A Kinetic Study on Aminolysis of *S*-4-Nitrophenyl Thiobenzoate in H₂O Containing 20 mol % DMSO and 44 wt % EtOH: Effect of Medium on Reactivity and Mechanism
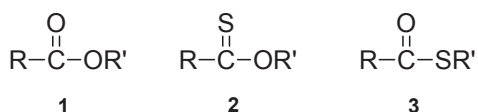
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Second-order rate constants (k_N) have been measured for nucleophilic substitution reactions of *S*-4-nitrophenyl thiobenzoate with a series of alicyclic secondary amines in H₂O containing 20 mol % DMSO at 25.0 ± 0.1 °C. The Brønsted-type plot exhibits a downward curvature, i.e., β_{nuc} decreases from 0.94 to 0.34 as the amine basicity increases. The reactions in the aqueous DMSO have also been suggested to proceed through a zwitterionic tetrahedral intermediate ($T^\pm$) with change in the RDS on the basis of the curved Brønsted-type plot. The reactions in the aqueous DMSO exhibit larger k_N values than those in the aqueous EtOH. The macroscopic rate constants (k_N) for the reactions in the two solvent systems have been dissected into the microscopic rate constants (k_1 and k_2/k_{-1} ratio) to investigate effect of medium on reactivity in the microscopic level. It has been found that the k_2/k_{-1} ratios are similar for the reactions in the two solvent systems, while k_1 values are larger for the reactions in 20 mol % DMSO than for those in 44 wt % EtOH, indicating that the larger k_1 is mainly responsible for the larger k_N. It has been suggested that the transition state is more stabilized in 20 mol % DMSO through mutual polarizability interaction than in 44 wt % EtOH through H-bonding interaction.

Key Words: Brønsted-type plot, Aminolysis, Medium effect, Polarizability.

Introduction

Aminolyses of esters have intensively been investigated and their mechanisms are well understood.[1-10] Reactions of carboxylic ester **1** with amines have generally been reported to proceed through a zwitterionic tetrahedral intermediate ($T^\pm$).[1-4] Curved Brønsted-type plots often reported for aminolyses of esters possessing a good leaving group (e.g., 2,4-dinitrophenoxide) have been interpreted as a change in the rate-determining step (RDS) of a stepwise mechanism.[1-4] It is well understood that RDS changes from breakdown of $T^\pm$ to its formation as the entering amine becomes more basic than the leaving group by 4 to 5 pK_a units.[1-4]

$$
\begin{array}{ccc}
\overset{\displaystyle O}{\underset{\displaystyle \|}{}} & \overset{\displaystyle S}{\underset{\displaystyle \|}{}} & \overset{\displaystyle O}{\underset{\displaystyle \|}{}} \\
R-C-OR' & R-C-OR' & R-C-SR' \\
\mathbf{1} & \mathbf{2} & \mathbf{3}
\end{array}
$$

Aminolyses of thiono esters **2** have often resulted in an upward curvature in the plot of observed rate constant (k_{obsd}) *vs.* amine concentration.[5-7] Since such an upward curvature indicates that the second amine molecule behaves as a general base catalyst, reactions of thiono esters with amines have been suggested to proceed through two intermediates (i.e., $T^\pm$ and its deprotonated form T^-).[5-7] A similar result has recently been reported for aminolyses of aryl phenyl thionocarbonates.[8]

