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Dissection of Activation Parameters in the Bell-Shaped α-Effect Following Solvent Modulation (DMSO−H_2O Media)

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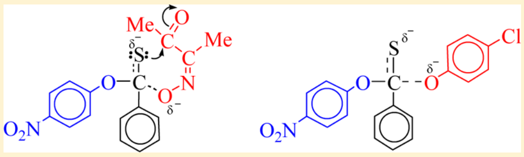
ABSTRACT: This paper comprises results of our investigation of the α-effect phenomenon for the reaction of *O*-*p*-nitrophenyl thionobenzoate (PNPTB) with butane-2,3-dione monoximate (Ox^-, α-nucleophile) and *p*-chlorophenoxide (*p*-$ClPhO^-$, normal-nucleophile) in DMSO−H_2O mixtures of varying compositions at 15.0 °C, 25.0 °C, and 35.0 °C. The reactivity of Ox^- and *p*-$ClPhO^-$ increases significantly as the DMSO content in the medium increases, although the effects of medium on reactivity are not the same for the reactions with Ox^- and *p*-$ClPhO^-$. Ox^- exhibits the α-effect in all solvent compositions and temperatures. The α-effect increases up to 50 mol % DMSO and then decreases thereafter, resulting in a bell-shaped α-effect profile. Dissection of the activation parameters (i.e., $\Delta H^\ddagger$ and $T\Delta S^\ddagger$) has revealed that the bell-shaped α-effect behavior is due to entropy of activation differences rather than enthalpy terms, although the enthalpy term controls almost entirely the solvent dependence of the reaction rate. Differences in the transition-state (TS) structures for the reactions with Ox^- (a six-membered cyclic TS) and *p*-$ClPhO^-$ (an acyclic TS) are consistent with the entropy-dependent α-effect behavior.



INTRODUCTION

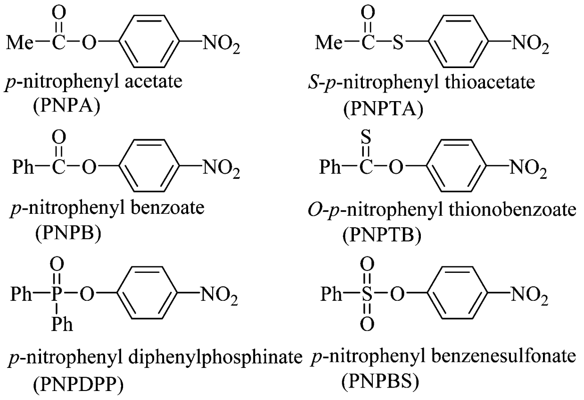
Nucleophiles possessing one or more nonbonding electron pairs at the atom α to the nucleophilic center have been termed α-nucleophiles.[1] Such α-nucleophiles often exhibit enhanced, even dramatically enhanced, reactivity toward a variety of electrophilic centers. Because of this enhancement they have been used effectively for nucleophilic breakdown of neurotoxins, antidotes for nerve gases, cleanup of contaminated sites, etc.[2−4] In analysis of the α-effect it has been pointed out that the effect must be carefully defined; as previously suggested here the ratio of the rate constant for reaction of α-nucleophile to the rate constant for a normal reference nucleophile *of the same or similar* pK_a defines the α-effect.[3b] Numerous studies have been performed to assess the factors that govern α-nucleophilicity so as to design better decontaminants, for example.[3−12]

The most common theories suggested to account for the α-effect phenomenon are ground-state (GS) destabilization, transition-state (TS) stabilization, thermodynamic stabilization of products, and solvent effects, while other possible specific origins include a TS having aromatic or radicaloid character.[3−24] However, none of these theories can decisively explain the α-effect phenomenon. Particularly controversial has been the solvent effect on the α-effect.[3b,12−24]

It has been reported that HOO^- does not exhibit any enhanced reactivity in the gas-phase reactions of methyl formate with HOO^- and OH^-.[12] Hence, the α-effect observed for various reactions with HOO^- in aqueous solutions has been attributed to a solvent effect,[12] because HOO^- was reported to be 12 kcal/mol less strongly solvated than OH^- in H_2O.[13] A similar conclusion (i.e., the α-effect is not due to an intrinsic property but instead due to a solvent effect) has been drawn from gas-phase reactions of alkyl chlorides with ClO^-, BrO^-, HOO^-, and RO^-.[14] However, recent developments of new instruments for gas-phase reactions and rapid advances in computational methods have shown that α-nucleophiles exhibit activation energies lower than those of isobasic normal nucleophiles (e.g., HOO^- vs MeO^- or EtO^-) in gas-phase S_N2 reactions of dimethyl methylphosphonate,[15] methyl formate,[16] or alkyl halides.[17,18] The discrepancies (i.e., the presence or absence of the α-effect in the gas-phase reactions) have been attributed to significant shifts in basicity of the nucleophiles between the solution and gas phases.[15−18]

We have found a remarkable solvent-dependent α-effect in nucleophilic substitution reactions of the substrates in Chart 1

Chart 1



p-nitrophenyl acetate (PNPA)

