DOI: 10.1002/chem.200801534

Effects on the Reactivity by Changing the Electrophilic Center from C=O to C=S: Contrasting Reactivity of Hydroxide, *p*-Chlorophenoxide, and Butan-2,3-dione Monoximate in DMSO/H_2O Mixtures

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Abstract: Second-order rate constants have been measured spectrophotometrically for the reactions of *O*-*p*-nitrophenyl thionobenzoate (**1**, PNPTB) with HO^-, butan-2,3-dione monoximate (Ox^-, α-nucleophile), and *p*-chlorophenoxide (*p*-$ClPhO^-$, normal nucleophile) in DMSO/H_2O of varying mixtures at (25.0 ± 0.1) °C. Reactivity of these nucleophiles significantly increases with increasing DMSO content. HO^- is less reactive than *p*-$ClPhO^-$ toward **1** up to 70 mol % DMSO although HO^- is over six pK_a units more basic in these media. Ox^- is more reactive than *p*-$ClPhO^-$ in all media studied, indicating that the α-effect is in effect. The magnitude of the α-effect (i.e., $k_{Ox^-}/k_{p\text{-ClPhO}^-}$) increases with the DMSO content up to 50 mol % DMSO and decreases beyond that point. However, the dependency of the α-effect profile on the solvent for reactions of **1** contrasts to that reported previously for the corresponding reactions of *p*-nitrophenyl benzoate (**2**, PNPB); reactions of **1** result in much smaller α-effects than those of **2**. Breakdown of the α-effect into ground-state (GS) and transition-state (TS) effects shows that the GS effect is not responsible for the α-effect across the solvent mixtures. The role of the solvent has been discussed on the basis of the bell-shaped α-effect profiles found in the current study as well as in our previous studies, that is, a GS effect in the H_2O-rich region through H-bonding interactions and a TS effect in the DMSO-rich media through mutual polarizability interactions.

Keywords: electrophilic addition · enthalpy of solution · kinetics · medium effect · polarizability

Introduction

Nucleophiles possessing an lone pair of electrons at the atom α to the nucleophilic center have been termed α-nucleophiles and exhibit enhanced reactivity compared with normal nucleophiles of similar basicity.[1] Numerous studies have been performed to investigate the cause of the enhanced reactivity (i.e., the α-effect) observed for α-nucleophiles.[2–22] The most prevalent theories on the α-effect phenomenon include ground-state (GS) destabilization, transition-state (TS) stabilization, thermodynamic stabilization of products, and solvent effects.[2–11] However, none of these hypotheses is able to explain the α-effect phenomenon.[2] Particularly, controversial are the hypotheses concerning solvent effect on the α-effect.[2a,8a,12–22]

The solvent effect of the α-effect has been suggested to be unimportant on the basis of the observation that the magnitude of the α-effect is similar for reactions performed in H_2O and in neat organic solvents (e.g., MeCN and toluene).[8a,12] Also controversial have been results of gas-phase studies and theoretical calculations into the origin of the α-effect.[13] In 1983, DePuy et al. performed gas-phase reactions of methyl formate with HOO^- and HO^- (as the reference nucleophile) and found that HOO^- does not exhibit any enhanced reactivity.[13a] Accordingly, the α-effect observed for various reactions with HOO^- in aqueous solutions was attributed to a solvent effect.[13] By contrast, α-nucleophiles have been reported to be intrinsically more reactive than normal nucleophiles of similar basicity in gas-phase reactions (e.g., HOO^- vs. EtO^-) again with methyl formate.[14] According to recent gas-phase studies including high-level theoretical calculations, α-nucleophiles exhibit

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801534.

lower activation energies than normal nucleophiles of similar basicity in gas-phase S_N2 reactions.[14–16] Thus, solvent effects on the α-effect have been suggested to be unimportant.[14–16]

We have found remarkable solvent effects on the α-effect in nucleophilic substitution reactions at various electrophilic centers.[17–22] In 1986, we initiated a systematic study to investigate solvent effects on the α-effect.[17a] Our first study showed a significant solvent effect on the α-effect for reactions of *p*-nitrophenyl acetate (PNPA) with butan-2,3-dione monoximate (Ox^-, α-nucleophile) compared with *p*-chlorophenoxide (*p*-$ClPhO^-$, normal nucleophile) in $DMSO/H_2O$ of varying compositions: the α-effect ($k_{Ox^-}/k_{p\text{-ClPhO}^-}$) increases with increasing DMSO content in the medium up to about 50 mol% DMSO and then decreases thereafter, that is, a bell-shaped profile.[17] Similar bell-shaped α-effect profiles have been obtained for the corresponding reactions of aryl acetates,[18] *p*-nitrophenyl benzoate,[19] *p*-nitrophenyl diphenylphosphinate,[20a] and *p*-nitrophenyl benzenesulfonate,[20b] although the magnitude of the α-effect is highly dependent on the nature of the electrophilic center of the substrates (C=O, P=O, and SO_2).[20]

