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Kinetic Studies of Bimolecular Nucleophilic Substitution. VII.*1 The Rates of the Menschutkin Reaction of Methyl Iodide with Various Primary, Secondary and Tertiary Amines in Benzene Solvent

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The nucleophilicity of a series of primary, secondary and tertiary amines, *i. e.*, methylamines, ethylamines, *n*-butylamines, ethanolamines and benzylamines, has been investigated by following the kinetics of the reaction of these amines with methyl iodide in benzene solvent. The effect of substituents attached to nitrogen atom on the nucleophilicity of these amines is interpreted in terms of the antagonism between steric retardation and inductive effect. The low nucleophilicity observed in the case of tertiary amines is ascribed to the steric retardation at the expense of the inductive acceleration by the substituents. No linear correlation of the nucleophilicity of amines with the pK_a values has been observed.

There have been published a number of kinetic studies[1] dealing with the nucleophilicity of primary, secondary and tertiary amines. There are, however, not enough data available for the systematic comparison of the effect of varying the amine structure from the primary to the tertiary. Therefore, we have conducted an investigation of the nucleophilicity of various aliphatic amines as reflected by the rate of S_N2 attack on methyl iodide. As a representative non-polar solvent for the Menschutkin reaction, benzene was chosen in order to avoid the complexity due to solvation of the nucleophiles.

One of the purposes of our investigation was to obtain more detailed information about the balance of inductive and steric effect of substituents attached to nitrogen atom. Concerning discrimination of both effects, the reported data indicate that in the case of methylamines[1a] the electronic effect of methyl substituents predominantly outweighs the steric effect in the reactions toward methyl iodide, whereas the reactions of *n*-propyl- and *n*-butyl-amines with ethyl iodide[1b] are controlled by the steric effect of these substituents.

Results and Discussion

The rates of reaction of methyl iodide with methyl-, ethyl-, *n*-butyl-, ethanol- and benzylamines were determined at appropriate temperatures in benzene solvent. Kinetics were followed by measuring the rate of formation of iodide ion by the usual Volhard procedure at 0°C. The rate data for the tertiary amines were interpreted by the standard second-order kinetic equation; the rate data for ammonia, primary and secondary amines were also interpreted by the second-order kinetic equation. However, in the case of the latter amines for which the reactions proceed consequtively, the rate constant values obtained at the early stage of the reaction were extrapolated to zero of the reaction time. As previously reported,[1a] the same approximation to obtain the initial rate constant was successful in the reactions

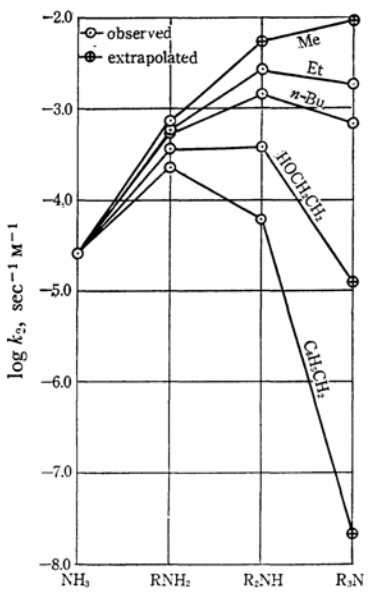

Fig. 1. Rates of the reactions of methyl iodide with various aliphatic amines in benzene solvent at 30.0°C.

*1 Presented at the 6th Organic Reaction Mechanism Symposium of the Chemical Society of Japan, Osaka, October, 1955.

1) a) Part VI of this series: K. Okamoto, S. Fukui and H. Shingu, This Bulletin, **40**, 1920 (1967); b) Wm. A. Henderson, Jr., and C. J. Schultz, *J. Org. Chem.*, **27**, 4643 (1962).

of methyl iodide with methylamine and dimethylamine.

The values of rate constants for the various amines at 30°C are listed in Table 1 together with the activation prarameters; the variation of rate constants due to alkyl substitution on nitrogen atom is illustrated in Fig. 1.

