The α Effect. II. Displacements on sp^3 Carbon

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Abstract: The aminolysis of methyl iodide in water has been determined to be first order in methyl iodide and first order in amine free base. The second-order rate constants can be related to the pK_a' of the amines *via* the conventional Brønsted equation for general base catalysis. Hydrazine, methylhydrazine, hydroxylamine, and methoxylamine show no significant positive deviations from the Brønsted plots for other amines, showing the α effect to be inoperative in these nucleophilic displacements on the sp^3 carbon of methyl iodide. This study represents the first attempt to determine if the α effect is operative in nucleophilic attack on sp^3 carbon by nonionic nucleophiles. The aminolysis of *p*-nitrophenyl acetate in acetonitrile has been investigated with the result that the α effect has been found to be operative in this aprotic solvent. This finding eliminates the possibility of solvation changes being responsible for the α effect.

In a previous paper[3] from this laboratory there was provided a summary of the reactions in which enhanced nucleophilicity was attributed to the α effect. Also included was a discussion of the various proposed causes of this effect. From this summary it was apparent that the types of substrates investigated were limited and for some of the cases in which the α effect was proposed not enough data were provided to completely justify its existence. We have, therefore, set about investigating the reactions of amines as nucleophiles and general bases with various types of substrates. In part I it was reported that amines having a heteroatom with an unshared pair of electrons next to the basic nitrogen atom ($HONH_2$, CH_3ONH_2, CH_3NHNH_2, NH_2NH_2) did not show enhanced reactivity as general bases in the conversion of nitroethane to its anion.[4] Thus, enhanced nucleophilicity of these amines due to the α effect is not apparent in this nucleophilic displacement on hydrogen.

According to Edwards and Pearson[5] the factors affecting nucleophilic reactivity, other than the α effect, are basicity and polarizability. In proton abstraction reactions it is anticipated that basicity and not polarizability would be important (but see ref 6). It is generally accepted that polarizability rather than basicity is important in nucleophilic displacements on sp^3 carbon (ref 7, p 42). Other factors of importance are solvation and steric effects. With ionic nucleophiles the separation of solvation and polarizability effects is often difficult since both factors are related to the size of the ion.[7]

In order to ascertain if the α effect is of importance in nucleophilic displacement reactions on sp^3 carbon we have investigated the alkylation of a series of amines with methyl iodide in aqueous solution. The α effect has been noted primarily in kinetic studies carried out in aqueous solution. The only previous justification of an α effect being operative in S_N2 displacements on sp^3 carbon stems from the observation that, in the nucleophilic displacement of Br^- from benzyl bromide, HOO^- was found to be much more effective than the more strongly basic HO^-.[8] In order to determine if the α effect is due to a solvation factor we have also investigated the reactions of *p*-nitrophenyl acetate, a substrate previously shown to be sensitive to the α effect,[9] with several amines in acetonitrile.

Experimental Section

Materials. Methyl iodide (City Chemical Corp.) was redistilled, bp 42–43°. Trifluoroethylamine hydrochloride was prepared according to Bruice, *et al.*[3] Methylamine (40% in water, Eastman Red Label) was diluted with water. Hydrazine was prepared from hydrazine hydrate.[10] Acetonitrile (Eastman Red Label) was distilled twice from phosphorus pentoxide. All other amines or their hydrochlorides were obtained from a previous study.[4]

Apparatus. Absorbance measurements were made on a Zeiss PMQII spectrophotometer equipped with a Zeiler automatic changer, a Zeiss linear-log converter, a Zeiss automatic slit-width adjuster, and a Honeywell recorder. pH Determinations were made with a Radiometer Model 22 pH meter equipped with a PHA 630 scale expander using a Radiometer G.K. 2021 C combined glass–calomel electrode.

