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Effect of Medium on Reactivity for Alkaline Hydrolysis of *p*-Nitrophenyl Acetate and *S*-*p*-Nitrophenyl Thioacetate in DMSO-H_2O Mixtures of Varying Compositions: Ground State and Transition State Contributions

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

Abstract

Second-order rate constants (k_N) for reactions of *p*-nitrophenyl acetate (**1**) and *S*-*p*-nitrophenyl thioacetate (**2**) with OH^- have been measured spectrophotometrically in DMSO-H_2O mixtures of varying compositions at 25.0 ± 0.1 °C. The k_N value increases from 11.6 to 32,800 $M^{-1}s^{-1}$ for the reactions of **1** and from 5.90 to 190,000 $M^{-1}s^{-1}$ for those of **2** as the reaction medium changes from H_2O to 80 mol % DMSO, indicating that the effect of medium on reactivity is more remarkable for the reactions of **2** than for those of **1**. Although **2** possesses a better leaving group than **1**, the former is less reactive than the latter by a factor of 2 in H_2O. This implies that expulsion of the leaving group is not advanced in the rate-determining transition state (TS), i.e., the reactions of **1** and **2** with OH^- proceed through a stepwise mechanism, in which expulsion of the leaving group from the addition intermediate occurs after the rate-determining step (RDS). Addition of DMSO to H_2O would destabilize OH^- through electronic repulsion between the anion and the negative-dipole end in DMSO. However, destabilization of OH^- in the ground state (GS) is not solely responsible for the remarkably enhanced reactivity upon addition of DMSO to the medium. The effect of medium on reactivity has been dissected into the GS and TS contributions through combination of the kinetic data with the transfer enthalpies ($\Delta\Delta H_{tr}$) from H_2O to DMSO-H_2O mixtures for OH^- ion.

Keywords: Medium effect, Alkaline hydrolysis, Polarizability, Destabilization of ground state, Stabilization of transition state

Introduction

Acyl-group transfer reaction is one of the most important substitution reactions at carbonyl centers.[1] Numerous studies have been performed to investigate the reactivity and reaction mechanism.[2-15] Some major factors reported to influence the reactivity and reaction mechanism are the type of solvents (e.g., protic vs. aprotic solvents), the nature of nucleophiles (e.g., neutral amine vs. anionic nucleophiles), basicity of nucleophiles and leaving groups, polarizability of reactants, etc.[2-15]

It is well known that anionic nucleophiles are more reactive upon changing the reaction medium from a protic solvent to a dipolar aprotic one (e.g., DMSO, DMF or HMPT) due to electronic repulsion between the anionic nucleophile and the negative-dipole end in the dipolar solvent.[2-4] Such medium effect on reactivity has been reported to be more significant for reactions with a smaller anionic nucleophile.[2-4]

It is generally understood that nucleophilic reactivity increases with increasing basicity of nucleophiles. However, nucleophiles bearing one or more nonbonding electron pairs on the atom α to the nucleophilic site have been reported to exhibit abnormally enhanced reactivity compared with the reference nucleophiles of similar basicity (or a positive deviation from a linear Brønsted-type plot).[5-15] Thus, the enhanced nucleophilic reactivity shown by these nucleophiles has been termed the α-effect.[5,6]

We have previously reported that butane-2,3-dione monoximate (Ox^-, an α-effect nucleophile) is ca. 100 times more reactive than *p*-chlorophenoxide (*p*-$ClPhO^-$, a reference nucleophile) toward *p*-nitrophenyl acetate (**1**) in H_2O, although the basicity of the two nucleophiles is similar.[7] Interestingly, we found that the magnitude of the α-effect (i.e., $k_N^{Ox-} / k_N^{p\text{-}ClPhO-}$) increases as the DMSO content in the reaction medium increases up to ca. 50 mol % DMSO and then decreases thereafter, resulting in a bell-shaped α-effect profile.[7] A similar medium dependent α-effect profile has been reported for the corresponding reactions of *S*-*p*-nitrophenyl thioacetae (**2**), *p*-nitrophenyl benzoate (**3**) and *O*-*p*-nitrophenyl thionobenzoate (**4**), although the magnitude of the α-effect was found to be dependent on the nature of the leaving group (e.g., *p*-nitrophenoxide in **1** vs. *p*-nitrothiophenoxide in **2**) and the electrophilic center (e.g., C=O in **3** vs. C=S in **4**).[8]

