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A Kinetic Study on Aminolysis of Benzyl 2-Pyridyl Thionocarbonate and *t*-Butyl 2-Pyridyl Thionocarbonate: Effects of Polarizability and Steric Hindrance on Reactivity and Reaction Mechanism

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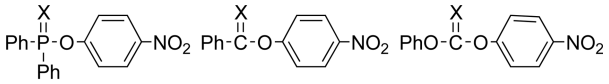
Second-order rate constants k_N have been measured for reactions of benzyl 2-pyridyl thionocarbonate (**4b**) and *t*-butyl 2-pyridyl thionocarbonate (**5b**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The k_N values for the reactions of **4b** and **5b** have been compared with those reported previously for the corresponding reactions of benzyl 2-pyridyl carbonate (**4a**) and *t*-butyl 2-pyridyl carbonate (**5a**) to investigate the effect of changing the electrophilic center from C=O to C=S on reactivity and reaction mechanism. The thiono compound **4b** is more reactive than its oxygen analogue **4a**. The Brønsted-type plots for the reactions of **4a** and **4b** are linear with β_{nuc} = 0.57 and 0.37, respectively. The reactions of **4a** were previously reported to proceed through a concerted mechanism, while those of **4b** in this study have been concluded to proceed through a stepwise mechanism with formation of an intermediate being the rate-determining step on the basis of the β_{nuc} value of 0.37. Enhanced polarizability upon changing the C=O in **4a** by C=S has been suggested to be responsible for the reactivity order and the contrasting reaction mechanisms. In contrast, the reactivity of **5a** and **5b** is similar, but they are much less reactive than **4a** and **4b**. Furthermore, the reactions of **5a** and **5b** have been concluded to proceed through the same mechanism (*i.e.*, a concerted mechanism) on the basis of linear Brønsted-type plots with β_{nuc} = 0.45 or 0.47. It has been concluded that the strong steric hindrance exerted by the *t*-Bu in **5a** and **5b** causes a decrease in their reactivity and forces the reactions to proceed through a concerted mechanism.

Key Words : Aminolysis, Polarizability, Intramolecular H-bonding, Forced concerted mechanism, Steric hindrance

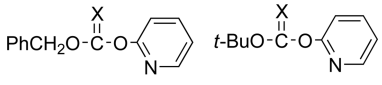
Introduction

Aminolysis of esters has intensively been investigated due to the importance in their biological processes as well as their synthetic applications.[1-11] The reactions of esters with amines have been reported to proceed through a concerted mechanism or through a stepwise pathway with one or two intermediates (*i.e.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}) depending on reaction conditions.[1-11] The linear Brønsted-type plots with β_{nuc} = 0.5 ± 0.1 obtained from aminolysis of 4-nitrophenyl diphenylphosphinate (**1a**) and 4-nitrophenyl diphenylphosphinothioate (**1b**) has been taken as evidence for a concerted mechanism.[7] The reactions of 4-nitrophenyl benzoate (**2a**) with a series of cyclic secondary amines have been concluded to proceed through a stepwise mechanism on the basis of a linear Brønsted-type plot with β_{nuc} = 0.81.[8h] In contrast, the corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**2b**) have been suggested to proceed through a stepwise mechanism with two intermediates $T^{\pm}$ and T^{-} on the basis of the fact that the plots of k_{obsd} *vs.* [amine] curve upward.[9] A similar result has been reported for the aminolysis of 4-nitrophenyl phenyl carbonate (**3a**) and *O*-4-nitrophenyl phenyl thionocarbonate (**3b**), *i.e.*, the reactions of **3a** proceed through stepwise mechanism with a change in the rate-determining step (RDS), while those of **3b** proceed through a stepwise mechanism with two intermediates $T^{\pm}$ and T^{-}.[10] These results demonstrate clearly that the nature of the electrophilic center (*e.g.*, P=O, P=S, C=O and C=S) controls the reaction mechanism.



