

Effect of Amine Nature on Reaction Mechanism: Aminolyses of O-4-Nitrophenyl Thionobenzoate with Primary and Secondary Amines

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Pseudo-first-order rate constants (k_{obs}) have been measured spectrophotometrically for reactions of O-4-nitrophenyl thionobenzoate (2) with a series of primary and acyclic secondary amines. The plots of k_{obs} vs amine concentration are linear for the reaction of **2** with primary amines. The slope of the Brønsted-type plot for the reaction of **2** with primary amines decreases from 0.77 to 0.17 as the amine basicity increases, indicating that the reaction proceeds through a zwitterionic addition intermediate in which the rate-determining step changes from the breakdown of the intermediate to the reaction products to the formation of the intermediate as the amine basicity increases. On the other hand, for reactions with all the acyclic secondary amines studied, the plot of k_{obs} vs amine concentration exhibits an upward curvature, suggesting that the reaction proceeds through two intermediates, e.g., a zwitterionic addition intermediate and an anionic intermediate. The microscopic rate constants (k_1 , k_{-1} , k_2 , and k_3 where available) have been determined for the reactions of **2** with all the primary and secondary amines studied. The k_1 value is larger for the reaction with the primary amine than for the reaction with the isobasic acyclic secondary amines, while the k_{-1} value is much larger for the latter reaction than for the former reaction. The k_3 value for the reaction with secondary amine is independent of the amine basicity. The small k_2/k_{-1} ratio is proposed to be responsible for the deprotonation process observed in aminolyses of carbonyl or thiocarbonyl derivatives.

Introduction

Aminolyses of carbonyl compounds have intensively been investigated, and their reaction mechanisms have been well clarified.¹⁻¹⁰ It has generally been suggested

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that aminolyses of carboxylic and carbonate esters (e.g., 1 and 3, respectively) proceed through a zwitterionic addition intermediate in which the rate-determining step (RDS) depends on the basicity of the attacking amine and the leaving group, i.e., the RDS changes from the breakdown of the intermediate to the reaction products to the formation of the intermediate as the attacking amine becomes more basic than the leaving group by 4-5 pK_a units.^{1,6–10}



However, aminolyses of thione esters (e.g., 2 and 4) have been much less investigated. The first kinetic study has been performed by Campbell et al. for the reaction of 2 with diethylamine and a series of primary amines in H₂O containing 20% CH₃CN.¹¹ The reaction with

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primary amines has been suggested to proceed through a zwitterionic addition intermediate on the basis of the nonlinear Brønsted-type plot obtained.¹¹ However, the microscopic rate constants involved in the aminolysis reaction have not been determined. Furthermore, the mechanism for the reaction with the secondary amine has not been elucidated either. More systematic studies for thiocarbonyl derivatives have been performed by Castro and Lee et al.^{12,13} Castro et al. have recently carried out the reaction of various thiocarbonyl derivatives (e.g., 4) with a series of pyridines and alicyclic secondary amines.^{12a} The reaction with pyridines has been suggested to proceed through an addition intermediate, while the one with alicyclic secondary amines has been proposed to proceed through one or two intermediates depending on the amine basicity, i.e., the reaction with strongly basic amines proceeds through a zwitterionic addition intermediate (T^{\pm}) , while the one with weakly basic amines proceeds through two intermediates, T^{\pm} and its deprotonated species $\widetilde{T}^{-,12a}$ Therefore, the amine basicity has been suggested to be an important factor in determining the presence or absence of the deprotonation process.¹² Lee et al. have performed kinetic studies for reactions of substituted phenyl dithioacetates with a series of anilines and benzylamines in CH₃CN.^{13a} The reactions have been suggested to proceed through a zwitterionic addition intermediate without the deprotonation process, which has often been observed in the aminolysis of thiono and dithio esters conducted in aqueous solution, indicating that a solvent effect is also an important factor in governing the deprotonation process.13a

Recently, we have performed a systematic kinetic study for the aminolysis of **2** with a series of alicyclic secondary amines in water containing 20 mol % dimethyl sulfoxide (DMSO) and found that the reaction proceeds through two intermediates (T^{\pm} and T^{-}) regardless of the amine basicity.¹⁴ We have extended our study to the reaction of **2** with a series of primary and acyclic secondary amines and found that the effect of the amine nature on the reaction mechanism is remarkable. Here we report a detailed reaction mechanism together with all the microscopic rate constants involved in the reactions of **2** with the primary and secondary amines.

