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The Origin of the α-Effect: Dissection of Ground-State and Transition-State Contributions

Ik-Hwan Um[1] and Erwin Buncel*

Department of Chemistry, Queen's University, Kingston, Canada K7L 3N6

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The origin of the α-effect has been probed through a combination of calorimetric and kinetic studies involving butane-2,3-dione monoximate as α-nucleophile and *p*-chlorophenoxide as normal nucleophile in the reaction with *p*-nitrophenyl acetate in DMSO−H_2O mixtures, which has been shown to exhibit a bell-shaped profile in the α-effect with solvent composition. The study, involving determination of enthalpies of solution and activation parameters, has allowed a dissection of contributions to the α-effect of ground-state destabilization and transition-state stabilization in these DMSO−H_2O solvent media. It has been found that over the solvent composition 0−50 mol % DMSO desolvation of the α-nucleophile is the main driving factor to the increasing α-effect. However, in solvent mixtures covering 50−90 mol % DMSO the thermodynamic activation parameters suggest an interplay of factors that result in the bell-shaped α-effect profile. Discussion is presented that includes possible medium-dependent nonsynchronicity of nucleophile desolvation and bond formation for the α-nucleophile.

Introduction

The origin of the α-effect, i.e., the enhanced reactivity of nucleophiles that have an unshared pair of electrons on the atom adjacent to the nucleophilic center, relative to a normal nucleophile of the same basicity, has been a source of continuing challenge to investigators since this phenomenon was brought to light by Edwards and Pearson.[2] The most popular general causes that have been advanced to account for the α-effect phenomenon are differential ground-state (GS) destabilization, transition-state (TS) stabilization, product stabilization, and solvent effects, while other possible specific origins include a transition state having aromatic or radicaloid character.[3−6] We have previously presented evidence in favor of TS stabilization,[7] and we have also described an unusual influence of solvent in α-effect systems,[8,9] but our work, in common with that of others, suffered from the fundamental deficiency that no quantitative data concerning ground-state energy levels was available. This information is particularly important as the solvent medium is systematically changed. In this paper, we present the first such pertinent evidence.

We reported in 1986 an unusual solvent effect: on changing the DMSO−water composition, the α-effect ($k^{\alpha-\mathrm{Nu}}/k^{\mathrm{normal-Nu}}$) for the reaction of *p*-nitrophenyl acetate (PNPA) with oximate as the α-Nu and aryloxide as normal-Nu exhibited a maximum at ca. 50 mol % DMSO.[8] More recently, we found a similar bell-shaped α-effect plot for the reaction of *p*-nitrophenyl diphenylphosphinate as a function of changing DMSO−H_2O mixtures.[10] However, a contrary result was reported with *o*-iodosylbenzoate as the α-nucleophile and *p*-chlorophenoxide as normal-nucleophile, in the reaction with PNPA, where *no maximum* in the α-effect−DMSO/H_2O profile was found, and in fact, the α-effect decreased steadily.[11] Clearly, more work on solvent effects was demanded.

It was shown some time ago that combining kinetic data with heats of solution could lead to a meaningful dissection in terms of GS versus TS stabilization/destabilization.[12] We report the first such results for an α-effect system in DMSO−H_2O, namely the determination of enthalpies of solution (ΔH_s) for the sodium salts of butane-2,3-dione monoximate (Ox^-) and *p*-chlorophenoxide (*p*-$ClPhO^-$) using a calorimetric technique and the activation parameters ($\Delta G^\ddagger$, $\Delta H^\ddagger$, and $T\Delta S^\ddagger$) in the

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[1] Permanent address: Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea.

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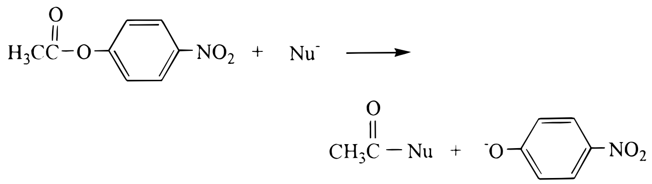
Scheme 1



Nu$^-$: *p*-ClPhO$^-$ (normal-Nu)

Ox$^-$ (α-Nu)

Solvent : 0, 10, 20, 30, … 80, 90 mole % DMSO in H_2O

Table 1. Enthalpies of Solutions (ΔH_s, kcal/mol) for Sodium Hydroxide, Sodium *p*-Chlorophenoxide (*p*-ClPhONa), and Sodium Butane-2,3-dione Monoximate (OxNa) in DMSO−H_2O Mixtures at 25.0 °C

