JOC *Article*

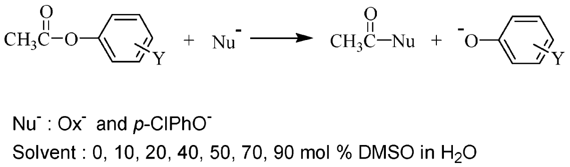
Solvent Effect on the α-Effect: Ground-State versus Transition-State Effects; a Combined Calorimetric and Kinetic Investigation

Ik-Hwan Um,*,[†] So-Jeong Hwang,[†] and Erwin Buncel*,[‡]

Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea, and
Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

ihum@mm.ewha.ac.kr; buncele@chem.queensu.ca

Received August 30, 2005



In a study of the solvent effect on the α-effect, second-order rate constants (k_{Nu^-}) have been determined spectrophotometrically for reactions of a series of substituted phenyl acetates with butan-2,3-dione monoximate (Ox^-, α-nucleophile) and *p*-chlorophenoxide (*p*-ClPhO^-, reference nucleophile) in DMSO−H_2O (DMSO = dimethyl sulfoxide) mixtures of varying compositions at 25.0 ± 0.1 °C. The magnitude of the α-effect, $k_{\mathrm{Ox}^-}/k_{p\text{−}\mathrm{ClPhO}^-}$, increases as the DMSO content in the medium increases up to 40−50 mol %, reaching 500, one of the largest α-effect values, and then decreases on further addition of DMSO, resulting in a bell-shaped α-effect profile regardless of the nature of the substrates. The magnitude of the α-effect is found to be significantly dependent on the substrates (or, more quantitatively, on β_{nuc}). Thus, β_{nuc} is an important predictor of the magnitude of the α-effect. The bell-shaped α-effect profile found in the present system is attributed to the differential change in the sensitivity of the medium effect on the Ox^- and *p*-ClPhO^- systems but not due to a change in the reaction mechanism or to a drastic change in the basicity of the two nucleophiles on addition of DMSO to the medium. Through application of calorimetric measurements of ground-state solvation combined with the diagnostic β_{nuc} values, it is shown that the transition-state effect is more dominant than the ground-state effect as the origin of the α-effect in the present system.

Introduction

Nucleophiles which bear one or more nonbonding electron pairs at the position α to the nucleophilic center have been termed α-nucleophiles and exhibit enhanced reactivity compared with normal nucleophiles of similar basicity (the α-effect).[1,2] Current interest in studying the reaction of α-nucleophiles has received major new impetus from the importance of the many applications of these highly reactive species.[3−7] For example, in the development of protocols for environmental decontamination of sites polluted with organophosphorus insecticides, α-nucleophiles such as oximates have been demonstrated to be highly effective.[4] The needs to develop efficient means to destroy stockpiles of organophophorus nerve agents have led a number of groups to investigate different approaches toward enhancing decomposition of these agents; α-nucleophiles can

---

* To whom correspondence should be addressed. Tel.: 82-2-3277-2349 (I.-H.U.); 1-613-533-2653 (E.B.). Fax: 82-2-3277-2844 (I.-H.U.); 1-613-533-6669 (E.B.).

[†] Ewha Womans University.

[‡] Queen's University.

(1) *Pure Appl. Chem.* **1979**, *51*, 1731.

(2) Reviews: (a) Buncel, E.; Um, I. H. *Tetrahedron* **2004**, *60*, 7801−7825. (b) Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313−319. (c) Curci, R.; Di Furia, F. *Int. J. Chem. Kinet.* **1975**, *7*, 341−349. (d) Grekov, A. P.; Veselov, V. Ya. *Russ. Chem. Rev.* **1978**, *47*, 631−648.

(3) (a) Balakrishnan, V. K.; Han, X.; VanLoon, G. W.; Dust, J. M.; Toullec, J.; Buncel, E. *Langmuir* **2004**, *20*, 6586−6593. (b) Couderc, S.; Toullec, J. *Langmuir* **2001**, *17*, 3819−3828. (c) Toullec, J.; Moukawin, M. *Chem. Commun.* **1996**, 221−222.

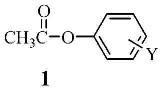
(4) (a) Terrier, F.; Degorre, F.; Kiffer, D.; Laloi, M. *Bull. Soc. Chim. Fr.* **1988**, *31*, 415−419. (b) Terrier, F.; Le Gue'vel, E.; Chatrousse, A. P.; Moutiers, G.; Buncel, E. *Chem. Commun. (Cambridge)* **2003**, 600−601. (c) Ashani, Y.; Cohen, S. *J. Med. Chem.* **1971**, *14*, 621−626.

