http://dx.doi.org/10.5012/bkcs.2014.35.7.2081

Kinetic Study on Aminolysis of Phenyl 2-Pyridyl Carbonate in Acetonitrile: Effect of Intramolecular H-bonding Interaction on Reactivity and Reaction Mechanism

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Received March 13, 2014, Accepted March 18, 2014

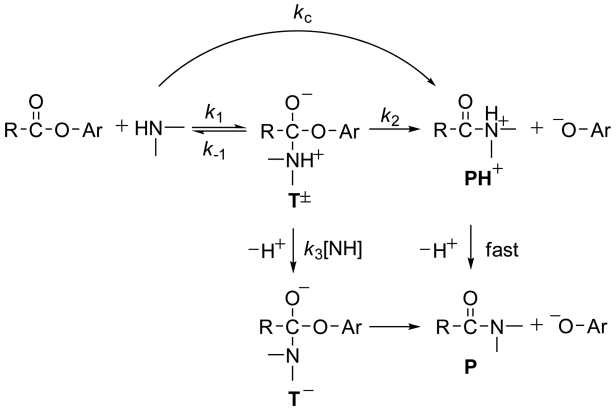
Second-order rate constants (k_N) have been measured spectrophotometrically for the reactions of phenyl 2-pyridyl carbonate (**6**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The Brønsted-type plot for the reaction of **6** is linear with $\beta_{nuc} = 0.54$, which is typical for reactions reported previously to proceed through a concerted mechanism. Substrate **6** is over 10^3 times more reactive than 2-pyridyl benzoate (**5**), although the reactions of **6** and **5** proceed through the same mechanism. A combination of steric hindrance, inductive effect and resonance contribution is responsible for the kinetic results. The reactions of **6** and **5** proceed through a cyclic transition state (TS) in which H-bonding interactions increase the nucleofugality of the leaving group (*i.e.*, 2-pyridiniumoxide). The enhanced nucleofugality forces the reactions of **6** and **5** to proceed through a concerted mechanism. In contrast, the corresponding reaction of 4-nitrophenyl 2-pyridyl carbonate (**7**) proceeds through a stepwise mechanism with quantitative liberation of 4-nitrophenoxide ion as the leaving group, indicating that replacement of the 4-nitrophenoxy group in **7** by the PhO group in **6** changes the reaction mechanism (*i.e.*, from a stepwise mechanism to a concerted pathway) as well as the leaving group (*i.e.*, from 4-nitrophenoxide to 2-pyridiniumoxide). The strong electron-withdrawing ability of the 4-nitrophenoxy group in **7** inhibits formation of a H-bonded cyclic TS. The presence or absence of a H-bonded cyclic TS governs the reaction mechanism (*i.e.*, a concerted or stepwise mechanism) as well as the leaving group (*i.e.*, 2-pyridiniumoxide or 4-nitrophenoxide).

Key Words : Aminolysis, Steric hindrance, Inductive effect, Resonance contribution, H-bonding interaction

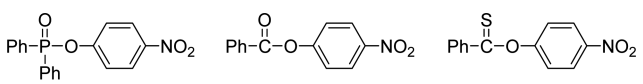
Introduction

Nucleophilic substitution reactions of esters with amines have been reported to proceed through a concerted mechanism or *via* a stepwise pathway with one or two intermediates (*i.e.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}) as shown in Scheme 1.[1-7] Numerous studies have been performed to investigate the reaction mechanism. Some important factors that control the reaction mechanism include the nature of the electrophilic center, reaction medium, stability of the intermediate, *etc*.[2-7]

Aminolysis of 4-nitrophenyl diphenylphosphinate (**1**) has been reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.5 \pm 0.1$.[5] In contrast, aminolysis of 4-nitrophenyl benzoate (**2a**) has been suggested to proceed through a stepwise mechanism, 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] The corresponding reaction of *O*-4-nitrophenyl thionobenzoate (**2b**) has been concluded to proceed through a stepwise mechanism with two intermediates on the basis of the fact that the plot of k_{obsd} *vs*. [amine] curves upward.[7] These demonstrate convincingly that the nature of the electrophilic center (*e.g.*, P=O, C=O and C=S) is an important factor that controls the reaction mechanism.