Our previous calorimetric studies on measurements of enthalpy of solution (ΔH_{sol}) for the sodium salts of Ox^- and *p*-$ClPhO^-$ have shown that Ox^- becomes more destabilized than *p*-$ClPhO^-$ upon addition of DMSO to H_2O, i.e., the difference in ΔH_{sol} between the two salts (i.e., $\Delta\Delta H_{sol} = \Delta H_{sol}^{OxNa} - \Delta H_{sol}^{p\text{-}ClPhONa}$) increases as the DMSO content in the medium increases up to ca. 40 mol % DMSO and then remains nearly constant at the maximum (i.e., 7.1 kcal mol^{-1}) upon further addition of DMSO to the medium.[7a] Thus, the calorimetric data combined with the kinetic results have led us to conclude that the differential GS destabilization between the two nucleophiles is mainly responsible for the increasing α-effect in the H_2O-rich region while the decreasing α-effect found in the DMSO-rich region is caused by the differential TS stabilization between the TS for the reactions of **1** with Ox^- and that for the corresponding reactions with *p*-$ClPhO^-$.[7a]

We have now extended our study to the reactions of **1** and **2** with OH^- in DMSO-H_2O mixtures of varying compositions to obtain further information on medium effects as shown in Scheme 1. We have found that the effect of medium on reactivity is more remarkable for the reactions of **2** than for those of **1**. We wish to report the kinetic evidence that the TS for the reactions of **2**, which possesses a polarizable S atom in the leaving group, is more stabilized than that for the corresponding reactions of **1** in DMSO-H_2O mixtures, and that the differential TS stabilization is responsible for the differential medium effect found in this study.

Experimental

Materials. Substrates **1** and **2** were prepared from reactions of acetyl chloride with *p*-nitrophenol and *p*-nitrothiophenol, respectively in the presence of triethylamine in anhydrous ether as reported previously.[7a] DMSO was distilled over calcium hydride at a reduced pressure (bp 64~66°C at 6~7mmHg) and stored under nitrogen. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. NaOH stock solution was standardized against potassium hydrogen phthalate (KHP, recrystallized from ethanol and dried under high vacuum). Other chemicals were of the highest quality available.

Kinetics. The kinetic studies were performed with a UV-Vis spectrophotometer for slow reactions ($t_{1/2}$ > 10s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \leq 10$ s) equipped with a constant temperature circulating bath (25.0 ± 0.1 °C). The reactions were followed by monitoring the appearance of *p*-nitrophenoxide ion for the reaction of **1** and *p*-nitrothiophenoxide ion for that of **2**. All the reactions were carried out under pseudo-first-order conditions in which the OH^- concentration was at least 20-fold excess over the substrate concentration. Other details in experimental methods were similar to those described previously.[7, 8]

Product Analysis. *p*-Nitrophenoxide (or *p*-nitrothiophenoxide) ion was identified as one of the reaction products by comparison of the UV-Vis spectrum after completion of the reaction with that of authentic sample under the same reaction condition.

Results

The kinetic study was performed spectrophotometrically under pseudo-first-order conditions in which the concentration of OH^- was in large excess over that of the substrate **1** or **2**. All reactions in this study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the slope of linear plots of ln ($A_\infty - A_t$) vs. time ($R^2 \geq 0.9999$). The second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} vs. concentration of OH^-. The kinetic data for the reactions of **1** and **2** with OH^- in DMSO-H_2O mixtures are summarized in Tables 1 and 2. The uncertainty in the k_N values is estimated to be less than 3 % from replicate runs.

