Aminolysis of 2,4-Dinitrophenyl and 3,4-Dinitrophenyl Benzoates: Effect of *ortho*-Nitro Group on Reactivity and Mechanism

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Received July 31, 2008

Second-order rate constants (k_N) have been measured spectrophotometrically for reactions of 3,4-dinitrophenyl benzoates (**5b**) with a series of alicyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The kinetic data have been compared with the data reported previously for the corresponding reactions of 2,4-dinitrophenyl benzoates (**5a**) to investigate the effect of changing the nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide on reactivity and mechanism. The kinetic results show that aminolyses of **5a** and **5b** proceed through the same mechanism, *i.e.*, a zwitterionic tetrahedral intermediate ($T^{\pm}$) with a change in the rate-determining step (RDS). Substrate **5a** is more reactive than **5b** when breakdown of $T^{\pm}$ is the RDS but less reactive when formation of $T^{\pm}$ is the RDS. Dissection of k_N values into the microscopic rate constants (*e.g.*, k_1 and k_2/k_{-1} ratio) has revealed that **5a** results in larger k_2/k_{-1} ratios but smaller k_1 values than **5b** for all the amines studied. Since 2,4-dinitrophenoxide is less basic and a better nucleofuge than 3,4-dinitrophenoxide, the larger k_2/k_{-1} ratios determined for the reactions of **5a** than for those of **5b** are as expected. The steric hindrance exerted by the *ortho*-nitro group on **5a** contributes to the smaller k_1 values found for the reactions of **5a** than for those of **5b**.

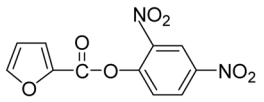
Key Words : Aminolysis, Brønsted-type plot, Steric hindrance, Reaction mechanism, *ortho*-Effect

Introduction

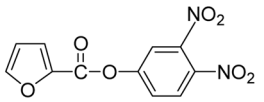
Aminolysis of esters has generally been understood to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate, $T^{\pm}$.[1-7] Curved Brønsted-type plots have often been reported for reactions of esters which possess a good leaving group (*e.g*, from a large β_{nuc} to a small one as the attacking amine becomes more basic than the leaving group by 4 to 5 pK_a units). Such a curved Brønsted-type plot has often been suggested as evidence for a change in rate-determining step (RDS) of a stepwise mechanism.[1-7]

Brønsted and Hammett equations have most commonly been employed to investigate reaction mechanism and/or to correlate reactivity with basicity or substituent constants.[8] It is well known that nucleophilicity increases with increasing the basicity of nucleophiles while nucleofugality decreases with increasing the basicity of nucleofuges. However, Gresser and Jencks found that 2,4-dinitrophenyl phenyl carbonate is less reactive than 3,4-dinitrophenyl phenyl carbonate toward quinuclidines,[1d] although 2,4-dinitrophenoxide is less basic than 3,4-dinitrophenoxide by *ca.* 1.3 pK_a units. Gresser and Jencks concluded that steric hindrance is responsible for the decreased reactivity of 2,4-dinitrophenyl phenyl carbonate compared to 3,4-dinitrophenyl phenyl carbonate, since the nitro group at the *ortho*-position may cause steric hindrance.[1d]

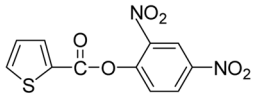
A similar result has been reported for aminolysis of 2,4-dinitrophenyl and 3,4-dinitrophenyl 2-furoates (**1a** and **1b**) and 2-thiophenecarboxylates (**2a** and **2b**).[9] We found that **1a** is only slightly more reactive than **1b** toward piperidine,[9a] while **2a** is even less reactive than **2b**.[9b] Dissection of the macroscopic second-order rate constant (k_N) into the microscopic rate constants (*e.g.*, k_1 and k_2/k_{-1}) has shown that **1a** and **2a** exhibit smaller k_1 values but larger k_2/k_{-1} ratios than **1b** and **2b**, respectively.[9] Our studies on the aminolyses of **1a**, **b** and **2a**, **b** have shown that steric hindrance contributes to the smaller k_1 values for the reactions of the substrates with an *ortho*-nitro group (*e.g.*, **1a** and **2a**).