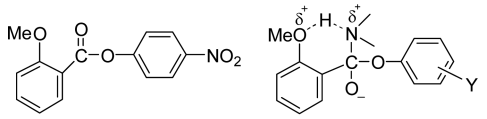
Scheme 1



1 **2a** **2b**

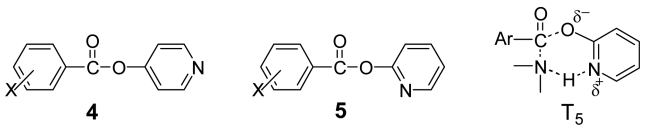
Solvent effect has also been reported to be important for the reaction mechanism. Aminolysis of 2,4-dinitrophenyl benzoate has been reported to proceed through a stepwise mechanism with a zwitterionic intermediate $T^{\pm}$ in H_2O[9a] but *via* a concerted pathway in MeCN.[9b] Since MeCN is a poor solvent for ionic species, $T^{\pm}$ would be highly unstable in the aprotic solvent. Accordingly, instability of $T^{\pm}$ in MeCN has been suggested to force the reaction to proceed through a concerted mechanism.[9b]

Intramolecular H-bonding interaction has been reported to be an important factor that controls the reaction mechanism for aminolysis of 4-nitrophenyl 2-methoxybenzoate (**3**) in MeCN.[10] We have previously proposed that the reaction of **3** in MeCN proceeds through a stepwise mechanism with an intermediate, which is stabilized through the H-bonding interaction as illustrated in T_3.[10] This idea has been further supported by the kinetic results that **3** is 20 and 74 times more reactive than 4-nitrophenyl 3-methoxybenzoate and 4-nitrophenyl 4-methoxybenzoate (*e.g.*, the isomers of **3**), respectively.[10]



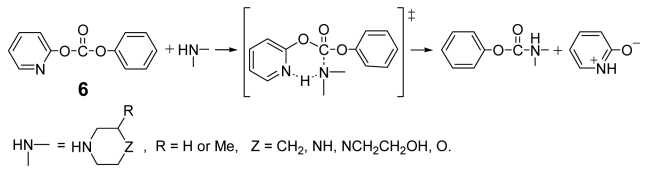
3 T_3

The importance of H-bonding interactions has been further examined from the reactions of 4-pyridyl X-substituted-benzoates (**4**)[11a] and 2-pyridyl X-substituted-benzoates (**5**)[11b] with a series of cyclic secondary amines in MeCN. We have reported that the aminolysis of **4** proceeds through a stepwise mechanism with one or two intermediates depending on the electronic nature of the substituent X, *i.e.*, with two intermediates $T^{\pm}$ and T^{-} when X is a strong electron-withdrawing group (EWG) but with $T^{\pm}$ only when X is a weak EWG or an electron-donating group (EDG).[11a] In contrast, the corresponding reaction of **5** has been suggested to proceed through a concerted mechanism with a transition-state (TS) structure similar to T_5 regardless of the electronic nature of the substituent X.[11b] The H-bonding interaction as illustrated in T_5, which is structurally not possible for the reaction of **4**, has been suggested to force the reaction to proceed through a concerted mechanism.[11b]



4 **5** T_5

Our study has now been extended to the reaction of phenyl 2-pyridyl carbonate (**6**) with a series of cyclic secondary amines in MeCN to obtain further information on the reaction mechanism (Scheme 2). The kinetic results have been compared with those reported recently for the corresponding reactions of **5**[11b] and 4-nitrophenyl 2-pyridyl carbonate (**7**)[12] to investigate factors that control the reaction mechanism as well as the reactivity.