S-*p*-nitrophenyl thioacetate (PNPTA)

p-nitrophenyl benzoate (PNPB)

O-*p*-nitrophenyl thionobenzoate (PNPTB)

p-nitrophenyl diphenylphosphinate (PNPDPP)

p-nitrophenyl benzenesulfonate (PNPBS)

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with butane-2,3-dione monoximate (Ox^-, α-nucleophile) and p-chlorophenoxide (p-$ClPhO^-$, normal-nucleophile) in DMSO−H_2O mixtures of varying compositions.[19−24] We have shown that the α-effect (i.e., $k_{Ox^-}/k_{p\text{-}ClPhO^-}$) for the reactions of p-nitrophenyl acetate (PNPA) with Ox^- and p-$ClPhO^-$ increases as the DMSO content in the medium increases up to ca. 50 mol % DMSO and then decreases thereafter, i.e., a bell-shaped α-effect profile.[19] Importantly, it has been shown that the basicity of Ox^- and p-$ClPhO^-$ in DMSO−H_2O mixtures increases in an almost parallel manner.[4d,19] This suggests that the bell-shaped α-effect profile is not due to a difference in basicity of the two nucleophiles.[19]

Similar bell-shaped α-effect profiles have been obtained for the corresponding reactions of aryl acetates,[20a] p-nitrophenyl benzoate (PNPB),[20b] O-p-nitrophenyl thionobenzoate (PNPTB),[21] p-nitrophenyl diphenylphosphinate (PNPDPP),[22a] and p-nitrophenyl benzenesulfonate (PNPBS).[22b] However, as shown in Figure 1, the magnitude of the α-effect is strongly dependent on the nature of the electrophilic centers for the C═O, P═O, and SO_2 electrophilic series.[22b]

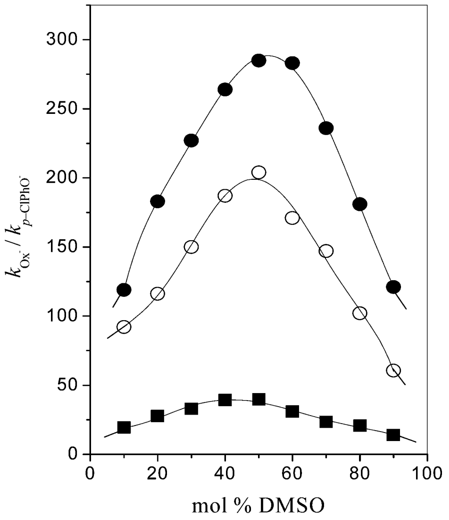


Figure 1. Plots showing the effect of medium on the α-effect for the reaction of PNPA (●), PNPBS (○), and PNPDPP (■) with Ox^- and p-$ClPhO^-$ in DMSO−H_2O mixtures at 25.0 °C. The kinetic data were taken from ref 22b.

An important parameter that provides insight into solution studies is the heat of solution (ΔH_{sol}) measured through calorimetry. Our previous calorimetric studies have shown that the difference in enthalpy of solution between the sodium salts of Ox^- and p-$ClPhO^-$ (i.e., $\Delta\Delta H_{sol}$ in eq 1) increases with increasing mol % DMSO up to ca. 40 mol % DMSO and then remains constant beyond that point (Figure 2).[19]

$$\Delta\Delta H_{sol} = \Delta H_{sol}{}^{OxNa} - \Delta H_{sol}{}^{p\text{-}ClPhONa} \tag{1}$$

Dissection of the α-effect into GS and TS contributions through combination of the kinetic data with the enthalpy of solution (ΔH_{sol}) data has previously led us to conclude that desolvation of the α-nucleophile (i.e., GS effect) is mainly responsible for the increasing α-effect up to 50 mol % DMSO while differential stabilization of TS contributes to the decreasing α-effect beyond 50 mol % DMSO.[19]

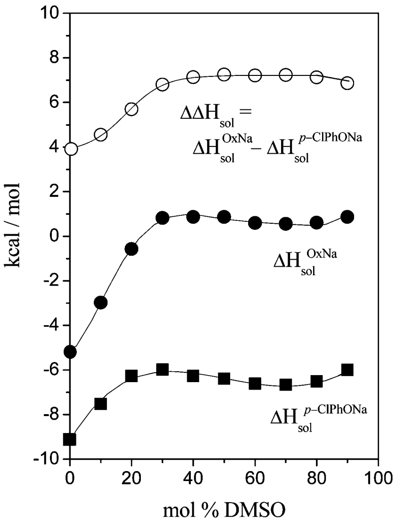
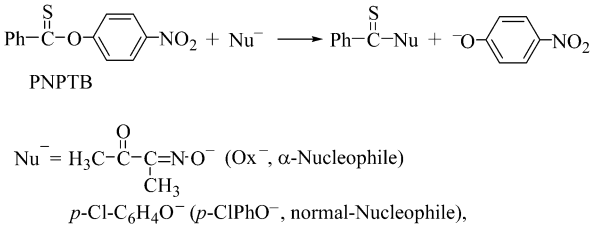


Figure 2. Plots of enthalpies of solution (ΔH_{sol}) as a function of mol % DMSO for the sodium salts of p-$ClPhO^-$ and Ox^- in DMSO−H_2O mixtures at 25.0 °C. The ΔH_{sol} data were taken from ref 19.

