8582 *J. Am. Chem. Soc.* **1995,** *117,* 8582−8585

La(III)−Hydrogen Peroxide Cooperativity in Phosphate Diester Cleavage: A Mechanistic Study

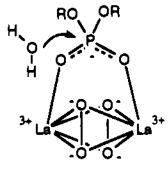
Bryan K. Takasaki[†] **and Jik Chin***

Contribution from the Department of Chemistry, McGill University, Montreal, Canada H3A 2K6

Received March 7, 1995[®]

Abstract: La(III), Pr(III), Nd(III), and Eu(III) (2 mM) can each combine with hydrogen peroxide to provide close to 9 orders of magnitude rate acceleration for hydrolyzing BNPP (bis(*p*-nitrophenyl) phosphate) at pH 7 and 25 °C. The rate of the reaction is second order each in [La(III)] and [H_2O_2], indicating that the active core **4** of the catalyst consists of two La(III) with two peroxides. The equilibrium constant for binding of BNPP to **4** ($K_1 = (1.3 \pm 0.1) \times 10^3\ M^{-1}$) and the rate constant for hydrolysis of the bound phosphate ($k_2 = (1.8 \pm 0.1) \times 10^{-2}\ s^{-1}$) have been determined. ^{18}O labeling studies reveal that the peroxide is a nucleophilic catalyst in cleaving the diester.

Currently there is much interest in developing artificial nucleases that hydrolyze the phosphate diester bonds in RNA and DNA. Since phosphate diesters are generally highly resistant toward hydrolytic cleavage, making catalysts reactive enough to hydrolyze the target bonds rapidly under physiological conditions represents a major challenge. Over the years many interesting catalysts that facilitate the hydrolysis of phosphate diesters have been reported.[1] Of particular interest are the lanthanides whose versatility in cleaving phosphates has been amply demonstrated even though the cleavage mechanisms are not clearly understood. Free Ln(III) ions[2] as well as those complexed to a variety of organic ligands[3] have been shown to be highly reactive for hydrolyzing phosphates including in some cases RNA[4] and DNA.[5] Lanthanides can cleave phosphates by monometallic or dimetallic,[6,7] paths and hydrogen peroxide[6,8] can enhance the reactivity of the lanthanides. For example, there is enormous cooperativity between hydrogen peroxide and La(III) ions in cleaving bis(*p*-nitrophenyl) phosphate (BNPP). Preliminary studies[6] indicated that the active core of the catalyst consists of two La(III) ions bridged by two peroxides. The mechanistic role of hydrogen peroxide in the system may simply be to form the dinuclear complex, thereby allowing phosphate diesters to bridge the two metal centers (**1**). Additionally, the peroxide may act as an intramolecular general base (**2**) or an intramolecular nucleophilic catalyst (**3**). Here we report a detailed kinetic and mechanistic analysis of the Ln(III)−peroxide system for hydrolyzing phosphate diesters. This analysis includes ^{18}O experiments which permit the unambiguous assignment of the role of hydrogen peroxide in this reaction.



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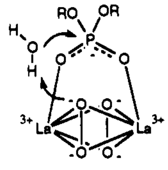

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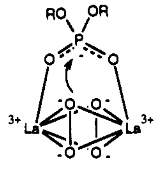

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Experimental Section

Materials. $La(ClO_4)_3{\cdot}6H_2O$ and other lanthanide ion salts were purchased from Strem Chemicals and used as purchased. Hydrogen peroxide (30%) was purchased from the A&C Chemical Co. The concentration of hydrogen peroxide of the stock solution was determined by titration with cerric ammonium nitrate. Bis(*p*-nitrophenyl) phosphate (BNPP) was purchased from Sigma Chemicals. $H_2{}^{18}O$ and $H_2{}^{18}O_2$ were purchased from ICON Chemicals Inc.

Kinetics. The cleavage of BNPP was followed by monitoring the increase in absorbance at 400 nm due to the formation of the *p*-nitrophenoxide ion. All absorbance measurements were made on a Hewlett-Packard HP 8452A UV−vis spectrophotometer equipped with a seven-cell transport and jacketed cells attached to a circulating water bath for temperature control. Rate constants were calculated by a nonlinear least-squares fit of the first-order rate equation to the absorbance data. All reported rate constants are based on the analysis of 30−300 points representing at least 3 half-lives of the reactions. Reactions were repeated at least three times in order to obtain standard deviations. All of the experiments in Figures 1−5 were done at pH 7.0 (0.1 M HEPES) and 25 °C.

