JOC *Article*

Effects of Amine Nature and Nonleaving Group Substituents on Rate and Mechanism in Aminolyses of 2,4-Dinitrophenyl X-Substituted Benzoates

Ik-Hwan Um,* Kyung-Hee Kim,[1] Hye-Ran Park, Mizue Fujio,† and Yuho Tsuno†

Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea, and Institute for Materials Chemistry and Engineering, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

ihum@mm.ewha.ac.kr.

Received February 23, 2004

Second-order rate constants have been measured for the reactions of 2,4-dinitrophenyl X-substituted benzoates (**1a**−**f**) with a series of primary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The Brønsted-type plot for the reactions of **1d** with primary amines is biphasic with slopes $\beta_1 = 0.36$ at the high pK_a region and $\beta_2 = 0.78$ at the low pK_a region and the curvature center at p$K_a° = 9.2$, indicating that the reaction proceeds through an addition intermediate with a change in the rate-determining step as the basicity of amines increases. The corresponding Brønsted-type plot for the reactions with secondary amines is also biphasic with $\beta_1 = 0.34$, $\beta_2 = 0.74$, and p$K_a° = 9.1$, indicating that the effect of amine nature on the reaction mechanism and pK_a° is insignificant. However, primary amines have been found to be less reactive than isobasic secondary amines. The microscopic rate constants associated with the aminolysis have revealed that the smaller k_1 for the reactions with primary amines is fully responsible for their lower reactivity. The electron-donating substituent in the nonleaving group exhibits a negative deviation from the Hammett plots for the reactions of **1a**−**f** with primary and secondary amines, while the corresponding Yukawa−Tsuno plots are linear. The negative deviation has been ascribed to stabilization of the ground state of the substrate through resonance interaction between the electron-donating substituent and the carbonyl functionality.

Introduction

Aminolysis of esters has generally been understood to proceed through an addition intermediate ($T^{\pm}$) with a change in the rate-determining step (RDS) from breakdown of $T^{\pm}$ to its formation as the amine becomes more basic than the leaving group by 4−5 pK_a units.[2−5] However, other factors have also been suggested to determine the reaction mechanism, i.e., aminolysis proceeds through one or two intermediates (e.g., $T^{\pm}$ and its deprotonated T^-) depending on amine basicity,[3a,b] reaction medium,[4a,b] and the nature of amines.[5a,b]

Another intriguing question is whether the substituent in the nonleaving group affects the reaction mechanism. Castro et al. have suggested that the electronic nature of the substituent in the nonleaving group affects the pK_a° value.[6,7] In pyridinolysis of 2,4-dinitrophenyl X-substituted benzoates (X = H, 4-Cl, and 4-NO_2) in aqueous ethanol, the Brønsted-type plot has been obtained to be curved with p$K_a° = 9.5$ for the reactions of the unsubstituted benzoate but linear for the corresponding reactions of the 4-chloro and 4-nitro derivatives (p$K_a° > 9.5$).[6] More recently, the pK_a° value has been suggested to increase as the substituent in the nonleaving group of the substrate becomes a stronger electron-withdrawing

---

† Kyushu University.

[1] Present address: Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, IN.

[2] (a) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622−2637. (b) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345−375. (c) Page, M. I.; Williams, A. *Organic and Bio-organic Mechanisms*; Longman: Harlow, U.K., 1997; Chapter 7. (d) Williams, A. *Adv. Phys. Org. Chem.* **1992**, *27*, 2−55.

[3] (a) Castro, E. A.; Galvez, A.; Leandro, L.; Santos, J. G. *J. Org. Chem.* **2002**, *67*, 4309−4315. (b) Castro, E. A.; Leandro, L.; Quesieh, N.; Santos, J. G. *J. Org. Chem.* **2001**, *66*, 6130−6135. (c) Castro, E. A.; Campodonico, P.; Toro, A.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 5930−5935. (d) Castro, E. A.; Andujar, M.; Toro, A.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 3608−3613. (e) Castro, E. A.; Andujar, M.; Campodonico, P.; Santos, J. G. *Int. J. Chem. Kinet.* **2002**, *34*, 309−315. (f) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505−3524.

[4] (a) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2002**, *67*, 8995−8998. (b) Oh, H. K.; Kim, S. K.; Cho, I. H.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2306−2310. (c) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2002**, *67*, 3874−3877. (d) Lee, H. W.; Guha, A. K.; Kim, C. K.; Lee, I. *J. Org. Chem.* **2002**, *67*, 2215−2222. (e) Oh, H. K.; Lee, J. Y.; Lee, H. W.; Lee, I. *New J. Chem.* **2002**, *26*, 473−476. (f) Koh, H. J.; Kang, S. J.; Kim, C. J.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2003**, *24*, 925−930. (g) Song, H. B.; Choi, M. H.; Koo, I. S.; Oh, H. K.; Lee, I. *Bull. Korean Chem. Soc.* **2003**, *24*, 91−94.

