Kinetics and Mechanism of the Aminolysis of *O*-Methyl-*S*-Phenylthiocarbonates in Methanol

Ho Bong Song, Moon Ho Choi, In Sun Koo,* Hyuck Keun Oh,† and Ikchoon Lee‡

Department of Chemistry, Kyung-Gi University, Suwon 440-760, Korea
**Department of Chemistry Education and Research Institute of Natural Sciences, Gyeongsang National University, Chinju 660-701, Korea*
†Department of Chemistry, Chonbuk National University, Chonju 561-756, Korea
‡Department of Chemistry, Inha University, Incheon 402-751, Korea
Received October 31, 2002

Kinetic studies of the reaction of *O*-methyl-*S*-phenylthiocarbonates with benzylamines in methanol at 45.0 °C have been carried out. The reaction proceeds by a stepwise mechanism in which the rate-determining step is the breakdown of the zwitterionic tetrahedral intermediate, $T^{\pm}$, with a hydrogen-bonded four-center type transition state (TS). These mechanistic conclusions are drawn based on (i) the large magnitude of ρ_X and ρ_Z, (ii) the normal kinetic isotope effects ($k_H/k_D > 1.0$) involving deuterated benzylamine nucleophiles, (iii) the positive sign of ρ_{XY} and the larger magnitude of ρ_{XZ} than that for normal S_N2 processes, and lastly (iv) adherence to the reactivity-selectivity principle (RSP) in all cases.

Key Words : *O*-Methyl-*S*-phenylthiocarbonates, Stepwise mechanism, Zwitterionic tetrahedral intermediate, Cross-interaction constant

Introduction

Aminolyses of acetate,[1] ester, and acyl compounds have been studied extensively, however, much less is known about the aminolysis of thiophenylcarbonates. In view of the importance of predicting the effects of the acyl group with thiophenyl leaving groups on the mechanism of aminolysis of thiophenyl compounds, we have used several different acyl group with thiophenyl leaving groups in our studies of the aminolysis mechanism.[2,3] In a previous work, we have studied the kinetics of the aminolysis of thiophenyl dimethylacetates and trimethylacetates.[2] We have found that the nucleophilic reaction of thiophenyl dimethylacetates and trimethylacetates in acetonitrile poroceeds by rate-limiting breakdown of a tetrahedral intermediate, $T^{\pm}$, with a hydrogen-bonded, four-center transition state.[2] The signs of cross-interaction constants, ρ_{ij} in eq. (1), where i and j are the substituents on the nucleophile (X), the substrate (Y) or the leaving group (Z), are opposite ($\rho_{XY} > 0$ and $\rho_{YZ} < 0$)[1,4] to those for normal S_N2 processes or for acyl transfers with rate-limiting formation of the tetrahedral intermediate, $T^{\pm}$ ($\rho_{XY} < 0$ and $\rho_{YZ} > 0$).[5] The deuterium kinetic isotope effects involving deuterated nucleophiles are normal, $k_H/k_D \simeq 1.0$.[1,2,4,6]

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (1a)$$

$$\rho_{XZ} = \partial\rho_Z/\partial\sigma_X = \partial\rho_X/\partial\sigma_Z \quad (1b)$$

In this work, we investigated the kinetics and mechanism of the aminolysis of *O*-methyl-*S*- phenylthiocarbonates with benzylamines in methanol at 45.0 °C, eq. (2). The objective of the present work is to elucidate the mechanism by determining $\beta_X(\beta_{nuc})$, $\beta_Z(\beta_{lg})$, cross-interaction constant β_{XZ}, eq. (1),[4] secondary kinetic isotope effects, and activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ where X and Z denote substituents in nucleophile and substrate, respectively.

$$2XC_6H_4CH_2NH_2 + CH_3OC(=O)SC_6H_4Z \xrightarrow[45.0^{\circ}C]{MeOH}$$

$$CH_3OC(=O)NHCH_2C_6H_4X + {}^{-}NH_3CH_2C_6H_4X + {}^{-}SC_6H_4Z \quad (2)$$

X = *p*-OCH_3, *p*-CH_3, *m*-CH_3, H, *p*-Cl, *m*-Cl,
Z = *p*-CH_3, H, *p*-Cl, *p*-Br, *m*-Cl, *m*-Br

