Bis(Zn^{II}–Cyclen) Complex as a Novel Receptor of Barbiturates in Aqueous Solution

Tohru Koike, Megumi Takashige, Eiichi Kimura,* Haruto Fujioka, and Motoo Shiro

Abstract: A new bis-zinc(II) receptor (Zn_2L), which has two macrocyclic 12-membered tetraamine (cyclen) Zn^{II} complexes connected through a *p*-xylene bridge, has been synthesized as a novel host molecule to recognize barbiturates (such as barbital (bar)) in aqueous solution. Each of the zinc(II) ions in the bis-zinc(II) receptor was originally intended to match the dianionic barbital anion (bar^{2-}) with supplementary hydrogen bonds between the cyclen NH's and the three carbonyl oxygens in complementary positions to yield a 1:1 complex, Zn_2L–bar^{2-}. From an aqueous solution of equimolar Zn_2L and barbital at pH 8, however, a cyclic 2:2 complex, $(Zn_2L$–$bar^{2-})_2$, was isolated and characterized by X-ray crystal analysis. The NMR study in 10% (v/v) D_2O/H_2O has revealed dissociation of $(Zn_2L$–$bar^{2-})_2$ solely into the original target 1:1 complex Zn_2L–bar^{2-} and established the dimerization constant for $2\,Zn_2L$–$bar^{2-} \rightleftharpoons (Zn_2L$–$bar^{2-})_2$, K_d ($= [(Zn_2L$–$bar^{2-})_2]/[Zn_2L$–$bar^{2-}]^2$) to be $10^{3.4}\,M^{-1}$. The thermodynamic parameters were evaluated from the NMR measurements at 25, 35, 45, and 55 °C: $\Delta G = -1.9 \times 10^4\,J\,mol^{-1}$, $\Delta H = -3.3 \times 10^4\,J\,mol^{-1}$, $\Delta S = -49\,J\,mol^{-1}\,K^{-1}$ at 25 °C. Potentiometric pH titration of Zn_2L (1 mM) and barbital (1 mM) disclosed extremely facile deprotonation of the two imido groups of barbital at pH less than 7 to form the dianionic barbital-bound Zn^{II} complexes Zn_2L–bar^{2-} and $(Zn_2L$–$bar^{2-})_2$, whereby the barbital binding affinity for Zn_2L was estimated to be K_{bar} ($= [Zn_2L$–$bar^{2-}]$/[uncomplexed Zn_2L][uncomplexed barbital]) $= 10^{5.8}\,M^{-1}$ at pH 8 and 25 °C with $I = 0.10$ ($NaNO_3$). The significance of the bis-zinc(II) receptor in stabilizing the dianionic barbital is evident by comparison with the interaction of Zn^{II}–cyclen complex (ZnL) with barbital, which yields only a 1:1 monoanionic barbital complex, ZnL–bar^- ($K_{bar} = [$ZnL–$bar^-]$/[uncomplexed ZnL][uncomplexed barbital] $= 10^{4.2}\,M^{-1}$ at pH 8 and 25 °C with $I = 0.10$ ($NaNO_3$)).

Keywords
barbiturates · macrocycles · molecular recognition · receptors · zinc complexes

Introduction

Many artificial supramolecular structures described in recent literature are principally based on the formation of directed hydrogen bonds, hydrophobic interactions, and π–π interactions between uncharged host and uncharged guest molecules.[1] Typical substrates are undeprotonated carboxylic acids, carboxyl amides, nucleic acid bases, ureas, or barbituric acid derivatives. However, those electrostatic bonds contribute only modestly to the free energy of association of uncharged molecules in a polar environment. For this reason, those individual bonds have hitherto played a limited role in molecular recognition in aqueous systems.

In 1987, Feibush et al. designed a complementary pair, a 2,6-diaminopyridine unit and an imido functional group interacting through three hydrogen bonds (see the recognition of thymine **1** and barbituric acid derivatives **2**).[2] This idea has since been adopted in designing artificial receptors for the clinically important drugs barbiturates (e.g., barbital **3**): Hamilton et al. synthesized macrocyclic receptors **4**, whose 1:1 complex stability constants K_{bar} ($=$ [barbiturate complex]/[barbiturate][receptor]) are 10^2–$10^6\,M^{-1}$ in $CDCl_3$;[3] Rebek et al. reported a receptor **5** ($K_{bar} = 10^{4.5}\,M^{-1}$ in $CDCl_3$) based on bis(Kemp's acid) derivatives separated by a naphthalene group;[4] Reinhoudt et al. introduced the UO_2^{2+} cation into a macrocyclic receptor **6** to bind one carbonyl group of a barbiturate ($K_{bar} = 10^{2.0}\,M^{-1}$ in 5% (v/v) [D_6]DMSO/$CDCl_3$);[5] and Picard et al. synthesized an open chain receptor **7** ($K_{bar} = 10^{2.9}\,M^{-1}$ in $CDCl_3$).[6] All of these barbiturate–receptor complexes are stable only in nonaqueous environments; they dissociate immediately in aqueous solution.

Previously, we reported that a zinc(II) complex of 12-membered macrocyclic tetraamine (cyclen) **8a** is a good receptor of deprotonated thymine and its derivatives such as AZT (3-azido-3-deoxythymidine), yielding stable 1:1 complexes (e.g., **9** for AZT) at physiological pH in aqueous solution.[7] We discovered strong interactions (e.g., $K = [\mathbf{9}]/[AZT^-][\mathbf{8a}] = 10^{5.6}\,M^{-1}$ for AZT) through the Zn^{II}–N^-(imido) bond as well as two complementary hydrogen bonds between cyclen NH's and both imido oxygens. The interaction is so strong that the complex is almost

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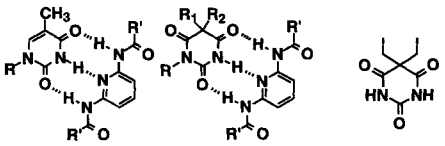
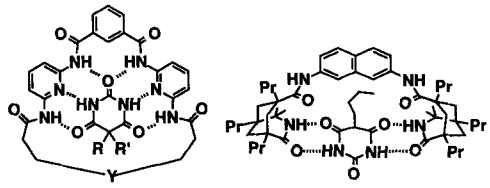