The rate sequence is in the order Me>Et>*n*-Bu>$HOCH_2CH_2$>$C_6H_5CH_2$ for the primary amines. The same order is also observed for secondary and tertiary amines. On the other hand, each series of mono-, di-, and tri-alkylamines falls off the line in the different order, *i. e.*, 3°>2°>1° for methylamines, 2°>3°>1° for ethylamines and *n*-butylamines, 2°>1°>3° for ethanolamines and 3°>2°>1° for benzylamines. These sequences are illustrated by broken lines in Fig. 1.

As is shown by inspection of the Taft's σ^*[2] values for alkyl, benzyl and β-hydroxyethyl substituents, these substituents are more electron-releasing as compared to hydrogen atom. This seems to be reflected on the fact that all primary amines employed have greater nucleophilicity or S_N2 reactivity than ammonia does. However, closer inspection of Fig. 1 reveals that the observed rate sequence for the alkyl substituents, *i. e.*, Me>Et>*n*-Bu, is different from the order which the electronic effect of these alkyl substituents would predict. The sequence indicates that the steric hindrance is surpassing the electronic acceleration.

The steric hindrance has been demostrated more clearly in the case of the secondary and the tertiary amines, as is shown in Fig. 1. Namely, the decrease in reaction rate on increasing the substituent size is greater for tertiary amines than for secondary amines. This phenomenon is obviously steric in nature, since the electronic effect of these substituents predicts the reaction rate increasing with increasing accumulation of the substituents on nitrogen atom. The origin of the steric hindrance may be attributed to the steric requirement of these substituents as previously revealed by Brown and Eldred[3] in the comparison of nucleophlicities of triethylamine and quinuclidine in the reactions toward alkyl iodides.

It is of interest to note that in the case of ethyl iodide, as observed by Henderson and Schultz,[1b] the rate sequence for *n*-butylamines and *n*-propylamines, *i. e.*, 1°>2°>3°, indicate the predominance of the steric hindrance, while the rate sequence for *n*-butylamines toward methyl iodide, *i. e.*, 2°>3°>1° (see Fig. 1), reveals survival of the electronic effect in the case of methyl iodide with less steric requirement.

From the values of activation parameters given in Table 1, it is pointed out that the steric requirements for the smaller substituents on nitrogen atom, *e. g.*, methyl and ethyl substituents, are reflected on the sequence of entropy of activation, whereas those for the larger substituents are shown in the increasing tendency of activation energies. The interpretation of these tendencies remains as a problem for the future.

The pK_a values[4] for various amines, when plotted against the number of the substituent attached to nitrogen atom, display similar tendencies to the case of nucleophilicity for the amines. This is shown by the comparison of Figs. 1 and 2. However, closer inspection of Fig. 2 shows the pK_a orders different from the nucleophilicity order for each series of secondary and tertiary amines. This is not surprising since, as is clearly demonstrated by Hall,[4] the pK_a values are largely controlled by solvation factors, *e. g.*, hydrogen bonding by water molecule, whereas the nucleophilicity is primarily controlled by steric factors as mentioned above.

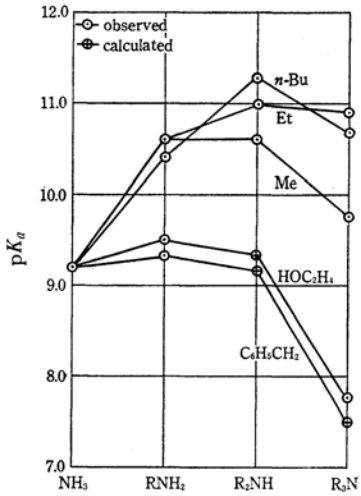

Fig. 2. The values of pK_a's for various aliphatic amines.