Experimental Section

Materials. *O*-4-Nitrophenyl thionobenzoate (**2**) was synthesized from the reaction of thiobenzoyl chloride with 4-nitrophenol as reported previously.^{11,14} The purity of **2** was checked by means of the melting point and spectral data such

(14) Um, I. H.; Kwon, H. J.; Kwon, D. S.; Park, J. Y. J. Chem. Res., Synop. **1995**, 301; J. Chem. Res., Miniprint **1995**, 1801–1817. as IR and ¹H NMR characteristics. Other chemicals used, including the amines, were of the highest quality available. The reaction medium was H₂O containing 20 mol % DMSO to eliminate solubility problems. DMSO was distilled over CaH₂ at a reduced pressure (bp 64–66 °C/6–7 mmHg) and stored under nitrogen. Doubly glass-distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed with a UV-vis spectrophotometer for slow reactions ($t_{1/2} \ge 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to keep the temperature in the reaction cell at 25.0 \pm 0.1 °C. The reaction was followed by monitoring the appearance of the leaving 4-nitrophenoxide at 410 nm (or 4-nitrophenol at 340 nm for the reaction with trifluoroethylamine). All reactions were carried out under pseudo-first-order conditions in which the amine concentrations were at least 30 times greater than the substrate concentration. The amine stock solution of ca. 0.2 M was prepared by dissolving 2 equiv of free amine and 1 equiv of standardized HCl solution (or 2 equiv of amine hydrochloride and 1 equiv of standardized NaOH solution) to keep the pH constant by making a self-buffered solution. All solutions were freshly prepared just before use under nitrogen and transferred by gastight syringes. Typically, the reaction was initiated by adding 5 μ L of a 0.02 M solution of 2 in CH₃CN by a 10 μ L syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and an aliquot of the amine stock solution.

Determination of pK_a. pK_as of the conjugate acids of amines were determined by measuring the pH of the solution containing equal amounts of free amine and amine hydrochloride with a glass electrode. The pK_a value was independent of the amine concentration in the range of $(10-100) \times 10^{-3}$ M, in which most of the rate constants were measured. The pK_a values so determined are listed in Tables 1 and 2.

Product Analysis. 4-Nitrophenoxide (and/or its conjugate acid) was identified as one of the products of the aminolysis of **2** by comparison of the UV–vis spectrum at the end of reaction with the authentic sample under the kinetic experimental conditions. The other product *N*-ethyl thiobenzoamide was analyzed by HPLC. The flow rate was 1 mL/min, and the eluent was 50% MeCN in MeOH (v/v). Quantitative analysis was performed by comparison of the HPLC peak area of the reaction mixture with that of the authentic sample.

Results

Reactions of **2** with the primary and secondary amines proceeded with quantitative liberation of 4-nitrophenoxide and/or its conjugate acid. The kinetic study was performed spectrophotometrically under pseudo-firstorder reaction conditions, e.g., the amine concentration in excess over the substrate concentration. All reactions obeyed first-order kinetics over 90% of the reaction. Pseudo-first-order rate constants (k_{obs}) were calculated from the equation $\ln(A_{\infty} - A_{t}) = -k_{obs}t + C$. The k_{obs} values obtained in this way are summarized in Table S1 (Supporting Information) along with the kinetic conditions. It is estimated from the replicate runs that the uncertainty in the rate constants is less than $\pm 3\%$. The plot of k_{obs} vs amine concentration is linear and passes through the origin for the reaction of **2** with all the primary amines studied. However, the corresponding plot for the reaction with all the secondary amines exhibits an upward curvature as the amine concentration increases (Figure S1, Supporting Information).

Discussion

Reactions with Primary Amines. Since the plots of k_{obs} vs [RNH₂] are linear and pass through the origin,

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FIGURE 1. Brønsted-type plot for the k_N (statistically corrected using p and q, see ref 15) for the reaction of **2** with primary amines in water containing 20 mol % DMSO at 25.0 \pm 0.1 °C. The identity of the points is given in Table 1. The solid line was calculated by eq 3.

