Kinetics and Reaction Mechanism of Aminolyses of Benzyl 2-Pyridyl Carbonate and *t*-Butyl 2-Pyridyl Carbonate in Acetonitrile

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Second-order rate constants (k_N) have been measured spectrophotometrically for the reactions of benzyl 2-pyridyl carbonate **3** and *t*-butyl 2-pyridyl carbonate **4** with a series of alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C. Substrate **4** is much less reactive than **3** and the steric hindrance exerted by the bulky *t*-Bu group in **4** has been attributed to its decreased reactivity. The Brønsted-type plots for the reactions of **3** and **4** are linear with $\beta_{nuc} = 0.57$ and 0.45, respectively. Thus, the reactions have been concluded to proceed through a concerted mechanism, although the current reactions were expected to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$. It has been proposed that the rate of leaving-group expulsion is accelerated by the intramolecular H-bonding interaction in $T^{\pm}$ and the "push" provided by the RO group through the resonance interaction. Thus, the enhanced nucleofugality forces the reactions to proceed through a concerted mechanism. The reactivity-selectivity principle (RSP) is not applicable to the current reaction systems, since the reaction of the less reactive **4** results in a smaller β_{nuc} than that of the more reactive **3**. Steric hindrance exerted by the bulky *t*-Bu group in **4** has been suggested to be responsible for the failure of the RSP.

**Key Words :** Aminolysis, Steric hindrance, H-bonding interaction, Reactivity-selectivity principle

Introduction

Aminolysis of carboxylic esters in H_2O has generally been reported to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$ as shown in Scheme 1.[1-10] The rate-determining step (RDS) has been suggested to be dependent on the basicity of the incoming amine and the leaving group, *e.g.*, it changes from breakdown of $T^{\pm}$ to its formation as the amine becomes more basic than the leaving group by 4 to 5 pK_a units.[1-10] A curved Brønsted-type plot found for aminolysis of esters possessing a good leaving group (*e.g.*, 2,4-dinitrophenoxide ion) has been taken as evidence for a change in the RDS of a stepwise reaction.[1-10]
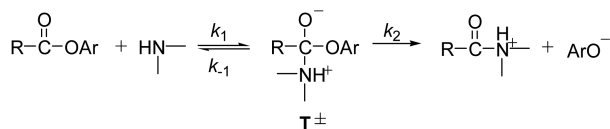
Scheme 1

On the other hand, aminolysis of 4-nitrophenyl benzoate **1** in MeCN has been concluded to proceed through a forced concerted mechanism due to instability of $T^{\pm}$ in the aprotic solvent.[11] However, we have recently shown that the
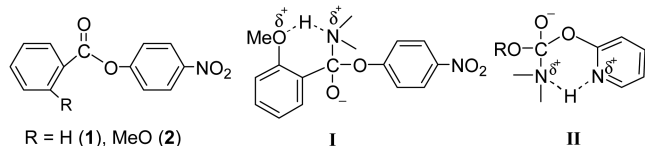
corresponding reaction of 4-nitrophenyl 2-methoxybenzoate **2** proceeds through a stepwise mechanism with an intermediate as modeled by I, which would be stabilized even in the aprotic solvent through the intramolecular H-bonding interaction.[12]

We have now extended our study to the reactions of benzyl 2-pyridyl carbonate **3** and *t*-butyl 2-pyridyl carbonate **4** with a series of alicyclic secondary amines in MeCN to get further information on the reaction mechanism in the aprotic solvent (Scheme 2). Substrates **3** and **4** have been chosen since their reactions are expected to proceed through a stabilized intermediate as modeled by II, which is similar to the intermediate I proposed for the corresponding reactions of **2**.
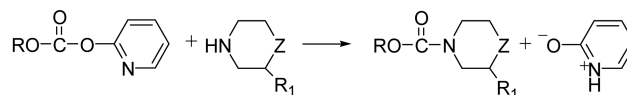

R = PhCH$_2$ (**3**), *t*-Bu (**4**)

R$_1$ = H or Me

Z = CH$_2$, NH, NCH$_2$CH$_2$OH, O

Scheme 2

The above idea can be further supported from the reports that reactions of **3** and its related compounds are strongly catalyzed in the reactions with alkali metal ethoxides EtOM (M = Li$^+$, Na$^+$ and K$^+$)[13] or with other organometallic reagents such as Grignard reagents, cupric bromide or lithium dialkylcuprate[14,15] through formation of a six-membered cyclic complex III or IV.

