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 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 because 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]

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

$$(CH_3)_2N(CH_2)_3NH\overset{+}{N}H_3 \rightleftharpoons (CH_3)_2N(CH_2)_3NHNH_2 + H^+ \quad (3)$$

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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

Leo R. Fedor,[2a] Thomas C. Bruice,[3] Kenneth L. Kirk,[2b] and Jerrold Meinwald

Contribution from the Departments of Chemistry, University of California at Santa Barbara, Santa Barbara, California,[4] and Cornell University, Ithaca, New York.
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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 $k_{\text{rate}} = 0.78\text{p}K_a - 8$) 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).

[2] (a) Postdoctoral Fellow, University of California, Santa Barbara, Calif.; (b) National Institutes of Health Postdoctoral Trainee, Cornell University, Ithaca, N. Y.

[3] To whom inquiries concerning this paper should be directed.

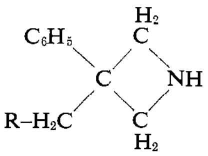
[4] The portion of this work carried out by L. R. F. and T. C. B. was supported by a grant from the National Institutes of Health to T. C. B.

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

Table I. Tabulation of Rate Data for the Reaction of Phenyl Acetate with 3-Hydroxymethyl-3-phenylazetidine (I) with 3-Methyl-3-phenylazetidine (II) and with Aziridine (III) in Water[a]

Nucleophile	pK_a'	Rate term	Rate constants[b]	pH range	No. of pH values	No. of k_{obsd}	Concn. range of nucleophile
I	9.95	k_2[I][E]	63	8.60–10.01	6	29	0.005–0.040
		k_3[I][OH$^\ominus$][E]	2.39 × 10^5				
II	10.38	k_2[II][E]	184	8.97–10.20	6	24	0.0015–0.012
		k_3[II][OH$^\ominus$][E]	5.48 × 10^5				
III	8.01	k_2[III][E]	3 ± 0.5	7.48–8.62	5	15	0.1–0.6

[a] $T = 30°$; $\mu = 1.0\ M$; aqueous solution. [b] The rate constants are given in units of minutes and M.



I, R = OH
II, R = H

tion by the hydroxyl group or to C–N–C bond angle constraint. To determine the magnitude and causitive factor of the enhanced nucleophilicity of I, the reactions of I and of 3-methyl-3-phenylazetidine (II) as well as aziridine (III) with phenyl acetate were examined. Phenyl acetate was chosen as substrate because its reactivity with a number of amines is known,[1d,6] providing a reference for evaluation of the nucleophilicities of the cyclic amines used in this study.

Experimental Section

Materials. Phenyl acetate, b.p. 195–196°, was distilled before use from a sample prepared for a previous study.[7] 3-Hydroxymethyl-3-phenylazetidine, m.p. 134.5–135.5° (lit.[5] m.p. 135–137°), and 3-methyl-3-phenylazetidine hydrochloride, m.p. 151–152° (lit.[8] m.p. 155°), as well as 1-acetyl-3-hydroxymethyl-3-phenylazetidine, m.p. 120–120.5° (lit.[5] m.p. 120–121°), were prepared by literature procedures and stored over P_2O_5. Aziridine, b.p. 56–57° (760 mm.) (lit.[9] b.p. 55–56°), was prepared by the method of Wenker[9] and was stored over sodium hydroxide pellets at 3° until used. Dead air space in the container was filled with dry nitrogen and caution was exercised in handling the amine which is toxic. Trimethylamine hydrochloride (Eastman White Label) was crystallized from methanol–ether and stored over P_2O_5 until used. Inorganic salts were Baker Analyzed reagent. Carbonate-free potassium hydroxide was prepared by the method of Albert and Serjeant.[10]

Apparatus. A Zeiss PMQ II Spectropho spectrophotometer equipped with a thermostated brass cuvette holder, through which was circulated water of constant temperature, was used for kinetic measurements. All pH measurements were made with a Radiometer Model 22 pH meter with a Model PHA 630 Pa scale expander. The combined glass calomel electrode (Radiometer G.K. 2021C) and electrode cell compartment were thermostated at 30 ± 0.1°. Addition and mixing of ester were accomplished as previously described.[11] An audible interval timer was used to signal time for optical density readings taken for rapid rates. pK_a' measurements were determined using a Radiometer TTT 1b autotitrator equipped with a PHA 630 Tá scale expander and a thermostated Metrohm microtitration cell and assembly as described by Bruice and Bradbury.[12]

