

Aminolysis of Benzyl 4-Pyridyl Carbonate in Acetonitrile: Effect of Modification of Leaving Group from 2-Pyridyloxy to 4-Pyridyloxy on Reactivity and Reaction Mechanism

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Received April 1, 2012, Accepted May 16, 2012

A kinetic study is reported for nucleophilic substitution reactions of benzyl 4-pyridyl carbonate **6** with a series of alicyclic secondary amines in MeCN. The plot of pseudo-first-order rate constant (k_{obsd}) vs. [amine] curves upward, which is typical for reactions reported previously to proceed through a stepwise mechanism with two intermediates (*i.e.*, a zwitterionic tetrahedral intermediate T^{\pm} and its deprotonated form T^{-}). Dissection of k_{obsd} into the second- and third-order rate constants (*i.e.*, Kk_2 and Kk_3 , respectively) reveals that Kk_3 is significantly larger than Kk_2 , indicating that the reactions proceed mainly through the deprotonation pathway (*i.e.*, the k_3 process) in a high [amine] region. This contrasts to the recent report that the corresponding aminolysis of benzyl 2-pyridyl carbonate **5** proceeds through a forced concerted mechanism. An intramolecular H-bonding interaction was suggested to force the reactions of **5** to proceed through a concerted mechanism, since it could accelerate the rate of leaving-group expulsion (*i.e.*, an increase in k_2). However, such H-bonding interaction, which could increase k_2 , is structurally impossible for the reactions of **6**. Thus, presence or absence of an intramolecular H-bonding interaction has been suggested to be responsible for the contrasting reaction mechanisms (*i.e.*, a forced concerted mechanism for the reaction of **5** vs. a stepwise mechanism with T^{\pm} and T^{-} as intermediates for that of **6**).

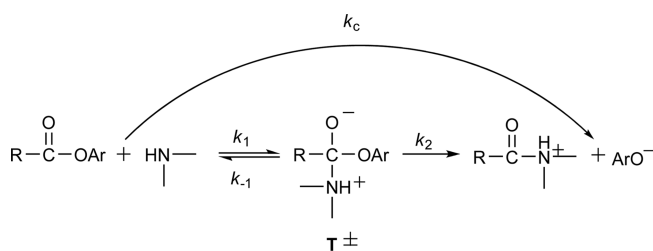
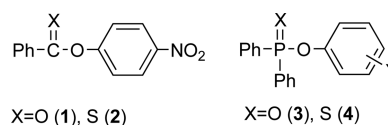
Key Words : Aminolysis, Brønsted-type plot, Nucleofuge, Reaction mechanism, Intramolecular H-bonding interaction

Introduction

Nucleophilic substitution reactions of esters with amines have intensively been studied due to their importance in biological processes as well as in synthetic applications.¹⁻¹⁰ As shown in Scheme 1, aminolysis of esters has been reported to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate T^{\pm} or through a concerted pathway depending on the reaction conditions (*e.g.*, the nature of the electrophilic centers, the basicity of the incoming amine and the leaving group, and the type of solvents).¹⁻¹⁰

Aminolysis of 4-nitrophenyl benzoate **1** in H₂O has been suggested to proceed through a stepwise mechanism with T^{\pm} as an intermediate, in which expulsion of the leaving group occurs in the rate-determining step (RDS) on the basis of a

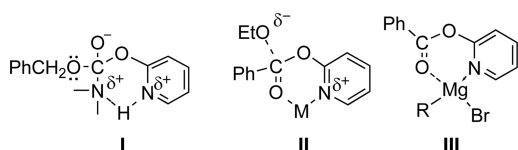
linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.81$.⁶ In contrast, the corresponding reactions in MeCN has been concluded to proceed through a concerted mechanism due to instability of T^{\pm} in the aprotic solvent,⁷ indicating that the nature of solvents is an important factor to determine reaction mechanisms. On the other hand, we have shown that the reactions of *O*-4-nitrophenyl thionobenzoate **2** with amines proceed through two intermediates (*i.e.*, T^{\pm} and its deprotonated form T^{-}) in H₂O as well as in MeCN,⁸ while aminolyses of aryl diphenylphosphinates (**3**) and diphenylphosphinothioates (**4**) have been concluded to proceed through a concerted mechanism,⁹ implying that the nature of the electrophilic center also determines the reaction mechanism.



