General Base Catalysis of the Aminolysis of Phenyl Acetate by Primary Alkylamines[1]

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Abstract: Rate constants are reported for the uncatalyzed (or water-catalyzed), amine-catalyzed, and hydroxide ion catalyzed reactions of phenyl acetate with methylamine, ethylamine, *n*-propylamine, and *n*-butylamine at 5° and ionic strength 1.0 *M*. The values of ΔH^* are 8500 and 3400 cal./mole and those of ΔS^*_{298} are -32.4 and -45.6 e.u. for the uncatalyzed and amine–catalyzed reactions of methylamine, respectively. In addition, general base catalysis of the reaction of phenyl acetate with *n*-butylamine at 25° in the absence of potassium chloride is detectable, if it is assumed that the salt effect of *n*-butylammonium chloride on the reaction is negligible. Tetrahydrofuran and ethanol inhibit, potassium chloride stimulates, and tetramethylammonium chloride has no effect on the reaction of methylamine with phenyl acetate.

General base catalysis by amines of the aminolysis and ammonolysis of esters was demonstrated independently by Bunnett and Davis,[2] by Jencks and Carriuolo,[3] and by Bruice and Mayahi.[4] Bunnett and Davis studied the aminolysis of formate esters in alcohol,[2] Jencks and Carriuolo studied the aminolysis of phenyl acetate by a number of amines in water and showed that general base catalysis was not significant for the corresponding reactions of *p*-nitrophenyl acetate,[3] and Bruice and Mayahi showed that the relative importance of general base catalysis decreased as the leaving group became better in a larger series of esters.[4] More recently Bruice and Willis re-examined the reaction of phenyl acetate with *n*-butylamine, one of the less reactive amines which was reported to show general base catalysis in the earlier study,[3] and were unable to find evidence for general base catalysis of this reaction.[5] As pointed out by these workers, the previously reported catalytic constant for this amine is so small that experimental errors make its determination difficult. Bruice and Willis were led to the conclusion that intermolecular general base catalysis is of no significance in the reaction of simple aliphatic amines with phenyl acetate. In view of the previously reported general base catalysis of the reactions of phenyl acetate with glycine, ammonia, glycylglycine, glycine ethyl ester, dimethylamine, and hydroxylamine,[3] all of which have considerably higher ratios of catalyzed to uncatalyzed reaction rates than does the sterically more demanding butylamine, it appeared desirable to re-examine the question of whether general base catalysis is significant in the reaction of simple amines with phenyl acetate.

Experimental Section

Materials and methods were essentially the same as described previously.[3] Deuterated methylammonium chloride was prepared by dissolving methylammonium chloride in deuterium oxide and evaporating to dryness in a rotary evaporator. For reactions at 5 ± 0.1° the reactants were preincubated in a water bath at 4.9°. The amine buffer solution, in 2.95 ml., was transferred to a cuvette in a brass block in the cell compartment of a Zeiss PMQ II spectrophotometer, through which water from the thermostat was circulated. The reaction was initiated by the addition of 0.05 ml. of 0.03 *M* phenyl acetate with a plastic rod with a flattened cup at one end, which was also used to mix the solution. It was shown that the temperature of the solution remained constant at 5 ± 0.1°. The reactions were followed spectrophotometrically at 270 mμ. Experiments with half-times of less than 1 min. generally were run in duplicate. Reactions with half-times of over 1 min. were generally run in Teflon-stoppered cuvettes, but it was shown that identical rate constants were obtained with open cuvettes. The ionic strength was maintained at 1.0 *M* with potassium chloride, unless noted otherwise.

At the end of the reaction the solutions were brought to 25° and the pH was determined with a Radiometer Model 4 pH meter. The rate constants which involve hydroxide ion are expressed in terms of hydroxide activities at the temperature at which the rate measurement was carried out. Hydroxide ion activities at 5° were calculated from the pH measurements at 25° and the heats of ionization of the amines and water[6]; these values are similar, so that the corrections are small. Values of pD were obtained from measurements with the glass electrode by adding 0.408 to the observed pH meter readings.[7] Deuteroxide ion activities were obtained from $pK_w = 14.089$ for deuterium oxide at 25°[7] and by assuming that the differences in the heats of ionization of the solvent and amines are the same in water and in deuterium oxide. This assumption does not introduce a significant uncertainty in the value of k_1 or k_{RNH_2} for methylamine in deuterium oxide, because the corrections of the observed rate constants for deuteroxide-catalyzed reactions were less than 10%.

