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

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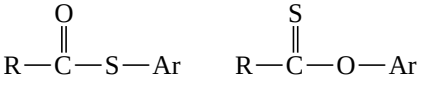
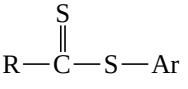
ABSTRACT: The kinetics and mechanism of the reactions of *O*-ethyl *S*-(*Z*)aryl thiocarbonates with (X)benzylamines in acetonitrile at 45.0°C are studied. Relatively small values of β_X (β_{nuc}) = 0.6 ~ 0.8 and β_Z (β_{lg}) = −0.5 ~ −0.7 together with a *negative* cross-interaction constant ρ_{XZ} (= −0.47) and failure of the reactivity–selectivity principle (RSP) are interpreted to indicate a concerted mechanism. The normal kinetic isotope effects (k_H/k_D = 1.3 ~ 1.8) involving deuterated benzylamine nucleophiles suggest a hydrogen-bonded, four-center-type transition state. © 2000 John Wiley & Sons, Inc. Int J Chem Kinet 32: 131–135, 2000

INTRODUCTION

The aminolyses of acyl compounds have been studied extensively. Brönsted plots were used in these reactions as mechanistic criteria [1,2]. In many of these nucleophilic reactions curved Brönsted-type plots have been found, which have been attributed to a change in the rate-determining step from breakdown ($\beta_{nuc} \cong 0.8 \sim 1.0$) to formation ($\beta_{nuc} \cong 0.1 \sim 0.3$) of a tetrahedral intermediate, $T^{\pm}$, in the reaction path as the basicity of the amine nucleophile increases [1–6]. The change in slope occurs at pK_a, where the leaving group and the nucleophile in the intermediate have the same leaving ability. Quite interestingly, however, concerted processes are found only in the reactions between *O*-ethyl *S*-aryl-thiocarbonates (structure I with R = EtO) with good leaving groups (Ar = 2,4-$(NO_2)_2$- and 2,4,6-$(NO_2)_3$-C_6H_2) and alicyclic secondary amines (β_{nuc} = 0.4 ~ 0.6) [7,8]. The concerted mechanism has been shown to be enforced by (i) instability incurred by the ArS group because ArS− is much less basic than ArO− and a better nucleofuge from $T^{\pm}$ than ArO− group [4]; (ii) stronger push provided by EtO, which enhances the nucleofugality of both the amine and arylthiolate ion from the intermediate relative to other R groups [9–11] (e.g., phenyl and alkyl); (iii) much faster expulsions of a given amine and ArS− from $T^{\pm}$ formed with structure I than those from $T^{\pm}$ with structures II and/or III due to a stronger π-bonding energy of the carbonyl group compared with thiocarbonyl [9]; and (iv) greater "push" to expel ArS− from $T^{\pm}$ provided by the secondary (alicyclic) amines than the tertiary (pyridines) amines [11].



Structure I **Structure II**



Structure III

To examine further the driving force for the con-

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certed aminolysis of the thiol derivatives, structure I, we carried out kinetic studies of the aminolysis of structure I with R = EtO and Ar = C_6H_4Z (Z = *p*-Me, H, *p*-Cl, and *p*-Br) using benzylamines ($XC_6H_4CH_2NH_2$; X = *p*-OMe, *p*-Me, H, *p*-Cl, and M-Cl) in acetonitrile at 45.0°C. Another important objective of this work is to determine the cross-interaction constant, ρ_{XZ} in Eq. (1) [12–14] where X and Z denote substituents in the nucleophile and leaving group, respectively. It has been postulated and experimentally found that in a stepwise acyl transfer

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

through a tetrahedral intermediate the sign of ρ_{XZ} is invariably positive and the reactivity–selectivity principle (RSP) [15,16] holds [17,18]. In contrast, the sign of ρ_{XZ} is normally negative and the RSP does not hold in the concerted acyl transfer reactions [17,18].

