

Unexpected stoichiometry in the cleavage of bis(4-nitrophenyl) phosphate and 4-nitrophenyl phosphorochloridate by alkaline hydrogen peroxide

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ABSTRACT: Reaction of alkaline hydrogen peroxide with bis(4-nitrophenyl) phosphate ion proceeds with simultaneous liberation of ca 2 equiv. of 4-nitrophenol per mole of substrate, and no evidence for build-up of an intermediate. Reaction of HO₂[−] with the more activated 4-nitrophenyl phosphorochloridate gives 4-nitrophenol in up to 40% yield with simple first-order kinetics and no indication of a long-lived intermediate. A fast intramolecular nucleophilic displacement of 4-nitrophenolate ion by peroxide in the initially formed 4-nitrophenyl peroxophosphate is proposed to explain this behavior. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: hydrogen peroxide; bis(4-nitrophenyl) phosphate; 4-nitrophenyl phosphorochloridate; cleavage; kinetics

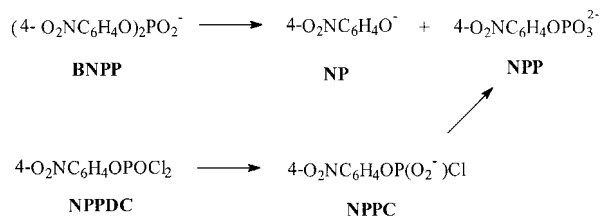
INTRODUCTION

Hydroperoxide anion is an α -nucleophile, with, in certain reactions, higher nucleophilicity than expected from its basicity, in terms of a Brønsted correlation.¹ In particular, HO₂[−], and other peroxy anions, show enhanced reactivity towards activated carboxylic and phosphoric acid esters.^{1,2} Recently a fast reaction of bis(4-nitrophenyl) phosphate ion [(4-O₂NC₆H₄O)₂PO₂[−], BNPP] with hydrogen peroxide in the presence of lanthanide(3+) cations was reported.³ Reaction of BNPP in the absence of lanthanide was stated to be 12-fold faster in a mixture of 0.1 M NaOH and 0.1 M H₂O₂ than in 0.1 M NaOH,^{3b} but no details of the kinetics of the uncatalyzed phosphodiester cleavage by alkaline H₂O₂ were given.

In preliminary experiments, we unexpectedly found that the reaction of HO₂[−] with BNPP, in contrast to that with OH[−], simultaneously liberates almost 2 equiv. of 4-nitrophenolate ion (NP). If the formation of each NP occurs as expected by nucleophilic attack of HO₂[−] on phosphorus, the first step should convert BNPP into a mono(4-nitrophenyl) peroxophosphate intermediate (**1**),

which could readily form 4-O₂NC₆H₄OPO₃^{2−} (NPP), which then might react rapidly with HO₂[−], but HO₂[−] does not react with NPP under our conditions. It appears that the peroxo intermediate, **1**, rapidly forms NP in addition to the expected NPP. In order to clarify the reaction mechanism we used another, more labile, substrate, 4-nitrophenyl phosphorodichloridate (4-O₂NC₆H₄OPOCl₂, NPPDC), which should produce the same intermediate as BNPP upon reaction with HO₂[−] after a very fast initial reaction with H₂O generating the monoanionic chloridate (NPPC).

This paper reports the results of a kinetic study of reactions of HO₂[−] with both BNPP and NPPDC, and kinetics of the hydrolysis of NPPDC (NPPC), and also extends the preliminary examination of the stoichiometry of the reactions with alkaline H₂O₂.



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EXPERIMENTAL

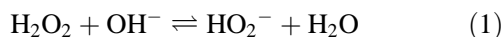
NPPDC was prepared as described⁴ from anhydrous

sodium 4-nitrophenolate and redistilled POCl_3 and was purified by recrystallization. Inorganic nucleophiles, BNPP and salts and organic solvents were analytical-grade reactants used as supplied.

Absorption spectra were monitored on a Hewlett-Packard model 8451A diode-array spectrophotometer with a thermostated cell holder. NMR spectra were recorded on a Varian INOVA 400 spectrometer, and ^{19}F chemical shifts were referred to CF_3Cl by using $\text{CF}_3\text{CO}_2\text{H}$ as an external reference.

