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References

- Gutsche, C. D. *Calixarenes*, Royal Society of Chemistry: Cambridge, 1989.
- Vicens, J.; Bohmer, V. *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Kluwer Eds., Dordrecht, 1991.
- Böhmer, V. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713.
- Zhang, L.; Godinez, L. A.; Lu, T.; Gokel, G. W.; Kaifer, A. E. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 235.
- Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Sching, M. J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767.
- Hofmeister, G. E.; Hahn, F. E.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 2318.
- (a) Arimura, T.; Edamitsu, S.; Shinkai, S.; Manabe, O.; Muramatsu, T.; Tashiro, M. *Chem. Lett.* **1987**, 2269. (b) Ferguson, G.; Gallagher, J. F.; Guinta, L.; Neri, P.; Pappalardo, S.; Parisi, M. *J. Org. Chem.* **1994**, *59*, 42.
- Verboom, W.; Bodewes, P. J.; van Essen, G.; Timmerman, T.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 499.
- Andreotti, G. D.; Bohmer, V.; Jordon, J. D.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, A. *J. Org. Chem.* **1993**, *58*, 4023.
- Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997.
- Bohmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 17.
- Nam, K. C.; Kim, J. M.; Kook, S. K.; Lee, S. J. *Bull. Korean Chem. Soc.* **1996**, *17*, 499.
- Kim, J. M.; Chun, J. C.; Nam, K. C. *Bull. Korean Chem. Soc.* **1997**, *18*, 409.
- Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675.
- Nam, K. C.; Kim, J. M.; Kim, D. S. *Bull. Korean Chem. Soc.* **1995**, *16*, 186.
- Gutsche, C. D.; Lin, L. G. *Tetrahedron* **1986**, *42*, 1633.
- Jaime, C.; Mendoza, J. D.; Parados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.
- Pappalardo, S.; Guinta, L.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611.
- Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.
- Nam, K. C.; Kim, D. S. *Bull. Korean Chem. Soc.* **1994**, *15*, 284.
- Sheldrick, G. M.; Shelxl-97: Program for the Solution and Refinement of Crystal Structures. University of Göttingen, Germany, 1997.
- International Table for X-ray Crystallography, Vol. C, Kynoch Press, Birmingham, England, 1980.

A Mechanistic Study on Addition Reactions of Alicyclic Amines to 3-Butyn-2-one

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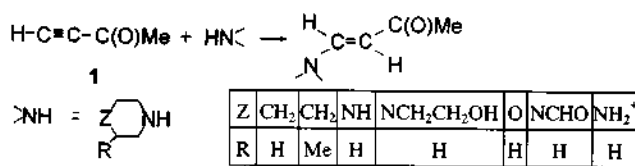
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Second-order rate constants have been measured spectrophotometrically for the addition reaction of a series of alicyclic amines to 3-butyne-2-one to yield their respective enamines at 25.0 °C. The reactivity of the amines increases with increasing the basicity of the amines. However, the Brønsted-type plot obtained exhibits a downward curvature as the basicity of the amines increases, *i.e.* β_{inc} decreases from 0.3 for low basic amines ($pK_a < 9$) and to 0.1 for highly basic amines ($pK_a > 9$). Such a curvature in the Brønsted-type plot is clearly indicative of a change in the reaction mechanism or transition state structure. From the corresponding reactions run in D_2O , the magnitude of kinetic isotope effect (KIE) has been calculated to be about 0.8 for highly basic amines and 1.21 for weakly basic amines. The difference in the magnitude of KIE also supports a change in the reaction mechanism or transition state structure upon changing the basicity of the amines. Furthermore, the small KIE clearly suggests that H^+ transfer is not involved in the rate-determining step, *i.e.* the addition reaction is considered to proceed via a stepwise mechanism in which the attack of the amines to the acetylene is the rate-determining step. The curvature in the Brønsted-type plot has been attributed to a change in the degree of bond formation between the amine and the acetylene.

