Aminolysis of 4-nitrophenyl phenyl carbonate and thionocarbonate: effects of amine nature and modification of electrophilic center from C=O to C=S on reactivity and mechanism†

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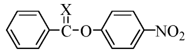
Received 25th January 2008, Accepted 27th February 2008
First published as an Advance Article on the web 14th March 2008
DOI: 10.1039/b801422a

A kinetic study is reported for the reactions of 4-nitrophenyl phenyl carbonate (**5**) and thionocarbonate (**6**) with a series of alicyclic secondary amines in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C. The plots of k_{obsd} *vs.* amine concentration are linear for the reactions of **5**. On the contrary, the plots for the corresponding reactions of **6** curve upward as a function of increasing amine concentration, indicating that the reactions proceed through two intermediates (*i.e.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^-). The Brønsted-type plot for the reactions of **5** with secondary amines exhibits a downward curvature, *i.e.*, the slope decreases from 0.98 to 0.26 as the pK_a of the conjugate acid of amines increases, implying that the reactions proceed through $T^{\pm}$ with a change in the rate-determining step (RDS). The k_N values are larger for the reactions of **5** with secondary amines than for those with primary amines of similar basicity. Dissection of k_N values for the reactions of **5** into the microscopic rate constants (*i.e.*, k_1 and k_2/k_{-1} ratio) has revealed that k_1 is larger for the reactions with secondary amines than for those with isobasic primary amines, while the k_2/k_{-1} ratio is nearly identical. On the other hand, for reactions of **6**, secondary amines exhibit larger k_1 values but smaller k_2/k_{-1} ratios than primary amines. The current study has shown that the reactivity and reaction mechanism are strongly influenced by the nature of amines (primary *vs.* secondary amines) and electrophilic centers (C=O *vs.* C=S).

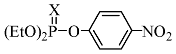
Introduction

Aminolysis of carboxylic esters has generally been understood to proceed through a zwitterionic tetrahedral intermediate $T^{\pm}$ with a change in the rate-determining step (RDS) on the basis of curved Brønsted-type plots reported for reactions of esters with a good leaving group.[1–5] The RDS has been suggested to change from breakdown of $T^{\pm}$ to its formation as the attacking amine becomes more basic than the leaving group by 4 to 5 pK_a units.[1–5]

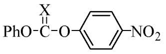
Aminolysis of thiono esters has been investigated much less intensively.[6–10] The first kinetic study was performed by Campbell and Lapinskas for the reactions of *O*-4-nitrophenyl thionobenzoate (**2**) with a series of primary amines.[6] They found that **2** is up to 200 fold more reactive than its oxygen analogue 4-nitrophenyl benzoate (**1**).[6] We have shown that reactions of **2** with a series of alicyclic secondary amines proceed through two intermediates (*i.e.*, $T^{\pm}$ and its deprotonated form T^-), while the corresponding reactions with primary amines proceed through $T^{\pm}$, indicating that the nature of amines (primary *vs.* secondary) determines the reaction mechanism of the aminolysis of **2**.[7]



X = O (**1**), S (**2**)



X = O (**3**), S (**4**)



X = O (**5**), S (**6**)

The effect of changing the electrophilic center from P=O to P=S on reactivity and reaction mechanism has also been investigated.[11–15] Hengge *et al.* have shown that 4-nitrophenyl diethyl phosphate (**3**) is *ca.* 10 fold more reactive than its sulfur analogue 4-nitrophenyl diethyl phosphorothioate (**4**) in alkaline hydrolysis conditions.[11] Besides, it has been concluded that the mono ester of **3** proceeds through A_ND_N mechanism while that of **4** proceeds through $D_N + A_N$ mechanism.[11j] We have shown that **3** is up to 2000 fold more reactive than **4** toward alkali metal ethoxide in anhydrous ethanol.[12a] Furthermore, alkali metal ions catalyze the reactions of **3** in the order $K^+ < Na^+ < Li^+$, while they inhibit the reactions of **4** in the order $K^+ < Na^+ < Li^+$.[12b,c] We have recently reported that aminolyses of aryl diphenylphosphinates and their sulfur analogues aryl diphenylphosphinothioates proceed through a concerted mechanism.[15] Besides, the reactions of the P=S compounds have been concluded to proceed through a tighter transition-state structure than those of the P=O compounds on the basis of β_{nuc}, β_{lg}, and activation parameters.[15a]

