

Phosphonate Ester Hydrolysis Catalyzed by Two Lanthanum Ions. Intramolecular Nucleophilic Attack of Coordinated Hydroxide and Lewis Acid Activation

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Abstract: (8-Hydroxy-2-quinolyl)methyl (8-hydroxy-2-quinolyl)methyl phosphonate (**I**) has been synthesized as a model compound and investigated in terms of catalysis of hydrolysis by two metal ions in concert. The divalent metal ions, Zn²⁺, Ni²⁺, Co²⁺, Cu²⁺ as well as Al³⁺, form only 1:1 complexes in which the metal ion is sequestered by coordination with the two 8-hydroxyquinoline moieties of **I**. In these complexes the >PO₂⁻ linker points away from the metal ion, and the latter does not act as a catalyst for hydrolysis. The spectrophotometric titration of **I** with La³⁺ indicates that the complexes (I)La and (I)La₂ exist in solution with association constant (log K_{as1}, 6.54; log K_{as2}, 4.81) greater than that (log K_{as}, < 4.0) for La³⁺ complexation of 8-hydroxy-2-methylquinoline. The large values of K_{as} with **I** suggest that La³⁺ interacts with both the 8-hydroxyquinoline ligands and the negative charge of the phosphonate linkage (>PO₂⁻). La³⁺ is a very effective catalyst for hydrolysis of **I**. Studies of the rates of hydrolysis of **I** as a function of [La³⁺] establish that the hydrolysis proceeds *via* two reaction paths: (i) spontaneous hydrolysis of a complex with (I)La₂ stoichiometry and (ii) La³⁺ promoted hydrolysis of the (I)La₂ complex. On the other hand, removal of one of two 8-hydroxyquinoline ligands of **I** to provide (8-hydroxy-2-quinolyl)methyl methylphosphonate (**II**) leads to the formation of the 1:1 complex (II)La, which is hydrolytically inert but subject to catalysis by free La³⁺. Thus, the remarkable spontaneous hydrolysis of (I)La₂ is due to double metal ion cooperativity in catalysis. The pH-rate profile supports a mechanism for the spontaneous hydrolysis of (I)La₂ which involves the intramolecular attack of HO⁻ ligated to one of the two La³⁺ in the complex (I)La₂(OH₂)_{n-1}(OH). The pK_a value of the water bound to La³⁺ in (I)La₂(OH₂)_n and rate constant for the hydrolysis of (I)La₂(OH₂)_{n-1}(OH) are determined as 7.19 and 1.36 × 10⁻³ s⁻¹, respectively. The [La³⁺] and [HO⁻] dependence of La³⁺ promoted hydrolysis of (I)La₂(X)_n and (II)La(X)_n {X = H₂O or HO⁻} is in accord with the transition state compositions of {(I)La₂(X)_n}{La(OH)²⁺} and {(II)La(X)_n}{La(OH)²⁺}, respectively. The bimolecular rate constant for the hydrolysis of (I)La₂(X)_n and (II)La(X)_n by La(OH)²⁺ were calculated as 2.62 × 10⁻¹ and 7.61 × 10⁻² M⁻¹ s⁻¹, respectively. The similarity of these second-order rate constants suggests that one 8-hydroxyquinoline {probably in leaving group} ligated La³⁺ is effectively associated with the leaving group oxyanion and negative charge of the >PO₂⁻ to activate **I** and **II** by Lewis-acid catalysis. Based on an estimation of the rate constant for hydroxide-catalyzed hydrolysis of **I** with P–O bond cleavage, a rate enhancement of ~10¹³ fold has been observed on the spontaneous hydrolysis of (I)La₂(OH₂)_{n-1}(OH). This is attributed to a combination of Lewis-acid activation {La³⁺ ligated to negative >PO₂⁻ and leaving oxygen} and intramolecular nucleophilic attack of hydroxide bound to the second La³⁺.

Introduction

The mechanisms of hydrolysis of phosphodiester are of interest because the subject relates to enzymatic hydrolysis of DNA and RNA. In neutral aqueous solution the hydrolysis of aliphatic phosphate diesters is much slower than hydrolysis of carboxylic acid esters, amides, nitriles, and phosphate mono and triesters. The rate of dimethyl phosphate hydrolysis at neutral pH and 25 °C is estimated to be 2 × 10⁻¹⁴ s⁻¹.¹ The half-life for hydrolytic cleavage of the phosphate diester bond of DNA has been assessed to be approximately 200 million years (pH 7, 25 °C).² On the other hand, DNA and RNA are completely hydrolyzed under physiological conditions within seconds in the presence of enzymes, many of which are activated by two metal ions. A role of metal ions has been considered to be Lewis-acid catalysis through coordination of the metal ions to substrate, rendering the latter more susceptible to nucleophilic attack. Substrate ligation to metal ion may also assist the departure of the incipient leaving group. In addition, a metal

ion ligated to substrate may act as a carrier of nucleophilic hydroxide ion. The pK_a of the water ligated to metal ion is considerably lower than that of H₂O itself so that at a given pH a higher concentration of hydroxide ion can be obtained in the presence of metal ion.

Evidence for the involvement of two metal ions in the 3'–5' exonuclease reaction mechanism comes from the X-ray crystal structure of the Klenow fragment of *Escherichia coli* DNA polymerase I and its complexes with a deoxynucleoside monophosphate product and a single-stranded DNA substrate.³ A mechanism proposed by Steitz is based on the structural information of Chart 1. Metal ion A, probably Zn²⁺, brings the attacking hydroxide into position for an in-line displacement of the 3' oxygen of leaving sugar. Another metal ion B, probably Mg²⁺, interacts with the 3' oxygen of the leaving sugar to facilitate the departure of the leaving group. In addition, one non-esterified oxygen of the scissile phosphate lies between two metal ions at a bonding distance capable of stabilizing the transition state. Other examples of two metal ion activation of enzymes that hydrolyze phosphate esters are *E. coli* alkaline

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(1) Guthrie, J. P. *J. Am. Chem. Soc.* 1977, 99, 3991.

(2) Chin, J.; Banaszczuk, M.; Jubian, V.; Zou, X. *J. Am. Chem. Soc.* 1989, 111, 186.

(3) Beese, L. S.; Steitz, T. A. *EMBO J.* 1991, 10, 25.

Chart 1

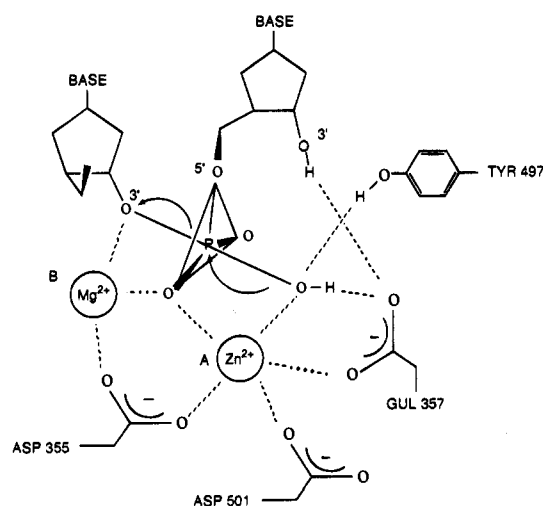
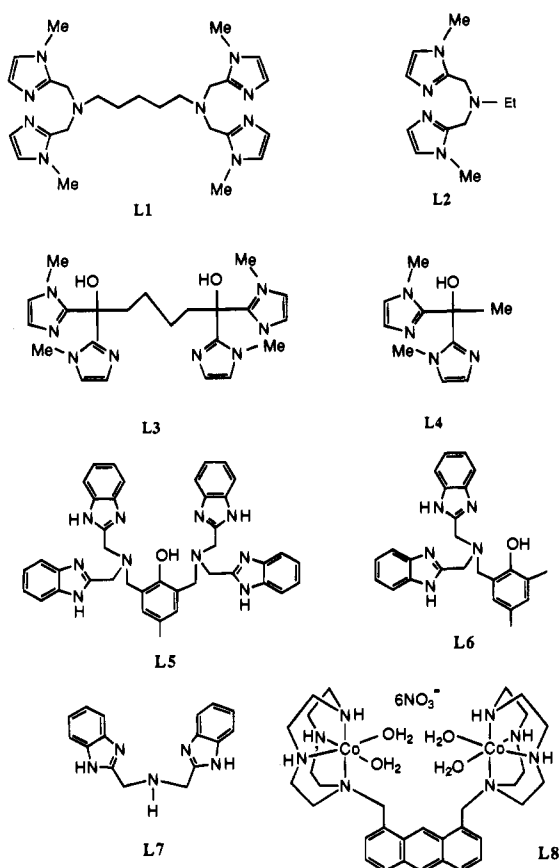


Chart 2

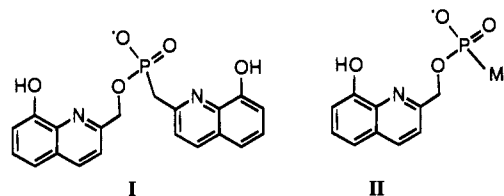


phosphatase,⁴ phospholipase C from *Bacillus cereus*,⁵ and RNases H from HIV reverse transcriptase.⁶

Recent reports of studies of putative two metal ion catalysis of phosphate ester hydrolysis are presented in Chart 2. Clewley and co-workers investigated two metal ion cooperativity in the hydrolysis of tris(4-nitrophenyl) phosphate by use of mono- and binucleating ligands (Chart 2, L2 and L1) complexed with Cu²⁺ and Zn²⁺,⁷ while Kesicki and co-workers have studied the

hydrolysis of bis(4-nitrophenyl) phosphate by Ni²⁺, Cu²⁺, and Zn²⁺ complexes of ligands L3 and L4.⁸ Both groups reported that no notable rate enhancement occurred by two metal ion cooperation. Wall and co-workers have demonstrated double Lewis-acid activation on the intramolecular transesterification of 2-hydroxypropyl 4-nitrophenyl phosphate (HPNP) using binuclear copper complex L5Cu₂, in which each Cu²⁺ is suggested to ligate to both oxygen atoms of the phosphate group.⁹ The rate constant (25 °C, pH 7) for cleavage of HPNP in the presence of L5Cu₂ was 50-fold larger than that in the case of mononucleating ligand complex L6Cu. They have also showed that dinuclear Cu²⁺ complex with ligand L7 catalyzed the transesterification of HPHP.¹⁰ Furthermore, in a study of bis(4-nitrophenyl) phosphate hydrolysis catalyzed by polyamine Co³⁺ complexes, Vance and Czarnik have observed that the reaction rate (25 °C, pH 7) of the hydrolysis with binucleating ligand-Co³⁺ complex, L8, is 10 times greater than that in the presence of 2 equiv of (cyclene)Co³⁺ complex (cyclene = 1,4,7,10-tetraazacyclododecane).¹¹ Another example of two metal ion catalysis recently reported is oxidative hydrolysis of bis(4-nitrophenyl) phosphate using La³⁺ and H₂O₂.¹²

Our interest is focused on the design and kinetic study of a model compound that demonstrates a remarkable catalysis of hydrolysis by two metal ions. We have synthesized (8-hydroxy-2-quinolyl)methyl (8-hydroxy-2-quinolyl)methylphosphonate (I)¹³ as a model which can hold two metal ions close to the >PO₂⁻ functionality like an enzyme-substrate complex and examined the complexation with La³⁺, Al³⁺, Zn²⁺, Ni²⁺, Co²⁺, and Cu²⁺ and hydrolysis of their metal complexes in detail. These results have been compared with those of (8-hydroxy-2-quinolyl)methyl methylphosphonate (II) which has only one 8-hydroxyquinoline moiety as a metal binding group.



We now report an intramolecular model which exhibits catalysis of the hydrolysis of an aliphatic phosphonate ester promoted by a combination of Lewis-acid and nucleophilic catalysis by two metal ions. A part of this work has been reported in our preliminary communication.¹⁴

Experimental Section

Organic Synthesis. (a) **General Methods.** Melting points were measured on a Laboratory Device Mel-Temp apparatus and are uncorrected. ¹H NMR spectra were recorded on Varian Gemini-200 and General Electric GN-500 spectrometers with trimethylsilane as an internal standard. When deuterium oxide (D₂O) was used as a solvent, the chemical shifts were reported relative to the signal of D₂O (4.63

(8) Kesicki, E. A.; DeRosch, M. A.; Freeman, L. H.; Walton, C. L.; Harvey, D. F.; Troglor, W. C. *Inorg. Chem.* **1993**, *32*, 5851.

(9) Wall, M.; Hynes, R. C.; Chin, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1633.

(10) Wahnou, D.; Hynes, R. C.; Chin, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1441.

(11) Vance, D. H.; Czarnik, A. W. *J. Am. Chem. Soc.* **1993**, *115*, 12165.

(12) Takasaki, B. K.; Chin, J. *J. Am. Chem. Soc.* **1993**, *115*, 9337.

(13) To differentiate each ionization state of I and II the following symbols are used: (I)H₂⁻ and (II)H⁻, monoanionic species; (I)H₂²⁻ and (II)²⁻, dianionic species; (I)³⁻, trianionic species. For metal ion (Mⁿ⁺) complexes of I and II, the symbols, (I)HM⁽ⁿ⁻²⁾⁺, (I)M₂⁽²ⁿ⁻³⁾⁺, and (II)M⁽ⁿ⁻²⁾⁺, etc. are used. The total charge of these compounds are, in some cases, omitted for clarity.

(14) Tsubouchi, A.; Bruce, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 11614.

(4) Kim, E. E.; Wyckoff, H. W. *J. Mol. Biol.* **1991**, *218*, 449.

