DOI 10.5012/bkcs.2010.31.10.2801

Single Electron Transfer (SET) Pathway: Nucleophilic Substitution Reaction of 4-Chloro-7-nitrobenzofurazan with Anilines in MeOH-MeCN Mixtures

Hojune Choi, Kiyull Yang,* Sang-Gyeong Lee,† Jong Pal Lee,‡ and In Sun Koo*

*Department of Chemistry Education and Research Institute of Natural Science, Gyeongsang National University, Jinju 660-701, Korea. *E-mail: iskoo@gnu.ac.kr*
†Department of Chemistry and Research Institute of Natural Science, Gyeongsang National University, Jinju 660-701, Korea
‡Department of Chemistry, Dong-A University, Pusan 604-714, Korea
Received August 19, 2010, Accepted August 28, 2010

A nucleophilic substitution reaction of 4-chloro-7-nitrobenzofurazan (NBF-Cl) with anilines in MeOH-MeCN mixtures was conducted at 25, 35, and 45 °C. Based on the higher β_{nuc} values (1.0 - 1.6) of the reaction and a good correlation of the rate constants with the reduction potentials of the aniline nucleophiles, the present reaction was initiated by a single electron transfer (SET). After this step, the reaction proceeds through a transition state similar to the normal S_NAr-Ad.E pathway.

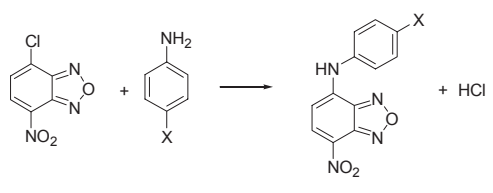
Key Words: Single electron transfer (SET) pathway, S_NAr-Ad.E mechanism, Structure-reactivity correlations, Hydrogen bond, Isodielectric solvents

Introduction

Nucleophilic aromatic substitution reactions are thought to involve four possible mechanisms: (i) bimolecular nucleophilic aromatic substitution, S_NAr-Ad.E (addition-elimination pathway);[1] (ii) an elimination-addition process, S_NAr-E.Ad or S_N1Ar (similar to a S_N1 mechanism);[1,2] (iii) bimolecular concerted aromatic nucleophilic substitution, S_N2Ar (similar to a S_N2 mechanism);[1] and (iv) a single electron transfer (SET) pathway.[3-5] In the SET mechanism, the reaction accompanies the formation of a σ-complex intermediate through an initial single electron transfer from a nucleophilic amine donor to an aromatic acceptor moiety having strong electron withdrawing substituents.[3-5] The nucleophilic aromatic substitution reaction of the aromatic compounds with amines generally involves the S_NAr-Ad.E mechanism (eq. 1).[6,7] However, the nucleophilic aromatic substitution reaction with high β_{nuc} (> 1.0) values involves the formation of an intermediate through the initial SET pathway.[3-5] The significance of structure-reactivity relationships such as Hammett ρ, Brønsted β coefficients, and cross-interaction constants ρ_{ij} as a mechanistic criterion for nucleophilic substitution or addition reactions as well as in the proton transfer process has been discussed by Jenks,[8] Terrier,[9] and Lee.[9,10] The β_{nuc} values are commonly accepted as measures of the degree of charge transfer from a base to an acid partner in the transition state (TS).[8,11] However, as pointed out by Bordwell and others, such β_{nuc} values indicate the degree of bond formation in the rate-determining TS of S_NAr-Ad.E and S_N2 reactions.[12] The normal range of β_{nuc} values would be between 0 and 1.[9] However, in previous works β_{nuc} values outside the normal range have often been observed.[9,13-15] In particular, a nucleophilic aromatic substitution reaction with high β_{nuc} values proceeds through the SET pathway rather than the normal S_NAr-Ad.E mechanism.