Scheme 2

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions in which the amine concentration was kept at least 20 times in excess of the substrate concentration. All the reactions in this study obeyed first-order kinetics and the pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{obsd}t + C$. As shown in Figure 1, the plot of k_{obsd} *vs.* [amine] is linear for the reactions of phenyl 2-pyridyl carbonate (**6**) with morpholine. The corresponding reaction of 2-pyridyl benzoate (**5**) results in also a linear plot (inset), indicating that general-base catalysis by a second amine molecule is absent. This is in contrast to the curved plot obtained from the corresponding reaction of 4-nitrophenyl 2-pyridyl carbonate (**7**), in which a second amine molecule behaves as a general-base catalyst.

The second-order rate constants (k_N) for the reactions of **6** were calculated from the slope of the linear plots of k_{obsd} *vs.* [amine]. The uncertainty in the k_N values is estimated to be less than ± 3% based on the replicate runs. The k_N values calculated in this way are summarized in Table 1 together with the k_N and Kk_2 values reported previously for the corresponding reactions of **5** and **7**, respectively, for compari-

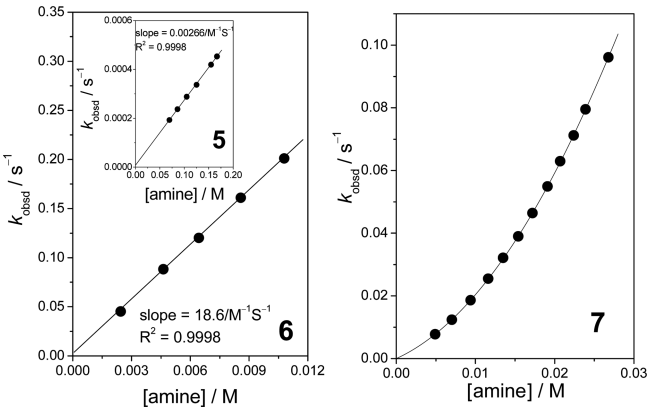


Figure 1. Plots of k_{obsd} *vs.* [amine] for the reaction of phenyl 2-pyridyl carbonate (**6**), 2-pyridyl benzoate (**5**, inset) and 4-nitrophenyl 2-pyridyl carbonate (**7**) with morpholine in MeCN at 25.0 ± 0.1 °C. The kinetic data for the reactions of **5** and **7** were taken from refs. 11b and 12, respectively.

Table 1. Summary of the Second-Order Rate Constants for the Reactions of Phenyl 2-Pyridyl Carbonate (**6**), 2-Pyridyl Benzoate (**5**) and 4-Nitrophenyl 2-Pyridyl Carbonate (**7**) with Cyclic Secondary Amines in MeCN at 25.0 ± 0.1 °C[a]

	amines	pK_a	k_N/M^{-1}s^{-1}		Kk_2/M^{-1}s^{-1}
			5	**6**	**7**
1	morpholine	16.6	2.66×10^{-3}	18.6	1.12
2	1-(2-hydroxyethyl)piperazine	17.6	8.59×10^{-3}	54.0	7.87
3	piperazine	18.5	43.3×10^{-3}	239	69.5
4	3-methylpiperidine	18.6	43.8×10^{-3}	228	96.2
5	piperidine	18.8	55.8×10^{-3}	261	173

[a]The pK_a values of amines in MeCN and kinetic data for the reactions of **5** and **7** were taken from refs. 11b and 12, respectively.

son.[11b,12]

Effect of Nonleaving Group on Reactivity and Reaction Mechanism. As shown in Table 1, the reactivity of amines increases with increasing their basicity, *e.g.*, the k_N value for the reaction of **6** increases from 18.6 $M^{-1}s^{-1}$ to 261 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the incoming amine increases from 16.6 to 18.8, respectively. Similar results are shown for the k_N and Kk_2 values for the reactions of **5** and **7**, respectively. However, **6** is significantly more reactive than **5** and **7** (*e.g.*, k_N or Kk_2 = 18.6, 2.66 × 10^{-3} and 1.12 $M^{-1}s^{-1}$ for the reactions of **6**, **5** and **7** with morpholine, respectively).