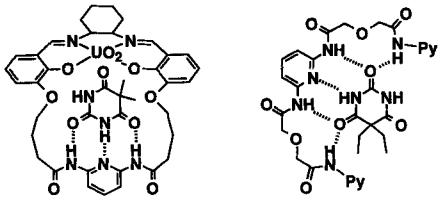
1 2 3

Feibush's Receptor barbital



4 5

Hamilton's Receptor Rebek's Receptor



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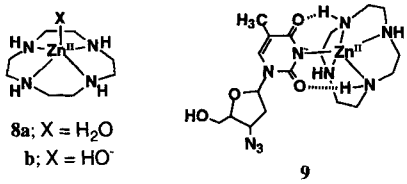
Reinhoudt's Receptor Picard's Receptor



8a; X = H_2O

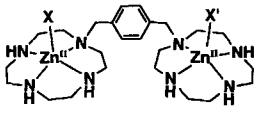
b; X = HO^-

Zn^{II}-cyclen

9

inert at physiological pH. Moreover, the Zn^{II}–cyclen complex **8a** is selective for the imido-containing thymine and uracil among the DNA and RNA bases.[7] That the cationic complex **8a** preferentially recognizes neutral uracil base over biological anions such as phosphates is remarkable; this is well illustrated by the formation of a stoichiometric complex with poly(U), whereby poly(U)–poly(A) hybridization is inhibited.[8]

We have now applied the host complex **8a** *in aqueous solution* to recognition of barbiturates with potentially double interaction sites (i.e., two imido groups). In order to produce a more efficient receptor, we have designed a new zinc(II) complex, bis(Zn^{II}–cyclen) (**10**) for barbiturate dianions. The recognition based on such metal-to-ligand interaction would offer special advantages in aqueous solution over the previous barbiturate receptors **4**–**7** that rely on weaker interactions such as hydrogen bonding, hydrophobic interactions, and π–π interactions.



10a; X = H_2O, X' = H_2O

b; X = HO^-, X' = H_2O

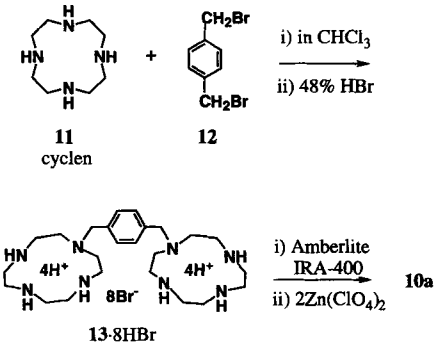
c; X = HO^-, X' = HO^-

Our Barbiturate Receptor

bis-(Zn^{II}-cyclen)

Results and Discussion

Syntheses of 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)-benzene (13) and the bis-zinc(II) complex bis(Zn^{II}–cyclen) (10): A sixfold excess of the macrocyclic tetraamine **11** (cyclen) was treated with 1,4-bis(bromomethyl)benzene (**12**) in $CHCl_3$ at room temperature overnight to obtain **13**, which was crystallized as its 8 HBr salt in 50% yield (see Scheme 1). After the HBr salt had been passed through an anion exchange column, the



11 cyclen **12**

i) in $CHCl_3$

ii) 48% HBr

i) Amberlite IRA-400

ii) $2Zn(ClO_4)_2$

10a

13·8HBr

Scheme 1. Syntheses of 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene (**13**) and bis(Zn^{II}–cyclen) (**10**).

acid-free ligand **13** (L) was mixed with two equivalents of $Zn(ClO_4)_2 \cdot 6H_2O$ in EtOH solution followed by crystallization from 0.1 M $NaClO_4$ aqueous solution to obtain the desired receptor complex, bis(Zn^{II}–cyclen) (Zn_2L), as colorless crystals. We characterized the bis-zinc(II) complex as **10a**·$(ClO_4)_4 \cdot 2H_2O$ by elemental analysis (C, H, N), NMR (^1H and ^{13}C), and following potentiometric pH titration studies.

Deprotonation constants of the Zn^{II}-bound water molecules in 10a and formation of the bis(Zn^{II}–cyclen) barbital^{2-} complexes 15 and 16: The acid–base properties of barbital **3** (1.0 and 2.0 mM) and bis(Zn^{II}–cyclen) **10a** (0.5, 1.0, and 2.0 mM) were determined by potentiometric pH titrations against 0.10 M NaOH aqueous solution with $I = 0.10$ ($NaNO_3$) at 25 °C. A typical pH titration curve for **10a** is shown in Figure 1b, which shows dissociation

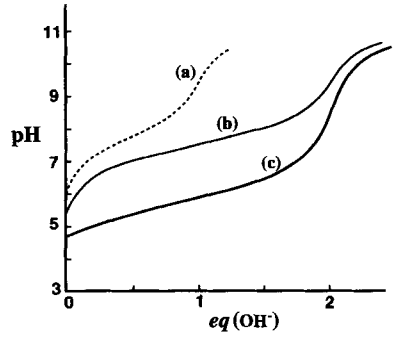


Fig. 1. Typical titration curves for barbital (**3**) and bis(Zn^{II}–cyclen) (**10a**) at 25 °C with $I = 0.10$ ($NaNO_3$); $eq(OH^-)$ is the number of equivalents of base added: a) 1.0 mM barbital; b) 1.0 mM bis(Zn^{II}–cyclen); c) 1.0 mM barbital + 1.0 mM bis(Zn^{II}–cyclen).

of two protons at $0 < eq(OH^-) < 2$. The deprotonation constants are estimated to be 7.23 ± 0.02 for the first deprotonation **10a** $\rightleftharpoons$ **10b** $+ H^+$ (pK_1) and 7.88 ± 0.02 for the second deprotonation **10b** $\rightleftharpoons$ **10c** $+ H^+$ (pK_2). The deprotonation constants of the Zn^{II}-bound water are not so different from those of Zn^{II}–cyclen **8a** ($pK_a = 7.86$)[9] and Zn^{II}–*N*-methylcyclen ($pK_a = 7.68$).[10] It is concluded that the two deprotonations of **10a** occur almost independently. The first deprotonation constant for barbital (**3**) $\rightleftharpoons$ bar^- (barbital monoanion) $+ H^+$ was also

