Medium Effect on the α -Effect for Nucleophilic Substitution Reactions of p-Nitrophenyl Acetate with Benzohydroxamates and m-Chlorophenoxide in DMSO-H₂O Mixtures as Contrasts with MeCN-H₂O Mixtures: Comparing Two Very Different Polar Aprotic Solvent Components

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¹This article is dedicated to Prof. Emeritus Erwin Buncl, Queen's University, for his numerous and significant life-long contributions to our understanding of mechanistic organic chemistry.

Abstract

A kinetic study is reported on nucleophilic substitution reactions of *p*-nitrophenyl acetate (**1a**) with three α -effect nucleophiles, benzohydroxamate (BHA^-), *p*-methylbenzohydroxamate (MBHA^-) and *p*-methyl-*N*-methylbenzohydroxamate (M_2BHA^-), and a reference nucleophile, *m*-chlorophenoxide ($m\text{-ClPhO}^-$) in DMSO- H_2O mixtures of varying compositions at 25.0 ± 0.1 °C. Second-order rate constants for the reactions with BHA^- and MBHA^- decrease upon addition of DMSO to the reaction medium up to 60 mol % DMSO and then increase thereafter only a little. In contrast, M_2BHA^- and $m\text{-ClPhO}^-$ become much more reactive as the DMSO content in the medium increases. Such contrasting medium effects on reactivity are consistent with the report that hydroxamic acids behave as OH acids in H_2O but as NH acids in dipolar aprotic solvents (e.g., DMSO and MeCN). It has been concluded that BHA^- and MBHA^- form an equilibrium of a reactive form I with less reactive species II in DMSO- H_2O mixtures and the position of the equilibrium is dependent on solvent compositions. BHA^- and MBHA^- exhibit the α -effect in H_2O but not in 90 mol % DMSO. In contrast, the α -effect yielded by M_2BHA^- increases steeply up to 70 mol % DMSO and then levels off thereafter.

Keywords: The α -Effect, Medium effect, Hydroxamates, Transition-state, Ground-state

Introduction

Nucleophiles possessing lone-pair electrons at the atom α to the nucleophilic site have been reported to exhibit higher nucleophilic reactivity than similarly basic normal nucleophiles.¹⁻¹⁸ Thus, the enhanced nucleophilic reactivity shown by these nucleophiles was termed the α -effect by Edward and Pearson.¹ Since this definition only refers to the structure of the α -nucleophiles, an alternative operational definition was given to the α -effect, i.e., a positive deviation exhibited by an α -nucleophile from a Brønsted-type nucleophilicity plot.²

Numerous studies have been carried out to investigate the origin of the α -effect and many theories have been proposed to account for the cause of the α -effect, e.g., ground-state (GS) destabilization, transition-state (TS) stabilization through aromatic or radicaloid character, thermodynamic stability of the reaction products, and solvent effects.¹⁻¹⁸ However, the effect of medium on the α -effect remains controversial although it has been studied most widely.⁹⁻¹⁸

DePuy et al. carried out the first gas-phase reaction of methyl formate with HOO^- and HO^- and found that HOO^- does not exhibit higher reactivity than HO^- ⁹ and, on this basis, concluded that the α -effect shown by HOO^- in aqueous reactions is due to solvent effect because HOO^- was previously reported to be 12 kcal/mol less strongly solvated than HO^- in H_2O .¹⁰ Bierbaum and coworkers have drawn a similar conclusion (i.e., the α -effect is not due to an intrinsic property but instead due to a solvent effect) from various gas-phase reactions with HOO^- , RO^- , and their microsolvated anions such as $\text{HOO}^-(\text{H}_2\text{O})$ and $\text{HOO}^-(\text{MeOH})$.¹² In contrast, other computational studies have shown that some α -nucleophiles exhibit lower activation energies than similarly basic normal nucleophiles (e.g., HOO^- vs. MeO^- or EtO^-) in gas-phase reactions of dimethyl methylphosphonate, methyl formate, or alkyl halides, indicating that the α -effect nucleophiles are intrinsically more reactive than the reference nucleophiles.^{14,15} The role of solvent in the α -effect, therefore, remains controversial.