Discussion

Effect of Medium on Reactivity. As shown in Table 1, the reactivity of OH^- increases as the DMSO content in the medium increases, i.e., k_N increases from 11.6 to 32,800 $M^{-1}s^{-1}$ for the reactions with **1** and from 5.90 to 190,000 $M^{-1}s^{-1}$ for those of **2** as the medium changes from H_2O to 80 mol % DMSO. Apparently, the effect of medium on reactivity is more significant for the reactions of **2** than for those of **1**.

We have previously reported that **2** is ca. 300 times more reactive than **1** toward *p*-chlorothiophenoxide ion (a soft polarizable nucleophile), i.e., k_N = 0.143 and 42.7 $M^{-1}s^{-1}$ for the reactions of **1** and **2** in H_2O, respectively.[8d] The contrast in the reactivity order found in the present work for the reactions of OH^- is striking; here **2** is less reactive than **1** by a factor of 2 in H_2O (Table 1). Furthermore, *p*-chlorothiophenoxide (k_N = 42.7 $M^{-1}s^{-1}$) is ca. 7 times more reactive than OH^- (k_N = 5.90 $M^{-1}s^{-1}$) for the reaction with **2**, although the former is less basic than the latter by 8.2 pK_a units.[16] This result indicates clearly that basicity of these nucleophiles does not control the reactivity for reactions involving polarizable reactants. Accordingly, one might suggest that the contrasting reactivity order found for the reactions of **1** and **2** with OH^- and for the corresponding reactions with *p*-chlorothiophenoxide is in accord with the HSAB principle.[17] However, the HSAB principle cannot explain the kinetic result that **2** becomes more reactive than **1** toward a hard base OH^- in DMSO-rich media (Table 1).

The effect of medium on the reactivity of OH^- toward substrates **1** and **2** are graphically illustrated in Figure 1. One can see that the logarithmic second-order rate constant increases as the mol % DMSO in the medium increases. It is also seen that **2** is less reactive than **1** up to 20 mol % DMSO but becomes more reactive thereafter. Consequently, the plot for the reactions of **2** exhibit a steeper slope than that for the corresponding reactions of **1**, although both plots are not quite linear.

One can suggest that H-bonding interaction is the most dominant for a small anion (e.g., OH^- or F^- ion) in H_2O. It is apparent that addition of DMSO to H_2O would decrease free H_2O molecules which can form H-bonding with anions. Because DMSO is known to form strong H-bonding with H_2O and the H-bonding interactions are stronger in DMSO-H_2O than in H_2O-H_2O.[2,3,18] Thus, OH^- would be destabilized upon addition of DMSO to H_2O due to a decrease in free H_2O molecules.

It is well known that the negative end of the dipole in DMSO is exposed while the positive one is buried in the middle of the molecule.[2,3,18] Accordingly, anions would experience strong electronic repulsion in DMSO-rich media. Such electronic repulsion between an anion and the negative dipole end in DMSO would be stronger for a smaller anion but insignificant for a large and polarizable anion in the DMSO-rich region. Moreover, DMSO could exert charge dispersion or mutual polarizability interactions toward a large and polarizable anion (e.g., picrate or I^- ion).[2, 3]

The negative charge in the TS for the reactions of **1** and **2** with OH^- would be dispersed whether the reactions proceed through a concerted mechanism or via a stepwise pathway. Hence, the TS for the current reactions could be stabilized through charge dispersion or mutual polarizability interactions in DMSO or in DMSO-rich media. Thus, one can suggest that both destabilization of OH^- in the GS and stabilization of the TS are responsible for the remarkable rate enhancement observed for the current reactions upon addition of DMSO to the medium.

Deduction of Reaction Mechanism from Leaving-Group Effect. It is believed that *p*-nitrothiophenoxide (pK_a = 4.52) is a better leaving group than *p*-nitrophenoxide (pK_a = 7.14) on the basis of their basicity.[16] Accordingly, one might expect that **2** would be more reactive than **1**. However, as mentioned in the preceding section (from Table 1 and Figure 1), **2** is less reactive than **1** by a factor of 2 in H_2O, indicating that leaving-group effect is absent. This is contrary to the expectation, if expulsion of the leaving group is advanced in the rate-determining TS whether the reactions proceed through a concerted mechanism or via a stepwise pathway. Thus, detailed information on the reaction mechanism is necessary to account for the absence of the leaving-group effect found in this study.

