A Kinetic Study of the Reaction of Substituted Benzyl Chlorides with Tertiary Amines

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Introduction

The kinetics of the bimolecular nucleophilic substitution of benzyl chlorides have been studied by many workers[1-9]. In a single stage process considered for the bimolecular substitution, bond formation between the central carbon atom and a nucleophilic reagent occurs simultaneously with bond fission between the central carbon atom and the halogen atom. The bond fission should be facilitated by electron releasing groups; however, the approach of the nucleophilic reagent, which is necessary for the bond formation is almost certain to be hindered by these substituents. The net result is a different effect and the polar effects of the substituents on the S_{N2} reaction can not be clear cut. In addition to the polar effect, the steric effect and the solvent effect to be considered in the reaction mechanism multiplies the difficulty for explaining the factors which determine the reactivity.

In the present experiment, the kinetics of the reaction of substituted benzyl chlorides with tertiary amines in benzyl alcohol solvent were studied in order to investigate the polar and the steric effects in the S_{N2} reaction by using the tertiary amines with bulky substituents as nucleophilic reagents.

Experimental

Materials.—Melting points, boiling points and literature references for benzyl chlorides, amines and benzyl alcohol are listed in Table I.

TABLE I

	M. p. or B. p. (°C)	Reference
Solvent		
Benzyl alcohol	112/20	
Amines		
Tri-*n*-butylamine	116/42	
Dimethylaminoethanol	135	
Diethylaminoethanol	42∼44/8	
Diisopropylaminoethanol	104/39	(a)
Diisobutylaminoethanol	84/9	(a)
Di-*n*-butylaminoethanol	99/10.5	(b)
Benzyl chlorides		
H	69∼70/17	
o-NO_2	[48]	(c)
p-NO_2	[71]	
o-Cl	94/10	
p-Cl	68/3	
o-CN	[60]	(d)
p-CN	[79]	(d)
o-CH_3	86∼88/16	(e)
p-CH_3	63∼65/5	(f)

a) Einhorn, Fiedler and Uhlfelder, *Ann.*, **371**, 145 (1909).

b) Kamm, Adams and Volwieler, U.S. Patent, 1,358, 750.

c) L. Vanino, "Handbuch der Präparativen Chemie", Bände II, 459.

d) C. Barkenbus and J.B. Holtzchaw, *J. Am. Chem. Soc.*, **47**, 2191 (1925).

e) I. Smith and L.J. Spillane, *J. Am. Chem. Soc.*, **62**, 2640 (1940).

f) M.G. Darzens and M.M. Delépine, *Compt. rend.*, **208**, 818 (1939).

Procedure.—In each run, 1 ml. of 0.1 N benzyl alcohol solutions of benzyl chlorides and amines were mixed into a 20 ml. reaction tube having a ground stopper. At appropriate intervals of time the reaction tubes placed in a thermostat were taken out and the reaction was stopped by rapid cooling with ice water. Then, the reaction mixture was washed out with 10 ml. of methanol and the chlorine ion formed was determined by titration with 0.01 N silver nitrate (Mohr's method). The temperature control was accurate to ±0.03° within the temperature ranges between 25°C–135°C.

The second order rate constant was calculated by equation 1

$$k_2 = \frac{1}{t} \cdot \frac{x}{a(a-x)} \tag{1}$$

where k_2 is the second order rate constant; t, the time in seconds; x, the amount of chlorine ion

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[1] D.H. Peacock, *J. Chem. Soc.*, **1924**, 1975; **1925**, 2177.

[2] P.P. Krichenko and V. Opotsky, *Ber.* 59B, 2131 (1926).

[3] H. Mc Combie, H.A. Scarborouch and F.P. Smith, *J. Chem. Soc.*, **1927**, 802.

[4] B.V. Tronov and A.I. Gershevich, *C. A.*, **22**, 3397 (1928).

[5] G.M. Bennett and B. Jones, *J. Chem. Soc.*, **1935**, 1815.