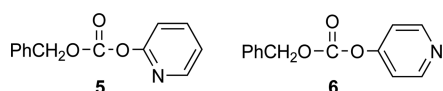
Scheme 1

We have recently reported that reactions of benzyl 2-pyridyl carbonate **5** with a series of alicyclic secondary amines proceed through a concerted mechanism in MeCN, although the reactions were predicted to proceed through a stepwise manner with a stabilized intermediate as modeled by I.¹⁰ This is because I is similar to the stable complexes II and III which were previously proposed for the reactions of **5** with alkali metal ethoxides EtOM (M = Li, Na, K)¹¹ or with

other organometallic reagents (*e.g.*, Grignard reagents, cupric bromide or lithium dialkylcuprate).^{12,13}



One might suggest solvent effect is responsible for the concerted mechanism since the ionic species I would be highly unstable in the aprotic solvent. However, this argument (*i.e.*, solvent effect) is little persuasive, since the corresponding reactions of **5** in H₂O were reported to proceed also through a concerted mechanism.¹⁴ Thus, we have concluded that an enhanced leaving-group ability through the H-bonding interaction shown in I forces the reactions to proceed through a concerted mechanism.¹⁰



We have now extended our study to the reactions of benzyl 4-pyridyl carbonate **6** with a series of alicyclic secondary amines in MeCN to examine the preceding argument that the H-bonding interaction in I forces the reactions of **5** to proceed through a concerted mechanism since such H-bonding interaction is not possible for the reaction of **6**. We wish to report that the effect of changing the leaving group from 2-pyridyloxide to 4-pyridyloxide (*i.e.*, **5** → **6**) on reactivity and reaction mechanism is indeed significant.

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions with the concentration of amines in excess over the substrate concentration. All the reactions obeyed first-order kinetics over 90% of the total reaction. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_{\infty} - A_t) = -k_{\text{obsd}}t + C$. It is estimated from replicate runs that the uncertainty in the rate constants is less than $\pm 3\%$. The k_{obsd} values with the reaction conditions are summarized in Tables S1-S5 in the Supporting Information.

As shown in Figure 1, the plot of k_{obsd} vs. [amine] for the

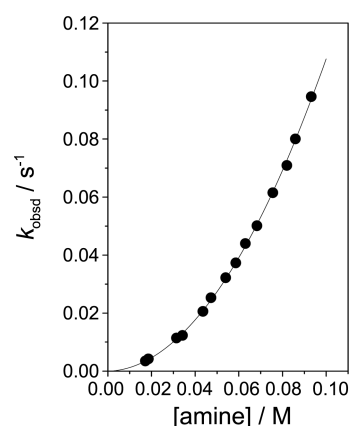


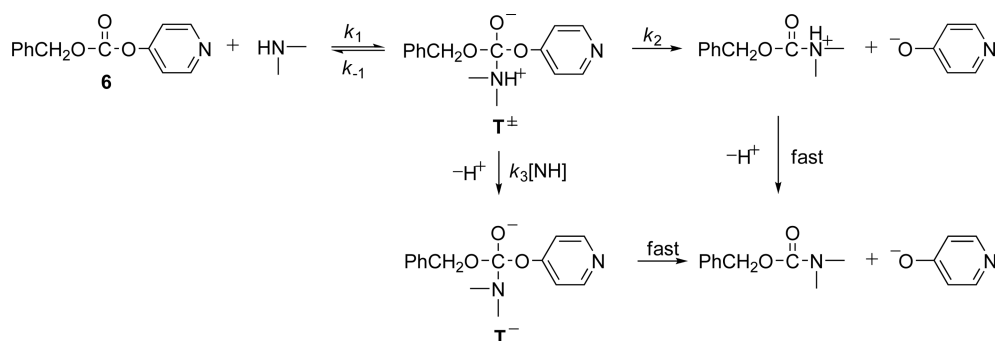
Figure 1. Plot of k_{obsd} vs. [amine] for the reaction of benzyl 4-pyridyl carbonate **6** with piperidine in MeCN at 25.0 ± 0.1 °C.

reactions of **6** with piperidine in MeCN curves upward as a function of increasing amine concentration. Similarly curved plots are obtained for the reactions with the other amines employed in this study (see Figures S1a-S4a in the supporting Information).

Effect of Modification of Nucleofuge on Reaction Mechanism. The upward curvature shown in Figure 1 is typical for aminolysis of esters reported previously to proceed through T^{\pm} and T^{-} as intermediates.^{1-5,8} Accordingly, one can suggest that the current aminolysis of **6** proceeds through a stepwise mechanism as shown in Scheme 2, in which a second amine molecule deprotonates from T^{\pm} as a general base catalyst.