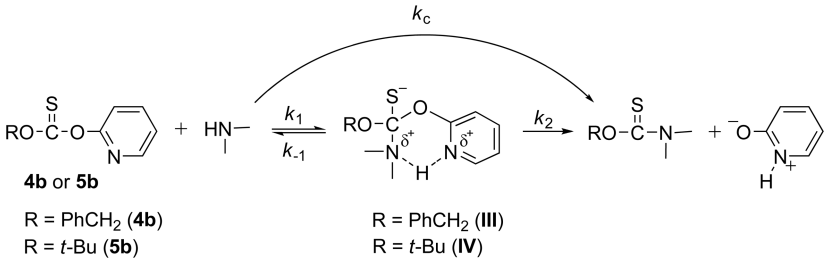
X = O (**1a**), S(**1b**) X = O (**2a**), S (**2b**) X = O (**3a**), S (**3b**)

We have recently carried out reactions of benzyl 2-pyridyl carbonate (**4a**) and *t*-butyl 2-pyridyl carbonate (**5a**) with a series of cyclic secondary amines in MeCN.[11a] The reactions were expected to proceed through a stepwise mechanism with an intermediate as modeled by I or II, since the intramolecular H-bonding interaction could stabilize the intermediate.



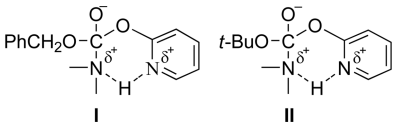
X = O (**4a**), S (**4b**) X = O (**5a**), S (**5b**)

However, the reactions have been concluded to proceed through a concerted mechanism on the basis of linear



Scheme 1

Brønsted-type plots with β_{nuc} = 0.57 and 0.45, respectively.[11a] We have proposed that the intramolecular H-bonding interaction forces the reactions to proceed through a concerted mechanism by increasing the nucleofugality of the leaving group, since the leaving group becomes *N*-protonated 2-pyridyloxide (*i.e.*, a zwitterionic form) upon the proton transfer from the aminium moiety.[11a]



We have now extended our study to the reactions of benzyl 2-pyridyl thionocarbonate (**4b**) and *t*-butyl 2-pyridyl thionocarbonate (**5b**) with a series of cyclic secondary amines in MeCN to investigate the effect of changing the nonleaving group on the reactivity and reaction mechanism (Scheme 1). We have also compared the kinetic data obtained in this study with those reported[11a] previously for the corresponding reactions of **4a** and **5a** to investigate the effect of changing the electrophilic center from C=O to C=S (*e.g.*, from **4a** to **4b** and from **5a** to **5b**) on the reactivity and reaction mechanism.

Results and Discussion

The aminolysis of **4b** and **5b** was followed spectrophotometrically by monitoring the appearance of 2-hydroxypyridine under pseudo-first-order conditions (*e.g.*, the concentration of amines was kept in excess over that of substrates). All of the reactions in this study obeyed first-order kinetics and the 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.* amine concentration were linear with excellent correlation coefficients (*e.g.*, $R^2 \geq 0.9995$) and passed through the origin, indicating that a general base catalysis by a second amine molecule is absent. Accordingly, the second-order rate constants (k_N) for the reactions of **4b** and **5b** were calculated from the slope of the linear plots and are summarized in Tables 1 and 2, respectively together with those reported previously for the corresponding reactions of **4a** and **5a** to investigate the effect of changing the electrophilic center from C=O to C=S on reactivity and reaction mechanism.

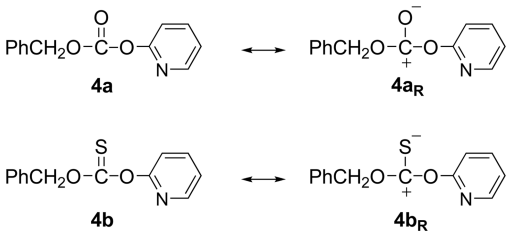
Effect of Changing Electrophilic Center from C=O to C=S on Reactivity. As shown in Table 1, the second-order rate constant decreases as the amine basicity decreases except piperazine, which shows a larger k_N than the more basic piperidine or 3-methylpiperidine. However, this is not surprising since piperazine possesses two nucleophilic sites. A similar reactivity trend is demonstrated for the reactions of **4a**, although the C=O compound **4a** is much less reactive than the C=S compound **4b**. This indicates that the effect of changing the electrophilic center from C=O to C=S on reactivity is significant.

