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Kinetic Studies of Bimolecular Nucleophilic Substitution. VI.*[1] Rates of the Menschtkin Reaction of Methyl Iodide with Methylamines and Ammonia in Aqueous Solutions

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The kinetics of the reactions of trimethylamine, dimethylamine, methylamine, and ammonia with methyl iodide in aqueous solutions have been investigated at temperatures ranging from 0 to 40°C. Kinetic analyses of the consecutive methylations of dimethylamine and methylamine have been conducted according to the method of French.[3] In the case of ammonia a standard second-order kinetic treatment can be successfully used because of the relative sluggishness of the first stage as compared with the succeeding stages. The observed rates are in the sequence: $Me_3N > Me_2NH > MeNH_2 > NH_3$. The factors which affect this rate sequence are discussed.

Although many investigations of the Menschtkin reaction have been reported in the literature, on the effect of varying the structure of amines from the primary to the tertiary there have been only fragmentary reports,[2] except for one relevant paper,[1] in which the nucleophlicities were investigated comparatively in each series of *n*-butyl- and *n*-propyl-amines.

We have measured the rates of the reactions of methyl iodide with a series of methylamines and ammonia in aqueous solutions in order to obtain an additional example for the comparions of the nucleophilicities of primary, secondary, and tertiary amines. The methylamines were chosen for study along with ammonia because of their representative structures in a homologous series of aliphatic amines, and also because it is, fortunately, feasible to make a kinetic analysis of their consecutive bimolecular reactions in view of the reported values for their ionization constants in aqueous solutions. Since methylamine, dimethylamine, and ammonia, expect for trimethylamine, react with methyl iodide consecutively, we treated the kinetic data using the method presented by French[3] for the kinetic analysis of consecutive, irreversible second-order reactions.

The Reaction of Methyl Iodide with Dimethylamine and Trimethylamine. The reactions of methyl iodide with trimethylamine were conducted in aqueous solutions at 0, 10, and 20°C. The rates were followed by titration with a standard aqueous nitric acid, and the data were interpreted by the standard second-order kinetic equation. The results are tabulated in Table 1.

In the case of dimethylamine, the situation is complicated by the possibility of succeeding reactions according to Eqs. (2)—(7):

$$Me_2NH + MeI \rightarrow Me_3\overset{+}{N}H + I^- \tag{1}$$

$$Me_3\overset{+}{N}H + H_2O \rightleftarrows Me_3N + H_3O^+;\quad K = 1.5 \times 10^{-10} \tag{2}$$

$$Me_3N + H_2O \rightleftarrows Me_3\overset{+}{N}H + OH^-;\quad K = 6.3 \times 10^{-5} \tag{3}$$

$$Me_2\overset{+}{N}H_2 + H_2O \rightleftarrows Me_2NH + H_3O^+;\quad K = 1.65 \times 10^{-11} \tag{4}$$

$$Me_2NH + H_2O \rightleftarrows Me_2\overset{+}{N}H_2 + OH^+;\quad K = 6.0 \times 10^{-4} \tag{5}$$

$$Me_3NH^+ + Me_2NH \rightleftarrows Me_3N + Me_2\overset{+}{N}H_2;\quad K = 9.5 \tag{6}$$

[*1] Part V: K. Okamoto, H. Matsuda, H. Kawasaki and H. Shingu, This Bulletin, **40**, 1917 (1967).

1) Wm. A. Henderson, Jr., and C. J. Schultz, *J. Org. Chem.*, **27**, 4643 (1962).

2) See the literature cited in footnote 6 of Ref. 1.

3) D. French, *J. Am. Chem. Soc.*, **72**, 4806 (1956).

TABLE 1. RATE CONSTANTS AND ACTIVATION PARAMETERS OF THE REACTIONS OF 0.05M METHYL IODIDE WITH METHYLAMINES AND AMMONIA IN AQUEOUS SOLUTIONS

Nucleophiles[a]	$10^5 k$ (sec^{-1} M^{-1}) Temp., 0.0°C	10.0°C	20.0°C	30.0°C	40.0°C	E_A kcal/mol	$\Delta S^{\ddagger}$ e. u.	log A
Me_3N	107	413	1410	—	—	20.55	0.986	13.44
Me_2NH	34.8	148	492	—	—	21.55	0.587	13.36
$MeNH_2$	7.25	30.0	113	—	—	21.80	0.436	13.32
NH_3	—	—	4.90	17.5	70.0	23.50	0.063	13.22
NaOH	—	—	3.53	—	—	—	—	—

a) Initial concentrations of the nucleophiles were about 0.100 M.