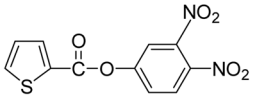
1a



1b

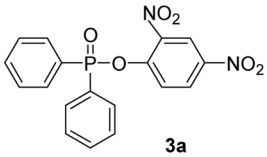


2a

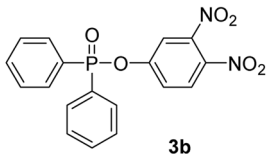


2b

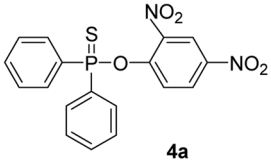
However, we have found that the steric hindrance reported for the reactions of the carbonyl esters (**1a** and **2a**) is absent for aminolyses of phosphorus centered esters, since 2,4-



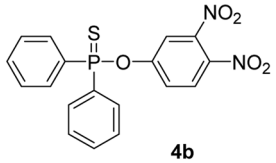
3a



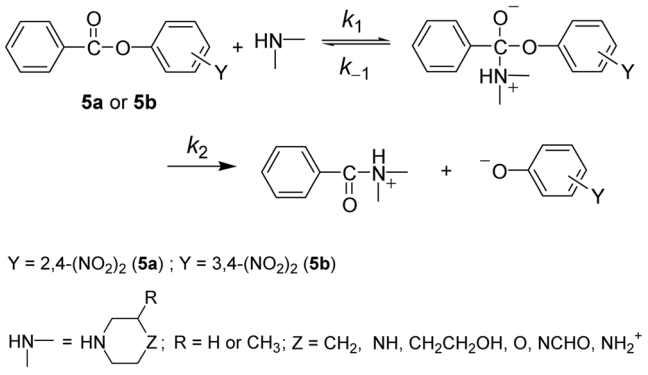
3b



4a



4b



Scheme 1

dinitrophenyl diphenylphosphinate (**3a**) and diphenylphosphinothioate (**4a**) are more reactive than 3,4-dinitrophenyl diphenylphosphinate (**3b**) and diphenylphosphinothioate (**4b**), respectively.[10a,b] Furthermore, the Brønsted-type plots have been found to be linear for aminolyses of Y-substituted phenyl diphenylphosphinates and diphenylphosphinothioates including **3a** and **4a**.[10a,b]

We performed a kinetic study on aminolysis of 2,4-dinitrophenyl benzoate (**5a**) and concluded that the reaction proceeds through $T^{\pm}$ with a change in the RDS on the basis of a curved Brønsted-type plot.[7a,b] The kinetic study has now been extended to reactions of 3,4-dinitrophenyl benzoate (**5b**) with a series of alicyclic secondary amines (Scheme 1). The kinetic data in the current study have been compared with those reported previously for the corresponding reactions of **5a** to investigate the effect of changing the nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide on the reactivity and reaction mechanism (*i.e.*, an *ortho*-substituent effect) in a microscopic rate constant level.

Results and Discussion

The reactions of **5b** with all the amines studied in this work obeyed first-order kinetics and proceeded with quantitative liberation of 3,4-dinitrophenoxide ion under pseudo-first-order conditions. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation, $\ln(A - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} *vs.* the 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^- ion from the hydrolysis of amines to k_{obsd} is negligible. Accordingly, the rate equation can be given as eq (1). The second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} *vs.* the amine concentration. Five different amine concentrations were used to determine k_N values. It is estimated from replicate runs that the uncertainty in the rate constants is less than 3%. The k_N values determined in this way are summarized in Table 1.

$$\text{rate} = k_{obsd}[\mathbf{5b}], \text{ where } k_{obsd} = k_N[\text{amine}] \quad (1)$$

Effect of *ortho*-Nitro Group on Reactivity and Mechanism. Table 1 shows that the second-order rate constant (k_N) for the reaction of **5b** decreases with decreasing the basicity of amines, *i.e.*, k_N decreases from 191 $M^{-1}s^{-1}$ to 10.0 and 0.0867 $M^{-1}s^{-1}$ as the pK_a of amines decreases from 11.02 to 8.65 and 5.95, respectively. A similar result is presented for the corresponding reactions of **5a**. It is noted that **5b** is less reactive than **5a** when the attacking amines are weakly basic (*i.e.*, $pK_a \leq 9.85$) but becomes more reactive as the amine basicity increases further (*i.e.*, $pK_a \geq 10.80$).