Table 1. Summary of Second-Order Rate Constants (k_N) for Aminolysis of Benzyl 2-Pyridyl Carbonate (**4a**) and Benzyl 2-Pyridyl Thionocarbonate (**4b**) in MeCN at 25.0 ± 0.1 °C[a]

	amines	pK_a	$k_N/M^{-1}s^{-1}$	
			4a	**4b**
1	piperidine	18.8	15.2	205
2	3-methylpiperidine	18.6	13.4	197
3	piperazine	18.5	14.2	252
4	1-(2-hydroxyethyl)piperazine	17.6	2.99	65.7
5	morpholine	16.6	0.940	35.3

[a]The data for the reactions of **4a** were taken from ref 11a.

It is well known that a C=S bond is more polarizable than a C=O bond, since the overlap between 2p and 3p orbitals in a C=S bond is not as strong as that between 2p and 2p orbitals in a C=O bond. Thus, the contribution of the resonance structure **4b$_R$** is expected to be more significant than that of **4a$_R$**. This idea is supported by the ^{13}C NMR spectra for **4a** and **4b**, *i.e.*, the chemical shifts for the carbon atoms of the C=O in **4a** and the C=S bond in **4b** are 157 and 194 ppm, respectively (*i.e.*, a 37 ppm downfield shift).[11c] This is consistent with the 30-50 ppm downfield shift reported for the C=S compounds **2b** and **3b** compared with the corresponding C=O compounds **2a** and **3a** (*e.g.*, the chemical shifts for the carbon atoms of the C=O in **2a** and **3a** are 163.8 and 150.7 ppm, respectively, while the chemical shifts for the C=S bond in **2b** and **3b** are 209.8 and 193.4 ppm, respectively).[10b] The 37 ppm downfield shift in the ^{13}C NMR spectrum for **4b** suggests that the carbon atom of the C=S bond in **4b** has a greater positive charge (or electrophilicity) than that of the C=O bond in **4a**. Thus, one might suggest that the high reactivity shown by **4b** is due to the enhanced electrophilicity of the polarizable electrophilic center (*i.e.*, C=S).



It is well known that anions are highly unstable in dipolar aprotic solvents such as MeCN and DMSO due to the repulsion between anionic solutes and the negative dipole end of dipolar solvents. Such repulsion would be more significant as the charge density of anions increases. Accordingly, a zwitterionic tetrahedral intermediate $T^{\pm}$ formed from the reactions of a C=O compound (*e.g.*, I in the Introduction section) would experience a stronger repulsion than that formed from the reactions of a C=S compound (*e.g.*, III in Scheme 1), since the negative charge is more concentrated on the small O atom in I than on the large S atom in III. Thus, one can suggest that III would be less unstable than I, which is responsible, at least in part, for the result that **4b** is more reactive than **4a** in MeCN.

Effect of Changing Electrophilic Center from C=O to C=S on Reaction Mechanism. To investigate the reaction mechanism, a Brønsted-type plot for the reactions of **4b** has been constructed in Figure 1. The plot for the corresponding reactions of **4a** is also demonstrated for comparison. The Brønsted-type plots for the reactions of **4a** and **4b** exhibit excellent linear correlations when the k_N and pK_a values are statistically corrected using p and q (*i.e.*, $p = 2$ and $q = 1$ except $q = 2$ for piperazine).[12] However, it is noted that the slopes of the linear plots are different from one another, *i.e.*, $\beta_{nuc} = 0.57$ and 0.37 for the reactions of **4a** and **4b**, respectively. The reactions of **4a** have recently been reported to proceed through a forced concerted mechanism with a TS structure similar to I on the basis of $\beta_{nuc} = 0.57$.[11a] In contrast, one can suggest that the reactions of **4b** proceed through a stepwise mechanism with formation of an intermediate (*i.e.*, III in Scheme 1) being the RDS. This is because a β_{nuc} value of 0.3 ± 0.1 is typical of reactions reported previously to proceed through a stepwise mechanism, in which formation of an intermediate is the RDS.