TABLE 2. THE REACTION OF METHYL IODIDE (0.05 M) WITH DIMETHYLAMINE (0.100 N) IN AN AQUEOUS SOLUTION AT 10.0±0.05°C

Time min	cc 0.0850 N HNO_3/5 cc	$(B_0-B)/A_0$	θ M·min	% Completion	k_1[b] min^{-1} M^{-1}	k^*_1[a] min^{-1} M^{-1}
0.0	3.492	—	—	8.4	—	—
10.0	3.328	0.0470	0.510	15.7	0.0880	0.0935
25.0	3.110	0.109	1.200	25.5	0.0880	0.0967
46.0	2.898	0.170	1.800	35.0	0.0880	0.1040
60.0	2.687	0.230	2.500	44.5	0.0890	0.1057
80.0	2.506	0.282	3.094	52.6	0.0889	0.1089
100	2.363	0.323	3.602	59.0	0.0880	0.1100
120	2.247	0.356	4.050	64.3	0.0890	0.1110
1500	1.450				Av. 0.0885±0.0110	
					Av. $(1.48\pm0.018)\times10^{-3}$ (sec^{-1} M^{-1})	

a) Calculated from $k^*_1 = \dfrac{2.303}{t(A_0-B_0)}\log\dfrac{(A_0-x)B_0}{(B_0-x)A_0}$.

b) $k_2 = 0.248$ (min^{-1} M^{-1}) (see text).

$$Me_3N + MeI \rightarrow Me_4N^+ + I^- \qquad (7)$$

However, by inspection of the values of the equilibrium constants[4] (K's in Eqs. (2)—(6)), especially of the value of K for Eq. (6), some of the equations can be eliminated; accordingly, the total reaction sequence can be represented as follows:

$$Me_2NH + MeI \xrightarrow{k_1} Me_3\overset{+}{N}H + I^- \qquad (1)$$

$$Me_3\overset{+}{N}H + Me_2NH \xrightarrow{\text{fast}} Me_3N + Me_2\overset{+}{N}H_2 \qquad (8)$$

$$Me_3N + MeI \xrightarrow{k_1} Me_4\overset{+}{N} + I^- \qquad (7)$$

In fact, the reaction rate of methyl iodide with hydroxide ion was found to be negligibly small (see Table 1) under the reaction conditions employed. The reaction of methyl iodide with water is also known to be extremely slow at 25°C, *i. e.*, $k=6.87\times10^{-8}$ (sec^{-1}).[5]

Since the reaction (8) proceeds rapidly, the overall reaction sequence may be simplified as follows:

$$Me_2NH + MeI \xrightarrow{k_1} Me_3N$$

$$Me_3N + MeI \xrightarrow{k_2} Me_4N^+$$

The respective rate equations will then be:

$$dA/dt = -2k_1AB \qquad (9)$$

$$dB/dt = -k_1AB - k_2CB \qquad (10)$$

$$dC/dt = k_1AB - k_2CB \qquad (11)$$

where $A=[Me_2NH]$, $B=[MeI]$, $C=[Me_3N]$, and $D=[Me_4N^+]$.

After the slow consumption of dimethylamine by the reaction (1), the rapid consumption of another mole of dimethylamine by the reaction (8) follows. Therefore, the rate of dimethylamine consumption according to the reaction (1) should be twice that shown in Eq. (9).

The analysis of Eqs. (9)—(11) was conducted according to the method of French[3] by introducing the parameter $\theta=\int_0^t Bdt$. Since $d\theta=Bdt$, Eqs. (9)—(11) may be converted into Eqs. (12)—(14):

$$dA/d\theta = -2k_1A \qquad (12)$$

$$dB/d\theta = -k_1A-k_2C \qquad (13)$$

$$dC/d\theta = k_1A-k_2C \qquad (14)$$

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[4] The ionization constants for trimethylamine and dimethylamine were taken to be 6.3×10^{-5} and $6.0\ 10^{-4}$ respectively (D. H. Everett and W. F. K. Wyne-Johnes, *Proc. Roy. Soc.*, **A177**, 499 (1941)).

[5] E. A. Moelwyn-Hughes, *Proc. Roy. Soc. (London)*, **A164**, 295 (1938).