SCHEME 1

$$\sum_{i=0}^{S} \frac{1}{C^{-}OAr + RNH_{2}} \xrightarrow{k_{1}} \sum_{k_{-1}} \frac{1}{C^{-}NH_{2}R} \xrightarrow{k_{2}} \sum_{i=0}^{S} \frac{1}{C^{-}NH_{2}R} \xrightarrow{i}{OAr}$$

$$2 \xrightarrow{i}{OAr} \xrightarrow{T^{\pm}} NO_{2}$$

the contribution of hydroxide and/or H_2O to the k_{obs} value is negligible under the present reaction conditions. The kinetic results and the product analysis suggest that the reaction of **2** with RNH₂ proceeds as depicted in Scheme 1. The kinetic law obtained is shown in eqs 1 and 2, where [S] and [P] represent the concentrations of substrate **2** and one of the reaction products, 4-nitrophenoxide (or 4-nitrophenol), respectively. The k_N values were determined from the slope of the linear plots of k_{obs} vs [RNH₂] and are summarized in Table 1.

$$-d[S]/dt = d[P]/dt = k_{obs}[S]$$
(1)

$$k_{\rm obs} = k_{\rm N} [{\rm RNH}_2]$$
, where $k_{\rm N} = k_1 k_2 / (k_{-1} + k_2)$ (2)

As shown in Table 1, the $k_{\rm N}$ value increases as the amine basicity increases. The effect of the amine basicity on the $k_{\rm N}$ value is graphically demonstrated in Figure 1. The Brønsted-type plot, which is statistically corrected using p and q,^{12,14,15} is nonlinear. Such a nonlinear Brønsted-type plot has often been observed for aminolyses of carboxylic esters with a good leaving group and used as evidence for a change in the RDS. The p $K_{\rm a}$ value at the center of the curvature of a nonlinear Brønsted-type plot has been defined p $K_{\rm a}^{\circ}$, where a change in the RDS occurs (e.g., $k_{-1} = k_2$ at $pK_{\rm a}^{\circ}$).^{1,12–14,16,17} The $pK_{\rm a}^{\circ}$ value in the present system has been determined to be

8.8, which is much smaller than the one reported for the corresponding aminolysis of 4-nitrophenyl benzoate, **1** (e.g., $pK_a^{\circ} > 11.0$).¹⁴ A similar result has been found by Campbell et al. in the aminolysis of **1** and **2** run in aqueous CH₃CN (e.g., $pK_a^{\circ} > 11$ for the reaction of **1** and $pK_a^{\circ} = 9.2$ for the reaction of **2**).¹¹ Jencks^{1c} and Castro¹⁶ have suggested that a smaller k_2/k_{-1} ratio is responsible for the smaller pK_a° value for the reaction of thiocarbonyl derivatives compared to their oxygen analogues.

One can get important information about the reaction mechanism from the magnitude of β_{nuc} values. Generally, $\beta_{\rm nuc}$ has been reported to be 0.8 \pm 0.2 when the breakdown of the addition intermediate to the reaction products is the RDS and 0.2 ± 0.1 when the formation of the addition intermediate is the RDS.^{1,6-10} The nonlinear Brønsted-type plot in Figure 1 has been analyzed using eq 3,^{1b,12} where β_1 and β_2 represent the slope of the Brønsted-type plot in Figure 1 for the reaction with strongly and weakly basic RNH₂, respectively. The parameters $k_{\rm N}^{\circ}$ and $pK_{\rm a}^{\circ}$ refer to a hypothetical amine, for which $k_{-1} = k_2$ in Scheme 1. The parameters determined are as follows: log $k_{\rm N}^{\circ} = 0.25$, p $K_{\rm a}^{\circ} = 8.8$, $\beta_1 =$ 0.17, and $\beta_2 = 0.77$. Therefore, one can suggest that the RDS for the reaction of 2 with RNH₂ changes from the k_2 to the k_1 step as the amine basicity increases on the basis of the magnitude of β_1 and β_2 values.

$$\log(k_{\rm N}/k_{\rm N}^{\circ}) = \beta_2(pK_{\rm a} - pK_{\rm a}^{\circ}) - \log[(1 + \alpha)/2]$$
$$\log \alpha = (\beta_2 - \beta_1) (pK_{\rm a} - pK_{\rm a}^{\circ})$$
(3)

