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Role of peroxophosphate intermediates in reactions of tris(4-nitrophenyl) phosphate and phenyl phosphorochloridate with alkaline hydrogen peroxide

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ABSTRACT: Reaction of alkaline hydrogen peroxide with tris(4-nitrophenyl) phosphate generates ca 1.5 equiv. of 4-nitrophenol per mole of substrate with no evidence of build-up of an intermediate, and reaction of bis(4-nitrophenyl) phosphate anion is too slow to give a product. The initially formed bis(4-nitrophenyl) peroxophosphate is assumed to decompose to the phosphate ester by reaction with H_2O_2 or to eliminate 4-nitrophenoxide ion with the formation of a transient cyclic peroxophosphate. Reaction of phenyl phosphorochloridate anion with ${HO_2}^-$ does not give phenoxide ion by this intramolecular reaction. Semi-empirical and *ab initio* simulations indicate that elimination of aryloxide ion from an aryl peroxophosphate should generate a cyclic rather than an open-chain peroxophosphate. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: hydrogen peroxide; tris(4-nitrophenyl) phosphate; phenyl phosphorochloridate; cleavage; kinetics; structure simulations

INTRODUCTION

The hydroperoxide anion is an effective dephosphorylating agent and readily displaces F^- and aryloxide and thiolate ions.[1,2] It is an α-effect nucleophile which is more reactive than predicted in terms of Brønsted correlations of nucleophilicity with basicity.[3] These reactions are practically important because ${HO_2}^-$ or peroxy anions are potentially useful in the decontamination of phosphonate nerve agents.[1,2–4]

We recently found that reaction of ${HO_2}^-$ with bis(4-nitrophenyl) phosphate ion $[(4\text{-}O_2NC_6H_4O)_2\ {PO_2}^-$ (BNPP)] generates more than 1 equiv. of 4-nitrophenoxide ion, although 4-nitrophenyl phosphate (NPP) is not an intermediate and reacts very slowly in these conditions.[5] The phosphate derivatives are illustrated (Chart 1) with their acronyms.

$(4\text{-}O_2NC_6H_4O)_3PO$	TNPP
$(4\text{-}O_2NC_6H_4O)_2{PO_2}^-$	BNPP
$4\text{-}O_2NC_6H_4{OPO_3}^{2-}$	NPP
$4\text{-}O_2NC_6H_4OPO \cdot Cl_2$	NPPDC
$4\text{-}O_2NC_6H_4OPO_2 \cdot Cl^-$	NPPC
$PhOPO \cdot Cl_2$	PPDC
$PhOPO_2 \cdot Cl^-$	PPC

Chart 1

These results were explained in terms of the reactions in Scheme 1, where the first-formed peroxomonophosphate **1** can either eliminate the second nitrophenoxide ion and form the short-lived peroxophosphate **2** or react with H_2O_2 giving oxygen and NPP. Reaction with OH^- also gives NPP, and allowance was made for its contribution.[5] Peroxomonophosphates are hydrolyzed with displacement of H_2O_2, but this reaction is slow except at low pH.[6]

Reaction of 4-nitrophenyl phosphorodichloridate (NPPDC) in alkaline hydrogen peroxide should also generate **1**, and subsequently **2**, because initial loss of Cl^- should be very fast[7] and the monochloridate anion [$4\text{-}O_2NC_6H_4OPO_2^- \cdot Cl$ (NPPC)] reacts in alkaline H_2O_2 with half-lives of ~2 s and loss of Cl^-.[5] In agreement with this model (Scheme 1), nitrophenoxide ion was formed in this reaction by decomposition of **1**, whereas reaction with OH^- gives no nitrophenoxide ion.[5]

In these reactions H_2O_2 (${HO_2}^-$) plays two roles (Scheme 1). It displaces Cl^- or nitrophenoxide ion from NPPC or BNPP, respectively, but it also reacts with the peroxophosphate **1**,[1b,6] giving unreactive NPP, in competition with cyclization which generates nitrophenoxide ion and the transient peroxophosphate **2**. Competition between these two reactions should depend in part on the leaving group ability of the aryloxide group. Intramolecular nucleophilic participation has been postulated in the peroxydolysis of bisaryl oxalates,[8] and intramolecular nucleophilic attack by an oxide moiety is common in dephosphorylations.[9] Therefore, we examined products

