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, carbonates, carbamates, and their thio analogs, 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.

\[
\begin{align*}
&\text{RC}^-'\text{X'Ar} \\
&\text{ROC}^-'\text{X'Ar} \\
&\text{RNHC}^-'\text{X'Ar}
\end{align*}
\]

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 and X' (O or S) in the aminolysis reactivity and mechanism of 1–3.

\[
\begin{align*}
&\text{2XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{H}_2\text{NC}^-'\text{OC}_6\text{H}_4\text{Z} \rightarrow \text{MeCN} \\
&10.0 \degree \text{C}
\end{align*}
\]

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

\[
\log(k_{2b}/k_0) = \rho_{XZ} \sigma_X + \rho_{XZ} \sigma_Z + \rho_{XZ} \sigma_X \sigma_Z
\] (2a)

\[
\rho_{XZ} = \partial \rho_{XZ}/\partial \sigma_X = \partial \rho_{XZ}/\partial \sigma_Z
\] (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 summarized in Table 1 together with selectivity parameters \( \rho \), \( \beta_X \), \( \beta_Z \), and \( \beta_{XZ} \). The \( \beta_X (\text{H}_2\text{O}) \) values are obtained by using the \( pK_a (\text{H}_2\text{O}) \) values, which are considered to be reliable since the \( pK_a \) values in MeCN and in H_2O vary in parallel.6 The \( \beta_Z (\text{H}_2\text{O}) \) values are obtained by multiplying a factor of 0.62 to all the \( \beta_Z \) values determined using the \( pK_a (\text{H}_2\text{O}) \) values.7

The rate \( (k_2 = 1.47 \times 10^{-3} \text{s}^{-1} \text{M}^{-1}) \) for X = Z = H at 10.0 \( \degree \text{C} \) is slower than that for the corresponding reaction of aryl thionocarbamate (ATC, \( k_2 = 81.6 \times 10^{-3} \text{s}^{-1} \text{M}^{-1}) \).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.

\[\text{O} \quad \text{O} \quad \text{S} \quad \text{S} \quad \text{S} \quad \beta \quad \beta \quad \beta \]

For given nonleaving group (R, RO, or RNH) and aromatic ring structure (Ar), the strength of positive charge on the functional center (carbonyl carbon), \( C_{\alpha} \), 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 \( C_{\alpha} \) will increase in the order, (5).

\[\text{a} < \text{b} < \text{c} < \text{d} \] (5)

Since in the concerted aminolysis (or in the stepwise reaction with rate-limiting formation of a zwitterionic tetrahedral intermediate, \( T^+ \)) the rate is faster for the substrate with a greater positive charge on \( C_{\alpha} \), the rate sequence predicted by (5) is which is indeed the sequence found experimentally. One might also argue that the stability of putative tetrahedral intermediate (\( T^+ \)) 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...
with ATC should be faster than ATNC (vide infra). In contrast, for the stepwise mechanism in which the expulsion of leaving group from T⁺ in eq. 7 is rate limiting, the stability of the intermediate, T⁺, will be important (vide infra) and the rate sequence will follow the sequence of T⁺ stability, (6), which is

\[ b < a < d < c \] (6)

quite different from sequence (5) for the concerted mechanism.

The stability of T⁺ is determined (i) by the acceptor ability of (C=S) 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 (C=O), and the donor ability of -O- is stronger than that of (C=X) and (ii) by the donor ability of -X' in

\[ \text{H}_2\text{N} - \text{C} - \text{X'Ar} + \text{RNH}_2 \xrightleftharpoons[k_a]{k_b} \text{H}_2\text{N} - \text{C} - \text{X'Ar} \]

\[ \xrightarrow[k_b]{k_a} \text{H}_2\text{N} - \text{C} - \text{X'Ar} \xrightarrow[k_b]{k_a} \text{HNH}_2 \]

\[ \text{T}^+ \]

\[ \text{H}_2\text{N} - \text{C} - \text{NHR} + \text{HXAr} \]

-S- leading to the T⁺ 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 Brønsted plots. The steeper linear part (βₓ > 0.9) for weakly basic pyridines changes to the smaller Brønsted slope (βₓ > 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⁺(k₅) to formation of T⁺(k₆). However, it is now apparent that the rate-limiting step actually changes from the intermediate (T⁺) stability, but not from k₅, to formation of T⁺(k₅). In accordance with this change, the rate order also changes from sequence 6 to sequence 5. For X = H (pKₐ of benzylamine = 5.37), the rate (k₅) order 6 applies.

\[ \text{O} \xrightarrow[\text{EtO}]{-\text{S}} \text{Ar} < \text{EtO} \xrightarrow[\text{S}]{-\text{S}} \text{Ar} < \text{EtO} \xrightarrow[\text{S}]{-\text{O}} \text{Ar} \]

