A Tris(Zn^{II}−1,4,7,10-tetraazacyclododecane) Complex as a New Receptor for Phosphate Dianions in Aqueous Solution

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Abstract: A new tris(Zn^{II}−cyclen) (Zn$_3$L^3), which has three Zn^{II}−macrocyclic tetraamine (cyclen) complexes connected through a 1,3,5-trimethylbenzene spacer, has been synthesized as a novel receptor for organic phosphate dianions in aqueous solution (cyclen = 1,4,7,10-tetraazacyclododecane and L^3 = 1,3,5-tris(1,4,7,10-tetraaza-cyclododecan-1-ylmethyl)benzene). The design of Zn$_3$L^3 was based on X-ray crystal structure analysis of the 1:3 complex of 4-nitrophenyl phosphate (NPP^{2-}) with Zn^{II}−cyclen (ZnL^1) complex. The potentiometric pH titration of Zn$_3$L^3·3H$_2$O revealed the deprotonation constants of the three Zn^{II}-bound H$_2$O molecules to be 6.1 (pK_1), 7.3 (pK_2), and 8.6 (pK_3) at 25 °C with I = 0.1 (NaNO$_3$). These three stepwise deprotonations and ^{1}H NMR spectra changes at various pD values in D$_2$O suggest that strong intramolecular hydrogen bonds link each adjacent Zn^{II}−OH$_2$ (or Zn^{II}−OH$^-$) at neutral pH in aqueous solution. At higher pH (>9), the hydrogen bond network disrupts. The ^{31}P NMR titration of Zn$_3$L^3·3H$_2$O with phenyl phosphate dianion (PP^{2-}) in D$_2$O confirmed the formation of a 1:1 complex (Zn$_3$L^3·PP^{2-}). By potentiometric pH titrations, the 1:1 complex affinity constants, log K_{aff} (K_{aff} = [phosphate complex]/[Zn^{II} complex][phosphate] (M^{-1})), were determined to be 5.8 with NPP^{2-}, 6.6 with PP^{2-}, 7.0 with α-D-glucose-1-phosphate, and 7.9 with phenyl phosphonate in aqueous solution. The tris(Zn^{II}−cyclen) complex is found to be a much better host toward phosphates than the parent Zn^{II}−cyclen (ZnL^1) (log K_{aff} = 3.3 for ZnL^1−NPP^{2-}) or a bis(Zn^{II}−cyclen) linked with a *m*-xylene spacer (Zn$_2$L^2) (log K_{aff} = 4.0 for Zn$_2$L^2−NPP^{2-}).

Introduction

Chemical design of efficient and selective host molecules for various biologically important types of phosphate anion guests has been attracting great interest. The majority of recently synthesized hosts are organic molecules equipped with acidic hydrogens at complementary positions to hydrogen bond with their guest phosphate oxyanions. The 1:1 affinity constants (K_{aff} = [phosphate complex]/[host][phosphate] (M^{-1})) are sometimes as high as 10^2-10^6 M^{-1} in *nonaqueous solutions* such as CHCl$_3$, CH$_3$CN, and DMSO.[1] These hydrogen bonds, however, cannot compete against the hydration of phosphate guests in water, resulting in the dissociation of the host−guest complexes. To date there have been only a limited number of phosphate receptors that work in the hostile environment of *an aqueous* system.[2−14] Representative examples are (i) multiprotonated or polycationic compounds such as polyamines[3−6] (e.g., log K_{aff} = 6.4 for **1**−ATP^{4-} complex[3a]), (ii) polyquarterny ammonium cations[7] (e.g., log K_{aff} = 2.1 for **2**−HPO$_4$$^{2-}$ complex), and

(iii) polyguanidinium cations[8,9] (e.g., log K_{aff} = 2.4 for **3**−PO$_4$$^{3-}$ complex[8]), or (iv) sapphyrins[10] (e.g., **4** with double-strand DNA). The attractive forces are essentially coulombic forces and strong hydrogen bonding between polycations of protonated (at neutral pH) amines and phosphate oxyanions.

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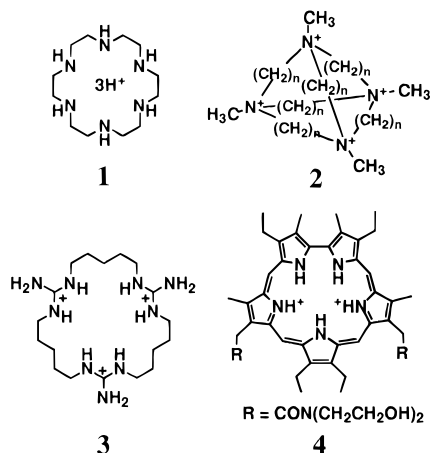
These 1:1 complexes are stable at neutral pH with appreciably high affinity constants.

1   **2**

3   **4**

R = CON(CH$_2$CH$_2$OH)$_2$

L^1 ZnL^1
cyclen   Zn^{II}–cyclen

5a: X = H$_2$O
b: X = OH$^-$

6

L^2
m-bis(cyclen)

7a: X=X'= H$_2$O
b: X= OH$^-$, X'= H$_2$O
c: X=X'= OH$^-$

Zn$_2$L^2
m-bis(Zn^{II}–cyclen)

Recently, Zn^{II}−macrocyclic polyamine complexes have emerged as a novel family of host molecules.[15] They were originally conceived from the fact that phosphates act as substrates (e.g., phosphomonoesters^{2-}) or inhibitors (e.g., HPO$_4{}^{2-}$) by reversibly coordinating to Zn^{II} in zinc enzymes.[16] The zinc(II) complexes of [12]aneN$_3$ ([12]aneN$_3$ = 1,5,9-triazacyclododecane)[17] and cyclen (cyclen = L^1 = 1,4,7,10-tetraazacyclododecane, ZnL^1 = **5**),[18] which were discovered to be good models for zinc enzymes such as carbonic anhydrase and alkaline phosphatase, reversibly bind phosphate dianions such as HPO$_4{}^{2-}$, phenyl phosphate (PP^{2-}), and 4-nitrophenyl phosphate (NPP^{2-}) to yield stable 1:1 complexes with affinity constants of log K_{aff} = 3.3 for **5**−NPP^{2-} complex.[18] However, metal-free cyclen (similarly dicationic species (L^1·2H$^+$) at neutral pH) had little interaction with these phosphate dianions. The recent X-ray crystal structure analysis of (Zn^{II}−alcohol-pendant-cyclen)$_3$−PO$_4{}^{3-}$ complex **6** showed that three phosphate oxygens could coordinate to each Zn^{II} as the apical donors to form a C_3-symmetric complex.[18] Moreover, a bis(Zn^{II}−cyclen) complex linked with a *m*-xylene spacer (**7**, Zn$_2$L^2) was found to bind with two oxyanions of NPP^{2-} with log K_{aff} = 4.0.[19] In all of these interactions, the P−O$^-$ moiety becomes a monodentate donor. A phosphate anion also acts as a monodentate
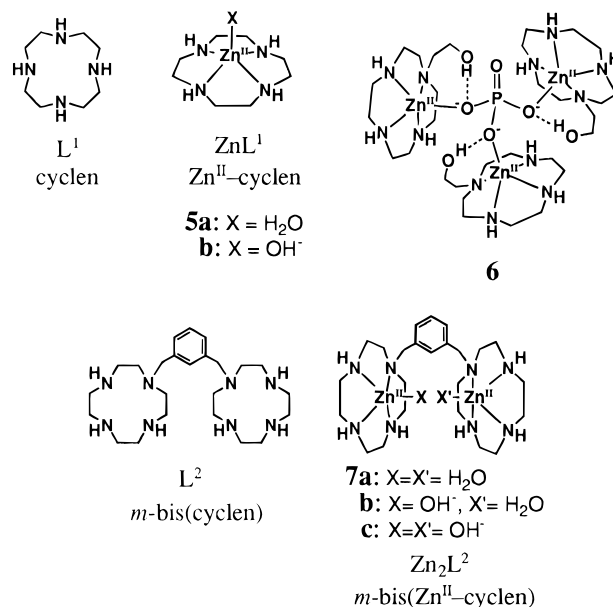
ligand to zinc(II) ions in carboxypeptidase A,[20] alkaline phosphatase,[21,22] and phospholipase C.[23] It must be noted that phosphate anions and hydroxyl anions compete for Zn^{II}, and hence, the solution pH critically affects the affinity of phosphate for Zn^{II}.[21] This would be particularly true when these anions interact with more than two zinc(II) ions, since these anions are potentially bidentate donors.

