Peroxyhydrolysis of nerve agent VX and model compounds and related nucleophilic reactions

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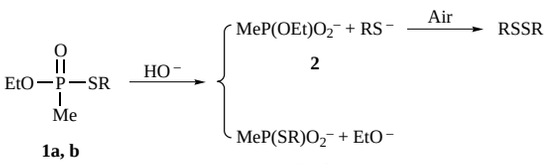
The exceedingly toxic agent VX [*O*-ethyl *S*-(diisopropylaminoethyl) methylphosphonothioate], 1a, and the midly toxic model compound *O*,*S*-diethyl methylphosphonothioate, 1b, react with HO^- to give parallel P–S and P–O bond cleavages; the P–O cleavage of VX produces relatively unreactive but very toxic anionic phosphonothioate. Peroxyhydrolysis of 1a,b with HO_2^- involves quantitative P–S cleavage at rates 30–40 times that with HO^- giving the corresponding phosphonate and sulfonate ions and disulfide as nontoxic products. In reaction of 1b with HO_2^- in $H_2{}^{18}O$, oxygen in these final products is not derived from water and HO_2^- exclusively displaces the thiolate ion at phosphorus. Reaction of 1b with HSO_5^- gives the same products, but *via* oxidatively promoted attack of $H_2{}^{18}O$ on phosphorus. Kinetic and isotopic labelling results on reactions of 1a,b and a range of related compounds with HO_2^-, HO^- and RO^- and an oximate ion are interpreted in terms of concerted $S_N2(P)$ reactions rather than stepwise reactions with formation of a trigonal bipyramidal (TBP) intermediate. Product selectivity depends on the *relative* basicities of the anionic nucleophile and the leaving anions.

Introduction

Chemical detoxification of the exceedingly toxic VX [*O*-ethyl *S*-(2-diisopropylaminoethyl) methylphosphonothioate] **1a** (Scheme 1) is more complex than the G-type nerve agents. GB



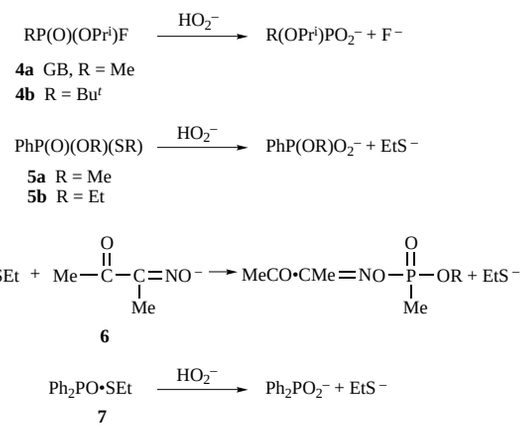
1a VX, R = $CH_2CH_2N(Pr^i)_2$
1b R = Et

Scheme 1

or Sarin (isopropyl methylphosphonofluoridate, **4a**) and related fluoridates are rapidly detoxified in relatively dilute alkali,[1,2] but VX reacts with HO^- at ambient temperatures to give nontoxic **2**, with P–S bond cleavage, and the highly toxic **3a**, with P–O bond cleavage.[2–5] The less toxic simulant of VX, *O*,*S*-diethyl methylphosphonothioate (**1b**), behaves similarly (Scheme 1). Some of the thiolate ions formed by alkaline P–S cleavage of **1a**,**b** are air oxidized, but the toxic phosphonothioate ions (**3a**,**b**) react only slowly with HO^-, as is typical of anionic phosphorus(v) esters.[6] Complete detoxification of VX (**1a**) by HO^- therefore requires high temperatures, which is impractical for decontamination, especially in the field.

Rapid detoxification of VX requires different chemistry. One effective approach is to use peroxyacids which oxidize sulfur and promote rapid P–S bond cleavage. Peroxymonosulfate ion, HSO_5^-, as OXONE ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), is especially useful, because protonation protects the amino group from oxidation and protonated VX is water soluble.[4] However, OXONE has a high molecular mass and relatively low solubility and is expensive. Hypochlorite ion, as bleaching powder, destroys VX, but this reaction is uneconomical because oxidant is wasted by reaction with the amino group.

In general these oxidants have relatively short shelf-lives and an alternative strategy is to use the more stable nucleophiles that give quantitative P–S bond cleavage. Iodosylbenzoate ions are effective towards phosphorus(v) centres,[2,7] and they are turnover catalysts in the overall hydrolysis of phosphonofluoridates.[7a] They quantitatively cleave P–S bonds, but the reaction is stoichiometric, rather than catalytic, probably because of reduction by thiolate ions.[7b] Peroxyanions are effective α-effect nucleophiles towards phosphorus(v) esters and related compounds,[8–11] and the hydroperoxide anion, HO_2^-, is considerably more reactive than HO^- in these reactions. Preliminary work showed that it gave quantitative P–S cleavage in reactions of VX, **1a**, and the simulant, **1b**.[5] Alkoxide ions in organic solvents initially give extensive P–S cleavage in reactions with **1a**,**b** and model compounds, *e.g. O*,*S*-dialkyl phenylphosphonothioate [PhP(O)(OR)SR, **5**] and do not produce toxic phosphonothioate ion.[12] However, it is best to avoid the use of large amounts of organic solvents for environmental reasons.