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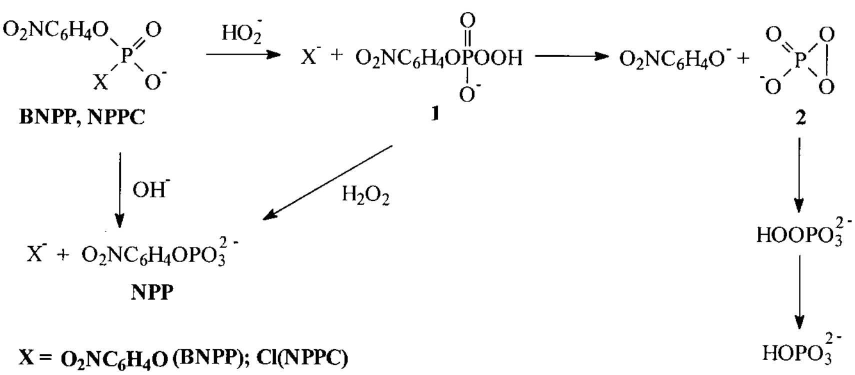
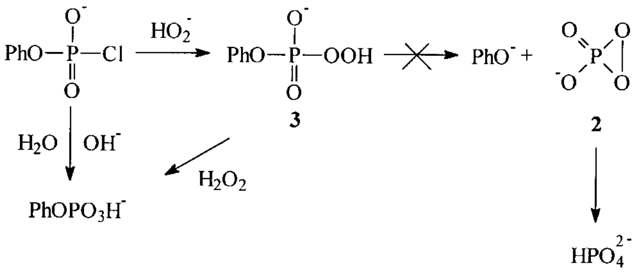


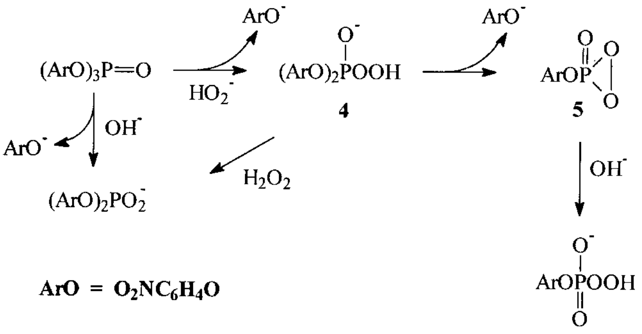
Scheme 1

of the reaction of alkaline H_2O_2 with phenyl phosphorodichloridate [$PhOPO{\cdot}Cl_2$ (PPDC)], which should be very rapidly hydrolyzed to the monochloridate anion [$PhOPO_2^-{\cdot}Cl$ (PPC)],[7] followed by displacement of the second Cl^- by HO_2^- giving phenyl peroxophosphate (**3**).[5] Reaction of H_2O_2 with **3** giving $O_2 +$ phenyl phosphate[1b,6] will compete with the formation of **2** and phenol, which should be disfavored by the lower leaving ability of phenoxide relative to nitrophenoxide ion. Therefore, we expected that relatively little phenol would be formed in the reaction of PPDC with HO_2^- (Scheme 2).



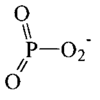
Scheme 2

We also examined reactions of tris(4-nitrophenyl) phosphate (TNPP) with the expectation that more than 1 mol of 4-nitrophenoxide ion would be formed in the reaction with HO_2^- owing to competition between cyclization and reaction of **4** with H_2O_2. Allowance was made for reactions of TNPP with $OH^- + H_2O$ which give nitrophenoxide ion (Scheme 3).



Scheme 3

We combined this experimental approach with simulations of structures of the intermediate peroxophosphate **2** and its conjugate acid **2a**, (Scheme 1) and compared them, and the heats of formation, with those of the hypothetical open-chain isomers, **6** and **6a**. We assume that displacement of nitrophenoxide ion from **1** involves nucleophilic participation by peroxo anion, but open-chain intermediates **6** and **6a** could be formed by P—O cleavage of **1** or **3** in reactions analogous to the spontaneous decompositions of monoalkyl and aryl phosphate monoanions.[5] We therefore compared predicted heats of formation of the hypothetical cyclic and open-chain peroxophosphates **2**, **2a** and **6**, **6a**.