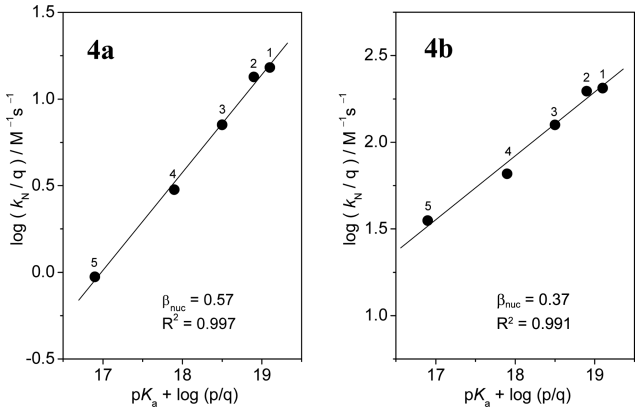


Figure 1. Brønsted-type plots for the reactions of benzyl 2-pyridyl carbonate (**4a**) and benzyl 2-pyridyl thionocarbonate (**4b**) with cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 1

The intermediate as modeled by I would be highly unstable due to the strong repulsion between the C–O$^-$ moiety of I and the negative dipole end of MeCN. Besides, the intramolecular H-bonding interaction shown in I could increase the nucleofugality of the leaving group, since it makes the leaving group as a protonated form (*i.e.*, 2-pyridiniumoxide). Thus, the reactions of **4a** have been reported to proceed through a forced concerted mechanism.[11a] In contrast, III would be less unstable even in MeCN since the negative charge of III (*i.e.*, the C–S$^-$ moiety) is highly dispersed on the large S atom. Furthermore, the ability of the C–S$^-$ moiety of III to form a C=S bond (and to expel the nucleofuge) would be much weaker than that of the C–O$^-$ moiety of I to form a C=O bond due to a weaker π-bonding energy of the thionocarbonyl group relative to the carbonyl group. This idea can account for the contrasting reaction mechanisms (*i.e.*, a forced concerted mechanism for the reactions of **4a** *vs*. a stepwise pathway for those of **4b**).

Aminolysis of thiono esters (*e.g.*, **2b** and **3b**) has often been reported to proceed through a stepwise mechanism with two intermediates, $T^{\pm}$ and its deprotonated form T^-.[9,10] However, the fact that the plots of k_{obsd} *vs*. [amine] for the aminloysis of **4b** in this study are linear indicates that the deprotonation process from $T^{\pm}$ to yield T^- (or a general base catalysis by a second amine molecule) is absent. One might suggest that absence of the deprotonation process (or a general base catalysis) is due to the H-bonding interaction shown in III. This is because the proton transfer through the intramolecular H-bonding would be more favorable than the deprotonation from the aminium moiety of III by a second amine molecule (*i.e.*, a general base catalysis). Furthermore, such H-bonding interaction could increase the nucleofugality significantly. Thus, one can suggest that the enhanced nucleofugality through the H-bonding interaction is responsible for the absence of the deprotonation process (or a general base catalysis) for the reactions of **4b**.

Effect of Steric Hindrance on Reactivity. To obtain further information on the reactivity and reaction mechanism, aminolysis of *t*-butyl 2-pyridyl thionocarbonate (**5b**) has

Table 2. Summary of Second-Order Rate Constants (k_N) for Aminolysis of *t*-Butyl 2-Pyridyl Carbonate (**5a**) and *t*-Butyl 2-Pyridyl Thionocarbonate (**5b**) in MeCN at 25.0 ± 0.1 °C[a]

	amines	pK_a	k_N / M^{-1}s^{-1}	
			5a	**5b**
1	piperidine	18.8	0.548	0.564
2	3-methylpiperidine	18.6	0.494	0.512
3	piperazine	18.5	0.631	0.622
4	1-(2-hydroxyethyl)piperazine	17.6	0.152	0.147
5	morpholine	16.6	0.0588	0.0566