Many researchers are interested in the nature of specific solvent effects on nucleophilic aromatic substitution in isodielectric solvents such as methanol-acetonitrile mixtures.[16,17] Rates of reactions between polar molecules are quite insensitive to change from a dipolar aprotic to a protic solvent of the same dielectric constant when there exists only electrostatic interactions between reactants (or TS) and solvents.[16,17] However, when specific solvation occurs between them, the rate is remarkably changed in isodielectric solvents such as methanol-acetonitrile mixtures.[16,18]

The reaction mechanism, reactivity, and solvents effects in these systems have been examined extensively,[19-21] and we have recently studied the nucleophilic displacement reaction of strongly activated chlorinated aromatic compounds in methanol-acetonitrile solvents.[22] It was assumed that electrophilic catalysis by methanol occurred, likely as a result of hydrogen bonding between alcoholic hydrogen, leaving chloride in the TS.[22] Therefore, mechanistic study on the nucleophilic substitution reaction between aromatic compounds having strong electron withdrawing substituents and amines is very important in examining the effects of protic solvents in the ground state (GS) or TS (or intermediate). In this work, we determined the second-order rate constants for the reaction of 4- chloro-7-nitrobenzofurazan (NBF-Cl, eq. 1) with anilines in MeOH-MeCN mixtures at 25, 35, and 45 °C. In order to discuss the reaction mechanism and solvent effects, we determined transition state parameters, ρ_N and β_{nuc}, using Hammett and simple Brönsted relationships, reduction potential (E^o) of amines, and activation parameters.



1 2 3 (1)

X = NH_2, OH, OCH_3, CH_3, H, Cl

Results and Discussion

The present reactions obey the kinetic law given in eq. 2. Plots of pseudo-first-order rate constants k_{obs} against [anilines] show a good linear relationship, as shown in Figure 1. The second-order rate constants k_2, were determined from the slopes of these plots and are summarized in Table 1. No third-order or higher-order terms were detected, and no complication was encountered in the determination of k_{obs} or in the linear plots of eq. (1b). This suggests that neither base-catalysis nor noticeable side reactions take place, and the overall reaction follows the route given by eq. 1.[21]

$$\text{Rate} = k_2\,[\text{anilines}][\text{substrates}] = k_{obs}\,[\text{substrates}] \quad (2a)$$

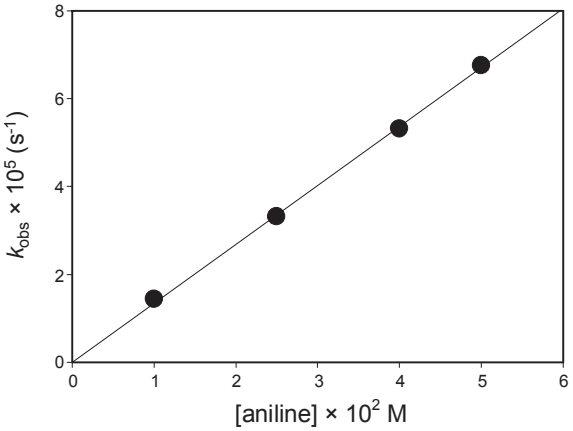


Figure 1. A plot of the observed first-order rate constant ($k_{obs} \times 10^5$ s^{-1}) against concentration of aniline for the reaction of 4-chloro-7-nitrobenzofurazan with aniline in 50% MeCN-50% MeOH solvents at 35 °C ($k_2 = 1.32 \times 10^{-3}$ $M^{-1}s^{-1}$).

Table 1. The second-order rate constants ($k_2 \times 10^3$) for the reaction of 4-chloro-7-nitrobenzofurazan with 4-X-anilines in MeCN-MeOH mixtures

	pK_a	Solvent (v/v)	$k_2 \times 10^3$ ($M^{-1}s^{-1}$)
4-Cl	3.81	MeOH	0.723 (r = 0.998)
		50% MeCN-50% MeOH	0.151(r = 0.999)
		MeCN	0.0117 (r = 0.999)
H	4.58	MeOH	2.67 (r = 0.999)
		50% MeCN-50% MeOH	0.851 (r = 0.981)
		MeCN	0.0687 (r = 0.999)
4-CH_3	5.07	MeOH	9.59 (r = 0.984)
		50% MeCN-50% MeOH	6.35 (r = 0.981)
		MeCN	0.351 (r = 0.997)
4-OCH_3	5.29	MeOH	29.3 (r = 0.995)
		50% MeCN-50% MeOH	16.8 (r = 0.999)
		MeCN	1.59 (r = 0.996)
4-OH	5.50	MeOH	57.1 (r = 0.999)
		50% MeCN-50% MeOH	26.6 (r = 0.999)
4-NH_2	6.08	MeOH	149 (r = 0.999)
		50% MeCN-50% MeOH	140 (r = 0.999)
		MeCN	49.9 (r = 0.999)