[6] S.C.J. Olivier and A. Ph. Weber, *Rec. trav. chim. Pay-Bas*, **53**, 869, 899 (1934).

[7] V.A. Hol'tsshmidt and N. K. Vorobev, *J. Phys. Chem.*, **13**, 473 (1939).

[8] J.W. Baker and W.S. Nathan, *J. Chem. Soc.*, **1933**, 1128; **1934**, 987; **1935**, 519, 1840, 1844, 1847; **1936**, 236.

[9] C.W.L. Bevan, E. D. Hughes and C. K. Ingold, *Nature*, **171**, 301 (1953).

formed at time t; a, the initial concentration of both benzyl chlorides and tertiary amines. As an example of a typical run, the reactions of benzyl chloride with diethylaminoethanol at the temperature between 55°C–95°C are shown in Fig. 1.

The rate constants of the reaction of benzyl chlorides with amines are shown in Table II.

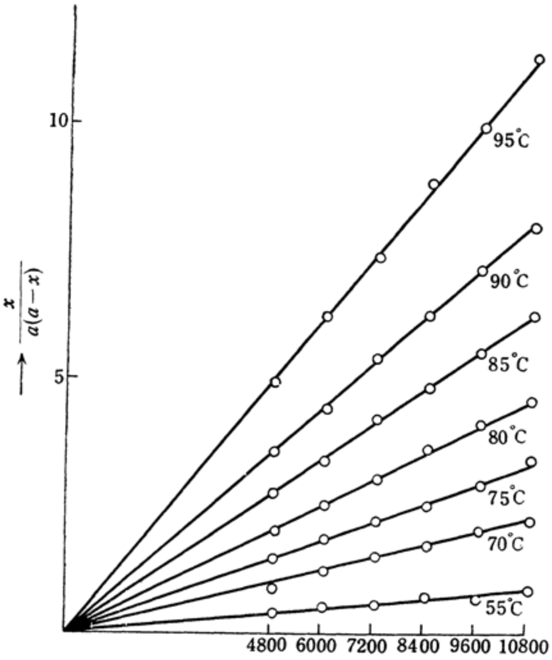


Fig. 1. Second order plots for the reaction of benzyl chloride with diethylaminoethanol.

The activation energies of the reactions were obtained from the linear relationship between log k and reciprocal absolute temperature. Typical runs are shown in Fig. 2. The rate constants, the activation energies and the entropies of activation obtained in this study are listed in Table III.

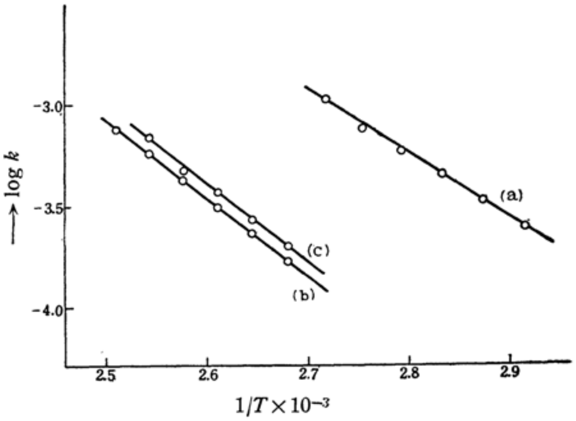


Fig. 2. The reaction of benzyl chloride with amines: the plot of log k against $1/T$. (a) diethylaminoethanol, (b) diisopropylaminoethanol, (c) diisobutylaminoethanol.

Results and Discussion

The experimental results listed in Table II are noted from the two different viewpoints, i. e. the effects of the substituents of amines (a) and those of benzyl chlorides (b), as follows.

