http://dx.doi.org/10.5012/bkcs.2011.32.11.4095

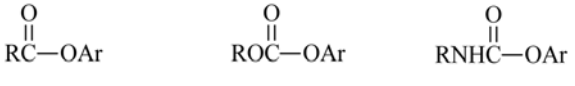
Kinetics and Mechanism of the Aminolysis of Aryl *N*-Isopropyl Thiocarbamates in Acetonitrile

Hyuck Keun Oh

Department of Chemistry, Research Institute of Physics and Chemistry, Chonbuk National University, Chonju 561-756, Korea
**E-mail: ohkeun@jbnu.ac.kr*
Received August 22, 2011, Accepted September 16, 2011

Key Words : Nucleophilic substitution, Aryl *N*-isopropyl thiocarbamates, Cross-interaction constant, Kinetic isotope effects, Concerted mechanism

Aryl esters, **1**, carbonates, **2**, and carbamates, **3**, are three classes of compounds which differ only in the acyl part, R, RO and RNH where R is alkyl or aryl. The aminolysis

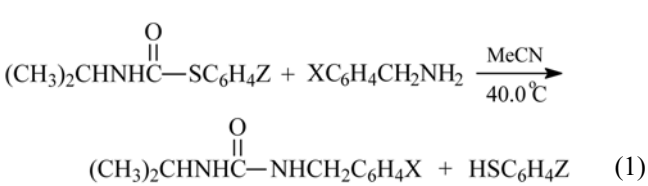


1 **2** **3**

mechanism of the carbonates is quite similar to that of esters, **1**, and carbonates, **2**, especially to the latter. For example, the aminolysis of aryl O-ethylcarbonates[1] (**2a**; R=Et) and aryl *N*-phenylcarbamates[2] (**3a**; R=C_6H_4Y) were found to proceed *via* two reaction pathway, uncatalyzed and catalyzed, through a zwitterionic tetrahedral intermediate, $T^{\pm}$. For the two (**2a** and **3a**) aminolysis reactions with benzylamines, the β_X values are large ($\beta_X > 1.0$) and the signs of ρ_{XY} (+1.10 for **3a**) and ρ_{XZ} (+0.16 for **2a**) are positive with adherence to the selectivity-reactivity principle (RSP).[3]

The stepwise aminolysis mechanism of **2a** through a tetrahedral intermediate, however, shifts to a concerted process where the leaving group is changed to a thiophenoxide[4] (**2b**; EtOC(=O)-SAr) instead of a phenoxide ($^-$OAr). The push provided by an EtO group to expel $^-$SAr in $T^{\pm}$ is now strong enough to make the intermediate so unstable that the intermediate can not exist. In view of the similar strong push expected from a $(CH_3)_2CNH$ group to expel the $^-$SAr group in $T^{\pm}$, it is of interest to see whether the aminolysis mechanism of the thiol analog of aryl *N*-isopropyl thiocarbamates, $(CH_3)_2CHNHC(=O)SC_6H_4Z$ (**3b**), also shifts to a concerted mechanism or not.

In order to pursue further the mechanistic similarities between carbamates and carbonates, we carried out kinetic studies on the aminolysis of aryl *N*-isopropyl thiocarbamates ($(CH_3)_2CHNHC(=O)SC_6H_4Z$) with benzylamines in acetonitrile, Eq. (1). The primary purpose of this work is to establish the aminolysis mechanism for Eq. (1) and to examine the effect of the nonleaving group, $(CH_3)_2CHNH$-, on the mechanism. We varied substituents in the nucleophile (X) and leaving group (Z) and the rate constants, k_2, are subjected to a multiple regression analysis to determine the cross-interaction constant,[5] ρ_{XZ} in Eq. (2). For a concerted mechanism the sign of ρ_{XZ} was found to be negative[5] and the reactivity-selectivity principle (RSP) failed.[6]



$$(CH_3)_2CHNHC(=O)SC_6H_4Z + XC_6H_4CH_2NH_2 \xrightarrow[40.0\,^{\circ}C]{MeCN} (CH_3)_2CHNHC(=O)NHCH_2C_6H_4X + HSC_6H_4Z \quad (1)$$