Scattered information on the aminolysis of carbonates and thionocarbonates is available.[8,9] However, the effect of changing

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† Electronic supplementary information (ESI) available: Tables S1–S14 for the reaction conditions and the kinetic results for reactions of **5** and **6** with secondary amines. Fig. S1–S7 for the plots of k_{obsd} *vs.* [amine] for reactions of **5** and **6** with secondary amines. Fig. S8 and S9 for the plots of k_{obsd}/[amine] *vs.* [amine] and [amine]/k_{obsd} *vs.* 1/[amine], respectively for the reaction of **6** with 1-formylpiperazine. Eqn S1–S6 used to calculate the k_2/k_{-1} ratio for reactions of **5** with secondary amines. See DOI: 10.1039/b801422a

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§ Present address: Advanced PKG Development Central R & D Institute, Samsung Electro-Mechanics, Suwon, Gyunggi-do 443–743, Korea the electrophilic center from C=O to C=S has not systematically been investigated. Thus, we have performed a systematic study for reactions of 4-nitrophenyl phenyl carbonate (**5**) and thionocarbonate (**6**) with a series of primary amines. The reactions have been proposed to proceed through $T^{\pm}$ with a change in the RDS on the basis of curved Brønsted-type plots.[10] Furthermore, we have found that the reactions of **6** exhibit a lower pK_a^{o} (*i.e.*, defined as the pK_a at the center of Brønsted curvature) than those of **5**.[10] The former reactions resulted in a smaller k_1 but a larger k_2/k_{-1} ratio than the latter reactions, which has been suggested to be responsible for the lower pK_a^{o} shown by the reactions of **6**.[10]

We have extended our study to the reactions of **5** and **6** with a series of alicyclic secondary amines to get further information. The microscopic rate constants (*i.e.*, k_1, k_2/k_{-1} and k_3/k_{-1} ratios) associated with the reactions of **5** and **6** have been determined to investigate the effect of modification of the electrophilic center from C=O to C=S (*i.e.*, **5** → **6**) on reactivity and reaction mechanism at the microscopic rate constant level. We also report the effect of amine nature (*e.g.*, primary *vs.* secondary) on reactivity and reaction mechanism by comparing the data in this study with those reported for the corresponding reactions with primary amines.[10]

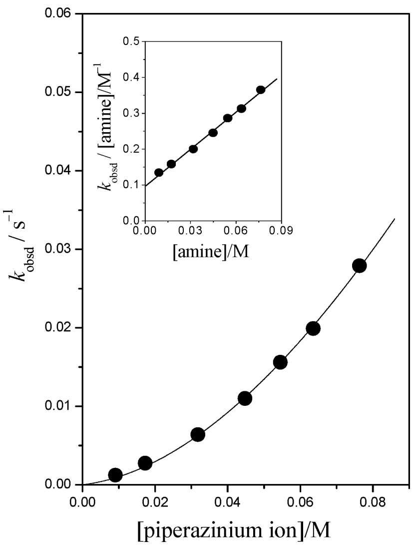


Fig. 1 Plots of k_{obsd} *vs.* [amine] and k_{obsd}/[amine] *vs.* [amine] (inset) for the reaction of 4-nitrophenyl phenyl thionocarbonate (**6**) with piperazinium ion in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C.

Results and discussion

Reactions of **5** and **6** with alicyclic secondary amines proceeded with quantitative liberation of 4-nitrophenoxide ion and/or its conjugate acid. The kinetic study was performed under pseudo-first-order conditions, *e.g.*, the amine concentration in excess over the substrate concentration. All reactions obeyed first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_{\infty} - A_t) = -k_{obsd}t + C$. The k_{obsd} values obtained are summarized in Tables S1–S14 in the electronic supplementary information (ESI). It is estimated from replicate runs that the uncertainty in the rate constant is less than 3%.

