

# Solvent Effect on the $\alpha$ -Effect for the Reactions of Aryl Acetates with Butane-2,3-dione Monoximate and *p*-Chlorophenoxide in MeCN–H<sub>2</sub>O Mixtures

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Second-order rate constants have been measured spectrophotometrically for the nucleophilic reactions of three substituted phenyl acetates with butane-2,3-dione monoximate (Ox<sup>-</sup>) as an  $\alpha$ -nucleophile and *p*-chlorophenoxide (ClPhO<sup>-</sup>) as corresponding normal nucleophile, in MeCN–H<sub>2</sub>O mixtures of varying compositions at 25.0 ± 0.1 °C. The reactivity of Ox<sup>-</sup> toward the aryl acetates decreases upon addition of MeCN to the reaction medium up to ca. 30 mol % MeCN, followed by a gradual increase in rate upon further addition of MeCN. A similar result has been obtained for the reaction of ClPhO<sup>-</sup> with the aryl acetates. However, the decrease in rate is more significant for the less reactive ClPhO<sup>-</sup> than for the more reactive Ox<sup>-</sup>. Thus, for all the aryl acetates studied, Ox<sup>-</sup> exhibits a sizable  $\alpha$ -effect ( $k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$ ) whose magnitude increases as the mol % MeCN in the reaction medium increases. The relative basicities ( $\Delta pK_a$ ) of Ox<sup>-</sup> and ClPhO<sup>-</sup> have been determined spectrophotometrically using piperazine as a reference base. The  $\Delta pK_a$  values increase on increasing the mol % MeCN in the medium for both Ox<sup>-</sup> and ClPhO<sup>-</sup>. The difference in the relative basicities of these nucleophiles ( $\Delta\Delta pK_a$ ) becomes larger with increasing mol % MeCN. The plots of  $\log k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$  vs  $\Delta\Delta pK_a$  for the three substrates are linear with near-unit slope, indicating that the difference in the relative basicity of the nucleophiles is largely responsible for the increasing  $\alpha$ -effect with medium composition in this system.

## Introduction

The term  $\alpha$ -effect was given to describe the abnormally enhanced nucleophilicity exhibited by nucleophiles having one or more nonbonding electron pairs at the position adjacent to the nucleophilic center relative to a nucleophile of the same basicity.<sup>1</sup> Numerous studies have been performed to account for the  $\alpha$ -effect phenomenon.<sup>2</sup> Theories suggested for the origin of the  $\alpha$ -effect include reactant destabilization through electronic repulsion between nonbonding electron pairs, transition-state stabilization, enhanced stability of the  $\alpha$ -product, solvent effect, as well as a transition state having aromatic or radicaloid character.<sup>2–10</sup> However, none of these factors alone can fully account for the  $\alpha$ -effect phenomenon.

Particularly, the effect of solvent on the  $\alpha$ -effect has been controversial.<sup>6–9</sup> While the effect of solvent on the  $\alpha$ -effect has been suggested to be unimportant on the basis of the similar magnitude of the  $\alpha$ -effect for reactions performed in H<sub>2</sub>O and in neat organic solvents,<sup>6</sup> gas-phase studies and theoretical calculations indicate a significant solvent effect on the  $\alpha$ -effect.<sup>7</sup>

To obtain more conclusive information on the role of solvent, we initiated a systematic study for the reactions

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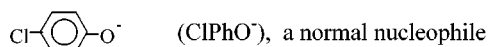
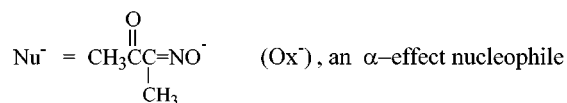
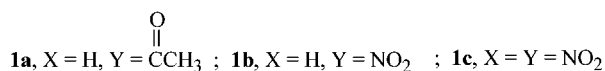
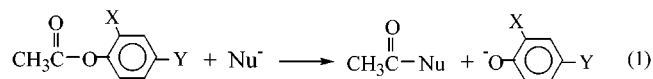
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of *p*-nitrophenyl acetate (PNPA) with butane-2,3-dione monoximate ( $\text{Ox}^-$ ) and *p*-chlorophenoxide ( $\text{ClPhO}^-$ ), as an  $\alpha$ -effect nucleophile and a corresponding normal nucleophile, respectively, in dimethyl sulfoxide (DMSO)– $\text{H}_2\text{O}$  mixtures of varying compositions, owing to the unique properties of this solvent system.<sup>11b</sup> Unexpectedly, the magnitude of the  $\alpha$ -effect ( $k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$ ) increased upon addition of DMSO in the reaction medium up to ca. 50 mol % DMSO and then decreased beyond that point, resulting in a bell-shaped dependence on solvent composition.<sup>8a,b</sup> A similar bell-shaped  $\alpha$ -effect profile with a maximum  $\alpha$ -effect at ca. 50 mol % DMSO was observed for the corresponding reactions of *p*-nitrophenyl diphenylphosphinate (PNPDPP) and *p*-nitrophenyl benzenesulfonate (PNPBS),<sup>8c,13</sup> suggesting that the bell-shaped  $\alpha$ -effect trend is general for the reactions of the carbonyl, phosphinyl, and sulfonyl esters with  $\text{Ox}^-$  and  $\text{ClPhO}^-$  in DMSO– $\text{H}_2\text{O}$  mixtures. However, Moss reported that the magnitude of the  $\alpha$ -effect for the reaction of PNPA with *O*-iodosylbenzoate ( $\text{IBO}^-$ ) and  $\text{ClPhO}^-$  in DMSO– $\text{H}_2\text{O}$  mixtures shows no maximum but decreases steadily as the DMSO content in the reaction medium increases.<sup>6a</sup> Terrier and co-workers reported that the  $\alpha$ -effect for the reaction of PNPA with  $\alpha,\alpha,\alpha$ -trifluoroacetophenone oximate ( $\text{TAOx}^-$ ) and  $\text{ClPhO}^-$  increases with DMSO content up to 70 vol %.<sup>4c</sup> Clearly, more work on solvent effects on the  $\alpha$ -effect is demanded.