Results and Discussion

The reactions were observed as first-order k_{obs} in both benzylamine, [N], and substrates, [S], as shown in eqs. (3) and (4), under the experimental conditions. Plots of k_{obs} against benzylamine concentration were linear accordance with eq. (4), where k_o and k_N are the rate coefficients for solvolysis and aminolysis.

$$\text{Rate} = k_{obs}[S] \quad (3)$$

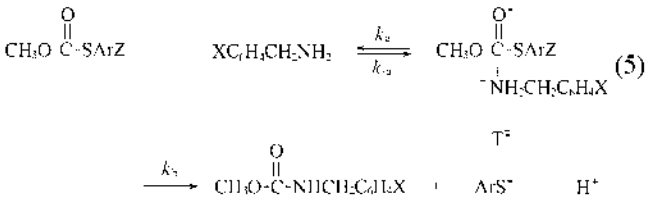
$$k_{obs} = k_o + k_N[N] \quad (4)$$

respectively, of the *O*-methyl-*S*-phenylthiocarbonates. The observed solvolysis rate constant was very small under the reaction condition ($k_o \approx 0$). The second-order rate constants for aminolysis (k_N) were obtained from the slopes of the plots [eq. (4)]. These values, together with the Hammett [$\rho_X(\rho_{nuc})$ and $\rho_Z(\rho_{lg})$] and Brönsted [$\beta_X(\beta_{nuc})$] coefficients, are shown in Table 1. The rate is faster with a strong

*Corresponding Author: e-mail: iskoo@nongae.gsnu.ac.kr

nucleophile ($\delta\sigma_X < 0$) and a better nucleofuge ($\delta\sigma_Z > 0$) as is expected from a typical nucleophilic substitution reaction.

The results in Table 1 reveal that the magnitude of the two parameters (ρ_X and β_X) are quite large. As we have pointed out previously, these β_X value can be considered to represent reliable values since although the absolute values of p*K*a in MeOH different from those in water.[2,8] The β_X values (1.6-2.45) obtained in this work are considerably larger than those for the corresponding reactions with benzylamines[9] proceeding by rate-limiting break-down of a zwitterionic tetrahedral intermediate, $T^{\pm}$, eq. (5). The large β_X values obtained the aminolysis of *O*-methyl-*S*-phenylthiocarbonates with benzylamines in methanol are most likely to occur by rate-determining expulsion of thiophenolate ion, ArS^-, from $T^{\pm}$ (k_b step). The large β_X values observed with benzylamine nucleophile in this work are considered to represent a very sensitive change in the benzylamine expulsion rate (k_{-a}) with substrate (X) variation due to the loss of a strong localized charge on the nitrogen atom of the benzylammonium in the $T^{\pm}$.



(5)

$$k_2 = \frac{k_a}{k_{-a}} k_b = K k_b \qquad (6)$$

The large ρ_X values (-0.80 ~ -1.05) observed in this work, which is an indication of rate-limiting leaving group expulsion mechanism. For example, the reaction thiophenyl dimethylacetates and trimethylacetates with benzylamines in acetonitrile at 55.0 and 60.0 °C have been proposed to proceed by rate limiting expulsion of thiophenylate ion from, $T^{\pm}$: the β_Z values for these reaction ranged from -0.80 to -1.7,[2] which is are quite similar to the values obtained in this work.

The cross-interaction constants ρ_{XZ} obtained are positive and is similar to that (0.53) for the reaction of Z-phenyl dithiobezoates with X-anilines in acetonitrile which is known to proceed by rate-limiting break-down of a zwitterionic tetrahedral intermediate, $T^{\pm}$.[10] The positive ρ_{XZ} and the larger magnitude of ρ_{XZ} than that for normal S_N2 processes and adherence to reactivity-selectivity principle (RSP) (Table 1) also support our proposed mechanism.