Table 1. Summary of Second-order Rate Constants (k_N, $M^{-1}s^{-1}$) for Reactions of 2,4-Dinitrophenyl Benzoate (**5a**) and 3,4-Dinitrophenyl Benzoate (**5b**) with Secondary Alicyclic Amines in 20 mol % DMSO at 25.0 ± 0.1°C[a]

Entry	Amines	pK_a	k_N / $M^{-1}s^{-1}$	
			5a	**5b**
1	piperidine	11.02	174	191
2	3-methylpiperidine	10.80	167	182
3	piperazine	9.85	82.1	61.7
4	morpholine	8.65	19.6	10.0
5	1-formylpiperazine	7.98	5.43	2.66
6	piperazinium ion	5.95	0.467	0.0867

[a] pK_a values and the data for reaction of **5a** were taken from ref. 7.

In Figure 1 is demonstrated the effect of amine basicity on reactivity as well as the effect of changing the nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrphenoxide. The Brønsted-type plot for the reactions of **5b** is curved downwardly, when k_N and pK_a are statistically corrected using p and q (*i.e.*, $p = 2$ except $p = 4$ for piperazinium ion and $q = 1$ except $q = 2$ for piperazine).[11] A similar result is shown for the corresponding reactions of **5a**. However, the slopes of the Brønsted-type plots are slightly different, *i.e.*, the slope decreases from 0.83 to 0.34 and from 0.74 to 0.34 as the

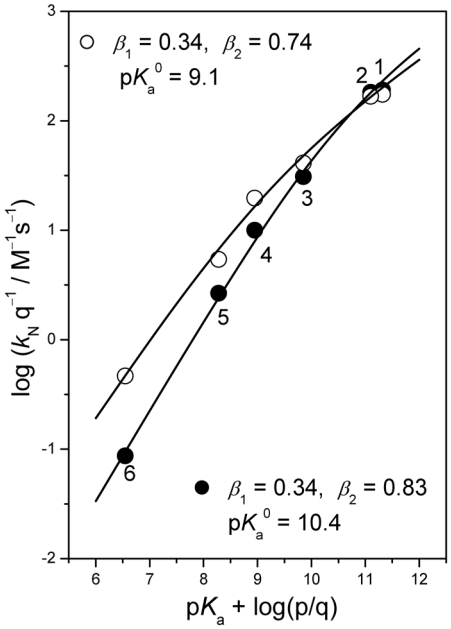


Figure 1. Brønsted-type plots for the reactions of **5a** (○) and **5b** (●) with secondary alicyclic amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

amine basicity increases for the reactions of **5b** and **5a**, respectively. It is also noted that **5a** is more reactive than **5b** when the attacking amine is weakly basic but becomes slightly less reactive when the amine is strongly basic (*e.g.*, $pK_a \geq 10.80$).

It is known that a change in RDS occurs at the center of the Brønsted curvature, defined as pK_a^o.[12] The pK_a^o for ester aminolysis has generally been reported to be 4 to 5 pK_a units higher than the pK_a of the conjugate acid of leaving group.[2-4] The center of the Brønsted curvature for the reactions of **5a** was determined to be 9.1, which is *ca.* 5 pK_a units higher than the pK_a of 2,4-dinitrophenol (*i.e.*, pK_a = 4.11), the conjugate acid of the leaving group. Thus, the curved Brønsted-type plot for the reactions of **5a** was interpreted as a change in the RDS.[7] The center of the Brønsted curvature for the reactions of **5b** determined is 10.4, which is also *ca.* 5 pK_a units higher than the pK_a of 3,4-dinitrophenol (*i.e.*, pK_a = 5.42). Thus, one can suggest that the reactions of **5b** proceed also through a stepwise mechanism with a change in the RDS on the basis of the curved Brønsted-type plot.

To test whether the aminolyses of **5a** and **5b** proceed through the same mechanism or not, a plot of log k_N for the reactions of **5a** *vs*. log k_N for the corresponding reactions of **5b** has been constructed. As shown in Figure 2, an excellent linear correlation is obtained (*i.e.*, $R^2 = 0.9992$) with a slope of 1.29. Such a good linear plot suggests that the reactions of **5a** and **5b** proceed through the same mechanism. The fact that the slope is larger than unity implies that **5b** is more sensitive than **5a** toward amine basicity. Accordingly, one can conclude that modification of the nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide influences the reactivity but not the reaction mechanism.