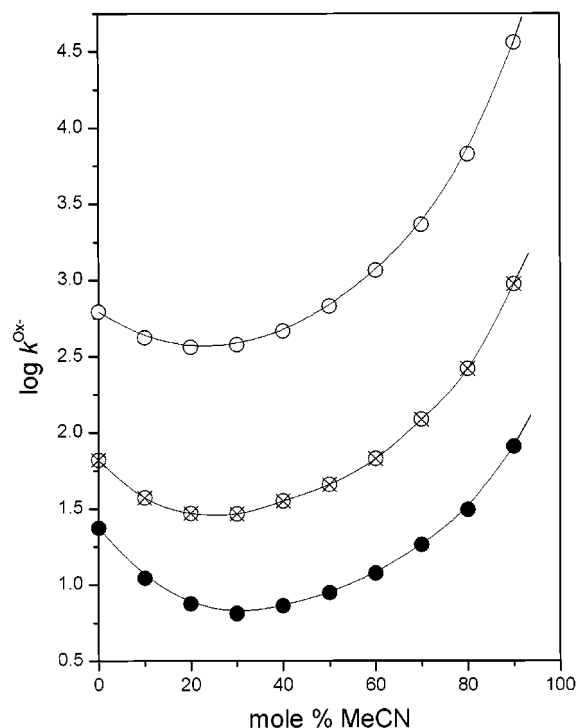
In view of the above, we have extended our studies to a different solvent system, namely acetonitrile (MeCN)– $\text{H}_2\text{O}$  mixtures, instead of DMSO– $\text{H}_2\text{O}$  mixtures.<sup>9</sup> Interestingly, we have found that the magnitude of the  $\alpha$ -effect increases as the mol % MeCN in the reaction medium increases.<sup>9e</sup> In the present paper, we report our results for the reactions of  $\text{Ox}^-$  and  $\text{ClPhO}^-$  with three aryl acetates, together with an analysis of the cause of this contrasting  $\alpha$ -effect profile in MeCN– $\text{H}_2\text{O}$  mixtures.



Solvent : 0, 10, 20 ... 80, 90 mole % MeCN in  $\text{H}_2\text{O}$

## Results

Kinetic studies were performed under pseudo-first-order conditions with the nucleophile in excess. Pseudo-first-order rate constants ( $k_{\text{obs}}$ ) were obtained from linear plots of  $\ln(A_\infty - A_t)$  vs  $t$ , where  $A_\infty$  and  $A_t$  are absorbances at infinite time and at time  $t$ , respectively. Generally, five different concentrations of nucleophile solutions were used to determine second-order rate constant from the



**Figure 1.** Plots of  $\log k^{\text{Ox}^-}$  vs mol % MeCN for the reactions of aryl acetates (**1a–c**) with  $\text{Ox}^-$  in MeCN– $\text{H}_2\text{O}$  mixtures at  $25.0 \pm 0.1$  °C: ● (**1a**), ⊗ (**1b**), ○ (**1c**).

slope of the plot of  $k_{\text{obs}}$  vs nucleophile concentration, which showed near-zero intercepts indicating that reaction with solvent was negligible. The correlation coefficients of the plots were usually higher than 0.9995 in all the solvent compositions studied. It is estimated from replicate runs that the uncertainty in the rate constants is less than  $\pm 3\%$ . The second-order rate constants determined in this way are presented graphically in Figures 1 and 2 as a function of medium composition.

Relative basicities of the present nucleophiles ( $\Delta pK_a = pK_a$  of the conjugate acid of nucleophiles –  $pK_a$  of the conjugate acid of the reference base) were determined spectrophotometrically with respect to piperazine as the reference base. This was done using the relationship in eq 2

$$\Delta pK_a = \log[\text{HA}]_{\text{eq}}[\text{B}]_{\text{eq}}/[\text{A}]_{\text{eq}}^2 \quad (2)$$

in which  $[\text{HA}]_{\text{eq}}$  represents the equilibrium concentration of the conjugate acid of the nucleophile and  $[\text{B}]_{\text{eq}}$  and  $[\text{A}^-]_{\text{eq}}$  represent the equilibrium concentration of the reference base (piperazine) and the nucleophile, respectively. The equilibrium concentration of the nucleophile was determined from the relationship  $[\text{A}^-]_{\text{eq}} = A/\epsilon$ , in which  $A$  and  $\epsilon$  represent the absorbance and molar absorptivity of the nucleophile at 290 nm for  $\text{Ox}^-$  and 299 nm for  $\text{ClPhO}^-$ , respectively. The advantages of piperazine as a reference base are as follows: (1) the basicity of piperazine is similar to that of  $\text{Ox}^-$  and  $\text{ClPhO}^-$  in  $\text{H}_2\text{O}$ ; (2) piperazine is stable under the experimental conditions and does not absorb in the UV light in the region of interest. The  $\Delta pK_a$  values determined in this way are summarized in Table 2.

