A NEW BIS(ZINC(II)-CYCLEN) COMPLEX AS A NOVEL CHELATOR FOR BARBITURATES AND PHOSPHATES[§]

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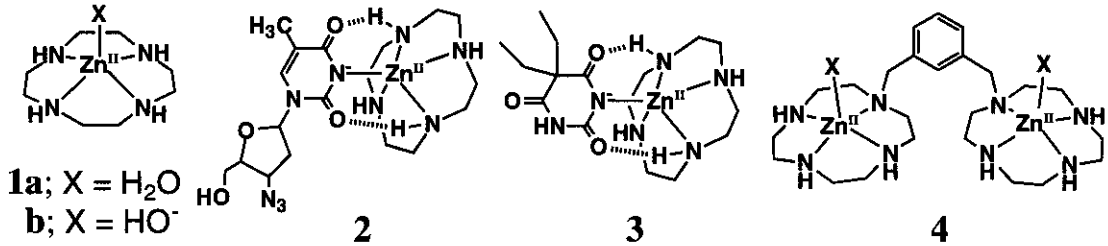
[§] This article is dedicated to the late Professor Yoshio Ban.

Abstract – A novel bis-zinc(II) receptor (bis(Zn^{II}–cyclen)), which has two macrocyclic tetraamine Zn^{II} complexes connected through a *m*-xylene bridge, has been synthesized as a potential host for barbiturates and phosphates in aqueous solution. The new zinc(II) complex, bis(Zn^{II}-cyclen) was proven to be an excellent host for barbital and forms a stable 1 : 1 complex (Zn_2L–barbital^{2-}) in aqueous solution (K_{Bar} = [Zn_2L–barbital^{2-}]/[uncomplexed Zn_2L][uncomplexed barbital] = $10^{5.6}$ M^{-1} at 25 °C and pH 8), wherein both imido groups of the barbital are deprotonated. The bis(Zn^{II}-cyclen) also has a strong affinity to a bidentate phosphomonoester dianion, 4-nitrophenyl phosphate (NP^{2-}) (K_{NP} = [Zn_2L–NP^{2-}]/[Zn_2L][NP^{2-}] = $10^{4.0}$ M^{-1} at 25 °C).

Molecular recognition of biological molecules and drugs has attracted much attention in recent years.[1] Earlier, we found that Zn^{II}-cyclen (cyclen = 1,4,7,10-tetraazacyclododecane) (**1**) is an efficient host for thymine (or uracil) derivatives (e.g., AZT)[2] and barbital[3] under physiological conditions. In aqueous solution Zn^{II}-cyclen forms N^-(imido)-bound Zn^{II} complexes, **2** with AZT^- and **3** with barbital$^-$ and both ternary complexes were isolated. The zinc(II) in cyclen is acidic enough to replace the imido proton and the resulting Zn^{II}–N^-(imido) bond is reinforced by two hydrogen bonds between the imido oxygens and NH groups of cyclen. The recognition based on such a strong Zn^{II}–anionic ligand interaction provides enough

stability to the host-guest complexes even in aqueous solution at physiological pH. The strengthened acidity of zinc(II) also bestows strong affinity to other anionic ligands such as hydroxide (to **1b**),[4] carboxylates,[4] and phosphates.[5]



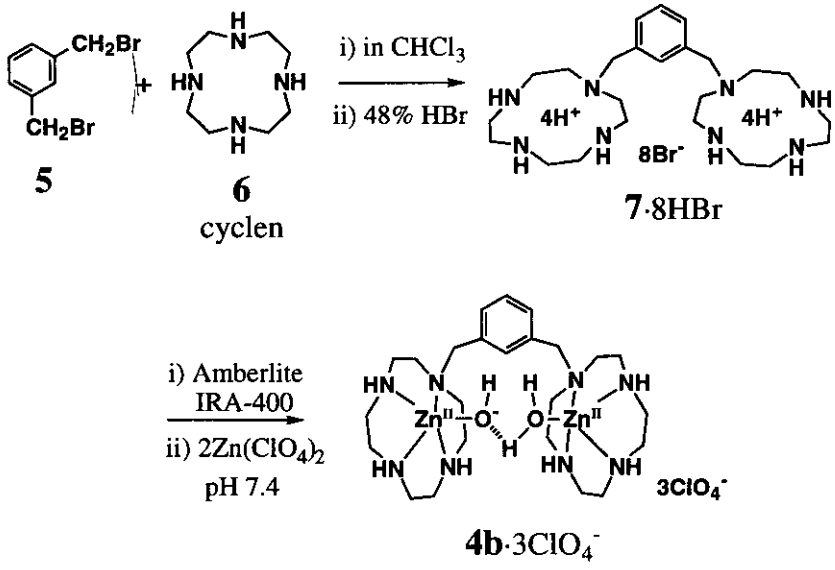
Zn^{II}-cyclen AZT$^-$–Zn^{II}-cyclen Barbital$^-$–Zn^{II}-cyclen Bis(Zn^{II}-cyclen)