Dissection of Macroscopic Rate Constants into Microscopic Rate Constants. On the basis of the mechanism proposed above, the curved Brønsted-type plot for the aminolysis of **5b** has been analyzed using a semiempirical equation (eq. 2).[1d,12] The parameters β_1 and β_2 represent the slope of the curved Brønsted plot for the reactions with strongly basic and weakly basic amines, respectively. Here $k_N°$ refers to the k_N value at $pK_a°$. The parameters determined from the fitting of eq. (2) to the experimental points are β_1 = 0.34, β_2 = 0.83, and pK_a^o = 10.4 for the reactions of **5b**.

$$\log (k_N/k_N°) = \beta_2(pK_a - pK_a°) - \log [(1 + \alpha)/2]$$

$$\text{where } \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a°) \quad (2)$$

The k_N values for the reactions of **5b** have been dissected into their microscopic rate constants through eqs. (3)-(10) as shown below. The macroscopic second-order rate constant k_N can be expressed as eq. (3) by applying the steady-state conditions to the intermediate on the basis of the proposed mechanism.

$$k_N = k_1k_2/(k_{-1} + k_2) \quad (3)$$

The k_2/k_{-1} ratios associated with the aminolysis of **5b** have been determined using eqs. (4)-(9). Eq. (3) can be simplified to eq. (4) or (5). Then, β_1 and β_2 can be expressed as eqs. (6) and (7), respectively.

$$k_N = k_1k_2/k_{-1}, \text{ when } k_2 << k_{-1} \quad (4)$$

$$k_N = k_1, \text{ when } k_2 >> k_{-1} \quad (5)$$

$$\beta_1 = d(\log k_1)/d(pK_a) \quad (6)$$

$$\beta_2 = d(\log k_1k_2/k_{-1})/d(pK_a) = \beta_1 + d(\log k_2/k_{-1})/d(pK_a) \quad (7)$$

Eq. (7) can be rearranged as eq. (8). Integral of eq. (8) from pK_a^o results in eq. (9). Since $k_2 = k_{-1}$ at pK_a^o, the term $(\log k_2/k_{-1})_{pKa^o}$ is zero. Therefore, one can calculate the k_2/k_{-1} ratios for the aminolysis of **5b** from eq. (9) using pK_a^o = 10.4, β_1 = 0.34, and β_2 = 0.83. The k_1 values have been determined from eq. (10) using the k_N values in Table 1 and the k_2/k_{-1} ratios calculated above. The k_2/k_{-1} ratios and k_1 values are summarized in Table 2 together with the data for the corresponding reactions of **5a**.

$$\beta_2 - \beta_1 = d(\log k_2/k_{-1})/d(pK_a) \quad (8)$$

$$(\log k_2/k_{-1})_{pKa} = (\beta_2 - \beta_1)(pK_a - pK_a^o) \quad (9)$$

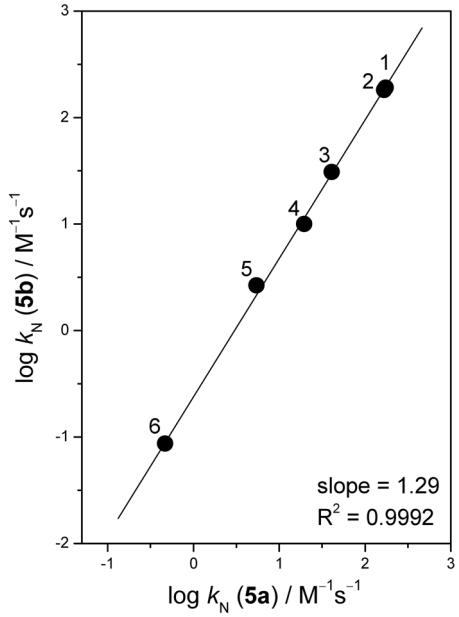


Figure 2. Plot of log k_N for the reactions of **5a** *vs*. log k_N for the reactions of **5b** in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

Table 2. Summary of Microscopic Rate Constants k_2/k_{-1} Ratios and k_1 values for the Reactions of **5b** and **5a** (in parentheses) with Secondary Alicyclic Amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

Entry	Amine	pK_a	k_2/k_{-1}	$k_1/M^{-1}s^{-1}$
1	piperidine	11.02	2.82(7.73)	258(197)
2	3-methylpiperidine	10.80	2.20(6.31)	265(193)
3	piperazine	9.85	0.538(2.00)	176(123)
4	morpholine	8.65	0.195(0.871)	61.3(42.1)
5	1-formylpiperazine	7.98	0.0915(0.470)	31.7(17.0)
6	piperazinium ion	5.95	0.0130(0.096)	6.76(5.36)

[a]The data in the parentheses for the reactions of **5a** were taken from ref. 7b.