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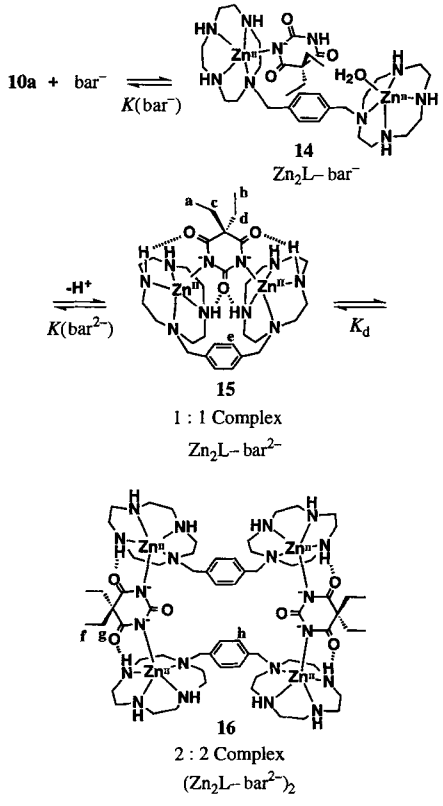
determined to be 7.85 ± 0.02 ($= -\log\{[\text{bar}^-]a_{H^+}/[\text{barbital}]\}$) under the same conditions (see Fig. 1a), while the second deprotonation did not occur at pH less than 12.

In order to observe the interaction between **10** and barbital, potentiometric pH titrations of **10a** (1.0 and 2.0 mM) in the presence of equimolar amounts of **3** were conducted against aqueous 0.10 M NaOH with $I = 0.10$ ($NaNO_3$) at 25 °C (Fig. 1c). The buffer pH region at $5 < pH < 7$, which corresponds to deprotonation of the two Zn^{II}-bound water molecules, is greatly lowered compared with those of the titration curves in Figures 1a for **3** and 1b for **10a**, indicating complexation with concomitant deprotonation of the two imido groups. Since **10** (1 mM) is stable at pH greater than 5.2 in 10% (v/v) D_2O/H_2O with 0.10 M $NaNO_3$ (see Experimental Section for **10**), the titration data at pH greater than 5.2 were analysed for possible 1:1 complexes, Zn_2L–bar^- [**14**, Eq. (1)] and Zn_2L–bar^{2-} [**15**, Eq. (2)], and a 2:2 complex $(Zn_2L\text{–}bar^{2-})_2$ [**16**, Eq. (3)], where bar^{2-} is the doubly deprotonated barbital dianion (see Scheme 2). The consideration of the 2:2 complex **16**



Scheme 2. Barbital complex formation.

resulted from its isolation from an aqueous solution of **10a** and **3** and its X-ray crystal analysis, as described below. The evidence for the 1:1 complex **15** was derived from the NMR study in aqueous solution (see below). No further deprotonation was observed at pH less than 12, indicating the stability of the barbital dianion complexes **15** and **16** under the given conditions. The barbital complex formation constants K_{bar^-}, $K_{bar^{2-}}$, and K_d are defined in Equations (1–3).

$$Zn_2L\ (\mathbf{10a}) + bar^- \rightleftharpoons Zn_2L\text{–}bar^-\ (\mathbf{14}) \qquad K_{bar^-} = [\mathbf{14}]/[\mathbf{10a}][bar^-] \qquad (1)$$

$$Zn_2L\text{–}bar^- \rightleftharpoons Zn_2L\text{–}bar^{2-}\ (\mathbf{15}) + H^+ \qquad K_{bar^{2-}} = [\mathbf{15}]a_{H^+}/[\mathbf{14}] \qquad (2)$$

$$2\,Zn_2L\text{–}bar^{2-} \rightleftharpoons (Zn_2L\text{–}bar^{2-})_2\ (\mathbf{16}) \qquad K_d = [\mathbf{16}]/[\mathbf{15}]^2 \qquad (3)$$

These values were calculated with the program BEST for pH titration analysis.[11] The results are summarized in Table 1. A typical distribution diagram for zinc(II) species as a function of pH with equimolar amounts of barbital and **10a** (1 mM) at 25 °C

Table 1. A comparison of pK_a values of Zn^{II}-bound water and barbital complexation constants for bis(Zn^{II}–cyclen) **10a** and Zn^{II}–cyclen **8a** at 25 °C with $I = 0.10$ ($NaNO_3$).

	10a	**8a**
pK_1	7.23 ± 0.02 [a]	7.86 [b]
pK_2	7.88 ± 0.02 [a]	
$\log K_{bar^-}$	5.5 ± 0.1 [c]	4.9 ± 0.1 [d]
$\log K_{bar^{2-}}$	−6.2 ± 0.1 [e]	
$\log K_d$	3.4 ± 0.1 [f]	
$\log K_{bar}$	5.8 [g]	4.2 [h]

[a] $pK_1 = -\log([\mathbf{10b}]a_{H^+}/[\mathbf{10a}])$, $pK_2 = -\log([\mathbf{10c}]a_{H^+}/[\mathbf{10b}])$. [b] $pK_1 = -\log([\mathbf{8b}]a_{H^+}/[\mathbf{8a}])$ from ref. [9a]. [c] $K_{bar^-} = [\mathbf{14}]/[\mathbf{10a}][bar^-]\,M^{-1}$. [d] $K_{bar^-} = [\mathbf{17}]/[\mathbf{8a}][bar^-]\,M^{-1}$. [e] $K_{bar^{2-}} = [\mathbf{15}]a_{H^+}/[\mathbf{14}]$ M. [f] $K_d = [\mathbf{16}]/[\mathbf{15}]^2\,M^{-1}$. [g] $K_{bar} = [\mathbf{15}]/[\text{uncomplexed } \mathbf{10}][\text{uncomplexed barbital}]\,M^{-1}$ at pH 8. [h] $K_{bar} = [\mathbf{17}]/[\text{uncomplexed } \mathbf{8}][\text{uncomplexed barbital}]\,M^{-1}$ at pH 8.

and $5 < pH < 10.5$ is displayed in Figure 2. It is evident that barbital is sequestered mostly as the dianionic guest (bar^{2-}) by the bis(Zn^{II}–cyclen) receptor **10a** (Zn_2L) either in the 1:1 (Zn_2L–bar^{2-} **15**) or the 2:2 complex ((Zn_2L–bar^{2-})$_2$ **16**) at