Oximate ions are α-effect nucleophiles and are potentially alternative decontaminants towards phosphorus(v) nerve agents.[2,13] We therefore examined the reaction of butane-2,3-

Table 1 Reactions of HO^- and HO_2^- [a]

Substrate	Nucleophile/ mol dm^{-3}	P–S (P–F) Cleavage (%)	$t_{1/2}$/ min	k_ψ/ 10^{-4} s^{-1}
1a,	0.1 HO^-	87	31	3.73
$MePO(OEt)SCH_2CH_2N(Pr^i)_2$	0.1 HO_2^-	100	*ca.* 0.75	
1b,	0.1 HO^-	74	48	2.42
MePO(OEt)SEt	0.1 HO_2^-	100	1.7	66.8
3a,	1.0 HO^-		1.1×10^4	0.011
$MePO_2^-{\cdot}SCH_2CH_2N(Pr^i)_2$	0.1 HO_2^-		400 [b]	
4b,	0.2 HO^-	100	111	1.05 [c]
$Bu^tPO(OPr^i)F$	0.1 HO_2^-	100	8.1	14.4 [c]
5b,	0.1 HO^-	81	18	6.45
PhPO(OEt)SEt	0.1 HO_2^-	100	V. fast	
8,	0.5 HO^-		126	0.92 [c]
$MePO(OEt)_2$	0.5 HO_2^-		V. slow	

[a] Followed by ^{31}P NMR spectrometry at 22–23 °C unless specified. [b] Based on initial rates. [c] At 25 °C.

Table 2 Relative amounts of P–S cleavage in reactions of HO^- in mixed solvents [a]

Conditions	**1a**, $MePO(OEt)SCH_2CH_2N(Pr^i)_2$	**1b**, MePO(OEt)SEt
1.0 M HO^-, H_2O [b]	87	75 (3.7 min)
0.1 M HO^-, 25 vol% Bu^tOH		78 (52 min)
0.1 M HO^-, 50 vol% MeCN		76
0.01 M HO^-, H_2O [c]	88 (31 min)	77 (5.6 h)
0.01 M HO^-, 50 vol% MeCN	86 (*ca.* 6.5 h)	

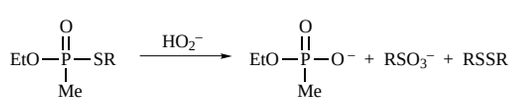
[a] P–S cleavage in mol% and $t_{1/2}$ in parentheses in water unless specified, followed by ^{31}P NMR spectrometry at 22–23 °C. [b] 0.010 mol dm^{-3} substrate. [c] 0.0010 mol dm^{-3} substrate.

dione monoximate ion (**6**) with **1b**. Based on our results and published work, we attempt to address the effect of the attacking nucleophile on the selectivity of P–S and P–O bond cleavages in **1a**,**b** and in related model compounds, *e.g.* **5**. Reactions are typically followed by NMR spectrometry which also provides definitive information on intermediates and products (Experimental). Some of these compounds, *e.g.* VX and GB (**4a**), are extremely toxic, so for routine kinetic studies, we prefer to use less toxic model compounds, *e.g.* **1b**, **4b**, **5** or **7**. For extensive quantitative kinetic investigation in dilute solutions, reactions of **7** were monitored by UV absorbance spectrometry (Experimental).

Results

Reactions of 1a,b and related compounds followed by NMR spectrometry

The major products of reactions of VX (**1a**) and **1b** with HO_2^-



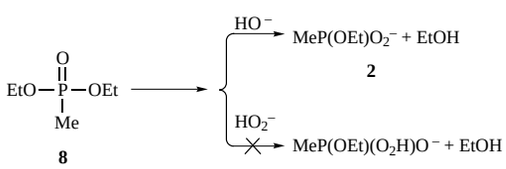
1a, b **2**

are the phosphonate and sulfonate ions and the disulfide. We saw no evidence of P–O (or C–O) bond cleavage. The initial attack of HO_2^- generates a peroxyacid (and its anion),[5,8,9] and they should be reduced by thiolate ions generating the corresponding sulfonate ions. Some disulfide is also formed, probably by oxidation of thiolate ion by air, or by O_2 generated by peroxide decomposition, which occurs readily in alkali.[14]

Values of $t_{1/2}$ or the first-order rate constant, k_ψ, for reactions of the various substrates with HO^- and HO_2^- are summarized in Table 1. For some experiments only half-lives are quoted, *e.g.* for the slow reactions of **3a**. Reactions of HO_2^- were generally followed in an aqueous solution of 0.9 mol dm^{-3} H_2O_2 and 0.1 mol dm^{-3} HO^- where HO^- is converted almost completely into HO_2^-. Where appropriate the amount of P–S cleavage is also quoted. Addition of organic solvents or a pH change from 12 to *ca.* 14 does not significantly change the product selectivity in reactions with HO^- (Table 2). In reactions of PhPO(OR)SR (**5**) with OH^-, we saw more P–O cleavage with methoxy (**5a**) than with the ethoxy derivatives (**5b**), as expected from the relative leaving group probabilities of MeO^- and EtO^- (Table 3).

Reactions of diethyl methylphosphonate (8)

Reactions of **8** with 0.5 mol dm^{-3} NaOH and 0.5 mol dm^{-3} NaOH + 0.9 mol dm^{-3} H_2O_2 were followed at 22 °C. For reaction of HO^-, $t_{1/2}$ = 2.1 h, *i.e.* **8** is less reactive than the thioethyl analogue (**1b**) under similar conditions (Table 1), and added H_2O_2 protonates HO^- and suppresses its reaction. There was little reaction with HO_2^-, and after 3 h only 3% conversion to **2** was observed from a slow reaction with residual HO^-. Therefore, HO_2^- does not displace EtO^- from **8**.