To shed more light on the reaction mechanism, the microscopic rate constants (k_1 , k_{-1} , and k_2) involved in the reaction of **2** with RNH₂ are required. As discussed above, the RDS of the reaction of **2** with RNH₂ is considered to change from the k_2 to the k_1 step as the basicity of RNH₂ increases. Therefore, eq 2 can be simplified to eqs 4 and 5. Then, β_1 and β_2 can be expressed as eqs 6 and 7, respectively.

$$k_{\rm N} = k_1 k_2 / k_{-1}$$
, when $k_2 \ll k_{-1}$ (4)

$$k_{\rm N} = k_1, \text{ when } k_2 \gg k_{-1} \tag{5}$$

$$\beta_1 = d(\log k_1)/d(pK_a) \tag{6}$$

$$\beta_2 = d(\log k_1 k_2 / k_{-1}) / d(pK_a)$$

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

Eq 7 can be rearranged as eq 8. The integral of eq 8 from pK_a° to pK_a results in eq 9. Since $k_2 = k_{-1}$ at pK_a° , the term $(\log k_2/k_{-1})_{pKa^{\circ}}$ is zero. Therefore, one can calculate the k_2/k_{-1} values for the reactions of **2** with all the primary amines studied from eq 9 using $\beta_1 = 0.17$, $\beta_2 = 0.77$, and $pK_a^{\circ} = 8.8$.

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

$$(\log k_2/k_{-1})_{pK_a} - (\log k_2/k_{-1})_{pK_a^\circ} = (\beta_2 - \beta_1)(pK_a - pK_a^\circ)$$
 (9)

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SCHEME 2

$$\sum_{i=1}^{S} \sum_{k=1}^{S} \sum_{k=1}^{k_{1}} \sum_{i=1}^{S} \sum_{j=1}^{k_{2}} \sum_{k=1}^{k_{2}} \sum_{i=1}^{S} \sum_{j=1}^{k_{2}} \sum_{i=1}^{S} \sum_{j=1}^{k_{2}} \sum_{i=1}^{N} \sum_{j=1}^{k_{2}} \sum_{i=1}^{N} \sum_{j=1}^{k_{2}} \sum_{j=1}^{N} \sum_{i=1}^{N} \sum_{j=1}^{k_{2}} \sum_{i=1}^{N} \sum_{j=1}^{N} \sum_{i=1}^{N} \sum_{i=1}^{N} \sum_{i=1}^{N} \sum_{j=1}^{N} \sum_{i=1}^{N} \sum_{i=1}$$

Eq 2 can be rewritten as eq 10, which allows one to calculate the k_1 value using the k_N and k_2/k_{-1} values determined above. The k_1 values calculated in this way are summarized in Table 1. It is shown that the k_1 value increases as the amine basicity increases. It is also noted that the k_1 value is always larger than the corresponding k_N value. However, the difference between the k_1 and k_N values becomes smaller with increasing amine basicity, as expected from eq 10 and the proposed reaction mechanism.

$$k_1 = k_{\rm N} \left(k_{-1}/k_2 + 1 \right) \tag{10}$$

To calculate the k_{-1} values from the k_2/k_{-1} values, the k_2 value should be determined. The k_2 value has been suggested to be dependent on the basicity of the leaving group and the structure of the acyl moiety but independent of the basicity and the nature of amines.^{1,13,14,17} Since the k_2 value cannot be measured directly, Castro et al. have estimated that $k_2 = 1.0 \times 10^8 \text{ s}^{-1}$ for aminolysis of S-4-nitrophenyl thioacetate^{17a} and $10^6 \text{ s}^{-1} < k_2 < 10^7 \text{s}^{-1}$ for aminolysis of phenyl dithioacetate.^{17b} The smaller k_2 value for the latter system was attributed to the decreased ability of $C-S^-$ to form a C=S bond compared to the ability of $C-O^-$ to form a C=O bond due to a weaker π -bonding energy of the thiocarbonyl (a $d\pi$ -p π bond) compared to the carbonyl group (a $p\pi$ - $p\pi$ bond).^{13a,17,18} We have recently estimated that $k_2 = 1.0 \times$ 10^6 s⁻¹ for the reaction of **2** with a series of alicyclic secondary amines.¹⁴ Since the k_2 value has been suggested to be independent of the nature of the amine,^{12,17} the k_2 value of 1.0×10^6 s⁻¹ has been used again for the reactions of 2 with the primary amines in order to calculate the k_{-1} value. The k_{-1} values calculated in this way are summarized in Table 1. It is shown that the k_{-1} value is larger than the k_2 value for the reactions with weakly basic amines but becomes smaller than the k_2 value for the reactions with strongly basic amines. This result clearly supports the preceding proposal that a change in the RDS occurs as the amine basicity increases. The effect of amine basicity on the k_1 , k_{-1} , and K values will be discussed later.