Meanwhile, the hydroxide-bound Zn^{II}–cyclen complex (**1b**), which is generated with a pK_a value of 7.9 at 25 °C,[4] catalytically promotes hydrolyses of carboxyesters,[4] phosphoesters[5] and β-lactam[6] in aqueous solution at physiological pH. Thus, it serves as zinc(II)-hydrolytic enzyme models.[7,8] With these two distinct functions of Zn^{II}–cyclen complex having become disclosed, we designed a bis(Zn^{II}–cyclen) complex connected with *m*-xylene bridge (**4**). We hoped to see (i) if a more stable ternary complex with barbital is formed, wherein the two zinc(II) ions simultaneously chelate with the two imido anions of a guest barbital and (ii) if hydrolysis of phosphoesters can be enhanced due to the fact that one zinc holds the phosphate dianion and the other zinc(II) ion provides a nucleophile Zn^{II}–OH^-. Herein, we present the synthesis, acidic properties, and molecular recognition properties of the newly designed zinc(II) complex (**4**).

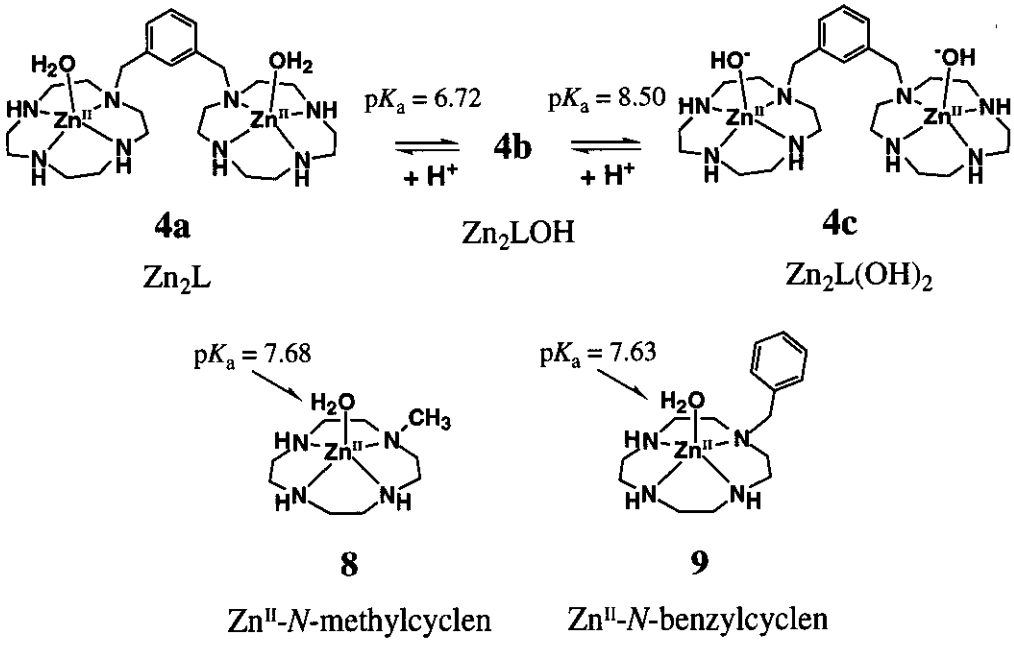
RESULTS AND DISCUSSION

Syntheses of 1,3-Bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene (7) and Its Zinc(II) Complex (4). 1,3-Bis(bromomethyl)benzene (**5**) was treated with six-fold excess amounts of macrocyclic tetraamine (**6**) (cyclen) in $CHCl_3$ to obtain 1,3-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl) benzene (**7**), which was crystallized from 48% HBr_{aq}/EtOH as its octahydrobromic acid salt in 35% yield. After the HBr salt was passed through an anion exchange column, the acid-free ligand (**7**) was mixed with two equivalent of $Zn^{II}(ClO_4)_2 \cdot 6H_2O$ and one equivalent NaOH in EtOH. After the solvent was evaporated, the residue was crystallized from pH 7.4 aqueous solution to get the desired product bis(Zn^{II}–

cyclen) as colorless needles in 68% yield. The bis(Zn^{II}–cyclen) was identified as **4b**·$(ClO_4)_3$ ($Zn_2L{\cdot}OH^-{\cdot}H_2O{\cdot}(ClO_4)_3$) by elemental analysis (C, H, N), nmr (^1H and ^{13}C) and potentiometric pH titration studies presented hereafter.