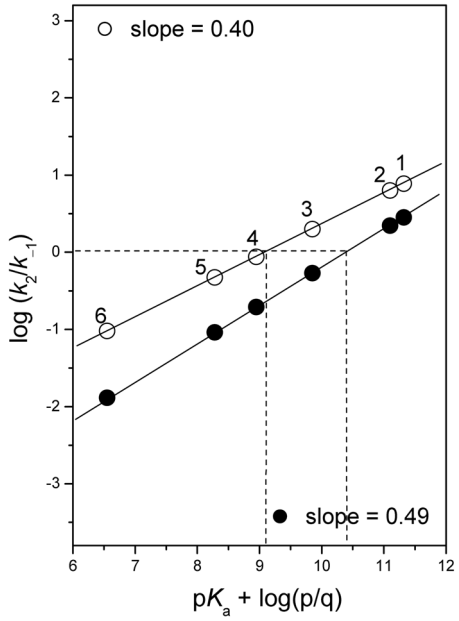


Figure 3. Plots of log k_2/k_{-1} versus pK_a for the reactions of **5a** (○) and **5b** (●) with secondary alicyclic amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

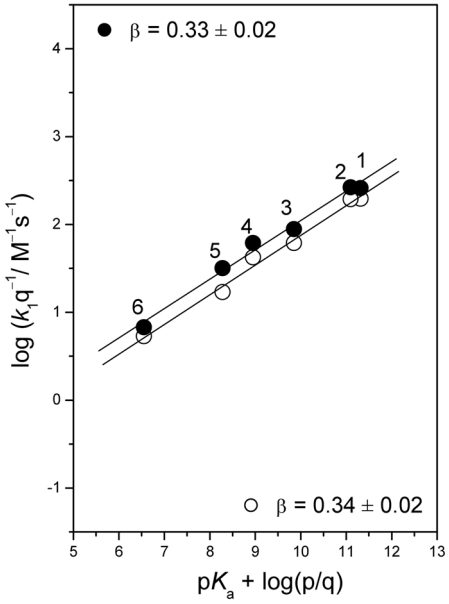


Figure 4. Brønsted-type plots for k_1 for the reactions of **5a** (○) and **5b** (●) with secondary alicyclic amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

$$k_N = k_1k_2/(k_{-1} + k_2) = k_1/(k_{-1}/k_2 + 1) \quad (10)$$

Effect of *ortho*-Nitro Group on Microscopic Rate Constants. As shown in Table 2, the k_2/k_{-1} ratio decreases as the amine basicity decreases. It is noted that $k_2/k_{-1} > 1$ when pK_a ≥ 10.80 but $k_2/k_{-1} < 1$ when pK_a ≤ 9.85 for the reactions of **5b**. On the other hand, $k_2/k_{-1} > 1$ when pK_a ≥ 9.85 but $k_2/k_{-1} < 1$ when pK_a ≤ 8.65 for the reactions of **5a**. This is in accord with the proposal that the RDS for the aminolysis of **5a** and **5b** changes at pK_a = 9.1 and 10.4, respectively.

The effect of amine basicity on the k_2/k_{-1} ratio is illustrated in Figure 3. The plots are linear with slopes of 0.40 and 0.49 for the reactions of **5a** and **5b**, respectively. The k_2 value has been suggested to be independent of amine basicity, since the push by the N atom of the aminium moiety of $T^{\pm}$ to expel the leaving group is absent.[1d] On the other hand, k_{-1} would decrease with increasing amine basicity. This idea is consistent with the positive slope shown in Figure 3.

It is noted that **5a** exhibits a larger k_2/k_{-1} ratio than **5b** for a given amine. Since 2,4-dinitrophenoxide is less basic and a better nucleofuge than 3,4-dinitrophenoxide, one can expect **5a** would exhibit a larger k_2 value than **5b**. In contrast, the leaving group basicity would not influence the k_{-1} value significantly. Therefore, the fact that **5a** results in a larger k_2/k_{-1} ratio than **5b** is consistent with the expectation on the basis of the basicity of the leaving groups.