(b: k₀=0.188 s⁻¹ M⁻¹)²f (d: kₓ=0.062 s⁻¹ M⁻¹)²f (c: kₓ=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, ρₓζ = -0.68 and failure of the RSP principle. We note that the magnitude of selectivity parameters (ρₓζ, βₓζ, ρₓζ and βₓζ) are greater for the more reactive systems indicating that the RSP does not hold (anti-RSP).5 The size of βₓζ is also in the range of values that are expected for a concerted aminolysis process.11 The βₓζ values are 0.93~1.24 which are rather larger than values normally expected for the concerted aminolysis reactions, βₓζ = 0.4~0.7.12 However βₓζ values smaller than 0.413 and larger than 0.714 have also been reported for the concerted aminolysis reactions. The larger βₓζ values are often obtained in solvents less polar than water15 so that the large βₓζ 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 HN₂ (in ATNC) to expel the leaving group destabilizes the putative tetrahedral intermediate, T⁺, to such an extent that the T⁺ cannot exist and results in a concerted process. (ii) The strong nucleofugality of benzylamine (large pKₐ) from T⁺ provides additional destabilization of the putative intermediate, which is also in favor of the concerted mechanism. (iii) The less polar (acetoniitrile) solvent used in the present work is also more conducive to a concerted mechanism compared with water16 (iv) As stated above, the C=S group is a better acceptor of electron from an

Table 1. The Second Order Rate Constants, kₓ × 10³ dm³ mol⁻¹ s⁻¹ for the Reactions of Z-Phenyl Thionocarbamates with X-benzylamines in Acetonitrile at 10.0 °C

<table>
<thead>
<tr>
<th>X</th>
<th>p-Me</th>
<th>H</th>
<th>p-Cl</th>
<th>p-Br</th>
<th>ρₓζ</th>
<th>βₓζ</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>0.703 ± 0.005</td>
<td>2.79 ± 0.06</td>
<td>29.3 ± 0.6</td>
<td>41.1 ± 0.9</td>
<td>4.32 ± 0.03</td>
<td>-1.88 ± 0.10f</td>
</tr>
<tr>
<td>p-Me</td>
<td>0.415 ± 0.003</td>
<td>2.11 ± 0.05</td>
<td>20.8 ± 0.4</td>
<td>29.4 ± 0.8</td>
<td>4.22 ± 0.03</td>
<td>-1.84 ± 0.11</td>
</tr>
<tr>
<td>H</td>
<td>0.367 ± 0.003</td>
<td>1.47 ± 0.04</td>
<td>13.3 ± 0.2</td>
<td>18.1 ± 0.3</td>
<td>4.13 ± 0.03</td>
<td>-1.81 ± 0.01</td>
</tr>
<tr>
<td>p-Cl</td>
<td>0.241 ± 0.002</td>
<td>0.886 ± 0.009</td>
<td>7.94 ± 0.08</td>
<td>10.1 ± 0.1</td>
<td>5.96 ± 0.07f</td>
<td>-1.76 ± 0.11f</td>
</tr>
<tr>
<td>m-Cl</td>
<td>0.176 ± 0.001</td>
<td>0.606 ± 0.006</td>
<td>5.02 ± 0.06</td>
<td>6.49 ± 0.05</td>
<td>3.85 ± 0.02</td>
<td>-1.69 ± 0.10f</td>
</tr>
<tr>
<td>ρₓζ</td>
<td>-0.93 ± 0.03</td>
<td>-1.01 ± 0.02</td>
<td>-1.15 ± 0.04</td>
<td>-1.23 ± 0.03</td>
<td>-1.01 ± 0.02</td>
<td>-1.69 ± 0.10f</td>
</tr>
<tr>
<td>βₓζ</td>
<td>0.93 ± 0.04</td>
<td>1.02 ± 0.03</td>
<td>1.16 ± 0.05</td>
<td>1.24 ± 0.04</td>
<td>ρₓζβₓζ = -0.68</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

- The σ values are taken from ref. 20c. Correlation coefficients were better than 0.997 in all cases. The pKₐ values were taken from ref. 20c. Z = p-Br was excluded from the Brønsted plot for βₓ due to an unreliable pKₐ values. Correlation coefficients were better than 0.997 in all cases. "At 0 °C." At -10 °C. Errors are average deviation. The σ values are the same as for footnote a. Correlation coefficients were better than 0.979 in all cases. "Correlation coefficients was 0.997." The pKₐ values were taken from ref. 20c. Correlation coefficients were better than 0.927 in all cases.
ether (-O-) or (-S-) than the C==O group and provides stronger stabilization to the (T±) 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 X CH2CH2ND3 are normal (kH/kD > 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.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{C} \quad \text{OAr} \\
\text{HN} & \quad \text{CH}_2 \\
\text{C}_6\text{H}_4\text{X} &
\end{align*}
\]