(5) (a) Domingos, J. B.; Longhinotti, E.; Brandao, T. A. S.; Santos, L. S.; Eberlin, M. N.; Bunton, C. A.; Nome, F. *J. Org. Chem.* **2004**, *69*, 7898−7905. (b) Moss, R. A.; Kanamathareddy, S.; Vijayaraghavan, S. *Langmuir* **2001**, *17*, 6108−6112.

10.1021/jo051823f CCC: $33.50

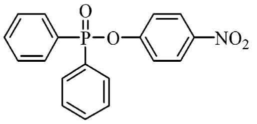
accelerate these decompositions.[5,6] In cases of poisoning by organophosphorus toxicants, standard medical procedure includes injection of oximate nucleophiles into the poisoned person.[7] No doubt the high reactivity of α-nucleophiles will also find uses in synthetic organic chemistry. In this regard, mildly basic α-nucleophiles could be used in deprotection steps in synthetic sequences, e.g., deprotection of alcohols by removing the protecting group.

Investigations of solvent effects, through enthalpies of solution and structural modification, have all formed part of an ongoing program of research into the reactivity of these versatile α-nucleophiles.[8−12] In 1986, we showed that there is a significant medium effect on the α-effect for the reactions of *p*-nitrophenyl acetate (**1a**) with butan-2,3-dione monoximate (Ox^-, $\mathrm{p}K_a^{\mathrm{OxH}} = 9.44$ in H_2O) as an α-nucleophile and *p*-chlorophenoxide ($p\text{-ClPhO}^-$, $\mathrm{p}K_a^{p\text{-ClPhOH}} = 9.38$ in H_2O) as reference nucleophile in DMSO−H_2O (DMSO = dimethyl sulfoxide) mixtures of varying compositions. The α-effect, $k_{\mathrm{Ox}^-}/k_{p\text{-ClPhO}^-}$, was found to increase with increasing DMSO content in the medium up to 50 mol % DMSO and then to decrease on further addition of DMSO, resulting in a bell-shaped α-effect profile.[8] The medium effect on the α-effect has recently been dissected into ground-state and transition-state effects from combination of the calorimetrically measured enthalpies of solution (ΔH_s) and the kinetically determined activation parameters ($\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$).[9] The effect of medium on the α-effect has also been studied by changing the medium from DMSO−H_2O to MeCN−H_2O mixtures,[10] the electrophilic center from C=O (**1a**) to P=O (**2**) and SO_2 (**3**),[11] and the leaving group from *p*-nitrophenoxide in **1a** to *p*-nitrothiophenoxide.[12] In all cases, the effect of medium on the α-effect has been found to be significant.

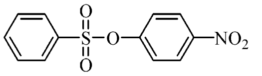


1

Y = 4-NO_2 (**1a**), 3-NO_2 (**1b**), 4-CHO (**1c**)
4-CH_3CO (**1d**), 3-CHO (**1e**)



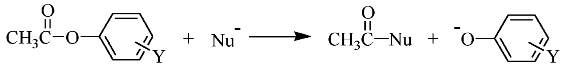
2



3

In the present study we have extended our investigation to the nucleophilic substitution reactions of **1b**−**e** with Ox^- and $p\text{-ClPhO}^-$ in DMSO−H_2O mixtures of varying compositions (Scheme 1). Our systematic investigation provides important clues rationalizing the bell-shaped α-effect profile and of the factors determining the magnitude of the α-effect and supports our analysis of ground-state and transition-state contributions to the α-effect.

SCHEME 1



Nu^- : Ox^- and $p\text{-ClPhO}^-$
Solvent : 0, 10, 20, 40, 50, 70, 90 mol % DMSO in H_2O

Results

All the reactions in this study obeyed pseudo-first-order kinetics in the presence of a large excess of nucleophile. Pseudo-first-order rate constants (k_{obsd}) were obtained from the plots of $\ln(A_\infty - A_t)$ vs t, which were linear over 90% of the reaction. Second-order rate constants (k_{Nu^-}) were determined from the slopes of the linear plots of k_{obsd} vs the nucleophile concentration. These plots had only small intercept values, indicating that the contribution of hydroxide and/or water to k_{obsd} was negligible (see Supporting Information). The k_{Nu^-} values determined are summarized in Table 1 and illustrated graphically in Figure 1 for the reactions of **1a**−**e** with Ox^- and $p\text{-ClPhO}^-$ in DMSO−H_2O mixtures of varying compositions.

