Revisiting the reactivity of oximate α-nucleophiles with electrophilic phosphorus centers. Relevance to detoxification of sarin, soman and DFP under mild conditions†

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Following a potentiometric determination of the relevant pK_a values of the $(R_1R_2)C{=}NOH$ functionality, the second order rate constants (k^{Ox}) for reaction of a large set of oximate bases with two model organophosphorus esters, *i.e.* bis-(4-nitrophenyl)phenylphosphonate (BNPPP) and bis-(4-nitrophenyl)methylphosphonate (BNPMP), and three toxic compounds, *i.e.*, sarin (GB), soman (GD) and diisopropylphosphorofluoridate (DFP), in aqueous as well as a 30 : 70 (v/v) H_2O–Me_2SO mixture have been measured. The corresponding Brønsted-type nucleophilicity plots of log k^{Ox} *vs.* pK_a^{Ox} reveal a clear tendency of the reactivity of the oximates to suffer a saturation effect with increasing basicity in aqueous solution. In the case of BNPMP and the three toxic esters, this behaviour is reflected in a levelling off at p$K_a \approx 9$ but a more dramatic situation prevails in the BNPPP system where the attainment of maximum reactivity at p$K_a \approx 9$ is followed by a clear decrease in rate at higher pK_a's. Interestingly, a number of data reported previously by different authors for the sarin, soman and DFP systems are found to conform rather well to the curvilinear Brønsted correlations built with our data. Based on this and previous results obtained for reactions at carbon centers, it can be concluded that the observed saturation effect is the reflection of an intrinsic property of the oximate functionality. An explanation of this behavior in terms of an especially strong requirement for desolvation of the oximates prior to nucleophilic attack which becomes more and more difficult with increasing basicity is suggested. This proposal is supported by the observed changes in pK_a^{Ox} and k^{Ox} brought about by a transfer from H_2O to a 30 : 70 H_2O–Me_2SO mixture. The implications of the saturation effect on the efficiency of oximates as nucleophilic catalysts for smooth decontamination are emphasized. Also discussed is the effect of basicity on the exalted (α-effect) reactivity of these bases.

Introduction

It has long been recognized that nucleophiles possessing a heteroatom with an unshared pair of electrons adjacent to the nucleophilic center exhibit a high nucleophilic reactivity compared with common nucleophiles of similar basicities. The origin of this behaviour, the so-called α-effect, has received considerable attention in the last two decades but it is as yet incompletely understood.[1–7] Recent work suggests, however, that ground-state and transition-state effects, together with solvation effects, play a major role in determining the exalted reactivity of α-nucleophiles.[8–13]

Among different α-nucleophiles, oximates have featured widely because they represent a class of nucleophilic catalysts which has proved to be very efficient in promoting such important processes as acyl, phosphyl and sulfyl transfers, as well as proton transfers.[10,14–18] However, we have discovered that the behaviour of oximates does not conform to the traditional finding that nucleophilicity increases regularly with increasing basicity.[9,10] Whereas Brønsted plots for normal nucleophiles reacting at electrophilic carbon centers have been found to be linear with slopes in the range 0.6–0.75 up to pK_a's ≈11, corresponding plots for oximates reacting at carbonyl centers display a levelling-off behaviour at much lower pK_a.[9,10,19] As shown in Fig. 1, which refers to their reactions with *p*-nitrophenylacetate (PNPA) in aqueous solution,[9,10] oximate bases of pK_a < 8 define a Brønsted line with a slope ($\beta_{nuc} = 0.70$) typical of acyl transfer reactions, but the Brønsted plot starts to curve around p$K_a \approx$ 8–8.5 and the observed curvature tends to define a limiting reactivity for the more basic oximate species. Other examples of acyl group transfers characterized by such a rapid saturation-type behaviour have been reported by Simanenko *et al.* as well as Tonnellato *et al.*[12,13] A similar tendency to a levelling-off in reactivity has been observed in the S_NAr displacement of the fluorine atom of 1-fluoro-2,4-dinitrobenzene by oximates.[20]

We have recently carried out a study of PNPA-oximate reactions, going from water to various H_2O–Me_2SO mixtures of increasing Me_2SO content.[19] While the levelling off in reactivity seen in water is still present in 70 : 30 (v/v) H_2O–Me_2SO, a complete change in behaviour occurs in Me_2SO-rich solutions where the linearity of the Brønsted correlation is restored over the whole range of

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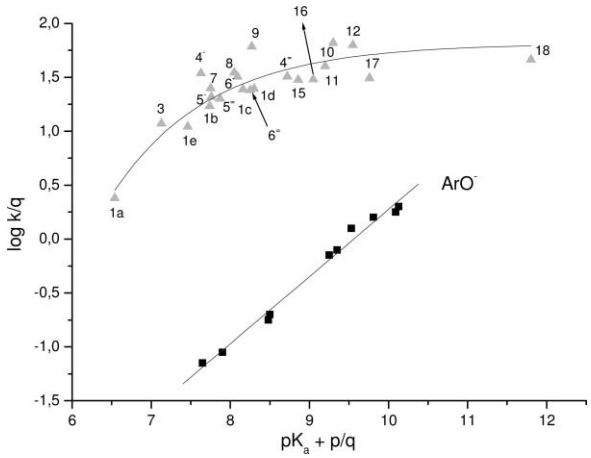
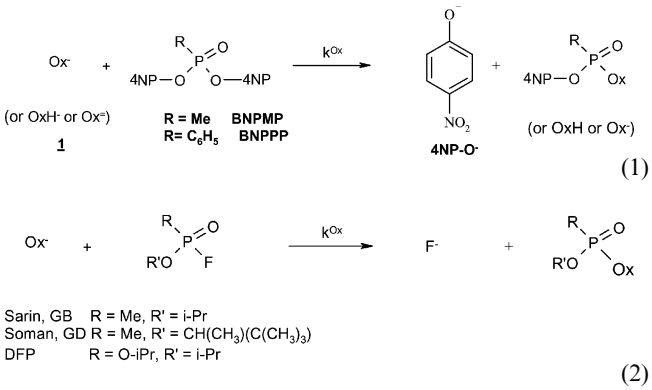


Fig. 1 Brønsted-type nucleophilicity plots for reactions of oximates and phenoxides with PNPA at T = 25 °C in aqueous solution showing the saturation behaviour of oximates (k in dm^3 mol^{-1} s^{-1}); see Chart 1 for the identification of the oxime structures.

oximate basicity studied. On this ground, we have suggested that the origin of the observed saturation of reactivity of oximates could arise from a special need for partial desolvation of these species prior to nucleophilic attack that becomes energetically more costly with increasing basicity.[19] 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.* pK_a > 11–12 for aryloxide ions, has been termed imbalance.[16,19–22]

In view of the use of oximates as catalysts for the hydrolysis of organophosphorus esters,[6,23–37] the question of whether the levelling off behaviour observed for reactions at carbon centers extends to processes involving other electrophilic centers, in particular phosphorus centers, was posed henceforth. In order to address this question, we have undertaken studies of the reactions of two model members of the phosphonate family, namely the bis(4-nitrophenyl)methyl- and bis(4-nitrophenyl)phenyl-phosphonates (BNPMP and BNPPP, respectively), with the series of oximates (Ox^-, OxH^-, $Ox^=$) derived from the ionization of monoxime (OxH) and dioxime (OxH_2) species **1–14** (Chart 1), according to eqn (1) in aqueous solution. As emphasized in a recent communication,[38] the results obtained have confirmed the strong tendency of the oximate reactivity to level off at p$K_a \approx 9$. This prompted us to consider the impact of this saturation effect for selecting the most efficient oximate nucleophiles in neutralization of toxic organophosphorus compounds such as sarin and soman—two chemical war agents commonly referred to as GB and GD, respectively—and the well-known insecticide diisopropylphosphorofluoridate (DFP) in aqueous solution (eqn (2)).[23–26,35–37]