We have carried out a systematic study on nucleophilic substitution reactions of 4-

nitrophenyl acetate (**1a**) with butane-2,3-dione monoximate (Ox^- , $\text{p}K_{\text{a}}^{\text{OxH}} = 9.44$ in H_2O) as an α -nucleophile and *p*-chlorophenoxide ($p\text{-ClPhO}^-$, $\text{p}K_{\text{a}}^{p\text{-ClPhOH}} = 9.38$ in H_2O) as a reference nucleophile in DMSO- H_2O mixtures of varying compositions to investigate effect of solvents on the α -effect.^{17a} We found that medium effect on the α -effect is significant, e.g., the magnitude of the α -effect (i.e., the $k_{\text{Ox}^-}/k_{p\text{-ClPhO}^-}$ ratio) increases as the DMSO content in the medium increases up to 50 mol % DMSO and then decreases upon further addition of DMSO (a bell-shaped α -effect profile).^{17a} Similarly bell-shaped α -effect profiles have been observed for the corresponding reactions of aryl acetates (**1b-1e**),^{17b} 4-nitrophenyl benzoate (**2**) and *O*-4-nitrophenyl thionobenzoate (**3**),^{17c} 4-nitrophenyl diphenylphosphinate (**4**) and 4-nitrophenyl benzenesulfonate (**5**),^{17d, 18} although the magnitude of the α -effect was dependent on leaving-group basicity^{17b} as well as on the nature of the electrophilic center (e.g., $\text{C}=\text{O}$, $\text{C}=\text{S}$, $\text{P}=\text{O}$ and SO_2).^{17d, 18}

It is important to note that the basicity of Ox^- and $p\text{-ClPhO}^-$ increases in an almost parallel manner as the DMSO content in the medium increases,^{17a} indicating that the bell-shaped α -effect profile is not due to any change in relative basicity of the two nucleophiles.^{17a} To dissect the α -effect into GS and TS contributions, we measured heat of solution (ΔH_{sol}) for the sodium salts of Ox^- and $p\text{-ClPhO}^-$ through calorimetry and activation parameters ($\Delta H^\ddagger$ and $\Delta S^\ddagger$) for the reactions of **1a** with Ox^- and $p\text{-ClPhO}^-$ in DMSO- H_2O mixtures.^{3b, 17a} Combination of the calorimetric data with activation parameters has led us to conclude that desolvation of Ox^- (i.e., GS effect) upon addition of DMSO to the medium is mainly responsible for the increasing α -effect up to 50 mol % DMSO and that the decreasing α -effect in the DMSO-rich medium is caused by differential TS stabilization.^{17a}

We have also carried out reactions of **1a** with Ox^- and $p\text{-ClPhO}^-$ in MeCN- H_2O mixtures of varying compositions and found that the α -effect increases as the MeCN content in the medium increases up to 90 mol % MeCN.^{17c} A comparable increasing α -effect profile has

been found for the reactions of **1a** with *p*-methyl-*N*-methylbezohydroxamate (M_2BHA^- , $pK_a^{M_2BHAH} = 8.50$ in H_2O) and *m*-chlorophenoxide ($m-ClPhO^-$, $pK_a^{m-ClPhOH} = 9.02$ in H_2O) in MeCN- H_2O mixtures of varying compositions.^{17f} Measurement of basicity of these nucleophiles in MeCN- H_2O mixtures has revealed that the α -nucleophiles Ox^- and M_2BHA^- become more basic than their reference nucleophiles *p*- $ClPhO^-$ and *m*- $ClPhO^-$, respectively, as the MeCN content in the medium increases.^{17e,17f} As a consequence, the magnitude of the α -effect increases almost linearly with increasing basicity difference, indicative of increasing GS destabilization throughout the range of media studied.^{17e,17f}