8 **2**

Reaction of 1b with butane-2,3-dione monoximate ion

The reaction of 0.01 mol dm^{-3} **1b** with 0.1 mol dm^{-3} butane-2,3-dione monoxime in 0.1 mol dm^{-3} NaOH was followed by decrease of the ^{31}P signal of **1b**, and $t_{1/2}$ = 5.2 h at 22 °C. The final products were ethyl methylphosphonate ion (**2**), and EtS^- and EtSSEt, identified by ^{31}P and ^{13}C NMR chemical shifts, showing that oximate ion displaces thiolate rather than ethoxide ion.[15]

Displacement by alkoxide ions

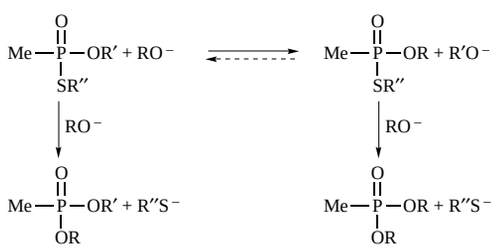
Consistent with earlier work [2–5,12] alkoxide ion largely displaces thiolate ion, but there is some loss of the *O*-alkyl group (Table 3). The reactivities of **1b** and **5** are similar to those of VX (**1a**) with alkoxide ions produced by dissolving sodium metal in the corresponding anhydrous alcohol. The relative amounts of P–S cleavage in reactions with alkoxide ions are greater than with aqueous HO^-, analogous to the quantitative P–S cleavage in reaction with HO_2^-. For some compounds the number of data points allowed calculation of first-order constants, *e.g.* for reaction of **5b** with 0.31 mol dm^{-3} MeO^- in MeOH, we obtained a

Table 3 Relative amounts of initial P–S cleavage in reactions of R′PO(OR)SR″[a]

R′, R, R″	Nucleophile, medium	$t_{1/2}$/ min	P–S cleavage (%)
Me, Et, Et (**1b**)	0.3 M HO^-, H_2O	16	74
	0.3 M MeO^-, MeOH	22.6	94
Me, Et	0.3 M HO^-, H_2O	10.4	88
$CH_2CH_2N(Pr^i)_2$	0.25 M MeO^-, MeOH	25	96
(VX or **1a**)	0.3 M PrO^-, PrOH	8.4	97
Ph, Me, Me (**5a**)	0.1 M HO^-, H_2O	4	53
	0.31 M EtO^-, EtOH[b]	2	95
Ph, Et, Et (**5b**)	0.1 M HO^-, H_2O	18	81
	0.31 M MeO^-, MeOH[b]	16.3	93

[a] At 22 °C unless specified. [b] At 25 °C.

good first-order plot and $k_\psi = 7.08 \times 10^{-4}$ s^{-1}. We saw no evidence for initial S_N2 reactions of alkoxide ions on either *S*- or *O*-alkyl groups. In reaction of VX with alkoxide ions in alcohols initial products are as shown in Scheme 2, but, with time,



Scheme 2

the major product MeP(O)(OR)(OR′) reacts with RO^- to give $MeP(O)(OR)_2$ and an alkyl methylphosphonate, *e.g.* **2**, also forms as the final product. In this anhydrous medium, **2** is probably produced by nucleophilic attack of RO^- on an alkyl group of the initial product, a dialkyl methylphosphonate, with C–O cleavage. When reaction of VX is carried out in a solution of 2 mol dm^{-3} KOH in EtOH at 22 °C, the toxic **3a** from reaction with trace HO^- has been detected. Hydroxide ion should be a better nucleophile in EtOH than in H_2O due to weaker hydrogen bonding. There is no reaction of HO^- when EtO^- is generated by adding sodium or potassium metal rather than KOH to EtOH.

Reactions of thiophosphonates with alkoxide ions give complete P–S cleavage under thermodynamically controlled conditions because attack of alkoxide ion (RO^-) on phosphorus is reversible (Scheme 2). Observation of first-order kinetics in reactions with alkoxide ion, and evidence that the initial reaction of EtO^- with PhP(O)(OMe)SMe (**5a**) is much faster than subsequent displacement of alkoxide ion,[12] indicate that in these cases products are kinetically controlled.

Hydroperoxide ion stability and the use of peroxyborate ion

Displacement of an ethoxy group from VX (**1a**) generates toxic **3a** (Scheme 1) and a major goal is either to avoid formation of **3a** or to decompose it rapidly. In order to test this second approach we examined the reaction of 0.01 mol dm^{-3} **3a** with 0.1 mol dm^{-3} NaOH and 0.3 mol dm^{-3} H_2O_2 and followed it at 22 °C by ^{31}P NMR spectrometry. Within 2 d 70% of **3a** was destroyed and from the initial rate, $t_{1/2}$ *ca.* 6.5 h (Fig. 1). This reaction is faster than that of HO^- by a factor of *ca.* 150, which is larger than those of 20–40 for reactions of HO_2^- and HO^- with nonionic phosphorus(v) esters, *e.g.* VX and **1b**. Two factors may contribute to this larger rate enhancement: (*a*) anionic attack upon **3a** is disfavoured by its negative charge, and this electrostatic effect may be less with HO_2^- than with HO^- because of differences in the charge densities of these ions and (*b*) unlike VX or **1b** which are unreactive towards oxidation by H_2O_2, **3a** is slowly oxidized by H_2O_2.

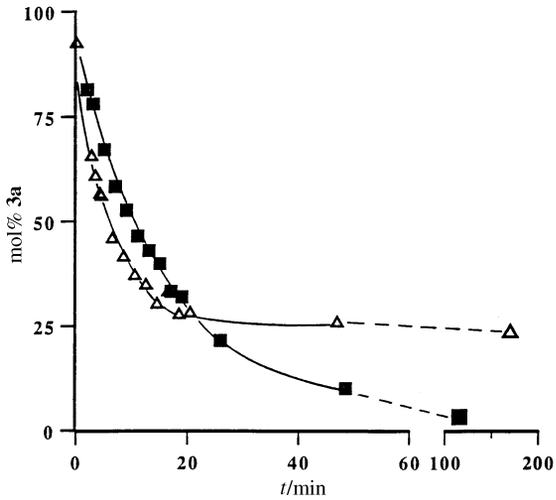


Fig. 1 Reaction of 0.01 mol dm^{-3} **3a** at 22 °C followed by ^{31}P NMR spectrometry. △, 0.1 NaOH, 0.3 H_2O_2; ■, 0.2 NaOH, 0.2 mol dm^{-3} $NaBO_3$.

