Kinetics and Mechanism of Addition of Benzylamines to Methyl α-Cyanocinnamates in Acetonitrile
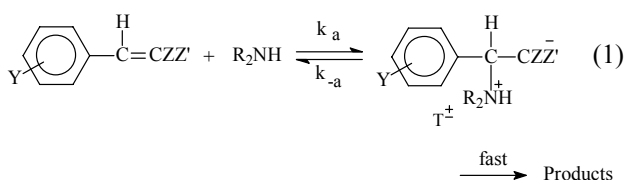
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Studies of substituent effects on the reactions of amine nucleophiles with olefins which are activated by electron-acceptors, Z and Z' in eq 1, have shown important difference

$$Y\text{---}\underset{}{\overset{H}{C}}=CZZ' + R_2NH \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} Y\text{---}\underset{\underset{T^{\pm}}{\overset{|}{R_2\overset{+}{N}H}}}{\overset{H}{\underset{|}{C}}}\text{---}C\bar{Z}Z' \quad (1)$$

$$\xrightarrow{\text{fast}} \text{Products}$$

in the mechanism between the reactions in aqueous solution and in acetonitrile. In aqueous solution, the reactions were found to proceed through a zwitterionic intermediate, $T^{\pm}$, with imbalanced transition states (TSs) in which the development of resonance into the ZZ' group lags behind charge transfer or bond formation.[1] The lag in resonance development has been expressed by a larger α_{nuc}, obtained by varying substituent Y (eq 1), than β_{nuc}, a Brönsted type coefficient based on variation of amine nucleophile.[1] The imbalance, $I_m = \alpha_{nuc} - \beta_{nuc}$, was
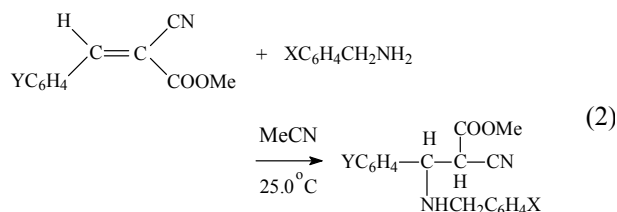

1   **2**
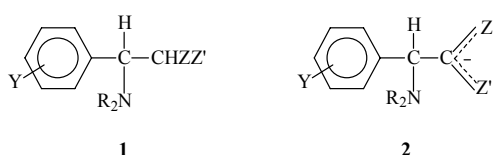
found to increase with increasing resonance stabilization of the carbanionic product, **2**, in aqueous solution, e.g., in the order CN, CN < H, NO₂.[1]

In contrast, however, the amine additions to olefins in acetonitrile were found to occur by a concerted formation of the C_α-N and C_β-H bonds in a single step process leading to a neutral product, **1**.[2] The rates of amine additions in acetonitrile are in general extremely slower than in aqueous solution ($k_a(aq) \cong 10^4 \cdot k_a(MeCN)$), but the relative order remains the same, $k_a(CN, CN) \gg k_a(H, NO_2)$.[1,2] An unexpected trend was observed in acetonitrile, however, that the α-carbon becomes more positive ($\rho_Y < 0$) in the TS than in the reactant for Z, Z'= CN, CN (benzylidenemalononitrile, BMN)[2b] in contrast to the negatively charged C_α ($\rho_Y > 0$) for Z, Z'= H, NO₂ (β-nitrostyrene, NS).[2a] The sign of ρ_Y is invariably positive in aqueous solution[1] as expected from an imbalanced TS in which a

greater degree of negative charge builds up C_α than that expected from a delocalized TS.

In view of this interesting trend, we conducted a similar amine addition reaction with methyl α-cyanocinnamate (MCC) in acetonitrile, eq 2. The purpose of the present paper is

$$\underset{YC_6H_4}{\overset{H}{>}}C=C\underset{COOMe}{\overset{CN}{<}} + XC_6H_4CH_2NH_2$$

$$\xrightarrow[25.0^{\circ}C]{MeCN} YC_6H_4\text{---}\underset{\underset{NHCH_2C_6H_4X}{\overset{|}{H}}}{\overset{H}{\underset{|}{C}}}\text{---}\underset{\overset{|}{H}}{\overset{COOMe}{\underset{|}{C}}}\text{---}CN \quad (2)$$

to further explore the different mechanism of the amine addition to olefin between the reactions in aqueous solution and in acetonitrile by examining the structure-reactivity behavior of olefins activated by cyano and keto groups, eq 2.