TABLE II

THE RATE CONSTANTS OF THE REACTION OF BENZYL CHLORIDES WITH TERTIARY AMINES

$k_2\times10^4$ (mol.•l.$^{-1}$•sec.$^{-1}$), t(°C)

1) The reaction of benzyl chloride with amines.

t	k_2	t	k_2
(Dimethylaminoethanol)		(Diethylaminoethanol)	
25.0	2.21	55.0	0.824
30.0	3.26	70.0	2.09
35.0	4.74	75.0	3.40
40.0	6.84	80.0	4.57
		85.0	5.79
		90.0	7.43
		95.0	10.8
(Diisopropylaminoethanol)		(Diisobutylaminoethanol)	
100.0	1.66	95.0	1.39
105.0	2.31	100.0	2.01
110.0	3.10	105.0	2.70
115.0	4.21	110.0	3.44
120.0	5.67	115.0	4.66
125.0	7.55	120.0	7.02
(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
80.0	2.44	80.0	0.622
85.0	3.24	85.0	0.834
90.0	4.23	90.0	1.11
95.0	5.52	95.0	1.46
100.0	7.48	100.0	1.93
120.0	21.22	105.0	2.36

2) The reaction of *o*-methylbenzyl chloride with amines.

t	k_2	t	k_2
(Dimethylaminoethanol)		(Diethylaminoethanol)	
25.0	2.68	60.0	1.29
30.0	4.10	65.0	1.83
35.0	5.99	70.0	2.59
40.0	9.00	75.0	3.56
		80.0	4.83
		85.0	6.50
(Diisopropylaminoethanol)		(Diisobutylaminoethanol)	
75.0	0.80	80.0	1.20
80.0	1.14	85.0	1.73
85.0	1.58	90.0	2.47
90.0	2.10	95.0	3.41
95.0	3.03	100.0	4.76
100.0	4.15	105.0	6.62

t	k_2	*t*	k_2
(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
75.0	2.21	54.5	0.740
80.0	3.02	60.0	1.16
85.0	4.05	65.0	1.67
90.0	5.81	70.0	2.67
95.0	7.85	75.0	3.40
100.0	10.55	80.0	5.04

3) The reaction of *p*-methylbenzyl chloride with amines.

(Dimethylaminoethanol)		(Diethylaminoethanol)	
20.0	2.85	60.0	2.40
25.0	4.27	65.0	3.44
30.0	6.46	70.0	4.96
35.0	9.77	75.0	6.66
		80.0	9.91
		85.0	13.5

(Diisopropylamino-ethanol)		(Diisobutylamino-ethanol)	
80.0	1.61	80.0	1.69
85.0	2.34	85.0	2.47
90.0	3.35	90.0	3.59
95.0	4.95	95.0	5.49
100.0	7.23	100.0	8.02
105.0	10.49	105.0	11.65

(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
60.0	1.50	50.0	1.20
65.0	2.11	55.0	2.06
70.0	2.88	60.0	2.54
75.0	3.85	65.0	3.93
78.0	4.65	70.0	4.95
83.0	6.33	75.0	6.94

4) The reaction of *o*-chlorobenzyl chloride with amines.

(Dimethylaminoethanol)		(Diethylaminothanol)	
35.0	2.25	80.0	1.14
40.0	3.33	90.0	2.24
45.0	4.82	100.0	4.11
50.0	7.10	105.0	5.49

(Diisopropylamino-ethanol)		(Diisobutylamino-ethanol)	
110.0	0.870	110.0	1.36
115.0	1.18	115.0	1.72
120.0	1.52	120.0	2.27
125.0	2.07	125.0	2.98
130.0	2.76	130.0	3.99
135.0	3.67	135.0	5.05

(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
95.0	1.76	85.5	3.45
100.0	2.33	90.0	4.17
105.0	2.80	95.0	4.89
115.0	4.65	100.0	7.06
120.0	5.99	105.0	8.66
125.0	8.21	110.0	11.3

5) The reaction of *p*-chlorobenzyl chloride with amines.

t	k_2	*t*	k_2
(Dimethylaminoethanol)		(Diethylaminoethanol)	
30.0	2.83	75.0	2.47
35.0	4.01	80.0	3.33
40.0	5.91	90.0	5.70
45.0	8.41	95.0	7.91
		100.0	11.25

(Diisopropylamino-ethanol)		(Diisobutylamino-ethanol)	
105.0	1.43	105.0	1.76
110.0	1.91	110.0	2.38
115.0	2.60	115.0	3.19
120.0	3.45	120.0	4.40
125.0	4.61	125.0	5.75

(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
85.0	2.26	85.5	6.15
90.0	3.00	90.0	7.96
95.0	4.02	95.0	10.3
100.0	5.30	100.0	14.3
105.0	6.78	105.0	18.1
		110.0	22.2

6) The reaction of *o*-cyanobenzyl chloride with amines.