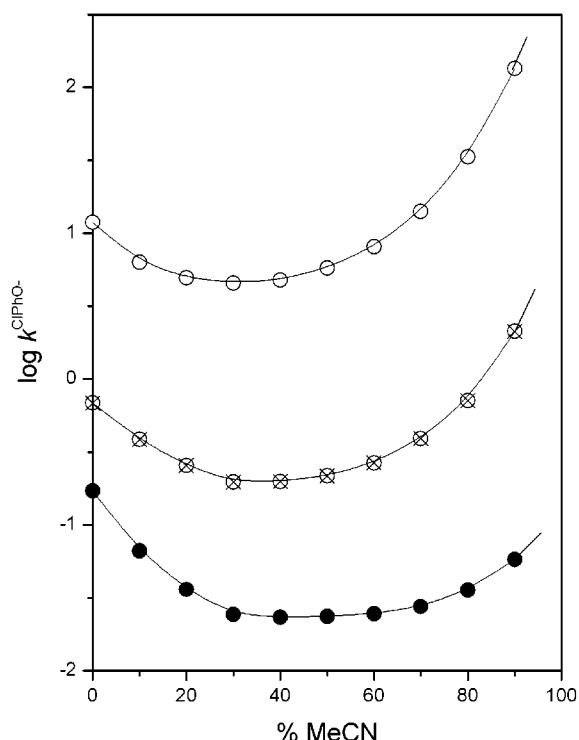
## Discussion

**Solvent Effect on Rate.** As shown in Figure 1, the reactivity of  $\text{Ox}^-$  decreases upon the initial addition of

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**Figure 2.** Plots of  $\log k^{\text{CIPhO}^-}$  vs mol % MeCN for the reactions of aryl acetates (**1a–c**) with  $\text{CIPhO}^-$  in MeCN– $\text{H}_2\text{O}$  mixtures at  $25.0 \pm 0.1$  °C: ● (**1a**), ⊗ (**1b**), ○ (**1c**).

**Table 1.** Magnitude of  $\alpha$ -Effect ( $k^{\text{Ox}^-}/k^{\text{CIPhO}^-}$ ) for the Reactions of Aryl Acetates (**1a–c**) with  $\text{Ox}^-$  and  $\text{CIPhO}^-$  in MeCN– $\text{H}_2\text{O}$  Mixtures at  $25.0 \pm 0.1$  °C

MeCN (mol %)	$k^{\text{Ox}^-}/k^{\text{CIPhO}^-}$		
	<b>1a</b>	<b>1b</b>	<b>1c</b>
0	138	96.1	52.5
10	166	96.6	66.2
20	208	116	73.3
30	266	148	82.8
40	314	180	96.9
50	375	210	117
60	484	254	144
70	665	312	165
80	868	369	202
90	1390	505	268

**Table 2.** Summary of the Relative Basicity of the Nucleophile ( $\Delta pK_a = pK_a$  of the Conjugate Acid of the Nucleophile –  $pK_a$  of the Conjugate Acid of the Reference Base, Piperazine) in MeCN– $\text{H}_2\text{O}$  Mixtures of Varying Compositions at  $25.0 \pm 0.1$  °C<sup>a</sup>

MeCN (mol %)	$\Delta pK_a (\text{Ox}^-)$	$\Delta pK_a (\text{CIPhO}^-)$	$\Delta \Delta pK_a^b$
0	–0.38	–0.44	0.06
10	0.58	0.43	0.15
20	1.17	0.90	0.27
30	1.80	1.44	0.36
40	2.32	1.89	0.43
50	2.69	2.19	0.50
60	3.43	2.84	0.59
70	3.90	3.20	0.70
80	4.96	4.18	0.78
90	5.85	4.90	0.95

<sup>a</sup> The uncertainty in  $\Delta pK_a$  values is estimated to be less than  $\pm 0.03$   $pK_a$  units. <sup>b</sup>  $\Delta \Delta pK_a = \Delta pK_a (\text{Ox}^-) - \Delta pK_a (\text{CIPhO}^-)$ .