The main product, $MePO_3^{2-}$, was detected by its ^{31}P NMR spectrum, δ_P 15.5 ($J_{H,P}$ 134), but there was a small unidentified signal at δ_P 42.0 (*ca.* 4% of the main peak with δ_P 42.0), which is not that of the *N*-oxide of **3a**, with δ_P 45.0. It may be generated from an impurity in VX which is greater than 95% pure by NMR spectrometry, but various contaminants are generally present. This minor product could be a cyclic peroxide anion [Me(O–O)P(SR)O^-], because compounds involving three-membered rings have been considered as intermediates in reactions of phosphonothionic acids with peroxyacids.[4,16]

Although HO_2^- destroys **3a** it is not a practical large-scale reagent for this relatively slow reaction because HO_2^- decomposes by reaction with H_2O_2,[14] and in the above conditions much of the peroxide had decomposed within 2 d. Peroxyborate ion ($NaBO_3 \cdot 4H_2O$) is much more stable than H_2O_2 under our reaction conditions and we used ^{31}P NMR spectrometry to follow the reaction of 0.01 mol dm^{-3} **3a** with 0.2 mol dm^{-3} NaOH and 0.2 mol dm^{-3} peroxyborate ion (based on active oxygen). The initial reaction is slower than that with HO^-–H_2O_2 (Fig. 1), but, because of the stability of peroxyborate ion, reaction goes almost to completion within 5 d, whereas that with HO_2^- is limited by its decomposition. Peroxyborate ion may therefore be a useful decontaminant, not only for **3a**, but also for VX.

Reactions of HO_2^- with phosphonofluoridates

The reaction of GB (**4a**) with HO^- and HO_2^- had been followed kinetically[8] by using an autotitrator and by colourimetric analysis of H_2O_2. This reaction is too fast to be followed by NMR spectrometry in aqueous media so we used the less toxic and less reactive *tert*-butyl analogue, **4b**, whose reaction can readily be followed by ^{31}P NMR spectrometry (Table 1). The relative reactivities of HO^- and HO_2^- are similar to those found for the other substrates.

Isotopic evidence on bond cleavage

When reaction of **1b** with HO_2^- was followed in $H_2{}^{18}O$ we detected no isotopic label in either the phosphonate or sulfonate ions (Experimental). This result confirms nucleophilic attack by HO_2^- on the phosphorus centre and indicates that oxygens of the sulfonate ion are not derived by nucleophilic attack of $H_2{}^{18}O$ or $H^{18}O^-$. This behaviour is different from that for reactions of thiophosphonates with HSO_5^- in $H_2{}^{18}O$ where initial oxidation at sulfur is followed by attack by $H_2{}^{18}O$ on the phosphorus centre (Experimental).

Acid dissociation of H_2O_2

Two methods have been used for estimation of the pK_a of H_2O_2.

Table 4 Reaction of HO_2^- with $Ph_2PO{\cdot}SEt$ (**7**)[a]

$[H_2O_2]$/ mol dm^{-3}	[NaOH]/ 10^{-3} mol dm^{-3}	$[HO_2^-]$/ 10^{-3} mol dm^{-3}	k_ψ/ 10^{-2} s^{-1}	k_{corr}/ 10^{-2} s^{-1}	k_{HO_2}/ dm^3 mol^{-1} s^{-1}
4.92	0.997	0.804	0.687	0.682	8.48
9.92	1.97	1.76	1.26	1.25	7.10
14.8	2.97	2.74	1.83	1.82	6.64[b]
14.8	2.96	2.73	1.81	1.80	6.59[c]
14.9	2.99	2.76	1.74	1.73	6.27
16.4	1.97	1.84	1.25	1.25	6.79
19.6	3.98	3.75	2.43	2.42	6.45
32.6	0.983	0.953	0.669	0.668	7.01[d]
32.6	1.97	1.91	1.26	1.26	6.60[d]
32.7	1.97	1.91	1.27	1.27	6.65
49.0	0.986	0.968	0.735	0.735	7.59
49.0	3.94	3.91	2.45	2.45	6.27

[a] At 25.0 °C with 3.50×10^{-5} mol dm^{-3} **7** and reaction followed at 230, 255 and 260 nm unless specified, k_{corr} is for reaction of HO_2^-. [b] 1.05×10^{-5} **7**. [c] 1.75×10^{-5} **7**. [d] 6.95×10^{-5} mol dm^{-3} **7**, reaction followed at 255 and 260 nm.

Evans and Uri based their value of pK_a *ca.* 11.8 on pH measurements.[17] Everett and Minkoff calculated values of K_a of H_2O_2 and alkyl hydroperoxides from spectral shifts as a function of pH and for H_2O_2 estimated pK_a *ca.* 11.6.[18] Some data were obtained by calculating absorbances from densities of photographic plates and others were obtained with an early model single-beam spectrophotometer. We followed the general procedure of Everett and Minkoff,[18] but with a wider range of wavelength, λ = 220–270 nm (Experimental) and like them did not correct for activity effects, because the conditions of measurement are similar to those of the kinetics. Our value of pK_a = 11.0 at 25 °C is lower than earlier values.[17,18]

Reaction of $Ph_2PO{\cdot}SEt$ (7) with HO_2^-

Reaction of **7** was followed spectrophotometrically at 230–260 nm in water over a range of stoichiometric [NaOH] and $[H_2O_2]$. There is almost no reaction with HO^- except in the most dilute H_2O_2 and first-order rate constants, k_ψ, with respect to **7** are then given by eqn. (1).