(Dimethylaminoethanol)		(Diethylaminoethanol)	
40.0	2.00	90.0	1.27
45.0	3.03	95.0	1.71
50.0	4.43	100.0	2.32
55.0	6.38	105.0	3.01
		110.0	3.82

(Diisopropylamino-ethanol)		(Diisobutylamino-ethanol)	
125.0	0.840	110.0	0.810
130.0	1.14	115.0	0.93
135.0	1.48	120.0	1.04
140.0	2.13	130.0	1.91
145.0	2.97	135.0	2.39
		140.0	3.01
		145.0	3.78

(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
100.0	1.19	90.0	2.10
105.0	1.61	95.0	2.69
110.0	2.09	100.0	3.70
115.0	2.71	105.0	4.68
120.0	3.28	110.0	5.93
125.0	3.97	115.0	7.27

7) The reaction of *p*-cyanobenzyl chloride with amines.

(Dimethylaminoethanol)		(Diethylaminoethanol)	
40.0	2.58	90.0	2.26
45.0	3.94	95.0	3.02
50.0	5.75	100.0	3.99
55.0	8.21	105.0	5.32
		109.8	6.70

t	k_2	t	k_2
(Diisopropylamino ethanol)		(Diisobutylamino-ethanol)	
110.0	0.660	110.0	0.580
115.0	0.810	120.0	0.890
120.0	1.13	130.0	1.52
130.0	1.80	135.0	1.99
135.0	2.40	140.0	2.65
140.0	3.00	145.0	3.54
145.0	3.78		
(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
100.0	1.80	90.0	2.86
105.0	2.35	95.0	3.63
110.0	3.10	100.0	4.81
115.0	4.11	105.0	6.42
120.0	5.00	110.0	7.93
		115.0	9.53

8) The reaction of *o*-nitrobenzyl chloride with amines.

t	k_2
(Tri-*n*-butylamine)	
105.0	3.66
110.0	4.75
115.0	6.34
120.0	8.38
125.1	11.3

9) The reaction of *p*-nitrobenzyl chloride with amines.

(Dimethylaminoethanol)		(Diethylaminoethanol)	
40.0	2.56	95.0	3.28
45.0	3.67	100.0	4.32
50.0	5.33	105.0	5.49
55.0	7.37	110.0	6.79
		115.0	8.79
(Di-*n*-butylaminoethanol)		(Tri-*n*-butylamine)	
90.0	0.810	105.0	6.10
100.0	1.54	110.0	7.97
105.0	2.08	115.0	10.1
110.0	2.61	120.0	11.8
115.0	3.77	125.1	14.9
120.0	6.15	130.0	18.1

TABLE III

THE SUMMARY OF RATE CONSTANTS ($k_2 \times 10^4$ mol.·l.$^{-1}$·sec.$^{-1}$ at 105°C), THE ACTIVATION ENERGIES (E kcal.) AND THE ENTROPIES OF ACTIVATION ($\Delta S^{\ddagger}$ e.u.)