In this paper, we report in detail the results of our investigations of reactions (1) and (2) in aqueous solution. Results regarding the course of reactions (1) in a 30 : 70 (v/v) H_2O–Me_2SO mixture are also reported. Altogether, the results obtained add to the evidence that the levelling off in nucleophilic reactivity of highly basic oximates arises from a need for partial desolvation of these oxyanions prior to nucleophilic attack, that is less important for weakly basic than for more strongly basic anions. The relevance of this solvational imbalance phenomenon to detoxification of organophosphorus esters under mild conditions is discussed.[27–31]



(1)

Sarin, GB R = Me, R' = i-Pr
Soman, GD R = Me, R' = CH(CH$_3$)(C(CH$_3$)$_3$)
DFP R = O-iPr, R' = i-Pr

(2)

Results

pK_a Values in H_2O–Me_2SO mixtures

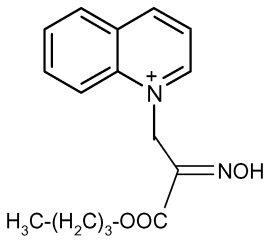
While the pK_a values for all oximes **1–14** were known in aqueous solution, only those for the oximes **7–10**, **12** and **13** were previously determined in H_2O–Me_2SO mixtures.[10] The acidity of the monoximes **1a–1d**, **3**, **10** and **14** (pK_{a1}) as well as that of the dioximes **4**, **5** and **6** (pK_{a1}, pK_{a2}) was therefore measured in 70 : 30 (v/v) H_2O–Me_2SO, 50 : 50 (v/v) H_2O–Me_2SO, and 30 : 70 (v/v) H_2O–Me_2SO, using the same potentiometric procedures as described earlier (see Experimental).[38–40] In view of their high significance for understanding reactivity, the pK_a values for ionization of all oximes **1–14** in water (I = 0.1 mol dm^{-3}) and H_2O–Me_2SO (I = 0.5 mol dm^{-3}) at 25 °C are collected in Table 1. For the purpose of comparison, the pK_a values of some phenols are also given in this table.[10,40]

Kinetic studies

Reactions of oximates 1–14 with BNPMP and BNPPP. Monoximate and dioximate bases derived from pyridinium and related cationic oximes are yellow-colored species the absorption spectra of which overlap with that of *p*-nitrophenoxide ion (4NP–O$^-$). However, we have found it possible to measure the rates of reactions (1) in all oximate buffers by following spectrophotometrically the appearance of 4NP–O$^-$ at the most appropriate wavelength in the range 410–440 nm in aqueous or 30 : 70 (v/v) H_2O–Me_2SO solution. For each buffer studied the reactions were conducted at 25 °C, varying the concentration of the acid and base buffer components at constant pH while maintaining pseudo-first-order conditions with the buffer always being in large excess throughout, *i.e.* [ester] $\approx 5 \times 10^{-5}$ mol dm^{-3}, [Ox^-], [OxH^-] or [$Ox^=$] = 10^{-3}–10^{-2} mol dm^{-3}. The ionic strength was kept constant at I = 0.1 mol dm^{-3} (KCl) in water and 0.5 mol dm^{-3} NMe_4Cl in 70% Me_2SO. In the case of the three dioximes studied, **4**, **5** and **6**, the reactivity of the mono and dioximate species could be assessed independently by investigating the kinetics of reactions (1) in buffer compositions of low pH to minimize the contribution of the dioximate base or of high pH to minimize that of the monoximate base (see Experimental).

Apart from the three pyridine aldoxime systems (**12–14**), excellent first-order kinetics up to about 90% of the total release of 1 eq. of 4NP–O$^-$ were obtained in all buffers studied. Plots of the corresponding first-order-rate constants k_{obs} *versus* the concentration of the reactive oximate species were linear with

1a R = SMe_2+
1b R = SOMe
1c R = SMe
1d R = H (MINA)
1e R = SO_2Me



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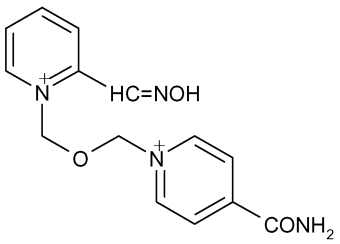
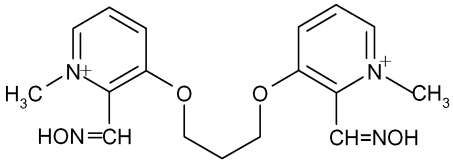
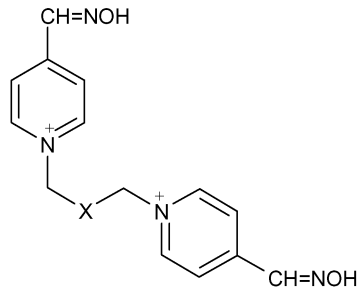


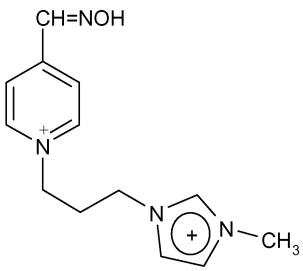
3 (HI6)



4 (R 665)



5 X = O (Toxogonine)
6 X = CH_2 (TMB4)



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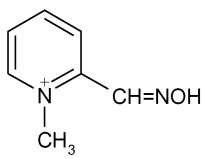

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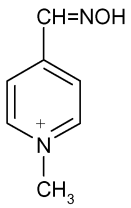

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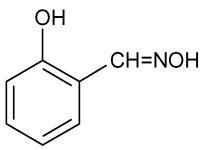

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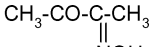

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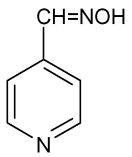

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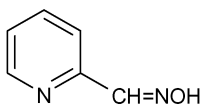

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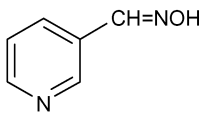

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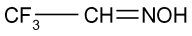

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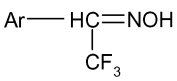

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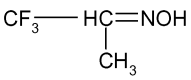

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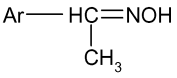

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Chart 1 Structures and numbering of oximes.

