

The α -Effect in Nucleophilic Substitution Reactions of Y-Substituted-Phenyl X-Substituted-Cinnamates with Butane-2,3-dione Monoximate

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Second-order rate constants (k_{Ox^-}) have been measured spectrophotometrically for nucleophilic substitution reactions of 4-nitrophenyl X-substituted-cinnamates (**7a-7e**) and Y-substituted-phenyl cinnamates (**8a-8e**) with butane-2,3-dione monoximate (Ox^-) in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C. The Hammett plot for the reactions of **7a-7e** consists of two intersecting straight lines while the Yukawa-Tsuno plot exhibits an excellent linearity with $\rho_X = 0.85$ and $r = 0.58$, indicating that the nonlinear Hammett plot is not due to a change in the rate-determining step but is caused by resonance stabilization of the ground state (GS) of the substrate possessing an electron-donating group (EDG). The Brønsted-type plot for the reactions of Y-substituted-phenyl cinnamates (**8a-8e**) is linear with $\beta_{\text{lg}} = -0.64$, which is typical of reactions reported previously to proceed through a concerted mechanism. The α -nucleophile (Ox^-) is more reactive than the reference normal-nucleophile (4-CIPhO $^-$). The magnitude of the α -effect (*i.e.*, the $k_{\text{Ox}^-}/k_{4\text{-CIPhO}^-}$ ratio) is independent of the electronic nature of the substituent X in the nonleaving group but increases linearly as the substituent Y in the leaving group becomes a weaker electron-withdrawing group (EWG). It has been concluded that the difference in solvation energy between Ox^- and 4-CIPhO $^-$ (*i.e.*, GS effect) is not solely responsible for the α -effect but stabilization of transition state (TS) through a cyclic TS structure contributes also to the Y-dependent α -effect trend (*i.e.*, TS effect).

Key Words : The α -effect, Solvent effect, Ground state, Transition state, Concerted mechanism

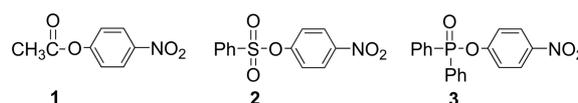
Introduction

Nucleophiles possessing one or more nonbonding electron pairs at the atom α to the nucleophilic center were termed α -nucleophiles.¹ Since such nucleophiles often exhibited higher reactivity than would be expected from their basicity, the term α -effect was given to their enhanced nucleophilic reactivity.¹ Numerous studies have been performed to investigate the origin of the α -effect.²⁻¹⁵ Important theories suggested as the origin of the α -effect are: (1) destabilization of the GS due to the electronic repulsion between the nonbonding electron pairs, (2) stabilization of the TS since the electronic repulsion can be diminished upon formation of a TS, (3) thermodynamic stability of reaction products, and (4) solvent effects.²⁻¹⁵

However, none of these theories alone can fully account for the α -effect phenomenon. Particularly, solvent effects on the α -effect is controversial. DePuy *et al.* carried out nucleophilic substitution reactions of methyl formate with HOO^- and OH^- in gas phase and found that HOO^- does not exhibit the α -effect.^{3e} Thus, solvent effect was suggested to be responsible for the α -effect shown by HOO^- in aqueous medium,³ since HOO^- was reported to be 12 kcal/mol less strongly solvated in H_2O than OH^- .⁴ On the contrary, recent advances of computational methods and developments of new instruments for gas-phase reactions have shown that solvent effect is unimportant for the α -effect, since α -nucleophiles (*e.g.*, HOO^- , FO^- , *etc.*) exhibit lower activation energies than normal nucleophiles of similar basicity in gas-