Introduction

Nucleophilic additions to carbon carbon triple bonds have been widely investigated due to synthetic interests.¹⁻⁵ Par-

ticularly, additions of nitrogenous nucleophiles to acetylenes with electron withdrawing groups such as COR, CO₂R, CN and SO₂R have been frequently employed as a route to a variety of heterocyclic compounds.⁵ The types of het-



erocyclic compounds prepared in this manner include pyrazoles, pyrroles, isoxazoles, etc. 3-Butyn-2-one (**1**), readily available from the oxidation of 3-butyn-2-ol, is one of the intensively studied acetylenes. Recently, we have investigated the reaction of **1** with NH_2NH_2 to form 3-methylpyrazole *via* a Michael-type addition intermediate.⁶ However, few mechanistic studies have been performed for the reaction of **1** with secondary amines which yield enamines.⁷ In order to obtain more reliable information about the reaction mechanism, we have studied the reactions of **1** with a series of alicyclic secondary amines whose pK_a range is over 5.5 in the pK_a unit as shown in Scheme 1.

Experimental

Materials. 3-Butyn-2-one (**1**) was obtained from Aldrich and distilled just before use. Other chemicals including the amines used in the present study were of the highest quality available from Aldrich (or Tokyo Kasei for 3-methylpiperidine) and generally recrystallized or distilled before use. Doubly glass distilled water was further boiled and cooled under a nitrogen atmosphere just before use.

Kinetics. The kinetic study was performed with a Hitachi U-2000 UV-VIS spectrophotometer equipped with a Neslab RTE-110 model constant temperature circulating bath to keep the reaction mixture at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of the products at a fixed wavelength corresponding to the maximum absorption (λ_{max}) of the respective enamines. All the reactions carried out under pseudo-first order conditions in which the concentration of amines was at least 20 times greater than that of **1**. The stock solutions of amines were prepared freshly with amine and 0.5 equivalent amount of HCl (or amine hydrochloride and 0.5 equivalent NaOH) to suppress formation of hydroxide by solvolysis.

Results and Discussion

All the reactions obeyed pseudo-first-order kinetics up to over 90% of the total reaction. The pseudo-first-order rate constants (k_{obs}) were measured from the well known equation, $\ln(A_{\infty} - A_t) = -k_{\text{obs}} \cdot t + c$. Apparent second-order rate constants (k_{app}) have been obtained from the slopes of the linear plots of k_{obs} vs amine concentration. The enamines formed in this way have been reported to be the trans isomer in most cases.^{7,8} The kinetic results are summarized in Table 1 and demonstrated in Figures 1-3.

In Figure 1 are graphically demonstrated the kinetic results for the addition reactions of **1** with 7 alicyclic amines. One can see that the reactivity of the amines increases with increasing their basicity. However, the Brønsted-type plot is not linear but exhibits a downward curvature upon increasing the basicity of amines. It has been generally

Table 1. Summary of Apparent Second-order Rate Constants (k_{app}) for Addition Reactions of Alicyclic Amines to 3-Butyn-2-one in H_2O at 25.0 ± 0.1 °C

Amines	pK_a ^a	k_{app} , $\text{M}^{-1}\text{s}^{-1}$
1. piperazinium ion	5.68	0.851 (0.705) ^c
2. 1-formylpiperazine	7.98 ^b	3.20 (3.18) ^c
3. morpholine	8.36	4.12 (4.07) ^c
4. 1-(2-hydroxyethyl)piperazine	9.38 ^b	6.00
5. piperazine	9.82	13.3 (15.3) ^c
6. 3-methylpiperidine	11.07	10.2 (12.9) ^c
7. piperidine	11.22	10.9 (12.7) ^c

^a pK_a data from reference 17, unless noted otherwise. ^b pK_a data from reference 11b. ^c The rate constant for the corresponding reaction run in D_2O .

known that a linearity in a Brønsted-type plot indicates a common reaction mechanism for a given series of reactants, while a break or curvature is suggestive of a change in reaction mechanism or transition state structure.^{9,10} Therefore, one might attribute the nonlinearity in Figure 1 to a change in reaction mechanism or transition state structure.