Aminolysis of thiol ester **3** has much less been studied than its oxygen analogue **1**.[9,10] The mechanism has been reported to proceed through either a concerted or a stepwise mechanism depending on reaction conditions. Lee and his coworkers performed reactions of *S*-aryl thiobenzoates with anilines in methanol, and concluded that the reactions proceed through a concerted mechanism.[9a] In contrast, reactions of the same substrates with benzylamines and pyridines in acetonitrile have been suggested to proceed through a stepwise mechanism, in which formation of $T^\pm$ is RDS.[9b] On the other hand, Castro *et al.* carried out reactions of *S*-4-nitrophenyl X-substituted thiobenzoate (X = 4-NO₂, 4-Cl, and H) with a series of alicyclic secondary amines in 44 wt% ethanol to investigate the effect of substituent X on the reaction mechanism.[10] They found that the Brønsted-type plot for the reactions of *S*-4-nitrophenyl 4-nitrothiobenzoate is linear with $\beta_{nuc} = 0.81$, while the plots for the corresponding reactions of *S*-4-nitrophenyl 4-chlorothiobenzoate and *S*-4-nitrophenyl thiobenzoate are curved downwardly.[10] They have reported that the pK_a^o, defined as the pK_a at the curvature center of a curved Brønsted-type plot in which a change in RDS occurs (i.e., $k_2 = k_{-1}$), is 10.0 and 10.4 when X = H and 4-Cl, respectively but larger than 11 when X = 4-NO₂.[10] Thus, it has been concluded that a strong EWG retards departure of the leaving group from $T^\pm$ but it accelerates departure of the amine from $T^\pm$.[10]

In contrast, we have shown that pK_a^o is independent of the substituent X in the benzoyl and benzenesulfonyl moieties for aminolyses of aryl benzoates[4] and benzenesulfonates[11] in H₂O containing 20 mol% DMSO. We have proposed that the k_2/k_{-1} ratio is not influenced by the electronic nature of the substituent X, since both the aryloxide and amine depart from $T^\pm$ with the bonding-electron pair.[4,11]

We have extended our study to reactions of *S*-4-nitrophenyl thiobenzoate with a series of alicyclic secondary amines in H₂O containing 20 mol% DMSO to investigate reaction mechanism (Scheme 1). We have also dissected the macroscopic second-order rate constants (k_N) into microscopic rate constants (i.e., k_1 and k_2/k_{-1} ratios) to investigate the effect of me-

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dium on reactivity and reaction mechanism in the microscopic level by comparing the current results with those in 44 wt% ethanol reported by Castro his coworkers.
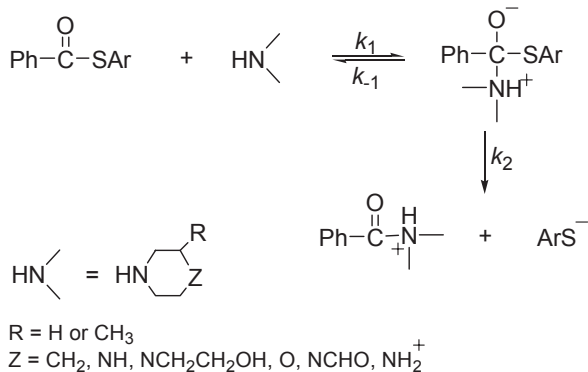
Results and Discussion

The kinetic study was performed under pseudo-first-order conditions with the concentration of nucleophile in excess over the substrate concentration. All reactions obeyed first-order kinetics with quantitative liberation of 4-nitrothiophen-oxide ion and/or its conjugate acid. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} *vs.* nucleophile concentration were linear passing through the origin, indicating that general base catalysis by a second amine molecule is absent. Thus, the rate equation can be given as eq (1). Second-order rate constants (k_N) have been determined from the slope of the linear plots of k_{obsd} *vs.* nucleophile concentration, and summarized in Table 1 together with the k_N values reported by Castro *et al.* for the corresponding reactions in 44 wt% EtOH for comparison. It is estimated from replicate runs that the uncertainty in the rate constants is less than ±3%.

$$\text{Rate} = k_{obsd}[\text{substrate}], \text{ where } k_{obsd} = k_N[\text{amine}] \qquad (1)$$

Reaction Mechanism from Brønsted-type Analysis. As shown in Table 1, the second-order rate constant (k_N) for the reactions in 20 mol% DMSO increases as the basicity of the incoming amine increases, e.g., k_N increases from 0.0146 M^{-1}s^{-1} to 2.14 and 61.4 M^{-1}s^{-1} as the pK_a of the conjugate acid of the amines increases from 5.95 to 8.65 and 11.02, in turn. A similar result is demonstrated for the corresponding reactions performed in 44 wt% EtOH. However, the k_N values are larger for the reactions in 20 mol% DMSO than for those in 44 wt% EtOH.

