Kinetic Study on Nucleophilic Displacement Reactions of 2-Chloro-4-Nitrophenyl X-Substituted-Benzoates with Primary Amines: Reaction Mechanism and Origin of the α-Effect

Tae-Il Um,[‡] Min-Young Kim, Tae-Eun Kim,[†] 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
[‡]Dongbuk High School, Seoul 134-060, Korea
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Second-order rate constants for aminolysis of 2-chloro-4-nitrophenyl X-substituted-benzoates (**1a-h**) have been measured spectrophotometrically in 80 mol % H_2O/20 mol % DMSO at 25.0 °C. The Brønsted-type plot for the reactions of 2-chloro-4-nitrophenyl benzoate (**1d**) with a series of primary amines curves downward, which has been taken as evidence for a stepwise mechanism with a change in rate-determining step (RDS). The Hammett plots for the reactions of **1a-h** with hydrazine and glycylglycine are nonlinear while the Yukawa-Tsuno plots exhibit excellent linearity with ρ_X = 1.22-1.35 and r = 0.57-0.59, indicating that the nonlinear Hammett plots are not due to a change in RDS but are caused by stabilization of substrates possessing an electron-donating group (EDG) through resonance interactions between the EDG and C=O bond of the substrates. The α-effect exhibited by hydrazine increases as the substituent X changes from a strong EDG to a strong electron-withdrawing group (EWG). It has been concluded that destabilization of hydrazine through the electronic repulsion between the adjacent nonbonding electrons is not solely responsible for the substituent dependent α-effect but stabilization of the transition state is also a plausible origin of the α-effect.

Key Words : The α-Effect, Ground state, Transition state, Intramolecular H-bonding, Yukawa-Tsuno plot

Introduction

Nucleophiles possessing one or more nonbonding electron pairs at the atom α to the reaction site have often been reported to exhibit significantly enhanced reactivity toward a variety of electrophiles.[1-14] Thus, the enhanced nucleophilic reactivity has been termed the α-effect by Edward and Pearson in 1962.[1] Numerous studies have been performed to investigate the origin of the α-effect.[1-14] Some important theories suggested as the origin of the α-effect are (1) destabilization of the ground state (GS) of the α-effect nucleophile due to the electronic repulsion between the adjacent nonbonding electron pairs, (2) stabilization of the transition state (TS), (3) thermodynamic stability of products, and (4) solvent effect.[2]

Among them, solvent effect on the α-effect has most intensively been studied. It has been reported that HOO^- does not exhibit any enhanced reactivity in the gas-phase reaction of methyl formate with HOO^- and OH^-.[3f] Accordingly, the α-effect observed in the reactions with HOO^- in

H_2O has been attributed to a solvent effect,[3f] because HOO^- was reported to be 12 kcal/mol less strongly solvated than OH^- in water.[4] In contrast, recent developments of computational methods have shown that the α-effect nucleophiles (*e.g.*, HOO^-, ClO^-, BrO^-, NH_2NH_2, *etc.*) exhibit lower activation energies than isobasic normal-nucleophiles in gas-phase S_N2 reactions of dimethyl methylphosphonate, methyl formate, or alkyl halides, indicating that solvent effect is not important as the origin of the α-effect.[5-7]

We have carried out nucleophilic substitution reactions of various esters with butane-2,3-dione monoximate (Ox^-, α-effect nucleophile) and 4-chlorophenoxide ($4\text{-}ClPhO^-$, normal-nucleophole) in H_2O/DMSO mixtures of varying compositions to investigate solvent effects on the α-effect.[9-14] Our systematic study has shown that the α-effect increases as the DMSO content in the medium increases up to 50 mol % DMSO and then decreases thereafter in the reactions of 4-nitrophenyl acetate, benzoate, benzenesulfonate and related esters with Ox^- and $4\text{-}ClPhO^-$ (*i.e.*, a bell-shaped α-effect profile) although the magnitude of the α-effect is strongly
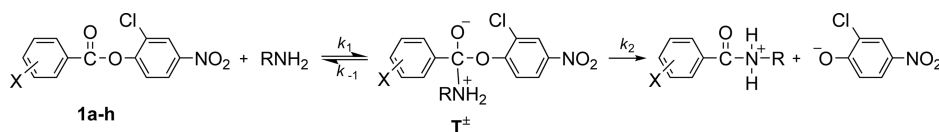
X = 3,5-$(NO_2)_2$ (**1a**), 4-Cl-3-NO_2 (**1b**), 3-Cl (**1c**), H (**1d**), 3-Me (**1e**), 4-Me (**1f**), 4-OMe (**1g**), 4-NMe_2 (**1h**).
RNH_2 = 9 primary amines including hydrazine.

