

The α -Effect in Hydrazinolysis of 4-Chloro-2-Nitrophenyl X-Substituted-Benzoates: Effect of Substituent X on Reaction Mechanism and the α -Effect

Min-Young Kim,[†] Tae-Eun Kim,[†] Jieun Lee,[‡] and Ik-Hwan Um^{*}

Department of Chemistry and [†]Department of Science Education, Ewha Womans University, Seoul 120-750, Korea
^{*}E-mail: ihum@ewha.ac.kr

[‡]Gocheok High School, Seoul 152-832, Korea

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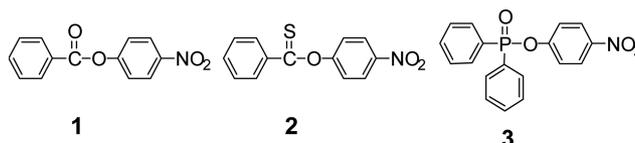
Second-order rate constants (k_N) have been measured spectrophotometrically for the reaction of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-6h**) with a series of primary amines including hydrazine in 80 mol % H₂O/20 mol % DMSO at 25.0 °C. The Brønsted-type plot for the reaction of 4-chloro-2-nitrophenyl benzoate (**6d**) is linear with $\beta_{\text{nuc}} = 0.74$ when hydrazine is excluded from the correlation. Such a linear Brønsted-type plot is typical for reactions reported previously to proceed through a stepwise mechanism in which expulsion of the leaving group occurs in the rate-determining step (RDS). The Hammett plots for the reactions of **6a-6h** with hydrazine and glycylglycine are nonlinear. In contrast, the Yukawa-Tsuno plots exhibit excellent linear correlations with $\rho_X = 1.29-1.45$ and $r = 0.53-0.56$, indicating that the nonlinear Hammett plots are not due to a change in RDS but are caused by resonance stabilization of the substrates possessing an electron-donating group (EDG). Hydrazine is *ca.* 47-93 times more reactive than similarly basic glycylglycine toward **6a-6h** (*e.g.*, the α -effect). The α -effect increases as the substituent X in the benzoyl moiety becomes a stronger electron-withdrawing group (EWG), indicating that destabilization of the ground state (GS) of hydrazine through the repulsion between the nonbonding electron pairs on the two N atoms is not solely responsible for the substituent-dependent α -effect. Stabilization of transition state (TS) through five-membered cyclic TSs, which would increase the electrophilicity of the reaction center or the nucleofugality of the leaving group, contributes to the α -effect observed in this study.

Key Words : The α -effect, Hydrazinolysis, Ground-state destabilization, Transition-state stabilization, Yukawa-Tsuno plot

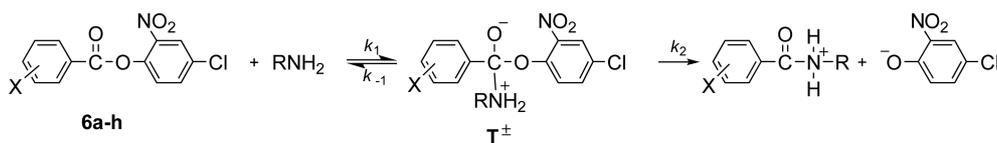
Introduction

Aminolysis of esters is an important class of reactions not only in organic syntheses but also in biological processes such as peptide biosynthesis and enzyme actions.¹ Reactions of esters with amines 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.*, nature of electrophilic centers, stability of intermediates, type of amines, *etc.*).²⁻⁹ Reactions of 4-nitrophenyl benzoate (**1**) with a series of cyclic secondary amines have been suggested to proceed through a stepwise mechanism with a zwitterionic tetrahedral intermediate (T^\pm) in which expulsion of the leaving group occurs in the rate-determining step (RDS) on the basis of a linear Brønsted-type plots with $\beta_{\text{nuc}} = 0.81$.⁵ The corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**2**) have been shown to proceed through a stepwise mechanism with two intermediates (*e.g.*, T^\pm and its deprotonated form T^-) on the basis of the experimental result that plots of k_{obsd} vs. [amine] curve upward.⁶ In contrast, aminolysis of 4-nitrophenyl diphenylphosphinate (**3**) has been reported to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.5 \pm 0.1$.⁷ These demonstrate convincingly that the nature of the electrophilic center (*e.g.*, C=O, C=S and P=O) is an important

factor that controls the reaction mechanism.