It is well known that both DMSO and MeCN destabilize charge localized anions due to the electronic repulsion between anions and the negative dipole end of these polar aprotic solvents.^{19,20} In contrast, DMSO can stabilize charge delocalized anions (e.g., picrate anion and anionic TS) through polarizability interaction, which is absent for MeCN.^{19,20} Our study has now been extended to reactions of **1a** with three α -nucleophiles (i.e., benzohydroxamate (BHA^-), *p*-methylbenzohydroxamate ($MBHA^-$) and *p*-methyl-*N*-methylbenzohydroxamate (M_2BHA^-)) and a reference nucleophile *m*- $ClPhO^-$ in MeCN- H_2O mixtures (Scheme 1) to investigate the effect of medium change from MeCN- H_2O to DMSO- H_2O mixtures on the α -effect.

Experimental

Materials. The benzohydroxamic acids used in this study were prepared readily from the reactions of benzoyl chloride (or *p*-methylbenzoyl chloride) with hydroxylamine (or *N*-methylhydroxylamine) as reported previously.^{17f} 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 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 the nucleophile concentrations were at least 10 times greater than the substrate concentration. The stock solution of nucleophiles (i.e., BHA⁻, MBHA⁻, M₂BHA⁻, and *m*-ClPhO⁻) were prepared by dissolving two equiv. of benzohydroxamic acids (or *m*-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.

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. One of the reaction products (*O*-acetyl benzohydroxamate, C₆H₅CONHOCOCH₃) was identified using an LC/Q-TOF Mass Spectrometer. The analytic methods and analysis report are given in the Supplementary material.

Results

All the reactions in this study obeyed pseudo-first-order kinetics and proceeded with quantitative liberation of *p*-nitrophenoxide anion. Pseudo-first-order rate constants (k_{obsd}) were calculated from the slope of linear plots of $\ln (A_{\infty} - A_t)$ vs. time, where the reaction was followed for at least 9 half-lives. The second-order rate constants were calculated from the slope of the linear plots of k_{obsd} vs. concentration of nucleophile (see the Supplementary material) and are summarized in Table 1 for the reactions with *m*-ClPhO⁻ and BHA⁻ and in Table 2 for those with MBHA⁻ and M₂BHA⁻ with standard deviations in the relevant rate constants. The reproducibility in the second-order rate constant is estimated to be higher than

97% based on at least three replicate runs.

Discussion

Medium Effect on Reactivity. As shown in Table 1, the second-order rate constant for the reaction of **1a** with $m\text{-ClPhO}^-$ ($k_{m\text{-ClPhO}^-}$) decreases from 0.362 to 0.260 $\text{M}^{-1}\text{s}^{-1}$ as the reaction medium changes from pure H_2O to 10 mol % DMSO, but increases upon further addition of DMSO to the reaction medium. A contrasting result is obtained for the corresponding reaction with BHA^- . Addition of DMSO to the reaction medium causes a decrease in the rate constant (i.e., k_{BHA^-}) but such decrease in the rate constant persists even into higher DMSO content regions, e.g., k_{BHA^-} decreases from 58.5 $\text{M}^{-1}\text{s}^{-1}$ in H_2O to 26.3 and 15.5 $\text{M}^{-1}\text{s}^{-1}$ in 30 and 60 mol % DMSO, respectively. It is also noted that k_{BHA^-} in 90 mol % DMSO (23.9 $\text{M}^{-1}\text{s}^{-1}$) is still smaller than that in H_2O .

It is well known that DMSO is highly polarizable and its negative dipole is exposed while the positive one is buried in the middle of the molecule.^{19,20} Thus, anionic nucleophiles, which can be stabilized in H_2O through H-bonding interaction, become destabilized upon addition of DMSO to the reaction medium due to the electronic repulsion between the anion and the negative dipole end of DMSO. Accordingly, one might expect that charge localized anionic nucleophiles, generally, should become more reactive as the DMSO content in the reaction medium increases.

