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Kinetic Study on Nucleophilic Substitution Reactions of 4-Chloro-2-nitrophenyl X-Substituted-benzoates with Cyclic Secondary Amines: Effect of Substituent X on Reactivity and Reaction Mechanism

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Second-order rate constants (k_N) have been measured spectrophotometrically for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**1a-1h**) with a series of cyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The Hammett plot for the reactions of **1a-1h** with piperidine consists of two intersecting straight lines, while the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_X = 1.25$ and $r = 0.58$, indicating that the nonlinear Hammett plot is not due to a change in the rate-determining step (RDS) but is caused by ground-state stabilization through resonance interactions for substrates possessing an electron-withdrawing group in the benzoyl moiety. The Brønsted-type plot for the reactions of 4-chloro-2-nitrophenyl benzoate (**1d**) with a series of cyclic secondary amines curves downward with $\beta_2 = 0.85$, $\beta_1 = 0.24$, and $pK_a^o = 10.5$, implying that a change in RDS occurs from the k_2 step to the k_1 process as the pK_a of the conjugate acid of the amine exceeds 10.5. Dissection of k_N into the microscopic rate constants k_1 and k_2/k_{-1} ratio associated with the reaction of **1d** reveals that k_2 is dependent on the amine basicity, which is contrary to generally held views.

Key Words : Aminolysis, Resonance stabilization, Yukawa-Tsuno plot, Hammett plot, Brønsted-type plot

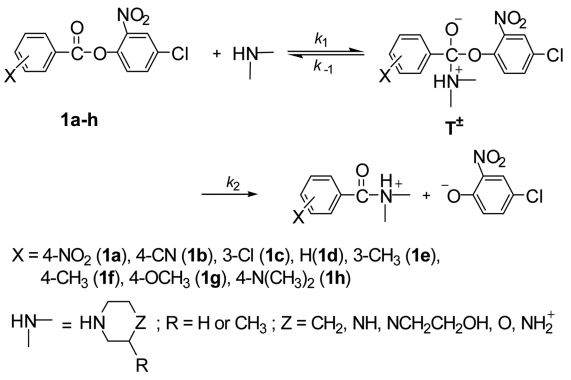
Introduction

Nucleophilic substitution reactions of esters with amines have intensively been studied due to their importance in biological processes as well as synthetic applications.[1-12] Aminolysis of esters has been reported to proceed through a concerted mechanism or *via* a stepwise pathway with one or two intermediates (*e.g.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form T^{-}) depending on the reaction conditions such as the nature of electrophilic center, the reaction medium, the basicity of leaving group and incoming amine, and the electronic nature of substituent in the nonleaving group.[1-12]

A curved Brønsted-type plot observed for aminolysis of esters possessing a weakly basic leaving group (*e.g.*, 2,4-dinitrophenoxide ion) has been suggested as evidence for a stepwise mechanism with a change in rate-determining step (RDS).[1-9] It has generally been reported that a change in RDS occurs as the incoming amine becomes more basic than the leaving group by 4 to 5 pK_a units (or the leaving group becomes less basic than the incoming amine by 4 to 5 pK_a units).[6-9]

However, the effect of nonleaving-group substituents on the reaction mechanism is controversial. Gresser and Jencks have reported that the electronic nature of the substituent X in the nonleaving group influences the k_2/k_{-1} ratio, *e.g.*, an EWG decreases the k_2/k_{-1} ratio by decreasing k_2 for reactions of X-substituted-phenyl 2,4-dinitrophenyl carbonates with quinuclidine.[6] A similar result has been reported by Castro *et al*. for pyridinolysis of diaryl carbonates and aminolysis of *S*-2,4-dinitrophenyl X-substituted-benzoates.[7,8] On the contrary, we have shown that the k_2/k_{-1} ratio is independent of the electronic nature of the substituent X in the nonleaving group for aminolysis of 2,4-dinitrophenyl X-substituted-benzoates and related esters.[9-12]

Our study has been extended to reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**1a-1h**) with a series of cyclic secondary amines in 80 mol % H_2O/20 mol % DMSO (Scheme 1). We have introduced various substituent X in the benzoyl moiety to investigate the effect of nonleaving-group substituents on the reaction mechanism. 4-Chloro-2-nitrophenoxide, which is slightly less basic than 4-nitrophenoxide, has been chosen as the leaving group to investigate the effect of leaving-group basicity on reaction mechanism.