Discussion

Medium Effect on Rate. In this section, the effect of added DMSO on the reaction rate will be analyzed in terms of H-bonding and polarizability interactions. The results given in Table 1 and illustrated in Figure 1A show clearly a significant increase in the second-order rate constant for the reaction of **1a**−**e** with Ox^- as the DMSO content in the medium increases. The rate enhancement is more significant in the DMSO-rich region; the second-order rate constant increases from 65.8 $M^{-1}\,s^{-1}$ to 1680 and 40500 $M^{-1}\,s^{-1}$ as the medium changes from pure water to 50 and 90 mol % DMSO, respectively for the reaction of **1a** with Ox^-. The least reactive substrate (**1e)** exhibits a small rate decrease as the medium changes from pure water to 10 mol % DMSO.

An initial decrease in rate upon addition of DMSO has also been observed for the corresponding reactions with $p\text{-ClPhO}^-$, as shown in Table 1 and Figure 1B. This decrease in rate constants persists into higher DMSO contents for the less reactive substrates. For example, the second-order rate constant for the reaction of **1a** with $p\text{-ClPhO}^-$ decreases from 0.685 $M^{-1}\,s^{-1}$ in H_2O to 0.653 $M^{-1}\,s^{-1}$ in 10 mol % DMSO, and the rate constants above 20 mol % DMSO exceed the value in H_2O. On the other hand, the second-order rate constant for the least reactive **1e** decreases from 0.091 $M^{-1}\,s^{-1}$ in H_2O to 0.038 $M^{-1}\,s^{-1}$ in 20 mol % DMSO, and the rate constant in 50 mol % DMSO (0.085 $M^{-1}\,s^{-1}$) is still smaller than that in H_2O.

Significant rate enhancements have often been observed for reactions with anionic nucleophiles on addition of DMSO to the reaction medium since anionic nucleophiles become desolvated in the aprotic solvent.[13] In fact, we have recently reported that $p\text{-ClPhO}^-$ and Ox^- become desolvated to the extent of 10.2 and 13.2 kcal/mol as the medium changes from pure water to 90 mol % DMSO.[9] The decrease in the rate

---

(6) (a) Um, I. H.; Jeon, S. E.; Baek, M. H.; Park, H. R. *Chem. Commun. (Cambridge)* **2003**, 3016−3017. (b) Nagelkerke, R.; Thatcher, G. R. J.; Buncel, E. *Org. Biomol. Chem.* **2003**, *1*, 163−167. (c) Buncel, E.; Nagelkerke, R.; Thatcher, G. R. J. *Can. J. Chem.* **2003**, *81*, 53−63. (d) Tsang, J. S. W.; Neverov, A. A.; Brown, R. S. *J. Am. Chem. Soc.* **2003**, *125*, 1559−1566.

(7) Wilson, I. B.; Ginsburg, S. *Arch. Biochem. Biophys.* **1995**, *54*, 569.

(8) Buncel, E.; Um, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 595.

(9) Um, I. H.; Buncel, E. *J. Org. Chem.* **2000**, *65*, 577−582.

(10) (a) Um, I. H.; Park, Y. M.; Buncel, E. *Chem. Commun. (Cambridge)* **2000**, *19*, 1917−1918. (b) Um, I. H.; Lee, E. J.; Buncel, E. *J. Org. Chem.* **2001**, *66*, 4859−4864.

(11) Um, I. H.; Hong, J. Y.; Buncel, E. *Chem. Commun. (Cambridge)* **2001**, 27−28.

(12) Um, I. H.; Buncel, E. *J. Am. Chem. Soc.* **2001**, *123*, 11111−11112.

(13) (a) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1−32. (b) Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133−202. (c) Buncel, E.; Wilson, H. *Acc. Chem. Res.* **1979**, *12*, 42−48.

TABLE 1. Summary of the Second-Order Rate Constants (k_{Nu^-}) for the Reaction of 1a−e with Ox$^-$ (and *p*-ClPhO$^-$ in Parentheses) in Various DMSO−H$_2$O Mixtures at 25.0 °C

	k_{Nu^-}/(M^{-1} s^{-1})				
mol % DMSO	**1a**[a]	**1b**	**1c**	**1d**	**1e**
0	65.8 (0.685)[b]	41.5 (0.320)	31.6 (0.302)	21.7 (0.171)	15.4 (0.0910)
10	77.8 (0.653)	47.3 (0.230)	34.2 (0.224)	23.6 (0.127)	13.9 (0.0500)
20	131 (0.76)	72.0 (0.241)	56.9 (0.232)	29.6 (0.117)	14.0 (0.0380)
40	746 (2.80)	275 (0.562)	208 (0.465)	89.0 (0.191)	26.2 (0.0520)
50	1680 (5.90)	499 (1.09)	399 (0.922)	160 (0.353)	37.5 (0.0850)
70	8200 (34.7)	1920 (4.88)	1530 (4.72)	541 (1.47)	104 (0.312)
90	40500 (335)	6460 (38.8)	5920 (36.4)	1620 (10.3)	330 (1.97)

[a] Data for the reactions of **1a** taken from ref 8. [b] The data in the parentheses are the second-order rate constants for the corresponding reactions with *p*-ClPhO$^-$. Data taken from ref 22.