Deprotonation Constants of Zn^{II}–bound Waters of Bis(Zn^{II}–Cyclen) (4). The acid-base properties of bis(Zn^{II}–cyclen) (**4**) was determined by potentiometric pH titrations of **4b**·$(ClO_4)_3$ (0.5 and 1 mM, 50 ml) (plus an equimolar amount of HNO_3) with 0.10 M NaOH and I = 0.10 ($NaNO_3$) at 25 °C. A typical pH titration curve is shown in Figure 1b, which demonstrates dissociation of two protons for $0 < \alpha(OH^-) < 2$. Any further deprotonation or precipitation of $Zn(OH)_2$ was not observed over pH 12, indicating the stability of the doubly deprotonated species (**4c**). The deprotonation constants are calculated to be 6.72 ± 0.02 for the first deprotonation **4a** ⇄ **4b** + H^+ (pK_1) and 8.50 ± 0.02 for the second deprotonation **4b** ⇄ **4c** + H^+ (pK_2). The pK_a value of Zn^{II}–bound water at 25 °C for Zn^{II}–cyclen (**1a**) is 7.86,[6] for Zn^{II}–*N*-methylcyclen (**8**) is 7.68,[4b] and for Zn^{II}–*N*-benzylcyclen (**9**) is 7.63 ± 0.03. Hence, the pK_1 value for **4a** ⇄ **4b** is concluded to be extraordinarily small, which is explained by postulating a strong intramolecular hydrogen bonding between the Zn^{II}–OH^- and Zn^{II}–OH_2 in **4b**. The pK_2 value of 8.50 is significantly higher than those of the mononuclear Zn^{II}–cyclens (**1a**, **8** and **9**) which is accounted for by the very stable hydrogen bond in **4b**. As aforementioned, **4b** was isolated at pH 7.4, which is between the pK_1 and pK_2 values. The ^1H and ^{13}C nmr spectra of **4b** disclosed a symmetric structure for the two Zn^{II}–cyclen moieties in DMSO solution.



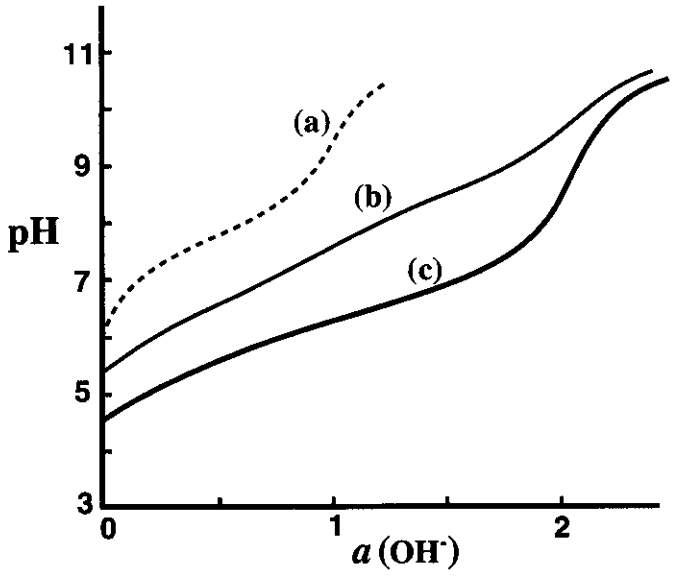


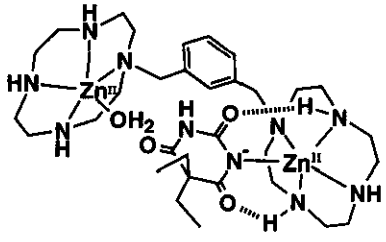
Figure 1. Typical titration curves for barbital and bis(Zn^{II}–cyclen) (**4**) at 25 °C with I = 0.10 ($NaNO_3$): (a) 1.0 mM barbital; (b) 1.0 mM **4b** + 1.0 mM HNO_3; (c) 1.0 mM barbital + 1.0 mM **4b** + 1.0 mM HNO_3. $a(OH^-)$ is the number of equivalents of base added.

Barbital Recognition of Bis(Zn^{II}–Cyclen) Complex (4). In order to see the interaction between the new bis(Zn^{II}–cyclen) (**4**) and barbital, potentiometric pH titrations of **4a** (0.5 and 1.0 mM, 50 ml,