Scheme 1

Results and Discussion

All of the reactions in this study 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 k_{obsd} *vs*. [amine] were linear and passed through the origin, indicating that general base catalysis by a second amine molecule is absent and the contribution of H_2O and/or OH^- from hydrolysis of amine to k_{obsd} is negligible. The second-order rate constants (k_N) were calculated from the slope of the linear plots of k_{obsd} *vs*. [amine]. The correlation coefficient for the linear regression was always higher than 0.9995. The uncertainty in the k_N values is estimated to be less than ± 3% from replicate runs. The k_N values calculated in this way are summarized in Table 1 for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**1a-1h**) with piperidine and in Table 2 for those of 4-chloro-2-nitrophenyl benzoate (**1d**) with a series of cyclic secondary amines.

Effect of Nonleaving-Group Substituent X on Reaction Mechanism. As shown in Table 1, the k_N value for the reactions of **1a-1h** decreases as the substituent X changes from a strong electron-withdrawing group (EWG) to a strong electron-donating group (EDG), *e.g.*, it decreases from 60.1 $M^{-1}s^{-1}$ to 5.91 and 0.232 $M^{-1}s^{-1}$ as the substituent X changes from 4-NO_2 to H and 4-$N(CH_3)_2$, in turn. One can attribute the decreasing reactivity of the substrates to a decrease in the electrophilicity of the reaction center (*i.e.*, the C=O bond in **1a-1h**) upon changing the substituent X in the benzoyl moiety from an EWG to an EDG.

The effect of the substituent X on reactivity is illustrated in Figure 1. The Hammett plot for the reactions of **1a-1h** with piperidine consists of two intersecting straight lines. Traditionally, such nonlinear Hammett plot has been interpreted as a change in rate-determining step (RDS).[1,13] Thus, one might suggest that the reactions of **1a-1h** with piperidine proceed through a stepwise mechanism with a change in RDS, *e.g.*, from breakdown of $T^{\pm}$ (the k_2 step in Scheme 1) to its formation (the k_1 step in Scheme 1) as the substituent X changes from EWGs to EDGs. This argument appears to be reasonable since an EWG in the benzoyl moiety would accelerate the rate of nucleophilic attack (*i.e.*, an increase in k_1) but would retard the rate of leaving-group departure (*i.e.*, a decrease in k_2) or *vice versa*.

Table 1. Summary of Second-Order Rate Constants for the Reactions of 4-Chloro-2-nitrophenyl X-Substituted-benzoates (**1a-1h**) with Piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C

	X	k_N / $M^{-1}s^{-1}$
1a	4-NO_2	60.1
1b	4-CN	46.4
1c	3-Cl	21.9
1d	H	5.91
1e	3-CH_3	4.91
1f	4-CH_3	3.51
1g	4-OCH_3	1.69
1h	4-$N(CH_3)_2$	0.232

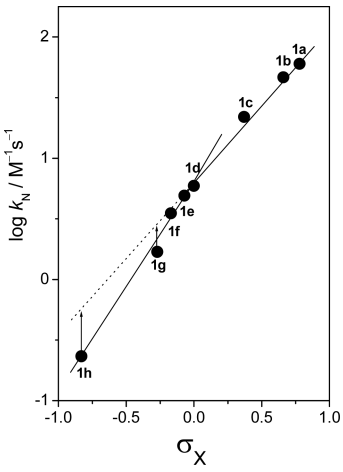
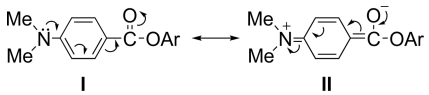


Figure 1. Hammett plot for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**1a-1h**) with piperidine in 80 mol % H_2O/ 20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

However, we propose that the nonlinear Hammett plot shown in Figure 1 is not due to a change in RDS. This is because RDS is not determined by the magnitude of the k_1 and k_2 values but it should be determined by the k_2/k_{-1} ratio (*e.g.*, RDS = the k_1 step when $k_2/k_{-1} > 1$ but RDS = the k_2 step when $k_2/k_{-1} < 1$). Moreover, k_1 and k_2 cannot be compared directly due to the difference in their units (*i.e.*, $M^{-1}s^{-1}$ for k_1 and s^{-1} for k_2).