The integration of Eqs. (12)—(14) gives Eqs. (15)—(17):

$$A = A_0 e^{-k_1\theta} \qquad (15)$$

$$(B_0-B) = A_0[1-e^{-2k_1\theta}-\{k_1(e^{-2k_1\theta}-e^{-k_2\theta})/(k_2-2k_1)\}] = A_0 f_{k_2,\theta}(k_1) \qquad (16)$$

$$C = k_1 A_0(e^{-2k_1\theta}-e^{-k_2\theta})/(k_2-2k_1) \qquad (17)$$

The value of k_2 in Eq. (16) has already been established by measuring the rate of the reaction of trimethylamine with methyl iodide. Since the relationship between θ and t can be established by plotting B against t and integrating graphically, the value of k for any θ may be obtained from Eq. (16) by plotting the value of $f_{k_2,\theta}(k_1)$ against appropriate values of k_1 and by seeking the matching point, one which satisfies the relation $(B_0-B)/A_0=f_{k_2,\theta}(k_1)$, on the $f_{k_2,\theta}(k_1)$ curve.

The k_1 values so calculated for the reactions carried out at 0, 10, and 20°C are tabulated in Table 1; the kinetic data for a representative run are shown in Table 2. An integrated second-order constant, *i. e.,* an apparent second-order rate constant, is calculated for the initial stage of the reaction; these results are also shown in Table 2.

It is of interest to note that the apparent second-order rate constant, k^*_1, which was obtained by extrapolating each rate constant at an appropriate interval to the zero point of the reaction time, is consistent with the value of the rate constant calculated from Eq. (16). This is illustrated in Fig. 1.

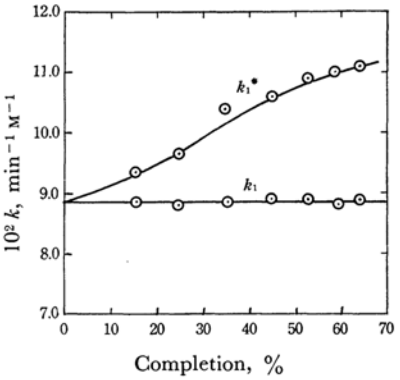

Fig. 1. The rate constants for the reaction of methyl iodide with methylamine in an aqueous solution at 10.0°C.

Reaction of Methyl Iodide with Methylamine. On the basis of an inspection similar to that made of equilibrium relations in the case of the reaction of dimethylamine, the consecutive reactions of methylamine may be expressed as follows:

$$\mathrm{MeNH_2 + MeI \xrightarrow{k_1} Me_2NH_2^+ + I^-} \qquad (18)$$

$$\mathrm{Me_2NH_2^+ + MeNH_2 \xrightarrow{fast} Me_2NH + MeNH_3^+} \qquad (19)$$

$$\mathrm{Me_2NH + MeI \xrightarrow{k_2} Me_3NH^+ + I^-} \qquad (20)$$

$$\mathrm{Me_3NH^+ + MeNH_2 \xrightarrow{fast} Me_3N + MeNH_3^+} \qquad (21)$$

$$\mathrm{Me_3N + MeI \xrightarrow{k_3} Me_3N^+ + I^-} \qquad (22)$$

The over-all rate equations will then be:

$$\mathrm{d}A/\mathrm{d}t = -2k_1AB-k_2CB \qquad (23)$$

$$\mathrm{d}B/\mathrm{d}t = -k_1AB-k_2CB-k_3DB \qquad (24)$$

$$\mathrm{d}C/\mathrm{d}t = k_1AB-k_2CB \qquad (25)$$

$$\mathrm{d}D/\mathrm{d}t = k_2CB-k_3DB \qquad (26)$$

where $A=[\mathrm{MeNH_2}]$, $B=[\mathrm{MeI}]$, $C=[\mathrm{Me_2NH}]$, and $D=[\mathrm{Me_3N}]$.