Trinuclear zinc(II) complexes are found at active sites in zinc enzymes[16] such as phospholipase C from *Bacillus cereus* (PLC$_{Bc}$)[23] (**8** in Scheme 1) and P1 nuclease.[24] An X-ray crystal structure of the complex **9** of PLC$_{Bc}$ with a competitive inhibitor (a phospholipid analog) revealed that the phosphate binds to all three zinc(II) ions by replacing two of zinc-bound water molecules in the native PLC$_{Bc}$.[23c,d]

Scheme 1

8   **9**
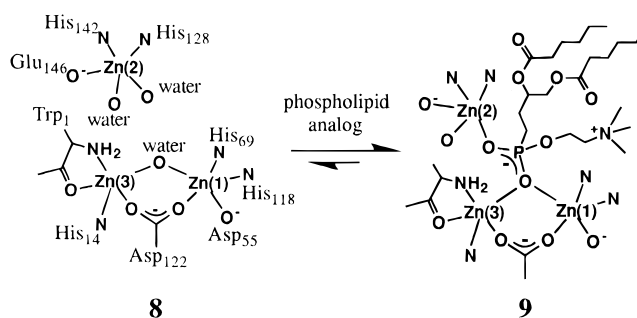
Since three coordination sites for water molecules (H$_2$O and/or OH$^-$) are present in the active site of PLC$_{Bc}$, the interaction with a phospholipid anion is seen to vary with pH, resulting in

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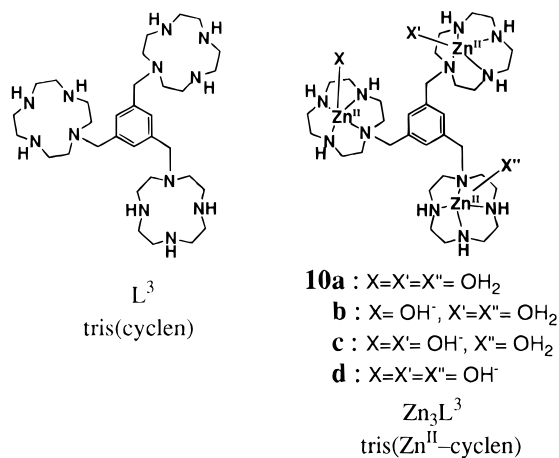
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pH-dependent enzyme activity. However, no systematic study on the cooperative phosphate recognition by three zinc(II) ions had been conducted in model systems. In this paper, we describe the synthesis of the novel trinuclear zinc(II) complex, tris(Zn^{II}−cyclen) (**10**, Zn$_3$L^3), having a 1,3,5-trimethylbenzene spacer (L^3 = 1,3,5-tris(1,4,7,10-tetraazacyclododecan-1-ylm-ethyl)benzene), and interesting new properties toward phosphates, which are dependent on pH in aqueous solution.

L^3
tris(cyclen)

10a : X=X'=X"= OH$_2$
b : X= OH$^-$, X'=X"= OH$_2$
c : X=X'= OH$^-$, X"= OH$_2$
d : X=X'=X"= OH$^-$

Zn$_3$L^3
tris(Zn^{II}−cyclen)

Results and Discussion

Isolation and X-ray Crystal Structure of a 1:3 Complex of 4-Nitrophenyl Phosphate (NPP^{2-}) with Three (Zn^{II}−cyclen) Complexes (11). Prior to developing a new phosphate receptor, we have characterized crystals precipitated from the mixture of 4-nitrophenyl phosphate (NPP^{2-}) and Zn^{II}−cyclen (ZnL^1). Colorless prisms were obtained by slow concentration under reduced pressure. The ^{1}H NMR data and elemental analysis (C, H, N) suggested that the complex was composed of one NPP^{2-} and three ZnL^1 units. The X-ray crystal structure analysis has revealed the structure of the trimeric complex **11** as shown in Figure 1, where each zinc(II) ions is bound to each phosphate oxygen (O48, O49, and O50).[25]

11
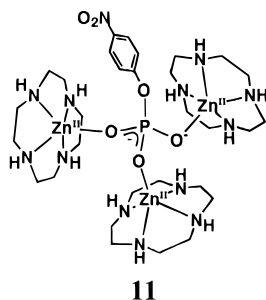
The three bond lengths between Zn^{II} and oxygen atom of NPP^{2-} in **11** are almost equivalent (1.92−1.94 Å) and are almost the same as those (ca. 1.92 Å) of the previous trimeric complex **6**.[18] Each Zn^{II} is in a distorted tetragonal-pyramidal environment constituted by four nitrogen atoms (N1, N4, N7, and N10) of cyclen and the phosphate oxygen (O48) of NPP^{2-}.

The 1:2 complexes of NPP^{2-} with zinc(II) complexes, in which two zinc(II) ions are linked by a O$^-$−P−O$^-$ bridge, have been isolated by several groups.[26,27] To our knowledge, **11** is

Figure 1. An ORTEP drawing (30% probability ellipsoides) of the 1:3 complex **11** of NPP^{2-} with Zn^{II}−cyclen. All hydrogen atoms, perchlorate anions, and water molecules are omitted for clarity. Selected bond lengths (Å): Zn(1)−O(48) 1.917(4), Zn(2)−O(49) 1.936(4), Zn(3)−O(50) 1.917(4), P(47)−O(46) 1.611(5), P(47)−O(48) 1.496(4), P(47)−O(49) 1.487(4), P(47)−O(50) 1.503(4). Selected bond angles (deg): C(37)−O(46)−P(47) 124.2(4), O(46)−P(47)−O(48) 105.5(2), O(48)−P(47)−O(49) 112.8(2), O(49)−P(47)−O(50) 112.6(3), O(50)−P(47)−O(46) 101.2(2), P(47)−O(48)−Zn(1) 130.8(2), P(47)−O(49)−Zn(2) 128.9(2), P(47)−O(50)−Zn(3) 127.6(2).

the first example of a 1:3 complex of dianionic phosphate with zinc(II) complexes. Three phosphorus−oxygen lengths (P−O(48), P−O(49), and P−O(50)) in NPP^{2-} are almost equivalent (ca. 1.5 Å), indicating that the dianionic charge of the NPP^{2-} is equally distributed over the three oxygen atoms of the phosphate, so that the phosphate dianion makes a C_3-symmetric guest having a 3-fold axis through the P−OAr bond. The examples of a similar C_3-symmetric structure of μ_3-carbonato-bridged trinuclear zinc(II) complexes have been also reported.[28]

Synthesis of Tris(cyclen) (L^3) and Its Trizinc(II) Complex (10). The X-ray crystal structure of the trimeric complex **11** and our previous complex **6**[18] led us to design a trinuclear zinc(II) complex for phosphate anions. Thus, we chose tris-(cyclen) (L^3) and its trizinc(II) complex **10** (Zn$_3$L^3) bearing a 1,3,5-trimethylbenzene spacer.

The Boc (*tert*-butyloxycarbonyl) group has been found to be effective protecting group for the synthesis of some derivatives of cyclic polyamines.[29] Hence, we used 1,4,7-tris(*tert*-butyl-oxycarbonyl)cyclen (**13**, 3Boc-cyclen) as shown in Scheme 2. The reaction of 1,3,5-tris(bromomethyl)benzene (**12**)[30] with 3.5 equiv of **13** in the presence of anhydrous Na$_2$CO$_3$ in CH$_3$CN slowly proceeded at 80 °C to give 9Boc-tris(cyclen) (**14**), which was purified by column chromatography after treating a mixture of **14** and the unreacted **13** with benzyl chloroformate (ZCl) to convert **13** to the less polar compound **15**. The recovered **15** can be converted to **13** by a conventional method (H$_2$, Pd/C) in 80−90%.

(25) For the crystal information files (CIFs) for the X-ray crystal structure analysis of **10**·(NO$_3$$^-$)$_6$·3H$_2$O and **11**·(ClO$_4$$^-$)$_4$·2H$_2$O, see the Supporting Information.