Effect of GS Resonance on Reactivity. We propose that stabilization of the GS of substrates possessing an EDG is responsible for the nonlinear Hammett plot, since substrates bearing an EDG in the benzoyl moiety could be stabilized through the resonance interaction as modeled by the resonance structures I and II. It is apparent that such resonance stabilization would cause a decrease in the reactivity of the substrates. This idea is consistent with the fact that the substrates possessing an EDG in the benzoyl moiety (*e.g.*, **1e-1h**) deviate negatively from the linear Hammett plot composed of the substrates bearing an EWG (*e.g.*, **1a-1d**). Furthermore, the negative deviation is more significant for the substrate possessing a stronger EDG.



I II

To examine the above argument, we have employed the Yukawa-Tsuno Eq. (1) in which the r value represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_X^+ - \sigma_X^o)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[15,16] Eq. (1) was originally derived to account for the kinetic results obtained from solvolysis of benzylic systems in which a partial positive charge develops in TS.[15,16] We have shown that Eq. (1) is highly effective in elucidation of ambiguities in the reaction mechanism not only for aminolysis of esters[9-12]

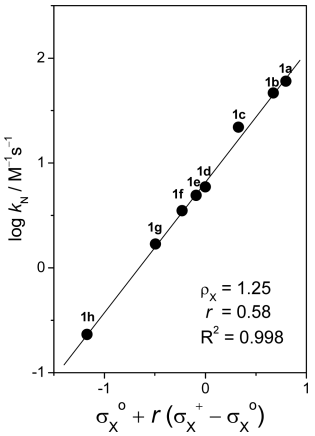


Figure 2. Yukawa-Tsuno plot for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**1a-1h**) with piperidine in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C.

but also for nucleophilic substitution reactions of various esters with anionic nucleophiles (*e.g.*, OH^-, CN^-, N_3^- and $CH_3CH_2O^-$).[17,18] Thus, a Yukawa-Tsuno plot has been constructed in Figure 2.

$$\log k^X/k^H = \rho_X[\sigma_X^o + r(\sigma_X^+ - \sigma_X^o)] \quad (1)$$

As shown in Figure 2, the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_X = 1.25$ and $r = 0.58$. Such good linear Yukawa-Tsuno plot indicates that the nonlinear Hammett plot shown in Figure 1 is clearly not due to a change in RDS but is caused by GS stabilization through resonance interactions. Thus, one can suggest that the electronic nature of the substituent X in the nonleaving group does not affect the k_2/k_{-1} ratio.

Effect of Amine Basicity on Reaction Mechanism. To investigate the effect of amine basicity on the reaction mechanism, the k_N values for the reactions of 4-chloro-2-nitrophenyl benzoate (**1d**) with a series of cyclic secondary amines have been measured and are summarized in Table 2. As shown in Table 2, the k_N value for the reaction of **1d** decreases as the amine basicity decreases, *e.g.*, it decreases from 5.91 $M^{-1}s^{-1}$ to 0.579 and 2.15 × 10^{-3} $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of amine decreases from 11.02 to 9.38 and 5.95, in turn.

The effect of amine basicity on reactivity is illustrated in Figure 3. Two Brønsted-type plots have been constructed for the aminolysis of **1d** using the kinetic data in Table 2, *e.g.*, a linear plot with $\beta_{nuc} = 0.72$ (a) and a curved one with β_{nuc} = 0.85 and 0.24 for the reactions with weakly basic amines and with strongly basic amines, respectively (b).

Table 2. Summary of Second-Order Rate Constants for the Reactions of 4-Chloro-2-nitrophenyl Benzoate (**1d**) with Cyclic Secondary Amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C[a]

	amines	pK_a	k_N / $M^{-1}s^{-1}$
1	piperidine	11.02	5.91
2	3-methylpiperidine	10.80	5.17
3	piperazine	9.85	2.16
4	1-(2-hydroxyethyl)piperazine	9.38	0.579
5	morpholine	8.65	0.305
6	piperazinium ion	5.95	0.00215

[a]The pK_a values in 80 mol % H_2O/20 mol % DMSO were taken from ref 19.