The nature of reaction mechanism is an important factor that controls reactivity of esters. It is apparent that reactivity of esters would increase by increasing the electrophilicity of the reaction center and/or the nucleofugality of the leaving group. However, enhanced nucleofugality would be effective only for reactions in which expulsion of the leaving group is involved in the RDS but would be ineffective for reactions in which expulsion of the leaving group occurs after the rate-determining step (RDS). As mentioned above, the linear plot of k_{obsd} *vs*. [amine] shown in Figure 1 indicates that general-base catalysis is absent for the reactions of **6**, but it does not give any further information on the reaction mechanism including the nature of RDS, *e.g.*, a concerted mechanism or a stepwise pathway.

To investigate the reaction mechanism, Brønsted-type plot for the reactions of **6** has been constructed in Figure 2. The Brønsted-type plots for the corresponding reactions of **5** and **7** are also illustrated for comparison. As shown in Figure 2, the plot for the reactions of **6** is linear with β_{nuc} = 0.54 when the k_N and pK_a values are statistically corrected using *p* and *q* (*i.e.*, *p* = 2 while *q* = 1 except *q* = 2 for piperazine).[13] This is similar to the linear Brønsted-type plot with β_{nuc} = 0.61 for the corresponding reactions of **5** (inset). However, the β_{nuc} for the reactions of **6** is much smaller than that for the reactions of **7** (β_{nuc} = 0.99), which was reported to proceed through a stepwise mechanism with two intermediates $T^{\pm}$ and T^{-}.[12]

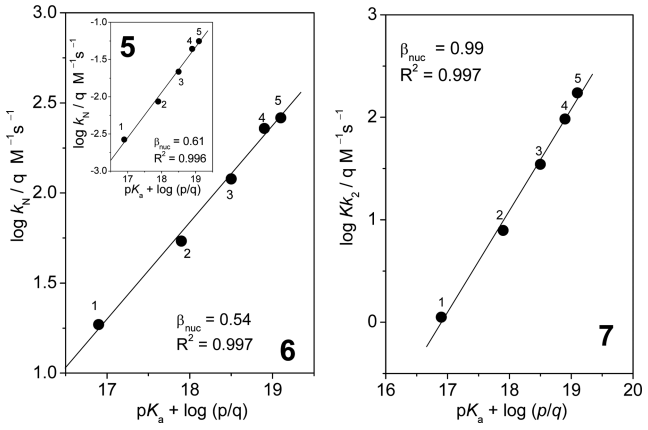
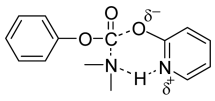


Figure 2. Brønsted-type plots for the reactions of phenyl 2-pyridyl carbonate (**6**), 2-pyridyl benzoate (**5**, inset) and 4-nitrophenyl 2-pyridyl carbonate (**7**) with a series of cyclic secondary amines in MeCN at 25.0 ± 0.1 °C.

A linear Brønsted-type plot with β_{nuc} = 0.5 ± 0.1 is typical for reactions reported previously to proceed through a concerted mechanism.[2-7] In fact, the aminolysis of **5** has recently been reported to proceed through a concerted mechanism on the basis of the linear Brønsted-type plot with β_{nuc} = 0.61.[11b] Thus, one can suggest that modification of the nonleaving group from the Ph group in **5** to the PhO group in **6** (*i.e.*, changing substrate from **5** to **6**) does not affect the reaction mechanism, but replacement of the 4-$NO_2C_6H_4O$ group in substrate **7** by the PhO group in **6** (*i.e.*, changing substrate from **7** to **6**) alters the reaction mechanism from a stepwise mechanism to a concerted pathway.