Aminolysis of esters possessing a C=S bond as an electrophilic center (*e.g.*, **2** and its derivatives) has often been reported to proceed through a stepwise mechanism with T^{\pm} and T^{-} as intermediates.^{8,15,16} In contrast, aminolysis of esters with a C=O bond as an electrophilic center (*e.g.*, **1** and **5**) has generally been reported to proceed without the deprotonation process.¹⁻⁷ In fact, the aminolysis of **5** has been concluded to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.57$.¹⁰ Thus, the finding that aminolysis of **6** proceeds through a stepwise mechanism with two intermediates even in the aprotic solvent is quite interesting, although it possesses a C=O bond as an electrophilic center.

Dissection of k_{obsd} into Kk_2 and Kk_3 . To support the



Scheme 2

above argument that the aminolysis of **6** proceeds through the two intermediates T^\pm and T^- as shown in Scheme 2, the k_{obsd} values have been dissected into the second-order rate constants (Kk_2) and the third-order rate constants (Kk_3). One can express the pseudo-first-order rate constant (k_{obsd}) for the reactions of **6** as Eq. (1) on the basis of the kinetic results and the mechanism proposed in Scheme 2. Equation (1) can be simplified as Eq. (2) under the assumption, $k_{-1} \gg k_2 + k_3[\text{amine}]$. Thus, one might expect that the plot of $k_{\text{obsd}}/[\text{amine}]$ vs. $[\text{amine}]$ is linear if the above assumption is valid.

$$k_{\text{obsd}} = (k_1 k_2 [\text{amine}] + k_1 k_3 [\text{amine}]^2) / (k_{-1} + k_2 + k_3 [\text{amine}]) \quad (1)$$

$$k_{\text{obsd}}/[\text{amine}] = Kk_2 + Kk_3[\text{amine}], \text{ where } K = k_1/k_{-1} \quad (2)$$

In fact, as shown in Figure 2, the plot of $k_{\text{obsd}}/[\text{amine}]$ vs. $[\text{amine}]$ is linear for the reaction with piperidine up to ca. 0.1 M. The corresponding plots for the reactions with the other amines are also linear (see Figures S1b-S4b in the Supporting Information), indicating that the current reactions proceed through T^\pm and T^- as shown in Scheme 2 and the assumption (*i.e.*, $k_{-1} \gg k_2 + k_3[\text{amine}]$) is valid. Accordingly, the Kk_2 and Kk_3 values were calculated from the intercept and the slope of the linear plots of $k_{\text{obsd}}/[\text{amine}]$ vs. $[\text{amine}]$, respectively and are summarized in Table 1 together with the second-order rate constants k_N reported recently for the corresponding reactions of **5** for comparison.¹⁰

As shown in Table 1, the Kk_3 value for a given amine is much larger than the corresponding Kk_2 value (*e.g.*, for reaction of **6** with piperidine, $Kk_2 = 0.00230 \text{ M}^{-1}\text{s}^{-1}$ and $Kk_3 = 1.05 \text{ M}^{-2}\text{s}^{-1}$). It is evident that the contribution of the $Kk_3[\text{amine}]^2$ term to the k_{obsd} value becomes more significant as the concentration of the incoming amine increases. This explains the reason why the plot of k_{obsd} vs. $[\text{amine}]$ curves significantly upward. Accordingly, one can suggest that the reactions of **6** with all the amines employed in this study proceed mainly through the k_3 process in a high amine concentration region.

Table 1 also shows that Kk_2 and Kk_3 increase as the basicity of amines increases. The effect of amine basicity on Kk_2 and Kk_3 is illustrated in Figures 1(a) and (b). The Brønsted-type plots exhibit excellent linear correlations when Kk_2 , Kk_3 and $\text{p}K_a$ were corrected statistically with p and q (*i.e.*, $p = 2$, while $q = 1$ except $q = 2$ for the Kk_2 of piperazine and $q = 4$ for the Kk_3 of piperazine).¹⁸ The slopes of the linear Brønsted-type plots (*i.e.*, β_{nuc}) are 0.66 and 0.82