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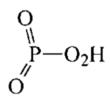


6a

Calculations were made at various levels, viz. AM1, PM3, HF 3–21G* and HF 6–31G*.

EXPERIMENTAL

Materials. Substrates and reagents were commercial materials (from ACROS and TCI America).

Methods. Solutions of dilute 35% H_2O_2 in water and substrates in dry THF were used and [H_2O_2] was measured by titration with $KMnO_4$. The pH of aqueous H_2O_2 was adjusted just before starting the reaction. Substrates were added to the stirred reaction solution at 25.0 °C by using a Hamilton syringe for the product experiments and a spring-loaded Hamilton syringe for the kinetics.

For product reactions starting with PPDC, absorbance of H_2O_2 in the UV region[10] interfered with the spectrum of the products. We used several methods to solve this problem. (i) After complete reaction the pH was reduced from 11.5 to 3.3 and the spectrum of the reaction mixture was compared with that of the corresponding solution of H_2O_2 at pH 3.3. The difference spectrum was that of phenyl phosphate, $\lambda_{max} = 264$ nm. (ii) The spectrum of the reaction mixture of PPDC + H_2O_2 (pH 11.5), after 30 min., was compared with that of an equivalent solution of PPDC (pH 11.5), to which H_2O_2 had been added after complete reaction. The spectra were almost identical, with no signal of phenol/phenoxide ion. (iii) The above reaction mixture with PPDC was left to stand overnight to allow decomposition of H_2O_2 and the spectrum was that of phenyl phosphate, with no other signals. A control experiment showed that phenoxide ion would not have fully decomposed under these conditions.

Hydrogen peroxide does not interfere with the signal of 4-nitrophenoxide ion at 400 nm, but TNPP is sparingly soluble in water and we used H_2O–THF (95:5, v/v) as solvent. Absorbances were compared after reactions of 6×10^{-6} M TNPP with OH^- or H_2O_2/HO_2^- in the pH range 10.9–11.5. Spectra were obtained on an HP model 8451A diode-array spectrophotometer at 25.0 °C, and solutions of H_2O_2 at the appropriate pH were used as reference. The pH was adjusted by addition of concentrated NaOH and H_2O_2/HO_2^- acted as buffer.

Formation of 4-nitrophenoxide ion was followed spectrophotometrically at 400 nm in H_2O–THF (95:5, v/v). The low solubility of TNPP forced us to use dilute (6×10^{-6} M) solutions, and observed absorbance changes during reaction were low (ca 0.05). There was also slight decomposition of H_2O_2, which prevented the use of a stopped-flow spectrometer. Formation of bubbles is not a serious problem when absorbance changes are large, although it introduced random scatter in the (linear) first-order rate plots, but the correlation coefficients were 0.99 over 2.5–3.5 half-lives. We could follow the spontaneous hydrolysis of 6×10^{-6} M TNPP in water (pH 8.2, 0.01 M borate) by neglecting the initial part of the rate plot to allow complete solubilization and $k_{obs} \approx 10^{-2}$ s^{-1}. The reaction with OH^- was followed in H_2O–THF (95:5, v/v) with the pH adjusted with OH^-.

Although the correlation coefficients are low, owing to scatter in the first-order rate plots there was no systematic deviation once mixing was complete, and no evidence for build-up of an intermediate.

Molecular modelling. Structures of intermediates from reactions of BNPP or NPDC[5] were modeled by using Spartan Plus software (Wavefunction)[11] with initial molecular mechanics minimization (MMFF) followed by semi-empirical or *ab initio* treatments. We generally used the HF 6–31G* level and geometries are very similar at this and the 3–21G* levels.

RESULTS AND DISCUSSION

Reaction products and kinetics

Reaction of PPDC with HO_2^- is very simple in that the only product is phenyl phosphate, with no signal of phenol (phenoxide ion), showing that intramolecular displacement of phenoxide ion does not compete with decomposition of the peroxophosphate **3** by reaction with H_2O_2 (Scheme **2**). These results were obtained under various reaction conditions (see Experimental).

Reaction of TNPP with H_2O_2/OH^- rapidly generates 4-nitrophenoxide ion, and we treated the data on the assumption that 5 vol.% THF would not significantly affect use of the pH scale or the value of the pK_a of H_2O_2 in water, which we took as 11.7.[5] The measured pH was not much lower than the pK_a and H_2O_2/HO_2^- acted as its own buffer. The concentration of THF involved a compromise between the low solubility of TNPP and medium effects on pH and pK_a. Initially we used 10^{-5} M TNPP, but the data were not reproducible and we subsequently decreased the concentration.