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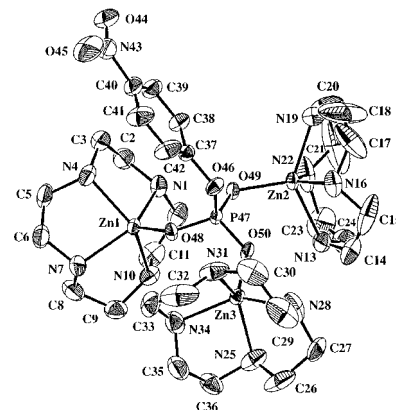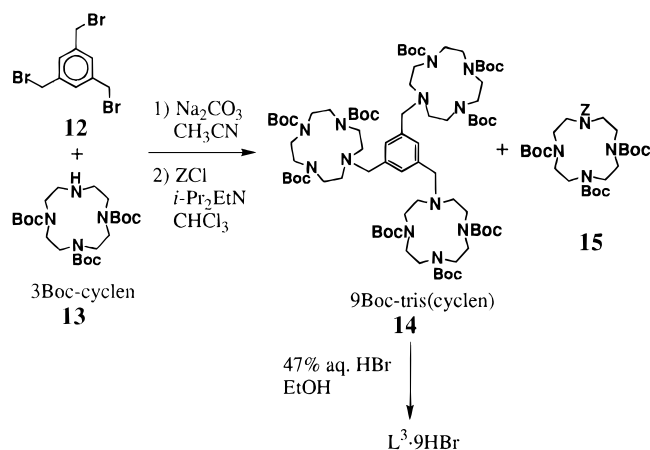
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Scheme 2

Figure 2. An ORTEP drawing (30% probability ellipsoides) of **10**. All hydrogen atoms, four external nitrate anions, and water molecules except a zinc(II)-bound water are omitted for clarity. Selected bond lengths (Å): Zn(1)−O(2a) 2.04(2), Zn(2)−O(6a) 2.00(1), Zn(3)−O(1w) 1.947(9), Zn(1)−N(1) 2.259(8), Zn(1)−N(4) 2.123(10), Zn(1)−N(7) 2.14(1), Zn(1)−N(10) 2.14(1), Zn(2)−N(13) 2.277(9), Zn(2)−N(16) 2.10(1), Zn(2)−N(19) 2.172(10), Zn(2)−N(22) 2.144(10), Zn(3)−N(25) 2.202(8), Zn(3)−N(28) 2.120(9), Zn(3)−N(31) 2.177(10), Zn(3)−N(34) 2.13(1). Selected bond angles (deg): Zn(1)−N(1)−C(37) 110.6(6), Zn(2)−N(13)−C(38) 108.8(8), Zn(3)−N(25)−C(39) 110.1(5), N(1)−Zn(1)−O(2a) 106.1(6), N(4)−Zn(1)−O(2a) 125.8(6), N(7)−Zn(1)−O(2a) 112.9(6), N(10)−Zn(1)−O(2a) 101.0(6).

The L^3·9HBr was obtained by the deprotection of **14** with aqueous HBr in EtOH and was converted to the free form by passing it through an anionic ion exchange resin column. The free ligand L^3 was allowed to react with Zn(NO$_3$)$_2$·6H$_2$O in EtOH/water to afford **10**·6(NO$_3^-$)·3H$_2$O·0.5EtOH as colorless needles after recrystallization from EtOH/water.

X-ray Crystal Structure of 10·6(NO$_3^-$)·3H$_2$O. The crystals of **10**·6(NO$_3^-$)·3H$_2$O were subjected to X-ray crystal structure analysis. An ORTEP drawing of **10**·6(NO$_3^-$)·3H$_2$O is shown in Figure 2 with 30% probability thermal ellipsoids.[25] Each Zn^{II}−cyclen unit has a distorted tetragonal-pyramidal structure, and zinc−nitrogen bond lengths are 2.10−2.28 Å, not unusual distances for Zn^{II}−cyclen complexes.[17,18,31] The apical coordination sites of two among three zinc(II) ions are occupied by two nitrate anions. An interesting feature is that the three Zn^{II}−cyclen moieties are orientated to face the same side of the molecule giving a pseudo-C_3-symmetrical molecule with three apical ligands of each three zinc(II) cations (one water molecule and two nitrate anions) located on the same face.

Determination of pK_a Values of Zinc(II)-Bound Waters of 10. The pK_a values of three zinc(II)-bound waters of **10** were determined by potentiometric pH titration against 0.10 M NaOH aqueous solution with $I = 0.10$ (NaNO$_3$) at 25 °C. Figure 3a shows a typical titration curve of isolated **10** (Zn$_3$L^3·3H$_2$O), showing dissociation of three protons at 0 < eq(OH$^-$) < 3eq(OH$^-$) is the number of equivalents of base added). Any further deprotonation or precipitation of Zn(OH)$_2$ was not observed over pH 11. The crystal structure analysis of **10** showed that two zinc(II) ions have nitrate anions at apical coordination site. Since it has been previously confirmed that nitrate anion has only negligible interaction with zinc(II) ion in aqueous solution,[32] we presume that the nitrate anions in **10** are replaced by water molecules, which reside on three zinc(II) ions of **10** in aqueous solution, and that the three dissociable protons can be assigned to the zinc(II)-bound water molecules. By calculation using the program "BEST"[33] and assuming eqs 1−3 (where a_{H^+} is the activity of H$^+$ and **10a** = Zn$_3$L^3·3H$_2$O, **10b** = Zn$_3$L^3·(OH$^-$)·2H$_2$O, **10c** = Zn$_3$L^3·2(OH$^-$)·H$_2$O, and **10d** = Zn$_3$L^3·3(OH$^-$)), the deprotonation constants of each water

molecules, pK_1, pK_2, and pK_3, were calculated to be 6.08 ± 0.03, 7.25 ± 0.03, and 8.63 ± 0.03, respectively.

$$\textbf{10a} \rightleftharpoons \textbf{10b} + \text{H}^+ \qquad K_1 = [\textbf{10b}]a_{H^+}/[\textbf{10a}] \qquad (1)$$

$$\textbf{10b} \rightleftharpoons \textbf{10c} + \text{H}^+ \qquad K_2 = [\textbf{10c}]a_{H^+}/[\textbf{10b}] \qquad (2)$$

$$\textbf{10c} \rightleftharpoons \textbf{10d} + \text{H}^+ \qquad K_3 = [\textbf{10d}]a_{H^+}/[\textbf{10c}] \qquad (3)$$

For comparison, the relevant pK_a values of zinc(II)-bound water in Zn^{II}−cyclen·H$_2$O (**5a**), Zn^{II}−N-benzylcyclen·H$_2$O (**16**, ZnL^4·H$_2$O),[18] bis(Zn^{II}−cyclen) linked with p-xylene spacer (**17**, Zn$_2$L^5·2H$_2$O),[31] and bis(Zn^{II}−cyclen) linked with m-xylene spacer (**7**, Zn$_2$L^2·2H$_2$O)[19] should be noted. Two reference complexes, **5** and **16**, have higher pK_a values of 7.9 (for **5a** $\rightleftharpoons$ **5b** + H$^+$) and 7.6, respectively.[17,18] The p-bis(Zn^{II}−cyclen)

16
ZnL^4
Zn^{II}−N-benzylcyclen

17
Zn$_2$L^5
p-bis(Zn^{II}−cyclen)
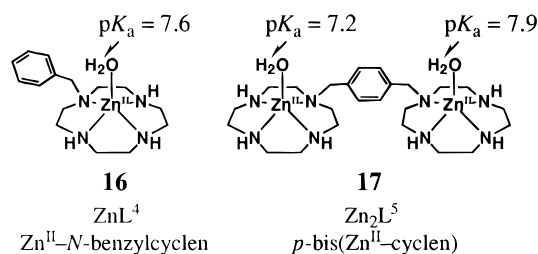
17 has two close values of 7.2 and 7.9.[31] On the other hand, the m-bis(Zn^{II}−cyclen) **7** has two more separate values: one is 6.7 (for **7a** $\rightleftharpoons$ **7b** + H$^+$) and the other is 8.5 (**7b** $\rightleftharpoons$ **7c** + H$^+$).[19] The reason of the lower pK_1 value and the higher pK_2 value with respect to pK_a of monomeric Zn^{II}−cyclen may be explained by strong intramolecular hydrogen bonding between the Zn^{II}−OH$^-$ and Zn^{II}−OH$_2$. In fact, **7b** was isolated as a stable crystalline 3(ClO$_4^-$) salt. Very recently, a similar type of L−Zn^{II}−OH$_2$···HO$^-$−Zn^{II}−L complex (L = a tris(pyrazoyl)-borate homologue) was isolated for X-ray crystal study and discussed in relevance to the hydrogen bond network at the active center of carbonic anhydrase.[34] These discussions should also be applicable for tris(Zn^{II}−cyclen) **10** (*vide infra*).

(31) Koike, T.; Takashige, M.; Kimura, E.; Fujioka, H.; Shiro, M. *Chem. Eur. J.* **1996**, *2*, 617−623.

(32) The pK_a value of zinc(II)-bound water in **5** with $I = 0.1$ (NaNO$_3$) at 25 °C has been found to be the same as that with $I = 0.1$ (NaClO$_4$) at 25 °C, indicating that nitrate anion has negligible interaction with Zn^{II}−cyclen.