Nucleophilic substitution reactions of aryl esters with anionic nucleophiles have been reported to proceed either through a concerted mechanism or via a stepwise pathway with an addition intermediate depending on reaction conditions.[19-26] Williams et al. have concluded that the reaction of **1** with a series of aryloxides proceeds through a concerted mechanism on the basis of a linear Brønsted-type plot.[20] If the reaction procceded through a stepwise mechanism, the Brønsted-type plot should have exhibited a break (or curvature) due to a change in the RDS when the pK_a of the incoming aryloxide corresponded to that of the leaving *p*-nitrophenoxide. Thus, absence of a break (or curvature) in the Brønsted-type plot has been taken as evidence for a concerted mechanism. The concerted mechanism was favored from the ^{18}O kinetic isotope effect studies on reactions of **1** with oxyanion nucleophiles by Hess and Hengge.[21] and from recent computational studies on alkaline hydrolyses of diaryl sulfates by Szeler et al.[22a] and aryl benzenesulfonates by Duarte et al.[22b]

In contrast, we have reported that nucleophilic substitution reactions of substituted phenyl acetates (**1** and its derivatives) with phenoxide ion proceed through a stepwise mechanism with an addition intermediate, in which expulsion of the leaving group from the addition intermediate occurs after the RDS.[23] The evidence provided was Hammett plots which exhibited a poor correlation with σ^- constants but a much better linear correlation with σ^o constants,[23] because this result indicates that no negative charge is developing on the O atom of the leaving group in the RDS. A similar conclusion has been drawn for the reactions of OH^- with aryl benzoates (**3** and its derivatives) and *O*-aryl thionobenzoate (**4** and its derivatives).[24] The stepwise mechanism was further supported from the theoretical studies on alkaline hydrolysis of esters in the gas phase by Pliego et al.[25a] and by Hori et al.[25b,c]

On the other hand, reactions of thiol esters have not been investigated as intensively as those of the analogous oxygen ester. However, one could deduce the mechanism for the current reactions of **1** and **2** on the basis of the kinetic results showing absence of the leaving-group effect. If the current reactions proceed through a concerted mechanism, attack of the nucleophile and expulsion of the leaving group occur simultaneously. In this case, **2**, which possesses a better leaving group (i.e., *p*-nitrothiophenoxide), should be more reactive than **1**, which bears a poorer leaving group (i.e., *p*-nitrophenoxide). On the contrary, if the reactions proceed through a stepwise mechanism, expulsion of the leaving group from the addition intermediate should occur after the RDS due to the large difference in basicity between OH^- and the leaving group (i.e., *p*-nitrophenoxide in **1** or *p*-nitrothiophenoxide in **2**). In this case, the leaving-group ability could not affect the reactivity of substrates **1** and **2**. Thus, the kinetic results shown in Table 1 and Figure 1 (i.e., absence of the leaving-group effect up to 20 mol % DMSO) imply that the current reactions proceed through a stepwise mechanism with an addition intermediate, in which expulsion of the leaving group occurs after the RDS. This is consistent with the report by Hupe and Jencks that nucleophilic substitution reactions of thiol esters proceed through a stepwise mechanism.[26]

Dissection of Medium Effect into GS and TS Contributions. In Table 2 are summarized the relative second-order rate constants (i.e., k_N in DMSO-H_2O / k_N in H_2O) for the reactions of **1** and **2** with OH^- together with the transfer enthalpy data from H_2O to DMSO-H_2O mixtures for OH^- ion (i.e., $\Delta\Delta H_{tr} = \Delta H_{sol}^{DMSO\text{-}H2O} - \Delta H_{sol}^{H2O}$), which represents the extent of desolvation of OH^- ion upon changing the medium from H_2O to DMSO-H_2O mixtures. Table 2 shows that $OH^–$ is destabilized up to 15.9 kcal $mol^{–1}$ as the medium changes from H_2O to 80 mol % DMSO, while the reactivity of **1** and **2** toward $OH^–$ increases 2,830 and 32,200 times, respectively, upon the medium change.