Aminolysis of 4-pyridyl X-substituted-benzoates (**4**) has been reported to proceed through a stepwise mechanism with one or two intermediates depending on the electronic nature of the substituent X (*e.g.*, two intermediates T^\pm and T^- when X = a strong EWG but T^\pm only when X = a weak EWG or an EDG).^{8a} In contrast, the corresponding reactions of 2-pyridyl X-substituted-benzoates (**5**, the isomers of **4**) have been suggested to proceed through forced a concerted mechanism with a TS structure similar to TS_1 , which is structurally not possible for the reaction of **4**, on the basis of a linear Brønsted-type plot $\beta_{\text{nuc}} = 0.58$.^{8b} One might expect that the H-bonding interactions as illustrated in TS_1 could change the leaving group from the highly basic 2-pyridyloxide ($pK_a = 11.62$ in H₂O) to the weakly basic 2-pyridiniumoxide or its tautomer 2-pyridone ($pK_a = 0.75$ in H₂O).⁹ Since the decreased basicity increases the nucleofugality of the leaving group significantly, the enhanced nucleofugality could force the reaction to proceed through a concerted

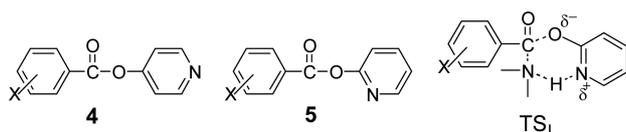


X = 4-NO₂ (**6a**), 4-CN (**6b**), 3-Cl (**6c**), H (**6d**), 3-Me (**6e**), 4-Me (**6f**), 4-OMe (**6g**), 4-NMe₂ (**6h**).

RNH₂ = 9 primary amines including hydrazine.

Scheme 1

mechanism through the H-bonding interaction shown in TS₁.



In aminolysis of esters, hydrazine has often been reported to be more reactive than similarly basic glycylglycine.¹⁰ Hydroxylamine and methoxyamine also exhibit higher nucleophilic reactivity than would be expected from their basicity. A common feature of these amines is possession of a nonbonding electron pair at the atom α to the reaction site. Thus, the enhanced reactivity shown by these nucleophiles has been termed the α -effect.¹¹ Numerous studies have been carried out to account for the α -effect.¹¹⁻¹⁵ Some important theories suggested as the origin of the α -effect include (1) destabilization of the ground state (GS) due to the repulsion between the nonbonding electron pairs, (2) TS stabilization, (3) thermodynamic stabilization of reaction products, and (4) solvent effects.¹¹⁻¹⁵

We have now carried out nucleophilic substitution reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-6h**) with a series of primary amines including hydrazine to investigate the origin of the α -effect as well as the reaction mechanism (Scheme 1). We wish to report that deduction of reaction mechanism based just on a linear or nonlinear Hammett plot can be misleading. A possible origin of the substituent-dependent α -effect found in this study is also reported.

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, $\ln(A_{\infty} - A_t) = -k_{\text{obsd}}t + C$. 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 contribution of H₂O and/or OH⁻ from hydrolysis of amines 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 $\pm 3\%$ from replicate runs. The k_N values calculated in this way are summarized in Table 1 for the reactions of 4-chloro-2-nitrophenyl benzoate (**6d**) with a series of primary amines and in Table 2 for those of 4-chloro-2-nitrophenyl X-

Table 1. Summary of Second-Order Rate Constants for the Reactions of 4-Chloro-2-nitrophenyl benzoate (**6d**) with Primary Amines in 80 mol % of H₂O/20 mol % DMSO at 25.0 \pm 0.1 °C

amine	pK _a ^a	10 ² k _N /M ⁻¹ s ⁻¹
1 ethylamine	10.67	203
2 ethylenediamine	10.32	108
3 ethanolamine	9.67	35.5
4 benzylamine	9.46	25.0
5 glycylglycine	8.31	3.78
6 hydrazine	8.20	246
7 glycine ethyl ester	7.68	1.82
8 1,2-diaminopropane-H ⁺	7.13	1.03
9 trifluoroethylamine	5.68	0.0273

^aThe pK_a data were taken from ref. 17b.

substituted-benzoates (**6a-6h**) with hydrazine and glycylglycine.