The basicity of Ox^- and *p*-$ClPhO^-$ in $DMSO/H_2O$ mixtures has been found to increase in almost parallel manner with increasing mol% DMSO, indicating that the bell-shaped α-effect profiles are not due to a difference in basicity of the two nucleophiles.[20a] Our calorimetric study for the two nucleophiles has shown that the difference in enthalpy of solution between Ox^-Na^+ and *p*-$ClPhO^-Na^+$ (i.e., $\Delta\Delta H_{sol} = \Delta H_{sol}^{Ox^-Na^+} - \Delta H_{sol}^{p\text{-ClPhO}^-Na^+}$) increases up to 30–40 mol% DMSO and then remains nearly unchanged upon further addition of DMSO.[17b] Breakdown of the α-effect into GS and TS contributions through combination of the kinetic data with enthalpy of solution (ΔH_{sol}) data has enabled us to conclude that desolvation of the α-nucleophile Ox^- is mainly responsible for the increasing α-effect up to 50 mol% DMSO (i.e., GS effect) while differential stabilization of TS contributes to the decreasing α-effect in the DMSO-rich solvent mixtures.[17b]

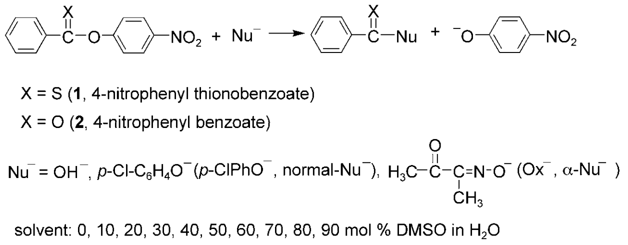
A remarkable GS effect on the α-effect has been found for reactions of *S*-*p*-nitrophenyl thioacetate (PNPTA) with Ox^- and *p*-$ClPhO^-$ in $DMSO/H_2O$.[22] The α-effect for the PNPTA system increases as the mol% DMSO increases up to 30–40 mol% and then remains nearly constant beyond that point.[22] Consequently, the α-effect trend in the PNPTA system is equal to the difference in enthalpy of solution between Ox^- and *p*-$ClPhO^-$ ($\Delta\Delta H_{sol}$), indicating clearly that the differential GS desolvation between the two nucleophiles is largely responsible for the α-effect profile over the whole medium range studied.[22]

Table 1. Summary of second-order rate constants for reactions of **1** (and **2** in parentheses) with Ox^-, *p*-$ClPhO^-$ and HO^- in $DMSO/H_2O$ of varying composition at (25.0 ± 0.1) °C.

Mol% DMSO	k_{Ox^-} [$M^{-1}s^{-1}$]		$k_{p\text{-ClPhO}^-}$ [$M^{-1}s^{-1}$]		k_{HO^-} [$M^{-1}s^{-1}$]		$k_{Ox^-}/k_{p\text{-ClPhO}^-}$	
0	48.9	(22.5)[a]	1.53	(0.255)[a]	0.470	(4.20)	32	(88)[a]
10	102	(20.0)[a]	2.20	(0.144)[a]	0.750	(6.40)	46	(139)[a]
20	254	(34.2)[a]	3.91	(0.185)[a]	1.62	(13.4)	65	(185)[a]
30	786	(75.7)[a]	9.57	(0.347)[a]	4.7	(34.8)	82	(218)[a]
40	2560	(186)[a]	25.4	(0.814)[a]	15.8	(88.0)	101	(229)[a]
50	7790	(455)[a]	63.8	(2.21)[a]	51.1	(251)	122	(206)[a]
60	20700	(1070)[a]	186	(5.73)[a]	159	(722)	111	(187)[a]
70	52300	(2360)[a]	511	(15.5)[a]	502	(2010)	102	(152)[a]
80	127000	(5360)[a]	1470	(44.8)[a]	1790	(6850)	86	(120)[a]
90	–	(11700)[a]	–	(162)[a]	–	(39300)	–	(72)[a]

[a] Data for the reactions of **2** were taken from ref. [19].

