References

1. (a) S. S. Mirvish, *Toxicology and App. Pharmacology*, **31**, 325 (1975); (b) P. Pademachcher and H. G. Gilde, *J. Chem. Educ.*, **53**, 7757 (1976); (c) J. S. Wishnok, *J. Chem. Educ.*, **54**, 440 (1977); (d) G. A. Digenis and C. I. Issidorides, *Bioorg. Chem.*, **8**, 97 (1979); (e) A. M. Crider, C. Lu, H. G. Floss, and J. M. Cassady, *J. Med. Chem.*, **22**, 32 (1979); (f) T. Suami, K. I. Tadano, and W. T. Brander, *J. Med. Chem.*, **22**, 314 (1979).

2. (a) T. P. Johnston, G. S. McCaleb, and J. A. Montgomery, *J. Med. Chem.*, **6**, 669 (1963); (b) T. P. Johnston, G. S. McCaleb, P. S. Opliger, and J. A. Montgomery, *J. Med. Chem.*, **9**, 892 (1966); (c) C. J. Cheng, S. Fujimura, D. Grunberger, and I. B. weinstein, *Cancer Res.*, **32**, 22 (1972); (d) T. Suami, T. Machinami, and T. Hisamatsu, *J. Med. Chem.*, **22**, 247 (1979).

3. (a) F. L. English, *Anal. Chem.*, **23**, 344 (1951); (b) R. N. Haszelidine and J. Jander, *J. Chem. Soc.*, 691 (1954); (c) H. Lund, Acta Chem. Scand., **11**, 990 (1957); (d) H. Burghar and H. Jager, *J. Electroanal. Chem.*, **17**, 191 (1968); (e) R. S. Nicholson and I. Shain, *Anal. Chem.*, 37 (1965); (f) F. Pulidori, G. Borghesani, and R. Pedrialli, *J. Electroanal. Chem.*, **27**, 385 (1970); (g) P. E. Iversen, *Acta Chem. Scand.*, **25**, 2337 (1971); (h) G. Jecob, C. Moinet, and A. Talles, *J. Electroanal. Chem.* **27**, 1417 (1982); (i) M. Studnickova, V. N. Flerov, and O. Fischer, *J. Electroanal. Chem.*, **187**, 307 (1985).