$$k_\psi = k_{HO}[HO^-] + k_{HO_2}[HO_2^-] \quad (1)$$

Values of k_{HO_2} (Table 4) were calculated with pK_a = 11.0 for H_2O_2 and k_{HO} = 0.27 dm^3 mol^{-1} s^{-1} for reaction of **7** with aqueous HO^- at 25.0 °C.[20] The correction for reaction of HO^- is negligible when $[H_2O_2] \gg K_w/K_a$ and HO^- is quantitatively protonated. The mean of all values of k_{HO_2} is 6.9 dm^3 mol^{-1} s^{-1} (Table 4). The value of k_{HO_2}/k_{HO} *ca.* 25 is similar to those of 40, 30, 27 and 22 for reactions of VX (**1a**, Table 1 and ref. 5), **1b**, **4b** and *p*-nitrophenyldiphenyl phosphate[19] respectively. These relative rate constants are lower than some estimated previously for reactions of GB and some phosphorus(v) esters, which were based on lower values of K_a,[8–10a] and were carried out under conditions of incomplete deprotonation.

Discussion

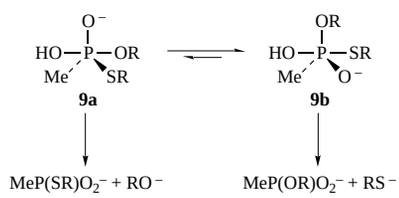
Peroxyanions, like oximate ions, are effective α-nucleophiles,[8–11,21] *i.e.* their nucleophilicities are higher than those predicted by linear free energy relations based on application of the Brønsted equation to nucleophilic reactions. One can question whether equilibrium basicity towards the hydronium ion should be related in any simple way to kinetic nucleophilicity, but the concept of the α-effect is widely accepted. An alternative treatment relates nucleophilicity to ionization potential, either vertical[22] or adiabatic.[23] Buncel *et al*. showed that anionic nucleophilicities towards activated carboxylic esters could be related to vertical ionization potentials, E_i*,[22] and Ritchie showed that activation free energies, $\Delta G^\ddagger$, of nucleophilic addition to preformed carbocations are linearly related to ionization potentials.[23] For deacylation of activated carboxylic esters plots of $\Delta G^\ddagger$ *versus* E_i* are linear,[22] and for reactions of HO^- and HO_2^-, $\Delta\Delta G^\ddagger$ *ca.* 14 kJ mol^{-1}. The corresponding values of $\Delta\Delta G^\ddagger$ for reactions of phosphorus(v) esters are slightly smaller, *viz*. *ca.* 10, 8.4, 7.9 and 8 kJ mol^{-1} for **1a**, **1b**, **7** and *p*-nitrophenyl diphenylphosphate respectively (Tables 1 and 4 and refs. 10 and 16).

Ritchie found $\Delta\Delta G^\ddagger$ *ca.* 15 kJ mol^{-1} for reactions of HO_2^- and HO^- with the pyronium cation.[23,24] This value is similar to that for deacylation.[22] Ritchie's N_+ scale of nucleophilicity fits nucleophilicities towards carbocations, activated carboxylic esters and activated aromatic compounds,[22,23] so that N_+ is linearly related to ionization potentials of nucleophiles. There is extensive discussion of the radicaloid character of transition states in nucleophilic reactions,[22–25] and Hoz has explained the α-effect in these terms.[26] His explanation can be applied to reactions of HO_2^- and other α-effect nucleophiles with phosphorus(v) esters and related compounds.

Nucleophilic displacement at phosphorus(v) centres can involve addition to form a trigonal bipyramidal intermediate (TBP) which may return to reactants, or dissociate to products.[6a,27] If the lifetime of the TBP is very short the reaction is essentially concerted and reactions may be strictly concerted but with varying extents of bond-making and breaking in the transition state.[28] Williams and co-workers have postulated that reactions of aryloxide ions upon aryloxy phosphorus(v) esters are concerted, *i.e.* follow an S_N2 (P) mechanism, based on their observation of linear Brønsted relations.[28a,b]

Rules that apply to bimolecular nucleophilic displacements at phosphorus(v) centres include:[6a,27] (1) groups occupy apical and equatorial positions which may rearrange by pseudorotation in a TBP. (2) Nucleophiles preferentially enter at and depart from apical positions. (3) Electronegative groups preferentially occupy apical positions. (4) Groups which are bulky, or are π-electron donors, preferentially occupy equatorial positions. As for the structures of transition states, they should be similar to those of related high-energy intermediates and Rules 2–4 should also apply to concerted S_N2(P) reactions, although pseudorotation is then precluded. We compare reactions of HO_2^- and HO^- with *O*-alkyl *S*-alkyl phosphorus(v) esters, *e.g.* **1a**,**b**, in the light of these rules, and first consider two limiting cases. (*a*) The TBP has a lifetime sufficient for pseudorotation to occur. (*b*) The lifetime of the TBP is very short so that bond-making and breaking are concerted so far as the kinetics are concerned.

Either model fits the data for reaction with HO^-. If as in (*a*) the lifetime of the TBP allows pseudorotation to occur intermediates **9a**,**b** will interconvert (Scheme 3). The first formed

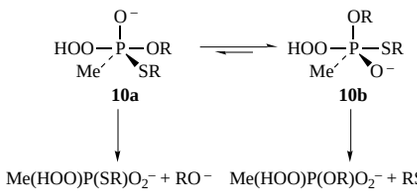


Scheme 3

intermediate will be **9a**, (Rule 3) and it will pseudorotate at equilibrium in the TBP. But RS^- should be a better leaving group than RO^-, so the final product will depend on a balance between apicophilicity and leaving group ability and in reactions of **1a**,**b** with HO^-, P–S is favoured over P–O cleavage by a factor of *ca.* 5.[2–5] Phosphorus(v) thiol esters are more reactive than the corresponding oxyesters towards HO^-, but rate differences are less than expected in terms of leaving group abilities of thiolate and oxide ions based on pK_a values.[20,29] (*b*) If reaction is concerted the transition states for P–O and P–S cleavage will have conformations similar to those of the (hypothetical)

TBP which, with the ease of breaking the P–O and P–S bonds will contribute directly to the free energies of activation of the two reactions.