Kinetics. All kinetic measurements were carried out at 30 ± 0.1°. For methyl iodide, the general procedure for determining pseudo-first-order rate constants (k_1) was that described previously.[4] The reaction was followed spectrophotometrically, using the absorption of iodide ion at 240 mμ [λ_{max} 227 mμ (ϵ 1.6×10^4)]. A plot of k_1 *vs.* $[N_T]$ (the concentration of amine both as free base and conjugate acid) provided the pH-dependent second-order rate constant (k_2'), which was multiplied by the reciprocal of the mole fraction of the free base present [*i.e.*, $(K_a + a_H)/K_a$] to give the true second-order rate constant (k_2). Each value of k_2 was determined by using four concentrations of N_T (0.5–0.1 *M*) at each of two pH values. Reactions of all amines with methyl iodide followed good first-order kinetics to three or four half-lives. A typical first-order plot is provided in Figure 1.

For *p*-nitrophenyl acetate, solutions of the amines as the free bases in acetonitrile were equilibrated at 30° in 2-ml ₮ cuvettes. One drop of a 10^{-2} *M* solution of the ester in anhydrous acetonitrile was added, and the variation in absorbance at 350 mμ was followed with time. Pseudo-first-order rate constants (k_1) were obtained in the usual fashion, and second-order rate constants (k_2) were obtained as the slopes of plots of k_1 *vs.* amine concentration. For imidazole the plot of k_1 *vs.* amine exhibited upward curvature indicating a term greater than the first power in imidazole. For this case k_1/[amine free base] *vs.* [amine free base] provided as intercept k_2 and as slope the third-order rate constant k_3.

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Results

The second-order rate constants for the reaction of ten amines with methyl iodide in water at 30° are given in Table I, and the relationship of these constants to the pK_a of the amines is shown in Figure 2. It can be seen that hydrazine, hydroxylamine, and methoxylamine show no significant positive deviation from the plot for primary amines and methylhydrazine exhibits but a twofold positive deviation from the line for secondary amines. The differentiation in the rates for primary and secondary amines is similar to that for the rates of the amine general base catalyzed ionization of nitroethane. In both cases the rates for hydrazine and methylhydrazine correlate with those for primary and secondary amines, respectively. The results with methylhydrazine point to the alkylated nitrogen as the nucleophilic seat. No α effect is apparent in the aminolysis of methyl iodide.

Table I. Second-Order Rate Constants for the Displacement of Iodide Ion from Methyl Iodide[a]

Amine	k_2, min^{-1} M^{-1}	pK_a'
1 Methylamine	1.85×10^{-1}	10.62[b]
2 Glycine	1.3×10^{-1}	9.63[c]
3 Hydrazine	1.3×10^{-1}	8.11[c]
4 Glycine ethyl ester	4.6×10^{-2}	7.75[c]
5 Hydroxylamine	2.0×10^{-2}	6.05[c]
6 Trifluoroethylamine	1.5×10^{-2}	5.63[b]
7 Methoxylamine	9.8×10^{-3}	4.85[c]
8 Piperidine	9.2×10^{-1}	11.10[c]
9 Morpholine	3.4×10^{-1}	8.59[c]
10 Methylhydrazine	5.0×10^{-1}	8.14[c]

[a] Solvent H_2O, $T = 30°$, $\mu = 1.0$ with KCl. [b] The pK_a' values for methylamine and 2,2,2-trifluoroethylamine are those employed in ref 3. [c] pK_a' values employed in ref 4. No significant reaction of Cl^- with CH_3I occurs at 1.0 M KCl in water at 30°.

The second-order rate constants for the reactions of six assorted amines with p-nitrophenyl acetate in acetonitrile are given in Table II. A Brønsted plot (not shown) for these rate constants, using the pK_a's of the amines in acetonitrile, shows considerable scatter. However, examination of Table II reveals that the nucleophilicity of hydrazine toward p-nitrophenyl acetate in acetonitrile is considerably greater than anticipated from its pK_a. The α effect is, therefore, apparently significant in this aprotic solvent.

Table II. Second-Order Rate Constants for the Aminolysis of p-Nitrophenyl Acetate in Acetonitrile at 30°

Amine	pK_a in acetonitrile[a]	k_2, min^{-1} M^{-1}
Imidazole	(13.8)[b]	0.2
Hydrazine	16.61	88
Morpholine	16.61	5.7
Benzylamine	16.76	2.3
Propylamine	18.22	18
Piperidine	18.92	170

[a] J. F. Coetzee and G. R. Padmanabhan, *J. Am. Chem. Soc.*, **87**, 5005 (1965). [b] Estimated value from a linear plot of pK_a in water *vs.* pK_a in acetonitrile.