MeCN into the reaction medium and then increases upon further addition of MeCN; the second-order rate constant for the reaction of **1a** with  $\text{Ox}^-$  decreases from  $23.6 \text{ M}^{-1} \text{ s}^{-1}$  in  $\text{H}_2\text{O}$  to  $6.46 \text{ M}^{-1} \text{ s}^{-1}$  in 30 mol % MeCN and then

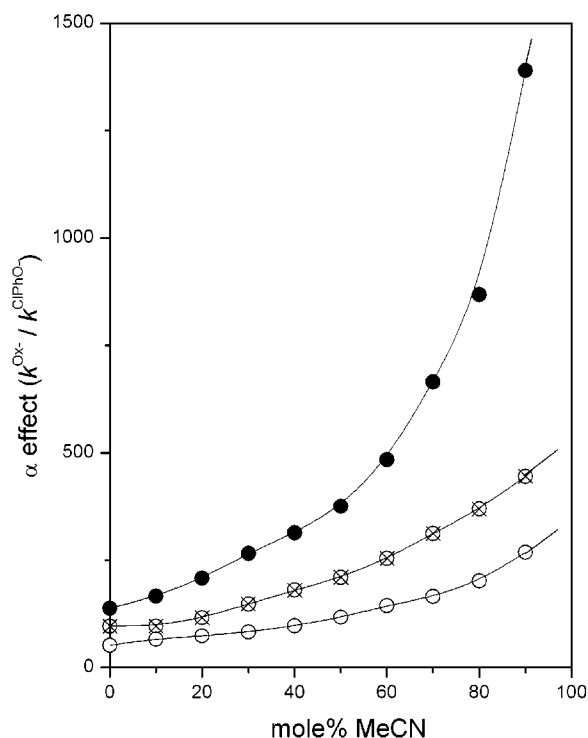
increases to  $80.8 \text{ M}^{-1} \text{ s}^{-1}$  on going to 90 mol % MeCN (see Table S1 in the Supporting Information). Similar rate behavior is obtained for the reactions of **1b** and **1c** with  $\text{Ox}^-$ . In all cases, the second-order rate constants exhibit a minimum at ca. 30 mol % MeCN. The reactivity of  $\text{CIPhO}^-$  exhibits a similar pattern, as shown in Figure 2. However, the rate decrease is more significant for the reaction of  $\text{CIPhO}^-$  than for  $\text{Ox}^-$ ; the second-order rate constant for the reaction of **1a** with  $\text{CIPhO}^-$  decreases from  $0.171 \text{ M}^{-1} \text{ s}^{-1}$  in  $\text{H}_2\text{O}$  to  $0.0232 \text{ M}^{-1} \text{ s}^{-1}$  in 40 mol % MeCN, and then increases to  $0.0580 \text{ M}^{-1} \text{ s}^{-1}$  (see Table S2 in the Supporting Information).

It is well-known that the negative end of the dipole in dipolar aprotic solvents such as MeCN and DMSO is exposed, whereas the positive end is buried within the molecule.<sup>11</sup> Since anions would be strongly destabilized in such dipolar aprotic solvents, one might expect a significant rate acceleration for the reactions of anionic nucleophiles upon addition of MeCN or DMSO to the reaction medium. In fact, in the latter case, the reactivities of  $\text{Ox}^-$  and  $\text{CIPhO}^-$  toward **1b** increase significantly as the mol % DMSO in the reaction medium increases, except for  $\text{CIPhO}^-$  from 0 to 10 mol % DMSO.<sup>8</sup> Therefore, the initial rate decrease upon addition of MeCN to the reaction medium up to ca. 30 mol % in the present system is an unexpected result based on the Hughes–Ingold rules of solvent effects.<sup>11,12</sup>

However, whereas DMSO is a highly polarizable solvent, MeCN is not so. Accordingly, DMSO can strongly stabilize polarizable anions (e.g., picrate) or anionic transition states that are expected to be highly polarizable through polarizability or charge dispersion interaction, while MeCN does not exert such strong interactions.<sup>11</sup> This difference in solvent property between MeCN and DMSO is likely largely responsible for the difference in the rate behavior between the reaction run in MeCN– $\text{H}_2\text{O}$  and that in DMSO– $\text{H}_2\text{O}$  mixtures (however, other difference may also contribute, e.g., H-bonding).<sup>11</sup> This argument can be further supported by similar results obtained for other reactions run in MeCN– $\text{H}_2\text{O}$  and in DMSO– $\text{H}_2\text{O}$  mixtures; the second-order rate constant for the reaction of **1b** with  $\text{OH}^-$  and benzohydroxamate anions in MeCN– $\text{H}_2\text{O}$  mixtures showed a minimum at ca. 30 mol % MeCN,<sup>9c</sup> while in DMSO– $\text{H}_2\text{O}$  mixtures the reactions of *p*-nitrophenyl diphenylphosphinate (PNPDPP) and *p*-nitrophenyl benzenesulfonate (PNPBS) with  $\text{Ox}^-$  and  $\text{CIPhO}^-$  exhibited increasing rate trends upon addition of DMSO to the reaction medium.<sup>8c,13</sup>

**Solvent Effect on the  $\alpha$ -Effect.** As shown in Table 1, for the reactions of **1a** with  $\text{Ox}^-$  and  $\text{CIPhO}^-$ , the magnitude of the  $\alpha$ -effect ( $k^{\text{Ox}^-}/k^{\text{CIPhO}^-}$ ) increases as the mol % MeCN in the reaction medium increases from 138 in  $\text{H}_2\text{O}$  to 375 and 1390 in 50 and 90 mol % MeCN, respectively. A similar result is obtained for the reactions of **1b** and **1c**, indicating that the effect of solvent on the  $\alpha$ -effect is general to this series. The effect of solvent on the  $\alpha$ -effect is graphically demonstrated in Figure 3. One can see that the plot of the  $\alpha$ -effect vs mol % MeCN exhibits upward curvature regardless of the substrate. The increasing  $\alpha$ -effect profile obtained in the present reaction is in contrast to the one obtained in the corresponding reactions run in DMSO– $\text{H}_2\text{O}$  mixtures. The magnitude of the  $\alpha$ -effect for the reaction of **1b**, PNPDPP and PNPBS with  $\text{Ox}^-$  and  $\text{CIPhO}^-$  in DMSO– $\text{H}_2\text{O}$  mixtures was found to increase upon addition of DMSO