Effect of Amine Basicity on Reactivity and Reaction Mechanism. As shown in Table 1, the k_N value for the reaction of **6d** decreases as the amine basicity decreases (except hydrazine), e.g., it decreases from 2.03 M⁻¹s⁻¹ to 3.78 $\times 10^{-2}$ and 2.73 $\times 10^{-4}$ M⁻¹s⁻¹ as the pK_a value for the conjugate acid of the incoming amine decreases from 10.67 to 8.31 and 5.68, in turn. Hydrazine exhibits a much larger k_N value than similarly basic glycylglycine (the α -effect). It is also noted that hydrazine is even more reactive than ethylamine which is over 2 pK_a units more basic than hydrazine.

The effect of amine basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot for the reactions of **6d** with the primary amines (except hydrazine, which deviates positively from the linearity) exhibits an excellent linear correlation ($R^2 = 0.996$) with $\beta_{\text{nuc}} = 0.74$ when the k_N and pK_a values are statistically corrected using p and q (e.g., $p = 3$ except $p = 6$ for 1,2-diaminopropane-H⁺ and $q = 1$ except $q = 2$ for ethylenediamine).¹⁶ This is similar to the linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.76$ for the corresponding reactions of 4-nitrophenyl benzoate but is contrasting to the curved Brønsted-type plots reported previously for the reactions of 2-chloro-4-nitrophenyl benzoate^{17a} and 2,4-dinitrophenyl benzoate.^{17b} The curved Brønsted-type plots have been interpreted as a change in RDS, e.g., from breakdown of T[‡] to its formation as the incoming amine becomes more basic than the leaving group by ca. 5 pK_a units.¹⁷ The pK_a⁰, defined as the pK_a at the center of the Brønsted curvature where a change in RDS occurs,² was reported to be 10.6 for the aminolysis of 2-chloro-4-nitrophenyl benzoate^{17a} and

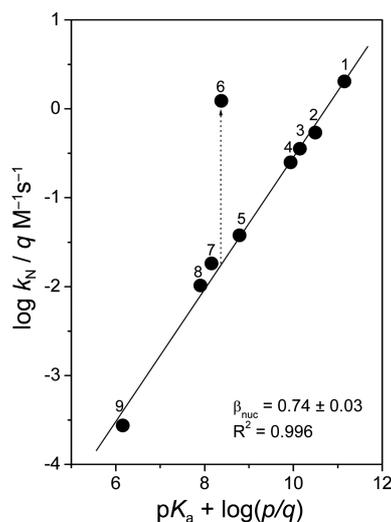


Figure 1. Brønsted-type plot for the reactions of 4-chloro-2-nitrophenyl benzoate (**6d**) with primary amines in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

9.2 for that of 2,4-dinitrophenyl benzoate.^{17b} Since $pK_a = 5.45$ and 4.11 for 2-chloro-4-nitrophenol and 2,4-dinitrophenol, respectively,⁹ the reported pK_a^0 values are consistent with the reports that the RDS changes from breakdown of T^\ddagger to its formation as the incoming amine becomes more basic than the leaving group by *ca.* 5 pK_a units.

The pK_a value of 4-chloro-2-nitrophenol (*i.e.*, the conjugate acid of the leaving group of **6d**) is 6.46.⁹ Thus, one might expect that the center of the Brønsted curvature (*i.e.*, pK_a^0) for the current reaction would be *ca.* 11.5, if the reaction proceeds through a stepwise mechanism with a change in the RDS. The pK_a value of the most basic amine used in this study (*i.e.*, ethylamine) is 10.67, which is *ca.* 0.5 pK_a units smaller than the expected pK_a^0 . This explains why the Brønsted-type plot shown in Figure 1 is not curved, although the current reaction is expected to proceed through a stepwise mechanism.

