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Kinetics and Mechanism of the Aminolysis of *O*-Methyl *S*-Aryl Thiocarbonates in Acetonitrile

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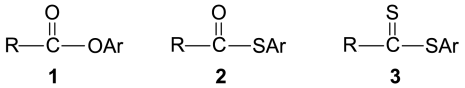
The aminolysis of *O*-methyl *S*-aryl thiocarbonates with benzylamines are studied in acetonitrile at −45.0 °C. The β_X (β_{nuc}) values are in the range 0.62-0.80 with a negative cross-interaction constant, $\rho_{XZ} = -0.42$, which are interpreted to indicate a concerted mechanism. The kinetic isotope effects involving deuterated benzylamine nucleophiles ($XC_6H_4CH_2ND_2$) are large, k_H/k_D = 1.29-1.75, suggesting that the N-H(D) bond is partially broken in the transition state by forming a hydrogen-bonded four-center cyclic structure. The concerted mechanism is enforced by the strong push provided by the MeO group which enhances the nucleofugalities of both benzylamine and arenethiolate from the putative zwitterionic tetrahedral intermediate.

Key Words : Nucleophilic substitution reaction, Concerted mechanism, Cross-interaction constant, Kinetic isotope effects, Four-center cyclic transition state

Introduction

The mechanism of aminolysis of esters and carbonates has been extensively investigated because of its relevance to the enzymatic catalysis of carbonyl group transfer reactions. In many of these nucleophilic substitution reactions curved Brönsted-type plots have been found, which have been attributed to a change in the rate-limiting step from breakdown ($\beta_{nuc} \cong$ 0.8-1.0) to formation ($\beta_{nuc} \cong$ 0.1-0.3) of a tetrahedral zwitterionic intermediate, $T^{\pm}$, in the reaction path as the basicity of the amine nucleophile increases.[1] Quite interestingly, however, concerted nucleophilic displacements are found only in the reactions *S*-aryl *O*-ethyl thiocarbonates (structure **2** with R = EtO) with good leaving groups[2] (**a**: Ar = C_6H_2-2,4,6-$(NO_2)_3$, or **b**: Ar = C_6H_3-2,4-$(NO_2)_2$) and alicyclic secondary amines ($\beta_{nuc} \cong$ 0.4-0.6).[3]



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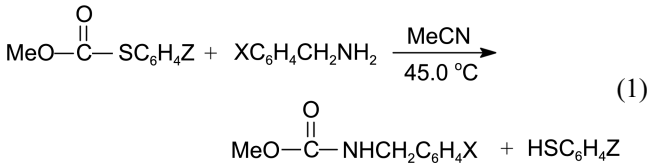
The concerted mechanism is enforced by (i) stronger push provided by R = EtO, which enhances the nucleofugality of both the amine and arylthiolate ion from $T^{\pm}$ relative to other acyl groups (R = alkyl or phenyl) and (ii) much faster expulsion of a given amine and ArS^- from $T^{\pm}$ formed with structure **2** than those from $T^{\pm}$ formed with structure **3** due to a stronger p-bonding energy of the carbonyl group (C=O) compared with thiocarbonyl (C=S) coupled with a greater nucleofugality of ArS^- incurred by much less basicity of ArS^- than ArO^-.

To examine further the driving force for the concerted aminolysis of the thiol derivatives, structure **2**, we carried out kinetic studies of aminolysis of *O*-methyl *S*-aryl thiocarbonates with R = MeO and Z = 4-Me, H, 4-Cl and 4-Br, using benzylamines ($XC_6H_4CH_2NH_2$; X = 4-OMe, 4-Me, H, 4-Cl and 3-Cl) in acetonitrile at 45.0 °C, eq. (1). In addition we are much interested in the mechanistic criteria based on the sign of ρ_{XZ}[4] in eq. (2) where X and Z are substituents in the nucleophile and leaving group, respectively. It has been postulated and experimentally confirmed that in a stepwise acyl transfer through a tetrahedral intermediate the sign of ρ_{XZ} is invariably *positive* and reactivity-selectivity principle



(1)

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

(RSP) holds.[5] In contrast, the sign of ρ_{XZ} is normally *negative* and the RSP is violated[6] in the concerted acyl transfer reactions.

Results and Discussion

The pseudo first order rate constants (k_{obs}) for all reactions obeyed eq. (3) with negligible k_0 ($\cong$ 0) in acetonitrile. The second-order rate constants, k_2 ($M^{-1}s^{-1}$), were obtains as the

$$k_{obs} = k_0 + k_2 [N] \quad (3)$$

slopes of the plots of k_{obs} *vs*. benzylamine concentration [N] and are summarized in Table 1. No third-order or higher order terms in amine were detected and no complications were found neither in the determination of k_{obs} nor in the linear plots of eq. (3). This suggests that there is no base catalysis or noticeable side reactions. The rate is fast with a stronger nucleophile and a better nucleofuge as normally

