

Origin of the α -Effect in Nucleophilic Substitution Reactions of Y-Substituted Phenyl Benzoates with Butane-2,3-dione Monoximate and Z-Substituted Phenoxides: Ground-State Destabilization vs. Transition-State Stabilization

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Received September 22, 2009, Accepted October 23, 2009

Second-order rate constants (k_{Nu}) have been measured for nucleophilic substitution reactions of Y-substituted phenyl benzoates (**1a-i**) with butane-2,3-dione monoximate (Ox^- , an α -nucleophile) and Z-substituted phenoxides in 80 mol% $\text{H}_2\text{O}/20$ mol% DMSO at 25.0 ± 0.1 °C. Hammett plots correlated with σ^0 and σ^- constants for reactions of **1a-h** with Ox^- exhibit many scattered points. In contrast, the Yukawa-Tsuno plot results in a good linear correlation with $\rho_Y = 2.20$ and $r = 0.45$, indicating that expulsion of the leaving group occurs in the rate-determining step (RDS). A stepwise mechanism with expulsion of the leaving-group being the RDS has been excluded, since Y-substituted phenoxides are less basic and better nucleofuges than Ox^- . Thus, the reactions have been concluded to proceed through a concerted mechanism. Ox^- is over 10^2 times more reactive than its reference nucleophile, 4-chlorophenoxide (4-ClPhO⁻). One might suggest that stabilization of the transition-state (TS) through intramolecular general acid/base catalysis is responsible for the α -effect since such general acid/base catalysis is not possible for the corresponding reactions with 4-ClPhO⁻. However, destabilization of the ground-state (GS) of Ox^- has been concluded to be mainly responsible for the α -effect found in this study on the basis of the fact that the magnitude of the α -effect is independent of the nature of the substituent Y.

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

Introduction

Nucleophiles possessing one or more nonbonding electron pairs on the atom α to the nucleophilic site have often been reported to exhibit abnormally enhanced reactivity than would be expected from their basicity.¹⁻¹⁹ Thus, the enhanced reactivity shown by these nucleophiles was termed the α -effect.¹ Numerous studies have been performed to investigate the cause of the α -effect.²⁻¹⁹ Many theories have been advanced to explain the α -effect, e.g., destabilization of the ground state (GS) due to electronic repulsion between the nonbonding electron pairs, transition state (TS) stabilization including general acid/base catalysis, thermodynamic stability of products, solvent effects.²⁻¹⁹ However, none of these theories is conclusive. Particularly, solvent effect on the α -effect remains controversial.⁸⁻¹⁹

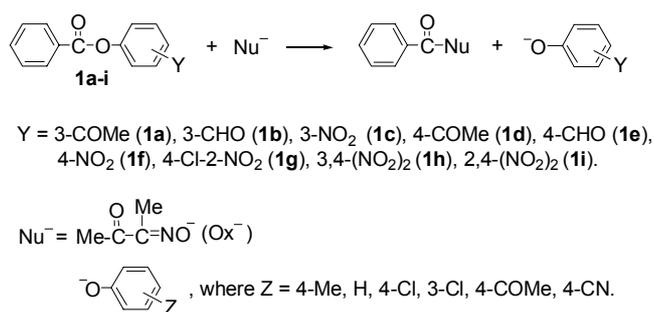
Solvent effect was suggested to be unimportant since the magnitude of the α -effects was found to be similar for reactions performed in H_2O and in organic solvents such as MeCN and toluene.⁸ Besides, it has been reported that α -nucleophiles are intrinsically more reactive than normal nucleophiles of similar basicity in gas-phase reactions.^{9,10} High-level theoretical calculations have also shown that α -nucleophiles (e.g., HOO^- , H_2NO^- , FO^- and ClO^-) exhibit lower activation energies than normal nucleophiles of similar basicity in gas-phase $\text{S}_{\text{N}}2$ reactions.¹¹ Accordingly, solvent effect on the α -effect has been concluded to be unimportant.⁸⁻¹¹ In contrast, DePuy *et al.* concluded that solvent effect is responsible for the α -effect shown by HOO^- in H_2O , since the α -nucleophile did not exhibit the α -effect in the gas-phase reaction with methyl formate.¹² Furthermore, from recent gas-phase ion-molecule studies, Bierbaum *et al.* have found that α -nucleophiles such as HOO^- , BrO^- and ClO^- do not exhibit enhanced reactivity in gas-phase reactions

with alkyl chlorides.¹³ Accordingly, they have concluded that the α -effect is due to solvent effect but not due to an intrinsic property.^{12,13}