Cleavage of 2′,3′-cAMP was monitored by HPLC using a Hewlett-Packard 1090 series II liquid chromatograph. In a typical run, the La(III) (5 mM), hydrogen peroxide (50 mM), and 2′,3′-cAMP were mixed in 0.1 HEPES buffer (pH 8.0). At regular intervals, 50 μL aliquots of the reaction solution were mixed with 50 μL of 0.2 M inorganic phosphate (pH 5.5). The lanthanum phosphate precipitate was spun down for 3 min at 13 200 rpm. A 1 μL sample of the supernatant was then injected onto a C-18 reversed-phase column (5 μm Hypersil maintained at 40 °C) and eluted for 5 min with $NH_4H_2PO_4$ (0.2 M pH 5.5) followed by a 0−100% linear gradient of $NH_4H_2PO_4$ (0.2 M pH 5.5) and methanol/water (3:2) solutions over 15 min with a flow rate of 0.5 mL/min. The retention times of 2′,3′-cAMP (7.58 min), 2′-

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[†] Current address: Beckman Institute, California Institute of Technology, Pasadena, CA 91125.

[®] Abstract published in *Advance ACS Abstracts,* July 15, 1995.

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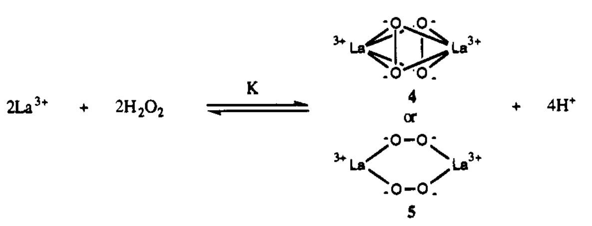
Scheme 1



AMP (8.12 min), and 3′-AMP (3.56) were all determined by injecting authentic samples of each compound.

^{31}P NMR. All ^{31}P NMR (Figure 5) were recorded using a Varian XL-300 spectrophotometer. Chemical shifts are with respect to an external reference of 85% H_3PO_4. The sample for Figure 5a was prepared by hydrolyzing BNPP (2 mM) with $La(ClO_4)_3$ (5 mM), $H_2{}^{18}O_2$ (25 mM), and H_2O_2 (25 mM) at pD 7.0 (0.1 M HEPES in D_2O) and 25 °C. The sample for Figure 5b was prepared by hydrolyzing BNPP (2 mM) with $La(ClO_4)_3$ (5 mM) and H_2O_2 (50 mM) at pD 7.0 (0.1 M HEPES in 50% $H_2{}^{18}O$ and 50% D_2O) and 25 °C. The reaction was quenched after 1/2 h by the addition of an excess of 2,6-pyridinedicarboxylic acid.

Results and Discussion

In a preliminary paper, we[6] recently showed that when 1 equiv or more of hydrogen peroxide is mixed with an aqueous solution of $La(ClO_4)_3$, 2 equiv of protons is released per equivalent of La(III) at neutral pH. The steepness of the titration curve indicated that at least a dimer or higher order aggregates are formed upon release of the protons (Scheme 1). It is not clear at this time whether the peroxides are bridging face-on (**4**) or end-on (**5**). An interesting crystal structure of a tetranuclear Sm(III) complex with face-on bridging peroxides has been reported.[9] A dinuclear Cu(II) complex with a face on bridging peroxide has also been reported.[10]

In an aqueous solution of $La(ClO_4)_3$ and H_2O_2, the rate of hydrolysis of BNPP increases with increasing solution pH and levels off at neutrality. The steepness of the pH−rate profile and the steepness of the titration curve indicated that a dinuclear La(III) (**4**) or a higher order aggregate is the active species for cleaving the phosphate diester.[6]

Second Order Reaction in [La(III)] and [H_2O_2]. If indeed **4** (or **5**) is the active species for cleaving BNPP, the rate of the reaction should be second order with respect to the concentrations of H_2O_2 and La(III). A plot of the logarithm of the pseudo-first-order rate constant for the cleavage of BNPP against the logarithm of the concentration of La(III) at 30 mM H_2O_2 and low concentrations of the metal (0.6−1.6 mM) gave a slope of 2.0 ± 0.1 (Figure 1).[8] Similarly, a plot of the logarithm of the pseudo-first-order rate constant for the cleavage of BNPP against the logarithm of the concentration of H_2O_2 at 2 mM La(III) and low concentrations of the peroxide (3−7 mM) gave a slope of 1.95 ± 0.05 (Figure 2). Hence the rate−concentration profiles (Figures 1 and 2), the pH−rate profile,[6] and the potentiometric titration data[6] are all consistent with **4** (or **5**) being the active species for cleaving the phosphate diester.