Kinetics. The appearance of phenolate anion with time was followed spectrophotometrically at 275 mμ ($T = 30°$). Trimethylamine hydrochloride (0.2 M) was used as external buffer to maintain pH in reactions of phenyl acetate with I and II; aziridine supplied its own buffer capacity. Solutions were brought to a calculated ionic strength of 1.0 M with potassium chloride. Deaerated water was used to prepare solutions and ₸ cuvettes of 2.5-ml. capacity were filled to the stopper level with solution. A solution in the reference cell identical with the reaction mixture (minus ester) was used to compensate for absorbance due to reactants. The concentration of nucleophile was always in excess of the concentration of ester (*ca.* 1 × 10^{-4} M) so that pseudo-first-order kinetics were obtained. Reaction rates were followed to a minimum of 3 half-lives. The pH of the reaction solution was always determined at the beginning of each run and was periodically checked after some runs to ensure constancy of pH during runs. Pseudo-first-order rate constants were calculated from the slopes of plots of log (O.D.$_\infty$/(O.D.$_\infty$ − O.D.$_t$)) *vs.* time.

In contrast to the phenyl acetate–azetidines systems, the kinetics of the reactions of phenyl acetate with aziridine at low amine concentrations were unsatisfactory. The difficulties were attributed to instability of aziridine in solution.[13] The following generalities concerning aqueous aziridine solutions in the pH range 7.48–8.62 apply: (1) at pH values >pK_a', pH increases with time; at pH values <pK_a', pH decreases with time; (2) pH increases or decreases with time are greatest for the most concentrated solution of a serial dilution; (3) solutions appear to be most stable at pH values close to the pK_a'. To minimize inaccuracies in the rate data for this system, reactions were run at high aziridine concentrations (Table I) and solutions were used as rapidly as possible after their preparation. For rapid reactions pseudo-first-order plots were linear to approximately 2 to 3 half-lives.

pK_a' Determinations. pK_a' determinations were performed potentiometrically ($T = 30°$ unless specified) by the method of Albert and Serjeant[10] employing a correction for hydroxide ions at a calculated ionic strength of 1.0 M with potassium chloride. The pH meter was calibrated at pH 9 and 7 with standard buffer solutions and the calibration was checked after each pK_a' determination. Runs in which the meter drift exceeded 0.02 pH unit during titration were discarded. The following pK_a' values were obtained: 3-hydroxymethyl-3-phenylazetidine, 9.95 ± 0.02 (six values); aziridine, 8.01 ± 0.04 (seven values) (lit.[14] 8.04, 25°); 3-methyl-3-phenylazetidine, 10.61 ± 0.05 (21°), 10.48 ± 0.05 (25°), 10.38 ± 0.05 (30°), 10.23 ± 0.05 (35°), 10.14 ± 0.04 (40°) (ten values for each determination). The pK_a' of trimethylamine at 30° is 10.08 extrapolated from the data of Bruice and Benkovic.[1b] The activity of hydroxide ion was calculated from K_w/a_H wherein K_w is the autoprotolysis constant for water. The following values of $-\log K_w$ were employed[15]: 14.133 (21°); 13.996 (25°); 13.833 (30°); 13.680 (35°); 13.534 (40°).

Results[16]

The reactions of phenyl acetate (aqueous 0.2 M trimethylamine buffer; $\mu = 1.0\ M$) at 30° with I

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(15) R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd Ed., Butterworth and Co. (Publishers) Ltd., London, 1959.

(16) Abbreviations used in this study are a_H, hydrogen ion activity determined at the glass electrode; a_{OH}, hydroxide ion activity determined from K_w/a_H wherein K_w is the autoprotolysis constant for

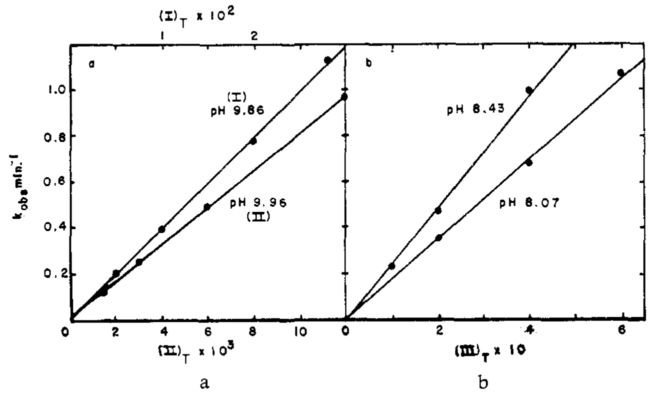

Figure 1. Plots of the pseudo-first-order rate constant *vs.* total concentration of amine for the reaction of phenyl acetate with 3-hydroxymethyl-3-phenylazetidine (I), with 3-methyl-3-phenylazetidine (II), and with aziridine (III) in water at 30°, $\mu = 1.0\ M$.