We have recently carried out nucleophilic substitution reactions of O-p-nitrophenyl thionobenzoate (PNPTB, Chart 1) with Ox^- and p-$ClPhO^-$ in DMSO/H_2O mixtures at 25.0 °C and found a bell-shaped α-effect profile.[21] The magnitude of the α-effect is smaller for PNPTB than for PNPB, its oxygen analogue, where C═S and C═O electrophilic centers are being compared.[21] The current study, reported herein, extends our analysis of the reactions of PNPTB with Ox^- and p-$ClPhO^-$ in DMSO−H_2O (Scheme 1) to the activation parameters (i.e., $\Delta H^‡$ and $T\Delta S^‡$) combining new kinetic data (15.0 °C and 35.0 °C) with those reported previously for the reactions at 25.0 °C. Scrutiny of the $\Delta H^‡$ and $T\Delta S^‡$ values has revealed that the $T\Delta S^‡$ term rather than the $\Delta H^‡$ term controls the *bell-shaped* α-effect profile as a function of solvent composition.

Scheme 1



Solvent : 0, 10, 20, 30, 40, 50, 60, 70, 80 mol % DMSO in H_2O
Temperature : 15.0, 25.0 and 35.0 °C

■ RESULTS AND DISCUSSION

The kinetic study was performed spectrophotometrically under pseudo-first-order conditions in which the concentration of Ox^- (or p-$ClPhO^-$) was in large excess over that of the substrate PNPTB. All of the reactions in this study obeyed pseudo-first-order kinetics and proceeded with quantitative liberation of p-nitrophenoxide ion. Pseudo-first-order rate constants (k_{obsd}) were calculated from the linear slopes of ln ($A_\infty - A_t$) vs time plots. Second-order rate constants (i.e., k_{Ox^-} and $k_{p\text{-}ClPhO^-}$) were calculated from the slope of the linear plots of k_{obsd} vs concentration of Ox^- (or p-$ClPhO^-$) and are

Table 1. Summary of Second-Order Rate Constants for the Reaction of PNPTB with Ox^- ($k_{Ox^-}/M^{-1}\ s^{-1}$) and p-$ClPhO^-$ ($k_{p\text{-}ClPhO^-}/M^{-1}\ s^{-1}$) Together with the α-Effect (i.e., the $k_{Ox^-}/k_{p\text{-}ClPhO^-}$ ratio) in Various DMSO−H_2O Mixtures at 15.0 °C, 25.0 °C, and 35.0 °C[a]

	15.0 °C			25.0 °C			35.0 °C		
mol % DMSO	k_{Ox^-}	$k_{p\text{-}ClPhO^-}$	α-effect	k_{Ox^-}	$k_{p\text{-}ClPhO^-}$	α-effect	k_{Ox^-}	$k_{p\text{-}ClPhO^-}$	α-effect
0	34.9	0.803	43	61.9	1.53	41	121	3.98	30
10	53.9	1.06	51	102	2.20	46	180	4.86	37
20	150	1.86	81	254	3.91	65	462	7.80	59
30	461	4.69	98	786	9.57	82	1290	17.6	73
40	1560	13.0	120	2560	25.4	101	3980	43.3	92
50	4890	35.2	139	7790	63.8	122	11300	112	101
60	13600	102	133	20700	186	111	29200	309	94
70	36500	302	121	52300	511	102	74100	860	86
80	95500	865	110	127000	1470	86	182000[b]	2380	76

[a] The data for reactions at 25.0 °C were taken from ref 21. [b] Because the reaction in 80 mol % DMSO was too fast to measure, the k_{Ox^-} value at 35.0 °C was extrapolated from the plot of log k_{Ox^-} vs mol % DMSO.

summarized in Table 1. The uncertainty in the k_{Ox^-} and $k_{p\text{-}ClPhO^-}$ values is estimated to be less than ±3% from replicate runs.

1. Effect of Temperature and Medium on the α-Effect: DMSO−H_2O Media. The effects of medium on the reactivity of Ox^- and p-$ClPhO^-$ are presented in Table 1. The rate constant increases as the DMSO content in the medium increases at all temperatures studied. The relative reactivity (k_{DMSO}/k_{H_2O}, i.e., the ratio of the second-order rate constant in a DMSO−H_2O mixture over the corresponding rate constant in pure H_2O) is 4.3, 140, and 2700 in 20, 50, and 80 mol % DMSO, respectively, for the reactions with Ox^- at 15.0 °C, while 2.3, 44, and 1100 in 20, 50, and 80 mol % DMSO, respectively, for the reactions with p-$ClPhO^-$ at 15.0 °C. A similar result is shown for the reactions run at 35.0 °C although the k_{DMSO}/k_{H2O} ratio is smaller for the reactions carried out at a higher temperature. It is noted that the relative reactivity is larger for the reaction with Ox^- than for the corresponding reaction with p-$ClPhO^-$ in all solvent compositions and reaction temperatures. The larger k_{DMSO}/k_{H_2O} ratio for the Ox^- system compared to p-$ClPhO^-$ appears to be mainly a reflection of the GS energies of the nucleophiles, because Ox^- was previously reported to be more destabilized than p-$ClPhO^-$ as the DMSO content in the medium increases.[19]