Table 1 pK_a Values for monoximes (OxH) and dioximes (OxH_2, OxH^-) in water and various H_2O–Me_2SO mixtures[a]

Oxime \ pK_a or phenol	H_2O	30% Me_2SO	50% Me_2SO	70% Me_2SO	ΔpK_a
1a[b]	6.54	6.78	6.78	7.14	0.60
2[b]	6.98	—	—	—	—
3[b]	7.13	7.03	7.20	7.72	0.59
4[b]	7.33	7.71	8.05	8.46	1.13
	9.02	9.03	9.29	9.80	0.78
5[b]	7.46	7.59	8.00	8.61	1.15
	8.17	8.49	8.70	9.45	1.28
2,4-Dichlorophenol[c]	7.65	8.01	8.31	9.08	1.43
1b[b]	7.74	7.98	8.41	9.36	1.62
7[c]	7.75	8.28	8.38	9.00	1.25
4-Cyanophenol[c]	7.80	8.17	8.45	9.31	1.51
6[b]	7.79	8.04	8.38	9.10	1.31
	8.55	8.83	9.28	9.89	1.44
3,5-Dichlorophenol[c]	8.03	8.27	8.53	9.38	1.35
8[c]	8.05	8.58	8.68	9.47	1.42
1c[b]	8.16	8.49	9.21	10.04	1.88
9[c]	8.27	8.70	9.22	10.16	1.89
1d[b]	8.30	8.70	9.37	10.27	1.97
3,4-Dichlorophenol[c]	8.51	8.78	9.10	10.08	1.57
10[b]	9.20	9.65	10.12	11.32	2.12
11[c]	9.30	9.97	10.62	12.07	2.77
4-Chlorophenol[c]	9.35	9.85	10.18	11.52	2.17
12[c]	9.55	10.22	10.98	12.40	2.85
3-Methoxyphenol[c]	9.65	10.35	11.05	12.24	2.59
13[c]	9.85	10.43	11.19	12.96	3.11
Phenol[c]	9.88	10.62	11.21	12.44	2.56
14	9.95	10.62	11.43	13.18	3.23

[a] $I = 0.1$ mol dm^{-3} in water, $I = 0.5$ mol dm^{-3} in H_2O–Me_2SO mixtures; $T = 25$ °C. [b] $pK^{H_2O}{}_a$ Values from ref. 10. [c] All pK_a values from ref. 10 and/or ref. 40.

negligible intercepts, indicating no appreciable contribution of hydroxide ion and/or water to the rates and suggesting that k_{obs} is simply given by eqn (3). Determination of the second-order-rate constants k^{Ox} from the slopes of the various buffer plots was straightforward (Fig. S1 and S2†).

$$k_{obs} = k^{Ox}[\text{oximate}] \quad (3)$$

In the three pyridinealdoxime systems, reactions (1) were found to be followed by the analogous but much slower displacement of 4NP–O^- from the resulting monosubstituted products. In these instances, the k_{obs} values pertaining to the first substitution process were obtained by recording the increase in absorbance at λ_{max} of 4NP–O^-— where the buffer species at hand do not absorb—as a function of time up to only 50% of the release of the first mole of this anion. In this way, excellent first-order kinetics were obtained with the k_{obs} values fitting eqn (3) nicely (Fig. S3†). No detailed kinetic investigation of the release of the second mole of 4NP–O^- has been made.

The various second-order rate constants k^{Ox} derived from eqn (3) in aqueous and 30 : 70 (v/v) H_2O–Me_2SO are collected in Table 2. Also given in this table are the rate constants k^{OH} for monosubstitution of BNPMP and BNPPP by hydroxide solutions (10^{-3}–10^{-2} mol dm^{-3}) in the two media.

Reactions of oximates with DFP, sarin and soman. The decomposition of the three organophosphorus esters GB, GD and DFP proceeds according to reactions (2) with no significant changes in the UV–visible absorbance, precluding a kinetic investigation of this process by conventional spectrophotometric procedures. The kinetics of reactions (2) were therefore studied by monitoring the increase in the concentration of the expelled fluoride ion by means of a potentiometric cell involving a fluoride ion selective electrode.[30,41–43] All details pertaining to this potentiometric technique, that we have adapted for the investigation of relatively fast kinetic processes ($t_{1/2} \approx 30$ s), have been previously reported, together with examples of its successful application to various types of reactions.[41] These include preliminary experiments regarding the decomposition of DFP in 2-pyridiniumaldoximate (**7**) buffers. In this instance, two different experimental approaches have been used, carrying out the reactions under common pseudo-first-order conditions in various 2-PAM 1 : 1 buffers, *i.e.* [DFP] = 10^{-3} mol dm^{-3}, [Ox$^-$] = 2–6 × 10^{-2} mol dm^{-3}, $I = 0.16$ mol dm^{-3} NaCl or at constant pH in external non-nucleophilic HEPES (pH = 7.49) or TAPS (pH = 8.30) buffers in order to achieve the decomposition in the presence of lower concentrations of the oximate reagents. These two approaches were found to afford similar values for the related $k^{2\text{-PAM}}$ rate constant, *i.e.* $k^{2\text{-PAM}}$ = 0.16 dm^3 mol^{-1} s^{-1}, for the oximate buffering approach, $k^{2\text{-PAM}}$ = 0.14 dm^3 mol^{-1} s^{-1} for the external buffer approach. Interestingly, these values compared well with that previously determined by Ashani and Cohen for the 2-PAM-DFP system, *i.e.* $k^{2\text{-PAM}}$ = 0.18 dm^3 mol^{-1} s^{-1}.[30]

The above successful potentiometric approach led us to use the same methodology to investigate the kinetics of decomposition of sarin and soman by oximates. Because these two organophosphorus esters decomposed in the range of a minute or less in most buffer solutions made up from the oximates themselves (0.01–0.10 mol dm^{-3}), all reactions (2) involving these two esters have been investigated with the external buffer procedure. For maximum consistency this approach has also been favored, using

Table 2 Second-order rate constants for nucleophilic substitution of BNPMP and BNPPP by oximates in aqueous and 30 : 70 (v/v) H_2O–Me_2SO solution at $T = 25\ ^\circ C$[a]

	H_2O		30 : 70 (v/v) H_2O–Me_2SO	
	BNPMP	BNPPP	BNPMP	BNPPP
Oxime	k^{ox}/dm^3 mol^{-1} s^{-1}	k^{ox}/dm^3 mol^{-1} s^{-1}	k^{ox}/dm^3 mol^{-1} s^{-1}	k^{ox}/dm^3 mol^{-1} s^{-1}
3	4.5	6.5	37	30
4	8.4	11.4	89	51
	33.2	51.0	—	215
5	9.2	12.4	92	103
	16.6	20.0	190	224
6	9.9	16.7	—	160
	26.2	39.4	—	380
7	11.1	14.3; 18.7	102	120
1b	6.3	11.5	—	91
8	10.1	19.0	145	180
1c	9.8	16.8	—	250
9	9.2	20.8	205	250
1d	9.8	20.6	260	240
10	—	—	330	470
11	20.1	26.0	900	550
12	15.0	19.8	800	270
13	21.0	14.2	855	265
14	18.1	14.7	760	240
OH^-	26.4	30.3	1350	290

[a] $I = 0.1$ mol dm^{-3} KCl in water; $I = 0.5$ mol dm^{-3} NMe_4Cl in 30 : 70 (v/v) H_2O–Me_2SO.

mainly monoximate species, for the DFP reactions. As illustrated by Fig. 2 and 3, which refer to experiments performed with the sarin-2-PAM-HEPES and soman-CEB1574-TAPS systems, respectively, as well as by Fig. S4† which refers to the soman-2-PAM-HEPES system, nice first-order kinetics were obtained in carrying out the decomposition of the esters under the following experimental conditions: [ester] = 10^{-3}mol dm^{-3}; total oxime concentration $[Ox]_0 = 2–8 \times 10^{-3}$ mol dm^{-3}; pH = 7.49 or 8.30, as maintained by 1 : 1 HEPES or TAPS buffers with a total buffer concentration of 0.1 mol dm^{-3}; $I = 0.16$ mol dm^{-3} (NaCl).