Reactions with Secondary Amines. As shown in Figure S1 (Supporting Information), the plot of k_{obs} versus [R₂NH] exhibits an upward curvature for the reaction of **2** with diethylamine. Such an upward curvature has also been obtained for the reaction of **2** with all the other acyclic secondary amines studied, indicating that the reaction proceeds through two intermediates, e.g., a zwitterionic addition intermediate (T[±]) and an anionic intermediate (T⁻) as shown in Scheme 2.

Under the assumption of steady-state conditions for the addition intermediate, one can derive eqs 11 and 12, where $[T^{\pm}]$ represents the concentration of the zwitterionic addition intermediate (T^{\pm}) .

$$d[P]/dt = k_2[T^{\pm}] + k_3[T^{\pm}][R_2NH]$$

= $k_1(k_2 + k_3[R_2NH])[R_2NH][S]/(k_{-1} + k_2 + k_3[R_2NH])$ (11)
 $k_{obs} = k_1(k_2 + k_3[R_2NH])[R_2NH]/(k_{-1} + k_2 + k_3[R_2NH])$ (12)

Since the first step in Scheme 2 is a preequilibrium, one can assume that $k_{-1} \gg k_2 + k_3$ [R₂NH]. Then, eq 12 can be simplified to eq 13.

$$k_{\text{obs}}/[R_2NH] = Kk_2 + Kk_3[R_2NH]$$
, where $K = k_1/k_{-1}$
(13)

The plots of $k_{obs}/[R_2NH]$ vs $[R_2NH]$ are linear for weakly basic secondary amines such as diallylamine (Figure S2, Supporting Information) and diethanolamine (Figure not shown), indicating that the assumption $k_{-1} \gg k_2 + k_3$ - $[R_2NH]$ is valid for the reaction of **2** with the weakly basic R₂NH. Therefore, the *Kk*₂ and *Kk*₃ values can be determined from the intercept and the slope of the linear plots of $k_{obs}/[R_2NH]$ vs $[R_2NH]$. However, as shown in Figure S2, the plot for the strongly basic R₂NH (diethylamine) is linear only at a low concentration region but exhibits a downward curvature as the amine concentration increases highly. Therefore, the assumption $k_{-1} \gg k_2 + k_2$ $k_3[R_2NH]$ appears to be valid only at a low concentration region for the reaction of **2** with the strongly basic R₂NH. This argument can be explained by the reasons given below. (1) The k_2 value has been suggested to be independent of the amine basicity.^{1,12,14,16,17} (2) The k_{-1} value would decrease as the amine basicity increases. (3) The k_3 value would be insensitive to the amine basicity since the proton transfer is from the aminium ion moiety of T^{\pm} to the corresponding free amine.^{14,16,17} However, the term $k_3[R_2NH]$ increases with increasing $[R_2NH]$.

Since the assumption $k_{-1} \gg k_2 + k_3[R_2NH]$ appears to be invalid for the reaction with strongly basic R_2NH at a high amine concentration region, one can assume that $k_2 \ll k_3[R_2NH]$. Then, eq 12 can be reduced to eq 14. The plots of $[R_2NH]/k_{obs}$ vs $1/[R_2NH]$ are linear for the reactions of **2** with the strongly basic R_2NH as shown in Figure S3 (Supporting Information). Therefore, $1/k_1$ and k_{-1}/k_1k_3 values can be determined from the intercept and the slope of the linear plots of $[R_2NH]/k_{obs}$ vs $1/[R_2NH]$, respectively.