The plots of k_{obsd} *vs.* amine concentration are linear and pass through the origin for the reactions of **5** (see Figs. S1–S7 in the ESI), indicating that general base catalysis by a second amine molecule is absent and the contribution of OH^- and/or water to k_{obsd} is negligible. However, as shown in Fig. 1, the plot of k_{obsd} *vs.* [amine] for the reaction of **6** with piperazinium ion exhibits an upward curvature. A similar upward curvature has been obtained for the reactions of **6** with the other secondary amines studied (see Figs. S2–S7 in the ESI). Such an upward curvature indicates that a second amine molecule behaves as a general base catalyst, and the reactions proceed through two tetrahedral intermediates (*i.e.*, $T^{\pm}$ and T^-).[7–9,16,17] Clearly, the current results show that the effect of modification of the electrophilic center (*i.e.*, **5** → **6**) on reaction mechanism is significant.

Mechanism of aminolysis of 4-nitrophenyl phenyl carbonate (5)

Since general base catalysis by a second amine molecule is absent and the contribution of OH^- and/or water to k_{obsd} is negligible for the reactions of **5**, the rate equation can be expressed as eqn (1), where [**5**] and [RR′NH] represent the concentration of substrate **5** and the amine used, respectively. The apparent second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} *vs.* [RR′NH], and are summarized in Table 1.

$$\text{rate} = k_{obsd}[\mathbf{5}], \text{ where } k_{obsd} = k_N[\text{RR}'\text{NH}] \qquad (1)$$

As shown in Table 1, the k_N value increases as the basicity of the amines increases. The effect of amine basicity on reactivity is illustrated in Fig. 2. The Brønsted-type plot for the reactions of **5** with secondary amines is curved when the pK_a and k_N values were statistically corrected using p and q (*i.e.*, $p = 2$ except $p = 4$ for piperazinium ion and $q = 1$ except $q = 2$ for piperazine).[18] A similar curved Brønsted-type plot is shown for the reactions of

Table 1 Summary of rate constants for reactions of 4-nitrophenyl phenyl carbonate (**5**) with alicyclic secondary amines in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C[a]

	Amine	pK_a	$k_N/M^{-1}\ s^{-1}$	$k_1/M^{-1}\ s^{-1}$	k_2/k_{-1}
1	Piperazinium ion	5.95	0.0622	22.4	0.00278
2	1-Formylpiperazine	7.98	1.68	36.0	0.0489
3	Morpholine	8.65	11.3	87.3	0.149
4	1-(2-Hydroxyethyl)-piperazine	9.38	27.6	83.0	0.498
5	Piperazine	9.85	108	271	0.661
6	3-Methylpiperidine	10.80	248	295	5.25
7	Piperidine	11.02	292	331	7.56

[a] The pK_a data in 80 mol% H_2O–20 mol% DMSO were taken from ref. 5.

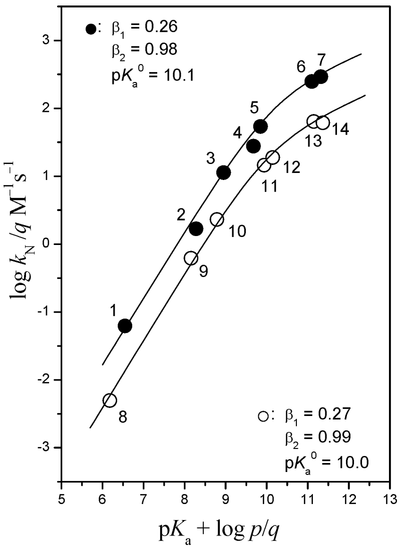
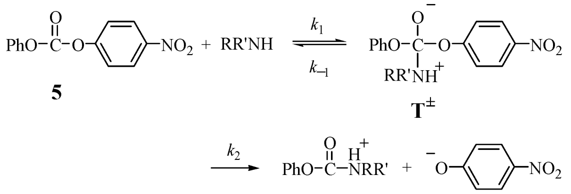


Fig. 2 Brønsted-type plots for reactions of 4-nitrophenyl phenyl carbonate (**5**) with primary amines (○) and alicyclic secondary amines (●) in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C. The identity of the numbers for the secondary amines is given in Table 1. For the primary amines: 8 = trifluoroethylamine, 9 = glycine ethyl ester, 10 = glycylglycine, 11 = benzylamine, 12 = ethanolamine, 13 = ethylamine, 14 = propylamine. The data for reactions with primary amines were taken from ref. 10.