Table 1. The Second Order Rate Constants, $k_N \times 10^4$ dm^3 mol^{-1} s^{-1} for the Reactions of *O*-Methyl *S*-Aryl Thiocarbonates with X-Benzylamines in Acetonitrile at 45.0 °C

X	Z				ρ_Z[a]	β_Z[b]
	p-Me	H	*p*-Cl	*p*-Br		
p-OMe	2.39	4.79	15.1	20.1	2.20 ± 0.20	−0.86 ± 0.03
	1.22[c]			10.2		
	0.615[d]			5.21		
p-Me	1.90	3.87	11.3	14.8	2.12 ± 0.18	−0.83 ± 0.05
H	1.48	3.01	8.48	11.4	2.09 ± 0.19	−0.81 ± 0.05
p-Cl	1.14	2.14	6.12	7.44	1.97 ± 0.15	−0.79 ± 0.02
	0.581			3.73		
	0.293			1.85		
m-Cl	0.901	1.70	4.58	5.73	1.92 ± 0.17	−0.76 ± 0.04
ρ_X[e]	−0.63 ± 0.04	−0.69 ± 0.02	−0.77 ± 0.05	−0.82 ± 0.04	ρ_{XZ}[f] = −0.42	
β_X[g]	0.62 ± 0.03	0.67 ± 0.01	0.75 ± 0.04	0.80 ± 0.02		

[a]The σ values were taken from J. A. Dean, *Handbook of organic Chemistry*, McGraw-Hill, New York, 1987, Table 7-1. Correlation coefficients were better than 0.992 in all cases. [b]The pK_a values were taken from ed., J. Bukingham, *Dictionary of Organic Chemistry*, Chapman and Hall, New York, 1982, 5th, ed. Z = *p*-Br was excluded from the Brönsted plot for β_Z due to an unreliable pK_a values. Correlation coefficients were better than 0.998 in all cases. [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. Correlation coefficients were better than 0.995 in all cases. [f]Correlation coefficients was 0.996. [g]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 0.993 in all cases. X = *p*-CH_3O were excluded from the Brönsted plot for β_X (benzylamine) due to an unreliable pK_a value listed.

expected from a nucleophilic substitution reaction. The Brönsted β_X (β_{nuc}) and β_Z(β_{lg}) and Hammet ρ_X (ρ_{nuc}) and ρ_Z (ρ_{lg}) values are also shown in Table 1. We note that the magnitudes of these selectivity parameters are in general considerably smaller than those for the aminolysis with benzylamines involving rate-limiting expulsion of the leaving group, ArS^-, from a tetrahedral intermediate, $T^{\pm}$. For example, for the aminolysis of thiophenyl benzoates (structure **2** with R = Ph) with benzylamines in acetonitrile,[7] which is believed to proceed by a stepwise mechanism with rate-limiting breakdown $T^{\pm}$, the magnitude of ρ_X (β_X) and ρ_Z (β_Z) values were much larger with −1.88 (1.86) and 3.84 (−1.63) for Z = H and X = H, respectively. These are larger by *ca.* 2-3 times than those corresponding values, −0.69 (0.67) and 2.09 (−0.81), in Table 1. The β_X values of 0.67 obtained in the present work is similar to those for the concerted reaction of structure (R = EtO) with alicyclic (secondary) amines[3] (β_X = 0.56 for Ar = 2,4-$(NO_2)_2C_6H_3$ and β_X = 0.48 for Ar = 2,4,6-$(NO_2)_3C_6H_2$ in structure **2**) in aqueous solution. These two derivatives of structure **2** (R = EtO) are, however, known to react with pyridines (tertiary amines) by a stepwise mechanism with rate-limiting breakdown of the intermediate, $T^{\pm}$, with β_X = 0.9 (pK_a^o = 8.6) and β_X = 0.8 (pK_a^o = 7.3) for Ar = 2,4-$(NO_2)_2C_6H_2$- and 2,4,6-$(NO_2)_3C_6H_2S$ in structure **2** (R = EtO), respectively.[8] This means that the change of amine from secondary to tertiary amines leads to an increase in the magnitude of β_X. On the other hand, the aminolysis of *O*-ethyl *S*-(Z-phenyl) dithiocarbonate (structure **3** with R = EtO and Ar = C_6H_4Z) with anilines in acetonitrile at 30.0°C was found to proceed by a concerted mechanism (β_X = 0.5-0.7 and ρ_{XZ} = −0.56).[9]

The cross-interaction constant, ρ_{XZ}, in the present work is determined by multiple regression of 20 k_2 values in Table 1. The negative sign of ρ_{XZ} is an indication of the concerted process.[10] It is also to be noted that faster rates are accompanied by a larger magnitude of selectivity parameters, ρ_X (β_X) and ρ_Z (β_Z). The failure of the RSP also supports the proposed mechanism.[10]