We have extended our study to reactions of the thiono ester *O*-*p*-nitrophenyl thionobenzoate (**1**, PNPTB) with HO^-, Ox^- and *p*-$ClPhO^-$ in $DMSO/H_2O$ (Scheme 1). The kinetic data have been compared with those for the corresponding reactions of *p*-nitrophenyl benzoate (**2**, PNPB) to examine the effect of modification of the electrophilic center from a C=O bond (**2**) to a polarizable C=S bond (**1**) on reactivity and the α-effect.



Scheme 1.

Results and Discussion

The kinetic study was performed under pseudo-first-order conditions with the concentration of nucleophile in excess over the substrate concentration. All reactions obeyed first-order kinetics with quantitative liberation of *p*-nitrophenoxide ion. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The plots of k_{obsd} versus nucleophile concentration were linear passing through the origin. Second-order rate constants have been determined from the slope of the linear plots and summarized in Table 1. It is estimated from additional runs that the uncertainty in the rate constants is less than ±3%. Detailed kinetic conditions and data are summarized in the Supporting Information.

Effect of medium on reactivity: Table 1 and Figure 1 show that the reactivity of the nucleophiles toward both **1** and **2** increases as the DMSO content increases. It is also seen for **1**, Ox^- is much more reactive than *p*-$ClPhO^-$ or HO^- in all solvents studied, indicating that a sizable α-effect is operative for the reactions of **1**. Interestingly, HO^- is less reactive than p-$ClPhO^-$ toward **1** up to about 70 mol% DMSO, although the former is over six pK_a units more basic than the latter in these media. In contrast, as shown in Figure 1 for the corresponding reactions of **2**, HO^- exhibits much higher reactivity than p-$ClPhO^-$, indicating that the unusual reactivity of HO^- is limited to the reactions of **1**.

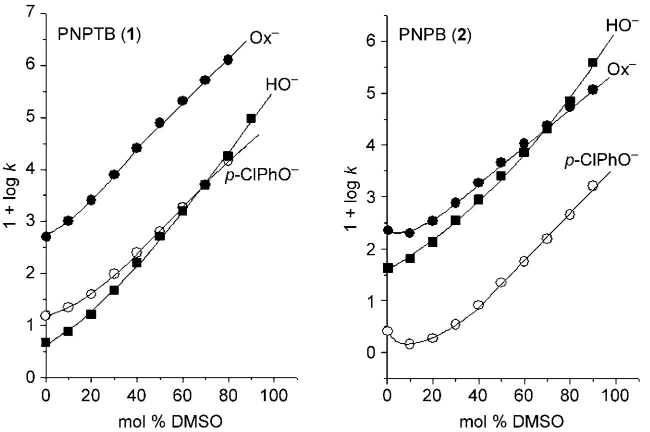


Figure 1. Plots of the logarithmic second-order rate constants versus mol% DMSO for the reaction of O-p-nitrophenyl thionobenzoate (**1**) and p-nitrophenyl benzoate (**2**) with Ox^-, p-$ClPhO^-$ and HO^- at (25.0 ± 0.1) °C.

The effect of the medium on the reactivity is illustrated in a different manner in Figure 2 (PNPTB), which shows the relative rate constants, that is, the ratio of the second-order rate constant in $DMSO/H_2O$ over the corresponding rate constant in H_2O, $k^{\mathrm{DMSO/H_2O}}/k^{\mathrm{H_2O}}$, as a function of mol% DMSO. It is apparent that Ox^- exhibits larger relative rate constants than p-$ClPhO^-$, which appears to be mainly a reflection of the GS energies of the nucleophiles. We have shown that Ox^- is more destabilized than p-$ClPhO^-$ as the DMSO content in the medium increases.[17b] Interestingly, HO^- shows smaller relative rate constants than Ox^- up to 60 mol% DMSO for the reactions of **1** although the degree of GS desolvation on addition of DMSO is more significant for HO^- than for Ox^-. A contrasting result is demonstrated for the corresponding reactions of **2**. As shown in Figure 2 (PNPB), HO^- exhibits significantly larger relative rate constants than Ox^- in all solvent compositions.