Another interest in this work is to examine the sign and magnitude of the cross-interaction constant,[3] ρ_{XY} in eqs 3

$$\log (k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (3a)$$

$$\rho_{XY} = \partial\rho_X/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_X \quad (3b)$$

where X and Y are substituents in amine (BA) and in the substrate (MCC), respectively, in eq 2. The ρ_{XY} has been shown to have a negative sign in addition processes, e. g., bond formation in the S_N2 reactions and in the addition of amines to an olefin with *ca.* $-0.6 \sim -0.8$.[3]

Results and Discussion

The reactions studied in this work (eq. 2) obeyed a simple rate law given by eqs 4 and 5 where k_2 is the rate constant for the benzylamine (BA) addition to the methyl α-cyanocinnamates (MCC). No catalysis by a second BA molecule was detected

$$-d[MCC]/dt = k_{obs}[MCC] \quad (4)$$

$$k_{obs} = k_2[BA] \quad (5)$$

in the present studies. Plots of k_{obs} *vs* [BA] were linear for *ca.*

10-fold increase in [BA]. The k_2 values obtained from the slopes of these plots are summarized in Table 1. The selectivity parameters, the Hammett ρ_X and ρ_Y values and the Brønsted β_X values, are also shown in Table 1 together with the corss-interaction constant ρ_{XY} (eq. 3). Although the β_X values are based on the plots of log k_2 (MeCN) against pK_a of the conjugate acid BAs in water, they are thought to be reliable since it was found both experimentally and theoretically that the absolute values of pK_a for conjugate acids of amines in MeCN differ from those in water by a reasonably constant value of ΔpK_a ($=^1pK_{MeCN} - pK_{H_2O}$) $\cong 7.5$.[4] Bruice and coworker[5] have investigated ester hydrolysis mechanism using *p*-nitrophenyl 2-cyano-3-(*p*-methoxyphenyl) propenoate (*p*-CH$_3$O-C$_6$H$_4$CH=C(CN)COOC$_6$H$_4$-*p*-NO$_2$). They found that the ester hydrolysis occurs with the expulsion of *p*-NO$_2$-phenoxide leaving group in aqueous solution. This step was found to have a substantially high

activation barrier, $\Delta H^{\neq} = 26.9 \pm 1.0$ kcal mol^{-1} with $\Delta S^{\neq} = -6.0 \pm 3.1$ e.u. In the present work, such ester aminolysis mechanism may also be a possibility, but in our product analysis we found no ester aminolysis product. The leaving group in the present case is MeO$^-$ group which is a very poor nucleofuge and the reaction medium is also an aprotic one (MeCN) so that such possibility can be safely ruled out.[6]

In general, rates of amine additions to activated olefins are over 10^2-fold faster in water than those for the corresponding reaction in acetonitrile.[1] Although the rate-limiting steps in both media are believed to be the initial nucleophilic addition, k_a in water and in acetonitrile, effects of the activating (electron-withdrawing) groups (Z,Z') on the rate are found to be different: In water the stabilization of the incipient sp^3 carbanionic center, **1**, (delocalization of which into the activating groups (Z,Z') lags behind the Cα-N bond formation) is important

Table 1. The Second Order Rate Constants, $k_2 \times 10^3$ dm^3 mol^{-1} s^{-1} for the Addition Reactions of Methyl α-Cyano-Y-cinnamates with X-Benzylamines in Acetonitrile at 25.0 °C