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (2a)$$

$$\rho_{XZ} = \partial\rho_Z/\partial\sigma_X = \partial\rho_Y/\partial\sigma_Z \quad (2b)$$

Results and Discussion

The reactions of aryl N-isopropyl thiocarbamates (AITC: $(CH_3)_2CHNHC(=O)SC_6H_4Z$) with X-benzylamines (BA) in acetonitrile follow a clear second-order kinetics, Eqs. (3). Unlike in the aminolysis of aryl *N*-phenylcarbamates[2] (APC: $PhNHC(=O)OC_6H_4Z$) we found no base

$$\text{rate} = k_{obs}\,[\text{AITC}] \quad (3a)$$

$$k_{obs} = k_2\,[\text{BA}] \quad (3b)$$

catalysis by the amine. The rate constants, k_2, determined are summarized in Table 1 together with selectivity parameters ρ_X, β_X, ρ_Z, and β_Z. The β_X (β_{nuc}) values are obtained by using the pK_a values of benzylamines in water. This procedure was found to be reliable since the pK_a values in acetonitrile and in water vary in parallel, although the absolute values are different.[7] For the β_Z (β_{lg}) values, a factor of 0.62 was multiplied to all the β_Z values determined using the pK_a (H_2O) values.[8]

Since strong destabilization of $T^{\pm}$ should be provided by a stronger push to expel the leaving group by the amino nonleaving group, R=NH_2 in **3b**, the aminolysis of AITC (**3b** with R=$(CH_3)_2CH$-) with benzylamines in acetonitrile is proposed to proceed concertedly. The β_Z values in Table 1 are within the range of values that are expected for a concerted mechanism.[9] Further supports for the concerted mechanism is provided by a negative ρ_{XZ} (−1.96) obtained, and failure of the reactivity-selectivity principle (RSP).[10] The selectivities (ρ and β values in Table 1) are greater for the faster reactions. This type of *anti*-RSP is considered another criterion for the concerted aminolysis.[6]

Table 1. The Second Order Rate Constants, k_2 (10^2 dm^3 mol^{-1} s^{-1}) for the Reactions of Z-Aryl *N*-Isopropyl Thiocarbamates with X-Benzylamines in Acetonitrile at 40.0 °C

X	Z				ρ_Z[a]	β_Z[b]
	p-Me	H	*p*-Cl	*p*-Br		
p-OMe	1.23	5.06	35.5	45.7	3.80 ± 0.15	-1.58 ± 0.08
p-Me	0.781	2.92	19.5	23.0	3.61 ± 0.10	-1.51 ± 0.06
H	0.411	1.32	7.05	8.42	3.21 ± 0.11	-1.34 ± 0.06
p-Cl	0.176	0.467	2.06	2.54	2.82 ± 0.14	-1.18 ± 0.05
m-Cl	0.0994	0.266	0.975	1.10	2.55 ± 0.06	-1.06 ± 0.06
ρ_X[a]	-1.68 ± 0.03	-1.99 ± 0.05	-2.3 ± 0.04	-2.49 ± 0.06	ρ_{XZ}[c] =	-1.96 ± 0.20
β_X[d]	1.65 ± 0.03	1.95 ± 0.03	2.38 ± 0.05	2.43 ± 0.05		

[a]The σ values were taken from C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.* **1991**, *91*, 166. Correlation coefficients were better than 0.997 in all cases. [b]The pK_a values were taken from A. Albert and E. P. Serjeant, "*The Determination of Ionization Constants*" 3rd Ed., Chapman and Hall, London, p 145. Correlation coefficients were better than 0.997 in all cases. [c]Calculated by a multiple regression analysis using eq (2a). r = 0.999, n = 20 and F_{calc} = 1410 (F_{tab} = 10.66 at the 99.9% confidence level). [d]The pK_a values were taken from A. Fischer, W. J. Galloway and J. Vaughan, *J. Chem. Soc.* **1964**, 3588. Correlation coefficients were better than 0.997 in all cases. For X = *p*-CH_3O an extrapolated value of pK_a = 9.64 was used.