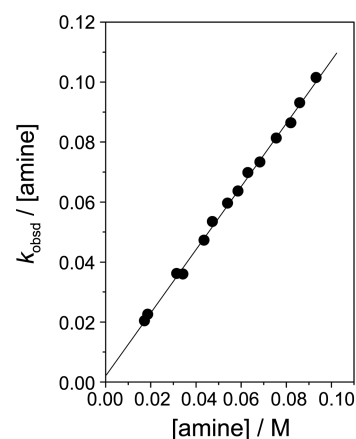


Figure 2. Plot of $k_{\text{obsd}}/[\text{amine}]$ vs. $[\text{amine}]$ for the reaction of benzyl 4-pyridyl carbonate **6** with piperidine in MeCN at 25.0 ± 0.1 °C.

for Kk_2 and Kk_3 , respectively, indicating that Kk_2 is less sensitive to the amine basicity than Kk_3 in the current reaction system. The β_{nuc} value of 0.82 is typical for reactions reported previously to proceed through a stepwise mechanism (*e.g.*, $\beta_{\text{nuc}} = 0.8 \pm 0.1$). However, the β_{nuc} value of 0.66 is slightly smaller than the lower limit of β_{nuc} value for aminolysis of esters reported to proceed through a stepwise mechanism with breakdown of T^\pm being the RDS.

Factors Governing Presence/Absence of Deprotonation Process. Castro *et al.* have reported that reactions of thiono esters (*e.g.*, *O*-phenyl thionoacetate and *O*-aryl *O*-4-nitrophenyl thionocarbonates) with weakly basic amines (*e.g.*, piperazinium ion and *N*-formylpiperazine) proceed through T^\pm and T^- in aqueous solution, while the corresponding reactions with strongly basic amines (*e.g.*, piperidine and piperazine) proceed without the deprotonation process from T^\pm .¹⁵ Thus, basicity of the attacking amine has been proposed to be a crucial factor that selects the mechanistic pathway.¹⁵ On the other hand, Lee *et al.* have reported that reactions of aryl dithiobenzoates with a series of aniline and benzylamine derivatives proceed only through T^\pm in MeCN.¹⁶ They have reported that the deprotonation process from T^\pm , which has often been observed for the reactions performed in H_2O , is absent in the aprotic solvent even for reactions with weakly basic anilines.¹⁶ Accordingly, the nature of the medium has been suggested to be also an important determinant of the presence/absence of the deprotonation process

Table 1. Summary of rate constants for nucleophilic substitution reactions of benzyl 2-pyridyl carbonate **5** and benzyl 4-pyridyl carbonate **6** with alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C^a

Amines	$\text{p}K_a$	5		6	
		$k_N/\text{M}^{-1}\text{s}^{-1}$	$10^3 Kk_2/\text{M}^{-1}\text{s}^{-1}$	$10^3 Kk_2/\text{M}^{-1}\text{s}^{-1}$	$Kk_3/\text{M}^{-2}\text{s}^{-1}$
1	piperidine	18.8	15.2	2.30	1.05
2	3-methylpiperidine	18.6	13.4	2.39	0.848
3	piperazine	18.5	14.2	2.30	1.48
4	1-(2-hydroxyethyl)piperazine	17.6	2.99	0.420	0.145
5	morpholine	16.6	0.940	0.0937	0.0171

^aThe $\text{p}K_a$ data were taken from ref. 17. ^bThe kinetic data for reactions of **5** were taken from ref. 10.

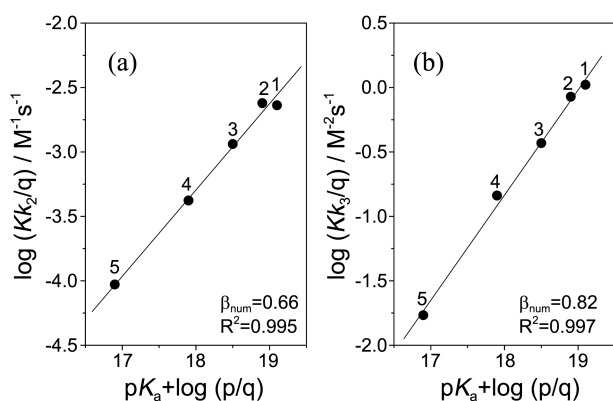


Figure 3. Brønsted-type plots for the reactions of benzyl 4-pyridyl carbonate **6** with alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C: $\log Kk_2$ vs. pK_a of amine (a) and $\log Kk_3$ vs. pK_a of amine (b). The identity of the points is given in Table 1.