We have initiated a systematic study to investigate the effect of solvent on the α -effect.¹⁴ Our study has shown that solvent effect on the α -effect is remarkable for nucleophilic substitution reactions of 4-nitrophenyl acetate (PNPA) with butane-2,3-dione monoximate (Ox^- , an α -nucleophile) and 4-chlorophenoxide (4-ClPhO⁻, a reference nucleophile) in DMSO- H_2O mixtures of varying compositions.¹⁴ It has been found that the α -effect (i.e., $k_{\text{Ox}^-} / k_{4\text{-ClPhO}^-}$) increases as the DMSO content in the medium increases up to ca. 50 mol% DMSO and then decreases thereafter, resulting in a bell-shaped α -effect profile.¹⁴ Similar bell-shaped α -effect profiles have been obtained for the corresponding reactions of aryl acetates, 4-nitrophenyl benzoate, thionobenzoate, benzenesulfonate, and diphenylphosphinate, although the magnitude of the α -effect is highly dependent on the nature of the electrophilic center.¹⁵⁻¹⁹

Our calorimetric study has revealed that Ox^- is ca. 4 kcal/mol less solvated than 4-ClPhO⁻ in H_2O .^{14b} Furthermore, it has been found that Ox^- becomes more destabilized than 4-ClPhO⁻ as the DMSO content in the medium increases up to ca. 50 mol% DMSO, and then the difference in their solvation energies remains nearly constant upon further addition of DMSO.^{14b} Dissection of the α -effect found in the reactions of PNPA into TS and GS contributions through combination of the kinetic data with calorimetric data has led us to conclude that destabilization of the α -nucleophile (i.e., Ox^-) is mainly responsible for the increasing α -effect up to 50 mol% DMSO (i.e., GS effect) while differential stabilization of TS contributes to the decreasing α -effect beyond 50 mol% DMSO.^{14b}

Our study has been extended to reactions of Y-substituted



Scheme 1

phenyl benzoates (**1a-i**) with Ox⁻ and Z-substituted phenoxides (Scheme 1) to investigate the origin of the α -effect. Comparison of the results obtained in the current study with those reported previously for the corresponding reactions with hydrazine and glycylglycine has shown that destabilization of Ox⁻ is more important than stabilization of TS for the α -effect in the current system.

Results and Discussion

Reactions were performed under pseudo-first-order conditions with the concentration of nucleophile in excess over the substrate concentration. All reactions obeyed first-order kinetics with quantitative liberation of Y-substituted phenoxide ion. 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. nucleophile concentration were linear with positive intercepts. Thus, the rate law is given as eq (1), in which k_0 represents the contribution of H₂O and/or OH⁻ from hydrolysis of the anionic nucleophiles to the k_{obsd} values. Accordingly, second-order rate constants (k_{Nu^-}) were determined from the slope of the linear plots and summarized in Tables 1 and 2. It is estimated from replicate runs that the uncertainty in the rate constants is less than $\pm 3\%$.

$$\text{Rate} = k_{\text{obsd}} [\text{substrate}], \text{ where } k_{\text{obsd}} = k_{\text{Nu}^-} [\text{nucleophile}] + k_0 \quad (1)$$

Reaction Mechanism. As shown in Table 1, second-order rate constant for reactions with Ox⁻, an α -nucleophile, increases as

the leaving-group basicity decreases, e.g., k_{Ox^-} increases from 0.703 M⁻¹s⁻¹ to 34.2 and 961 M⁻¹s⁻¹ as the pK_a of the conjugate acid of the leaving group decreases from 10.4 to 7.79 and 5.60, in turn. A similar result is shown for the corresponding reactions with 4-ClPhO⁻ (a reference nucleophile), although it is much less reactive than Ox⁻. The α -effect shown by Ox⁻ will be discussed in the following section.