One can propose that the reactions of **6** proceed through a forced concerted mechanism with a TS structure similar to T_6, which is similar to T_5 suggested previously for the corresponding reactions of **5**.[11b] The intramolecular H-bonding interactions illustrated in T_5 and T_6 would cause a significant decrease in the leaving-group basicity by changing the highly basic 2-pyridyloxide (*e.g.*, the pK_a = 11.62 in H_2O)[14] to the weakly basic 2-pyridiniumoxide (*e.g.*, the pK_a = 0.75 in H_2O)[14] or its tautomer 2-pyridone. It is apparent that the decreased basicity of the leaving group would cause a remarkable increase in its nucleofuglaity. Thus, one can suggest that the intramolecular H-bonding interaction forces the reactions of **6** and **5** to proceed through a concerted mechanism.



T_6

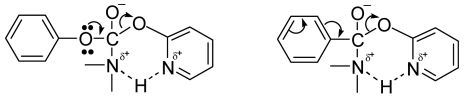
Factors Influencing Reactivity: Reactions of 6 and 5. Table 1 shows that substrate **6** is over 10^3 times more reactive than substrate **5**. However, the high reactivity of **6** compared to that of **5** is not due to the nature of the reaction mechanism, since the reactions of both **6** and **5** appear to proceed through the same mechanism (*i.e.*, a forced concerted mechanism). Clearly, other factors are responsible for the kinetic results.

The reactivity of **6** and **5** would be affected by the inductive effect exerted by the PhO and Ph groups. Since the σ_I values of PhO and Ph are 0.38 and 0.10, respectively,[15] the former is a little stronger EWG than the latter. Thus, replacement of the Ph group in **5** by the stronger electron-withdrawing PhO group would increase the electrophilicity of the reaction center (*i.e.*, an inductive effect), and the enhanced electrophilicity could be an explanation for the higher reactivity of **6**. However, the inductive effect alone cannot be fully responsible for the result that **6** is over 10^3 times more reactive than **5**, since the difference in the σ_I value between the PhO and Ph groups is only 0.28.

It is well known that steric hindrance is also an important factor that affects the reactivity of esters. The E_S values of Ph and *t*-Bu are –2.55 and –1.54, respectively,[15] indicating that the Ph group exerts much stronger steric hindrance than the bulky *t*-Bu group. The E_S value of PhO is not available but is expected to be similar to the E_S value of $PhCH_2$ (*i.e.*,

–0.38).[15]Accordingly, one can suggest that the Ph group in **5** would exert significantly stronger steric hindrance than the PhO group in **6**, and that the strong steric hindrance exerted by the Ph group in **5** causes a significant decrease in its reactivity. This argument can be further supported by the k_N value of 0.940 $M^{-1}s^{-1}$ reported previously for the reaction of benzyl 2-pyridyl carbonate with morpholine in MeCN[16] (*i.e.*, *ca.* 353 times increase in reactivity upon replacing the strongly hindered Ph group in **5** by the weakly hindered $PhCH_2$ group).

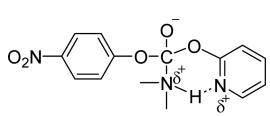
Finally, resonance effect would also contribute to the enhanced reactivity of substrates **6**. As illustrated in T_{6R}, expulsion of the leaving-group would be facilitated by the "push" provided by the PhO group through the resonance interaction. The Ph group in T_5 could also facilitate expulsion of the leaving group through the resonance interaction as illustrated in T_{5R} but not as strongly as the PhO in T_6. Because the former is a weaker EDG than the latter (*e.g.*, σ_R = –0.11 and –0.58 for Ph and PhO, respectively).[15] Thus, one can suggest that the stronger "push" provided by the PhO in T_{6R} also contributes to the kinetic result that **6** is more reactive than **5**.



T_{6R} T_{5R}

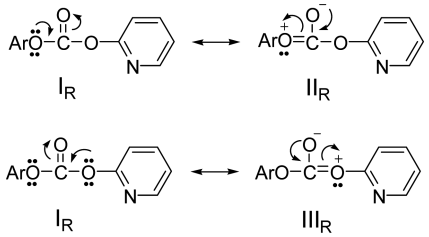
Importance of H-Bonding Interaction: Reactions of 6 and 7. The aminolysis of **7** has been reported to proceed through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and T^{-}) on the basis of the curved plot of k_{obsd} *vs.* [amine] (*e.g.*, Figure 1). This is in contrast to the reaction of **6**, which proceeds through a forced concerted mechanism with a TS structure similar to T_6.