Since we have already established that in practice k_3 is as much as about three times k_2, one would expect $\mathrm{d}D/\mathrm{d}t$ to be approximately zero under our reaction conditions. Thus, Eqs. (23)—(26) may be converted into the Eqs. (27)—(29) series:

$$\mathrm{d}A/\mathrm{d}t = -2k_1AB-k_2CB \qquad (27)$$

$$\mathrm{d}C/\mathrm{d}t = k_1AB-k_2CB \qquad (28)$$

$$\mathrm{d}B/\mathrm{d}t = -k_1AB-2k_2CB \qquad (29)$$

In a manner similar to that used in the case of dimethylamine, these equations are converted to those of the first-order type by the introduction of the $\theta=\int_0^t B\mathrm{d}t$ parameter:

$$\mathrm{d}A/\mathrm{d}\theta = -2k_1A-k_2C \qquad (20)$$

$$\mathrm{d}B/\mathrm{d}\theta = k_1A-k_2C \qquad (31)$$

$$\mathrm{d}C/\mathrm{d}\theta = -k_1A-2k_2C \qquad (32)$$

After the integration of these equations, A, B and C may be obtained as the functions of θ, μ and m (see Eqs. (33)—(35)) if we express μ and m as follows:

$$\mu = -(2k_1+k_2)/2;\quad m = \{(3/4)k_2^2-(k_1-k_2)^2\}^{1/2}.$$

$$A = e^{\mu\theta}(A_0\cos m\theta + A_0'\sin m\theta) \qquad (35)$$

$$B = B_0-A_0[1-(\sin m\theta)e^{\mu\theta}\{(1/\tan m\theta)+(k_2/2m)\}] \qquad (34)$$

$$C = -e^{\mu\theta}[\{(-2k_1-\mu)A_0-mA_0'\}\cos m\theta+\{(-2k_1-\mu)A_0'+mA_0\}\sin m\theta]/k_2 \qquad (35)$$

where $A_0'=(-2k_1-\mu)A_0/m$.

To the initial stage of the reaction we may apply the following conditions: $\sin m\theta \risingdotseq m$ and $\tan m\theta \risingdotseq m$. Therefore, Eq. (34) may be converted to Eq. (36).

$$B_0-B = A_0[1-e^{\mu\theta}\{1+(k_2\theta/2)\}] \qquad (36)$$

From Eq. (36) we can obtain the following expression for the k_1 value:

$$k_1 = -2.303\{\log 2+\log(a/A_0)-\log(2+k_2\theta)\}(1/\theta)-(1/2)k_2 \qquad (37)$$

where $a=(A_0-B_0+B)$ is the total amount of

TABLE 3. THE REACTION OF METHYL IODIDE (0.05 M) WITH METHYLAMINE (0.100 N) IN AN AQUEOUS SOLUTION AT 10.0±0.05°C

Time min	cc 0.08013 N HNO_3/5 cc (a)	θ M·min	% Completion	k_1 b) $min^{-1} M^{-1}$	k^*_1 a) $min^{-1} M^{-1}$
0.0	6.377	—	3.76	—	—
20.0	6.254	1.021	7.41	0.0182	0.0190
50.0	6.072	2.480	12.80	0.0177	0.0198
110	5.701	5.125	23.80	0.0177	0.0221
170	5.332	7.440	34.80	0.0182	0.0246
230	5.042	9.410	43.45	0.0179	0.0256
290	4.809	11.11	50.30	0.0173	0.0262
∞	3.132 c)			Av. 0.0180	
				Av. 3.00×10^{-4} ($sec^{-1} M^{-1}$)	

a) Calculated from $k^*_1=\dfrac{2.303}{t(A_0-B_0)}\log\dfrac{(A_0-x)B_0}{(B_0-x)A_0}$.

b) $k_2=8.85\times10^{-2}$ ($min^{-1} M^{-1}$) (see text).

c) Measured in a sealed ampoule after 5-hr reaction at 80°C.

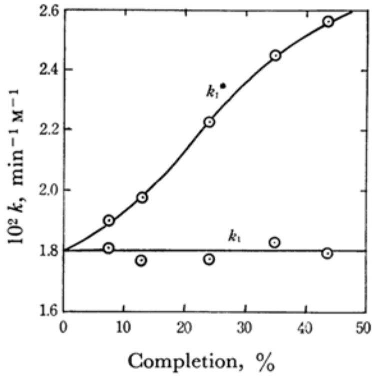

Fig. 2. The rate constants for the reaction of methyl iodide with methylamine in an aqueous solution at 10.0°C.

