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The levelling effect of solvational imbalances in the reactions of oximate α-nucleophiles with electrophilic phosphorus centers. Relevance to detoxification of organophosphorus esters

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Received (in Cambridge, UK) 6th December 2002, Accepted 23rd January 2003
First published as an Advance Article on the web 4th February 2003

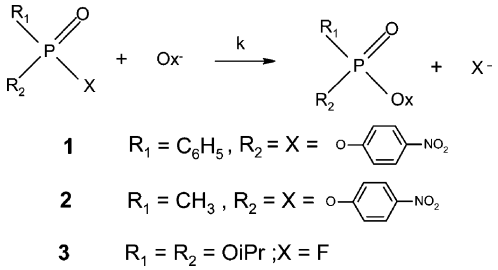
A study of the reactions of oximate α-nucleophiles with diisopropylphosphorofluoridate (DFP) and two model phosphonates, has revealed either a levelling-off in reactivity or a bell-shaped behaviour in accordance with a critical decoupling of desolvation and bond formation (solvational imbalances); the relevance of these results to detoxification is emphasized.

Oximates are nucleophiles of special interest because of the presence of an unshared electron pair adjacent to the nucleophilic center; as α-nucleophiles they exhibit an exalted reactivity in different processes, including as potential reactivators of AChE inhibited by organophosphorus toxics.[1–5] However, we and others have observed a rapid saturation-type behaviour for oximates reacting at carbonyl centers, with no increase in reactivity of oximates of pK_a > 8–8.5.[6–8] Recently, the origin of this observed levelling-off was identified as arising from a special need for partial desolvation of these species prior to nucleophilic attack that becomes energetically more costly with increasing basicity.[9] Such a decoupling of desolvation and bond formation, which also occurs with other types of nucleophiles but at much higher pK_a's, *i.e.* p$K_a \geq 12$, has been termed *imbalance*.[10–12]

The question, whether the levelling-off behaviour observed for acyl transfer extends to processes involving other electrophilic centers, in particular phosphorus centers, has not been addressed so far. Should this actually be the case, this would be of major interest for selecting the most efficient oximate catalysts in neutralization of toxic organophosphorus compounds under mild conditions.[5]

In order to address this question, we have undertaken studies of two model members of the phosphonate family, namely the bis(4-nitrophenyl) phenyl and methyl phosphonates **1** and **2** .The results obtained with these two compounds, as elaborated below, prompted us to extend the study to the well known insecticide diisopropylphosphorofluoridate **3**, commonly denoted as DFP.

The reactions of **1** and **2** with an extended set of oximates (Ox^-) according to eqn. (1) were studied spectrophotometrically by monitoring the appearance of the leaving *p*-nitrophenoxide ion. Under the experimental conditions employed, the results revealed that the departure of the two *p*-nitrophenoxy leaving groups occurs in two distinct stages. In the following, results are presented only for departure of the first *p*-nitrophenoxide ion which was found to proceed more rapidly than the second. All reactions were conducted in buffer solutions made up of the respective oximates, varying the concentration of the conjugate acid and base components at constant pH while maintaining pseudo-first-order conditions with the buffer in large excess.[12] The extended set of oximates used was the same as that employed in previous studies of the hydrolysis of *p*-nitrophenyl acetate (PNPA).[12,13] Similar conditions were used in the case of DFP, but in this instance the kinetics were conducted using a potentiometric technique described elsewhere.[14]



(1)

The results are summarized in the form of the Brønsted-type plots in Figs. 1 and 2; these encompass two distinct types of

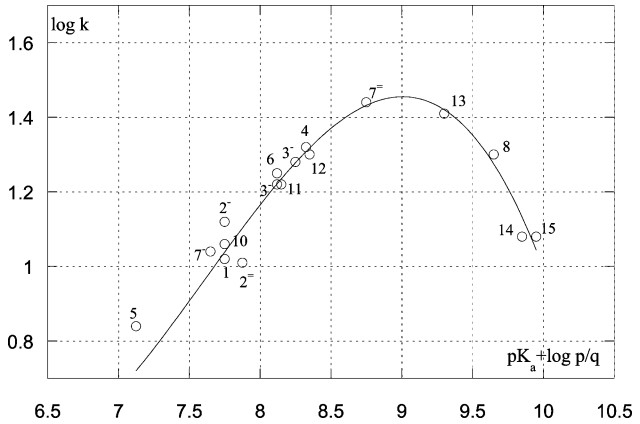


Fig. 1 Brønsted-type nucleophilicity plot for the reaction of the oximates with the phosphonate **1** at 25 °C in aqueous solution (k in dm^3 mol^{-1} s^{-1}). See ref. 17 for identification of the oximate species.