Reactions were initiated by adding 10–50 μl of a stock solution of the substrate in water for BNPP and in THF for NPPDC to a 3.0 ml solution of the other reactants at 25.0 °C, with a large excess of H_2O_2 or other nucleophile assuring first-order kinetics. Observed first-order rate constants (k_{obs}) were calculated by a non-linear least-squares fitting of the absorbance vs time profiles to the rate equation with the Origin 5 program. Values of k_{obs} for reactions with NPPC with HO_2^- followed at 312 and 402 nm were within 5% and all values of k_{obs} are means of two values within 5%.

The base deprotonation constant of H_2O_2 [Eqn. (1)] was determined spectrophotometrically.



Aliquots of 0.2 M NaOH were added to 0.01 M H_2O_2 to a final concentration of 0.02 M NaOH. Absorbances (A) in the range 280–320 nm were measured after each addition and fitted the equation

$$A = A_0 + 0.5\Delta\varepsilon(K^{-1} + [\text{H}_2\text{O}_2]_{\text{T}} + [\text{NaOH}]_{\text{T}} - \{(K^{-1} + [\text{H}_2\text{O}_2]_{\text{T}} + [\text{NaOH}]_{\text{T}})^2 - 4[\text{H}_2\text{O}_2]_{\text{T}}[\text{NaOH}]_{\text{T}}\}^{0.5}) \quad (2)$$

by a non-linear least-squares routine with the Origin 5 program, where A_0 is the initial absorbance, $\Delta\varepsilon$ is the difference in molar absorptivities of HO_2^- and H_2O_2 at a given wavelength, concentrations are total analytical concentrations of H_2O_2 and NaOH after each addition and $K = [\text{HO}_2^-]/([\text{H}_2\text{O}_2][\text{OH}^-])$.

RESULTS AND DISCUSSION

Kinetics of BNPP cleavage

Kinetics of BNPP cleavage were followed by appearance of 4-nitrophenolate ion at 400 nm in mixtures of H_2O_2 (0.07–0.7 M) and NaOH (0.08–0.6 M). Equilibrium concentrations of OH^- and HO_2^- were calculated from total concentrations and the equilibrium constant of reaction (1), $K = 200 \pm 20 \text{ l mol}^{-1}$ (Experimental), corresponding to $\text{p}K_{\text{a}} = 11.7$ for H_2O_2 in agreement with published values⁵ but higher than the value obtained with H_2O_2 in large excess over NaOH.^{2a}

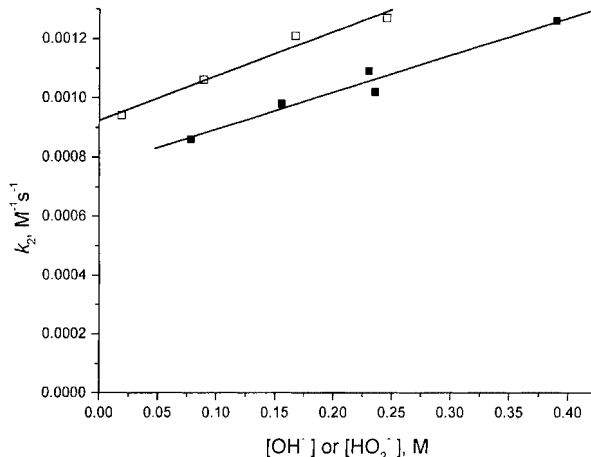


Figure 1. Plots of k_2 for the cleavage of BNPP by HO_2^- vs $[\text{OH}^-]$ at constant $[\text{HO}_2^-] = 0.07 \text{ M}$ and $[\text{HO}_2^-]$ at $[\text{OH}^-] < 0.01 \text{ M}$ (open and closed points, respectively) at 25.0 °C

