Ground-State versus Transition-State Effects on the α-Effect as Expressed by Solvent Effects

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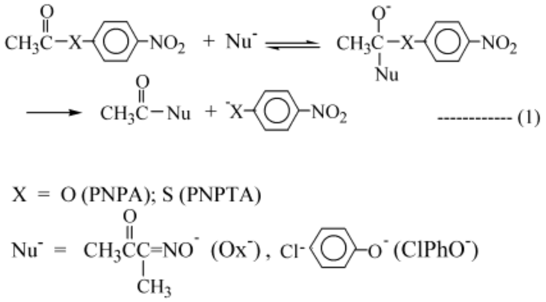
Since the first observations, close to 50 years ago, of the enhanced reactivity of nucleophiles having an atom with an unshared electron pair adjacent to the nucleophilic center, i.e., the α-effect, hypotheses as to its origin have abounded.[1−14] An early point of view focused on destabilization of the α-nucleophile through pair−pair repulsion and this type of ground-state (GS) explanation received support in molecular orbital (FMO) representations.[2] However, a variety of evidence became forthcoming that transition-state (TS) stabilization could largely contribute to the α-effect phenomenon and TS models such as an aromatic-like TS, radicaloid TS, and a TS in which the extent of nucleophilic bonding exceeded leaving group departure were proposed.[3−6] The possibility of product stabilization has also received support.[7−9] Most contentious, perhaps, was the proposal that solvation effects could in part or wholly be responsible for manifestation of the α-effect.[10−14] However, systematic studies of solvent effects on the α-effect were lacking.[10−12]

In our work we have utilized the well-known enhancement of nucleophilicity of oxygen anions induced by addition of a dipolar aprotic solvent such as DMSO or MeCN to aqueous media.[15] Interestingly, this type of solvent effect manifests itself differentially with respect to α- and normal-nucleophiles, resulting in varied, characteristic profiles of the α-effect ($k_{\alpha-\mathrm{Nu}}/k_{\mathrm{normal-Nu}}$) with solvent composition.[10−12] We report herein a novel type of profile for the dependence of the α-effect on solvent composition.

In the first systematic study of the effect of solvent on the α-effect, we reported in 1986 the bell-shaped profile, curve A in Figure 1, for the reaction of *p*-nitrophenyl acetate (PNPA) with butane-2,3-dione monoximate (Ox^-) as α-nucleophile and *p*-chlorophenoxide ($ClPhO^-$) as corresponding normal nucleophile, as a function of DMSO−H_2O composition.[10a] Importantly, the basicities (pK_a values) of Ox^- and $ClPhO^-$ increase in almost parallel manner with mole % DMSO.[6c,11b,12a] This bell-shaped rate ratio profile when combined with heats of solution data was recently dissected into TS and GS contributions.[10b] Contrastingly, Moss and co-workers reported that k_{IO^-}/k_{ClPhO^-}, where IO^- represents the α-nucleophile *o*-iodosylbenzoate, follows a steadily diminishing trend as a function of mole % DMSO, i.e., curve B in Figure 1.[16] However, the pK_a dependence of the *o*-iodosylbenzoate anion as function of medium composition was not known.

We now report a novel type of dependence of the α-effect on solvent composition, namely curve C in Figure 1, corresponding to the reaction of *S*-*p*-nitrophenyl thioacetate (PNPTA) with Ox^- and $ClPhO^-$ in DMSO−H_2O mixtures (eq 1). In this case, the magnitude of the α-effect increases up to ca. 30 mol % DMSO and then levels off. In the following it is argued that this α-effect profile arises largely from a GS effect.



(1)

Kinetic studies were performed spectrophotometrically by monitoring the leaving *p*-nitrothiophenoxide ion under pseudo-first-order conditions with the nucleophile in excess. Generally, five different concentrations of nucleophile solutions were used to determine second-order rate constants. It is estimated from replicate runs that the uncertainty in rate constant is less than ±3%. The second-order rate constants determined in this way are summarized in Table 1 together with data for the corresponding reaction of PNPA.

Dissection of the α-effect into GS and TS effects in this system can be accomplished through combination of the kinetic data with enthalpy of solution (ΔH_s) data as recently reported.[10b] It was shown that while ΔH_s for Ox^-Na^+ greatly exceeds that for $ClPhO^-Na^+$ over the entire DMSO−H_2O solvent composition, the difference in enthalpy of solution for Ox^- and $ClPhO^-$ ($\Delta\Delta H_s$) increases up to near 30 mol % DMSO and then remains nearly constant upon further addition of DMSO to the medium.[10b] Thus the trend of the α-effect in the PNPTA system is identical to the ΔH_s difference between Ox^- and $ClPhO^-$. It follows that differential GS desolvation between Ox^- and $ClPhO^-$ is largely responsible for the α-effect profile over the whole medium range studied.

The above conclusion is illustrated pictorially in Figure 2, which shows that for the PNPTA system the magnitude of the

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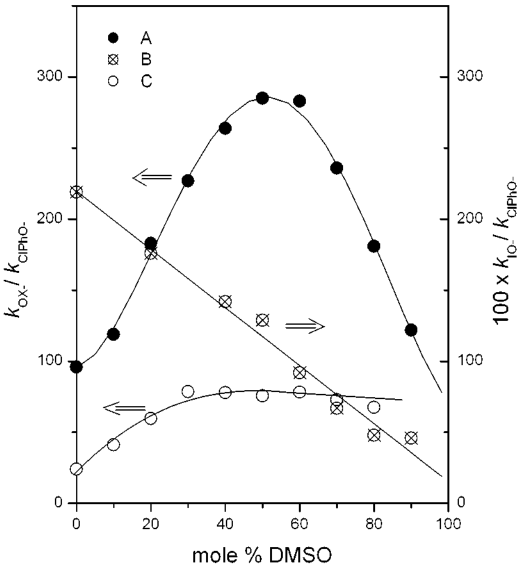

Figure 1. Illustration of the contrasting rate ratio profiles for the α-effect as a function of mole % DMSO at 25 °C: (A) reaction of *p*-nitrophenyl acetate (PNPA) with butane-2,3-dione monoximate (Ox^-) and *p*-chlorophenoxide ($ClPhO^-$); (B) reaction of PNPA with *o*-iodosylbenzoate (IO^-) and $ClPhO^-$; and (C) reaction of *S*-*p*-nitrophenyl thioacetate (PNPTA) with Ox^- and $ClPhO^-$.