(33) Martell, A. E.; Motekaitis, R. J. *Determination and Use of Stability Constants,* 2nd ed.; VCH: New York, 1992.
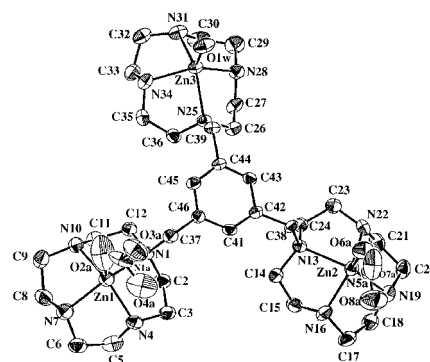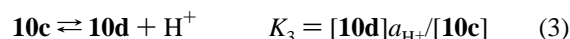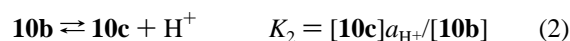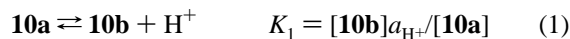
(34) Ruf, M.; Weis, K.; Vahrenkamp, H. *J. Am. Chem. Soc.* **1996**, *118*, 9288−9294.
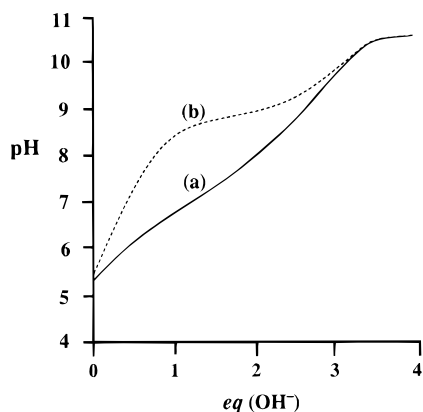
Figure 3. Typical titration curves of 1 mM **10** (a) in the absence and (b) in the presence of 1 mM phenyl phosphate disodium salt in water at 25 °C with $I = 0.10$ (NaNO$_3$), where eq(OH$^-$) is the number of equivalents of base added.
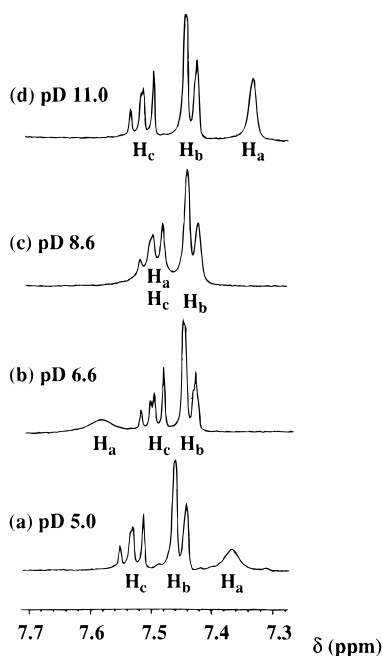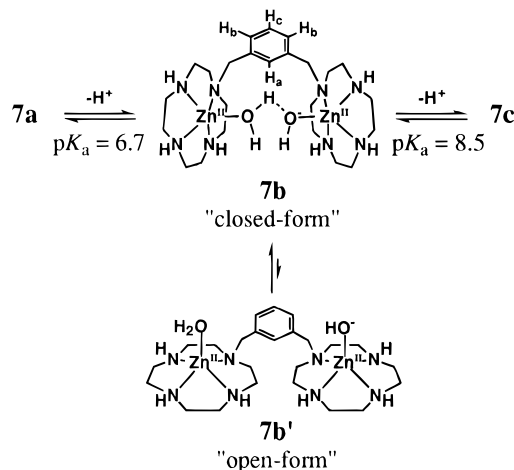

Figure 4. Aromatic regions of ^{1}H NMR spectra of *m*-bis(Zn^{II}−cyclen) **7** (5 mM) at different pD values at 35 °C. For the assignment of each peak, see text.

^{1}H NMR Behaviors of Zn^{II}−*N*-benzylcyclen (16), *m*-Bis-(Zn^{II}−cyclen) (7), and Tris(Zn^{II}−cyclen) (10) in Aqueous Solution at Various pD Values. It was expected that the pH-dependent conformational change of *m*-bis(Zn^{II}−cyclen) **(7)** and tris(Zn^{II}−cyclen) **(10)**, which we assumed in the previous section, should cause pH(pD)-dependent changes on ^{1}H NMR spectra in D$_2$O solution. Hence, the ^{1}H NMR spectra of monomeric **16**, dimeric **7**, and trimeric **10** (all at 5 mM) at various pD values in D$_2$O were taken at 35 °C.

The chemical shifts of the aromatic ring protons of monomeric **16** did not change with pD (=5.9, 7.7, and 11.0), indicating that little conformational change was induced by deprotonation of the zinc(II)-bound water. In comparison, the ^{1}H NMR spectra of the dimeric complex **7**[35] dramatically changed as shown in Figure 4, illustrating the aromatic protons (H$_a$, H$_b$, and H$_c$ of **7**, see Scheme 3) at pD (a) 5.0, (b) 6.6, (c) 8.6, and (d) 11.0. While H$_b$ and H$_c$ did show little change, the broad peak of H$_a$ exhibited a downfield shift from δ 7.37 at pD 5.0 to δ 7.59 at pD 6.6 with broadening and became overlapped

Scheme 3

7b
"closed-form"

7b'
"open-form"

by two other peaks at pD 8.6. When more base was added, the H$_a$ peak showed an upfield shift back to δ 7.34 with sharpening at pD 11.0.

An explanation of this behavior is presented graphically in Scheme 3. It is assumed that **7a** predominantly takes an "open-form" (as in **7b'**) at low pD (<5), since both of the zinc(II)-bound waters are not deprotonated and have negligible interaction toward each other. Upon deprotonation of one of the zinc(II)-bound waters, **7b** favors a "closed-form" in which intramolecular hydrogen bonding between the zinc(II)-bound water and the zinc(II)-bound hydroxide bridges the two Zn^{II}−cyclen moieties.[36,37] The downfield shift of H$_a$ peak is probably induced by the shielding effect of zinc(II) ions fixed close to H$_a$. The second deprotonation generates **7c**, which takes an "open-form" as in **7a**. A repulsive interaction between the two hydroxide anions may assist the "opening" of the structure. Above pD 11, the two zinc(II)-bound waters in **7** are considered to be completely deprotonated.

The pH-dependent ^{1}H NMR experiment of **10** in D$_2$O at 35 °C has been carried out at pD 4.9, 6.1, 7.4, 8.5, 9.3, and 11.4 (see Figure 5, respectively). The second (6.1), third (7.4), and fourth (8.5) pD values were adjusted to match the three pK_a values of zinc(II)-bound waters in **10** (Zn$_3$L^3·3H$_2$O) at 35 °C.[38] The aromatic protons (all three are equivalent) at pD 4.9 (Figure 5a) exhibit a somewhat broad shape at δ 7.42. As pD is increased to 6.1, 7.4, and 8.5, this peak moved downfield with broadening (broadest at pD 8.5 and δ 7.48). Further pD increases caused an upfield shift to δ 7.38 at pD 9.3 and δ 7.37 at pD 11.4 with peak sharpening.

By analogous consideration for the pH-dependent structural change of **7** presented in Scheme 3, we propose two main

(35) In this study, **7** was synthesized via *N*-alkylation of **13** with α,α′-dibromo-*m*-xylene.

(36) An equivalent structure which has two zinc(II) ions bridged by an OH$^-$ anion is not excluded. Very recently, Gutneh et al. has reported that the dinuclear zinc(II) complex having a *m*-xylyl connectivity similar to that of **7** has Zn$-^-$OH$-$Zn bridge structure in the solid state: Gultneh, Y.; Allwar; Ahvazi, B.; Blaise, D.; Butcher, R. J.; Jasinski, J.; Jasinski, J. *Inorg. Chim. Acta* **1996**, *241*, 31−38.

(37) Several crystal structures of "Zn$_2$(μ-OH)$_2$" structures have been reported. (a) Chaudhuri, P.; Stockheim, C.; Wieghardt, K.; Deck, W.; Gregorzik, R.; Vahrenkamp, H.; Nuber, B.; Weiss, J. *Inorg. Chem.* **1992**, *31*, 1451−1457. (b) Alsfasser, R.; Vahrenkamp, H. *Chem. Ber.* **1993**, *126*, 695−701.

(38) The pK_a values of zinc(II)-bound waters of **10** at 35 °C with $I = 0.10$ (NaNO$_3$) were determined to be 6.00 ± 0.03 (pK_1), 7.20 ± 0.03 (pK_2), and 8.47 ± 0.03 (pK_3), respectively, by potentiometric pH titration.

(39) The trimeric structure of [{η_2-H$_2$B(3-Bu^{t}pz)$_2$}Zn(μ-OH)]$_3$ (3-Bu^{t}pz denotes 3-C$_3$N$_2$Bu^{t}H$_2$), which possesses approximately C_3 symmetry with each OH$^-$ group bridging to zinc(II) ions, has been isolated and characterized [Gorrell, I. B.; Looney, A.; Parkin, G.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 4068−4069]. We also reported the trimeric structure of (Zn^{II}−[12]aneN$_3$−OH$^-$)$_3$·3(ClO$_4$$^-$)·HClO$_4$, which was precipitated from pH 8 solution (ref 17a).