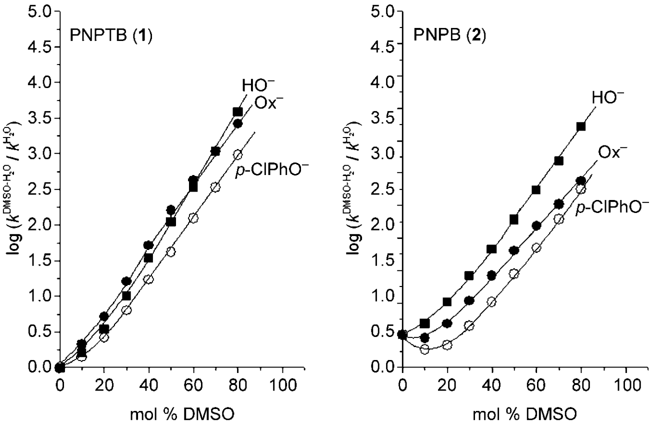


Figure 2. Plots of logarithmic relative rate constants, $\log k^{\mathrm{DMSO/H_2O}}/k^{\mathrm{H_2O}}$, versus mol% DMSO for reactions of **1** and **2** with Ox^-, p-$ClPhO^-$ and HO^- at (25.0 ± 0.1) °C.

The enthalpy of transfer from H_2O to $DMSO/H_2O$ for a nucleophile, which can be expressed as $\Delta\Delta H_{tr} = \Delta H_{sol}^{\mathrm{DMSO/H_2O}} - \Delta H_{sol}^{\mathrm{H_2O}}$, represents the degree of desolvation of the nucleophile upon changing the medium from H_2O to $DMSO/H_2O$.[17b] Figure 3 illustrates the relationship between $\Delta\Delta H_{tr}$ and the relative reactivity for the reactions of **1** with Ox^-, p-$ClPhO^-$ and HO^-. It is seen that logarithmic relative rate constants for the three nucleophiles follow a similar trend in the region where $\Delta\Delta H_{tr} < 5$ kcal mol^{-1}, indicating that the effect of GS desolvation on reactivity is similar for the three nucleophiles in that region. However, in the region where $\Delta\Delta H_{tr} > 5$ kcal mol^{-1}, p-$ClPhO^-$ exhibits the largest while HO^- the smallest relative rate constant. This result indicates that GS desolvation on addition of DMSO cannot be solely responsible for the increasing relative rate constants. Accordingly, differential stabilization of TS on addition of DMSO to the medium is considered to contribute to the increasing rate constants in the reactions of **1**. The fact that p-$ClPhO^-$ exhibits the largest relative reactivity where $\Delta\Delta H_{tr} > 5$ kcal mol^{-1}, while HO^- is subject to the smallest rate enhancement, shows that TS stabilization on addition of DMSO is most significant for p-$ClPhO^-$ but least for HO^-.

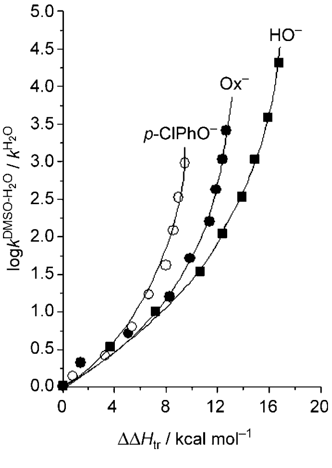


Figure 3. Plots of the logarithmic relative rate constants, $\log k^{\mathrm{DMSO/H_2O}}/k^{\mathrm{H_2O}}$ versus $\Delta\Delta H_{tr}$ for the reaction of **1** with Ox^-, p-$ClPhO^-$ and HO^- at (25.0 ± 0.1) °C. The $\Delta\Delta H_{tr}$ data were taken from ref. [17b].

Effect of medium on the α-effect: As shown in Figure 1, Ox^- is more reactive than p-$ClPhO^-$ toward **1** throughout the $DMSO/H_2O$ solvent region. The α-effect for the current reactions of **1** is illustrated in Figure 4 as a function of mol% DMSO together with the one reported previously for the corresponding reactions of **2** for comparison.[19] Figure 4 clearly demonstrates a solvent composition dependent α-

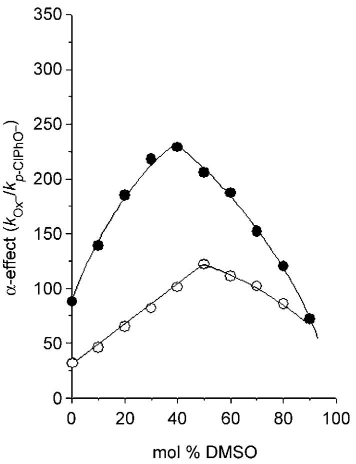


Figure 4. Plots of the α-effect ($k_{Ox^-}/k_{p\text{-ClPhO}^-}$) versus mol % DMSO for reactions of **1** with Ox^- and p-ClPhO$^-$ (○) and **2** with Ox^- and p-ClPhO$^-$ (●) at (25.0 ± 0.1) °C.