$$k_{obs} = k_2\,[\text{anilines}] \quad (2b)$$

Solvent effects. Table 1 shows that the second-order rate constant (k_2) for the reaction of NBD-Cl with anilines increases as the methanol volume percent rises, i.e., increases from 1.17×10^{-5} $M^{-1}s^{-1}$ in acetonitrile to 72.3×10^{-5} $M^{-1}s^{-1}$ in methanol for *p*-chloroaniline nucleophile. Converse results are obtained for the reaction of 4-substituted-2,6-dinitrochloro benzenes with pyridines[12(c)] and benzylamines[23] in MeOH-MeCN mixtures at 25 °C. It is noted that the solvation effect on TS or intermediate by methanol is more important than the hydrogen bonded effect on aniline by methanol in GS. However, hydrogen bonded pyridines and benzylamines by methanol are less reactive than free pyridine and benzylamine in acetonitrile solvent: attacking pyridine is a weak nucleophile in methanol, but becomes more reactive in acetonitrile.[12(c)] The increases in the second-order rate constant (k_2) by increasing the volume percent of methanol indicate that the stabilization of the TS or Meisenheimer σ complex due to the hydrogen bond with methanol is greater than stabilization of ground state (GS). The specific rate ratio, k_{MeOH}/k_{MeCN}, varied significantly over the full range of 4-substituted aniline nuclophiles. The ratios decrease from 61.8 to 38.8, 27.3, 18.4, and 2.98 as the pK_a values of anilines increase from 3.83 (for 4-Cl) to 4.58 (for 4-H), 5.07 (for 4-CH_3), 5.29 (for 4-OCH_3), and 6.08(for 4-NH_2), respectively. This may be attributed to the reduced nucleophilicity of anilines in methanol solvent, which stems from enhanced hydrogen bonding ability between aniline and methanol at higher pK_a values.

Structure-reactivity correlations. Table 1 shows that the rate constant increases in the order of X = 4-Cl < H < 4-CH_3 < 4-OCH_3 < 4-OH < 4-NH_2, where X is aniline substituents. The β_{nuc} values were determined by plotting log k_2 (MeCN-MeOH) against pK_a (H_2O) of anilines.[24,25] Both the Hammett and Brönsted plots show good linearity, as presented in Figures 2 and 3. The transition parameters, Hammett ρ_N values, and Brönsted β_{nuc} values are summarized in Table 2. The ρ_N values are −2.70, −3.45, and −4.17 in MeOH, 50% MeOH-50% MeCN, and MeCN, respectively (Table 2). These results are comparable with the values of −3.70 reported by Ryan for substitutions of picryl chloride by a similar set of anilines in a 75 - 25 (v/v) EtOH-H_2O mixture,[26] and are also similar to the results for the substitution reaction of 4-X-2,5-dinitrochlorobenzene with anilines, benzylamines, and pyridines in MeOH-MeCN (v/v) mixtures.[12(c),23,27] The β_{nuc} values are 1.08, 1.36, and 1.62 in MeOH, 50% MeOH-50% MeCN, and MeCN, respectively (Table 2). The large negative ρ_N and large positive β_{nuc} values obtained in the present work are consistent with significant development of a positive charge at the nitrogen atom of the aniline moiety and the negative charge developed in the substrate aromatic

Table 2. Hammett ρ_N values and Brönsted β_{nuc} values for the reaction of 4-chloro-7-nitrobenzofurazan with 4-X-anilines in MeOH-MeCN mixtures at 25 °C

Solvent (v/v)	ρ_N	β_{nuc}
MeOH	−2.70	1.08
50% MeCN-50% MeOH	−3.45	1.36
MeCN	−4.17	1.62

