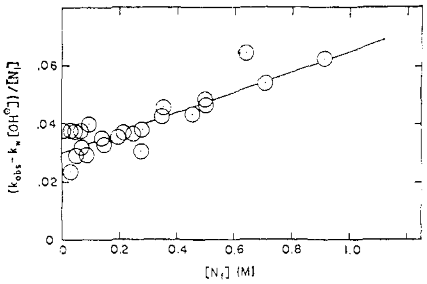


Figure 11. Plot of $(k_{\text{obsd}} - k_w[\text{OH}^-])/[\text{N}_f]$ *vs.* $[\text{N}_f]$ for the reaction of morpholine with phenyl acetate [H_2O, 30°, μ = 1.0 with KCl].

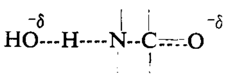
and (4) *n*-butyl- and *n*-propylamines; only k_n and k_{gb} terms (μ = 1.0 with KCl), (1) N- and N,N′-dimethylhydrazine, (2) ethylamine, (3) amino acid derivatives (glycine, glycine ethyl ester, glycylglycine, lysine-H^+), and (4) morpholine; only k_n and k_{ga} terms (μ = 1.0 with KCl), (1) methoxylamine; and amines with k_n, k_{ga}, and k_{gb} terms, (1) *n*-alkylamines (except *n*-butyl- and *n*-propylamines), fluoralkylamines, ammonia (μ = 1.0 with KCl), (2) all *n*-alkylamines, ammonia (μ = 1.0 with $(CH_3)_4NCl$), and (3) hydroxylamine, hydrazine.

These various cases may be considered separately. That secondary amines do not generally exhibit k_{ga} or k_{gb} terms is consistent with the suggestion[4] that the transition states for these mechanisms are considerably more crowded than for simple nucleophilic attack. This also explains the decreasing values of k_{gb} and k_{ga} with increasing chain length for *n*-alkylamines (Table V). The low values of the rate constants for ammonia also provided in Table V may be due to its known hydration[41] which also decreases its pK'_{a_1}. That the transition state for k_{ga} is more crowded than that for k_{gb} is shown by the fact that N-methyl- and N,N-dimethylhydrazine exhibit only k_{gb} terms while hydrazine exhibits all terms, and that the amino acid derivatives (in which the amino group is on a secondary carbon) and ethylamine exhibit k_{gb} but not k_{ga} terms. The transition states associated with k_{ga} and k_{gb} in the aminolysis of thiol esters and lactones may be less crowded than with PA aminolysis, for the secondary amines piperidine and morpholine exhibit k_{ga} and k_{gb} terms with the former substrates.[46,52] The lack of k_{ga} and k_{gb} terms in the case of *n*-propyl- and *n*-butylamines in KCl solutions and the appearance of these terms in $(CH_3)_4NCl$ solutions have been discussed. These same factors may perhaps apply to the α,ω-diaminoalkanes.[1e] Methoxylamine with only k_n and k_{ga} terms is an anomaly.[53] From the values of k_n and k_{ga}[53] it is clear that a k_{gb} term would be expected. Those amines exhibiting all catalytic terms are the primary amines, hydroxylamine, hydrazine, and ammonia. These apparently provide the minimum of steric requirements.

From the Hammond postulate[54] it follows that for reactions passing through a metastable intermediate, the transition states must closely resemble the intermediate I if both k_1/k_2 and k_3 are of kinetic significance. If the rate-limiting step is k_1 or k_3, then the transition state associated with the nonrate-determining step will still closely resemble the intermediate, while the transition state for the rate-determining step must possess a structure intermediate between that of the intermediate and reactant or product, respectively, but resemble most the intermediate.