In Figure 4 are demonstrated Brønsted-type plots for k_1 for the reactions of **5a** and **5b**. The plots are linear with similar slopes, *i.e.*, β_1 = 0.33 and 0.34 for the reactions of **5a** and **5b**, respectively. Interestingly, **5b** exhibits slightly larger k_1 values than **5a** for all the amines studied. This is an unexpected result, since the C=O bond of **5b** would be less electrophilic than that of **5a** on the basis of the fact that 3,4-dinitrophenoxide is more basic than 2,4-dinitrophenoxide. Accordingly, the basicity difference between the two leaving groups cannot account for the difference in k_1 values determined for the aminolyses of **5a** and **5b**.

The *ortho*-NO_2 in the nucleofuge of **5a** would exert steric hindrance when the amine approaches to the electrophilic center to form an intermediate, $T^{\pm}$ (*i.e.*, the k_1 step). Thus, one can suggest that steric hindrance exerted by *ortho*-NO_2 is responsible for the fact that **5a** results in smaller k_1 values than **5b**.

However, the steric hindrance exerted by *ortho*-NO_2 is insignificant when the k_2 step is RDS. This is because **5a** results in larger k_N values than **5b** when the k_2 step is the RDS (*i.e.*, pK_a < 10.4) but smaller k_N values when the k_1 step is the RDS (*i.e.*, pK_a > 10.4). This argument can be further supported by the fact that $k_N = k_1k_2/k_{-1}$ when the k_2 step is the RDS and the k_2/k_{-1} ratios have been shown to be larger for the reactions of **5a** than those of **5b** (see Table 2 and Figure 3).

Conclusions

The current study has allowed us to conclude the following: (1) Modification of nucleofuge from 2,4-dinitrophenoxide to 3,4-dinitrophenoxide influences reactivity but does not affect mechanism for the aminolyses of **5a** and **5b**. (2) Substrate **5a** is more reactive than **5b** when the k_2 step is the RDS but less reactive when the k_1 step is the RDS. (3) Steric hindrance exerted by the *ortho*-nitro group is responsible for the fact that k_1 is smaller for the reactions of **5a** than for those of **5b**. (4) Substrate **5a** exhibits larger k_2/k_{-1} ratios th-an **5b** as expected from the fact that 2,4-dinitrophenoxide is less basic and a better nucleofuge than 3,4-dinitrophenoxide.

Experimental Section

Materials. Substrate **5b** was readily prepared from the reaction of 3,4-dinitrophenol and benzoyl chloride in the presence of triethylamine in anhydrous ether and purified by column chromatography: mp = 110-111 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54-7.60 (t, J = 7.5 Hz, 2H), 7.65-7.69 (dd, J_1 = 10.0 Hz, J_2 = 2.5 Hz, 1H), 7.76-7.70 (t, J = 7.5 Hz, 1H), 7.85-7.86 (d, J = 2.5 Hz, 1H), 8.06-8.10 (d, J = 10.0 Hz, 1H), 8.18-8.21 (d, J = 7.5 Hz, 2H). Anal. Calcd for $C_{13}H_8N_2O_6$: C, 54.17; H, 2.80. Found: C, 54.08; H, 2.82. Other chemicals including amines were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. Due to the low solubility of **5b** in pure H_2O, 20 mol % DMSO/80 mol % H_2O was used as the reaction medium for the kinetic study. The kinetic studies were performed with a Scinco S-3100 UV-Vis spectrophotometer equipped with a constant temperature circulating bath at 25.0 ± 0.1 °C for slow reactions (*e.g.*, $t_{1/2}$ > 10 s) or with an Applied Photophysics Stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2}$ < 10 s). The reactions were performed under pseudo-first-order conditions, *i.e.*, the amine concentration was at least 20 times greater than that of the substrate **5b** and followed by monitoring the appearance of the leaving 3,4-dinitrophenoxide ion at 410 nm.

Products Analysis. 3,4-Dinitrophenoxide ion was liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra after the completion of the reactions with those of the authentic samples under the same reaction conditions.

Acknowledgments. This work was supported by a grant from Korea Research Foundation (KRF-2005-015-C00256). Jin-A Seo is also grateful for the BK 21 Scholarship.

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