Scheme 1

dependent on the nature of the electrophilic center (*e.g.*, C=O, C=S, SO$_2$, and P=O centered esters).[9-14] The bell-shaped α-effect profile has been attributed to differential destabilization of GS up to 50 mol % DMSO and to differential stabilization of TS in the DMSO-rich region.[9-14]

Our study has now been extended to nucleophilic substitution reactions of 2-chloro-4-nitrophenyl X-substituted-benzo-ates (**1a-h**) with a series of primary amines including hydrazine to investigate the origin of the α-effect. We have also studied the reaction mechanism of the aminolysis of **1a-h** through linear free energy relationships such as Brønsted-type, Hammett, and Yukawa-Tsuno plots.

Results and Discussion

All of the reactions in this study were performed under pseudo-first-order conditions in which the amine concentration was kept at least 20 times in excess of the substrate concentration. The reactions obeyed first-order kinetics in all cases and the 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 concentrations are linear and pass through the origin, indicating that general-base catalysis by a second amine molecule is absent. The second-order rate constants (k_N) were calculated from the slope of the linear plots. The k_N values calculated in this way are summarized in Tables 1 and 2 for the reactions of 2-chloro-4-nitrophenyl benzoate (**1d**) with a series of primary amines and for those of 2-chloro-4-nitrophenyl X-substituted-benzoates (**1a-h**) with hydrazine and glycylglycine, respectively. The uncertainty in the k_N values is estimated to be less than ± 3% based on the replicate runs.

Effect of Amine Basicity on Reactivity and Reaction Mechanism. As shown in Table 1, the k_N values for the reactions of 2-chloro-4-nitrophenyl benzoate (**1d**) with primary amines decreases as the amine basicity decreases (except for the reaction with hydrazine), *e.g.*, k_N decreases from 4.52 M^{-1}s^{-1} to 0.139 and 0.00124 M^{-1}s^{-1} as the pK_a of the conjugate acid of the incoming amine decreases from 10.67 to 8.31 and 5.68, in turn. However, hydrazine exhibits *ca.* 50 times larger k_N than similarly basic glycylglycine. This is consistent with the previous reports that hydrazine is
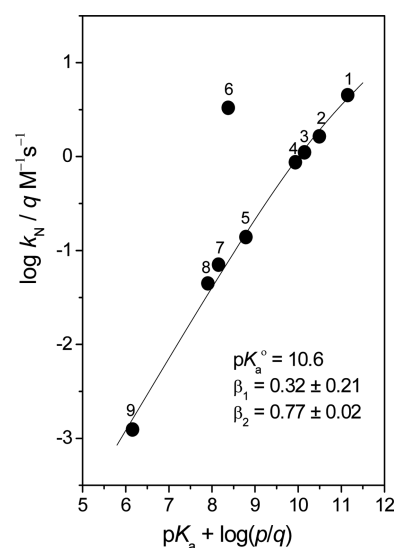

Figure 1. Brønsted-type plot for the reactions of 2-chloro-4-nitrophenyl benzoate (**1d**) with primary amines in 80 mol % of H$_2$O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1, and hydrazine is excluded in the correlation.

much more nucleophilic than would be expected from its basicity (*i.e.*, the α-effect).[2,13]

The effect of amine basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot for the reactions of **1d** with the amines (except hydrazine) curves downward 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).[15] Such curved Brønsted-type plot is typical of reactions reported to proceed through a stepwise mechanism with a change in RDS.[16-19] In fact, the reactions of 2,4-dinitrophenyl benzoate with the primary amines used in this study have been suggested to proceed through a stepwise mechanism with a change in RDS on the basis of a nonlinear Brønsted-type plot.[13,18a] Thus, one can suggest that the aminolysis of **1d** proceeds also through a stepwise mechanism with a change in RDS.

