The effect of solvent on the α-effect: the MeCN–H_2O solvent system†

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The increasing α-effect observed in MeCN–H_2O solvent mixtures, which contrasts with the previously found bell-shaped dependence on solvent composition in the DMSO–H_2O system, is attributed to the differential solvent effect on basicities of the α- and normal nucleophiles in the former case.

Among the possible causes of the α-effect, that is the enhanced reactivity of nucleophiles having an unshared pair of electrons adjacent to the nucleophilic centre,[1] the effect of solvent has been particularly controversial.[2–9] As one possible approach to the problem, in 1986 we examined the reactivities of an α-nucleophile, butane-2,3-dione monoximate (Ox^-), and a normal nucleophile, *p*-chlorophenoxide ($ClPhO^-$) with *p*-nitrophenyl acetate (PNPA) in dimethyl sulfoxide (DMSO)–H_2O mixtures,[7a] due to the unique properties of this solvent system.[10] Unexpectedly, we observed a bell-shaped profile for the dependence of the α-effect on solvent composition, with a maximum at *ca.* 50 mol % DMSO.[7a] More recently, we observed a similar bell-shaped α-effect trend for the corresponding reactions of *p*-nitrophenyl diphenyl phosphinate (PNPDPP).[7b] However, a contrary result was reported for the reaction of PNPA with *O*-iodosylbenzoate (IBO^-) and $ClPhO^-$: the α-effect showed no maximum but decreased steadily as the DMSO content in the reaction medium increased.[9] Clearly, more work is called for in order to understand the effect of solvent on the α-effect.

We have now extended our study to a different solvent system, acetonitrile (MeCN)–H_2O mixtures, and have found a new type of solvent effect on the α-effect, namely an increasing α-effect. A plausible cause of this trend for the reaction of PNPA with Ox^- and $ClPhO^-$ (eqn. 1) in MeCN–H_2O mixtures is herein presented.

$$CH_3C(O)OC_6H_4NO_2\text{-}p + Nu^- \longrightarrow CH_3C(O)\text{-}Nu + p\text{-}NO_2C_6H_4O^-$$
$$Nu^- = CH_3C(O)C(CH_3){=}NO^-\ (Ox^-),\ \text{an } \alpha\text{-nucleophile}$$
$$p\text{-}ClC_6H_4O^-\ (ClPhO^-),\ \text{a normal nucleophile} \qquad (1)$$

Kinetic studies were performed spectrophotometrically under pseudo-first-order conditions with the nucleophile in excess. Pseudo-first-order rate constants (k_{obs}) were obtained from linear plots of ln ($A_\infty - A_t$) *vs.* *t*. Second-order rate constants (k^{Ox-} and k^{ClPhO-}) were calculated from the slope of the linear plot of k_{obs} *vs.* nucleophile concentration. As shown in Fig. 1, the magnitude of the α-effect (k^{Ox-}/k^{ClPhO-}) increases as the mol % MeCN in the medium increases, from *ca.* 100 in H_2O to 500 in 90 mol % MeCN. Recently, we found a decreasing α-effect trend for the reaction of PNPA with hydroxamates in MeCN–H_2O mixtures, and a shift in equilibrium from an OH acid to an NH acid upon addition of MeCN to H_2O was attributed as responsible for the observed α-effect trend.[8b]

Transition-state stabilization is one possible cause of the α-effect[11] and recently the bell-shaped α-effect trend observed for the reaction of PNPA in DMSO–H_2O mixtures has been explained through a dissection of ground-state and transition-state contributions.[7c] In that system the basicities of the α-Nu (Ox^-) and normal-Nu ($ClPhO^-$) exhibit a parallel dependence on the DMSO–H_2O composition.[7]

The addition of MeCN to H_2O could influence not only the reaction rate but also the basicity of the anionic nucleophiles. Although the pK_a values for some phenols, carboxylic acids and amines in pure MeCN are available,[12a,b] very few pK_a data have been reported for MeCN–H_2O mixtures.[8b] Therefore, we have measured the relative basicity of Ox^- and $ClPhO^-$ in MeCN–H_2O mixtures using piperazine as a reference base. One can define ΔpK_a as the pK_a difference between the conjugate acids of the nucleophile (Ox^- or $ClPhO^-$) and piperazine, *i.e.* ΔpK_a = pK_a of the conjugate acid of the nucleophile (Ox^- or $ClPhO^-$) − pK_a of the conjugate acid of the reference base (piperazine). Hence, the magnitude of ΔpK_a represents the relative basicities of these nucleophiles. We determined ΔpK_a values spectrophotometrically using the relationship: $\Delta pK_a = \log\, [HA]_{eq}[B]_{eq}/[A^-]_{eq}{}^2$, in which $[HA]_{eq}$ represents the equilibrium concentration of the conjugate acid of the nucleophile, and $[B]_{eq}$ and $[A^-]_{eq}$ represent the equilibrium concentration of the reference base (piperazine) and the nucleophile, respectively. The ΔpK_a values thus determined in MeCN–H_2O mixtures are summarized in Table 1. As shown in the table, the ΔpK_a values of Ox^- and $ClPhO^-$ in H_2O are −0.38 and −0.44, respectively. The pK_a values of the conjugate acids of Ox^-, $ClPhO^-$ and piperazine in H_2O at 25 °C, have been reported to be 9.44,[7b] 9.38[12c] and 9.82,[12c] respectively, *i.e.* the ΔpK_a data determined in H_2O in the present study are identical to the literature values. It is also noted that Ox^- and $ClPhO^-$ are less basic than piperazine in H_2O but appear to be more basic upon addition of MeCN. This is consistent with the report that the increase in pK_a values upon changing medium from H_2O to MeCN is more significant for phenols than for amines: the pK_a enhancements were reported to be 12–17 and 7–8 in pK_a units for phenols and for the conjugate acids of alicyclic secondary