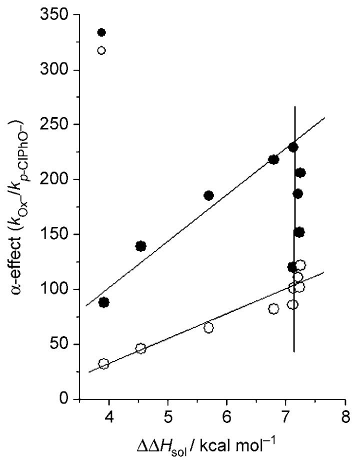


Figure 5. Plots for the α-effect behavior of **1** (○) and **2** (●), as a function of the differential enthalpy of solution of Ox^- versus p-ClPhO$^-$ in DMSO/H$_2$O mixtures. The break in the plot occurs at 40 mol % DMSO. Data for $\Delta\Delta H_{sol}$ were taken from ref. [17b].

effect for the reactions of **1** and **2**. The α-effect for both systems increases with increasing the DMSO content in the medium up to 40 or 50 mol % DMSO, and then decreases upon further increase in mol % DMSO. However, the shape and magnitude of the α-effect profiles are contrasting, that is, **1** exhibits smaller α-effect than **2** and the increase (or decrease) in the α-effect on changing the medium composition is less significant for **1** than for **2**.

Dissection of the α-effect into GS and TS effects can be accomplished through combination of the kinetic data with enthalpy of solution (ΔH_{sol}) data reported previously by our group.[17b]

It was shown that while ΔH_{sol} for Ox^-Na^+ greatly exceeds that for p-ClPhO$^-$Na$^+$ over the entire range of DMSO/H$_2$O solvent composition, the difference in enthalpy of solution for Ox^- and p-ClPhO$^-$ (i.e., $\Delta\Delta H_{sol} = \Delta H_{sol}^{Ox^-Na^+} - \Delta H_{sol}^{p\text{-ClPhO}^-Na^+}$) increases up to near 40 mol % DMSO and then remains nearly constant upon further addition of DMSO.[17b] Thus, if $\Delta\Delta H_{sol}$ (i.e., the difference in GS energy between Ox^- and p-ClPhO$^-$) were responsible for the α-effect, the α-effect should increase up to near 40 mol % DMSO and then remain nearly constant beyond that point. Besides, one might expect that reactions of **1** and **2** should result in a similar α-effect in magnitude, since $\Delta\Delta H_{sol}$ is constant for Ox^- and p-ClPhO$^-$ for the two systems. However, the α-effect shown in Figure 4 increases up to 40 or 50 mol % DMSO and then decreases as the DMSO content in the medium increases further. Thus, the current results indicate that GS effect (i.e., $\Delta\Delta H_{sol}$) cannot solely be responsible for the α-effect found for the reactions of **2**.

The above argument can be further supported by Figure 5, which shows that the magnitude of the α-effect increases linearly with increasing $\Delta\Delta H_{sol}$ up to about 40 or 50 mol % DMSO but thereafter the α-effect becomes independent of $\Delta\Delta H_{sol}$. This result indicates that GS effect could be partially responsible for the increasing α-effect up to 40 or 50 mol % DMSO but clearly not for the decreasing α-effect in the DMSO-rich region. It is also noted that the α-effect for reactions of **1** exhibits lower sensitivity to $\Delta\Delta H_{sol}$ than that for **2** up to near $\Delta\Delta H_{sol} = 7$ kcal mol^{-1}. As well **1** exhibits much smaller variation in the magnitude of the α-effect at $\Delta\Delta H_{sol} = \approx 7$ kcal mol^{-1}, than **2**. Thus, one can conclude that another effect than GS contributes to the contrasting α-effect profiles shown in Figure 4. This is considered below.