Reactions were first-order in BNPP and k_{obs} was independent of $[\text{H}_2\text{O}_2]$ and proportional to $[\text{HO}_2^-]$ with a small positive deviation from linearity. There was a small increase in k_{obs} at constant $[\text{HO}_2^-]$ with increased $[\text{NaOH}]$. Figure 1 shows dependences of the second-order rate constant $k_2 = k_{\text{obs}}/[\text{HO}_2^-]$ on $[\text{OH}^-]$ (at constant $[\text{HO}_2^-] = 0.07 \text{ M}$ with excess of NaOH over H_2O_2) and $[\text{HO}_2^-]$ (at low $[\text{OH}^-] < 0.01 \text{ M}$ with excess of H_2O_2 over NaOH). These effects of increased $[\text{OH}^-]$ and $[\text{HO}_2^-]$ are similar to those observed on addition of NaCl or Na_2HPO_4 at similar ionic strengths (I) and the direction and magnitude of these salt effects are those expected for a reaction between co-ions, and fit a Debye–Hückel equation of the form

$$\log k_2 = \log k_2^0 + (0.78 \pm 0.06)I^{1/2}/(1 + I^{1/2}) \quad (3)$$

The second-order rate constant of the cleavage of BNPP by HO_2^- , extrapolated to zero ionic strength, $k_2^0 = (7.9 \pm 0.1) \times 10^{-4} \text{ l mol}^{-1} \text{ s}^{-1}$ at 25 °C is 23-fold higher than that of the alkaline hydrolysis (k_1) of BNPP ($3.5 \pm 0.3) \times 10^{-5} \text{ l mol}^{-1} \text{ s}^{-1}$ (lit. $5.8 \times 10^{-6} \text{ l mol}^{-1} \text{ s}^{-1}$ in 20% EtOH^{6a} and $2.4 \times 10^{-5} \text{ l mol}^{-1} \text{ s}^{-1}$ in water^{6b}). Values of k_2/k_1 in the range 10–30 are typical for other reactions with activated carboxylic and phosphate esters.^{1,2}

The yield of 4-nitrophenolate ion (NP) determined spectrophotometrically was $180 \pm 10 \text{ mol}\%$ with respect to initial [BNPP], i.e. almost 2 equiv. of NP are liberated, but even at the highest $[\text{HO}_2^-]$ employed, ca 0.4 M, the yield of NP did not reach the theoretical limit of 200 mol%. Cleavage of the first NP converts BNPP into the peroxyphosphate, **1**, $(4\text{-O}_2\text{NC}_6\text{H}_4\text{O})\text{P}(=\text{O})(\text{OOH})\text{O}^-$. We expected this intermediate to have a reactivity similar to that of 4-nitrophenyl phosphate anion (NPP), or to generate it rapidly however, under a range of conditions,

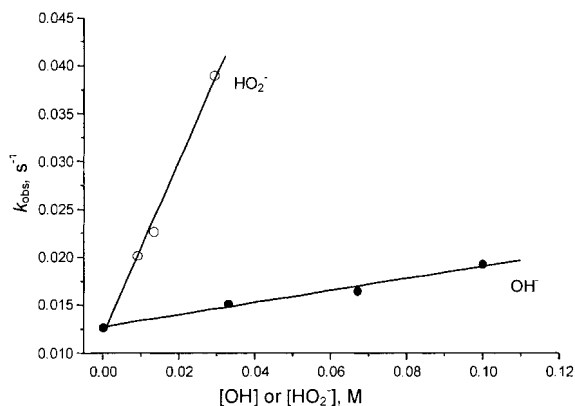
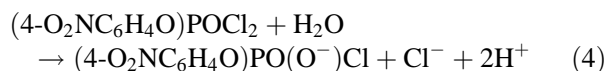


Figure 2. Plots of k_{obs} for the cleavage of NPPC vs $[\text{OH}^-]$ and $[\text{HO}_2^-]$ at 25.0°C

NPP reacts very slowly with HO_2^- . Also, cleavage of BNPP follows clean first-order kinetics with no indication of any intermediate in significant concentration. Therefore, the peroxy analog **1**, of NPP reacts much faster in these conditions than the starting BNPP while NPP is essentially unreactive. This observation was unexpected in view of the similar structures of NPP and the peroxy intermediate, **1**. We therefore examined the products and kinetics of reaction of the highly activated phosphorodichloridate, NPPDC, with alkaline hydrogen peroxide; initial P—Cl cleavage should be fast and reaction of the monochloridate anion, NPPC, will be rate limiting and generate the peroxophosphate, **1**, which then might be detectable.