The relationship between $\Delta\Delta H_{tr}$ and logarithmic relative-rate constants for the reactions of **1** and **2** with $OH^–$ is demonstrated graphically in Figure 2. It is noted that the plots are nonlinear for both reactions of **1** and **2**. We propose that the nonlinear plots shown in Figure 2 are not due to a change in the reaction mechanism upon addition of DMSO to the reaction medium. Because we have previously reported that reactions of **1** with a series of aryloxide ions proceed through a common TS over the medium range 40 ~ 90 mol % DMSO on the basis of a novel Brønsted-type plot showing an excellent linear correlation.[23]

Figure 2 shows that the logarithmic relative-rate constant increases slowly up to near $\Delta\Delta H_{tr}$ = 10 kcal $mol^{–1}$ but rapidly thereafter for both reactions of **1** and **2**. It is also notable that the reactions of **2** result in larger relative-rate constants than those of **1**, and the difference in the relative rate constants becomes larger as $\Delta\Delta H_{tr}$ increases (or as the DMSO content in the reaction medium increases). If the increasing relative-rate constants for the reactions of **1** and **2** were caused solely by destabilization of $OH^–$ upon addition of DMSO to the medium, one should have observed similarly linear plots. This is because $OH^–$ is the common nucleophile used in this study. Thus, the nonlinear plots shown in Figure 2 suggest that an additional factor (e.g., stabilization of TS) contributes to the enhanced reactivity upon addition of DMSO to the medium.

The IR and ^{13}C NMR spectra taken from substrates **1** and **2** in this study have revealed that the C=O stretching vibration for **2** (1680 $cm^{–1}$) is 70 $cm^{–1}$ lower than that for **1** (1750 $cm^{–1}$), and the ^{13}C NMR chemical shift of the carbonyl carbon in **2** (191.6 ppm) is 23 ppm downfield compared to that in **1** (168.6 ppm). These spectral data imply that the C=O bond in **2** has a weaker double-bond character and is more polarizable than that in **1**. Thus, one might expect that the reactions of **2** would proceed through a more polarizable TS than the corresponding reactions of **1**.

As mentioned in the preceding section, DMSO could stabilize charge dispersed TSs through charge dispersion or mutual polarizability interactions. It is apparent that the more polarizable TS would be more stabilized than the less polarizable TS in the DMSO-H_2O mixtures and such differential TS stabilization would be greater as the DMSO content in the medium increases. Thus, one can suggest that (1) stabilization of TS in the DMSO-rich region is responsible for the nonlinear plots shown in Figure 2 and (2) the differential stabilization of TSs leads to the differential medium effect found in this study for the reactions of **1** and **2**.

Conclusions

Our study has led us to conclude the following: (1) The effect of medium on reactivity is more remarkable for the reactions of **2** than for those of **1**. (2) Substrate **2** is less reactive than **1** by a factor of 2 in H_2O, although the former bears a better leaving group than the latter. This indicates that expulsion of the leaving group is not advanced in the RDS. (3) Destabilization of OH^- is not solely responsible for the enhanced reactivity upon addition of DMSO to the medium. (4) The TS for the reactions of **2** is more stabilized than that for the corresponding reactions of **1** through charge dispersion or mutual polarizability interactions with DMSO. (5) The differential TS stabilization, which becomes more significant as the DMSO content in the medium increases, is mainly responsible for the differential medium effects found in this study.