	$\Delta H_{s,}$ kcal/mol		
mol % DMSO	NaOH[a]	*p*-ClPhONa[b]	OxNa[b]
0	−10.5	−9.12	−5.20
10	−10.4	−7.53	−2.98
20	−7.3	−6.27	−0.57
30	−5.6	−5.98	0.82
40	−3.7	−6.27	0.86
50	−3.4	−6.39	0.86
60	−2.7	−6.62	0.59
70	−2.1	−6.67	0.56
80	−1.5	−6.51	0.61
90	−0.8	−6.00	0.86

[a] Data taken from ref 13. [b] This work.

reaction of these nucleophiles with PNPA in DMSO−H_2O mixtures, Scheme 1.

Results

The enthalpies of solution (ΔH_s) for the sodium salts *p*-chlorophenoxide (*p*-ClPhONa) and oximate (OxNa) have been measured at 25.0 ± 0.1 °C in various DMSO−H_2O mixtures. The concentration range of the salts in a given solvent medium was $2-8 \times 10^{-3}$ M. No dependence of the molar enthalpy of solution on concentration was observed within this concentration range. The precision of the Tronac model 1250 calorimeter in typical measurement of enthalpies of solution (ΔH_s) on 2 calories was ±0.5%, while temperature control of ±0.0001 °C was maintained when a standard instrument with a 50 mL Dewar vessel was used. In Table 1 are presented ΔH_s values for the salts listed above together with the literature data for NaOH.[13a]

The transfer enthalpy for a given compound from one solvent to another ($\Delta\Delta H_{tr}$) is defined as the difference in ΔH_s in the two solvents. Thus:

$$\Delta\Delta H_{tr} = \Delta H_s(\text{in DMSO}-H_2O) - \Delta H_s(\text{in } H_2O) \quad (1)$$

The single ion transfer enthalpies from H_2O to DMSO−H_2O mixtures ($\Delta\Delta H_{tr}$) for *p*-ClPhO$^-$ and Ox$^-$ have been calculated from the measured ΔH_s values of sodium salts of these anions and the known data for Na$^+$,[13a] according to eqs 2 and 3.

$$\Delta\Delta H_{tr}(p\text{-ClPhO}^-) = \Delta\Delta H_{tr}(p\text{-ClPhONa}) - \Delta\Delta H_{tr}(\text{Na}^+) \quad (2)$$

$$\Delta\Delta H_{tr}(\text{Ox}^-) = \Delta\Delta H_{tr}(\text{OxNa}) - \Delta\Delta H_{tr}(\text{Na}^+) \quad (3)$$

In Table 2 are presented the transfer enthalpies ($\Delta\Delta H_{tr}$) from H_2O to DMSO−H_2O mixtures for the single ions *p*-ClPhO$^-$, Ox$^-$, and Na$^+$.

The observed rate constants (k_{obs}) of the reactions of PNPA with *p*-ClPhO$^-$ and Ox$^-$, present in exess, in various DMSO−H_2O mixtures were determined spectrophotometrically. All the reactions in the present system obeyed pseudo-first-order kinetics. Generally five different concentrations of nucleophilic solutions were used to obtain second-order rate constants from the slope of the plot of k_{obs} vs concentration of nucleophile, which showed negligible intercept indicating that the reaction with OH$^-$ or solvent did not occur to a significant extent. The correlation coefficient of the plot was usually higher than 0.9995 in all solvents studied. It is estimated from replicate runs that the uncertainty in any particular measured rate constant is less than ±3%. In Tables 3 and 4 are presented the second-order rate constants for the reactions of PNPA with *p*-ClPhO$^-$ and Ox$^-$ in DMSO−H_2O mixtures at 25.0, 35.0, and 45.0 °C. The magnitudes of the α-effect ($k^{\text{Ox}^-}/k^{p\text{-ClPhO}^-}$) values are presented in Table 5, and the activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $T\Delta S^{\ddagger}$) for the reactions of PNPA with *p*-ClPhO$^-$ and Ox$^-$ in various DMSO−H_2O mixtures are summarized in Tables 6 and 7, respectively.