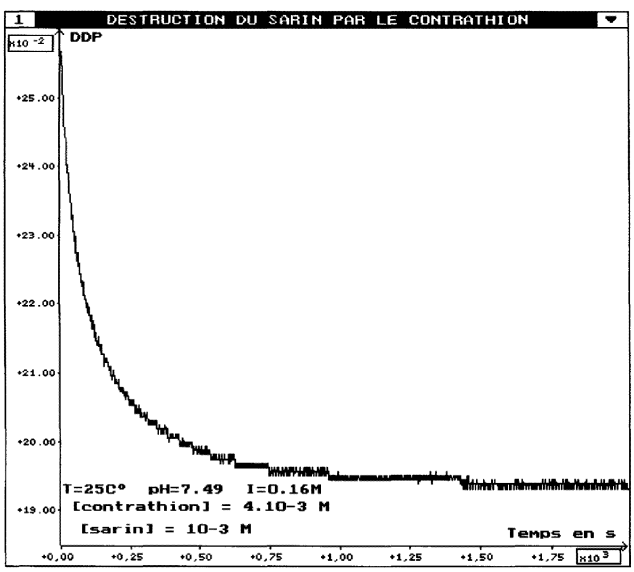

Fig. 2 Oscilloscope trace illustrating the first-order decomposition of sarin by the 2-pyridiniumaldoxime **7** at pH = 7.49 in a 1 : 1 HEPES buffer, as derived from a potentiometric monitoring of the resulting increase in the F^- concentration. See text.

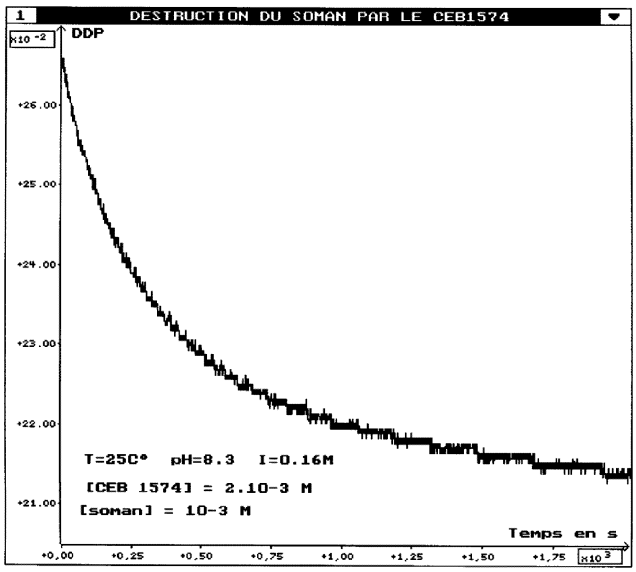

Fig. 3 Oscilloscope trace illustrating the first order decomposition of soman by the oxime **8** (CEB 1574) at pH = 8.30 in a 1 : 1 TAPS buffer, as derived from a potentiometric monitoring of the resulting increase in the F^- concentration. See text.

Neglecting in a first approximation the contribution of hydroxide ion as well as of water to the decomposition process at the pH at hand the expected reaction rate law may be written as:

$$\frac{d[F^-]}{dt} = k^{Ox^-}[Ox^-][ester] \quad (4)$$

where the concentration of the reactive oximate species at time t is given by the equation:

$$[Ox^-] = \frac{[Ox]_0 - x}{1 + 10^{pK_a^{Ox} - pH}} \quad (5)$$

In this equation, $[Ox]_0$ is the total concentration of the oxime introduced in the solution and x, the concentration of the fluoride ion generated by the reaction at time t, *i.e.* we have $x = [F^-]_{tot} - [F^-]_0$ with an initial F^- concentration $[F^-]_0 = 10^{-4}$ mol dm^{-3} and $[F^-]_{tot}$ at time t as given by eqn (6).[41] E is the potential of the cell measured at time t, Δ a constant deduced from the calibration of the cell and $\Im$ the Faraday constant.[41]

$$[F^-]_{tot} = 10^{((E - \Delta)\Im)/(2.303RT)} \quad (6)$$

$$k_{.t}^{ox} = \frac{1 + 10^{(pK_a^{ox} - pH)}}{[Ox]_0 - C_0} \ln \frac{C_0([Ox]_0 - x)}{(C_0 - x)[Ox]_0} = Z \quad (7)$$

Integration of eqn (4) then leads to eqn (7) which predicts that a plot of the right side term, denoted Z for simplicity, *versus* time should afford a straight line passing through the origin. As illustrated by Fig. 4 which refers to the sarin and soman 2-PAM-HEPES systems, as well as by Fig. S5,† which refers to the DFP-2-PAM-HEPES system, plots of Z *versus* t corresponding to the various experiments carried out with the series of oximates studied were in fact all linear with zero intercepts, allowing a straightforward determination of the corresponding k^{ox} values from the slopes of these plots.[41] For a given phosphorus ester oximate system, very consistent k^{ox} values were derived from experiments carried out with different total concentrations of the oximes (Table S1†).

In the case of the decomposition of DFP, the rate constants k^{ox} for R-744 (**2**), HI-6 (**3**) and 2-PAM (**7**) systems have also been determined through experiments conducted in oximate buffers.

$$\frac{d[F^-]}{dt} = k^{Ox}[Ox^-][DFP] = k_{obs}[DFP] \quad (8)$$

In agreement with the rate law of eqn (8), plots of the observed first-order rate constants k_{obs} *versus* the oximate concentration were linear with zero intercepts as shown in Fig. S6† for the decomposition of DFP in 1 : 1 HI6 buffers. The second-order rate constants k^{ox} derived from these measurements, *e.g.* k^{HI6} = 0.059 dm^3 mol^{-1} s^{-1} agreed very well with those obtained with the external buffer methodology, *e.g.* $k^{HI6} = 0.062$ dm^3 mol^{-1} s^{-1}.

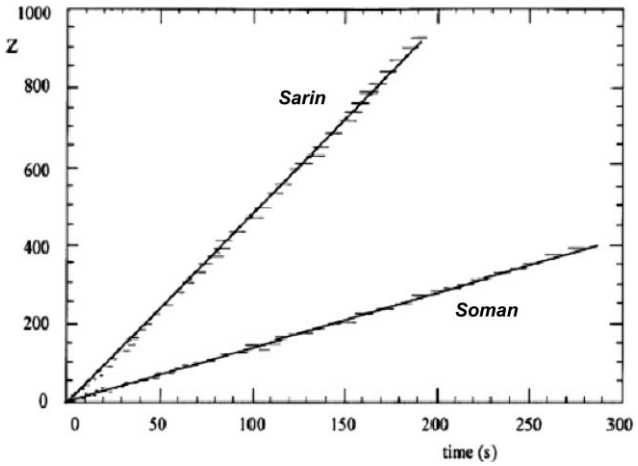

Fig. 4 Graphs according to eqn (7) illustrating the decomposition of sarin and soman in an external HEPES buffer, containing total pyridinealdoxime (**7**) concentrations of 2×10^{-3} and 4×10^{-3} mol dm^{-3}, respectively (pH = 7.49; $T = 25$ °C).

The various second-order rate constants k^{ox} pertaining to the decomposition of sarin, soman and DFP by oximates at 25 °C in aqueous solution are collected in Table 3. All kinetic data obtained for reactions (1) and (2) in aqueous solution are displayed in the form of Brønsted-type nucleophilicity plots in Fig. 5–8.