Equilibrium Constant for Formation of 4. The equilibrum constant for formation of **4** (Scheme 1) is given by eq 1.

$$K = \frac{[\mathbf{4}][\mathrm{H}]^4}{[\mathrm{La}]^2[\mathrm{H_2O_2}]^2} \qquad (1)$$

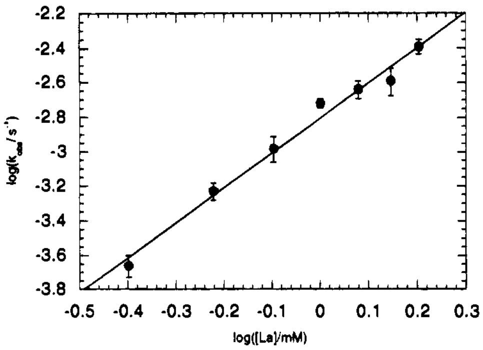


Figure 1. Dependence of the logarithm of the pseudo-first-order rate constant for the cleavage of BNPP on the logarithm of [La(III)] in 30 mM H_2O_2 (slope 2.0 ± 0.1).

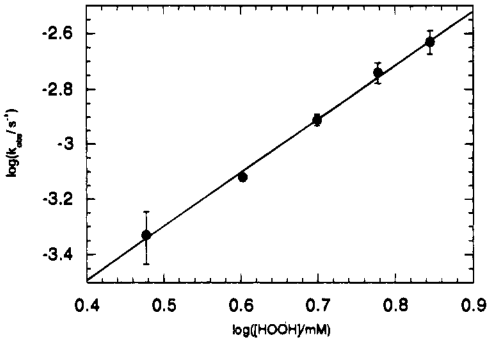


Figure 2. Dependence of the logarithm of the pseudo-first-order rate constant for the cleavage of BNPP on the logarithm of [H_2O_2] in 2 mM $La(ClO_4)_3$ (slope 1.95 ± 0.05).

Rearranging eq 1 and solving for [**4**] gives eq 2 where $[\mathrm{La}]_t$ represents the total La concentration. We[6] showed that the value

$$[\mathbf{4}] = \frac{[\mathrm{H}]^4 + 4[\mathrm{La}]_t K[\mathrm{H_2O_2}]^2 - [\mathrm{H}]^2([\mathrm{H}]^4 + 8[\mathrm{La}]_t K[\mathrm{H_2O_2}]^2)^{1/2}}{8K[\mathrm{H_2O_2}]^2} \qquad (2)$$

of K (1.4 × 10^{-23} M) can be obtained by fitting the potentiometric titration of a solution of La(III) according to eq 3 where $[\mathrm{OH}]_t$ represents the concentration of OH^- consumed.

$$[\mathrm{OH}]_t = 4[\mathbf{4}] = \frac{[\mathrm{H}]^4 + 4[\mathrm{La}]_t K[\mathrm{H_2O_2}]^2 - [\mathrm{H}]^2([\mathrm{H}]^4 + 8[\mathrm{La}]_t K[\mathrm{H_2O_2}]^2)^{1/2}}{2K[\mathrm{H_2O_2}]^2} \qquad (3)$$

Substrate Binding. As mentioned above, the rate of hydrolysis of BNPP is second order in [La] (Figure 1) at low concentrations of the metal ion (0.1−1.4 mM) when there is a large excess of H_2O_2 (30 mM). However, with a moderate increase in the concentration of La(III) (3−6 mM) the rate of hydrolysis of BNPP begins to level off (Figure 3). This saturation behavior (eq 4) is consistent with a mechanism which

$$k_{\mathrm{obs}} = \frac{K_1 k_2[\mathbf{4}]}{K_1[\mathbf{4}] + 1} \qquad (4)$$

involves the formation of a complex between the substrate and **4** followed by the reaction of the complex (Scheme 2). Figure 3 was fit according to the equation obtained by substituting eq 2 into eq 4.