and with II in the pH range 8.6 to 10.2 are described by eq. 1. At constant pH a plot of k_{obsd} *vs.* total amine

$$d(\text{phenol})/dt = (k_{\text{OH}}[\text{OH}^\ominus] + k_{\text{MA}}[\text{N(CH}_3)_3] + k_2[\text{amine}] + k_3[\text{amine}][\text{OH}^\ominus])[\text{ester}] \quad (1)$$

$$k_{\text{obsd}} = k_{\text{OH}}[\text{OH}^\ominus] + k_{\text{MA}}[\text{N(CH}_3)_3] + k_2[\text{amine}] + k_3[\text{amine}][\text{OH}^\ominus]$$

concentration is linear (Figure 1a) with intercept $k_{\text{OH}}[\text{OH}^\ominus] + k_{\text{MA}}[\text{N(CH}_3)_3]$ and slope $k_2' = k_2(K_a'/(K_a' + a_{\text{H}})) + k_3(K_a'/(K_a' + a_{\text{H}}))[\text{OH}^\ominus]$. No terms second order in amine were detected although the use of low amine concentrations (Table I) in this study might preclude the detection of such terms. The second-order rate constant at 30° for the reaction of phenyl acetate with trimethylamine (k_{MA}) is 0.016 M^{-1} min.$^{-1}$ calculated from the Arrhenius activation energy and the rate constant determined at 20° by Bruice and Benkovic.[1b] The contribution of trimethylamine to the pseudo-first-order rate constants in the pH range examined is practically negligible. Also, no significant rate increase, beyond that anticipated from an ionic strength effect, was observed in 0.1 to 0.4 M trimethylamine solutions containing I or II.[17] The second-order rate constant for alkaline hydrolysis of phenyl acetate is 223 M^{-1} min.$^{-1}$.[1a]

At each constant pH, plots of k_2', divided by the mole fraction of free amine $(K_a'/(K_a' + a_{\text{H}}))$ *vs.* K_w/a_{H} are linear with intercept k_2 and slope k_3 (Figure 2). For I, $k_2 = 63\ M^{-1}$ min.$^{-1}$ and $k_3 = 2.39 \times 10^5$ M^{-2} min.$^{-1}$; for II, $k_2 = 184\ M^{-1}$ min.$^{-1}$ and $k_3 = 5.48 \times 10^5\ M^{-2}$ min.$^{-1}$. The values for the rate constants were determined by the method of least squares and the rate data are given in Table I.

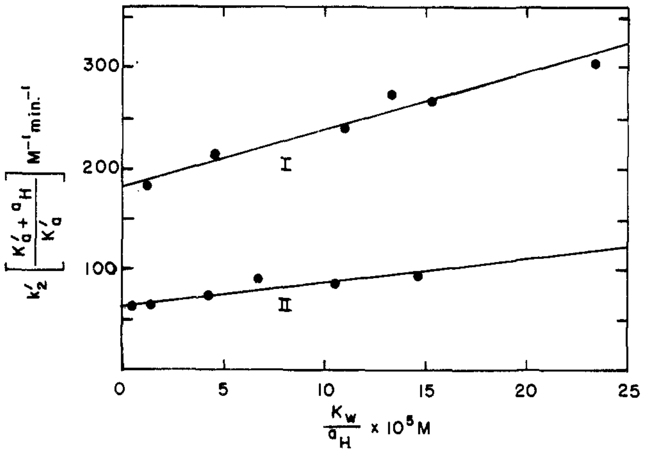

Figure 2. Plots of the acidity-dependent apparent second-order rate constants *vs.* K_w/a_H for the reaction of phenylacetate with 3-hydroxymethyl-3-phenylazetidine (I) and with 3-methyl-3-phenylazetidine (II) in water at 30°, $\mu = 1.0\ M$.