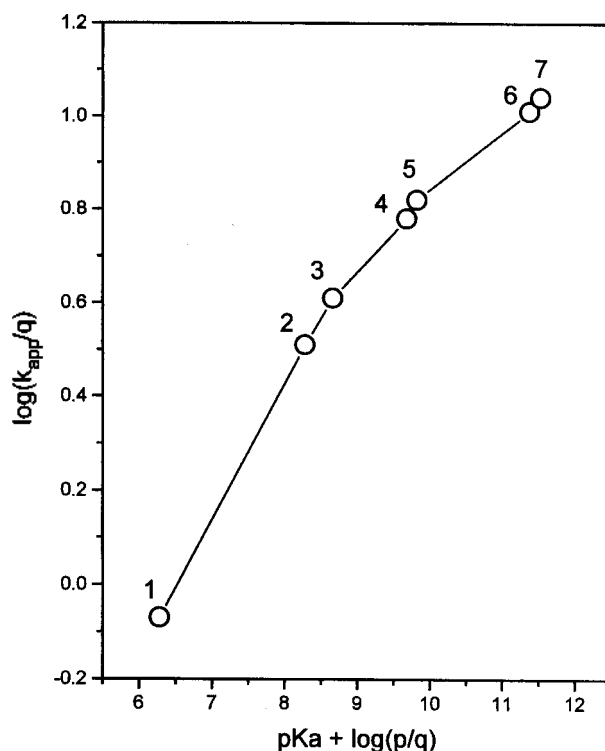
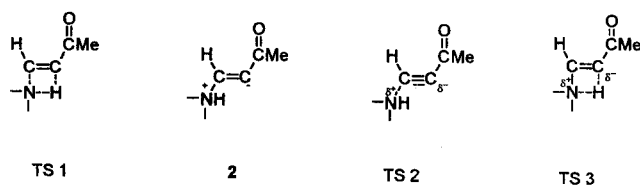


Figure 1. A Brønsted-type plot for the addition reaction of alicyclic amines to 3-butyn-2-one in water at 25.0 °C. $\log k_{\text{app}}$ and pK_a 's are statistically corrected by using p and q , i.e. $p=2$ (except $p=4$ for piperazinium ion) and $q=1$ (except $q=2$ for piperazine). See references 11b and 13.

The present reaction could proceed *via* one step concerted mechanism with a transition state similar to TS1, *i.e.* the nucleophilic attack by >NH and proton transfer from the nitrogen atom to the carbon atom occur concertedly. The reaction could also proceed in a stepwise mechanism with an addition intermediate **2**. In a stepwise mechanism, the transition state structure would resemble either TS2 or TS3 depending on the rate-determining step (RDS). It is noted that both TS2 and TS3 experience partial charge separation while TS1 does not.

One might suggest that the reaction proceeds *via* TS1 based on the fact that only the trans isomers have been obtained. In this mechanism, proton transfer is involved in the RDS, and therefore, primary kinetic isotope effect (KIE) is expected. In order to determine the magnitude of KIE, the reactions have been performed in D₂O. In Figure 2 are demonstrated the kinetic results for the reactions of **1** with piperazinium ion and piperidine in H₂O and D₂O. The magnitudes of KIE have been calculated to be 1.21 and 0.86 for the reaction with piperazinium ion and piperidine, respectively. The KIE values of other amines are about 0.8 for strongly basic amines but about 1.0 for weakly basic amines. The KIE value of 1.2 is too small to be primary KIE. Moreover, the inverted KIE (<1.0) clearly suggests that proton transfer is not involved in the RDS. Therefore, one can eliminate a possibility of a concerted mechanism (TS1).