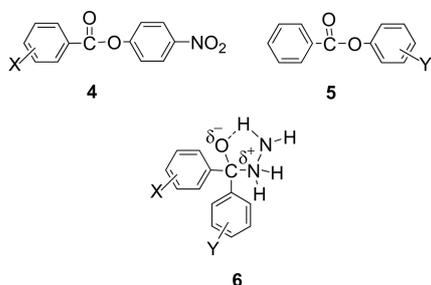
phase reactions.⁵⁻⁷

We have reported that the α -effect is strongly dependent on the solvent composition for the reactions of 4-nitrophenyl acetate (**1**) with butane-2,3-dione monoximate (Ox^- , α -nucleophile) and 4-chlorophenoxide (4-CIPhO $^-$, normal-nucleophile) in $\text{H}_2\text{O}/\text{DMSO}$ mixtures and in $\text{H}_2\text{O}/\text{MeCN}$ mixtures of varying compositions, *e.g.*, the magnitude of the α -effect (*i.e.*, $k_{\text{Ox}^-}/k_{4\text{-CIPhO}^-}$) increases as the mol % DMSO in the medium increases up to *ca.* 50 mol % and then decreases beyond that point (a bell-shaped α -effect profile),¹¹ while the α -effect for the reactions performed in aqueous MeCN increases with increasing mol % MeCN in the medium.¹² These results indicate that solvent effect on the α -effect is indeed important. Similar bell-shaped α -effect profiles have been reported for the reactions of 4-nitrophenyl benzenesulfonate (**2**) and 4-nitrophenyl diphenylphosphinate (**3**) with Ox^- and 4-CIPhO $^-$ in $\text{H}_2\text{O}/\text{DMSO}$ mixtures, although the magnitude of the α -effect decreases as the electrophilic center changes from C=O to SO_2 and P=O.^{13,14}

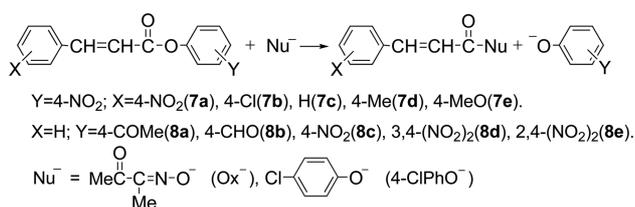


Stabilization of TS has also been examined as an origin of the α -effect for nucleophilic substitution reactions of 4-nitrophenyl X-substituted-benzoates (**4**) and Y-substituted-phenyl benzoates (**5**) with NH_2NH_2 (an α -nucleophile) and glycylglycine (a normal-nucleophile).¹⁵ We have shown that the α -effect (*i.e.*, $k_{\text{NH}_2\text{NH}_2}/k_{\text{glycylglycine}}$) increases as the sub-

stituents X and Y become a weaker electron-withdrawing group (EWG).¹⁵ Accordingly, stabilization of the TS through intramolecular H-bonding interaction (e.g., **6**) has been suggested to be responsible for the substituent-dependent α -effect.¹⁵



Our study has been extended to the nucleophilic substitution reactions of 4-nitrophenyl X-substituted-cinnamates (**7a-7e**) and Y-substituted-phenyl cinnamates (**8a-8e**) with Ox^- in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C (Scheme 1). The kinetic data have been analyzed through LFERs (e.g., Brønsted, Hammett, and Yukawa-Tsuno plots) to deduce the reaction mechanism. The kinetic data in this study have also been compared with those reported previously for the corresponding reactions with 4-ClPhO⁻ to investigate the origin of the α -effect.



Scheme 1

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions in which the concentration of Ox^- was kept in excess over the substrate concentration. All of the reactions in this study obeyed first-order kinetics and pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln(A - A_t) = -k_{\text{obsd}}t + C$. The plots of k_{obsd} vs. $[\text{Ox}^-]$

Table 1. Summary of Second-Order Rate Constants for the Reactions of 4-Nitrophenyl X-Substituted-Cinnamates (**7a-7e**) with Butane-2,3-dione Monoximate (Ox^-) and 4-Chlorophenoxide (4-ClPhO⁻) in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C^a

X	$k_{\text{Ox}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{4\text{-ClPhO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$	
7a	4-NO ₂	134	0.844	159
7b	4-Cl	38.7	0.224	173
7c	H	28.9	0.177	163
7d	4-Me	17.4	0.0958	182
7e	4-MeO	10.8	0.0614	176

^aThe pK_a values and kinetic data for the reactions with 4-ClPhO⁻ were taken from ref. 16.

were linear and passed through the origin. Thus, the second-order rate constants (k_{Ox^-}) were calculated from the slope of the linear plots. Based on replicate runs, it is estimated that the uncertainty in the k_{Ox^-} values is less than $\pm 3\%$. The k_{Ox^-} values calculated in this way are summarized in Table 1 for the reactions of 4-nitrophenyl X-substituted-cinnamates (**7a-7e**) with Ox^- together with the $k_{4\text{-ClPhO}^-}$ values reported previously for the corresponding reactions with 4-ClPhO⁻ to calculate the magnitude of the α -effect (i.e., the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratio). In Table 2 are summarized the k_{Ox^-} and $k_{4\text{-ClPhO}^-}$ values for the reactions of Y-substituted-phenyl cinnamates (**8a-8e**) together with the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratios.