The reaction of phenyl acetate with aziridine (III) in the pH range 7.48 to 8.62 is described by

$$d(\text{phenol})/dt = k_2[\text{amine}][\text{ester}] \quad (2)$$

$$k_{\text{obsd}} = k_2[\text{amine}]$$

At constant pH (see the Experimental Section) plots of k_{obsd} *vs.* total amine concentration are linear (Figure 1b) with 0 intercept and slope $k_2' = k_2(K_a'/(K_a' + a_{\text{H}}))$. For several pH values $k_2'[(K_a' + a_{\text{H}})/K_a'] = k_2$ is constant and has the value $3 \pm 0.5\ M^{-1}$ min.$^{-1}$ (Table I). No term first order in aziridine and first order in hydroxide ion *i.e.*, k_3, was detected above the aminolysis term k_2.

The relationship of log K_a' to absolute temperature for 3-methyl-3-phenylazetidine (see the Experimental Section) is given by the least-squares equation from which may be calculated $\Delta H_i = 10.46$ kcal. mole^{-1}.

$$\log K_a' = -2.286 \times 10^3 \frac{1}{T} - 2.83 \quad (3)$$

At 25° $\Delta S_i = -12.9$ e.u.

Discussion

The stable product obtained on extraction of I from aqueous ethyl acetate solution is the amide.[18] The ease with which this displacement of ethoxide from ethyl acetate occurs suggested that possibly the hydroxyl group of I participates in the aminolysis reaction. Perhaps the simplest way of determining the role of the hydroxyl group of I in the aminolysis reaction is to compare the kinetics for the aminolysis of phenyl acetate by I and II.

The Brønsted plot for the aminolysis of phenyl acetate by primary and secondary aliphatic amines is described by eq. 4.[1d,2] On the basis of this equation,

$$\log k_{\text{rate}}\ (25°) = 0.78\text{p}K_a' - 8 \quad (4)$$

the pK_a' values for I and II, and the values for k_2 in Table I, it can be shown that I is *ca.* 120 times and II is *ca.* 180 times more reactive than is predicted from the Brønsted plot. The fact that the deoxy compound II

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water; k_{obsd}, the pseudo-first-order rate constant in units of min.$^{-1}$; K_a', the apparent dissociation constant for the conjugate acid of an amine; k_{OH}, the second-order rate constant for alkaline hydrolysis of phenyl acetate; k_{MA}, the second-order rate constant for reaction of phenyl acetate with trimethylamine; k_2', the acidity-dependent apparent second-order rate constant derived from slopes of plots of k_{obsd} *vs.* total amine concentration; k_2, the true second-order rate constant for reaction of phenyl acetate with amines; k_3, the third-order rate constant for reaction of phenyl acetate with 3,3-disubstituted azetidines catalyzed by hydroxide ion.

(17) In 0.007 M (I) solutions at pH 9.47, the pseudo-first-order rate constants for phenol appearance are 0.124, 0.124, and 0.132 min.$^{-1}$ in 0.1, 0.2, and 0.4 M trimethylamine solutions, respectively; in 0.003 M (II) solutions at pH 9.47 the pseudo-first order rate constants for phenol appearance are 0.080, 0.085, and 0.085 min.$^{-1}$ in 0.1, 0.2, and 0.4 M trimethylamine solution, respectively.

(18) 1-Acetyl-3-hydroxymethyl-3-phenylazetidine has an infrared absorption at 1650 cm.$^{-1}$ (C=O) and 3-acetoxymethyl-3-phenylazetidine hydrochloride has an infrared absorption at 1735 cm.$^{-1}$ (C=O).[5]

exhibits a slightly greater nucleophilicity than I suggests that the hydroxyl group of I does not assist the reaction. On the contrary, there is a tendency for the hydroxyl group to decrease the nucleophilicity of I. Support for this may be found in a comparison of the pK_a' values of I and II which are 9.95 and 10.38, respectively. Thus the greater acidity of the conjugate acid of I may be due to intramolecular hydrogen bonding between the hydroxyl and amine functions. Hence there is no evidence for hydroxyl group participation in the aminolysis of phenyl acetate by I.

The term $k_3[\text{amine}][\text{OH}^\ominus][\text{ester}]$, in the case of I, might be due to hydroxide ion catalyzed aminolysis as generally found at high pH for primary or secondary amines[1d] or alternatively to hydroxide ion catalyzed transesterification as found unequivocally with tris(hydroxymethyl)aminomethane.[19] The near identity of the values of k_3 for I and II establishes this term to represent specific base-catalyzed aminolysis. Therefore, the hydroxymethyl group of I participates not at all in its modes of reaction with ester.