(5) Hough, E.; Hansen, L. K.; Birknes, B.; Jynge, K.; Hansen, S.; Hordvik, A.; Little, C.; Dodson, E.; Derewenda, Z. *Nature* **1989**, *338*, 357.

(6) Davies, J. F.; Hostomska, Z.; Hostomsky, Z.; Jordan, S. R.; Matthews, D. A. *Science* **1991**, *252*, 88.

(7) Clewley, R. G.; Slebocka-Tilk, H.; Brown, R. S. *Inorg. Chem. Acta* **1989**, *157*, 233.

ppm). IR spectra were obtained on a Perkin-Elmer 1330 spectrophotometer. Mass spectrometry was performed on a VG analytical spectrometer (Model VGII-250) using electron impact (EI) and fast atom bombardment (FAB) techniques with *m*-nitrobenzyl alcohol or glycerol as a matrix. Elemental analysis was carried out by Galbraith Laboratories, Inc. (Knoxville, TN). All reagents for synthesis were purchased from commercial vendors and used without further purification. Dimethylformamide (DMF) was dried over CaH₂ overnight and distilled under reduced pressure. 1,4-Dioxane and benzene were dried by refluxing with Na metal and methylene dichloride (CH₂Cl₂) with P₂O₅ and were distilled before use. Acetonitrile (MeCN) was refluxed and distilled from CaH₂. Acetone was dried over 4A molecular sieves and used without distillation. All nonaqueous reactions were run under argon atmosphere.

(b) **8-*tert*-Butyldiphenylsilyloxy-2-methylquinoline (2)**. A mixture of 8-hydroxy-2-methylquinoline (**1**) (10.0 g, 62.8 mmol), *tert*-butylchlorodiphenylsilane (TBDPSCI) (28.9 g, 105 mmol), and imidazole (10.5 g, 154 mmol) in DMF (90 mL) was stirred for 72 h at room temperature. The reaction was quenched with 5% aqueous NaHCO₃ (300 mL), and the mixture was extracted with hexane. The extract was washed with water and dried over anhydrous Na₂SO₄. After evaporating the solvent, the residue was dissolved in CH₂Cl₂ (40 mL), and methanol (40 mL) was added to this solution. The solvent was concentrated to appropriate volume (ca. 20 mL), and the precipitated solid was collected by filtration to give 21.0 g (84.1%) of **2** as a white solid: mp 97.0–97.5 °C; ¹H NMR (CDCl₃) δ 7.96–7.12 (m, 15 H, aromatic), 2.29 (s, 3 H, 2-CH₃), 1.15 (s, 9H, C(CH₃)₃); MS (EI) *m/z* 397 (calcd for C₂₆H₂₇NOSi (M⁺) 397).

(c) **8-*tert*-Butyldiphenylsilyloxyquinoline-2-carbaldehyde (3)**. Compound **2** (20.0 g, 50.3 mmol) was added under argon at 60 °C to a suspension of SeO₂ (5.71 g, 51.4 mmol) in 1,4-dioxane (120 mL). The temperature was raised to 75 °C, and the mixture was stirred for 24 h. After removal of residue by filtration, solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 95/5) to give 15.9 g (76.7%) of **3** as a white solid: mp 78.0–78.5 °C; IR (KBr) 1700 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 9.67 (s, 1 H, CHO), 8.22–7.22 (m, 15 H, aromatic), 1.21 (s, 9 H, C(CH₃)₃); MS (EI) *m/z* 354 (calcd for C₂₂H₁₆NO₂Si (M⁺ - C₄H₉) 354).

(d) **8-*tert*-Butyldiphenylsilyloxy-2-quinolyl)methanol (4)**. NaBH₄ (0.416 g, 11.0 mmol) was added to an ice-cooled solution of **3** (15.8 g, 38.4 mmol) in absolute ethanol (60 mL). After stirring for 6 h, the solvent was removed under reduced pressure, and water was added to the residue. The crude product was extracted with diethyl ether, and the solution was dried over anhydrous Na₂SO₄. Ether solvent was reduced to one-fifth of the initial volume, and the precipitated product was collected by filtration and washed with hexane. Some product remains in the filtrate which was chromatographed on silica gel (gradient of 30–50% ether in hexane). The fraction containing product was collected and reduced under vacuum, and the residue was combined with the major fraction of the product. A total of 14.9 g (93.8%) of **4** was obtained as a white solid: mp 107.0–107.5 °C; IR (KBr) 3400 (OH) cm⁻¹; ¹H NMR (CDCl₃) δ 8.03 (d, *J* = 8.6 Hz, 1 H, quinoline 4-H), 7.81–7.02 (m, 14 H, aromatic), 4.70 (s, 2 H, CH₂OH), 4.13 (bs, 1 H, OH), 1.19 (s, 9 H, C(CH₃)₃); MS (EI) *m/z* 413 (calcd for C₂₆H₂₇NO₂Si (M⁺) 413).

(e) **8-*tert*-Butyldiphenylsilyloxy-2-quinolyl)methyl Bromide (5)**. A solution of **4** (7.00 g, 16.9 mmol) in benzene (200 mL) was placed into a distillation apparatus, and 60 mL of benzene was distilled off under argon to remove moisture by azeotropy. Thionyl bromide (3.88 g, 1.87 mmol) was carefully added to this solution at ~0 °C. After the mixture was stirred for 1.5 h at 5 °C, the reaction was stopped by adding 5% aqueous NaHCO₃. The organic layer was extracted with ether, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 2/5) to give 6.20 g (77.0%) of **5** as a white solid: mp 74–75 °C; ¹H NMR (CDCl₃) δ 8.15–7.08 (m, 15 H, aromatic), 4.24 (s, 2 H, CH₂), 1.17 (s, 9 H, C(CH₃)₃); MS (EI) *m/z* 475 (calcd for C₂₆H₂₆NOBrSi (M⁺) 475).

(f) **Dimethyl (8-*tert*-Butyldiphenylsilyloxy-2-quinolyl)methylphosphonate (6)**. A mixture of **5** (6.20 g, 1.30 mmol) and trimethylphosphite (5.60 g, 45.1 mmol) was heated to 80 °C under argon for 24 h

with stirring. Excess trimethylphosphite was removed *in vacuo*, and the residue was chromatographed on silica gel (hexane/EtOAc = 1/1) to give 4.52 g (68.7%) of **6** as a white solid: mp 95–96 °C; IR (KBr) 1250 (P=O), 1050 and 1015 (P–OC) cm⁻¹; ¹H NMR (CDCl₃) δ 8.02 (d, *J* = 8.4 Hz, 1 H, quinoline 4-H), 7.82–7.78 (m, 4 H, 2 × phenyl *m*-H), 7.49–6.94 (m, 10 H, aromatic), 3.65 (d, *J*_{P–H} = 11.1 Hz, 6 H, P(OCH₃)₂), 3.42 (d, *J*_{P–H} = 22.0 Hz, 2 H, PCH₂), 1.17 (s, 9 H, C(CH₃)₃); MS (EI) *m/z* 505 (calcd for C₂₈H₃₂NO₄PSi (M⁺) 505).

(g) **(8-Hydroxy-2-quinolyl)methylphosphonic Acid (8)**. TBDPSCI (2.70 g, 9.82 mmol) was added under argon to a mixture of **6** (2.26 g, 4.47 mmol) and KI (1.85 g, 11.1 mmol) in MeCN (7 mL), and the mixture was heated at 50 °C for 27 h. After adding MeCN (5 mL), KCl was removed by filtration. The filtrate was concentrated *in vacuo*, and the yellow residue was purified by flash column chromatography (silica gel, CH₂Cl₂) to afford a yellow glassy solid of **7**. This was dissolved in methanol (40 mL)–water (4 mL), and the solution was stirred for 24 h at room temperature. The solvent was evaporated *in vacuo*, and a small amount of methanol was added. The precipitated yellow solid was collected by filtration and washed with methanol to give 0.725 g (67.8%) of **8** as a yellow solid: mp 271–272 °C dec; IR (KBr) 3400 (OH), 1590 and 1625 (PO–H), 1000 (P–OH) cm⁻¹; ¹H NMR (D₂O) δ 8.70 (d, *J* = 8.6 Hz, 1 H, 4-H), 7.71 (d, *J* = 7.7 Hz, 1 H, 3-H), 7.50 (d, *J* = 4.1 Hz, 2 H, 5,7-H), 7.24 (t, *J* = 4.6 Hz, 1 H, 6-H), 3.56 (d, *J* = 22.3 Hz, 2 H, PCH₂); MS (FAB) *m/z* 240 (calcd for C₁₀H₁₁NO₄P (M + H⁺) 240).

(h) ***O*-(*tert*-Butyldiphenylsilyloxy-2-quinolyl)methyl-*N,N'*-dicyclohexylisourea (9)**. A mixture of the alcohol **4** (2.50 g, 6.04 mmol), dicyclohexylcarbodiimide (1.25 g, 6.06 mmol), and a catalytic amount of CuCl (3.75 mg) in benzene (2.5 mL) was stirred for 1 h at 50 °C. After additional stirring for 24 h at room temperature, the volume of the reaction mixture was doubled with hexane, and the solution was applied to a filter pad of neutral aluminum to remove copper salts. The product was eluted with hexane. Evaporating the solvent gave 3.31 g (88.4%) of **9** as a white solid, which was pure enough to use for the next reaction: mp 116–117 °C; IR (KBr) 3450 (NH), 1665 (N=C) cm⁻¹; ¹H NMR (CDCl₃) δ 8.00 (d, *J* = 8.6 Hz, 1 H, quinoline 4-H), 7.82–7.78 (m, 4 H, 2 × phenyl *m*-H), 7.42–6.99 (m, 10 H, aromatic), 5.09 (s, 2 H, CH₂O), 3.60–3.40 (bm, 2 H), 2.86 (bs, 1 H, NH), 1.98–1.23 (m, 20 H, cyclohexyl), 1.46 (s, 9 H, C(CH₃)₃); MS (FAB) *m/z* 620 (calcd for C₃₉H₅₀N₃O₂Si (M + H⁺) 620).

(i) **Bis[(8-*tert*-butyldiphenylsilyloxy-2-quinolyl)methyl] (8-Hydroxy-2-quinolyl)methylphosphonate (10)**. A suspension of **8** (0.580 g, 2.43 mmol) and **9** (3.16 g, 5.10 mmol) in DMF (20 mL)–benzene (60 mL) was heated at 80 °C for 42 h. The reaction mixture was cooled to room temperature, and dicyclohexylurea was removed by filtration. The filtrate was concentrated under reduced pressure and the crude product purified by column chromatography (silica gel, hexane/EtOAc = 2/3) to give 1.28 g (51.1%) of **10** as glassy solid, mp 62–64 °C; IR (KBr) 3400 (OH), 1250 (P=O), 1035 (P–OC) cm⁻¹; ¹H NMR (CDCl₃) δ 8.00–7.05 (m, 35 H, aromatic), 4.83 (d, *J*_{P–H} = 8.5 Hz, 2 H, POCH₂), 4.82 (d, *J*_{P–H} = 8.0 Hz, 2 H, POCH₂), 3.62 (d, *J*_{P–H} = 22.2 Hz, 2 H, PCH₂), 1.13 (s, 9 H, C(CH₃)₃); MS (FAB) *m/z* 1030 (calcd for C₆₂H₆₁N₃O₆PSi₂ (M + H⁺) 1030).

(j) **(8-Hydroxy-2-quinolyl)methyl (8-Hydroxy-2-quinolyl)methylphosphonate (I)**. The compound **10** (1.24 g, 1.20 mmol) was dissolved in acetone (51 mL), and then 1 N HCl (24 mL) was added to this solution at room temperature. After stirring for 24 h, the solvent was removed under vacuum, and the residue was washed with chloroform to give the crude product. The latter was dissolved in methanol, and then MeCN was slowly added. The precipitating solid was collected by filtration to afford 0.306 g (55.5% as I·HCl^{1/2}(H₂O)) of **I** as a yellow solid: mp > 151 °C dec; IR (KBr) 3400 (OH), 1635 and 1600 (PO–H), 1250 and 1205 (P=O), 1065 (P–OC) cm⁻¹; ¹H NMR (D₂O) δ 8.66 (d, *J* = 9.0 Hz, 1 H), 8.64 (d, *J* = 8.5 Hz, 1 H), 7.82 (d, *J* = 9.0 Hz, 1 H), 7.33 (d, *J* = 8.5 Hz, 1 H), 7.62 (t, *J* = 8.5 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.40 (t, *J* = 7.5 Hz, 1 H), 7.34 (d, *J* = 7.5 Hz, 1 H), 7.22 (d, *J* = 7.5 Hz, 1 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 5.30 (d, *J*_{P–H} = 10.5 Hz, 2 H, POCH₂), 3.83 (d, *J*_{P–H} = 21.5 Hz, 2 H, PCH₂); MS (FAB) *m/z* 397 (calcd for C₂₀H₁₈N₂O₅P (M + H⁺) 397). Anal. Calcd for C₂₀H₁₇N₂O₅P·HCl^{1/2}(H₂O): C, 52.24; H, 4.60; N, 6.09. Found: C, 52.54; H, 4.46; N, 6.40.