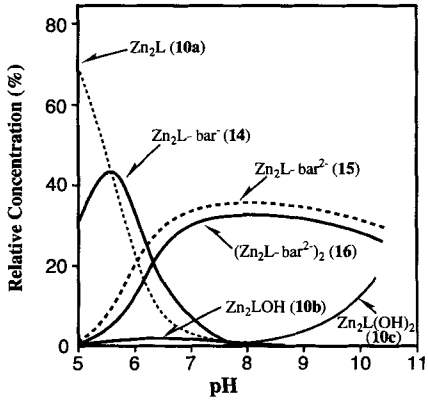


Fig. 2. Distribution diagram for the zinc(II) species in a 1 mM bis(Zn^{II}–cyclen)/1 mM barbital system as a function of pH at 25 °C with $I = 0.10$ ($NaNO_3$).

physiological pH. We can estimate the complexation constant of **15**, $\log K_{bar}$ ($K_{bar} = [\mathbf{15}]/[\text{uncomplexed } \mathbf{10}][\text{uncomplexed barbital}]\,M^{-1}$) to be 5.8 at pH 8 and 25 °C, where [uncomplexed **10**] = [**10a**] + [**10b**] + [**10c**] and [uncomplexed barbital] = [**3**] + [bar^-]. Higher concentrations afford the 2:2 complex **16** [$K_d = 10^{3.4}\,M^{-1}$ for Eq. (3)] through intermolecular interactions, and the barbital receptor **10a** becomes a stronger host for the barbital dianion, as shown by the greater conditional complexation constant of bar^{2-} complexes **15** and **16**, K'_{bar} (= ([**15**] + [**16**])/[uncomplexed **10**][uncomplexed barbital]M^{-1} (e.g., $\log K'_{bar} = 7.2$ at [**15**] = 10 mM, pH 8, and 25 °C).

As a control experiment, the interaction between barbital (1.0 mM) and Zn^{II}–cyclen (**8a**, 1.0, 2.0, and 3.0 mM) was investigated by potentiometric pH titration under the same conditions (see typical titration curves in Fig. 3c). In this case, only 1:1 ZnL–bar^- complex **17** was formed at $5 < pH < 11$ with no sub-

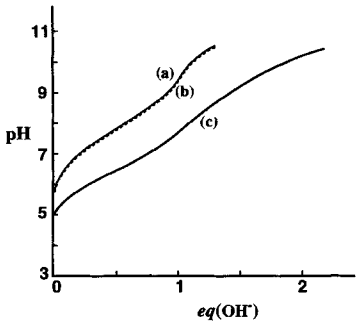
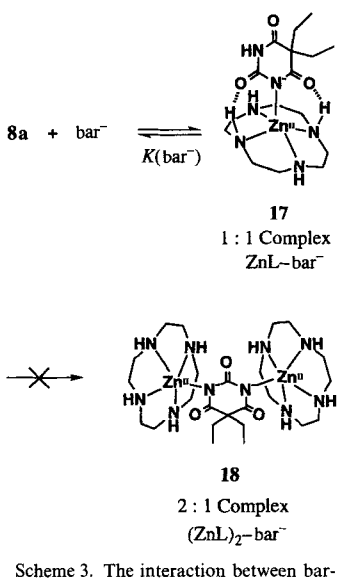


Fig. 3. Typical titration curves for barbital (**3**) and Zn^{II}–cyclen (**8a**) at 25 °C with $I = 0.10$ ($NaNO_3$); $eq(OH^-)$ is the number of equivalents of base added: a) 1.0 mM **8a**; b) 1.0 mM **3**; c) 1.0 mM **3** + 1.0 mM **8a**.

sequent 2:1 $(ZnL)_2$-bar^{2-} complex **18** (see Scheme 3). The barbital monoanion complex **17** was independently synthesized as its monoperchlorate salt by treating equimolecular amounts of **8a** and barbital sodium salt in aqueous solution. The $\log K_{bar}$-($= \log([\mathbf{17}]/[\mathbf{8a}][bar^-]\,M^{-1})$) and $\log K_{bar}$ ($= \log[\mathbf{17}]/[$uncomplexed **8**$][$uncomplexed barbital$]\,M^{-1}$) at pH 8) values were, respectively, 4.9 ± 0.1 and 4.2 ± 0.1 at 25 °C with $I = 0.10$ ($NaNO_3$), where [uncomplexed **8**] = [**8a**] + [**8b**]. These values are much smaller than the corresponding K_{bar}- and K_{bar} ($< K'_{bar}$ at physiological pH) for bis(Zn^{II}–cyclen) complex **10a** (see Table 1), enabling us to confirm that more effective recognition of barbital is achieved by the two Zn^{II}–cyclen units linked in the same molecule.



Scheme 3. The interaction between barbital and Zn^{II}–cyclen (**8a**).

Synthesis and X-ray crystal structure of (bis(Zn^{II}–cyclen)–bar^{2-})$_2$ complex (16): The bis(Zn^{II}–cyclen)–bar^{2-} complex was crystallized as its perchlorate salt from an aqueous solution (pH 8) of equimolar amounts of **10a**·$(ClO_4)_4$ and barbital sodium salt. After drying under 1 mmHg at 40 °C for 5 h, the colorless crystals changed to white powder, which indicated that some lattice water molecules in the crystal are easily removed. The elemental analysis (C, H, N) of the obtained powder suggested the formula $(Zn_2L\text{–}bar^{2-}\cdot(ClO_4)_2\cdot H_2O)_n$. The crystal of the bis(Zn^{II}–cyclen)–bar^{2-} complex was subjected to X-ray structure analysis at 25 ± 1 °C. The crystal structure provided unequivocal evidence for the cyclic 2:2 $(Zn_2L\text{–}bar^{2-})_2$ complex **16**, which is shown in Figure 4. Selected crystal data and collection parameters are given in the Experimental Section.[12] The methylene carbons of the cyclen ring, the perchlorates, and the ethyl groups of the barbital dianions are very disordered; this is reflected in the comparatively large R value of 0.104. We attempted to determine the X-ray crystal structure of **16** at a lower temperature using liquid nitrogen, but were unsuccessful owing to the formation of cracks in the crystal. We failed to isolate the originally intended 1:1 complex **15** with various other counteranions such as PF_6^-, Cl^-, NO_3^-, etc.