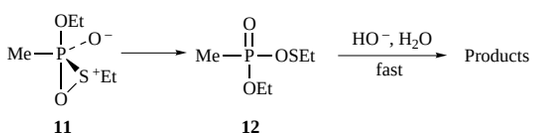
If intermediates rapidly interconvert by pseudorotation, the situation will be different for reaction with HO_2^- (Scheme 4).



Scheme 4

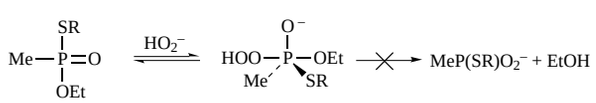
The equilibrium between **10a**,**b** should be similar to that between **9a**,**b**, as should relative rates of loss of RO^- and RS^- (Scheme 3), whereas we observe quantitative loss of RS^-.[5] We therefore consider a reaction path in which a TBP with equatorial RS can undergo P–S cleavage,[5] and an alternative explanation with a concerted S_N2(P) reaction.

In earlier work we considered a mechanism for reactions of HO_2^- that involved pseudorotation of a TBP and gave complete P–S cleavage.[5] It involved formation of a cyclic sulfonium ion (**11**) and generation of a very labile mixed anhydride (**12**).



This mechanism is now excluded for several reasons. If **12** is an intermediate, its hydrolysis in $H_2{}^{18}O$ must introduce the isotopic label into either the phosphonate or the sulfonate ion products, but no such label was detected (Experimental). In addition, the disulfide is always a major initial product which then slowly converts to the sulfonate.[30] It is formed by oxidation by oxygen of thiolate ion displaced from phosphorus(v) by HO_2^-, but hydrolysis of **12** would not generate thiolate ion.

Our results indicate that the TBP is probably not a long-lived intermediate in reactions of phosphorus(v) thiol esters with aqueous HO_2^-. We could explain the absence of P–O cleavage in reactions with HO_2^- on the assumption that a TBP with HO_2^- and RO^- groups in apical positions always reverts to reactants (Scheme 5), *i.e.* it is a dead-end species (**13**).



Scheme 5

But in that event it is difficult to explain the similar values of k_{HO_2}/k_{HO} for reactions of a variety of phosphorus(v) derivatives with very different substituents and leaving groups. For example, attack of HO^- or HO_2^- upon **7** should generate a TBP with EtS in the apical position and it could go directly to products. Direct attack of HO^- upon **1a**,**b**, or similar substrates would generate species that could also go directly to products with departure of either RS^- or RO^-, but attack of HO_2^- on the same substrates would preferentially generate an unproductive TBP with an apical RO group (Scheme 5). However, the relative rates of these two reactions, *i.e.* values of k_{HO_2}/k_{HO}, do not differ significantly, not only for **7** and **1a**,**b**, but also for substrates with very different leaving groups, *e.g.* F^-, ArO^-, RS^- and substituents, *e.g.* R, Ph, PhO, RO, at the reaction centre (Tables 1 and 4 and refs. 5, 8, 10, 16, 20 and 29).† Values of k_{HO_2}/k_{HO} for deacylation and carbocation addition are also similar to those for reactions at phosphorus(v).[22–24]

Our kinetic and isotopic data for reactions of HO_2^- with phosphorus(v) derivatives are understandable in terms of a concerted S_N2(P), reaction with no intermediate in the initial displacement of thiolate ion. This mechanism has been proposed for a variety of nucleophilic displacements at phosphorus(v) centres.[28] Nucleophilic [S_N2(P)] displacements of RO^- or RS^- involve distinct reaction paths but the structures of the transition states should be similar to those of the corresponding TBP intermediates. The free energy of activation involves an intrinsic, kinetic, barrier term which would be present in a symmetrical exchange reaction, and a thermodynamic term, which depends on the free energy of reaction. This approach, as exemplified by the Marcus equation, has been applied successfully to S_N2 reactions of alkyl halides and other substitutions.[31]

The thermodynamic barrier term depends, in part, upon the relative basicities of the nucleophiles, Nuc^- and the leaving anions, LG^- (RO^- and RS^-), *i.e.* upon pK_a (LGH) − pK_a (NucH). This term is strongly positive for displacement of RO^- by HO_2^- and this reaction does not take place. On the other hand, it is small or negative for the displacement of RS^- by HO_2^-. For example, the pK_a of $Et_2NCH_2CH_2SH$, a model for the leaving group in VX, is 8.25,[3] and is significantly lower than for ROH, H_2O or H_2O_2. The increased P–S cleavage when HO^- is replaced by RO^- (Table 3) and especially by HO_2^-, fits these concepts.

The kinetic contribution to the activation free energy is influenced by the higher apicophilicity of RO over RS,[6a,27] which should affect the free energies of an S_N2(P) transition state and a TBP similarly. In reaction with HO^- this term partially offsets the thermodynamic term, which strongly favours P–S over P–O cleavage. As a result, both RS^- and RO^- are displaced in reactions of HO^- with VX (**1a**), **1b** and related compounds (Table 3 and refs. 2–5). In addition phosphorus(v) esters of thiols are not much more reactive than the corresponding oxyesters towards nucleophiles, despite the large differences in pK_a of RSH and ROH.[20,29]