Discussion

Dissection of Solvent Effect on Ground-State and Transition-State Contributions: Methodology.[12] In principle, a reaction pathway in a given solvent may be represented by a qualitative two-dimensional energy profile. Figure 1 shows such a profile for a reaction carried out in two different media, H_2O and a DMSO−H_2O mixture. In Figure 1, the standard free energy of the reactant, R, in H_2O is designated as $G_o{}^R$ and in the DMSO−H_2O mixture as $G_s{}^R$. The difference in free energies between the two solvents ($G_s{}^R - G_o{}^R$) is termed the transfer free energy $\delta G_{tr}{}^R$.

$$\delta G_{tr}{}^R = G_s{}^R - G_o{}^R \quad (4)$$

Similarly, for the transition state T one obtains

$$\delta G_{tr}{}^T = G_s{}^T - G_o{}^T \quad (5)$$

The difference in free energies of activation for the two solvents is designated $\delta\Delta G^{\ddagger}$, and from Figure 1 it is apparent that

$$\delta\Delta G^{\ddagger} = \Delta G_s{}^{\ddagger} - \Delta G_o{}^{\ddagger} = (G_s{}^T - G_s{}^R) - (G_o{}^T - G_o{}^R) \quad (6)$$

which simplifies to

$$\delta\Delta G^{\ddagger} = \delta G_{tr}{}^T - \delta G_{tr}{}^R \quad (7)$$

$\delta G_{tr}{}^T$ can be evaluated from the measurable transfer free energies of reactants ($\delta G_{tr}{}^R$) and the kinetic activation parameters ($\delta\Delta G^{\ddagger}$). The foregoing arguments apply

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Table 2. Transfer Enthalpies ($\Delta\Delta H_{tr}$, kcal/mol) from 0 to 90 mol % DMSO for Single Ions of Na^+, p-ClPhO$^-$, and Ox$^-$ at 25.0 °C

	$\Delta\Delta H_{tr}$, kcal/mol		
mol % DMSO	$Na^{+\,a}$	p-ClPhO$^{-\,b}$	Ox$^{-\,b}$
0	0	0	0
10	0.8	0.8	1.4
20	−0.5	3.3	5.1
30	−2.3	5.4	8.3
40	−3.9	6.7	9.9
50	−5.3	8.0	11.4
60	−6.1	8.6	11.9
70	−6.6	9.0	12.4
80	−6.9	9.5	12.7
90	−7.1	10.2	13.2

[a] Data taken from ref 13. [b] Calculated from calorimetric data using eqs 2 and 3.

Table 3. Second-Order Rate Constants (k, $M^{-1}\ s^{-1}$) for the Reaction of PNPA with p-ClPhO$^-$ in DMSO−H_2O Mixtures of Varying Composition at 25.0, 35.0, and 45.0 °C

	k, $M^{-1}\ s^{-1}$		
mol % DMSO	25.0 °C	35.0 °C	45.0 °C
0	0.685[a]	1.50	2.71
10	0.653		
20	0.760[a]	1.69	3.26
30	1.36		
40	2.86[a]	5.77	10.7
50	5.90[a]	11.1	21.7
60	13.6		
70	34.7[a]	60.0	120
80	94.8		
90	334[a]	560	935

[a] Data taken from ref 8.

Table 4. Second-Order Rate Constants (k, $M^{-1}\ s^{-1}$) for the Reaction of PNPA with Ox$^-$ in DMSO−H_2O Mixtures of Varying Composition at 25.0, 35.0, and 45.0 °C

	k, $M^{-1}\ s^{-1}$		
mol % DMSO	25.0 °C	35.0 °C	45.0 °C
0	65.8[a]	102	160
10	77.8		
20	130[a]	230	393
30	309		
40	740[a]	1250	1990
50	1680[a]	2750	4160
60	3850		
70	8200[a]	12 200	17 300
80	17 200		
90	40 500[a]	b	b

[a] Data taken from ref 8. [b] Rates were too fast to measure. Therfore, rate constants could not be measured at 35.0 and 45.0 °C; instead the following values and temperatures were determined: 28 000 $M^{-1}\ s^{-1}$ at 15.0 °C; 34 300 $M^{-1}\ s^{-1}$ at 20.0 °C; 50 800 $M^{-1}\ s^{-1}$ at 30.0 °C.

Table 5. Magnitude of the α-Effect ($k^{Ox^-}/k^{p\text{-ClPhO}^-}$) for the Reaction of PNPA with Ox$^-$ and p-ClPhO$^-$ in DMSO−H_2O Mixtures of Varying Composition at 25.0, 35.0, and 45.0 °C

	α-effect ($k^{Ox^-}/k^{p\text{-ClPhO}^-}$)		
mol % DMSO	25.0 °C	35.0 °C	45.0 °C
0	96	68	59
10	119		
20	183	136	121
30	227		
40	264	217	186
50	285	248	192
60	283		
70	236	203	144
80	181		
90	121	100[a]	83[a]

[a] Graphically extrapolated value.

