Transition State Structure in the Reaction of Benzyl Bromides with Imidazoles and Pyridines

Hee-Soon Lee, Duk-Young Cheong, Soo-Dong Yoh,[*] Woo-Sik Kim,[†]
Young-Woo Kwak,[‡] Yong-Tae Park,[‡] and Jae-Keun Lee[‡]

Department of Chemistry Education, Kyungpook National University, Taegu 702-701, Korea
[†]Department of Polymer Science, Kyungpook National University, Taegu 702-701, Korea
[‡]Department of Chemistry, Kyungpook National University, Taegu 702-701, Korea
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The Menschuckin reaction of benzyl derivatives with pyridine have been studied many researchers[1-14] in various solvents and at both atmospheric and high pressure. From these reactions, such researchers attempted to gain a detailed mechanism by checking mainly substituent effects. Imidazole contains both a pyridine-type nitrogen in the five membered ring and a pyrrole-type nitrogen. Imidazole ($pK_a = 7.1$) is a much stronger base than pyridine ($pK_a = 5.2$) and an important compound among its various derivatives is the biologically active histidine.

There is a few report[15-17] in regards to the Menschutkin reaction attacking the nucleophilic imidazole. In this connection, the Menschutkin reaction of substituted benzyl bromides with substituted imidazoles and pyridines has been studied[16,18] in acetonitrile in order to investigate the substituent effect in substrate and both nucleophiles. The mechanistic information was gained from the linear free energy relationships using both notable Hammett and Brönsted type parameters and *ab initio* MO calculations were performed by using the GAUSSIAN 98 program to optimize stable and TS structure at the RHF/6-31+G(d) level[19] for the reaction of benzyl chloride with both nucleophiles.

The Hammett and Brönsted coefficients (ρ and β) are the first derivatives of log k as shown in Eqs. (1) and (2), respectively, both reflect the TS structures involved in a series of reactions with structural changes affecting the reaction center, and measure the degree of bond formation.

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

$$\beta = \partial \log k / \partial pK \qquad (2)$$

In this paper, the variation of the TS structure for imidazole and pyridine within the above reactions has been reported. Detailed results will be reported in due course.

Results and Discussion

The Second-order rate constants, two Brönsted $\beta_{nu,}$ and Hammett ρ_Y of pyridine, are summarized in Table 1. The substituent effect was accelerated by an electron-donation to both the substrate and nucleophiles of imidazole and pyridine, while electron-withdrawing reversed the effects in the

Table 1. Second-order Rate Constants $[10^4 \cdot k_2]$(L/mol·s) and Hammett ρ_Y (or Brönsted β_{Nu}) Constants for the Reactions (Z)-Substituted Benzyl Bromides with (Y)-Substituted Imidazoles and (Y)-Pyridines in Acetonitrile at 45 °C[a]

Nucleophile, (Y)		(Z)=4-CH₃	H	4-Br	3-NO₂
Imidazole	H	62.12	49.42	42.52	32.69
	1-CH₃	76.35	60.62	52.83	41.67
	4-CH₃	90.95	72.31	64.00	51.72
(β_{Nu})		(0.29)	(0.29)	(0.31)	(0.35)
β_{Nu} R		0.999	0.999	0.999	0.999
Pyridine	H	50.87	29.89	25.45	15.51
	3-CH₃	73.31	46.02	39.81	24.85
	4-NH₂	768.3	513.6	527.3	419.3
β_Y (β_{Nu})		-1.88 (0.30)	-1.95 (0.31)	-2.08 (0.33)	-2.27 (0.36)
β_{Nu} R		0.999	0.999	0.999	0.999

[a]Determined conductimetically in duplicate; average deviation $\leq \pm 3\%$.

substrate and both nucleophiles. Meanwhile, the second-order rate constants for the reaction of imidazole are larger than those of pyridine, due to mainly a larger basicity of imidazole without 4-amino pyridine.

