Kinetics and Mechanism of the Aminolysis of Aryl Thionocarbamates in Acetonitrile

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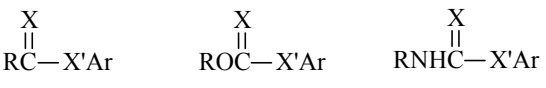
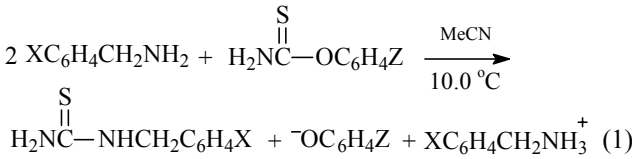
In spite of the large amount of research that has been carried out, there are still many facets of the aminolysis of aryl esters,[1] carbonates,[2] carbamates,[3] and their thio analogs, **1** ~ **3**, that are not well understood. These include the effects of the nonleaving group R, RO or RNH, and the combined or cooperative effects of the atom pairs, X and X', on the aminolysis reactivity and mechanism of **1** ~ **3**.



1 **2** **3**

R = alkyl, aryl, or arylalkyl group
X, X' = O or S

In an attempt to clarify some of these problems, we have undertaken an examination of the effects of atom pairs X, X' on the reactivity which is reflected in the mechanism. In this work, we carried out kinetic studies of the aminolysis of aryl thionocarbamates (ATNC: **3** with R = H, X = S and X' = O) with benzylamines (BAs) in acetonitrile, eq (1). We varied



(1)

substituents in the nucleophile (X) and leaving group (Z), and the rate constant,[4] k_2 are subjected to a multiple regression analysis to determine the cross-interaction constant, ρ_{XZ}, in eqs 2. It has been shown that for a concerted reaction series the sign of ρ_{XZ} is negative and the reactivity-selectivity principle (RSP) fails.[5]

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

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

Results and Discussion

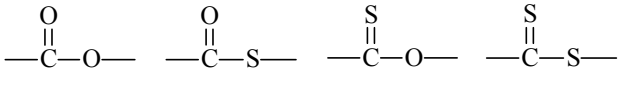
The reaction of aryl thionocarbamates (ATNC) with benzylamines (BAs) in acetonitrile follow clean, second-order kinetics given by eqs 3 and 4, where k_{obs} is the pseudo-first-order rate constant and k_2 is the second-order rate constant for the aminolysis of the substrate. The rate constant, k_2 values are

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

$$k_{obs} = k_2\,[\text{BA}] \quad (4)$$

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 (H_2O) values, which are considered to be reliable since the pK_a values in MeCN and in H_2O vary in parallel.[6] The β_Z (β_{eg}) values are obtained by multiplying a factor of 0.62 to all the β_Z values determined using the pK_a (H_2O) values.[7]

The rate ($k_2 = 1.47 \times 10^{-3}$ s^{-1} M^{-1} for X = Z = H at 10.0 °C) is slower than that for the corresponding reaction of aryl thiocarbamate (ATC, $k_2 = 81.6 \times 10^{-3}$ s^{-1} M^{-1}).[8] This rate sequence is an indication of the concerted mechanism as corroborated below: There are four kinds of structures (**a**~**d**) according to different combinations of atom pairs X and X' (O or S) in **1**~**3**.



a **b** **c** **d**

For given nonleaving group (R, RO, or RNH) and aromatic ring structure (Ar), the strength of positive charge on the functional center (carbonyl carbon), C_α, will depend on the sum of electronegativity of O and S atom pairs. The electronegativity of O (3.41) is larger than that of S (2.58),[9] and since an electron is transferred from ether oxygen (X' = O) to carbonyl oxygen (C=O),[10] the carbonyl oxygen is more electronegative than the ether oxygen (and similarly with X = S and X' = S), and hence the positive charge on C_α will increase in the order, (5).

$$\mathbf{d} < \mathbf{c} < \mathbf{b} < \mathbf{a} \quad (5)$$

Since in the concerted aminolysis (or in the stepwise reaction with rate-limiting formation of a zwitterionic tetrahedral intermediate, $T^{\pm}$) the rate is faster for the substrate with a greater positive charge on C_α, the rate sequence predicted by (5) is which is indeed the sequence found experimentally. One might

$$\text{ATNC } (\mathbf{c}) < \text{ATC } (\mathbf{b})$$

also argue that the stability of putative tetrahedral intermediate ($T^{\pm}$) is the most stable with ATNC (**c**) and the least stable with ATC (**b**), and the fact that nucleofugality of the leaving group is greater with ATC (**b**) so that the rate of concerted reaction