The effect of amine basicity and medium on reactivity is illustrated in Figure 1. One can see that the reactions in 20 mol% DMSO exhibit higher reactivity than those in 44 wt% EtOH. The Brønsted-type plots for the reactions performed in both mixed solvents exhibit a downward curvature when the k_N and pK_a values are statistically corrected using q and p ($p = 2$ except $p = 4$ for piperazinium ion and $q = 1$ except $q = 2$ for pipe-razine),[12] i.e., as the amine basicity increases, the slope of the Brønsted-type plot (β_{nuc}) decreases from 0.93 to 0.34 for the

reactions in 20 mol% DMSO and from 0.86 to 0.27 for those in 44 wt% EtOH. Such nonlinear Brønsted-type plots are typical for reactions which proceed through a stepwise mechanism with a change in RDS.[1-4] In fact, Castro *et al.* have concluded that the reactions in the aqueous EtOH proceed through a zwitterionic tetrahedral intermediate (T$^\pm$) with a change in RDS on the basis of the curved Brønsted-type plot. Thus, one can suggest that the reactions in 20 mol% DMSO proceed also through T$^\pm$ with a change in RDS (Scheme 1). It follows that the medium change form 44 wt% EtOH to 20 mol % DMSO causes an increase in reactivity but does not influences the reaction mechanism in the aminolysis of *S*-4-nitrophenyl thiobenzoate.

Dissection of Macroscopic Rate Constants into Microsco-pic Rate Constants. The nonlinear Brønsted-type plots shown

Table 1. Summary of second-order rate constants for reactions of *S*-4-nitrophenyl thiobenzoate with alicyclic secondary amines in H$_2$O containing 20 mol% DMSO and 44 wt% ethanol at 25.0 ± 0.1°C

Amine	20 mol% DMSO		44 wt% EtOH[b]	
	pK_a[a]	$10\,k_N$ / M^{-1}s^{-1}	pK_a	$10^2\,k_N$ / M^{-1}s^{-1}
1. piperazinium ion	5.95	0.146 ± 0.003	5.37	0.0870
2. 1-formylpiperazine	7.98	2.83 ± 0.01	7.63	2.80
3. morpholine	8.65	21.4 ± 0.4	8.48	25.0
4. 1-(2-hydroxyethyl)-piperazine	9.38	-	9.09	47.0
5. piperazine	9.85	173 ± 4	9.71	150
6. 3-methyl piperidine	10.80	515 ± 7	-	-
7. piperidine	11.02	614 ± 5	10.82	390

[a]The pK_a data in 20 mol% DMSO were taken from ref. 4f. [b]The data for reactions in 44 wt% EtOH were taken from ref. 10a.
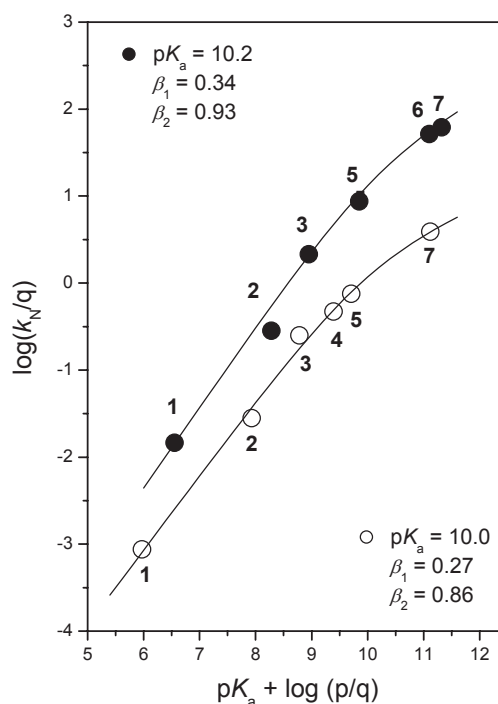

Figure 1. Brønsted-type plots for reactions of *S*-4-nitrophenyl thio-benzoate with alicyclic secondary amines in H$_2$O containing 20 mol % DMSO (●) and 44 wt% ethanol (○) at 25.0 ± 0.1°C. The identity of points is given in Table 1.