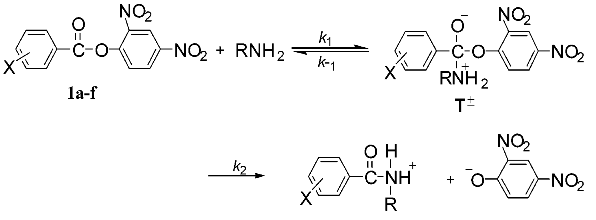
[5] (a) Um, I. H.; Seok, J. A.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2003**, *68*, 7742−7746. (b) Um, I. H.; Lee, S. E.; Kwon, H. J. *J. Org. Chem.* **2002**, *67*, 8999−9005. (c) Um, I. H.; Hong, J. Y.; Kim, J. J.; Chae, O. M.; Bae, S. K. *J. Org. Chem.* **2003**, *68*, 5180−5185. (d) Um, I. H.; Min, J. S.; Ahn, J. A.; Hahn, H. J. *J. Org. Chem.* **2000**, *65*, 5659−5663. (e) Um, I. H.; Park, H. R.; Kim, E. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 1251−1255. (f) Um, I. H.; Lee, E. J.; Lee, J. P. *Bull. Korean Chem. Soc.* **2002**, *23*, 381−384.

[6] (a) Castro, E. A.; Santander, C. L. *J. Org. Chem.* **1985**, *50*, 3595−3600. (b) Castro, E. A.; Valdivia, J. L. *J. Org. Chem.* **1986**, *51*, 1668−1672. (c) Castro, E. A.; Steinfort, G. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 453−457.

[7] Castro, E. A.; Bessolo, J.; Aguayo, R.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 8157−8161.

10.1021/jo049694a CCC: $27.50

SCHEME 1



X = 4-NO$_2$ (**1a**), 4-CN (**1b**), 4-Cl (**1c**), H (**1d**), 4-Me (**1e**), 4-MeO (**1f**)

substituent (EWS) for the reactions of *S*-4-nitrophenyl X-substituted thiobenzoates in aqueous ethanol (i.e., $pK_a°$ = 10.0, 10.4, and >10.8, as the substituent changes from H to 4-Cl and 4-NO$_2$, respectively).[7] Their finding is in accordance with the results of Gresser and Jencks for the reactions of quinuclidines with diaryl carbonates.[8] It has been reported that electron attraction from the nonleaving group favors amine expulsion (e.g., k_{-1} in Scheme 1) compared with ArO$^-$ expulsion (e.g., k_2 in Scheme 1),[8] indicating that the $pK_a°$ value increases with increasing electron-withdrawing ability of the nonleaving group substituents by increasing the k_{-1}/k_2 ratio.

However, we have recently proposed that the effect of nonleaving group substituents on the reaction mechanism is insignificant.[5c,d,9,10] We have shown that the k_{-1}/k_2 ratio remains nearly constant on changing the electronic nature of the substituent in the nonleaving group for the reactions of 2,4-dinitrophenyl X-substituted benzoates with a series of alicyclic secondary amines.[9] Although the Hammett plots have been found to be nonlinear for aminolyses of 4-nitrophenyl[5d] and 2,4-dinitrophenyl X-substituted benzoates[9] and 2,4-dinitrophenyl X-substituted benzenesulfonates,[5c] the corresponding Yukawa–Tsuno plots are linear. A similar result has been found for alkaline hydrolysis of *O*-4-nitrophenyl X-substituted thionobenzoates[10a] and for nucleophilic substitution reactions of 2,4-dinitrophenyl X-substituted benzoates with anionic nucleophiles such as OH$^-$, CN$^-$, and N$_3^-$ in 80 mol % H$_2$O/20 mol % DMSO.[10b] Traditionally nonlinear Hammett plots have been interpreted as a change in the reaction mechanism or the RDS of a stepwise reaction.[11,12] However, we have proposed another explanation for the nonlinear Hammett plots, e.g., stabilization of the ground state (GS) of the substrate through resonance interaction between the electron-donating substituent (EDS) and the carbonyl, thionocarbonyl, and sulfonyl functionalities on the basis of the linear Yukawa–Tsuno plots.[5c,d,9,10]

TABLE 1. Summary of Apparent Second-order Rate Constants (k_N) for Aminolysis of 2,4-Dinitrophenyl Benzoate (1d) in 80 mol % H$_2$O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

entry	amine	pK_a	$10^1\,k_N$ ($M^{-1}\,s^{-1}$)
1	trifluoroethylamine	5.68	0.178 ± 0.004
2	glycine ethyl ester	7.68	4.25 ± 0.08
3	glycylglycine	8.31	12.2 ± 0.1
4	benzylamine	9.46	52.5 ± 0.5
5	ethanolamine	9.67	62.1 ± 0.9
6	glycine	10.06	126 ± 3
7	ethylenediamine	10.32	146 ± 2
8	propylamine	10.89	204 ± 2
9	ethylamine	10.67	204 ± 4
10	piperazinium ion	5.95	4.67 ± 0.1[a]
11	1-formyl piperazine	7.98	54.3 ± 0.1[a]
12	morpholine	8.65	196 ± 3[a]
13	piperazine	9.85	821 ± 8[a]
14	3-methylpiperidine	10.8	1670 ± 17[a]
15	piperidine	11.02	1740 ± 26[a]

[a] The k_N values for the reactions with the secondary amines were taken from ref 9.