Reference to Table 1 reveals that the β_X values are 1.65-2.43 which are rather greater than the values normally expected for the concerted aminolysis processes, β_X = 0.4 ~ 0.7[10] However, β_X values smaller than 0.4[11] as well as those larger than 0.7[12] have also been observed for the concerted reactions. Especially in solvents less polar than water, larger β_X (1.3-1.6)[13] are often obtained for the concerted processes. Thus the large β_X values in the present work may be due to the less polar solvent used, acetonitrile. The relatively large β_X values may reflect rather tight bond formation in the TS.

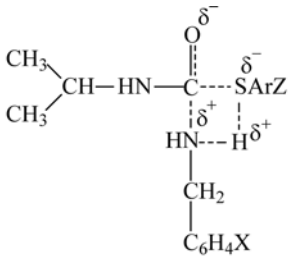
Strong destabilization incurred by powerful nucleofugality of benzylamines from $T^{\pm}$ is known to cause the aminolysis to proceed by a concerted mechanism.[14] The order of the increasing rate of expulsion of amines from $T^{\pm}$ is reported as[6] pyridines < anilines < secondary alicyclic amines < quinuclidines < benzylamines. Moreover, it has been shown that carbonyl (C=O) has a greater proclivity for the concerted mechanism than thiocarbonyl (C=S) group[15] due to a narrower energy gap between π^* and σ^* levels, $\Delta\varepsilon = \varepsilon(\pi^*_{C=O}) - \varepsilon(\sigma^*_{C-S}) < \Delta\varepsilon = \varepsilon(\pi^*_{C=S}) - \varepsilon(\sigma^*_{C-S})$, enabling efficient mixing of the two antibonding orbitals.[15] Thus, concerted mechanisms are found for the aminolyses of *S*-(2,4-dinitrophenyl)[15] and *S*-(2,4,6-trinitrophenyl)[17] *O*-ethyl thiocarbonates in contrast to the stepwise mechanisms for the corresponding dithiocarbonates.[18] Less polar solvents are also conducive to a concerted mechanism as observed for the aminolysis of carbonates from stepwise in water to concerted in acetonitrile.[19] For example, the aminolysis of 2,4,6-trinitrophenyl O-ethyl dithiocarbonates is stepwise[20] (biphasic Brönsted plot) in water, but is concerted (β_X = 0.53) in a less polar solvent (44 wt % aqueous EtOH).[21] The change of solvent from water to a less polar solvent such as MeCN destabilizes the zwitterionic intermediate by enhancing the rate of expulsion of the amine from $T^{\pm}$, and renders the intermediate, $T^{\pm}$, more unstable kinetically so that a concerted mechanism is enforced.[21]

The kinetic isotope effects (k_H/k_D) involving deuterated benzylamines[22] ($XC_6H_4CH_2ND_2$) are presented in Table 2. We note that the isotope effects are normal with k_H/k_D > 1.0 suggesting there is a hydrogen bond formed by the amino

Table 2. The Kinetic Isotope Effects for the Reactions of Z-Phenyl *N*-Isopropyl Thiocarbamates with X-Benzylamines in Acetonitrile at 40.0 °C

X	Z	k_H (× 10^2 M^{-1} s^{-1})	k_D(× 10^2 M^{-1} s^{-1})	k_H/k_D
p-OMe	*p*-Me	1.23(± 0.02)	0.911(± 0.01)	1.35 ± 0.02[a]
p-OMe	H	5.06(± 0.06)	3.58(± 0.05)	1.41 ± 0.02
p-OMe	*p*-Cl	35.0(± 0.7)	23.8(± 0.4)	1.47 ± 0.03
P-OMe	*p*-Br	45.7(± 0.9)	29.5(± 0.6)	1.55 ± 0.03
p-Cl	*p*-Me	0.176(± 0.002)	0.127(± 0.001)	1.38 ± 0.03
p-Cl	H	0.467(± 0.003)	0.319(± 0.003)	1.46 ± 0.02
p-Cl	*p*-Cl	2.06(± 0.04)	1.34(± 0.02)	1.53 ± 0.02
p-Cl	*p*-Br	2.54(± 0.05)	1.57(± 0.03)	1.61 ± 0.03

[a]Standard deviations.