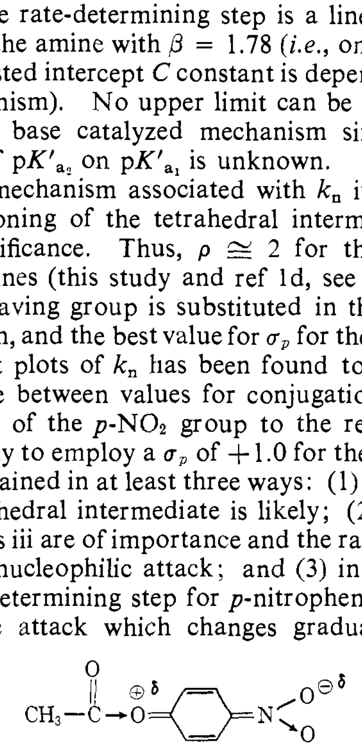
$$\text{A} + \text{B} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{I} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \text{C} + \text{D} \qquad (8)$$

For the term k_{OH}, the rate-determining step is most likely k_1 and the transition state for this step must resemble ii. Support for k_1 being rate determining is derived from the fact that $>N^-$ could not compete with $C_6H_5O^-$ as a leaving group from the tetrahedral intermediate. Structure ii is in agreement with expectations derived from the salt effect studies. Of the various rate terms for aminolysis the k_{OH} constant is associated with the largest Brønsted β constant. Whether the proton in ii is completely removed in the transition state (specific base catalysis) or not (general base catalysis) is not determinable from existing data. Thus, differentiation between these mechanisms cannot be made on the basis of deuterium solvent isotope effects (where $k_{OH}{}^{H_2O}/k_{OH}{}^{D_2O} = 2.24$ for methylamine at 5°)[5] owing to the fact that for general catalysis $k_r{}^{H_2O}/k_r{}^{D_2O}$ should exceed 2.0 and for specific catalysis $K'_{a_2}{}^{H_2O}/K'_{a_2}{}^{D_2O}$ would most assuredly exceed 2.0.[55] Regardless of the mechanism, the log of the rate constant for the rate-determining step is a linear function of pK'_{a_1} of the amine with β = 1.78 (*i.e.*, only the value of the Brønsted intercept *C* constant is dependent on the type mechanism). No upper limit can be set on β for the specific base catalyzed mechanism since the dependence of pK'_{a_2} on pK'_{a_1} is unknown.



ii

For the mechanism associated with k_n it is possible that partitioning of the tetrahedral intermediate is of kinetic significance. Thus, $\rho \cong 2$ for this term for various amines (this study and ref 1d, see Table XIV) when the leaving group is substituted in the *meta* and *para* position, and the best value for σ_p for the NO_2 group in Hammett plots of k_n has been found to be +1.0,[1d] intermediate between values for conjugation and nonconjugation of the *p*-NO_2 group to the reaction seat. The necessity to employ a σ_p of +1.0 for the NO_2 group may be explained in at least three ways: (1) partitioning of the tetrahedral intermediate is likely; (2) resonance structures as iii are of importance and the rate-determining step is nucleophilic attack; and (3) in addition to 2 the rate-determining step for *p*-nitrophenyl acetate is nucleophilic attack which changes gradually to partitioning for phenyl acetate so that a curved Hammett plot is obtained and a special value of σ_p for the nitro group must be employed in order to obtain a linear plot. That the rate-determining step is nucleophilic



iii

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[52] T. C. Bruice, J. R. Bruno, and W. S. Chou, *J. Am. Chem. Soc.*, **85**, 1659 (1963).

[53] This reaction initially studied by Jencks and Carriuolo[4] has been reinvestigated in our laboratory (Mr. Barton Holmquist). Our kinetic results are nearly identical with those reported in the literature (*i.e.*, k_n = 0.0015 *vs.* too small to determine; and k_{ga} = 0.087 *vs.* 0.113).

[54] G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

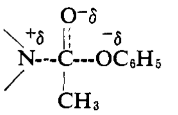
[55] N. C. Li, P. Tang, and R. Mathur, *J. Phys. Chem.*, **65**, 1074 (1961).

