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Kinetic Study on Aminolysis of 4-Nitrophenyl Isonicotinate in Acetonitrile: Effect of Amine Basicity on Reactivity and Reaction Mechanism

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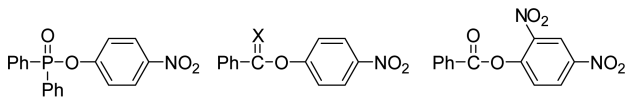
A kinetic study is reported on nucleophilic substitution reactions of 4-nitrophenyl isonicotinate (**7**) with a series of cyclic secondary amines in MeCN. The plots of k_{obsd} *vs*. [amine] curve upward for the reactions with weakly basic amines (*e.g.*, morpholine, 1-(2-hydroxyethyl)piperazine, and piperazine) but are linear for those with strongly basic amines (*e.g.*, piperidine and 3-methylpiperidine). The curved plots for the reactions with the weakly basic amines are typical for reactions reported previously to proceed through uncatalyzed and catalyzed routes with two intermediates (*e.g.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}). In contrast, the linear plots for the reactions with the strongly basic amines indicate that the catalytic route (*i.e.*, the deprotonation process to yield T^{-} from $T^{\pm}$ by a second amine molecule) is absent. The Brønsted-type plots for Kk_2 and Kk_3 (*i.e.*, the rate constants for the uncatalyzed and catalyzed routes, respectively) exhibit excellent linear correlations with $\beta_{nuc} = 0.99$ and 0.69, respectively. The effect of amine basicity on the reaction mechanism is discussed in detail.

Key Words : Aminolysis, 4-Nitrophenyl isonicotinate, Energy profile, Stepwise mechanism, Catalysis

Introduction

Aminolysis of esters is a fundamental reaction not only in organic synthesis but also in biological processes such as biosynthesis of peptides and enzyme actions.[1] Nucleophilic substitution reactions of esters have been reported to proceed through a concerted mechanism or *via* a stepwise pathway with one or two intermediates depending on the reaction conditions (*e.g.*, the nature of the electrophilic center, the substituent in the leaving- and nonleaving-groups, the reaction medium, *etc.*).[1-9]

Aminolysis of 4-nitrophenyl diphenylphosphinate (**1**) has been suggested to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.4 \pm 0.1$.[5] However, the reactions of 4-nitrophenyl benzoate (**2a**) with a series of cyclic secondary amines have been proposed to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate $T^{\pm}$, in which expulsion of the leaving group from $T^{\pm}$ occurs in rate-determining step (RDS), on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.81$.[6] In contrast, the corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**2b**) have been shown to proceed through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and its deprotonated form T^{-}),[7] indicating that the nature of the electrophilic center (*e.g.*, P=O, C=O and C=S) governs the reaction mechanism.



1 X=O (**2a**), S (**2b**) **3**

Chart 1

The nature of solvents is also known to be an important factor which affects the reaction mechanism,[8] *e.g.*, aminolysis of 2,4-dinitrophenyl benzoate (**3**) has been reported to proceed through a stepwise mechanism with a change in RDS in H_2O on the basis of a curved Brønsted-type plot[9a] but through a concerted mechanism in MeCN on the basis of a linear Brønsted-type plot with $\beta_{nuc} = 0.40$.[9b] Instability of $T^{\pm}$ in MeCN has been proposed to force the reaction to proceed through a concerted mechanism, since the zwitterionic $T^{\pm}$, which could be stabilized in the aqueous medium through H-bonding interactions with H_2O molecules, becomes highly unstable in the aprotic solvent due to the repulsion between the $C–O^{-}$ moiety of $T^{\pm}$ and the negative dipole end of MeCN.[9b] This idea is consistent with the computational studies.[10-12] Recent computational studies have questioned the existence of $T^{\pm}$ in gas-phase or in aprotic solvents, *e.g.*, Illieva *et al.* failed to identify $T^{\pm}$ for the reaction of methyl formate with ammonia in the gas phase,[11] while Sung *et al.* reported that at least five H_2O molecules are required to stabilize $T^{\pm}$ in the reaction of phenyl acetate with ammonia.[12]