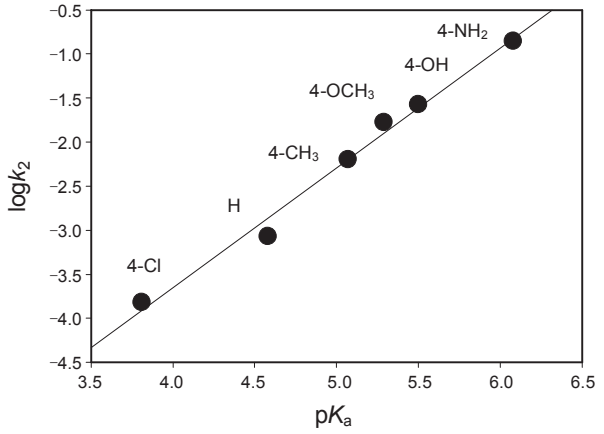


Figure 2. Typical Brönsted plot for the reaction of 4-chloro-7-nitrobenzofurazan with 4-X-anilines in 50% MeCN-50% MeOH solvents at 25 °C (β_{nuc} = 1.36, r = 0.988).

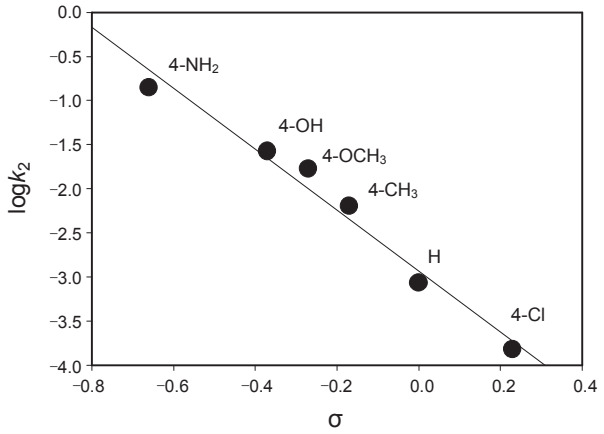
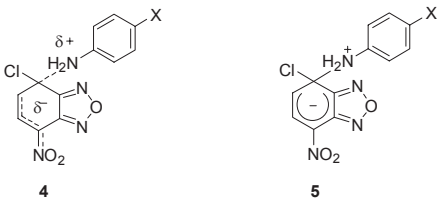
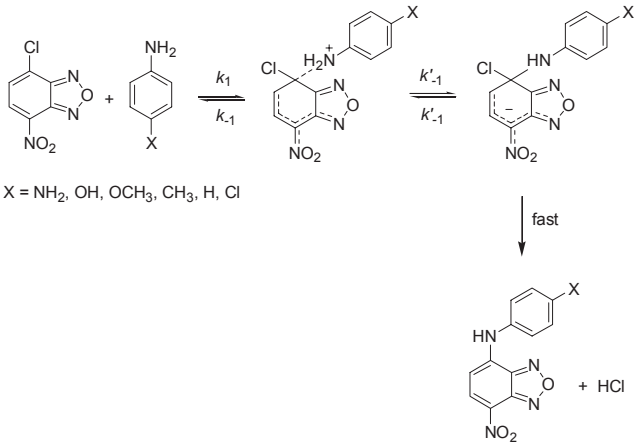


Figure 3. Typical Hammett plot for the reaction of 4-chloro-7-nitrobenzofurazan with 4-X-anilines in 50% MeCN-50% MeOH solvents at 25 °C (ρ_N = −3.45, r = 0.974).



Scheme 1. Transition state (**1**) and Meisenheimer complex (**2**)



Scheme 2

ring in the TS **4** for formation of a zwitterionic intermediate σ-complex **5**. The zwitterionic intermediate (Meisenheimer σ-complex) is stabilized through declocalization of negative charge by resonance, as shown in Scheme 1.