RESULTS AND DISCUSSION

The pseudo-first-order rate constants (k_{obs}) for all reactions obeyed Eq. (2) with negligible k_0 (≅0) in acetonitrile. The second-order rate constants, k_2 ($M^{-1}s^{-1}$), were obtained as

$$k_{obs} = k_0 + k_2 [N] \quad (2)$$

the slopes of the plots of k_{obs} vs. benzylamine concentration [N] and are summarized in Table I. 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. (2). This suggests that there is no base catalysis or noticeable side reactions. The rate is faster with a stronger nucleophile and a better nucleofuge as normally expected from a nucleophilic substitution reaction. The Brönsted β_X (β_{nuc}) and β_Z (β_{lg}) and Hammett ρ_X (ρ_{nuc}) and ρ_Z (ρ_{lg}) values are also shown in Table I. 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 thiolphenyl benzoates (structure I with R = Ph) with benzylamines in acetonitrile [11], 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

Table I The Second-Order Rate Constants, $k_2 \times 10^3$ dm^3 mol^{-1} s^{-1} for the Reactions of *O*-Ethyl *S*-Aryl Thiocarbonates with X-Benzylamines in Acetonitrile at 45.0°C

	Z					
X	*p*-Me	H	*p*-Cl	*p*-Br	ρ_Z[a]	β_Z[b]
p-OMe	18.4	31.7	75.4	85.6	1.63 ± 0.09[e]	−0.66 ± 0.03[c]
	7.51[d]			38.7[d]		
	3.06[e]			17.4[e]		
p-Me	16.8	26.9	65.1	71.8	1.56 ± 0.11	−0.64 ± 0.01
H	13.2	21.8	50.0	53.1	1.51 ± 0.07	−0.63 ± 0.02
	9.70[d]			36.1[d]		
	4.81[e]			18.8[e]		
p-Cl	2.35	15.5	31.6	9.02	1.37 ± 0.09	−0.55 ± 0.03
m-Cl	7.80	12.4	25.2	26.7	1.32 ± 0.05	−0.54 ± 0.03
ρ_X[f]	−0.60 ± 0.01[c]	−0.63 ± 0.01	−0.76 ± 0.02	−0.78 ± 0.01	ρ_{XZ}[g] =	−0.47 ± 0.14[c]
β_X[h]	0.62 ± .02[h]	0.63 ± 0.02	0.78 ± 0.01	0.79 ± 0.03		

[a] The σ values were taken from Dean, J. A. Handbook of Organic Chemistry; McGraw-Hill: New York, 1987; Table 7-1. Correlation coefficients were better than 0.995 in all cases.

[b] The pK_a values were taken from Buckingham, J., Ed.; Dictionary of Organic Chemistry, 5th ed. Chapman and Hall: New York, 1982; Z = *p*-Br was excluded from the Brönsted plots for β_Z due to an unreliable pK_a values. Correlation coefficients were better than 0.998 in all cases.

[c] Errors shown are standard deviations.

[d] At 35°C.

[e] At 25°C.

[f] The σ values were taken from McDaniel, D. H.; Brown, H. C. J Org Chem 1958, 23, 420. Correlation coefficients were better than 0.998 in all cases.

[g] Correlation coefficient was 0.997.

[h] The pK_a values were taken from Fischer, A.; Galloway, W. J.; Vaughan, J. J Chem Soc 1964, 3588. Correlation coefficients were better than 0.997 in all cases. X = *p*-CH_3O was excluded from the Brönsted plots for β_X due to an unreliable pK_a value listed.

(−1.63) for Z = H and X = H, respectively. These are larger by ca. three times than those corresponding values, −0.63 (0.63) and 1.51 (−0.63), in Table I. The β_X value of 0.63 obtained in the present work is similar to those for the concerted reaction of structure (R = EtO) with alicyclic (secondary) amines [7,8] (β_X = 0.56 for Ar = 2,4-$(NO_2)_2C_6H_3$ and β_X = 0.48 for Ar = 2,4,6-$(NO_2)_2C_6H_2$ in structure I) in aqueous solution. These two derivatives of structure I (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-$(NO_2)_2$- and 2,4,6-$(NO_2)_3$-C_6H_2S in structure I (R = EtO), respectively [19]. 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*-ethlyl *S*-(*Z*-phenyl) dithiocarbonate (structure III 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) [20].

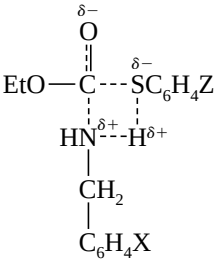
The cross-interaction constant, ρ_{XZ}, in the present work is determined by multiple regression of 20 k_2 [k_{XZ} in Eqs. (1) and (3)] values in Table I, Eq. (3). The negative sign

$$\log (k_{XZ}/k_{HH}) = -(0.65 \pm 0.03)\sigma_X + (1.49 \pm 0.03)\sigma_Z - (0.47 \pm 0.14)\sigma_X\sigma_Z \quad (3)$$

of ρ_{XZ} is an indication of the concerted process [17,18]. 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 concerted mechanism [17,18].