The low activation enthalpies, $\Delta H^\ddagger$, and highly negative activation entropies, $\Delta S^\ddagger$, (Table 3) are also in line with the proposed TS. Especially, the $\Delta H^\ddagger$ values are somewhat lower and the $\Delta S^\ddagger$ 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±. This will lower the $\Delta H^\ddagger$ value, but the TS becomes structured and rigid (low entropy process) which should lead to a large negative.

<table>
<thead>
<tr>
<th>X</th>
<th>Z</th>
<th>$k_\text{H} \times 10^3$ (M$^{-1}$s$^{-1}$)</th>
<th>$k_\text{D} \times 10^3$ (M$^{-1}$s$^{-1}$)</th>
<th>$k_\text{H}/k_\text{D}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>p-Me</td>
<td>0.703 (± 0.005)</td>
<td>0.411 (± 0.004)</td>
<td>1.71 ± 0.03*</td>
</tr>
<tr>
<td>p-OMe</td>
<td>H</td>
<td>2.79 (± 0.06)</td>
<td>1.67 (± 0.02)</td>
<td>1.67 ± 0.02</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Cl</td>
<td>29.3 (± 0.6)</td>
<td>18.1 (± 0.2)</td>
<td>1.61 ± 0.04</td>
</tr>
<tr>
<td>P-OMe</td>
<td>p-Br</td>
<td>41.1 (± 0.9)</td>
<td>26.5 (± 0.4)</td>
<td>1.55 ± 0.03</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Me</td>
<td>0.241 (± 0.002)</td>
<td>0.138 (± 0.001)</td>
<td>1.74 ± 0.02</td>
</tr>
<tr>
<td>p-Cl</td>
<td>H</td>
<td>0.886 (± 0.009)</td>
<td>0.527 (± 0.005)</td>
<td>1.68 ± 0.02</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Cl</td>
<td>7.94 (± 0.08)</td>
<td>4.87 (± 0.05)</td>
<td>1.63 ± 0.03</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Br</td>
<td>10.1 (± 0.1)</td>
<td>6.43 (± 0.07)</td>
<td>1.57 ± 0.02</td>
</tr>
</tbody>
</table>

*Standard deviations.

Table 3. Activation Parameters$^\ddagger$ for the Reactions of Z-Phenyl Thionocarbamates with X-Benzylamines in Acetonitrile

<table>
<thead>
<tr>
<th>X</th>
<th>Z</th>
<th>$\Delta H^\ddagger$/kcal mol$^{-1}$</th>
<th>$\Delta S^\ddagger$/cal mol$^{-1}$ K$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>p-Me</td>
<td>7.1</td>
<td>48</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Br</td>
<td>7.4</td>
<td>38</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Me</td>
<td>7.4</td>
<td>47</td>
</tr>
<tr>
<td>p-Cl</td>
<td>p-Br</td>
<td>7.1</td>
<td>42</td>
</tr>
</tbody>
</table>

$^\ddagger$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 $\Delta H^\ddagger$ and $\Delta S^\ddagger$, 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)-O- < -C(=O)-S- < -C(=O)-S-, and our results are consistent with this order. The negative cross-interaction constant, $\beta_{xz} = -0.68$, the size of $\psi_z$ (= 0.69~0.88) and failure of the RSP are in accord with the concerted mechanism. The normal kinetic isotope effects, $k_\text{H}/k_\text{D} = 1.55 ~ 1.74$, 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 A. Williams.18 These substrates 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 1H and 13C NMR (JEOL 400 MHz) data were found to agree well with the literature values.19

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 ($5 \times 10^3$ mole) was reacted with excess $p$-chlorobenzylamine ($5 \times 10^2$ 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.

$$\text{H}_2\text{NCO}(\equiv\text{S})\text{NHCH}_2\text{C}_6\text{H}_4\text{OCH}_3-p; \text{ m.p. 110-112 °C, IR(KBr), 3281(N-H), 1511(C-C, aromatic), 1497(C=\equiv C, aromatic), 1459(C-H, CH\_2), 1254(C-O), 1186(C=S), 708(C-H, aromatic); 1H 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); 13C 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\text{\textsubscript{10}}H\text{\textsubscript{14}}N\text{\textsubscript{2}}O\text{\textsubscript{2}}S: C, 55.1; H, 6.21. Found: C, 55.3; H, 6.22.**

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**References**