Discussion

Oximate reactivity

As can be seen in Fig. 5–8, all Brønsted-type nucleophilicity plots pertaining to the five phosphorus compounds studied reveal a clear tendency of the reactivity of oximates to suffer a saturation

Table 3 Rate constants for nucleophilic substitution of sarin, soman and DFP by oximates in aqueous solution

		Sarin	Soman	DFP
Oxime	$pK^{H_2O}{}_a$	k^{Ox}/dm^3 mol^{-1} s^{-1}	k^{Ox}/dm^3 mol^{-1} s^{-1}	k^{Ox}/dm^3 mol^{-1} s^{-1}
1a	6.54	0.32	0.14	—
2	6.98	—	0.25	0.050
3	7.13	1.47	0.43	0.062; 0.059[b]
4	7.33	2.39	—	0.125
	9.02	20.20	—	1.000
5	7.46	—	—	0.13[c]
	8.17	—	—	0.30[e]
7	7.75	4.75; 2.00[d]	1.42	0.14; 0.18[e]
6	7.79	5.90	1.65	0.25; 0.32[e]
	8.55	10.05	3.60	0.40; 0.53[e]
8	8.05	8.00	2.20	0.30
9	8.27	6.45; 6.33[d]	—	—
1d	8.30	5.00; 4.16[d]	1.90	0.28
11	9.30	8.80; 6.83[d]	4.35	0.60
12	9.55	13.40	5.59	0.64
13	9.85	14.70; 28.00[d]	5.50	0.64
14	9.95	13.10; 16.50[d]	—	—
OH^-	15.74	23.70[e]; 27.50[f]	10.15[f]	0.31[e]

[a] $T = 25$ °C, $I = 0.16$ mol dm^{-3} KCl, k^{Ox} derived from the external buffer approach, unless otherwise stated (see text); the quoted k^{Ox} values are the average of two or three determinations (see Table S1†). [b] k^{Ox} derived from the oximate buffer approach. [c] Ref. 30. [d] Ref. 29. [e] Ref. 28. [f] Ref. 31.

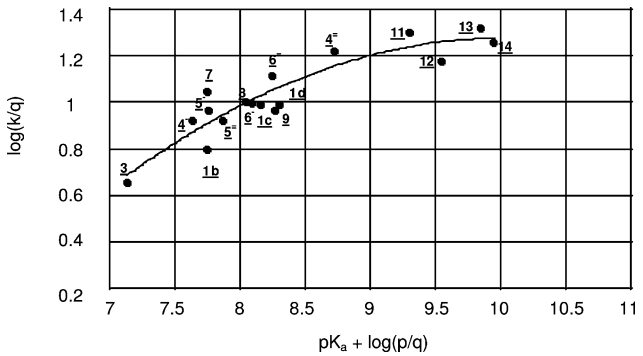

Fig. 5 Statistically corrected Brønsted-type nucleophilicity plot for the reactions of the oximates with BNPMP at 25 °C in aqueous solution (k in dm^3 mol^{-1} s^{-1}). See Chart 1 for the structures of oximates.

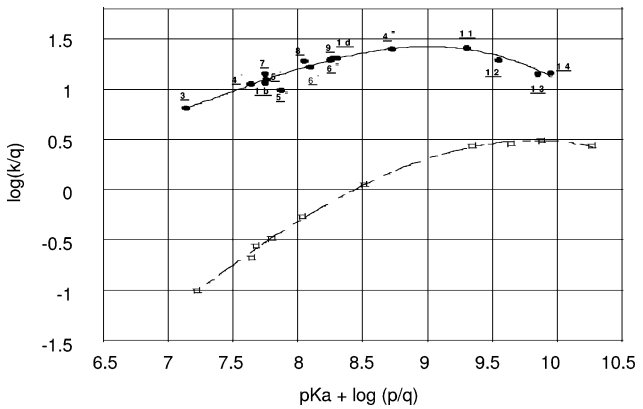

Fig. 6 Statistically corrected Brønsted-type nucleophilicity plot for the reaction of the oximates (●, this work) and phenoxide ions (□, ref. 40) with BNPPP at 25 °C in aqueous solution (k in dm^3 mol^{-1} s^{-1}). See Chart 1 for the structures of the oximates.

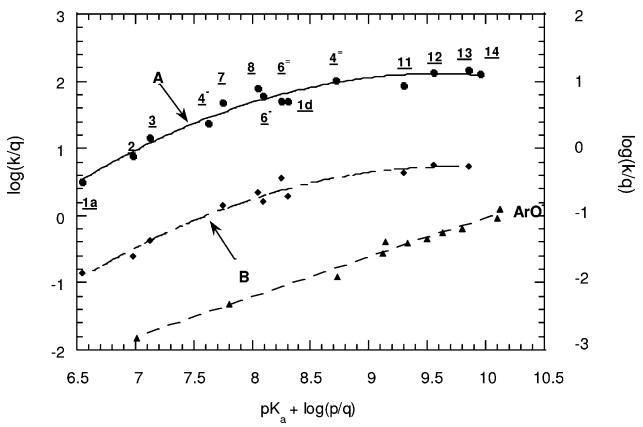

Fig. 7 Brønsted-type nucleophilicity plots for the reactions of oximates with sarin (graph **A**, right Y axis) and soman (graph **B**, left Y axis) at 25 °C in aqueous solution (k in dm^3 mol^{-1}s^{-1}). The structures of oximates are given in Chart 1. The lower line refers to the reactions of phenoxides with sarin (left Y axis, ref. 27).

effect with increasing basicity. In the case of the two model phosphonates, BNPMP and BNPPP, as well as the three toxic esters, GB, GD and DFP, this behaviour is reflected by a levelling of at p$K_a^{Ox} \approx 9$. Interestingly, a more dramatic situation is observed in the bis (4-nitrophenyl)phenylphosphonate (BNPPP) system. In this instance, the reactivity is characterized by a bell-shaped profile where the attainment of maximum reactivity is followed by a clear decrease in rate at p$K_a^{Ox} > 9$.

So far, the finding that the reactivity of oximates can be subject to a saturation effect has been firmly established only for reactions occurring at electrophilic carbon centers,[9,10,12,13] *e.g.* Fig. 1. The present discovery that such a behaviour also holds for reactions at electrophilic phosphorus centers is therefore of major significance, suggesting in fact that the occurrence of curvature in the Brønsted plots of Fig. 1 and Fig. 5–8 is the reflection of an intrinsic property of the oximate functionality. In this regard, it is intriguing that such a levelling off behaviour has not emerged from earlier studies of the decomposition of organophosphorus esters by oximates in aqueous solution.[27–31] Monitoring by titration the production of acid (HF) associated with the reactions, Green and Saville reported in 1956 a thorough kinetic investigation of the decomposition of sarin (GB) by a series of oximates of different basicities and noted that there was *surprisingly* little change in reactivity with varying the oximate structure.[29] Even though the agreement is far from being perfect, the results of these authors conform in fact rather well to the curvilinear Brønsted correlation built on the basis of our data, confirming in particular the levelling off observed at p$K_a \geq 9$ (see Table 3). On the other hand, Ashani and Cohen have investigated the decomposition of DFP by a large set of pyridinium and structurally related aldoximates (see structures in Chart 2) but they failed to correlate their kinetic data in terms of a meaningful Brønsted plot.[30] Again, a re-analysis of these data on the basis of statistically corrected rate constants and pK_a^{Ox} values for the dioxime reagents leads to a nice fit with the curvilinear behaviour depicted in Fig. 8. Thus, the reactivity of the moderately basic oximates (p$K_a \leq 8$) defines a linear Brønsted plot with a slope, $\beta_{nuc} = 0.65$, which is intermediate between those associated in the same pK_a^{Ox} range to the correlations pertaining to the decomposition of BNPMP and BNPPP ($\beta_{nuc} = 0.45$) and to that of sarin and soman on the other hand ($\beta_{nuc} = 0.75$–0.80). Furthermore, the reactivity of the most basic oximates toward