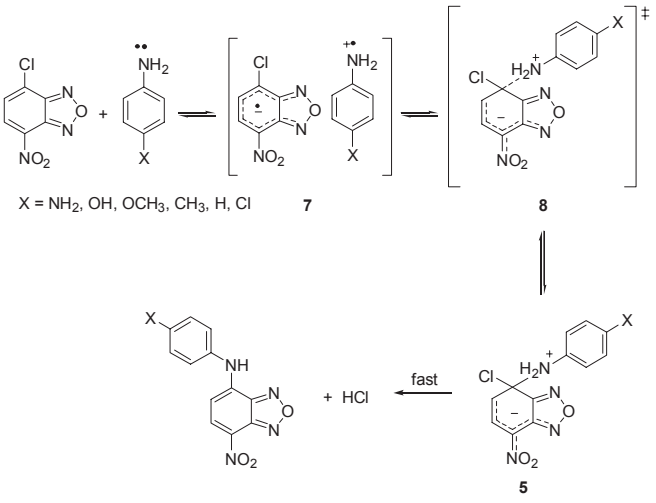
The large negative ρ_N and large positive β_{nuc} values are in keeping with the traditional interpretation of nucleophilic aromatic substitution by amines, and this behavior accords well with the S_NAr-Ad.E mechanism shown in Scheme 2, where

Table 3. Additional rate constants ($M^{-1}s^{-1}$) for the reaction of 4-chloro- 7-nitrobenzofurazan with 4-X-anilines in MeCN-MeOH mixtures at various temperatures and enthalpies ($kJ \cdot mol^{-1}$) and entropies ($J \cdot K^{-1} \cdot mol^{-1}$) of activation

	pK_a	Solvent (v/v)	t (°C)	$k_2 \times 10^3$ ($M^{-1}s^{-1}$)	$\Delta H^{\neq}$ ($kJ \cdot mol^{-1}$)	$-\Delta S^{\neq}$ ($J \cdot K^{-1} \cdot mol^{-1}$)
4-Cl	3.81	MeOH	25 °C	0.723	19.3	241
			35 °C	0.900		
			45 °C	1.26		
H	4.58	MeOH	25 °C	2.67	42.3	152
			35 °C	4.51		
			45 °C	8.36		
		50% MeCN-50% MeOH	25 °C	0.851	36.9	180
			35 °C	1.32		
			45 °C	2.32		
4-CH_3	5.07	50% MeCN-50% MeOH	25 °C	6.35	38.2	159
			35 °C	9.90		
			45 °C	17.9		
		MeCN	25 °C	0.351	41.2	172
			35 °C	0.820		
			45 °C	1.06		
4-OCH_3	5.29	MeCN	25 °C	1.59	44.4	150
			35 °C	2.78		
			45 °C	5.24		

rate-limiting formation of the intermediate σ complex is followed by fast expulsion of the chloride leaving group.[2(a),6,7,9,24] This indicates that deprotonation of complex **5** to give conjugate base **6** as well as subsequent re-aromatization of these species is a fast process relative to the nucleophilic addition step.[9,24] The reactions of NBF-Cl with 4-X-subsiututed anilines have also been performed at 25.0, 35.0, and 45 °C to determine activation parameters. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values determined in the present system are summarized in Table 3. Such large negative $\Delta S^{\ddagger}$ values and small positive $\Delta H^{\ddagger}$ values suggest that the reaction takes place through a typical rate-determining nucleophilic addition in the present study.[28,29]

Single electron transfer (SET) pathway. The β_{nuc} values are close to or greater than unity for various nucleophilic aromatic substitution reactions. The large β_{nuc} values show greater sensitivity to substituent changes on the reaction at hand relative to the reference ionization equilibrium,[9,1(a),30] or in the case of S_N2 reactions in terms of the advent of a SET pathway, where full electronic transfer occurs prior to the coupling of electrophilic and nucleophilic partners.[3-5] The high β_{nuc} values associated with the present reactions may be a reflection of a SET pathway, as described in Scheme 3.[9] As in Scheme 3, one of the electrons of the lone pair in aniline (donor) is transferred to the nitrobenzofurazan acceptor moiety (**7**), and subsequent coupling between the resulting cation and the anion radicals within the solvent cage takes place. The transition state for the coupling reaction might be structure **8**, and σ-complex intermediate **5** will be formed as a result.