4. J. C. Kim and I. S. Cho, *J. Pharm. Soc. (Korea)*, **27**, 177 (1983).

5. Selected data; **3**: mp. 113-115℃, IR (KBr); 3350, 3330 cm^{-1} (-NH, s), 1640 cm^{-1} (C=O), 1570 cm^{-1} (-NH, b). ^{1}H-NMR (CDCl$_3$); δ 3.5 (2H, s, -NH$_2$), δ 3.7-3.8 (4H, m, -CH$_2$CH$_2$Cl), δ 7.0-7.2 (5H, m, -C$_6$H$_5$), δ 8.4-8.5 (1H, s, Ar-NH-). MS; m/z 213 (27%), 215 (M+2, 9%). Elemental analysis, Tound; C 51.25%, H 5.70%, N 18.74%. Calcd.; C 50.59%, H 5.66%, N 19.67%. **4**: mp. 123-125℃. IR; 3370 cm^{-1} (-NH, s), 1640 cm^{-1} (-NH, b). ^{1}H-NMR (CDCl$_3$); δ 3.4-3.6 (4H, m, -CH$_2$CH$_2$Cl), δ 6.1-6.4 (1H, t, -NH-CH$_2$-), δ 6.6-7.3 (5H, m, -C$_6$H$_5$), δ 8.30 (1H, s, Ar-NH-). **5**: IR; 3340, 3296 cm^{-1} (-NH$_2$, s) 1646 cm^{-1} (C=O), 1586 cm^{-1} (-NH, b), 1118 cm^{-1} (C-N, s). ^{1}H-NMR (Acetone-D$_6$); δ 3.77 (2H, s, -NH$_2$, δ 6.87-7.47 (5H, m, C$_6$H$_5$-), δ 7.92 (1H, s, -NH). MS; m/z 165, 150 (M-CH$_3$), 92 (M-C$_2$H$_5$N$_2$O). **6**: mp. 145℃. IR; 3420 cm^{-1} (-NH, s), 1650 cm^{-1} (C=O), 1580 cm^{-1} (-NH, b). ^{1}H-NMR (CDDl$_3$), δ 5.69 (1H, s, -NH-), δ 7.17-7.60 (5H, m, -C$_6$H$_5$) δ 7.91 (1H, s, Ar-NH). MS; m/z 150, 93 (MC$_2$H$_4$NO). Elemental Analysis, found; C 63.32%, H 6.82%, N 18.13%, Calcd.; C 63.98%, H 6.71%, N 18.65%. **7**: mp. 80℃. ^{1}H-NMR (CDCl$_3$); δ 1.15-1.40 (3H, t, -CH$_2$CH$_3$), δ 4.00-4.25 (2H, q, -CH$_2$CH$_3$) δ 7.02-7.21 (5H, m, C$_6$H$_5$-), δ 9.7-9.9 (1H, s, Ar-NH). IR; 3360 cm^{-1} (-NH, s), 1705 cm^{-1} (C=O), 1540 cm^{-1} (-NH, b). **8**: mp. 154℃. IR; 3370 cm^{-1} (-NH, s), 1630 cm^{-1} cm^{-1} (C=O), 1095 cm^{-1} (-C$_6$H$_5$Cl, s), 795 cm^{-1} (1,4 disubstituted benzene). ^{1}H-NMR (CDCl$_3$); δ 3.66-4.20 (4H, m, CH$_2$CH$_2$Cl), δ 6.65 (1H, s, HN-CH$_2$CH$_2$Cl), δ 7.32-8.07 (4H, q, C$_6$H$_5$-), δ 9.21 (1H, s, Ar-NH). MS; m/z 234, 127 (M-C$_3$H$_5$NOCl, 20.5%), 129 (6.4%), 107 (M-C$_6$H$_5$N, 100%). **9**: mp. 204-205℃. IR; 3330, 3310 cm^{-1} (-NH, s), 1645 cm^{-1} (C=O), 1550 cm^{-1} (-NH, b), 1092 cm^{-1} (Ar-Cl), 837 cm^{-1} (1,4 -disubstituted

benzene). ^{1}H-NMR (CDCl$_3$); δ 2.67-2.83 (3H, d, -CH$_3$), δ 5.68 (1H, s, -NHC=O), δ 7.03-7.53 (4H, q, ArNH), δ 8.47 (1H, s, ArNH). MS; m/z 184, 127 (M-C$_2$H$_4$NO, 100%), 129 (33%).

Nucleophilic Substitution Reactions of Benzyl bromides with N-Methylanilines in Methanol-Acetonitrile Mixtures

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In our previous work, we have shown that benzyl derivatives react by a dissociative S_N2 mechanism with a relatively loose transition state (TS)[1]. The cross-interaction constants between X-substituted nucleophiles and Z substituted leaving groups, ρ_{XZ} (Scheme 1), in Eq. (1)[2] were negative[1] indicating that a stronger nucleophile ($\delta\sigma_X<0$) and a better leaving group ($\delta\sigma_Z>0$) lead to a later TS[2] ($\delta\rho_Z>0$) and $\delta\rho_X<0$, respectively in Eq. (2).

$$\log k_{ij}/k_{HH} = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \tag{1}$$

where i, j=X, Y or Z

$$\rho_{XZ} = \frac{\partial^2 \log k_{XZ}}{\partial\sigma_X\partial\sigma_Z} = \frac{\partial\rho_Z}{\partial\sigma_X} = \frac{\partial\rho_X}{\partial\sigma_Z} \tag{2}$$