We have extended our work to reactions of 2,4-dinitrophenyl X-substitued benzoates (**1a**–**f**) with a series of primary amines in 80 mol % H$_2$O/20 mol % DMSO to investigate (1) the effect of nonleaving group substituents on the reaction mechanism and (2) the effect of amine nature on rates and mechanism by comparing the kinetic results obtained in this study with those reported previously for the corresponding reactions with secondary amines.[9]

Results

Reactions of **1a**–**f** with the primary amines proceeded with quantitative liberation of 2,4-dinitrophenoxide. All reactions studied in this work obeyed pseudo-first-order kinetics under excess amine. Pseudo-first-order rate constants (k_{obsd}) were obtained from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + c$. Correlation coefficients of the linear regressions were usually higher than 0.9995. The plots of k_{obsd} vs amine concentrations are linear and pass through the origin, indicating that general base catalysis by the second amine molecule is absent and the contribution of OH$^-$ and H$_2$O to k_{obsd} is negligible. Five different amine concentrations were used to determine second-order rate constants (k_N) from the slope of the linear plots. The second-order rate constants determined in this way are summarized in Tables 1 and 3. The kinetic conditions together with the pseudo-first-order rate constant k_{obsd} values are given in Tables S2–S21 in Supporting Information.

Discussion

Reaction Mechanism. As shown in Table 1, the reactivity increases as the amine basicity increases, i.e., as the amine changes from weakly basic trifluoroethylamine to more basic benzyl and ethylamine, the second-order rate constant (k_N) for the reaction of **1d** increases from 0.0178 to 5.25 and 20.4 M^{-1} s^{-1}, respectively. The effect of amine basicity on reactivity is illustrated in Figure 1. The statistically corrected Brønsted-type plot using p and q[13] for the reactions of **1d** with primary

---

(8) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963–6970.

(9) Um, I. H.; Chung, E. K.; Lee, S. M. *Can. J. Chem.* **1999**, *77*, 659–666.

(10) (a) Um, I. H.; Lee, J. Y.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2004**, *69*, 2436–2441. (b) Um, I. H.; Han, H. J.; Ahn, J. A.; Kang, S.; Buncel, E. *J. Org. Chem.* **2002**, *67*, 8475–8480.

(11) (a) Swansburg, S.; Buncel, E.; Lemieux, R. P. *J. Am. Chem. Soc.* **2000**, *122*, 6594–6600. (b) Carrol, F. A. *Perspectives on Structures and Mechanism in Organic Chemistry*; Brooks/Cole: New York, 1998; pp 371–386. (c) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins Publishers: New York, 1987; pp 143–151.

(12) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; pp 480–483.

(13) Bell, R. P. *The Proton in Chemistry*; Methuen: London, 1959; p 159.

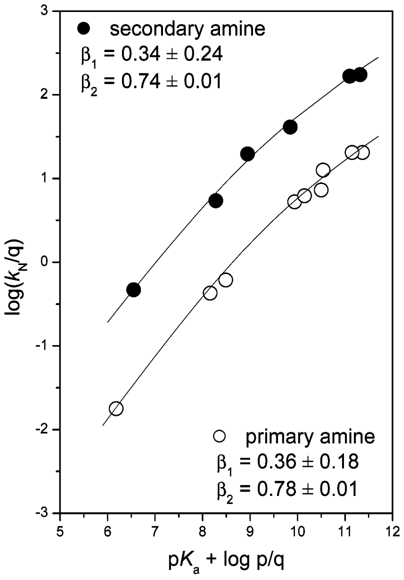


FIGURE 1. Brønsted-type plots for reactions of 2,4-dinitrophenyl benzoate (**1d**) with primary and secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The solid lines were calculated by eq 1.

amines exhibits a downward curvature, i.e., β_{nuc} decreases from 0.78 to 0.36 as the basicity of amines increases. A similar result is demonstrated for the corresponding reaction with secondary amines. Because such a biphasic Brønsted-type plot is typical for reactions that proceed through an addition intermediate ($T^{\pm}$),[2-5] one can suggest that the present reaction proceeds as shown in Scheme 1 with a change in the RDS from breakdown of $T^{\pm}$ to its formation as the basicity of amines increases.