TS

proton (N-H or N-D) in the TS, most probably with the negatively charged S atom in the leaving group. Since the large β_X and β_Z values suggest that the TS is a late type with a large degree of bond formation and bond cleavage the hydrogen bonding seems to be rather strong with relatively large values of k_H/k_D > 1.0. This is supported by a larger k_H/k_D value for a stronger nucleophilie ($\delta\sigma_X$ < 0) and a stronger nucleofuge ($\delta\sigma_Z$ > 0) which will lead to a later TS in accordance with the negative ρ_{XZ}; a stronger nucleophile, $\delta\sigma_X$ < 0, gave a larger ρ_Z value $\delta\rho_Z$ > 0 so that $\rho_{XZ} = \delta\rho_Z/\delta\sigma_X$ < 0, while a stronger nucleofuge, $\delta\sigma_Z$ > 0, gave a larger negative ρ_X value $\delta\sigma_Z$ > 0 so that $\rho_{XZ} = \delta\rho_Z/\delta\sigma_X$ < 0, while a stronger nucleofuge ($\delta\sigma_Z$ > 0) gave a larger negative ρ_X ($\delta\rho_X$ > 0) leading to ρ_{XZ} < 0.

In summary, we propose a concerted mechanism with a

hydrogen bonded cyclic transition state for the aminolysis of aryl *N*-isopropyl thiocarbamates with benzylamines in acetonitrile based on the negative cross-interaction constant, failure of RSP and the kinetic isotope effects greater than unity. The four conducive factors for the concerted aminolysis mechanism for the present reaction series are: (i) strong (strongest) push provided to expel ArS^- by the nonleaving group, $(CH_3)_2CHNH$, (ii) destabilization of the intermediate, $T^{\pm}$, by a powerful expulsion rate of the benzylamine from $T^{\pm}$, (iii) greater leaving ability of ^-SAr than ^-OAr due to the greater electron acceptor ability of $\sigma^*_{C\text{-}S}$ than $\sigma^*_{C\text{-}O}$ bond orbital, and (iv) instability of the intermediate, $T^{\pm}$, in a less polar solvent, MeCN than in water due to the ionic nature of $T^{\pm}$.

Experimental Section

Experimental.

Materials: GR grade acetonitrile was used after three distillations. GR grade benzylamine nucleophiles were used after recrystallization.

Substrates.

Phenyl *N*-Isopropyl Thiocarbamate: A solution of thiophenol (0.01 mol) in dry toluene (10 mL) was added to a solution of isopropyl isocyanate (0.01 mol). A catalytic quantity (0.5 mL) of pyridine was added and the solution refluxed for 1 h. On evapolation of the solvent *in vacuo*, the thiocarbamate precipitated and was recrystalized from chloroform-pentane. The other substituted phenyl *N*-isopropyl thiocarbamates were prepared in an analogous manner and recrystallized from chloroform-pentane. The substrates synthesized were confirmed by spectral and elemental analysis as follows.

$(CH_3)_2CHNHC(=O)SC_6H_4$-*p*-CH_3: mp 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.15 (6H, d, -$(CH_3)_2$), 1.80 (1H, d, -CH-), 2.41 (3H, d, CH_3), 6.42 (1H, s, NH), 7.19-7.47 (4H, m, C_6H_4); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 165.2, 139.5, 135.1, 129.9, 125.0, 43.7, 22.4, 21.2; ν_{max} (KBr), 3301 (NH), 2972 (CH, aliphatic), 2923 (CH, aromatic), 1648 (C=O), 620 (C-S); MS *m/z* 209 (M^+). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.1; H, 7.20. Found; C, 63.3; H, 7.21.