Effect of Substituent X on Reactivity and Reaction Mechanism. To investigate the effect of nonleaving-group substituent on the reactivity and reaction mechanism, the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a–6h**) with hydrazine and glycyglycine have been carried out. As shown in Table 2, the k_N value for the reaction with hydrazine decreases as the substituent X in the benzoyl moiety changes from an EDG to an EWG, *e.g.*, it decreases from $36.2 \text{ M}^{-1}\text{s}^{-1}$ to 2.46 and $0.0602 \text{ M}^{-1}\text{s}^{-1}$ as X changes from 4-NO₂ to H and 4-NMe₂, in turn. A similar result is demonstrated for the corresponding reactions with glycyglycine. However, hydrazine is much more reactive than glycyglycine in all cases, indicating that hydrazine exhibits the α -effect regardless of the electronic nature of the substituent X.

The effect of substituent X on the reactivity of substrates **6a–6h** is illustrated in Figure 2. The Hammett plots are nonlinear. Each Hammett plot consists of two intersecting

Table 2. Summary of Second-Order Rate Constants for the Reactions of 4-Chloro-2-nitrophenyl X-Substituted-benzoates (**6a–6h**) with Hydrazine and Glycyglycine in 80 mol % H₂O/20 mol % DMSO at 25 ± 0.1 °C

	X	$k_N/\text{M}^{-1}\text{s}^{-1}$		α -Effect
		hydrazine	glycyglycine	
6a	4-NO ₂	36.2	0.387	93.5
6b	4-CN	26.2	0.313	83.7
6c	3-Cl	11.3	0.139	81.3
6d	H	2.46	0.0378	65.1
6e	3-Me	1.97	0.0301	65.4
6f	4-Me	1.25	0.0191	65.4
6g	4-MeO	0.595	0.0101	58.9
6h	4-NMe ₂	0.0602	0.00127	47.4

straight lines, *e.g.*, $\rho_X = 1.97$ for the hydrazinolysis of substrates possessing an EDG (**6e–6h**) and $\rho_X = 1.49$ for the reaction of substrates possessing an EWG or no substituent (**6a–6d**). A similar result is shown for the corresponding reactions with glycyglycine. Traditionally, such nonlinear Hammett plots have been interpreted as a change in RDS.¹⁸ Thus, one might suggest that the reactions of **6a–6h** proceed through a stepwise mechanism with a change in RDS upon changing the substituent X, *e.g.*, from formation of T^\ddagger (*i.e.*, the k_1 step in Scheme 1) to its breakdown (*i.e.*, the k_2 step in Scheme 1) as the substituent X changes from EDGs to EWGs. This idea appears to be reasonable, since an EDG in the benzoyl moiety would decrease k_1 but would increase k_2 by increasing the electron density of the reaction center, or *vice versa*.

However, we propose that the nonlinear Hammett plots are not due to a change in RDS. Because RDS is not determined by the magnitude of the k_1 and k_2 values. Furthermore, k_1 and k_2 cannot be compared directly due to the

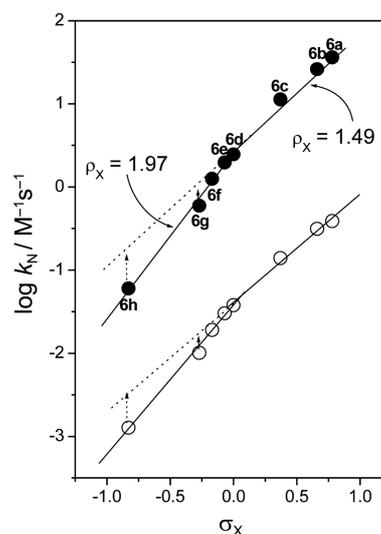
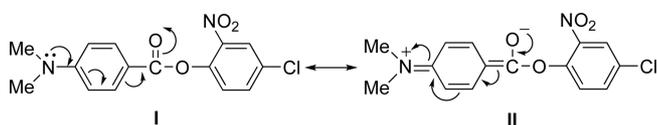


Figure 2. Hammett plots for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a–6h**) with hydrazine (●) and glycyglycine (○) in 80 mol % H₂O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

difference in their units (*i.e.*, $M^{-1}s^{-1}$ for the second-order rate constant k_1 and s^{-1} for the first-order rate constant k_2). The RDS should be determined by the k_2/k_{-1} ratio (*i.e.*, RDS = the k_2 step when $k_2/k_{-1} < 1$ while RDS = the k_1 step when $k_2/k_{-1} > 1$).