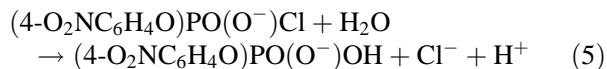
Kinetics of NPPDC cleavage

Addition of a THF solution of NPPDC to water to give a final concentration of 0.11 mM immediately releases 2 equiv. of H^+ , monitored by pH, and then 1 equiv. of H^+ in a slower reaction, which is complete after ca 10 min, confirming fast cleavage of the first P—Cl bond:



and subsequent slower hydrolysis of 4-nitrophenyl

phosphorochloridate anion (NPPC):



When this reaction is followed spectrophotometrically, the initial spectrum, with $\lambda_{\text{max}} = 282$ nm, changed after approximately 10 min into one with $\lambda_{\text{max}} = 292$ nm and a clean isosbestic point at 286 nm. Subsequent addition of 0.01 M NaOH shifts the maximum of the final spectrum to 312 nm. The wavelength maxima of last two spectra correspond to the absorption spectra of anionic and dianionic NPP, respectively.

When a THF solution of NPPDC was added to an aqueous mixture of H_2O_2 and NaOH, both NPP and NP were formed. The first-order rate constants (k_{obs}) calculated from the kinetics of formation of NPP or NP, followed at 312 and 402 nm, respectively, agree within the limits of experimental error, indicating that these products are formed in parallel reactions. Figure 2 shows dependences of k_{obs} on the concentrations of OH^- and HO_2^- , giving second-order rate constants k_1 and k_2 , and that of the spontaneous hydrolysis of NPPC k_0 (from the intercept) (Table 1).

Although, as expected, HO_2^- reacts much faster with NPPC than with BNPP, formation of NP again follows simple first-order kinetics, with no indication of any long-lived intermediate. The half-life of a putative intermediate $(4\text{-O}_2\text{NC}_6\text{H}_4\text{O})\text{P}(=\text{O})(\text{OOH})\text{O}^-$, **1**, must be therefore less than 1 min. The yield (Y) of NP increases with an increase in $[\text{HO}_2^-]$ [Fig. 3 (curve A)], but is consistently lower than that calculated from kinetic data as

$$Y_{\text{kinet}} = 100k_2[\text{HO}_2^-]/(k_2[\text{HO}_2^-] + k_1[\text{OH}^-] + k_0) = 100k_2[\text{HO}_2^-]/k_{\text{obs}} \quad (6)$$

on the assumption that NP and NPP are formed through simple parallel reactions with HO_2^- , OH^- or H_2O [Fig. 3 (curve B)]; Y_{kinet}/Y is approximately constant, at 1.75 ± 0.25 in up to 0.032 M HO_2^- . Such behavior can be rationalized by assuming that the peroxy intermediate decomposes in fast parallel reactions, one forming NP and probably inorganic peroxophosphate, **2**, and the other unreactive NPP and oxygen (Scheme 1).

Table 1. Rate constants of the spontaneous (k_0), and alkaline hydrolyses (k_1) and hydroperoxidolysis (k_2) of NPPC in different media at 25.0°C

Medium	$k_0(\text{s}^{-1})$	k_1 ($1 \text{ mol}^{-1} \text{ s}^{-1}$)	k_2 ($1 \text{ mol}^{-1} \text{ s}^{-1}$)	E_{T}^{N} ^a
Water	0.013 ± 0.001	0.065 ± 0.007	0.91 ± 0.08	1.000
D ₂ O	0.0098 ± 0.0005	0.046 ± 0.004	0.75 ± 0.07	
50 vol.% MeCN	0.0012 ± 0.0001	0.0093 ± 0.0009	0.20 ± 0.04	0.816
50 vol.% dioxane	0.0014 ± 0.0001	0.019 ± 0.002	0.82 ± 0.07	0.703
50 vol.% THF	0.00073 ± 0.00005	0.038 ± 0.004	0.28 ± 0.03	0.655