(k) **Bis[(8-*tert*-butyldiphenylsilyloxy-2-quinolyl)methyl] Methylphosphonate (11)**. A solution of methylphosphonic dichloride (0.159 g, 1.20 mmol) in CH_2Cl_2 (1 mL) was added over 20 min to a solution of **4** (1.00 g, 2.42 mmol) and triethylamine (0.215 g, 2.42 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 1 h, triethylammonium hydrogen chloride was removed by filtration, and the product was purified by column chromatography (silica gel, hexane/EtOAc = 3/2) to give 0.81 g (76%) of **11** as a glassy solid: mp 54–55 °C; $^1\text{H NMR}$ (CDCl_3) δ 7.92 (d, J = 8.6 Hz, 2 H, 2 \times quinoline 4-H), 7.76–7.72 (m, 8 H, 4 \times phenyl m-H), 7.36–7.08 (m, 20 H, aromatic), 4.82 (d, $J_{\text{P-H}}$ = 8.2 Hz, 4 H, 2 \times POCH_2), 1.48 (d, $J_{\text{P-H}}$ = 17.7 Hz, 3 H, PCH_3), 1.14 (s, 9 H, $\text{C}(\text{CH}_3)_3$); MS (FAB) m/z 887 (calcd for $\text{C}_{53}\text{H}_{56}\text{N}_2\text{O}_5\text{PSi}_2$ ($\text{M} + \text{H}^+$) 887).

(l) **Sodium (8-Hydroxy-2-quinolyl)methyl Methylphosphonate (II)**. A solution of **11** (0.80 g, 0.90 mmol) in acetone (40 mL)–1 N HCl (20 mL) was stirred for 24 h at room temperature to remove the silyl protecting group. After evaporation of acetone, the aqueous solution was washed with diethyl ether and neutralized with 1 N KOH. Deprotected product, bis[(8-hydroxy-2-quinolyl)methyl] methylphosphonate (**12**), was extracted with EtOAc: $^1\text{H NMR}$ (CDCl_3) δ 8.13 (bs, 2 H, 2 \times OH), 8.11 (d, J = 8.5 Hz, 2 H, 2 \times 4-H), 7.53 (d, J = 8.6 Hz, 2 H, 2 \times 3-H), 7.42 (t, J = 7.7 Hz, 2 H, 2 \times 6-H), 7.29 (d, J = 7.7 Hz, 2 H), 7.18 (d, J = 7.2 Hz, 2 H), 5.36 (d, $J_{\text{P-H}}$ = 9.2 Hz, 4 H, 2 \times POCH_2), 1.70 (d, $J_{\text{P-H}}$ = 17.4 Hz, 3 H, PCH_3). This product was used in the following reaction without purification.

To a solution of **12** (0.30 g, 0.73 mmol) in acetone (2 mL) was added NaI (0.106 g, 0.73 mmol) at room temperature. The mixture was stirred at 40 °C for 24 h. The product was precipitated out as a yellow solid. After filtration the solid was dissolved in water and precipitated by addition of acetone to give **II** as a white solid (85 mg, 33% based on **11**): mp >145 °C dec; IR (KBr) 3500 (OH), 1175 (PO_2^-), 1040 (PO_2^- , P–OC) cm^{-1} ; $^1\text{H NMR}$ (D_2O) δ 8.19 (d, J = 8.5 Hz, 1 H, 4-H), 7.53 (d, J = 8.6 Hz, 1 H, 3-H), 7.32 (d, J = 3.3 Hz, 2 H, 5,7-H), 7.04 (t, J = 4.0 Hz, 1 H, 6-H), 4.98 (d, $J_{\text{P-H}}$ = 7.8 Hz, 2H, POCH_2), 1.17 (d, $J_{\text{P-H}}$ = 16.5 Hz, 3H, PCH_3); MS (FAB) m/z 252 (calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{P}$ (M^+) 252). Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{PNa}^{1/2}(\text{H}_2\text{O})$: C, 46.49; H, 4.26; N, 4.39. Found: C, 46.07; H, 4.57; N, 4.81.

Kinetic and Equilibrium Studies. (a) **Materials.** Buffers and metal chlorides were of the highest purity available and used as received from the suppliers. The solution of KCl, used to maintain constant ionic strength, was demetallated by passing through a Chelex 100 resin (Bio-Red) column. Glass distilled deionized water was used for all kinetic and equilibrium studies.

(b) **Metal Binding Equilibria.** The equilibrium constants for binding of **I** and **II** with lanthanum ion were spectrophotometrically determined at 30 °C with constant ionic strength (μ = 1.0 with KCl). All solutions used were buffered with 0.1 M HEPES (*N*-(2-hydroxyethyl)piperazine-*N'*-3-propanesulfonic acid). The concentrations of **I** and **II** were always held constant (**I**, 2.0×10^{-5} M; **II**, 3.8×10^{-5} M) and the metal concentration varied from 2.0×10^{-5} to 1.0×10^{-1} M. High concentrations of LaCl_3 cause the pH of buffered stock metal ion solutions to shift downwards. The pH was adjusted to its original value by the addition of aliquots of a concentrated KOH solution prior to incorporation of esters. In practice aliquots of stock solutions of the phosphonate esters were added to thermally equilibrated cuvettes containing buffer solution of lanthanum chloride and absorbances recorded (**I**, 264 nm; **II**, 260 nm). A Perkin-Elmer 553 spectrophotometer with thermostat cuvette holder was employed. Hydrolysis of phosphonate esters was negligible during the time required for the measurement (30 s). A Radiometer Model 26 pH meter and a combination glass electrode were used for pH measurement.

Binding of **I** (2.0×10^{-5} M) to Zn^{2+} , Ni^{2+} , Co^{2+} , Cu^{2+} , and Al^{3+} was studied at pH 7.1 and 30 °C (μ = 1.0) using the method provided for studies with La^{3+} . The absorbances were measured at 261 nm for Zn^{2+} , Cu^{2+} , and Al^{3+} , 263 nm for Ni^{2+} , and 259 nm for Co^{2+} in the range of the metal ion concentration from 0 to 6.0×10^{-5} M.

(c) **Potentiometric and Spectrophotometric Titration.** The pK_a values for **I** were determined by potentiometric pH titration at 30 °C (μ = 1.0). A solution of **I**·HCl (1.1×10^{-3} M) in water (20 mL) was

titrated with 0.1 N KOH, and the titration curve was analyzed by a literature procedure.¹⁵

The pK_a (phenolic proton ionization) of **II** was determined spectrophotometrically at 30 °C (μ = 1.0). All solutions were buffered with 0.1 M CHES (2-(cyclohexylamino)ethanesulfonic acid). The pH values of the solutions varied from 8.3 to 10.9. The final concentration of **II** was held constant (4.0×10^{-5} M). Aliquots of the stock solution of **II** were added to the buffer solution and absorbances recorded at 241 and 258 nm. The plots of the absorbance at two wavelengths vs pH were fit to a theoretical equation for a single pK_a .

(d) **Kinetic Measurements Were Carried out by HPLC.** Ionic strength was kept constant (μ = 1.0) with KCl. HEPES and MES (2-(*N*-morpholino)ethanesulfonic acid) buffers (0.1 M) were used within 1 pH unit of their pK_a values to maintain constant pH. pH values of solutions were measured prior to initiation of the hydrolysis. The stock solution (5.0×10^{-3} M) of **I** was made with methanol and that (1.0×10^{-2} M) of **II** with water. The hydrolyses were performed in glass screw-capped vials using a total volume of 1 mL and an initial concentration of 2.0×10^{-5} M of phosphonate esters. The glass vials containing solutions of the buffer and metal chloride were thermally equilibrated in a thermostated compartment, and the reactions were initiated by addition of the stock solution (4 μL) of phosphonate esters. The vials were quickly shaken and returned to the compartment. The hydrolysis was monitored by high performance liquid chromatography (HPLC): a Perkin-Elmer series 100 pump module equipped with a Beckman reverse phase ODS column (particle size 5 μm ; 250 \times 4 mm) was used, and chromatograms were recorded on a Hewlett-Packard HP 3392A integrator connected to a Hewlett-Packard HP 1050 variable wavelength detector. Aliquots of the reaction solutions were periodically taken up by a glass syringe and directly injected (20 μL). The samples were eluted with water–methanol (**I**, 42:58; **II**, 55:45, v/v) containing EDTA (5.0×10^{-3} M) and phosphate buffer (5.0×10^{-3} M, pH 4.0) at constant flow rate of 2.5 mL/min. Detector wavelength was chosen to be 254 nm for **I** and 310 nm for **II**. The hydrolyses were followed for approximately 3 half-lives by observing the disappearance of the esters. The calibration curve, the plot of the peak area against the concentration of the ester, was a straight line passing through the origin in the range from initial concentration of the esters to final one. Therefore, the pseudo-first-order rate constants were obtained from the plots of the peak area (A_t) for phosphonate esters vs time by fitting the data points by use of eq 1, where A_0 is the initial peak area.

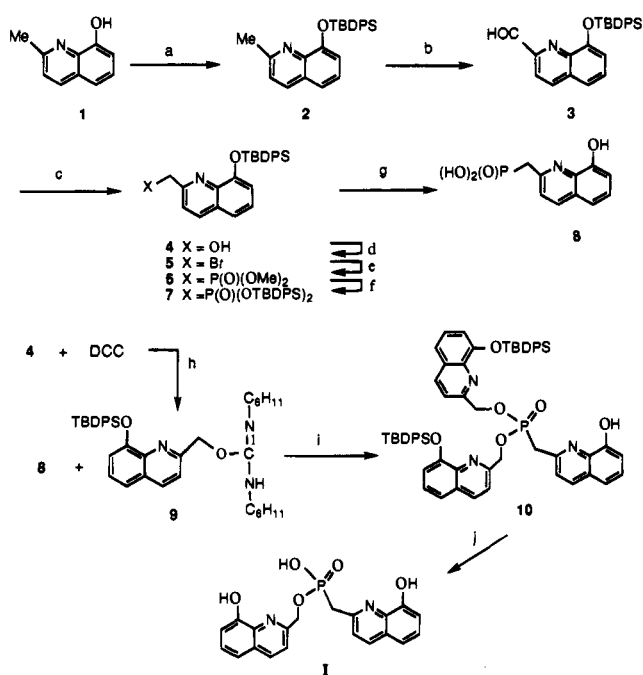
$$A_t = A_0 \exp(-k_{\text{obsd}} \times t) \quad (1)$$

Results

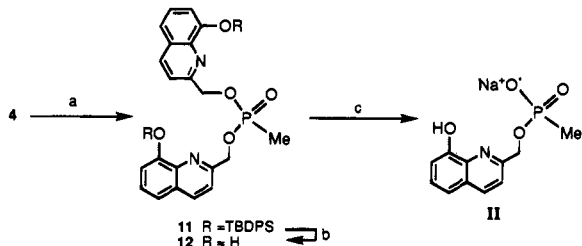
Synthesis. The synthesis of the phosphonate **I** was achieved as shown in Scheme 1. The alcohol **4**, which is an intermediate common to the synthesis of the phosphonic acid and the ester moieties of **I**, was prepared in good yield from 8-hydroxy-2-methylquinoline (**1**) in three steps; protection of 8-hydroxyl group with TBDPS (*tert*-butyldiphenylsilyl) group, oxidation of the 2-methyl group with SeO_2 , and finally reduction of the resulting aldehyde. Arbuzov reaction of trimethylphosphite with the bromide **5**, obtained by bromination of the alcohol **4** with SOBr_2 , gave the dimethyl phosphonate **6**, which was converted to the disilylester **7**, with TBDPSCl . Removal of the TBDPS protecting groups of **7** to provide the phosphonic acid **8**, was accomplished by hydrolysis in methanol–water (10:1). The isourea derivative **9** was prepared from **4** by reaction with DCC. The ester **10** was obtained on reaction of the phosphonic acid **8** with the isourea derivative **9**. Acidic hydrolysis of **10** gave the desired phosphonate **I**.

The synthesis of the phosphonate **II** was achieved in three steps from **4** as shown in Scheme 2. The reaction of the alcohol **4** with methylphosphonic dichloride followed by removal of the TBDPS protecting groups by acidic hydrolysis gave the

(15) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hill: New York, 1984.

Scheme 1^a

^a Reagents and conditions: (a) TBDPSCl, imidazole, DMF, room temperature, 72 h; (b) SeO₂, 1,4-dioxane, 75 °C, 24 h; (c) NaBH₄, EtOH, room temperature, 6 h; (d) SOBr₂, benzene, 5 °C, 1.5 h; (e) P(OMe)₃, 80 °C, 24 h; (f) TBDPSCl, KI, MeCN, 50 °C, 27 h; (g) MeOH–H₂O (10:1), room temperature, 24 h; (h) CuCl, benzene, room temperature, 24 h; (i) DMF–benzene (1:3), 80 °C, 42 h; (j) 1 N HCl/acetone, room temperature, 24 h.

Scheme 2^a

^a Reagents and conditions: (a) MeP(O)Cl₂, Et₃N, CH₂Cl₂, 0 °C, 1 h; (b) 1 N HCl, acetone, room temperature, 24 h; (c) NaI, acetone, 40 °C, 24 h.

phosphonate diester **12**, which was converted into the target phosphonate **I** by reaction with NaI.

Metal Binding Studies. Complexation of the 8-hydroxyquinoline moieties of **I** to lanthanum ion was monitored spectrophotometrically at 30 °C ($\mu = 1.0$ with KCl) by the increase in the absorbance at 264 nm. A plot of A_{264} vs $[La^{3+}]$ at pH 7.1 is provided in Figure 1(a). Examination of the plot shows two regions separated by a deflection point ($[La^{3+}] = \sim 8 \times 10^{-4}$ M). In the first region, the absorbance increases rapidly in an almost linear manner with increasing $[La^{3+}]$ and gently approaches the maximum value in the second region. In what follows we show that the change in A_{264} is explained in terms of noncooperative binding of two La^{3+} to **I** (Scheme 3).

