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A Kinetic Study on Aminolysis of *t*-Butyl 4-Pyridyl Carbonate and Related Compounds: Effect of Leaving and Nonleaving Groups on Reaction Mechanism

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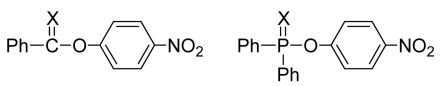
Second-order rate constants k_N have been measured spectrophotometrically for nucleophilic substitution reactions of *t*-butyl 4-pyridyl carbonate **8** with a series of alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C. The Brønsted-type plot for the reactions of **8** is linear with $\beta_{nuc} = 0.84$. The β_{nuc} value obtained for the reactions of **8** is much larger than that reported for the corresponding reactions of *t*-butyl 2-pyridyl carbonate **6** (*i.e.*, $\beta_{nuc} = 0.44$), which was proposed to proceed through a forced concerted mechanism. Thus, the aminolysis of **8** has been concluded to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$, in which expulsion of the leaving-group from $T^{\pm}$ occurs at the rate-determining step (RDS). In contrast, aminolysis of benzyl 4-pyridyl carbonate **7** has been reported to proceed through two intermediates, $T^{\pm}$ and its deprotonated form T^{-} on the basis of the fact that the plots of pseudo-first-order rate constant k_{obsd} *vs*. amine concentration curve upward. The current study has demonstrated convincingly that the nature of the leaving and nonleaving groups governs the reaction mechanism. The contrasting reaction mechanisms have been rationalized in terms of an intramolecular H-bonding interaction, steric acceleration, and steric inhibition.

Key Words : Aminolysis, Mechanism, H-bonding interaction, Steric acceleration, Steric inhibition

Introduction

Nucleophilic substitution reactions of esters have intensively been investigated due to their importance in biological processes as well as synthetic applications.[1-15] Reactions of esters with amines have been reported to proceed through a concerted mechanism or through a stepwise pathway with one or two intermediates depending on reaction conditions (*e.g.*, reaction medium, the nature of electrophilic center, and the type and basicity of amines).[1-3,9-15] The reaction of 4-nitrophenyl benzoate **1** with a series of alicyclic secondary amines in H_2O has been reported to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$, in which expulsion of the leaving group from $T^{\pm}$ occurs at the rate-determining step (RDS), on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.81$.[12c] In contrast, the corresponding reaction in MeCN has been suggested to proceed through a concerted mechanism, since the ionic intermediate $T^{\pm}$ would be highly unstable in the aprotic solvent.[12d]

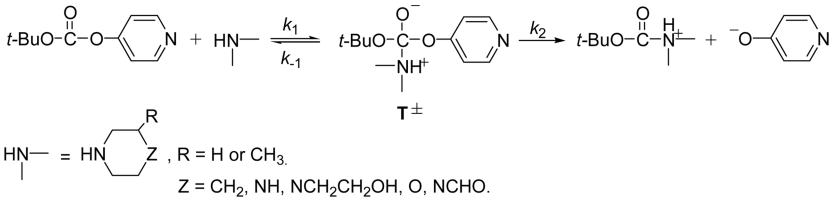


X= O (**1**), S (**2**) X= O (**3**), S (**4**)

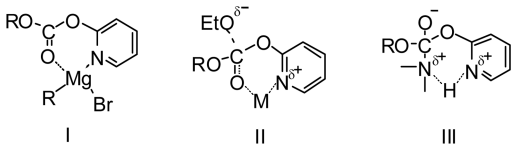
On the other hand, we have shown that aminolysis of *O*-4-nitrophenyl thionobenzoate **2** proceeds through two intermediates (*i.e.*, $T^{\pm}$ and its deprotonated form T^{-}).[13a] However, the corresponding reactions of 4-nitrophenyl diphenylphosphinate **3** and diphenylphosphinothioate **4** have been reported to proceed through a concerted mechanism with no intermediate,[14a,b] indicating that the nature of the electrophilic center (*e.g.*, C=O, C=S, P=O, P=S) is also an important factor to determine the reaction mechanism. We have also shown that the nature of amines governs the reaction mechanism for the reaction of **2** with primary amines, *i.e.*, the reaction with weakly basic amines proceeds through $T^{\pm}$ and T^{-} but the deprotonation process from $T^{\pm}$ to yield T^{-} is absent for the reaction with strongly basic amines.[13c]