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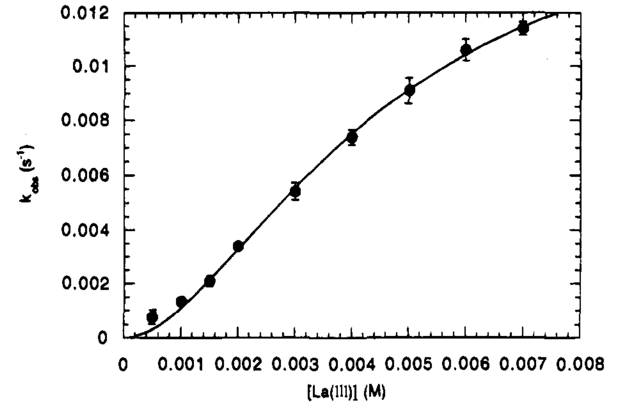


Figure 3. Dependence of the pseudo-first-order rate constant for the cleavage of BNPP on [La(III)] in 20 mM H_2O_2.

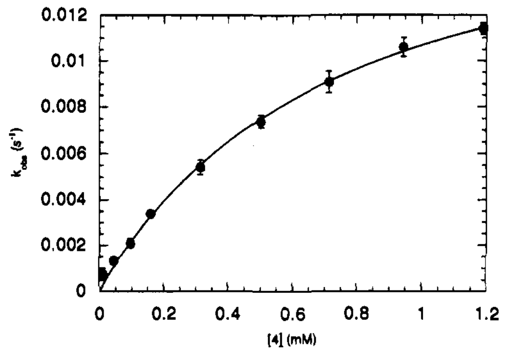
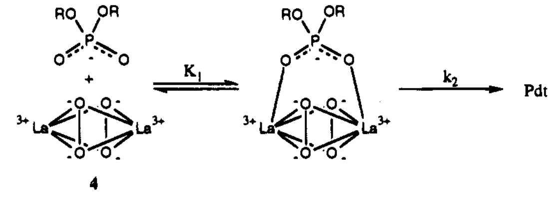


Figure 4. Dependence of the pseudo-first-order rate constant for the cleavage of BNPP on [4] in 20 mM H_2O_2 (eq 4).

Scheme 2



When k_{obs} in eq 4 is plotted against the concentration of **4** rather than that of La(III), the sigmoidal curve (Figure 3) is converted to a simple saturation curve (Figure 4). The concentration of **4** was calculated from eq 2 using the K (1.4 × 10^{-23} M) value obtained from the potentiometric titration. The values for K_1 ((1.3 ± 0.1) × 10^3 M^{-1}) and k_2 ((1.8 ± 0.1) × 10^{-2} s^{-1}) were obtained by fitting Figure 4 according to eq 4. The first-order rate constant (k_2) for the reaction of BNPP bound to **4** is approximately 10^9 times greater than that observed for the hydrolysis of BNPP in the absence of any catalyst. This value is comparable to that observed for *cis*-diaqua–cobalt(III) complexes.[11] The equilibrium constant (K_1) for binding of BNPP to **4** is about 2–3 orders of magnitude greater than that for monodentate coordination of phosphate diesters to *cis*-diaqua–cobalt(III) complexes.[11] The unusually high K_1 value suggests that BNPP may be coordinating to **4** as a bidentate ligand rather than as a monodentate ligand.

Role of La(III). The dinuclear La(III) complex **4** may provide double Lewis acid activation for cleaving BNPP by forming the bridging phosphate diester complex (**1**). Such a double Lewis acid activation mechanism has been recently implicated in a dinuclear Cu(II) complex promoted transesterification of a phosphate diester.[12] Interestingly, there are many enzymes that hydrolyze phosphate mono- and diesters that are activated by two or more metal ions.[13] Double Lewis acid activation (**5**) should provide far greater rate acceleration than single Lewis acid activation (**6**) for hydrolyzing phosphate diesters since the developing negative charge during the reaction in the former case is stabilized by the metal while in the latter case the developing negative charge is not stabilized by the metal.

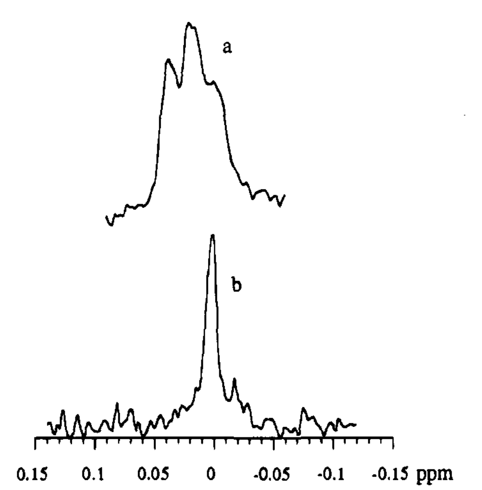
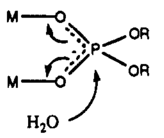


Figure 5. ^{31}P NMR spectrum showing the product of BNPP (2 mM) hydrolysis promoted by La(III) (5 mM) and hydrogen peroxide (50 mM) using (a) H_2O_2 and $H_2{}^{18}O_2$ (1:1) in D_2O and (b) H_2O_2 in $H_2{}^{18}O$ and D_2O (1:1).