It has been reported that a typical dissociative S_N2 process has relatively narrow range of the magnitude of ρ_{XY} (0.6-0.8)[1d] suggesting a similar degree of bond formation is involved in the TS. In this work, we report the results of kinetic studies on the nucleophilic substitution reactions of benzyl bromides with N-methylanilines in methanol-acetonitrile mixtures at two temperatures of 45.0 and 55.0℃, Eq. (3).
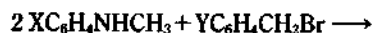

Typical S$_N$2 TS

Scheme 1

Notes

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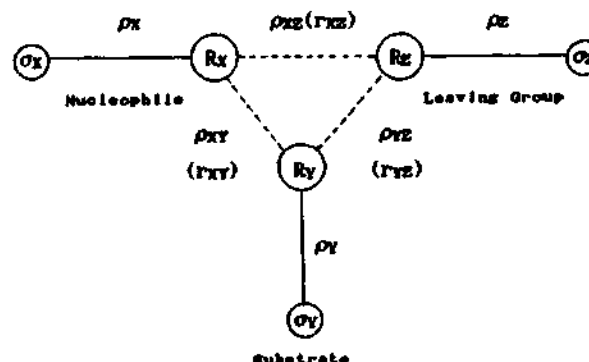
Table 1. Second Order Rate Constants ($k_2 \times 10^{-3}$ M^{-1}s^{-1}) for the Reaction of Y-Substituted Benzyl Bromides with X-Substituted N-Methylanilines in MeOH-MeCN Mixtures at 45.0 and 55.0℃

MeOH (V/V)%	X=	Y=p-CH$_3$		H		p-Cl		p-NO$_2$	
		T(℃)							
		45.0	55.0	45.0	55.0	45.0	55.0	45.0	55.0
100	p-OCH$_3$	91.2	159	43.9	77.9	42.3	72.0	17.7	30.6
	H	29.9	49.9	12.4	22.6	10.4	19.3	4.01	6.96
	p-Cl	13.0	25.3	4.96	9.07	3.95	7.30	1.12	2.25
90	p-OCH$_3$	93.2	162	45.0	80.2	44.4	78.8	19.5	34.1
	H	30.7	54.1	12.3	23.0	11.0	19.9	4.01	7.13
	p-Cl	13.3	25.3	5.10	9.50	4.03	8.25	1.19	2.36
80	p-OCH$_3$	90.3	159	44.3	79.2	45.1	76.0	21.2	35.9
	H	29.0	47.9	12.0	21.4	10.9	18.9	4.08	7.52
	p-Cl	12.6	22.9	4.84	9.05	4.10	7.52	1.21	2.37
70	p-OCH$_3$	89.1	151	43.9	78.4	44.2	75.8	21.1	35.9
	H	26.4	43.2	11.5	20.0	10.5	18.0	4.19	7.53
	p-Cl	11.9	21.1	4.67	8.52	3.93	7.34	1.18	2.34
50	p-OCH$_3$	85.0	143	41.3	70.0	41.4	70.0	20.8	35.6
	H	21.6	37.2	9.07	16.8	9.18	14.9	3.64	6.48
	p-Cl	8.85	17.4	3.98	7.37	3.39	6.21	1.16	2.23

Table 2. The Hammett ρ_Y^+ Values[a] for the Reaction of X-Substituted N-Methylanilines with Y-Substituted Benzyl Bromides in MeOH-MeCN Mixtures at 45.0 and 55.0℃

MeOH (V/V)%	X=p-OCH$_3$		H		p-Cl	
	T (℃)					
	45.0	55.0	45.0	55.0	45.0	55.0
100	−0.62	−0.62	−0.75	−0.75	−0.93	−0.91
90	−0.59	−0.59	−0.76	−0.77	−0.92	−0.90
80	−0.54	−0.56	−0.74	−0.70	−0.89	−0.86
70	−0.53	−0.54	−0.69	−0.66	−0.88	−0.83
50	−0.52	−0.51	−0.66	−0.65	−0.78	−0.78

[a] Corre. Coeff.; $r = 0.985 \pm 0.015$.