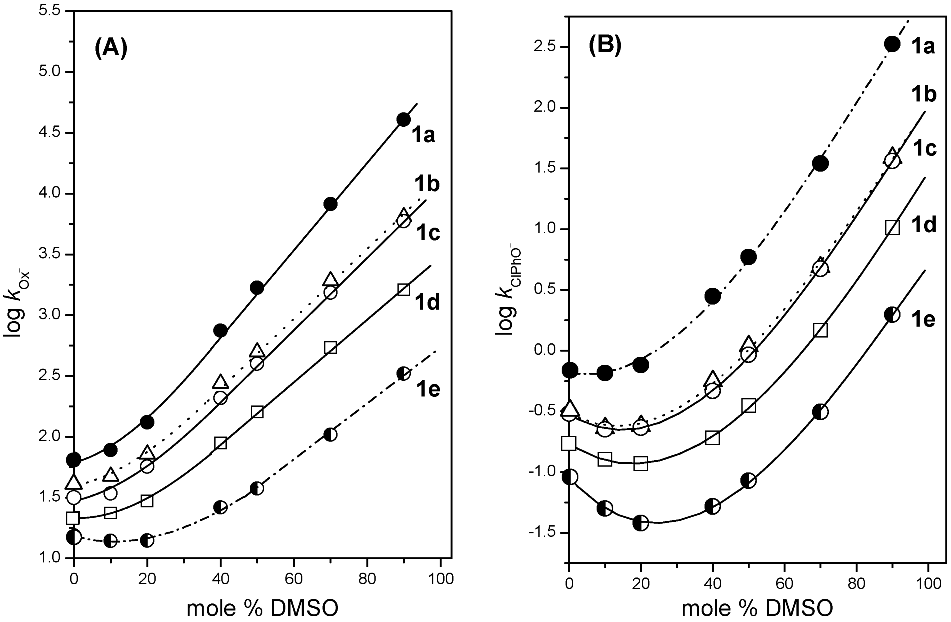


FIGURE 1. Plots of the logarithmic second-order rate constants vs mole percent DMSO for the reactions of **1a−e** with Ox$^-$ (A) and *p*-ClPhO$^-$ (B) at 25.0 ± 0.1 °C.

constant in the water-rich region found in the present system is hence unexpected.

Various changes are attendant upon addition of anionic solutes to a bulk solvent, whether pure water or DMSO−H$_2$O mixtures.[9,13] H-bonding is an important interaction between solvent molecules and anionic solutes in the H$_2$O-rich region. Thus, addition of DMSO to the reaction medium would destabilize anionic solutes (both anionic nucleophiles and anionic transition states) due to decreased H-bonding interaction. The fact that Ox$^-$ exhibits decreased reactivity toward the least reactive **1e** in 10 mol % DMSO suggests that the transition state becomes more desolvated than the ground state. On the contrary, in the DMSO-rich region, free H$_2$O molecules for H-bonding become limited;[9,13] accordingly, H-bonding is diminished in importance. Instead, polarizability interaction becomes dominant in the DMSO-rich region.[9,13] Since DMSO is highly polarizable, it can stabilize a polarizable transition state through the polarizability interaction. This argument is consistent with the large rate enhancement observed in the DMSO-rich region. It follows from the evidence presented here that decreased H-bonding and enhanced polarizability interactions are responsible for the initial rate retardation in the H$_2$O-rich region and the major rate enhancement in the DMSO-rich region, respectively.

Medium Effect on the α-Effect. Factors influencing the magnitude of the α-effect will be discussed here. As illustrated in Figure 2, the α-effect ($k_{Ox^-}/k_{p-ClPhO^-}$) increases as the solvent is changed up to ca. 40−50 mol % DMSO, in which the maximum α-effect is observed, and then it decreases upon further additions of DMSO, resulting in a bell-shaped α-effect profile. It is noted that the magnitude of the α-effect in pure water is similar to that in pure DMSO in all cases. Thus, if the reaction were performed solely in the two pure solvents, one would not have found the medium-dependent α-effect profile. Clearly, the present result shows that the effect of medium on the α-effect is significant and supports the argument that a two-point analysis of the α-effect could be misleading.[14]

It is shown in Figure 2 that the reactions of **1a−e** and **2** with Ox$^-$ and *p*-ClPhO$^-$ exhibit a maximum α-effect at 40 or 50 mol % DMSO in all cases. However, the magnitude of the α-effect is dependent on the substrate; in the phenyl acetate series the maximum α-effect found at 40 mol % DMSO is ca. 500 for the reaction of **1e**, but only ca. 40 for the diphenylphosphinate **2**, i.e., over 1 order of magnitude smaller.