X	Y					$\rho_Y{}^a$
	p-OMe	*p*-Me	H	*p*-Cl	*p*-Br	
p-OMe	12.7 ± 0.1^b 8.86 ± 0.09 6.35 ± 0.05^c	11.1 ± 0.1	16.8 ± 0.2	27.5 ± 0.6	44.5 ± 1.2 31.6 ± 0.9 22.7 ± 0.5	1.05 ± 0.05
p-Me	6.95 ± 0.07	8.67 ± 0.08	12.7 ± 0.1	20.1 ± 0.4	23.2 ± 0.6	0.990 ± 0.05
H	4.70 ± 0.04	5.67 ± 0.05	8.15 ± 0.08	12.4 ± 0.2	14.3 ± 0.3	0.910 ± 0.05
p-Cl	4.41 ± 0.05 3.09 ± 0.03 2.23 ± 0.02	3.59 ± 0.03	4.98 ± 0.05	7.40 ± 0.07	11.3 ± 0.1 8.01 ± 0.07 5.53 ± 0.04	0.810 ± 0.03
$\rho_X{}^d$	-0.920 ± 0.04	-0.990 ± 0.03	-1.06 ± 0.05	-1.15 ± 0.06	-1.20 ± 0.04	$\rho_{XY}{}^e = -0.490$ (± 0.01)
$\beta_X{}^f$	0.880 ± 0.04	0.940 ± 0.04	1.01 ± 0.04	1.09 ± 0.05	1.14 ± 0.03	

[a]The σ values were taken from Hansch, C.; Leo, A. A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. Correlation coefficients were better than 0.995 in all cases. [b]At 35.0 °C. [c]At 15.0 °C. [d]The source of σ is the same as for footnote a. Correlation coefficients were better than 0.997 in all cases. [e]Correlation coefficients was 0.997. [f]The pK_a values were taken from Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. Correlation coefficients were better than 0.997 in all cases. pK_a = 9.67 was used for X = p-CH$_3$O.(reference Oh, H. K.; Lee, J. Y.; Lee, I. *Bull. Korean Chem. Soc.* **1998**, *19*, 1198).

Table 2. Comparisons of Reactivity Parameter for the Addition Reaction, YC$_6$H$_4$CH=CZZ′+XC$_6$H$_4$CH$_2$NH$_2$, in Acetonitrile at 25.0 °C

Entry	$k_2{}^a$/M^{-1}s^{-1}	log.$k_0{}^b$	$\rho_X{}^c$	$\rho_Y{}^c$	$\rho_{XY}{}^d$	$\Sigma\sigma^e$	$\Sigma\sigma^{-f}$
1 (BMN)^g	1.48	4.94*	-1.62	-0.550	-0.310	1.32	2.00
2 (BID)^h	1.48	4.20	-1.10	0.410	-0.330	0.830	2.08
3 (NS)^i	2.63×10^{-2}	2.55	-1.22	1.73	-0.400	0.780	1.27
4 (NSB)^j	2.69×10^{-2}	1.42	-0.820	1.27	-0.520	0.770	1.27^l
5 (MCC)^k	8.15×10^{-3}	-	-1.06	0.910	0.490	1.11	1.75
6 (CNS)^j	1.26×10^{-3} (30 °C)	≈ 3.35	-1.15	1.10	-0.670	0.920	1.00^m

[a]For X=Y=H at 25.0 °C unless otherwise noted in parentheses. *Extrapolated value. [b]Intrinsic rate constants, k_0, for carbanion forming reactions (k_a in eq. 1) in 50% DMSO-50% H$_2$O at 20.0 °C with amines.[2b] [c]For Y=H and X=H, respectively. [d]Correlation coefficients are better than 0.997 in all cases. [e]Normal Hammett substituent constant (s_p). [f]Exalted substituent constant (s_p^-) for direct conjugation with anionic functional center.[6] [g]Benzylidenemalononitrile.[1b] [h]Benzylidene-1,3-indandione.[1c] [i]β-Nitrostyrene.[1a] [j]β-Nitrostilbene and β-cyano-β-4-nitrostilbene.[1d] [k]This work. [l]The value of Ph group is excepted.[1d] [m]The value of *p*-NO$_2$Ph group is excepted.[1d]