Table 1. The Second Order Rate Constants, k_N x 10^3 dm^3 mol^{-1} s^{-1} for the Reactions of Z-Phenyl Thionocarbamates with X-benzylamines in Acetonitrile at 10.0 °C

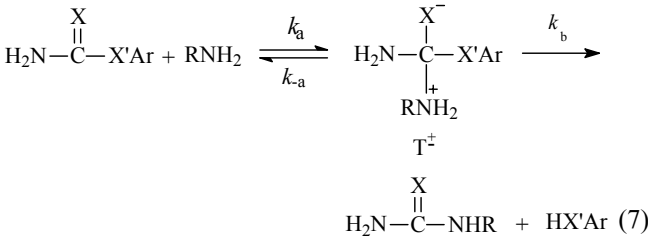
X	Z				ρ_Z[a]	β_Z[b]
	p-Me	H	*p*-Cl	*p*-Br		
p-OMe	0.703 ± 0.005 0.415 ± 0.003[c] 0.249 ± 0.002[d]	2.79 ± 0.06	29.3 ± 0.6	41.1 ± 0.9 23.8 ± 0.5[c] 14.0 ± 0.2[d]	4.32 ± 0.03	-1.88 ± 0.10[e]
p-Me	0.548 ± 0.004	2.11 ± 0.05	20.8 ± 0.4	29.4 ± 0.8	4.22 ± 0.03	-1.84 ± 0.11
H	0.367 ± 0.003	1.47 ± 0.04	13.3 ± 0.2	18.1 ± 0.3	4.13 ± 0.03	-1.81 ± 0.01
p-Cl	0.241 ± 0.002 0.142 ± 0.001[c] 0.0824 ± 0.0008[d]	0.886 ± 0.009	7.94 ± 0.08	10.1 ± 0.1 5.96 ± 0.07[c] 3.58 ± 0.04[d]	4.00 ± 0.02	-1.76 ± 0.11
m-Cl	0.176 ± 0.001	0.606 ± 0.006	5.02 ± 0.06	6.49 ± 0.05	3.85 ± 0.02	-1.69 ± 0.10
ρ_X[f]	-0.93 ± 0.03	-1.01 ± 0.02	-1.15 ± 0.04	-1.23 ± 0.03	ρ_{XZ}[g] =	-0.68
β_X[h]	0.93 ± 0.04	1.02 ± 0.03	1.16 ± 0.05	1.24 ± 0.04		

[a]The σ values were taken from ref. 20a. Correlation coefficients were better than 0.967 in all cases. [b]The pK_a values were taken from ref. 20b. Z = *p*-Br was excluded from the Brönsted plot for β_Z due to an unreliable pK_a values. Correlation coefficients were better than 0.997 in all cases. [c]At 0 °C. [d]At -10 °C. [e]Errors are everage deviation. [f]The source of σ is the same as for footnote a. Correlation coefficients were better than 0.998 in all cases. [g]Correlation coefficients was 0.997. [h]The pK_a values were taken from ref. 20c. Correlation coeffcients were better than 0.997 in all cases.

with ATC should be faster than ATNC (vide infra). In contrast, for the stepwise mechanism in which the expulsion of leaving group from $T^{\pm}$ in eq. 7 is rate limiting, the stability of the intermediate, $T^{\pm}$, will be important (vide infra) and the rate sequence will follow the sequence of $T^{\pm}$ stability, (6), which is

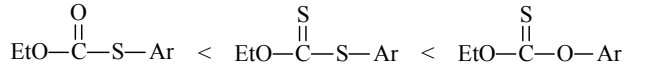
$$\mathbf{b} < \mathbf{a} < \mathbf{d} < \mathbf{c} \qquad (6)$$

quite different from sequence (5) for the concerted mechanism. The stability of $T^{\pm}$ is determined (i) by the acceptor ability of (C=X) and (ii) by the donor ability of -X'- in **1** ~ **3**. It has been shown that the acceptor ability of (C=S) is stronger than that of (C=O), and the donor ability of -O- is stronger than that of



(7)

-S- leading to the $T^{\pm}$ stability sequence given as (6). According to this sequence the rate of ATNC (**c**) is predicted to be faster than that of ATC (**b**); **b** < **c** which is a reverse of the order experimentally found so that the present reaction series is unlikely to proceed by a stepwise mechanism. An example of such stepwise aminolysis reaction series which is consistent with rate order 6 is found in the pyridinolysis of 2,4-dinitrophenyl O-ethyl carbonates.[2d,e,f] These reactions are reported to exhibit biphasic Brönsted plots. The steeper linear part (β_X > 0.9) for weakly basic pyridines changes to the smaller Brönsted slope (β_X > 0.2) for strongly basic pyridines, which has been interpreted to indicate a change in the rate-limiting step from expulsion of the leaving group from $T^{\pm}$(k_b) to formation of $T^{\pm}$(k_a). However, it is now apparent that the rate-limiting step actually changes from the intermediate ($T^{\pm}$) stability, but not from k_b, to formation of $T^{\pm}$(k_a). In accordance with this change, the rate order also changes from sequence 6 to sequence 5. For X = H (pK_a of benzylamine = 5.37), the rate (k_2) order 6 applies.