The enhanced nucleophilicity of I and of II may be attributed to steric constraint of the covalent bonds in the four-membered ring. The resulting enhancement in nucleophilicity is comparable to that produced by the α-effect.[20] If the suggestion that enhanced nucleophilicity of I and of II toward phenyl acetate is due to constraint of covalent bonds in azetidines, then enhanced nucleophilicity is anticipated for aziridine (III) toward phenyl acetate since bond angles in III are more constrained than in I and II. On the basis of the Brønsted equation (4) and the pK_a' of aziridine, the predicted second-order rate constant for aminolysis is *ca.* $10^{-2}\ M^{-1}\ \text{min.}^{-1}$; experimentally its value is *ca.* $3\ M^{-1}\ \text{min.}^{-1}$ (Table I). The enhanced nucleophilicity of I, II, and III based on pK_a' must be due to constraint of the C–N–C bond angle. The result of the C–N–C bond angle constraint in I, II, and III is a decrease in pK_a' (compare dimethylamine ($pK_a' = 10.64$) to aziridine ($pK_a' = 8.04$) and diethylamine ($pK_a' = 10.98$)[21] to 3-methyl-3-phenylazetidine ($pK_a' = 10.38$) due to the increased s character of the lone pair of electrons. This decrease in basicity toward the proton is accompanied by an increase in nucleophilicity toward the ester carbonyl carbon. Thus aziridine has a nucleophilicity anticipated for an amine of $pK_a' =$ *ca.* 11. Increased nucleophilicity with decrease of C–N–C bond angle is a probable explanation for the greater nucleophilicity of imidazoles compared with pyridines.[22,23]

Decrease in "F strain"[24] as a contributing factor to the enhanced nucleophilicity of aziridine and of 3,3-disubstituted azetidines is difficult to establish. Thus ammonia ($pK_a' = 9.21$, $k_2 = 0.14\ M^{-1}\ \text{min.}^{-1}$)[6] and dimethylamine ($pK_a' = 10.64$, $k_2 = 4.5\ M^{-1}\ \text{min.}^{-1}$)[6] fit a single Brønsted plot for primary and secondary amines. However, it is known[25] that the hydrogens of ammonia are heavily solvated *via* hydrogen bonding to water molecules and, therefore, their effective size may approach that of a methyl group. In contrast trimethylamine exhibits a large negative deviation from the Brønsted plot of eq. 4.

The entropy of dissociation of 3-methyl-3-phenylazetidinium ion determined in this study (−12.9 e.u. at 25°) is not markedly different from that of dimethylamine (−9.5 e.u. at 25°).[26] Thus enhanced nucleophilicity of azetidines probably is not due to any abnormal ground-state solvation.[25] Searles, *et al.*,[14] have determined the entropies and enthalpies of dissociation of several cyclic amines. While aziridine and azetidine have identical $\Delta H°$ values (10.5 kcal. mole^{-1}), these compounds possess markedly different entropies of dissociation, −2 and −16 e.u., respectively. Searles, *et al.*, have correlated this result with the electron density on the nitrogen atoms of the respective amines and have suggested that the acidity of aziridine is due to electron delocalization in the three-membered ring. The increased value of $\Delta S°$ for aziridine compared with that of azetidine suggests solvation effects may be operative in the ground-state solvation of the former.

Although the Brønsted coefficient β ($\log k_{\text{rate}} = \beta pK_a + C$) has been discussed widely in terms of the position of the transition state along the reaction coordinant,[27] the interpretation of C, which is characteristic for a given type nucleophile reacting with a particular substrate, is more difficult. Thus, the reaction of α,ω-diaminoalkanes or their mono conjugate acids with phenyl acetate is characterized by the same β value found for primary and secondary amines, but a C constant on a Brønsted plot which is *ca.* 1 logarithm unit greater than the intercept constant for the reaction of primary and secondary amines with phenyl acetate.[1d] Since the number of methylene groups separating the amino groups or amino and protonated amino groups vary from $n = 2$ to $n = 6$, intramolecular catalysis does not serve as an explanation. Most likely if a series of azetidines of varying pK_a values were treated with phenyl acetate, the Brønsted β value would be found to be quite similar while C would be 2 logarithm units greater than that established for primary and secondary amines. The inability to generally rationalize the magnitude of C would appear to make an explicit explanation of the enhanced nucleophilicity of I, II, and III tenuous. We feel, however, that the greatest contributing factor to the enhanced nucleophilicity of I, II, and III toward the ester carbonyl group resides in a lessened crowding in the formation of the transition state. This lessened crowding is of greater importance than the increased s character of the nitrogen lone pair in reactions at the ester carbonyl groups but of little importance in determining pK_a. Hence, though pK_a decreases on C–N–C bond angle constraint, nucleophilicity increases.

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