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

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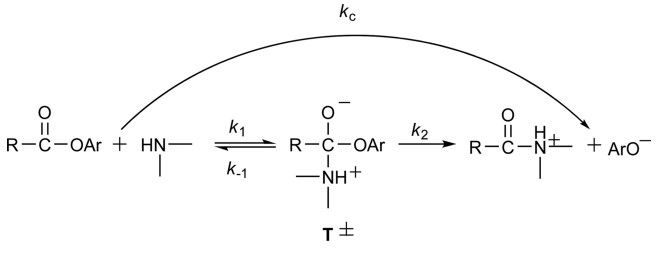
A kinetic study is reported for nucleophilic substitution reactions of benzyl 4-pyridyl carbonate **6** with a series of alicyclic secondary amines in MeCN. The plot of pseudo-first-order rate constant (k_{obsd}) *vs*. [amine] curves upward, which is typical for reactions reported previously to proceed 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

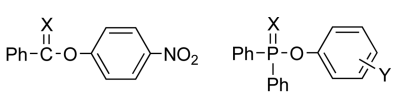
Introduction

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 H_2O 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 $\beta_{nuc} = 0.81$.[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 H_2O 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.



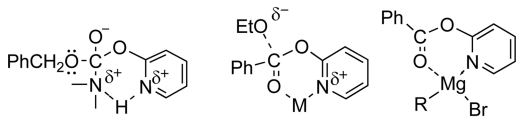
Scheme 1



X=O (**1**), S (**2**) X=O (**3**), S (**4**)

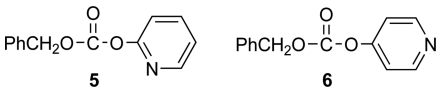
We have recently reported that reactions of benzyl 2-pyridyl carbonate **5** with a series of alicyclic secondary amines proceed through a concerted mechanism in MeCN, although the reactions were predicted to proceed through a stepwise manner with a stabilized intermediate as modeled by I.[10] This is 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]



I II III

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 H_2O 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]



5 **6**

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 $\ln (A_\infty - A_t) = -k_{obsd}t + C$. It is estimated from replicate runs that the uncertainty in the rate constants is less than ± 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 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).

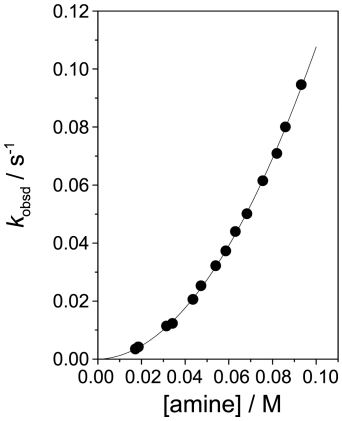
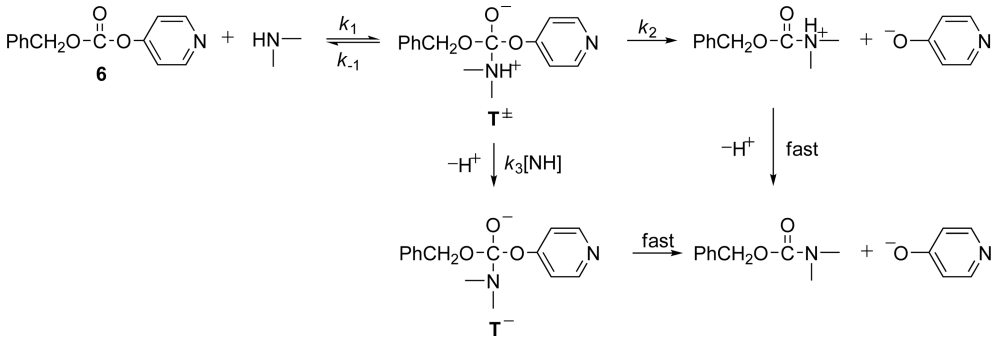


Figure 1. Plot of k_{obsd} *vs.* [amine] for the reaction of benzyl 4-pyridyl carbonate **6** with piperidine in MeCN at 25.0 ± 0.1 °C.

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 $\beta_{nuc} = 0.57$.[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, $k_{-1} >> k_2 + k_3$[amine]. Thus, one might expect that the plot of k_{obsd}/[amine] *vs*. [amine] is linear if the above assumption is valid.

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

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

In fact, as shown in Figure 2, the plot of k_{obsd}/[amine] *vs*. [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.*, $k_{-1} >> k_2 + k_3$[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_{obsd}/[amine] *vs*. [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, $Kk_2 = 0.00230$ $M^{-1}s^{-1}$ and $Kk_3 = 1.05$ $M^{-2}s^{-1}$). It is evident that the contribution of the Kk_3[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*. [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 pK_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

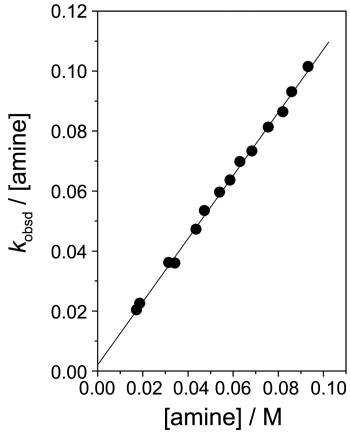


Figure 2. Plot of k_{obsd}/[amine] *vs*. [amine] for the reaction of benzyl 4-pyridyl carbonate **6** with piperidine in MeCN at 25.0 ± 0.1 °C.

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.*, $\beta_{nuc} = 0.8 \pm 0.1$). 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	pK_a	**5**	**6**	
			$k_N/M^{-1}s^{-1}$	$10^3Kk_2/M^{-1}s^{-1}$	$Kk_3/M^{-2}s^{-1}$
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

[a]The pK_a data were taken from ref. 17. [b]The kinetic data for reactions of **5** were taken from ref. 10.

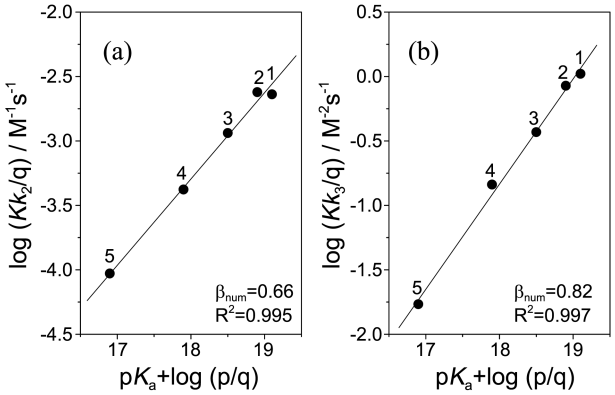


Figure 3. Brønsted-type plots for the reactions of benzyl 4-pyridyl carbonate **6** with alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C: log Kk_2 *vs*. pK_a of amine (a) and log Kk_3 *vs*. pK_a of amine (b). The identity of the points is given in Table 1.

(*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 $\beta_{nuc} = 0.57$.[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 intramolecula 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 ^{1}H 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.

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