The effect of medium on the reactivity of $m\text{-ClPhO}^-$ and BHA^- is graphically illustrated in Figure 1. One can see that the reactivity of $m\text{-ClPhO}^-$ toward **1a** increases with increasing DMSO content in the medium except at 10 mol % DMSO. Such an increasing reactivity pattern has previously been reported for reactions of Z-substituted-phenyl acetates (**1b-1e**) with anionic nucleophiles (e.g., aryloxides and oximates) in DMSO- H_2O mixtures.^{17a,17b} However, BHA^- exhibits a different reactivity pattern, i.e., k_{BHA^-} decreases as the DMSO

content in the medium increases up to 60 mol % DMSO and then increases from 70 to 90 mol %, but only to a small degree. The decreasing rate-constant pattern shown by BHA^- is quite unexpected on the basis of the Hughes and Ingold's qualitative solvent-effect rule,²¹ where a transition state (TS) that is more dispersed, less polar than the ground state (GS) should lead to an increase in rate constant as the medium becomes less polar as a result of addition of DMSO.²¹

Medium Effect on Structures of BHA^- . Hydroxamic acids have previously been reported to act as OH or NH acids depending on the nature of solvents.²²⁻²⁶ Bordwell et al. have concluded that hydroxamic acids behave as OH acids in hydroxylic solvents but as NH acids in DMSO by comparing acidities of 6 series of analogous oxygen, nitrogen, and carbon acids in DMSO and in the gas phase.²² A similar conclusion has been drawn from spectrometric data, chemoselectivity of methylation of hydroxamic acids, and computational studies (i.e., OH acids in H_2O but NH acids in the gas phase or in dipolar aprotic solvents).²³⁻²⁶ Thus, one might expect that BHA^- would exist mainly as I in H_2O but its tautomeric form II in DMSO. Furthermore, BHA^- would rapidly establish a prototropic equilibrium²⁷ between I and its tautomer II in the DMSO- H_2O mixtures (Scheme 2) and the position of such an equilibrium would be strongly dependent on the DMSO- H_2O composition.

In examining Scheme 2 it is clear that intramolecular hydrogen bonding, shown in tautomer I as a four-member ring, could not be very effective in stabilizing I in water-rich media. In fact, amphiprotic water would stabilize I through numerous effective H-bonding interactions with I; *I does not need intramolecular H-bonding*. Contrariwise, in DMSO-rich solvent region intramolecular H-bonding forming a five-membered ring system in II could replace stabilization by the medium expected in H_2O dominant media. Result: the tautomeric equilibrium, K_t , should shift towards II as a function of increasing concentration of DMSO in

the medium.

The nucleophilicity of II in DMSO-rich media depends upon interplay of factors including the relative contributions of the resonance forms of II (Scheme 2). If form IIa makes a dominant contribution to the resonance hybrid, II, then, in principle, not only should product analysis reveal that BHA^- reacts primarily as a N-nucleophile, but that yield should be reduced as a result of steric hindrance of the nucleophilic site.

In fact, it has been reported that only *O*-acylated product, e.g., $\text{C}_6\text{H}_5\text{C}(\text{O})\text{NHOC}(\text{O})\text{CH}_3$, is formed from the reaction of benzohydroxamic acid with acetylating agents (e.g., acetyl chloride or acetic anhydride),^{17f} and that *O*-methylation occurs predominantly in the reaction of benzohydroxamic acid with diazomethane.^{26a} Finally, ab initio calculations performed on the hydroxamate ions at RHF level using 6-311G (d,p) basis set have also revealed that the O atom is the nucleophilic site toward $\text{C}=\text{O}$ and $\text{P}=\text{O}$ centered esters.^{26b}

On the other hand, in form IIb the strong electrostatic attraction of $=\text{N}-\text{O}-\text{H}$ for $\text{C}-\text{O}^-$ should lead to a five-membered H-bonded ring that would account for a greater contribution to II from IIb than from IIa. The dominant contributor to the overall hybrid form would then be IIb. In this case, II no longer meets the definition of an α -nucleophile; *in IIb no lone pair resides on the atom α to the nucleophilic center*. This translates into *a decrease in nucleophilic reactivity as K_t shifts to II as a function of increasing DMSO in the medium and as II is better described by IIb*.