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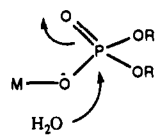

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Role of Peroxide. The function of the peroxides in **4** may simply be to bring the two La(III) ions close enough to bridge the phosphate diester. The peroxides may additionally act as general base or nucleophilic catalysts for cleaving the phosphate diester. In order to distinguish the mechanistic possibilities, ^{18}O labeling experiments were performed. The incorporation of ^{18}O into inorganic phosphate can be detected by ^{31}P NMR spectroscopy. Incorporation of ^{18}O into inorganic phosphate results in a 0.02 ppm upfield shift of the phosphate signal.[14] When BNPP (2 mM) was allowed to react with La(III) (5 mM), $H_2{}^{18}O_2$ (25 mM) and H_2O_2 (25 mM) for 30 min in D_2O, the product inorganic phosphate peak appeared as a triplet (Figure 5a) with a 1:2:1 ratio of $PO_4{}^{3-}$ to $PO_3{}^{18}O^{3-}$ to $PO_2{}^{18}O_2{}^{3-}$, clearly demonstrating the incorporation of ^{18}O from $H_2{}^{18}O_2$ into the product. The incorporation of two labeled oxygen atoms into the inorganic phosphate product and the 1:2:1 ratio of the products suggest that each *p*-nitrophenyl group of BNPP is released through nucleophilic attack of hydrogen peroxide. As a control experiment, BNPP (2 mM) was also allowed to react with La(III) (5 mM) and H_2O_2 (50 mM) in 50:50 $H_2{}^{18}O/D_2O$ for 30 min. In this case, the inorganic phosphate product peak appeared as a sharp singlet (Figure 5b), indicating that solvent water is not the nucleophile in the cleavage reaction. Therefore, the peroxide group in **4** must be acting as a nucleophilic catalyst

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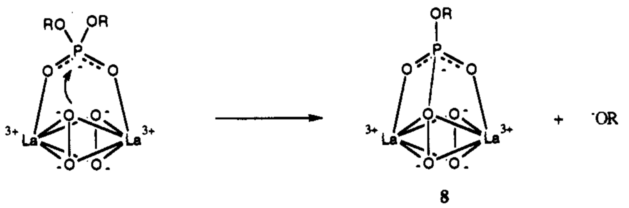
Table 1. Pseudo-First-Order Rate Constants (s^{-1}) for Ln(III) (2 mM) Promoted Cleavage of BNPP with or without Added Hydrogen Peroxide (20 mM) at pH 7.0 (0.1 M HEPES) and 25 °C.

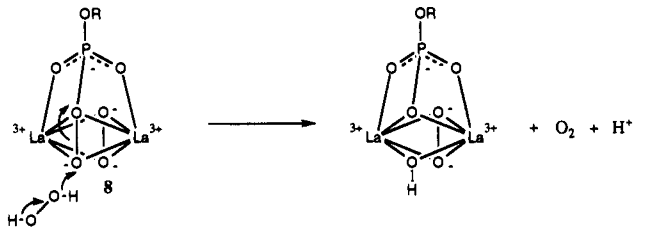
Ln(III)	no HOOH	relative rate	HOOH	relative rate
none[a]	$(1.1 \pm 0.1) \times 10^{-11}$	1	$(1.3 \pm 0.1) \times 10^{-10}$	1.2×10^{1}
La(III)	$(1.4 \pm 0.1) \times 10^{-7}$	1.3×10^{4}	$(3.4 \pm 0.1) \times 10^{-3}$	3.1×10^{8}
Pr(III)	$(5.1 \pm 0.3) \times 10^{-6}$	4.6×10^{5}	$(7.2 \pm 0.2) \times 10^{-3}$	6.5×10^{8}
Nd(III)	$(5.3 \pm 0.3) \times 10^{-6}$	4.8×10^{5}	$(7.2 \pm 0.2) \times 10^{-3}$	6.5×10^{8}
Eu(III)	$(9.4 \pm 0.5) \times 10^{-6}$	8.5×10^{5}	$(3.7 \pm 0.1) \times 10^{-3}$	3.4×10^{8}

[a] Extrapolated from the rate measured at 0.1 M NaOH with or without 0.1 M HOOH.

