http://dx.doi.org/10.5012/bkcs.2014.35.2.638

Kinetic Study on Aminolysis of 4-Nitrophenyl 2-Pyridyl Carbonate in Acetonitrile: Kinetic Evidence for a Stepwise Mechanism with Two Intermediates

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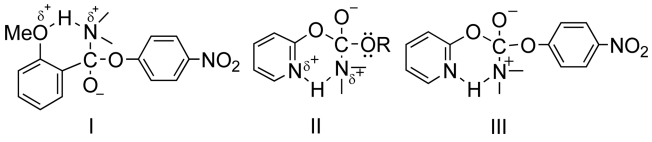
Received October 23, 2013, Accepted November 11, 2013

Key Words : Aminolysis, Intermediate, Electrophilicity, Nucleofugality, Basicity

Nucleophilic substitution reactions of esters are an important class of reactions in biological processes and organic syntheses. Numerous studies on aminolysis of esters have been performed to investigate the reaction mechanism.[1-6] Aminolysis of C=O centered esters has generally been reported to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate ($T^{\pm}$).[1-6] However, stability of $T^{\pm}$ has been suggested to be an important factor which governs the reaction mechanism, *e.g.*, a forced concerted mechanism with an unstable $T^{\pm}$ but a stepwise pathway with a stable $T^{\pm}$.[2-6]

We have recently reported that the reactions of 4-nitrophenyl 2-methoxybenzoate with a series of cyclic secondary amines in MeCN proceed through a stepwise mechanism with a stable $T^{\pm}$ as modeled by I, in which the intramolecular H-bonding interactions provide a high stability to the cyclic intermediate.[3a] In contrast, the corresponding reactions of benzyl 2-pyridyl carbonate and *t*-butyl 2-pyridyl carbonate have been suggested to proceed through a forced concerted mechanism, although the reactions were predicted to proceed through a stepwise mechanism with a stable intermediate as modeled by II.[3b]



I II III

It is noted that I and II are structurally similar (*e.g.*, a six-membered intramolecular H-bonding structure). However, scrutiny of their structures reveals that the H-bonding sites are different (*e.g.*, between the NH of the aminium moiety and the O atom of the 2-MeO group in model I, and between the NH of the aminium moiety and the N atom of the 2-pyridyl moiety in model II). The H-bonding interaction in model I has previously been suggested to increase its stability[3a] while that in model II decreases its stability by increasing the nucleofugality of the leaving 2-pyridyloxide.[3b] Thus, the difference in the stability of $T^{\pm}$ has been reported to be responsible for the contrasting reaction mechanisms.[3b]

Our study has now been extended to the reaction of 4-nitrophenyl 2-pyridyl carbonate with a series of cyclic secondary amines in MeCN to obtain further information on the reaction mechanism. It was expected that the reaction would proceed through a stepwise mechanism with a stable intermediate as modeled by III. Because the H-bonding interactions in III would cause a change in the nucleofuge from 4-nitrophenoxide to the weakly basic *N*-protonated 2-pyridiniumoxide (*e.g.*, pK_a of the conjugate acid of *N*-protonated 2-pyridiniumoxide is 0.75 in H_2O).[4] However, unexpectedly, we wish to report that the leaving group is the more basic 4-nitrophenoxide but not the less basic *N*-protonated 2-pyridiniumoxide.

Experimental Section

As shown in Figure 1, the plot of k_{obsd} *vs.* [amine] for the reaction with morpholine is nonlinear. Similarly curved plots are obtained for the reactions with all the amines studied in this work as shown in Figures S1(a)-S4(a) in the Supporting Information (SI) section. Such nonlinear plot has often been reported for aminolysis of C=S centered esters (*e.g.*, *O*-4-nitrophenyl thionobenzoate), in which a second amine molecule behaves as a general-base catalyst,[5] but is very rare for aminolysis of C=O centered esters.[6]