Polarizability effect on the α-effect: Different studies have shown that the contrasting α-effect found for the reactions of **1** and **2** is unlikely due to a difference in the reaction mechanism. We have recently shown that reactions of aryl benzoates including **2** with three representative anionic nucleophiles (i.e., HO$^-$, CN$^-$ and N$_3^-$) proceed through a stepwise mechanism.[23] Alkaline hydrolysis of **1** has also been reported to proceed through a stepwise mechanism.[24] Besides, studies on reactions of **1** and **2** with primary amines have shown that the aminolysis of these esters proceeds through the same stepwise mechanism.[25]

The major factor influencing reactivities in the present system is polarizability. Thus, enhanced polarizability of the thiono ester compared with its oxygen analogue is considered to be responsible for the contrasting α-effect between the two systems, since replacing the C=O bond in **2** by C=S is accompanied by a significant increase in polarizability.[26] The enhanced polarizability of the C=S bond in **1** is well reflected in the ^{13}C NMR chemical shift of the thiono carbonyl carbon. The chemical shifts are $\delta = 163.8$ ppm for the carbonyl carbon in **2** and 209.8 ppm for the thio carbonyl carbon in **1**, that is, a 46 ppm downfield shift in the ^{13}C NMR.[26] This is in good agreement with the literature value 30–50 ppm downfield shift reported for various sulfur compounds compared with the corresponding oxygen analogues.[27] In addition to ^{13}C NMR spectroscopy, significant deshielding influences have been observed in the ^{1}H NMR and ^{19}F NMR chemical shifts for a series of thionyl acid fluorides, RC(S)F.[28] Such a deshielding effect is not surprising since an electron deficiency on the thio carbonyl carbon would be expected to result from inefficient orbital overlap and/or the ability of sulfur to stabilize a negative charge in the substrate by distributing the electron cloud through the 3d orbitals.

Consequently, one might expect a greater reactivity of a nucleophile at the electrophilic center of **1** compared with **2**. In fact, as shown in Figure 6, the relative reactivity of **1** to **2** (i.e., $k_{C=S}/k_{C=O}$) for the reactions with p-ClPhO$^-$ and Ox$^-$ is much larger than unity and it increases with increasing mol% DMSO. In contrast, the thiono ester is less reactive than its oxygen analogue toward HO$^-$ ($k_{C=S}/k_{C=O} = 0.11$–0.26) in all solvent compositions, indicating that the reactivity of the polarizable **1** is strongly dependent on the nature of the nucleophiles.

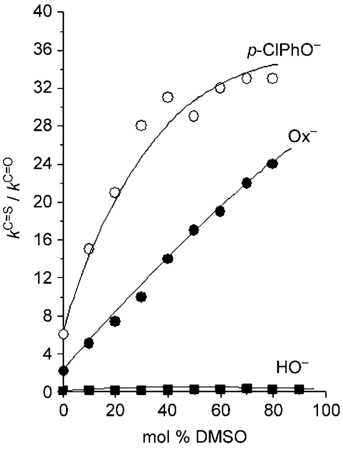
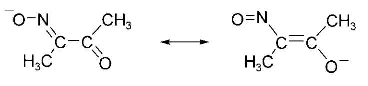


Figure 6. Plots of the relative reactivity of **1** to **2**, $k_{C=S}/k_{C=O}$ versus mol% DMSO. Note that $k_{C=S}/k_{C=O} = 0.11$–0.26 for the reaction with HO$^-$.

The above results agree well expectations based on the HSAB principle.[29] It is noted that while HO$^-$ is a hard nucleophile, Ox$^-$ and p-ClPhO$^-$, although they are oxygen nucleophiles, are considered to be relatively polarizable. The negative charge on the oxygen atom in Ox$^-$ and p-ClPhO$^-$ can be delocalized through resonance interactions as shown in the resonance structures I and II for Ox$^-$ and III through VI for p-ClPhO$^-$. The following argument shows that this delocalization is more effective for p-ClPhO$^-$ than for Ox$^-$.



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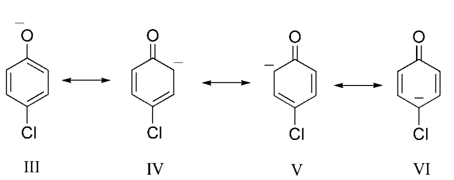

III IV V VI

Figure 6 demonstrates that upon increasing the mol% DMSO, the $k_{C=S}/k_{C=O}$ ratio increases more significantly for the reactions with p-ClPhO$^-$ than for Ox$^-$. A similar result is shown in Figure 3, that is, p-ClPhO$^-$ exhibits much larger $k^{DMSO/H_2O}/k^{H_2O}$ ratios than Ox$^-$ for the reaction of **1** in the region where $\Delta\Delta H_{tr} > 5$ kcal mol^{-1}. These results suggest that p-ClPhO$^-$ is relatively more polarizable than Ox$^-$. Thus, one can conclude that the contrasting relative reactivity and the α-effect profile found for the reactions of **1** and **2** is mainly due to the enhanced polarizability of the electrophilic center upon replacing the C=O bond in **2** by a polarizable C=S bond.