As shown in Table 1, Ox^- is much more reactive than p-$ClPhO^-$ toward PNPTB in all DMSO−H_2O mixtures, indicating that the α-effect is operative in the current reactions. The α-effects for the reactions of PNPTB are illustrated in Figure 3 together with those for the corresponding reactions of PNPA for comparison. It is noted that the reactions of PNPTB exhibit an α-effect smaller than that of the corresponding reactions of PNPA, and the increase (or decrease) in the α-effect on changing the medium composition is less significant for PNPTB than for PNPA.

Our calorimetric study has previously revealed that Ox^-Na^+ is less strongly solvated than p-$ClPhO^-Na^+$ in all DMSO−H_2O compositions, and that the difference in the enthalpy of solution for Ox^- and p-$ClPhO^-$ (i.e., $\Delta\Delta H_{sol}$) increases up to near 40 mol % DMSO and then remains nearly constant upon further increase in mol % DMSO (Figure 2).[19] Thus, if the difference in the GS solvation between Ox^- and p-$ClPhO^-$ is the cause of the α-effect, one might expect that the $k_{Ox^-}/k_{p\text{-}ClPhO^-}$ ratio increases up to 40 mol % DMSO and then remains nearly constant beyond that point. In fact, we have previously shown that the α-effect for the reactions of S-p-nitrophenyl thioacetate (PNPTA, the thio analogue of PNPA in Chart 1) with Ox^- and p-$ClPhO^-$ increases up to near 40 mol % DMSO and then remains constant thereafter.[24] However, the α-effect for the current reactions of PNPTB increases up to 50 mol % DMSO and then decreases as the DMSO content in the medium increases further, although the decrease in the α-effect is modest. Furthermore, the magnitude of the α-effect is much smaller for the reactions of PNPTB than for the corresponding reactions of PNPA. The current results show that GS effects as revealed by $\Delta\Delta H_{sol}$ cannot be solely responsible for the bell-shaped α-effect profile found for the reactions of PNPTB.

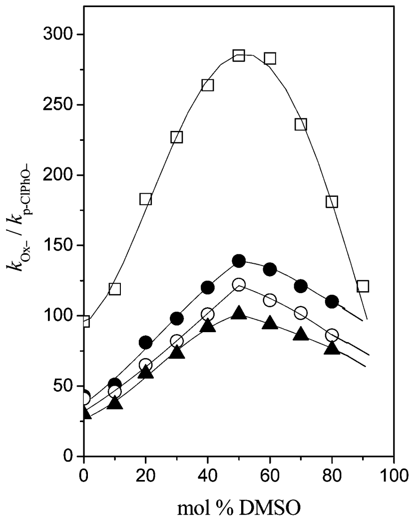


Figure 3. Plots of the magnitude of the α-effect ($k_{Ox^-}/k_{p\text{-}ClPhO^-}$) vs mol % DMSO for the reaction of PNPTB with Ox^- and p-$ClPhO^-$ at 15.0 (●), 25.0 (○), and 35.0 °C (▲). The α-effect data for the reactions of PNPA at 25.0 °C (□) were taken from ref 19.

2. Effect of Medium on $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$. To dissect the α-effect in this study into GS and TS contributions, the activation parameters (i.e., $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$) have been calculated from the kinetic data for the reactions of PNPTB with Ox^- and p-$ClPhO^-$ at 15.0 °C, 25.0 °C, and 35.0 °C. The Arrhenius equation, $k = Ae^{-E_a/RT}$, was used to calculate enthalpies of activation values. Equation 2 is derived from the Arrhenius equation. The slope of the linear plot of ln k vs $1/T$ is equal to $-E_a/R$. The enthalpy of activation ($\Delta H^{\ddagger}$) was then calculated using eq 3. Entropies of activation ($\Delta S^{\ddagger}$) were calculated from eq 4. The $\Delta H^\ddagger$ and $T\Delta S^\ddagger$ values calculated in this way are summarized in Table 2.

$$\ln k_{\mathrm{Ox}^-}\ (\text{or } k_{p\text{-ClPhO}^-}) = -E_a/RT + \ln A \qquad (2)$$

$$\Delta H^\ddagger = E_a - RT \qquad (3)$$

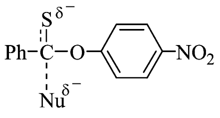
$$\Delta S^\ddagger = R(\ln A - \ln T - \ln K_B/h - 1) \qquad (4)$$

Table 2. Summary of Activation Parameters for the Reaction of PNPTB with Ox^- and p-$ClPhO^-$ in Various DMSO/H_2O Mixtures at 25.0 °C