Amines	Dimethylaminoethanol			Diethylaminoethanol		
Benzyl chlorides	k_2	E	$\Delta S^{\ddagger}$	k_2	E	$\Delta S^{\ddagger}$
H	32.3	14.0	−28.8	19.2	15.5	−30.5
o-CH$_3$	596	15.2	−24.4	24.0	15.3	−30.9
p-CH$_3$	740	14.4	−25.7	46.0	16.7	−25.6
o-Cl	21.4	15.1	−26.7	5.52	15.9	−31.9
p-Cl	27.9	13.9	−29.4	13.6	14.9	−32.7
o-CN	7.38	16.0	−26.5	3.05	16.0	−32.8
p-CN	8.63	15.5	−27.5	5.32	15.6	−32.8
o-NO$_2$						
p-NO$_2$	6.56	14.4	−30.9	5.55	14.7	−35.1
	Diisopropylaminoethanol			Diisobutylaminoethanol		
H	2.30	17.8	−28.5	2.70	18.5	−26.4
o-CH$_3$	5.59	16.7	−29.7	6.58	18.1	−25.8
p-CH$_3$	9.57	18.9	−23.0	11.5	20.6	−18.0
o-Cl	0.650	17.4	−32.2	0.100	16.7	−33.2
p-Cl	1.43	17.4	−30.7	1.76	17.8	−29.1
o-CN	0.212	20.4	−26.5	0.526	15.5	−37.7
p-CN	0.459	16.9	−34.2	0.348	18.0	−31.9
o-NO$_2$						
p-NO$_2$						
	Di-*n*-butylaminoethanol			Tri-*n*-butylamine		
H	9.68	14.6	−34.2	2.36	14.1	−33.6
o-CH$_3$	14.3	16.5	−28.4	22.9	16.6	−27.2
p-CH$_3$	13.0	14.6	−33.6	41.3	16.2	−31.7
o-Cl	2.90	14.0	−38.3	0.866	15.2	−32.8
p-Cl	6.98	15.1	−33.6	1.81	15.1	−33.2
o-CN	1.59	15.9	−38.9	0.506	14.2	−41.2
p-CN	2.38	15.1	−35.7	0.642	14.1	−40.9
o-NO$_2$				0.370	16.1	−32.1
p-NO$_2$	2.07	17.2	−30.4	0.600	13.2	−38.8

I—a) The rate constants of the reaction of amines with benzyl chlorides at 105°C increase in the following order,

diisopropylaminoethanol, diisobutylaminoethanol $\ll$ di-*n*-butylaminoethanol, tri-*n*-butylamine, diethylaminoethanol $\ll$ dimethylaminoethanol.

As noted in the above sequence, dimethylaminoethanol reacts much faster than the other amines and amines with normal alkyl groups react faster than those with branched alkyl groups. I—b) The rate constants of benzyl chlorides with amines at 105°C increase in the following order,

$$p\text{-CH}_3 > o\text{-CH}_3 > \text{H} > p\text{-Cl} > o\text{-Cl} > p\text{-CN} > o\text{-CN} > p\text{-NO}_2 > o\text{-NO}_2 .$$

The rates of reaction decrease by introducing the electron attracting groups and the *para* derivatives react faster than the corresponding *ortho* derivatives.

II—a) The activation energies for amines increase in the following order,

dimethylaminoethanol, diethylaminoethanol, di-*n*-butylaminoethanol, tri-*n*-butylamine $\ll$ diisopropylaminoethanol, diisobutylaminoethanol.

Amines with the branched alkyl groups, such as isopropyl and isobutyl groups, require more energy than amines with normal alkyl groups, such as methyl, ethyl and *n*-butyl groups. The activation energies required for the latter four amines are nearly equal.

II—b) The activation energies for benzyl chlorides do not show the characteristic variation of the substituents as found in the rate constant, in which regular sequences are shown according to their polar effects.

The following relations are found for *ortho* and *para* derivatives of benzyl chlorides according to the nature of the attacking amines. *Ortho* derivatives require more energy of activation than *para* derivatives in the reaction with four amines with normal alkyl groups and the reversed order is found in the reaction with amines with branched alkyl groups.

