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Reactions of Oximate α-Nucleophiles with Esters: Evidence from Solvation Effects for Substantial Decoupling of Desolvation and Bond Formation

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Deviations from linearity in Brønsted-type plots have been recognized as major indicators of mechanistic features and hence of potential energy surfaces, governing such important processes as acyl, phosphyl, and sulfyl transfers, as well as proton transfers.[2−8] In particular, the observation of deviations from Brønsted-type nucleophilicity plots has provided new insights into the origin of the exalted reactivities of nucleophiles possessing a heteroatom with an unshared electron pair adjacent to the nucleophilic center, the so-called α-effect.[9−23] Among different α-nucleophiles, oximate anions have featured widely because they have long been used as potential reactivators of acetylcholinesterase inhibited by organophosphorus toxics.[4,15,24,25] However, whereas the Brønsted-type plots for normal nucleophiles reacting at carbon, sulfur, or phosphorus electrophilic centers have been found to be linear with slopes in the range of 0.6−0.75 up to $pK_a \approx 10-11$, corresponding plots for oximates display a leveling-off behavior at much lower pK_a.[15,22,23] As shown in Figure 1 which refers to their reactions with *p*-nitrophenylacetate (PNPA) in aqueous solution, oximates of different structures fall on somewhat different curves for $pK_a <$ 7.5−8 but they all coalesce to a common plateau at high pK_a.[15]

The origin of the special properties of oximates has received considerable attention though it is as yet incompletely understood.[10−19] Recent work suggests, however, that ground-state and transition-state effects, together with solvation effects, play a major role in determining reactivity in these systems.[15,20−23]

A most reasonable explanation of the observed leveling-off in the reactivity of the oximate functionality has been in terms of the models proposed by Jencks and by Bernasconi to account for the downward curvatures observed in Brønsted-type plots for acyl transfers involving strongly basic aryloxide or alkoxide anions and for ionization of carbon acids by carboxylate bases.[2,6−8,15,26] Thus, the saturation effect would result from a special need for partial desolvation of oximates prior to nucleophilic attack, that is less important for weakly basic than for more strongly basic anions.[6,8,15,22] This lack of synchronization between two concurrent events in an elementary process has been commonly referred to as an imbalance.[2b,6,8]

The question was posed henceforth: how could one change the solvational imbalance pertaining to the oximates and thereby reverse their leveling-off in reactivity? It appeared that one approach would be to change from aqueous medium to Me_2SO-rich media in view of previous findings of the modulation of basicities and nucleophilicities through the use of H_2O-Me_2SO mixtures.[27]

The results of the experiments undertaken to test this hypothesis for the oximate−PNPA systems are displayed in Figure 2.[28] While the characteristic leveling-off in reactivity seen in H_2O is still present in 70% H_2O−30% Me_2SO (Figure S1), a dramatic change in behavior is observed on going to 30% H_2O−70% Me_2SO (Figure 2, plot A) where the Brønsted correlation has become linear once again, as found for the weakly basic oximates in aqueous solution.[30] In addition, the differences observed in the reactivity of the various families of oximates at low pK_a (Figure 1) are no longer present in this mixture. Similar results are obtained in 20% H_2O−80% Me_2SO (Figure S1).

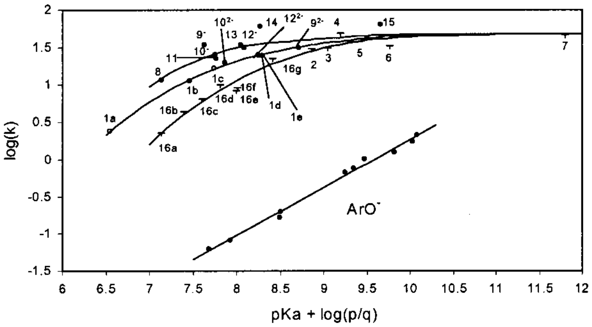

Figure 1. Brønsted-type nucleophilicity plots for reactions of oximates and phenoxides (ArO^-) with PNPA at 25 °C in aqueous solution (see Figure S2 for identification of the oximate families).[8,15,25] Data for ArO^- ions are taken from ref 26.

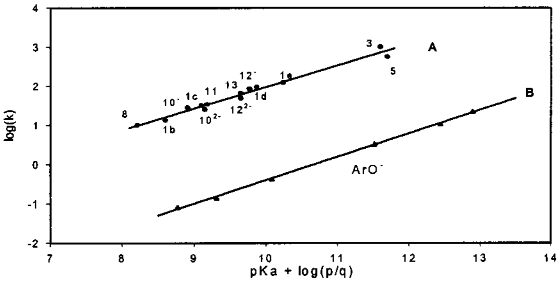

Figure 2. The contrasting plot A illustrating the metamorphosis in Brønsted-type reactivity for PNPA−oximates systems at 25 °C in 30% H_2O−70% Me_2SO (v/v) with reference to ArO^- reactivities[8,31] in this mixture (plot B).