The nonlinear Brønsted-type plots shown in Figure 1 have been analyzed using a semiempirical equation (eq 1)[8,9,14] on the basis of the proposed mechanism in Scheme 1, where β_1 and β_2 represent the slope of the Brønsted-type plot in Figure 1 for the reactions with strongly basic and weakly basic amines, respectively.

$$\log\left(\frac{k_N}{k_N{}^\circ}\right) = \beta_2(\mathrm{p}K_a - \mathrm{p}K_a{}^\circ) - \log\left(\frac{1+\alpha}{2}\right)$$

$$\text{where } \log \alpha = (\beta_2 - \beta_1)(\mathrm{p}K_a - \mathrm{p}K_a{}^\circ) \qquad (1)$$

The $k_N°$ refers to the k_N value at $pK_a°$, the center of the curvature in the curved Brønsted-type plot, where $k_{-1}/k_2 = 1$. The $pK_a°$ value has been determined to be 9.2 and 9.1 for the reactions with primary and secondary amines, respectively, indicating that $pK_a°$ is not significantly influenced by the amine nature. The $pK_a°$ value in the aminolysis of **1d** is ca. 5 pK_a units higher than the pK_a of the conjugate acid of the leaving group. This is consistent with the general report that the RDS changes as the amine becomes more basic than the leaving group by 4−5 pK_a units.[2-5] However, the present result contrasts to the proposal that $pK_a°$ is independent of the leaving group basicity but significantly influenced by the amine nature.[4a,c] Lee et al. have recently shown $pK_a° \geq 9.7$ for the reactions of substituted phenyl furan-2-carbodithioates with benzylamines in CH_3CN, whereas $pK_a° = 5.2$ for the corresponding reactions with pyridines in CH_3CN.[4a] A similar result has been reported for the reactions of substituted phenyl dithioacetates with pyridines in CH_3CN (e.g., $pK_a° = 5.2$ regardless of the leaving group basicity).[4c]

Effect of Amine Nature on Reactivity. Figure 1 shows that primary amines are less reactive than secondary amines of similar basicity. This is consistent with the report that primary amines exhibit reactivity lower than that of secondary or tertiary amines of similar basicity in various reactions, i.e., in deprotonation of carbon acids such as nitroethane,[15a] 4-nitrophenyl, and 2,4-dinitrophenylacetonitriles,[16] and in nucleophilic displacement on chloramine[17] and in aminolysis of various esters.[15b,18] Since solvation energy has been reported to increase in the order $R_3NH^+ < R_2NH_2^+ < RNH_3^+$, solvent effect has generally been suggested to be responsible for the decreasing reactivity order.[15,16,19]

However, Castro et al. have explained the reactivity order using the k_1/k_{-1} ratio, since k_2 would be independent of the nature of amines.[20] It has been shown that quinuclidines are more reactive than isobasic alicyclic secondary amines in the reactions with methyl 2,4-dinitrophenyl carbonate and phenyl 2,4-dinitrophenyl carbonate in water.[20a] Similarly, pyridines have been reported to be more reactive than isobasic alicyclic secondary amines toward 4-methylphenyl 4-nitrophenyl thionocarbonate in 44% ethanol/water.[20b] In all cases the k_1/k_{-1} ratios for quinuclidines and pyridines have been suggested to be larger than those for the isobasic alicyclic secondary amines.[20]

$$\text{rate} = \frac{k_1k_2[\text{substrate}][\text{amine}]}{(k_{-1} + k_2)} \qquad (2)$$

$$k_N = \frac{k_1k_2}{k_{-1} + k_2} = \frac{k_1}{\dfrac{k_{-1}}{k_2} + 1} \qquad (3)$$

We have determined the microscopic rate constants (e.g., k_1 and k_{-1}/k_2 ratio) associated with the reactions of **1d** with primary and secondary amines to investigate which is responsible for the lower reactivity shown by primary amines between k_1 and k_{-1}/k_2 (or k_{-1}). The apparent second-order rate constant k_N can be expressed

---

[14] Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153−2159.

[15] (a) Gregory, M. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 2327−2330. (b) Bruice, T. C.; Donzel, A.; Huffman, R. W.; Butler, A. R. *J. Am. Chem. Soc.* **1967**, *89*, 2106−2121.

[16] Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343−4348.

[17] Yagil, G.; Anbar, M. *J. Am. Chem. Soc.* **1962**, *84*, 1797−1803.

[18] (a) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209−3216. (b) Benkovic, S. J.; Benkovic, P. A. *J. Am. Chem. Soc.* **1966**, *88*, 5504−5511.

[19] Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373−1383.