so that the rate (intrinsic rate) increases with the sum of electron accepting power of the activating groups, $\Sigma\sigma_p$.[1] In acetonitrile, however, the rate was found to increase with the sum of electron-accepting ability of Z,Z′ through π-orbitals i.e., the sum of through conjugative electron-accepting power, $\Sigma\sigma_p^-$. This is of course a manifestation of the mechanistic difference in the two media, i.e., the amine addition reaction in water proceeds through an intermediate, whereas that in acetonitrile proceeds by a single step addition. The rates of amine additions to various activated olefins in water and in acetonitrile are compared in Table 2. The available rate data in aqueous solution show general parallelism between the intrinsic rate (log k_0)[7] and the sum of the normal substituent constants ($\Sigma\sigma_p$). For MCC the data in aqueous solution are not available, but we can predict that the log k_0 values will fall in between benzylidenemalononitrile (BMN) and benzylideneindanedione (BID). In acetonitrile, however, only the through conjugative electron shift, i.e., the electron shift through π-orbital, is important, and β-nitrostyrene (NS) and β-nitrostilbene (NSB) have nearly the same rate constants since in the latter the benzene ring has negligible π-electron accepting effect due to non-coplanarity of the ring with the vinylic π-orbital.[1d,3] Again the rate for β-cyano-β-4-nitrostilbene (CNS) is the lowest due to the non-coplanarity of the p-nitrobenzene ring. The rate for MCC is faster than CNS but is slower than NSB ($\cong$ NS), which indicates that the through conjugative electron-withdrawing power of the COOMe group ($\sigma_p^- = 0.75$) is not fully operative.

The cross-interaction constants, ρ_{XY} in eqs. 3, are all negative for the six series in Table 2. This shows that the cross-interaction constants, ρ_{XY}, in the bond formation process is negative.[1c,3] The size of ρ_{XY} for MCC has again an intermediate value, but is well within the range of the ρ_{XY} values found for S_N2 processes ($\rho_{XY} = -0.6 \sim -0.8$) provided the fall-off factor of ca. 0.47[8] for an intervening CH_2 group in the benzylamine is accounted for $\rho_{XY} \cong 0.42$. It is also notable that the magnitude of ρ_{XY} (-0.49) as well as ρ_Y (+0.91) value for MCC is larger than those for BMN ($\rho_{XY} = -0.31$)[1c] and BID ($\rho_{XY} = -0.33$).[1d] These are consistent with somewhat higher degree of N-Cα bond formation in the TS than for the BA addition to other activated olefins listed in Table 2.[3]

The kinetic isotope effects, k_H/k_D (Table 3), involving deuterated benzylamine nucleophiles[9] ($XC_6H_4CH_2ND_2$) are greater than one, $k_H/k_D = 1.8 \sim 2.1$, suggesting a possibility of hydrogen-bond formation (**3** and/or **4**) as have been proposed for the BA additions in acetonitrile to other activated olefins listed in Table 2. The hydrogen bonding of the N-H proton toward one of the oxygen atoms in the COOMe group, **3**, (mostly toward the ester oxygen, since the trans C=C/C=O form is more stable) is also a possibility, albeit such hydrogen-bonding may involve a too long H-bond as the lone pair on N (n_N) of BA approaches to the $C\alpha = C\beta$ π-bond almost vertically from above (or below) the molecular plane of MCC.

The k_H/k_D (> 1.0) values increase with an electron acceptor Y and an electron donor X, which is in line with the C_α-N bond formation in the TS with a greater degree of bond making by a stronger electron-donor X, $\delta\sigma_X < 0$ (with a larger positive Y, $\delta\rho_Y > 0$) and by a stronger electron-accepter Y, $\delta\sigma_Y > 0$ (with a larger negative X, $\delta\rho_X < 0$) leading to a negative cross-interaction constant ρ_{XY}, eq. 3b.

3   **4**
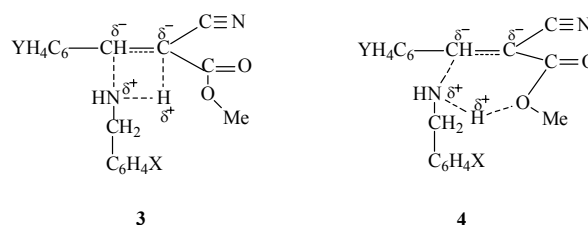
The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (Table 4), are quite similar to those for the corresponding reaction of other activated olefins in Table 2 in acetonitrile with low $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values. These are consistent with the concurrent N-C$_\alpha$ and H-C$_\beta$ bond formation in the TS, **3**. Since exclusion repulsion energy in the N-C$_\alpha$ bond making is partially offset by the bond energy of the partial bond formed, and also by the H-C$_\beta$ bond formation, barrier to bond formation in the rate determining step should be low with little variation depending on X and/or Y. This is because the higher barrier for a weaker nucleophile ($\delta\sigma_x > 0$) is partially offset by a stronger acidity of the N-H proton in the H-bond formation. The large negative entropy of activation is in line with four-centered constrained TS structure, **3**.