Secondary kinetic isotope effects involving deuterated benzylamine nucleophiles are summarized in Table 3. Benzylamines have two mobile protons so that in a general base-catalyzed nucleophilic attack in S_N2 type concerted processes one of the mobile hydrogens on the N atom will cause an inverse isotope effect due to steric hindrance to N-H bending vibration.[2] Thus, in such cases, the k_H/k_D values are either less than unity (inverse effect) or marginally greater than unity (normal effect) due to cancellation of the primary kinetic effect of deprotonation process.[2] The k_H/k_D values observed in Table 3 is all greater than 1.0. It means that deprotonation will cause a decrease in the N-H vibration frequencies and k_H/k_D values will be grater than 1.0. Thus, the normal k_H/k_D values (k_H/k_D>1.0) alone do not allow us to predict the correct mechanism. Previously we have noted that the k_H/k_D values are close to 1.0 in the rate-limiting breakdown of $T^{\pm}$.[10] The k_H/k_D values in Table 3 are somewhat larger than those for such a mechanism. This can be rationalized by a cyclic four-center TS of types shown as I and II, respectively, for stepwise and concerted mechanism. In such four-center cyclic proton transfer, leaving group departure is facilitated in addition to charge dispersion. The assistance to bond cleavage of the leaving group is especially

Table 1. Rate constants, k_2 $10^{-4}M^{-1}s^{-1}$, for the reactions of O-Methyl-S-Arylthiocarbonates with X-benzylamines in MeOH at 45

	Z						ρ_Z[a]	ρ_Z[b]
	Z = *p*-CH_3	H	*p*-Cl	*p*-Br	*m*-Cl	*m*-Br		
p-OCH_3	1.50	3.13	8.57	9.76	17.2	19.5	1.99 ± 0.04	-0.81 ± 0.14
	1.08[c]			7.10		14.3		
	0.783[d]			5.19		10.4		
p-CH_3	0.894	2.04	5.90	6.42	11.9	13.4	2.09 ± 0.03	-0.875 ± 0.14
p-CH_3	0.589	1.47	4.39	4.81	9.03	10.3	2.20 ± 0.04	-0.93 ± 0.14
H	0.435	0.984	3.08	3.69	6.82	8.16	2.26 ± 0.07	-0.91 ± 0.14
p-Cl	0.181	0.492	1.51	1.83	3.48	4.29	2.40 ± 0.07	-
	0.122[c]			1.29		2.91		
	0.087[d]			0.912		2.02		
m-Cl	0.101	0.279	0.954	1.13	2.41	2.84	2.56 ± 0.06	-1.04 ± 0.14
ρ_X[e]	-1.79 ± 0.05	-1.61 ± 0.05	-1.49 ± 0.04	-1.43 ± 0.03	-1.33 ± 0.04	-1.28 ± 0.04	ρ_{XZ} = 0.53 ± 0.13	
β_X[f]	2.34 ± 0125	2.10 ± 0.07	1.97 ± 0.08	1.89 ± 0.06	1.74 ± 0.08	1.68 ± 0.07		

[a]The ρ_X and ρ_Z values were calculated using σ values, which were found in J. A. Dean, *Handbook of Organic Chemistry*, McGraw-Hill, New York, 1987, Table 7-1. [b]The β_X and β_Z values were calculated *pK*a values, which were found in J. Bukingham, *Dictionary of Organic Chemistry*, Chapman and Hall, New York, 1982, 5th, ed. Z=*p*-Br was excluded from Bronsted plot for β_Z due to an unreliable *p*Ka values. [c]At 35 °C. [d]At 25 °C. [e]The σ values were taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **1958**, *23*, 420. [f]The *pK*a values were taken from A. Fischer, W. J. Galloway and J. Vaughan, *J. Chem. Soc.* **1964**, 3588. Correlation coefficients are better than 0.992. pKa = 9.67 was used for X = *p*-CH_3O. (reference H. K. Oh, J. Y. Lee and I. Lee, *Bull Korean Chem. Soc.* **1998**, *19*, 1198.)