Observed first-order rate constants, k_{obs}, and second-order rate constants, k_{HO_2} and k_{OH}, are given in Table 1. They are corrected for the contribution of the spontaneous water reaction, k_{H_2O}, and where necessary, for

Table 1. Rate constants of reaction of TNPP with OH^- and HO_2^- [a]

	Nucleophile			
	OH^-		HO_2^-	
pH	k_{obs} (s^{-1})	k_{OH}, (l mol^{-1} s^{-1})[b]	k_{obs} (s^{-1})	k_{HO_2}, (l mol^{-1} s^{-1})[b]
11.08	0.036	21		
11.31	0.044	17		
10.85			0.47	300
10.89			0.40	233
10.32			0.16	300

[a] The solvent was H_2O–THF (95:5, v/v) and stoichiometric $[H_2O_2] = 0.012$ M.

[b] After correction for contributions of reactions with H_2O and, where necessary, with OH^-. $k_{H_2}O = 1.07 \times 10^{-2}$ s^{-1}.

reaction with OH^-. Concentrations of HO_2^- and OH^- were, of necessity, kept low to slow the reaction and that with H_2O could not be neglected, especially at low pH where reactions of OH^- and HO_2^- became less important. The concentration of H_2O_2 was kept low because otherwise reactions became too fast. Corrections and the high rates of reaction with HO_2^- are such that values of k_{HO_2} are approximate and we quote rate constants to only two significant figures. Reactions of BNPP are very much slower than those of TNPP, and do not contribute to formation of nitrophenoxide ion. Second-order rate constants of reactions of BNPP with HO_2^- and OH^- are 7.9×10^{-4} and $3.5 \times 10^{-5}\ \mathrm{l\,mol^{-1}\,s^{-1}}$, respectively, in water at 25.0 °C.[5] Literature values of pK_a for dilute H_2O_2 in water range from 11.5 to 11.7,[5,10,12] and use of the lower value decreases k_{HO_2} by a factor of ca 1.5. Relative values of k_{HO_2}, k_{OH} and k_{H_2O} are similar to those for reactions with BNPP,[5] and for k_{HO_2} and k_{OH} are similar to those for many reactions.[1–3]

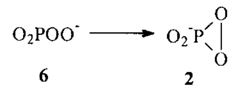
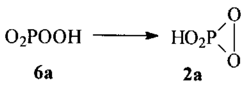
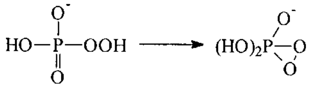
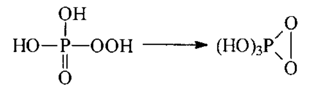
We use higher [H_2O_2], ca 0.1 M at pH 11, for the product than for the kinetic experiments to reduce contributions of reactions of TNPP with H_2O and OH^-, although decomposition of **4** by attack of H_2O_2 is accelerated (Scheme 3). Formation of nitrophenoxide ion was monitored by comparing the absorbances after reactions of equimolar TNPP with OH^- and HO_2^-. Approximately 1.5 equiv. of nitrophenoxide ion were formed in the reaction of TNPP with HO_2^-, and as with BNPP,[5] a transient intermediate can generate additional nitrophenoxide ion or decompose unproductively by reaction with H_2O_2 to a phosphate ester which is unreactive under our conditions (Scheme 3).

The yield of nitrophenoxide ion depends largely upon competition between decomposition of the first-formed peroxophosphate, **1** or **4**, with intramolecular displacement of nitrophenoxide ion, and reaction with H_2O_2/ HO_2^- which gives a nitrophenyl phosphate. Reaction of HO_2^- with BNPP generates between 1 and 2 equiv. of nitrophenoxide ion, and that with NPPC generates up to ca 0.5 equiv. of nitrophenoxide ion,[5] depending, in part, upon competition by the reaction with OH^-.[5] However, reaction of TNPP could generate more than 2 equiv. of nitrophenoxide ion by subsequent reactions of **1** and **5**. Formation of ca 1.5 equiv. of 4-nitrophenoxide ion indicates that the unproductive reaction of **4** with H_2O_2/HO_2^- limits the yield. We could not study the reaction of TNPP over a wide range of conditions in order to establish the relationship between rate constants and products, as in the earlier work,[5] or the extent to which attack of a peroxyanion with a hydroperoxide[1b,6] is affected by the structure of peroxophosphate, **4**, for example.