Table 3. The Hammett ρ_X Values[a] for the Reaction of X-Substituted N-Methylanilines with Y-Substituted Benzyl Bromides in MeOH-MeCN Mixtures at 45.0 and 55.0℃

MeOH (V/V)%	Y=p-CH$_3$		H		p-Cl		p-NO$_2$	
	T (℃)							
	45.0	55.0	45.0	55.0	45.0	55.0	45.0	55.0
100	−1.70	−1.60	−1.90	−1.87	−2.07	−1.99	−2.40	−2.27
90	−1.69	−1.62	−1.90	−1.86	−2.09	−1.97	−2.43	−2.33
80	−1.71	−1.69	−1.93	−1.89	−2.09	−2.02	−2.49	−2.37
70	−1.75	−1.72	−1.95	−1.94	−2.11	−2.04	−2.51	−2.38
50	−1.97	−1.84	−2.04	−1.97	−2.18	−2.12	−2.52	−2.42

[a] Corre. Coeff.; $r = 0.997 \pm 0.003$.

$$2\ XC_6H_4NHCH_3 + YC_6H_4CH_2Br \longrightarrow$$

$$YC_6H_4CH_2NCH_3C_6H_4X + XC_6H_4\overset{+}{N}H_2CH_3 + Br^{-1} \qquad (3)$$

X = p-OCH$_3$, H or p-Cl

Y = p-CH$_3$, H, p-Cl or p-NO$_2$

We are interested primarily in the effects of nucleophiles, temperature and solvent composition on the magnitude of ρ_{XY} which is a measure of the degree of bond formation.

Results and Discussion

The second order rate constants, k_2, for the reactions of benzyl bromides and N-methylanilines in MeOH-MeCN mixtures are summarized in Table 1. Although the solvolysis (methanolysis) of benzyl bromides will take place in parallel with the aminolysis reaction (Eq. (3)), we can disregard it safely since it does not interfere with the aminolysis as we

have pointed out for the similar types of reaction.[3]

The rate shows a slight maximum at around 70-90% methanol. The rate increases with a stronger nucleophile and with a more electron donating substituent in the substrate (e.g. Y=p-CH$_3$). The latter suggests substantial positive charge development at the benzylic carbon center in the TS. This is supported by the relatively large negative ρ_Y^+ values (Scheme 1) in Table 2. The magnitude of $|\rho_Y^+|$ tends to increase with a weaker nucleophile (X=p-Cl) and with a MeOH content of the solvent mixture.

This can be rationalized as a lesser degree of bond formation with a weaker nucleophile and a greater degree of bond breaking in a methanol-rich solvent leading to a greater positive charge development at the reaction center.

The Hammett ρ_X values for the substituent changes in the nucleophile are collected in Table 3. The negative sign reflects correctly the positive charge development at the nitrogen atom of the nucleophile in the TS. The size of the

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Table 4. The Cross-Interaction Constants, ρ_{XY}, for the Reaction of Benzyl Bromides with N-Methylanilines in MeOH-MeCN Mixtures at 45.0 and 55.0℃

MeOH	ρ_X		ρ_Y^+		ρ_{XY}		Corre Coeff. (r)	
			T (℃)					
(V/V)%	45.0	55.0	45.0	55.0	45.0	55.0	45.0	55.0
100	−1.94	−1.87	−0.78	−0.77	−0.64	−0.59	0.994	0.993
90	−1.95	−1.87	−0.76	−0.76	−0.67	−0.64	0.993	0.994
80	−1.97	−1.92	−0.73	−0.71	−0.71	−0.61	0.993	0.993
70	−2.00	−1.95	−0.71	−0.68	−0.69	−0.59	0.993	0.993
50	−2.03	−2.00	−0.66	−0.65	−0.53	−0.58	0.990	0.991

negative value increases with a more electron withdrawing substituent in the substrate (Y=p-NO$_2$) indicating a greater degree of bond formation.