To further test the idea, MBHA^- and M_2BHA^- have been used as a new set of α -effect nucleophiles for the reactions with **1a**. Note that MBHA^- could also form comparable tautomeric structure to II, described by canonical forms analogous to those shown in Scheme 2 in the DMSO- H_2O mixtures. Accordingly, MBHA^- and BHA^- would exhibit a similar reactivity pattern upon addition of DMSO to the medium. However, M_2BHA^- should show a quite different reactivity pattern in the DMSO- H_2O mixtures since M_2BHA^- is structurally

unable to undergo tautomerization to give a prototropic isomer analogous to II.

As shown in Table 2, the second-order rate constant for the reactions with MBHA^- , k_{MBHA^-} , decreases as the DMSO content in the reaction medium increases up to ca. 60 mol % DMSO and is followed by a small increase in k_{MBHA^-} upon further addition of DMSO. It is noted that the rate constant for the reaction with MBHA^- in 90 mol % DMSO is still smaller than that in pure H_2O . This reactivity pattern is almost the same as that observed in the corresponding reaction with BHA^- , in accord with the foregoing reasoning (*vide supra*). In contrast, $k_{\text{M}_2\text{BHA}^-}$ increases significantly as the DMSO content in the reaction medium increases, e.g., it increases from 15.3 to 90,700 $\text{M}^{-1}\text{s}^{-1}$ as the reaction medium changes from pure H_2O to 90 mol % DMSO, an impressive 5930-fold increase in reactivity.

A similar result was previously reported for the corresponding reactions carried out in MeCN- H_2O mixtures, e.g., the rate constant for the reaction of **1a** with MBHA^- decreased with increasing MeCN content in the reaction medium up to 60 mol % MeCN and then increased marginally thereafter.^{17f} The rate constant for the reaction with M_2BHA^- exhibited also a small decrease up to 30 mol % MeCN and increased beyond that point, e.g., $k_{\text{M}_2\text{BHA}^-}$ decreased from 15.3 in H_2O to 12.0 $\text{M}^{-1}\text{s}^{-1}$ in 30 mol % MeCN and thence increased to 574 $\text{M}^{-1}\text{s}^{-1}$ in 90 mol % MeCN.^{17f} It is noteworthy that the increase in reactivity of M_2BHA^- is only 37.5-fold upon changing the reaction medium from pure H_2O to 90 mol % MeCN, a moderate “two-point” rate enhancement.

The effect of medium on reactivity of MBHA^- and M_2BHA^- is illustrated in Figure 2. The logarithmic second-order rate constant for the reaction with MBHA^- (i.e., $\log k_{\text{MBHA}^-}$) decreases as the DMSO content in the medium increases up to 60 mol % DMSO and then increases thereafter, although the decrease or increase in the rate constant appears to be small. In contrast, the logarithmic rate constant for the reaction with M_2BHA^- (i.e., $\log k_{\text{M}_2\text{BHA}^-}$) increases linearly with increasing DMSO content in the reaction medium. Consequently,

MBHA⁻, which is more reactive than M₂BHA⁻ in H₂O and 10 mol % DMSO, becomes less reactive than M₂BHA⁻ beyond 20 mol % DMSO. Such contrasting reactivity patterns shown in Figure 2 clearly support the preceding idea that the unusual reactivity shown by BHA⁻ is caused by the equilibrium shift from more reactive I to the less reactive tautomeric species II as the DMSO content in the reaction medium increases. Furthermore, our current kinetic results are consistent with the conclusion drawn from various experimental and computational studies, i.e., hydroxamic acids behave as OH acids in H₂O but as NH acids in gas phase or in dipolar aprotic solvents.²²⁻²⁶