Table 2. Activation Parameters[a] for the Reaction of *O*-Methyl-*S*-Arylthiocarbonates with X-benzylamines in Methanol

X	Z	ΔH/kcal mol^{-1}	ΔS/cal mol^{-1} K^{-1}
p-OMe	*p*-Me	5.6 ± 0.1[b]	58 ± 1[b]
	p-Br	5.4 ± 0.1[b]	55 ± 1[b]
	m-Br	5.4 ± 0.1[b]	54 ± 1[b]
p-Cl	*p*-Me	6.4 ± 0.1[b]	60 ± 1[b]
	p-Br	6.1 ± 0.1[b]	56 ± 1[b]
	m-Br	6.6 ± 0.1[b]	53 ± 1[b]

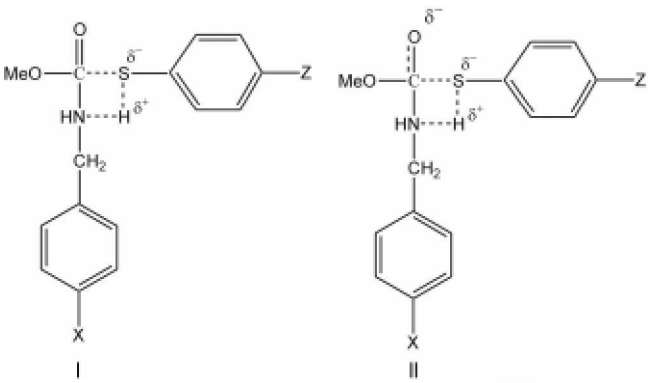
[a]Calculated by the Eyring equation. [b]Errors shown are standard deviation.

Table 3. The Secondary Kinetic Isotope Effects for the Reactions of *O*-Methyl-*S*-Arylthiocarbonates with Deuteratated X-benzylamines in MeOD

X	Z	k_H 10^4 (M^{-1}s^{-1})[b]	k_D 10^4 (M^{-1}s^{-1})[b]	k_H/k_D
p-OMe	*p*-Me	1.50	1.26	1.19
	H	3.13	2.57	1.22
	p-Cl	8.57	6.41	1.34
	p-Br	9.76	7.69	1.27
	m-Cl	17.2	13.3	1.29
	m-Br	19.5	14.9	1.31
p-Cl	*p*-Me	0.181	0.163	1.11
	H	0.492	0.428	1.15
	p-Cl	1.51	1.28	1.18
	p-Br	1.83	1.53	1.20
	m-Cl	3.48	2.82	1.23
	m-Br	4.29	3.43	1.25

[a]Determined conductimetrically in duplicate. [b]Averge deviation typically 3%. [c]Maximum standard deviations are 0.05.

important in protic solvents since the solvent cannot stabilize the TS by hydrogen bonding. It is difficult to choose one from two cyclic TS, but the favor I rather than II because of the larger magnitude of ρ_{XZ} than that for normal S_N2 processes and electron donating OCH_3 group.



Activation parameters for the reaction of *O*-methyl-*S*-phenylthiocarbonates with benzylamines are shown in Table 2. The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were obtanied from the slope and intercept, respectively, of Eyring plots, by least-squares analysis. Although the relatively low positive $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values are in line with the stepwise mechanism,[7] they can also be interpreted as supportive of a concerted mechanism.

In summary, the reaction of *O*-methyl-*S*-phenylthiocarbonates with benzylamines in methanol proceed by a steowise mechanism in which the rate-determining step is breakdown of the zwitterionic tetrahedral intermediate with a hydrogen bonded four-center type TS.

These mechanistic conclusions are drawn based on (i) the large magnitude of ρ_N and ρ_Z, (ii) the normal kinetic isotope effects ($k_H/k_D > 1.0$) involving deuterated benzylamine nucleophiles, (iii) a small positive enthalpy of activation, $\Delta H^{\neq}$, and a large negative entropy of activation, $\Delta S^{\neq}$, (iv) the positive sign of ρ_{XZ} and the larger magnitude of ρ_{XZ} than that for normal S_N2 processes, and lastly (v) adherence to the RSP in all cases.

Experimental Section

Materials. Merck GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. The GR grade of thiophenols and methyl chloroformate were purchased from Tokyo Kasei.

Preparations of *O*-Methyl *S*-Aryl Thiocarbonates. Thiophenol derivatives and methyl chloroformate were dissolved in anhydrous ether and added pyridine carefully keeping temperature to 0-5 °C. Ice was then added to the reaction mixture and ether layer was separated, dried on $MgSO_4$ and distilled under reduced pressure to remove solvent. IR (Nicolet 5BX FT-IR) and ^{1}H and ^{13}C NMR (JEOL 400 MHz) data are as follows:

***O*-Methyl *S*-Phenyl Thiocarbonate**: Liquid, IR (KBr), 2945 (C-H, CH_3), 1736 (C=O), 1591, 1475 (C=C, aromatic), 1138, 1092 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 3.72 (3H, s, CH_3), 7.29-7.45 (5H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 170.1 (C=O), 134.7, 129.5, 129.1, 127.5 (aromatic), 53.4.