We therefore conclude that the aminolysis of thiophenyl derivatives, structure I (R = EtO), 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 = EtO has a stronger electron-releasing effect (σ_R = −0.50) than R = Me (σ_R = −0.18)) [21]; (ii) by a strong "push" provided by a primary amine in $T^{\pm}$ (the push provided by amines in the putative intermediate, $T^{\pm}$, decreases in the order, primary > secondary > tertiary due to stabilization provided by the cationic charge dispersion by the amines within $T^{\pm}$) [11]; (iii) by a relatively strong leaving ability of the ArS group (lower pK_a than the corresponding ArO group), and (iv) by a destabilizing effect of $T^{\pm}$ by the solvent, acetonitrile [3].

The kinetic isotope effects (k_H/k_D) determined with deuterated benzylamine nucleophiles are collected in Table II. The k_H/k_D values are all substantially greater than unity, suggesting that a four-center-type TS (structure IV) is involved [14]. In agreement with the negative ρ_{XZ} [13], which can be alternatively defined as Eq. (4), the magnitude of k_H/k_D is greater due to a



Structure IV

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 ($\delta\rho_Z > 0$)

$$\rho_{XZ} = \partial\rho_Z/\partial\sigma_X = \partial\rho_X\partial\sigma_Z < 0 \quad (4)$$

and bond making ($\delta\rho_X < 0$), respectively. The activation parameters in Table III are also in line with those for a typical S_N2-type concerted reaction.

Table II The Secondary-Kinetic Isotope Effects for the Reactions of *O*-Ethyl *S*-Aryl Thiocarbonates with Deuterated X-Benzylamines in Acetonitrile at 45.0°C[a]

X	Z	$k_H \times 10^3$ ($M^{-1}s^{-1}$)	$k_D \times 10^3$ ($M^{-1}s^{-1}$)	k_H/k_D
p-Me	*p*-Me	16.8 ± 0.08	12.3 ± 0.06	1.37 ± 0.01
p-Me	H	26.9 ± 0.1	19.1 ± 0.09	1.41 ± 0.01
p-Me	*p*-Cl	65.2 ± 0.5	39.8 ± 0.2	1.63 ± 0.02
p-Me	*p*-Br	71.8 ± 0.6	41.9 ± 0.4	1.71 ± 0.02
p-Cl	*p*-Me	9.70 ± 0.02	7.52 ± 0.05	1.28 ± 0.01
p-Cl	H	15.5 ± 0.06	10.4 ± 0.07	1.49 ± 0.01
p-Cl	*p*-Cl	31.6 ± 0.2	18.9 ± 0.1	1.67 ± 0.02
p-Cl	*p*-Br	36.1 ± 0.3	20.2 ± 0.2	1.78 ± 0.03

[a] Errors shown are standard deviations.

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

X	Z	$\Delta H^{\pm}$/kcal mol^{-1}	$-\Delta S^{\pm}$/cal mol^{-1} K^{-1}
p-OMe	*p*-Me	16.3 ± 0.1	15 ± 1
p-OMe	*p*-Br	14.4 ± 0.1	18 ± 1
p-Cl	*p*-Me	12.7 ± 0.1	28 ± 1
p-Cl	*p*-Br	12.5 ± 0.1	26 ± 1

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

In summary, the reactions of *O*-ethyl *S*-(*Z*)aryl thiocarbonates with (X) benzylamines in acetonitrile proceed by a concerted displacement mechanism. This conclusion is based on (i) the relatively small β_X (0.6 ~ 0.8) and β_Z (−0.5 ~ −0.7) values, (ii) a negative ρ_{XZ} (−0.47) 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, as found with secondary amines (alicyclic amines in water), but not with tertiary amines (pyridines in water).

EXPERIMENTAL

Materials

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

Preparations of *O*-Ethyl *S*-Aryl Thiocarbonates [22]

Thiophenol derivatives and ethyl chloroformate were dissolved in anhydrous ether and pyridine added carefully, keeping the temperature to 0 ~ 5°C. Ice was then added to the reaction mixture and the ether layer was separated, dried on $MgSO_4$, and distilled under reduced pressure to remove the solvent. IR (Nicolet 5BX FT-IR) and ^{1}H and ^{13}C NMR (JEOL 400 MHz) data are cited next.