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Tables 1 and 2 for cjc-2020-0503

Table 1. Summary of second-order rate constants (k_N) for the reactions of *p*-nitrophenyl acetate (**1**) and *S*-*p*-nitrophenyl thioacetate (**2**) with OH^- in DMSO-H_2O mixtures of varying compositions at 25.0 ± 0.1 °C.

mol % DMSO	k_N (**1**) / $M^{-1}s^{-1}$	k_N (**2**) / $M^{-1}s^{-1}$	k_N(**2**) / k_N(**1**)
0	11.6	5.90	0.51
10	19.2	11.6	0.60
20	46.1	39.7	0.86
30	114	180	1.58
40	298	706	2.37
50	879	2860	3.25
60	2,630	10,700	4.07
70	8,350	41,700	4.99
80	32,800	190,000	5.79

Table 2. Transfer enthalpies ($\Delta\Delta H_{tr}$ / kcal mol^{-1}) from H_2O to DMSO-H_2O mixtures for OH^- and relative second-order rate constants ($k_N^{DMSO\text{-}H2O}$ / k_N^{H2O}) for the reactions of **1** and **2** with OH^- in DMSO-H_2O mixtures of varying compositions at 25.0 ± 0.1 °C.[a]

mol % DMSO	$\Delta\Delta H_{tr}$	**1**	**2**
0	0	1.00	1.00
10	–0.8	1.66	1.97
20	3.7	3.97	6.73
30	7.2	9.83	30.5
40	10.7	26.0	119
50	12.4	76.0	485
60	13.9	227	1,810
70	14.9	720	7,070
80	15.9	2,830	32,200

[a]The $\Delta\Delta H_{tr}$ data were taken from ref. 27.

Figures 1 and 2 for cjc-2020-0503

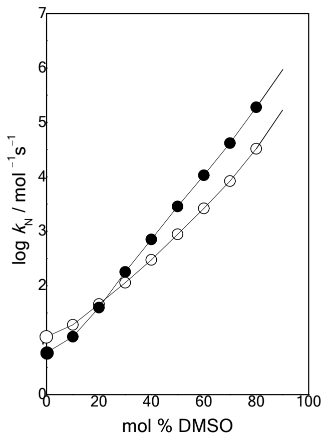


Figure 1. Plots of logarithmic second-order rate constants vs. mol % DMSO for the reactions of **1** (○) and **2** (●) with OH⁻ in DMSO-H_2O mixtures of varying compositions at 25.0 ± 0.1 °C.

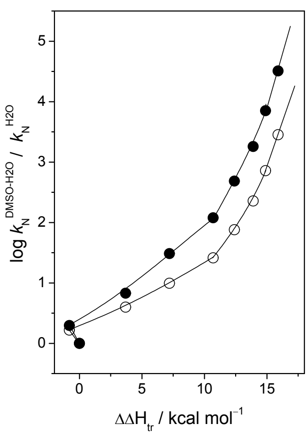
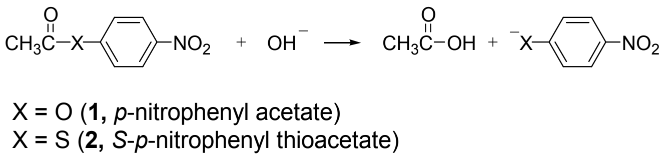


Figure 2. Plots of logarithmic relative-rate constants ($k_N^{DMSO\text{-}H2O}/k_N^{H2O}$) vs. $\Delta\Delta H_{tr}$ for the reactions of **1** (○) and **2** (●) with OH⁻ in DMSO-H_2O mixtures of varying compositions at 25.0 ± 0.1 °C.

Scheme 1 for cjc-2020-0503



Scheme 1. Nucleophilic substitution reactions of *p*-nitrophenyl acetate (**1**) and *S*-*p*-nitrophenyl thioacetate (**2**) with OH^- in various DMSO-H_2O mixtures.

Chart 1 for cjc-2020-0503

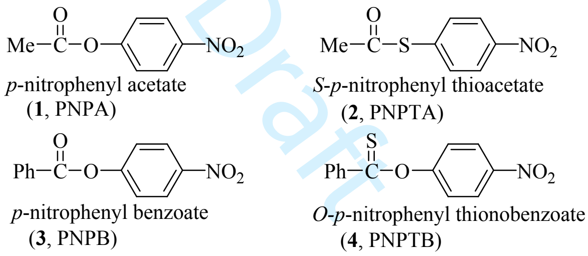


Chart 1. Structures of substrates studied previously.