Scheme 3

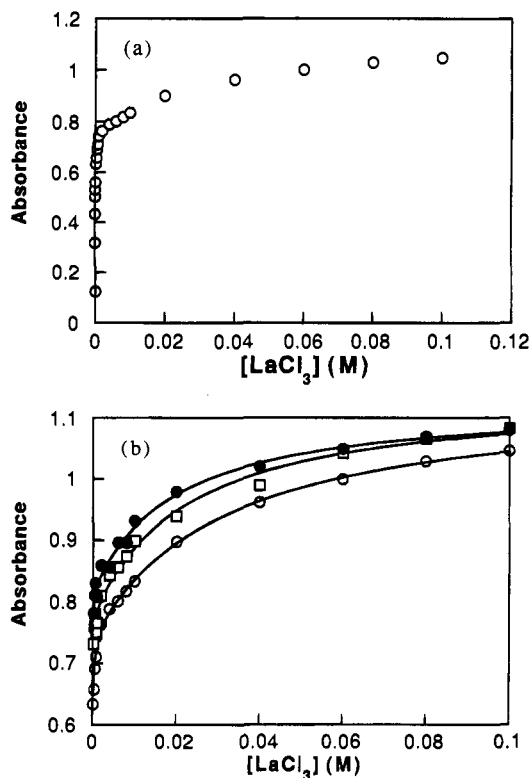
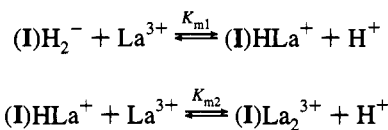


Figure 1. Plots of absorbance of **I** (2.0×10^{-5} M) at 264 nm vs $[La^{3+}]$ at 30 °C ($\mu = 1.0$); (a) whole plot at pH 7.1; (b) partial plot ($[La^{3+}] > 2.0 \times 10^{-4}$ M) at pH 7.1 (O), pH 7.4 (□), and pH 7.6 (●). The solid lines best fit to the data points were generated by use of eqs 6 or 7.

Considering the existence of only three spectral species, $(I)H_2^-$, $(I)HLa^+$, and $(I)La_2^{3+}$ at the working pH range of 7–8, the absorbance (A) of the solution of **I** in the presence of La^{3+} at any wavelength is provided by eq 2 where ϵ_0 , ϵ_1 , and ϵ_2 are molar extinction coefficients of corresponding species at a given wavelength. The spectral species for each complex may contain

$$A = \epsilon_0[(I)H_2^-] + \epsilon_1[(I)HLa^+] + \epsilon_2[(I)La_2^{3+}] \quad (2)$$

spectrophotometrically identical hydroxo complexes formed by ionization of a water molecule ligated to La^{3+} . The equilibrium constants of eqs 3a and 3b, derived from Scheme 3, were

$$K_{m1} = \frac{[(I)HLa^+]a_H}{[(I)H_2^-][La^{3+}]} \quad (3a)$$

$$K_{m2} = \frac{[(I)La_2^{3+}]a_H}{[(I)HLa^+][La^{3+}]} \quad (3b)$$

combined with the material balance of the total ester concentration ($[(I)_T]$) in eq 4a to provide eqs 4b, 4c, and 4d. On rearrangement of eqs 4b, 4c, and 4d, the concentrations of each

$$[(I)_T] = [(I)H_2^-] + [(I)HLa^+] + [(I)La_2^{3+}] \quad (4a)$$

$$= [(I)H_2^-] \{ 1 + K_{m1}[La^{3+}]/a_H + K_{m1}K_{m2}[La^{3+}]^2/a_H^2 \} \quad (4b)$$

$$= [(I)HLa^+] \{ a_H/K_{m1}[La^{3+}] + 1 + K_{m2}[La^{3+}]/a_H \} \quad (4c)$$

$$= [(I)La_2^{3+}] \{ a_H^2/K_{m1}K_{m2}[La^{3+}]^2 + a_H/K_{m2}[La^{3+}] + 1 \} \quad (4d)$$

species are expressed by eqs 5a, 5b, and 5c. By combination of eqs 5a, 5b, and 5c with eq 2, the dependence of the absorbance on the concentration of La^{3+} may be represented as eq 6 where A_0 , A_1 , and A_2 refer to the absorbances of $(I)H_2^-$,

$$[(\text{I})\text{H}_2^-] = \frac{a_{\text{H}}^2}{a_{\text{H}}^2 + a_{\text{H}}K_{\text{m1}}[\text{La}^{3+}] + K_{\text{m1}}K_{\text{m2}}[\text{La}^{3+}]^2}[(\text{I})_{\text{T}}] \quad (5a)$$

$$[(\text{I})\text{HLa}^+] = \frac{a_{\text{H}}K_{\text{m1}}[\text{La}^{3+}]}{a_{\text{H}}^2 + a_{\text{H}}K_{\text{m1}}[\text{La}^{3+}] + K_{\text{m1}}K_{\text{m2}}[\text{La}^{3+}]^2}[(\text{I})_{\text{T}}] \quad (5b)$$

$$[(\text{I})\text{La}_2^{3+}] = \frac{K_{\text{m1}}K_{\text{m2}}[\text{La}^{3+}]^2}{a_{\text{H}}^2 + a_{\text{H}}K_{\text{m1}}[\text{La}^{3+}] + K_{\text{m1}}K_{\text{m2}}[\text{La}^{3+}]^2}[(\text{I})_{\text{T}}] \quad (5c)$$

$(\text{I})\text{HLa}^+$, and $(\text{I})\text{La}_2^{3+}$, respectively, at the concentration equal

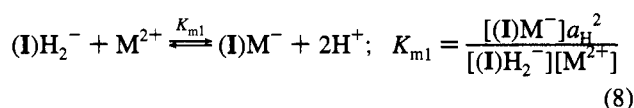
$$A = \frac{A_0 a_{\text{H}}^2 + A_1 a_{\text{H}} K_{\text{m1}} [\text{La}^{3+}] + A_2 K_{\text{m1}} K_{\text{m2}} [\text{La}^{3+}]^2}{a_{\text{H}}^2 + a_{\text{H}} K_{\text{m1}} [\text{La}^{3+}] + K_{\text{m1}} K_{\text{m2}} [\text{La}^{3+}]^2} \quad (6)$$

to $[(\text{I})_{\text{T}}]$. This equation was used to generate a line to fit each series of experimental data points {pH 7.1 and 7.2} in plots of A_{264} vs $[\text{La}^{3+}]$ $\{[\text{La}^{3+}] > 2.0 \times 10^{-4} \text{ M}\}$. A nonlinear least-squares fitting of eq 6 to the data points of the plot of A_{264} vs $[\text{La}^{3+}]$ is provided in Figure 1(b). In eq 6, A_0 is the absorbance when $[\text{La}^{3+}] = 0$ and $[\text{La}^{3+}]$ may be replaced by the total metal concentration ($[\text{La}^{3+}] \gg [(\text{I})_{\text{T}}]$). Beyond pH 7.4, however, the $(\text{I})\text{H}_2^-$ species was fully complexed with La^{3+} even at La^{3+} concentrations only a few times larger than $[(\text{I})_{\text{T}}]$. In this instance eq 6 reduces to eq 7. The values of A_0 , A_1 , A_2 , K_{m1} , and K_{m2} obtained in this way at several different pH values

$$A = \frac{A_1 a_{\text{H}} + A_2 K_{\text{m2}} [\text{La}^{3+}]}{a_{\text{H}} + K_{\text{m2}} [\text{La}^{3+}]} \quad (7)$$

between 7 and 8 were identical, within experimental error, and their mean values are listed in Table 1.

Binding of **I** to Zn^{2+} , Ni^{2+} , Co^{2+} , Cu^{2+} , and Al^{3+} was also examined spectrophotometrically at pH 7.1 and 30 °C ($\mu = 1.0$). Figure 2 shows plots of absorbances vs metal ion concentrations for each metal ion. For the divalent metal ions tested, the absorbances increase linearly with increase in the metal ion concentration and reach saturation levels depending on the metal ions at the concentration equal to that of **I** ($2.0 \times 10^{-5} \text{ M}$). These results indicate that the divalent metal ions form 1:1 complexes in which two 8-hydroxyquinolines of **I** presumably ligate to one central metal ion. Considering the following equilibria (eq 8), the absorbance (A) at an arbitrary wavelength was given by eq 9 derived in the same manner as described above. In eq 9, A_0 is the absorbance when $[\text{M}^{2+}] = 0$ and A_1 is the absorbance at saturation. The equilibrium concentration of metal ions in eq 9 cannot be approximately replaced by the



$$A = \frac{A_0 a_{\text{H}}^2 + A_1 K_{\text{m1}} [\text{M}^{2+}]}{a_{\text{H}}^2 + K_{\text{m1}} [\text{M}^{2+}]} \quad (9)$$

total metal concentration used because the condition $[\text{metal ion}] \gg [(\text{I})_{\text{T}}]$ does not pertain. The concentration $[\text{M}^{2+}]$ was then

Table 1. Absorbances^a and Binding Equilibrium Constants {30 °C, $\mu = 1.0$ } at pH 7.1

complex ^b	A_0^c	A_1	A_2	K_{m1}	K_{m2}
(I)La ₂	0.121 ^d	0.751 ^d	1.14 ^d	1.55×10^{-3} ^d	2.42×10^{-6} ^d
(I)Zn	0.125	1.12		7.38×10^{-6}	
(I)Ni	0.125	1.035		3.69×10^{-5}	
(I)Co	0.126	1.01		8.08×10^{-7}	
(I)Cu	0.120	0.926		6.01×10^{-7}	
(I)Al	0.123	0.887		4.26×10^{-9}	
(II)La	0.072	0.891		1.26×10^{-4}	
(III)La	0.123	<i>e</i>		$< 1.0 \times 10^{-6}$	

^a At 259 nm for (I)Co ($2.0 \times 10^{-5} \text{ M}$), 260 nm for (II)La ($3.8 \times 10^{-5} \text{ M}$) and (III)La ($2.0 \times 10^{-5} \text{ M}$), 261 nm for (I)Zn, (I)Cu, and (I)Al ($2.0 \times 10^{-5} \text{ M}$), 263 nm for (I)Ni ($2.0 \times 10^{-5} \text{ M}$), and 264 nm for (I)La₂ ($2.0 \times 10^{-5} \text{ M}$). The values in parentheses are concentration of phosphonate esters. ^b Charges of complexes are omitted. ^c The observed values at $[\text{metal ion}] = 0$. ^d Average of values obtained at several pH from 7 to 8. ^e Not obtained.

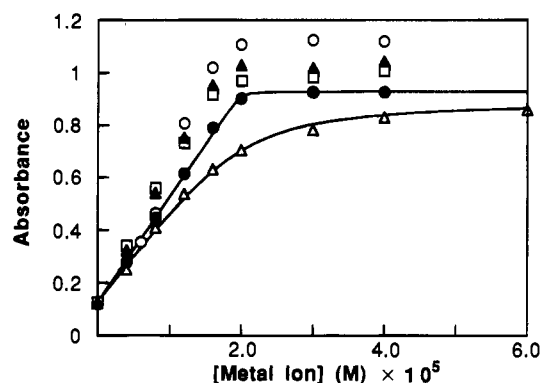


Figure 2. Plots of absorbance of **I** ($2.0 \times 10^{-5} \text{ M}$) vs $[\text{metal ion}]$ at pH 7.1 and 30 °C ($\mu = 1.0$); metal ion = Zn^{2+} (○, 261 nm), Ni^{2+} (▲, 263 nm), Co^{2+} (□, 259 nm), Cu^{2+} (●, 261 nm), and Al^{3+} (△, 261 nm). The lines providing best fits to the data points for Cu^{2+} and Al^{3+} were constructed by use of eq 9.

presented by eq 11 derived from a material balance (eq 10) of metal ions where $P = \{[(\text{I})_{\text{T}}] - [\text{M}^+]\}K_{\text{m1}} + a_{\text{H}}^2$. Equation 9

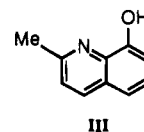
$$[\text{M}^+] = [\text{M}^{2+}] + [(\text{I})\text{M}^-] =$$

$$[\text{M}^{2+}] + \frac{K_{\text{m1}}[\text{M}^{2+}]}{a_{\text{H}}^2 + K_{\text{m1}}[\text{M}^{2+}]}[(\text{I})_{\text{T}}] \quad (10)$$

$$[\text{M}^{2+}] = \frac{-P + (P^2 + 4a_{\text{H}}^2 K_{\text{m1}} [\text{M}^+])^{1/2}}{2K_{\text{m1}}} \quad (11)$$

was fit to the data points for divalent metal ions as well as Al^{3+} in Figure 2 with constants listed in Table 1. The lines, constructed by eq 9, for only Cu^{2+} and Al^{3+} are included in Figure 2; the others are omitted to prevent confusing the data presentation.

The complexation of **II** and 8-hydroxy-2-methylquinoline (**III**) with lanthanum ion was also investigated spectrophotometrically at pH 7.1 and 30 °C ($\mu = 1.0$) in a manner similar to that described for **I**. Assuming the formation of only a 1:1



complex, we may apply the theoretical eq 6 {where $K_{\text{m2}} = 0$ }

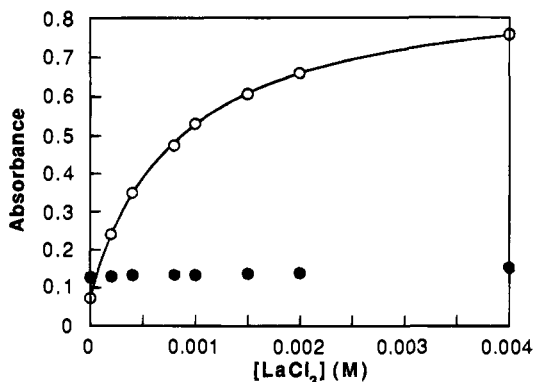


Figure 3. Plots of absorbances of **II** (O, 3.8×10^{-5} M) and **III** (●, 4.0×10^{-5} M) at 260 nm vs $[\text{La}^{3+}]$ at 30 °C ($\mu = 1.0$) at pH 7.1. The curve which best fit the data points was created using eq 6 on assumption of formation of a 1:1 complex ($K_{m2} = 0$).