Many factors have been suggested to influence the magnitude of the α-effect: the basicity of α-nucleophiles, the type of hybridization of the electrophilic centers, and the magnitude of β_{nuc}, among them.[4,15−19] Aubort and Hudson have reported that highly basic α-nucleophiles (e.g., acetone oximate anion) do

---

(14) Hoz, S.; Buncel, E. *Tetrahedron Lett.* **1984**, *25*, 3411−3414.

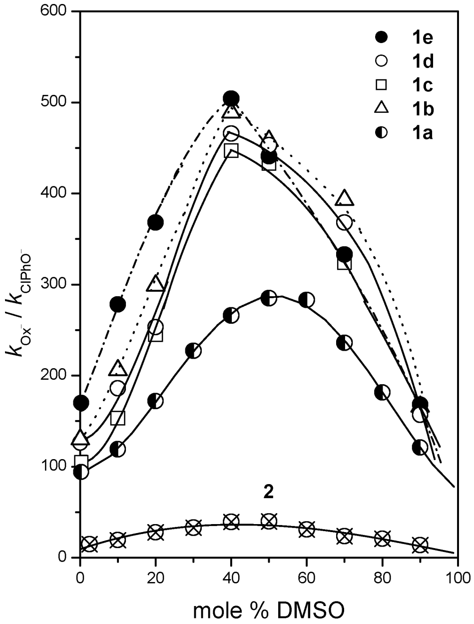


FIGURE 2. Plots showing solvent effect on the α-effect for the reactions of **1a**−**e** and **2** with Ox^- and *p*-$ClPhO^-$ in DMSO−H_2O mixtures of varying compositions at 25.0 °C.

not exhibit the α-effect in the reaction with **1a**.[15] A similar result has recently been reported for the reaction of **1a** with a series of substituted oximate anions.[4,16] Terrier et al. observed that the Brønsted-type plot is linear for low basic oximates ($pK_a < 8$) but levels off for the more basic oximates ($pK_a \geq 8$).[4,16] The hybridization type of the electrophilic center was proposed to be an important factor in determining the magnitude of the α-effect, based on the observation of a large rate constant ratio (k_{HOO^-}/k_{HO^-}).[17] For example, Wiberg reported that HOO^- is 22 000 to 66 000 times more reactive than HO^- toward the sp-hybridized carbon of benzonitriles in 50% aqueous acetone.[17a] However, we have recently found an α-effect ($k_{NH_2NH_2}/k_{glycylglycine}$) of only 7−10 with $\beta_{nuc} = 0.32$ for the reactions at the sp-hybridized carbon atom of 3-butyn-2-one with primary amines including hydrazine and methoxylamine. This result suggests that the α-effect is not necessarily large for the reactions at an sp-hybridized carbon when β_{nuc} is small,[18] indicating that the magnitude of β_{nuc} is a more important predictor of the magnitude of the α-effect. This is consistent with the finding by Bruice and Dixon that the magnitude of the α-effect increases with increasing β_{nuc} value for the reactions of 17 substrates with hydrazine as α-nucleophile and glycylglycine or glycinamide as the corresponding reference nucleophile.[19]

While the reactions of **2** with aryloxides proceed with $\beta_{nuc} = 0.21$,[11] much larger β_{nuc} values have been reported for the reactions of the aryl acetates with aryloxides, being 0.78 for **1a** and 0.90 ± 0.03 for **1b**−**e**.[20] The correlation between the magnitude of the β_{nuc} values and the magnitude of the α-effect can be also found in the present system. As shown in Figure 2, the magnitude of the α-effect is very small for the reaction of **2**, while that for **1b**−**e** is much larger. Now, the β_{nuc} value of 0.90 ± 0.03 is close to unity; hence, the α-effect of ca. 500 found for **1e** represents the maximum α-effect found so far for the reaction of an sp^2 carbon. It follows from the evidence presented here that β_{nuc} is an important predictor to determine the magnitude of the α-effect.

TABLE 2. Hammett ρ Values and Correlation Coefficients (R^2) with Various σ Constants for the Reactions of 1a−e with Ox^- in DMSO−H_2O Mixtures at 25.0 °C

	ρ		
mol % DMSO	σ	σ°	σ^-
0	1.26 (0.909)[a]	1.26 (0.968)	0.52 (0.763)
10	1.43 (0.906)	1.46 (0.964)	0.62 (0.782)
20	1.89 (0.876)	1.88 (0.933)	0.87 (0.822)
40	2.70 (0.873)	2.68 (0.925)	1.28 (0.842)
50	3.03 (0.867)	3.00 (0.918)	1.48 (0.859)
70	3.33 (0.846)	3.33 (0.903)	1.72 (0.887)
90	3.67 (0.847)	3.77 (0.915)	2.19 (0.912)

[a] The data in the parentheses are correlation coefficients in the plot log *k* vs σ (σ° or σ^-).