Effect of Medium on the α -Effect. It is well known that HOO⁻ is more nucleophilic than HO⁻ in H₂O. Since the former was reported to be 12 kcal/mol less strongly solvated than the latter in H₂O, the enhanced reactivity shown by HOO⁻ was attributed to the solvation effect.^{9,10} In contrast, BHAs⁻ were reported to be more strongly solvated than *m*-ClPhO⁻ in H₂O.²⁸ Nevertheless, Table 3 shows that the three BHAs⁻ exhibit the α -effect in H₂O. Thus, BHAs⁻ appear to be intrinsically more nucleophilic than *m*-ClPhO⁻ toward **1a**. This idea is in accord with the conclusion drawn from recent gas-phase experiments and computational studies that α -effect nucleophiles are intrinsically more reactive than similarly basic normal-nucleophiles in gas-phase reactions.^{14,15}

It is noted that BHA⁻ and MBHA⁻ are less reactive than *m*-ClPhO⁻ in 90 mol % DMSO (i.e., absence of the α -effect), while the α -effect shown by M₂BHA⁻ increases from 42.3 to 1270 as the reaction medium changes from pure H₂O to 90 mol % DMSO. Our results indicate that the absence of the α -effect for the reactions with BHA⁻ and MBHA⁻ likely arises from the equilibrium shift from I to the less reactive tautomer II, described by increasingly greater contributions of resonance form IIb, upon addition of DMSO to the reaction medium. Accordingly, the effect of medium on the α -effect will be discussed only for the reactions with M₂BHA⁻ and *m*-ClPhO⁻.

In Figure 3 are illustrated the α -effect for the reactions of **1a** with M_2BHA^- and $m\text{-ClPhO}^-$ in the DMSO- H_2O mixtures together with that reported for the corresponding reactions carried out in MeCN- H_2O mixtures^{17f} for comparison. Interestingly, the α -effect profiles contrast, e.g., the α -effect in DMSO- H_2O mixtures increases steeply upon addition of DMSO up to ca. 70 mol % DMSO and levels off subsequently, whereas that in MeCN- H_2O mixtures increases only a little up to ca. 70 mol % MeCN but increases rapidly beyond that point. The contrasting α -effect profiles shown in Figure 3 clearly indicate that medium effect on the α -effect is indeed remarkable. Though likely fortuitous, it is striking that the two α -effect versus medium curves almost appear to be mirror images of one another. This emphasizes the differences in behavior found with the two solvents, DMSO and MeCN, even though these are generally grouped together as being polar and aprotic.^{19,20}

We have previously concluded that the increasing basicity difference between the two nucleophiles is responsible for the significant increasing α -effect in the MeCN-rich region since M_2BHA^- was found to be more basic than $m\text{-ClPhO}^-$ with increasing the MeCN content in the MeCN-rich region.^{17f} In contrast, it has previously been reported that basicity of $p\text{-ClPhO}^-$ and oximate anions (e.g., Ox^- and α,α,α -trifluoroacetophenone oximate anion) increases in a parallel manner upon addition of DMSO to H_2O .^{11,17a} Thus, one might suggest that any difference in basicity between $m\text{-ClPhO}^-$ and M_2BHA^- is not likely responsible for the α -effect profile observed in the DMSO- H_2O mixtures.

We have reported that reactions of **1a** with Ox^- and $p\text{-ClPhO}^-$ in DMSO- H_2O mixtures yield a bell-shaped α -effect profile, i.e., the α -effect increases up to 50 mol % DMSO and then decreases thereafter.^{17a} From combination of our calorimetric studies of the two nucleophiles with activation parameters for the two series of reactions in DMSO- H_2O mixtures, it has been concluded that differential GS destabilization between the two nucleophiles is responsible for the increasing α -effect in the H_2O -rich region while differential enthalpy of activation (TS

effect) causes the decreasing α -effect trend in the DMSO-rich region.^{17a} This was because Ox^- became more destabilized than $p\text{-ClPhO}^-$ up to 50 mol % DMSO but the TS for the reaction with $p\text{-ClPhO}^-$ became more stabilized than that for the reaction with Ox^- in the DMSO-rich region.^{17a}

A similar argument can be applied to the current α -effect profile. One might expect that the negative charge in M_2BHA^- is localized mainly on its O atom. In contrast, the negative charge in $m\text{-ClPhO}^-$ should be delocalized on the aryl ring through resonance interaction. This idea is consistent with the report that BHAs^- are more strongly solvated than $m\text{-ClPhO}^-$ in H_2O .²⁸ Thus, M_2BHA^- would be more stabilized than $m\text{-ClPhO}^-$ in H_2O through the H-bonding interaction, but would be more destabilized upon addition of DMSO to the medium. This idea is in accord with the increasing α -effect trend up to 70 mol % DMSO found here.