Figure 5. The pD-dependent change of aromatic protons in **10** (5 mM) in D$_2$O at 35 °C.
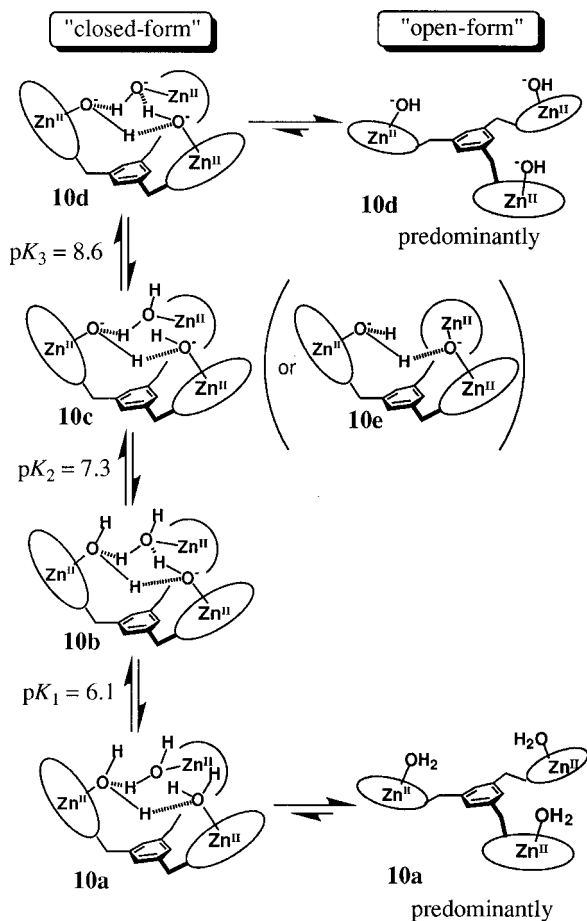

Figure 7. Change in the ^{31}P NMR chemical shift of PP^{2-} (5 mM) with increasing concentration of **10** in D$_2$O (pD 7.1 ± 0.1).

Zn^{II}−OH$_2$ and Zn^{II}−OH$^-$, fixing **10** into a "closed-form" for L^3·[Zn(OH$_2$)]$_2$·[Zn(OH$^-$)] (**10b**) and for L^3·[Zn(OH$_2$)]·[Zn(OH$^-$)]$_2$ (**10c**). The structure of **10c** may be equivalent to L^3·[Zn(OH$_2$)]·[Zn−OH−Zn)] (**10e**), in which two zinc(II) ions are bridged by a hydroxide anion. (iii) Above pH 9 (pK_3 = 8.6), the hydrogen-bonding network starts to collapse due to repulsive intramolecular interactions among all the Zn^{II}−OH$^-$, changing to an "open-form".

We may consider the existence of "half-closed-form" which has two Zn^{II}−cyclen moieties on the upside of the molecule and the other sitting horizontally as shown in **10f**. However, the pK_1 value of 6.1 for the first equilibrium (**10a** ⇌ **10b** + H$^+$) is significantly lower than the corresponding pK_1 (6.7) for **7** (**7a** ⇌ **7b** + H$^+$). We therefore presume that the first

Figure 6. Schematic model of conformational change of **10** dependent on pH in aqueous solution. Round circles in all structures denote cyclen rings in **10**.

deprotonation is promoted by the presence of the other two zinc(II)-bound waters. The CPK model studies of **10** suggest that three zinc(II)-bound water molecules could come close to each other, enough to allow direct hydrogen bonding between three Zn^{II}−$^-$OH (or OH$_2$) and/or Zn^{II}−$^-$OH−Zn^{II} bridging. This cooperative assembly of three Zn^{II}−cyclen units was anticipated to offer a suitable recognition site for C_3-symmetrical guests such as phosphate anions.

Affinity Constants of 1:1 Complex of 10 with Organic Phosphate and Phosphonate Dianions in Aqueous Solutions. To investigate complex formation between **10** and phosphates, we conducted a ^{31}P NMR titration experiment of 5 mM phenyl phosphate dianion (PP^{2-}) (pK_4 = 5.9 = −log[PP^{2-}]a_{H^+}/[HPP$^-$], where HPP$^-$ is phenyl hydrogen phosphate, see eq 4) with varying concentrations (0−10 mM) of **10** in D$_2$O at pD 7.1 ± 0.1 and 35 °C (Figure 7). Under these conditions, the

$$\text{HPP}^- \rightleftharpoons \text{PP}^{2-} + \text{H}^+ \qquad K_4 = [\text{PP}^{2-}]a_{H^+}/[\text{HPP}^-] \quad (4)$$

phosphorus chemical shift of PP^{2-} moved from δ ca. 0 to δ −1.3 during the addition of 1 equiv of **10**. No further change in chemical shift at higher concentration of **10** strongly suggests 1:1 complexation.

For comparison, we obtained the ^{31}P NMR of PP^{2-} in D$_2$O (pD 8.5 ± 0.1) in the presence of zinc(II)-free ligand L^3, which

conformations of **10** as shown in Figure 6. (i) At low pH (ca. 5), **10a** is a major species and its conformation is not fixed by intramolecular interaction between zinc(II)-bound waters. The X-ray crystal structure of **10** (Figure 2) obtained from pH 5 solution may suggest that an "open-form" predominates over a "closed-form". (ii) As pH is raised to 6−8 (pK_1 = 6.1 and pK_2 = 7.3), deprotonation of the zinc(II)-bound waters starts to form an intramolecular hydrogen-bonding network between
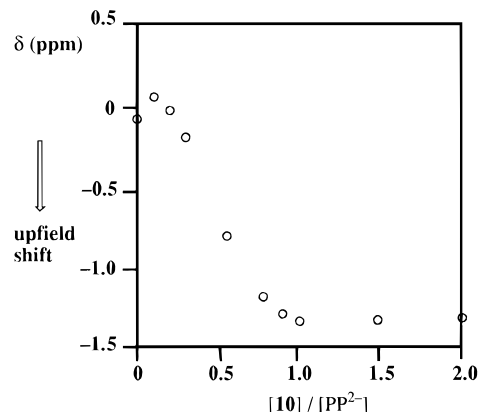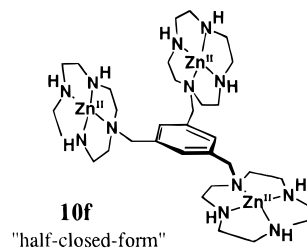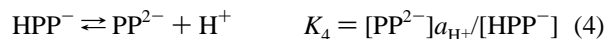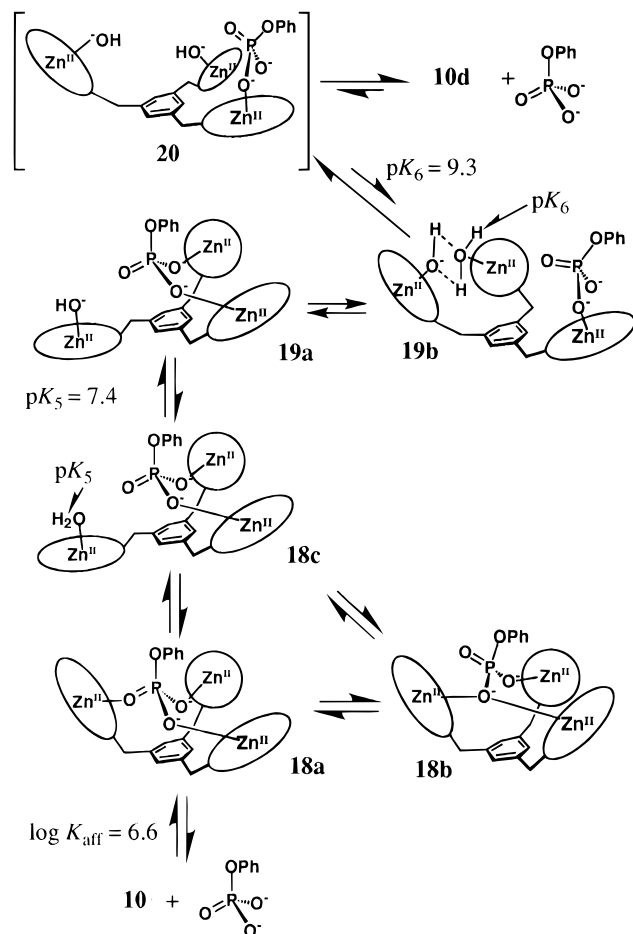
Figure 8. Proposed structural change of the 1:1 complex of **10** and PP²⁻ at various pH. Round circles denote cyclen rings in **10**.

was considered to exist as the tris(cyclen·2H⁺) (L³·6H⁺) at this pH. It was found that L³·6H⁺ induced only a negligible change in the chemical shifts of phosphorus. This fact confirmed that L³·6H⁺ has little interaction with phosphate anions and that the three zinc(II) ions in **10** are necessary for effective recognition of phosphates.