$$[\mathbf{R}_2 \mathbf{N}\mathbf{H}]/k_{\text{obs}} = k_{-1}/k_1 k_3 [\mathbf{R}_2 \mathbf{N}\mathbf{H}] + 1/k_1 \qquad (14)$$

The microscopic rate constants $(k_1, k_{-1}, \text{ and } k_3)$ have also been determined from a nonlinear least-squares fitting of eq 12 to the experimental data using the same k_2 value used for the reactions with the primary amines $(k_2 = 1.0 \times 10^6 \text{ s}^{-1})$. The microscopic rate constants determined in this way have been found to be identical to those obtained from the graphical method using eqs 13 and 14 within an experimental error range. The k_1 ,

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TABLE 1. Summary of Apparent Second-Order Rate Constants (k_N) and Microscopic Rate Constants for the Reaction of 2 with Primary Amines in Water Containing 20 Mol % DMSO at 25.0 \pm 0.1 °C^a

Amine	$\mathrm{p}K_{\mathrm{a}}{}^{b}$	$k_{\rm N}/{ m M}^{-1}{ m s}^{-1}$	$k_1/M^{-1}s^{-1}$	$k_{-1}/10^6 \ { m s}^{-1}$	$K/10^{-6} {\rm M}^{-1}$
1. trifluoroethylamine	5.70	0.0261	1.00	37.3	0.0268
2. glycineethylester	7.68	0.876	3.00	2.42	1.24
3. glycylglycine	8.31	1.68	3.38	1.01	3.34
4. benzylamine	9.46	3.70	4.47	0.207	21.6
5. ethanolamine	9.67	4.10	4.74	0.155	30.6
6. glycine	10.06	12.5	14.2	0.137	104
7. ethylamine	10.67	7.16	7.44	0.0389	191

^{*a*} $k_2 = 1.0 \times 10^6$ s⁻¹. ^{*b*} The p K_a of the conjugate acid of amines determined in 20 mol % DMSO at 25.0 ± 0.1 °C. The uncertainty in the p K_a values is estimated to be less than ± 0.1 in p K_a unit.

TABLE 2.Summary of Microscopic Rate Constants Involved in the Reaction of 2 with Acyclic and Alicyclic SecondaryAmines in Water Containing 20 Mol % DMSO at 25.0 \pm 0.1 °C^a

Amine	pKa ^b	$k_1/M^{-1}s^{-1}$	$k_{-1}/10^6 \ { m s}^{-1}$	$K/10^{-6} \mathrm{M}^{-1}$	$k_3/10^9 \mathrm{~M^{-1}s^{-1}}$
Acyclic secondary amine					
8. diethanolamine	9.24	0.0643	242	$2.66 imes10^{-4}$	0.997
9. diallylamine	9.37	0.852	197	$4.32 imes10^{-3}$	0.886
10. N-benzylmethylamine	9.77	16.6	72.8	0.228	1.02
11. diethylamine	11.14	2.29	52.5	0.0436	0.878
Alicyclic secondary amine ^c					
12. piperazinium ion	5.95	1.42	740	$1.92 imes10^{-3}$	0.737
13. morpholine	8.65	18.3	91.0	0.201	1.61
14. piperazine	9.85	104	37.0	2.81	1.53
15. 3-methyl piperidine	10.80	153	12.3	12.4	0.790
16. piperidine	11.02	173	10.3	16.8	1.07

 a k_{2} = 1.0×10⁶ s⁻¹. b The p K_{a} of conjugate acid of amines determined in 20 mol % DMSO at 25.0 ± 0.1 °C. c The data for the reaction of **2** with alicyclic amines are taken from ref 14. The uncertainty in the p K_{a} values is estimated to be less than ± 0.1 in p K_{a} unit.

 k_{-1} , and k_3 values determined from the nonlinear regression method are summarized in Table 2 along with the corresponding data in the literature¹⁴ for the reactions of **2** with a series of alicyclic secondary amines for comparison. The effect of the amine nature on these microscopic rate constants will be discussed in the following section.