***O*-Methyl *S*-*p*-Methylphenyl Thiocarbonate**: Liquid, IR (KBr), 2952 (C-H, CH_3), 1732 (C=O), 1592, 1486 (C=C, aromatic), 1135, 1086 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 2.39 (3H, s, CH_3), 3.84 (3H, s, CH_3), 7.22-7.45 (4H, dd, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 170.5 (C=O), 139.8, 134.8, 129.9, 124.0 (aromatic), 54.3, 21.2.

***O*-Methyl *S*-*p*-Chlorophenyl Thiocarbonate**: Liquid, IR (KBr), 2964 (C-H, CH_3), 1732 (C=O), 1548, 1471 (C=C, aromatic), 1135, 1092 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 3.85 (3H, s, CH_3), 7.57-7.31 (4H, dd, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 170.1 (C=O), 136.7, 132.8, 126.3, 124.5 (aromatic), 54.2.

***O*-Methyl *S*-*p*-Bromophenyl Thiocarbonate**: Liquid, IR (KBr), 2964 (C-H, CH_2), 1732 (C=O), 1571, 1472 (C=C, aromatic), 1135, 1092 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 3.83 (3H, s, CH_3), 7.52-7.36 (4H, dd, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 169.5 (C=O), 136.2, 132.4, 126.7, 124.3 (aromatic), 54.7.

***O*-Methyl *S*-*m*-Chlorophenyl Thiocarbonate**: Liquid, IR (KBr), 2964 (C-H, CH_3), 1732 (C=O), 1548, 1471 (C=C, aromatic), 1135, 1092 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 3.85 (3H, s, CH_3), 7.21 7.37 (4H, m, aromatic ring); ^{13}C

NMR (100.4 MHz, $CDCl_3$), 170.1 (C=O), 136.7, 132.8, 126.3, 124.5 (aromatic), 54.2.

***O*-Methyl *S*-*m*-Bromophenyl Thiocarbonate**: Liquid, IR (KBr), 2964 (C-H, CH_2), 1732 (C=O), 1571, 1472 (C=C, aromatic), 1135, 1092 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 3.83 (3H, s, CH_3), 7.25-7.39 (4H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 169.5 (C=O), 136.2, 132.4, 126.7, 124.3 (aromatic), 54.7.

Kinetic Measurement. Rates were measured conductrically at 45 ± 0.05 °C. The conductivity bridge used in this work was a self-made computer automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs}, were determined by Guggenheim method[11] with large excess of benzylamine. Second-order rate constants, k_N, were obtained from the slope of a plot of k_{obs} *vs.* benzylamine with more than five concentrations of more than two runs and were reproducible to within ± 3%, to within 3%.

Product Analysis. Substrate (0.05 mole) and benzylamine (0.5 mole) were added to acetonitrile and reacted 45.0 °C under the same condition as the kinetic measurements. After more than 15 half lives, solvent was removed under reduced pressure and product was separated by column chromatography (silica gel, 10% ethylacetate-*n*-hexane). A representative product analysis for *p*-OCH_3 (nucleophile) is given as follows.

$CH_3OC(=O)NHCH_2C_6H_4OCH_3$: Liquid, IR (KBr), 3313 (N-H), 2975 (C-H, benzyl), 2961 (C-H, CH_2), 2943 (C-H, CH3), 1685 (C=O), 1544 (C=C, aromatic), 1521 (N-H), 1262, 1036 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$), 1.93 (3H, s, CH_3), 2.36 (3H, s, OCH_3), 4.07 (2H, d, CH_2), 7.02-7.42 (4H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 170.1 (C=O), 157.5, 156.8, 131.7, 127.9, 53.6, 51.8, 50.2.

Acknowledgment. This study was supported by the research grants of Kyung-Gi University in 2000.

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