Effect of Substituent X on Reactivity and Reaction Mechanism. As shown in Table 1, the second-order rate constant for the reactions of **7a-7e** with Ox^- is dependent on the electronic nature of the substituent X in the cinnamoyl moiety, e.g., k_{Ox^-} decreases from $134 \text{ M}^{-1}\text{s}^{-1}$ to 28.9 and 10.8 $\text{M}^{-1}\text{s}^{-1}$ as the substituent X changes from 4-NO₂ to H and 4-MeO, respectively. A similar result is shown for the corresponding reactions with 4-ClPhO⁻ although Ox^- is much more reactive than 4-ClPhO⁻, indicating that the α -effect is operative in the current reactions.

The effect of the substituent X on the reactivity of 4-nitrophenyl X-substituted-cinnamates (**7a-7e**) is illustrated in Figure 1. The Hammett plot consists of two intersecting straight lines. Traditionally, such nonlinear Hammett plot has been taken as evidence for a change in the rate-determining step (RDS) of a stepwise reaction.¹⁷ Thus, one might suggest that the reactions proceed through a stepwise mechanism with a change in the RDS upon changing the substituent X in the cinnamoyl moiety, e.g., from breakdown of an addition intermediate to its formation as the substituent X changes from EWGs to EDGs.

The above idea appears to be reasonable since an EWG in the cinnamoyl moiety could accelerate the rate of nucleophilic attack (i.e., k_1) by increasing the electrophilicity of the

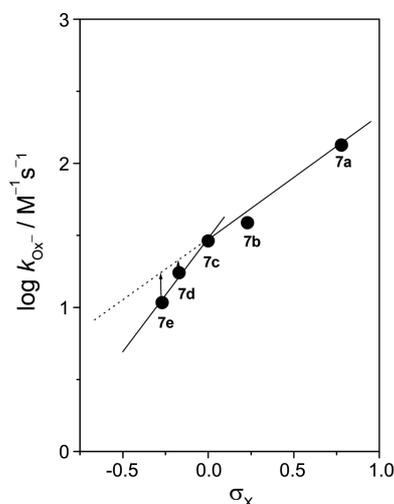
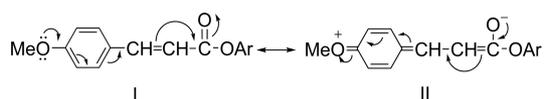


Figure 1. Hammett plot for the reactions of 4-nitrophenyl X-substituted-cinnamates (**7a-7e**) with Ox^- in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

reaction center but would retard the rate of leaving-group departure (*i.e.*, k_2), while an EDG would decrease k_1 but would increase k_2 . However, we propose that the nonlinear Hammett plot shown in Figure 1 is not due to a change in the RDS since the RDS is not determined by the magnitude of the k_1 and k_2 values. Moreover, the k_1 and k_2 values 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).

We propose that the nonlinear Hammett plot shown in Figure 1 is caused by stabilization of the GS of the substrate possessing an EDG in the cinnamoyl moiety through resonance interactions as modeled by resonance structures I and II. This is because such resonance interaction could stabilize the GS of the substrate and would cause a decrease in reactivity. This argument can be supported by the fact that the substrates possessing an EDG (*e.g.*, **7b**, **7d** and **7e**) exhibit negative deviation from the linear line composed of the substrates bearing no EDG (*e.g.*, **7a** and **7c**). Furthermore the deviation is more significant for the substrate possessing a stronger EDG.



To examine the above argument, the Yukawa-Tsuno equation has been employed. Eq. (1) has originally been derived to account for the kinetic data obtained from solvolysis of benzylic systems, in which a partial positive charge develops in the TS.¹⁸ The magnitude of the r value in the Yukawa-Tsuno equation 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.^{18,19}

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

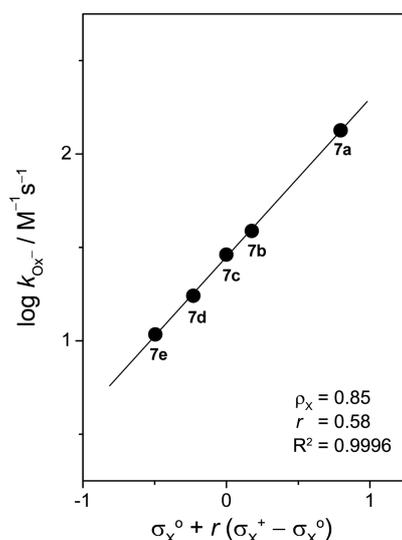


Figure 2. Yukawa-Tsuno plot for the reactions of 4-nitrophenyl X-substituted cinnamates (**7a-7e**) with Ox^- in 80 mol % $H_2O/20$ mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