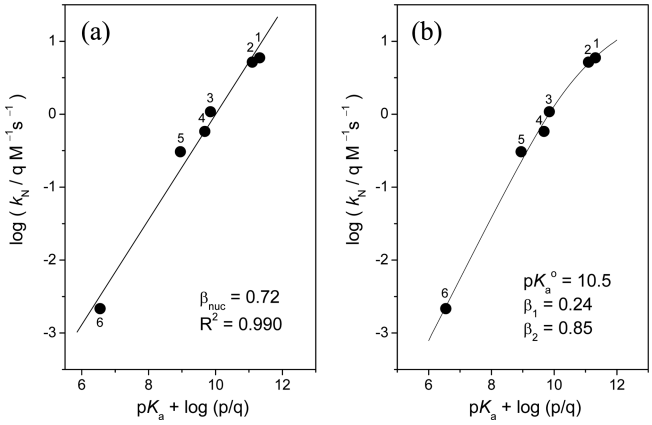


Figure 3. Brønsted-type plots for the reactions of 4-chloro-2-nitrophenyl benzoate (**1d**) with cyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2. The plots were statistically corrected using p and q (*i.e.*, $q = 1$ except $q = 2$ for piperazine while $p = 2$ except $p = 4$ for piperazinium ion).

The β_{nuc} value of 0.72 for the linear Brønsted-type plot is an upper limit for reactions reported previously to proceed through a concerted mechanism.[1-8] Thus, one might suggest that the aminolysis of **1d** proceeds through a concerted mechanism. However, we propose that the current aminolysis does not proceed through a concerted mechanism on the basis of the following reasons: (1) The linear Brønsted-type plot exhibits more scattered points than the curved one. (2) A small ρ_X value has often been reported (*e.g.*, 0.2-0.5) for reactions which proceed through a concerted mechanism.[13] Accordingly, the ρ_X value of 1.25 shown in Figure 2 appears to be too large for a concerted reaction. (3) The reactions of Y-substituted-phenyl benzoates with the cyclic secondary amines used in this study have been reported to proceed through a stepwise mechanism, in which the RDS is dependent on the basicity of the incoming amine and the leaving Y-substituted-phenoxide ion, *e.g.*, a change in RDS occurs when the amine becomes more basic than the leaving group by 4 to 5 pK_a units (or the leaving Y-substituted-phenoxide ion becomes less basic than the incoming amine by 4 to 5 pK_a units).[6,9] The pK_a of the conjugate acid of the leaving group in this study (*i.e.*, 4-chloro-2-nitrophenol) was reported to be 6.46.[20] Accordingly, one might expect that a change in the RDS would occur at pK_a between 10.46 and 11.46, if the reaction proceeds through a stepwise mechanism.

Dissection of k_N into Microscopic Rate Constants k_1 and k_2/k_{-1}. The nonlinear Brønsted-type plot shown in Figure 3(b) has been analyzed using a semiempirical equation, Eq. (2), in which β_1 and β_2 represent the slope of the nonlinear Brønsted-type plot for the strongly basic and weakly basic amines, respectively, while k_N^o refers to the k_N value at

pK_a^o, defined as the pK_a at the center of the Brønsted curvature.[6] The β_1, β_2, and pK_a^o calculated are 0.24, 0.85, and 10.5, respectively. These β_1 and β_2 values are typical of reactions reported previously to proceed through a stepwise mechanism with a change in RDS. Besides, the pK_a^o value of 10.5 is also within the expected pK_a^o range (*i.e.*, 10.46-11.46), indicating that the nonlinear Brønsted-type plot is not artificial but is due to a change in RDS.

$$\log (k_N/k_N^o) = \beta_2(pK_a - pK_a^o) - \log [(1 + \alpha)/2]$$
$$\text{where } \log \alpha = (\beta_2 - \beta_1)(pK_a - pK_a^o) \quad (2)$$

Thus, the k_N values have been dissected into the microscopic rate constants associated with the reactions of **1d** (*e.g.*, the k_1 values and the k_2/k_{-1} ratios) using the following equations. Eq. (3) can be simplified to Eqs. (4) and (5). Then, β_1 and β_2 can be expressed as Eqs. (6) and (7), respectively.