Table 2. Acid Dissociation Constants of **I**, **II**, and **III** {30 °C, $\mu = 1.0$ }

compd	pK _a (for OH)	pK _a (for NH ⁺)
I	10.43, 9.35	4.92, 2.87
II	9.61	<i>a</i>
III	9.96 ^b	5.70 ^b

^a Not determined. ^b From ref 17 (25 °C, $\mu = 0.5$).

to the fitting of a line to the data points for **II**. The change in A_{260} following increases in concentration of La^{3+} and the best fit of the resultant curve for **II** are shown in Figure 3. The values of A_0 , A_1 , and K_{m1} $\{= [(\text{II})\text{La}^+]/[(\text{II})\text{H}^-][\text{La}^{3+}]\}$ used to create the best fit are included in Table 1. In contrast, no significant increase in absorbance was observed for 8-hydroxy-2-methylquinoline at $[\text{La}^{3+}]$ in the range from 0 to 4.0×10^{-3} M (Figure 3). We assessed the value of K_{m1} as less than 1.0×10^{-6} corresponding to 5% complexation at pH 7.1 and $[\text{La}^{3+}] = 4.0 \times 10^{-3}$ M.

Acid dissociation constants of I and II were determined by potentiometric pH titration and spectrophotometric titration, respectively, at 30 °C ($\mu = 1.0$). The values obtained are reported as pK_a in Table 2. In the case of **I**, two pK_a values attributable to the quinoline nitrogen and phenol group were obtained for each 8-hydroxyquinoline moiety of structure **I**. The more acidic conjugated acid of quinoline nitrogen and phenolic proton would be expected to be present in the quinoline ring attached to the phosphorus atom by a methylene group, since it is reasonable to expect that the electron-withdrawing effect of the $>\text{PO}_2^-$ group is transmitted best to the quinoline ring by the methylene group rather than through the $-\text{OCH}_2-$ group.¹⁶

Hydrolysis of Phosphonates in the Absence of Metal Ions. EDTA (1.0×10^{-3} M) was incorporated into reaction solutions to sequester trace metal ion impurities, and the hydrolysis was studied at pH 7.0, 7.5, and 8.0 at 30 °C ($\mu = 1.0$). The concentrations of **I** and **II** remained unchanged for the time periods employed {6 months for **I** and 3 months for **II**}.

Lanthanum Ion Promoted Hydrolysis. Hydrolysis of **I** was followed by HPLC at 30 °C ($\mu = 1.0$) and constant pH in the range of 6.5–7.8 with increasing $[\text{La}^{3+}]$. The rate of the hydrolysis was dramatically increased by the presence of La^{3+} . The reaction produced two compounds, (8-hydroxy-2-quinolyl)-methyl phosphonic acid (**8**) eluted with the retention time of 3 min and (8-hydroxy-2-quinolyl)methanol with an elution time of 4 min. The identity of these products was established by comparison of their retention times with those of authentic samples. The reaction followed pseudo-first-order kinetics for at least 3 half-lives. A plot of the pseudo-first-order rate constants (k_{obsd}) vs $[\text{La}^{3+}]$ at pH 7.4 (Figure 4) may be explained

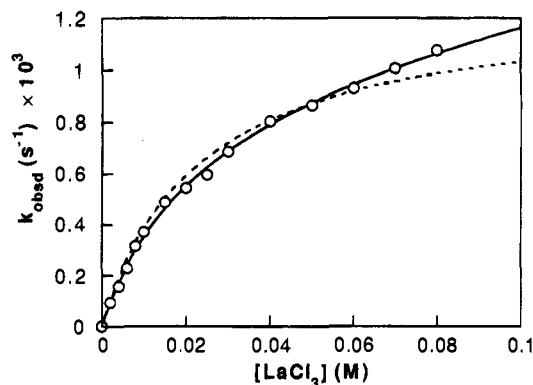
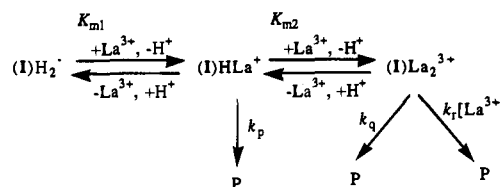


Figure 4. The dependence of the pseudo-first-order rate constant (k_{obsd}) for hydrolysis of **I** on $[\text{La}^{3+}]$ at pH 7.4 and 30 °C ($\mu = 1.0$). Theoretical curves were fit to the data points using eq 12 when (i) $k_r = 0$ (—) and (ii) $k_r \neq 0$ (---). The assumption (ii) provides the better fit.

Scheme 4



$$k_{\text{obsd}} = \frac{k_p a_{\text{H}} K_{m1} [\text{La}^{3+}] + (k_q + k_r [\text{La}^{3+}]) K_{m1} K_{m2} [\text{La}^{3+}]^2}{a_{\text{H}}^2 + a_{\text{H}} K_{m1} [\text{La}^{3+}] + K_{m1} K_{m2} [\text{La}^{3+}]^2} \quad (12)$$

via Scheme 4 from which eq 12 was derived. In fitting the data points of k_{obsd} vs $[\text{La}^{3+}]$ by eq 12 the values of K_{m1} (1.55×10^{-3}) and K_{m2} (2.42×10^{-6}) are those determined from the equilibrium binding studies. Referring to Scheme 4, two different assumptions have been used in the fitting of the experimental points by eq 12: (i) kinetically active species have ester:metal compositions of 1:1 and 1:2, and the hydrolysis of these species does not involve free metal ion (i.e., $k_r = 0$) and (ii) all reaction paths (i.e., k_p , k_q , and k_r) are operative. When k_p was varied in the range from 0 to 1.0×10^{-5} s⁻¹, no significant difference in the calculated values of k_q and k_r was found regardless of the use of assumption of (i) or (ii). Thus, k_p , the specific rate constant for the 1:1 complex is too small to be accurately estimated. Comparison of the two fits to the experimental values (Figure 4) indicates that the only detectable reactions are associated with k_q and k_r . Furthermore, when K_{m2} was allowed to vary in the iterative calculation as a parameter, the fit to the kinetic points became better as the value of K_{m2} approached that determined in the equilibrium study.

The measurement of k_{obsd} as a function of $[\text{La}^{3+}]$ was repeated at several different pH values to establish the pH-rate profile for k_q and k_r {Scheme 4 with $k_p = 0$ }. A plot of $\log k_q$ vs pH is provided in Figure 5(a). The curve which provides the best fit to the experimental data points is constructed by eq 13 employing the values of 1.36×10^{-3} s⁻¹ for k_1 and $6.41 \times$

$$k_q = k_1 K_c / (K_c + a_{\text{H}}) \quad (13)$$

10^{-8} for K_c . On the other hand, k_r increases with a first-order dependence on $[\text{HO}^-]$ in the pH range 7–8, exhibiting a unit slope in the plots of $\log k_r$ vs pH (Figure 5(b)). One explanation for this observation involves hydrolysis of $(\text{I})\text{La}_2^{3+}$ by nucleophilic attack of hydroxide bound to free lanthanum ion.

The rate of the hydrolysis of **II** was also increased by the presence of La^{3+} . The reaction proceeded with release of (8-

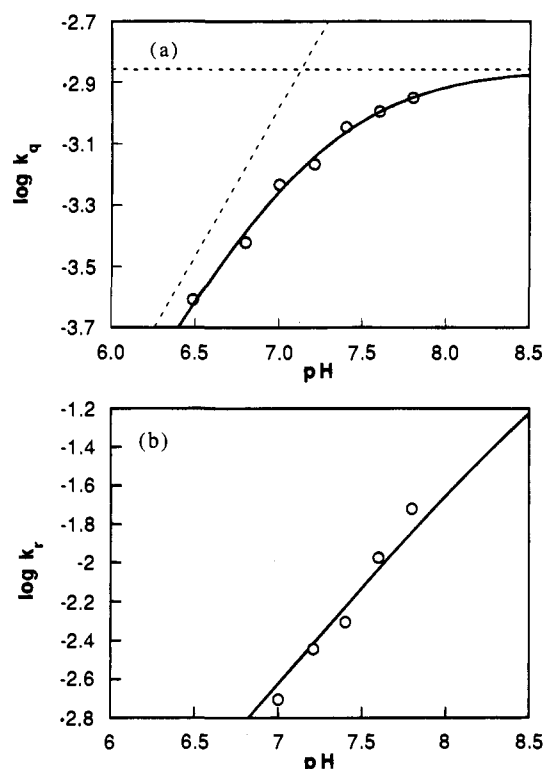


Figure 5. The pH-rate profiles of the rate constant k_q (a, top) and k_r (b, bottom) at 30 °C ($\mu = 1.0$, $k_p = 0$) for hydrolysis of **I**. The theoretical curves of plots a and b (top and bottom) were generated by use of eqs 13 and 19, respectively.

hydroxy-2-quinolyl)methanol, which was identified by its retention time by HPLC analysis. The values of k_{obsd} were measured at constant pH (30 °C and $\mu = 1.0$) between 7.2 and 7.8 as a function of $[\text{La}^{3+}]$ by monitoring the disappearance of **II**. The concentration of La^{3+} was changed in the range from 5.0×10^{-3} to 7.0×10^{-2} M, where **II** was entirely converted to the 1:1 complex. Plots of k_{obsd} vs $[\text{La}^{3+}]$ at each pH show a linear relationship as seen in Figure 6(a). The slopes of the plots represent the pH dependent apparent second-order rate constants (k_s) for hydrolysis of the 1:1 complex catalyzed by a second La^{3+} . The intercepts in these plots are zero, thus indicating that the rate of spontaneous hydrolysis of the 1:1 complex is not detected. In Figure 6(b), values of $\log k_s$ were plotted against the pH values at which they were determined. The slope of this plot is unity so that the composition of the transition state is $\{(\text{II})\text{La}^+\}(\text{La}^{3+})(\text{HO}^-)$ which is kinetically equivalent to $\{(\text{II})\text{La}^+\}(\text{La}^{3+}\text{HO}^-)$. The latter transition state composition would suggest nucleophilic attack of HO^- ligated to La^{3+} upon the 1:1 complex of **II** and La^{3+} .

The influence of the buffer concentration on the rates of La^{3+} promoted hydrolysis of **I** and **II** was examined at pH 7.2 and 7.6 at metal concentrations of 1.0×10^{-2} and 6.0×10^{-2} M. Rates of hydrolysis (k_{obsd}) were constant over the 10-fold change in the buffer (HEPES) concentration.

The effect of other metal ions on the hydrolysis of I and II was also investigated at pH 7.0 and 30 °C ($\mu = 1.0$) for Ce^{3+} (1.0×10^{-2} M), Al^{3+} (1.0×10^{-3} M), Zn^{2+} (3.0×10^{-3} M), Ni^{2+} (1.0×10^{-2} M), Co^{2+} (1.0×10^{-2} M), and Cu^{2+} (3.0×10^{-4} M). With the exception of Ce^{3+} the concentrations of the metal ions were chosen to be high enough to saturate **I** and **II** without any precipitation. At this concentration of Ce^{3+} ester **I** is not saturated. For the hydrolysis of **I**, neither Zn^{2+} , Ni^{2+} , nor Al^{3+} were active, and no hydrolysis products were observed by HPLC after 3 months for Zn^{2+} and Ni^{2+} and 1 month for Al^{3+} . The reaction of **I** with Co^{2+} and Cu^{2+} produced a few

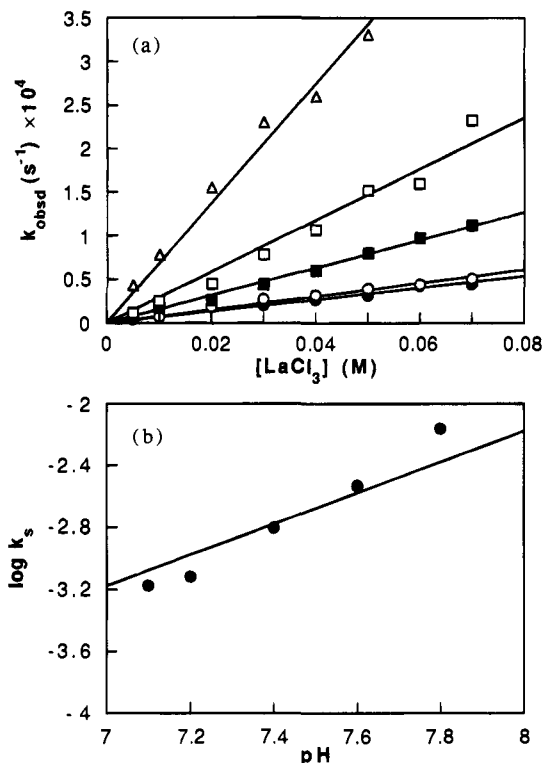


Figure 6. (a) The dependence of the pseudo-first-order rate constant (k_{obsd}) for hydrolysis of **II** on $[\text{La}^{3+}]$ at pH 7.1 (\bullet), pH 7.2 (\circ), pH 7.4 (\blacksquare), pH 7.6 (\square), and pH 7.8 (\triangle) and (b) the plot of the second-order rate constant (k_s) vs pH at 30 °C ($\mu = 1.0$). The lines of plots a (top) and b (bottom) were drawn by use of the equations $k_{\text{obsd}} = k_s[\text{La}^{3+}]$ and $k_s = k_4K_x/a_{\text{H}}$, respectively. When $k_4 = 0.262 \text{ M}^{-1} \text{ s}^{-1}$, the line with slope +1 best fit the data points of plot b.

unidentified products in 3 months. Furthermore, no observable rate enhancement was found for the hydrolysis of **II** in the presence of Zn^{2+} , Ni^{2+} , Co^{2+} , Cu^{2+} , and Al^{3+} . In the presence of Ce^{3+} , however, the hydrolysis of both **I** and **II** proceeded with rate constants, k_{obsd} (**I**, $3.2 \times 10^{-3} \text{ s}^{-1}$; **II**, $1.6 \times 10^{-5} \text{ s}^{-1}$), comparable to those (**I**, $1.2 \times 10^{-3} \text{ s}^{-1}$; **II**, $9.1 \times 10^{-6} \text{ s}^{-1}$) in the presence of La^{3+} under the same conditions (1.0×10^{-2} M) and pH 7.0.