5 with primary amines, although primary amines are less reactive than secondary amines of similar basicity. Such a curved Brønsted-type plot has often been reported for reactions which proceed through a stepwise mechanism with a change in the RDS, *i.e.*, from breakdown of T$^{\pm}$ to its formation as the amine basicity increases as shown in Scheme 1.



RR'NH = 7 different alicyclic secondary amines

Scheme 1

The nonlinear Brønsted-type plot shown in Fig. 2 has been analyzed using a semiempirical equation [eqn (2)], in which β_1 and β_2 represent the slope of the Brønsted-type plot at the high and the low pK_a region, respectively.[19] The curvature center of the curved Brønsted-type plot has been defined as pK_a^o, the pK_a where the RDS changes.[19] The k_N^o refers to the k_N value at pK_a^o. The parameters determined from the fitting of eqn (2) to the experimental points are $\beta_1 = 0.26$, $\beta_2 = 0.98$, and p$K_a^o = 10.1$ for the reactions of **5** with secondary amines, which are nearly identical to those reported for the corresponding reactions with primary amines (*i.e.*, $\beta_1 = 0.27$, $\beta_2 = 0.99$, and p$K_a^o = 10.0$). Thus, one can suggest that secondary amines are more reactive than isobasic primary amines, but the nature of amines does not influence the mechanism of the reactions of **5**.

$$\log(k_N/k_N^o) = \beta_2(pK_a - pK_a^o) - \log[(1 + \alpha/2)], \text{ where } \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a^o) \quad (2)$$

Effect of amine nature on reactivity

The fact that secondary amines are more reactive than isobasic primary amines in this study is consistent with the reports that primary amines are less reactive than secondary or tertiary amines of similar basicity, *e.g.*, in deprotonation of carbon acids such as nitroethane,[20a] 4-nitrophenyl and 2,4-dinitrophenylacetonitriles,[21] in nucleophilic displacement on chloramines,[22] in aminolysis of various esters,[20b,23] and in reactions with benzhydrylium ions.[24] Since solvation energy increases in the order $R_3NH^+ < R_2NH_2^+ < RNH_3^+$, solvent effect has been suggested to be responsible for the low reactivity shown by primary amines.[20,21]

More systematic analysis has been performed in terms of the k_1/k_{-1} ratio.[25] Castro *et al.* found that quinuclidines are more reactive than isobasic alicyclic secondary amines in the reactions of methyl 2,4-dinitrophenyl carbonate and phenyl 2,4-dinitrophenyl carbonate in water.[25a] Similarly, pyridines were shown to be more reactive than alicyclic secondary amines of similar basicity toward 4-methylphenyl 4-nitrophenyl thionocarbonate in 44% ethanol–water.[25b] In all cases the k_1/k_{-1} ratios for quinuclidines and pyridines have been calculated to be larger than those for the isobasic alicyclic secondary amines.[25] Since the k_2 value was suggested to be independent of the nature of amines, Castro *et al.* have concluded that the larger k_1/k_{-1} ratio for the reactions with tertiary amines is responsible for their higher reactivity.[25]

A large k_1/k_{-1} ratio is possible either by increasing k_1 or by decreasing k_{-1}. Thus, we have dissected the k_N values into the microscopic rate constants (*e.g.*, k_1 and k_2/k_{-1} ratio) to investigate which term (*i.e.*, k_1 *vs.* k_{-1}) is more responsible for the higher reactivity shown by the secondary amines in this study. The second-order rate constant k_N can be represented as eqn (3) by applying a steady-state condition for the addition intermediate T$^{\pm}$. The k_2/k_{-1} ratios have been calculated using the method reported by Castro and Ureta (see also eqn S1–S6 in the ESI).[19] The k_1 values have been determined from eqn (4) using the k_N values in Table 1 and the k_2/k_{-1} ratios determined above. The k_1 values and k_2/k_{-1} ratios calculated in this way are summarized in Table 1.

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

$$k_1 = k_N(k_{-1}/k_2 + 1) \quad (4)$$

As shown in Table 1, the k_2/k_{-1} ratio increases as the amine basicity increases. The effect of amine basicity on the k_2/k_{-1} ratio is illustrated in Fig. 3. The plots are linear with the same slope for the reactions with secondary and primary amines. Besides, the k_2/k_{-1} ratios for the reactions of **5** with secondary amines are almost the same as those for the reactions with isobasic primary amines. Thus, one can suggest that the k_2/k_{-1} ratio is not responsible for the reactivity difference between the primary and secondary amines.