Role of solvent—Gas-phase reactions: Our present work is ideal for commenting on the role of the solvent in nucleophilic reactions, noting that the DMSO/H_2O solvent system provides the characteristics of both protic (H_2O) and aprotic (DMSO) media, that is, hydrogen bonding in the H_2O-rich region and polarizability interactions in the DMSO-rich domain.[30,31] These characteristics, when combined with present experimental results showing bell-shaped α-effect profiles (Figure 4), have enabled us to discuss GS and TS solute–solvent interactions in a more detailed manner (cf. ref. [15]).

As noted in other publications, hydrogen-bonding interactions are believed to be dominant for anionic solutes in H_2O-rich region.[30,31] However, charge dispersion or mutual polarizability interactions between solutes and solvent molecules become the more important interactions in the DMSO-rich region.[30,31] Our calorimetric study has shown that in H_2O, Ox$^-$ is less strongly solvated than p-ClPhO$^-$ by 4 kcal mol^{-1}, and that on addition of DMSO to the medium up to 40 to 50 mol% DMSO, both Ox$^-$ and p-ClPhO$^-$ become greatly desolvated.[17b] However, as mentioned in the preceding section, the difference in enthalpy of solution for Ox$^-$ and p-ClPhO$^-$ (i.e., $\Delta\Delta H_{sol}$) increases on addition of DMSO to H_2O up to about 40 mol% DMSO and then remains nearly constant thereafter.[17b] The increasing $\Delta\Delta H_{sol}$ follows a similar pattern to the increasing α-effect profile; thus, the GS effect is shown to be mainly responsible for the α-effect profile up to 40 or 50 mol% DMSO.

The above interpretation is supported by the measured activation parameters for reactions of PNPA with Ox$^-$ and p-ClPhO$^-$ in various DMSO/H_2O mixtures, where it was found that the reactions are mainly governed by the enthalpy of activation, $\Delta H^{\ddagger}$; beyond 20 mol% DMSO $\Delta H^{\ddagger}$ decreases on addition of DMSO to the medium while $\Delta S^{\ddagger}$ remains nearly unchanged for both Ox$^-$ and p-ClPhO$^-$ systems.[17b] An interesting finding was that the decrease in $\Delta H^{\ddagger}$ for p-ClPhO$^-$ is steeper than that for Ox$^-$ in the medium range 50–90 mol% DMSO, which indicates that the TS for the p-ClPhO$^-$ system becomes relatively more stabilized than the TS for Ox$^-$ in the DMSO-rich region.[17b] Thus, differential TS stabilization has been demonstrated to be responsible for the decreasing α-effect profile in the DMSO-rich region (see above).[17b]

Since the difference in polarizability of the TS between the Ox$^-$ and p-ClPhO$^-$ systems contributes to their differential TS stabilization in the DMSO-rich region, it follows that the TS for the p-ClPhO$^-$ system is more polarizable than the TS for the Ox$^-$ system. This is consistent with the above proposal on the basis of the respective resonance structures and relative rate constants that p-ClPhO$^-$ is more polarizable than Ox$^-$.

The bell-shaped α-effect profile found in the current study (Figure 4) as well as in our previous studies,[17–20] has revealed a differential GS/TS solvent effect, that is, a GS effect in the H_2O-rich region through H-bonding interactions and a TS effect in the DMSO-rich media through mutual polarizability interactions.[17–20]