[20] (a) Castro, E. A.; Aliaga, M.; Campodonico, P.; Santos, J. G. *J. Org. Chem.* **2002**, *67*, 8911−8916. (b) Castro, E. A.; Garcia, P.; Leandro, L.; Quesieh, N.; Rebolledo, A.; Santos, J. G. *J. Org. Chem.* **2000**, *65*, 9047−9053.

TABLE 2. Summary of Microscopic Rate Constants Associated with Aminolysis of 2,4-Dinitrophenyl Benzoate (1d) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

entry	amine	pK_a	k_{-1}/k_2	k_1 (M^{-1} s^{-1})
1	trifluoroethylamine	5.68	18.6	0.348
2	glycine ethyl ester	7.68	2.73	1.59
3	glycylglycine	8.31	1.99	3.64
4	benzylamine	9.46	0.489	7.82
5	ethanolamine	9.67	0.399	8.69
6	glycine	10.06	0.274	16.0
7	ethylenediamine	10.32	0.284	18.8
8	propylamine	10.89	0.123	22.9
9	ethylamine	10.67	0.152	23.5
10	piperazinium ion	5.95	10.5	5.36
11	1-formylpiperazine	7.98	2.13	17.0
12	morpholine	8.65	1.15	42.1
13	piperazine	9.85	0.501	123
14	3-methylpiperidine	10.8	0.158	193
15	piperidine	11.02	0.129	197

[a] pK_a values in 80 mol % H_2O/20 mol % DMSO taken from refs 5d and 9.

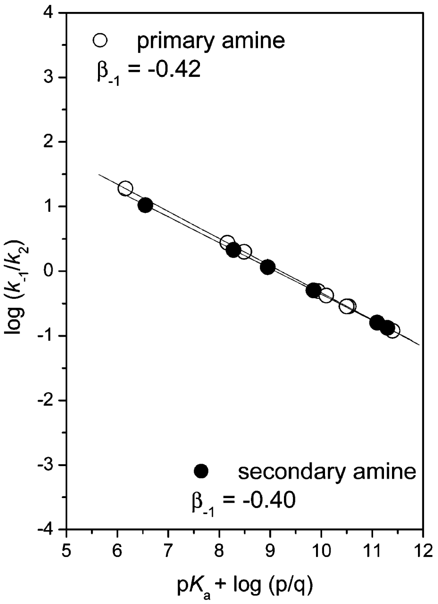


FIGURE 2. Brønsted-type plots for reactions of 2,4-dinitrophenyl benzoate (**1d**) with primary and secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

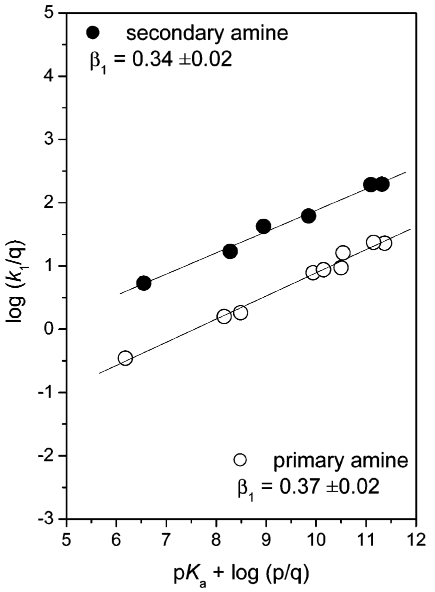


FIGURE 3. Brønsted-type plots for reactions of 2,4-dinitrophenyl benzoate (**1d**) with primary and secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

as eq 3 by applying the steady-state conditions to the intermediate on the basis of the proposed mechanism in Scheme 1. The k_{-1}/k_2 ratios for the reactions of **1d** with primary amines have been calculated using the methods reported previously by Castro et al. (see also eqs S1− S6 in Supporting Information).[3d,14] The k_1 values have been determined from eq 3 using the k_N values in Table 1 and the k_{-1}/k_2 ratios determined above. Using the same method, we have recalculated the k_{-1}/k_2 ratios and k_1 values for the reactions of **1d** with secondary amines from the k_N values reported previously.

Table 2 shows that the k_{-1}/k_2 ratio decreases as the basicity of amines increases, i.e., $k_{-1}/k_2 > 1$ for p$K_a \leq 8.31$ and $k_{-1}/k_2 < 1$ for p$K_a \geq 9.46$ for the reactions of **1d** with primary amines. A similar result can be seen for the corresponding reactions with secondary amines, i.e., $k_{-1}/k_2 > 1$ for p$K_a \leq 8.65$ and $k_{-1}/k_2 < 1$ for p$K_a \geq 9.85$. This result is in accordance with the preceding proposal that the RDS changes at pK_a ca. 9.2 and 9.1 for the reactions of **1d** with primary and secondary amines, respectively.