The effect of amine basicity on k_1 values is illustrated in Fig. 4. The Brønsted-type plot for the reactions with secondary amines is linear with $\beta_1 = 0.26$. The corresponding plot for the reactions with primary amines is also linear with the same slope. However, secondary amines exhibit larger k_1 values than primary amines. Thus, one can suggest that the larger k_1 for the reactions of **5** with secondary amines is mainly responsible for the fact that secondary amines are more reactive than primary amines of similar basicity.

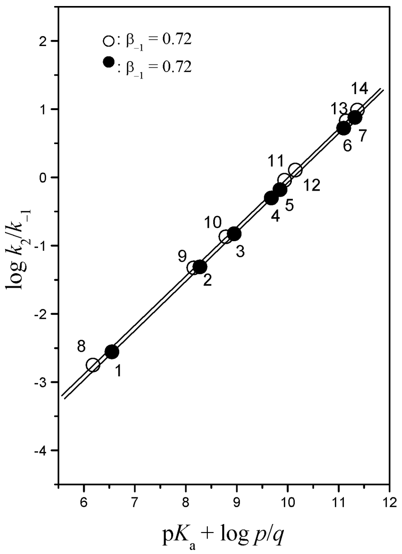


Fig. 3 Plots of log k_2/k_{-1} *vs.* pK_a for reactions of 4-nitrophenyl phenyl carbonate (**5**) with primary amines (○) and alicyclic secondary amines (●) in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C. The identity of the numbers is the same as in Fig. 2. The data for the reactions with primary amines were taken from ref. 10.

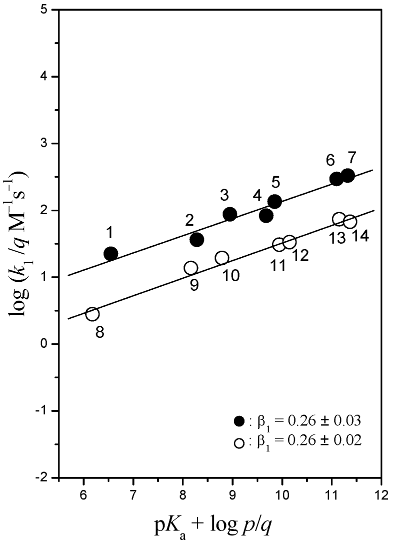
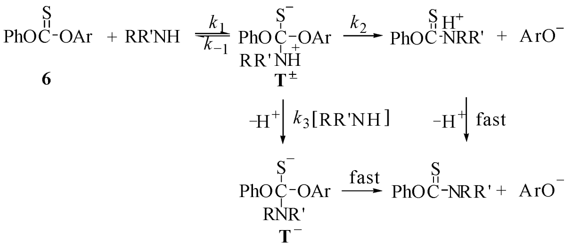


Fig. 4 Brønsted-type plots for reactions of 4-nitrophenyl phenyl carbonate (**5**) with primary amines (○) and alicyclic secondary amines (●) in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C. The identity of numbers is the same as in Fig. 2. The data for the reactions with primary amines were taken from ref. 10.

Mechanism of aminolysis of 4-nitrophenyl phenyl thionocarbonate (6)

The fact that the plot of k_{obsd} *vs.* [amine] exhibits an upward curvature for the reactions of **6** with secondary amines suggests that the reactions proceed through two intermediates ($T^\pm$ and T^-) as shown in Scheme 2. Accordingly, under the assumption of a steady-state condition for the zwitterionic intermediate $T^\pm$, rate equations can be expressed as eqn (5) and (6), in which [$T^\pm$], [**6**] and [RR′NH] represent the concentration of the zwitterionic intermediate $T^\pm$, substrate **6**, and the amine used, respectively.