**Figure 3.** Plots of  $\alpha$ -effect ( $k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$ ) vs mol % MeCN for the reactions of aryl acetates (**1a–c**) with  $\text{Ox}^-$  and  $\text{ClPhO}^-$  in MeCN– $\text{H}_2\text{O}$  mixtures at  $25.0 \pm 0.1$  °C: ● (**1a**), ⊗ (**1b**), ○ (**1c**).

to the medium up to ca. 50 mol % DMSO, and then decrease beyond that point, resulting in a bell-shaped  $\alpha$ -effect profile.<sup>8,13</sup> Therefore, the increasing  $\alpha$ -effect profile obtained in the MeCN– $\text{H}_2\text{O}$  mixtures in the present study is a noteworthy finding and suggests that the role of solvent on the  $\alpha$ -effect is significant.

The enhanced reactivity of an  $\alpha$ -effect nucleophile compared to that of a corresponding normal nucleophile can result from destabilizing the ground-state (GS) and/or by stabilizing the transition state (TS) of the  $\alpha$ -effect nucleophile system. The  $\alpha$ -nucleophile  $\text{HOO}^-$  was reported to be 12 kcal/mol less solvated than  $\text{OH}^-$  in  $\text{H}_2\text{O}$ <sup>14</sup> and up to  $10^2$ – $10^4$  times more reactive than  $\text{HO}^-$  in various addition reactions, although  $\text{HOO}^-$  is less basic than  $\text{HO}^-$  by over 4  $\text{pK}_a$  units.<sup>5,15,16</sup> However, DePuy et al. found that  $\text{HOO}^-$  shows no enhanced nucleophilicity in the gas-phase reaction with methyl formate.<sup>7a</sup> Furthermore, Wolfe et al. in an extensive ab initio study found no unusual geometrical or energetic effect for the transition state in gas-phase  $\text{S}_{\text{N}}2$  reactions with  $\text{HOO}^-$  and  $\text{FO}^-$ .<sup>7b</sup> Jorgensen et al. obtained a similar result through ab initio study of  $\text{S}_{\text{N}}2$  reactions of  $\text{HOO}^-$  and  $\text{HO}^-$  with  $\text{CH}_3\text{Cl}$ .<sup>7c</sup> Therefore, it has been suggested that  $\text{HOO}^-$  is not intrinsically more reactive than  $\text{HO}^-$ , but that the enhanced reactivity of  $\text{HOO}^-$  in solution is mostly due to a solvation effect.<sup>7</sup> A similar conclusion has been drawn by Terrier et al. who found that highly basic oximates of various structures show small or no  $\alpha$ -effect for the reactions with **1b**, and suggested that differential solvation (i.e., solvational imbalance for highly basic

oximates) is mainly responsible for the cause of the vanishing  $\alpha$ -effect with increasing oximate basicity.<sup>4,17</sup>

The GS of  $\text{Ox}^-$  and  $\text{ClPhO}^-$  would be also destabilized upon the addition of MeCN in the medium, consequent to the repulsion between the negative dipole end of MeCN and the anionic species. However, the difference in the GS solvation energy between  $\text{Ox}^-$  and  $\text{ClPhO}^-$  in MeCN– $\text{H}_2\text{O}$  mixtures will be practically constant for the reactions of **1a**, **1b**, and **1c**. Therefore, if the difference in the GS solvation energy were mainly responsible for the  $\alpha$ -effect, the magnitude of the  $\alpha$ -effect should be about the same, regardless of the substrate. In fact, the magnitude of the  $\alpha$ -effect is strongly dependent on substrate, as shown in Table 1 and Figure 3. Therefore, the present results clearly suggest that while the solvent effect on the  $\alpha$ -effect is significant, the difference in the GS energy of  $\text{Ox}^-$  and  $\text{ClPhO}^-$  cannot be solely responsible for the  $\alpha$ -effect in the present system. This argument is consistent with our recent report which found  $\text{Ox}^-$  to be 3.92 kcal/mol less solvated than  $\text{ClPhO}^-$  in  $\text{H}_2\text{O}$ ,<sup>8b</sup> equivalent to an  $\alpha$ -effect of 750. However, the  $\alpha$ -effect observed in the present system in  $\text{H}_2\text{O}$  is found to be only 138, 96, and 52 for the reaction of **1a**, **1b**, and **1c**, respectively, indicating that the differential GS energy is not fully reflected in the  $\alpha$ -effect.

Many factors have been suggested to influence the magnitude of the  $\alpha$ -effect, e.g., basicity of nucleophile,<sup>4</sup> hybridization type of electrophilic center,<sup>5</sup> solvent,<sup>6</sup> and  $\beta_{\text{nuc}}$  value.<sup>3,8c,15</sup> The importance of  $\beta_{\text{nuc}}$  in influencing the  $\alpha$ -effect can be demonstrated as follows.