Experimental

Materials. Gaseous ammonia, methylamine, dimethylamine, trimethylamine and ethylamine were generated by adding concentrated aqueous solution of the hydrochloride of the respective amine into 50% aqueous sodium hydroxide, and were absorbed in dry benzene; the benzene solution was diluted to the appropriate concentration with dry benzene. The amine hydrochlorides employed were a reagent grade quality and were used as received. Diethylamine (bp 55.0—56.0°C), triethylamine (bp 88.0—89.0°C), *n*-butylamine

2) R. W. Taft, in "Steric Effects in Organic Chemistry," M. S. Newman (Ed.), John Wiley and Sons, New York (1956), Chap. 13; see also Ref. 4.

3) H. C. Brown and N. R. Eldred, *J. Am. Chem. Soc.*, **71**, 445 (1949).

4) For the values of pK_a see H. K. Hall, Jr., *ibid.*, **79**, 5441 (1957). The pK_a values for diethanolamine, di- and tri-benzylamines are calculated by using the Hall's equation.

Table 1. Rate constants and activation parameters of the reactions of methyl iodide with various aliphatic amines in benzene solvent at 30.0°C[a]

R		RNH_2	R_2NH	R_3N
Me	k_2[c]	7.28×10^{-4}	4.87×10^{-3}[f]	8.89×10^{-3}[f]
	E_A[d]	9.10	7.31	7.0
	$\Delta S^{\neq}$[e]	−43.8	−47.0	−46.9
Et	k_2	5.62×10^{-4}	2.78×10^{-3}	1.85×10^{-3}
	E_A	12.8	10.7	9.1
	$\Delta S^{\neq}$	−33.2	−36.9	−42.9
n-Bu	k_2	5.53×10^{-4}	1.49×10^{-3}	6.87×10^{-4}
$HOCH_2CH_2$[b]	k_2	3.75×10^{-4}	3.83×10^{-4}	1.29×10^{-5}[f]
	E_A	11.2	11.4	13.1
	$\Delta S^{\neq}$	−39.4	−38.8	−39.8
$C_6H_5CH_2$	k_2	2.24×10^{-4}	5.96×10^{-5}	2.09×10^{-3}[f]
	E_A	12.5	14.3	19.7
	$\Delta S^{\neq}$	−35.8	−32.7	−30.9
(NH_3)	$k_2=2.61\times10^{-5}$ at 30.0°C			

a) Initial concentrations of amines and methyl iodide were respectively 0.10 M, except when otherwise noted.
b) Initial concentrations of the amines were 0.01—0.02 M.
c) k_2 ($sec^{-1}M^{-1}$) at 30.0°C
d) E_A (kcal/mol)
e) $\Delta S^{\neq}$ 30° (e. u.)
f) Extrapolated from data at the other temperatures.

Table 2. The second-order rate constants[a] of the reactions of 0.10 M methyl iodide with methylamines, ethylamines, ethanolamines and benzylamines in benzene solvent

Temp. °C	$MeNH_2$	Me_2NH	Me_3N
10.0	2.58×10^{-4}	2.05×10^{-3}	3.88×10^{-3}
15.0	3.34×10^{-4}	2.60×10^{-3}	4.83×10^{-3}
20.0	4.27×10^{-4}	3.22×10^{-3}	5.97×10^{-3}
30.0	7.28×10^{-4}	—	—
	$EtNH_2$	Et_2NH	Et_3N
10.0	—	7.85×10^{-4}	—
20.0	—	1.50×10^{-3}	1.10×10^{-3}
30.0	5.62×10^{-4}	2.78×10^{-3}	1.85×10^{-3}
40.0	1.09×10^{-3}	—	2.98×10^{-3}
50.0	2.08×10^{-3}	—	—
	$HOCH_2CH_2NH_2$	$(HOCH_2CH_2)_2NH$	$(HOCH_2CH_2)_3N$
30.0	3.75×10^{-4}	3.83×10^{-4}	—
40.0	6.77×10^{-4}	6.92×10^{-4}	—
50.0	1.19×10^{-3}	1.23×10^{-3}	4.93×10^{-5}
60.0	—	—	9.13×10^{-5}
70.0	—	—	1.63×10^{-4}
	$C_6H_5CH_2NH$	$(C_6H_5CH_2)_2NH$	$(C_6H_5CH_2)_3N$
30.0	2.24×10^{-4}	5.96×10^{-5}	—
80.0	4.30×10^{-3}	1.68×10^{-3}	—
110.0	—	—	1.91×10^{-5}
120.0	—	—	7.54×10^{-5}