One might expect that a partial negative charge develops on the oxygen atom of the leaving aryloxy when expulsion of the leaving group occurs either in a concerted or stepwise mechanism. Such negative charge can be delocalized on the substituent Y through resonance interactions. Thus, σ^- constants would exhibit a good Hammett correlation if expulsion of the leaving group occurs at rate-determining step (RDS). In contrast, σ^0 constants would result in a better Hammett correlation than σ^- constants if expulsion of the leaving group occurs after RDS. Thus, Hammett plots have been constructed for reactions of Y-substituted phenyl benzoates (**1a-h**) with Ox⁻ using σ^- and σ^0 constants to deduce the reaction mechanism. As shown in Figure 1, the Hammett plot correlated with σ^- constants exhibits a slightly better correlation coefficient than that correlated with σ^0 constants (inset). However, both Hammett plots show many scattered points. Accordingly, one cannot get any conclusive information from these plots.

Yukawa-Tsuno plots have been reported to be highly informative to clarify ambiguities in reaction mechanism for nucleophilic substitution reactions of various esters (e.g., aryl benzoates, thionobenzoates, and diphenylphosphinates).²¹⁻²³ Thus, a Yukawa-Tsuno plot has been constructed for reactions of **1a-h** with Ox⁻ in Figure 2. One can see that the Yukawa-Tsuno plots exhibit a good linear correlation with $\rho_Y = 2.20$ and $r = 0.45$. The r value in the Yukawa-Tsuno equation (eq 2) represents the extent of resonance contribution between the reaction site and substituent Y.^{24,25} Thus, the r value of 0.45 indicates that a negative charge develops partially on the oxygen atom of the leaving aryloxy. Thus, one might suggest two different mechanisms to account for the result, i.e., a concerted mechanism and a stepwise pathway in which departure of the leaving group occurs in the RDS. However, one can exclude the latter mechanism since the leaving Y-substituted phenoxides are less basic and better nucleofuges than the incoming Ox⁻. Accordingly, one can conclude that the current reactions proceed through a concerted mechanism.

Table 1. Summary of Second-order Rate Constants for Reactions of Y-Substituted Phenyl Benzoates (**1a-i**) with Butane-2,3-dione Monoximate (Ox⁻) and 4-Chlorophenoxide (4-ClPhO⁻) in 80 mol% H₂O / 20 mol% DMSO at 25.0 \pm 0.1 $^{\circ}$ C.^a

	Y	pK _a ^{Y-PhOH}	$k_{\text{Ox}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{4\text{-ClPhO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{Ox}^-}/k_{4\text{-ClPhO}^-}$
1a	3-COMe	10.4	0.703	3.45×10^{-3}	204
1b	3-CHO	10.1	1.22	6.10×10^{-3}	200
1c	3-NO ₂	9.32	9.78	4.16×10^{-2}	235
1d	4-COMe	8.94	4.01	2.36×10^{-2}	170
1e	4-CHO	8.45	8.39	5.52×10^{-2}	152
1f	4-NO ₂	7.79	34.2	1.85×10^{-1}	185
1g	4-Cl-2-NO ₂	6.92	47.1	2.15×10^{-1}	219
1h	3,4-(NO ₂) ₂	5.60	961	7.19	134
1i	2,4-(NO ₂) ₂	4.11	-	6.50	-

^aThe pK_a values in 20 mol% DMSO and kinetic data for reactions with 4-ClPhO⁻ were taken from ref. 20.

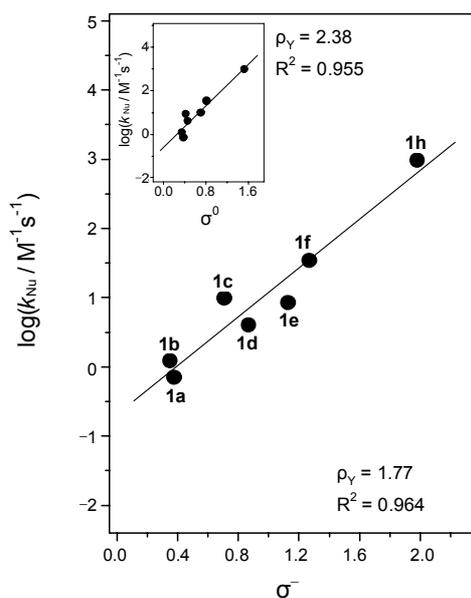


Figure 1. Hammett plots correlated with σ^- and σ^0 (inset) for reactions of Y-substituted phenyl benzoates (**1a-h**) with Ox^- in 80 mol% H_2O / 20 mol% DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