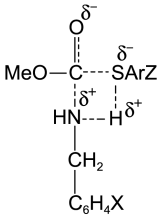
We therefore conclude that the aminolysis of thiophenyl derivatives, structure **2** (R = MeO), is enforced to proceed through a concerted mechanism due to destabilization of the putative tetrahedral intermediate, $T^{\pm}$, (i) by a strong electron releasing power of the R group (R = MeO has a stronger electron releasing effect (σ_R = −0.43) than R = Me (σ_R = −0.18))[11]; (ii) by a strong 'push' provided by a primary amine in $T^{\pm}$ (the push provided by amines in the putative intermediate, $T^{\pm}$, decrease in the order, primary > secondary > tertiary due to stabilization provided by the cationic charge dispersion by the amines within)[7]; (iii) by a relatively strong leaving ability of the ArS group (lower pK_a than the corresponding ArO group), and (iv) by a destabilizing effects of $T^{\pm}$ by the solvent, acetonitrile.

The kinetic isotope effects (k_H/k_D) determined with deuterated benzylamine nucleophiles are collected in Table 2. The (k_H/k_D) values are all substantially greater than unity, sug-

Table 2. The Secondary Kinetic Isotope Effects for the Reactions of *O*-Methyl *S*-Aryl Thiocarbonates with Deuterated X-Benzylamines in Acetonitrile at 45.0 °C

X	Z	$k_H \times 10^4$ ($M^{-1}s^{-1}$)	$k_D \times 10^4$ ($M^{-1}s^{-1}$)	k_H/k_D
p-Me	*p*-Me	2.39(± 0.03)	1.81(± 0.01)	1.32 ± 0.02[a]
p-Me	H	4.79(± 0.05)	3.47(± 0.03)	1.38 ± 0.02
p-Me	*p*-Cl	15.1(± 0.20)	9.74(± 0.08)	1.55 ± 0.02
P-Me	*p*-Br	20.1(± 0.30)	11.9(± 0.20)	1.69 ± 0.04
p-Cl	*p*-Me	1.14(± 0.03)	0.884(± 0.01)	1.29 ± 0.04
p-Cl	H	2.14(± 0.04)	1.45(± 0.02)	1.48 ± 0.03
p-Cl	*p*-Cl	6.12(± 0.05)	3.77(± 0.04)	1.62 ± 0.02
p-Cl	*p*-Br	7.44(± 0.06)	4.25(± 0.05)	1.75 ± 0.03

[a]Standard deviations.



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gesting that a four-center type TS (**4**) is involved.[4] In agreement with the negative ρ_{XZ},[4] which can be alternatively defined as eq. (4), the magnitude of (k_H/k_D is greater due to a greater degree of proton transfer for a stronger nucleophile ($\delta\sigma_X < 0$) and nucleofuge ($\delta\sigma_Z > 0$), which lead to a greater degree of bond cleavage ($\delta\rho_Z > 0$) and bond making ($\delta\rho_X < 0$), respectively.

$$\rho_{XZ} = \partial\rho_Z/\partial\sigma_X = \partial\rho_X/\partial\sigma_Z \quad (4)$$

Finally the activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, are summarized in Table 3, The $\Delta H^{\neq}$ values are relatively low and $\Delta S^{\neq}$ values are large negative, which are consistent with the concerted mechanism.[12]

Table 3. Activation Parameters[a] for the Reactions of *O*-Methyl *S*-Aryl Thiocarbonates with X-Benzylamines in Acetonitrile

X	Z	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1} K^{-1}
p-OMe	*p*-Me	12.1	37
p-OMe	*p*-Br	12.1	33
p-Cl	*p*-Me	12.2	38
p-Cl	*p*-Br	12.5	34

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg, *Physical Organic Chemistry*; Wiley: New York, 1964; p 378) are ± 0.6 kcal mol^{-1} and ± 2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

In summary, the reactions of *O*-methyl *S*-(Z)-aryl thiocarbonates with (X)-benzylamines in acetonitrile by a concerted displacement mechanism. This conclusion is based on (i) the relatively small β_X (0.6-0.8) and β_Z (−0.7 ~ −0.9) values, (ii) a negative ρ_{XZ} (−0.42) value, and (iii) the failure of the RSP. The kinetic isotope effects, (k_H/k_D) > 1.0, suggest that the TS has a four-center type hydrogen-bonded structure. It is notable that primary amines (benzylamine) and acetonitrile as solvent destabilize the putative tetrahedral intermediate, $T^{\pm}$, so strongly as to enforce a concerted mechanism.

Experimental

Materials. Merk GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification. Thiophenols and methyl chloroformate were Tokyo Kasei GR grade.

Preparartions of *O*-Methyl *S*-Aryl Thiocarbonates[13]. 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.

Kinetic Measurement. Rates were measured conductometrically at 45.0 ± 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 the Guggenheim method[14] 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 three runs and were reproducible 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). Analysis of the product gave the following results.

$CH_3OC(=O)NHCH_2C_6H_4$-OCH_3: Liquid, IR (KBr), 3313 (N-H), 2975 (C-H, benzyl), 2961 (C-H, CH_2), 2943 (C-H, CH_3), 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.

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