Rate constants were calculated from the dependence on amine concentration and pH of the observed pseudo-first-order rate constants as described previously.[3] In most experiments, both amine catalysis and hydroxide ion catalysis contributed significantly to the observed rates, so that it was necessary to calculate the catalytic constants by a series of successive approximations. However, the experiments were set up in such a manner that the correction for hydroxide ion catalysis would be small when the experiment was designed to measure amine catalysis, and *vice versa*. The corrections for the k_1 and k_{OH^-} terms amounted to approximately 20%; no significant correction was necessary for the k_{RNH_2} terms. The concentration of free amine was calculated from the amount added and the amount of amine hydrolysis. Amine hydrolysis was significant only in the most alkaline solutions and in all cases resulted in less than a 10% decrease in the concentration of free amine.

Results

In Figure 1 the open circles show the dependence on amine buffer concentration of the pseudo-first-order

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[1] Supported by grants from the National Science Foundation and the National Institute of Child Health and Human Development of the National Institutes of Health (HD-01247).

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

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

[4] T. C. Bruice and M. F. Mayahi, *ibid.*, **82**, 3067 (1960).

[5] T. C. Bruice and R. G. Willis, *ibid.*, **87**, 531 (1965).

[6] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 371; J. T. Edsall and J. Wyman, "Biophysical Chemistry," Vol. 1, Academic Press Inc., New York, N. Y., 1958, p. 452.

[7] P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Am. Chem. Soc.*, **86**, 1 (1964).

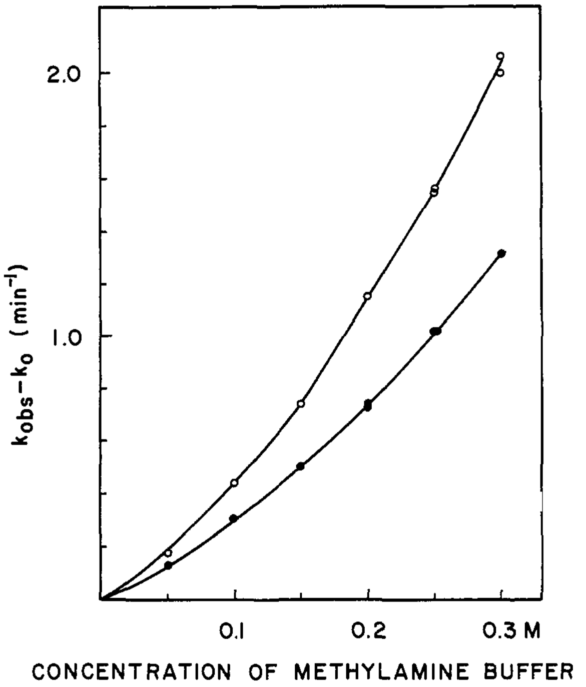

Figure 1. Pseudo-first-order rate constants for the reaction of phenyl acetate with methylamine as a function of methylamine buffer concentration at 5°, ionic strength 1.0 *M*. The buffer is 40% free base: upper curve, in water; lower curve, in deuterium oxide solution.

rate constants for the reaction of methylamine with phenyl acetate in aqueous solution at 5°, with the ionic strength maintained at 1.0 with potassium chloride. The observed rate constants are corrected for the rate of alkaline hydrolysis of phenyl acetate[3] at the same pH; this correction is less than 5% of the observed rates. The reaction with methylamine is more than first order in respect to amine concentration, as shown by the fact that the pseudo-first-order rate constants increase more rapidly than the first power of the amine concentration at constant pH. The apparent second-order rate constants, obtained by dividing the pseudo-first-order rate constants by the concentration of free amine, increase with increasing amine concentration (Figure 2, open circles). The slope of this line is the catalytic constant, k_{RNH_2}, for amine catalysis of the reaction, and the intercept, after correction for hydroxide ion catalysis, is the rate constant k_1 for the uncatalyzed (or water-catalyzed) aminolysis, according to the rate law of eq. 1. This is essentially the same

$$k_{obsd} - k_0 = k_1[RNH_2] + k_{RNH_2}[RNH_2]^2 + k_{OH^-}[RNH_2][OH^-] \quad (1)$$

type of behavior as was previously observed for glycine.[3] In deuterium oxide solution the observed pseudo-first-order rate constants are decreased (Figure 1, closed circles) and it is apparent that the amine-catalyzed reaction, measured by the slope of the line in Figure 2 (closed circles), is decreased more than the uncatalyzed (or water-catalyzed) reaction, measured by the intercept.