Table XIV. Hammett ρ and Deuterium Solvent Kinetic Isotope Effects for the Aminolysis of Phenyl Acetates

Amine	k_n ρ	k_n k^{H_2O}/k^{D_2O} [b]	k_{gb} ρ	k_{gb} k^{H_2O}/k^{D_2O} [b]	k_{ga} ρ	k_{ga} k^{H_2O}/k^{D_2O} [b]
NH_3	2.1[a]	1.0[d]	0.55[a]	1.5[d]	...	...
NH_2OH	...	...	...	1.94[f]	...	1.63[f]
NH_2NH_2	2.9[a]	1.1[a]	0.55[a]	1.2[a]	0.65[a]	2.3[a]
Imidazole	1.8[a]	1.1[a]	0.5[a]	2.2[a]	...	...
$(CH_3)_3N$	2.1[a]	0.9[c]	...	...	...	...
CH_3ONH_2	...	...	...	...	0.57[d,e]	1.9[f]

[a] Reference 1d. [b] For phenyl acetate itself. [c] M. L. Bender, E. J. Pollock, and M. C. Nevew, *J. Am. Chem. Soc.*, **84**, 595 (1962). [d] Reference 4. [e] Based on the rate constants for phenyl acetate and *p*-nitrophenyl acetate. [f] Determined by Dr. Leigh Auleb in this laboratory.

attack for *p*-nitrophenyl acetate is most likely based on the results of the following paper[56] (*i.e.*, rate constants for reaction of a series of nucleophiles with *p*-nitrophenyl acetate and 2,2,2-trifluoroethyl thiolacetate are almost identical; therefore no element effect is evident, a result hardly compatible with partitioning being of significance for 17 nucleophiles). Assuming partitioning to be important in k_n for PA and from the Hammond[54] postulate, N–C bond formation is essentially complete and C–OPh bond rupture has not proceeded far in the transition states. For cases in which k_1/k_2 and k_3 are of kinetic significance, a single structure resembling the tetrahedral intermediate suffices to provide the salient features of the transition states. In iv solvent water is undoubtedly involved in solvation



iv

of the charged centers and some O–H and H–N stretching must occur in reaching the transition state. The values of $k_n^{H_2O}/k_n^{D_2O}$ are very nearly 1.0 (Table XIV) reflecting probable cancellation of isotopic solvent effects between ground and transition states. Reactions such as the aqueous solvolysis of methyl sulfonates[57] and alkyl halides[58] proceeding from neutral ground states through charge-dispersed transition states are known which do not exhibit significant deuterium solvent isotope effects. The polar nature of iv is in agreement with the values of $k_n^{K^+}/k_n^{N^+(CH_3)_4}$.

In discussing structures for transition states associated with k_{gb} and k_{ga} the question arises of whether catalysis is involved in addition of amine or elimination of phenoxide. Since no change of mechanism with increase in amine concentration has been noted in the aminolysis of PA it is most reasonable to assume symmetrical mechanisms (for discussion of this topic see ref 59).

k_{gb}:

$$N_f + E \underset{k_2NH^+}{\overset{k_1N_f}{\rightleftharpoons}} T^- \xrightarrow{k_3NH^+} \text{product} \qquad (9)$$

k_{ga}:

$$N_f + E \underset{k_2N_f}{\overset{k_1NH^+}{\rightleftharpoons}} TH \xrightarrow{k_3N_f} \text{product} \qquad (10)$$

