Contrasting Solvent Effect Profiles for Alkaline Hydrolyses of Paraoxone and Parathione in DMSO-H_2O Mixtures

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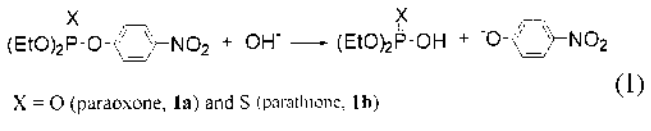
Acyl-transfer reactions have been suggested to proceed either through a concerted mechanism or through a stepwise mechanism, depending on the nature of the nucleophile and the leaving group of substrates.[1-11] It has generally been understood that the reaction of esters with amine nucleophiles proceeds through a stepwise mechanism with an addition intermediate.[3,4] However, the reaction of esters with anionic nucleophiles has not been completely understood, *i.e.*, some studies have suggested a concerted mechanism[5-8] while others have proposed a stepwise mechanism.[9-11]

Williams *et al.* have concluded that acyl-transfer reactions between anionic nuclephiles proceed through a concerted mechanism, based on the linear Brϕnsted-type plot obtained from the reaction of 4-nitrophenyl acetate with a series of substituted phenoxide anions.[5] A similar conclusion was drawn for phosphoryl- and sulfonyl-transfer reactions with anionic nucleophiles.[5] However, Buncel *et al.* have suggested that acyl-transfer reactions proceed through an addition intermediate, based on the poor Hammett correlation obtained from reactions of a series of substituted phenyl acetates, phosphinates and sulfonates with anionic nucleophiles.[9]

Linear free energy relationships (LFERs) have been employed as one of the most popular probes for determination of reaction mechanisms. However, the conclusion drawn based on LFERs alone has been suggested to be inconclusive.[2a] Additional evidence (*e.g.*, kinetic isotope effect,[2a] oxygen isotope exchange,[10] direct observation or isolation of intermediates.[11]) should be required to get more conclusive information about the reaction mechanism. We have recently reported spectral evidence for a stable intermediate along with kinetic evidence for the nucleophilic substitution reaction of a cyclic sulfinate ester, dibenzo[1,2]oxathiin-6-oxide, with ethoxide anion in anhydrous ethanol.[11a] To obtain further information on the reaction mechanisms, we have now expanded our study to alkaline hydrolyses of paraoxone (**1a**) and parathione (**1b**) in dimethyl sulfoxide (DMSO)-H_2O mixtures of varying compositions, eq. (1), and found contrasting solvent effect profiles. A plausible cause of the contrasting solvent effect profile together with the TS structure is herein presented.



(1)

X = O (paraoxone, **1a**) and S (parathione, **1b**)

Solvent : 15, 30, 45, 60, 75 and 90 mole % DMSO in H_2O

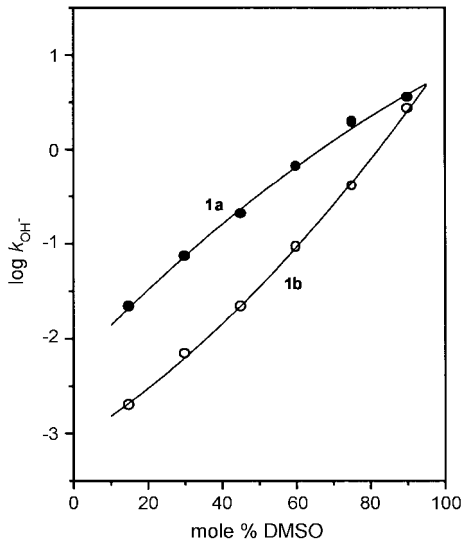
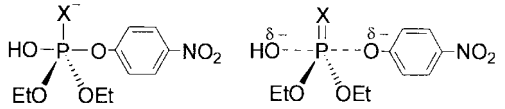


Figure 1. Plots showing contrasting solvent effect profiles for alkaline hydrolyses of paraoxone (**1a**) and parathione (**1b**) in DMSO-H_2O mixtures at 25.0 ± 0.1 °C.