Scheme 1

in Figure 1 have been analyzed using a semiempirical equation (eq 2)[1d,13] on the basis of the proposed mechanism shown in Scheme 1. The parameters β_1 and β_2 represent the slope of the curved Brønsted plots in Figure 1 for the reactions with strongly basic and weakly basic amines, respectively. Here $k_N°$ refers to the k_N value at $pK_a°$ where $k_2/k_{-1} = 1$. The parameters determined from the fitting of eq (2) to the experimental points are $\beta_1 = 0.34$, $\beta_2 = 0.93$ and $pK_a° = 10.2$ for the reactions in 20 mol% DMSO. Castro *et al.* reported that $\beta_1 = 0.27$, $\beta_2 = 0.86$, and $pK_a° = 10.0$ for the corresponding reactions in 44 wt% EtOH.

$$\log (k_N/k_N°) = \beta_2(pK_a - pK_a°) - \log (1 + \alpha)/2$$

$$\text{where } \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a°) \qquad (2)$$

The macroscopic rate constant k_N values have been dissected into their microscopic rate constants (i.e., k_1 and k_2/k_{-1} ratios) to investigate the effect of medium on reactivity in a microscopic level. The apparent second-order rate constant k_N can be expressed as eq (3) by applying the steady-state conditions to the intermediate on the basis of the proposed mechanism.

$$k_N = k_1k_2 / (k_{-1} + k_2) \qquad (3)$$

The k_2/k_{-1} ratios associated with the reactions in aqueous DMSO and EtOH have been determined using eqs (4) – (9) and the kinetic data in Table 1. Eq (3) can be simplified to eq (4) or (5). Then, β_1 and β_2 can be expressed as eqs (6) and (7), respectively.

$$k_N = k_1k_2 / k_{-1}, \text{ when } k_2 \ll k_{-1} \qquad (4)$$

$$k_N = k_1, \text{ when } k_2 \gg k_{-1} \qquad (5)$$

$$\beta_1 = d(\log k_1) / d(pK_a) \qquad (6)$$

$$\beta_2 = d(\log k_1k_2 / k_{-1}) / d(pK_a) = \beta_1 + d(\log k_2 / k_{-1}) / d(pK_a) \qquad (7)$$

Eq (7) can be rearranged as eq (8). Integral of eq (8) from $pK_a°$ to pK_a results in eq (9). Since $k_2 = k_{-1}$ at $pK_a°$, the term (log $k_2 / k_{-1})_{pKa}°$ is zero. Therefore, one can calculate the k_2/k_{-1} ratios from eq (9) using $pK_a° = 10.2$, $\beta_1 = 0.34$, and $\beta_2 = 0.93$ for the reactions in 20 mol% DMSO, and $pK_a° = 10.0$, $\beta_1 = 0.27$, and $\beta_2 = 0.86$ for the reactions in 44 wt% EtOH.

$$\beta_2 - \beta_1 = d(\log k_2 / k_{-1}) / d(pK_a) \qquad (8)$$

$$(\log k_2 / k_{-1})_{pKa} = (\beta_2 - \beta_1)(pK_a - pK_a°) \qquad (9)$$

The k_1 values have been determined from eq (10) using the k_N values in Table 1 and the k_2/k_{-1} ratios calculated above. The k_2/k_{-1} ratios and k_1 values for the reactions in 20 mol% DMSO and in 44 wt% EtOH are summarized in Table 2.

$$k_N = k_1k_2 /(k_{-1} + k_2) = k_1 /(k_{-1}/k_2 + 1) \qquad (10)$$

Medium Effect on Reactivity and Mechanism. Table 2 shows that the k_2/k_{-1} ratio and k_1 value increase as the amine basicity increases for reactions in both aqueous DMSO and aqueous EtOH. The effect of amine basicity on the k_2/k_{-1} ratio

Table 2. Microscopic rate constants for reactions of *S*-4-nitrophenyl thiobenzoate with alicyclic secondary amines in H_2O containing 20 mol% DMSO and 44 wt% ethanol at $25.0 \pm 0.1°C$.