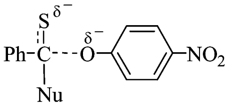
	Ox^-		p-$ClPhO^-$	
mol % DMSO	$\Delta H^\ddagger$, kcal mol^{-1}	$T\Delta S^\ddagger$, kcal mol^{-1}	$\Delta H^\ddagger$, kcal mol^{-1}	$T\Delta S^\ddagger$, kcal mol^{-1}
0	10.4 ± 0.7	−4.6 ± 0.7	13.5 ± 1.9	−3.6 ± 1.9
10	10.0 ± 0.2	−4.7 ± 0.2	12.8 ± 0.6	−4.1 ± 0.6
20	9.3 ± 0.6	−4.8 ± 0.6	12.1 ± 0.0	−4.6 ± 0.0
30	8.5 ± 0.0	−5.0 ± 0.0	11.1 ± 0.3	−5.0 ± 0.3
40	7.7 ± 0.1	−5.1 ± 0.1	10.0 ± 0.5	−5.5 ± 0.5
50	6.8 ± 0.3	−5.4 ± 0.4	9.6 ± 0.0	−5.4 ± 0.0
60	6.1 ± 0.2	−5.4 ± 0.2	9.2 ± 0.3	−5.2 ± 0.3
70	5.7 ± 0.1	−5.4 ± 0.1	8.6 ± 0.1	−5.1 ± 0.1
80	5.1 ± 0.5	−5.4 ± 0.5	8.3 ± 0.1	−4.8 ± 0.1

Table 2 shows that the enthalpies of activation decrease over 5 kcal/mol as the medium changes from H_2O to 80 mol % DMSO, e.g., $\Delta H^\ddagger$ decreases from 10.4 to 5.1 kcal/mol for the reactions with Ox^- and from 13.5 to 8.3 kcal/mol for those with p-$ClPhO^-$. In contrast, the entropy change in the same medium range is only about 1 kcal/mol at 25.0 °C for the reactions with both Ox^- and p-$ClPhO^-$. Thus, one can suggest that the enthalpy term controls almost entirely the solvent dependence of the reaction rate.

We have recently shown that reactions of PNPTB with three representative anionic nucleophiles (i.e., OH^-, CN^-, and N_3^-) proceed through a stepwise mechanism.[25] Thus, one might expect that the reactions of PNPTB with Ox^- and p-$ClPhO^-$ proceed also through a stepwise mechanism with a partial negative charge on the sulfur atom in the TS as modeled by TS_I or TS_{II} depending on the rate-determining step.



TS_I



TS_{II}

It is apparent that the negatively charged TS_I and TS_{II} would not be strongly solvated in H_2O because the H-bonding interaction between the H_2O molecules and a negatively charged sulfur atom is expected to be poor. This idea is consistent with the fact that HS^- is not very soluble in H_2O, and H_2S is a gas at room temperature while H_2O is liquid. In contrast, the charge dispersion (or mutual polarizability) interaction would become more important as the DMSO content in the medium increases.[26] Thus, the TSs for the reactions of PNPTB would be more solvated with increasing the concentration of DMSO in the medium, because the increased DMSO content enhances the polarizability of the reaction medium. This idea is consistent with the fact that the $\Delta H^\ddagger$ terms for the reactions of PNPTB with both Ox^- and p-$ClPhO^-$ decrease gradually with increasing mol % DMSO (Table 2).

Table 2 shows that the $T\Delta S^\ddagger$ terms also decrease as the DMSO content in the reaction medium increases up to a certain mol % DMSO, although the decreases are small and are not the same for the reactions with Ox^- and p-$ClPhO^-$. The decrease in $T\Delta S^\ddagger$ is clearly a reflection of the increasing TS solvation in that medium range. Interestingly, beyond 50 mol % DMSO, $T\Delta S^\ddagger$ for the reaction with Ox^- remains virtually constant, while $T\Delta S^\ddagger$ for that with p-$ClPhO^-$ increases gradually upon further increase in the DMSO content. Therefore, it is the differential entropy effect that controls TS stabilization as it impacts the observed bell-shaped α-effect profile.

3. Modulation of TS Structures: Effect on $\Delta H^\ddagger$ and $T\Delta S^\ddagger$. How can the differential activation energy parameters arise? Figure 4 illustrates the changes in $\Delta H^\ddagger$ and $T\Delta S^\ddagger$ upon changing mol % DMSO for the reactions of PNPTB with p-$ClPhO^-$ and Ox^-. As shown in Figure 4A, the plot consists of two intersecting straight lines. The $\Delta H^\ddagger$ for the reactions with both Ox^- and p-$ClPhO^-$ decreases as the mol % DMSO increases. Interestingly, $\Delta H^\ddagger$ decreases more rapidly for the reaction with p-$ClPhO^-$ than for that with Ox^- up to 40 mol % DMSO (slope = 1.26) but more slowly beyond that point (slope = 0.80). This indicates that the TS for the reaction with p-$ClPhO^-$ becomes more strongly solvated than that for the reaction with Ox^- as the DMSO content in the medium increases up to 40 mol % DMSO but less strongly solvated upon further increase in the DMSO content. Thus, if the $\Delta H^\ddagger$ term controls the magnitude of the α-effect in this study, one might expect that the α-effect decreases up to 40 mol % DMSO and then increases beyond that point. However, the α-effect profile shown in Figure 3 is opposite to the expectation, i.e., it increases up to ca. 50 mol % DMSO and decreases beyond that point. This clearly indicates that the bell-shaped α-effect profile observed for the reactions of PNPTB is not controlled by the $\Delta H^\ddagger$ term.