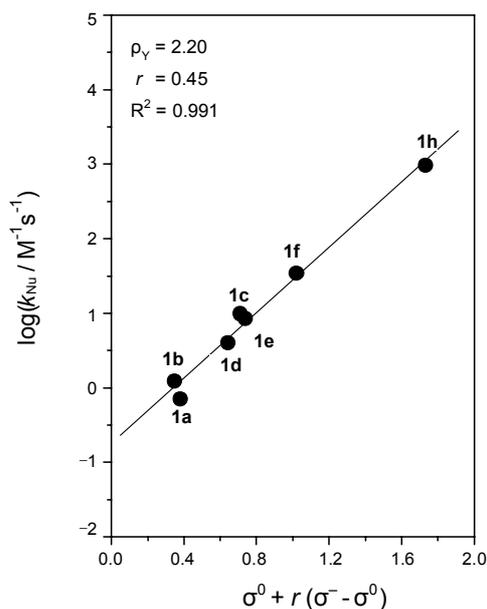


Figure 2. Yukawa-Tsuno plots for reactions of Y-substituted phenyl benzoates (**1a-h**) with Ox^- in 80 mol% H_2O / 20 mol% DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

$$\log k^Y/k^H = \rho_Y (\sigma^0 + r(\sigma^- - \sigma^0)) \quad (2)$$

Origin of the α -Effect: GS Destabilization vs. TS Stabilization. As mentioned in the preceding section, Ox^- is over 10^2 times more reactive than its reference nucleophile, 4-CIPhO $^-$, although the basicity of the two nucleophiles is known to be similar (e.g., the $\text{p}K_a$ values of the conjugate acids of Ox^- and 4-CIPhO $^-$ in 20 mol% DMSO were reported to be 10.68 and 10.58, respectively).¹⁶ Interestingly, Table 1 shows that the mag-

Table 2. Summary of Second-order Rate Constants ($k_{Z-\text{PhO}^-}$) for Reactions of Y-Substituted Phenyl Benzoates (Y = 4-NO $_2$, **1f**; Y = 4-Cl-2-NO $_2$, **1g**; Y = 3,4-(NO $_2$) $_2$, **1h**; Y = 2,4-(NO $_2$) $_2$, **1i**) with Z-Substituted Phenoxides in 80 mol% H_2O / 20 mol% DMSO at 25.0 ± 0.1 °C.^a

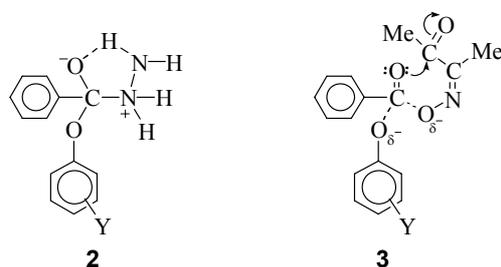
Entry	Z	$\text{p}K_a^{\text{Z-PhOH}}$	$10^2 k_{Z-\text{PhO}^-} / \text{M}^{-1}\text{s}^{-1}$			
			1f	1g	1h	1i
1	4-Me	11.7	92.5	84.1	2080	2170
2	H	11.3	45.2	35.5	1580	1160
3	4-Cl	10.5	18.5	21.5	719	650
4	3-Cl	10.2	9.03	11.2	424	397
5	4-COMe	8.94	0.888	0.945	36.0	36.8
6	4-CN	8.60	0.510	0.656	18.6	29.4

^aThe $\text{p}K_a$ values in 20 mol% DMSO and kinetic data for the reactions of 4-nitrophenyl benzoate (**1f**) were taken from ref. 20.

nitude of the α -effect is independent of the electronic nature of the substituent Y in the leaving group. This is in contrast to our previous report that the α -effect increases linearly with increasing the basicity of the leaving group for reactions of Y-substituted phenyl benzoates with hydrazine (an α -nucleophile) and glycylglycine (a reference nucleophile).²⁶

Stabilization of transition state (TS) through intramolecular H-bonding as modeled by **2** has been suggested to be responsible for the substituent dependent α -effect for the reactions with hydrazine, since such 5-membered H-bonding interaction is not possible for the corresponding reactions with glycylglycine.²⁶ One might draw a similar conclusion that TS stabilization is responsible for the α -effect shown by Ox^- in the current study. This is because TS stabilization through intramolecular general acid/base catalysis as modeled by **3** is possible for the reactions with Ox^- , while such general acid/base catalysis is impossible for the reactions with 4-CIPhO $^-$.

