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Kinetics and Reaction Mechanism of Aminolyses of Benzyl 2-Pyridyl Carbonate and *t*-Butyl 2-Pyridyl Carbonate: Effect of Nonleaving Group on Reactivity and Reaction Mechanism

Ji-Sun Kang, Jae-In Lee,† and Ik-Hwan Um*

*Department of Chemistry and Nano Science, Ewha Womans University, Seoul 120-750, Korea. *E-mail: ihum@ewha.ac.kr*
†Department of Chemistry and Plant Resources Research Institute, Duksung Women's University, Seoul 132-714, Korea
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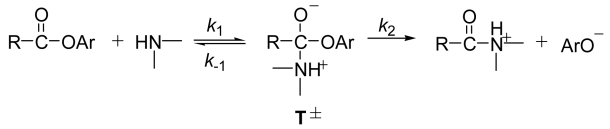
Second-order rate constants (k_N) have been measured spectrophotometrically for the reactions of benzyl 2-pyridyl carbonate **7** and *t*-butyl 2-pyridyl carbonate **8** with a series of alicyclic secondary amines in H_2O at 25.0 °C. Substrate **8** is less reactive than **7**. Steric hindrance exerted by the bulky *t*-Bu group of **8** has been suggested to be responsible for the decreased reactivity. The Brønsted-type plots for the reactions of **7** and **8** are linear with β_{nuc} = 0.49 and 0.44, respectively, which is typical for reactions reported previously to proceed through a concerted mechanism. Aminolyses of **7** and **8** were expected to proceed through a zwitterionic tetrahedral intermediate $T^{\pm}$, which would be stabilized through an intramolecular H-bonding interaction. However, the kinetic results suggest that the reactions proceed through a concerted mechanism. The H-bonding interaction in $T^{\pm}$ has been suggested to accelerate the rate of leaving-group expulsion from $T^{\pm}$. Another factor that might accelerate expulsion of the leaving group is the "push" provided by the RO group in $T^{\pm}$ through resonance interactions. Thus, it has been concluded that the enhanced nucleofugality through the H-bonding interaction and the "push" provided by the RO group forces the reactions to proceed through a concerted mechanism.

Key Words : Aminolysis, Steric hindrance, H-bonding interaction, Nonleaving group, Brønsted-type plot

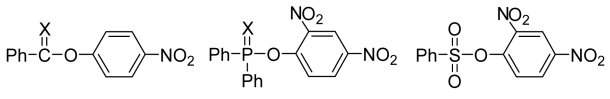
Introduction

Aminolysis of esters has been reported to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$ as shown in Scheme 1 or through a concerted pathway depending on the reaction conditions (*e.g.*, the type of solvents, the basicity of the incoming amine and the leaving group, and the nature of the electrophilic centers).[1-10] Aminolysis of 4-nitrophenyl benzoate **1** in H_2O has been reported to proceed through a stepwise mechanism, in which breakdown of $T^{\pm}$ is the rate-determining step (RDS) on the basis of a linear Brønsted-type plot with β_{nuc} = 0.81.[6] In contrast, the corresponding reaction of **1** in MeCN has been concluded to proceed through a concerted mechanism based on a linear Brønsted-type plot with β_{nuc} = 0.40.[7] Instability of $T^{\pm}$ in the aprotic solvent has been suggested to force the reaction to proceed through a concerted mechanism.[7]



Scheme 1

We have shown that aminolysis of *O*-4-nitrophenyl thionobenzoate **2** proceeds through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and its deprotonated form T^{-}) in H_2O as well as in MeCN.[8] On the other hand, aminolyses of 2,4-dinitrophenyl diphenylphosphinate **3** and 2,4-dinitrophenyl diphenylphosphinothioate **4** in H_2O have been reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with β_{nuc} = 0.45 ± 0.07,[9] while the corresponding aminolysis of 2,4-dinitrophenyl benzenesulfonate **5** has been concluded to proceed through a stepwise mechanism with a change in the RDS based on a curved Brønsted-type plot (*e.g.*, β_{nuc} changes from 0.86 to 0.38 as the amine basicity increases),[10] indicating that the nature of electrophilic center is also an important factor to determine reaction mechanism.