Effect of Substituent X on Reactivity and Reaction Mechanism. To investigate the effect of substituent X on

Table 1. Summary of Second-Order Rate Constants for the Reactions of 2-Chloro-4-Nitrophenyl Benzoate (**1d**) with Primary Amines in 80 mol % of H$_2$O/20 mol % DMSO at 25.0 ± 0.1 °C

	amine	pK_a	$10^2\, k_N$/M^{-1}s^{-1}
1	ethylamine	10.67	452
2	ethylenediamine	10.32	328
3	ethanolamine	9.67	111
4	benzylamine	9.46	86.9
5	glycylglycine	8.31	13.9
6	hydrazine	8.20	662
7	glycine ethyl ester	7.68	7.06
8	1,2-diaminopropane-H$^+$	7.13	4.45
9	trifluoroethylamine	5.68	0.124

Table 2. Summary of Second-Order Rate Constants for the Reactions of 2-Chloro-4-Nitrophenyl X-Substituted-Benzoates (**1a-h**) with Hydrazine and Glycylglycine in 80 mol % H$_2$O/20 mol % of DMSO at 25 ± 0.1 °C

	X	k_N/M^{-1}s^{-1}		α-Effect[a]
		hydrazine	glycylglycine	
1a	3,5-(NO$_2$)$_2$	550	7.70	71.4
1b	4-Cl-3-NO$_2$	130	1.88	69.1
1c	3-Cl	27.9	0.495	56.4
1d	H	6.62	0.139	47.6
1e	3-Me	5.73	0.118	48.6
1f	4-Me	3.66	0.0852	42.9
1g	4-MeO	1.78	0.0419	42.5
1h	4-NMe$_2$	0.177	0.00542	32.7

[a]The α-Effect in this study is defined as the $k_N^{hydrazine}/k_N^{glygly}$ ratio.

reactivity and reaction mechanism, the k_N values for the reactions of 2-chloro-4-nitrophenyl X-substituted-benzoates (**1a-h**) with hydrazine and glycylglycine have been measured. As shown in Table 2, the k_N value for the reactions with hydrazine 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 550 $M^{-1}s^{-1}$ to 6.62 and 0.177 $M^{-1}s^{-1}$ as the substituent X changes from 3,5-$(NO_2)_2$ to H and 4-NMe_2, in turn. A similar result is shown for the corresponding reactions with glycylglycine. It is also noted that hydrazine is much more reactive than similarly basic glycylglycine (*i.e.*, the α-effect) toward all the substrates studied.

The effect of substituent X on reactivity is demonstrated in Figure 2. One can see that each Hammett plot in Figure 2 consists of two intersecting straight lines, *e.g.*, the reactions of substrates possessing an EDG result in a larger ρ_X than those bearing an EWG for the reactions with both hydrazine and glycylglycine. Such nonlinear Hammett plots have traditionally been taken as evidence for a change in RDS.[20] In fact, Jencks has previously concluded that the reactions of X-substituted-benzaldehydes with semicarbazide in a weakly acidic medium (*e.g.*, pH = 3.9) proceed through a stepwise mechanism with a change in RDS on the basis of a nonlinear Hammett plot (*e.g.*, a large ρ_X when X = EDGs but a small ρ_X when X = EWGs).[20] Thus, one might suggest that the RDS for the current reactions also changes from the first step (the k_1 process) to the second step (the k_2 process) as the substituent X changes from EDGs to EWGs.

The above idea appears to be reasonable. Because an EDG in the benzoyl moiety would increase the electron density of the reaction center, which would cause a decrease in k_1 but an increase in k_2. On the contrary, an EWG in the benzoyl moiety would increase k_1 but decrease k_2 by decreasing the electron density of the reaction center. 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 k_1 and k_2 but it should be governed by the k_2/k_{-1} ratio (*i.e.*, RDS = the k_1 step when $k_2/k_{-1} > 1$ but RDS = the k_2 step when $k_2/k_{-1} < 1$). Furthermore, k_1 and k_2 cannot be compared directly due to the 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).