We have shown that aminolysis of 4-pyridyl X-substituted-benzoates (**4**) with a series of cyclic secondary amines in MeCN 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 = a strong electron-withdrawing group (EWG) such as 4-NO_2 or 4-CN but without the deprotonation process to form T^{-} from $T^{\pm}$ when X = a weak EWG or an electron-donating group (EDG).[13a] In contrast, the corresponding reaction of 2-pyridyl X-substituted-benzoates (**5**) has been reported to proceed through a concerted mechanism with a transition state (TS) structure similar to **6**,[13b] which is structurally not

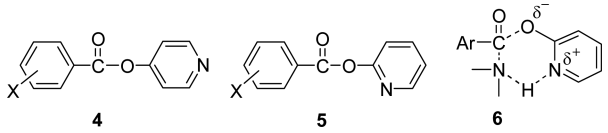


Chart 2

possible for the reaction of **4**. The H-bonding interaction illustrated in **6** has been suggested to force the reaction to proceed through a concerted mechanism by increasing the nucleofugality of the leaving group.[13b] Because, the intramolecular H-bonding interaction would decrease the leaving-group basicity by changing the highly basic 2-pyridyloxide (pK_a = 11.62 in H_2O) to the weakly basic 2-pyridiniumoxide (pK_a = 0.75 in H_2O) or to its tautomer 2-pyridone.[14]

Our study has now been extended to reactions of 4-nitrophenyl isonicotinate (**7**) with a series of cyclic secondary amines in MeCN to investigate the reaction mechanism. Although substrate **7** was often used to test catalytic host systems involving metal ions,[15] detailed information on the reaction mechanism is lacking. We wish to report that the reaction proceeds through a stepwise mechanism with one or two intermediates depending on the basicity of the incoming amine as shown in Scheme 1.

Results and Discussion

The kinetic study was carried out under pseudo-first-order conditions in which the amine concentration was kept in excess of the substrate concentration. All of the reactions in this study proceeded with quantitative liberation of 4-nitrophenoxide ion and obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The plots of $\ln (A_\infty - A_t)$ *vs*. t were linear over 90% of the total reaction. The uncertainty in the k_{obsd} values is estimated to be less than ± 3% from replicate runs. As shown in Figure 1, the plot of k_{obsd} vs. [amine] curves upward for the reaction with weakly basic amines (*e.g.*, morpholine), but is linear for the reaction with strongly basic amines (*e.g.*, piperidine).

Effect of Amine Basicity on Reaction Mechanism. As shown in Figure 1, the plot of k_{obsd} *vs*. [amine] for the reaction with morpholine curves upward. Similarly curved plots were obtained for the reactions with 1-(2-hydroxyethyl)-piperazine and piperazine (Figures S1 and S2 in the Supporting Information). Such upward curvature is typical for reactions reported previously to proceed through a stepwise mechanism with two intermediates ($T^{\pm}$ and T^-).[2,7] In contrast, the linear plot for the reactions with strongly basic amines (*e.g.*, piperidine and 3-methylpiperidine) indicates that the deprotonation process to form T^- from the aminium moiety of $T^{\pm}$ by a second amine molecule is absent. This demonstrates convincingly that the amine basicity governs the reaction mechanism for the aminolysis of **7**. Thus, one can suggest that the reaction of **7** in this study proceeds through a stepwise mechanism with one or two intermediates depending on the amine basicity (*i.e.*, through the catalyzed and/or uncatalyzed routes as shown in Scheme 1).