^a Parameters from Ref. 7

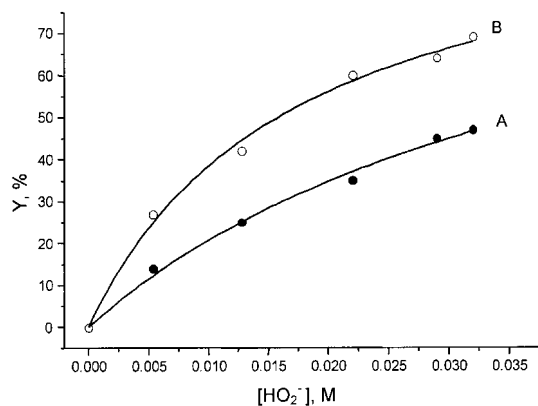


Figure 3. Yield (Y , mol%) of NP as a function of $[\text{HO}_2^-]$ in the reaction of NPPC. Curve A, experimental values; curve B, calculated from rate constants as $Y_{\text{kinet}} = 100k_2[\text{HO}_2^-]/k_{\text{obs}}$.

The steady-state approximation to the peroxy intermediate (Scheme 1) gives for the yield of NP

$$Y = 100k_2[\text{HO}_2^-]/\{k_{\text{obs}}(1 + k_4/k_3)\} \quad (7)$$

where $k_{\text{obs}} = k_2[\text{HO}_2^-] + k_1[\text{OH}^-] + k_0$. Therefore,

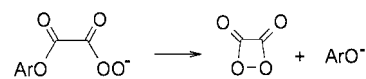
$$Y_{\text{kinet}}/Y = 1 + k_4/k_3 \quad (8)$$

and $k_4/k_3 = 0.75$. If reactions of BNPP and NPPC with HO_2^- proceed through the same intermediate, this result indicates that the yield of NP in the reaction with BNPP should be ca 175 mol%, in good agreement with experiment (see above).

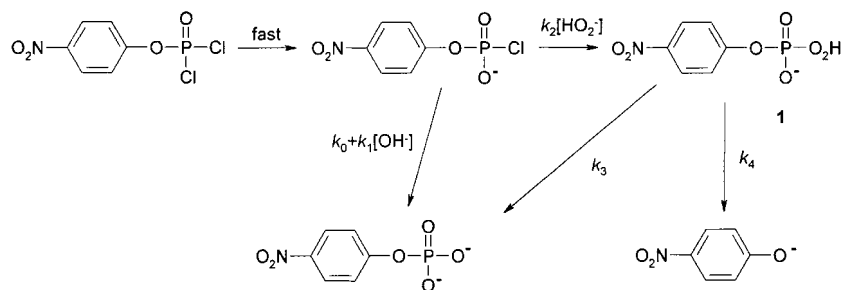
However, two observations indicate that this treatment is oversimplified. First, when 1×10^{-4} M H_2O_2 was reacted with a large excess of NPPC (0.01 M) in 0.05 M NaOH, 1 equiv. of NP per equivalent of H_2O_2 was formed, showing that the first-formed peroxyphosphate, **1**, can decompose spontaneously to NP without intervention of a second hydroperoxy species, e.g. HO_2^- . In addition, the decomposition reaction represented in Scheme 1 by step k_3 is an intermolecular interaction of the intermediate with excess of HO_2^- (H_2O_2), as proposed for decomposition of the structurally related intermediate $(\text{EtO})_2\text{P}(=\text{O})\text{OOH}$ in the reaction of

paraoxon with H_2O_2 giving $(\text{EtO})_2\text{PO}_2^-$.⁸ We note that ethoxy is a poor leaving group and would not be displaced in decomposition of a peroxyphosphate. The apparent approximate constancy of Y_{kinet}/Y and, consequently, k_4/k_3 , in conditions of variable H_2O_2 concentration [Fig. 3 and Eqn. (8)] is over-simplified and the yield of NP decreases at higher HO_2^- reflecting differences in the dependences of steps k_3 and k_4 on concentration of HO_2^- . In particular, the step indicated by k_3 should not be independent of $[\text{H}_2\text{O}_2]$,⁸ and with 0.065 M HO_2^- k_{obs} increases to 0.069 s^{-1} (cf. Fig. 2) and Y_{kinet} increases modestly to 82% but Y decreases to 23% (cf. Fig. 3).