Structure predictions

Heats of formation and geometries of the hypothetical peroxophosphate cyclic intermediates, **2** and **2a**, are compared with those of the open-chain isomers, **6** and **6a**, in terms of various levels of calculation. The results, summarized in Table 2, indicate that the cyclic structure

Table 2. Relative heats of formation of intermediate peroxophosphates[a]

Intermediates	AM1	PM3	3–21G*	6–31G*
 **6** **2**	−24.1		−39.5	−36.6
 **6a** **2a**	+5.1		−24.5	−13.6
 **8** **7**	+3.8	−3.1	+16.2	+18.2
 **8a** **7a**	+8.0	−3.7		+11.1

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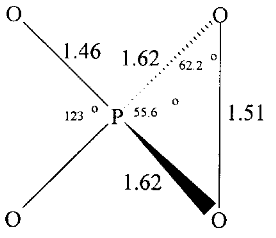
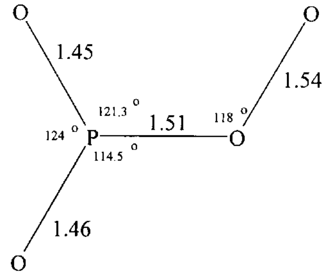
[a] Relative heats of formation ($\mathrm{kcal\,mol^{-1}}$) in the left to right direction.



2



6

is preferred for the anion **2**, and from HF *ab initio* methods for the protonated from **2a**. The open-chain species, **6** and **6a**, akin to metaphosphates, would be formed if elimination of 4-nitrophenoxide ion did not require nucleophilic participation by the peroxo moiety.[5]

Predicted geometries of the anions from calculation at the 6–31G* level are illustrated for **2** and **6** and O—O bond lengths of the cyclic intermediates are similar to those in H_2O_2 and peroxocomplexes of transition metals, which are 1.49 and ca 1.47 Å, respectively.[13] Predicted geometries calculated at the 3–21G* level are almost identical with those shown illustrated for **2** and **6**. Calculations neglect hydration, but its contribution should be similar for species of like charge. The negative charge on **6** is localized but that on **2** is delocalized, which offsets the stronger hydration of cyclic as compared with extended ions.

The postulated intermediate **2** can break down by attack of H_2O or OH^- on phosphorus generating the strained cyclic species, **7** and **7a**, but they are disfavored relative to the open-chain peroxophosphates, **8** and **8a** (Table 2), which form inorganic phosphate by reaction with H_2O_2.[6] Therefore, we conclude that **2** ring opens by attack of H_2O OH^- on phosphorus rather than by addition giving **7** and **7a**, followed by ring opening. Our calculations relate to intermediates, not transition states, but in fast reactions conversion barriers are low and changes in geometries small. On the assumption that the semi-empirical are less reliable than the *ab initio* treatments, it appears that the general conclusions do not depend on the charge of the intermediates, but it is reasonable to assume that elimination of nitrophenoxide ion from a peroxophosphate involves an anionic intermediate (Scheme 1). The various methods of structure simulations have been critically analyzed,[11,14] and the semi-empirical AM1 and PM3 methods appear to be less reliable than the HF *ab initio* methods.

Predicted dimensions of the hypothetical peroxo intermediates **2** and **6** are shown on the structures. We expect the peroxo intermediates to be extensively deprotonated in our reaction conditions, and the cyclic peroxophosphate **2** is predicted to be symmetrical. These structures are from 6–31G* calculations, but essentially identical structures were obtained from 3–21G* calculations.

CONCLUSIONS

The initially formed peroxophosphate from the reaction of HO_2^- with PPC decomposes by reaction with H_2O_2/HO_2^- rather than by eliminating phenoxide ion, but the peroxophosphate from reaction of TNPP eliminates 4-nitrophenoxide ion in competition with decomposition by reaction with H_2O_2/HO_2^-. Quantum mechanical calculations indicate that elimination of aryloxide ion from the initially formed peroxophosphate ester generates a labile cyclic, rather than an open-chain, peroxophosphate.

Acknowledgements

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