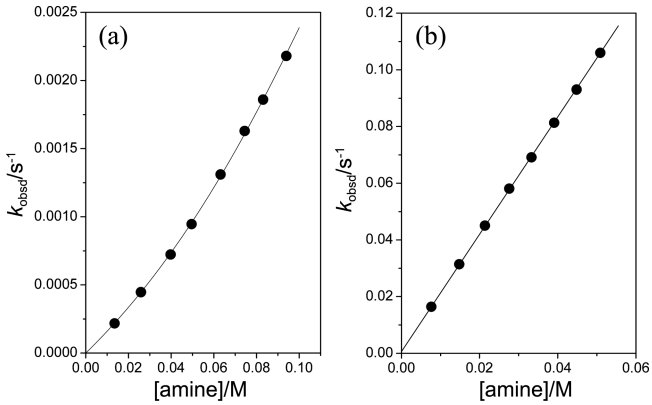


Figure 1. Plots of k_{obsd} *vs.* [amine] for the reactions of 4-nitrophenyl isonicotinate (**7**) with morpholine (a) and piperidine (b) in MeCN at 25.0 ± 0.1 °C.

To account for the kinetic result that the reaction mechanism is governed by the basicity of the incoming amine, a

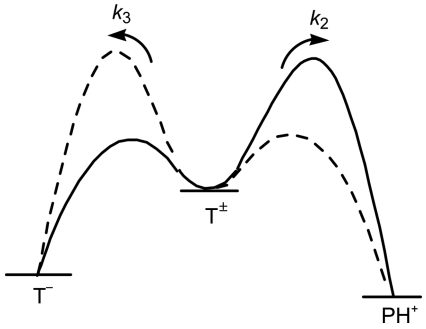
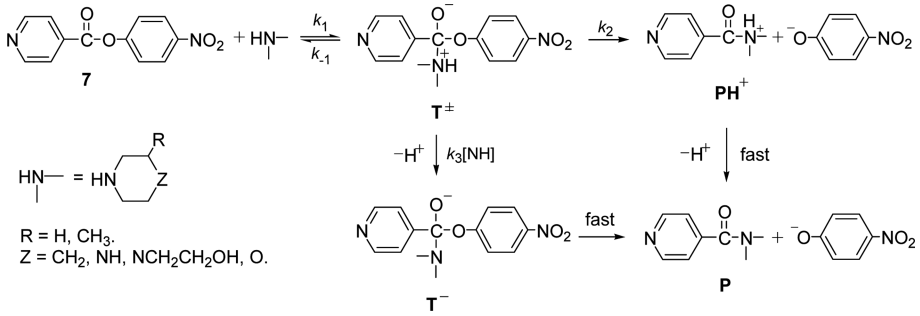


Figure 2. A qualitative energy profile for the processes that yield T^- and PH^+ from $T^{\pm}$.



Scheme 1

qualitative energy profile is illustrated in Figure 2 for the processes that yield T^- and PH^+ from $T^\pm$ (see Scheme 1 for the definition of $T^\pm$, T^-, PH^+ and the other terms). It is apparent that the reaction would proceed through the k_2 path (*i.e.*, the uncatalyzed route) when the energy barrier to form T^- from $T^\pm$ is higher than that to yield PH^+ (*i.e.*, the dotted line) but *via* the k_3 path (*i.e.*, the catalyzed route) when the energy barrier to form PH^+ from $T^\pm$ is higher than that to yield T^- (*i.e.*, the solid line).

The fact that the reaction mechanism is governed by the amine basicity suggests that the amine basicity would affect the energy barrier for the k_2 and k_3 processes. It is apparent that a more basic amine would deprotonate more rapidly from the aminium moiety of $T^\pm$, while the aminium ion would tend to hold the proton more strongly as the amine becomes more basic. Consequently, k_3 would be little influenced by the amine basicity. In contrast, the effect of amine basicity on k_2 is not clearly understood. Gresser and Jencks have concluded 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 leaving group.[16] Castro *et al.* have drawn a similar conclusion for aminolyses of ethyl phenyl thionocarbonate, methyl 4-nitrophenyl thionocarbonate, and 3-methoxyphenyl 4-nitrophenyl thionocarbonate.[17] However, we propose that the amine basicity affects k_2 through an inductive effect on the basis of the fact that the reactions of **7** with the weakly basic amines proceed through the k_3 process but the catalytic route (*i.e.*, the k_3 process) is absent for the reactions with the strongly basic amines.