Table 6. Activation Parameters (kcal/mol) for the Reaction of PNPA with p-ClPhO$^-$ in DMSO−H_2O Mixtures of Varying Composition at 25.0 °C

	kcal/mol		
mol % DMSO	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$
0	17.7	12.3	−5.4
20	17.7	13.1	−4.5
40	16.9	12.0	−4.9
50	16.5	11.7	−4.8
70	15.4	10.7	−4.7
90	14.1	9.1	−5.0

Table 7. Activation Parameters (kcal/mol) for the Reaction of PNPA with Ox$^-$ in DMSO−H_2O Mixtures of Varying Composition at 25.0 °C

	kcal/mol		
mol % DMSO	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$
0	15.0	8.0	−7.0
20	14.6	9.2	−5.4
40	13.6	8.6	−5.0
50	13.1	7.7	−5.4
70	12.2	6.4	−5.7
90	11.2	6.1	−5.1

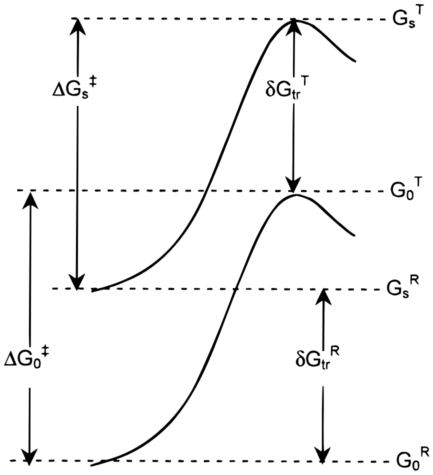

Figure 1. Illustration of relationship between the transfer free energies of reactants and the transition state and the free energies of activation for a reaction occurring in the two solvent systems.

equally to the derived thermodynamic functions, i.e., equations corresponding to δG_{tr}^R or δG_{tr}^T can readily be written for $\Delta\Delta H_{tr}^R$ or $\Delta\Delta H_{tr}^T$.

The purpose of this methodology is to dissect the relative contribution of the overall solvent effect on the GS and on the TS as the solvent composition is systematically changed from H_2O to 90 mol % DMSO and to understand the origin of the bell-shaped α-effect versus solvent composition plots that have frequently been reported in this and related systems.[8,10]

Ground-State Contribution. The enthalpy of solution data for sodium p-chlorophenoxide (p-ClPhONa) and sodium butane-2,3-dione monoximate (OxNa) are presented in Table 1 together with the data for sodium hydroxide in the literature.[13] The enthalpies of solution (ΔH_s) of both p-ClPhONa and OxNa are negative, or exothermic, except those for OxNa beyond ca. 20 mol % DMSO. ΔH_s values increase as the mol % DMSO in-

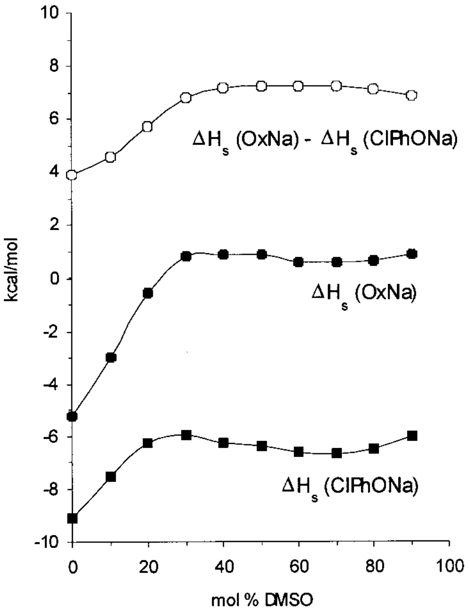

Figure 2. Plots of enthalpies of solution (ΔH_s) as a function of mol % DMSO for the sodium salts of p-ClPhO$^-$ and Ox$^-$ in DMSO$-$H$_2$O mixtures at 25.0 °C.