The complex **16** has a cyclic structure constructed with two barbital dianions (bar^{2-}) and two host complexes. The barbital dianion bridges the two Zn_2L units through the Zn^{II}–N(bar^{2-}) bonds. Each zinc(II) ion is surrounded in a distorted tetragonal

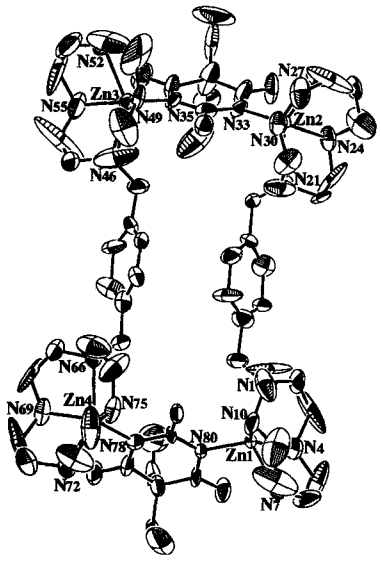
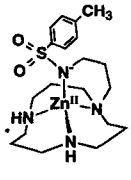


Fig. 4. ORTEP diagram (30% probability ellipsoids) of **16**. Hydrogen atoms, waters, and perchlorates are omitted for clarity. Selected bond lengths (Å): Zn1–N1 2.19(1), Zn1–N4 2.11(1), Zn1–N7 2.17(2), Zn1–N10 2.14(2), Zn1–N80 1.95(1), Zn2–N21 2.21(1), Zn2–N24 2.10(2), Zn2–N27 2.13(2), Zn2–N30 2.13(1), Zn2–N33 1.96(1), Zn3–N35 1.99(1), Zn3–N46 2.22(1), Zn3–N49 2.03(1), Zn3–N52 2.21(2), Zn3–N55 2.04(2), Zn4–N66 2.21(1), Zn4–N69 2.09(2), Zn4–N72 2.19(1), Zn4–N75 2.15(1), Zn4–N78 1.98(1). Selected bond angles (°): N1-Zn1-N80 109.8(5), N4-Zn1-N80 117.9(5), N7-Zn1-N80 113.4(5), N10-Zn1-N80 113.0(5), N21-Zn2-N33 109.7(5), N24-Zn2-N33 113.9(5), N27-Zn2-N33 111.4(6), N30-Zn2-N33 114.6(5), N46-Zn3-N35 113.5(5), N49-Zn3-N35 107.5(6), N52-Zn3-N35 111.9(6), N55-Zn3-N35 121.5(7), N66-Zn4-N78 112.9(4), N69-Zn4-N78 119.5(6), N72-Zn4-N78 106.8(5), N75-Zn4-N78 109.4(6).

pyramidal environment by the four nitrogen atoms of each cyclen and an anionic barbital nitrogen. The structure around the zinc(II) ions in **16** is similar to that of the previous five-coordinate Zn^{II}–cyclen–AZT$^-$ complex **9**.[7a] The average Zn^{II}–N^- (bar^{2-}) bond length of 1.97 Å is shorter than that of the Zn^{II}–N (cyclen) bond length of 2.15 Å. Such a high affinity of a Zn^{II} macrocyclic polyamine complex to anionic amines has been observed in the Zn^{II}–N^- (sulfonamide) bond length (1.925 Å) of Zn^{II}–tosylamidopropyl[12]aneN$_3$ complex **19**[13] and Zn^{II}–N^- (thymine) bond length (1.987 Å) of Zn^{II}–(acridine-pendant-cyclen)(1-methylthymine) complex **20**.[7b] The present structure is compatible with our earlier findings that the strongly acidic zinc(II) in macrocyclic polyamine complexes prefers N^- anions over neutral nitrogen donors.[7, 9, 13] Although the distances between the barbital carbonyl oxygens and the secondary nitrogens of the cyclen units (about 2.9–3.2 Å) seem long for hydrogen-bond formation, a little wagging of the barbital dianion in solution would permit closer contacts between them for the formation of direct (or indirect through water molecules) hydrogen bonds.



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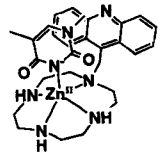

20

NMR study of the 2:2 complex 16 in DMSO and aqueous solution: Because of the poor solubility (< 20 mM) of **16** in aqueous solution, we first conducted the ^1H and ^{13}C NMR study using a [D_6]DMSO solution of **16** (25 mM) at 25 °C. The NMR spectra of **16** in [D_6]DMSO showed *two* carbonyl carbon signals at $\delta = 165.3$ and 182.5, two aromatic carbon signals at $\delta = 130.7$ and 131.5, and one methyl carbon signal at $\delta = 10.1$; one aro-

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matic singlet proton signal at $\delta = 6.88$ and one triplet methyl proton signal at $\delta = 0.74$, which supports the symmetrical $(Zn_2L-bar^{2-})_2$ structure **16** (see Scheme 2 and Experimental Section). As a reference experiment, the ^{13}C NMR data of the 1:1 Zn^{II}–cyclen–bar^- complex **17** (50 mM) in [D_6]DMSO showed *three* carbonyl carbon signals ($\delta = 156.6$, 174.9 and 180.1), supporting an asymmetric barbital monoanion binding mode as shown in **17** (see Scheme 3 and Experimental Section).

However, the ^1H NMR spectral behavior of **16** differed significantly in aqueous solution. A typical ^1H NMR spectrum of **16** (0.63 mM) in D_2O (pD 8) is shown in Figure 5. The spectrum revealed three barbital methyl signals (H_a, H_b, and H_f), three barbital methylene signals (H_c, H_d, and H_g), two aromatic singlet signals (H_e and H_h) and multiplet signals (δ = 2.5–4.2) for methylene protons of cyclen units and benzyl groups. The integral ratios of $H_h/2H_e$, $H_f/2(H_a+H_b)$ and $H_g/2(H_c+H_d)$ gave a constant value of 2.0 at 2.5 mM **16**, for instance, at 25 °C with $I = 0.10$ ($NaNO_3$) in D_2O, where the integral values of H_a and H_c were equal to those of H_b and H_d, respectively. Furthermore, the integral ratios for $H_h/2(H_e)^2$ at different concentrations of **16** (0.63, 1.25, 2.5, and 5.0 mM) gave a constant value of 2.0 ± 0.1 under the same conditions. These results led us to conclude that the 2:2 complex **16** equilibrates with the 1:1 complex **15** in aqueous solution, as shown in Scheme 2. Accordingly, the barbital diethyl group (H_a, H_b, H_c, H_d for **15**, and H_f, H_g for **16**) and the aromatic protons of the bis(Zn^{II}–cyclen) (H_e for **15** and H_h for **16**) were assigned with the assistance of an NOE experiment (see Experimental Section). The integral ratio of the former ($H_h/2H_e$) serves as an index of the concentration ratio of [**16**]/[**15**]. The clear separation of the barbital ethyl signals ($H_f \rightarrow H_a$ and H_b, $H_g \rightarrow H_c$ and H_d) accompanied by the disproportionation of **16** to the postulated monomeric complex **15** is reasonable if one considers the tighter bonding (i.e., restricted conformational flexibility) of the guest barbital in **15** on the NMR time scale.