a) k_2 ($sec^{-1}M^{-1}$); the initial concentrations of amines were 0.100 M, except ethanolamines (0.01—0.02 M).

Table 3. Kinetics of the reaction of methyl iodide with ammonia in benzene solvent at 30.02±0.02°C

$(MeI)_0=0.100$ M; $(NH_3)_0=0.100$ M

Time min	cc 0.0511 N KSCN/2.00 cc[b]	Completion %	10^5k_2 $sec^{-1}M^{-1}$
	(1.979)	0.00	—
0[e]	1.962	0.62	2.61[a]
160	1.890	2.39	2.66
260	1.832	3.96	2.75
380	1.770	5.63	2.72
525	1.685	7.92	2.83
∞[d]	(0.250)[c]	100	

a) Extrapolated from the k_2 values plotted against the percentage of completion.
b) 1.000 cc of 0.1031 N $AgNO_3$ was added before the titration at 0°C.
c) 2.000 cc of 0.1031 N $AgNO_3$ was added before the titration at 0°C.
d) Two days at 120°C.
e) The time when the first ampoule was removed for the interruption of the reaction.

Table 4. Kinetics of the reaction of methyl iodide with benzylamine in benzene solvent at 30.02±0.02°C

$(MeI)_0=0.0990$ M; $(Benzylamine)_0=0.0920$ M

Time min	0.0515 N KSCN/2.00 cc[b]	Completion %	10^4k_2 $sec^{-1}M^{-1}$
0	1.985	0.00	2.24[a]
22.5	1.857	3.17	2.28
35.0	1.773	5.25	2.48
51.0	1.681	7.54	2.51
60.0	1.637	8.62	2.47
71.0	1.570	10.28	2.54
90.0	1.454	13.18	2.64
100	1.424	13.92	2.53
∞[d]	(1.915)[c]		

a) Extrapolated from the k_2 values plotted against the percentage of completion.
b) 1.000 cc of 0.10 N $AgNO_3$ was added before the titration at 0°C.
c) 3.000 cc of 0.10 N $AgNO_3$ was added before the titration at 0°C.
d) Twelve hours at 120°C.

(bp 78.0°C), di-*n*-butylamine (bp 159.0°C), tri-*n*-butylamine (bp 216°C), ethanolamine (bp 69.0—72.0°C/8 mmHg), diethanolamine (bp 151—152°C/11 mmHg), triethanolamine (bp 201—203°C/10 mmHg), benzylamine (bp 68.0—68.3°C/6 mmHg), dibenzylamine (bp 143.0—143.5°C/5 mmHg) and methyl iodide (42.4—43.2°C) were purified by fractional distillation. Tribenzylamine, mp 92.2—92.9°C, corr., was purified by recrystallization with ethanol. Benzene was fractionated over sodium.

Kinetic Measurements. The reactions carried out at 10, 15 and 20°C were followed by pipetting 2 cc aliquots from 25 cc glass-stoppered flask into 5 cc of ice-water. For the reactions at the temperatures higher than 30°C a sealed ampoule technique was employed; each ampoule contained 2-cc of aliquot. The ampoule was cooled in ice-water for the interruption of the reaction. The iodide ion liberated during the reaction was titrated by the Volhard method at 0°C. The rate data were interpreted as described in text. The results are listed in Tables 1—4. The kinetic data for the typical runs for ammonia and for benzylamine are illustrated in Tables 3 and 4, respectively.