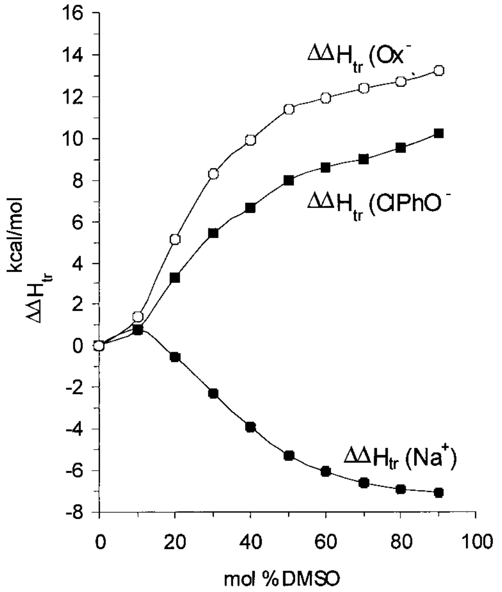

Figure 3. Plots of transfer enthalpies ($\Delta\Delta H_{tr}$) from H$_2$O to DMSO$-$H$_2$O mixtures as a function of mol % DMSO for the single ions Ox$^-$, p-ClPhO$^-$, and Na$^+$ at 25.0 °C.

creases in all cases. However, the increase in ΔH_s is most pronounced for NaOH and least pronounced for p-ClPhONa. In Figure 2 is plotted the variation of ΔH_s as a function of mol % DMSO for p-ClPhONa and OxNa. One can see that the ΔH_s value increases at first and reaches maximum as the DMSO concentration increases, close to 30 mol % DMSO, the overall increase for p-ClPhONa and OxNa being ca. 3 and 6 kcal/mol, respectively. Importantly, ΔH_s appears to be almost constant beyond 30 mol % DMSO for both salts. Such a behavior, showing a maximum ΔH_s value near 30 mol % DMSO, is not specific to the present system but, rather, is consistent with many unusual phenomena observed near 30$-$40 mol % DMSO, such as a maximum in energy$-$volume coefficient,[14] viscosity and density,[15] and a minimum in freezing point,[16] adiabatic compressibility,[17] and excess free energy of mixing[18] of DMSO with H$_2$O.

H-bonding interactions are believed to be the most important for anionic solutes in H$_2$O. Since DMSO forms strong H-bonding with H$_2$O, addition of DMSO to H$_2$O would decrease the concentration of free H$_2$O molecules,[19,20] and this would diminish the extent of H-bonding between free H$_2$O molecules and the anions of p-ClPhO$^-$ and Ox$^-$. Therefore, one can attribute the increased ΔH_s values of these salts to a decrease in H-bonding interactions over the solvent range 0$-$30 mol % DMSO. When the DMSO concentration exceeds 30 mol %, the H-bonding interaction with H$_2$O molecules becomes diminished, but importantly, DMSO plays an increasingly important role in solvent$-$solute interactions, e.g., through charge dispersion or mutual polarizability interaction.[19,20] Since the negative end of the dipole in DMSO is exposed while the positive one is buried within the molecule, DMSO is ineffective in solvating anions but can strongly solvate cations through ion$-$dipole interactions.[19,20] Therefore, small variations in ΔH_s values for the sodium salts of p-ClPhO$^-$ and Ox$^-$ beyond 30 mol % DMSO likely originate from opposite influences, i.e., an unfavorable interaction between the solvent and the anionic solutes and a favorable one between the solvent and the Na$^+$ cation, as the mol % DMSO increases.

The above argument gains support from the transfer enthalpies from H$_2$O to DMSO$-$H$_2$O mixtures ($\Delta\Delta H_{tr}$) for single ions, Na$^+$, p-ClPhO$^-$, and Ox$^-$. $\Delta\Delta H_{tr}$ values for p-ClPhO$^-$ and Ox$^-$ can be calculated using the known data for Na$^+$,[13a] via the extrathermodynamic assumption,[13] $\Delta\Delta H_{tr}(\mathrm{Ph_4As^+}) = \Delta\Delta H_{tr}(\mathrm{Ph_4B^-})$. Hence, $\Delta\Delta H_{tr}$(p-ClPhO$^-$) = $\Delta\Delta H_{tr}$(p-ClPhONa) $-$ $\Delta\Delta H_{tr}$(Na$^+$) and $\Delta\Delta H_{tr}$(Ox$^-$) = $\Delta\Delta H_{tr}$(OxNa) $-$ $\Delta\Delta H_{tr}$(Na$^+$), as stated in the Results. The $\Delta\Delta H_{tr}$ values for the single ions obtained in this way are summarized in Table 2 and illustrated graphically in Figure 3. The $\Delta\Delta H_{tr}$ value for Na$^+$ decreases (e.g., -7.1 kcal/mol upon solvent change from H$_2$O to 90 mol % DMSO), indicating that ion$-$dipole interactions between the cation and the negative end of the dipole in DMSO become stronger as the DMSO content increases. The $\Delta\Delta H_{tr}$ values for the anions exhibit a steep increase as the DMSO content increases up to near 30$-$40 mol %. This increase in $\Delta\Delta H_{tr}$ clearly indicates that these anions become strongly desolvated upon the solvent change, due to reduced H-bonding interaction between the anions and H$_2$O molecules in the H$_2$O-rich media. However, the degree of desolvation is not so steep in the DMSO-rich media, probably due to the combination of the increase in charge dispersion and the decrease in H-bonding interactions. In contrast, $\Delta\Delta H_{tr}$ for OH$^-$ exhibits a steeper dependence than Ox$^-$ or p-ClPhO$^-$ in the DMSO-rich region,[13] which is in accord with nonpolarizable nature of the small "hard" anion.