Figure 4B demonstrates the effect of medium on the entropy of activation ($T\Delta S^\ddagger$) for the reactions of PNPTB with p-$ClPhO^-$ and Ox^- at 25.0 °C. The plot exhibits a break between 40 and 50 mol % DMSO. From 0 to 40 mol % DMSO, $T\Delta S^\ddagger$ decreases more rapidly for the reaction with p-$ClPhO^-$ than for that with Ox^-, indicating that the TS becomes more ordered for the reaction with p-$ClPhO^-$ than for that with Ox^- as the DMSO content increases up to 40 mol %. This idea is also consistent with the preceding argument that the TS becomes more strongly solvated for the reaction with p-$ClPhO^-$ than for the reaction with Ox^- as the DMSO content in the medium increases up to 40 mol %. Interestingly, the $T\Delta S^\ddagger$ for the reaction with Ox^- remains constant beyond 50 mol % DMSO. In contrast, the $T\Delta S^\ddagger$ for the reaction with p-$ClPhO^-$ increases gradually with increasing mol % DMSO beyond 50 mol %, indicating that the TS for the reaction with p-$ClPhO^-$ gains more freedom in this medium range.

4. TS Structures and $T\Delta S^\ddagger$. Such contrasting changes in the $T\Delta S^\ddagger$ terms can be readily understood from the TS models outlined. Our recent study has shown that reactions of aryl thionobenzoates including PNPTB with anionic nucleophiles (i.e., OH^-, CN^-, and N_3^-) as well as with amines proceed through a stepwise mechanism, in which the rate-determining step (RDS) is dependent on the basicity of the incoming nucleophile and the leaving aryl oxide.[25] Because both Ox^- and p-$ClPhO^-$ are more basic than the leaving p-nitrophenoxide,

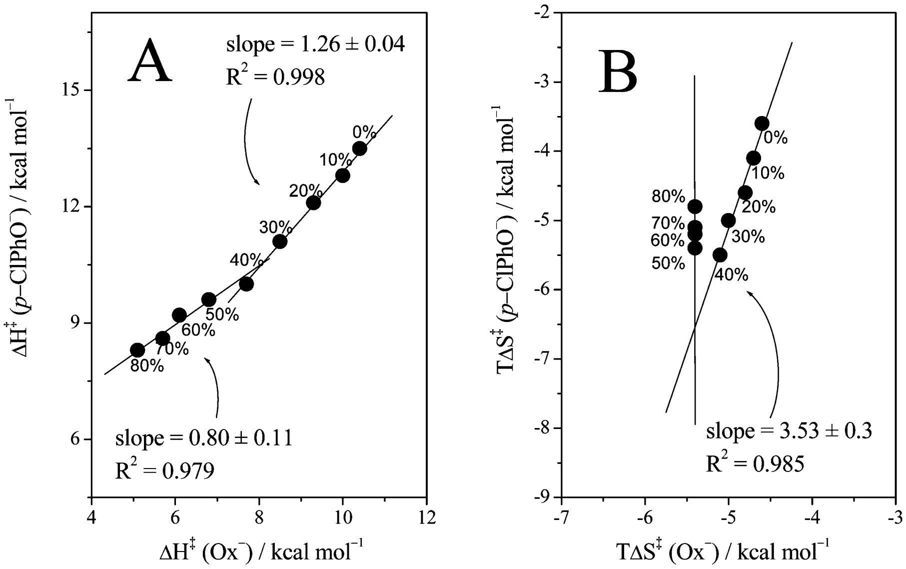
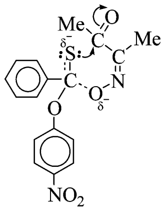
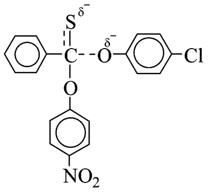


Figure 4. Plots showing changes in $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ upon changing mol % DMSO for the reactions of PNPTB with Ox^- and p-$ClPhO^-$ in DMSO/H_2O mixtures at 25.0 °C: (A) $\Delta H^{\ddagger}$ (p-$ClPhO^-$) versus $\Delta H^{\ddagger}$ (Ox^-) and (B) $T\Delta S^{\ddagger}$ (p-$ClPhO^-$) versus $T\Delta S^{\ddagger}$ (Ox^-). The identity of points is given in Table 2.

expulsion of the leaving group would occur after the RDS. Thus, one can propose $TS_{Ox}-$ and $TS_{p\text{-}ClPhO^-}$ as the TS structures for the reactions of PNPTB with Ox^- and p-$ClPhO^-$, respectively.