To rationalize the above proposal, a $T^\pm$ structure, which shows three different processes under the presence of a cyclic amine, is illustrated in Figure 3. The electronic nature of the "Z" moiety in the cyclic amine affects its basicity (*e.g.*, the pK_a of the conjugate acid of the amines in MeCN 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).[18] Moreover, the electronic nature of the Z moiety in the aminium moiety of $T^\pm$ would influence 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. Consequently, modification of the Z moiety from CH_2 to an electron-withdrawing O atom (*i.e.*, from strongly basic piperidine to weakly basic morpholine) would decrease k_2 by decreasing the electron density of the reaction center (or by increasing the energy barrier to form PH^+ from $T^\pm$). This idea is consistent with the fact that the reactions with weakly basic amines proceed through the catalytic route (*i.e.*, the k_3 process) but the catalytic process is absent for the reactions with the strongly basic amines.

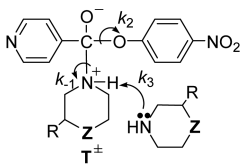


Figure 3. $T^\pm$ structure with an amine showing three different processes (*i.e.*, k_{-1}, k_2 and k_3).

Another factor that might account for the kinetic result that the aminolysis of **7** proceeds through a stepwise mechanism with two intermediates is the nature of the pyridine ring in **7**. Since a pyridine ring is considered as an analogue of benzene ring that carries a strong EWG, it would decrease the electron density of the reaction center through an inductive effect. Thus, modification of the nonleaving group from benzoyl to isonicotinyl would increase the acidity of the aminium moiety of $T^\pm$, which decreases the energy barrier for the k_3 process (*i.e.*, an increase in k_3). In contrast, the pyridine ring in **7** would increase the energy barrier for the k_2 process by decreasing the electron density of the reaction center (*i.e.*, a decrease in k_2). This idea explains the fact that the aminolysis of **7** with weakly basic amines proceeds through a stepwise mechanism with two intermediates while the corresponding reaction of 4-nitrophenyl benzoate proceeds through a stepwise mechanism with only one intermediate $T^\pm$.

Dissection of k_{obsd} into Rate Constants Kk_2 and Kk_3. To examine the above proposal that the amine basicity affects k_2, the k_{obsd} values have been dissected into the rate constants for the uncatalyzed and catalyzed routes (*i.e.*, Kk_2 and Kk_3, respectively) using the following equations. Eq. (1) can be derived on the basis of the kinetic results and the mechanism proposed in Scheme 1. Under the assumption $k_2 << k_3$[amine], Eq. (1) can be simplified to Eq. (2). Thus, one might expect that the plot of [amine]/k_{obsd} *vs.* 1/[amine] would be linear if the assumption is valid. In fact, as shown in Figure 4(a), the plot of [amine]/k_{obsd} *vs.* 1/[amine] for the reaction with morpholine is linear when the amine concentration is high but exhibits negative deviation as the amine concentration decreases. This indicates that the above assumption is valid only when the amine concentration is high, but 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.

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

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

It is noted that the first step in Scheme 1 is a preequilibrium. Thus, one can assume that $k_{-1} >> k_2 + k_3$[amine]. In this case, Eq. (1) can be simplified to Eq. (3). Accordingly, one might expect that the plot of k_{obsd}/[amine] *vs.* [amine] would be linear. In fact, as shown in Figure 4(b), the plot of k_{obsd}/[amine] *vs.* [amine] for the reaction with morpholine exhibits an excellent linear correlation with a positive intercept. The corresponding plots for the reactions with 1-(2-hydroxyethyl)-piperazine and piperazine are also linear (Figures S1b and S2b in the Supporting Information), indicating that the proposed reaction mechanism and the assumption $k_{-1} >> k_2 + k_3$[amine] are correct for the reactions

