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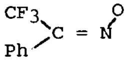
ENHANCED REACTIVITY OF AN α-NUCLEOPHILE IN WATER-DIMETHYL SULFOXIDE MIXTURES. A TRANSITION STATE EFFECT.

Marguerite LALOI-DIARD*, Laboratoire de Physicochimie des Solutions, ENSCP, 11 rue Pierre et Marie Curie, 75231 - Paris Cédex 05 France
Jean-François VERCHERE, Patrick GOSSELIN and François TERRIER*, Département de Chimie, Faculté des Sciences de Rouen - 76130 Mont Saint Aignan France

Summary - The reactivity of the anion of α,α,α-trifluoroacetophenone oxime towards p-nitrophenylacetate is considerably enhanced relative to that of the similarly basic p-chlorophenoxide anion on addition of Me_2SO *to aqueous solutions. This is shown to be due to an enhanced stabilization of the transition state for the oxime reaction.*

Whether the extra reactivity of α-nucleophiles results essentially from ground state destabilization of the nucleophile or extra stabilization of the transition state remains a subject of active discussion.[1-4] In a recent theoretical analysis, Buncel and Hoz[5] have concluded that the latter effect must contribute predominantly to the manifestation of the α-effect. A comparison of the reactivity of the anions of p-chlorophenol ($ClPhO^-$), i.e. a normal nucleophile, and of (Z) α,α,α-trifluoroacetophenone oxime (TFA-Ox$^-$), i.e. an α-nucleophile,[6] towards p-nitrophenylacetate (PNPA) not only in water but also in water-Me_2SO mixtures of varying composition strongly supports this proposal :

$$p\text{-}NO_2\text{-}C_6H_4\text{-}OCOCH_3\text{(PNPA)} + A^- \xrightarrow{k^{A^-}} CH_3CO\ A + p\text{-}NO_2\text{-}C_6H_4\text{-}O^-$$

Reaction (1) : $A^-=Cl\text{-}C_6H_4\text{-}O^-=ClPhO^-$; Reaction (2) : A^-=TFA-Ox$^-$ = 

$$\begin{matrix}CF_3 & & O^- \\ & \!\!>C = N & \\ Ph & & \end{matrix}$$

The choice of reactions (1) and (2) was dictated by our finding that the hydrogen basicities of these two anions are not only similar in H_2O [6] but also throughout the whole range of the solvent composition studied ; (Table). Also important is that both anions remain more basic than the leaving p-nitrophenoxide ion in all solvent mixtures.[7] Thus, the addition of Me_2SO is not expected to affect the mechanism of reactions (1) and (2), which has been shown to involve rate-determining attack of the nucleophile followed by rapid breakdown of the resulting tetrahedral intermediate in aqueous solution.[8] The rates of reactions (1) and (2) were determined spectrophotometrically under pseudo-first-order conditions, i.e. $[A^-] >> [PNPA]$ using oximate and p-chlorophenoxide buffers. No contribution of the OH^- reaction was found in our experiments, i.e. $k_{obsd} = k^{A^-}[A^-]$ in all cases. The measured k^{A^-} values are given in the Table together with the values of the ratio $k^{TFA\text{-}Ox^-}/k^{ClPhO^-}$ which measures the α-effect exhibited by TFA-Ox$^-$ in the various H_2O-Me_2SO mixtures.[11] As can be seen, the reactivity of the oxime anion is considerably enhanced relative to that of the similarly basic $ClPhO^-$ anion on Me_2SO addition to aqueous solutions : the α-effect changes from 52 in water to 345 in 70% Me_2SO.

Table : Effect of Me_2SO on the rate-equilibrium behaviour of $TFA\text{-}Ox^-$ and $ClPhO^-$ in Reactions (1) and (2) ; t = 25°C , I = 0.5 M NMe_4Cl.[a]

% Me_2SO by volume	$pK_a^{ClPhO^-}$	k^{ClPhO^-}	$pKa^{TFA\text{-}Ox^-}$	$k^{TFA\text{-}Ox^-}$	$k^{TFA\text{-}Ox^-}/k^{ClPhO^-}$
0	9.35	0.57	9.05	30	52.6
10	9.45	0.52	9.21	31	59.6
20	9.65	0.50	9.42	34	68
30	9.90	0.54	9.85	43	79.6
40	10.15	0.66	10.15	57	86.3
50	10.55	0.84	10.65	106	126
60	10.95	1.38	10.95	360	261
70	11.60	2.90	11.60	1000	345

(a) The pK_a values were measured according to a potentiometric procedure previously described.[9]

The similarity of the pKa values of $TFA\text{-}Ox^-$ and $ClPhO^-$ in $H_2O\text{-}Me_2SO$ mixtures implies that the free energy ΔG_{exch} associated with the p-chlorophenol-oxime exchange reaction (3) is essentially insensitive to solvent ($\Delta G_{exch} \sim 0$). This observation suggests that the larger rate acceleration observed for the oxime anion-PNPA reaction is not the result of a significant ground-state destabilization of $TFA\text{-}Ox^-$ relative to $ClPhO^-$ on transfer from H_2O to $H_2O\text{-}Me_2SO$ solutions. Should such a destabilization occur, it should be paralleled by a similar destabilization of TFA-OxH relative to ClPhOH in order to account for the similar pKa values. Such a situation is extremely difficult to envision since Me_2SO is known to commonly discriminate much more between anionic than neutral species.[10] Thus, we conclude that the enhanced reactivity of $TFA\text{-}Ox^-$ is the reflection of an enhanced stabilization of the transition state for the $TFA\text{-}Ox^-$- reaction relative to that for the $ClPhO^-$-PNPA reaction. Then, as far as the effect of Me_2SO on reactions (1) and (2) is concerned, our results lend much support to the Buncel and Hoz proposal.[5]

$$ClPhOH + TFA - Ox^- \overset{\Delta G_{exch}}{\rightleftharpoons} ClPhO^- + TFA - OxH \qquad (3)$$

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(11) The k^{A^-} values are accurate to ± 3% ; the pKa values are accurate to ± 0.01.

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