(i.e., $T^\pm \rightarrow T^-$).¹⁶

However, we have shown that the reaction of *O*-4-nitrophenyl thionobenzoate **2** with secondary amines (either cyclic or acyclic) proceeds through T^\pm and T^- in MeCN as well as in H_2O , indicating that the nature of solvents is not an important factor to determine the reaction mechanism.⁸ We have also shown that reactions of *O*-Y-substituted phenyl thionobenzoates (**2** and its derivatives) with primary amines proceed through a stepwise mechanism with one or two intermediates depending on the basicity of the incoming amine and the nucleofuge (i.e., the reaction proceeds through T^\pm when the leaving Y-substituted phenoxide is less basic than the incoming amine but through T^\pm and T^- when the leaving group is more basic than the incoming amine).⁸

One can find from the aminolyses mentioned above that the reactions with weakly basic amines or aminolyses of substrates possessing a strongly basic nucleofuge proceed through T^\pm and T^- . It is apparent that reactions with weakly basic amines would increase k_{-1} , while those of substrates possessing a strongly basic leaving group would decrease k_2 . Accordingly, one might suggest that reactions proceeding through T^\pm and T^- would result in a small k_2/k_{-1} ratio by decreasing k_2 and/or by increasing k_{-1} .

Aminolysis of **5** in MeCN was expected to proceed through an intermediate as modeled by I, since it can be stabilized through an intramolecular H-bonding interaction.¹⁰ However, the reactions of **5** have been concluded to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.57$.¹⁰ We have suggested that the intramolecular H-bonding interaction accelerates the rate of leaving-group expulsion (i.e., an increase in k_2), which forces the reactions to proceed through a concerted mechanism.¹⁰ It is evident that the intramolecular H-bonding interaction shown in model I for the reactions of **5** is not possible for the reactions of **6**. Accordingly, one might expect that the k_2 (or the k_2/k_{-1} ratio) would be much smaller for the reactions of **6** than for those of **5**. This idea is consistent with the fact that the k_N for the reactions of **5** is much larger than the Kk_2 for those of **6**, although 4-pyridyloxide in **6** is *ca.* 0.4 pK_a units

less basic and a better nucleofuge than 2-pyridyloxide in **5**.¹⁹

Conclusions

The current study has allowed us to conclude the following: (1) The plots of k_{obsd} vs. [amine] curve upward, indicating that the reactions of **6** proceed through two intermediates T^\pm and T^- . (2) Dissection of k_{obsd} into Kk_2 and Kk_3 reveals that Kk_3 is significantly larger than Kk_2 , implying that the reactions proceed mainly through the k_3 process in a high [amine] region. (3) It is common that the reactions reported previously to proceed through T^\pm and T^- show a small k_2/k_{-1} ratio by decreasing k_2 and/or by increasing k_{-1} . (4) Although 4-pyridyloxide in **6** is a weaker base and a better nucleofuge than 2-pyridyloxide in **5**, the Kk_2 for the reactions of **6** is much smaller than the k_N for the corresponding reactions of **5**. This is because the intramolecular H-bonding interaction, which was suggested to increase the k_2 for the reactions of **5**, is absent for the reactions of **6**. (5) Aminolysis of **6** would result in a small k_2 (or a small k_2/k_{-1} ratio), which causes the reaction to proceed through T^\pm and T^- .

Experimental Section

Materials. Substrate **6** was synthesized from the reaction of 4-hydroxypyridine with benzyl chloroformate in methylene chloride, which was generated from the reaction of phosgene and benzyl alcohol as reported previously.²⁰ The crude products were purified by recrystallization and their purity was checked by their melting points and 1H and ^{13}C NMR spectra. Amines and other chemicals were of the highest quality available. MeCN was distilled over P_2O_5 and stored under nitrogen.

Kinetics. Kinetic study was performed using a UV-vis spectrophotometer equipped with a constant-temperature circulating bath. All the reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than the substrate concentration. 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. The reactions were followed by monitoring the appearance of the leaving 4-pyridyloxide at 275 nm. Reactions were followed generally for 9-10 half-lives and k_{obsd} were calculated using the equation, $\ln(A_\infty - A_t)$ vs. t .

Product Analysis. 4-Pyridyloxide was liberated quantitatively and identified as one of the reaction products by comparison of the UV-Vis spectra after completion of the reactions with those of the authentic samples under the reaction conditions.

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0075488). A. R.

Bae is also grateful for the BK 21 Scholarship.

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