An explanation for this metamorphosis follows from further consideration of Jencks' and Bernasconi's models for solvational imbalances.[6,26] Using the straight Brønsted line of slope β_{nuc} defined by the points at low pK_a as reference and assuming that the desolvation occurs in an equilibrium step ($K_d < 1$) which precedes nucleophilic attack (eq 1),

$$\mathrm{RO}^-_{\mathrm{solv}} \overset{K_d}{\rightleftharpoons} \mathrm{RO}^-_{\mathrm{des}} \xrightarrow{\mathrm{PNPA}} [\ ]^{\neq} \tag{1}$$

curved Brønsted plots of the type shown in Figure 1 will be the reflection of negative deviations of the points at high basicity that may be expressed in terms of eq 2.

$$\Delta \log(k) = (1 - \beta_{\mathrm{nuc}}) \log(K_d) \tag{2}$$

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This clearly shows that as desolvation becomes energetically more expensive, the increasingly more negative $\log(K_d)$ values render $\Delta \log(k)$ more negative as well, accounting for the observed leveling-off in strongly aqueous media.

According to Bernasconi,[6] a more general way to visualize the situation is to assume that partial desolvation of the nucleophile and bond formation actually occur in the same step but that desolvation has progressed further than bond formation in the transition state (TS). Thus, the change in $\log(k)$ is described by an equation of the form:

$$\Delta \log(k) = (\alpha_{des} - \beta_{nuc}) \log(K_d) \tag{3}$$

where $1 \geq \alpha_{des} \geq 0$ measures the progress of desolvation in the TS. For $\alpha_{des} > \beta_{nuc}$, desolvation is ahead of bond formation and $\Delta \log(k)$ is again negative. For $\alpha_{des} = 1$, the situation becomes identical to that expressed in eqs 1 and 2. A most important message from eqs 2 and 3 is that for curvature to be observed in a Brønsted plot, not only must partial desolvation of the nucleophile become energetically more demanding with increasing pK_a, but this desolvation must also occur ahead of bond formation, that is, $\alpha_{des} - \beta_{nuc} > 0$.

In keeping with this model, it is clear that for the present system, this decoupling must prevail for oximates in aqueous solution and in media of low Me_2SO content. In contrast, the recovery of linearity of the Brønsted plots in Me_2SO-rich media implies that the extent of imbalance between desolvation and bond formation is no longer sufficiently significant to result in detectable curvature in the Brønsted plot. With respect to the aqueous solutions, it is interesting that the three linear correlations defined at low pK_a for the various classes of oximates studied exhibit rather high and similar slopes, that is, $\beta_{nuc} \approx 0.7$. This implies that in aqueous solution the pronounced curvature can only be understood if the negative $\log K_d$ values associated with the partial desolvation of the most basic oximates are operating in conjunction with a significant value of the $(\alpha_{des} - \beta_{nuc})$ term, which in fact requires $\alpha_{des} \approx 1$. In other words, we must be dealing with an essentially complete decoupled situation, as formulated by Jencks in eqs 1 and 2 for a number of acyl transfers.[26]

On the other hand, the poor ability of dipolar aprotic solvents in hydrogen-bonding makes it reasonable to anticipate that the ground state of the oxyanion will be more prone for nucleophilic attack in Me_2SO-rich media.[27] This will avoid the need for an energetically costly additional desolvation prior to bond formation, thereby reducing nonsynchronicity.

Thus, the results of the present study point to a situation in which there is clear evidence of a practically complete decoupling of nucleophile desolvation and bond formation for acyl transfers involving oximates in aqueous solution but not in media of high Me_2SO content.[32] The decisive evidence for this conclusion is provided herein by the early onset of curvature in the oximate plots as compared with the much later appearance of saturation behavior with the more strongly basic normal oxyanions in aqueous solution. It follows also from the present results that the disappearing α-effect at high pK_a in aqueous solution will become restored in Me_2SO-rich media.

As a consequence of the above behavior, it may be noted that consideration of the efficiency of oximates as decontaminating agents will need to take cognizance of the present work highlighting the fact that any advantage which one would normally expect to accrue in using highly basic oximates becomes nullified in aqueous solution for $pK_a > 8$.

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Supporting Information Available: Brönsted plots for PNPA-oximates and phenoxides systems at 25 °C in 70−30% and 20−80% H_2O-Me_2SO mixtures (Figure S1); structures and numbering of the oximate species quoted in this work (Figure S2) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) A reviewer has pointed out that the observed leveling off in rate and change in rate-determining step, could be more properly viewed in terms of a preassociation process, i.e.,

$$\mathrm{PNPA} + \mathrm{RO^-}_{solv} \xrightleftharpoons{\text{assoc.}} \mathrm{PNPA{\cdot}RO^-}_{solv} \xrightleftharpoons[k_{solv.}]{k_{desolv.}} \mathrm{PNPA{\cdot}RO^-}_{desolv.} \rightarrow \mathrm{TS}$$

We thank this reviewer for this interesting comment which does not, however, alter the argument about the relative coupling between desolvation and bond formation processes.

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