In multiple-step reactions as 9 and 10 the experimentally determined Hammett ρ_{expt} value and the Brønsted general base β_{expt} and general acid α_{expt} constants are necessarily complex functions of each kinetically important step. Knowing that β values are positive and α values are negative numbers it can be shown that

$$\log k_{rate} = \rho_1\sigma - \log(1 + \delta) + A \qquad (11)$$

$$\log k_{rate} = \beta_1 pK_a - \log(1 + BK_a^{\alpha_3 - \alpha_2}) + C \qquad (12)$$

where subscripts 1, 2, and 3 refer to constants k_1, k_2, and k_3; δ is the partition coefficient k_2/k_3; A, B, and C are constants. If $k_2 \gg k_3$ so that k_3 is the rate-determining step then[60]

$$\log k_{rate} = \sigma(\rho_1 + \rho_3 - \rho_2) + E \qquad (13)$$

$$\log k_{rate} = (\beta_1 + \alpha_3 - \alpha_2)pK_a + F \qquad (14)$$

Only in the case where k_1 is rate determining are the Hammett ρ and Brønsted β constants easily interpretable.

$$\log k_{rate} = \sigma\rho_1 + A \qquad (15)$$

$$\log k_{rate} = \beta_1 pK_a + C \qquad (16)$$

In cases where a change of rate expression occurs with change of amine concentration or acidity it is possible to stipulate which step is rate controlling.[61] Nothing of this nature has been noted with the aminolysis reaction, nor would it be expected if symmetrical mechanisms as 9 and 10 were operative. Therefore, it is obvious that β_{expt} and ρ_{expt} serve best as parameters which describe the over-all reaction.

For k_{gb}, ρ is much smaller than for k_n (Table XIV) while β is identical with that for k_n (eq 6a and 8). Since the basicity of the amine is important in determining both nucleophilicity and catalytic ability one might anticipate a greater dependence of k_{gb} on the pK'_{a_1} of

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(56) M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, **89**, 2121 (1967).

(57) R. E. Robertson and P. M. Laughton, *Can. J. Chem.*, **35**, 1319 (1957).

(58) P. M. Laughton and R. E. Robertson, *ibid.*, 37, 1491 (1959).

(59) T. C. Bruice and L. R. Fedor, *J. Am. Chem. Soc.*, **86**, 4886 (1964).

(60) For nucleophilic displacements it can be shown that $(\alpha + \phi) = \beta$ where $\delta\Delta F_K/\delta\Delta F_{AH} = \phi$ and ΔF_K is the free energy of the equilibrium constant for

$$A + \text{substrate} \overset{K}{\rightleftharpoons} \text{product} + B$$

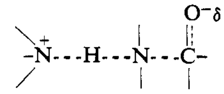
and ΔF_{AH} is the change in free energy for

$$AH \overset{K_a}{\rightleftharpoons} A + H^+$$

For nucleophilic displacement reactions it can not be assumed that $\phi = 1$ as in the case of general acid–base catalysis. If $\phi = 1$, eq 14 reduces to $\log k_{rate} = (\alpha_3 + 1)pK_a + F = \beta_4 pK_a + F$. This point was brought to our attention by Dr. M. J. Gregory.

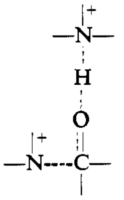
(61) For an extensive listing of references see footnote 3 in A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, **87**, 3217 (1965); also, P. M. Mader, *ibid.*, **87**, 3191 (1965); G. L. Schmir, *ibid.*, **87**, 5692 (1965); **88**, 551 (1966); R. L. Schowen and G. W. Zuorick, *ibid.*, **88**, 1223 (1966).

the amine and consequently a larger β might be expected for k_{gb} as compared to k_n. The fact that ρ_{expt} is quite small, that $k_{ga}^{H_2O}/k_{ga}^{D_2O}$ may approach 2.0, and that the β_{expt} values for k_n and k_{gb} are identical would be in accord with k_1 being rate determining and the transition state for k_1 being in free energy much higher than the tetrahedral intermediate. A transition state with less N-C bond formation than for that associated with k_n and partial proton transfer would be in accord with experimental results.