(**b** : k_2=0.018 s^{-1} M^{-1})[2d] (**d** : k_2=0.062 s^{-1} M^{-1})[2f] (**c** : k_2=0.31 s^{-1} M^{-1})[2f]

The concerted mechanism proposed for the aminolysis of ATNC in MeCN is supported by the negative cross-interaction constant,[5] ρ_{XZ} = -0.68 and failure of the RSP principle. We note that the magnitude of selectivity parameters (ρ_X, β_X, ρ_Z and β_Z) are greater for the more reactive systems indicating that the RSP does not hold (anti-RSP).[5] The size of β_Z is also in the range of values that are expected for a concerted aminolysis process.[11] The β_X values are 0.93~1.24 which are rather larger than values normally expected for the concerted aminolysis reactions, β_X = 0.4~0.7.[12] However β_X values smaller than 0.4[13] and larger than 0.7[14] have also been reported for the concerted aminolysis reactions. The larger β_X values are often obtained in solvents less polar than water[15] so that the large β_X values in the present work may be due to the MeCN used.

Of the five factors that are known to influence the aminolysis mechanism of **1** ~ **3**, three (i ~ iii) are in favor, but two (iv ~ v) are in disfavor of the concerted mechanism for the present reactions: (i) The strong push provided by H_2N (in ATNC) to expel the leaving group destabilizes the putative tetrahedral intermediate, $T^{\pm}$, to such an extent that the $T^{\pm}$ can not exist and results in a concerted process. (ii) The strong nucleofugality of benzylamine (large pK_a) from $T^{\pm}$ provides additional destabilization of the putative intermediate, which is also in favor of the concerted mechanism. (iii) The less polar (acetonitrile) solvent used in the present work is also more conducive to a concerted mechanism compared with water.[16] (iv) As stated above, the C=S group is a better acceptor of electron from an

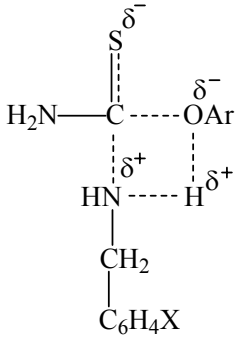
Table 2. The Kinetic Isotope Effects for the Reactions of Z-Phenyl Thionocarbamates with Deuterated X-Benzylamines in Acetonitrile at 10.0°C

X	Z	k_H x 10^3($M^{-1}s^{-1}$)	k_D x 10^3($M^{-1}s^{-1}$)	k_H/k_D
p-OMe	*p*-Me	0.703 (± 0.005)	0.411 (± 0.004)	1.71 ± 0.03[a]
p-OMe	H	2.79 (± 0.06)	1.67 (± 0.02)	1.67 ± 0.02
p-OMe	*p*-Cl	29.3 (± 0.6)	18.1 (± 0.2)	1.61 ± 0.04
P-OMe	*p*-Br	41.1 (± 0.9)	26.5 (± 0.4)	1.55 ± 0.03
p-Cl	*p*-Me	0.241 (± 0.002)	0.138 (± 0.001)	1.74 ± 0.02
p-Cl	H	0.886 (± 0.009)	0.527 (± 0.005)	1.68 ± 0.02
p-Cl	*p*-Cl	7.94 (± 0.08)	4.87 (± 0.05)	1.63 ± 0.03
p-Cl	*p*-Br	10.1 (± 0.1)	6.43 (± 0.07)	1.57 ± 0.02

[a]Standard deviations.

ether (-O-) or (-S-) than the C=O group and provides stronger stabilization to the ($T^{\pm}$) intermediate. Therefore, thiocarbonyl (in ATNC) is less likely to lead to a concerted mechanism than the carbonyl group. (v) The leaving ability of $^{-}$OAr is weaker than that of $^{-}$SAr, which is in disfavor of a concerted mechanism. The above three factors (i ~ iii) together with the combined or cooperative effects of O and S atom pairs discussed above in conjunction with the rate orders (5) and (6) provide strong supports for the concerted mechanism for the reactions (eq 1) studied in this work.