The effect of amine basicity on the k_{-1}/k_2 ratio is illustrated in Figure 2. One can see linear Brønsted-type plots with a β_{-1} value of −0.42 and −0.40 for reactions of **1d** with primary and secondary amines, respectively. Interestingly, the magnitude of the k_{-1}/k_2 ratio is almost the same for the reactions of **1d** with primary and secondary amines, indicating that the k_{-1}/k_2 ratio (or k_{-1}) cannot be responsible for the reactivity difference between primary and secondary amines.

As shown in Table 2 and Figure 3, the k_1 value increases linearly as the amine basicity increases for the reactions of **1d** with primary and secondary amines. Interestingly, the k_1 value is smaller for the reactions with primary amines than for those with secondary amines of similar basicity. This result suggests that the smaller k_1 value for the reactions with primary amines is fully responsible for their lower reactivity.

One should have expected an opposite result (e.g., larger k_1 for the reactions with primary amines than for those with isobasic secondary amines) if steric effect were significant for the present reactions. Steric effect would be significant for reactions in which bond formation between the electrophile and nucleophile in the TS is greatly advanced. Because the magnitude of β_1 represents the extent of bond formation in the TS,[11b,c] the small β_1 value obtained in the aminolysis of **1d** (e.g., 0.37 and 0.34 for the reactions with primary and secondary amines, respectively) suggests that the extent of bond formation is insignificant. Accordingly, the steric effect in the present system appears to be insignificant. This argument is in accordance with the report that tertiary amines are less reactive than secondary or primary amines of similar basicity in the nucleophilic substitution reaction of phenyl acetate in which $\beta_{nuc} = 1.05$,[15b] while

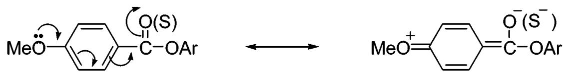
TABLE 3. Summary of Second-Order Rate Constants (k_N) for Aminolysis of 2,4-Dinitrophenyl X-Substituted Benzoates (1a−f) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

X	$10^3\ k_N$ ($M^{-1}\ s^{-1}$) trifluoroethylamine	$10^1\ k_N$ ($M^{-1}\ s^{-1}$) glycylglycine	k_N ($M^{-1}\ s^{-1}$) ethylamine
4-MeO	4.71 ± 0.06	2.76 ± 0.01	4.86 ± 0.01
4-Me	8.89 ± 0.04	6.06 ± 0.07	10.7 ± 0.04
H	17.8 ± 0.4	12.2 ± 0.1	20.4 ± 0.4
4-Cl	31.9 ± 0.3	23.7 ± 0.2	48.1 ± 0.04
4-CN	124 ± 1	116 ± 1	273 ± 0.6
$4-NO_2$	153 ± 1	152 ± 2	384 ± 1

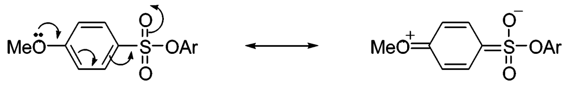
the reverse is true in the reactions of phosphate and sulfate esters in which $\beta_{nuc} = 0.20^{18a}$ and $0.13,^{18b}$ respectively.

Effect of Nonleaving Group Substituent on Rate and Mechanism. Nonlinear Hammett plots have traditionally been interpreted as a change in reaction mechanism or RDS depending on the shape of the curvature.[11,12] An upward curvature has been ascribed to a change in reaction mechanism and is typified by a nucleophilic substitution in benzylic systems where EDSs are located on the large negative slope portion corresponding to the S_N1 mechanism, which then changes to the S_N2 mechanism for the EWSs found on the small negative (or even positive) slope portion of the plot.[11] In contrast, a downward curvature has been understood as a change in the RDS within a given mechanism upon changing the electronic nature of substituents.[12]

However, we have recently suggested a different explanation for the nonlinear Hammett plots obtained from aminolyses of 4-nitrophenyl X-substituted benzoates[5d] and 2,4-dinitrophenyl X-substituted benzenesulfonates[5c] as well as alkaline hydrolysis of *O*-4-nitrophenyl X-substituted thionobenzoates[10a] and nucleophilic substitution reactions of 2,4-dinitrophenyl X-substituted benzoates with OH^-, CN^-, and N_3^-.[10b] In all cases, EDSs in the nonleaving group exhibit negative deviations from Hammett plots. We have ascribed the negative deviations to stabilization of the ground state (GS) of the substrate through resonance interaction between the EDS and the carbonyl, thionocarbonyl, and sulfonyl functionalities as illustrated by resonance structures I ↔ II and III ↔ IV.[5c,d,10]