Table 1. Summary of Second-Order Rate Constants for the Reactions of PNPTA and PNPA[a] with Ox^- and $ClPhO^-$ in DMSO−H_2O Mixtures at 25.0 °C

mole %	k_{Ox^-}, $M^{-1} s^{-1}$		k_{ClPhO^-}, $M^{-1} s^{-1}$		k_{Ox^-}/k_{ClPhO^-}	
DMSO	PNPA[a]	PNPTA	PNPA[a]	PNPTA	PNPA[a]	PNPTA
0	65.8	61.0	0.685	2.53	96.1	24.1
10	77.8	91.5	0.653	2.22	119	41.2
20	139	208	0.760	3.48	183	59.8
30	309	565	1.36	7.18	227	78.7
40	740	1,560	2.80	20.0	264	78.0
50	1,680	4,080	5.90	54.0	285	75.6
60	3,850	10,500	13.6	134	283	78.4
70	8,200	26,000	34.7	356	236	73.0
80	17,200	63,000	94.8	931	181	67.7
90	40,500	[b]	334		122	

[a] The data for the reaction of PNPA were taken from ref 10. [b] Rate too fast to be measured.

α-effect increases linearly with increasing $\Delta\Delta H_s$. However, for the PNPA system a bilinear plot is revealed in Figure 2. Up to ca. 50 mol % DMSO the α-effect is linearly dependent on $\Delta\Delta H_s$, but thereafter the α-effect becomes almost independent of $\Delta\Delta H_s$, implying that in that region the α-effect does not originate from differential GS desolvation. This argument is consistent with our recent discussion that for PNPA reacting with Ox^- and $ClPhO^-$, $\Delta\Delta H_s$ is responsible for the increasing α-effect up to ca. 50 mol % DMSO, as a GS effect, while differential TS stabilization is responsible for the deceasing α-effect beyond ca. 50 mol % DMSO.[10b]

Further confirmation of these conclusions derives from evaluation of β_{nuc}; it has been shown that β_{nuc} is an important predictor of the magnitude of the α-effect, with a direct proportionality between these two quantities.[7−9,11a,12] The results of kinetic studies for PNPTA with substituted phenoxides (p-X-$C_6H_4O^-$, X = Me, H, Cl, CN) in 20, 50, 80 mol % DMSO at 25.0 °C are summarized in Table S1 (Supporting Information).

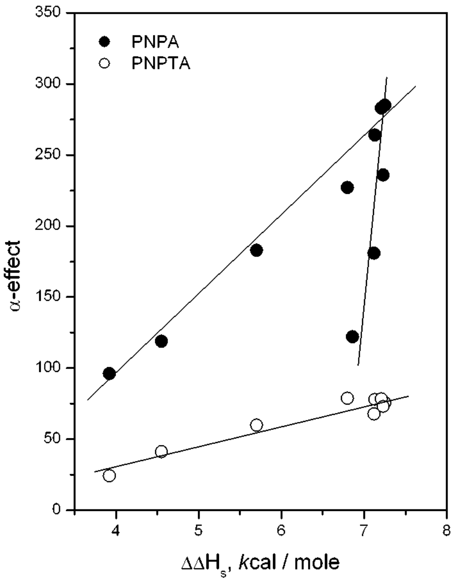

Figure 2. Illustration of the bilinear plot for the α-effect behavior of PNPA, contrasting with the linear plot for PNPTA, as a function of the differential heat of solution of Ox^- vs $ClPhO^-$ in DMSO−H_2O mixtures. The break in the plot for PNPA occurs at ca. 50 mol % DMSO.

Good linear Brønsted-type correlations are obtained for the reactions of PNPTA with various substituted phenoxides in all DMSO−H_2O mixtures studied ($r \geq 0.995$ in all cases). The β_{nuc} value decreases monotonically as the mole % DMSO increases, i.e., β_{nuc} values are 0.60, 0.51, and 0.41 in 20, 50, and 80 mol % DMSO, respectively. Extrapolation of the plot of β_{nuc} values against mole % DMSO to pure water gives a β_{nuc} value of 0.67, which is in good agreement with the reported value of 0.68 by Hupe and Jencks.[17] The β_{nuc} values obtained for the reaction of PNPTA are considerably smaller than those for the corresponding reactions of PNPA reported previously (e.g., 0.75, 0.72, 0.65, and 0.59 in H_2O, 20, 50, and 90 mol % DMSO, respectively),[18] which accounts for the smaller α-effect for the PNPTA than the PNPA system and is in accord with the above prediction.

Our studies have demonstrated that the role of solvent on the α-effect is indeed remarkable, and that both the GS and TS can be thus influenced. Interestingly the present study with *S*-*p*-nitrophenyl thioacetate (PNPTA) has shown that in this system the GS contribution to the α-effect is dominant. While this is reminiscent of the generally accepted paradigm as to the origin of the α-effect (vide supra),[1−13] it is noteworthy that it is through study of the solvent effect on the α-effect that the historical parallel could be revived.

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