R = H (**1**), MeO (**2**)   **I**   **II**

III   **IV**
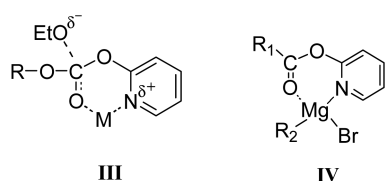
Results and Discussion

The kinetic study was performed spectrophotometrically by monitoring the appearance of the leaving 2-pyridyloxide at 302 nm under pseudo-first-order conditions (*e.g.*, the concentration of amines was kept in excess over that of substrates **3** and **4**). 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. Thus, the second-order rate constants (k_N) for the reactions of **3** and **4** with amines were calculated from the slope of the 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 $\pm 3\%$.

Effect of Replacing PhCH$_2$ in 3 by *t*-Bu on Reactivity. As shown in Table 1, k_N decreases slightly as the amine basicity decreases except piperazine (*e.g.*, the k_N value for the reactions of **3** decreases from 15.2 $M^{-1}s^{-1}$ to 2.99 and 0.940 $M^{-1}s^{-1}$ as the pK_a of the amine decreases from 18.8 to 17.6 and 16.6, in turn). Piperazine is more reactive than 3-methylpiperidine although the former is less basic than the latter. However, it is not surprising since piperazine possesses two nucleophilic sites. A similar reactivity pattern is shown for the corresponding reactions of **4** although **4** is up to *ca.* 30 times less reactive than **3**.

Many factors would influence the reactivity of **3** and **4** (*e.g.*, electronic effects, steric hindrance and reaction mechanism). The electronic effects such as inductive and resonance effects can be represented by σ_I and σ_R, respectively. 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,[17] one can suggest that the electronic effects for the PhCH$_2$ and *t*-Bu groups are similar. Thus, the electronic effects would be

Table 1. Summary of second-order rate constants (k_N) for aminolysis of benzyl 2-pyridyl carbonate **3** and *t*-butyl 2-pyridyl carbonate **4** in MeCN at 25.0 $\pm$ 0.1 °C[a]

	Amines	pK_a	k_N / $M^{-1}s^{-1}$	
			3	**4**
1	piperidine	18.8	15.2	0.548
2	3-methylpiperidine	18.6	13.4	0.494
3	piperazine	18.5	14.2	0.631
4	1-(2-hydroxyethyl)piperazine	17.6	2.99	0.152
5	morpholine	16.6	0.940	0.0588

[a]The pK_a data in MeCN were taken from ref. 16.

little responsible for the difference in the reactivity between **3** and **4**.

It is evident that the *t*-Bu moiety in substrate **4** would exhibit significantly stronger steric hindrance than the PhCH$_2$ group in **3** since the steric factor $E_s = -1.54$ and -0.38 for *t*-Bu and PhCH$_2$, respectively.[17a] Thus, it is apparent that the steric hindrance exerted by the bulky *t*-Bu group is mainly responsible for the fact that **4** is less reactive than **3**.

Another plausible factor that might account for the reactivity order is the nature of the reaction mechanism including the reaction sites. The reactions of **3** and **4** with amines could proceed through an S_N1 mechanism in H$_2$O as shown in Scheme 3. However, the current aminolysis in MeCN would not proceed through an S_N1 mechanism since the ionic intermediates for an S_N1 reaction would be highly unstable in the aprotic solvent. This idea is consistent with the fact that k_{obsd} increases linearly with increasing amine concentration as mentioned in the result section. An S_N2 reaction would not occur at the bulky *t*-Bu group of **4** but would be possible at the benzylic carbon of **3**. However, *N*-benzylpiperidine (*i.e.*, one of the S_N2 products for the reaction of **3** with piperidine) has not been detected in the reaction mixture. Thus, one can suggest that the aminolysis of **3** does not proceed through an S_N2 pathway either. To investigate the reaction mechanism, Brønsted-type analysis has been performed in the following section.
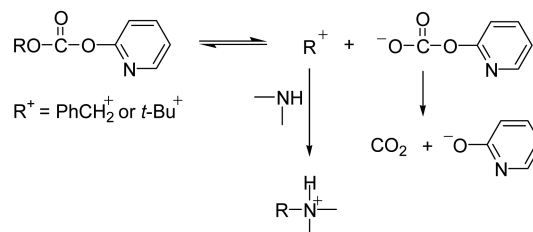
Scheme 3

Reaction Mechanism. Analysis of Brønsted-type plots is one of the most common methods in deducing reaction mechanisms, *e.g.*, a linear Brønsted-type plot with $\beta_{nuc} = 0.5 \pm 0.1$ has often been reported for reactions proceeding through a concerted mechanism, while $\beta_{nuc} = 0.8 \pm 0.1$ for those proceeding through a stepwise pathway with expulsion of the leaving group from $T^\pm$ being the RDS.[1-10] 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.