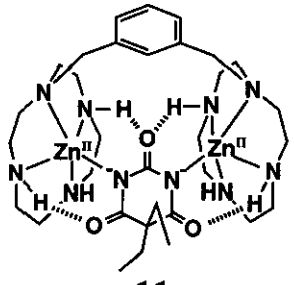
prepared from **4b** and equivalent HNO_3) in the presence of an equimolar amount of barbital were conducted with 0.10 M NaOH and I = 0.10 ($NaNO_3$) at 25 °C. A typical titration curve is shown in Figure 1c. The buffer region ($0 < \alpha(OH^-) < 2$), which corresponds to double deprotonation from the two Zn^{II}–bound waters (or from two imido functions of barbital), is greatly lowered from those of the titration curves in Figure 1a for barbital (1 mM) and 1b for **4a** (1 mM) indicating a strong barbital recognition with concomitant double deprotonation. Since **4a** (Zn_2L) is stable at pH > 5, the titration data at pH > 5.3 were analyzed for the formation of two 1 : 1 complexes; Zn_2L–barbital$^-$ (**10**) (eq 1) and Zn_2L–barbital^{2-} (**11**) (eq 2). The latter complex (**11**) was isolated as a crystalline perchlorate salt from H_2O/DMSO solution of equimolar amounts of **4b** and barbital sodium salt. The elemental analysis (C, H, N) and nmr data suggested its structure as 1 : 1 complex (**11**) with a symmetric barbital dianion (see Experimental Section).[9] The supporting evidence for the barbital^{2-}–bound structure comes from the amide ν_{CO} change from 1698, 1669 (undeprotonated imido) and 1553 cm^{-1} (deprotonated imido) for barbital sodium salt (Na^+·barbital$^-$) and 1707, 1682 (undeprotonated imido) and 1613 cm^{-1} (deprotonated imido) for Zn^{II}–cyclen–barbital$^-$ (**3**)[3] to 1597 and 1576 cm^{-1} (deprotonated imido) for **11**. No further deprotonation was observed at pH < 12, indicating the stability of the barbital^{2-} complex (**11**) under the given conditions. The first deprotonation constant for free barbital (to yield barbital$^-$) is 7.85 at 25 °C with I = 0.10 ($NaNO_3$), while the second deprotonation (to barbital^{2-}) does not occur at pH < 12 (see Figure 1a).[3] Thus, the barbital complex formation constants K(barbital$^-$) and K(barbital^{2-}) are defined as follows:

$$Zn_2L\ (\mathbf{4a}) + \text{barbital}^- \rightleftarrows Zn_2L\text{–barbital}^-\ (\mathbf{10}) \qquad : K(\text{barbital}^-) = [\mathbf{10}]/[\mathbf{4a}][\text{barbital}^-] \qquad (1)$$

$$Zn_2L\text{–barbital}^- \rightleftarrows Zn_2L\text{–barbital}^{2-}\ (\mathbf{11}) + H^+ \qquad : K(\text{barbital}^{2-}) = [\mathbf{11}]a_{H^+}/[\mathbf{10}] \qquad (2)$$



10
Zn_2L–barbital$^-$



11
Zn_2L–barbital^{2-}

These ternary complex formation constants were calculated with the program BEST for pH titration analysis.[10] The results are summarized in Table 1. It is evident that the dianionic barbital (barbital^{2-}) is firmly chelated by bis(Zn^{II}–cyclen) (**4a**) at physiological pH (see Figure 1c). Molecular mechanics (MM2) calculation at 300 K suggested a very good fitting between the guest barbital^{2-} and the host bis(Zn^{II}–cyclen), as shown by the minimum-energy structure (**11**) in Figure 2. The pH titration allowed us to calculate the complexation constant for **11**, log K_{Bar} (= log([**11**]/[uncomplexed **4**][uncomplexed barbital])) = 5.6 ± 0.1 at 25 °C and pH 8, where [uncomplexed **4**] = [**4a**] + [**4b**] + [**4c**] and [uncomplexed barbital] = [barbital] + [barbital$^-$].

Table 1. A Comparison of pK_a Values of Zn^{II}–bound Water and Barbital Complexation Constants for Bis(Zn^{II}–Cyclen) (**4a**) and Zn^{II}–Cyclen (**1a**) at 25 °C with I = 0.10 ($NaNO_3$)

	4a	**1a**
pK_1	6.72 ± 0.02[a]	7.86[b]
pK_2	8.50 ± 0.02[a]	
log K(barbital$^-$)	5.6 ± 0.1[c]	4.9 ± 0.1[d]
log K(barbital^{2-})	–6.3 ± 0.1[e]	
log K_{Bar}	5.6 ± 0.1[f]	4.2 ± 0.1[g]
log K_{NP}	4.0 ± 0.1[h]	3.3 ± 0.1[i]

[a] pK_1 = –log ([**4b**]a_{H^+}/[**4a**]), pK_2 = –log ([**4c**]a_{H^+}/[**4b**]). [b] pK_1 = –log ([**1b**]a_{H^+}/[**1a**]) from ref 6 with I = 0.10 ($NaClO_4$). [c] K(barbital$^-$) = [**10**]/[**4a**][barbital$^-$] M^{-1}. [d] K(barbital$^-$) = [**3**]/[**1a**][barbital$^-$] M^{-1}. [e] K(barbital^{2-}) = [**11**]a_{H^+}/[**10**] M. [f] K_{Bar} = [**11**]/[uncomplexed **4**][uncomplexed barbital] M^{-1} at pH 8. [g] K_{Bar} = [**3**]/[uncomplexed **1**][uncomplexed barbital] M^{-1} at pH 8. [h] K_{NP} = [**12**]/[**4a**][NP^{2-}] M^{-1}. [i] K_{NP} = [NP^{2-}–Zn^{II}–cyclen]/[**1a**][NP^{2-}] M^{-1}.