As shown in Figure 2, the Yukawa-Tsuno plot exhibits an excellent linear correlation with $\rho_X = 0.85$ and $r = 0.58$. The ρ_X value of 0.85 is almost identical to the ρ_X value of 0.89 reported for the corresponding reactions with 4-ClPhO⁻ but is much smaller than that reported previously for the reactions of 2,4-dinitrophenyl X-substituted-benzoates with anions (*e.g.*, $\rho_X = 1.93, 1.72$ and 1.75 for the reactions with OH^- , CN^- and N_3^- , respectively).²⁰ The small ρ_X value found in this study is consistent with the report that insertion of one $-CH_2-$ or $-CH=CH-$ group between the reaction site and the phenyl ring causes a decrease in ρ_X by a half.²¹ Accordingly, the linear Yukawa-Tsuno plot with $\rho_X = 0.85$ and $r = 0.58$ supports our preceding proposal that the nonlinear Hammett plot is not due to a change in the RDS but is caused by GS stabilization through resonance interactions.

The reactions of **7a-7e** with 4-ClPhO⁻ have recently been reported to proceed through a concerted mechanism.¹⁶ Accordingly, one might suggest that the reactions with Ox^- proceed through the same mechanism on the basis of the fact that the ρ_X values for the two series of reactions are almost identical. However, the ρ_X value of 0.85 alone does not give any conclusive information on the reaction mechanism.

Effect of Substituent Y on Reactivity and Reaction Mechanism. To get further information on the reaction mechanism, second-order rate constants for the reactions of Y-substituted-phenyl cinnamates (**8a-8e**) with Ox^- have been measured. As shown in Table 2, k_{Ox^-} increases as the basicity of the leaving group decreases except for the reaction of **8e** (*e.g.*, from $4.19 M^{-1}s^{-1}$ to 28.9 and $577 M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the leaving aryloxyde decreases from 8.94 to 7.79 and 5.60, in turn). It is noted that 2,4-dinitrophenyl cinnamate (**8e**) is less reactive than 3,4-dinitrophenyl cinnamate (**8d**), although the former possesses a less basic leaving group than the latter. However, this is consistent with the report by Gresser *et al.* that the steric hindrance exerted by the 2-NO₂ in the leaving aryloxyde is responsible for the decreased reactivity shown by esters possessing a 2,4-dinitrophenoxy group.²²

The effect of leaving-group basicity on reactivity is illustrated in Figure 3. It is shown that the Brønsted-type plot exhibits an excellent linear correlation with $\beta_{lg} = -0.64$ when the point for 2,4-dinitrophenyl cinnamate is excluded. The β_{lg} value found in this study is a little smaller than that reported

Table 2. Summary of Second-Order Rate Constants for Reactions of Y-Substituted-phenyl Cinnamates (**8a-8e**) with Butane-2,3-dione Monoximate (Ox^-) and 4-Chlorophenoxide (4-ClPhO⁻) in 80 mol % $H_2O/20$ mol % DMSO at 25.0 ± 0.1 °C^a

Y	pK_a	$k_{Ox^-}/M^{-1}s^{-1}$	$k_{4-ClPhO^-}/M^{-1}s^{-1}$	$k_{Ox^-}/k_{4-ClPhO^-}$	
8a	4-COMe	8.94	4.19	0.0188	223
8b	4-CHO	8.45	8.99	0.0446	202
8c	4-NO ₂	7.79	28.9	0.177	163
8d	3,4-(NO ₂) ₂	5.60	577	5.52	105
8e	2,4-(NO ₂) ₂	3.94	434	5.45	79.6

^aThe pK_a values and kinetic data for the reactions with 4-ClPhO⁻ were taken from ref. 16.

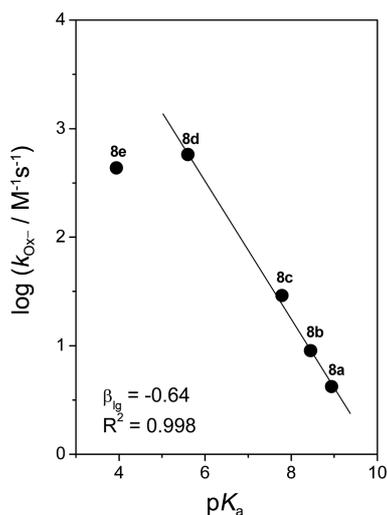


Figure 3. Brønsted-type plot for reactions of Y-substituted-phenyl cinnamates (**8a-8e**) with Ox^- in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

for the corresponding reactions with 4-ClPhO^- (*i.e.*, $\beta_{\text{lg}} = -0.74$)¹⁶ but is typical of reactions reported previously to proceed through a concerted mechanism.²³⁻²⁵ Thus, one can suggest that the reactions of **8a-8e** with Ox^- proceed through a concerted mechanism.