The kinetic isotope effects (Table 2) involving deuterated nucleophile,[17] $XC_6H_4CH_2ND_2$, are normal ($k_H/k_D > 1.0$) suggesting a possibility of forming hydrogen-bonded four-center type TS as has often been proposed. Since no base catalysis was found (the rate law is first order with respect to [BA], eq. 3), the proton transfer occurs concurrently with the rate-limiting expulsion of ArO^- in the TS but not catalyzed by benzylamine. The consumption of proton by the excess benzylamine should therefore take place in a subsequent rapid step.



TS

The low activation enthalpies, $\Delta H^{\neq}$, and highly negative activation entropies, $\Delta S^{\neq}$,(Table 3) are also in line with the proposed TS. Especially, the $\Delta H^{\neq}$ values are somewhat lower and the $\Delta S^{\neq}$ values are higher negative values than other carbamates of aminolysis systems. The expulsion of ArO^- anion in the rate determining step (an endoergic process) is assisted by the hydrogen-bonding with an amino hydrogen of the benzylammonium ion within the intermediate, $T^{\pm}$. This will lower the $\Delta H^{\neq}$ value, but the TS becomes structured and rigid (low entropy process) which should lead to a large negative.

Table 3. Activation Parameters[a] for the Reactions of Z-Phenyl Thionocarbamates 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	7.1	48
p-OMe	*p*-Br	7.4	38
p-Cl	*p*-Me	7.4	47
p-Cl	*p*-Br	7.1	42

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg, K. B.[21]) are ± 0.4 kcal mol^{-1} and ± 2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

In summary, the aminolysis reactions of aryl thionocarbamates (ATNC) with benzylamines in acetonitrile are investigated at 10.0 °C. The rate of ATNC is slower than the corresponding aminolysis of aryl thiocarbamate (ATC), which has been interpreted in terms of cooperative effects of atom pairs O and S on the reactivity and mechanism. For concerted processes, these effects predict a rate sequence, -C(=S)-S- < -C(=S)-O- < -C-(=O)-S- < -C-(=O)-O-, and our results are consistent with this order. The negative cross-interaction constant, ρ_{XZ} = -0.68, the size of β_Z (= 0.69~0.88) and failure of the RSP are in accord with the concerted mechanism. The normal kinetic isotope effects, k_H/k_D = 1.55 ~ 1.74, involving deuterated benzylamines suggest a hydrogen bonded cyclic transition state.

Experimental Section

Materials. Acetonitrile (Merck, GR) was used after three-time distillations. The benzylamine nucleophiles, Aldrich GR, were used after recrystallization. Phenols and potassium thiocyanate were Tokyo Kasei GR grade.

Substrates. Phenyl Thionocarbamates. Phenyl thionocarbamates were prepared by the literature method of H. Al-Rawi and A. Williams.[18] These substrates were prepared by adding acetic acid (1 mL) over a period of 5 min to a stirred suspension of phenol (1 g) and potassium thiocyanate (0.8 g) in water (10 mL). After about 15 min, precipitate formed which was filtered and recrystallized. Melting point, IR (Nicolet 5BX FT-IR) and ^{1}H and ^{13}C NMR (JEOL 400 MHz) data were found to agree well with the literature values.[18]

Kinetic Measurement. Rates were measured conductometrically at 10.0 ± 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[19] with large excess of benzylamine. Second-order rate constants, k_2, 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, phenyl thionocarbamate (5×10^{-3} mole) was reacted with excess *p*-chlorobenzylamine (5×10^{-2} mole) with stirring for more than 15 half-lives at 10.0 °C in acetonitrile, and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was treated with column chromatography (silica gel, 20% ethyl acetate-*n*-hexane). Analysis of the product gave the following results.

$H_2NC(=S)NHCH_2C_6H_4OCH_3$-*p*: m.p. 110-112 °C, IR(KBr), 3281(N-H), 1511(C-C, aromatic), 1497(C=C, aromatic), 1459 (C-H, CH_2), 1254(C-O), 1186(C=S), 708(C-H, aromatic); ^{1}H NMR(400 MHz, $CDCl_3$), 3.88(3H, s, CH_3), 4.48(2H, s, CH_2), 7.05(2H, d, J = 8.75 MHz, meta H), 7.30(2H, d, J = 8.30 MHz, ortho H) ; ^{13}C NMR(100.4 MHz, $CDCl_3$), 216.7, 159.4, 129.2, 128.7, 114.1, 55.3, 43.3.; Mass, *m/z* 196(M^+). Anal. Calcd. For $C_9H_{12}N_2OS$: C, 55.1; H, 6.21. Found: C, 55.3; H, 6.22.

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