Bruice showed that the magnitude of the  $\alpha$ -effect decreases as the  $\beta_{\text{nuc}}$  value decreases for reactions of a variety of substrates with hydrazine and glycyglycine.<sup>15</sup> We found that the reaction of an sp-hybridized carbon center in which the  $\beta_{\text{nuc}}$  value is 0.32 exhibits an unexpectedly small  $\alpha$ -effect.<sup>5a</sup> Furthermore, Bernasconi observed no  $\alpha$ -effect for the addition reaction of a series of primary amines to Meldrum's acid, a system for which  $\beta_{\text{nuc}} = 0.22$ .<sup>3</sup> For nucleophilic substitution reactions of a series of aryloxides with **1a**, **1b**, and **1c**, the  $\beta_{\text{nuc}}$  values have been reported to be 0.89, 0.79, and 0.38, respectively.<sup>18</sup> Hence, in the present reactions of **1a–c**, the  $\beta_{\text{nuc}}$  value follows the same order as the  $\alpha$ -effect in magnitude. Similarly, we recently found that the magnitude of the  $\alpha$ -effect is strongly dependent on the  $\beta_{\text{nuc}}$  value for reactions of  $\text{Ox}^-$  and  $\text{ClPhO}^-$  at three different electrophilic centers (i.e., **1b**, PNPBS and PNPDP) in 50 mol % DMSO– $\text{H}_2\text{O}$  mixture: the  $\alpha$ -effects were ca. 300, 200, and 40 while the  $\beta_{\text{nuc}}$  values were 0.64, 0.54, and 0.21 for the carbonyl, sulfonyl, and phosphinyl ester, respectively.<sup>8c</sup>

Since the magnitude of the  $\beta_{\text{nuc}}$  value has been understood as a measure of bond formation between the nucleophile and the substrate in the TS of the rate-determining step, the TS structure of **1a**, **1b**, and **1c** systems would vary according to the different  $\beta_{\text{nuc}}$  values. One can expect that the TS stabilizing effect would be proportional to the degree of bond formation at the TS. It follows that the TS stabilizing effect would be most significant for the reaction of **1a** and least significant for

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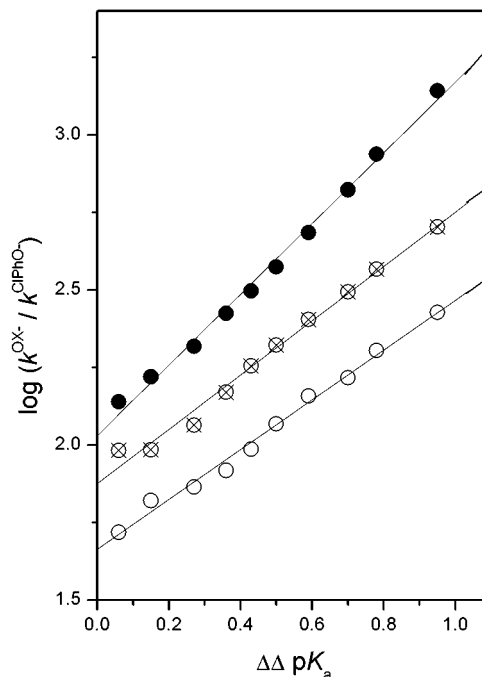
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the reaction of **1c**, based on their  $\beta_{\text{nuc}}$  values. This would explain the finding that the magnitude of the  $\alpha$ -effect and the  $\beta_{\text{nuc}}$  value follow a direct relationship in the present and other systems as mentioned above.

**Solvent Effect on Basicity.** The addition of MeCN to H<sub>2</sub>O would also influence the basicity of the present anionic nucleophiles. It is well-known that carboxylic acids and phenols become significantly weaker acids in MeCN than in H<sub>2</sub>O.<sup>19</sup> Although the  $\text{p}K_{\text{a}}$  values for some phenols and carboxylic acids in pure MeCN are available,<sup>19</sup> very few  $\text{p}K_{\text{a}}$  data have been reported for MeCN–H<sub>2</sub>O mixtures.<sup>9c</sup> As part of the present study, we have measured the relative basicity of Ox<sup>−</sup> and ClPhO<sup>−</sup> in MeCN–H<sub>2</sub>O mixtures using piperazine as a reference base. One can define  $\Delta\text{p}K_{\text{a}}$  as the  $\text{p}K_{\text{a}}$  difference between the conjugate acids of the nucleophile (Ox<sup>−</sup> or ClPhO<sup>−</sup>) and piperazine, i.e.,  $\Delta\text{p}K_{\text{a}} = \text{p}K_{\text{a}}$  of the conjugate acid of the nucleophile (Ox<sup>−</sup> or ClPhO<sup>−</sup>) –  $\text{p}K_{\text{a}}$  of the conjugate acid of the reference base (piperazine). Therefore, the magnitude of  $\Delta\text{p}K_{\text{a}}$  values represents the relative basicities of these nucleophiles. The  $\Delta\text{p}K_{\text{a}}$  values determined spectrophotometrically in MeCN–H<sub>2</sub>O mixtures of varying compositions (see the Results) are summarized in Table 2.