If the reactions in this study proceed through a concerted mechanism as proposed above, a partial negative charge would develop on the O atom of the leaving aryloxide. Since such negative charge can be delocalized to the substituent Y through resonance interactions, σ_{Y^-} constants should result in a better Hammett correlation than σ_{Y^0} constants. On the contrary, if the reactions proceed through a stepwise mechanism, departure of the leaving group would occur after the RDS. This is because Ox^- is more basic and a poorer nucleofuge than the leaving-aryloxides employed in this study. Thus, no negative charge would develop on the O atom of the leaving group if the reactions proceed through a stepwise mechanism. In this case, σ_{Y^0} constants should result in a better Hammett correlation than σ_{Y^-} constants.

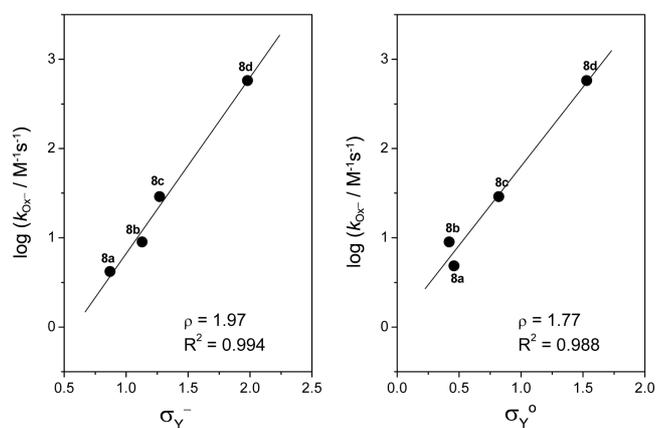


Figure 4. Hammett plots correlated with σ_{Y^-} and σ_{Y^0} constants for the reactions of Y-substituted-phenyl cinnamates **8a-8d** with Ox^- in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C.

To examine whether a partial negative charge develops on the O atom of the leaving group, Hammett plots have been constructed using σ_{Y^-} and σ_{Y^0} constants. As shown in Figure 4, the Hammett plot correlated with σ_{Y^-} constants exhibits much better linearity than that correlated with σ_{Y^0} constants. This is only possible when a partial negative charge develops on the O atom of the leaving group. Thus, one can conclude that the current reactions proceed through a concerted mechanism.

Origin of the α -Effect. Our calorimetric study has previously shown that Ox^- is 6.70 kcal/mol less strongly solvated than 4-ClPhO^- in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO (*i.e.*, the reaction medium used in this study).^{11b} Thus, if the difference in the solvation energy between Ox^- and 4-ClPhO^- (*e.g.*, the GS effect) is responsible for the α -effect observed in the current reactions, the magnitude of the α -effect (*i.e.*, the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratio) should be independent of the electronic nature of the substituents X and Y. This is because the two nucleophiles (*i.e.*, Ox^- and 4-ClPhO^-) were used throughout the reactions. In fact, Table 1 shows that the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratio is independent of the electronic nature of the substituent X for the reactions of 4-nitrophenyl X-substituted-cinnamates. However, Table 2 shows that the $k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ ratio for the reactions of Y-substituted-phenyl cinnamates decreases as the substituent Y becomes a weaker EWG. Furthermore, the plot of $\log k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$ vs. pK_a of the conjugate acid of the leaving aryloxides exhibits an excellent linear correlation (Figure 5), indicating that the GS effect is not solely responsible for the α -effect observed in this study.