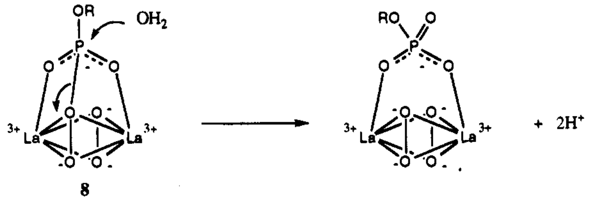
Scheme 3



Scheme 4



Scheme 5



in cleaving the phosphate diester, forming the peroxyphosphate intermediate **8** (Scheme 3).

Peroxyphosphates are known to be reduced by hydrogen peroxide to the corresponding phosphates.[15] We propose that **8** is also reduced by hydrogen peroxide to the phosphate (Scheme 4). Since ^{18}O is incorporated into the inorganic phosphate product when $H_2{}^{18}O_2$ is used but not when $H_2{}^{18}O$ is used, the rate of reduction of **8** by H_2O_2 must be faster than the rate of hydrolysis of **8** (Scheme 5) under our experimental conditions.

Other Phosphate Diesters. It is difficult to study the La(III)−peroxide cooperativity for phosphate diesters that are less reactive than BNPP since the dinuclear La(III) complex **4** is unstable and loses activity after about 30 min. The La(III)−peroxide cooperativity can be studied for hydrolyzing 2′,3′-cAMP (2′,3′-cyclic adenosine monophosphate). Although the phosphate diester in 2′,3′-cAMP consists of poor leaving groups, the five-membered-ring strain makes the diester highly reactive.[16] In the absence of H_2O_2, the pseudo-first-order rate constant for $La(ClO_4)_3$ (5 mM) promoted cleavage of 2′,3′-cAMP is $(1.4 \pm 0.1) \times 10^{-3}\ s^{-1}$ at pH 8.0 and 25 °C. However, with added peroxide (50 mM), the pseudo-first-order rate constant for the cleavage reaction is $(2.5 \pm 0.2) \times 10^{-2}\ s^{-1}$. Although the La(III)−peroxide cooperativity is significant for cleaving 2′,3′-cAMP, it is less than that observed for cleaving BNPP. It may be that the efficiency of the metal−peroxide nucleophile diminishes for cleaving phosphate diesters with poorer leaving groups.

Other Lanthanides. La(III), Pr(III), Nd(III), and Eu(III) all show comparable cooperativities with hydrogen peroxide for cleaving BNPP (Table 1).[17] Lanthanides by themselves provide about 4−6 orders of magnitude rate acceleration for hydrolyzing BNPP. Close to 9 orders of magnitude rate acceleration can be obtained for the hydrolysis reaction by combining the lanthanides with hydrogen peroxide (Table 1).

In conclusion, the rate−concentration profiles (Figures 1 and 2), the pH−rate profile, and the potentiometric titration data are all consistent with the dinuclear La(III) complex **4** being the reactive species for cleaving BNPP. The equilibrium constant for binding of BNPP to **4** ($K_1 = (1.3 \pm 0.1) \times 10^{3}\ M^{-1}$) and the rate constant for hydrolysis of the bound phosphate ($k_2 = (1.8 \pm 0.1) \times 10^{-2}\ s^{-1}$) have been determined. ^{18}O labeling studies reveal that the bridging peroxide in **4** acts as an efficient intramolecular nucleophilic catalyst in cleaving the phosphate diester. The dinuclear La(III) complex **4** is reactive for hydrolyzing phosphate diesters with good (BNPP) or poor (2′,3′-cAMP) leaving groups. La(III), Pr(III), Nd(III), and Eu(III) can each combine with hydrogen peroxide to provide a close to 9 order of magnitude rate acceleration for hydrolyzing BNPP.

Acknowledgment. We thank NSERC, Pioneer Hi-Bred International Inc., and the U.S. Army research office for support of this work. B.T. gratefully acknowledges a postgraduate fellowship from NSERC.

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[17] The dinuclear complexes of Tm(III) and Lu(III) with bridging peroxides are less stable at neutral pH than those of the other lanthanides reported in Table 1.