R= $PhCH_2$ (**5**), *t*-Bu (**6**) R= $PhCH_2$ (**7**), *t*-Bu (**8**)

We have recently performed aminolyses of benzyl 2-pyridyl carbonate **5** and *t*-butyl 2-pyridyl carbonate **6** to investigate the reaction mechanism.[15] It has been reported that esters possessing a 2-pyridyl moiety (*e.g.*, **5** and **6**) are an excellent acylating agent in reactions with Grignard reagents as well as in reactions with cupric bromide or lithium dialkylcuprate.[16,17] The reactions have been suggested to proceed through a 6-membered cyclic complex (*e.g.*, I), in which Mg^{2+} ion acts as a strong Lewis acid catalyst.[16,17] We have also shown that alkali metal ions catalyze the reaction of **5** with alkali metal ethoxides EtOM (M = Li, Na, K) through a transition state similar to II.[18] Thus, it was expected that aminolysis of **5** and **6** would proceed through a stepwise mechanism with an intermediate as modeled by III, which is structurally similar to I or II. However, we have reported that the intramolecular H-bonding interaction shown in III forces the reactions of **5** and **6** to proceed through a concerted mechanism by accelerating the rate of the leaving-group expulsion from $T^{\pm}$.[15]



Scheme 1



To examine the above idea, we have performed aminolysis of benzyl 4-pyridyl carbonate **7** in H_2O, which was expected to proceed through a different mechanism since a six-membered cyclic H-bonding interaction is not possible for the reaction of **7**. In fact, the reaction has been concluded to proceed through two intermediates $T^{\pm}$ and T^{-} on the basis of the fact that plots of k_{obsd} *vs*. [amine] curve upward.[19]

Our study has now been extended to the reaction of *t*-butyl 4-pyridyl carbonate **8** with a series of alicyclic secondary amines in H_2O to get more information on the reaction mechanism. Our kinetic results suggest that the aminolysis of **8** proceeds through a stepwise mechanism with $T^{\pm}$ as an intermediate (Scheme 1). We wish to account for the contrasting reaction mechanisms for the aminolyses of **6**, **7**, and **8** in terms of an intramolecular H-bonding interaction, steric acceleration, and steric inhibition.

Results and Discussion

The reactions were followed spectrophotometrically by monitoring the disappearance of substrate **8** at 275 nm under pseudo-first-order conditions (*e.g.*, the concentration of amines was kept in excess over that of **8**). All reactions 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 a large positive intercept as shown in Figure 1, indicating that (1) general base catalysis by a second amine molecule is absent, and (2) the contribution of H_2O and/or OH^- from hydrolysis of amines to k_{obsd} is significant (*e.g.*, $k_o = 1.6 \times 10^3\ s^{-1}$).

Accordingly, k_{obsd} can be expressed as Eq. (1), in which [NH], k_N and k_o represent the concentration of amine, the second-order rate constant and the contribution of H_2O and/or OH^- from hydrolysis of amines to k_{obsd}, respectively. The k_N values for the reactions of **8** with amines were calculated from the slope of linear plots of k_{obsd} *vs*. [NH], and are summarized in Table 1. From replicate runs, the uncertainty in the k_N values is estimated to be less than ± 3%.

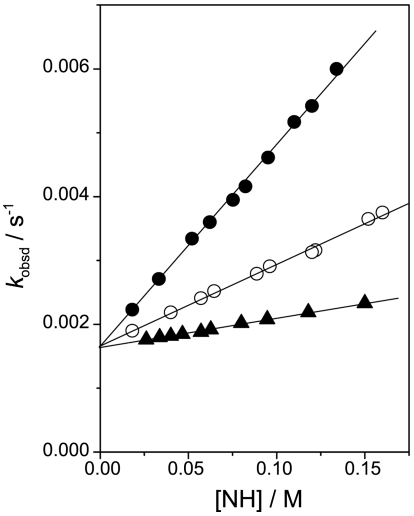


Figure 1. Plots of k_{obsd} *vs*. [NH] for the reactions of *t*-butyl 4-pyridyl carbonate **8** with 1-(2-hydroxyethyl)piperazine (●), morpholine (○) and *N*-formylpiperazine (▲) in H_2O at 25.0 ± 0.1 °C.