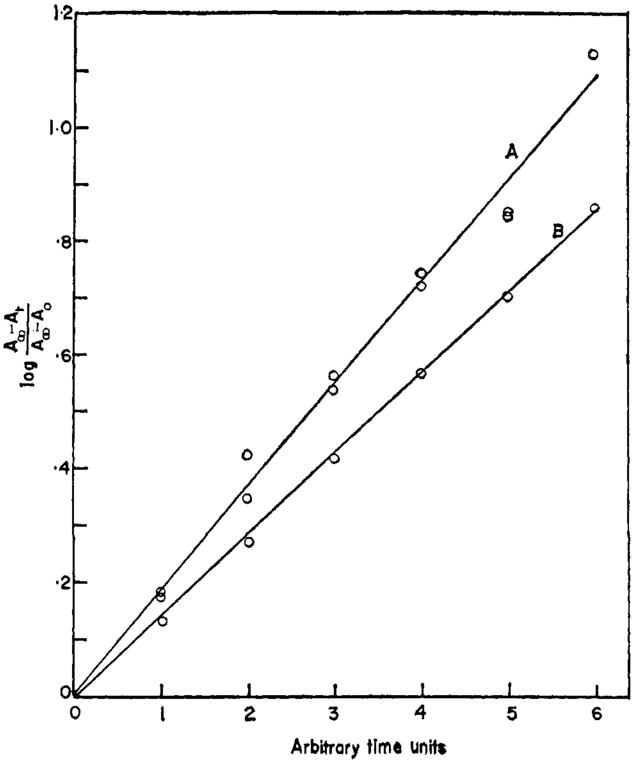

Figure 1. A representative example of the first-order rate plots for the reaction of amines with methyl iodide as followed spectrophotometrically; hydroxylamine at pH 6.87, $\mu = 1.0$, 30°; plot A, $[N_T] = 0.5$ M; plot B, $[N_T] = 0.35$ M.

Discussion

The reaction of all amines investigated with methyl iodide has been found to be first order in amine and first order in substrate. This finding may be compared to the often noted amine or amine conjugate acid general catalyzed aminolysis of phenyl acetate (for a compilation of references see ref 3) and thiolesters.[11-13] If the mechanism of general base catalyzed aminolysis of these esters involves a proton abstraction in the transition state from the nucleophilic amine by the catalyzing amine molecule, then one wonders why this mechanism is not seen with methyl iodide since the free energies of activation for aminolysis of methyl iodide and phenyl acetate are comparable.

The fact that amines which exhibit the α effect do not do so in displacements on methyl iodide or in the general base catalyzed ionization of nitroethane suggests that the α effect is associated with particular types of transition states. A compilation of proposed causes for the α effect has been given elsewhere.[3]

Changes in hydration of the α heteroatom in nucleophilic attack which are greater than the hydration changes on protonation of the amines can also be discarded as causes of the α effect, as the enhanced reactivity of hydrazine toward p-nitrophenyl acetate is still apparent in acetonitrile where this type of stabilization cannot occur. The changes in hydration on protonation for hydrazines and aliphatic amines are comparable as indicated by the values of ΔS_i.[3,14]