In summary, the kinetics of the addition of X-substituted benzylamines(BA) to Y-substituted methyl α-cyanocinnamate(MCC) in acetonitrile at 25.0 °C have been studied. The

Table 3. Kinetic Isotope Effects on the Second-Order Rate Constants (k_2) for the Reactions of Methyl α-Cyano-Y-cinnamates with Deuterated X-Benzylamines in Acetonitrile at 25.0 °C

X	Y	$k_H \times 10^3$ $(M^{-1}s^{-1})$	$k_D \times 10^3$ $(M^{-1}s^{-1})$	k_H/k_D
p-OMe	p-OMe	8.86 ($\pm$ 0.09)	4.84 ($\pm$ 0.05)	1.83 $\pm$ 0.03[a]
p-OMe	p-Me	11.1 ($\pm$ 0.10)	5.81 ($\pm$ 0.06)	1.91 $\pm$ 0.03
p-OMe	H	16.8 ($\pm$ 0.25)	8.48 ($\pm$ 0.08)	1.98 $\pm$ 0.03
p-OMe	p-Cl	27.5 ($\pm$ 0.30)	14.3 ($\pm$ 0.21)	2.06 $\pm$ 0.04
p-OMe	p-Br	31.6 ($\pm$ 0.88)	14.9 ($\pm$ 0.35)	2.12 $\pm$ 0.04
p-Cl	p-OMe	3.09 ($\pm$ 0.02)	1.74 ($\pm$ 0.01)	1.78 $\pm$ 0.02
p-Cl	p-Me	3.59 ($\pm$ 0.03)	1.94 ($\pm$ 0.01)	1.85 $\pm$ 0.02
p-Cl	H	4.98 ($\pm$ 0.05)	2.59 ($\pm$ 0.02)	1.92 $\pm$ 0.02
p-Cl	p-Cl	7.40 ($\pm$ 0.06)	3.68 ($\pm$ 0.02)	2.01 $\pm$ 0.02
p-Cl	p-Br	8.01 ($\pm$ 0.08)	3.85 ($\pm$ 0.03)	2.08 $\pm$ 0.03

[a]Standard deviations.

Table 4. Activation Parameters[a] for the Reactions of Methyl α-Cyano-Y-cinnamates with X-Benzylamines in Acetonitrile

X	Y	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1} K^{-1}
p-OMe	p-OMe	5.6	49
p-OMe	p-Br	5.4	47
p-Cl	p-OMe	5.6	51
p-Cl	p-Br	6.8	49

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg, K. B. *Physical Organic Chemistry*; Wiley: New York, 1964; p 378) are $\pm$ 0.5 kcal mol^{-1} and $\pm$ 2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

reaction is studied under pseudo-first-order conditions by keeping a large excess of BA over MCC, respectively. The addition of BA to MCC occurs in a single step in which the additon of BA to C_α of MCC and proton transfer from BA to C_β of MCC take place concurrently with a four-membered cyclic transition state structure. The sign and magnitude of the cross-interaction constant, ρ_{XY} (= 0.49), are comparable to those found in the normal bond formation processes in the S_N2 and addition reactions. The normal kinetic isotope effect ($k_H/k_D >$ 1.0) and relatively low $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values are also consistent with the mechanism proposed.

Experimental

Materials. Merk GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used after recrystallization. Methyl cyanoacetate and benzaldehydes were Aldrich reagent.