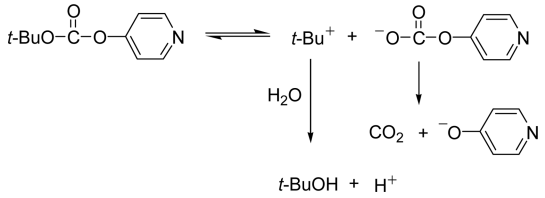
$$k_{obsd} = k_N[NH] + k_o \quad (1)$$

Reaction Mechanism. Since *t*-butyl cation is stable in H_2O, one might suggest that the reaction of **8** would proceed through an S_N1 mechanism (Scheme 2) as well as through an ordinary nucleophilic substituion at the C=O center. Thus, one might attribute the large positive intercept shown in Figure 1 to the nature of the reaction mechanism (*i.e.*, S_N1). This idea can be further supported by the fact that the intercept is almost the same for the reactions with the three different amines.

To examine the above argument, the reaction of **8** with

Table 1. Summary of kinetic data for the reactions of *t*-butyl 4-pyridyl carbonate **8** with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C

	Amines	pK_a	[NH]/mM	$10^3\ k_{obsd}/s^{-1}$	$10^2\ k_N\ /M^{-1}s^{-1}$
1	*N*-formylpiperazine	7.98	26.1 ~ 150	1.76 ~ 2.33	0.467
2	morpholine	8.36	18.2 ~ 160	1.90 ~ 3.75	1.28
3	1-(2-hydroxyethyl)piperazine	9.38	18.2 ~ 134	2.23 ~ 6.00	3.19
4	piperazine	9.82	18.4 ~ 134	4.53 ~ 24.5	17.3
5	3-methylpiperidine	11.07	3.13 ~ 20.0	9.17 ~ 42.8	202
6	piperidine	11.22	3.19 ~ 22.7	10.7 ~ 57.6	242



Scheme 2

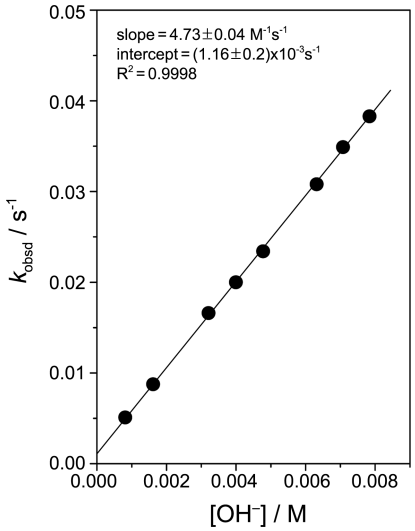


Figure 2. Plot of k_{obsd} *vs*. [OH^-] for the reaction of *t*-butyl 4-pyridyl carbonate **8** with OH^- in H_2O at 25.0 ± 0.1 °C.

OH^- has been performed. If the reaction proceeds through an S_N1 mechanism as shown in Scheme 2, formation of *t*-butyl cation is the RDS. Then, one might expect that k_{obsd} would be independent of the hydroxide concentration if the reaction proceeds through an S_N1 mechanism. As shown in Figure 2, the k_{obsd} value for the reaction of **8** with OH^- increases linearly as [OH^-] increases, indicating that the reaction does not proceed through an S_N1 mechanism. Thus, one can suggest that the slope and intercept of Figure 1 represent the second-order rate constant (k_N) and the contribution of H_2O and/or OH^- to the k_{obsd} value (k_o), respectively.

Table 1 shows that the k_N value for aminolysis of **8** increases with increasing the amine basicity, *e.g.*, it increases from 4.67×10^{-3} $M^{-1}s^{-1}$ to 3.19×10^{-2} and 2.42 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the amine increases from 7.98 to 9.38 and 11.22, in turn. The effect of the amine basicity on k_N is illustrated in Figure 3. The Brønsted-type plot for the reaction of **8** exhibits a linear correlation with β_{nuc} = 0.84, when k_N and pK_a are corrected statistically by *p* and *q* (*i.e.*, *p* = 2 while *q* = 1 except *q* = 2 for piperazine).[20] Such a linear Brønsted-type plot with β_{nuc} = 0.8 ± 0.1 is typical for reactions reported previously to proceed through a stepwise mechanism with expulsion of the leaving group being the RDS,[1-3,21] *e.g.*, reactions of *S*-phenyl 4-nitrophenyl thiocarbonate with secondary alicyclic amines (β_{nuc} = 0.85),[21a] reactions of 4-methylphenyl 4-nitrophenyl carbonate with anilines (β_{nuc} = 0.85),[21b] reactions of *S*-2,4-dinitrophenyl 4-nitrothiobenzoate with pyridines (β_{nuc} = 0.95).[21c] Thus, one