Effect of Amine Nature on Rate, Equilibrium, and Reaction Mechanism. As shown in Tables 1 and 2, the k_1 value for the reaction with the acyclic secondary amine is much smaller than the one for the reaction with the isobasic primary amine. On the contrary, the k_{-1} value for the reaction with the acyclic secondary amine is much larger than the one for the reaction with the primary amines, implying that the zwitterionic addition intermediate for the reaction with the secondary amines is more unstable than the one for the reaction with the primary amines. It is also noted that the *K* value for the reaction with the secondary amines is much smaller than the one for the reaction with the primary amines.

The effect of amine basicity on the k_1 , k_{-1} , and K values is illustrated in Figures 2, 3, and 4, respectively, for the reactions of **2** with the primary amines along with the corresponding data for the reactions with the alicyclic secondary amines for comparison. However, the data for the reactions of **2** with the acyclic secondary amines are not demonstrated due to a poor correlation.

As shown in Figure 2, the magnitude of the k_1 value increases linearly with increasing amine basicity, resulting in good linear Brønsted-type plots for both the primary and alicyclic secondary amine systems. The slope of the linear Brønsted-type plot (β_1) has been calculated to be 0.17 and 0.44 for the reactions with the primary and secondary amines, respectively, indicating that the k_1 value for the reaction with the primary amines is much



FIGURE 2. Brønsted-type plots for k_1 (statistically corrected using p and q, see ref 15) for the reaction of **2** with primary (\bigcirc) and alicyclic secondary (\bigcirc) amines in water containing 20 mol % DMSO at 25.0 \pm 0.1 °C. The identity of the points is given in Tables 1 and 2.

less sensitive to amine basicity than for the reaction with the alicyclic secondary amines. However, the β_1 value of 0.17 is compatible with the ones obtained for aminolyses of various carbonyl and thiocarbonyl esters in which the RDS is the formation of an addition intermediate (the k_1 step).^{1,12,16,17}

Figure 3 shows the effect of amine basicity on the k_{-1} value for the reactions of **2** with the primary and alicyclic secondary amines. One can see that the k_{-1} value increases linearly with decreasing amine basicity. The



FIGURE 3. Brønsted-type plots for k_{-1} (statistically corrected using p and q, see ref 15) for the reaction of **2** with primary (\bigcirc) and alicyclic secondary (\bigcirc) amines in water containing 20 mol % DMSO at 25.0 \pm 0.1 °C. The identity of the points is given in Tables 1 and 2.



FIGURE 4. Brønsted-type plot for *K* (statistically corrected using p and q, see ref 15) for the reaction of **2** with primary (\bigcirc) and alicyclic secondary (\bullet) amines in water containing 20 mol % DMSO at 25.0 \pm 0.1 °C. The identity of the points is given in Tables 1 and 2.

slope of the linear Brønsted-type plots (β_{-1}) has been determined to be -0.60 and -0.39 for the reactions with the primary amines and with the alicyclic secondary amines, respectively, indicating that the k_{-1} process is influenced more sensitively by the amine basicity for the reaction with the primary amines than for the reaction with the secondary amines.

The effect of amine basicity on the equilibrium constant $K (= k_1/k_{-1})$ is demonstrated in Figure 4 for the reaction of **2** with the primary and the alicyclic secondary amines. One can see good linear Brønsted-type plots for both the primary and the alicyclic secondary amine systems. The

slopes of the linear Brønsted-type plots (β_{eq}) have been calculated to be 0.77 and 0.84 for the reactions of **2** with the primary amines and with the alicyclic secondary amines, respectively, indicating that the positive charge developed on the N atom would be slightly larger for the reaction with the secondary amines than for the reaction with the primary amines.

As shown in Table 2, the magnitude of k_3 values has been determined to be ca. 1 \times 10 $^9~M^{-1}~s^{-1}$ for the reactions of 2 with the acyclic and alicyclic secondary amines and remains nearly constant upon changing the amine basicity. This result is consistent with the suggestion that the k_3 value is insensitive to amine basicity.^{14,16,17} Castro et al. have estimated the k_3 value of 1 imes $10^{10}\,M^{-1}\,s^{-1}$ for aminolyses of various thiocarbonyl esters in H_2O .^{12,16,17} Therefore, the k_3 value determined in the present aminolysis carried out in 20 mol % DMSO appears to be smaller than the one estimated by Castro et al. for the aminolyses performed in $H_2O.^{12,16,17}$ However, this is not an unexpected result. Since proton mobility in H₂O has been suggested to be abnormally high,¹⁹ the addition of DMSO to H₂O would decrease proton mobility significantly. Accordingly, one can expect a decrease in the k_3 value upon changing the solvent from pure H₂O to H₂O containing 20 mol % DMSO. This argument is consistent with recent reports that the k_3 value for aminolysis of thiocarbonyl esters is smaller in aqueous ethanol $(k_3 = 4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1})$ than in pure H₂O $(k_3 = 1 \times 10^{10} \,\mathrm{M}^{-1}\,\mathrm{s}^{-1})^{12a}$ and that the k_3 process becomes absent in an aprotic solvent, CH₃CN.^{13a}