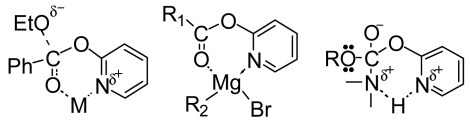
X= O (**1**), S (**2**) X= O (**3**), S (**4**) **5**

We have recently reported that aminolysis of 2-pyridyl benzoate **6** in H_2O proceeds through a stepwise mechanism based on a linear Brønsted-type plot with β_{nuc} = 0.77.[11] On the contrary, aminolyses of benzyl 2-pyridyl carbonate **7** and *t*-butyl 2-pyridyl carbonate **8** in MeCN have been concluded to proceed through a concerted mechanism since the Brønsted-type plots are linear with β_{nuc} = 0.57 and 0.45 for the reactions of **7** and **8**, respectively.[12]

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

Substrates **6-8** are known to be excellent acylating

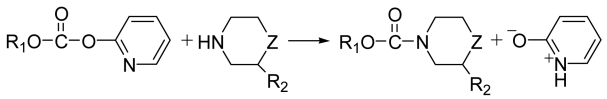
agents,[13-15] since the reactions of these compounds with alkali metal ethoxides EtOM (M = Li, Na, K)[13] or with other organometallic reagents (*e.g.*, Grignard reagents, cupric bromide or lithium dialkylcuprate)[14,15] are catalyzed remarkably through formation of a six-membered cyclic complex I or II. Accordingly, aminolyses of **7** and **8** in MeCN were expected to proceed through a stepwise mechanism with an intermediate as modeled by III, which would be highly stabilized even in the aprotic solvent through the intramolecular H-bonding interaction.



I II III

However, we have suggested that the H-bonding interaction in III accelerates expulsion of the leaving 2-pyridyloxide.[12] Another factor that would facilitate expulsion of the leaving group is the "push"[16] provided by the RO moiety of III through a resonance interaction. Accordingly, we have concluded that the enhanced nucleofugality through the H-bonding interaction and the "push" provided by the RO group forces the reaction to proceed through a concerted mechanism.

We have now extended our study to the reactions of **7** and **8** with a series of alicyclic secondary amines in H_2O (Scheme 2) to get further information on the reaction mechanism. We have also investigated the effect of changing the nonleaving group from benzoyl (**6**) to benzyloxycarbonyl (**7**) and *t*-butyloxycarbonyl (**8**) on reactivity and reaction mechanism by comparing the kinetic data obtained from the current reactions with those reported recently for the corresponding reactions of **6**.[11]



R_1 = $PhCH_2$ (**7**), *t*-Bu (**8**)

R_2 = H or Me

Z = CH_2, NH, NCH_2CH_2OH, O, NCHO, NH_2^+

Scheme 2

Results and Discussion

The rate constants were measured spectrophotometrically by monitoring the appearance of the leaving 2-pyridyloxide at 293 nm under pseudo-first-order conditions (*e.g.*, the concentration of amines was kept in excess over that of substrate **7** or **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 passing through the origin, indicating that general base catalysis by a second amine molecule is absent, and the contribution of H_2O and/or OH^- from hydrolysis of amines to the k_{obsd} value is negligible. Accordingly, the second-order rate constants (k_N) for the reactions of **7** and **8** with amines were calculated from the slope of linear plots of k_{obsd} *vs*. amine concentration, and are summarized in Table 1. From replicate runs, the uncertainty in the k_N values is estimated to be less than ± 3%.

Effect of Changing Nonleaving Group from Benzoyl (6) to Benzyloxycarbonyl (7) and *t*-Butyloxycarbonyl (8) on Reactivity. As shown in Table 1, k_N decreases as the basicity of the incoming amine decreases regardless of the nature of the nonleaving groups. However, the dependence of k_N on the basicity of amines is much less significant for the reactions of **7** and **8** than for those of **6** (*e.g.*, as the pK_a decreases from 11.22 to 7.98, k_N decreases from 3.68 to 9.06 × 10^{-3} $M^{-1}s^{-1}$, from 37.9 to 1.09 $M^{-1}s^{-1}$, and from 0.735 to 0.0279 $M^{-1}s^{-1}$, for the reactions of **6**, **7**, and **8**, in turn). It is also noted that the reactivity is dependent on the nature of the nonleaving group, *e.g.*, **7** is the most reactive regardless of the amine basicity, while **6** is more reactive than **8** toward highly basic piperidine and 3-methylpiperidine but is less reactive toward weakly basic amines (*e.g.*, p$K_a \leq 9.82$). The fact that the reactions of **6** exhibit higher sensitivity than those of **7** and **8** is responsible for the reactivity patterns together with a difference in the reaction mechanism (the reaction mechanism will be discussed in the following section).