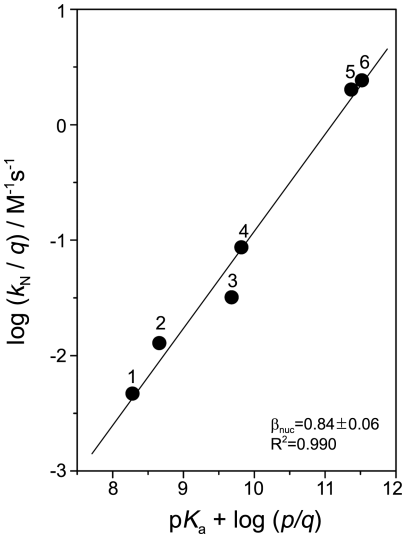
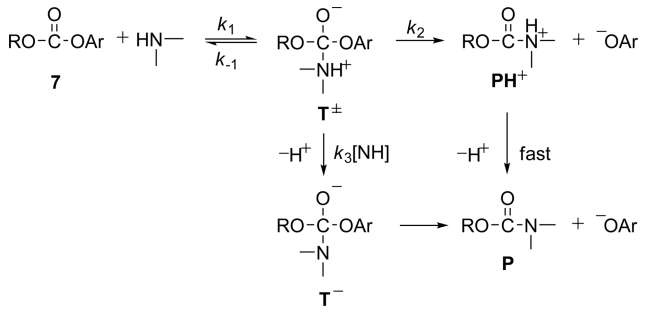


Figure 3. Brønsted-type plot for the reaction of *t*-butyl 4-pyridyl carbonate **8** with a series of alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

can suggest that the aminolysis of **8** proceeds through a stepwise mechanism as shown in Scheme 1, in which the expulsion of the leaving group occurs at the RDS.

Effect of Leaving and Nonleaving Groups on Reaction Mechanism. The aminolysis of **8** in this study has been concluded to proceed through a stepwise mechanism with $T^{\pm}$ as an intermediate on the basis of a linear Brøneted-type plot with β_{nuc} = 0.84. In contrast, the corresponding reaction of **6** has been concluded to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with β_{nuc} = 0.5 ± 0.1.[15] The H-bonding interaction in III, which was proposed as an intermediate for the reaction of **6**, has been reported to force the reactions to proceed through a concerted mechanism, since such an intramolecular H-bonding interaction would accelerate the rate of leaving-group expulsion (*i.e.*, an increase in the nucleofugality of 2-pyridyloxide).[15] However, it is apparent that such an intramolecular H-bonding interaction is structurally impossible for the reaction of **8**. This accounts for the contrasting reaction mechanisms for the aminolyses of **6** and **8**.

The reaction of benzyl 4-pyridyl carbonate **7** with a series of alicyclic secondary amines has been reported to proceed through two intermediates $T^{\pm}$ and T^- as shown in Scheme 3, since the plots of k_{obsd} *vs*. [amine] curve upward.[19] In con-



Scheme 3

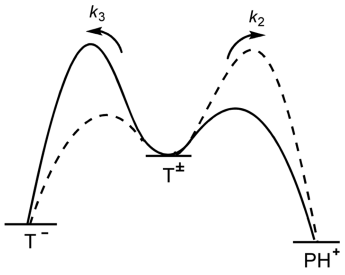


Figure 4. Qualitative energy profile for the process from $T^{\pm}$ to T^- and PH^+.

trast, the corresponding plots for the aminolysis of **8** are linear as shown in Figure 1, indicating that the deprotonation process from $T^{\pm}$ to yield T^- is absent upon changing the R in the nonleaving group from $PhCH_2$ to *t*-Bu (*i.e.*, **7** → **8**).