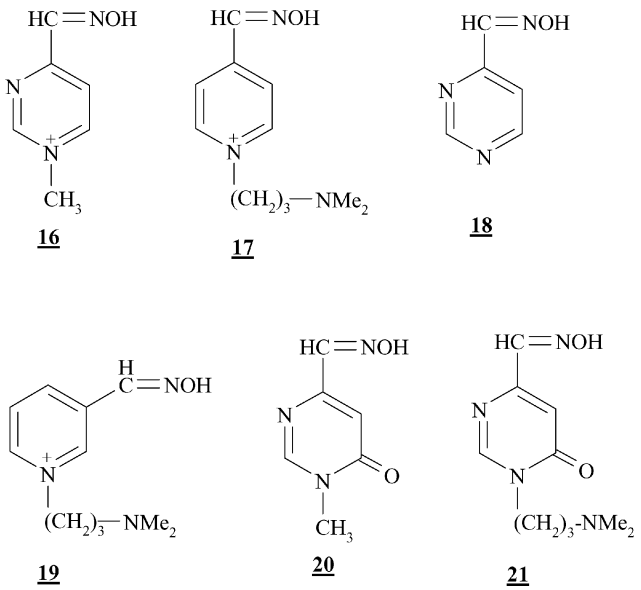

Chart 2

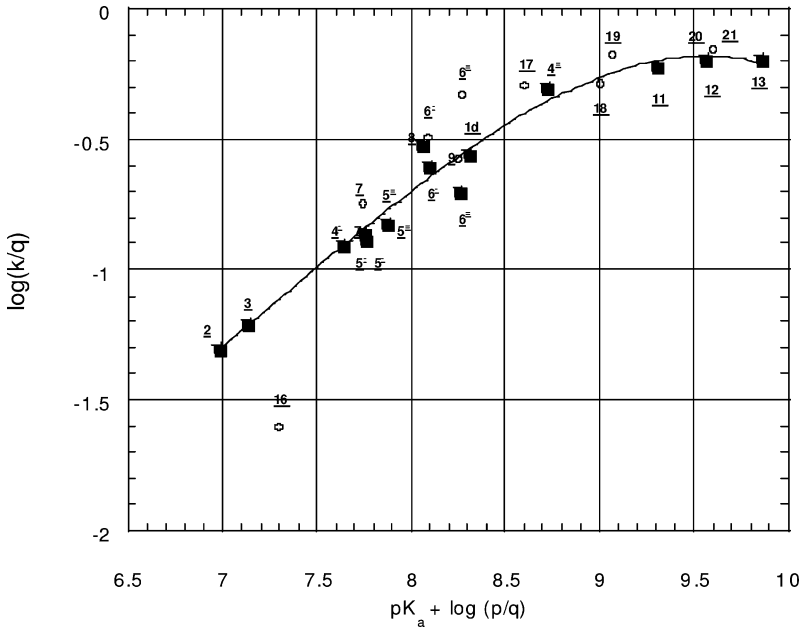

Fig. 8 Brønsted-type nucleophilicity plot for the reaction of oximates with DFP at 25 °C in aqueous solution (k in $dm^3\ mol^{-1}\ s^{-1}$). The structures of oximates are given in Chart 1 and Chart 2. (■) Data obtained in this work; (○) data from ref. 30.

DFP is clearly subject to a saturation effect, as it does for the other systems.

Returning to the β_{nuc} values, it is noteworthy that they vary so much within our family of phosphorus electrophiles. Since the magnitude of β_{nuc} is commonly recognized as a measure of the extent of bond formation between the nucleophile and the substrate in the transition state of the rate determining step, it follows that the TS stabilizing effect must be smaller for the BNPMP and BNPPP systems, which involve the departure of a 4NP–O^- ion, than for the DFP, sarin and soman systems, which involve the departure of a F^- ion.[2] Interestingly, previous studies by Um *et al.*, have emphasized that β_{nuc} is also very dependent of the nature of the electrophilic center.[2,11]

Oximate *vs.* phenoxide reactivity

Confirming the generality of the behaviour emphasized in previous studies of acyl group transfers, *e.g.* the PNPA reactions in Fig. 1,[9,10,12,13] a most important feature emerging from Fig. 5–8 is that, for a given phosphorus electrophile, the reactivity of oximates tends to level off much more rapidly than that of phenoxide ions. Using the sarin system as a reference, the Brønsted correlation of oximates is seen to define a limiting reactivity at $pK_a \geq 9$–9.5. At the same time no significant curvature can be detected up to $pK_a \approx 10.5$ in the corresponding correlation for phenoxide ions, in accord with previous reports that it is only for $pK_a > 11$–12 that normal oxyanions like phenoxide or alkoxide anions display a levelling off behaviour.[14,17] In this regard, however, an interesting situation is the one depicted in Fig. 6 which refers to the BNPPP system. In this instance, the levelling off observed in the reactivity of oximates at $pK_a \approx 9$ is followed by a decrease in rate at higher pK_a. Significantly, the Brønsted plot describing the reactivity of phenoxides with BNPPP has been previously found to curve earlier ($pK_a \approx 9.5$–10) than usually found for these normal oxyanions ($pK_a > 11$–12).[16,17,44] In this particular system, it is possible that the presence of the phenyl group induces a greater steric hindrance to the approach of the most basic and therefore more solvated oximate or phenoxide nucleophiles to the phosphorus center, as compared with the methyl group in the related BNPMP system.

To be noted is that the decreasing oximate reactivity at $pK_a^{Ox} > 9$ in Fig. 6 corresponds to a negative β_{nuc} value. So far, 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*-nitrophenylphosphates.[16] A last message from Fig. 5–8 is that there is no significant difference up to $pK_a \approx 9$ in the development of curvature in the correlations pertaining to the reactions of oximates with sarin, soman and DFP on the one hand, BNPMP and BNPPP on the other hand. This suggests that the nature of the leaving group, F^- or 4NP–O^-, is not here a predominant factor determining the extent of the levelling off, at least up to $pK_a \approx 9$. In view of the very different pK_a values for these two leaving anions (3.45 and 7.15, respectively), this result is very important since it supports the idea that the observed non-linearity of the Brønsted plots cannot be the reflection of a change in the rate-limiting step of the substitutions.[14]

Imbalanced transition states

We have previously suggested that the observation of curvature in the Brønsted-type nucleophilicity plots for the reactions of oximates with esters could be reasonably accounted for in terms of an earlier proposal by Jencks and Hupe that strongly hydrogen-bonded species like oxyanions must undergo some desolvation prior to being involved in nucleophilic attacks.[9,16,19,44] Such de-solvation will occur ahead of bond formation in the transition state and will become energetically more expensive with increasing basicity, simply because solvation is usually stronger for most basic anions.[39,40,46] This will decrease the reactivity of basic nucleophiles, accounting for the observed curvature in the Brönted plots. This

lack of synchronization between desolvation and bond formation has frequently been called an "*imbalance*".[16,21,45]

This explanation can be visualized as follows. Using the straight Brønsted lines of slope β_{nuc} defined by the points at low pK_a as references, and assuming that the desolvation of the basic reagents occurs in an equilibrium step ($K_d < 1$) which precedes nucleophilic attack (eqn 9), curved Brønsted plots will be the reflection of negative deviations of the points at high basicity that may be expressed by eqn (10).

$$RO^-_{solv} \underset{\text{-----}}{\overset{K_d}{\rightleftharpoons}} RO^-_{des} \xrightarrow[k^{RO}]{\text{Electrophile}} []^{\#} \quad (9)$$

$$\Delta\log(k^{RO}) = (1 - \beta_{nuc})\log K_d \quad (10)$$

The accumulated evidence, however, is that it is more appropriate to view the situation in term of a more sophisticated but more general model which has been the subject of considerable discussion in the context of the imbalances encountered in proton transfer reactions on carbon atoms.[10,21,45–47] Instead of assuming that desolvation and bond formation occur in two different steps, this model considers that the two events take place in the same step but that desolvation has progressed further than bond formation in the transition state. Then, the decrease in $\log(k^{RO})$ is described by an equation of the form:

$$\Delta\log(k^{RO}) = (a_{des} - \beta_{nuc})\log K_d \quad (11)$$

where $1 \geq a_{des} \geq 0$ measures the progress of desolvation in the transition state. If desolvation is ahead of bond formation, we have $a_{des} > \beta_{nuc}$ so that $\Delta\log(k^{RO})$ is again negative. For $a_{des} \approx 1$, the situation corresponds to a total decoupling of the two events, as depicted by Jencks' model. Importantly, eqn (10) and (11) deliver the same important message, *i.e.* that for curvature to be generated by solvation effects 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: $a_{des} - \beta_{nuc} > 0$.[16,21,44–47]

Based on eqn (11), two different explanations can be suggested to account for the differences observed in the Brønsted behaviour of oximate (Ox) and phenoxide (ArO) reactions.