Recently, we quantitatively investigated the interaction between barbital and Zn^{II}–cyclen (**1a**) (ZnL) by potentiometric pH titration under the same conditions.[3] In this case, only 1 : 1 ZnL–barbital$^-$ complex (**3**) was formed at 5 < pH < 11 with no sign of the subsequent 2 : 1 $(ZnL)_2$–barbital^{2-} complex. Thus, strong

chelation by the two intramolecular Zn^{II}–cyclen units made possible an otherwise impossible double deprotonation of barbital. The log K_{Bar} (= log([**3**]/[uncomplexed **1**][uncomplexed barbital])) is 4.2 at 25 °C and pH 8, where [uncomplexed **1**] = [**1a**] + [**1b**]. The corresponding K_{Bar} for bis(Zn^{II}–cyclen) (**4a**) is *ca.* 25 times larger than that for Zn^{II}–cyclen, quantitatively ensuring us that more effective recognition of barbital is achieved by the present two Zn^{II}–cyclen units linked within the same molecule.

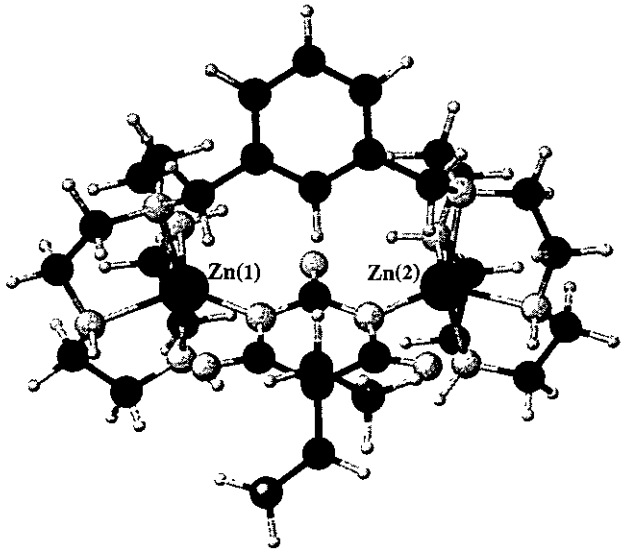
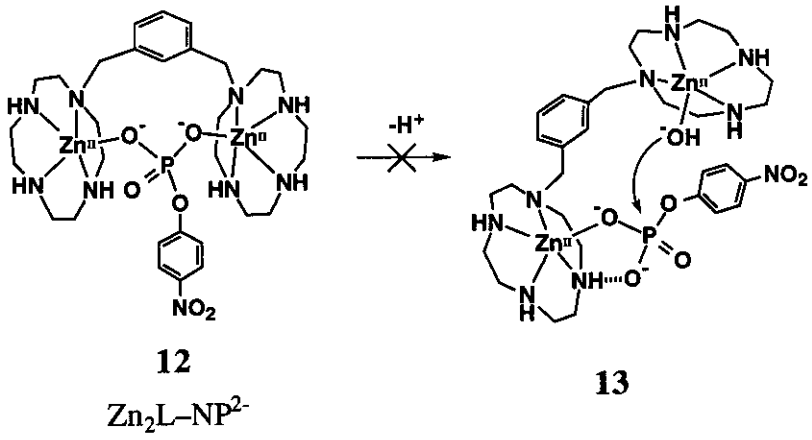


Figure 2. Minimum-energy structure of **11** calculated by MM2.

Phosphomonoester Dianion Recognition of Bis(Zn^{II}–Cyclen) Complex (4). In previous papers,[4,6,8] we found that Zn^{II}–cyclen (**1**) has a unique anion (e.g., acetate, halide anions) binding trend which is almost comparable with that of a zinc(II)-containing enzyme, carbonic anhydrase. Phosphomonoester dianions are often good inhibitors for Zn^{II}–containing hydrolytic enzymes,[11] and become substrates for alkaline phosphatase which requires two zinc(II) ions at the catalytic center.[12] In order to see if the 4-nitrophenyl phosphate dianion (NP^{2-}) first binds with **4a** to yield 1 : 1 Zn_2L–NP^{2-} complex (**12**), which then deprotonates a water molecule to form **13**, we have conducted the potentiometric pH titration with **4a** (0.5 and 1.0 mM) in the presence of equimolar NP^{2-} (see Figure 3 and eq 3). As known to alkaline phosphatase, if one zinc in **4** holds the phosphate dianion and the other zinc(II) ion provides a nucleophile Zn^{II}–OH^- (see **13**), the phosphate hydrolysis might be greatly enhanced by **4**.

$$Zn_2L\ (\mathbf{4a}) + NP^{2-} \rightleftarrows Zn_2L\text{–}NP^{2-}\ (\mathbf{12}): \quad K_{NP} = [Zn_2L\text{–}NP^{2-}]/[Zn_2L][NP^{2-}] \tag{3}$$