The reactivity of substrates **7** and **8** would be affected by many factors (*e.g.*, electronic effects such as inductive and resonance effects, steric hindrance, and reaction mechanism). Although the σ_I and σ_R values of $PhCH_2O$ and *t*-BuO are not

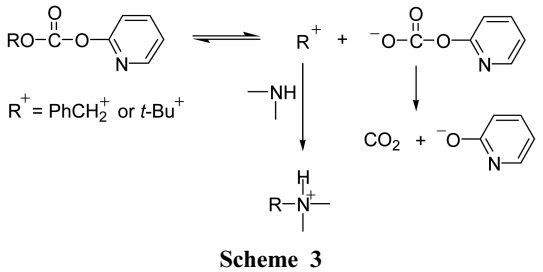
Table 1. Summary of kinetic data for the reactions of 2-pyridyl benzoate **6**, benzyl 2-pyridyl carbonate **7** and *t*-butyl 2-pyridyl carbonate **8** with alicyclic secondary amines in H_2O at 25.0 ± 0.1 °C [a]

	Amines	pK_a	**6**[b]	**7**	**8**
			$k_N/M^{-1}s^{-1}$	$k_N/M^{-1}s^{-1}$	$k_N/M^{-1}s^{-1}$
1	piperidine	11.22	3.68	37.9	0.735
2	3-methylpiperidine	11.07	2.80	44.0	0.748
3	piperazine	9.82	0.279	19.1	0.443
4	1-(2-hydroxyethyl)piperazine	9.38	0.0851	5.03	0.119
5	morpholine	8.36	0.0342	3.07	0.0828
6	*N*-formylpiperazine	7.98	0.00906	1.09	0.0279
7	piperazinium ion	5.68	–	0.110	0.00387

[a]pK_a data were taken from ref. 17. [b]The kinetic data for the reactions of **6** were taken from ref. 11.

available, one might expect that the electronic effects of these substituents would be similar to those of MeO. Thus, one might suggest that $PhCH_2O$ and *t*-BuO are inductively electron withdrawing ($\sigma_I = 0.27$ for MeO)[18] but are electron donating in a resonance manner ($\sigma_R = -0.61$ for MeO).[18] However, the difference in the electronic effects of $PhCH_2O$ and *t*-BuO groups 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 $PhCH_2$ and *t*-Bu.[18] In contrast, *t*-Bu would exert significantly stronger steric hindrance than $PhCH_2$ since $E_s = -0.38$ and –1.54 for $PhCH_2$ and *t*-Bu, respectively.[18] Thus, one might suggest that the strong steric hindrance exerted by the bulky *t*-Bu group is mainly responsible for the decreased reactivity of **8**.

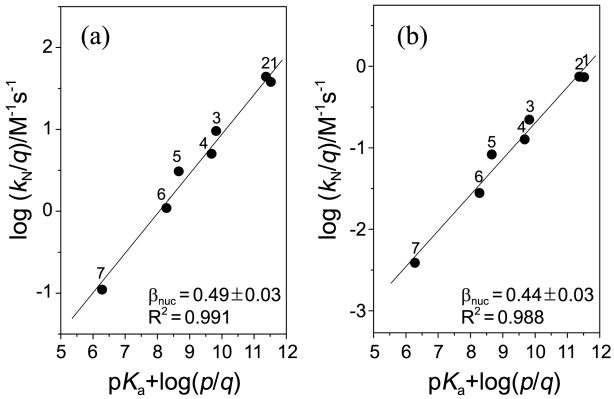
Another possibility that might account for the reactivity pattern found in the current study is the nature of the reaction mechanism. The reactions of **7** and **8** (but not **6**) with amines could proceed through an S_N1 mechanism as shown in Scheme 3, since the ionic intermediates would be stable in H_2O. If the reaction proceeds through an S_N1 mechanism, one might expect that the pseudo-first-order rate constant (k_{obsd}) would be independent of the amine concentrations. However, the k_{obsd} value has been found to increase linearly with increasing the amine concentration, indicating that the reactions do not proceed through an S_N1 mechanism. An S_N2 reaction would not occur at the phenyl ring of **6** or at the bulky *t*-Bu group of **8** but would be possible at the benzylic carbon of **7**. However, *N*-benzylpiperidine (*i.e.*, one of the S_N2 reaction products of **7** with piperidine) has not been detected in the reaction mixture, indicating that the aminolysis of **7** does not proceed through an S_N2 pathway either. Thus, one can suggest that the only reaction center is the carbon atom of the C=O bond of **7** and **8**.