(1) Desolvation has progressed similarly in the transition states for oximate and phenoxide reactions, *i.e.* $a^{Ox}_{des} = a^{ArO}_{des}$. Since β_{nuc} is found to be essentially the same for a given electrophile reacting with oximates and phenoxides (see Fig. 1, 6 and 7) the desolvation of oximates must be significantly more difficult than that of phenoxides to account for the more rapid appearance of curvature in the Brønsted plots for oximate ions. The situation is qualitatively the same as that suggested by Jencks' model for a complete decoupling of the desolvation and bond formation steps.

(2) The K_d values are similar for similarly basic phenoxide and oximate species. In this case, the magnitude of the deviation from the Brønsted plot drawn at low pK_a will depend on the ($a_{des} - \beta_{nuc}$) term. Then, the more rapid levelling off in the reactivity of oximates implies $a^{Ox}_{des} > a^{ArO}_{des}$, *i.e.* the Brønsted behaviour of oximates is the reflection of greater solvational imbalances in the related transition states as compared with the situation for phenoxide reactions.

That the latter situation prevails in our system can be demonstrated by comparing the changes in acidity suffered by oximes and phenols on going from water to 30 : 70 (v/v) H_2O–Me_2SO.

Solvent effects on pK^{Ox}_a and pK^{ArOH}_a

Due to their poor ability to provide hydrogen-bond solvation, dipolar aprotic solvents are known to strongly destabilize anionic species with a localized or relatively localized negative charge as compared to protic solvents.[48,49] In accord with this idea, the acidity of oxygen acids like carboxylic acids and phenols has been reported to decrease markedly upon addition of increasing amounts of Me_2SO to aqueous solutions.[39,40,46,50] Consistent with these findings, Table 1 shows that the acidity of all oximes **1–14** also decreases with increasing Me_2SO content of H_2O–Me_2SO mixtures. However, a close inspection of the pK_a variations in Table 1 reveals two significant features: (1) a phenol and an oxime of similar $pK^{H_2O}_a$ values undergo comparable changes in acidity on transfer to Me_2SO-rich solutions; (2) the solvent effect on the acidity of the two functionalities is a function of the acidity measured in aqueous solution, becoming more and more important with increasing $pK^{H_2O}_a$, as previously observed and discussed in detail by Bernasconi for carboxylate ions.[46,47] Thus, for the change from H_2O to 70% Me_2SO, we have the following decreases in acidity, as measured by $\Delta pK_a = pK^{70\%}_a - pK^{H_2O}_a$ values: $\Delta pK_a = 1.43$ for 2,4-dichlorophenol ($pK^{H_2O}_a = 7.65$) *vs.* $\Delta pK_a = 1.62$ for the oxime **1b** ($pK^{H_2O}_a = 7.74$); $\Delta pK_a = 2.17$ for 4-chlorophenol ($pK^{H_2O}_a = 9.35$) *vs.* $\Delta pK_a = 2.12$ for the oxime **10** ($pK^{H_2O}_a = 9.20$); $\Delta pK_a = 2.59$ for 3-methoxyphenol ($pK^{H_2O}_a = 9.65$) *vs.* $\Delta pK_a = 2.85$ for the oxime **12** ($pK^{H_2O}_a = 9.55$) and $\Delta pK_a = 3.11$ for the oxime **13** ($pK^{H_2O}_a = 9.85$).

In as much as they are primarily the reflection of the desolvation of phenoxide or oximate functionalities caused by the addition of Me_2SO to aqueous solutions,[48–50] the above ΔpK_a values may be considered as being a good index of the relative degrees of solvation of the ArO^- or Ox^- anions in aqueous solutions. Then, the regular increase in ΔpK_a with increasing $pK^{H_2O}_a$ fits well with Jencks and Hupe's proposal that desolvation requirements in the transition states of nucleophilic substitution processes become energetically more expensive when the basicity of the nucleophile is increased.[16,17,44] In contrast, the fact that the ΔpK_a values measuring the solvent effect are roughly similar for oximates and phenoxides of similar basicities in aqueous solution is difficult to reconcile with the idea that the more rapid appearance of curvature in the Brønsted plots for oximates is the reflection of more unfavourable energetics of partial desolvation of these species in the related transition states as compared with the situation for phenoxide reactions. Hence, the above suggestion that the oximate reactions proceed through strongly imbalanced transition states in aqueous solution is reinforced.

Solvent effect on rates

The fact that the addition of Me_2SO decreases the solvation of oxyanions also suggested that desolvation requirements should become less and less important in determining the reactivity of these species on going from H_2O to Me_2SO-rich solvents. On this ground, one could reasonably expect that the curvature of the Brønsted plots will be attenuated or will even disappear in solvents of high Me_2SO content. As a matter of fact, we have recently reported a study of the PNPA-oximates reactions, going from water to 70 : 30 (v/v) H_2O–Me_2SO, 30 : 70 (v/v) H_2O–Me_2SO and 20 : 80 (v/v) H_2O–Me_2SO. While the characteristic levelling

off in reactivity seen in water is still present in 70 : 30 (v/v) H_2O–Me_2SO, a dramatic change in behaviour was observed on going to the two Me_2SO-rich solutions where the Brønsted correlation has become linear once again, as found for the weakly basic oximates in aqueous solution.[19]

Fig. 9 shows the Brønsted plots describing the reactivity of oximates with BNPMP and BNPPP in 30 : 70 (v/v) H_2O–Me_2SO. Even though the points for the two most basic oximates employed suggest that some curvature starts to develop at $pK_a \geq 13$, it is clear that the effect of going from water to 70% Me_2SO is to largely restore the linearity of the correlation pertaining to the BNPMP reactions. As pointed out for the PNPA systems, the metamorphosis can be explained as follows. Being less solvated in Me_2SO-rich media, the ground state of the oxyanions is now more prone for nucleophilic attack. This avoids the need for an energetically costly additional desolvation prior to bond formation, thereby reducing the non-synchronicity between the two events, as found in aqueous solution.[19]

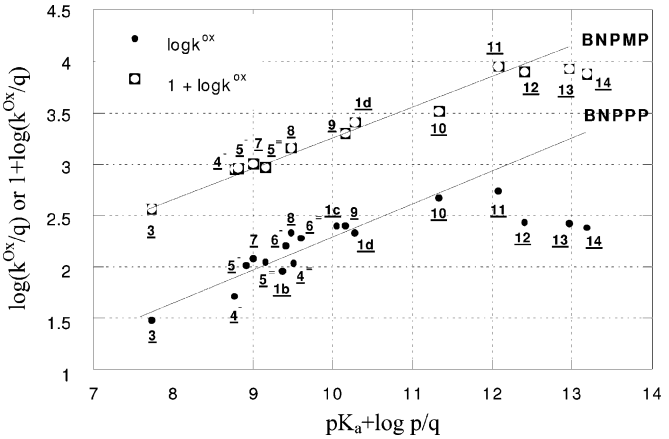

Fig. 9 Statistically corrected Brønsted-type nucleophilicity plots for the reactions of oximates with BNPMP and BNPPP at 25 °C in 30% H_2O–70% Me_2SO; k in $dm^3\ mol^{-1}\ s^{-1}$. See Chart 1 for identification of the oximate species.

