Solvent Effects on the Benzylation with Substituted Imidazoles in Acetonitrile and Methanol

Soo-Dong Yoh,* Oh-Seuk Lee,† Jong-Hwan Park, Sung-Hong Kim, and Yung-Duk Lee

Department of Chemistry Education, Kyungpook National University, Taegu 702-701, Korea
†Department of Chemistry, Andong National University, Andong 760-380, Korea
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Solvolytic and nucleophilic reactions of benzyl halides with a variety of aromatic and aliphatic amines have been studied by many workers.[1~7] They have attempted to gain an insight into S_N reaction mechanism for these reactions by checking mainly substituent effects.

In this connection, we have studied the reaction of substituted benzyl bromides with substituted imidazoles in acetonitrile and methanol (Eq. 3) in order to investigate the solvent dependence of the rate and the substituent effect in substrate and nucleophile. This yielded detailed information on the transition state.

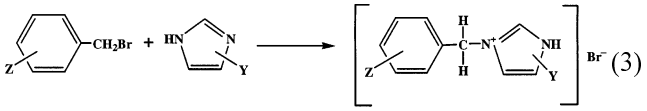
The linear free energy relationships (LFERs), the notable Hammett and Brönsted types, have been used as an empirical means of characterizing transition state (TS) structures.[8~10] The Hammett and Brönsted coefficients (ρ and β) are first derivatives of log k as shown in Eqs. (1) and (2), respectively, and reflect TS structures involved in a series of reactions with structural changes affecting the reaction center.

$$\rho = \partial \log k/\partial\sigma \quad (1)$$

$$\beta = \partial \log k/\partial \mathrm{pK} \quad (2)$$

The magnitudes of the ρ and β values in the nucleophile can measure the degree of bond formation.

In this paper, we report the results of the relationship of substituent and solvent effect on the substrate (Z) and nucleophile (Y). The pressure effect and detailed results will be reported in due course.



(3)

Z = 4-CH_3, H, 4-Br, 3-NO_2, Y = H, 1-CH_3, 4-CH_3, 2-CH_3

Results and Discussion

The pseudo first-order rate constants and second-order rate constants in acetonitrile are summarized in Table 1 and also the pseudo first-order rate constants for this reaction in methanol are listed in Table 2.

The reaction rate is increased with the electron-donating ability in substrate and nucleophile, while electron-withdrawing one reversed effects in the substrate on both solvents in Tables 1 and 2. As shown in Figure 1, in acetonitrile, the plots of k_{obs} value *vs.* [imidazole] passed through the origin within experimental uncertainty, indicating the accurately first-order reaction to imidazole concentration. For all the more electron-withdrawing substituents than Z=4-CH_3, the

Table 1. Pseudo First-order Rate Constants[a] $[10^4 \cdot k_{obs}](s^{-1})$ and Second-order Rate Constants[b] $[10^4 \cdot k_2](l/mol \cdot s)$ for the Reactions of (Z)-Substituted Benzyl Bromides with (Y)-Substituted Imidazoles in Acetonitrile at 45 °C

Z	Y[a] [Nu]	H	Z	Y[b] H	1-Me	4-Me	2-Me
4-Me	0.30	18.78	4-Me	62.12[C]	76.35	90.95	84.21
	0.25	16.01					
	0.20	12.65	H	49.42	60.61	72.31	64.86
	0.10	6.436	4-Br	42.52	52.83	64.00	57.87
	0.05	3.234	3-NO_2	32.69	41.67	51.72	44.55
	0.01	0.6547					

[C]The second-order rate constants, k_2(62.12) was calculated from Eq. (4) after substitution the concentration of nucleophile, 0.30, 0.25, 0.20..... and the pseudo first--order rate constants, 18.78, 16.01, 12.65..... Other pseudo first-order rate constants were omitted.

Table 2. Pseudo First-order Rate Constants $[10^4 \cdot k_{obs}](s^{-1})$ for the Reactions of (Z)-Substituted Benzyl Bromides with (Y)-Substituted Imidazoles in Methanol at 45 °C

Z \ Y	[Nu]	H	1-Me	4-Me	2-Me
4-Me	0.30	2.944	2.932	2.928	2.475
	0.25	2.582	2.589	2.587	2.164
	0.20	2.265	2.266	2.237	1.916
	0.10	1.516	1.486	1.478	1.320
	0.05	1.132	1.122	1.107	1.046
	0.03	0.9691	0.9668	0.9670	0.9173
	0.01	0.8360	0.8314	0.8351	0.8298
H	0.30	1.495	1.483	1.452	1.193
	0.25	1.230	1.239	1.227	0.9789
	0.20	1.029	1.026	1.013	0.8314
	0.15	0.8275	0.8218	0.7972	0.6680
	0.10	0.6006	0.5990	0.5981	0.4946
	0.075	0.4992	0.4933	0.4832	0.4152
	0.0375	0.3494	0.3478	0.3219	0.2831
	0.03	0.3021	0.3111	0.2946	0.2736
4-Br	0.30	1.187	1.182	1.204	0.9081
	0.20	0.8236	0.8066	0.8140	0.6340
	0.10	0.4565	0.4517	0.4614	0.3631
	0.01	0.1371	0.1351	0.1403	0.1207
3-NO_2	0.30	0.6690	0.6695	0.6654	0.4863
	0.20	0.4651	0.4578	0.4581	0.3254
	0.10	0.2269	0.2284	0.2254	0.1702