Scheme 3

Reaction Mechanism. To get further information on the reaction mechanism, Brønsted-type analysis has been performed, since it is one of the most powerful tools in deducing reaction mechanisms.[1-9] A linear Brønsted-type plot with $\beta_{nuc} = 0.5 \pm 0.1$ has often been reported for reactions proceeding through a concerted mechanism,[7-9] while $\beta_{nuc} = 0.8 \pm 0.1$ for those reported to proceed through a stepwise pathway, in which expulsion of the leaving group from $T^{\pm}$ is the RDS.[1-5] A curved Brønsted-type plot (*e.g.*, from a large slope to a small one as the amine basicity increases) has been taken as evidence for a change in the RDS of a stepwise reaction.[1-5]

Aminolysis of **6** has recently been reported to proceed through a stepwise mechanism with breakdown of $T^{\pm}$ being the RDS on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.77$.[11] If the aminolyses of **7** and **8** proceed also through a stepwise pathway, expulsion of the leaving group would be the RDS. This is because amines are known to be a better leaving group than isobasic aryloxides[1-5] and 2-pyridyloxide is even more basic than the most basic piperidine.[17] Thus, one might expect a linear Brønsted-type plot with $\beta_{nuc} = 0.8 \pm 0.1$, if the reactions of **7** and **8** proceed through a stepwise mechanism. However, as shown in Figures 1(a) and (b), the Brønsted-type plots are linear with $\beta_{nuc} = 0.49$ and 0.44 for the reactions of **7** and **8**, respectively, when k_N and pK_a values are corrected statistically by *p* and *q* (*i.e.*, $q = 1$ except $q = 2$ for piperazine while $p = 2$ except $p = 4$ for piperazinium ion).[19] Since a linear Brønsted-type plot with $\beta_{nuc} = 0.5 \pm 0.1$ is typical for reactions reported previously to proceed through a concerted mechanism,[7-9] one can suggest that the aminolyses of **7** and **8** proceed through a concerted pathway.

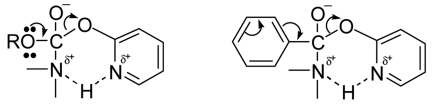


Figures 1. (a) and (b) Brønsted-type plots for the reactions of benzyl 2-pyridyl carbonate **7** (a) and *t*-butyl 2-pyridyl carbonate **8** (b) with amines in H_2O at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

The aminolyses of **7** and **8** in MeCN have been concluded to proceed through a forced concerted mechanism on the basis of linear Brønsted-type plots with $\beta_{nuc} = 0.57$ and 0.45, respectively.[12] One might suggest that solvent effect is responsible for the concerted mechanism since the ionic species $T^{\pm}$ would be highly unstable in the aprotic solvent. However, this argument appears to be little persuasive, since the reactions of **7** and **8** in H_2O also proceed through a concerted mechanism as discussed above.

We have proposed that the H-bonding interaction in III would accelerate the rate of the leaving-group expulsion.[12] Another factor that might facilitate expulsion of the leaving group is the "push"[16] provided by the RO group through a resonance interaction (*e.g.*, III_R). The Ph group in **6** would also accelerate the leaving-group expulsion through a resonance interaction (*e.g.*, IV_R) but not as strongly as the RO group in **7** and **8** since the former is much weaker electron donating than the latter (*e.g.*, $\sigma_R = -0.11$ and –0.61 for Ph and MeO, respectively).[18] Furthermore, the aromaticity of the phenyl ring in IV_R would disappear through the resonance interaction. This argument can be further supported

by the fact that **6** is much less reactive than **7**. Thus, one might suggest that the enhanced nucleofugality through the H-bonding interaction and the strong "push" provided by the RO group forces the reactions of **7** and **8** to proceed through a concerted mechanism in H_2O as well as in MeCN.



III_R **IV_R**

Conclusions

The current study has allowed us to conclude the following: (1) Substrate **8** is less reactive than **7**. Steric hindrance is responsible for the decreased reactivity of **8**. (2) The Brønsted-type plots for the reactions of **7** and **8** are linear with β_{nuc} = 0.49 and 0.44, respectively, indicating that the reactions proceed through a concerted mechanism, which contrasts to the stepwise mechanism reported for the corresponding reactions of **6**. (3) Since the reactions of **7** and **8** in H_2O proceed also through a concerted mechanism, the argument that instability of $T^{\pm}$ in the aprotic solvent causes the reactions of **7** and **8** in MeCN to proceed through a concerted mechanism is little persuasive. (4) Enhanced nucleofugality through the H-bonding interaction and the "push" provided by the RO group forces the reactions of **7** and **8** to proceed through a concerted mechanism.

Experimental Section

Materials. Substrate **7** was prepared as reported in the preceding paper (*e.g.*, **7** was synthesized from the reaction of 2-hydroxypyridine with benzyl chloroformate in methylene chloride, which was generated from the reaction of phosgene and benzyl alcohol, in the presence of pyridine).[20] Substrate **8** was prepared by the reaction of 2-pyridyl chloroformate, generated from phosgene and 2-hydroxypyridine in the presence of pyridine, with equimolar amounts of *t*-butyl alcohol and pyridine in methylene chloride. 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. 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 appearance of the leaving 2-pyridyloxide ion at 293 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. 2-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. No S_N2 products (*e.g.*, *N*-benzylpiperidine) were detected in the reaction products.

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