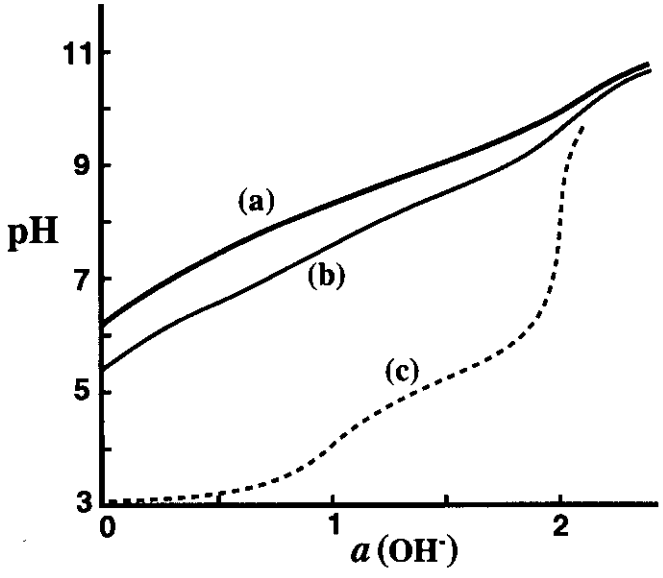


Figure 3. Typical titration curves for 4-nitrophenyl phosphate (NP^{2-}) and bis(Zn^{II}–cyclen) (**4**) at 25 °C with I = 0.10 ($NaNO_3$): (a) 1.0 mM NP^{2-} + 1.0 mM **4b** + 1.0 mM HNO_3; (b) 1.0 mM **4b** + 1.0 mM HNO_3; (c) 1.0 mM NP^{2-} + 2.0 mM HNO_3. $a(OH^-)$ is the number of equivalents of base added.

The titration data (Figure 3a for 1 mM **4a** in the presence of an equimolar amount of NP^{2-}) and its analysis have established only the equilibrium (3) with the 1 : 1 affinity constants log K_{NP} = 4.0 ± 0.1 for **4a** at 25 °C with I = 0.10 ($NaNO_3$), but no further deprotonation to other phosphate anion binding species such as

13. The deprotonation constants (pK_a) for 4-nitrophenylphosphoric acid are <3 and 5.15 ± 0.02 at 25 °C with I = 0.10 ($NaNO_3$). A typical distribution diagram for zinc(II) species as a function of pH with equimolar amounts of 4-nitrophenyl phosphate and **4a** (1 mM) at 25 °C and 5 < pH < 11 is displayed in Figure 4. The reference log K_{NP} value for Zn^{II}–cyclen **1a** is 3.3 ± 0.1 under the same conditions, where K_{NP} = [ZnL–NP^{2-}]/ [ZnL][NP^{2-}]. Accordingly, the dimeric effect on the NP^{2-} recognition ability (*ca.* 5 times) is not as great as on the barbital^{2-} recognition (*ca.* 25 times). The anticipated species (**13**) was not found and the 1 : 1 phosphate-bound complex (**12**) is inert against water and hydroxide ion. Hence, enhanced hydrolysis of 4-nitrophenyl phosphate (NP^{2-}) with **4** was not observed at 7 < pH < 11 and 25 °C.

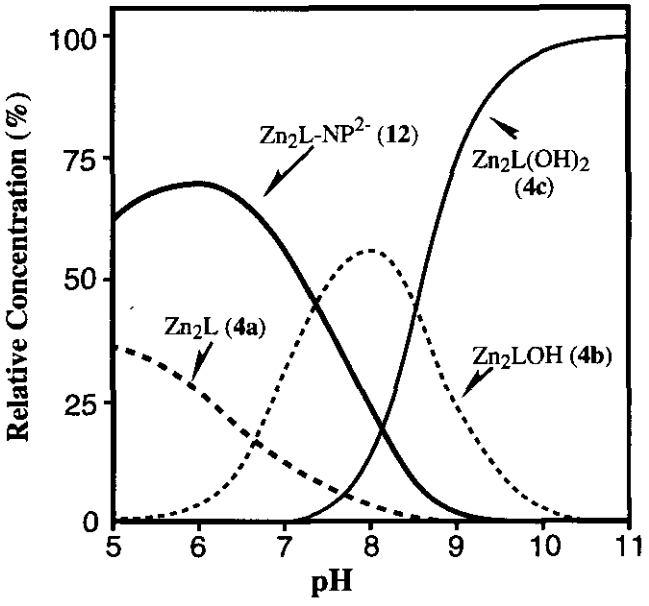


Figure 4. Distribution diagram for the zinc(II) species in 1 mM bis(Zn^{II}–cyclen)/1 mM 4-nitrophenyl phosphate system as a function of pH at 25 °C with I = 0.1 ($NaNO_3$).