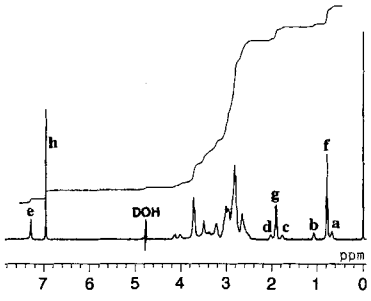

Fig. 5. Typical ^1H NMR spectra for the mixture of the 1:1 and 2:2 bis(Zn^{II}–cyclen)–bar^{2-} complexes **15** and **16** (0.63 mM as **16**) at 25 °C with $I = 0.10$ ($NaNO_3$) in D_2O (pD = 8).

In order to determine the K_d value ($= [\mathbf{16}]/[\mathbf{15}]^2\,M^{-1}$), ^1H NMR spectra for 5.0, 2.5, 1.25, and 0.63 mM of **16** were recorded at 25, 35, 45, and 55 °C with $I = 0.10$ ($NaNO_3$) in 10% (v/v) D_2O/H_2O solution, where the ^1H NMR signal patterns are similar to those in Figure 5. From the total concentration of zinc(II) species and the complex ratio of [**16**]/[**15**], we estimated the concentration of **15** and **16**, which then allowed calculation of $\log K_d$, which was 3.38 ± 0.05 (at 25 °C), 3.19 ± 0.05 (35 °C), 3.01 ± 0.05 (45 °C), and 2.86 ± 0.05 (55 °C): the lower the temperature, the greater the K_d value. The K_d value at 25 °C is almost the same as that determined by the potentiometric pH titration (see Table 1). The thermodynamic parameters for the equilibrium $2(\mathbf{15}) \rightleftharpoons \mathbf{16}$ were determined from the temperature dependency of those $\log K_d$ values. The van't Hoff plot of $\ln K_d$ against $1/T$ (K^{-1}) gives a line which affords estimated values of $\Delta G = -(1.9 \pm 0.1) \times 10^4\,J\,mol^{-1}$, $\Delta H = -(3.3 \pm 0.1) \times 10^4\,J\,mol^{-1}$ and $\Delta S = -49 \pm 2\,J\,mol^{-1}\,K^{-1}$ at 25 °C. The dimerization reaction of **15** to **16** is exothermic, possibly as a result of release of the strain energy of **15**, as indicated by the somewhat hindered barbital binding mode (Scheme 2).

Molecular mechanics (MM2) calculations revealed the minimum-energy structures for **15** and **16** at 300 K (Fig. 6). One mole of **16** is more stable than two moles of **15** by -73.9 kJ, calculated from E_{total} values for **15** ($-151.3\,kJ\,mol^{-1}$) and **16** ($-376.5\,kJ\,mol^{-1}$). The breakdown of E_{total} into seven energy terms is shown in the Experimental Section. The greatest contribution for the stability difference between **15** and **16** is the difference in bond angle energy ΔE_{ba} of -57.2 kJ.

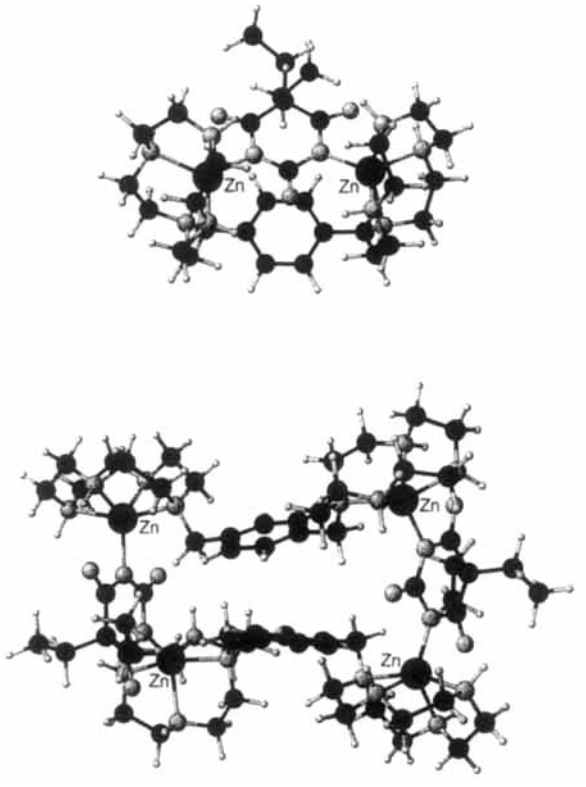

Fig. 6. Minimum-energy structures of 1:1 complex **15** (above) and 2:2 complex **16** (below) calculated by MM2.

Since the X-ray crystal structure of **16** revealed a new macrocyclic cavity with two composite benzene rings (approx. 4 Å distance), we tested whether this space could accommodate aromatic compounds such as 1,4-dinitrobenzene and *p*-toluene sulfonate, which would favor dimerization to form **16**. However, the ^1H NMR spectra (in D_2O) of **16** (2.5 mM) in the presence of the potential guest molecules (e.g., saturated 1,4-dinitrobenzene (ca. 0.5 mM) or *p*-toluene sulfonate (10 mM)) did not show any unusual chemical shifts. We interpret this to mean that the macrocyclic cavity of **16** is too small to sandwich aromatic guests.

Conclusions

A new bis(Zn^{II}–cyclen) complex **10a**, which consists of two Zn^{II}–cyclen complexes and a *p*-xylene bridge, has been synthesized for the recognition of dianionic forms of barbiturates *in aqueous solution*. As anticipated, **10a** very firmly chelates with barbital (**3**, as the dianion) at physiological pH in the 1:1 complex **15** and also in the 2:2 cyclic complex **16**. The latter complex **16** was obtained as crystals and its structure confirmed by X-ray

diffraction study. Although we failed to isolate the originally intended 1:1 complex **15**, we identified it in equilibrium with **16** in aqueous solution by NMR. pH-metric titration of **10a** and **3** established the 1:1 and 2:2 complex stability constants, which showed that the formation of the host–guest complexes **15** and **16** was favored over the 1:1 (Zn^{II}–cyclen)–bar^- complex **17**.