This analysis applies to other reactions involving putative alkoxy leaving groups and the thermodynamic barrier term is more favourable for reactions in which aryloxide or fluoride, rather than alkoxide ions, is displaced by either HO^- or HO_2^-.[2–4,8–11,20,29] Consistent with the above analysis and based on relative pK_a, oximate ions (pK_a of butane-2,3-dione monoxime is 9.38),[32] also give a quantitative P–S cleavage in reaction with **1b** and similar compounds.[33] In addition, HO_2^- does not displace EtO^- from diethyl methylphosphonate, **8** (Table 1). The ability of HO_2^- to displace RS^- rather than RO^- at phosphorus(v) centres is similar to that seen in other systems, *e.g.* HO^- displaces F^- rather than Pr^iO^- from GB (**4a**),[2] consistent with the relative leaving group abilities. There is however, significant loss of Pr^iO^- in the reaction of GB in water at near neutrality, but it is probably due to an S_N1 reaction at the isopropyl group.[34]

Conclusions

Relative to the strongly corrosive bleach and alkoxide systems, various milder methods can be used for solution detoxification of VX. Several of them involve initial oxidation at sulfur followed by hydrolysis at the P–S bond.[2,4,34] An alternative strategy is to use α-effect nucleophiles such as peroxyanions or oximate ions (or iodosylbenzoate ions as reported previously)[7b] to give

† The only exceptions to this generalization of which we are aware are reactions of $(EtO)_2PO{\cdot}SEt$ where HO^- is more reactive than HO_2^-. These reactions may not be concerted and this question will be discussed elsewhere.

quantitative P–S cleavage under relatively mild conditions. Our results indicate that substitution of VX and related compounds by nucleophiles is of a concerted $S_N2(P)$ mechanism rather than step-wise reactions with formation of a trigonal bipyramical (TBP) intermediate. Product selectivity depends on the relative basicities of the anionic nucleophile and the leaving anions. The instability of H_2O_2 at high pH may be a problem for largescale applications, but peroxyborate ion is more stable in these conditions and, although it is less nucleophilic than HO_2^-, its stability is an advantage.

Experimental

Reactions of most of the substrates were followd by ^{31}P NMR spectrometry, which also identifies products.[2,4] Reaction of the model compound, **7**, with HO_2^- can be monitored by UV absorbance spectrometry, which is convenient for extensive kinetic work. Hydroperoxides are weak acids,[14,15] and reactions of H_2O_2 are generally followed at high pH. In large excess H_2O_2, it quantitatively protonates HO^-, the concentration of H_2O_2 is that of added HO^- and is independent of the pK_a of H_2O_2.[16] In other conditions, calculation of second-order rate constants depends on the extent of H_2O_2 deprotonation, which can be estimated from the pK_a value.

Materials

Solutions of alkoxide in alcohol were prepared by dissolving a weighed amount of sodium metal in the corresponding anhydrous alcohol. OXONE and H_2O_2 were used as received, as were $H_2{}^{18}O$ (70% Cambridge Isotope Labs and 99% MSD Isotopes) and butane-2,3-dione monoxime (Aldrich). For reactions followed spectrophotometrically solutions were made up in redistilled, deionized, CO_2-free water. Solutions of NaOH and H_2O_2 were regularly reanalysed. Preparations of VX (**1a**), *O*,*S*-diethyl methylphosphonothioate (**1b**), *O*,*S*-dialkyl phenylphosphonothioate (**5a** and **5b**), *S*-ethyl diphenylphosphinothioate (**7**) and *O*-isopropyl *tert*-butyl fluorophosphonate (**4b**) have been described,[2,7,20,29a] and *O*,*S*-diethyl methylphosphonothioate (^{13}C labelled) was prepared from $^{13}CH_3{}^{13}CH_2SH$ by standard methods.[2] **CAUTION:** Several of these compounds, or the intermediates used in their preparations, are extremely toxic and can only by handled in controlled environments.[2]

Instrumentation

NMR spectra were recorded on a Bruker AC250 or a Varian Gemini 200 FTNMR spectrometer. NMR spectra were recorded at 22–23 or 25 °C for some of the kinetic experiments. ^{31}P Spectra were recorded with at least 16 transients with ^{1}H decoupling and 85% H_3PO_4 as external reference. ^{13}C NMR spectra (^{1}H decoupled) were recorded with $SiMe_4$ in $CDCl_3$ as the external reference. In some reactions ^{13}C enriched substrates were used to improve the sensitivity of product detection. Gas-liquid chromatography–mass spectrometry (GC–MS) and direct-exposure probe (DEP) mass spectrometry were also used to examine products of some of the reactions on a Finnegan 5100 GC–MS instrument with chemical ionization by using CH_4 and a source temperature of 100 °C. The capillary column (DB-1701, J and W Scientific, Folsom, CA) was 15 m × 0.25 mm and was programmed from 60 to 270 °C at 10 °C min^{-1} and 200 °C as the injector temperature. Both phosphonic and sulfonic acids were detected with the DEP. Absorbance spectra were measured on HP diode array single beam (8451) or double beam (8450) spectrophotometers.

Products and isotopic labelling

Product composition was determined after complete reaction from ^{31}P or ^{13}C NMR spectra, generally with *ca*. 0.01–0.02 mol dm^{-3} substrate. In the experiments with *O*,*S*-diethyl methylphosphonothioate (**1b**) in $H_2{}^{18}O$ and H_2O_2 we used 0.2 mol dm^{-3} NaOH and 0.7 mol dm^{-3} H_2O_2 in 1 cm^3 solution volume, giving *ca*. 35% $H_2{}^{18}O$ in the final solution, or 0.1 mol dm^{-3} NaOH and 1 mol dm^{-3} H_2O_2 in 1 cm^3 total solution volume, giving *ca*. 90% $H_2{}^{18}O$ in the final solution. For experiments with HSO_5^- we used 0.5 cm^3 of 0.4 mol dm^{-3} HSO_5^- (added as OXONE) in 0.5 cm^3 of 70% $H_2{}^{18}O$. In H_2O, the only ^{31}P signal observed (detection limit: 0.5 area% or 1 × 10^{-4} mol dm^{-3}) was at 31.5 ppm due to formation of ethylmethylphosphonic acid. In $H_2{}^{18}O$, there was also a peak at 31.53 ppm due to incorporation of ^{18}O. Its area was 35% of the main peak indicating quantitative attack of water on phosphorus. Consistently GC–MS gave signals at *m/z* = 125 and 127.