Cause of Nonlinear Hammett Plot. A careful examination of the nonlinear Hammett plots shown in Figure 2 reveals that substrates possessing an EDG in the benzoyl moiety deviate negatively from the linear line composed with those bearing no EDG. Moreover, the negative deviation is more significant for the substrate possessing a stronger EDG (*e.g.*, **1h**). It is apparent that an EDG in the benzoyl moiety could stabilize the GS of the substrate through the resonance interactions between the EDG and C=O bond as illustrated by the resonance structures I and II. Thus, we propose that resonance stabilization of the substrate in the GS is responsible for the nonlinear Hammett plots.
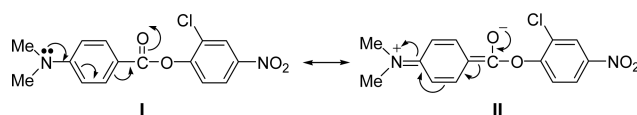
To examine the validity of the above argument, the Yukawa-Tsuno equation is employed. Eq. (1) was originally derived to account for the kinetic results obtained from solvolysis of benzylic systems, in which a positive charge develops partially in the transition state (TS).[21,22] The r value in Eq. (1) represents the resonance demand of the reaction center or the extent of resonance contribution, while the term $(\sigma_X^+ - \sigma_X^o)$ is the resonance substituent constant that measures the capacity for π-delocalization of the π-electron donor substituent.[21,22]
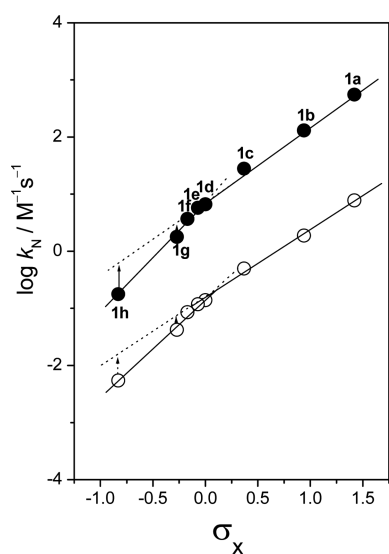

Figure 2. Hammett plots for the reactions of 2-chloro-4-nitrophenyl X-substituted-benzoates (**1a-h**) with hydrazine (●) and glycylglycine (○) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.
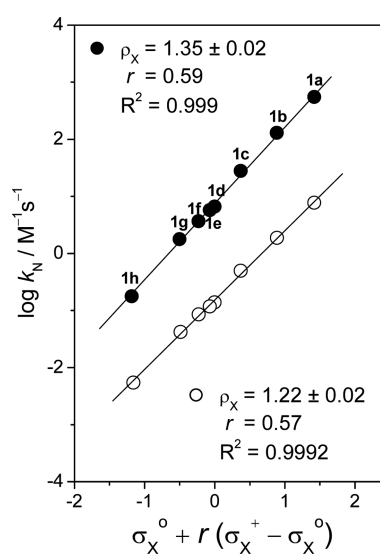
Figure 3. Yukawa-Tsuno plots for the reactions of 2-chloro-4-nitrophenyl X-substituted-benzoates (**1a-h**) with hydrazine (●) and glycylglycine (○) in 80 mol % H_2O/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of the points is given in Table 2.

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

The Yukawa-Tsuno plots in Figure 3 exhibit excellent linear correlations with $\rho_X = 1.35$ and $r = 0.59$ for the reactions with hydrazine and with $\rho_X = 1.22$ and $r = 0.57$ for the reactions with glycylglycine. Such linear Yukawa-Tsuno plots clearly indicate that the nonlinear Hammett plots are not due to a change in RDS but are caused by stabilization of the substrates possessing an EDG through resonance interactions. It is also noted that the ρ_X and r values for the reactions of hydrazine and glycylglycine are similar, indicating that the two series of reactions proceed through the same mechanism with a similar TS structure. Thus, one can suggest that the α-effect in this study is not due to any difference in the reaction mechanism between the reactions with hydrazine and glycylglycine.

Origin of the α-Effect. Since reactivity is governed by the GS and TS energies, our discussion will be limited to the GS and TS effects. The origin of α-effect has been suggested to be destabilization of the GS due to the electronic repulsion between the adjacent nonbonding electrons and/or due to desolvation of the α-effect nucleophiles, *e.g.*, HOO⁻ and butane-2,3-dione monoxime were reported to be 12 and 3.9 kcal/mol less strongly solvated in H_2O than their respective normal-nucleophile OH⁻ and 4-chlorophenoxide, respectively.[4,9]