Origin of Bell-Shaped α-Effect. Possible causes for the bell-shaped α-effect profile will be examined in this section. One possibility is that a change in the reaction mechanism on addition of DMSO to the reaction medium might be responsible for the bell-shaped α-effect. In fact, change of solvent from water to an aprotic solvent such as MeCN has often been suggested to result in a change in the reaction mechanism.[21] For example, Lee et al. have concluded that the change of solvent from water to MeCN causes a mechanistic change in the aminolysis of aryl chloroformates and chlorothionoformates, from stepwise to concerted.[21]

Hammett correlations have been performed to examine whether addition of DMSO to the reaction medium causes a change in the reaction mechanism or not. As shown in Table 2, σ^- constants give the poorest Hammett correlation, while σ° results in the best correlation for the reactions of **1a**−**e** with Ox^- in all DMSO−H_2O mixtures. A similar result is seen in Table S29 in the Supporting Information for the corresponding reactions with *p*-$ClPhO^-$.

If leaving group departure is involved in the rate-determining step (RDS), whether the reaction proceeds through a stepwise or concerted mechanism, a partial negative charge would develop on the oxygen atom of the leaving aryl oxides. Since negative charge can be delocalized on the substituent in the leaving group through resonance, one would expect σ^- constants to give the best Hammett correlation. The fact that σ^- constants result in the poorest Hammett correlation suggests that leaving group departure is not involved in the rate-determining step in the DMSO−H_2O mixtures studied. This argument is consistent with our previous proposal that the reactions of **1a** with substituted phenoxides in DMSO−H_2O mixtures proceed through a tetrahedral intermediate with its formation as the RDS.[22] Addition of DMSO to the reaction medium does not

---

(15) (a) Aubort, J. D.; Hudson, R. F. *J. Chem. Soc. D* **1970**, 938−939. (b) Aubort, J. D.; Hudson, R. F. *J. Chem. Soc. D* **1970**, 1378−1379.

(16) (a) Buncel, E.; Cannes, C.; Chatrousse, A. P.; Terrier, F. *J. Am. Chem. Soc.* **2002**, *124*, 8766−8767. (b) Moutiers, G.; Le Guevel, E.; Cannes, C.; Terrier, F.; Buncel, E. *Eur. J. Org. Chem.* **2001**, *17*, 3279−3284.

(17) (a) Wiberg, K. B. *J. Am. Chem. Soc.* **1955**, *77*, 2519−2522. (b) Mclssac, J. E., Jr.; Subbaraman, J.; Mulhausen, H. A.; Behrman, E. J. *J. Org. Chem.* **1972**, *37*, 1037−1041.

(18) Um, I. H.; Lee, J. S.; Yuk, S. M. *J. Org. Chem.* **1998**, *63*, 9152−9153.

(19) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 6592−6597.

(20) Kwon, D. S.; Lee, G. J.; Um, I. H. *Bull. Korean Chem. Soc.* **1990**, *11*, 262−264.

(21) Oh, H. K.; Ha, J. S.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2004**, *69*, 8219−8223.

(22) Buncel, E.; Um, I. H.; Hoz, S. *J. Am. Chem. Soc.* **1989**, *111*, 971−975.

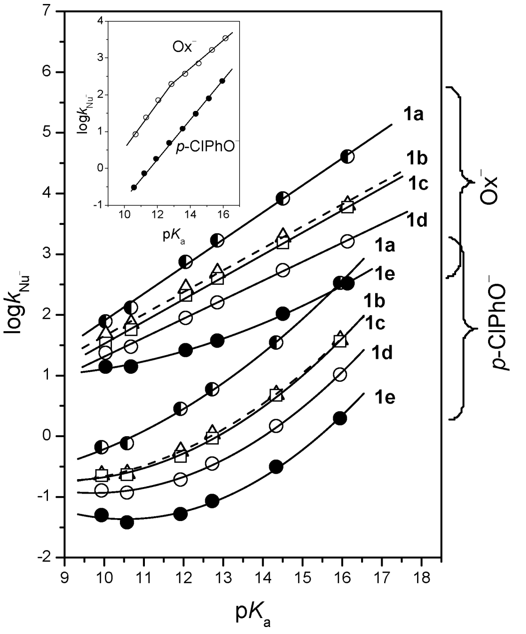


FIGURE 3. Novel Brønsted-type plots for the reactions of **1a**−**e** and **2** (inset) with Ox^- and *p*-$ClPhO^-$ in DMSO−H_2O mixtures of varying compositions at 25 ± 0.1 °C.

cause a mechanism change since the novel Brønsted-type plot, in which the pK_a change of phenols is brought about by changes in the reaction medium, is linear over the whole range of DMSO−H_2O composition.[22] Accordingly, the evidence tends to rule out the bell-shaped α-effect profile being due to a change in reaction mechanism.