TABLE 4. THE REACTION OF METHYL IODIDE (0.05M) WITH AMMONIA (0.100 N) IN AN AQUEOUS SOLUTION AT 20.0±0.05°C

Time min	cc 0.08013 N HNO_3/5 cc	% Completion	k^*_2 a) $min^{-1} M^{-1}$
0.0	6.137	2.00	—
12.0	6.129	2.24	0.00294
32.0	6.107	2.80	0.00294
92.0	6.055	4.47	0.00286
152	6.000	6.15	0.00294
192	5.960	7.35	0.00299
∞ c)	2.900		
			0.00294 b)

a) Calculated from

$$k^*_2=\frac{2.303}{t(A_0-B_0)}\log\frac{(A_0-x)B_0}{(B_0-x)A_0}.$$

b) Extrapolated to $t=0$; 4.90×10^{-5} ($sec^{-1} M^{-1}$).

c) Measured in a sealed ampoule after two-days reaction at 80°C.

unchanged amines, an amount which we can determine by titration. Thus we may calculate the value of k_1 from k_2, a and θ. The results obtained from the reactions at 0, 10, and 20°C are listed in Table 1. Simple kinetic data for a representative run are shown in Table 3; the plots of the apparent second-order rate constants, k^*_1, against the completion % are shown in Fig. 2 in order to show that the value of k^*_1 extrapolated to zero conversion is consistent with value of k_1 calculated from Eq. (37).

Reaction of Methyl Iodide with Ammonia. Since ammonia was found to be less reactive toward methyl iodide than the other methylamines, and since the extrapolation method of the apparent second-order rate constants has already given satisfactory results in the cases of methylamine and dimethylamine (see Figs. 1 and 2), we treated the rate data at the initial stage of the reaction by a standard second-order expression. For three runs, carried out at 20, 30, and 40°C respectively, the apparent second-order rate constants were invariable to at least 10% completion. The results are listed in Table 1, while the data for a representative run are shown in Table 4.

The S_N2 Reactivity of Methylamines and Ammonia toward Methyl Iodide. A linear relation is found between the rate constants of the reaction of methyl iodide with methylamines and ammonia and those of the reaction of cyanogen iodide[6] with the same nucleophiles in aqueous solutions. The logarithms of the rate constants are plotted in Fig. 3.

The reactivity sequence, *i. e.*, $Me_3N>Me_2NH>MeNH_2>NH_3$, found in both reactions might be explained in either of two ways; *i. e.*, the inductive effect of methyl substituents on nitrogen, or the polarizability factor of these amines. The plot

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[6] R. O. Griffith, R. S. Jobin and A. McKeown, *Trans. Faraday Soc.*, **34**, 316 (1938).

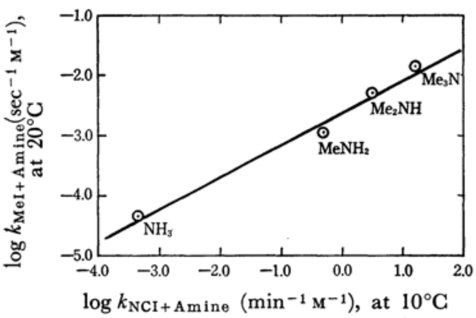

Fig. 3. A comparison of the reactions of methylamines in aqueous solutions.

of the logarithms of the rate constants against Taft's $\sum\sigma^*$,⁷⁾ *i. e.*, a measure of the inductive effect, shows a parallelism between the rates of the reaction of methyl iodide and the inductive effects for amines (Fig. 4). Furthermore, a similar plot against the electric polarization⁸⁾ for these amines, *i. e.*, a measure of the polarizability, also indicates a qualitative correlation almost identical with the $\log k-\sum\sigma^*$ relationship (Fig. 5). However, definitely-curved lines are obtained from the plots in both Figs. 4 and 5. Therefore, both the factors are insufficient to explain the downward drift of the lines from the linearity; the incursion of steric hindrance by methyl substituents should also be taken into consideration. In this connection, it should be noted that, contrary to the rate sequence for methylamines, the rate constants in the reactions of *n*-propyl- and *n*-butyl-amines with ethyl iodide are in the sequence: primary>secondary>tertiary amines.¹⁾ This clearly indicates the existence of a steric retardation in these reactions with ethyl iodide; this problem will be the subject of a forthcoming paper.