The $|\rho_Y|$ values are increased toward to electron-withdrawing substituents and also are accord with the β_{nu} values in the Y-substituted pyridine series. The magnitudes of the $|\rho_Y|$ and β_{nu} values are degree of bond formation of benzyl α-carbon with N atom of mucleophile (C···N).[20] Therefore, this is the reason why the electron withdrawing group, Z = *p*-NO₂, has a large $|\rho_Y|$ and $\beta_{nu.}$
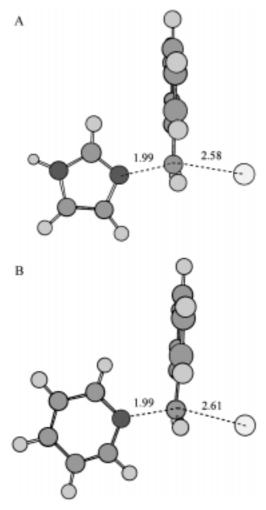
A comparison of β_{nu} of imidazole to that of pyridine is shown in Table 1. The values are very similar within the range of 0.29-0.36 both, suggesting that the degree of bond formation within both nucleophiles is similar in TS structure.

In Table 2, the negative ρ_Z value for the entire range of substituents indicates the dominance of bond fission in the transition state. When the ρ_Z value of imdazole is compared with that of pyridine, the former is less negative than that of pyridine, indicating that the degree of bond breaking is more advanced in the reaction of pyridine than in that of imidazole. These results are confirmed by the bond distance (C$_\alpha$··· Cl) as shown in the final column of Table 3, using the RHF/

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Notes

Table 2. Apparent Reaction Constants $(\rho_Z)^{1)}$ for the Reaction of (Z)-Substituted Benzyl Bromides with (Y)-Substituted Imidazoles and Pyridines in Acetonitrile at 45 °C

Nucleophile, (Y)		(Z)=4-CH$_3$	H	4-Br	3-NO$_2$
Imidazole	H	-0.34	-0.30	-0.27	-0.20
	1-CH$_3$	-0.34	-0.29	-0.25	-0.18
	4-CH$_3$	-0.34	-0.28	-0.23	-0.14
Pyridine	H	-0.72	-0.59	-0.52	-0.28
	3-CH$_3$	-0.64	-0.53	-0.47	-0.26
	4-NH$_2$	-0.43	-0.32	-0.26	-0.05

$^{1)}\rho_Z$ values are calculated from the partial differential of (log $k_2 = \rho_Z\sigma^+ + \rho_{ZZ}\sigma^{+2}$) in the reaction of (Z)-benzyl bromide with respective nucleophile.

Figure 1. Optimized TS structures of benzyl chloride with Imidazole (A) and Pyridine (B) by RHF/6-31+G(d) level.

6-31+G(d) basis set.

As shown in Table 3, the magnitude of the Mulliken charge of N on the imidazole is larger than that of pyridine, while the (C$_\alpha$) of benzyl fragments and the (Cl) of leaving fragments are smaller. The large positive charge of the N atom in imidazole indicates that the larger electron transfer from imidazole to the reaction center, and also shows that the positive charge of substrate (C$_\alpha$) is smaller than that of pyridine.

Table 3. Calculated Parameters of Optimized TS Structure for the Reaction of Benzyl Chloride with Imidazole and Pyridine by RHF/6-31+G(d) level

Substrate	Nucleophile	Mulliken Charge (sum=0)			Distance (Å)$^{1)}$	
		N of Nu.	C$_\alpha$ of Sub.	Cl	N⋯C$_\alpha$	C$_\alpha$⋯Cl
Benzyl Chloride	Imidazole	0.570	0.155	-0.725	1.99	2.58
	Pyridine	0.453	0.289	-0.742	1.99	2.61

$^{1)}$N⋯C and N⋯Cl bond length (Å) in the TS structure.

In conclusion, in the reaction of benzyl bromides with pyridines and imidazoles and the degree of bond formation between the two nucleophiles in the transition state is similar. In regards to the bond breaking of these reactions, the former is more advanced the latter as shown in the transition state structure in Figure 1.

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