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The enthalpy of solution difference between Ox^- and p-$ClPhO^-$ ($\Delta\Delta H_s$) can be calculated using the following relationship

$$\Delta\Delta H_s = \Delta H_s(\mathrm{OxNa}) - \Delta H_s(p\text{-}\mathrm{ClPhONa}) \qquad (8)$$

since the enthalpy of solution of Na^+ cancels. The results in Figure 2 show that $\Delta\Delta H_s$ increases over 3 kcal/mol upon addition of DMSO up to nearly 50 mol % DMSO and remains almost constant beyond that point: thus, Ox^- experiences much greater desolvation than p-$ClPhO^-$ upon addition of DMSO to the medium.

Interestingly, the increasing trend in $\Delta\Delta H_s$ values up to 50 mol % DMSO parallels the increasing α-effect trend observed over that medium range. Thus, the greatly increasing desolvation of Ox^- over p-$ClPhO^-$ appears to be the dominant factor in the increasing α-effect trend up to 50 mol % DMSO. However, if the difference in the GS desolvation were mainly responsible for the α-effect throughout the whole range of DMSO−H_2O mixtures studied, one would have expected the α-effect to remain constant, at the maximum value, in the DMSO-rich region. In fact, the magnitude of the α-effect decreases beyond 50 mol % DMSO in this and related systems.[8,10] Since the pK_a values of p-$ClPhO^-$ and Ox^- change in parallel manner upon addition of DMSO to the medium;[10] therefore, the bell-shaped α-effect cannot be due to differential change in pK_a values of the two nucleophiles, and an additional factor must be operating in the DMSO-rich region.

Transition-State Contribution. To aid in the investigation of the effect of solvent on the TS, activation parameters have been determined from rate constants obtained at 25.0, 35.0, and 45.0 °C for the reactions of PNPA with Ox^- and p-$ClPhO^-$ in DMSO−H_2O mixtures. In Tables 3 and 4 are summarized the rate constant data. The effect of temperature on the reaction rates is larger for the slower reaction (p-$ClPhO^-$ with PNPA) than for the faster one (Ox^- with PNPA). For example, the rate accelerations in H_2O at 35.0 and 45.0 °C compared to those at 25.0 °C, k(35.0 °C)/k(25.0 °C) and k(45.0 °C)/k(25.0 °C), are 2.2 and 4.0 for p-$ClPhO^-$ and 1.6 and 2.4 for Ox^-, respectively. This differential temperature effect on the reaction rate is similar throughout the solvent range studied. Consequently, the magnitude of the α-effect becomes smaller on increasing the reaction temperature over the whole solvent range, which is in accord with the reactivity-selectivity principle.[21] However, the α-effect trend obtained from the reactions run at 35.0 and 45.0 °C shows the same general characteristics as that obtained at 25.0 °C, i.e., a bell-shaped plot with maximum located near 50 mol % DMSO (Figure 4).

The activation parameters for the reaction of PNPA with Ox^- and p-$ClPhO^-$ are summarized in Tables 6 and 7 and illustrated graphically in Figure 5 as a function of mol % DMSO. In accord with the rate data, the free energy of activation ($\Delta G^‡$) decreases as the DMSO content increases, by about 4 kcal/mol for both the Ox^- and p-$ClPhO^-$ systems upon the solvent change from 0 to 90 mol % DMSO. Interestingly, the entropy term ($T\Delta S^‡$) increases initially by 1−1.5 kcal/mol but remains almost constant beyond 20 mol % DMSO, for both the Ox^- and p-$ClPhO^-$ systems. The enthalpy of activation ($\Delta H^‡$) exhibits an initial increase upon the solvent change from 0 to 20 mol % DMSO for both systems. However, unlike the entropy term, $\Delta H^‡$ decreases for both systems upon further addition of DMSO, suggesting that beyond 20 mol % DMSO the reaction rate is mainly governed by the enthalpy term.