O-*Ethyl* S-*Phenyl Thiocarbonate.* The data include liquid, IR(KBr), 2979 (C—H, CH_2), 1735 (C═O), 1592, 1478 (C—C, aromatic), 1135, 1087 (C—O); ^{1}H NMR (400 MHz, $CDCl_3$), 1.32 (3H, t, J = 7.32 MHz, CH_3), 4.30 (2H, q, J = 7.08 MHz, CH_2), 7.39 ~ 7.55 (5H, m, aromatic ring); and ^{13}C NMR (100.4 MHz, $CDCl_3$), 168.7 (C═O) 136.2, 133.4, 127.5, 125.2 (aromatic), 64.1, 14.2.

O-*Ethyl* S-p-*Methylphenyl-Thiocarbonate.* The data include liquid, IR(KBr), 2979 (C—H, CH_2), 2939 (C—H, CH_3), 1737 (C═O), 1596, 1488 (C═C, aromatic), 1139, 1092 (C—O); ^{1}H NMR (400 MHz, $CDCl_3$), 1.31 (3H, t, J = 7.08 MHz, CH_3), 2.37 (3H, s, CH_3), 4.29 (2H, q, J = 7.08 MHz, CH_2), 7.21–7.42 (4H, dd, J = 7.81 MHz, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 169.9 (C═O), 139.8, 134.8, 129.9, 124.3 (aromatic), 63.9, 21.3, 14.3.

O-*Ethyl* S-p-*Chlorophenyl Thiocarbonate.* Data include liquid, IR(KBr), 2979 (C—H, CH_2), 1723 (C═O), 1582, 1475 (C═C, aromatic), 1132, 1092 (C—O); ^{1}H NMR (400 MHz, $CDCl_3$), 1.32 (3H, t, J = 7.32 MHz, CH_3), 4.30 (2H, q, J = 7.08 MHz, CH_2), 7.47 ~ 7.26 (4H, dd, 8.50 MHz, aromatic ring); and ^{13}C NMR (100.4 MHz, $CDCl_3$), 168.9 (C═O), 136.0, 135.9, 129.3, 126.4 (aromatic), 64.3, 14.3.

O-*Ethyl* S-p-*Bromophenyl Thiocarbonate.* Data include liquid, IR(KBr), 2979 (C—H, CH_2), 1730 (C═O), 1575, 1474 (C═C, aromatic), 1152, 1092 (C—O); ^{1}H NMR (400 MHz, $CDCl_3$), 1.32 (3H, t, J = 7.08 MHz, CH_3), 4.30 (2H, q, J = 7.08 MHz, CH_2), 7.54 ~ 7.38 (4H, dd, 8.50 MHz, aromatic ring); and ^{13}C NMR (100.4 MHz, $CDCl_3$), 168.5 (C═O), 136.0, 132.1, 126.8, 124.0 (aromatic), 64.1, 14.1.

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. Pseudo-first-order rate constants, k_{obs}, were determined by the Guggenheim method [23] with a large excess of benzylamine, [substrate] ≅ 0.001 M and [benzylamine] ≅ 0.05 ~ 0.1 M. Second-order rate constants, k_2, were obtained from the slope of a plot of k_{obs} vs. benzylamine with more than five concentrations in more than three runs and were reproducible to within ± 3%.

Product Analysis

Substrate (0.05 mol) and benzylamine (0.5 mol) were added to acetonitrile and reacted 45.0°C under the same condition as the kinetic measurements. After more than 15 half-lives, the solvent was removed under reduced pressure and the product was separated by

column chromatography (silica gel, 10% ethylacetate-*n*-hexane). Analysis of the product gave the results cited next.

$CH_3CH_2OC(=O)NHCH_2C_6H_4-OCH_3$. Data include mp 45 ~ 46°C, IR(KBr), 3315 (N—H), 2972 (C—H, benzyl), 2963 (C—H, CH_2), 2946 (C—H, CH_3), 1683 (C=O), 1549 (C=C, aromatic), 1522 (N—H), 1260, 1038 (C—O); ^{1}H NMR (400 MHz, $CDCl_3$), 1.99 ~ 1.18 (3H, m, CH_3), 3.73 (3H, s, OCH_3), 4.08 (2H, q, J = 7.08, OCH_2), 4.23 (2H, d, J = 5.86, CH_2^- N), 5.55 (1H, s, NH), 7.18 ~ 6.80 (4H, dd, J = 8.30 MHz, aromatic ring); and ^{13}C NMR (100.4 MHz, $CDCl_3$), 171.1 (C=O), 158.9, 156,9, 131.1, 128.9 (aromatic ring), 60.7, 55.2 (OCH_3), 44.4 (CH_2), 14.7 (CH_3).

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