One might further suggest that a drastic change in pK_a of the conjugate acid of Ox^- and *p*-$ClPhO^-$ is responsible for the bell-shaped α-effect, since nucleophilicity is strongly influenced by the basicity of nucleophiles. In fact, we have recently reported that the α-effect for the reactions of aryl acetates (including **1a** and **1d**) with Ox^- and *p*-$ClPhO^-$ in MeCN−H_2O mixtures increases as the MeCN content in the medium increases.[10] The pK_a values of the conjugate acids of Ox^- and *p*-$ClPhO^-$ have been found to increase as the MeCN content in the medium increases. However, Ox^- has been shown to be more basic than *p*-$ClPhO^-$ in media of higher MeCN content and the increasing pK_a difference between the conjugate acid of Ox^- and *p*-$ClPhO^-$ has been attributed to be responsible for the increasing α-effect profile in this case.[10] In contrast, the pK_a's of the conjugate acids of Ox^- and *p*-$ClPhO^-$ have been found to increase in a parallel manner upon addition of DMSO.[9,23]

Novel Brønsted-type plots, log k_{Nu^-} vs pK_a, where pK_a changes are brought about by change in solvent composition, have been constructed for the present system. As shown in Figure 3, the Ox^- system exhibits linear correlations beyond 10 mol % DMSO. On the contrary, the *p*-$ClPhO^-$ system exhibits an initial decrease on addition of DMSO followed by steep upward curvature. We have recently reported contrasting novel Brønsted-type plots for the corresponding reactions of **2**.[23] As shown in the inset of Figure 3, the novel Brønsted-type plot for the reaction with Ox^- exhibits downward curvature while that for the reaction with *p*-$ClPhO^-$ gives rise to a linear plot. This downward curvature was taken to be indicative of nonperfect syncronization in the transition state (PNS).[23,24] In contrast, the lack of such curvature for the current system suggests that no such imbalance exists here, indicating that the origin of the α-effect is likely to be different for the reactions of **1a**−**e** and **2**. Interestingly, a common feature exhibited in the novel Brønsted-type plots is that Ox^- shows higher sensitivity of the medium effect than *p*-$ClPhO^-$ in the H_2O-rich region, but the reverse is true in the DMSO-rich region regardless of the nature of substrates. It follows from the evidence presented here, that the origin of the bell-shaped α-effect is the differential sensitivity of the medium effect on the Ox^- and *p*-$ClPhO^-$ systems but not a change in reaction mechanism or a drastic change in the basicity of the two nucleophiles on addition of DMSO to the medium.

Ground-State vs Transition-State Effect: Evidence from Enthalpies of Solution. Finally, the effect of medium on the α-effect will be dissected into ground-state and transition-state contributions. We have recently shown through measurements of heats of solution that both Ox^- and *p*-$ClPhO^-$ are desolvated upon addition of DMSO and the former experiences higher desolvation than the latter.[9] The difference in the desolvation energy between Ox^- and *p*-$ClPhO^-$ ($\Delta\Delta H_s$) has been found to increase up to ca. 40 mol % DMSO but to remain nearly constant beyond that point. Thus, $\Delta\Delta H_s$ increases from 0 to 0.6, 1.8, and 3.2 kcal/mol as the medium changes from pure water to 10, 20, and 40 mol % DMSO, in turn, but remains nearly constant upon further addition of DMSO.[9]

If the ground-state energy difference between Ox^- and *p*-$ClPhO^-$ (e.g., $\Delta\Delta H_s$) were responsible for the α-effect, then the magnitude of the α-effect should have remained constant at the maximum beyond 40 mol % DMSO. The fact that the α-effect decreases in the DMSO-rich region suggests that the ground-state effect cannot be responsible for the α-effect in this region. In our previous report for the reactions of **1a** with Ox^- and *p*-$ClPhO^-$, we have shown through a kinetic study and dissection of rate data, that the transition-state for the reaction with Ox^- becomes less solvated than the one for reaction with *p*-$ClPhO^-$ in the DMSO-rich region, and that the differential solvation of the two transition-states is responsible for the decreasing α-effect trend beyond the break point of 40−50 mol % DMSO.[9]

The above argument can be further supported from the substrate dependent α-effect shown in Figure 2. Since Ox^- and *p*-$ClPhO^-$ were employed as the common nucleophiles for all the reactions of **1a**−**e** and **2**, the ground-state effect will be constant for the nucleophiles. Besides, the ground-state effect for the substrates is plausibly expected to be similar. Therefore, one would expect similar magnitudes of the α-effect if the ground-state effect governs the α-effect in these systems. Thus, the fact that the α-effect is significantly dependent on the substrates (or, more quantitatively, on the β_{nuc} value), clearly leads to the conclusion that the transition-state effect is more important than the ground-state effect for the α-effect in the present system.