For reactions with HO_2^- in $H_2{}^{18}O$ the only ^{31}P signal was at 27.7 ppm due to formation of the ethylmethylphosphonate ion, and there was no incorporation of ^{18}O within the detection limit of the instrument. We saw no change in ^{13}C signals of the other product, $CH_3CH_2SO_3^-$. This result indicates that $CH_3CH_2SO_2{}^{18}O^-$ was probably not formed although ^{13}C–S–^{18}O coupling in this system might have been too small to be detected.[35] No signal corresponding to incorporation of ^{18}O into the sulfonate ion product was detected by GC–MS. Control experiments with HO_2^- (and HSO_5^-) in isotopically normal H_2O gave only the main ^{31}P and ^{13}C signals.

Reactions of **1b** with nucleophiles initially generate EtS^- which may be oxidized to EtSSEt by O_2 from air or decomposing H_2O_2 or peroxyacid. Some O_2 was derived from decomposing H_2O_2,[17] because EtSSEt was formed even when reaction was followed under N_2. These compounds were identified by their ^{13}C chemical shifts which are: EtS^-; CH_2, 26.2; CH_3, 12.6 ppm; and for EtSSEt; CH_2, 35.2; CH_3, 16.6 ppm.

The reaction of 0.01 mol dm^{-3} **1b** with 0.1 mol dm^{-3} sodium butane-2,3-dione monoximate was monitored by following the ^{31}P signals of **1b** (δ_P 63.9) and the product **2** (δ_P 27.6) at 22 °C. The half-life was 5.2 h and no reaction intermediate was observed by ^{31}P NMR spectrometry. The non-phosphonylated products were EtS^- and EtSSEt. There were no changes in the ^{13}C oximate signals during reaction [$CH_3CO{\cdot}C(CH_3){=}NO^-$, CH_3CO, 27.4; CH_3CO, 205.9; $C(CH_3){=}N{-}O^-$, 162.2; $C(CH_3){=}N{-}O^-$, 10.5]. Chemical shifts (^{13}C and ^{31}P) for compounds discussed here and related compounds are available as supplementary data (Suppl. No. 57212) from the British Library.‡

Kinetics

Only the reaction of **7** could be followed spectrophotometrically because the other substrates do not absorb at kinetically useful wavelengths. Their reactions were followed by ^{31}P NMR spectrometry at 22–25 °C on a Bruker AC 250 spectrometer as described earlier. In some cases only a few data points were taken and then $t_{1/2}$ values are quoted, but when more points were taken (*ca*. 10) first-order kinetics were followed. Reaction of **9** was generally followed on an HP single beam diode-array spectrophotometer at 25.0 °C, as described for reaction of **7** with OH^-.[20] The concentration of **7** was 1–7.5 × 10^{-5} mol dm^{-3} and it was added as a solution in MeCN with a Hamilton spring-loaded syringe so that the final solution contained 0.4 vol% MeCN. The initial decrease of absorbance fitted first-order kinetics and was followed by a much slower, small, decrease of absorbance that did not complicate the initial kinetics. We used the wavelength range 230–260 nm except at high [H_2O_2] where absorbance at 230 nm was inconveniently high and then we followed reactions at 255 and 260 nm. Values of k_ψ were independent of wavelength and [**7**] and [H_2O_2]. For example, reaction of 3.5 × 10^{-5} mol dm^{-3} **5b** in 2.96 × 10^{-3} NaOH and 14.8 × 10^{-3} mol dm^{-3} H_2O_2, gave 10^2k_ψ = 1.77, 1.69 and 1.77 s^{-1} when measured at 230, 255 and 260 nm. For reaction of 2.97 × 10^{-3} mol dm^{-3} HO^- and 14.8 × 10^{-3} mol dm^{-3}

‡ For details of the Supplementary Publication Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1.

H_2O_2 mean values of 10^2k_ψ were 1.81, 1.83 and 1.76 with 1.05, 1.75 and 3.5×10^{-5} mol dm^{-3} **7** respectively.

Acid dissociation of H_2O_2

The general method of Everett and Minkoff[15] was followed, except that we made measurements over a wider wavelength range, λ = 220, 240, 260 and 270 nm. The value of K_a was calculated from the linear eqn. (2) where A and $A_{H_2O_2}$ are the measured

$$[H^+](A - A_{H_2O_2}) = K_aA_{HO_2^-} - K_aA \qquad (2)$$

absorbances at various pH and in neutral solution and $A_{HO_2^-}$, the absorbance of HO_2^-, is assumed to be independent of pH. Over the whole wavelength range pK_a values were 11.0 ± 0.05, without activity correction (*cf.* refs. 14 and 15). We also used the Henderson equation[15] with the extinction coefficients measured at 240 nm and plotted log $(\varepsilon - \varepsilon_{H_2O_2}) - \log(\varepsilon_{HO_2^-} - \varepsilon)$ against pH, where ε is the overall extinction coefficient, $\varepsilon_{H_2O_2}$ is that of H_2O_2 and $\varepsilon_{HO_2^-}$ is that of HO_2^- at high pH. Plots were linear and had slope = 1.03, and gave pK_a = 11.0.

Note added in proof. Examination of the ^{31}P NMR spectra of **3a**,**b** from reaction of **1a**,**b** in $H_2{}^{18}O$ (unbuffered, pH 13 or 4 mol dm^{-3} NaOH) shows that there is no C–O cleavage. Control experiments show that **3a**,**b** do not exchange with $H_2{}^{18}O$.

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