v

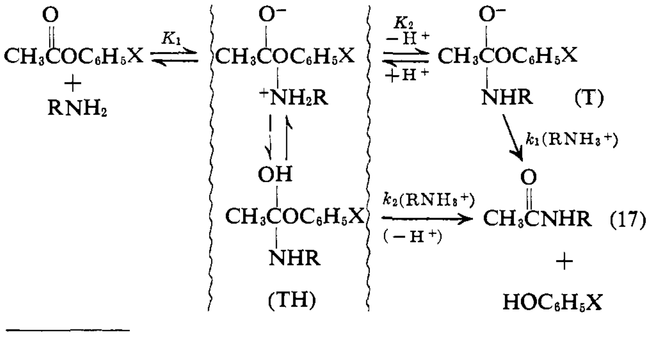
The ρ value for k_{ga} is also much smaller than for k_n and about equivalent to that for k_{gb}. Comparison of the Brønsted equations of 6a and 8c reveals that k_{ga} is less sensitive to pK'_{a_1} than k_n. If k_1 is rate controlling for k_{ga}, the conjugate acid of the amine is the catalyst and the amine free base the nucleophile; therefore, the value of β must be a composite of negative and positive constants and should be smaller than for k_n. Also, the smaller value of ρ would be in accord with k_1 being rate determining. If N-C bond formation has proceeded in k_{ga} to a greater extent than in k_{gb} then one would have an explanation for the greater steric hindrance found in k_{ga} as compared to k_{gb}. The values of $k_{ga}^{H_2O}/k_{ga}^{D_2O}$ suggest considerable proton transfer in the transition state (Table XIV).



vi

Structures v and vi are in accord with the values of $k^{K^+}/k^{N^+(CH_3)_4}$ determined for k_{gb} and k_{ga}, respectively.

From the discussion of the complexity in determining the meaning of ρ, β, and α constants for reactions proceeding through metastable intermediates and the knowledge that exact interpretations of deuterium solvent isotope effects is questionable,[62] it is obvious that the provided transition states are not unique. The fact that these mechanisms do serve to explain the dependence of the rate constants on electronic effects in the leaving group, the basicity of nucleophile and catalyst, deuterium solvent isotope effects and salt effects may be coincidental. The k_{ga} and k_{gb} terms, their isotope effects, and Hammett ρ and Brønsted β values may also be rationalized in terms of a multiple-step reaction involving only general acid catalysis of the departure of the leaving group in which the catalytic steps are both of the general acid type (see eq 17 and 18).



(17)

$$\frac{d[\text{amide}]}{dt} = \left[\frac{K_1(k_2a_H + K_2k_1)}{K_1[RNH_2](K_2 + a_H) + a_H}\right] \times [PA][RNH_2][RNH_3^+] \quad (18)$$

Since K_1 and K_2 are very small numbers and the concentration of amine is less than 1.0 *M*

$$k_{obsd} = (K_1/K_{a_1})(k_2K'_{a_1}[RNH_3^+] + K_2k_1[RNH_2])[RNH_2] \quad (19)$$

so that

$$k_{gb} = K_1K_2k_1/K_a \qquad k_{ga} = K_1k_2 \quad (20)$$

The small $+\rho$ associated with substituents in the leaving group for both k_{ga} and k_{gb} would be in accord with electron-attracting substituents decreasing susceptibility of the leaving group to slow proton transfer. Rationalization of the isotope effects for this mechanism requires consideration of the deuterium solvent thermodynamic isotope effects of K_{a_1} and K_2 [*i.e.*, for hydrazine: $k_{ga}^{H_2O}/k_{ga}^{D_2O} = (K_1^{H_2O}/K_1^{D_2O})(k_2^{H_2O}/k_2^{D_2O}) = (1.1)\cdot(2) = 2.2$; $k_{gb}^{H_2O}/k_{gb}^{D_2O} = (K_1^{H_2O}/K_1^{D_2O})(K_{a_1}^{D_2O}/K_{a_1}^{H_2O})(K_2^{H_2O}/K_2^{D_2O})(k_1^{H_2O}/k_1^{D_2O}) = (1.1)(0.194)(3.52)\cdot(2) = 1.37$, where the values of $K_a^{D_2O}/K_a^{H_2O}$ are obtained from a Rule and La Mer plot[63] (see Table XIV)].