CONCLUSIONS

A new bis(Zn^{II}–cyclen) complex (**4**), which consists of two Zn^{II}–cyclen complexes and a *m*-xylene bridge, has been synthesized for the recognition of dianionic forms of barbiturates and phosphomonoesters in aqueous solution. As anticipated, **4a** very firmly chelates with barbital (as dianion) and 4-nitrophenyl phosphate at physiological pH to form the stable 1 : 1 complexes (**11** and **12**). The former complex was isolated as its diperchlorate salt. The pH-metric titrations of **4** with barbital and 4-nitrophenyl phosphate

have established the 1 : 1 complex stability constants, which showed the greater stability of the host-guest complexes (**11** and **12**) over the reference host Zn^{II}–cyclen (**1**).

EXPERIMENTAL SECTION

General Information. All reagents used were of analytical reagent grade (purity > 99%) and used without further purification. All aqueous solutions were prepared using deionized and distilled water. Ir spectra were recorded on a Shimadzu FTIR-4200 spectrophotometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) nmr spectra were recorded on a JEOL α-400 spectrometer at 25 °C. 3-(Trimethylsilyl) propionic-2,2,3,3-d_4 acid sodium salt in D_2O and tetramethylsilane in DMSO-d_6 were used as internal references for ^{1}H and ^{13}C nmr measurements. A reference zinc(II) complex (**9**) was synthesized as its perchlorate salt (**9**·$(ClO_4)_2$) in 40% yield by the same method for Zn^{II}–cyclen complex (**1a**)[6] except with 1-benzyl-1,4,7,10-tetraazacyclododecane,[13] which was identified by potentiometric pH titration and nmr (^{1}H and ^{13}C) study. ^{1}H Nmr (D_2O): δ 2.68 (2H, ddd, J = 3, 7, 13 Hz, NCHCN), 2.75–2.89 (8H, m, NCHCN), 2.95–3.02 (4H, m, NCHCN), 3.19 (2H, ddd, J = 3, 8, 14 Hz, NCHCN), 4.01 (2H, s, Ar CH), 7.39–7.50 (5H, m, ArH). ^{13}C Nmr (D_2O): δ 45.0, 46.5, 47.3, 51.9, 58.8, 131.5, 131.6, 134.1, 134.6.

1,3-Bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl) benzene Octahydrobromic Acid Salt, 7·8HBr·3H_2O. A solution (25 ml) of 1,3-bis(bromomethyl)benzene (1.32 g, 5.0 mmol) in $CHCl_3$ (25 ml) was added dropwise in a $CHCl_3$ solution (100 ml) of 1,4,7,10-tetraazacyclododecane (5.17 g, 30 mmol) and the reaction mixture was stirred at room temperature for 7 h. After the solution was washed with two 50-ml portions of water to recover excess amount of cyclen, the organic solvent was evaporated. The oily residue was purified by silica gel column chromatography (eluent: 28% NH_{3aq}/MeOH/$CHCl_3$ = 1 : 5 : 25) followed by crystallization from 48% HBr_{aq}/EtOH to obtain colorless crystals of 1,3-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl) benzene as its octahydrobromic acid salt (**7**·8HBr·3H_2O) (2.00 g, 35%). Ir (KBr pellet) 3445, 2994, 2926, 2870, 2784, 2664, 1626, 1586, 1491, 1431, 1418, 1306, 997, 829 cm^{-1}. ^{1}H Nmr (D_2O): δ 2.98 (8H, t, J = 5.4 Hz, NCH), 3.05 (8H, br, NCH), 3.20 (8H, t, J = 5.4 Hz, NCH), 3.25 (8H, br, NCH), 3.97 (4H, s, Ar CH), 7.39 (1H, s, ArH), 7.44 (2H, d, J = 7.7 Hz, ArH), 7.54 (1H, t, J = 7.7 Hz, ArH). ^{13}C Nmr (D_2O): δ 44.9, 45.0, 47.2, 50.8, 59.5, 132.6, 132.8, 135.0, 138.0. Anal. Calcd for $C_{24}H_{46}N_8$·8HBr·3H_2O: C, 25.1; H, 5.3; N, 9.8. Found:C, 24.9; H, 5.1; N, 9.7. The protonation constants (log([H_nL]/[$H_{n-1}L$]a_{H^+})) are 11.1 ± 0.1, 10.1 ± 0.1, 8.9 ± 0.1, 8.3 ± 0.1, 2.7 ± 0.2 and < 2 at 25 °C with I = 0.10 ($NaNO_3$).