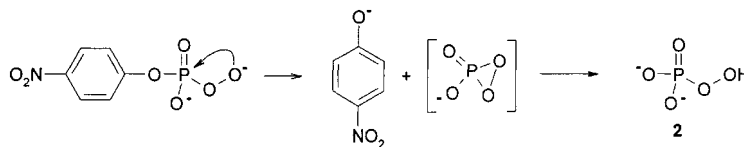
The mechanism of the step leading to NP from the peroxyphosphate, **1**, has to be considered. It is too fast to be a simple nucleophilic displacement of NP by the second HO_2^- anion, bearing in mind the very slow reaction of HO_2^- with the structurally similar NPP, and evidence of a spontaneous reaction. Expulsion of NP may occur simultaneously with decomposition of $(4\text{-O}_2\text{NC}_6\text{H}_4\text{O})\text{P}(=\text{O})(\text{OOH})\text{O}^-$ to oxygen and NPP via a common intermediate, possessing an enhanced electronic density on the phosphoryl group after an electron transfer from HO_2^- , but this reaction is intermolecular. More probable is an intramolecular nucleophilic attack of the anionic peroxy moiety on phosphorus, as shown in Scheme 2. Indeed, intramolecular nucleophilic substitutions are typically much faster than the corresponding intermolecular reaction;¹ in particular, the high hydrolytic reactivity of phosphodiester bearing a β -hydroxyl group is attributed to intramolecular attack of O^- on phosphorus.⁹ A fast intramolecular substitution by a peroxide ion was postulated in the peroxydolysis of bisaryl oxalates, e.g. bis(2,4-dinitrophenyl)oxalate, leading to formation of a cyclic peroxyoxalate: although the detailed reaction mechanism is uncertain.¹⁰



In the dephosphorylation mechanism (Scheme 2), a strained three-membered ring is formed in the transition state. However, fast intramolecular substitutions by oxygen nucleophiles through three-membered rings are



Scheme 1



Scheme 2

well known, e.g. in epoxide formation from chlorohydrins in alkali.⁹ In addition, the peroxy group in the first-formed intermediate (Scheme 2) is well placed to displace the 4-nitrophenolate ion in a transition state akin to a trigonal bipyramid with apical entering and leaving groups.¹¹ The cyclic peroxophosphate ion will probably rapidly generate inorganic phosphate by attack of water on phosphorus followed by decomposition of **2** by reaction with H₂O₂.

Hydrolysis of NPPC

An interesting feature of the NPPC hydrolysis is the large contribution of a water reaction relative to that of OH⁻. For BNPP k_{obs} for the water reaction was estimated as ca. $1.1 \times 10^{-11} \text{ s}^{-1}$,^{3b} i.e. 10⁹-fold lower than for hydrolysis of NPPC, but the rate constants of OH⁻ reactions for these substrates differ by only 10³-fold. At the same time, the relative rate constants of the HO₂⁻ and OH⁻ reactions are similar for both substrates, i.e. 23 for BNPP and 14 for NPPC. It seems, therefore, that spontaneous water reactions follow different mechanisms with BNPP and NPPC.

In an earlier kinetic study of the hydrolyses of PO₂Cl₂^{-12a} and EtOPO(O⁻)Cl,^{12b} an S_N1-like mechanism with a polar transition state and positive charge on the entering H₂O and negative charge on the leaving Cl⁻ was proposed. Reaction kinetics were not studied in detail, but the PO₂Cl₂⁻ hydrolysis showed a positive salt effect and negligible reaction with OH⁻, and hydrolysis