The mechanism of eq 17 is essentially that proposed by Bunnett and Davis.[64] From the concept of microscopic reversibility the retrograde mechanism for steps k_1 and k_2 of eq 17 must involve amine general base catalyzed attack of phenol on amide and protonated amide, respectively. It has been argued[4] that eq 17 is incorrect on the basis that at pH values where phenol exists as phenolate ion the implausible assumption must be made that phenolate ion must first associate with a proton and then have this proton removed by amine in the transition state. This does not appear to be a reasonable argument.

There are multiple mechanisms (1) for the forward reaction and each of these must have its retrograde counterpart. As in the forward direction, the importance of each mechanistic path must be dependent on the concentration of the reactant species. At pH values above the pK_a' of the phenol the retrograde terms for k_{ga} and k_{gb} would not be of importance, but direct attack of phenolate ion on amide might. The latter is the retrograde mechanism associated with k_n in the forward reaction. For phenolysis of amide the retrograde of eq 17 could be of importance at pH values below that of the pK_a' of the phenol. To date no investigation of phenolysis of an amide has been made.

In mechanisms 9 and 10 the same amine species involved as a catalyst in the k_1 steps may also be involved as its conjugate acid or base in the k_2 and k_3 steps. This would be so, if the rate constant for diffusion of the catalyst from the tetrahedral intermediate was less

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(62) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 42, 3207 (1961).

(63) R. P. Bell, "The Proton in Chemistry," Cornell University Press, New York, N. Y., 1959, p 188.

(64) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960).

than the rate constant for collapse of the tetrahedral intermediate. A mechanism of this type would be for all practical purposes concerted and in accord with a previously proposed mechanism.[1a]

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Nucleophilic Displacement Reactions at the Thiol Ester Bond. V. Reactions of 2,2,2-Trifluoroethyl Thiolacetate[1]

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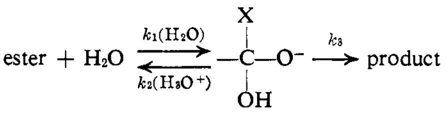
Contribution from the Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. Received October 28, 1966

Abstract: The kinetics for the reactions of 16 nucleophiles with 2,2,2-trifluoroethyl thiolacetate have been determined (30°, $\mu = 1.0$ with KCl in water). For hydrazine, morpholine, glycine, ethanolamine, hydroxide ion, carbonate ion, and the anions of pentaerythritol, 2,2,2-trifluoroethanol, and cyanide the reactions were found to be only first order in both the ester and nucleophile (k_n[E][B]). The first authenticated case for a reaction of an amine with an ester which is first order in the ester and first order in the conjugate acid of the base (k_{BH^+}[E][BH$^+$]) has been found for tris(hydroxymethyl)aminomethane. This nucleophile also exhibits a simple nucleophilic term (k_n[B][E]). The base hydroxylamine exhibits the terms (k_n[B][E] + k_{gb}[B]^2[E] + k_{ga}[B][BH$^+$][E]). The value of log k_n for the reaction of 13 nucleophiles exhibiting this constant with the thiol ester and with *p*-nitrophenyl acetate follow quite precisely the equation $\log k_n = \log k_{n_{p\text{-NPA}}} + 0.6$. From the equation and the lack of a significant element effect, it is argued that the rate-determining step for the thiol and nitrophenyl esters is nucleophilic attack of the base species at the carbonyl carbon. For piperidine the rate terms for reaction with the thiol ester are (k_{gb}[B]^2[E] + k_1[OH$^-$][E]) where $k_1 = 158 \times k_{OH}$ and k_{OH} is the true second-order rate constant for the reaction of hydroxide with the thiol ester in the absence of piperidine. Consistent with this finding is mechanism 15 (see text) where $k_2[\text{pipH}^+] \gg k_3$ and $k_1 = K_a'k_1k_3/k_2K_w$. The reaction of the thiol ester with imidazole is complicated by a reverse reaction.