I II



III IV

As shown in Table 3, the second-order rate constant increases as the substituent X in the nonleaving group changes from a strong EDS to a strong EWS. The effect of substituent X on rates has been illustrated in Figure 4. One can see that the Hammett plots are curved downwardly, i.e., the points for 4-MeO and 4-Me exhibit negative deviations from the linear Hammett plots in all cases. A similar result has been obtained for the corresponding reactions with secondary amines (see Figure S1 in Supporting Information). However, the Yukawa−Tsuno plots in Figure 5 (and in Figure S2) exhibit good linear correlation, indicating that the curved Hammett plots in Figure 4 and Figure S1 in Supporting Information are due not to a change in the RDS but to stabilization of the GS through resonance interaction between the EDS and the carbonyl group as illustrated by resonance structures I ↔ II. Thus, the present study further confirms our previous proposal that determination of reaction mechanism based just on a linear or nonlinear Hammett plot can be misleading.[5c,d,10]

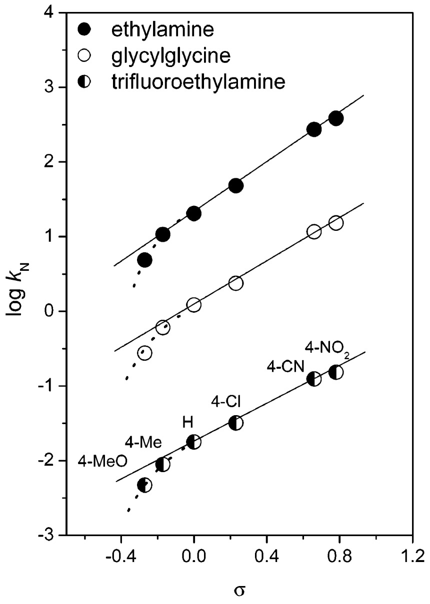


FIGURE 4. Hammett plots for reactions of 2,4-dinitrophenyl X-substituted benzoates (**1a**−**f**) with three primary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

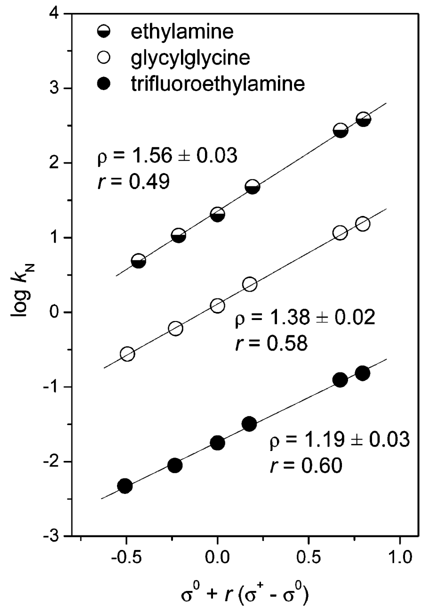


FIGURE 5. Yukawa−Tsuno plots for reactions of 2,4-dinitrophenyl X-substituted benzoates (**1a**−**f**) with three primary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

The Yukawa–Tsuno equation (eq 4) has been applied to numerous reactions in which a partial positive charge develops in the transition state (TS) of the RDS.[21–24] The magnitude of the r value represents the resonance demand of the reaction center or the extent of resonance contribution, and the term $(\sigma^+ - \sigma^\circ)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[21]

$$\log\left(\frac{k^{\mathrm{X}}}{k^{\mathrm{H}}}\right) = \rho[\sigma^\circ + r(\sigma^+ - \sigma^\circ)] \qquad (4)$$

The r value has been found to be as large as 1.53 for solvolysis of 1-aryl-2,2,2-trifluoroethyl tosylates, in which the resonance demand is significantly high due to the strong electron-withdrawing ability of the α-CF_3 group.[23] On the other hand, the r value decreases when the coplanarity of the aryl moiety and the reaction center is hindered by twisting the aryl moiety.[21–24] However, it has been reported that a large r value always accompanies a large ρ value or vice versa for S_N1 reactions.[21–24]

In contrast, the r value in the present reaction increases as the ρ value decreases, i.e., the r value increases from 0.49 to 0.58 and 0.60 as the ρ decreases from 1.56 to 1.38 and 1.19 for the reaction of **1d** with ethylamine, glycylglycine, and trifluoroethylamine, respectively (see Figure 5). Such an inverse relationship between r and ρ is more significant for the reactions with secondary amines, i.e., the r value increases from 0.36 to 0.65 and 0.89 as the ρ decreases from 1.48 to 1.04 and 0.71 for the reactions of **1d** with piperidine, morpholine and piperazinium ion, respectively (see Figure S2 in Supporting Information). The same trend in the magnitude of the r and ρ values has been found for reactions of 4-nitrophenyl-substituted benzoates with alicyclic secondary amines, i.e., the r values are 0.75, 1.05, 1.20, 1.29, and 1.38 while the ρ values are 0.75, 0.54, 0.51, 0.44, and 0.42 for the reaction with piperidine, piperazine, 1-(2-hydroxyethyl)piperazine, morpholine, and 1-formylpiperazine, respectively. It is noted that the r value increases while the ρ value decreases as the basicity of amines decreases, indicating that the magnitude of the r and ρ values is associated with the RDS of ester aminolyses.