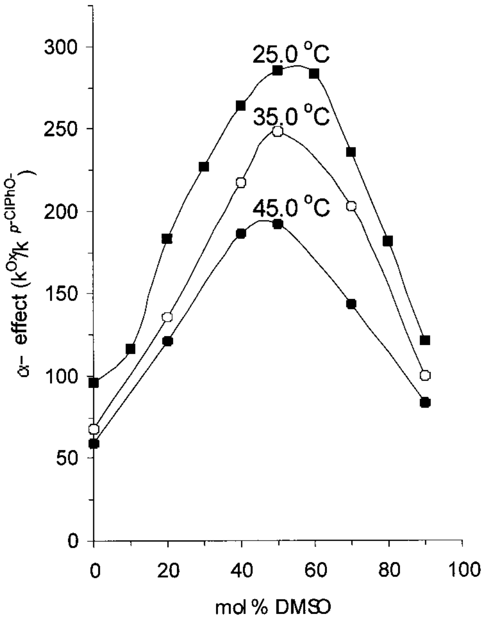

Figure 4. Plots of the α-effect ($k^{Ox^-}/k^{p\text{-}ClPhO^-}$) as a function of mol % DMSO for the reaction of PNPA with p-$ClPhO^-$ and Ox^- at 25.0, 35.0, and 45.0 °C.

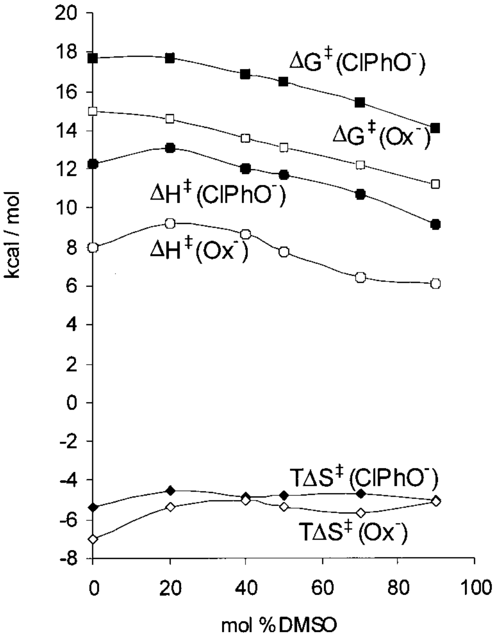

Figure 5. Comparative plots of activation parameters ($\Delta G^‡$, $\Delta H^‡$, and $T\Delta S^‡$) as a function of mol % DMSO for the reaction of PNPA with p-$ClPhO^-$ and Ox^- at 25.0 °C.

A noteworthy observation is that the decrease in $\Delta H^‡$ for the p-$ClPhO^-$ system is steeper than that for the Ox^- system in the medium range 50−90 mol % DMSO (Figure 5), which suggests that the TS for the p-$ClPhO^-$ system becomes more stabilized than the one for the Ox^- system in the DMSO-rich region. One possibility is that this stabilization in the DMSO-rich region results from a greater polarizability of p-$ClPhO^-$ as compared to Ox^-.

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In that case, the differential trend in $\Delta H^{\ddagger}$ between the Ox^- and *p*-$ClPhO^-$ systems beyond 50 mol % DMSO could account for the decreasing α-effect in the DMSO-rich region (Figure 4).

In discussion of the origin of the α-effect in the *p*-nitrophenyldiphenyl phosphinate (PNPDPP) system[10] we found that the TS for the Ox^- reaction is significantly imbalanced[22] as a result of nonsynchronicity[23] in desolvation and bond formation. The key point here is that the extent of nonsynchronicity for the Ox^- reaction varies as the solvent composition varies, whereas it is constant for the *p*-$ClPhO^-$ reaction.[10] While a definitive analysis of the degree of nonsynchronicity in the current system awaits quantitative treatment[23] the similarity in the bell-shaped α-effect plot versus DMSO−H_2O composition, is suggestive of having a similar origin.