One might expect that the reaction of **7** would proceed through a concerted mechanism with a TS structure similar to T_7. If the reaction proceeds through T_7, in which the proton is H-bonded between the two N atoms, the deprotonation process from $T^{\pm}$ to yield T^{-} by a second amine molecule would not be possible. Because the proton in the aminium moiety of T_7 would be transferred to the N atom of the leaving group. Furthermore, the H-bonding interaction in T_7 would alter the leaving group from the more basic 4-nitrophenoxide (*e.g.*, pK_a = 7.14 in H_2O) to the significantly less basic 2-pyridiniumoxide (or its tautomer 2-pyridone). However, in fact, the aminolysis of **7** proceeds through a stepwise mechanism with two intermediates. Besides, the leaving group is 4-nitrophenoxide but not 2-pyridiniumoxide, indicating clearly that the reaction does not proceed through T_7.



T_7

Aryl 2-pyridyl carbonates can be represented by three different resonance structures as illustrated in the resonance structures I_R, II_R and III_R. One might expect that the resonance structure II_R would be the minor contributor when ArO = 4-$NO_2C_6H_4O$ due to the strong electron-withdrawing ability of the NO_2 group. In contrast, the resonance structure III_R becomes the major contributor when OAr = 4-$NO_2C_6H_4O$. It is apparent that the positively charged O atom in III_R would inhibit formation of T_7. This idea explains why the reaction of **7** does not proceed through T_7 and accounts for the contrasting reaction mechanism (*i.e.*, a forced concerted mechanism for reactions of **5** and **6** *vs.* a stepwise pathway for the reaction of **7**) as well as the contrasting leaving group (*i.e.*, 2-pyridiniumoxide *vs.* 4-nitrophenoxide).



I_R II_R

I_R III_R

Conclusions

The current study has led us to conclude the following: (1) The Brønsted-type plots for the reactions of **6** and **5** are linear with β_{nuc} = 0.54 and 0.61, respectively, indicating that the reactions proceed through the same mechanism (*i.e.*, a concerted mechanism). (2) Substrate **6** is over 10^3 times more reactive than substrate **5**. A combination of steric hindrance, inductive effect and resonance contribution is responsible for the kinetic result that **6** is over 10^3 times more reactive than **5**. (3) The aminolysis of **6** proceeds through a TS structure similar to T_6, which forces the reaction to proceed through a concerted mechanism by increasing the nucleofugality of the leaving group. (4) Resonance structure III_R becomes the major contributor when ArO = 4-$NO_2C_6H_4O$. The positively charged O atom in III_R inhibits formation of the H-bonding structure T_7. (5) The presence or absence of the intramolecular H-bonding interactions controls the leaving group (*i.e.*, the less basic 2-pyridiniumoxide *vs.* the more basic aryloxide) and the reaction mechanism (*i.e.*, a forced concerted mechanism for reactions of **5** and **6** *vs.* a stepwise pathway for the reactions of **7**).

Experimental Section

Materials. Substrate **6** was prepared from the reaction of phenyl chloroformate and 2-hydroxypyridine in the presence of triethylamine in methylene chloride at 0 °C. The crude product was purified by column chromatography. The purity of **6** was confirmed from the melting point and ^1H and ^{13}C NMR characteristics (Supporting Information). MeCN was distilled over P_2O_5 and stored under nitrogen. The amines and other chemicals used were of the highest quality available.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All of the reactions in this study 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 0.02 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 amine. The reactions were followed by monitoring the appearance of 2-pyridiniumoxide up to *ca*. 9 half-lives.

Product Analysis. 2-Pyridiniumoxide (or 2-pyridone) was liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra obtained after completing the reactions with those of authentic samples under the same kinetic conditions.

Acknowledgments. This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2012-R1A1B-3001637, IHU) and (NRF-2009-0094017, JIL).

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