Accordingly, one can suggest that TS stabilization is also responsible for the α -effect in this study. One can suggest two plausible TS structures as illustrated by TS_{I} and TS_{II} . The former would increase the electrophilicity of the reaction center while the latter would enhance the nucleofugality of the leaving aryloxide. Since such cyclic TS structures are

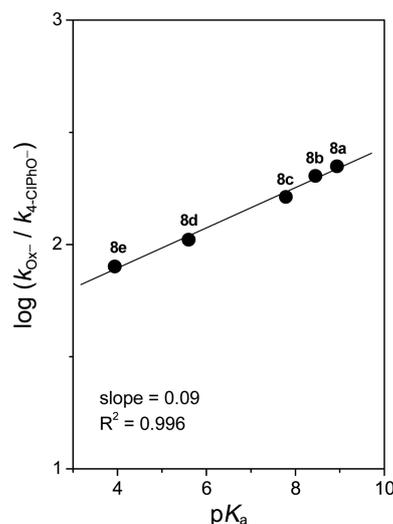
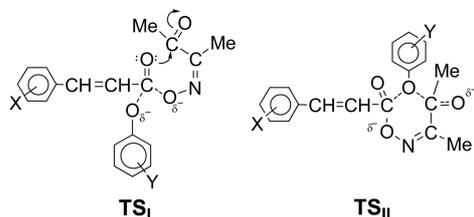


Figure 5. Plot showing dependence of the α -effect on the leaving-group basicity for the reactions of Y-substituted-phenyl cinnamates (**8a-8e**) with Ox^- and 4-ClPhO^- in 80 mol % $\text{H}_2\text{O}/20$ mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

not possible for the reactions with 4-ClPhO⁻, TS stabilization through an increase in the electrophilicity (*i.e.*, TS_I) or nucleofugality (*i.e.*, TS_{II}) is considered to be responsible for the α -effect shown by Ox⁻.



If the reactions with Ox⁻ proceed through TS_I, the magnitude of the α -effect would be similarly dependent on the electronic nature of the substituents X and Y. This is because the substituents X and Y are similarly away from the reaction center. The fact that the magnitude of the α -effect is independent of the substituent X but is dependent on the substituent Y indicates that the reactions do not proceed through TS_I. In contrast, if the reactions with Ox⁻ proceed through TS_{II}, the magnitude of α -effect would be more influenced by the substituent Y in the leaving group than by the substituent X in the cinnamoyl moiety. This is because the substituent Y is much closer (*e.g.*, proximal) to the C=O bond in the Ox⁻ nucleophile than the substituent X (*e.g.*, distal). The fact that the magnitude of the α -effect is linearly dependent on the substituent Y but is independent of the substituent X suggests that the reactions with Ox⁻ would proceed through TS_{II}.

Conclusions

The current study has allowed us to conclude the following: (1) The Hammett plot for the reactions of **7a-7e** with Ox⁻ consists of two intersecting straight lines, while the Yukawa-Tsuno plot is linear with $\rho_X = 0.85$ and $r = 0.58$. This indicates that the nonlinear Hammett plot is not due to a change in the RDS but is caused by GS stabilization of the substrates possessing an EDG in the cinnamoyl moiety. (2) The Brønsted-type plot for the reactions of Y-substituted-phenyl cinnamates (**8a-8d**) with Ox⁻ is linear with $\beta_{lg} = -0.64$, a typical β_{lg} value for reactions reported previously to proceed through a concerted mechanism. (3) The fact that σ_Y^- constants result in a much better Hammett correlation than σ_Y^0 constants supports also a concerted mechanism. (4) The difference in solvation energies between Ox⁻ and 4-ClPhO⁻ is not solely responsible for the σ -effect. (5) The enhanced nucleofugality through TS_{II} is considered to be responsible for the dependence of the σ -effect on the electronic nature of the substituent Y.

Experimental Section

Materials. Y-Substituted-phenyl X-substituted-cinnamates were prepared from the reactions of Y-substituted-phenol and X-substituted-cinnamoyl chloride in anhydrous ether in the presence of triethylamine as reported previously.²¹ The

crude product was purified by column chromatography (silica gel, methylene chloride/*n*-hexane 50/50). The purity was checked by the melting point and ¹H NMR spectrum. Butane-2,3-dione monoxime 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 % H₂O/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.*, $t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2} \leq 10$ s) equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of the leaving Y-substituted-phenoxide ion. All reactions were carried out under pseudo-first-order conditions in which the Ox⁻ concentration was at least 20 times greater than the substrate concentration. The Ox⁻ stock solution was prepared by dissolving 2 equiv. of butane-2,3-dione monoxime and 1 equiv. of standardized NaOH solution to make a self-buffered solution in a 25.0 mL volumetric flask.

Products Analysis. Y-Substituted-phenoxide ion was identified as one of the products in the reaction by comparison of the UV-vis spectra after completion of the reaction with the authentic sample under the same reaction conditions.

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