Since DMSO is highly polarizable, it can stabilize charge dispersed anions (e.g., picrate anion and negatively charged TSs) through polarizability interaction, which is absent for MeCN.^{19,20} This idea is consistent with the kinetic results that rate enhancement is more significant upon medium change from H_2O to DMSO than to MeCN, *even though both DMSO and MeCN are categorized as polar aprotic solvents*,²⁰ e.g., the $k_{\text{M}_2\text{BHA}^-}$ for the reaction of **1a** with M_2BHA^- increases 5930- and 37.5-fold upon medium change from H_2O to 90 mol % DMSO and MeCN, respectively.

It is obvious that the negative charge in the TS of the current reactions is dispersed partially on the nucleophile and partially on the substrate whether the reaction proceeds either through a concerted mechanism or via a stepwise pathway. We have previously shown that the TS formed from the reaction of **1a** with $p\text{-ClPhO}^-$ is more stabilized than that formed from the corresponding reaction with Ox^- in the DMSO-rich region. As mentioned above, M_2BHA^- would be more destabilized than $m\text{-ClPhO}^-$ in the whole range of DMSO- H_2O mixtures. In contrast, the TS formed from the reaction of **1a** with $m\text{-ClPhO}^-$ is expected to be more

stabilized than that formed from the corresponding reaction with M_2BHA^- in the DMSO-rich region. Thus, one can suggest that the opposing medium effects on the GS and TS in the DMSO-rich region are responsible for the kinetic result that the α -effect levels off beyond 70 mol % DMSO.

Conclusions

Our kinetic study on nucleophilic substitution reactions of **1a** with $m\text{-ClPhO}^-$, BHA^- , $MBHA^-$ and M_2BHA^- in DMSO- H_2O mixtures of varying compositions has demonstrated that medium effect on the α -effect is indeed significant and led us to conclude the following: (1) BHA^- and $MBHA^-$ form an equilibrium of I with its tautomeric form II in DMSO- H_2O mixtures. (2) Equilibrium shift from I to the less reactive II upon addition of DMSO to the reaction medium is responsible for the unusual reactivity pattern shown by BHA^- and $MBHA^-$. Tautomer II is less reactive than I as a result of an increasingly greater contribution of the non- α -nucleophilic resonance form IIb, which is stabilized in DMSO through formation of a good five-membered intramolecular hydrogen bond, to the description of the resonance hybrid II. (3) M_2BHA^- becomes more strongly destabilized than $m\text{-ClPhO}^-$ upon addition of DMSO to the medium, which is the cause of the increasing α -effect profile up to 70 mol % DMSO. (4) The TS formed from the reaction with $m\text{-ClPhO}^-$ becomes more stabilized through the polarizability interaction with DMSO than that formed from the reaction with M_2BHA^- beyond 70 mol % DMSO. This accounts for the result that the α -effect levels off beyond 70 mol % DMSO.

Supplementary material: kinetic data for the reactions of PNPA (**1a**) with $m\text{-ClPhO}^-$, BHA^- , $MBHA^-$ and M_2BHA^- in DMSO- H_2O mixtures of varying compositions and the product analysis report. Supplementary material is available with the article through the journal Web site at <http://nrcresearchpress>.