The nucleophilic attack process would be accelerated with increasing the basicity of amines, while the proton transfer process from the nitrogen atom to the carbon atom in the present system (*e.g.* TS3) would be decelerated as the amine becomes more basic. Consequently, the effect of amine basicity on rate would be insignificant for the reac-

tions in which proton transfer is involved in the RDS. As shown in Figure 1, the reactivity of the amines used in the present study appears to be not so sensitive to the basicity of the amines, *i.e.* β_{nuc} values have been calculated to be about 0.3 for the weakly basic amines and about 0.1 for the strongly basic amines. Therefore, one might suggest that the present reactions proceed *via* TS3 based on the small β_{nuc} values. However, this mechanism also requires primary KIE. The small KIE values clearly rule out the possibility of TS3.

TS2 is the transition state structure for the reactions in which proton transfer occurs after the RDS. In this mechanism, no primary KIE is expected. Therefore, one can propose that the present reactions proceed *via* TS2, based on the absence of primary KIE. In order to examine this proposal, the reaction of **1** with piperazinium ion has been performed in 3 different pHs (pH=5.38, 5.68, 5.98) by changing buffer ratio. The kinetic results are demonstrated in Figure 3. One can see that the plots of k_{obs} vs amine concentration are linear and the slope of the plots (k_{app}) appears to be slightly different upon changing pH of the reaction medium. However, the difference in k_{app} values is considered to be insignificant and within the experimental error ($\pm 3\%$). If piperazinium ion or its conjugate acid behaved as a general base or acid catalyst, one should have observed significant difference in the k_{app} value with upward curvatures in Figure 3. Therefore, the linearity shown in Figure 3 suggests that proton transfer is definitely not involved in the RDS of the present reaction.

The magnitude of β_{nuc} value has been generally understood to represent the degree of bond formation or charge transfer from a nucleophile to an electrophile at the transition state. Since the degree of charge transfer would be

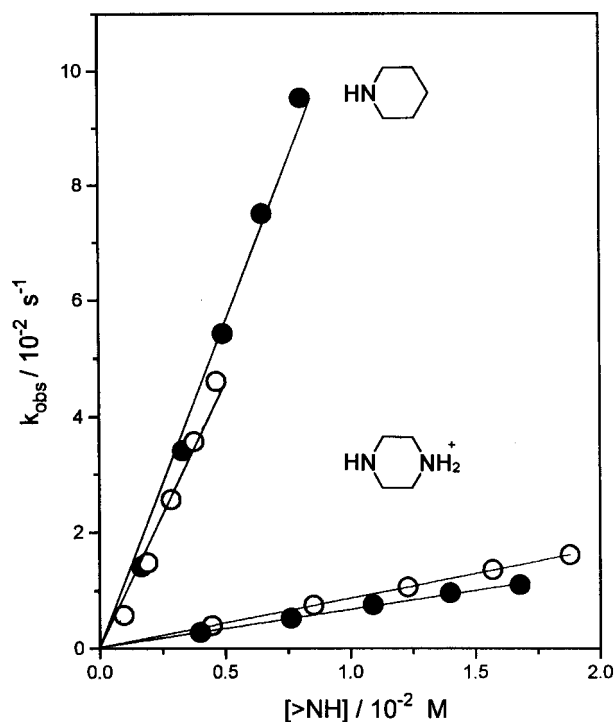


Figure 2. Plots showing kinetic isotope effect for the addition reaction of piperidine and piperazinium ion to 3-buten-2-one in H₂O (●) and D₂O (○) at 25.0 °C.