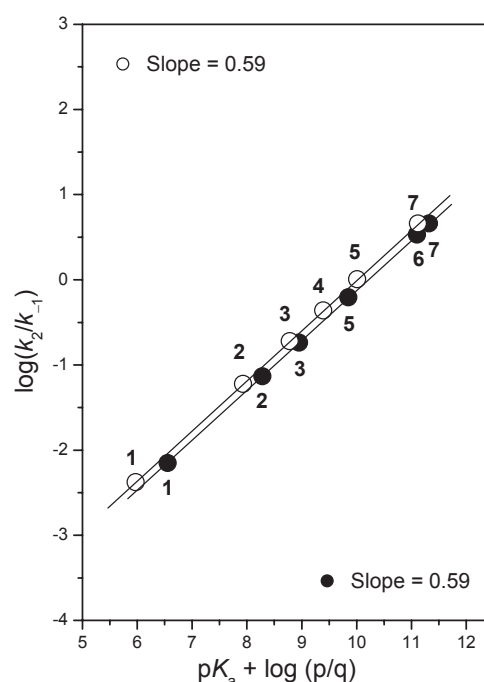| Amines	20 mol% DMSO		44 wt% EtOH	
	k_2/k_{-1}	k_1 / $M^{-1}s^{-1}$	k_2/k_{-1}	k_1 / $M^{-1}s^{-1}$
1. piperazinium ion	0.00704	2.09	0.00420	0.208
2. 1-formylpiperazine	0.0738	4.12	0.0602	0.493
3. morpholine	0.183	13.8	0.191	1.56
4. 1-(2-hydroxyethyl)-piperazine	-	-	0.437	1.54
5. piperazine	0.622	45.1	0.674	3.72
6. 3-methyl piperidine	3.40	66.6	-	-
7. piperidine	4.59	74.7	4.59	4.75

Figure 2. Plots of log k_2/k_{-1} *vs.* pK_a for reactions of *S*-4-nitrophenyl thiobenzoate with alicyclic secondary amines in H_2O containing 20 mol % DMSO (●) and 44 wt % ethanol (○) at 25.0 ± 0.1 °C. The identity of numbers is given in Table 2.

is illustrated in Figure 2. The plots of log k_2/k_{-1} vs. pK_a of the conjugate acid of amines results in excellent linearity with a slope of 0.59 for the reactions in both solvent systems when pK_a is statistically corrected using q and p.[12] Figure 2 shows that the k_2/k_{-1} ratio is similar for the reactions in both solvent systems. It is apparent that the k_2/k_{-1} ratio is not influenced upon changing the medium from 44 wt% EtOH to 20 mol % DMSO.

The effect of amine basicity on k_1 is illustrated in Figure 3. The statistically corrected Brønsted-type plots are linear for the reactions in both solvent mixtures. The slope of the linear plots (β_1) is slightly larger for the reactions in aqueous DMSO than in aqueous EtOH, i.e., 0.34 and 0.27 for the reactions in 20 mol % DMSO and 44 wt% EtOH, respectively. This is consistent with the fact that the slope in Figure is slightly larger for the reactions in the aqueous DMSO than for those in the aqueous EtOH. More interestingly, the k_1 value is much larger for
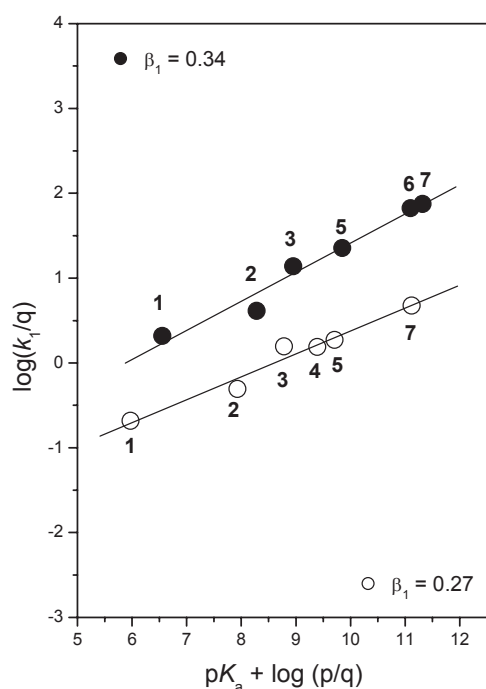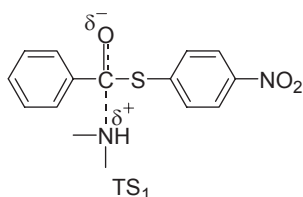
Figure 3. Brønsted-type plots for reactions of *S*-4-nitrophenyl thiobenzoate with alicyclic secondary amines in H_2O containing 20 mol% DMSO (●) and 44 wt% ethanol (○) at 25.0 ± 0.1 °C. The identity of numbers is given in Table 2.