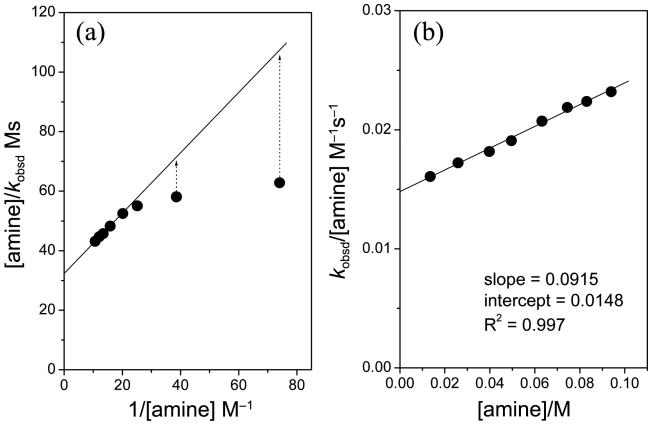


Figure 4. Plots of [amine]/k_{obsd} *vs.* 1/[amine] (a) and k_{obsd}/[amine] *vs.* [amine] (b) for the reaction of 4-nitrophenyl isonicotinate (**7**) with morpholine in MeCN at 25.0 ± 0.1 °C.

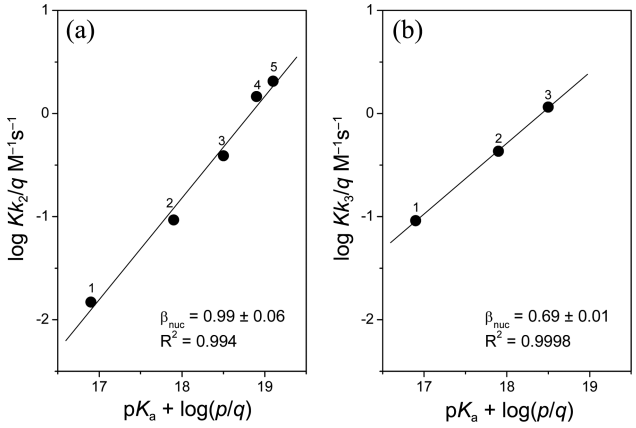


Figure 5. Brønsted-type plots of Kk_2 (a) and Kk_3 (b) for the reactions of 4-nitrophenyl isonicotinate (**7**) with cyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

with weakly basic amines. However, k_{-1} would become smaller as the amine basicity increases. This can explain why the reactions with strongly basic amine result in linear plots of k_{obsd} *vs*. [amine].

$$k_{obsd}/[amine] = k_1k_2/k_{-1} + k_1k_3[amine]/k_{-1}$$
$$= Kk_2 + Kk_3[amine], \text{ where } K = k_1/k_{-1} \quad (3)$$

Thus, the Kk_2 and Kk_3 values for the reactions with morpholine, 1-(2-hydroxyethyl)piperazine and piperazine were determined from the intercept and slope of the linear plots of k_{obsd}/[amine] *vs*. [amine], respectively. Under the assumption $k_{-1} >> k_2$, the second-order rate constants (Kk_2) for the reactions with piperidine and 3-methylpiperidine were calculated from the slope of the linear plots of k_{obsd} *vs*. [amine] and are summarized in Table 1 together with the Kk_2 and Kk_3 values for the reactions with the weakly basic amines.

As shown in Table 1, the Kk_2 values decrease as the amine basicity decreases, *e.g.*, Kk_2 decreases from 2.06 M^{-1}s^{-1} to 0.0929 and 0.0148 M^{-1}s^{-1} as the pK_a of the conjugate acid of the amine decreases from 18.8 to 17.6 and 16.6, in turn. A similar result is demonstrated for Kk_3 although the Kk_3 values for the reactions with piperidine and 3-methylpiperidine are not available due to the absence of the catalytic route (*i.e.*, the k_3 process). The effects of amine basicity on Kk_2 and Kk_3 are illustrated in Figure 5. The Brønsted-type plot for the uncatalyzed reaction (*i.e.*, Kk_2) exhibits an excellent linear correlation when the Kk_2 and pK_a values were corrected statistically using p and q (*i.e.*, $p = 2$ while $q = 1$ except $q = 2$ for piperazine).[19] The Brønsted-type plot for the catalyzed reaction (*i.e.*, Kk_3), although only three points are used to construct the plot, results in also an excellent linear correlation, indicating that the Kk_2 and Kk_3 values calculated are considered to be highly reliable. The β_{nuc} values for the uncatalytic and catalytic routes are 0.99 and 0.69, respectively, implying that k_2 is more sensitive to the amine basicity than k_3. A similar result has been reported for the corresponding reactions of 4-pyridyl 3,5-dinitrobenzoate (*e.g.*, $\beta_{nuc} = 0.98 \pm 0.03$ for Kk_2 and $\beta_{nuc} = 0.79 \pm 0.04$ for Kk_3).[13a] Thus, the fact that Kk_2 results in a larger β_{nuc} value than Kk_3 supports the preceding proposal that k_2 is affected by the amine basicity through an inductive effect while k_3 is little influenced by the amine basicity.