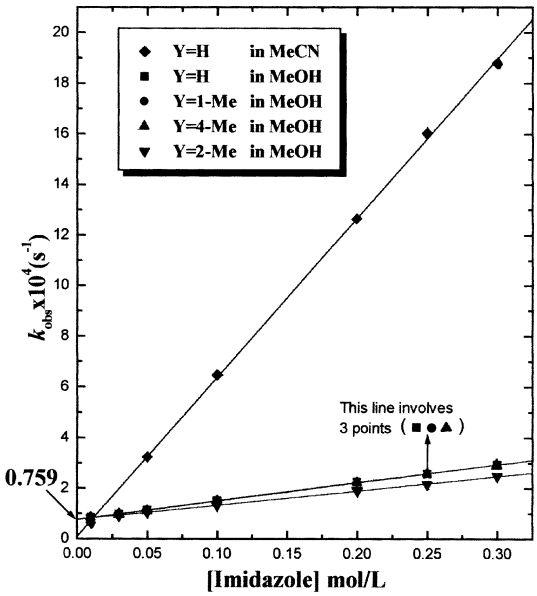


Figure 1. Plots of pseudo first-order rate constants (k_{obs}) *vs.* nucleophile concentration for the reactions of 4-Me-benzyl bromide with (Y)-substituted imidazoles in acetonitrile and methanol at 45 °C.

Table 3. First-order (k_1) and Second-order (k_2) Rate Constants for the Reactions of (Z)-Substituted Benzyl Bromides with (Y)-Substituted Imidazoles in Methanol at 45 °C

Substituents		Slope	Intercept	$100 \times k_1$[a]
Z	Y	$10^4 k_2$ ($s^{-1}M^{-1}$)	$10^5 k_1$ (s^{-1})	[0.1] k_2+k_1
4-Me	H	7.310	0.7675	51.2
	1-Me	7.329	0.7576	50.8
	4-Me	7.308	0.7528	50.7
	2-Me	5.695	0.7593	57.1
H	H	4.317	0.1751	28.9
	1-Me	4.295	0.1767	29.1
	4-Me	4.270	0.1636	27.7
	2-Me	3.365	0.1616	32.4
4-Br	H	3.626	0.0981	21.3
	1-Me	3.605	0.0941	20.7
	4-Me	3.655	0.0976	21.1
	2-Me	2.715	0.0925	25.4
3-NO_2	H	2.211	0.0116	4.98
	1-Me	2.206	0.0108	4.67
	4-Me	2.200	0.0096	4.18
	2-Me	1.581	0.0112	6.62

[a]Percent of S_N1 process in a whole reaction at [Y-Imidazole] = 0.1 M.

entire reaction proceeded accurately according to second-order process. The reaction follows the simple kinetic rate law of Eq. 4. In this study, the second-order rate constants, k_2, are calculated from the slope of k_{obs} *vs.* [imidazole] plots using least-squares method.

$$k_{obs} = k_2[\text{imidazole}] \quad (4)$$

In the methanol, however, the plots of k_{obs} *vs.* [imidazole] for typical electron donating 4-CH_3- substituted substrate with Y-substituted imidazoles are a significant positive intercept which corresponds to a zeroth-order reaction to imidazole. The constant positive intercept which is independent of the nature or concentration of the nucleophile indicates first-order process in the substrate as demonstrated by the convergency at the same intercept in the k_{obs} *vs.* [imidazole] plots for the various Y-substituents. On the other hand, the second-order rate constant, k_2, obtained from the slope of the linear parts of plots in Figure 1, is very small and not so largely dependent of nature of nucleophile, indicating through a competitive methanolysis and nucleophilic displacement by Y-imidazoles. Above results in methanol revealed a kinetic dependence expected for a simultaneous occurrence of independent unimolecular and bimolecular process.[11-12]

The first-order rate constants, k_1 values are determined from the intercepts of the linear part of k_{obs} *vs.* [imidazole] plots and the second-order rate constants, k_2 values are determined from its slope. Rate data are listed in Table 3 for k_1 and k_2. The k_1 values are independent on the nucleophilicity of imidazole while the values are increased extensively with the electron-donating Z-substituent, that is, with delocalized stabilization of positive charge on benzyl carbon by Z-substituent and the k_1 values obtained from the reacction with various Y-imidazoles are mostly constant for each Z-substituent with experimental uncertainty. The change of k_2 value with the Z-substituent from 3-NO_2 to 4-Me produces *ca.* 3.30-fold rate enhancement in the reaction with H-imidazole. On the other hand, the change of k_1 value with the Z-aryl substituent from 3-NO_2 to 4-Me produces *ca.* 66.2-fold rate enhancement which is far larger than the above values for bimolecular reaction and the k_1 values in the same Z-substituent are constant independent of nucleophilic nature. Therefore, the k_1 values reveal the rate constant of S_N1 reaction mechanism.