The rate of the reaction of phenyl acetate with methylamine also increases more rapidly with increasing pH than can be accounted for by the increase in the concentration of free amine, even if allowance is made for amine catalysis of the reaction. The apparent second-order rate constants for the reaction are plotted as a function of hydroxide ion activity in Figure 3. The

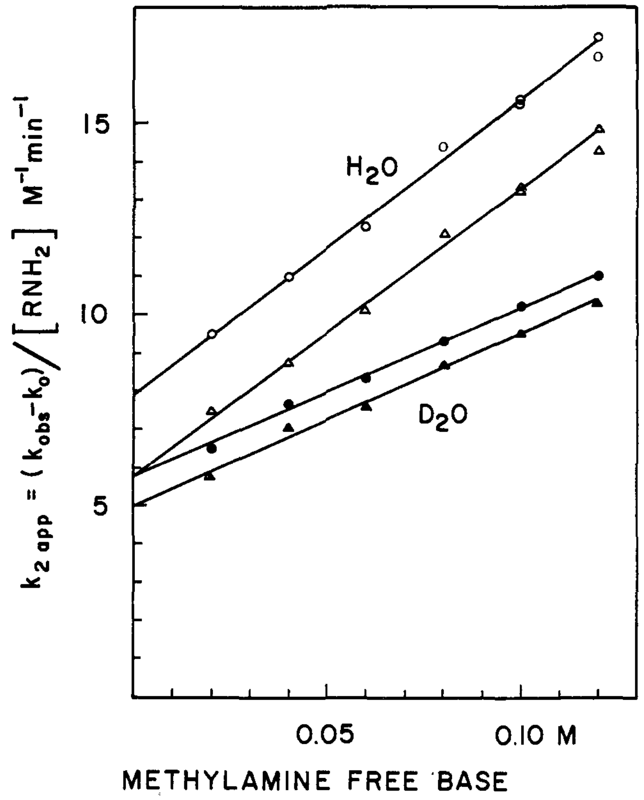

Figure 2. Apparent second-order rate constants for the reaction of phenyl acetate with methylamine at 5°, ionic strength 1.0 *M*: circles, uncorrected values; triangles, corrected for hydroxide ion catalysis; open symbols, in water; closed symbols, in deuterium oxide.

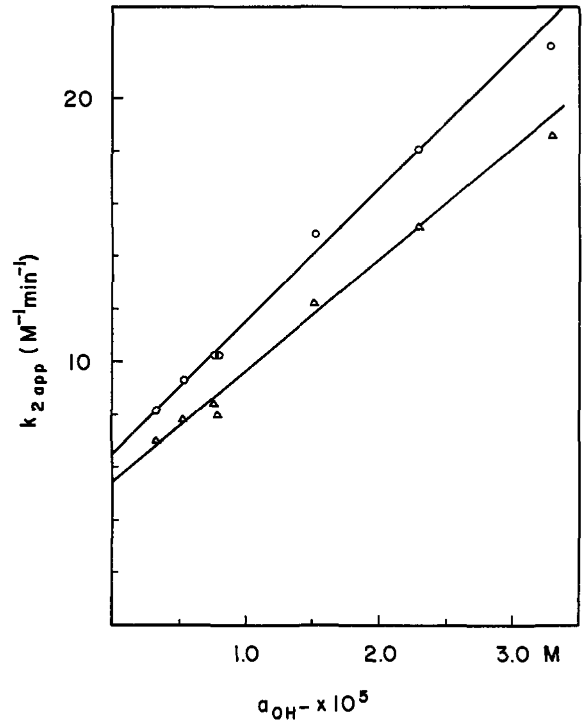

Figure 3. Apparent second-order rate constants, $k_{2app} = (k_{obsd} - k_0)/[RNH_2]$, for the reaction of methylamine (total buffer concentration 0.05 *M*) with phenyl acetate as a function of hydroxide ion activity at 5°, ionic strength 1.0 *M*: circles, uncorrected values; triangles, corrected for amine catalysis.