The magnitude of the β_{nuc} value has been understood as a measure of bond formation between the nucleophile and the substrate in the transition state of the RDS;[22,25] hence the transition-state structure for the reactions of **1a**−**e** and **2** would vary according to the different β_{nuc} values. One can expect that

---

(23) Tarkka, R. M.; Buncel, E. *J. Am. Chem. Soc.* **1995**, *117*, 1503−1507.

(24) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119−238.

(25) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; pp 107−111.

the transition-state stabilizing effect would be more significant for the reaction system in which the degree of bond formation between nucleophile and substrate in the transition state is more advanced and vice versa. Accordingly, it is plausible that the transition-state stabilizing effect would be larger for the reactions of **1b**−**e** ($\beta_{nuc} = 0.90 \pm 0.03$) compared with the corresponding reactions of **1a** ($\beta_{nuc} = 0.78$) or **2** ($\beta_{nuc} = 0.21$), on the basis of their β_{nuc} values. This would account for the large α-effect found for the reactions of **1b**−**e** and the small α-effect observed for **2**, consistent with the preceding conclusion that transition-state effect is more dominant than the ground-state effect as the origin of the α-effect.

Conclusions

The results of the kinetic study for the reactions of **1a**−**e** and **2** with Ox^- and p-$ClPhO^-$ as the α and normal nucleophiles, respectively, have allowed us to conclude the following. (1) The bell-shaped α-effect profile obtained for the reactions of **1a**−**e** and **2** suggests that the effect of medium on the α-effect is significant and a two-point analysis could be misleading. (2) The reactions of **1a**−**e** with Ox^- and p-$ClPhO^-$ proceed through a tetrahedral intermediate with its formation being the RDS in all the DMSO−H_2O mixtures studied. (3) The contrasting novel Brønsted-type plots for the reactions of **1a**−**e** and **2** suggest that the origin of the α-effect is likely to be different for these systems. (4) Differential change in the sensitivity of the medium effect on the Ox^- and p-$ClPhO^-$ systems is responsible for the bell-shaped α-effect profile found for the reactions of **1a**−**e** and **2**. (5) The magnitude of the α-effect is significantly dependent on β_{nuc} values. (6) Through application of calorimetric measurements of ground-state solvation combined with the diagnostic β_{nuc} values, it is proposed that the transition-state effect is more dominant than the ground-state effect for the α-effect in the present system.

Experimental Section

Materials. Y-substituted phenyl acetates (**1a**−**e**) were readily prepared from the reactions of the Y-substituted phenol and acetyl chloride in anhydrous ether in the presence of triethylamine. Their purity was checked by their melting points and ^{1}H NMR spectra. Butan-2,3-dione monoxime (OxH) and the phenols used are of the highest quality available and were recrystallized before use. DMSO was refluxed over calcium hydride, distilled, collecting the fraction of bp 64−66 °C (6−7 mmHg), and stored under nitrogen. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetics. Kinetic studies were performed with a UV−vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) and a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) with a constant-temperature circulating bath at 25.0 ± 0.1 °C. Typically, the reaction was initiated by adding 5 μL of ca. 0.02 M of substrate solution in MeCN by 10 μL gastight syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostated reaction mixture made up of reaction medium and an aliquot of the nucleophile stock solution. The nucleophile stock solution of ca. 0.2 M was prepared by dissolving 2 equiv of OxH and 1 equiv of standardized NaOH solution to make a self-buffered solution. Generally, the nucleophile concentration was varied over the range $(1-100) \times 10^{-3}$ M, while the substrate concentration was 4×10^{-5} M. All the solutions were transferred by gastight syringes under nitrogen. The reactions were followed by monitoring the appearance of Y-substituted phenoxide ions at a fixed wavelength corresponding to the λ_{max}.

Product Analysis. Y-substituted phenoxide ion was liberated quantitatively and identified as one of the reaction products in the reactions of **1a**−**e** with Ox^- by comparison of the UV−vis spectra after completion of the reactions with those of the authentic samples under the same reaction conditions.

Acknowledgment. The authors are grateful for the financial support from the Korea Science and Engineering Foundation (Grant KOSEF-F01-2005-000-10033-0) and NSERC of Canada (E.B.).

Supporting Information Available: Tables of kinetic data for the reactions of **1a**−**e** with Ox^- in DMSO−H_2O mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051823F