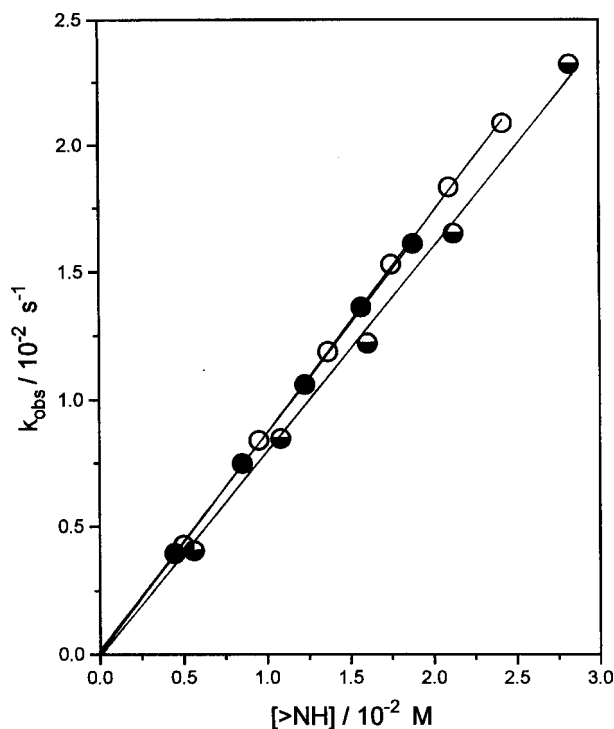


Figure 3. Plots showing dependence of rate on pH for the addition reaction of piperazinium ion to 3-buten-2-one at 25.0 °C. (pH 5.38 (●), 5.68 (○) and 5.98 (◐)).

less significant for neutral amines than anionic nucleophiles, one can expect smaller β_{nuc} value for the reactions with amines than with anionic nucleophiles. Therefore, one might consider that the small β_{nuc} values in the present system are simply due to the use of neutral amines as the nucleophile. However, a change in the reaction mechanism has been also suggested to influence the magnitude of β_{nuc} values significantly. For example, aminolysis of carboxylic esters has been generally understood to proceed in a stepwise mechanism and the magnitude of β_{nuc} values has been reported to be in the range of 0.7-1.0 for the reactions whose RDS is the second step (e.g. leaving group departure).¹¹⁻¹³ However, the magnitude of β_{nuc} has been reported to decrease up to 0.1-0.3 when the RDS changes from the second step to the first step (e.g. nucleophilic attack to form an addition intermediate).¹¹⁻¹³ The β_{nuc} value of 0.1-0.3 in the present system is similar to the one observed in aminolysis of carboxylic esters in which the nucleophilic attack process is the RDS, supporting that the present reactions proceed *via* TS2.

It has been well known that the effect of solvent on rate is dependent on the charge type of reactants and transition states.^{14,15} Significant rate enhancements have been often reported for the reactions with anionic nucleophiles upon solvent change from H₂O to dipolar aprotic solvents such as MeCN and DMSO due to destabilization of the ground state.^{14,15} However, on the contrary, the reactions with neutral nucleophiles (e.g. amines) have been reported to exhibit rate retardation in dipolar aprotic solvents.¹⁶ The reactants in the present system are neutral in charge but the transition state would develop partial charge (e.g. TS2). Such a charged transition state would be less solvated in MeCN than in H₂O. Accordingly, the rate in the present system would decrease upon solvent change from H₂O to MeCN. However, such a rate decrease would be expected to be less significant for the reactions proceeding with less charge developed transition state. As mentioned in the preceding section, one might consider that the degree of charge transfer (or charge development) would be less significant for the reactions with more basic amines based on the smaller β_{nuc} value for the more basic amines (e.g. 0.1 for strongly basic amines and 0.3 for weakly basic amines in Figure 1).

In order to examine this argument, the reactions of **1** with morpholine and piperidine have been performed in MeCN. Both reactions with morpholine and piperidine have been found to be less reactive in MeCN than in H₂O as expected. Besides, the rate decrease has been found to be less significant for the more basic piperidine system (e.g. 10.9 M⁻¹s⁻¹ in H₂O and 5.62 M⁻¹s⁻¹ in MeCN) than the less basic morpholine system (e.g. 4.12 M⁻¹s⁻¹ in H₂O and 0.52 M⁻¹s⁻¹ in MeCN), indicating that the charge development in the transition state is less significant for the more basic amine system. This is completely consistent with the proposal made from the magnitude of β_{nuc} value in the preceding section.