Jencks et al. have found that aminolyses of carboxylic esters proceed through one or two intermediates depending on the nature of the leaving group, i.e., the reaction of carboxylic esters possessing a poor leaving group proceeds through the deprotonation of a zwitterionic addition intermediate (T^{\pm}) , which can be deprotonated to yield an anionic intermediate (T⁻).^{1a} Castro et al. have suggested that aminolyses of various thiocarbonyl esters proceed through deprotonation of T^{\pm} to give T^{-} for reactions with weakly basic amines but without the deprotonation process for those with strongly basic amines.^{12,16,17} Accordingly, the basicity of amines has been suggested to be an important factor that governs the presence or absence of the deprotonation process (the k_3 path) for aminolyses of thiocarbonyl esters.^{12,16,17} Interestingly, the present result has clearly showed that the reaction of **2** with the primary amines proceeds without the k_3 path, while the reaction with the secondary amines (for both acyclic and alicyclic amines) proceeds through the k_3 path regardless of the amine basicity, suggesting that the amine nature (primary vs secondary) is another important factor that determines the k_3 path.

A common feature for the aminolysis reaction, which proceeds through the k_3 path, is that the k_2/k_{-1} ratio is small. The introduction of a poor leaving group as in Jencks' system^{1a} would decrease the k_2 value but would not affect the k_{-1} value. On the other hand, a decrease in the amine basicity as in Castro's system^{12,16,17} would increase the k_{-1} value but would not influence the k_2 value. For both systems, the k_2/k_{-1} ratio becomes small. As shown in Tables 1 and 2, the k_{-1} value is much larger for the reaction with the secondary amine than for the

⁽¹⁹⁾ Eigen, M. Angew. Chem., Int. Ed. Engl. 1964, 3, 1.

reaction with the isobasic primary amine, while the k_2 value remains constant. Consequently, the k_2/k_{-1} ratio becomes smaller for the reaction with the secondary amine (both acyclic and alicyclic amines) than for the reaction with the isobasic primary amine. Therefore, it is proposed that a small k_2/k_{-1} ratio is a plausible cause of the deprotonation process observed in aminolyses of carbonyl and thiocarbonyl derivatives.

Conclusions

The present study has allowed us to conclude the following. The reaction of **2** with primary amines proceeds through an addition intermediate, in which the RDS changes from the breakdown of the addition intermediate to the products to the formation of the intermediate as the amine basicity increases ($pK_a^\circ = 8.8$). However, the reaction of **2** with secondary amines proceeds through two intermediates, e.g., a zwitterionic addition intermediate (T^{\pm}) and an anionic intermediate (T^{-}). The effect of the amine basicity on the microscopic rate constants (k_1 , k_{-1} , and K) shows a good linear correlation for the reaction of **2** with primary amines but a poor correlation

for the reactions with acyclic secondary amines. The k_1 value is larger for the reaction of **2** with primary amines than for the one with acyclic secondary amines, while the k_{-1} value is much smaller for the former reaction than for the latter reactions. The small k_2/k_{-1} ratio is considered to be responsible for the deprotonation process observed in the aminolyses of carbonyl and thiocarbonyl derivatives.

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Supporting Information Available: Experimental conditions and k_{obs} values for the reaction of **2** with primary and acyclic secondary amines (Table S1), plots of k_{obs} vs amine concentration for the reaction of **2** with benzylamine and diethylamine (Figure S1), and plots of $k_{obs}/[amine]$ vs [amine] for the reaction of **2** with diethylamine and diallylamine (Figure S2), plots of [amine]/ k_{obs} vs 1/[amine] for the reaction of **2** with diethylamine (Figure S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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