Figure 1 shows that the second-order rate constant increases with increasing mole % DMSO in the reaction medium for both reactions of **1a** and **1b**. However, surprisingly, the effect of solvent on rates is contrasting, *i.e.*, the second-order rate constant for the reaction of **1a** exhibits a downward curvature while the one for the reaction of **1b** shows an upward curvature.

Significant rate enhancements have often been reported for nucleophilic substitution reactions involving anionic nucleophiles as the solvent changes from H_2O to DMSO.[12,13] Such rate enhancements upon addition of DMSO to the reaction medium have been rationalized by postulates such as desolvation of the anionic nucleophile and/or stabilization of the transition state (TS).[12,13] The negative end of the dipole of DMSO is exposed whereas the positive end is buried within the molecule. Therefore, DMSO stabilizes cations, whereas it strongly destabilizes anions due to the repulsion between the anion and the negative end of the dipole. It has generally been understood that destabilization of anionic species is more significant for small and charge localized anions than large and charge delocalized ones.[12] Since earlier

studies on ester hydrolysis have concluded that substrate solvation changes are not responsible for rate enhancements in DMSO,[12] one can suggest that destabilization of OH^- is largely responsible for the rate enhancement upon addition of DMSO to the reaction medium. However, OH^- is the common nucleophile for the reactions of **1a** and **1b**. Therefore, the contrasting solvent effect profile (Figure 1) is clearly not due to the ground-state (GS) but due to differential solvent effect on the TS.



2 **3**

The TS of the present reaction would be negatively charged either the reaction proceeds concertedly or stepwisely. Let **2** and **3** represent the addition intermediate of a stepwise mechanism and the TS structure of a concerted mechanism, respectively. If the present reaction proceeds through a stepwise mechanism, the TS structure would be similar to the intermediate **2**. In this case, the negative charge on the TS would be developed partially on the X atom of the P=X moiety, whether the rate determining step (RDS) is the formation or the breakdown of the intermediate **2**. Such an anionic TS would also be destabilized upon addition of DMSO to the reaction medium. Therefore, one can expect that the destabilization of the anionic TS would diminish the rate accelerating effect caused by destabilization of OH^- ion upon addition of DMSO to a certain degree. Destabilization of the anionic TS would be more significant for the reaction of **1a** than for that of **1b**, since the negative charge on the TS of a stepwise mechanism (*e.g.*, a TS similar to **2**) is expected to be significantly more localized on the P-O^- bond than on the P-S^- bond due to the high polarizability of the S atom. Therefore, one can expect that the rate enhancement upon solvent change from H_2O to DMSO would be less significant for the reaction of **1a** than for that of **1b** if the present reaction proceeds through the intermediate **2**. In fact, the rate enhancement upon solvent change from 15 mole % DMSO to 90 mole % DMSO is much smaller for the reaction of **1a** than for that of **1b** as mentioned above. Such difference in solvent effect on rates can only be obtain when the TS structure is similar to the intermediate **2** in which a partial negative charge is developed on the X atom of the P=X bond.

However, if the present reaction proceeds through a concerted mechanism, the negative charge on the TS **3** would be dispersed on the two O atoms, but clearly not on the X atom of the P=X moiety. In this case, one cannot expect significant difference in the TS destabilization between the hydrolysis of **1a** and **1b**. However, as shown in Figure 1, the effect of solvent on rate is significantly different, indicating that the hydrolysis of **1a** and **1b** does not proceed concertedly *via* **3**.

Therefore, the contrasting solvent effect profile obtained in the present study suggests that the alkaline hydrolyses of **1a** and **1b** proceed through an addition intermediate **2**. This argument is consistent with the conclusion drawn from LFERs that acyl-, phosphinyl- and sulfonyl-group transfer reactions between anions proceed in a stepwise mechanism with an addition intermediate.[9-11, 14]

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