Table I. Rate Constants for the Aminolysis of Phenyl Acetate[a]

Amine	Temp., °C.	Fraction of free base	No. of points[b]	Concn. range,[c] M	k_1, M^{-1} min.$^{-1}$	k_{RNH_2}, M^{-2} min.$^{-1}$	k_{OH^-}, M^{-2} min.$^{-1}$
CH_3NH_2	5	0.4	6	0.05–0.3	5.6	75	
	5	0.3–0.9	7	0.05			4500
	25	0.4	6	0.05–0.3	17	122	
	25	0.3–0.9	4	0.05			7000
in D_2O	5	0.4	6	0.05–0.3	4.9	44	
	5	0.3–0.9	4	0.1			2010
$C_2H_5NH_2$	5	0.4	6	0.1–0.6	2.1	9.5	
	5	0.3–0.9	4	0.1			770
n-$C_3H_7NH_2$	5	0.4	6	0.1–0.6	1.8	5.7	
	5	0.3–0.9	4	0.1			730
n-$C_4H_9NH_2$	5	0.4	9	0.1–1.0	2.5	4.2	
	5	0.3–0.9	4	0.1			510

[a] Ionic strength maintained at 1.0 M with potassium chloride. [b] Reactions with half-times of less than 1 min. were generally run in duplicate. [c] Total buffer concentration.

upper line (circles) represents the uncorrected rate constants and the lower line (triangles) shows the rate constants after correction for catalysis by free amine. The slope of the lower line is k_{OH^-}, the rate constant for catalysis of the aminolysis by hydroxide ion (eq. 1). This value and a corresponding value for k_{OD^-}, which was obtained from similar experiments in deuterium oxide, were used to correct the data shown in Figure 2 for the contribution of hydroxide ion catalysis to the observed rate; the corrected values are shown by the triangles in Figure 2.

The final values of k_1, k_{RNH_2}, and k_{OH^-} for the methylamine reaction are summarized in Table I. The results of similar experiments with ethylamine, n-propylamine, and n-butylamine are also given in Table I. The values of k_{OH^-} are not of high precision because of assumptions regarding the dependence of equilibrium constants on salt effects and temperature (see the Experimental Section and Discussion). However, they are sufficient to demonstrate the existence and approximate magnitude of this term and to make the relatively small corrections required for the calculation of k_1 and k_{RNH_2} (see Figure 2).

The effects of added solvents and salts on the rate of the reaction of phenyl acetate with 0.1 M methylamine buffer are shown in Table II. The effect of tetrahydrofuran and ethanol is to *decrease* the rate. The rate acceleration that is observed with increasing amine concentration, therefore, does not appear to be a nonspecific solvent effect caused by the replacement of water by a less polar molecule. The effect of 1 M potassium chloride is to increase the rate, while tetramethylammonium chloride, which may be a model for the amine hydrochlorides in the reaction mixtures, has little effect on the rate. These salt effects are considerably larger than those observed with the charged amine, glycine.[3] The fact that potassium chloride increases the rate, while tetramethylammonium chloride has little effect, indicates that the rate increases which have been ascribed to general base catalysis are not caused by the replacement of potassium chloride by amine hydrochloride in the reaction mixtures as the buffer concentration is increased. In fact, the changing composition of the salt in the reaction mixture will tend to mask general base catalysis. This effect is of little importance for reactions which are fast and which show much catalysis; the methylamine data shown in Figures 1 and 2, for example, were obtained with reaction mixtures in which the potassium chloride concentration varied only from 0.82 to 0.97 M. However, for bulkier, less reactive amines, such as n-butylamine, which were studied in more concentrated solution, this effect is expected to be of greater significance.