Conclusions

The present study has allowed us to conclude the following: (1) The reaction of **1d** with primary amines proceeds through $T^\pm$ in which the RDS changes from breakdown of $T^\pm$ to its formation as the basicity of amines increases (e.g., $pK_a^\circ = 9.2$). (2) Primary amines are less reactive than isobasic secondary amines toward **1d**. The k_1 value is smaller for the reactions with primary amines than for those with secondary amines of similar basicity, while the k_{-1}/k_2 ratios are almost the same for both reactions with primary and secondary amines. Accordingly, the smaller k_1 value has been suggested to be fully responsible for the lower reactivity of primary amines. (3) The Hammett plots for the aminolyses of **1a–f** are nonlinear, but the corresponding Yukawa–Tsuno plots are linear. The nonlinear Hammett plots have been ascribed to resonance stabilization of the GS of the substrate as illustrated by the resonance structures I ↔ II.

Experimental Section

Materials. Compounds (2,4-dinitrophenyl X-substituted benzoates, **1a–f**) were prepared from the reaction of X-substituted benzoyl chlorides with 2,4-dinitrophenol in anhydrous ether in the presence of triethylamine as reported previously.[9] Their purity was checked by means of melting point and spectral data such as IR and ^{1}H NMR characteristics. Amines and other chemicals were of the highest quality available. Distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed with a UV–vis spectrophotometer for the slow reactions ($t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for the fast reactions ($t_{1/2} \leq 10$ s) equipped with a constant temperature circulating bath at 25.0 ± 0.1 °C. All solutions were transferred by gastight syringes. The reactions were followed by monitoring the appearance of the leaving 2,4-dinitrophenoxide ion. All reactions were carried out under pseudo-first-order conditions in which amine concentrations were at least 100 times greater than the substrate concentration. The reaction medium was 80 mol % H_2O/20 mol % DMSO to eliminate the problem of low solubility of the substrates in pure H_2O.

Typically, a reaction was initiated by adding 5 μL of a 0.01 M solution of 2,4-dinitrophenyl benzoate in acetonitrile by syringe to a 10-mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of solvent and an aliquot of the amine stock solution. Generally, the amine concentration was varied over the range $(1–100) \times 10^{-3}$ M, while the substrate concentration was 1×10^{-5} M. Pseudo-first-order rate constants (k_{obsd}) were calculated from the well-known equation $\ln(A_\infty - A_t) = -k_{\mathrm{obsd}}t + c$. The plots of $\ln(A_\infty - A_t)$ vs time were linear over ca. 90% reaction. Usually, five different amine concentrations were employed, and replicate values of k_{obsd} were determined to obtain the second-order rate constants (k_{N}) from the slope of linear plots of k_{obsd} versus amine concentrations.

Products Analysis. 2,4-Dinitrophenoxide was liberated quantitatively and identified as one of the products in the aminolysis of **1a–f** by comparison of the UV–vis spectra after completion of the reactions with those of the authentic sample under the same reaction conditions. Other products such as *N*-ethylbenzamide and *N*-(*n*-propyl)benzamide have been identified by GC–MS.

Acknowledgment. This work was supported by Korea Research Foundation (KRF-2002-070-C00061). I.H.U. is also grateful for a JSPS fellowship (L-03709).

Supporting Information Available: Method to determine the k_{-1}/k_2 ratios for the reactions of **1d** with primary and secondary amines; Table S1 for the second-order rate constants for the reactions of **1d** with secondary amines taken from reference 9; Figures S1 and S2 for Hammett and Yukawa–Tsuno plots, respectively, for the reactions of **1d** with secondary amines; and Tables S2–S21 of the kinetic results for the reactions of **1a–f** with primary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049694A

---

[21] (a) Tsuno, Y.; Fujio, M. *Adv. Phys. Org. Chem.* **1999**, *32*, 267–385. (b) Tsuno, Y.; Fujio, M. *Chem. Soc. Rev.* **1996**, *25*, 129–139. (c) Yukawa, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 965–970.

[22] (a) Fujio, M.; Rappoport, Z.; Uddin, M. K.; Kim, H. J.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 163–169. (b) Nakata, K.; Fujio, M.; Nishimoto, K.; Tsuno, Y. *J. Phys. Org. Chem.* **2003**, *16*, 323–335. (c) Uddin, M. K.; Fujio, M.; Kim, H. J.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1371–1379.

[23] Murata, A.; Sakaguchi, S.; Mishima, M.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1129–1137.

[24] (a) Nakashima, T.; Fujiyama, R.; Kim, H. J.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 429–438. (b) Nakashima, T.; Fujiyama, R.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1043–1047. (c) Nakashima, T.; Fujiyama, R.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* **1999**, *40*, 539–542.