Kinetic evidence for the formation of tetrahedral intermediates in the reaction of nucleophiles with thiol esters has been obtained from previous studies in this laboratory. The kinetics for the reaction of δ-thiolvalerolactone, γ-thiolbutyrolactone, *n*-butyl thiolacetate, isopropyl thiolacetate, and *t*-butyl thiolacetate with methoxylamine and hydroxylamine are explicable on the basis of the formation of tetrahedral intermediates along parallel general base and general acid catalyzed reaction paths, these intermediates being in acid-base equilibria.[1c] Since the acid-base equilibria of tetrahedral intermediates allow crossing over from the reaction pathway of one symmetrical mechanism to another, the term "cross-over" mechanism was offered for this phenomenon. In the hydrolysis of ethyl trifluorothiolacetate the pH-rate profile was interpreted as due to an unsymmetrical mechanism involving general base (by water) catalyzed addition of water to the ester carbonyl group, acid (by $\mathrm{H^{-}{}_{3}O}$) catalyzed collapse of intermediate to starting ester, and spontaneous conversion of the tetrahedral intermediate to products (eq 1).[1d] The proposed mechanism, which requires the presence of a tetrahedral intermediate, has recently been confirmed by Bender using O^{18} exchange techniques.[4] The decrease in k_{obsd} with increasing hydrogen ion concentration has been shown, through experiments with LiCl solutions, not to be due to a decrease in $a_{\mathrm{H_2O}}$.[5] A similar pH-rate profile has recently been obtained for the hydrolysis of benzoyl and *p*-chlorobenzoyl cyanide by Hibbert and Satchell.[6] These investigators have interpreted their results *via* eq 1. In the cross-over mechanism and that of type 1 we have, therefore, evidence for tetrahedral intermediates along the reaction path in both symmetrical and unsymmetrical general catalyzed reactions on thiol esters.



$$\text{ester} + \mathrm{H_2O} \underset{k_2(\mathrm{H_3O^+})}{\overset{k_1(\mathrm{H_2O})}{\rightleftarrows}} -\overset{\overset{\displaystyle \mathrm{X}}{|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{O}^- \xrightarrow{k_3} \text{product} \qquad (1)$$

The present study deals with the reaction of nucleophiles with 2,2,2-trifluoroethyl thiolacetate. In contrast to ethyl trifluorothiolacetate, electron-attracting substituents for this ester are present on the thiol rather than acyl moiety. The objective of this study is to determine something of the nature of the mechanism of nucleophilic displacement on an aliphatic thiol ester with a good leaving group particularly in regard to the formation of tetrahedral intermediates and the nature of the rate-determining step.

Experimental Section

Apparatus. Absorbance measurements were made on a Zeiss PMQ II spectrophotometer or Gilford Model 2000 or 220 recording

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(1) For previous papers in this series see: (a) T. C. Bruice, J. J. Bruno, and W. S. Chou, *J. Am. Chem. Soc.*, **85**, 1659 (1963); (b) L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 4117 (1964); (c) T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 738, 739, 4886 (1964); (d) L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 5697 (1964); **87**, 4138 (1965).

(2) Postdoctoral Fellow, University of California at Santa Barbara, Santa Barbara, Calif.

(3) To whom inquiries concerning this paper should be directed.

(4) M. L. Bender, private communication.

(5) T. C. Bruice and M. J. Gregory, unpublished results.

(6) F. Hibbert and D. P. N. Satchell, *Chem. Commun.*, 516 (1966).