TS_{Ox^-}



$TS_{p\text{-}ClPhO^-}$

A six-membered cyclic TS is proposed for the reaction with Ox^-, because the negatively charged S atom in the TS_{Ox-} is expected to be a good nucleophilic site. This idea can be supported by the report that SO_3^{2-} is an excellent nucleophile toward carbonyl carbon and its nucleophilic center is the polarizable sulfur atom rather than the negatively charged oxygen atom.[27] The cyclic TS structure can be further supported from the kinetic results shown in Table 2 in that $T\Delta S^{\ddagger}$ is more negative for the reaction with Ox^- than with p-$ClPhO^-$ in the H_2O-rich region (e.g., up to near 30 mol % DMSO), where the solvent polarizability is not great. Furthermore, the change in $T\Delta S^{\ddagger}$ upon changing solvent compositions would be less significant for the cyclic TS, because the rotational and vibrational degrees of freedom are restricted to a certain degree in such a cyclic TS structure. In fact, Table 2 and Figure 4B show that $T\Delta S^{\ddagger}$ decreases less rapidly for the reaction with Ox^- than with p-$ClPhO^-$ up to 40 mol % DMSO.

One might expect that the bond formation between the nucleophile and the electrophilic center becomes less advanced with increasing mol % DMSO on the basis of the normal Hammond effect.[28] It is apparent that a decrease in bond formation upon increasing mol % DMSO would cause an increase in entropy term. In fact, Table 2 shows that the $T\Delta S^{\ddagger}$ term for the reaction with p-$ClPhO^-$ increases gradually with increasing the DMSO content in the medium beyond 50 mol % DMSO. This implies that the increased $T\Delta S^{\ddagger}$ by the decreased bond formation in the DMSO−rich region exceeds the decreased $T\Delta S^{\ddagger}$ by the increased TS solvation for the reaction with p-$ClPhO^-$. However, such medium effect on $T\Delta S^{\ddagger}$ would not be significant for the reaction with Ox^-, which is proposed to proceed through a cyclic TS (i.e., $TS_{Ox}-$). This idea is consistent with the fact that the $T\Delta S^{\ddagger}$ term for the reaction with Ox^- remains constant beyond 50 mol % DMSO (Table 2). Thus, one can attribute the contrasting $T\Delta S^{\ddagger}$ behavior to the difference in TS structures (i.e., the cyclic TS_{Ox^-} vs the acyclic $TS_{p\text{-}ClPhO^-}$).

5. Measurement of Brønsted β_{nuc}. It is well-known that β_{nuc} represents a relative degree of bond formation between the nucleophile and the electrophilic center in the rate-determining TS. Thus, the Brønsted β_{nuc} values for the reactions of PNPTB in DMSO/H_2O mixtures have been measured to examine the preceding argument that the bond formation becomes less advanced with increasing mol % DMSO. In Table 3 are summarized the second-order rate constants ($k_{p\text{-}XPhO^-}$) for reactions of PNPTB with a series of p-X-substituted-phenoxides in 20, 50, and 80 mol % DMSO at 25.0 °C together with the Brønsted β_{nuc} values calculated from the kinetic data. Table 3 shows that the Brønsted β_{nuc} decreases from 0.56 to 0.54 and 0.51 as the DMSO content in the medium increases from 20 to

Table 3. Summary of pK_a of Phenols and Second-Order Rate Constants ($k_{p\text{-}XPhO^-}$/M^{-1} s^{-1}) for the Reactions of PNPTB with p-X-Substituted Phenoxides in Various DMSO/H_2O Mixtures at 25.0 ± 0.1 °C

	20 mol %		50 mol %		80 mol %	
X	pK_a	$k_{p\text{-}XPhO^-}$	pK_a	$k_{p\text{-}XPhO^-}$	pK_a	$k_{p\text{-}XPhO^-}$
CH_3	11.7	8.44	14.0	185	16.3	4990
H	11.3	4.54	13.5	85.7	15.7	2200
Cl	10.5	3.91	12.5	63.8	14.5	1470
CN	8.6	0.151	10.1	1.32	11.5	17.4
	β_{nuc} = 0.56		β_{nuc} = 0.54		β_{nuc} = 0.51	

50 and 80 mol % DMSO, in turn. This confirms the above argument that the bond formation for the reactions of PNPTB becomes less advanced as the mol % DMSO increases.

6. Origin of the Bell-Shaped α-Effect Profile. Table 2 shows that, as the medium changes from 0 to 40 mol % DMSO, the $\Delta H^{\ddagger}$ for the reaction with Ox^- decreases from 10.4 ± 0.7 to 7.7 ± 0.1 kcal/mol (i.e., $\Delta\Delta H^{\ddagger} = -2.7$ kcal/mol), while the $\Delta H^{\ddagger}$ for the reaction with p-$ClPhO^-$ decreases from 13.5 ± 1.9 to 10.0 ± 0.5 kcal/mol (i.e., $\Delta\Delta H^{\ddagger} = -3.5$ kcal/mol). Thus, the enthalpy term is 0.8 kcal/mol more favorable for the reaction with p-$ClPhO^-$ than for that with Ox^- upon changing the medium from 0 to 40 mol % DMSO. On the other hand, in the same medium range, $T\Delta S^{\ddagger}$ decreases from −4.6 ± 0.7 to −5.1 ± 0.1 kcal/mol for the reaction with Ox^- (i.e., $T\Delta\Delta S^{\ddagger} = -0.5$ kcal/mol) and from −3.6 ± 1.9 to −5.5 ± 0.5 kcal/mol for that with p-$ClPhO^-$ (i.e., $T\Delta\Delta S^{\ddagger} = -1.9$ kcal/mol), indicating that the entropy term is 1.4 kcal/mol more favorable for the reaction with Ox^- than for that with p-$ClPhO^-$. Overall, the reaction with Ox^- is 0.6 kcal/mol more favorable than that with p-$ClPhO^-$ upon the medium change from 0 to 40 mol % DMSO. This accounts for the fact that the α-effect increases from 41 to 101 as the DMSO content in the reaction medium increases from 0 to 40 mol % DMSO.