Scheme 2

Further assumption $k_{-1} >> k_2 + k_3$[RR′NH] simplifies eqn (6) to eqn (7).

$$\text{rate} = k_2[\text{T}] + k_3[\text{T}][\text{RR'NH}] = (k_1k_2[\text{RR'NH}] + k_1k_3[\text{RR'NH}]^2)[\mathbf{6}]/(k_{-1} + k_2 + k_3[\text{RR'NH}]) \quad (5)$$

$$k_{obsd} = (k_1k_2[\text{RR'NH}] + k_1k_3[\text{RR'NH}]^2)/(k_{-1} + k_2 + k_3[\text{RR'NH}]) \quad (6)$$

$$k_{obsd}/[\text{RR'NH}] = k_1k_2/k_{-1} + k_1k_3[\text{RR'NH}]/k_{-1} \quad (7)$$

In fact, as shown in the inset of Fig. 1, the plot of k_{obsd}/[RR′NH] *vs.* [RR′NH] is linear for the reaction of **6** with piperazinium ion, indicating that the above assumption (*i.e.*, $k_{-1} >> k_2 + k_3$[RR′NH]) is valid for the reaction with this weakly basic amine. Therefore, the k_1k_2/k_{-1} and k_1k_3/k_{-1} values have been determined from the intercept and the slope of the linear plot, respectively. However, the corresponding plots for reactions with more basic secondary amines are linear only in a low amine concentration region but curved as the amine concentration increases (see Fig. S8 in the ESI for the reaction of **6** with 1-formylpiperazine). Therefore, the assumption $k_{-1} >> k_2 + k_3$[RR′NH] is invalid for the reactions with the basic amines. This argument is consistent with the idea that the k_{-1} value decreases with increasing the amine basicity and the term k_3[RR′NH] increases with increasing [RR′NH], while the k_3 value was suggested to be insensitive to the amine basicity since the proton transfer is from the aminium ion moiety of $T^\pm$ to the corresponding free amine.[7,8]

One can reduce eqn (6) to eqn (8) under the assumption $k_2 << k_3$[RR′NH] at the high amine concentration region. In fact, the plot of [RR′NH]/k_{obsd} *vs.* 1/[RR′NH] is linear at a high amine concentration region but exhibits negative deviations at a low concentration region as expected (see Fig. S9 in the ESI for the reaction of **6** with 1-formylpiperazine). A similar result has been obtained for the reactions of **6** with all the other basic amines studied, indicating that the assumption $k_2 << k_3$[RR′NH] is valid only at a high amine concentration region. Therefore, the $1/k_1$ value has been estimated from the intercept of the linear part of the plot. More reliable values of k_1, k_2/k_{-1} and k_3/k_{-1} ratios have been determined through the nonlinear least-squares fitting of eqn (6) to the experimental data using the estimated k_1 values as input values. The k_3/k_2 ratio has also been calculated from the k_2/k_{-1} and k_3/k_{-1} ratios. The k_1, k_2/k_{-1}, k_3/k_{-1} and k_3/k_2 ratios obtained in this way are summarized in Table 2.

$$[\text{RR'NH}]/k_{obsd} = 1/k_1 + k_{-1}/k_1k_3[\text{RR'NH}] \quad (8)$$

As shown in Table 2, $k_2/k_{-1} < 1$ regardless of amine basicity, indicating that formation of $T^\pm$ occurs before the RDS. Besides, the k_3/k_2 ratio of *ca.* 10^2 implies that the deprotonation process (the k_3 step in Scheme 2) becomes dominant when the amine

Table 2 Summary of microscopic rate constants for reactions of 4-nitrophenyl phenyl thionocarbonate (**6**) with alicyclic secondary amines in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C

	Amine	pK_a	$k_1/M^{-1}\ s^{-1}$	k_2/k_{-1}	$k_3/k_{-1}/M^{-1}$	$k_3/k_2/M^{-1}$
1	Piperazinium ion	5.95	1.84	0.0307	2.81	91.5
2	1-Formylpiperazine	7.98	7.38	0.140	14.8	106
3	Morpholine	8.65	13.4	0.247	60.5	245
4	1-(2-Hydroxyethyl)-piperazine	9.38	16.9	0.411	40.1	97.6
5	Piperazine	9.85	39.1	0.554	145	262
6	3-Methylpiperidine	10.80	41.4	0.861	136	158
7	Piperidine	11.02	35.2	0.867	104	120

concentration is high enough (*e.g.*, [RR′NH] >> 0.01 M). Thus, the microscopic rate constants in Table 2 are consistent with the proposed mechanism.