We then conducted a potentiometric pH titration for **10** (1 mM) and PP²⁻ (1 mM) in water ($I = 0.1$ (NaNO₃)) with 0.1 M NaOH at 25 °C to determine the 1:1 affinity constant (see Figure 3b). The phosphate complexes considered (**18**−**20**) are shown in Figure 8. The 1:1 complexation constant log K_{aff} and the deprotonation constants pK_5 and pK_6, defined by eqs 5−7, respectively, were determined to be 6.6, 7.4, and 9.3 by using the program BEST.[33]

$$10 + PP^{2-} \rightleftarrows 18 \qquad K_{aff} = [18]/[10][PP^{2-}] \qquad (5)$$

$$18 \rightleftarrows 19 + H^+ \qquad K_5 = [19]a_{H^+}/[18] \qquad (6)$$

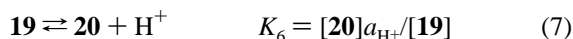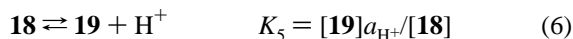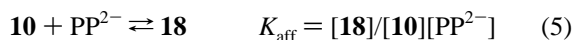$$19 \rightleftarrows 20 + H^+ \qquad K_6 = [20]a_{H^+}/[19] \qquad (7)$$

Figure 9 shows the distribution diagram of five species (**10c**, **10d**, **18** (**18a** and/or **18b** and/or **18c**), **19** (**19a** and/or **19b**), and PP²⁻) for a 5 mM **10**/5 mM PP²⁻ mixture (the same concentration as in the ¹H NMR experiment described above) as a function of pH at 25 °C with $I = 0.10$ (NaNO₃). The population of **10**−PP²⁻ (1:1) complex **18** is over 90% below pH 6.4 (see also Figure 8). As pH is raised, the population of **18** decreases and the population of monohydroxide form **19** increases. The concentration of the monohydroxide form reaches a maximum
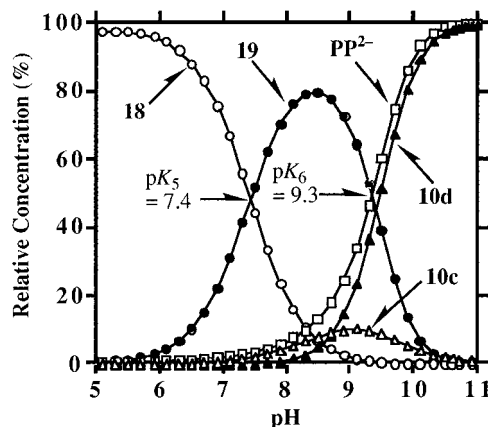

Figure 9. Distribution diagram for the species **18** (**18a** and/or **18b** and/or **18c**), **19** (**19a** and/or **19b**), **10c**, **10d**, and PP²⁻ for a 5 mM **10**/5 mM PP²⁻ mixture as a function of pH at 25 °C with $I = 0.1$ (NaNO₃). The two other species which exist in less than 5% (**10a** and **10b**) are omitted for clarity.

Table 1. Phosphate (Phosphonate) Affinity Constants (log K_{aff}) of *m*-Bis(Zn^II−cyclen) **7** and Tris(Zn^II−cyclen) **10** for NPP²⁻, PP²⁻, **21**, and **22** at 25 °C and $I = 0.10$ (NaNO₃)

phosphate (phosphonate)	(pK_4[b])	log K_{aff}[a]	
		7	**10**
NPP²⁻	(5.2)	4.0[c]	5.8
PP²⁻	(5.8)	4.6	6.6
21	(6.1)		7.0
22	(7.0)		7.9

[a] $K_{aff} = [Zn_2L^2−RPO_3{}^{2-}$ complex]/[Zn_2L^2][$RPO_3{}^{2-}$] (M⁻¹) for **7** or [$Zn_3L^3−RPO_3{}^{2-}$ complex]/[Zn_3L^3][$RPO_3{}^{2-}$] (M⁻¹) for **10**. [b] p$K_4 = -\log$ ([$RPO_3{}^{2-}$]a_{H^+}/[RPO_3H^-]) obtained by pH titration at 25 °C with $I = 0.10$ (NaNO₃). [c] From ref 19 with $I = 0.10$ (NaClO₄).

at pH 8.4. The deprotonation constant pK_5 value of 7.4 for zinc(II)-bound water in **18** is considerably higher than the pK_1 (= 6.1) of **10a** in the absence of phosphate. This is due to the competing phosphate interaction with this zinc(II) site. In the light of the extremely high affinity constant of 1:1 complexation of **10** with PP²⁻ in comparison to that of 1:1 complexation of *m*-bis(Zn^II−cyclen) (**7**) with PP²⁻ (log $K_{aff} = 4.6$), we conclude that **10** acts as a tripodal host. It has been shown that the complex of PLC_{Bc} with an inorganic phosphate has an **18b** type of structure, namely, two of the three zinc(II) ions are bridged by one oxygen of phosphate and the other zinc(II) binds to the second oxygen of phosphate.[23a,b] Hence, the species **18a** and/or **18b** are more favorable structures of **18** and dramatically stabilize the phosphate complex. It is also implied in Figure 9 that the second deprotonation of zinc(II)-bound water in **19b** occurs with a pK_a of 9.3 to afford **20** which dissociates to phosphate and **10d**. In conclusion, tris(Zn^II−cyclen) efficiently recognizes PP²⁻ in slightly acidic solution and the complex dissociates at higher pH.
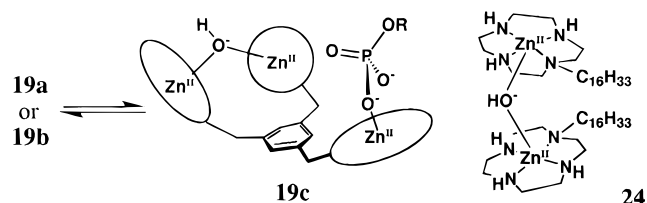
The 1:1 complexation constants with other phosphates such as 4-nitrophenyl phosphate (NPP²⁻), α-D-glucose-1-phosphate **21**, and phenyl phosphonate **22** were similarly determined under the same conditions as above and summarized in Table 1. For complexation with NPP²⁻, the trimeric effect of **10** is about 300 times greater as compared to that of monomeric Zn^II−cyclen (**5**) and 60 times greater as compared to that of *m*-bis(Zn^II−cyclen) (**7**). For complexation with PP²⁻, **10** has 100 times greater affinity constants than **7**. The affinity sequence of **10** is **22** (log $K_{aff} = 7.9$) > **21** (log $K_{aff} = 7.0$) > PP²⁻ (log $K_{aff} = 6.6$) > NPP²⁻ (log $K_{aff} = 5.8$). This sequence seems to parallel order of basicity of these phosphates described by pK_4 defined in eq 4: **22** (7.0) > **21** (6.1) > PP²⁻ (5.8) > NPP²⁻ (5.2).

Hydroxyl groups of **21** may have negligible effects on the complexation. It was unfortunate that we failed to isolate the 1:1 complexes as crystals of sufficient quality for X-ray crystal structure study. However, in the light of the actual P−O bonding to three Zn^{II}−cyclen complexes in Figure 1 and the size of the 1,3,5-trimethylbenzene spacing unit between the three Zn^{II}−cyclen units, we consider **18a** and/or **18b** to be feasible for the 1:1 complex.

Since the trizinc(II) center of PLC$_{Bc}$ (**8**) strongly interacts with phospholipids (phosphodiesters), we also checked if the interaction of **10** with phosphodiester monoanion could occur. The pH titration of **10** in the presence of di-*n*-butyl phosphate monoanion **23** (pK_a is below 4), however, gave almost the same curve as the titration curve in the absence of **23** (see Figure 3a) within experimental error. This implies little interaction between tris(Zn^{II}−cyclen) and phosphodiester monoanion.[40] We conclude that **10** is a receptor selective for dianionic phosphates and phosphonates.