Table II. Effect of Salts and Solvents on the Reaction of Phenyl Acetate with 0.1 M Methylamine Buffer, 40% Free Base, at 5°

	k_{obsd}, min.$^{-1}$
Control	0.33
+ Tetrahydrofuran, 10% (v./v.)	0.18
+ Ethanol, 10% (v./v.)	0.21
+ KCl, 1 M	0.43
+ $(CH_3)_4NCl$, 1 M	0.30

Our results are in agreement with those of Bruice and Willis[5] in that general base catalysis of the n-butylamine reaction is difficult to measure at 25° and an ionic strength maintained at 1.0 M with potassium chloride, because of the small magnitude of the catalytic constant for this amine. However, if tetramethylammonium chloride, which has little effect on the rate, is accepted as a model for butylammonium chloride, it may be more valid to measure the reaction in the absence of potassium chloride and neglect the effect of the changing ionic strength on the rate. The results of such an experiment at 25° are shown in Figure 4. It is apparent that the reaction is more than first order in respect to n-butylamine under these conditions (lower line) and that the apparent second-order rate constants increase with increasing amine concentration before and after correction for the hydroxide ion catalyzed reaction (upper lines). The increase in the apparent second-order rate constants is not strictly linear in respect to amine concentration, and the arbitrary straight line which is drawn through the corrected points gives values of k_1 and k_{RNH_2} of 5.0 M^{-1} min.$^{-1}$ and 6.2 M^{-2} min.$^{-1}$, respectively. It is possible that the leveling off of these points with increasing amine concentration reflects an inhibition of the reaction which is caused by a nonspecific solvent effect of concentrated butylamine, similar to that observed with tetrahydrofuran and ethanol. If this interpretation is correct, the true value of k_1 would be slightly smaller and that of k_{RNH_2} larger than these values. The dashed line in Figure 4 shows the contribution of the uncatalyzed reaction to the observed pseudo-first-order rate constants; the difference between this line and the observed rate constants represents the amount of catalysis of the reaction.

The reaction of the still more hindered amine, isopropylamine, with phenyl acetate at 25° and ionic strength 1.0 *M* was found to proceed at a rate which is linear in respect to buffer concentration, 40% free base, from 0.1 to 1.0 *M* with a second-order rate constant of 0.46 M^{-1} min.$^{-1}$ and no evidence for general base catalysis. Solutions of *n*-hexylamine buffers, 40% free base, were found to be clear at 0.1 *M* and above 0.4 *M*, but were turbid at intermediate concentrations. The pseudo-first-order rate constants for the reaction of phenyl acetate were found to be constant at 2.4 ± 0.2 min.$^{-1}$ in buffer solutions between 0.4 and 1.0 *M*. This unexpectedly rapid reaction probably represents a reaction which occurs within a micellar phase,[8] as well as the reaction with free amine in solution.

Discussion

Our experimental results are in agreement with those of Bruice and Willis in that the contribution of general base catalysis to the rate of the reaction of butylamine with phenyl acetate is sufficiently small that it is difficult to be certain whether such catalysis exists at 25° and an ionic strength maintained at 1.0 *M* with potassium chloride.[5] However, this situation appears to represent a special case and, in contrast to these workers, we are led to the conclusion that general base catalysis is significant for the reaction of simple alkylamines with phenyl acetate, unless special circumstances mask its significance. This conclusion is based on the following points.

1. General base catalysis is readily detectable with methylamine, ethylamine, *n*-propylamine, and *n*-butylamine at 5°. In this series, as well as that studied previously,[3] the ratio k_1/k_{RNH_2} increases with increasing size of the alkyl substituent(s) on the amine. Molecular models suggest that a transition state for general base catalyzed aminolysis which contains the elements of phenyl acetate and two molecules of amine is crowded, so that it is not surprising that the k_{RNH_2} term, for general base catalysis, decreases more rapidly than the k_1 term with increasing size of the amine.

2. The rate constants for the amines examined in this study were measured at 5°, rather than at 25°, in order to permit measurement of the reaction rates of such reactive amines as methylamine without the use of special equipment. Since the temperature dependence of the general base catalyzed reaction is considerably smaller than that of the uncatalyzed reaction, the contribution of the catalyzed reaction is increased and becomes easier to measure at low temperatures. The values of ΔH^* and ΔS^* for the amine-catalyzed reaction of phenyl acetate with methylamine are 3400 cal./mole and -45.6 e.u., while the corresponding values for the uncatalyzed reaction are 8500 cal./mole and -32.4 e.u., respectively. Bruice and Benkovic have shown previously that both the enthalpy and entropy of activation are decreased in the general base catalyzed reactions of hydrazine and imidazole with phenyl acetate, as compared to the uncatalyzed reactions.[9] The large negative entropy presumably reflects the orientation requirements of the several participating molecules in the catalyzed reaction[10] and the decreased enthalpy in the k_{RNH_2}, compared to the k_1 term, reflects the more facile reaction path which is made possible by amine catalysis; if no such decrease in enthalpy occurred, the catalyzed reaction would occur at too slow a rate to be detectable.[9]