Conclusions

The present kinetic study has allowed us to conclude the following. (1) The present reaction proceeds in a stepwise mechanism with the transition state similar to TS2. (2) The degree of bond formation between the nucleophile and sub-

strate becomes smaller as the amine basicity increases, which is responsible for the curvature in Figure 1.

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References

1. Patai, S., Ed.; *The Chemistry of Carbon Carbon Triple Bond*, Part 2; John Wiley and Sons: 1978; pp 813-976.
2. (a) Truce, W. E.; Markley, L. M. *J. Org. Chem.* **1970**, *35*, 3275. (b) Ruder, S. M.; Kulkarni, V. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2119. (c) Seyferth, D.; Wood, T. G. *Organometallics.* **1988**, *7*, 714.
3. Singaram, B.; Rangaishenvi, M. V.; Brown, H. C.; Goraliski, C. T.; Hasha, D. L. *J. Org. Chem.* **1991**, *56*, 1543.
4. (a) Mueller, R. H.; Thompson, M. E. *Tetrahedron Lett.* **1980**, *21*, 1093. (b) Breus, V. A.; Neklyudov, S. A.; Solomov, B. N.; Kanovalove, A. I. *Zh. Org. Khim.* **1983**, *19*, 1613.
5. (a) Sinskey, M. S.; Bass, R. G. *J. Heterocyclic Chem.* **1984**, *21*, 759. (b) Acheson, R. M.; Woollard, J. J. *Chem. Soc., Perkin I.* **1975**, 446.
6. Um, I. H.; Lee, J. S.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1997**, *18*, 268.
7. (a) Um, I. H.; Kim, K. H.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1993**, *14*, 307. (b) Singaram, B.; Goraliski, C. T.; Fisher, G. B. *J. Org. Chem.* **1991**, *56*, 5691. (c) Marshall, J. A.; Flynn, D. A. *J. Org. Chem.* **1979**, *44*, 1391. (d) Wender, P. A.; Eissenstat, M. A. *J. Am. Chem. Soc.* **1978**, *100*, 292.
8. (a) Truce, W. E.; Gorbaty, M. L. *J. Org. Chem.* **1970**, *35*, 2113. (b) Truce, W. E.; Tichenor, G. J. W. *J. Org. Chem.* **1972**, *37*, 2391.
9. Chapman, N. B.; Shorter, J., Eds.; *Advances in Linear Free Energy Relationships*; Plenum: London, 1972.
10. (a) Um, I. H.; Chung, E. K.; Kwon, D. S. *Tetrahedron Lett.* **1997**, *38*, 4787. (b) Um, I. H.; Hong, Y. J.; Kwon, D. S. *Tetrahedron* **1997**, *53*, 5073. (c) Um, I. H.; Oh, S. J.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1996**, *17*, 802.
11. (a) Castro, E. A.; Pizarro, M. I.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 5982. (b) Castro, E. A.; Santos, J. G.; Tellez, J.; Umana, M. I. *J. Org. Chem.* **1997**, *62*, 6568.
12. (a) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. (b) Campbell, P.; Lapinskas, B. A. *J. Am. Chem. Soc.* **1977**, *99*, 5378.
13. Um, I. H.; Kim, M. J.; Min, J. S.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1997**, *18*, 523.
14. Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.
15. (a) Um, I. H.; Lee, G. J.; Yoon, H. W.; Kwon, D. S. *Tetrahedron Lett.* **1992**, *33*, 2023. (b) Um, I. H.; Oh, S. J.; Kwon, D. S. *Tetrahedron Lett.* **1995**, *36*, 6903. (c) Um, I. H.; Hahn, G. J.; Lee, G. J.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1992**, *13*, 642. (d) Um, I. H.; Lee, G. J.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1989**, *10*, 620.
16. Um, I. H.; Shin, E. H.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1996**, *17*, 234.
17. Jencks, W. P.; Regenstein, F. *Handbook of Biochemistry. Selected Data for Molecular Biology*; Sober, H. A. Ed.; The Chemical Rubber Co., 1968.