Scheme 3

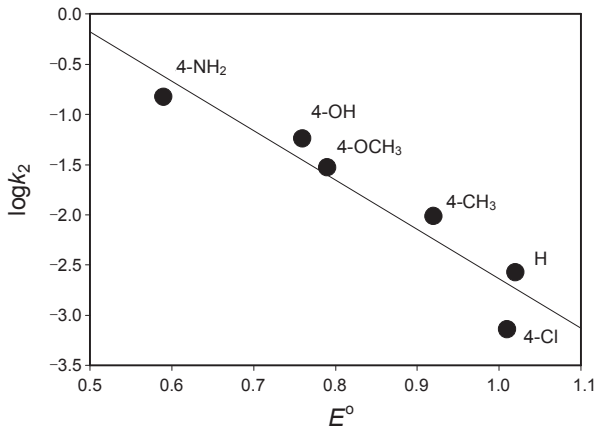


Figure 4. The influence of the reduction potential E^{o} of anilines on the rates of reaction of 4-chloro-7-nitrobenzofurazan with 4-X-anilines in MeOH solvents at 25 °C (r = 0.899).

One electron reduction potentials E^{o} of 4-X-anilines in aqueous solutions were measured by Jonsson *et al.*[30] Both the E_o and σ_p^+, and pK_a and σ_p^+, plots show good linearity.[30(a)] This indicates that the β_{nuc} values are associated with one electron reduction (or oxidation potential), E^{o}. Plots of log k_2 against E^{o} values of 4-substituted anilines show a good linear relationship, as indicated in Figure 4. These results are clearly consistent with the SET pathway, as shown in Scheme 3.

Conclusions

A nucleophilic substitution reaction of 4-chloro-7-nitrobenzofurazan with anilines in MeOH-MeCN mixtures was conducted. Based on the higher β_{nuc} values (1.0 - 1.6) of the reaction and a good correlation of the rate constants with the reduction potentials of the aniline nucleophiles, the reaction was initiated by a single electron transfer (SET) mechanism, where one of the electrons in aniline is transferred to nitrobenzofurazan. After this step, the reaction of the present nitrobenzofurazan, which is an electrophilic benzenoide system such as 2,4,6-trinitochlorobenzene, proceeds through a transition state similar to the normal S_NAr-Ad.E pathway.

Experimental Section

Materials. The 4-chloro-7-nitrobenzofurazan (Aldrich-GR), aniline (Aldrich-GR), *p*-anisidine (Aldrich-GR), *p*-chloroaniline (Aldrich-GR), and *p*-toludine (Aldrich-GR) were used commercial grade (> 98%). Merck HPLC grade (< 0.1% water) methanol and acetonitrile were used without further purification.

Kinetics. Rates were measured conductimetrically at least in duplicate as in previous work.[21,22,24]

Product analysis. Anilinium salts were liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra after the completion of the reaction with those of authentic samples under same reaction conditions. For example, ε = 18992 M^{-1} cm^{-1} at 476 nm for anilinium salt (X = OCH_3). And also the products identified by ^{1}H NMR spectrum (Bruker 300 Mhz).

References

1. Wu, Z.; Glaser, R. *J. Am. Chem. Soc.* **2004**, *126*, 10632.
2. (a) Miller, J. *Aromatic Nucleophilic Substitution Reaction*; Elsevier: London, 1968. (b) Ross, S. D. *Prog. Phys. Org. Chem.* **1963**, *1*, 31.
3. Bordwell, F. G.; Branca, J. C.; Cripe, T. A. *Isr. J. Chem.* **1985**, *26*, 357.
4. Bordwell, F. G.; Clemens, A. H. *J. Org. Chem.* **1981**, *46*, 1037.
5. Bordwell, F. G.; Hugues, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991.
6. Terrier, F. *Aromatic Nucleophilic Substitution Reaction*; VCH publisher: New York, 1991, Chapers 1 and 2.