As shown in Table 2, the  $\Delta\text{p}K_{\text{a}}$  values of Ox<sup>−</sup> and ClPhO<sup>−</sup> in H<sub>2</sub>O are  $-0.38$  and  $-0.44$ , respectively. The  $\text{p}K_{\text{a}}$  values of the conjugate acids of Ox<sup>−</sup>, ClPhO<sup>−</sup>, and piperazine have been reported as 9.44,<sup>13</sup> 9.38,<sup>20</sup> and 9.82,<sup>20</sup> respectively; i.e., the  $\Delta\text{p}K_{\text{a}}$  data determined in H<sub>2</sub>O in the present study are identical to the literature values. It is also noted that Ox<sup>−</sup> and ClPhO<sup>−</sup> are less basic than piperazine in H<sub>2</sub>O but appear to be more basic upon addition of MeCN to H<sub>2</sub>O. This is consistent with the reports that the increase in  $\text{p}K_{\text{a}}$  values upon changing the medium from H<sub>2</sub>O to MeCN is more significant for phenols than for amines. Thus, the  $\text{p}K_{\text{a}}$  enhancements were reported to be 12–17 and 7–8  $\text{p}K_{\text{a}}$  units for phenols and the conjugate acids of alicyclic secondary amines (e.g., piperidine and morpholine), respectively, upon solvent change from H<sub>2</sub>O to MeCN.<sup>19</sup>

The difference in the relative basicity between Ox<sup>−</sup> and ClPhO<sup>−</sup> can be expressed as  $\Delta\Delta\text{p}K_{\text{a}}$ , i.e.,  $\Delta\Delta\text{p}K_{\text{a}} = \Delta\text{p}K_{\text{a}}$  (Ox<sup>−</sup>) –  $\Delta\text{p}K_{\text{a}}$  (ClPhO<sup>−</sup>). As shown in Table 2,  $\Delta\Delta\text{p}K_{\text{a}}$  increases as the mol % MeCN increases in the medium; i.e., Ox<sup>−</sup> is more basic than ClPhO<sup>−</sup> by 0.06, 0.50, and 0.95 in  $\text{p}K_{\text{a}}$  units in H<sub>2</sub>O, 50 and 90 mol % MeCN, respectively. However, interestingly, the  $\Delta\Delta\text{p}K_{\text{a}}$  trend determined in MeCN–H<sub>2</sub>O mixtures in the present study is in contrast to that determined in DMSO–H<sub>2</sub>O mixtures. The  $\Delta\text{p}K_{\text{a}}$  values of the conjugate acids of Ox<sup>−</sup> and ClPhO<sup>−</sup> increase in a parallel manner as the mol % DMSO in the medium increases, while  $\Delta\Delta\text{p}K_{\text{a}}$  remains nearly constant upon the change in medium from H<sub>2</sub>O to 90 mol % DMSO.<sup>8b,13,21</sup> Therefore, we propose that the differential solvent effect on the relative basicity is the cause of the contrasting  $\alpha$ -effect profile for the reaction run in MeCN–H<sub>2</sub>O, compared with DMSO–H<sub>2</sub>O mixtures.



**Figure 4.** Plots of  $\log k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$  vs  $\Delta\Delta\text{p}K_{\text{a}}$  for the reactions of aryl acetates with Ox<sup>−</sup> and ClPhO<sup>−</sup> in MeCN–H<sub>2</sub>O mixtures at  $25.0 \pm 0.1$  °C. ● (**1a**), ⊗ (**1b**), ○ (**1c**).

To confirm the above argument, we have correlated  $\Delta\Delta\text{p}K_{\text{a}}$  values with  $\log k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$  values obtained in the present study. As shown in Figure 4, the  $\log k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$  value increases linearly with  $\Delta\Delta\text{p}K_{\text{a}}$ , indicating that the increasing  $\Delta\Delta\text{p}K_{\text{a}}$  value is responsible for the increasing  $\alpha$ -effect profile upon addition of MeCN in the medium. The slope of the linear plots in Figure 4 is near unity, which indicates that the increase in the  $\Delta\Delta\text{p}K_{\text{a}}$  values is fully reflected in the increasing  $\alpha$ -effect profile for the reactions of **1a–c** with Ox<sup>−</sup> and ClPhO<sup>−</sup> in MeCN–H<sub>2</sub>O mixtures