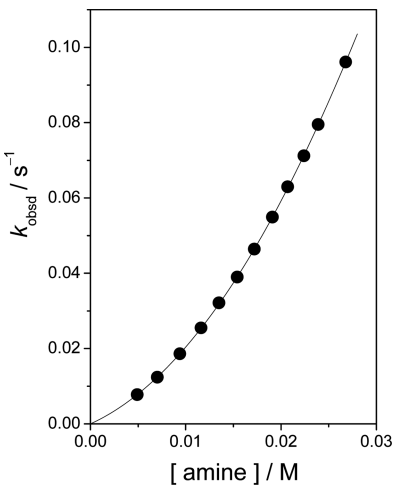
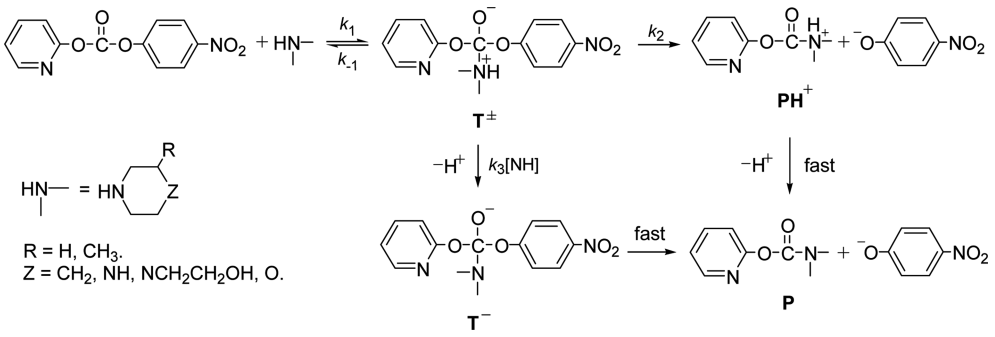


Figure 1. Plot of k_{obsd} *vs.* [amine] for the reaction of 4-nitrophenyl 2-pyridyl carbonate with morpholine in MeCN at 25.0 ± 0.1 °C.



Scheme 1

If the reaction proceeds through an intermediate (or a transition state) as modeled by III, general-base catalysis by a second amine molecule would not be necessary. This is because the H^+ transfer occurs from the aminium moiety of III to the N atom of the leaving 2-pyridyloxide. Thus, if the reaction proceeds through III, one might expect that plot of k_{obsd} *vs.* [amine] should be linear. However, the plots are nonlinear (Figure 1 and Figures S1a-S4a in the SI section), indicating that the reaction does not proceed through III but proceeds via a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and its deprotonated form T^-) as shown in Scheme 1.

One can derive Eq. (1) on the basis of the kinetic results and the mechanism proposed in Scheme 1. Eq. (1) can be simplified to Eq. (2) under the assumption $k_2 << k_3$[amine]. Thus, one might expect the plot of [amine]/k_{obsd} *vs.* 1/[amine] is linear if the above assumption is valid. As shown in Figure 2(a), the plot of [amine]/k_{obsd} *vs.* 1/[amine] is linear only when the amine concentration is high but curves downward as the amine concentration decreases. This indicates that the above assumption is invalid when the amine concentration is low. However, this is not surprising because the k_3[amine] term becomes smaller as the amine concentration decreases.

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

$$[\text{amine}] / k_{obsd} = 1/k_1 + k_1k_3/k_{-1}[\text{amine}] \quad (2)$$

Since the first step in Scheme 1 is a preequilibrium, one can assume that $k_{-1} >> k_2 + k_3$[amine]. Then, Eq. (1) can be simplified to Eq. (3). Thus, if the above assumption is valid, one might expect that the plot of k_{obsd}/[amine] *vs.* [amine] is linear. In fact, as shown in Figure 2(b), the plot exhibits an excellent linear correlation with a positive intercept. The plots for the reactions with all the other amines used in this study are also linear as shown in Figures S1(c)-S4 (c) in the SI section, indicating that the proposed reaction mechanism and the assumption $k_{-1} >> k_2 + k_3$[amine] are correct in all cases.

$$k_{obsd}/[\text{amine}] = k_1k_2/k_{-1} + k_1k_3[\text{amine}]/k_{-1} \quad (3)$$

Thus, the k_1k_2/k_{-1} and k_1k_3/k_{-1} values were determined from the intercept and slope of the linear plot, respectively, while the k_3/k_2 ratios were calculated from the k_1k_2/k_{-1} and k_1k_3/k_{-1} values. As shown in Table 1, the k_1k_2/k_{-1} and k_1k_3/k_{-1} values increase as the amine basicity increases, *e.g.*, k_1k_2/k_{-1} increases from 1.12 $M^{-1}s^{-1}$ to 7.87 and 173 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the amine increases from 16.6 to 17.6 and 18.8, in turn. The statistically corrected Brønsted-type plots[7] shown in Figure S5 in the SI section exhibit excellent linear correlations, indicating that the k_1k_2/k_{-1} and k_1k_3/k_{-1} values calculated are highly reliable. It is noted that the k_3/k_2 ratio decreases as the amine basicity increases. Besides, the maximum k_3/k_2 ratio is only *ca.* 80 for the reaction with the least basic morpholine. This explains why the plot of [amine]/k_{obsd} *vs.* 1/[amine] shown in Figure 2(a) curves downward in a low amine concentration region.