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Tables for cjc-2018-0103

Table 1. Summary of the second-order rate constants for the reactions of **1a** with *m*-ClPhO[−] and BHA[−] in DMSO-H₂O mixtures of varying compositions at 25.0 ± 0.1 °C

mol % DMSO	$k_{m\text{-ClPhO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{BHA}^-}/\text{M}^{-1}\text{s}^{-1}$
0	0.362 ± 0.007	58.5 ± 1.7
10	0.260 ± 0.002	47.6 ± 0.3
20	0.338 ± 0.007	37.0 ± 0.3
30	0.545 ± 0.002	26.3 ± 0.1
40	0.933 ± 0.020	19.0 ± 0.5
50	2.13 ± 0.01	16.8 ± 0.04
60	4.29 ± 0.10	15.5 ± 0.2
70	9.75 ± 0.18	17.5 ± 0.4
80	27.2 ± 0.5	20.3 ± 0.2
90	71.6 ± 3.1	23.9 ± 0.3

Table 2. Summary of the second-order rate constants for the reactions of **1a** with MBHA[−] and M₂BHA[−] in DMSO-H₂O mixtures of varying compositions at 25.0 ± 0.1 °C

mol % DMSO	$k_{\text{MBHA}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{M}_2\text{BHA}^-}/\text{M}^{-1}\text{s}^{-1}$
0	63.8 ± 0.8	15.3 ± 0.3
10	59.7 ± 1.4	31.8 ± 0.4
20	49.4 ± 0.7	93.1 ± 0.6
30	34.6 ± 0.9	284 ± 4
40	29.4 ± 1.2	780 ± 11
50	24.8 ± 0.8	2080 ± 50
60	23.7 ± 0.6	4880 ± 110
70	23.7 ± 0.3	12100 ± 500
80	27.7 ± 0.9	34000 ± 600
90	36.2 ± 0.2	90700 ± 3600

Table 3. Summary of the α -effect for the reactions of **1a** with *m*-ClPhO[−], BHA[−], MBHA[−] and M₂BHA[−] in DMSO-H₂O mixtures of varying compositions at 25.0 ± 0.1 °C

mol % DMSO	$k_{\text{BHA}^-}/k_{m\text{-ClPhO}^-}$	$k_{\text{MBHA}^-}/k_{m\text{-ClPhO}^-}$	$k_{\text{M}_2\text{BHA}^-}/k_{m\text{-ClPhO}^-}$
0	162	176	42.3
10	183	230	122
20	109	146	275
30	48.3	63.5	521
40	20.4	31.5	836
50	7.89	11.6	977
60	3.61	5.52	1140
70	1.79	2.43	1240
80	0.746	1.02	1250
90	0.334	0.506	1270

Figures for cjc-2018-0103

Chart 1. Structures of substrates studied previously. **Scheme 1.** Reactions of **1a** with $m\text{-ClPhO}^-$, BHA^- , MBHA^- and M_2BHA^- . **Scheme 2.** A prototropic equilibrium between I and its tautomer II.

Figure 1. Plots of $\log k$ vs. mol % DMSO for the reactions of **1a** with $m\text{-ClPhO}^-$ and BHA^- in DMSO- H_2O mixtures of varying compositions at 25.0 ± 0.1 °C.

Figure 2. Plots of $\log k$ vs. mol % DMSO for the reactions of **1a** with MBHA⁻ and M₂BHA⁻ in DMSO-H₂O mixtures of varying compositions at 25.0 ± 0.1 °C.

Figure 3. Medium effect on the α -effect (i.e., $k_{\text{M}_2\text{BHA}^-}/k_{\text{m-ClPhO}^-}$) for the reactions of **1a** with M₂BHA⁻ and *m*-ClPhO⁻ in DMSO-H₂O (●) and in MeCN-H₂O (○) mixtures of varying compositions at 25.0 ± 0.1 °C. The α -effect data for the reactions in MeCN-H₂O mixtures were taken from ref. 17f.

Medium Effect on the α -Effect for Nucleophilic Substitution Reactions of *p*-Nitrophenyl Acetate with Benzohydroxamates and *m*-Chlorophenoxide in DMSO-H₂O Mixtures as Contrasts with MeCN-H₂O Mixtures: Comparing Two Very Different Polar Aprotic Solvent Components¹

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