Preparartions of methyl α-cyanocinnamates. The methyl α-cyanocinnamates were prepared by the literature method of Zabicky.[10] A 0.1 M ethanolic solution of both benzaldehyde and methyl cyanoacetate with few drops of piperidine was refluxed for 4 ~ 6 hours. The solvent was quickly evaporated, and the residue cooled, filtered off, and purified by repeated recrystallisations from ethanol (yield > 85%). Melting point, IR (Nicolet 5BX FT-IR) and ^1H and ^{13}C NMR (JEOL 400 MHz) data were found to agree well with the literature values.[10]

Kinetic measurement. The reaction was followed spectrophotometrically by monitoring the decrease in the concentration of methyl-α-cyanocinnamate, [MCC], at λ_{max} of the substrate to over 80% completion. The reaction was studied under pseudo-first-order condition, [MCC] = 8.0×10^{-5} M and [BA] = 0.1 ~ 0.4 M at 25.0 ± 0.1 °C. The pseudo first-order rate constant, k_{obs}, was determined form the slope of the plot (r > 0.994) ln[MCC] (2.303 log [MCC]) *vs* time. Second-order rate constants, k_N, were obtained from the slope of a plot (r > 0.993) of k_{obs} *vs.* benzylamine with more than four concentrations of more than three runs and were reproducible to within ± 3%.

Product analysis. The analysis of final products was difficult due to partial decomposition during product separation and purification. We therefore analysed the reaction mixture by NMR (JEOL 400 MHz) at appropriate intervals under exactly the same reaction conditions as the kinetic measurement in CD_3CN at 25.0 °C. Initially we found a peak for CH in the reactant, p-$ClC_6H_5CH=C(CN)COOMe$ at 8.23 ppm, which was gradually reduced, and a new two peaks for CH-CH in the product, p-$ClC_6H_5(MeOC_6H_4CH_2NH)CH-CH(CN)COOMe$, grew at 3.79 and 4.78 ppm as the reaction proceed. No other peaks or complications were found during the reaction except the 3 peak height changes indicating that the reaction proceeds with no other side reactions.

References

1. (a) Oh, H. K.; Yang, J. H.; Sung, D. D.; Lee, I. *J. Chem. Soc. Perkin Trans*. **2000**, *2*, 101. (b) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2000**, *65*, 2188. (c) Oh, H. K.; Kim, T. S.; Lee, H. W.; Lee, I. *J. Chem. Soc. Perkin Trans*. **2002**, *2*, 282. (d) Oh, H. K.; Yang, J. H.; Hwang, Y. H.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2002**, *23*, 221. (e) Oh, H. K.; Kim, T. S.; Lee, H. W.; Lee I. *Bull. Korean Chem. Soc.* **2003**, *24*, 193. (f) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2000**, *65*, 5391. (g) Oh, H. K.; Kim, I. K.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2004**, *69*, 3806.(f) Oh, H. K.; Ku, M. H.; Lee, H. W. *Bull. Korean Chem. Soc.* **2005**, *26*, 935.
2. (a) Bernasconi, C. F. *Acc. Chem. Res*. **1987**, *20*, 301. (b) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017.
3. (a) Lee, I. *Chem. Soc. Rev*. **1990**, *19*, 317. (b) Lee, I. *Adv. Phys. Org. Chem*. **1992**, *27*, 57. (c) Lee, I.; Lee, H. W. *Coll. Czech. Chem. Commun*. **1999**, *64*, 1529.
4. Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302.
5. Inoue, M.; Bruice, T. C. *J. Am. Chem. Soc*. **1982**, *104*, 1644.
6. Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2002**, *23*, 221.
7. Bernasconi, C. F.; Ketner, R. J. *J. Org. Chem*. **1998**, *63*, 6266.
8. (a) Page, M.; Williams, A. *Organic and Bio-organic Mechanisms*; Longman: London, 1977; p 250. (b) Hansch, C.; Hoekman, D.; Gao, H. *Chem. Rev*. **1996**, *96*, 1045.
9. Lee, I. *Chem. Soc. Rev*. **1995**, *24*, 223.
10. (a) Zabicky, I. *J. Chem. Soc*. **1961**, 683. (b) Ku, M. H.; Oh, H. K.; Ko, S. *Bull. Korean Chem. Soc.* **2007**, *83*, 1217. (c) Oh, H. K. *Bull. Korean Chem. Soc.* **2008**, *29*, 1195.