It is well known that k_3 is independent of the amine basicity.[5,6] Because a more basic amine would deprotonate more rapidly from the aminium moiety of $T^{\pm}$, while the

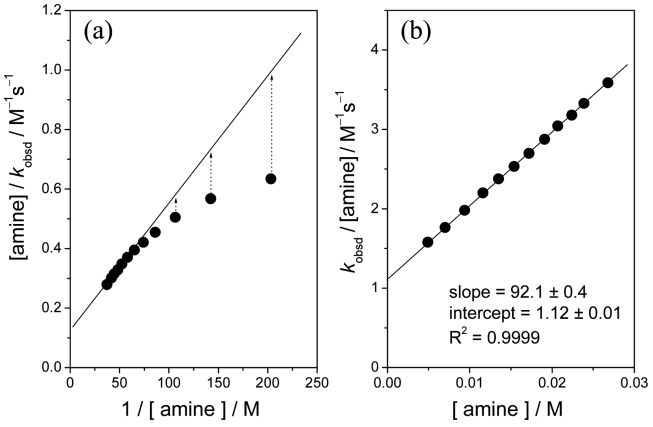


Figure 2. Plots of [amine]/k_{obsd} *vs.* 1/[amine] (a) and k_{obsd}/[amine] *vs.* [amine] (b) for the reaction of 4-nitrophenyl 2-pyridyl carbonate with morpholine in MeCN at 25.0 ± 0.1 °C.

Table 1. Summary of Kinetic Data for Aminolysis of 4-Nitrophenyl 2-Pyridyl Carbonate in MeCN at 25.0 ± 0.1 °C[a]

	amines	pK_a	k_1k_2/k_{-1}	k_1k_3/k_{-1}	k_3/k_2
1	morpholine	16.6	1.12	92.1	82.2
2	1-(2-hydroxyethyl)-piperazine	17.6	7.87	301	38.2
3	piperazine	18.5	69.5	2870	41.3
4	3-methylpiperidine	18.6	96.2	1420	14.8
5	piperidine	18.8	173	1730	10.0

[a]The pK_a values in MeCN were taken from refs. 3a and 9, and the units of k_1k_2/k_{-1}, k_1k_3/k_{-1} and k_3/k_2 are $M^{-1}s^{-1}$, $M^{-2}s^{-1}$ and M^{-1}, in turn.

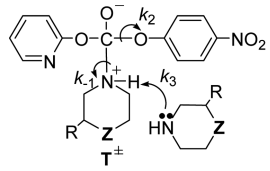


Figure 3. $T^{\pm}$ structure and three different reaction routes.

aminium ion would tend to hold the proton more strongly as the amine becomes more basic. In contrast, the effect of amine basicity on k_2 is not clearly understood.[6,8] Gresser *et al*. reported that amine basicity does not affect k_2 in aminolysis of diaryl carbonates, since there is little or no electron donation from the aminium moiety of $T^{\pm}$ to push out the nucleofuge.[8] However, we have proposed that the amine basicity affects k_2 through an inductive effect, although the "push" by the aminium moiety of $T^{\pm}$ is absent.[6]

It is apparent that the basicity of the amines used in this study is affected by the "Z" moiety of the cyclic amines (*e.g*., the pK_a of the conjugate acid of amine decreases from 18.8 to 17.6 and 16.6 as the "Z" changes from CH_2 to NCH_2CH_2OH and O, in turn). Furthermore, the electronic nature of the Z moiety in the aminium moiety of $T^{\pm}$ would affect the electron density of the reaction site (*i.e*., the central carbon atom) through an inductive effect, although the effect would not be significant because of the long distance between the Z moiety and the reaction site. Accordingly, k_2 would decrease as the Z moiety changes from CH_2 to an electron-withdrawing oxygen atom (*i.e*., from a strongly basic piperidine to a weakly basic morpholine). This idea is consistent with the fact that the k_3/k_2 ratio increases as the amine becomes less basic or *vice versa* (Table 1).

In summary, (1) aminolysis of 4-nitrophenyl 2-pyridyl carbonate proceeds through a stepwise mechanism with two intermediates $T^{\pm}$ and T^{-}, (2) the assumption $k_{-1} >> k_2 + k_3$[amine] is valid in the experimental conditions, (3) the k_3/k_2 ratio is dependent on the amine basicity.

Acknowledgments. This research was supported by 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).

Supporting Information: Experimental Section including the kinetic conditions and results.

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