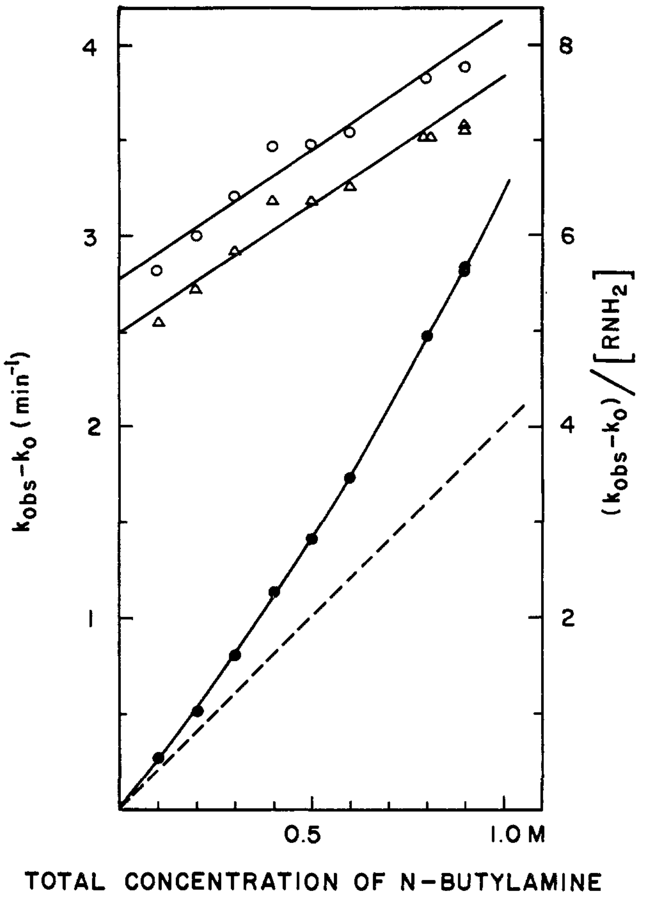

Figure 4. The reaction of phenyl acetate with *n*-butylamine, 40% free base, at 25°: lower line, pseudo-first-order rate constants; upper lines, apparent second-order rate constants; open circles, uncorrected values; triangles, corrected for hydroxide ion catalysis; dashed line, contribution of the uncatalyzed reaction to the observed pseudo-first-order rate constants.

3. The rate of the aminolysis of phenyl acetate by methylamine is decreased by the addition of tetrahydrofuran and ethanol and is increased by the addition of potassium chloride to the reaction medium. This suggests that the transition state is more polar than the reactants. The addition of relatively high concentrations of butylamine to the reaction mixture is expected to cause an inhibition of the rate by a similar nonspecific solvent effect, and this inhibition will tend to mask catalysis by butylamine.

4. Measurements of aminolysis rates are generally carried out with increasing concentrations of amine–

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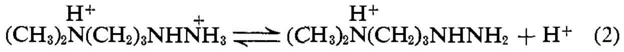
[8] M. T. A. Behme, J. G. Fullington, R. Noel, and E. H. Cordes, *J. Am. Chem. Soc.*, 87, 266 (1965).

[9] T. C. Bruice and S. J. Benkovic, *ibid.*, 86, 418 (1964).