1,3-Bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene Dizinc(II) Complex, 4b·$(ClO_4)_3$. A solution of **7**·8HBr·$3H_2O$ (1.6 g, 1.4 mmol) in water (10 ml) was passed through an anion exchange column (Amberlite IRA-400) and the solvent was evaporated. To the obtained acid-free ligand (**7**) was added a solution of $Zn(ClO_4)_2 \cdot 6H_2O$ (1.2 g, 3.2 mmol) in EtOH (30 ml) and 1 M NaOH (0.7 ml). After the solvent was evaporated, the residue was crystallized from 0.1 M $NaClO_4$ solution to give 1,3-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene dizinc(II) complex as colorless needles (**4b**·$(ClO_4)_3$) (0.87 g, 68%). Ir (KBr pellet) 3430, 3200, 2928, 2878, 1630, 1455, 1358, 1296, 1254, 1144, 1115, 1092, 986, 910, 855, 627 cm^{-1}. ^1H Nmr (DMSO-d_6): δ 2.50 – 3.00 (32H, m, NCH), 3.21 (1H, s, OH), 3.29 (2H, s, H_2O) 3.75 (4H, s, ArCH), 3.90 (2H, m, NH), 4.02 (4H, m, NH), 7.34 (2H, d, J = 6.9 Hz, ArH), 7.42 (1H, t, J = 6.9 Hz, ArH), 7.91 (1H, s, ArH). ^{13}C Nmr: δ (DMSO-d_6) 41.8, 42.6, 44.7, 50.6, 59.2, 127.6, 132.2, 133.6, 134.8. Anal. Calcd for $C_{24}H_{49}N_8O_2Zn_2 \cdot 3ClO_4$: C, 31.7; H, 5.4; N, 12.3. Found: C, 31.8; H, 5.1; N, 12.1.

1,3-Bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene Dizinc(II) Barbital^{2-} Complex, 11·$(ClO_4)_2$. To a solution of **4b**·$(ClO_4)_3$ (0.23 g, 0.25 mmol) in water (50 ml) was added barbital sodium salt (52 mg, 0.25 mmol) to give a white precipitate, which was crystallized from H_2O/DMSO to afford barbital^{2-}–bound complex as colorless needles (**11**·$(ClO_4)_2 \cdot 3H_2O$) (0.15 g, 60 %). Ir (KBr pellet) 3445, 2965, 2932, 2878, 1597, 1576, 1445, 1393, 1327, 1298, 1248, 1143, 1131, 1090, 976, 951, 856, 818, 793, 762, 737, 708 cm^{-1}. ^1H Nmr (DMSO-d_6): δ 0.81 (6H, t, J = 7.3 Hz, CH_3), 1.83 (4H, q, J = 7.3 Hz, CH_2), 2.50 – 3.21 (32H, m, NCH), 3.61 (4H, br, NH), 3.90 – 4.03 (6H, m, ArCH, NH), 6.71 (1H, s, ArH), 6.90 (2H, d, J = 7.7 Hz, ArH), 7.03 (1H, t, J = 7.7 Hz, ArH). ^{13}C Nmr (DMSO-d_6): δ 10.1, 32.0, 42.2, 43.8, 44.2, 48.8, 55.2, 128.2, 129.9, 131.6, 132.2, 165.2, 182.5. Anal. Calcd for $C_{32}H_{56}N_{10}O_3Zn_2 \cdot 2ClO_4 \cdot 3H_2O$: C, 38.0; H, 6.2; N, 13.8. Found: C, 37.8; H, 5.9; N, 13.8.

Potentiometric pH Titrations. The preparation of the test solutions and the calibration of the electrode system were described earlier.[8b] All test solutions (50 ml) were kept under an argon (>99.999% purity) atmosphere at 25.0 ± 0.1 °C. The potentiometric pH titrations were carried out with I = 0.10 ($NaNO_3$), and at least three independent titrations were made. Deprotonation constants of Zn^{II}–bound water (= [HO^-–bound species][H^+]/[H_2O–bound species]), formation constant for Zn_2L–barbital$^-$ (= [Zn_2L–barbital$^-$]/[Zn_2L][barbital$^-$]), deprotonation constant for Zn_2L–barbital$^-$ (= [Zn_2L–barbital^{2-}][H^+]/[ZnL–barbital$^-$], and formation constant for Zn_2L–NP^{2-} (= [Zn_2L–NP^{2-}]/[Zn_2L][NP^{2-}]) were determined using the program BEST.[10] The K_w (= $a_{H^+} \cdot a_{OH^-}$), K_w' (= [H^+][OH^-]), and f_{H^+} values are $10^{-14.00}$, $10^{-13.79}$ and 0.825,

respectively. The corresponding mixed constants are calculated using $[H^+] = a_{H^+}/f_{H^+}$.

Molecular Mechanics Calculation. Structure minimization for **11** was accomplished using the molecular dynamics (MD) and molecular mechanics (MM2) packages provided by the CAChe System, Version 3.5 (Tektronix). Structure was first minimized using MM2 at 300 K, and the resulting structure was submitted to MD simulation at 800 K. The lowest energy structure for **11** (Figure 2) was obtained by further optimization using MM2 at 300 K using block-diagonal Newton-Raphson method until the change of the total energy became less than 0.001 kJ mol^{-1}. The energy terms (kJ mol^{-1}) for the MM2 force field are bond stretch (50.8), bond angle (271.9), dihedral angle (39.1), improper torsion (0.2), van der Waals (11.8), electrostatics (–529.0) and hydrogen bond (–9.3).

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