of EtOPO(O⁻)Cl was accelerated by an increase in the water content of aqueous acetone. Such kinetic behavior is atypical of hydrolyses of phosphate di- and triesters which usually proceed with bimolecular mechanisms.¹¹ The spontaneous hydrolysis of NPPC has some common features with those of PO₂Cl₂⁻ and EtOPO(O⁻)Cl. There is a positive salt effect (Fig. 4) and addition of organic solvents inhibits the reaction while log k_0 correlates with the E_{T}^{N} parameter for the solvent mixtures (Table 1) with a dependence consistent with a spontaneous hydrolysis.¹³ At the same time, reactions with OH⁻ and especially HO₂⁻ are much less sensitive to solvent composition (Table 1). The second-order rate constants for reaction of HO₂⁻ are approximate because the solvent effect on deprotonation of H₂O₂ is neglected. The solvent isotope effect $k_0(\text{H}_2\text{O})/k_0(\text{D}_2\text{O}) = 1.33$ (Table 1) is small, indicating little if any proton transfer in the transition state. Reactions with OH⁻ and HO₂⁻ also show small, probably secondary, isotope effects of 1.4 and 1.2 respectively (Table 1). (There will be a contribution due to the isotope effect on the deprotonation of H₂O₂, but it should not be large). Addition of a strong acid inhibits the spontaneous hydrolysis (Fig. 4) after a correction for a positive salt effect. These results strongly favor an S_N1-like mechanism, because protonation should assist water attack but inhibit expulsion of Cl⁻.

In an S_N1-like mechanism the phosphoryl group should generate 4-nitrophenyl metaphosphate, which could be trapped by F⁻.¹⁴ Reaction of NPPC with NaF indeed affords the expected (4-O₂NC₆H₄O)P(=O)OF⁻ as shown by the ¹⁹F NMR spectrum of a reaction mixture of 0.01 M NPPDC and 0.5 M NaF in H₂O [doublet at -76.092 ppm with $J_{\text{P,F}} = 949 \text{ Hz}$, typical of ³¹P splitting; cf. $\delta_{\text{F}} = -73.48 \text{ ppm}$ and $J_{\text{P,F}} = 932 \text{ Hz}$ for PhOP(O)OF⁻.^{14c} However, F⁻ appears to react nucleophilically with NPPC. Figure 4 shows the dependence of k_{obs} on [NaF], giving $k_{\text{F}} = 0.017 \text{ l mol}^{-1} \text{ s}^{-1}$ after correction for the salt effect. Therefore the formation of (4-O₂NC₆H₄O)P(=O)OF⁻ does not necessarily involve metaphosphate trapping by F⁻. We note that although the spontaneous hydrolysis of NPPC is S_N1-like both OH⁻ and F⁻ react bimolecularly, and the second-order rate constants for reactions of OH⁻ and F⁻ differ by a factor of 3, which is typical of reactions at phosphorus(V) centers.¹⁵ Relative reactivities of HO₂⁻ and OH⁻ are also similar to those observed in other reactions at these centers.¹⁶

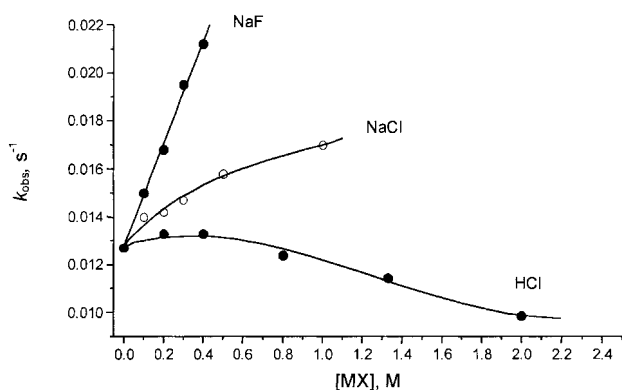


Figure 4. Rate constants of the spontaneous hydrolysis of NPPC as functions of NaCl, HCl and NaF concentrations

CONCLUSIONS

Reaction of BNPP with HO_2^- involves the formation of a very reactive intermediate after substitution of the first NP, which decomposes with liberation of ca 80% mol of the remaining NP. Nucleophilic attack on NPPC by HO_2^- proceeds ca 1000-fold faster than on BNPP, in accordance with the higher lability of the P—Cl compared with the P— $\text{OC}_6\text{H}_4\text{NO}_2$ bond, but NP is released simultaneously with overall substitution without formation of a long-lived intermediate, as with the much less reactive BNPP. This observation, indicating very high lability of the peroxy intermediate, **1**, is rationalized in terms of an intramolecular nucleophilic substitution by the peroxy group at phosphorus. The enhanced reactivity of HO_2^- relative to OH^- or F^- towards NPPC is observed even when reaction with H_2O is $\text{S}_{\text{N}}1$ -like, and should be rather insensitive to nucleophilicity.

Acknowledgements

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