[a]The data for the reactions of **5a** were taken from ref 11a.

been carried out. The second-order rate constants k_N are summarized in Table 2 together with the k_N values reported for the corresponding reactions of *t*-butyl 2-pyridyl carbonate (**5a**)[11a] for comparison. As shown in Table 2, the reactivity of **5b** is similar to that of **5a**, indicating that the effect of changing the electrophilic center from C=O to C=S on reactivity is negligible. Interestingly, this is in contrast to the result obtained from the reactions of **4a** and **4b** (Table 1). However, comparison of Tables 1 and 2 reveals that **5a** and **5b** are much less reactive than **4a** and **4b**, respectively, implying that modification of the nonleaving group from benzyloxythionocarbonyl to *t*-butoxythionocarbonyl on reactivity is significant.

Many factors could affect the reactivity of esters (*e.g.*, electronic effects, steric hindrance and reaction mechanism). The σ_I and σ_R constants represent the electronic effects such as inductive and resonance effects, respectively. The σ_I values for $PhCH_2$ and *t*-Bu are 0.03 and −0.03, respectively, while $\sigma_R = -0.12$ for both $PhCH_2$ and *t*-Bu,[13] indicating that the electronic effects for the $PhCH_2$ in **4a-4b** and the *t*-Bu in **5a-5b** are similar. Thus, one can suggest that the electronic effects would be little responsible for the experimental results that **4a** and **4b** are significantly more reactive than **5a** and **5b**, respectively.

It is apparent that the *t*-Bu moiety in substrates **5a** and **5b** would exhibit significantly stronger steric hindrance than the $PhCH_2$ group in **4a** and **4b**, since the steric factor $E_s = -1.54$ and −0.38 for *t*-Bu and $PhCH_2$, respectively.[13a] Thus, one can suggest that the steric hindrance exerted by the bulky *t*-Bu is mainly responsible for the fact that **5a** and **5b** are much less reactive than **4a** and **4b**, respectively.

Steric hindrance would be even more significant for the reactions of **5b** than for those of **5a**, since the C=S bond in **5b** is much larger than the C=O bond in **5a**. This idea is consistent with the fact that the rate retardation upon replacing the $PhCH_2$ in **4a** and **4b** by the *t*-Bu in **5a** and **5b** is more significant for the reactions of the C=S compounds than the C=O compounds, *e.g.*, as shown in Tables 1 and 2 for the reactions with piperidine, the k_N(**4a**)/k_N(**5a**) ratio is 28 and the k_N(**4b**)/k_N(**5b**) is 360.

As discussed in the preceding section, the C=S compound **5b** possesses a more electrophilic center than the C=O compound **5a**. Besides, the intermediate for the reactions of **5b** (*i.e.*, IV in Scheme 1) would be less unstable than that for the reactions of **5a** (*i.e.*, II) due to a weaker repulsion between the C–S$^-$ moiety and the negative dipole end of MeCN. Accordingly, **5b** is expected to be more reactive than **5a**. However, Table 2 shows that the reactivity of **5a** and **5b** is similar, indicating that the factors which increase the reactivity of **5b** are compensated by the strong steric hindrance exerted by the C=S bond.

Effect of Steric Hindrance on Reaction Mechanism. To investigate the reaction mechanism, Brønsted-type plots have been constructed for the reactions of **5a** and **5b**. As shown in Figure 2, the Brønsted-type plots are linear with $\beta_{nuc} = 0.45$ and 0.47 for the reactions of **5a** and **5b**, respectively. Aminolysis of **5a** has recently been reported to