As shown in Figures 1(a) and (b), the Brønsted-type plots are linear with $\beta_{nuc} = 0.57$ and 0.45 for the reactions of **3** and **4**, respectively when k_N and pK_a are corrected statistically by p and q (*i.e.*, $q = 1$ except $q = 2$ for piperazine while $p = 2$).[18] 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,[1-5,11] one can suggest that the current aminolyses of **3** and **4** proceed through a concerted mechanism. This is quite unexpected since the reactions of **3** and **4**
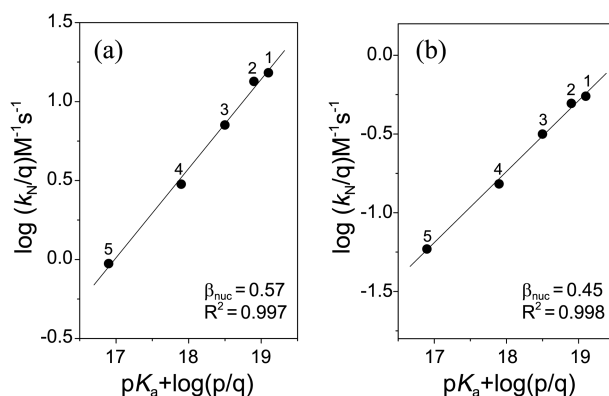
Figures 1. (a) and (b). Brønsted-type plots for the reactions of benzyl 2-pyridyl carbonate **3** (a) and *t*-butyl 2-pyridyl carbonate **4** (b) with alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

were predicted to proceed through a stepwise mechanism with a stabilized intermediate as modeled by II.

It is noted that intermediates I and II are structurally similar (*e.g.*, a six membered intramolecular H-bonded structure). However, a careful examination of their structures reveals that the H-bonding sites are different (*e.g.*, between the NH of the aminium moiety and the oxygen atom of the 2-MeO group in model I, and between the NH and the nitrogen atom of the 2-pyridyl moiety in model II). Accordingly, one might expect that the H-bonding interaction in model II would increase the nucleofugality of the leaving 2-pyridyloxide, while the one in model I could not increase the nucleofugality of the leaving group.

Another factor that accelerates expulsion of the leaving group from model II is the "push"[5b,6a] provided by the RO group through the resonance interaction as shown in the resonance structure II_R. It is evident that an increase in the rate of the leaving-group expulsion would shorten the lifetime of the intermediate II. Thus, one can conclude that the enhanced nucleofugality through the H-bonding interaction and the "push" provided by the RO group shortens the lifetime of II and forces the reactions of **3** and **4** to proceed through a concerted mechanism.
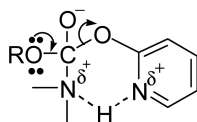
$$II_R$$

Failure of Reactivity-Selectivity Principle. It has often been reported that a less reactive reaction system exhibits a higher selectivity than a more reactive system (*e.g.*, a larger β_{nuc} for a less reactive system or *vice versa*), which is in accord with the reactivity-selectivity principle (RSP).[19] However, as shown in Figures 1(a) and (b), the β_{nuc} value is smaller for the reactions of the less reactive **4** than for those of the more reactive **3**. Accordingly, one can suggest that the RSP is not applicable to the current reaction systems.

The magnitude of the β_{nuc} value has also been understood

to represent a degree of bond formation between the nucleophile and the electrophile in the transition state (TS). Thus, bond formation in the TS is considered to be less advanced for the reactions of **4** than for those of **3** on the basis of the β_{nuc} values. It is noted that that **4** possesses a bulky *t*-Bu group near the reaction site. It is apparent that the bulky *t*-Bu group prevents to form a tight bond between the incoming amine and the electrophilic center of **4**. Thus, the steric hindrance exerted by the bulky *t*-Bu group is proposed to be responsible for the fact that the reactions of **4** result in a smaller β_{nuc} (or less bond formation) than those of **3**, (*i.e.*, a failure of the RSP).

Conclusions

The current study has allowed us to conclude the following: (1) Compound **4** is less reactive than **3**. Steric hindrance exerted by the bulky *t*-Bu group rather than electronic effects is responsible for the decreased reactivity of **4**. (2) The reactions of **3** and **4** proceed through a forced concerted mechanism, indicating that the difference in reactivity is not due to the nature of their reaction mechanism. (3) Enhanced nucleofugality through H-bonding interaction and the "push" provided by the RO group forces the reactions to proceed through a concerted mechanism. (4) The reactions of less reactive **4** result in a smaller β_{nuc} than those of more reactive **3**, indicating that the RSP is not applicable to the current systems. (5) Steric hindrance exerted by *t*-Bu group is responsible for the failure of the RSP.

Experimental Section

Materials. Substrate **3** was prepared as reported previously,[13a] while **4** was synthesized from 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 ^{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 the reaction medium and the amine nucleophile. The reactions were followed by monitoring the appearance of the leaving 2-pyridyloxide at 302 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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