Contrasting with the BNPMP system, the solvent transfer does not lead to the recovery of an extended linear correlation for the BNPPP reactions. This behaviour follows the more pronounced decrease in reactivity observed at high pK_a in aqueous solution (Fig. 6) and the idea that the presence of the phenyl group induces a greater steric hindrance to the approach of a nucleophile to the phosphorus center, as compared to a methyl group (*vide supra*). 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 BNPPP than BNPMP. This would account for the observed decrease in reactivity of BNPPP at high pK_a in water and the greatest difficulty to restore a normal behaviour in 70% Me_2SO.

Conclusion—relevance to detoxification of organophosphorus esters

As a first major consequence of the levelling off observed in Fig. 5–8, the gain in reactivity reflecting the related α-nucleophile character of the oximate functionality in aqueous solution decreases regularly with increasing pK_a in the series. Table 4 presents the α-effects calculated by comparing the reactivity of a few oximates of increasing pK_a's with that of similarly basic phenoxide ions in the case of the sarin and BNPPP systems. As can be seen, the enhanced reactivity factor, k_{ox}/k_{ArO}, decreases progressively from about 70–80 for the two systems in the low pK_a region to about 10 for sarin and 5 for BNPPP at high pK_a.

Table 4 The effect of basicity on the exalted α-reactivity of oximates towards sarin and BNPPP in aqueous solution

Oxime	$pK^{H_2O}{}_a$	k_{ox}/k_{ArO}	
		Sarin	BNPPP
3 (HI-6)	7.13	80	70
7 (2-PAM)	7.75	80	50
1d (MINA)	8.30	50	31
11 (DAM)	9.30	22	10
12 (4-PAD)	9.55	25	7
13 (2-PAD)	9.85	12	4.6

Overall the experimental evidence leaves no doubt that the levelling off in reactivity of the most basic oximates is an intrinsic property of the oximate functionality. As a result, it is evident that consideration of the efficiency of oximates as nucleophilic decontaminating catalysts will need to take cognizance of this saturation effect since any advantage which one would normally expect to accrue in using highly basic oximates tends to nullify in aqueous solution for $pK_a > 8$–9.

Experimental

Materials

All the oxime and phenol precursors of the nucleophiles used in this work were available from previous studies and were recrystallized from methanol or hexane before use.[9,10,19,20] The phosphonates BNPMP and BNPPP were prepared according to literature methods.[5,51] Sarin, soman and DFP were provided by the Centre d'Etude du Bouchet and used without further purification. Dimethylsulfoxide was refluxed over calcium hydride and distilled, and the fraction of 32–35 °C (under 2 mmHg) was collected and stored under nitrogen. Me_2SO–water solutions were prepared as described previously.[10] Only freshly prepared solutions were used in the kinetic and potentiometric studies.

Acidity measurements

The unknown acidity constants (pK_a) of the monoximes **1a–1d**, **3**, **10** and **14** in 70 : 30 (v/v) H_2O–Me_2SO, 50 : 50 (v/v) H_2O–Me_2SO and 30 : 70 H_2O–Me_2SO were measured by potentiometry at 25 °C, using a procedure previously employed for the determination of the pK_a's of carboxylic acids, phenols and a number of nitrogen acids in the same solvent mixtures.[39,40] Thus the pK_{a1} values were determined from buffer solutions with $[Ox^-]$–[OxH] ratios equal to 1 : 2, 1 : 1, 2 : 1. These solutions were prepared so that the molarity of the oximate species was in all cases equal to 0.01 mol dm^{-3}. The ionic strength was maintained constant at 0.5 mol dm^{-3} by adding NMe_4Cl in H_2O–Me_2SO mixtures. Under these experimental conditions, the pK_{a1} values at the corresponding ionic strength were in each solvent obtained from the measured pH values of the

buffers by means of eqn (12). Calibration of the cell used to obtain the pH measurements was carried out as previously described.[39]

$$pK_a = pH - \log \frac{[Ox^-]}{[OxH]} \quad (12)$$

The pK_{a1} and pK_{a2} values for ionization of the three dicationic dioximes **4**, **5** and **6** (OxH_2) were too close to be independently determined in a similar way. For a reliable determination of these pK_a's, potentiometric titrations of 0.01 mol dm^{-3} solutions of the dioximes in the H_2O–Me_2SO mixtures at hand by a 0.1 mol dm^{-3} NMe_4OH solution in the same solvent mixture were carried out at $T = 25$ °C and $I = 0.5$ mol dm^{-3}, following the same procedure successfully employed in aqueous solution.[10] Then, the pK_{a1} and pK_{a2} values were readily derived from the titration data according to the Speakman equation.[52]

Kinetic measurements

The potentiometric method used to determine the kinetics of the sarin, soman and DFP reactions according to eqn (2) by monitoring the appearance of F^- under the various experimental conditions described in the text has been presented in detail elsewhere with particular illustrations taken from the DFP systems.[41] Spectrophotometric determinations of the rates of decomposition of the phosphonates PNPMP and PNPPP according to eqn (1) were carried out under pseudo-first-order conditions with excess buffer base (10^{-3}–10^{-2} mol dm^{-3}) over the ester concentration ($\approx 5 \times 10^{-5}$ mol dm^{-3}) and at constant ionic strength (I = 0.1 mol dm^{-3} KCl in H_2O, I = 0.5 mol dm^{-3} NMe_4Cl in 30 : 70 (v/v) H_2O–Me_2SO). Measurements were made by monitoring the appearance of the resulting 4-nitrophenoxide ion ($4NP–O^-$) at the wavelengths found to be the most appropriate for minimizing interference between the UV–vis spectrum of this anion and that of the relevant oximate buffers, *i.e.* in the 410–440 nm region. For a given buffer, at least six values of the base reagent were employed at constant pH and each individual experiment was performed in triplicate. Apart from the three pyridinealdoxime systems (**12–14**), excellent first-order kinetics up to 90% of the total release of 1 equiv of $4NP–O^-$ were obtained (see Fig. S1 and S2†). In the three pyridinealdoxime systems, reactions (1) were found to be followed by a much slower displacement of $4NP–O^-$ originating from the decomposition of the resulting monosubstituted phosphonate. However, in these instances, where there is no overlap in the UV–visible absorption of the *p*-nitrophenoxide ion and the buffer acid or base species, nice first order behaviour was found to prevail up to 50% of release of the first mole of $4NP–O^-$ (see text and Fig. S3†).

In the case of the three dioxime systems (**4**, **5**, **6**), the reactivity of the mono- and dioximate was assessed independently, first at low pH with $[OxH^-]$–$[OxH_2]$ ratios of 1 : 4 or 1 : 3 to minimize the contribution of the dioximate base and then at high pH, working with $[Ox^=]$–$[OxH^-]$ ratios of 3 : 1 or 4 : 1 to maximize the contribution of the dioximate base, and then analyzing the data as previously described for other reactions.

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