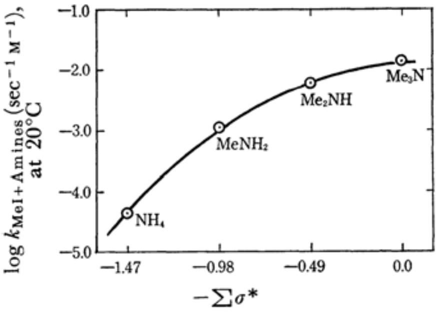

Fig. 4. Relation between the rates of the reactions of methyl iodide with methylamines and Taft's σ^*.

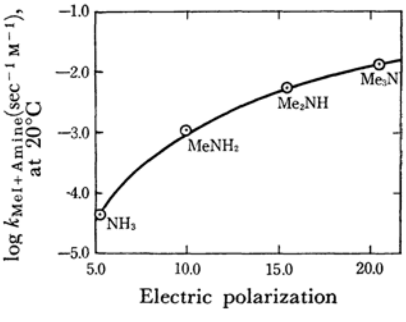

Fig. 5. Relation between the rates of the reactions of methyl iodide with methylamines and the electric polarizations of the amines.

Interestingly, the A constant of the Arrhenius equation (*i. e.*, $\log k=Ae^{-E_a/RT}$) for these reactions are estimated to be about 10^{13} (see Table 1), indicating that the rates for these reactions are not "slow" in aqueous solutions, but are rather "normal." Contrary to this observation in aqueous solutions, most of the Menschtkin reactions previously carried out in such organic solvents as benzene, acetone, ethanol and nitrobenzene, are "slow" reactions, with low Arrhenius constants in the range of 10^3—10^8.⁹⁾

There is no parallelism between the S_N2 reactivity and the pK_a of the conjugate acid of these amines. That is, the rate constants are in the order: $Me_3N>Me_2NH>MeNH_2>NH_3$, whereas the pK_a sequence for these amines is $Me_2NH>MeNH_2>Me_3N>NH_3$.⁴⁾ This discrepancy seems not unexpected, since the nucleophilicity data reflect a kinetic phenomenon, while the basicity data are concerned with an equilibrium phenomenon.

TABLE 5. THE REACTION OF METHYL IODIDE (0.05 M) WITH TRIMETHYLAMINE (0.100 N) IN AN AQUEOUS SOLUTION AT 10.0±0.05°C

Time min	cc 0.08500 N HNO_3/5 cc	% Completion	k_2 $min^{-1} M^{-1}$
0.0	4.403	21.2	—
10.0	4.086	33.9	0.242
20.0	3.813	44.8	0.255
35.0	3.533	56.0	0.249
60.0	3.207	69.0	0.248
80.0	3.025	76.3	0.249
100	2.889	77.6	0.250
120	2.773	86.4	0.249
140	2.736	87.7	0.240
160	2.682	90.0	0.236
2000	2.429		Av. 0.248±0.0012
			Av. $(4.13\pm0.0021)\times10^{-3}$ $(sec^{-1} M^{-1})$

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7) For the values of $\sum\sigma^*$, see H. K. Hall, Jr. *J. Am. Chem. Soc.*, **79**, 5441 (1957).

8) For ammonia, see J. M. A. de Bruyne and C. P. Smith, *ibid.*, **57**, 1203 (1935); for methylamines, see L. G. Grove and S. Sugden, *J. Chem. Soc.*, **1937**, 1779.

9) For a summary, see E. A. Moelwyn-Hughes, "The Kinetics of Reactions in Solution," 2nd ed., Clarendon Press, Oxford (1947), p. 76.

Experimental

Materials. Gaseous methylamines were generated by adding concentrated aqueous solutions of the respective hydrochlorides into 50% aqueous sodium hydroxide, and were then absorbed into water; the concentrated aqueous amine solutions were diluted to an appropriate concentration for each kinetic run. The respective amine hydrochlorides were of a reagent-grade quality and were used as received. A reagent-grade aqueous ammonia was used after appropriate dilution. Methyl iodide, bp 42.0°C, was purified by fractional distillation.

Kinetic Measurements. The reactions carried out at 0 and 10°C were followed by pipetting 5-cc aliquots from the reaction vessel, maintained with ±0.05°C in a thermostat, into a cooled flask and titrating them with standard aqueous nitric acid, using bromothymol blue as an indicator. For the reactions at 40 and 30°C, a sealed-ampoule technique was employed; each ampoule contained a 5-cc aliquot. The rate data were treated as has been described in the text. In the case of trimethylamine, the data were treated by a standard second-order rate equation. The kinetic data for a typical run for trimethylamine are listed in Table 5.