$$k_N = k_1k_2/(k_{-1} + k_2) = k_1/(k_{-1}/k_2 + 1) \quad (3)$$
$$k_N = k_1k_2/k_{-1}, \text{ when } k_2 << k_{-1} \quad (4)$$
$$k_N = k_1, \text{ when } k_2 >> k_{-1} \quad (5)$$
$$\beta_1 = d(\log k_1)/d(pK_a) \quad (6)$$
$$\beta_2 = d(\log k_1k_2/k_{-1})/d(pK_a) = \beta_1 + d(\log k_2/k_{-1})/d(pK_a) \quad (7)$$

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} ratio for the reactions of **1d** from Eq. (9) using $\beta_1 = 0.24$, $\beta_2 = 0.85$ and $pK_a^o = 10.5$. The k_1 values have been calculated from Eq. (3) using the k_N values in Table 2 and the k_2/k_{-1} ratios calculated above.

$$\beta_2 - \beta_1 = d(\log k_2/k_{-1})/d(pK_a) \quad (8)$$
$$(\log k_2/k_{-1})_{pKa} = (\beta_2 - \beta_1)(pK_a - pK_a^o) \quad (9)$$

The k_1 and k_2/k_{-1} values calculated in this way are summarized in Table 3. As shown in Table 3, the k_1 value decreases as the amine basicity decreases, *e.g.*, it decreases from 7.78 $M^{-1}s^{-1}$ to 2.41 and 0.554 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the amine decreases from 11.02 to 9.38 and 5.95, in turn. A similar result is shown for the k_2/k_{-1} ratio, although the k_2/k_{-1} ratio decreases more rapidly than the k_1 value as the amine basicity decreases.

The effects of amine basicity on the microscopic rate constants are illustrated in Figure 4. The Brønsted-type plot for k_1 is linear with $\beta_1 = 0.24$, although the correlation coefficient is not excellent ($R^2 = 0.978$). The β_1 value of 0.24 shown in Figure 4(a) is typical of reactions which were reported to proceed through a stepwise mechanism with the k_1 step being the RDS.[1-6] On the other hand, the slope of the linear plot for the k_2/k_{-1} ratio shown in Figure 4(b) is 0.61, which is much larger than the β_1 value of 0.24.

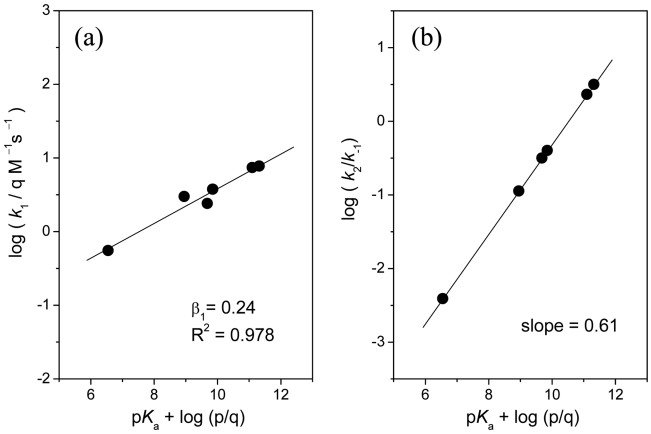


Figure 4. Brønsted-type plots for the reactions of 4-chloro-2-nitrophenyl benzoate (**1d**) with cyclic secondary amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1°C. The identity of points is given in Table 3. The plots were statistically corrected using p and q (*i.e.*, $q = 1$ except $q = 2$ for piperazine while $p = 2$ except $p = 4$ for piperazinium ion).

One might expect that k_1 and k_{-1} would be similarly sensitive to the basicity of amine on the basis of the principle of microscopic reversibility.[22] Thus, if k_2 is independent of amine basicity, the slopes of the Brønsted-type plots for k_1 and k_2/k_{-1} should be similar. However, Figure 4 shows that the slope for k_2/k_{-1} is much larger (*i.e.*, 0.61) than that for k_1 (*i.e.*, 0.24), implying that k_2 is dependent on the amine basicity. This argument is consistent with our recent report that k_2 is dependent on the basicity of amines through an inductive effect in aminolysis of 4-pyridyl 3,5-dinitrobenzoate,[9a] but is in contrast to the report by Gresser and Jencks that the k_2 value in aminolysis of diaryl carbonates is independent of amine basicity.[6] Gresser and Jencks have concluded that there is little or no electron donation from the aminium moiety of $T^{\pm}$ to push out the leaving group.[6] A similar conclusion has been drawn by Castro *et al*. for aminloysis of ethyl phenyl thionocarbonate,[21a] methyl 4-nitrophenyl thionocarbonate,[21b] 4-methylphenyl 4-nitrophenyl thionocarbonate,[21c] and 3-methoxyphenyl 4-nitrophenyl thionocarbonate.[21d]