One might expect that both hydrazine and glycylglycine would not be strongly solvated in the aqueous medium since they are neutral amines. Thus, the electronic repulsion between the adjacent nonbonding electrons would be an important factor which could increase the reactivity of hydrazine. However, if the GS effects (through the electronic repulsion and/or desolvation energy) are mainly responsible for the enhanced reactivity of hydrazine, one might expect that the α-effect should be independent of the electronic nature of the substituent X. This is because hydrazine and glycylglycine are used as the α-effect nucleophile and its reference nucleophile throughout the whole reactions (*i.e.*, a constant GS effect). However, as shown in Table 2, the magnitude of the α-effect (*i.e.*, $k_N^{\text{hydrazine}}/k_N^{\text{glygly}}$) increases as the substituent X changes from a strong EDG to a strong EWG. Thus, one can suggest that the GS effect is not solely responsible for the α-effect observed in this study.

Stabilization of TS through intramolecular H-bonding interactions as modeled by III, IV and V has previously been suggested to be responsible for the α-effects exhibited by NH_2NH_2, NH_2OH and HOO⁻, respectively.[13,14] We have previously reported that the α-effect for the reactions of 4-nitrophenyl X-substituted-benzoates with hydrazine and glycylglycine increases as the substituent X changes from a strong EWG to a strong EDG.[13] Thus, TS stabilization through intramolecular H-bonding interaction as modeled by III has been suggested to be responsible for the substituent dependent α-effect, since such H-bonding interaction would be stronger as the substituent X becomes a stronger EDG.[13] However, the α-effect in this study decreases as the substituent X becomes a stronger EDG (Table 2), which is in

contrast to the α-effect reported previously for the corresponding reactions of 4-nitrophenyl benzoate. Thus, one might suggest that the presence of the 2-Cl in the leaving group, which could exert steric hindrance in formation of such a cyclic structure, would be a plausible reason for the contrasting α-effect behaviors.
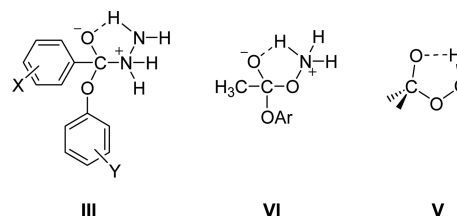
Conclusions

The current study has allowed us to conclude the following: (1) Hydrazine is 33-71 times more reactive than similarly basic glycylglycine toward 2-chloro-4-nitrophenyl X-substituted-benzoates (**1a-h**). (2) The Brønsted-type plot for the reaction of 2-chloro-4-nitrophenyl benzoates (**1d**) with a series of primary amines curves downward, which has been taken as evidence for a stepwise mechanism with a change in RDS. (3) Hammett plots for the reactions of **1a-h** with hydrazine and glycylglycine are nonlinear, while the Yukawa-Tsuno plots result in excellent linear correlations with $\rho_X = 1.22\text{-}1.35$ and $r = 0.57\text{-}0.59$, indicating that nonlinear Hammett plots are not due to a change in RDS but are caused by stabilization of the substrate possessing an EDG through resonance interactions. (4) The α-effect increases as the substituent X changes from a strong EDG to a strong EWG, indicating that GS effect is not solely responsible for the substituent dependent α-effect. (5) Stabilization of TS is also responsible for the α-effect.

Experimental Section

Materials. Substrates **1a-h** were readily prepared from the reaction of the respective X-substituted-benzoyl chloride with 2-chloro-4-nitrophenol in anhydrous ether in the presence of triethylamine as reported previously.[14] Their purity was confirmed from melting points and ¹H NMR characteristics. Doubly glass distilled H_2O was further boiled and cooled under nitrogen just before use. The amines and other chemicals used were of the highest quality available.

Kinetics. The rate constants were measured using a UV-vis spectrophotometer for slow reactions (*e.g.*, $t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions (*e.g.* $t_{1/2}$ 10 s) equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. All reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than the substrate concentration. Typically, the reaction was initiated by adding 5 μL of a 0.02 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and amine. The

reactions were followed by monitoring the appearance of 2-chloro-4-nitrophenoxide up to 9 half-life.

Product Analysis. 2-Chloro-4-nitrophenoxide (and/or its conjugate acid) was liberated quantitatively and identified as one of the reaction products by comparison of the UV-vis spectra obtained after completing the reactions with those of authentic samples under the same kinetic conditions.

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