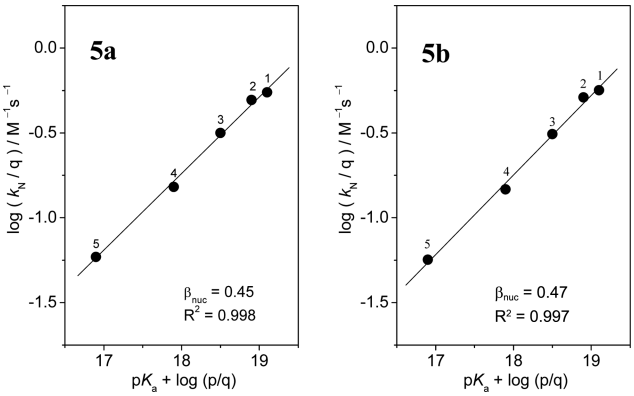


Figure 2. Brønsted-type plots for the reactions of *t*-butyl 2-pyridyl carbonate (**5a**) and *t*-butyl 2-pyridyl thionocarbonate (**5b**) with alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 2.

proceed through a forced concerted mechanism,[11a] since $\beta_{nuc} = 0.5 \pm 0.1$ is typical of reactions reported previously to proceed through a concerted mechanism. Thus, one can suggest that aminolysis of **5b** proceeds also through a concerted mechanism on the basis of the linear Brønsted-type plot with $\beta_{nuc} = 0.47$. Interestingly, this is in contrast to the result obtained from the reactions of **4a** and **4b**, *i.e.*, the reaction mechanism changes from a forced concerted mechanism to a stepwise pathway upon changing the electrophilic center from C=O (**4a**) to C=S (**4b**).

It is apparent that the steric hindrance for the reactions of **5b** would be more significant on going from the ground state (GS) to the intermediate, since the hybridization of the reaction center changes from sp^2 to sp^3. Consequently, the enhanced steric hindrance would destabilize the intermediate formed from the reactions of **5b** (*i.e.*, IV). Thus, one can suggest that the strong steric hindrance exerted by the *t*-Bu group in IV forces the reactions of **5b** to proceed through a concerted mechanism.

Conclusions

The aminolysis of **4b** and **5b** has allowed us to conclude the following: (1) The reactions of **4b** proceed through a stepwise mechanism with formation of $T^{\pm}$ being the RDS, while the corresponding reactions of **4a** proceed through a concerted pathway. Besides, **4b** is more reactive than **4a**. (2) The enhanced polarizability (or electrophilicity) upon changing the electrophilic center from the C=O in **4a** to the C=S in **4b** is responsible for the reactivity order and the contrasting reaction mechanisms. (3) The reactions of **5a** and **5b** proceed through a concerted mechanism and their reactivity is similar. (4) In contrast, **5a** and **5b** are much less reactive than **4a** and **4b**, indicating that steric hindrance exerted by the bulky *t*-Bu is responsible for the decreased reactivity. (5) Since steric hindrance is expected to be more significant on going from the GS to the intermediate IV, the enhanced steric hindrance forces the reactions of **5b** to proceed through a concerted mechanism.

Experimental Section

Materials. Substrates **4b** and **5b** were prepared in THF through the reaction of di-2-pyridyl thionocarbonate with benzyloxymagnesium bromide and potassium *t*-butoxide, respectively, as reported previously.[11c,14] The crude products were purified by short pathway silica gel column chromatography or recrystallization. Their purity was checked by their melting point, ^{1}H and ^{13}C NMR spectra. Amines and other chemicals were of the highest quality available.

Kinetics. Kinetic study was carried out by using a UV-Vis spectrophotometer for slow reactions (*e.g.*, $t_{1/2} \geq 10$ s) or a stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2} <$ 10 s) equipped with a constant-temperature circulating bath to maintain the reaction temperature at 25.0 ± 0.1 °C. All reactions were performed under pseudo-first-order conditions in which the concentration of amines was kept at least 20 times greater than that of the substrate. Typically, the reaction was initiated by adding 5 μL of a 0.01 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of MeCN and the amine nucleophile. Reactions were followed generally up to 9 half-lives and k_{obsd} were calculated using the equation, ln ($A_\infty - A_t$) *vs*. *t*.

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