It is apparent that the amines used in this study is affected by the electronic nature of the Z moiety of the amines, *e.g.*, the pK_a of the conjugate acid of the amines decreases from 11.02, 9.38 and 5.95 as the Z in the cyclic amines used in this study changes from CH_2, NCH_2CH_2OH and NH_2^+, in turn. Moreover, the Z in the aminium moiety of $T^{\pm}$ would influence the electron density of the reaction center through an inductive effect, although the effect would not be signi-

Table 3. Summary of Microscopic Rate Constants for the Reactions of 4-Chloro-2-nitrophenyl Benzoate (**1d**) with Cyclic Secondary Amines in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1°C

	amines	pK_a	k_1 / $M^{-1}s^{-1}$	k_2/k_{-1}
1	piperidine	11.02	7.78	3.16
2	3-methylpiperidine	10.80	7.40	2.32
3	piperazine	9.85	7.54	0.401
4	1-(2-hydroxyethyl)piperazine	9.38	2.41	0.316
5	morpholine	8.65	3.00	0.113
6	piperazinium ion	5.95	0.554	0.00390

ficant due to the long distance between the Z and the reaction site. Consequently, k_2 would decrease as the basicity of amine decreases or *vice versa*. This accounts for the kinetic results shown in Table 3 and Figure 4 that the k_2/k_{-1} ratio decreases more rapidly than k_1 as the amine basicity decreases.

Conclusions

The current study has allowed us to conclude the following: (1) The Hammett plot for the reactions of **1a-1h** with piperidine consists of two intersecting straight lines, while the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_X = 1.25$ and $r = 0.58$. (2) The nonlinear Hammett plot is not due to a change in the RDS but is caused by GS stabilization through resonance interactions for substrates possessing an EDG in the benzoyl moiety. Thus, the k_2/k_{-1} ratio is not affected by the electronic nature of the substituent X. (3) Analysis of the Brønsted-type plot for the aminolysis of **1d** suggests that the reaction proceeds through a stepwise mechanism with a change in RDS (*i.e*., from the k_2 step to the k_1 process as the pK_a of the conjugate acid of the amine exceeds 10.5). (4) The basicity of amines can influence k_2 through an inductive effect, which is contrary to generally held views. (5) The current study has also demonstrated that deduction of reaction mechanism based just on a linear or nonlinear plot can be misleading.

Experimental Section

Materials. 4-Chloro-2-nitrophenyl X-substituted-benzoates (**1a-1h**) were readily prepared from the reaction of the respective benzoyl chloride with 4-chloro-2-nitrophenol in anhydrous ether under the presence of triethylamine as reported previously.[23] The crude products were purified by column chromatography and their purity was checked by their melting points and spectral data such as ^{1}H and ^{13}C NMR spectra. DMSO and other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. Due to low solubility of the substrates in pure water, aqueous DMSO (80 mol % H_2O/20 mol % DMSO) was used as the reaction medium.

Kinetics. The kinetic study was performed using a UV-Vis spectrophotometer for slow reactions (*e.g*., $t_{1/2} \geq 10$ s) or a stopped-flow spectrophotometer for fast reactions (*e.g*., $t_{1/2} <$ 10 s) 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-chloro-2-nitrophenoxide ion. All of the reactions in this study were carried out under pseudo-first-order conditions, in which the concentration of the amine was kept in excess over that of the substrate.

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, which was prepared by adding 2 equiv. of amine and 1 equiv. of standardized HCl solution to make a self-buffered solution. All solutions were transferred by gas-tight syringes. Generally, the amine concentration in the reaction mixtures was varied over the range $(2 - 50) \times 10^{-3}$ M, while the substrate concentration 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. Usually, five different amine concentrations were employed to obtain the second-order rate constants (k_N) from the slope of linear plots of k_{obsd} *vs*. amine concentrations.