$(CH_3)_2CHNHC(=O)SC_6H_5$: mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.21 (6H, d, -$(CH_3)_2$), 1.66 (1H, d, -CH-), 6.32 (1H, s, NH), 7.37-7.57 (5H, m, C_6H_5); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 164.6, 135.1, 129.1, 129.0, 128.5, 43.8, 22.4; ν_{max} (KBr), 3265 (NH), 2970 (CH, aliphatic), 2920 (CH, aromatic), 1662 (C=O), 629 (C-S); MS *m/z* 195 (M^+). Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.5; H, 6.71. Found; C, 61.3; H, 6.70.

$(CH_3)_2CHNHC(=O)SC_6H_4$-*p*-Cl: mp 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.27 (6H, d, -$(CH_3)_2$), 1.62 (1H, d, -CH-), 6.38 (1H, s, NH), 7.34-7.49 (4H, m, C_6H_4); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 163.8, 136.3, 135.5, 129.2, 126.9, 44.1, 22.5; ν_{max} (KBr), 3300 (NH), 2974 (CH, aliphatic), 2924 (CH, aromatic), 1649 (C=O), 630 (C-S); MS *m/z* 229 (M^+). Anal. Calcd for $C_{10}H_{12}ClNOS$: C, 52.3; H, 5.31. Found; C, 52.5; H, 5.32.

$(CH_3)_2NC(=O)SC_6H_4$-*p*-Br: mp 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.32 (6H, d, -$(CH_3)_2$), 1.61 (1H, d, -CH-), 6.36 (1H, s, NH), 7.37-7.55 (4H, m, C_6H_4); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 163.7, 136.5, 132.1, 127.6, 123.7, 44.1, 22.6; ν_{max} (KBr), 3302 (NH), 2972 (CH, aliphatic), 2916 (CH, aromatic), 1649 (C=O), 625 (C-S); MS *m/z* 274 (M^+). Anal. Calcd for $C_{10}H_{12}BrNOS$: C, 43.8; H, 4.41. Found; C, 43.9; H, 4.43.

Kinetic Measurement. Rates were measured conductometrically in acetonitrile. The conductivity bridge used in this work was a homemade computer-automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obsd}, were determined by the Guggenheim method[23] with large excess of pyridine. Second order rate constants, k_2, were obtained from the slope of a plot of k_{obsd} *vs*. [BA] with more than five concentrations of benzylamine. The k_2 values in Table 1 are the averages of more than three runs and were reproducible to within ± 3%.

Product Analysis. The substrate *p*-chlorophenyl *N*-isopropyl thiocabamate (0.01 mole) was reacted with excess benzylamine (0.1 mole) with stirring for more than 15 half-lives at 40.0 °C in acetonitrile (*ca*. 200 mL) and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was subjected to column chromatography (silica gel, 20% ethyl acetate-*n*-hexane). Analysis of the product gave the following results.

$(CH_3)_2CHNHC(=O)NHCH_2C_6H_4$: mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.24 (6H, d, -$(CH_3)_2$), 3.86 (1H, m, -CH-), 4.27 (2H, d, CH_2), 6.32 (1H, s, NH), 7.10-7.37 (5H, m, C_6H_5); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 157.9, 139.4, 128.3, 127.2, 126.9, 44.2, 41.9, 23.4; ν_{max} (KBr), 3332 (NH), 2965 (CH, aliphatic), 2922 (CH, aromatic), 1620 (C=O); MS *m/z* 192 (M^+). Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.7; H, 8.41. Found; C, 68.9; H, 8.42.

Acknowledgments. This paper was supported by Chonbuk National University in 2011.