Discussion

The metal binding equilibrium constants (K_{m1} and K_{m2} of Scheme 4) of I and II were determined by spectrophotometric titration with La^{3+} as well as other metal ions (Zn^{2+} , Ni^{2+} , Co^{2+} , Cu^{2+} , and Al^{3+}). One might expect that K_{m1} and K_{m2} are pH-dependent if the spectral species $\{(\text{I})\text{HLa}^+$ and $(\text{I})\text{-La}_2^{3+}\}$ of La^{3+} complexes involve coordinated water which ionizes to provide hydroxo complexes. In the following, however, we will discuss the values of K_{m1} and K_{m2} (Table 1) as being pH-independent. The validity of this treatment is assured by the argument described in the Appendix.

For comparison with other metal–ligand systems, values of K_{m1} and K_{m2} are first converted to the association constant K_{as} as shown in eqs 14, 15, and 16.¹⁸ The values of K_{as} for **II** and **III** were also calculated.¹⁹ The log of the association constants for the metal complexes of **I**, **II**, and **III** are listed in Table 3. An interaction between metal ions and the $>\text{PO}_2^-$ functionality

(16) The difference in the electronic effects of the $>\text{PO}_2^-$ group upon PCH_2^- and POCH_2^- groups is seen in the rate of deuterium exchange reactions of the $-\text{CH}_2-$ protons. In the ^1H NMR spectrum of **I**, the proton signal of former disappeared after a few days at 25 °C and that of latter after a week at 50 °C.

(17) Smith, R. M.; Martell, A. *Critical Stability Constants*; Plenum Press: New York, 1989; Vol. 2.

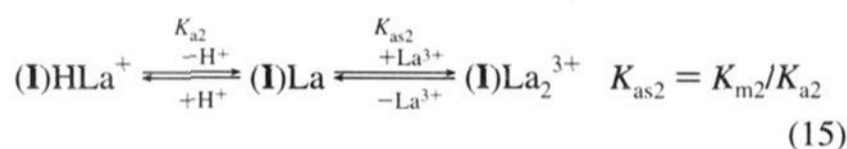
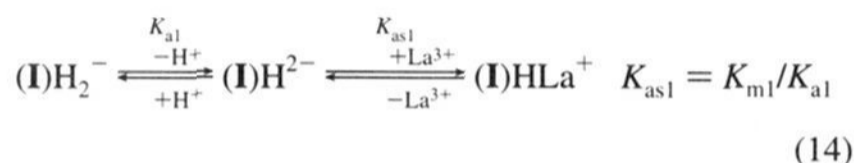
Table 3. Association Constants of Various Metal Ion Complexes of **I**, **II**, and **III** {30 °C, $\mu = 1.0$ }

constant		value		
		I	II	III
$\log K_{as1}$	(La ³⁺)	6.54	5.71	<3.98
$\log K_{as2}$	(La ³⁺)	4.81		
$\log K_{as1}$	(Zn ²⁺)	14.6		9.82 ^a
$\log K_{as1}$	(Ni ²⁺)	15.3		9.41 ^a
$\log K_{as1}$	(Co ²⁺)	13.7		9.63 ^a
$\log K_{as1}$	(Cu ²⁺)	13.5		12.48 ^a
$\log K_{as1}$	(Al ³⁺)	11.4		

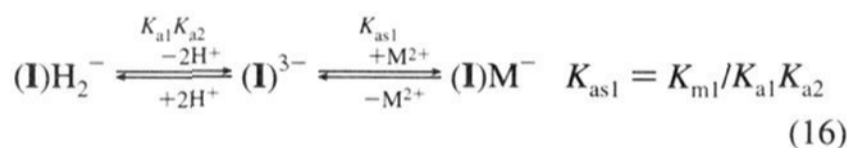
^a From ref 20 at 25 °C (50% dioxane).

in the metal complexes of **I** and **II** would be expected to be reflected in the association constants of the complexes when the K_{as} values were compared with those for **III**. The RO-(PO₂⁻)CH₂- and R(PO₂⁻)OCH₂- substituents at the 2-position

For complexation of **I** with La³⁺

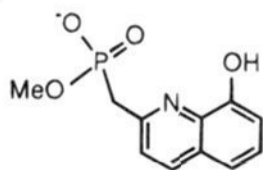


For complexation of **I** with divalent metal ions



of the quinoline rings of **I** and **II** likely provide greater steric hindrance to metal binding than does the methyl group of **III**. In addition, electron-withdrawing by these substituents lowers the pK_a values for **I** and **II** as shown by comparison to the pK_a of **III** (Table 2). Both these steric and electronic effects of the substituents would be expected to make the metal association constants of **I** and **II** smaller than that of **III**. The values of K_{as1} and K_{as2} for **I** with La³⁺ are greater than that of K_{as1} for the 1:1 complex of **III** with La³⁺ by roughly 2 and 1 orders of magnitude, respectively. The K_{as1} for the complex (**II**)La is also 2 orders of magnitude greater than that for (**III**)La. The large values of K_{as} for the La³⁺ complexes of **I** and **II** are,

(18) In the calculation for the complex of **I**, we assumed that ligation of one quinoline ligand to a metal ion causes no change of the pK_a value for the phenolic proton of the unligated 8-hydroxyquinoline moiety. In addition, based on our knowledge that methyl (8-hydroxy-2-quinolyl)methylphosphonate (**IV**) is a better ligand than **II** in coordination to La³⁺, we are allowed to suppose that the first binding site of **I** is the 8-hydroxyquinoline moiety which is linked to the phosphorus atom *via* a methylene group. Log K_{as} {30 °C, $\mu = 1.0$ } of the 1:1 complex of **IV** with La³⁺ is ~6.3 greater than that of the 1:1 complex (**II**)La and close to K_{as1} for the 1:1 complex (**I**)La, unpublished result.



IV

(19) For complexation of **II** with metal ions, $K_{as} = [(\mathbf{II})\text{La}^+]/[(\mathbf{II})^{2-}][\text{La}^{3+}] = K_{m1}/K_a$ { K_a : acid dissociation constant of phenolic proton of **II**} and for complexation of **III**, $K_{as} = [(\mathbf{III})\text{La}^{2+}]/[(\mathbf{III})^-][\text{La}^{3+}] = K_{m1}/K_a$ { K_a : acid dissociation constant of phenolic proton of **III**}.

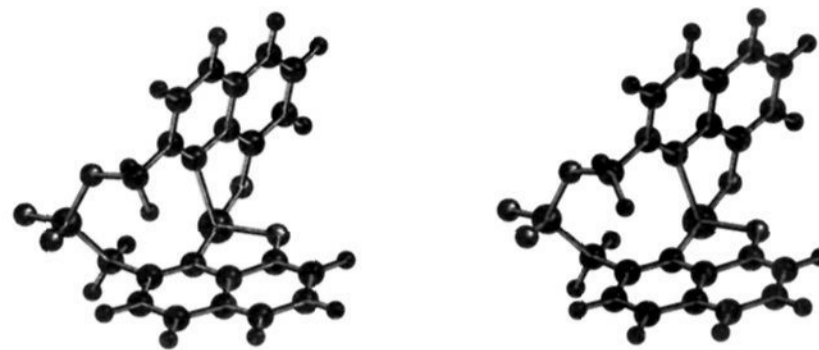


Figure 7. Stereoview of an illustrative drawing for a possible structure of the 1:1 complex of **I** with divalent metal ions and Al³⁺. In this structure the phosphonate oxygen is in the opposite side to the central atom, which is sequestered by two 8-hydroxyquinoline ligands.

therefore, attributable to an association of La³⁺ to the negative charge of the phosphonate group in the complexes. Such interaction is a desirable feature for La³⁺ catalysis. Thus, the ligation of the >PO₂⁻ moiety to La³⁺ upon complexation would reduce the negative charge of the oxyanion and increase susceptibility to nucleophilic attack, leading to a rate enhancement for the hydrolysis of **I** and **II**.

Divalent metal ions (Zn²⁺, Ni²⁺, CO²⁺, and Cu²⁺) form 1:1 complexes with **I** in which two 8-hydroxyquinolines of **I** coordinate to a single metal ion. The values of $\log K_{as1}$ for formation of these 1:1 complexes with **I** are 4–5 orders of magnitude larger than K_{as1} values (50% dioxane)²¹ for formation of the (**III**)M (M = divalent metal ions) except for Cu²⁺; the K_{as1} value for (**I**)Cu is one order of magnitude larger than that of (**III**)Cu. This finding is indicative of the participation of both 8-hydroxyquinolines in the complexation of M²⁺ species with **I**. The value of K_{m1} for Cu²⁺ is probably less than one might estimate due to the formation of nonligatable copper hydroxide ($pK_a = \sim 7$)²² at the pH (7.1) employed.

By molecular modeling (Figure 7) we find that two 8-hydroxyquinoline ligands of **I** can be located around a distorted octahedral metal ion within bonding distance; one of them shares two equatorial positions and another equatorial and apical positions. In these complexes the >PO₂⁻ linkage is directed away from the central metal ion which can, therefore, not act as a Lewis-acid catalyst. In addition, ligation of two anionic ligands (phenoxide) to a divalent metal ion neutralizes the positive charge on the metal ions to reduce its Lewis-acid ability. In the case of Al³⁺, saturation occurs at a 2:1 ratio of metal ion to **I**. In contrast to La³⁺, however, the titration curve for Al³⁺ complexation shows no deflection point which differentiates between the formation of 1:1 and 2:1 complexes. The association constant of Al³⁺ to **I** is close to those for divalent metal ion associating with **I** and significantly great in comparison to that for La³⁺. These observations support Al³⁺ forming a 1:1 complex and not a complex with a stoichiometry of 2:1 metal to **I**.

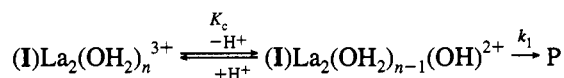
Metal Ion Catalysis of Hydrolysis of Phosphonate Esters.

The ligation of La³⁺ to **I** has a large effect on the rate of the hydrolysis of **I** at pH between 6.5 and 7.8. There are two reaction paths for catalysis of hydrolysis of **I**. One involves hydrolysis (k_q) of the (**I**)La₂ complex and another the La³⁺ catalyzed hydrolysis (k_r) of the (**I**)La₂ complex (Scheme 4). It is known that La³⁺ catalyzes the hydrolysis of activated phosphonate monoesters.²³ On the other hand, there is no influence of divalent metal ions (Zn²⁺, Ni²⁺, Co²⁺, and Cu²⁺) and Al³⁺ on the hydrolysis of **I**. This can be clearly explained by our finding that these metal ions form 1:1 complexes which are hydrolytically inert (*loc. cit.*).

A plot of $\log k_q$ vs pH (Figure 5(a)) is biphasic going from slope +1 to slope 0 with the break at pH ~7. Since the phosphonate **I** has no functional group with pK_a near 7, the

rate constant k_q may be interpreted in terms of intramolecular nucleophilic catalysis by hydroxide which is ligated to an La^{3+} complexed by **I** (Scheme 5). The pH dependence of the rate

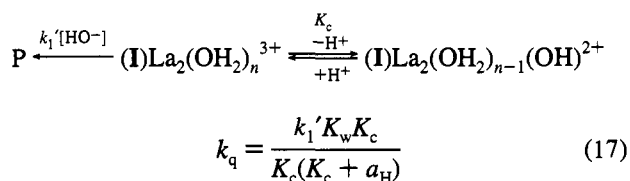
Scheme 5



constant k_q can be described by eq 13 based on this mechanism. The rate constant k_1 is $1.36 \times 10^{-3} \text{ s}^{-1}$ corresponding to a half-life of 8.5 min. The acid dissociation constant K_c for the 1:2 complex was determined as 6.41×10^{-8} [$\text{p}K_c = 7.19$], which is considerably smaller than the $\text{p}K_a$ of H_2O ligated to lanthanum ion ($\text{p}K_a = 9.06$).²⁴ It is difficult, in general terms, to state the relationship between the $\text{p}K_a$ of water coordinated to a metal ion and the $\text{p}K_a$ of this water molecule when the metal is held by various ligating systems. A $\text{p}K_a$ value of 7.4 for La^{3+} complexed H_2O has been reported when the La^{3+} is held by a Schiff base macrocyclic ligand.^{25a} This is close to the $\text{p}K_a$ of $(\text{I})\text{La}_2(\text{OH}_2)_n^{3+}$. Even though the ligand types are different, the sharing of a common value of $\text{p}K_a$ (7.19) allows some insurance of the acceptability of a $\text{p}K_a$ for $(\text{I})\text{La}_2(\text{OH}_2)_n^{3+}$ near neutrality.