An opposite result is obtained beyond 50 mol % DMSO. As the medium changes from 50 to 80 mol % DMSO, $\Delta H^{\ddagger}$ decreases from 6.8 ± 0.3 to 5.1 ± 0.5 kcal/mol for the reaction with Ox^- ($\Delta\Delta H^{\ddagger} = -1.7$ kcal/mol), and from 9.6 ± 0.0 to 8.3 ± 0.1 kcal/mol for that with p-$ClPhO^-$ ($\Delta\Delta H^{\ddagger} = -1.3$ kcal/mol). Thus, the enthalpy term is 0.4 kcal/mol more favorable for the reaction with Ox^- than that with p-$ClPhO^-$ upon the medium change from 50 to 80 mol % DMSO. On the other hand, $T\Delta S^{\ddagger}$ increases from −5.4 ± 0.0 to −4.8 ± 0.1 kcal/mol for the reaction with p-$ClPhO^-$ (i.e., $T\Delta\Delta S^{\ddagger} = 0.6$ kcal/mol) but remains constant for the reaction with Ox^- (i.e., $T\Delta\Delta S^{\ddagger} = 0$ kcal/mol), indicating that the entropy term is 0.6 kcal/mol is more favorable for the reaction with p-$ClPhO^-$ than for the reaction with Ox^-. Overall, the reaction with Ox^- is 0.2 kcal/mol less favorable than that with p-$ClPhO^-$ as the medium changes from 50 to 80 mol % DMSO, which is responsible for the decreasing α-effect from 122 to 86 in the medium range.

CONCLUSIONS

Our study of the reactions of O-p-nitrophenyl thionobenzoate (PNPTB) with Ox^- and p-$ClPhO^-$ in DMSO/H_2O mixtures of varying compositions at 15.0 °C, 25.0 °C, and 35.0 °C has allowed us to conclude the following:

(1) Addition of DMSO to the reaction medium results in significant increases in the reactivity of Ox^- and p-$ClPhO^-$, although the effects of medium on reactivity are not the same for the reactions with Ox^- and p-$ClPhO^-$, which results in a bell-shaped α-effect profile.

(2) As the medium changes from H_2O to 80 mol % DMSO, $\Delta H^{\ddagger}$ decreases over 5 kcal/mol while $T\Delta S^{\ddagger}$ decreases only about 1 kcal/mol for the reactions of PNPTB with both Ox^- and p-$ClPhO^-$, indicating that the enthalpy term controls almost entirely the solvent dependence of the reaction rate.

(3) From 0 to 40 mol % DMSO, the reaction with Ox^- is 0.8 kcal/mol less favorable by the $\Delta H^{\ddagger}$ term but 1.4 kcal/mol more favorable by the $T\Delta S^{\ddagger}$ term. Thus, the reaction with Ox^- is 0.6 kcal/mol more favorable than those with p-$ClPhO^-$ (due to the favorable $T\Delta S^{\ddagger}$ term), which is responsible for the increasing α-effect trend in that medium range.

(4) For the reaction with Ox^- beyond 50 mol % DMSO, the $\Delta H^{\ddagger}$ term is 0.4 kcal/mol more favorable but the $T\Delta S^{\ddagger}$ term is 0.6 kcal/mol less favorable. Accordingly, the reaction with Ox^- is 0.2 kcal/mol less favorable than that with p-$ClPhO^-$ (due to the unfavorable $T\Delta S^{\ddagger}$ term), which is responsible for the decreasing α-effect behavior in that medium range.

(5) Overall, it is shown that the $T\Delta S^{\ddagger}$ term rather than the $\Delta H^{\ddagger}$ term controls the bell-shaped α-effect profile, which is contrary to generally held views. Differences in TS structures (i.e., a cyclic TS for the reaction with Ox^- versus an acyclic TS for that with p-$ClPhO^-$) cause the contrasting $T\Delta S^{\ddagger}$ behaviors.

EXPERIMENTAL SECTION

Materials. PNPTB was prepared as reported previously.[21,25] Butane-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.

Kinetics. The kinetic study was performed with a UV−vis spectrophotometer for the slow reactions ($t_{1/2} > 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \leq 10$ s) equipped with a constant temperature circulating bath to maintain the temperature in the reaction cell. 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 the 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 1 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.

Product Analysis. p-Nitrophenoxide ion 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.

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Notes

The authors declare no competing financial interest.

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