A careful examination of the nonlinear Hammett plots shown in Figure 2 reveals that substrates possessing an EDG in the benzoyl moiety (*e.g.*, **6e-6h**) exhibit negative deviation from the linear line composed of substrates bearing an EWG or no substituent (*e.g.*, **6a-6d**). Substrates possessing an EDG can be stabilized through resonance interactions as illustrated by the resonance structures I \leftrightarrow II. Since such stabilization of the substrates in the GS would decrease their reactivity, we propose that the nonlinear Hammett plots are due to the resonance stabilization. This idea is consistent with the fact that the substrate possessing a stronger EDG (*e.g.*, **6h**) deviates more negatively from the linear line.



To examine the above proposal, the Yukawa-Tsuno equation has been employed. Eq. (1) was originally derived to account for the kinetic results obtained from solvolysis of benzylic systems, in which a positive charge develops partially in the TS.¹⁹ The r value in Eq. (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_X^+ - \sigma_X^0)$ is the resonance substituent constant that measures the capacity for π -delocalization of the π -electron donor substituent.^{19,20} We have reported that Eq. (1) is highly effective to clarify ambiguities in the reaction mechanism for nucleophilic substitution reactions of esters with anionic nucleophiles (*e.g.*,

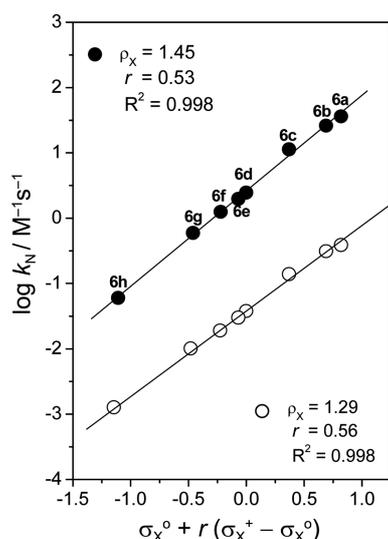


Figure 3. Yukawa-Tsuno plots for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-6h**) with hydrazine (●) and glycyglycine (○) in 80 mol % $H_2O/20$ mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

OH^- , CN^- and N_3^-)²¹ as well as aminolysis of esters.⁵⁻⁸

$$\log k^X/k^H = \rho_X[\sigma_X^0 + r(\sigma_X^+ - \sigma_X^0)] \quad (1)$$

The Yukawa-Tsuno plots in Figure 3 result in excellent linear correlations with $\rho_X = 1.45$ and $r = 0.53$ for the reactions with hydrazine and $\rho_X = 1.29$ and $r = 0.56$ for those with glycyglycine. Such linear Yukawa-Tsuno plots with an r value of 0.53 or 0.56 supports the preceding proposal that the nonlinear Hammett plots shown in Figure 2 are not due to a change in RDS but are caused by the resonance stabilization of the substrates possessing an EDG in the benzoyl moiety. Thus, the current study demonstrates convincingly that deduction of reaction mechanism based just on a linear or nonlinear Hammett plot can be misleading.

Effect of Substituent X on the α -Effect. As shown in Figure 1, hydrazine exhibits positive deviation from the linear Brønsted-type plot. It is manifestation of the α -effect but not due to the nature of the reaction mechanism for the reactions with hydrazine and glycyglycine. Because we have shown in the preceding section that the reactions of **6a-6h** with the two amines proceed through the same mechanism on the basis of the linear Yukawa-Tsuno plots with a similar ρ_X and r values.

It is apparent that the electronic repulsion between the nonbonding electron pairs on the two adjacent N atoms in hydrazine could destabilize its GS. Thus, destabilization of the GS has previously been suggested to be responsible for the enhanced reactivity shown by hydrazine.^{1,2} However, if GS destabilization is solely responsible for the enhanced reactivity of hydrazine, the α -effect should have been independent of the electronic nature of the substituent X. Because hydrazine and glycyglycine are used as the α - and normal-nucleophiles throughout the whole reaction series.