If TS stabilization through **3** is responsible for the enhanced reactivity shown by Ox^- , the α -effect should be dependent on the nature of the substituent Y in the leaving group as reported previously for the reactions with hydrazine and glycylglycine.²⁶



However, in fact, the magnitude of the α -effect is independent of the substituent Y (see Table 1), indicating that TS stabilization through general acid/base catalysis is not responsible for the α -effect found in this study.

Ox^- has been reported to be 5.7 kcal/mol less solvated than 4-CIPhO $^-$ in 20 mol% DMSO,^{14b} which is the reaction medium in this study. Since Ox^- and 4-CIPhO $^-$ have been employed as a pair of nucleophiles throughout the reactions of **1a-i**, the difference in the GS solvation energy of the two nucleophiles remains constant at 5.7 kcal/mol. Accordingly, if the difference

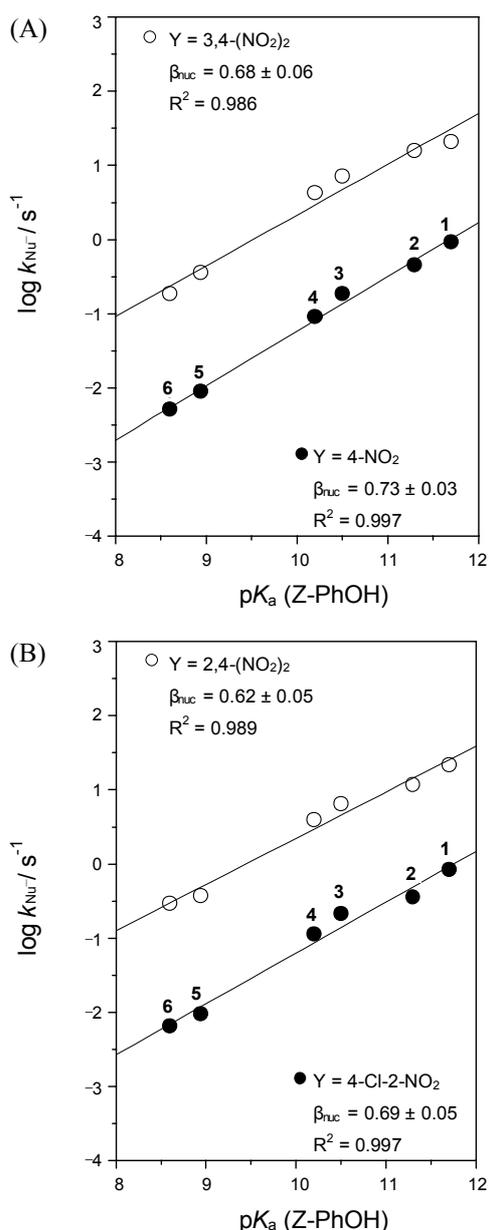


Figure 3. Brønsted-type plots for reactions of Y-substituted phenyl benzoates with Z-substituted phenoxies in 80 mol% H₂O / 20 mol% DMSO at 25.0 ± 0.1 °C. **A:** Y = 4-NO₂ (**1f**) and 3,4-(NO₂)₂ (**1h**); **B:** Y = 4-Cl-2-NO₂ (**1g**) and 2,4-(NO₂)₂ (**1i**). The identity of points is given in Table 2.

in the GS solvation energies of the two nucleophiles is mainly responsible for the α -effect, one can expect that the magnitude of the α -effect remains nearly constant upon changing the substituent Y in the leaving group. In fact, the α -effect is independent of the nature of Y. Thus, one can suggest that the α -effect found in this study is mainly due to destabilization of Ox⁻ in the GS.