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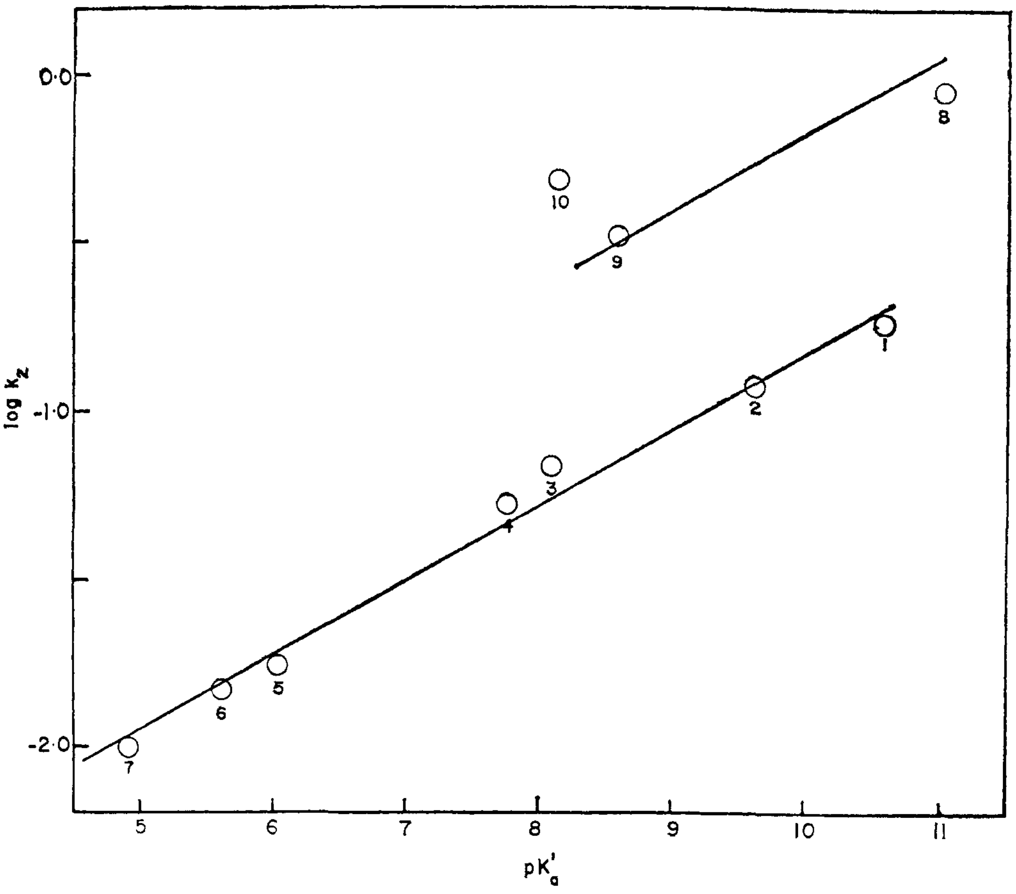

Figure 2. Brønsted plot for the reactions of ten amines with methyl iodide. The numbers refer to the compounds in Table I. The rate constants for hydrazine has been divided by two.

From this work it is impossible to provide any explanation for the *α* effect for hydrazine, hydroxylamine, methoxylamine, or methylhydrazine. Additional studies with the series of amines dealt with herein and other types of substrates are required. From what is presently known it can be stated that the *α* effect is associated with displacement reactions highly dependent on the basicity of the nucleophile (*i.e.*, large Brønsted slope). These reactions include displacements on phosphoryl halides,[15] thiolesters,[11-13] and phenyl acetates.[3] Reactions in which neither the *α* effect nor basicity (as measured by the Brønsted slope) are of great importance include the aminolyses of methyl iodide and sulfate[16] and phosphate[17] esters. The amine general base catalyzed ionization of nitroethane (Brønsted slope 0.5)[4] may be a special case since nucleophilic attack is on hydrogen. Those substances sensitive to both the *α* effect and basicity represent unsaturated systems which readily undergo addition reactions. The large Brønsted slopes associated with nucleophilic displacements on these substances have generally been considered to indicate a high degree of bond formation in the transition state. This assumption is based on an analogy with the Brønsted treatment of proton transfer reactions.[18] Though this analogy may not be quite correct it follows from the Hammond postulate[19] and the fact that metastable tetrahedral intermediates are formed that bond formation is essentially complete in the transition state. On the basis that the retrograde of the aminolysis of methyl iodide is much slower than the reaction in the forward direction, little bond formation has occurred in the transition state for the forward reaction (assuming a simple one-step S_N2 displacement). Arguments have been presented elsewhere that little bond formation occurs in the transition states associated with the aminolysis of phosphate and sulfate esters.[17,18]

In summary, experiments to date associate the *α* effect with considerable bond formation in the transition state. This statement does not apply to proton abstraction from carbon. We have shown the *α* effect not to be due to a solvation phenomenon. Further experimental work is required in order to determine if these statements apply equally well to nucleophiles other than amines.

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