However, Table 1 shows that hydrazine is *ca.* 47-93 times more reactive than glycyglycine depending on the electronic

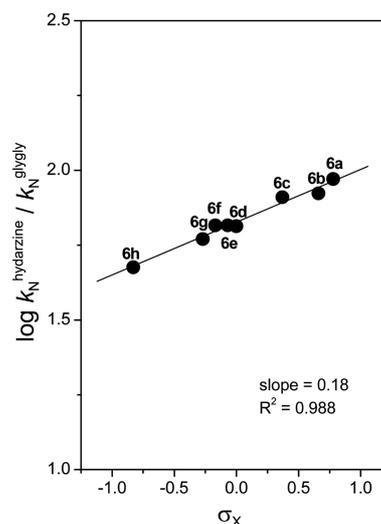
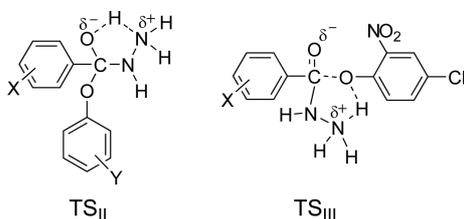


Figure 4. Plot showing dependence of the α -effect on the substituent X for the reactions of 4-chloro-2-nitrophenyl X-substituted-benzoates (**6a-6h**) in 80 mol % of $H_2O/20$ mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

nature of the substituent X in the benzoyl moiety. Furthermore, the α -effect shown in Figure 4 is linearly dependent on the electronic nature of the substituent X. This implies that GS destabilization is not solely responsible for the α -effect observed in this study.

Stabilization of TS through TS_{II} has previously been suggested to be responsible for the enhanced reactivity of hydrazine, since such a five-membered cyclic TS is not possible for the reaction with glycylglycine.^{11,17c} One can suggest a similar TS structure to account for the substituent-dependent α -effect, *i.e.* TS_{III}. It is expected that the H-bonding interaction in TS_{II} and TS_{III} would be influenced by the electronic nature of the substituent X. This might account for the kinetic result that the α -effect found in this study is dependent on the electronic nature of the substituent X.



The intramolecular H-bonding interaction in TS_{III} would increase the nucleofugality of the leaving group. Enhanced nucleofugality would be ineffective for reactions in which expulsion of the leaving group occurs after RDS but would be highly effective when the expulsion of the leaving group is involved in RDS. As discussed from the linear Brønsted-type plot with $\beta_{\text{nuc}} = 0.74$, the current reaction has been suggested to proceed through a stepwise mechanism with expulsion of the leaving group being the RDS. Thus, we propose that the enhanced nucleofugality through TS_{III} is also responsible for the substituent dependent α -effect observed in this study.

Conclusions

The current study has led us to conclude the following: (1) The Brønsted-type plot for the aminolysis of **6d** is linear $\beta_{\text{nuc}} = 0.74$, which is typical for reactions reported to proceed through a stepwise mechanism in which expulsion of the leaving group occurs in the RDS. (2) Hydrazine exhibits positive deviation from the linear Brønsted-type plot (the α -effect). (3) Hammett plots for the reactions of **6a-6h** with hydrazine and glycylglycine are nonlinear, while the Yukawa-Tsuno plots exhibit excellent linear correlation with $\rho_X = 1.29-1.45$ and $r = 0.53-0.56$. Thus, the nonlinear Hammett plots are not due to a change in RDS but are caused by resonance stabilization of substrates possessing an EDG in the benzoyl moiety. (4) The magnitude of the α -effect increases linearly with increasing the electron-withdrawing ability of the substituent X. (5) Destabilization of the GS through the electronic repulsion is not solely responsible for the substituent-dependent α -effect. Stabilization of the TS through the intramolecular H-bonding interactions shown in TS_{II} and TS_{III} are also responsible for the α -effect observed

in the current reaction.

Experimental Section

Materials. 4-Chloro-2-nitrophenyl X-substituted-benzoates (**6a-6h**) 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.²⁰ The crude products were purified by column chromatography and their purity was checked by their melting points and spectral data such as ¹H and ¹³C NMR spectra. Amines and other chemicals were of the highest quality available.

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 2-chloro-4-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 μ L 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 amine concentration in the reaction mixtures was varied over the range $(2 - 100) \times 10^{-3}$ M, while the substrate concentration was *ca.* 4×10^{-5} M. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A_\infty - A_t) = -k_{\text{obsd}}t + C$. 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.

Product 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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