the reactions in 20 mol% DMSO than for those in 44 wt% EtOH, indicating that the larger k_1 is mainly responsible for the larger k_N value for the reactions in the former solvent than for those in the latter solvent.

It is apparent that both basicity of amines and transition-state solvation can influence k_1 values. As shown in Table 1, the basicity of amines is similar in both solvent systems, indicating that the amine basicity cannot be responsible for the difference in the k_1 values obtained from the two different mixed solvents. Thus, differential solvation of transition state is considered to be responsible for the difference in the k_1 values.

The transition-state structure for the k_1 process would be similar to TS$_1$. Hydrogen-bonding interaction would be important between the partially charged TS$_1$ and EtOH, while mutual polarizability interaction between polarizable DMSO and the charge dispersed transition-state TS$_1$ would be the major interaction between the solvent and solute.[14] The fact that k_1 is larger for the reactions in 20 mol % DMSO than in 44 wt % EtOH indicates that the partially charged TS$_1$ is more strongly stabilized through mutual polarizability interaction than through H-bonding interaction.

Conclusions

The current study has allowed us to conclude the following:

(1) Aminolyses of *S*-4-nitrophenyl thiobenzoate proceed through a stepwise mechanism with a change in RDS in both 20 mol % DMSO and 44 wt % EtOH, i.e., the medium change from the aqueous DMSO to the aqueous EtOH does not influence reaction mechanism. (2) Reactions in the aqueous DMSO exhibit larger k_N values than those in the aqueous EtOH. (3) Dissection of k_N values into k_1 and k_2/k_{-1} has revealed that the k_2/k_{-1} ratio is similar for the two solvent systems but k_1 is much larger for the reactions in the aqueous DMSO than for those in the aqueous EtOH. (4) The larger k_1 value is mainly responsible for the larger k_N value determined in the aqueous DMSO. (5) 20 mol % DMSO stabilizes TS$_1$ more strongly through mutual polarizability interaction than 44 wt% EtOH through H-bonding interaction.

Experimental Section

Materials. *S*-4-Nitrophenyl thiobenzoate was readily prepared from the reaction of 4-nitrothiophenol and benzoyl chloride in the presence of triethylamine in anhydrous ether as reported previously.[10] Amines and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic studies were performed at 25.0 ± 0.1 °C with a UV-Vis spectrophotometer equipped with a constant temperature circulating bath for slow reactions (e.g., $t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions (e.g., $t_{1/2} < 10$ s). The reactions were followed by monitoring the appearance of 4-nitrothiophenoxide ion (or its conjugate acid). All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than that of the substrate. The amine stock solution of *ca.* 0.2M was prepared in a 25.0mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized HCl solution in order to obtain a self-buffered solution. All the transfers of reaction solutions were carried out by means of gas-tight syringes.

Product Analysis. *S*-4-Nitrophenoxide (and/or its conjugate acid 4-nitrothiophenol) was liberated quantitatively and identified as one of the products by comparison of the UV-Vis spectrum at the end of reaction with the authentic sample under the experimental condition.

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