Products Analysis. 4-Chloro-2-nitrophenoxide ion 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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References

1. (a) Page, M. I.; Williams, A. *Organic and Bio-organic Mechanisms*; Longman: Singapore, 1997; Chapt. 7. (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins Publishers: New York, 1987; Chapt. 8. (c) Jencks, W. P. *Catalysis in Chemistry and Enzymology*, McGraw Hill: New York, 1969; Chapt. 10.
2. (a) Castro, E. A. *Pure Appl. Chem.* **2009**, *81*, 685-696. (b) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505-3524. (c) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511-527. (d) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345-375. (e) Jencks, W. P. *Acc. Chem. Res*. **1980**, *13*, 161-169.
3. (a) Castro, E. A.; Aliaga, M.; Campodonico, P. R.; Cepeda, M.; Contreras. R.; Santos, J. G. *J. Org. Chem*. **2009**, *74*, 9173-9179. (b) Castro, E. A.; Ramos, M.; Santos, J. G. *J. Org. Chem*. **2009**, *74*, 6374-6377. (c) Castro, E. A.; Ugarte, D.; Rojas, M. F.; Pavez, P.; Santos, J. G. *Int. J. Chem. Kinet.* **2011**, *43*, 708-714. (d) Castro, E. A.; Aliaga, M.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 2679-2685. (e) Castro, E. A.; Gazitua, M.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 8088-8092.
4. (a) Sung, D. D.; Koo, I. S.; Yang, K.; Lee, I. *Chem. Phys. Lett*. **2006**, *432*, 426-430. (b) Sung, D. D.; Koo, I. S.; Yang, K.; Lee, I. *Chem. Phys. Lett*. **2006**, *426*, 280-284. (c) Oh, H. K.; Oh, J. Y.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2005**, *70*, 5624-5629. (d) Oh, H. K.; Jin, Y. C.; Sung, D. D.; Lee, I. *Org. Biomol. Chem.* **2005**, *3*, 1240-1244.
5. (a) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824-3829. (b) Llinas, A.; Page, M. I. *Org. Biomol. Chem.* **2004**, *2*, 651-654. (c) Perreux, L.; Loupy, A.; Delmotte, M. *Tetrahedron* **2003**, *59*, 2185-2189. (d) Menger, F. M.; Brian, J.; Azov, V. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2581-2584. (e) Fife, T. H.; Chauffe, L. *J. Org. Chem*. **2000**, *65*, 3579-3586.
6. Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6970-6980.
7. (a) Castro, E. A.; Valdivia, J. L. *J. Org. Chem.* **1986**, *51*, 1668-1672. (b) Castro, E. A.; Santander, C. L. *J. Org. Chem.* **1985**, *50*, 3595-3600. (c) Castro, E. A.; Steinfort, G. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 453-457. (d) Castro, E. A.; Aguayo, R.; Bessolo, J.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 7788-7791. (e) Castro, E. A.;

Aguayo, R.; Bessolo, J.; Santos, J. G. *J. Org. Chem*. **2005**, *70*, 3530-3536. (f) Castro, E. A.; Aguayo, R.; Santos, J. G. *J. Org. Chem*. **2004**, *69*, 5399-5404. (g) Castro, E. A.; Aguayo, R.; Santos, J. G. *J. Org. Chem*. **2003**, *68*, 8157-8161.