α-D-glucose-1-phosphate
21

phenyl phosphonate
22

di-*n*-butyl phosphate
23

We initially suspected that the zinc(II)-bound hydroxide in the complex **19a** and **19b** in Figure 8 might be well positioned to attack the phosphorus atom of phosphate to cleave the P−OR ester bond.[41] However, acceleration of NPP^{2-} cleavage hardly

occurred at pH 7.0, 8.0, or 9.0 at 37 °C. The failure of intramolecular OH$^-$ attack at the zinc(II)-bound phosphate may be attributable to the inert nature of complex **19c** (equivalent to **19a** and **19b**). We recently showed that the μ-OH$^-$-bridged bis(Zn^{II}−cyclen) species **24** is kinetically inactive as a nucleophile toward 4-nitrophenyl acetate.[19,42]

Conclusions

The 1:3 complex (**11**) consisting of one molecule of NPP^{2-} and three Zn^{II}−cyclen complexes was isolated, and its X-ray crystal structure analysis was carried out. On the basis of the structure of **11**, a new tris(Zn^{II}−cyclen) (**10**) was synthesized via 3Boc-cyclen (**13**) as a potential host for C_3-symmetrical phosphate guests. The crystal structure of **10** (obtained at pH 5) was determined by X-ray crystal structure analysis. The three

(40) Earlier, we showed that the Zn^{II}−macrocyclic triamine ([12]aneN$_3$) complex has more interaction with anionic phosphates than **5**.[17b] Hence, we are now synthesizing homologues of **10** with [12]aneN$_3$ as trizinc(II) enzyme models.

(41) Kimura, E.; Kodama, Y.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1995**, *117*, 8304−8311.

(42) Kimura, E.; Hashimoto, H.; Koike, T. *J. Am. Chem. Soc.* **1996**, *118*, 10963−10970.

pK_a values of zinc(II)-bound water of **10** in aqueous solution have been determined by potentiometric pH titration, and the formation of strong intramolecular hydrogen bonds yields a "closed-form" of **10** at neutral pH, as suggested by three stepwise deprotonation of the zinc(II)-bound waters and unique ^{1}H NMR behavior of **10** dependent on pH (pD). By potentiometric pH titrations, we found **10** to be an effective receptor for C_3-symmetric organic phosphates (and a phosphonate) in slightly acidic pH solutions with high 1:1 affinity constants (log K_{aff}), resulting from the cooperative recognition of three zinc(II) ions. The cooperative recognition with trinuclear zinc(II) complex may apply to other multidentate anions in aqueous solution. The study of tris(zinc(II)−macrocyclic polyamine) complexes may also be useful in understanding phosphate substrate interactions with three zinc(II) center phosphatases (e.g., phospholipase C).

Experimental Section

General Information. All reagents and solvents used were purchased at the highest commercial quality and used without further purification. All aqueous solutions were prepared using deionized and distilled water. IR spectra were recorded on a Shimadzu FTIR-4200 spectrometer. ^{1}H NMR spectra were recorded on a JEOL Alpha (400 MHz) spectrometer. Tetramethylsilane in CDCl$_3$ and 3-(trimethylsilyl)-propionic-*2,2,3,3-d$_4$* acid sodium salt in D$_2$O were used as internal references for ^{1}H and ^{13}C NMR measurements. The pD values in D$_2$O were corrected for a deuterium isotope effect using pD = [pH-meter reading] + 0.40.[17c] ^{31}P NMR spectra were recorded on a JEOL Lambda (202 MHz) spectrometer. A D$_2$O solution of 80% phosphoric acid was used as an external reference for ^{31}P NMR. Elemental analysis was performed on a Perkin Elmer CHN Analyzer 2400. Thin-layer (TLC) and silica gel column chromatographies were performed using Merck Art. 5554 (silica gel) TLC plates and Fuji Silysia Chemical FL-100D (silica gel), respectively.

Crystallization of the 1:3 Complex of 4-Nitrophenyl Phosphate (NPP^{2-}) and Three Zinc(II)−1,4,7,10-tetraazacyclododecane (Zn^{II}−cyclen) (11). 4-Nitrophenyl phosphate disodium salt hexahydrate (25 mg, 67 μmol) was added to a solution of 1,4,7,10-tetraazacyclododecane−zinc(II) diperchlorate complex monohydrate (182 mg, 0.40 mmol) in water (3 mL) at room temperature. This mixture was concentrated slowly under reduced pressure to provide a 1:3 complex of 4-nitrophenyl phosphate with Zn^{II}−cyclen **11**·(ClO$_4^-$)$_4$·2H$_2$O (55 mg, 61%) as colorless prisms. For **11**·(ClO$_4^-$)$_4$·2H$_2$O: IR (KBr pellet) 3300, 3177, 2955, 2919, 1611, 1591, 1518, 1485, 1445, 1375, 1578, 1256, 1134, 1092 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.75−2.82 (24H, m, CH$_2$), 2.89−2.96 (24H, m, CH$_2$), 7.35 (4H, d, *J* = 9.3 Hz, ArH), 8.27 (4H, d, *J* = 9.3 Hz, ArH). Anal. Calcd for C$_{30}$H$_{64}$N$_{13}$O$_{22}$PCl$_4$Zn$_3$·2H$_2$O: C, 26.42; H, 5.03; N, 13.35. Found: C, 26.00; H, 5.07; N, 13.33.

1,4,7-Tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (3Boc−cyclen) (13). A solution of di-*tert*-butyl dicarbonate (7.9 g, 36 mmol) in CHCl$_3$ (100 mL, passed through Al$_2$O$_3$) was added slowly (in 3 h) to a solution of cyclen (2.2 g, 13 mmol) and triethylamine (5.5 mL, 39 mmol) in CHCl$_3$ (120 mL) at room temperature (*slow addition of a (Boc)$_2$O solution is necessary for good chemical yields*). The reaction mixture was stirred for 24 h at room temperature, and the organic solvent was removed under reduced pressure. The remaining residue was purified by silica gel column chromatography (hexanes/AcOEt) to provide **13** as a colorless amorphous solid (4.4 g, 72%). For **13**: IR (KBr pellet) 3522, 2976, 2818, 1691, 1464, 1418, 1366, 1272, 1250, 1171, 1100 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.45 (18H, brs, C(CH$_3$)$_3$), 1.47 (9H, brs, C(CH$_3$)$_3$), 2.80−2.90 (4H, m, CH$_2$), 3.17−3.43 (8H, m, CH$_2$), 3.54−3.72 (4H, m, CH$_2$); ^{13}C NMR (CDCl$_3$) δ 28.51, 28.70, 45.01, 46.01, 48.85, 49.12, 49.49, 49.90, 50.52, 51.00, 79.22, 79.35, 79.51, 155.43, 155.62, 155.85.

1,3,5-Tris[4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecan-1-ylmethyl]benzene (9Boc−tris(cyclen), 14) and 1-(Benzyloxycarbonyl)-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (15). A solution of 1,3,5-tris(bromomethyl)benzene (**12**)[30] (0.82 g, 2.3 mmol) and 3Boc−cyclen (**13**) (3.5 g, 7.4 mmol) in CH$_3$CN (100 mL) was stirred at 80 °C under Ar in the presence of

anhydrous Na_2CO_3 (1.57 g, 14.8 mmol). After 3 days of stirring, insoluble inorganic salts were filtered off and the filtrate was concentrated under reduced pressure. The resulting crude product was dissolved in $CHCl_3$ (50 mL), to which *N,N*-diisopropylethylamine (0.40 mL, 2.3 mmol) and benzyl chloroformate (0.33 mL, 2.31 mmol) were added at 0 °C. After being stirred overnight at room temperature, the reaction mixture was concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography to afford **15** (0.54 g, 12% yield based on used **13**) and 9Boc−tris(cyclen) (**14**, 3.0 g, 85% based on used **12**) as colorless amorphous solids. For **15**: IR (KBr pellet) 3520, 2977, 2810, 1692, 1480, 1416, 1366, 1269, 1171 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.46 (18H, brs, C(CH$_3$)$_3$), 1.47 (9H, brs, C(CH$_3$)$_3$), 3.25−3.50 (16H, m, CH$_2$), 5.12 (2H, s, ArCH$_2$), 7.30−7.38 (5H, m, ArH); ^{13}C NMR (CDCl$_3$) δ 28.33, 28.37, 28.45, 50.40, 67.20, 78.10, 126.95, 127.61, 128.08, 128.26, 128.48, 128.54, 136.41, 157.55. For **14**: IR (KBr pellet) 2977, 2810, 1692, 1480, 1416, 1366, 1316, 1269, 1171 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.42, 1.46, 1.47 (27H, 3 brs, C(CH$_3$)$_3$), 3.17−3.70 (16H, m, CH$_2$), 5.12 (2H, s, ArCH$_2$), 7.30−7.38 (5H, m, ArH); ^{13}C NMR (CDCl$_3$) δ 28.51, 28.69, 47.35, 47.63, 49.79, 53.47, 54.89, 79.37, 79.49, 131.70, 135.45, 155.36, 155.37, 155.39, 155.69.