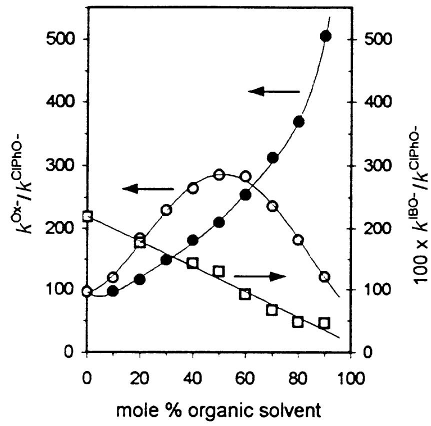

Fig. 1 Plots showing the effect of solvent on the α-effect ($k^{\alpha-Nu}/k^{normal-Nu}$) for the reaction of PNPA at 25.0 °C: k^{Ox-}/k^{ClPhO-} in MeCN–H_2O (●); k^{Ox-}/k^{ClPhO-} in DMSO–H_2O (○);[7b] k^{IBO-}/k^{ClPhO-} in DMSO–H_2O (□).[9]

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† Electronic supplementary information (ESI) is available: second-order rate constants for the reaction of *p*-nitrophenyl acetate with butane-2,3-dione monoximate and *p*-chlorophenoxide in MeCN–H_2O mixtures at 25 °C. See http://www.rsc.org/suppdata/cc/b0/b005610n/

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Table 1 Summary of the relative basicity of the nucleophile (ΔpK_a = pK_a of the conjugate acid of the nucleophile—pK_a of the conjugate acid of the reference base, piperazine) in MeCN–H_2O mixtures of varying compositions at 25.0 ± 0.1 °C[a]

Mol % MeCN	ΔpK_a (Ox^-)	ΔpK_a ($ClPhO^-$)	$\Delta\Delta pK_a$[b]
0	−0.38	−0.44	0.06
10	0.58	0.43	0.15
20	1.17	0.90	0.27
30	1.80	1.44	0.36
40	2.32	1.89	0.43
50	2.69	2.19	0.50
60	3.43	2.84	0.59
70	3.90	3.20	0.70
80	4.96	4.18	0.78
90	5.85	4.90	0.95

[a] The uncertainty in ΔpK_a values is estimated to be less than ±0.03 pK_a units. [b] $\Delta\Delta pK_a$ = ΔpK_a (Ox^-) − ΔpK_a ($ClPhO^-$).

amines (*e.g.* piperidine and morpholine), respectively, upon solvent change from H_2O to MeCN.[12a,b]

The difference in the relative basicity between Ox^- and $ClPhO^-$ can be expressed as $\Delta\Delta pK_a$, *i.e.* $\Delta\Delta pK_a$ = $\Delta pK_a(Ox^-)$ − ΔpK_a ($ClPhO^-$). As shown in Table 1, $\Delta\Delta pK_a$ increases as the mol % MeCN in the medium increases, *i.e.* Ox^- is more basic than $ClPhO^-$ by 0.06, 0.50 and 0.95 pK_a units in H_2O, 50 and 90 mol % MeCN, respectively, which contrasts with the situation, noted above, for DMSO–H_2O mixtures. We propose therefore, that the differential solvent effect on the basicity of these nucleophiles is the cause of the contrasting α-effect trends observed for the reaction of PNPA with Ox^- and $ClPhO^-$ in DMSO–H_2O and in MeCN–H_2O mixtures.

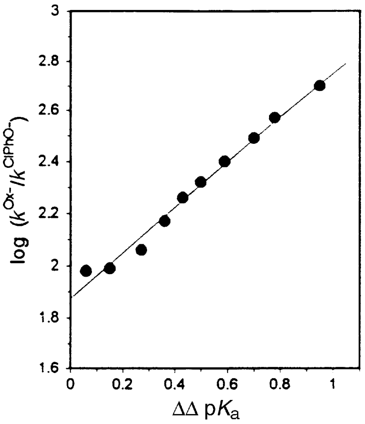

Fig. 2 Plot of log k^{Ox^-}/k^{ClPhO^-} *vs.* $\Delta\Delta pK_a$ for the reaction of PNPA with Ox^- and $ClPhO^-$ in MeCN–H_2O mixtures at 25.0 ± 0.1 °C.

Furthermore, it is found that a plot of log k^{Ox^-}/k^{ClPhO^-} against $\Delta\Delta pK_a$ is linear with a slope of 0.85 (Fig. 2). This provides evidence that the increase in the $\Delta\Delta pK_a$ values is almost fully reflected in the increase in the α-effect for the reaction of PNPA with Ox^- and $ClPhO^-$ upon addition of MeCN into the reaction medium.

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