To examine the above idea, second-order rate constants ($k_{\text{Z-PhO}^-}$) have been measured for reactions of 4 different Y-substituted phenyl benzoates with 6 different Z-substituted phenoxides (Z-PhO⁻). The $k_{\text{Z-PhO}^-}$ values are summarized in Table 2 and illustrated graphically in Figures 3A and 3B. Table 2 shows that $k_{\text{Z-PhO}^-}$ decreases as the basicity of Z-PhO⁻ decreases in all

cases. It is also noted that the $k_{\text{Z-PhO}^-}$ values for the reactions of **1i** are not always larger than those for the corresponding reactions of **1h**, although 2,4-dinitrophenoxide in **1i** is less basic than 3,4-dinitrophenoxide in **1h**. Similarly, **1g** is not always more reactive than **1f**, although the former possesses a much less basic leaving group (i.e., 4-chloro-2-nitrophenoxide) than the latter does (i.e., 4-nitrophenoxide). One might suggest that steric hindrance caused by the substituent on the 2-position of **1i** and **1g** is responsible for the unusual reactivity order.²⁷

The effect of basicity of Z-PhO⁻ on reactivity is illustrated in Figures 3A and 3B. The Brønsted-type plots are linear with β_{nuc} values varying from 0.73 to 0.69, 0.68 and 0.62 as the substituent Y changes from 4-NO₂ to 4-Cl-2-NO₂, 3,4-(NO₂)₂, and 2,4-(NO₂)₂ in turn, which is in accordance to reactivity-selectivity principle.²⁸

It is well known that the magnitude of the α -effect increases with increasing β_{nuc} values when TS stabilization is responsible for the α -effect.^{2,5-8} The β_{nuc} values determined in this study exhibit a linear correlation with the basicity of the leaving Y-substituted phenoxides (Figure not shown). Thus, one might expect that the α -effect increases with increasing the leaving-group basicity, if TS stabilization (through general acid/base catalysis as modeled by **3**) contributes to the current α -effect. However, in fact, the α -effect is independent of the leaving-group basicity, indicating that stabilization of TS is not responsible for the α -effect. This is consistent with the preceding argument that the α -effect found in current study is mainly due to GS destabilization.

Conclusions

The current study has allowed us to conclude the following: (1) The Yukawa-Tsuno plot for the reactions of Y-substituted phenyl benzoates (**1a-h**) with Ox⁻ exhibits good linearity with $\rho_Y = 2.20$ and $r = 0.45$, indicating that expulsion of the leaving group occurs in RDS. (2) A concerted mechanism or a stepwise pathway, in which expulsion of the leaving-group occurs in RDS, can account for the results. However, the latter mechanism has been excluded since Y-substituted phenoxides are less basic and better nucleofuges than the incoming Ox⁻ ion. (3) Ox⁻ is over 10² times more reactive than 4-ClPhO⁻ toward **1a-h** (i.e., the α -effect). (4) TS stabilization through intramolecular general acid/base catalysis has been ruled out as the origin of the α -effect found in the current reactions, since the magnitude of the α -effect is independent of the nature of substituent Y and of β_{nuc} values. (5) Since Ox⁻ has been reported to be 5.7 kcal/mol less solvated than 4-ClPhO⁻ in 20 mol% DMSO, GS destabilization of Ox⁻ has been concluded to be mainly responsible for the α -effect found in this study.

Experimental Section

Materials. Y-Substituted phenyl benzoates were readily prepared from reactions of benzoyl chloride with Y-substituted phenol in anhydrous ether under the presence of triethylamine. The crude products were purified through column chromatography. Other chemicals including butane-2,3-dione monoxime

and phenols were of the highest quality available. Doubly glass-distilled water was further boiled and cooled under nitrogen just before use to exclude dissolved CO₂. Since solubility of the substrates is low in pure water, 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 ($t_{1/2} > 10$ s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \leq 10$ s) equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of Y-substituted phenoxide at a fixed wavelength corresponding the maximum absorption.

Typically, the reaction was initiated by adding 5 μ L of a 0.02 M substrate stock solution in MeCN by a 10 μ L syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and nucleophile. The nucleophile stock solution of ca. 0.2 M for the reactions was prepared in 25.0 mL volumetric flask under nitrogen by adding 2 equiv. of butan-2,3-dione monoxime (or Z-substituted phenol) to 1 equiv. of standardized NaOH solution to obtain a self-buffered solution. Transfers of solutions were carried out by means of gas-tight syringes. All reactions were carried out under pseudo-first-order conditions in which nucleophile concentrations were at least 20 times greater than the substrate concentration.

Product Analysis. Y-substituted phenoxide (and/or its conjugate acid) was identified as one of the products by comparison of the UV-Vis spectra at the end of reactions with the authentic sample.

Acknowledgments. The authors are grateful for the financial support from the Korea Research Foundation (KRF-2008-313-C00500) and BK 21 Scholarship.

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