In conclusion, our study has shown that differential ground-state desolvation for the α- and the normal-nucleophile is the main factor responsible for the increasing α-effect trend in the H_2O-rich media (up to ca. 50 mol % DMSO). On the other hand, differential stabilization of the transition state in the DMSO-rich media contributes to the decreasing α-effect over that range. Clearly, a single factor such as GS destabilization, or even TS stabilization, is not by itself sufficient to explain origin of the α-effect and its variation with solvent composition in the DMSO−H_2O system.

Extension of the present work to related compounds, with different eletrophilic centers, as well as a full analysis of potential nonsynchronicity in these systems, is underway.

Experimental Section

Materials. PNPA, *p*-chlorophenol (*p*-ClPhOH), and butane-2,3-dione monoxime (OxH) were obtained from Aldrich and recrystallized before use. Sodium butane-2,3-dione monoximate (OxNa) was prepared by mixing equivalent amounts of sodium ethoxide solution and OxH. Typically, 10.51 g of OxH (103.9 mmol) was placed in a 250 mL round-bottom flask and 100.0 mL of 1.039 M of sodium ethoxide solution was added. The mixture was stirred for 1 h under nitrogen, the bulk solvent removed on a rotary evaporator and the residue was dried overnight under high vacuum (mp 234 °C dec). A similar method was used for the preparation of sodium *p*-chlorophenoxide (*p*-ClPhONa, mp 305−306 °C).

Doubly glass distilled water was boiled and cooled under nitrogen just before use. DMSO was refluxed and distilled over CaH_2 at reduced pressure (64−66 °C at 6−7 mmHg) and stored under nitrogen. DMSO−H_2O mixtures of varying compositions (mol %) were prepared by adding the calculated weight of H_2O to the weighed dry DMSO in a flask. The mixed solvents were stored under nitrogen but no longer than 2 days.

Calorimetric Studies. A Tronac 1250 calorimeter was used for measurement of enthalpies of solution. Depending on the magnitude of enthalpies of solution, generally 20− 80 mg of an accurately weighed sample was inserted in a ca. 1.5 cm diameter fragile glass ampule, and the ampule neck was sealed using a micro torch. The ampule was placed in the ampule holder, and the Dewar vessel containing 50.0 mL of solvent was assembled to the calorimeter header. The header was immersed in the water bath, whose temperature was controlled at 25.000 ± 0.003 °C. The temperature of the solvent in the dewar vessel was adjusted to equilibrate using a micro electric heater and a mechanical stirrer provided on the header. Once the electric heater was turned off, the temperature increased very slowly due to the mechanical stirrer. From this point, an electrical calibration was done to determine the initial heat capacity of the system. When the temperature reached 25.0 °C, the ampule was broken using the breaker located on the header and was followed by a final electrical calibration to determine the final heat capacity of the system. The heat evolved by dissolution of the sample salt (Q_s) was calculated by multiplying the mean heat capacity (C_p) of the system and the temperature change (ΔT) due to the sample dissolution, $Q_s = C_p\Delta T$. The enthalpy of solution (ΔH_s) was obtained by dividing Q_s by the number of moles of sample used, i.e., $\Delta H_s = Q_s/$(number of moles of sample).

Kinetics. The kinetic study was performed using a Perkin-Elmer 552 spectrophotometer for the slow reactions ($t_{1/2} > 10$ s) or a Can-Tech stopped-flow spectrophotometer for the fast reactions ($t_{1/2} \leq 10$ s). The temperature inside the 10 mm quarts cells in the UV−vis spectrophotometer and the fluid handling system of the stopped-flow apparatus could be set anywhere between 10.0 ± 0.1 and 45.0 ± 0.1 °C.

All the kinetic studies were performed under pseudo-first-order conditions in which the concentration of nucleophile is generally 20-fold but at least 10-fold greater than the substrate concentration. Nucleophile stock solutions of ca. 0.2 M were prepared in 25.0 mL volumetric flasks in a glovebox under a nitrogen atmosphere by adding 2 equiv of *p*-chlorophenol or butane-2,3-dione monoxime to 1 equiv of base in order to achieve self-buffered solutions. For reasons of solubility, above 40 mol % DMSO Me_4NOH was used as the base, while below 40 mol % NaOH could be used. The reactions were followed by monitoring the appearance of *p*-nitrophenoxide ion at the appropriate fixed wavelength (λ_{max}: 400−432 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_∞ 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 the kinetic method were reported previously.[24]

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