Recent gas-phase studies including high-level theoretical calculations have shown that α-nucleophiles are intrinsically more reactive, lower enthalpies of activation, than normal nucleophiles of similar basicity (e.g., HOO$^-$ vs. EtO$^-$).[14–16] Patterson and Fountain have reported on the basis of a theoretical study for gas-phase reactions of methyl formate with HO$^-$, EtO$^-$, and HOO$^-$ that the α-nucleophile HOO$^-$ exhibits 3.6 kcal mol^{-1} lower activation barrier than the gas-phase-acidity-matched normal nucleophile EtO$^-$, as evidence for a gas-phase α-effect.[14] They found that HOO$^-$ does not exhibit enhanced reactivity toward methyl formate when compared with HO$^-$, which is much more basic than HOO$^-$ in the gas phase.[14] Yamataka et al. performed theoretical studies at the G2(+) level on gas-phase S_N2 reactions of alkyl halides with 11 anionic nucleophiles.[15] They found that normal nucleophiles exhibit linear plots of the calculated activation barrier versus proton affinity for the reactions with EtCl and *i*PrCl, while α-nucleophiles exhibit negative deviations.[15] The negative deviations exhibited by α-nucleophiles were considered as evidence of a gas-phase α-effect in gas-phase reactions.[15]

An interesting study by McAnoy et al. of the gas-phase reactions of dimethyl methylphosphonate with CD_3O^- and HOO$^-$ anions in an ion-trap mass spectrometer showed four parallel reactions (i.e., deprotonation which yields a carbanion, S_N2 at carbon, nucleophilic substitution at phosphorus, and a reductive elimination process), nucleophilic substitution at carbon predominant for the HOO$^-$ reaction but proton transfer dominating for CD_3O^-.[16] The difference in the observed reactivities of the two nucleophiles was suggested as evidence for an interesting α-effect in the gas-phase.[16]

Conclusion

Our study of the reactions of *O*-*p*-nitrophenyl thionobenzoate (**1**) with HO$^-$, p-ClPhO$^-$, and Ox$^-$ has revealed major reactivity differences on changing the electrophilic center from C=O (**2**) to C=S (**1**):

1) HO$^-$ is more reactive than p-ClPhO$^-$ toward **2**, but less reactive toward **1** up to 70 mol % DMSO although the former is over six pK_a units more basic in these media.
2) Ox$^-$ is more reactive than p-ClPhO$^-$ toward **1** throughout the whole medium range (i.e., the α-effect), but the α-effect profile for the reactions of **1** contrasts to that previously reported for the reactions of **2**.
3) Dissection of the α-effect into GS and TS effects shows that the GS effect is not responsible for the α-effect over the entire solvent composition for reactions of **1**.
4) The dominant factor influencing reactivity in the present system is polarizability: a) p-ClPhO$^-$ and Ox$^-$ are up to 33 times more reactive toward the C=S compound **1** than toward its oxygen analogue **2**, whereas HO$^-$ is 4–9 times less reactive toward the former than the latter. b) Enhanced polarizability of the electrophilic center is responsible for the contrasting reactivity as well as the difference in the α-effect profile for reactions of **1** and **2**.
5) The bell-shaped α-effect profile obtained in this work has provided unique opportunity for discussion of the role of solvent with respect to GS and TS stabilization/destabilization through H-bonding versus polarizability interactions in the DMSO-H_2O solvent system.

Experimental Section

Materials: Compound **1** was prepared as reported previously.[24,25] Butan-2,3-dione monoxime and p-chlorophenol were recrystallized before use. DMSO was distilled over CaH_2 under reduced pressure just before use. Other chemicals were of the highest quality available. Doubly glass distilled water was further boiled and cooled under nitrogen just before use.

Kinetic measurements: The kinetic study was performed with a UV/Vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to maintain the temperature in the reaction cell at (25.0 ± 0.1) °C. The reaction was followed by monitoring the appearance of the leaving p-nitrophenoxide ion. All reactions were carried out under pseudo-first-order conditions in which nucleophile concentrations were at least 20 times greater than the substrate concentration. The Ox$^-$ and p-ClPhO$^-$ stock solutions of ca. 0.2 M were prepared by dissolving two equiv of OxH (or p-ClPhOH) and one equiv of standardized NaOH solution to keep the pH constant in this self-buffered solution. All solutions were prepared freshly just before use under nitrogen and transferred by gas-tight syringes. Typically, the reaction was initiated by adding 5 μL of a 0.02 M solution of the substrate in CH_3CN by a 10 μL syringe to a 10 mm quartz UV cell containing 2.50 mL of the thermostatted reaction mixture made up of solvent and aliquot of the nucleophile stock solution.

Product analysis: p-Nitrophenoxide was liberated quantitatively and identified as one of the products by comparison of the UV/Vis spectrum at the end of reaction with the authentic sample under the experimental condition.

Acknowledgements

The authors are grateful for the financial support from Korea Research Foundation (KRF-2005-015-C00256) and from NSERC of Canada.

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Received: July 28, 2008