Experimental Section

General information: All reagents were of analytical reagent grade (purity > 99%) and were used without further purification. All aqueous solutions were prepared with deionized and distilled water. IR spectra were recorded on a Shimadzu FTIR-4200 spectrophotometer. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL α-400 spectrometer at the desired temperature ±0.5 °C. [2,2,3,3-D_4]-3-(Trimethylsilyl)propionic acid sodium salt in aqueous solution and tetramethylsilane in [D_6]DMSO were used as internal references for ^1H and ^{13}C NMR measurements.

Synthesis of 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene octahydrobromic acid salt (13·$(HBr)_8$·$4H_2O$): A $CHCl_3$ solution (25 mL) of 1,4-bis(bromomethyl)benzene **12** (1.32 g, 5.0 mmol) was added dropwise in a $CHCl_3$ solution (100 mL) of 1,4,7,10-tetraazacyclododecane **11** (5.17 g, 30 mmol). The mixture was allowed to react at room temperature overnight. After the solution had been washed with two 50 mL portions of water to remove excess **11**, the organic phase was separated and evaporated. The oily residue was purified by silica gel column chromatography (eluent: 28% aqueous NH_3/MeOH/$CHCl_3$ = 1:5:25) followed by crystallization from 48% aqueous HBr/EtOH to obtain colorless crystals of 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene **13** as its octahydrobromic acid salt (**13**·$(HBr)_8$·$4H_2O$) in 50% yield. IR (KBr pellet): $\tilde{\nu}$ = 3507, 3437, 2996, 2818, 2683, 1607, 1572, 1491, 1431, 1413, 1251, 1206, 1016, 993, 959, 829, 815, 771 cm^{-1}; ^1H NMR (D_2O): δ = 2.93 (t, J = 5.2 Hz, 8H, NCH), 3.02 (br, 8H, NCH), 3.17 (t, J = 5.2 Hz, 8H, NCH), 3.24 (br, 8H, NCH), 3.89 (s, 4H, ArCH), 7.44 (s, 4H, ArH); ^{13}C NMR (D_2O): δ = 44.8, 45.0, 47.3, 50.6, 59.0, 133.4, 137.6. Anal. ($C_{24}H_{62}N_8O_4Br_8$): calcd C 24.7, H 5.4, N 9.6; found C 24.8, H 5.5, N 9.6.

Synthesis of 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene bis(zinc(II)) complex (10a·$(ClO_4)_4$·$2H_2O$): An aqueous solution (10 mL) of **13**·8HBr·$4H_2O$ (0.47 g, 0.40 mmol) was passed through an anion exchange column (Amberlite IRA-400). To the obtained acid-free ligand **13** was added an EtOH solution (30 mL) of $Zn(ClO_4)_2$·$6H_2O$ (0.38 g, 1.0 mmol) and the mixture was heated to 60 °C. After the solvent had been evaporated, the residue was crystallized from 0.1 M $NaClO_4$ aqueous solution to afford 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)-benzene) bis(zinc(II)) complex as colorless crystals (**10a**·$(ClO_4)_4$·$2H_2O$) in 60% yield [14]. IR (KBr pellet): $\tilde{\nu}$ = 3436, 3200, 2928, 2880, 1620, 1460, 1356, 1294, 1251, 1144, 1117, 1090, 982, 855, 733, 627 cm^{-1}; ^1H NMR (D_2O): δ = 2.82–3.13 (m, 32H, NCH), 4.01 (s, 4H, ArCH), 7.42 (s, 4H, ArH); ^{13}C NMR (D_2O): δ = 45.0, 46.5, 47.3, 52.0, 58.4, 134.1, 135.1. Anal. ($C_{24}H_{54}N_8O_{20}Cl_4Zn_2$): calcd C 27.5, H 5.2, N 10.7; found C 27.7, H 5.4, N 10.6. The stability of **10** in 10% (v/v) D_2O/H_2O was determined by ^1H NMR and pH change of the solution at 25 °C and pH = 5.2, 7.8, and 10.0. Each ^1H NMR spectrum of **10** (1 mM) was assignable to one species (e.g., the data at pH 5.2 are almost the same as the above ^1H NMR data for **10** in D_2O). The solution pH remained unchanged to within 0.05 pH unit after 2 h (a standard pH titration time) under an argon atmosphere.

Synthesis of 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene bis(zinc(II)) barbital^{2-} complex (16·$(ClO_4)_4$): To an aqueous solution (50 mL) of **10a**·$(ClO_4)_4$·$2H_2O$) (0.52 g, 0.50 mmol) was added barbital sodium salt (0.10 g, 0.50 mmol) and the solution pH was adjusted to 8 with 10 M NaOH aqueous solution at room temperature. Colorless crystals of 1,4-bis(1,4,7,10-tetraazacyclododecan-1-ylmethyl)benzene bis(zinc(II)) barbital^{2-} complex **16** as its tetraperchlorate salt containing three lattice water molecules (determined by X-ray crystal structure analysis) were obtained in 80% yield by slow evaporation at 25 °C. After drying the crystals under 1 mmHg at 40 °C for 5 h, a water molecule was removed from the asymmetric crystal unit. IR (KBr pellet): $\tilde{\nu}$ = 3420, 3300, 2966, 2930, 2878, 1599, 1578, 1456, 1445, 1390, 1325, 1144, 1115, 1090, 976, 856, 818, 795, 625 cm^{-1}; ^1H NMR ([D_6]DMSO, 25 mM as the 2:2 complex **16**): δ = 0.74 (t, J = 7.2 Hz, 6H, CH_3), 1.77 (q, J = 7.2 Hz, 4H, CH_2), 2.5–3.2 (m, 16H, NCH), 3.56 (br, 4H, NH), 3.90–4.03 (br, 6H, ArCH, NH), 6.88 (s, 4H, ArH), where small signals of unremovable impurity were observed at δ = 1.00 (t), 1.63 (q), 1.91 (q), and 7.13 (s) [15]; ^1H NMR (D_2O, 2.5 mM as the 2:2 complex): δ = 0.68, 0.79, and 1.07 (CH_3); 1.78, 1.90, and 2.02 (CH_2); 2.5–4.2 (NCH), 6.96 and 7.29 (ArH). The ^1H NMR signal in D_2O was assigned by an NOE experiment (upon irradiation of aromatic protons H_e) in which 1.2% NOE for $H_e \rightarrow H_b$ was observed. ^{13}C NMR ([D_6]DMSO, 25 mM as the 2:2 complex): δ = 10.1, 32.2, 42.1, 43.8, 44.2, 48.5, 54.5, 55.2, 130.7, 131.5, 165.3, 182.5. Anal. ($C_{64}H_{116}N_{20}O_{24}Cl_4Zn_4$): calcd C 39.4, H 6.0, N 14.3; found C 39.1, H 5.8, N 14.2.