A kinetically equivalent process would involve HO^- attack on the species $(\text{I})\text{La}_2(\text{OH}_2)_n^{3+}$ (Scheme 6). From eqs 13 and 17, $k_1 = k_1'K_w/K_c$, and since, at 30 °C, $K_w = 1.47 \times 10^{-14}$, $k_1 = 1.36 \times 10^{-3} \text{ s}^{-1}$, and $K_c = 6.41 \times 10^{-8}$, the value of k_1' (30 °C) would be $5.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. Two considerations disfavor Scheme 6. Comparison of the calculated values of k_1 (Scheme 5) and k_1' (Scheme 6) shows that the effective molarity of the La^{3+} complexed nucleophilic HO^- (Scheme 5) would be equal to 10^{-6} M . There is no apparent reasoning that an intramolecular reaction should be so disfavored. Also, the value of k_1' corresponds to 10^6 times that for the second-order rate constant

Scheme 6



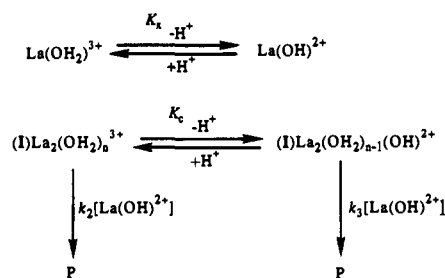
($2.6 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$, 25 °C)²⁶ for HO^- attack upon dibenzyl methylphosphonate. The latter is a neutral ester whose leaving group basicity is similar to that for **I**. If the mechanism of Scheme 6 was in effect, the enhanced sensitivity to HO^- attack would be due solely to the double Lewis-acid activation by the two La^{3+} ions. According to this logic, the double Lewis-acid activation would be lost by ionization of the water ligated to one La^{3+} of the complex. Even though the total charge of the complex reduces to 2+ from 3+ by the ionization, such a drastic change of the activity cannot be rationalized. In fact, it has been observed that such an ionization has no effect on the rate of lanthanum hydroxide $\{\text{La}(\text{OH})^{2+}\}$ catalyzed hydrolysis of the 1:2 complex {see following}. Therefore, the mechanism in Scheme 5 must be favored.

(20) *Stability Constants of Metal-Ion Complexes*; Supplement No. 1; Special Publication 25; Chemical Society London: Alden Press: Oxford, 1971.

(21) The association constants of metal ion complexes of the 8-hydroxyquinoline derivatives in 50% dioxane are usually *ca.* 1 order magnitude larger than those in water (see ref 20). Therefore, enhancement of K_{as} would be 5–6 order magnitude in water medium.

(22) Burgess, J. *Metal Ions in Solution*; Wiley and Sons: New York, 1978.

Scheme 7



$$v = k_t[\text{La}^{3+}][(\text{I})\text{La}_2^{3+}] = \left\{ \frac{K_x}{K_x + a_{\text{H}}} \right\} \left\{ \frac{k_3K_c + k_2a_{\text{H}}}{K_c + a_{\text{H}}} \right\} [\text{La}^{3+}][(\text{I})\text{La}_2^{3+}] \quad (18)$$

$$\text{at pH} < 8, \quad k_t = \frac{K_x \{k_3K_c + k_2a_{\text{H}}\}}{a_{\text{H}} \{K_c + a_{\text{H}}\}} \quad (19)$$

$$\text{where } [(\text{I})\text{La}_2^{3+}] = [(\text{I})\text{La}_2(\text{OH}_2)_n^{3+}] + [(\text{I})\text{La}_2(\text{OH}_2)_{n-1}(\text{OH})^{2+}] \text{ and } [\text{La}^{3+}] = [\text{La}(\text{OH}_2)^{3+}] + [\text{La}(\text{OH})^{2+}]$$

The hydrolysis of the 1:2 complex of **I** with La^{3+} is subject to La^{3+} catalysis $\{k_t(\text{I})\text{La}_2\}[\text{La}^{3+}]$. Rare-earth metal ion catalysis of hydrolysis of phosphonate and phosphate esters in a homogeneous system^{23,25a,27,28} as well as in hydroxide gels^{29,30} is known where there is no metal ion chelating functions in the molecules. In such instances, the metal ion catalysis has been attributed to metal hydroxide $\{\text{M}^{n+}(\text{H}_2\text{O})_m(\text{HO}^-)\}$ acting as a nucleophile. Association of metal ion with phosphonate or phosphate groups brings the nucleophilic hydroxide close to the phosphorus atom. This kind of metal ion catalysis has also been shown for the hydrolysis of 4-nitrophenyl methylphosphonate³¹ with Ca^{2+} and isopropyl methylphosphonofluoridate³² with Mg^{2+} , Cu^{2+} , and Mn^{2+} . The pH-dependent second-order rate constant (k_t) for hydrolysis of $(\text{I})\text{La}_2$ by La^{3+} exhibits a first-order dependence on hydroxide concentration at pH 7.0–7.8 (Figure 5(b)). This pH dependence is in agreement with a mechanism in which $\text{La}(\text{OH})^{2+}$ is an effective nucleophile. Unfortunately we could not, due to lanthanum hydroxide precipitation, extend the kinetic studies to pH value > 8 where k_t would begin to saturate [$\text{p}K_a$ for $\text{La}(\text{OH}_2)^{3+} = 9.06$]. Hence, our experimental data do not exclude the possibility for another mechanism which involves HO^- attack upon a 1:3 complex $(\text{I})\text{La}_3$ $\{k_{\text{HO}^-}[(\text{I})\text{La}_2][\text{La}^{3+}][\text{HO}^-]\}$.

The pH-dependence of the apparent bimolecular rate constant, k_t (pH < 8.0) may be expressed by eq 19 (Scheme 7) in which $\text{La}(\text{OH})^{2+}$ is a nucleophile. The linearity of the plot of $\log k_t$ vs pH (Figure 5(b)) requires that the value of k_2 should be equal to that of k_3 , indicating that the ionization of a water molecule

(23) Withey, R. J. *Can. J. Chem.* **1969**, *47*, 4383.

(24) *Stability Constants of Metal-Ion Complexes*; IUPAC Chemical Data Series No. 22; Part B; Pergamon Press: 1979.

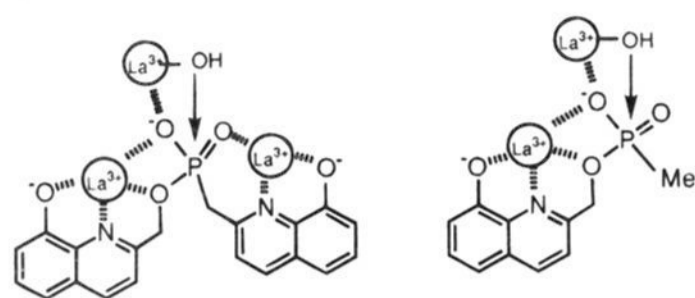
(25) (a) Hay, R. W.; Govan, N. *J. Chem. Soc., Chem. Commun.* **1990**, 714. For some other examples of acidity constants for La^{3+} complexes, see: (b) Ethylene diaminodiacetic acid- La^{3+} ($\text{p}K_a = 9.44$): Chang, C. A.; Garg, B. S.; Manchanda, V. K.; Ochaya, V. O.; Sekhar, V. C. *Inorg. Chem. Acta* **1986**, *115*, 101. (c) Ethylene diaminetetraacetic acid- La^{3+} ($\text{p}K_a = > 11$): Southwood-Jones, R. V.; Merbach, A. E. *Inorg. Chem. Acta* **1978**, *30*, 77. (d) 3,3'-Bis[*N,N*-bis(carboxymethyl)aminomethyl]thymolsulphophthalein- La^{3+} ($\text{p}K_a = 8.60$): Nayan, R. *J. Inorg. Nucl. Chem.* **1980**, *42*, 1743.

(26) Hudson, R. F.; Harper, D. C. *J. Chem. Soc.* **1958**, 1356.

(27) Blewett, F. M.; Watts, P. *J. Chem. Soc. (B)* **1971**, 881.

(28) Sumaoka, J.; Yashiro, M.; Komiya, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1707.

Chart 3



of $(\text{I})\text{La}_2(\text{OH}_2)_n^{3+}$ has no effect on the rate of the reaction of this species with $\text{La}(\text{OH})^{2+}$. By fitting eq 19 to the data points, we obtained the bimolecular rate constant $k_2 (= k_3)$ of $0.262 \text{ M}^{-1} \text{ s}^{-1}$, which corresponds to one-fiftieth of a bimolecular rate constant ($14 \text{ M}^{-1} \text{ s}^{-1}$)³³ for the reaction of $\text{La}(\text{OH})^{2+}$ with 4-nitrophenyl methylphosphonate. The value of k_2 is exceedingly large when considering the difference of 7 $\text{p}K_a$ units in the acidity of leaving groups of **I** and 4-nitrophenol. The notable reactivity of $(\text{I})\text{La}_2(\text{X})_n$ $\{\text{X} = \text{H}_2\text{O} \text{ or } \text{HO}^-\}$ with $\text{La}(\text{OH})^{2+}$ nucleophile must be provided by Lewis-acid catalysis by La^{3+} in the 1:2 complex. Comparing the rate constant (k_2) for this reaction with that (k_1 , Scheme 5) for the intramolecular reaction of $(\text{I})\text{La}_2(\text{OH}_2)_{n-1}(\text{OH})^{2+}$ shows that only a $5 \times 10^{-3} \text{ M}$ concentration of $\text{La}(\text{OH})^{2+}$ is required to give the same first-order-rate as the intramolecular reaction. This small effective molarity suggests that $\text{La}(\text{OH})^{2+}$, catalyzing the hydrolysis of $(\text{I})\text{La}_2(\text{X})_n$, weakly associates with phosphonate anion of the 1:2 complex and behaves as an intramolecular nucleophile. The binding constant of La^{3+} to the phosphonate moiety of $(\text{I})\text{La}_2(\text{X})_n$ is so small that the plot of k_{obsd} vs $[\text{La}^{3+}]$ in Figure 4 did not level-off until $[\text{La}^{3+}] \approx 0.08 \text{ M}$. It is worthy to note that, to the best of our knowledge, the $\text{La}(\text{OH})^{2+}$ catalyzed hydrolysis of the $(\text{I})\text{La}_2(\text{X})_n$ complexes of **I** is the first example of catalysis of hydrolysis involving three metal ions.

The 1:1 complex $(\text{II})\text{La}(\text{X})_n$ $\{\text{X} = \text{H}_2\text{O} \text{ or } \text{HO}^-\}$ also enters into a bimolecular reaction with La^{3+} which leads to catalysis of hydrolysis (eq 20). The first-order dependence (Figure 6(b))



of the rate constant, k_s on $[\text{HO}^-]$ establishes that $(\text{II})\text{La}(\text{X})_n$ like $(\text{I})\text{La}_2(\text{X})_n$ is hydrolyzed by $\text{La}(\text{OH})^{2+}$ (Chart 3). The calculated bimolecular rate constant (k_4 , Figure 5(b)) for reaction of $(\text{II})\text{La}(\text{X})_n$ with $\text{La}(\text{OH})^{2+}$ is $7.61 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$, indicating that the $\text{La}(\text{OH})^{2+}$ reacts with $(\text{I})\text{La}_2(\text{X})_n$ only four times faster than with $(\text{II})\text{La}(\text{X})_n$. Thus, in the reaction of $(\text{I})\text{La}_2(\text{X})_n$ with $\text{La}(\text{OH})^{2+}$, La^{3+} chelated to the leaving 8-hydroxyquinoline is essential for the catalytic process and, presumably, activates the substrate toward the attack of the metal ligated hydroxide by Lewis-acid catalysis. On the other hand, the complex $(\text{I})\text{La}_2(\text{X})_n$ is entirely active for spontaneous hydrolysis, but the complex $(\text{II})\text{La}(\text{X})_n$ is not at all. This observation confirmed that, in the 1:2 complex $(\text{I})\text{La}_2(\text{X})_n$, La^{3+} ligated to nonleaving 8-hydroxyquinoline brings in the nucleophilic hydroxide acting as an intramolecular nucleophile. Consequently, it becomes apparent that the remarkable reactivity of the 1:2 complex $(\text{I})\text{La}_2(\text{X})_2$ results from cooperativity of the two metal ions in catalysis, combination of Lewis-acid and intramolecular nucleophilic catalysis.

(29) Butcher, W. W.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2420.

(30) Bamann, E.; Meisenheimer, M. *Chem. Ber.* **1938**, *71*, 1711, 1980, 2086, 2233.

(31) Behrman, E. J.; Biallas, M. J.; Brass, H. J.; Edwards, J. O.; Isaks, M. *J. Org. Chem.* **1970**, *35*, 3063.

(32) Epstein, J.; Mosher, W. A. *J. Phys. Chem.* **1968**, *72*, 622.