III—a) The entropies of activation for amines increase in the following order,

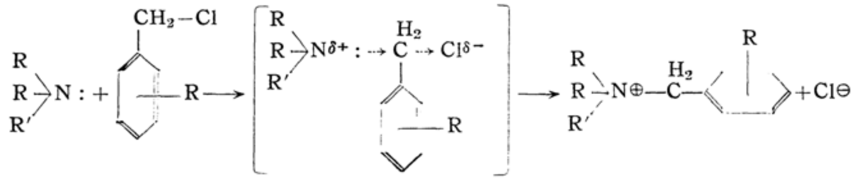
tri-*n*-butylamine, di-*n*-butylaminoethanol, diethylaminoethanol $<$ diisobutylaminoethanol, diisopropylaminoethanol $<$ dimethylaminoethanol.

The entropy of activation for dimethylaminoethanol is less negative than the other amines. The slow rates of amines with normal alkyl groups, such as ethyl and *n*-butyl groups, which require the nearly equal energies of activation with dimethylaminoethanol are attributed to the more negative entropies of activation.

III—b) The linear relationship between the activation energy and the entropy of activation could not be found for benzyl chlorides; however, the results show a combined increase in the activation energy and decrease in the entropy of activation. Benzyl chlorides with electron attracting groups show more negative entropy of activation than those with the electron releasing groups.

Ortho derivatives show more negative entropy of activation than *para* derivatives in the reaction with amines with branched alkyl groups and the reversed relation is found in the reaction with the other four amines.

The single stage process is considered for the bimolecular nucleophilic substitution and, in the transition state, by the approach of the nucleophilic reagent, the bond formation occurs simultaneously with bond fission, in which chlorine atom ionizes by the interaction of the solvent molecule.



Assuming the above mechanism for the reaction, the effects of the substituents of amines are considered as follows. The electron density of the nitrogen atom in amines increases from methyl to *n*-butyl by an inductive effect, which is favorable for bond formation, but, the frontal strain considered in the transition state increases by the same sequence, which is unfavorable for the reaction. The simple explanation becomes difficult because of these two opposing effects, i. e.; polar effect and steric effect; however, the results that amines with bulky substituents always require 2–3 kcal. more activation energy than the other four amines may be due to the increased F-strain considered in the transition state.

As shown in II—b), the relative order of activation energies for *ortho* and *para* derivatives of benzyl chlorides are changed by the nature of the attacking amines. The lower activation energies for the reaction of *ortho* derivatives with bulky amines may be explained by assuming the increased F-strain between *ortho* derivatives and the amines with bulky groups in the transition state, which causes the dissociation of chlorine atoms more readily.

The activation energies for the reaction of benzyl chlorides with electron attracting groups or electron releasing groups are nearly equal. These results may be due to the two opposing effects which are considered in the single stage process, namely the ionization of chlorine atom facilitated by the electron releasing groups and the approach of amine molecule to the central carbon atom retarded by the same substituents.

As shown in III—a), the entropy of activation for dimethylaminoethanol is less negative than the other four amines studied. This may be explained by assuming the solvation of amines, e.g. the interaction of protonic solvent with amines, in the ground state, which must be lost in the transition state. Dimethylaminoethanol solvates more than the other amines in which solvation is hindered by the increased B-strain due to their bulky substituents. Therefore, the entropies of activation for the latter amines are more negative than dimethylaminoethanol.

The results shown in III—b) are explained by a similar consideration in which the differences of the entropies of activation in the benzyl chloride series depend on the degree of solvation in their ground state. The solvation of benzyl chlorides to the chlorine atom by the protonic solvent, in the ground state, increases by introducing the electron releasing group, such as methyl group, but, in the transition state, the solvent interaction with the ionizing chlorine atom is nearly the same irrespective of the nature of their substituents. Therefore, the more negative entropies of activation of benzyl chlorides with electron attracting groups are expected.

In bimolecular nucleophilic substitution, the polar effects are not clearly shown as mentioned above, but, it can be concluded that the steric effect and the solvent effect play an important role for the reaction.

Summary

(1) The rate constants, the activation energies and the entropies of activation of the reaction of benzyl chlorides with tertiary amines in benzyl alcohol were determined.

(2) In the single stage process for the bimolecular nucleophilic substitution, the polar effects of the substituents are not clearly shown.

(3) Both steric and solvent effects play important roles on the reaction studied in this experiment.

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