The size, however, slightly decreases in the solvent with a greater methanol content, which should be normally interpreted as a lesser degree of bond formation in a MeOH-rich solvent. We note that the variation in the size of ρ_X is relatively small with the solvent composition. On the other hand, the size of ρ_X tends to decrease with an increase in the temperature implying that bond formation decreases with an increase in the temperature. This is in contrast to the insignificant change of $|\rho_Y^+|$ with the temperature in Table 2.

The cross-interaction constants, ρ_{XY} obtained by the multiple linear regression of the rate data, k$_2$, using Eq. 1 are summarized in Table 4. We note that the ρ_X and ρ_Y^+ values listed are in good agreement with the values independently determined for X=H and Y=H in Tables 2 and 3, which implies that the ρ_{XY} values are reliable.[2b]

The magnitute of $|\rho_{XY}|$ in MeOH at 45.0℃ (0.64) is well within the range of $|\rho_{XY}|$ values for a normal dissociative S$_N$2 reactions (0.6-0.8).[1a] The magnitude tends to exhibit a small maximum at 80-90% MeOH, which is the range for rate maxima in Table 1. Since a greater value of $|\rho_{XY}|$ indicates a greater degree of bond formation,[2] the maximum can be taken to reflect a maximum degree of bond formation at 80-90% MeOH. This can be rationalized with a greater degree of bond breaking due to a maximum concentration of free MeOH normally predicted for this solvent composition leading to a maximum degree of electrophilic bond-breaking assistance by the hydrogen bonding of MeOH. If we consider the negative sign of ρ_{XZ} for the aminolysis of benzyl derivatives,[1d,2] a greater bond breaking should lead to a grea-

ter degree of bond formation. Thus a greater $|\rho_Y^+|$ (a greater degree of bond breaking accompanied by a greater degree of bond formation[2]) together with a smaller $|\rho_X|$ (a lesser degree of bond formation) in the methanol-rich solvent act in a compensating manner to give a maximum behavior in degree of bond formation in the 80-90% MeOH range.

The magnitude of $|\rho_{XY}|$ tends to decrease with an increase in temperature, suggesting a lesser degree of bond formation at higher temperature as we noted with the change in $|\rho_X|$ above.

We conclude that the degree of bond formation exhibits a maximum at 80-90% MeOH solvent and decreases with increase in temperature. In general, the size of $|\rho_{XY}|$ found in this work is in the general range of 0.6-0.8 found for the dissociative type S$_N$2 reactions with loose TS.

Experimental

Meterials. Solvents and benzyl bromides used are the same as described previously.[1d] N-Methylanilines are commercially available compounds, which were purified before use.[4]

Rates Measurements. The rates were measured by the conductivity method. Determination of rate constants, k$_2$, is as described in the previous reports.[1]

References

1. (a) I. Lee, H. W. Lee, S. C. Sohn, and C. S. Kim, *Tetrahedron*, **41**, 2635 (1985); (b) I. Lee, S. C. Sohn, C. H. Kang, and Y. J. Oh, *J. Chem. Soc., Perkin Trans.*, 2, 1631 (1986); (c) I. Lee, S. C. Sohn, Y. J. Oh, and B. C. Lee, *Tetrahedron*, **42**, 4713 (1986); (d) I. Lee, C. S. Shim, S. Y. Chung, H. Y. Kim, and H. W. Lee, *J. Chem. Soc., Perkin Trans, 2*, 1919 (1988).
2. (a) I. Lee, *Chem. Soc. Rev.*, **19**, 317 (1990); (b) I. Lee, *Adv. Phys. Org. Chem.*, **27**, 57 (1991).
3. (a) I. Lee, W. H. Lee, H. W. Lee, and B. C. Lee, *J. Chem. Soc., Perkin Trans*, 2, 785 (1991); (b) I. Lee, W. H. Lee, and H. W. Lee, *J. Org. Chem.*, **56**, 4682 (1991); (c) I. Lee, H. K. Kang, and H. W. Lee, *J. Am. Chem. Soc.*, **109**, 7472 (1987).
4. D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, *"Purification of Laboratory Chemicals"*, 2nd ed., Pergamon Press, 1990.