Table 1. Summary of Kinetic Data for the Reactions of 4-Nitrophenyl Isonicotinate (**7**) with Cyclic Secondary Amines in MeCN at 25.0 ± 0.1 °C

	amine	pK_a[a]	Kk_2/M^{-1}s^{-1}	Kk_3/M^{-2}s^{-1}
1	morpholine	16.6	0.0148	0.0915
2	1-(2-hydroxyethyl)piperazine	17.6	0.0929	0.431
3	piperazine	18.5	0.777	4.62
4	3-methylpiperidine	18.6	1.46	–
5	piperidine	18.8	2.06	–

[a]The pK_a data were taken from ref. 18.

Conclusions

The kinetic study on the aminolysis of **7** in MeCN has shown that the reaction proceeds through uncatalytic and catalytic routes depending on the amine basicity: (1) The curved plot of k_{obsd} *vs.* [amine] for the reactions with the weakly basic amines indicates that the reactions proceed through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and T^{-}), while the linear plot for the reactions with strongly basic amines implies that the deprotonation process by a second amine molecule to form T^{-} from $T^{\pm}$ is absent. (2) The energy barrier for the uncatalyzed route (*i.e.*, the k_2 process) increases as the amine basicity decreases. This accounts for the kinetic result that the reactions with the weakly basic amines proceed through the catalytic route (*i.e.*, the k_3 process). (3) The Brønsted-type plots for the Kk_2 and Kk_3 are linear with β_{nuc} values of 0.99 and 0.69, respectively. The larger β_{nuc} value for Kk_2 than for Kk_3 further supports the proposal that the amine basicity affects k_2 while k_3 is little influenced by the amine basicity.

Experimental Section

Materials. 4-Nitrophenyl isonicotinate (**7**) was readily prepared from the reaction of isonicontinyl chloride with 4-nitrophenol in anhydrous ether under the presence of triethylamine as reported previously.[20] The crude product was purified by column chromatography and the purity was checked by the melting point and spectral data such as ^{1}H and ^{13}C NMR spectra. MeCN and other chemicals were of the highest quality available.

Kinetics. The kinetic study was carried out using a UV-Vis spectrophotometer equipped with a constant temperature circulating bath to maintain the reaction mixture at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of 4-nitrophenoxide ion. All of the reactions in this study were performed under pseudo-first-order conditions, in which the concentration of the amine was kept in excess of the substrate concentration.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of the substrate in acetonitrile to a 10-mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and aliquot of the amine stock solution. All solutions were transferred by gas-tight syringes. Generally, the concentration of amines in the reaction mixtures was *ca.* (1–10) × 10^{-2} M, while the concentration of the substrate was *ca*. 4 × 10^{-5} M. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, ln ($A_\infty - A_t$) = $-k_{obsd}t + C$. The plots of ln ($A_\infty - A_t$) *vs.* time were linear over 90 % of the total reaction.

Products Analysis. 4-Nitrophenoxide ion (and/or its conjugate acid, 4-nitrophenol) was liberated quantitatively and identified as one of the products by comparison of the UV-Vis spectrum after completion of the reaction with that of authentic sample under the same reaction condition.

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Supporting Information. Kinetic conditions and results.

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