[10] The "uncatalyzed" reaction may, in fact, be a water-catalyzed reaction. If the rate constant for this reaction is expressed as a third-order constant by dividing k_1 by the water concentration, ΔS^* will be correspondingly more negative; this will have the effect of reducing the difference between ΔS^* for this term and for k_{RNH_2}.

amine hydrochloride buffers and with the ionic strength maintained at a constant value with potassium chloride, in an attempt to separate specific buffer effects from ionic strength effects on the reaction. The data shown in Table II suggest that specific salt effects, particularly the greater salting-out effect of potassium chloride than of alkylammonium chlorides,[11] may be significant in such rate measurements. The importance of this effect will vary with the reaction conditions but, in general, it will tend to mask general base catalysis if the potassium chloride concentration is decreased at the same time that the amine buffer concentration is increased. If it is assumed that *n*-butylamine hydrochloride, like tetramethylammonium chloride, has no significant effect on the rate of phenyl acetate aminolysis, general base catalysis by even this relatively unreactive amine becomes detectable in the absence of potassium chloride at 25° (Figure 4). If tetramethylammonium chloride is taken as a model for all amine hydrochlorides, it might be desirable generally to determine rate constants for general base catalysis in a medium in which the ionic strength is maintained constant with this salt. It is probable that rate constants for general base catalysis, measured under these conditions, would be somewhat larger than those reported in Table I, which were determined in the presence of potassium chloride for comparison with previous results.[3] In general, the absolute values of rate constants for the relatively complex kinetic behavior of reactions of this kind will be dependent on the experimental conditions used for their determination and on assumptions regarding the nature of specific salt and solvent effects. Thus, it may be relatively easy to demonstrate the existence of general base or hydroxide ion catalysis of a reaction, but impossible to determine precise rate constants which are independent of the conditions of measurement.

Bruice and Willis measured the rate constant for the reaction of 3-dimethylaminopropylhydrazine with phenyl acetate and suggested that this reaction occurred at a rate which is 10^3 faster than expected, because of intramolecular general base catalysis by the dimethylamino group of the attack of hydrazine. This factor of 10^3 was based on a pK_a' value of 6.83 for the dissociation of the protonated hydrazine portion of the dication of the molecule according to eq. 2. Since the reaction of the neutral molecule was studied, a more



$$(CH_3)_2\overset{H^+}{N}(CH_2)_3NH\overset{+}{N}H_3 \rightleftharpoons (CH_3)_2\overset{H^+}{N}(CH_2)_3NHNH_2 + H^+ \quad (2)$$

appropriate comparison would be based on the pK_a' value for the hydrazine portion of the species which contains a neutral dimethylamine group (eq. 3). This dissociation constant cannot be measured directly be-

$$(CH_3)_2N(CH_2)_3NHN\overset{+}{H}_3 \rightleftharpoons (CH_3)_2N(CH_2)_3NHNH_2 + H^+ \quad (3)$$

cause of the greater basicity of the dimethylamino group but, in the absence of the perturbing effect of the protonated dimethylamino group, it would be expected to be similar to that of hydrazine itself. The rate constant for the reaction with phenyl acetate of 3-dimethylaminopropylhydrazine is also similar to that of hydrazine itself, and is less than one order of magnitude larger than that of methylhydrazine. It would appear that the possible existence and magnitude of intramolecular general base catalysis have not yet been clearly evaluated for this reaction.[12]

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[11] F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).

[12] This point was brought to our attention by Dr. Michael Caplow.

Aminolysis of Phenyl Acetates in Aqueous Solutions. V.[1] Hypernucleophilicity Associated with Constraint of Bond Angles

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Abstract: The reactions of phenyl acetate with 3-hydroxymethyl-3-phenylazetidine, 3-methyl-3-phenylazetidine, and aziridine in water ($T = 30°$, $\mu = 1.0$) are characterized by large positive deviations from a Brønsted plot (log $k_{\text{rate}} = 0.78pK_a - 8$) derived for primary and second aryaliphatic amines. The enhanced nucleophilicity of the cyclic amines is attributed to C–N–C bond angle constraint.

The observation of Testa and co-workers[5] that 3-hydroxymethyl-3-phenylazetidine (I) is acetylated at the 1-position on extraction from aqueous solution by ethyl acetate suggested that the unusually high reactivity of the cyclic amine might be due to participa-

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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 S. J. Benkovic, *ibid.*, **85**, 1 (1963); (c) *ibid.*, **86**, 418 (1964); (d) T. C. Bruice and R. G. Willis, *ibid.*, **87**, 531 (1965).

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[4] The portion of this work carried out by L. R. F. and T. C. B. was supported by a grant from the National Institutes of Health to T. C. B.

[5] E. Testa, L. Fontenella, and M. Bovara, *Ann.*, **671**, 97 (1964).