7. Bernasconi, C. F. *MTP Int. Rev. Sci. Org. Chem. Ser. 1* **1973**, *3*, 33.
8. (a) Jenks, W. P. In *Nucleophilicity*; Harris, J. M., Mc Manus, S. P., Eds.; Advances in Chemistry Series 215, American Chemical Society: Washington, DC, 1987; p 155.
9. Terrier, F.; Mokhtari, M.; Goumony, R.; Hallé, J.-C.; Buncel, E. *Org. Biomol. Chem.* **2003**, *1*, 1757.
10. (a) Lee, I. *Chem. Soc. Rev*. **1990**, *19*, 317. (b) Lee, I. *Adv. Phy. Org. Chem*. **1992**, *27*, 57.
11. (a) Williams, A. *Chem. Soc. Rev*. **1994**, 93. (b) Page, A.; Williams, A. In *Organic and Bio-organic Mechanisms*; Longman: Harlow, Chapter 3. (c) Kresge, A. *J. Chem. Soc. Rev*. **1973**, *2*, 475.
12. (a) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991. (b) Moutiers, G.; Guével, E. L.; Cannes, C.; Terrier, F.; Buncel, E. *Eur. J. Org. Chem.* **2001**, 3279. (c) Sung, R. Y.; Choi, H.; Lee, J. P.; Park, J. K.; Yang, K.; Koo, I. S. *Bull. Korean Chem. Soc*. **2009**, *30*, 1579.
13. (a) Bordwell, F. G.; Boyle, W. J. *J. Am. Chem. Soc*. **1972**, *94*, 3907. (b) Bordwell, F. G.; Hautala, J. A. *J. Org. Chem*. **1978**, *43*, 3116.
14. Jenks, W. P.; Haber, M. T.; Herschlag, D.; Nazaretian, K. L. *J. Am. Chem. Soc*. **1986**, *108*, 479.
15. Bernasconi, C. F. *Adv. Phy. Org. Chem*. **1992**, *27*, 119.
16. Lee, H. W.; Lee, I. *J. Korean Chem. Soc*. **1978**, *22*, 221.
17. (a) Koniglio, B. O. *et al*. *J. Chem. Soc*. **1966**, 152. (b) Parker, A. J. *Ibid* **1961**, 4398.
18. (a) Kingsbury, C. A. *J. Org. Chem.* **1964**, *29*, 3262. (b) Ballestreri, F. P. *et al. J. Org. Chem*. **1977**, *42*, 1415.
19. Banjoko, O.; Babatunde, I. A. *Tetrahedron* **2004**, *60*, 4645.
20. Mancini, P. M.; Fortunato, G. G.; Votlero, L. R. *J. Phys. Org. Chem.* **2004**, *17*, 138.
21. Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *J. Org. Chem*.**1998**, *63*, 9834.
22. Kang, D. H.; Koo, I. S.; Lee, J. G.; Lee, I. *J. Korean Chem. Soc*. **1985**, *29*, 565.
23. Koo, I. S. *et al.* Unpublished results.
24. Hwang, J.; Yang, K.; Koo, I. S.; Sung, D. S.; Lee, I. *Bull. Korean Chem. Soc*. **2006**, *27*, 733.
25. (a) Ritchie, C. D. In *Solute-Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Chapter 4. (b) Coetzee, J. F. *Progress in Physical Organic Chemistry*; Streitwieser, A., Jr., Taft, R. W., Eds.; Wiley; New York, 1967; Vol. 4, pp 54-92. (c) Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2099. (d) Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302.
26. Ryan, J. J.; Humffray, A. A. *J. Chem. Soc. B* **1967**, 1300. (Introduction ref. 2 추가)
27. Sung, R. Y.; Choi, H.; Lee, J. P.; Park, J. K.; Koo, I. S. *Bull. Korean Chem. Soc*. **2009**, *30*, 1579.
28. Shin, G.-C.; Hwang, J.; Yang, K.; Koo, I. S.; Lee, I. *Bull. Korean Chem. Soc*. **2005**, *26*, 1981.
29. Bernasconi, C. F.; Stronach, M. W. *J. Am. Chem. Soc.* **1993**, *115*, 1341.
30. (a) Jonsson, M.; Lind, J.; Ericksen, T. E.; Merényi, G. *J. Am. Chem. Soc.* **1994**, *116*, 1423. (b) Bacon, J.; Adams, R. N. *J. Am. Chem. Soc*. **1968**, *90*, 6596.