The % contribution of S_N1 process at 0.1 M concentration of Y-imidazole are calculated from the Eq. 5 and are listed in the last column of Table 3.

$$S_N1\ \% = 100\, k_1/(k_1 + k_2\,[\text{imidazole}]) \quad (5)$$

The percentage of S_N1 in the reaction of benzyl bromide with Y-substituted imidazoles are generally increased with weaker nucleophile and that of the large steric effects such as 2-Me- imidazole. Going to the electron-donating substituents of Z-substituted benzyl bromides, its percentages are remarkably large, 51.2%, 28.9% 21.3% and 4.98% for Z=4-Me, H, 4-Br and 3-NO_2 in the case of Y=H, respectively. It is indicated that the less nucleophilic imidazole derivatives brings about the higher activation energy for bimolecular process and the more activated phenyl substituent make lower the activation energy for leading to preferential unimolecular over concerted bimolecular process.

In the case of typical S_N2 reaction, rate constants are determined under pseudo first-order condition and the reaction rates are given by Eq. 4. Therefore, the k_2 value is usually obtained from dividing k_{obs} by nucleophile concentration because the second-order rate constant, as listed in Table 1a, should be constant independent of nucleophile concentration.

As clearly shown in Table 2, however, the k_2 values in methanol are not constant for the resspective concentrations

Table 4. The Brönsted β^a Values for the Reactions of (Z)-Substituted Benzyl Bromides with (Y)-Substituted Imidazoles at 45 °C

Solvent \ Z	4-Me	H	4-Br	3-NO_2
acetonitrile	0.29	0.29	0.31	0.35
methanol	(0.0001)	(0.008)	(0.009)	(0.005)

[a]Except for Y; 2-CH_3

of nucleophile and increased significantly with low imidazole concentration in the reaction of electron-donating Z=4-CH_3. This indicates that the reaction proceeds through a competitive unimolecular and bimolecular reacction mechanism already-described.

Generally, Menschutkin reaction as shown Equation 3, typical S_N2 reaction, was formed charge separated activated complex from neutral reactants. So the polar complex[13] is easier to solvate with a more polar acetonitrile and hence its activation energy will be lowered which in turn the reaction will be promoted. In methanol, there is, however, not followed the tendencies observed in the case of acetonitrile. This may be explained that methanol solvates most readily with imidazole, thus lowers the free energy of imidazole, which increases the activation energy and reduces the reaction rate. The activated complex at transition state will also solvate with methanol but less effective than the starting amine does at ground state since the activated complex has penta coordinated structure and sterically more hindered. Reactivity by an S_N1 is favored by solvents of high ionizing power, that is, by polar protic methanol solvents that helps to pull the leaving group of -Br with hydrogen bond. This facts are in fair agreement with the experimental data as shown in Table 3, that is, the reaction of 4-methyl benzyl bromide with imidazole reacts predominantly an S_N1 mechanism than that of other electron-withdrawing benzyl bromides, so the ratio of the rate constants of acetonitrile/methanol are decreased with going to 4-CH_3 from 3-NO_2.

The k_1 values in Table 3 show a linear correlation with $\rho^+ = -1.75$ (R=0.997), mean that the intercept is related with S_N1 character. On the other hand, a plot of log k_2 *vs.* σ^+ gives a smooth curved correlation with negative ρ value in both solvents. The curved Hammett plot means that the change of the carbocationic character by the contribution of decreased bond formation to the nucleophile and/or increased bond cleavage.

In Table 4, the value of β in acetonitrile is very larger than that in methanol. Thus, from the sign of ρ and β value, this reaction leads to a dissociative S_N2 mechanism in acetonitrile, while in methanol, the reaction leads to an S_N1 or more dissociative S_N2 mechanism.

Experimental Section

Materials. All materials were purchased from Wako (Japan) or Merck (Germany). Acetonitrile and methanol was purified by distillation after adding anhydrous potassium carbonate for three days at room temperature. *p*-Bromobenzyl imidazolium bromide; imidazole (1.02 g, 0.015 mol) was added to a solution of *p*-bromobenzyl bromide (3.75 g, 0.015 mol) in anhydrous acetonitrile (50 mL). The mixture was heated under reflux for 3 h and then left overnight at room temperature. The product was separated from the solvent and washed with anhydrous ether,colorless crystals, mp 174-175 °C (recrystalized from acetone-hexane), $\delta_H(CDCl_3)$ 5.4 (CH_2, 2H, s), 7.6-7.7 (Ph-H, 4H, m), 7.7-7.8 (imidazole-H, 3H, m), 9.3 (N-H, 1H, s).

Kinetics. The reaction kinetics were followed by a conductometric method previously reported.[11-12]

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