To account for the presence/absence of the deprotonation process, a qualitative energy profile is illustrated in Figure 4. The reaction would proceed through the deprotonation process (*i.e.*, the k_3 path through the dotted line) when the energy barrier to form T^- from $T^{\pm}$ is lower than that to form PH^+. On the contrary, the reaction would proceed through the k_2 step through the solid line when the energy barrier to form PH^+ from $T^{\pm}$ is lower than that to form T^-.

It is apparent that the energy barrier to form PH^+ from $T^{\pm}$ (*i.e.*, the k_2 step) is mainly dependent on the basicity of the leaving group. Since 4-pyridyloxide is a common leaving group for the reactions of **7** and **8**, the energy barrier for the k_2 step would not be affected by the leaving group. Accordingly, one might suggest that the nature of the R in the nonleaving groups of **7** and **8** (*i.e.*, $PhCH_2$ in **7** and *t*-Bu in **8**) affects the energy barrier for the k_2 and k_3 processes. The difference in the electronic effects of $PhCH_2$ and *t*-Bu would be negligible since $\sigma_I = 0.03$ and -0.03 for $PhCH_2$ and *t*-Bu, respectively while $\sigma_R = -0.12$ for both of them.[22] Thus, one can suggest that the electronic effects of the nonleaving groups of substrates **7** and **8** are not responsible for the contrasting reaction mechanisms.

It is well known that *t*-Bu exerts significantly stronger steric effect than $PhCH_2$ since $E_s = -0.38$ and -1.54 for $PhCH_2$ and *t*-Bu, respectively.[21] Thus, one might suggest that the strong steric effects exerted by the bulky *t*-Bu are responsible for the contrasting reaction mechanisms. It is evident that the steric hindrance becomes more significant as the hybridization of the central carbon changes from sp^2 to sp^3. Thus, the steric hindrance exerted by *t*-Bu would become stronger upon formation of the tetrahedral intermediate $T^{\pm}$, but would become weaker upon breakdown of $T^{\pm}$ to yield PH^+. Consequently, the bulky *t*-Bu would favor to expel the leaving group from $T^{\pm}$ to decrease the steric hindrance (*i.e.*, an increase in k_2). On the contrary, the *t*-Bu in $T^{\pm}$ would prevent the approach of the second amine molecule which deprotonates from $T^{\pm}$ (*i.e.*, a decrease in k_3). Thus, one might suggest that modification of the R in the nonleaving group from $PhCH_2$ to *t*-Bu causes a change in the reaction mechanism by lowering the energy barrier for the k_2 step (*i.e.*, steric acceleration) and/or by raising the energy barrier for the k_3 process (*i.e.*, steric inhibition).

Conclusions

The current study has allowed us to conclude the following: (1) Aminolysis of **8** proceeds through a stepwise mechanism in which expulsion of the leaving group from $T^{\pm}$ occurs at the RDS. (2) Modification of the leaving group from 2-pyridyloxide to 4-pyridyloxide (*i.e.*, from **6** to **8**) causes a change in the reaction mechanism (*i.e.*, from a forced concerted mechanism to a stepwise pathway). Presence or absence of an intramolecular H-bonding interaction determines the reaction mechanism. (3) Replacement of $PhCH_2$ by the bulky *t*-Bu in the nonleaving group (*i.e.*, from **7** to **8**) prevents the deprotonation process from $T^{\pm}$ by raising the energy barrier for the k_3 process (*i.e.*, steric inhibition) and/or by lowering the energy barrier for the k_2 process (*i.e.*, steric acceleration).

Experimental Section

Materials. Substrate **8** was prepared by the reaction of di-*tert*-butyl dicarbonate and 4-hydroxypyridine in the presence of 0.1 equiv. of 4-(dimethylamino)pyridine in methylene chloride. The crude product was purified by recrystallization and its purity was checked by its melting point and ^1H and ^{13}C NMR spectra. Amines and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

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 H_2O and the amine nucleophile. The amine stock solution of *ca.* 0.2 M was prepared in a 25.0 mL volumetric flask by adding 2 equiv. of amine and 1 equiv. of HCl solution to make a self-buffered solution. The reactions were followed by monitoring the disappearance of *t*-butyl 4-pyridyl carbonate 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*.

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Supporting Information. ^1H and ^{13}C NMR spectra of

compound **8**.

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