1,3,5-Tris(1,4,7,10-tetraazacyclododecan-1-ylmethy)benzene Non-ahydrobromide Dihydrate, L^3·9(HBr)·2H$_2$O. To a solution of 9Boc−tris(cyclen) (**14**, 3.29 g, 2.1 mmol) in EtOH (100 mL) at 0 °C was added slowly 47% aqueous HBr (12.5 mL, 0.73 mol). After being stirred overnight at room temperature, the reaction mixture was concentrated under reduced pressure below 40 °C. The resulting crude powder was crystallized from EtOH/24% aqueous HBr to afford L^3·9(HBr)·2H$_2$O as fine crystals (2.6 g, 88%): mp 266 °C (dec); IR (KBr pellet) 3500, 2955, 2714, 1584, 1440, 1359, 1073 cm^{-1}; ^{1}H NMR (D$_2$O) δ 2.92−3.08 (24H, m, CH$_2$), 3.08−3.42 (24H, m, CH$_2$), 3.40 (6H, s, ArCH$_2$), 7.33 (3H, s, ArH); ^{13}C NMR (D$_2$O) δ 42.13, 42.46, 44.87, 47.64, 56.15, 132.34, 135.35. Anal. Calcd for C$_{33}$H$_{66}$N$_{12}$·9HBr·2H$_2$O: C, 28.41; H, 5.71; N, 12.05. Found: C, 28.50; H, 5.85; N, 11.82.

1,3,5-Tris((1,4,7,10-tetraazacyclododecan-1-yl)methyl)benzene Tri-zinc(II) Complex, 10·6(NO$_3$$^-$)·3H$_2$O·0.5EtOH. The acid-free ligand L^3 was obtained by passing L^3·9(HBr)·2H$_2$O (1.0 g, 0.72 mmol) through an anionic exchange resin (Amberlite IRA-400, OH$^-$ form) and concentrating under reduced pressure. The resulting free L^3 was dissolved in 20 mL of 66% (v/v) aqueous EtOH, and a solution of zinc(II) nitrate hexahydrate (0.69 g, 2.28 mmol) was added at 60 °C. After being stirred overnight at 60 °C, the reaction mixture was concentrated under reduced pressure. The resulting colorless powder was crystallized from EtOH/water to afford **10**·6(NO$_3$$^-$)·3H$_2$O·0.5EtOH (0.62 g, 67%) as colorless needles: mp >280 °C; IR (KBr pellet) 3491, 3197, 1607, 1385, 1094 cm^{-1}; ^{1}H NMR (D$_2$O) δ 2.63−3.12 (36H, m), 3.18−3.33 (6H, m), 3.82−3.90 (3H, m), 4.05−4.20 (12H, m), 7.38 (3H, s, ArH); ^{13}C NMR (D$_2$O) δ 40.94, 41.05, 43.45, 43.56, 48.23, 118.13, 132.88. Anal. Calcd for C$_{33}$H$_{66}$N$_{18}$O$_{18}$Zn$_3$·3H$_2$O·0.5EtOH: C, 32.00; H, 5.92; N, 19.76. Found: C, 32.16; H, 5.85; N, 19.75. The colorless prisms suitable for X-ray structure analysis were obtained by recrystallization from EtOH/water.

Potentiometric pH Titrations. The preparation of the test solutions and the calibration method of the electrode system (Orion Research Expandable Ion Analyzer EA920 and Orion Research Ross Combination pH Electrode 8102BN) were described earlier.[18] All test solutions (50 mL) were kept under an argon (>99.999% purity) atmosphere. The potentiometric pH titrations were carried out with $I = 0.10$ (NaNO$_3$) at 25.0 ± 0.1 °C (or 35.0 ± 0.1 °C), and at least three independent titrations were performed. Deprotonation constants of Zn^{II}-bound water K'_n (=[HO$^-$-bound species][H$^+$]/[H$_2$O-bound species], phosphate complex affinity constants K_{aff} (= [phosphate complex]/[host][phosphate], where host is **7** or **10**) were determined by means of the the program BEST.[33] All σ fit values defined in the program are smaller than 0.005. The K_W (=$a_{H^+}a_{OH^-}$), K'_W (=[H$^+$][OH$^-$]), and f_{H^+} values used at 25 and 35 °C are $10^{-14.00}$, $10^{-13.79}$, and 0.825, and $10^{-13.68}$, $10^{-13.48}$, and 0.823, respectively. The corresponding mixed constants, K_n (=[HO$^-$-bound species]a_{H^+}/[H$_2$O-bound species]), are derived using [H$^+$] = a_{H^+}/f_{H^+}. The species distribution values (%) against pH (=$-\log$[H$^+$] + 0.084) were obtained using the program SPE.[33]

Crystallographic Study of 11·4(ClO$_4$$^-$)·2H$_2$O. A colorless prismatic crystal of **11**·4(ClO$_4$$^-$)·2H$_2$O (C$_{30}H_{68}N_{13}O_{24}PCl_4Zn_3$, M_r = 1363.87) having approximate dimensions of 0.35 × 0.20 × 0.15 mm was sealed in a glass capillary and used for data collection. All measurements were made on a Rigaku RAXIS IV imaging plate area detector with graphite monochromated Mo Kα radiation. Indexing was performed from three 2.0° oscillation images which were exposed for 4.0 min. The data were collected at a temperature of 25 ± 1 °C to a maximum 2θ value of 48.7°. A total of 454.0° oscillation images were collected, each being exposed for 30.0 min. The crystal-to-detector distance was 110.0 mm. The detector swing angle was 0.0°. Readout was performed in the 100 μm pixel mode. The structure was solved by direct methods (SIR 92) and expanded by means of Fourier techniques (DIRDIF 94). All calculations were performed with the teXsan crystal structure analysis package developed by Molecular Structure Corporation (1992, 1994). Crystal data for **11**·4(ClO$_4$$^-$)·2H$_2$O: monoclinic, space group P2$_1$/a (No. 14), a = 18.481(8) Å, b = 13.901(3) Å, c = 22.556(6) Å, β = 111.80(3)°, V = 5380.7 Å^3, Z = 2, D_{calcd} = 1.683 g/cm^3, $2\theta_{max}$ = 48.7°, total number of reflections = 7700. Three of the four perchlorate ions were disordered at the two locations indicated by the corresponding unprimed and primed numbers of the oxygen atoms, respectively. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 6568 observed reflections ($I > 3.00\sigma(I)$) and 767 variable parameters and converged (largest parameter shift was 0.03 times its esd) with unweighted and weighted agreement factors of R (=$\sum||F_o| - |F_c||/\sum|F_o|$) = 0.061 and R_w (=$(\sum w(|F_o| - |F_c|)^2/\sum wF_o^2)^{0.5}$) = 0.096.

Crystallographic study of 10·6(NO$_3$$^-$)·3H$_2$O. A colorless prismatic crystal of **10**·6(NO$_3$$^-$)·3H$_2$O (C$_{33}H_{72}N_{18}O_{21}Zn_3$, M_r = 1253.18) having approximate dimensions of 0.35 × 0.15 × 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS IV imaging plate area detector with graphite monochromated Mo Kα radiation. Indexing was performed from three 1.0° oscillation images which were exposed for 4.0 min. The data were collected at a temperature of 25 ± 1 °C to a maximum 2θ value of 52.8°. A total of 44.5° oscillation images were collected, each being exposed for 30.0 min. The crystal-to-detector distance was 125.0 mm. The detector swing angle was 0.0°. Readout was performed in the 100 μm pixel mode. The structure was solved by direct methods (SHELXS 86) and expanded by Fourier techniques (DIRDIF 94). All calculations were performed with the teXsan crystal structure analysis package developed by Molecular Structure Corporation (1992, 1994). Crystal data for **10**·6(NO$_3$$^-$)·3H$_2$O: monoclinic, space group P1 (No. 1), a = 15.668(6) Å, b = 15.914(3) Å, c = 15.614(2) Å, α = 91.730(10)°, β = 111.80(3)°, γ = 116.85(2)°, V = 3001.2 Å^3, Z = 2, D_{calcd} = 1.387 g/cm^3, $2\theta_{max}$ = 52.8°, total number of reflections = 10 717. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 7488 observed reflections ($I > 3.00\sigma(I)$) and 1367 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of R (=$\sum||F_o| - |F_c||/\sum|F_o|$) = 0.051 and R_w = ($(\sum w(|F_o| - |F_c|)^2/\sum wF_o^2)^{0.5}$) = 0.071.

Supporting Information Available: Tables crystallographic parameters, atomic coordinates, equivalent isotropic temperature factors, anisotropic temperature factors, bond distances, and bond angles in CIF format for **10**·6(NO$_3$$^-$)·3H$_2$O and **11**·4(ClO$_4$$^-$)·2H$_2$O (40 pages). See any current masthead page for ordering and Internet access instructions.

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