## Conclusions

The results of the kinetic study for the reaction of aryl acetates (**1a–c**) with Ox<sup>−</sup> and ClPhO<sup>−</sup> and of the relative basicity measurements of these nucleophiles in various MeCN–H<sub>2</sub>O mixtures, have allowed us to conclude the following. (1) The reactivity of Ox<sup>−</sup> and ClPhO<sup>−</sup> toward **1a–c** decreases upon addition of MeCN up to ca. 30 mol % MeCN and then increases upon further addition of MeCN to the reaction medium. (2) The magnitude of the  $\alpha$ -effect ( $k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$ ) increases as the mol % MeCN in the reaction medium increases, indicating a significant solvent effect on the  $\alpha$ -effect. (3) Differential GS solvation between Ox<sup>−</sup> and ClPhO<sup>−</sup> cannot be solely responsible for the  $\alpha$ -effect in the present system. (4)  $\beta_{\text{nuc}}$  values in the present system are in the same order as the  $\alpha$ -effect in magnitude, indicating that TS stabilization is a significant contributor to the  $\alpha$ -effect. (5) The relative basicity ( $\Delta\text{p}K_{\text{a}}$ ) of Ox<sup>−</sup> and ClPhO<sup>−</sup> with respect to piperazine as reference base increases as the mol % MeCN increases, and the difference in the relative basicity between Ox<sup>−</sup> and ClPhO<sup>−</sup> ( $\Delta\Delta\text{p}K_{\text{a}}$ ) becomes larger with increasing mol % MeCN in the medium. (6) Plots of  $\log k^{\text{Ox}^-}/k^{\text{ClPhO}^-}$  vs  $\Delta\Delta\text{p}K_{\text{a}}$  are linear with near unit slope, indicating that the increasing  $\Delta\Delta\text{p}K_{\text{a}}$  values

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is largely responsible for the increasing  $\alpha$ -effect trend observed in the present system.

### Experimental Section

**Materials.** PNPA, butane-2,3-dione monoxime, *p*-chlorophenol, and other chemicals used were obtained from Aldrich and recrystallized before use. MeCN was distilled over P<sub>2</sub>O<sub>5</sub> under a nitrogen atmosphere. Doubly glass-distilled water was further boiled and cooled under nitrogen just before use. MeCN–H<sub>2</sub>O mixtures of varying compositions (mol %) were prepared by adding the calculated weight of H<sub>2</sub>O to the weighed, dry MeCN in a flask. The mixed solvents were stored under nitrogen but no longer than 2 days.

**Product Analysis.** 4-Acetylphenoxide, 4-nitrophenoxide, and 2,4-dinitrophenoxide were identified as one of the final products of the corresponding reactions by comparison of the UV–vis spectra after completion of the reactions with those of authentic samples at the same experimental conditions. The other products, 4-chlorophenyl acetate and 2,3-butanedione mono-(*O*-acetyl oxime), were indentified by HPLC using a Waters 600 liquid chromatograph equipped with a Waters 996 photodiode array detector, a Rheodyne 7725i manual injector, and a column of Nova-Pak C18 60 Å (4  $\mu$ m) (3.9 i.d.  $\times$  150 mm length). The flow rate was 1 mL/min, and the eluent was 50% MeCN in MeOH (v/v). Quantitative analysis was performed by comparison of the HPLC peak area of the reaction mixture with that of the authentic sample.

**Kinetics.** Kinetic studies were performed with a Scinco S-2100 UV–vis spectrophotometer for slow reactions ( $t_{1/2} > 10$  s) or for fast reactions ( $t_{1/2} \leq 10$  s), with an Applied Photophysics SX-17MV stopped-flow spectrophotometer, equipped with a Neslab RTE-110 constant temperature circulating bath to keep the temperature in the reaction chamber at 25.0  $\pm$  0.1 °C. All the reactions were carried out under pseudo-first-order conditions in which the concentrations of nucleophiles were generally over 20 times, but at least 10 times, greater than that of the substrate. Nucleophile stock solutions of ca. 0.2 M were prepared in 25.0 mL volumetric flasks by adding 0.5 equiv of base in order to achieve self-buffered solutions. For reasons of solubility, standardized NaOH solution (solvent composition  $\leq 40$  mol % MeCN) or Me<sub>4</sub>NOH·5H<sub>2</sub>O

(solvent composition  $\geq 50$  mol % MeCN) was used as the base. The reactions were followed by monitoring the appearance of the leaving aryloxide ion (e.g., *p*-nitrophenoxide ion at 400 nm). Each reaction was monitored up to 10 half-lives. The pseudo-first-order rate constants were obtained from the slopes of plots of  $\ln(A_{\infty} - A_t)$  versus time, where  $A_{\infty}$  and  $A_t$  represent the absorbance reading at 10 half-lives and at time  $t$  (generally taken up to 3 half-lives), respectively. Other details of kinetic methods were reported previously.<sup>22</sup>

**Relative Basicity Measurements.** Relative basicities of Ox<sup>−</sup> and ClPhO<sup>−</sup> were determined spectrophotometrically. Piperazine was chosen as reference base. Determinations of relative basicity were done by measuring the absorbance of Ox<sup>−</sup> or ClPhO<sup>−</sup> which is at equilibrium with the conjugate acid of the base, i.e., piperazinium ion, using the same UV–vis spectrophotometer as used for the kinetic study at the appropriate fixed wavelength. Standard 1.0 cm quartz cells (Hellma) closed on top with a rubber septum were used. Hamilton gastight syringes were used to transfer solutions. All the solutions were prepared in 25.0 mL volumetric flasks sealed with a rubber septum just before use under a nitrogen atmosphere. Other details of relative basicity measurements are similar to the those in the literature.<sup>9c,23</sup>

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**Supporting Information Available:** Second-order rate constants for the reactions of aryl acetates (**1a–c**) with Ox<sup>−</sup> in MeCN–H<sub>2</sub>O mixtures at 25.0  $\pm$  0.1 °C (Table S1) and the rate constants for the corresponding reactions with ClPhO<sup>−</sup> (Table S2). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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