The values of k_3 and k_2 have been suggested to be independent of the basicity of amines.[7,8] However, the reactions with morpholine and piperazine exhibit larger k_3/k_{-1} and k_3/k_2 ratios than the other amines. One might attribute this result to their structures, *i.e.*, piperazine has two basic nitrogen atoms, while morpholine has one nitrogen and one oxygen atom. Thus, piperazine exhibits larger k_3/k_{-1} and k_3/k_2 ratios. The larger k_3/k_{-1} and k_3/k_2 ratios shown by morpholine might indicate that the oxygen atom in the morpholine participates in the k_3 process although it is not as basic as the nitrogen atom.

Effect of amine nature on k_1

As shown in Fig. 5, the plot of log k_1 *vs.* pK_a is linear with $\beta_1 = 0.27$ for the reactions of **6** with secondary amines. The corresponding plot for the reactions with primary amines is also linear with $\beta_1 = 0.16$. These β_1 values are consistent with the β_1 values reported for reactions which proceed through rate-determining formation of an intermediate (*i.e.*, $\beta_1 = 0.2 \pm 0.1$).[1–6]

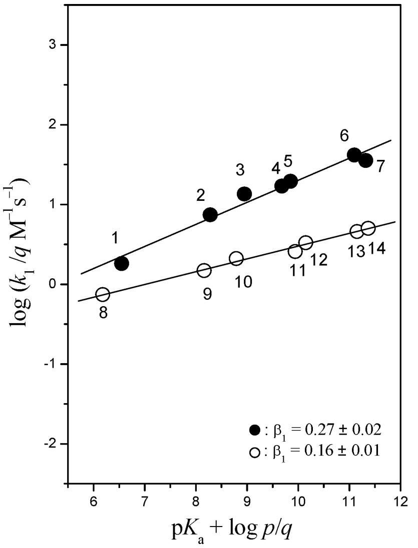


Fig. 5 Brønsted-type plots for reactions of 4-nitrophenyl phenyl thionocarbonate (**6**) with primary amines (○) and alicyclic secondary amines (●) in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C. The identity of the numbers is the same as in Fig. 2. The data for the reactions with primary amines were taken from ref. 10.

Interestingly, the magnitude of k_1 values is larger for the reactions of **6** with secondary amines than for those with primary ones. A similar result is shown in Fig. 4 for the reactions of **5**. One should have observed an opposite result if steric hindrance was an important factor to determine the reactivity of amines.

Steric hindrance would not be significant for reactions in which the bond formation between the nucleophile and the substrate is not greatly advanced in the transition state (TS). Since the β_1 values in this study are very small (*i.e.*, $\beta_1 = 0.16$–0.27), one can suggest that the bond formation is advanced only a little in the TS. Thus, steric hindrance appears to be insignificant for the aminolysis of **5** and **6**. This argument is consistent with the reports that primary amines are more reactive than secondary or tertiary amines of similar basicity in the nucleophilic substitution reaction of phenyl acetate in which $\beta_{nuc} = 1.05$,[20b] while the reverse is true in the reactions of phosphate and sulfate esters in which $\beta_{nuc} = 0.20$[23a] and 0.13,[23b] respectively.

Effect of k_2/k_{-1} ratio on reaction mechanism

It has generally been understood that aminolysis of esters proceeds through one or two intermediates (*i.e.*, $T^{\pm}$ and its deprotonated form T^-) depending on reaction conditions. Satterthwait and Jencks have found that aminolysis of esters possessing a poor leaving group proceeds through two intermediates, $T^{\pm}$ and T^-.[16a] Castro *et al.* have reported that reactions of various thiono esters with weakly basic secondary amines proceed through $T^{\pm}$ and T^-, while the reaction with strongly basic piperidine proceeds through $T^{\pm}$ only. Thus, the basicity of amines has been suggested to be also an important factor to determine reaction mechanism.[8] However, the current study has shown that the reactions of **6** with secondary amines proceed through $T^{\pm}$ and T^- regardless of amine basicity, while the corresponding reactions with primary amines proceed through $T^{\pm}$ only. Accordingly, the nature of amines appears to be another factor that governs the deprotonation process (*i.e.*, the k_3 step in Scheme 2).