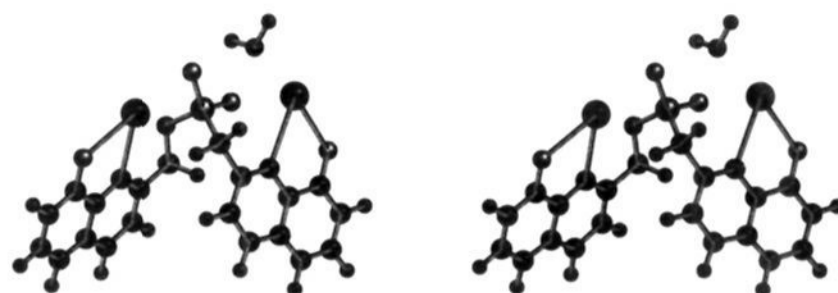
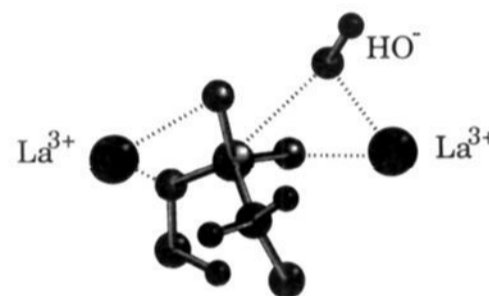


Figure 8. Stereoview of a model of the complex of **I** with two La^{3+} . The structure of the complex was generated on a Silicon Graphics 4D/340GTX workstation with the graphics program QUANTA 4.0 (Molecular Simulations, Waltham, MA) in the following manner. The X-ray structure of the complex of Zn^{2+} with 8-hydroxyquinoline was transferred from the Cambridge structural data base and connected to each end of a QUANTA-generated $-\text{CH}_2\text{O}(\text{PO}_2^-)\text{CH}_2-$ portion. Zn^{2+} was replaced by La^{3+} and the $\text{La}-\text{O}$ and $\text{La}-\text{N}$ bond distances adjusted to 2.55 and 2.67 Å, respectively, which was taken from the X-ray structure of La^{3+} complex with pyridine-2,6-dicarboxylic acid.³⁴ The torsion angles of the $\text{RCH}_2\text{O}(\text{PO}_2^-)\text{CH}_2\text{R}'$ portion were manipulated to give a possible interaction between La^{3+} and negative charge of the phosphonate group and incipient leaving oxygen without appearance of undesirable eclipse conformation. A water molecule was located at the proper distance³⁵ (2.48 Å) for ligation to La^{3+} and oriented close to P.

Chart 4



A stereoview of a model of the complex of **I** with two La^{3+} is provided in Figure 8 (see caption for construction of the model). Inspection of the structure of the complex $(\text{I})\text{La}_2(\text{OH}_2)$ shows that the structural coordinates are ideal for intramolecular double metal ion catalysis of the hydrolysis of the P—O bond. The distances from La^{3+} to ligated water and phosphonate oxygen are ideal for catalysis. Thus, the water oxygen is essentially in line with the leaving group and located 2.76 Å from P. The second La^{3+} is 2.65 Å from the departing oxygen. In addition, the first and second La^{3+} ions are located 2.50 and 2.54 Å, respectively, from the two partially negatively charged $>\text{PO}_2^-$ oxygens.

Based on the result of the modeling as well as the foregoing argument, we may propose a concerted two metal ion mechanism for the spontaneous hydrolysis of the 1:2 complex (Chart 4). In this mechanism, one La^{3+} associates with both the negative charge on $>\text{PO}_2^-$ and the departing incipient oxygen of the leaving group to stabilize a transition state, while the second La^{3+} ligates to the negative charge on the $>\text{PO}_2^-$ moiety and HO^- , which is in alignment for a virtual in-line nucleophilic attack on P.

By use of certain X-ray structural data for the Klenow fragment of a DNA polymerase, Stietz and co-workers³ have proposed a mechanism for 3'-5' exonuclease in which two metal ions (Zn^{2+} and Mg^{2+}) are intimately involved in the catalytic process for phosphate ester hydrolysis (Chart 1). Comparison of Chart 1 and our proposal of mechanism for spontaneous hydrolysis of $(\text{I})\text{La}_2(\text{OH}_2)_{n-1}(\text{OH})$ (Chart 4) establishes their essential identity. The remarkable catalytic power of La^{3+} may be related to its electronegativity, nonrigid stereochemistry of ligation, and the high coordination number over 8. These properties are accounted for by inner orbital shielding of outer electrons, filled d-orbitals, and comparatively

large ionic radius.³⁶ This behavior is in contrast to d-transition metal complexes where the involvement of the d-orbital in the bonding imparts strong directional characteristics and produces the well-defined geometry such as square planar or octahedral. The flexibility of the lanthanum complexes may satisfy the geometrical requirements of ligation of the ground and transition states in catalysis.

One must know the rate constant for hydrolysis of **I** in order to estimate the increase in rate constant for hydrolysis of **I** upon conversion into (I)La₂(OH)₂(OH)_{n-1}(OH)²⁺. Unactivated phosphonate monoesters are relatively unreactive toward nucleophiles such as hydroxide. Indeed, no hydrolysis of **I** can be detected after 6 months at pH 7. An estimation of the rate of hydrolysis of **I** was made in the following manner. A linear relationship between pK_a of the leaving group and the bimolecular rate (k_{HO⁻}, M⁻¹ s⁻¹) of the hydroxide-catalyzed hydrolysis of phosphate diesters, possessing both alkyl and aryl leaving group, is given in eq 21.² This relationship also holds for the HO⁻ catalyzed

$$\log k_{\text{HO}^-} = 0.69 - 0.76 \text{ p}K_a \quad (21)$$

hydrolysis of methylphosphonate monoesters, because k_{HO⁻} for methylphosphonate monoester and phosphate diesters are comparable when the leaving groups are the same.³⁷ The pK_a value of (8-hydroxy-2-quinolyl)methanol is not readily determined. The pK_a of benzyl alcohol is 15.48,³⁸ and a consideration of the difference in electronic effect between phenyl and 8-hydroxyquinoline leads to an approximation of a pK_a of 14.5 for (8-hydroxy-2-quinolyl)methanol.³⁹ The bimolecular rate constant for HO⁻ catalyzed hydrolysis of **I** at 30 °C would be ~5.0 × 10⁻¹¹ M⁻¹ s⁻¹ based on eq 21. From this, at pH 8 and 30 °C, the pseudo-first-order rate constant of hydrolysis of **I** would be ~5.0 × 10⁻¹⁷ s⁻¹. Since at pH 8, k_q (≈k₁) = 1.36 × 10⁻³ s⁻¹, a rate enhancement of 10¹³ has been observed.

Conclusion

From thermodynamic studies of metal ion complexation and comparison of the kinetics of hydrolysis of **I** and **II** in the presence of metal ions, we conclude the following. The phosphonate ester **I** forms a hydrolytically active 1:2 complex (I)La₂ with La³⁺ but inert 1:1 complexes with Zn²⁺, Ni²⁺, Co²⁺, Cu²⁺, and Al³⁺. The La³⁺ in the (I)La₂ complex serve to (i) facilitate the formation of metal ligated hydroxide as an intramolecular nucleophile; (ii) stabilize the transition state of the hydrolysis by neutralization of the phosphonate negative charge; and (iii) interact with an incipient oxyanion of the leaving alcohol (Chart 4). The two La³⁺ functions operate in concert and provide ~10¹³ rate enhancement. Consequently the 1:2 complex (I)La₂(OH)₂(OH)_{n-1}(OH) may serve as a model for the 3'-5' exonuclease reaction of *E. coli* DNA polymerase I, and our result offers a chemical reality for the proposed two metal ion mechanism of this enzyme.

(33) This value was calculated based on the data in the literature (ref 23) using the pK_a value of 9.06 for H₂O ligated La³⁺.

(34) Guerriero, P.; Casellato, U.; Siran, S.; Vigato, P. A.; Graziani, R. *Inorg. Chem. Acta* **1987**, *133*, 337.

(35) Glaser, J.; Johansson, G. *Acta Chem. Scand., Ser. A* **1981**, *35*, 639.

(36) Sinha, S. P. *Structure and Bonding*; Springer-Verlag: New York, 1989; Vol. 25, p 69.

(37) This can be appreciated by comparison of experimental (30 °C)³¹ and computed {by eq 21} values of k_{HO⁻} for hydrolysis of methylphosphonate monoesters: phenyl methylphosphonate, 5.6 × 10⁻⁷ M⁻¹ s⁻¹ vs 1.8 × 10⁻⁷ M⁻¹ s⁻¹; 4-nitrophenyl methylphosphonate, 5.0 × 10⁻⁵ M⁻¹ s⁻¹ vs 1.8 × 10⁻⁵ M⁻¹ s⁻¹.

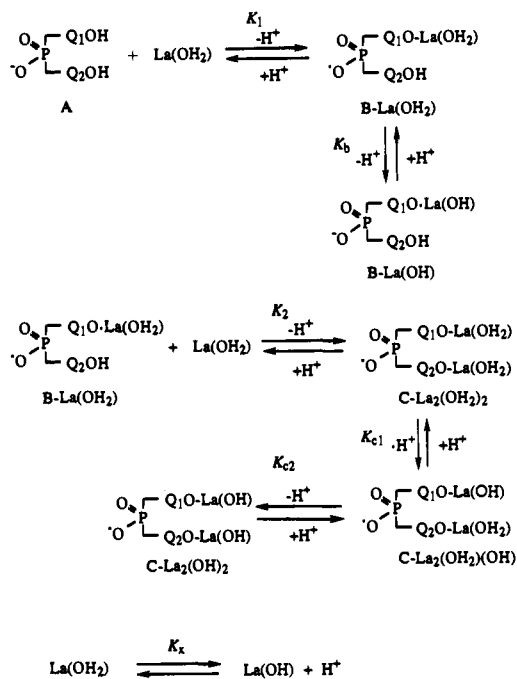
(38) Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205.

(39) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.

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Appendix

The following equilibria include the formation of hydroxo complexes. Charges of each complex and lanthanum ion are omitted for clarity and HOQ₁-PO₂⁻-Q₂OH symbolizes **I**, etc.



Assuming that ionization of a water molecule ligated to La³⁺ in a particular complex does not alter the UV/vis spectrum of the complex, we may define three spectral species: a {=(I)H₂⁻} = A; b {=(I)HL_a⁺} = B-La(OH)₂ + B-La(OH); C {=(I)-La₂³⁺} = C-La₂(OH)₂ + C-La₂(OH)₂(OH) + C-La₂(OH)₂. Considering that [La³⁺] (total lanthanum ion concentration) is greater than total ester concentration [(I)_T] {=[a] + [b] + [c]}, the concentrations of each species are given by eqs A-1, A-2, and A-3, respectively. Titration was carried out spectrophotometrically at constant pH by observing the conversion of a to b to c. Defining K_{m1} = [b]a_H/[a][La³⁺]; K_{m2} = [c]a_H/[b][La³⁺],

$$[\text{a}] \{=[(\text{I})\text{H}_2^-\}\} = \frac{a_{\text{H}}^2}{P} [(\text{I})_{\text{T}}] \quad (\text{A-1})$$

$$[\text{b}] \{=[(\text{I})\text{HL}_a^+\}\} = \frac{a_{\text{H}} K_1 \frac{a_{\text{H}}}{K_x + a_{\text{H}}} [\text{La}^{3+}] \left(1 + \frac{K_b}{a_{\text{H}}}\right)}{P} [(\text{I})_{\text{T}}] \quad (\text{A-2})$$

$$[\text{c}] \{=[(\text{I})\text{La}_2^{3+}\}\} = \frac{K_1 K_2 [\text{La}^{3+}]^2 \left(\frac{a_{\text{H}}}{K_x + a_{\text{H}}}\right)^2 \left(1 + \frac{K_{c1}}{a_{\text{H}}} + \frac{K_{c1} K_{c2}}{a_{\text{H}}^2}\right)}{P} [(\text{I})_{\text{T}}] \quad (\text{A-3})$$

$$P = a_{\text{H}}^2 + a_{\text{H}} K_1 \frac{a_{\text{H}}}{K_x + a_{\text{H}}} [\text{La}^{3+}] \left(1 + \frac{K_b}{a_{\text{H}}}\right) + K_1 K_2 [\text{La}^{3+}]^2 \left(\frac{a_{\text{H}}}{K_x + a_{\text{H}}}\right)^2 \left(1 + \frac{K_{c1}}{a_{\text{H}}} + \frac{K_{c1} K_{c2}}{a_{\text{H}}^2}\right)$$

metrically at constant pH by observing the conversion of a to b to c. Defining K_{m1} = [b]a_H/[a][La³⁺]; K_{m2} = [c]a_H/[b][La³⁺],

then the pH-dependent association constants, K_{m1} and K_{m2} , are provided by eqs A-4 and A-5, respectively. In the pH range

$$K_{m1} = K_1 \frac{a_H}{K_x + a_H} \left(1 + \frac{K_b}{a_H} \right) \quad (\text{A-4})$$

$$K_{m2} = \frac{K_2 \left(\frac{a_H}{K_x + a_H} \right) \left(1 + \frac{K_{c1}}{a_H} + \frac{K_{c1}K_{c2}}{a_H^2} \right)}{1 + \frac{K_b}{a_H}} \quad (\text{A-5})$$

between 7 and 8, $a_H/(K_x + a_H)$ is nearly equal to 1 since $K_x = 10^{-9.06}$, therefore eqs A-4 and A-5 can be reduced to eqs A-6 and A-7, respectively. The spectrophotometrically determined K_{m2} values of **I** are identical at several pH between 7 and 8. According to eq A-7, the values of K_{m2} become pH-independent

$$K_{m1} = K_1 \left(1 + \frac{K_b}{a_H} \right) \quad (\text{A-6})$$

$$K_{m2} = \frac{K_2 \left(1 + \frac{K_{c1}}{a_H} \left(1 + \frac{K_{c2}}{a_H} \right) \right)}{1 + \frac{K_b}{a_H}} \quad (\text{A-7})$$

at pH below 8 when $K_b = K_{c1}$ and $K_{c2} \ll 10^{-8}$. In this instance, K_{m2} is equal to K_2 . On the other hand, the values of K_{m1} of **I** were obtained at only pH 7.1 and 7.2 so that their pH-dependence was not quantified. The value of K_{m1} at pH 7 is only *ca.* two times that of K_1 because $K_b (=K_{c1})$ would be $\sim 10^{-7}$ {kinetically determined K_{c1} is $10^{-7.19}$ } so that the term $(1 + K_b/a_H)$ in eq A-6 at pH 7 is *ca.* 2. Therefore, we are allowed to discuss the K_{m1} and K_{m2} values as K_1 and K_2 , respectively. The errors in these association constants do not exceed one order of magnitude. The same logic is applied for complexation of **II**.

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