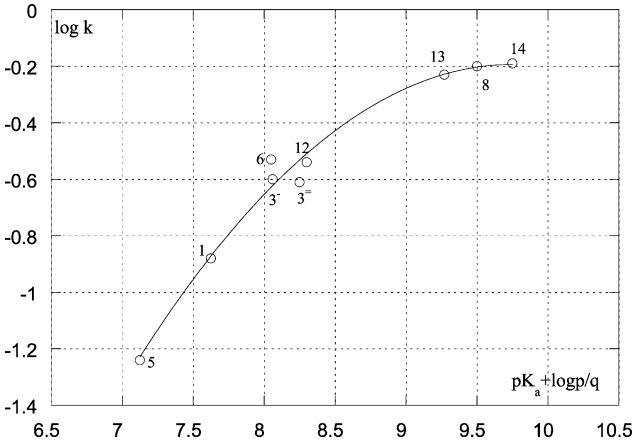


Fig. 2 Brønsted-type nucleophilicity plot for the reaction of the oximates with theDFP at 25°C in aqueous solution (k in dm^3 mol^{-1} s^{-1}). See ref. 17 for identification of the oximate species.

DOI: 10.1039/b212160n

behaviour. In the case of the phosphonate **1** (Fig. 1) the reactivity is characterized by a bell-shaped profile where the attainment of maximum reactivity (k_{obs}^{max} 25 $dm^3mol^{-1}s^{-1}$) is followed by a clear decrease in rate at $pK_a > 9 - 9.5$. In contrast, the phosphonate **2** and DFP exhibit only a levelling off in reactivity in this pK_a region, as exemplified for DFP in Fig. 2, with k_{obs}^{max} = 0.66 $dm^3mol^{-1}s^{-1}$ for DFP[15,16] and k_{obs}^{max} = 20 $dm^3mol^{-1}s^{-1}$ for **2**.

The present results differ in several important ways when compared to PNPA. Thus, while the profiles observed with DFP and **2** resemble qualitatively that found in the case of PNPA,[9,12] the levelling-off here occurs at somewhat greater pK_a values, *i.e.* pK_a ~ 9.5–10 instead of pK_a ~ 8–8.5. While this finding does not alter fundamentally the idea that the levelling-off is the reflection of decoupling of nucleophile desolvation and bond formation,[9–12] it reveals nevertheless that the imbalance phenomenon depends to some extent on the nature of the electrophilic center. This notion is confirmed by the behaviour of the phosphonate **1**, as seen in Fig. 1 where the levelling-off is found to occur around pK_a ~ 9 but is followed by a decrease in rate at higher pK_a. This decreasing reactivity corresponds to a negative β_{nuc} value;[10b,17] to our knowledge, there is only one major precedent for negative β_{nuc} values, as reported by Jencks and also referring to reactions at a phosphorus center, *i.e.* for substituted quinuclidines reacting with a series of *p*-nitrophenyl phosphates.[10b]

As a possible explanation for the present negative β_{nuc}, it seems reasonable to anticipate that the presence of the phenyl group in **1** will induce a greater steric hindrance to the approach of the oximate nucleophile to the phosphorus center, as compared to the methyl group in **2**. The most basic oximates being the most solvated, the need for desolvation of these species prior to nucleophilic attack would then be greater and therefore more energetically costly in the case of **1** than of **2**. This would account for the observed decreasing reactivity of **1** at high pK_a. In this regard, it will be important to extend the present study to other phosphorus electrophilic centers and varying the nature of the substituents in order to obtain more information on how steric factors can affect the rate-basicity profile.

In conclusion, our work provides definitive evidence for the levelling off in nucleophilic reactivity of highly basic oximates at phosphorus centers, arising from a critical decoupling of desolvation and bond formation. However, in addition, we have shown that this phenomenon is itself modulated by the nature of the electrophilic center, in comparison with carbonyl centers (PNPA), for example. Finally, the curved plots in Figs. 1 and 2 strikingly demonstrate the lack of an obvious parallel relationship between the basicities of oximates and their potential efficiency for detoxification under mild conditions.[17]

We are grateful for the financial support of this research by C.N.R.S. (F. T.) and N.S.E.R.C. (E. B.).

Notes and references

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13 The oximes and dioximes numbered **1**–**8** in Figs. 1 and 2 are the same as those identified in ref. 12; other oximes are the following: **9** = $CH_3SO_2CH_2COCH{=}NOH$; **10** = $CH_3SOCH_2COCH{=}NOH$; **11** = $CH_3SCH_2COCH{=}NOH$; **12** = $CH_3COCH{=}NOH$(MINA); **13** = $CH_3COC(=NOH)CH_3$; **14** = Pyridine-2-carbaldehyde oxime;[8] **15** = Pyridine-3-carbaldehyde oxime (pK_a values in ref. 3*a*, 6*a* and 8. Using the methodology detailed in ref. 12, both mono- (Ox^-)and di-oximate (Ox^{2-}) species have been used as α-nucleophiles in the case of the dioximes **2**, **3** and **7**. The pK_a and rate data for the (Ox^{2-}) species have been statistically corrected in plotting Figs. 1 and 2.
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