A common feature for aminolyses of carbonyl and thiocarbonyl esters which proceed through $T^{\pm}$ and T^- is that the k_2/k_{-1} ratio is small. Introduction of a poor leaving group as in Satterthwait and Jencks' system decreases k_2 but would not influence k_{-1}. On the other hand, a weakly basic amine as in Castro's system increases k_{-1} but would not affect k_2. Both systems would cause a decrease in the k_2/k_{-1} ratio. The current study has also demonstrated that the reactions of **6** with secondary amines proceed through $T^{\pm}$ and T^- and result in a smaller k_2/k_{-1} ratio than those with isobasic primary amines (see Fig. 6). Thus, it is proposed that a small k_2/k_{-1}

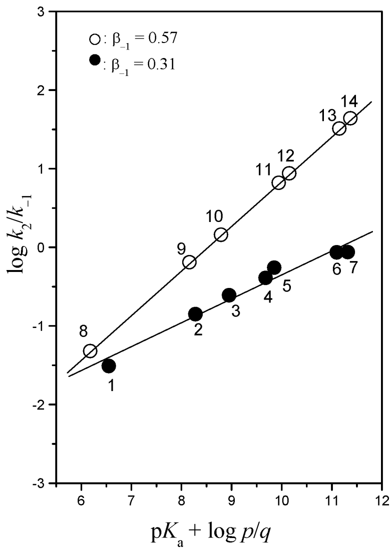


Fig. 6 Plots of log k_2/k_{-1} *vs.* pK_a for reactions of 4-nitrophenyl phenyl thionocarbonate (**6**) with primary amines (○) and alicyclic secondary amines (●) in 80 mol% H_2O–20 mol% DMSO at 25.0 ± 0.1 °C. The identity of the numbers is the same as in Fig. 2. The data for the reactions with primary amines were taken from ref. 10.

ratio is a credible cause of the deprotonation process observed for reactions of thiocarbonyl esters with secondary amines.

Conclusions

Our systematic study has shown that the reactivity and reaction mechanisms are strongly influenced by the nature of amines (primary *vs.* secondary amines) and electrophilic centres (C=O *vs.* C=S). (1) For reactions of **5**, the deprotonation process (*i.e.*, the k_3 step) is absent regardless of the amine nature. Secondary amines are more reactive and exhibit lager k_1 values than isobasic primary amines, while the k_2/k_{-1} ratio is nearly identical for reactions with both primary and secondary amines. (2) Reactions of **6** with secondary amines proceed through $T^{\pm}$ and T^-, while the corresponding reactions with primary amines proceed through $T^{\pm}$ only. Secondary amines exhibit smaller k_2/k_{-1} ratios than primary amines of similar basicity, which is a credible cause for the deprotonation process observed for reactions of thiocarbonyl esters with secondary amines.

Experimental

Materials

4-Nitrophenyl phenyl carbonate (**5**) and thionocarbonate (**6**) were prepared as reported previously.[10] Amines and other chemicals were of the highest quality available and were recrystallized or distilled before use whenever necessary. The reaction medium was H_2O containing 20 mol% DMSO to eliminate solubility problems. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics

The kinetic studies were performed using a UV-vis spectrophotometer equipped with a constant-temperature circulating bath for slow reactions ($t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \le 10$ s). The reactions were followed by monitoring the appearance of 4-nitrophenoxide ion (and/or 4-nitrophenol for the reaction with piperazinium ion). Typically, the reaction was initiated by adding 5 μL of a 0.02 M substrate stock solution in CH_3CN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine: [substrate] = *ca.* 4×10^{-5} M, [amine] = *ca.* $(4–82) \times 10^{-3}$ M. The amine stock solution of *ca.* 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen by adding 2 equiv. of amine to 1 equiv. of standardized HCl solution to obtain a self-buffered solution. All the transfers of solutions were carried out by means of gastight syringes. Concentrations of amines and pseudo-first-order rate constants (k_{obsd}) for the individual kinetic experiment are given in Tables S1–14 in the ESI.

Product analysis

4-Nitrophenoxide ion (and/or its conjugate acid) was liberated quantitatively and identified as one of the products by comparison of the UV-vis spectra after completion of the reactions with those of the authentic sample under the same reaction conditions.

Acknowledgements

This work was supported by a grant from the Korea Research Foundation (KRF-2005–015-C00256).

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