References

1. Koh, H. J.; Lee, J.-W.; Lee, H. W.; Lee, I. *Can. J. Chem*. **1998**, *76*, 710.
2. Koh, H. J.; Kim, O. S.; Lee, H. W.; Lee, I. *J. Phys. Org. Chem*. **1997**, *10*, 725.
3. (a) Pross, A. *Adv. Phys. Org. Chem*. **1997**, *14*, 69. (b) Buncel, E.; Wilson, H. *J. Chem. Educ*. **1987**, *64*, 475.
4. Oh, H. K.; Lee, Y. H.; Lee, I. *Int. J. Chem. Kinet*. **2000**, *32*, 131.
5. (a) Lee, I. *Chem. Soc. Rev*. **1990**, *19*, 317. (b) Lee, I. *Adv. Phys. Org. Chem*. **1992**, *27*, 57.
6. Lee, I.; Sung, D. D. *Curr. Org. Chem*. **2004**, *8*, 557.
7. (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. *Prog. Phys. Org. Chem*. **1967**, *4*, 54. (c) Spillane, W. J.; Hagan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc. Perkin Trans. 2* **1996**, 2099.
8. Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 3874.
9. (a) Castro, E. A.; Pavez, P.; Santos, J. G. *J. Org. Chem*. **2001**, *66*, 3129. (b) Stefanidas, D.; Cho, S.; Dhe-Paganon, S.; Jencks, W. P. *J. Am. Chem. Soc*. **1993**, *115*, 1650.

10. Skoog, M. T.; Jencks, W. P *J. Am. Chem. Soc*. **1984**, *106*, 7597.
11. (a) Ba-Saif, S.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1989**, *111*, 2647. (b) Colthurst, M. J.; Nanni, M.; Williams, A. *J. Chem. Soc. Perkin Trans. 2* **1996**, 2285.
12. (a) Maude, A. B.; Williams, A. *J. Chem. Soc. Perkin Trans. 2* **1997**, 179. (b) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem*. **1998**, *63*, 6820.
13. Castro, E. A. *Chem. Rev.* **1991**, *99*, 3505.
14. (a) Yamabe, S.; Minato, T. *J. Org. Chem*. **1983**, *48*, 2972. (b) Lee, I.; Lee, D.; Kim, C. K. *J. Phys. Chem. A* **1997**, *101*, 879. (c) Lee, I.; Kim, C. K.; Li, H. G.; Sohn, C. K.; Kim, C. K.; Lee, H. W.; Lee, B.-S. *J. Am. Chem. Soc.* **2000**, *122*, 11162. (d) Lee, I. *Int. Rev. Phys. Chem.* **2003**, *22*, 263.
15. Castro, E. A.; Ibanez, F.; Salas, M.; Santos, J. G.; Sepulveda, P. *J. Org. Chem*. **1993**, *58*, 459.
16. (a) Castro, E. A.; Ruiz, M. G.; Santos, J. G. *Int. J. Chem. Kinet*. **2001**, *33*, 281. (b) Yew, K. H.; Koh, H. J.; Lee, H. W.; Lee, I. *J. Chem. Soc. Perkin Trans. 2* **1995**, 2263. (c) Castro, E. A.; Ruiz, M. G.; Salinas, S.; Santos, J. G. *J. Org. Chem*. **1999**, *64*, 4817.
17. Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem*. **2001**, *66*, 6000.
18. Oh, H. K.; Lee, J.-Y.; Park, Y. S.; Lee, I. *Int. J. Chem. Kinet*. **1998**, *30*, 419.
19. Castro, E. A.; Cubillas, M.; Munoz, G.; Santos, J. G. *Int. J. Chem. Kinet*. **1994**, *26*, 571.
20. Dewar, M. J. S.; Dougherty, R. C. *The PMO Theory of Organic Chemistry*; Plenum: New York, 1975; Chapter 5.
21. Lee, I. *Chem. Soc. Rev.* **1995**, *24*, 571.
22. Lee, I. *Chem. Soc. Rev.* **1994**, *24*, 223.
23. (a) Guggenheim, E. A. *Philos, Mag.* **1926**, *2*, 538. (b) Oh, H. K.; Hong, S. K. *Bull. Korean Chem. Soc*. **2009**, *30*, 2453. (c) Lee, H.; Oh, H. K. *Bull. Korean Chem. Soc*. **2010**, *31*, 475. (d) Oh, H. K. *Bull. Korean Chem. Soc*. **2010**, *31*, 1785.