8. (a) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 8995-8998. (b) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 3874-3877. (c) Oh, H. K.; Kim, S. K.; Lee, H. W.; Lee, I. *New J. Chem*. **2001**, *25*, 313-317.
9. (a) Um, I. H.; Bea, A. R. *J. Org. Chem*. **2012**, *77*, 5781-5787. (b) Um, I. H.; Kim, K. H.; Park, H. R.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* **2004**, *69*, 3937-3942. (c) Um, I. H.; Jeon, S. E.; Seok, J. A. *Chem. Eur. J.* **2006**, *12*, 1237-1243.
10. (a) Um, I. H.; Lee, S. E.; Kwon, H. J. *J. Org. Chem.* **2002**, *67*, 8999-9005. (b) Um, I. H.; Seok, J. A.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2003**, *68*, 7742-7746. (c) Um, I. H.; Hwang, S. J.; Yoon, S.; Jeon, S. E.; Bae, S. K. *J. Org. Chem.* **2008**, *73*, 7671-7677.
11. (a) Um, I. H.; Akhtar, K.; Shin, Y. H.; Han, J. Y. *J. Org. Chem.* **2007**, *72*, 3823-3829. (b) Um, I. H.; Shin, Y. H.; Han, J. Y.; Mishima, M. *J. Org. Chem.* **2006**, *71*, 7715-7720. (c) Um, I. H.; Han, J. Y.; Shin, Y. H. *J. Org. Chem.* **2009**, *74*, 3073-3078.
12. Um, I. H.; Lee, J. Y.; Ko, S. H.; Bae, S. K. *J. Org. Chem*. **2006**, *71*, 5800-5803.
13. (a) Carroll, F. A. *Perspectives on Structure and Mechanism in Organic Chemistry*, Brooks/Cole: New York, 1988; pp 371-386. (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins Publishers: New York, 1987; pp 143-151.
14. (a) Um, I. H.; Hong, J. Y.; Seok, J. A. *J. Org. Chem.* **2005**, *70*, 1438-1444. (b) Um, I. H.; Chun, S. M.; Chae, O. M.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* **2004**, *69*, 3166-3172. (c) Um, I. H.; Hong, J. Y.; Kim, J. J.; Chae, O. M.; Bae, S. K. *J. Org. Chem.* **2003**, *68*, 5180-5185.
15. (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.
16. (a) Kaljurand, I.; Lilleorg, R.; Murumaa, A.; Mishima, M.; Burk, P.; Koppel, I.; Koppel, I. A.; Leito, I. *J. Phys. Org. Chem.* **2013**, *26*, 171-181. (b) Basheer, A.; Mishima, M.; Marek, I. *Org. Lett*. **2011**, *13*, 4076-4079. (c) Than, S.; Badal, M.; Itoh, S.; Mishima, M. *J. Phys. Org. Chem.* **2010**, *23*, 411-417. (d) Itoh, S.; Badal, M.; Mishima, M. *J. Phys. Org. Chem.* **2009**, *113*, 10075-10080.
17. (a) Um, I. H.; Han, H. J.; Ahn, J. A.; Kang, S.; Buncel, E. *J. Org. Chem.* **2002**, *67*, 8475-8480. (b) Um, I. H.; Lee, J. Y.; Kim, H. T.; Bae, S. K. *J. Org. Chem.* **2004**, *69*, 2436-2441. (c) Um, I. H.; Kim, E. H.; Lee, J. Y. *J. Org. Chem.* **2009**, *74*, 1212-1217.
18. (a) Um, I. H.; Kang, J. S.; Shin, Y. H.; Buncel, E. *J. Org. Chem.* **2013**, *78*, 490-497. (b) Um, I. H.; Shin, Y. H.; Park, J. E.; Kang, J. S.; Buncel, E. *Chem. Eur. J*. **2012**, *18*, 961-968. (c) Um, I. H.; Han, J. Y.; Hwang, S. J. *Chem. Eur. J.* **2008**, *14*, 7324-7330. (d) Um, I. H.; Park, J. E.; Shin, Y. H. *Org. Biomol. Chem.* **2007**, *5*, 3539-3543.
19. Im, L. R.; Min, J. S.; Akhtar, K.; Um, I. H. *Bull. Korean Chem. Soc*. **2011**, *32*, 2117-2120.
20. Jencks, W. P.; Regenstein, J. *Handbook of Biochemistry*, 2nd ed.; Sober, H. A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1970; p J-195.
21. (a) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem*. **1996**, *61*, 3501-3505. (b) Castro, E. A.; Saavedra, C.; Cubillos, M.; Santos, J. G.; Umana, M. I. *J. Org. Chem*. **1999**, *64*, 5401-5407. (c) Castro, E. A.; Garcia, P.; Leandro, L.; Quesieh, N.; Rebolledo, A.; Santos, J. G. *J. Org. Chem*. **2000**, *65*, 9047-9053. (d) Castro, E. A.; Leandro, L.; Quesieh, N.; Santos, J. G. *J. Org. Chem*. **2001**, *66*, 6130-6135.
22. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins Publishers: New York, 1987; pp 178-179.
23. (a) Cadogan, J. I. G. *J. Chem. Soc.* **1959**, 2844-2846. (b) Effenberger, F.; Muck, A. C.; Bessey, E. *Chem. Ber.* **1980**, *113*, 2086-2099.