Synthesis of (Zn^{II}–cyclen)–bar^- complex (17·ClO_4): Barbital sodium salt (0.10 g, 0.5 mmol) and Zn^{II}–cyclen·$(ClO_4)_2$·H_2O (0.23 g, 0.5 mmol) [9a] were dissolved in distilled water (20 mL) at 60 °C. When the solution was concentrated to approx. 5 mL, (Zn^{II}–cyclen)–bar^- complex (**17**·ClO_4) was obtained as colorless needles in 60% yield. IR (KBr pellet): $\tilde{\nu}$ = 3450, 3299, 2967, 2932, 1707, 1682, 1613, 1447, 1402, 1373, 1331, 1255, 1179, 1121, 1092, 972, 868, 812, 625 cm^{-1}; ^1H NMR ([D_6]DMSO, 50 mM): δ = 0.73 (t, J = 7.3 Hz, 6H, CH_3), 1.77 (q, J = 7.3 Hz, 4H, CH_2), 2.60–2.80 (m, 16H, NCH), 3.75 (4H, NH(cyclen)), 10.8 (1H, NH(barbital)); ^{13}C NMR ([D_6]DMSO, 50 mM): δ = 9.51, 31.5, 43.6 (cyclen), 55.7, 156.6, 174.9, 180.1. Anal. ($C_{16}H_{31}N_6O_7ClZn$): calcd C 36.9, H 6.0, N 16.2; found C 37.3, H 6.1, N 16.5.

Potentiometric pH titrations: The preparation of the test solutions and the calibration of the electrode system were described earlier [9a,10,13,16]. 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 performed. Deprotonation constants of Zn^{II}-bound water (K_n = [HO^--bound species][H^+]/[H_2O-bound species]), barbital complex formation constants K_{bar^-} (= [bar^--bound complex]/[receptor][bar^-]) and $K_{bar^{2-}}$ (= [bar^{2-}-bound complex][H^+]/[bar^--bound complex]), and dimerization constant K_d were determined by means of the program BEST [11]. All sigma fit values defined in the program are smaller than 0.005. The K_w (= $a_{H^+} \cdot a_{OH^-}$), K'_w (= [H^+][OH^-]) and f_{H^+} values used are $10^{-14.00}$, $10^{-13.79}$, and 0.825, respectively. The mixed constants (K_n = [HO^--bound species]a_{H^+}/[H_2O-bound species] and $K_{bar^{2-}}$ = [bar^{2-}-bound complex]a_{H^+}/[bar^--bound complex]) are derived from K'_n and $K'_{bar^{2-}}$ by [H^+] = a_{H^+}/f_{H^+}.

Crystallographic study: A colorless prismatic crystal (0.35 × 0.20 × 0.10 mm) of **16**·$(ClO_4)_4$·$3H_2O$ ($C_{64}H_{118}N_{20}O_{25}Cl_4Zn_4$, M_r = 1971.1) sealed in a glass capillary was used for data collection. The lattice parameters and intensity data were measured on a Rigaku Raxis II area detector with graphite monochromated $Mo_{K\alpha}$ radiation (μ = 11.14 cm^{-1}) at 25 ± 1 °C. Indexing was performed from 3 stills which were exposed for 10 min. A total of 40 oscillation (5.0°) images were collected, each being exposed for 60 min. The crystal-to-detector distance was 90 mm and the detector swing angle was 0.0°. Readout was performed in the 105 μm pixel mode. The structure was solved by direct methods (SHELXS86) and expanded by means of Fourier techniques (DIRDIF92). All calculations were performed with the teXsan crystal structure analysis package developed by Molecular Structure Corporation (**1985**, **1992**). Crystal data: triclinic, space group $P\bar{1}$ (No.2), a = 17.127(5) Å, b = 21.552(4) Å, c = 14.229(6) Å, α = 102.36(2)°, β = 99.34(3)°, γ = 86.02(2)°, V = 5058(2) Å^3, Z = 2, D_{calcd} = 1.294 g cm^{-3}, $2\theta_{max}$ = 46.2°, total no. of reflns = 8895. Non-hydrogen atoms of the 2:2 complex unit **16** and three water oxygen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms, except those of water molecules, were included but not refined. The final cycle of full-matrix least-squares refinement was based on 6154 observed reflns (I > 5.00 $\sigma(I)$) and 927 variable parameters, and converged (largest parameter was 0.02× its esd) with R (= $\sum||F_o| - |F_c||/\sum|F_o|$) of 0.104 and Rw (= $(\sum w(|F_o| - |F_c|)^2/\sum wF_o^2)^{0.5}$) of 0.132. The O atoms of the Cl1 perchlorate ion are disordered at the two positions (occupancy = 0.5 and 0.5), but those of Cl2 are not disordered. The other two perchlorate ions are disordered at the four locations Cl3, Cl4, Cl5, and Cl6 with an occupancy ratio of 0.60:0.69:0.43:0.28. The disordered structures of the cyclen groups were suggested by consideration of the large anisotropy in the temperature factors of the carbon atoms, but could not be confirmed on a difference Fourier map. The uncertainty in these disordered structures might lead to a comparatively large R value.

Molecular mechanics calculations: Structure minimization for **15** and **16** was accomplished with the molecular dynamics (MD) and molecular mechanics (MM2) packages provided by the Tektronix CAChe System, Version 3.5. The structure was first minimized by MM2 at 300 K and the resulting structure submitted to MD simulation at 800 K. The lowest energy structures for **15** and **16** (Fig. 6) were obtained by further optimization by MM2 at 300 K with the block-diagonal Newton–Raphson method until the change in total energy (ΔE_{total}) became less than 0.001 kJ mol^{-1}. The energy terms (kJ mol^{-1}) for the MM2 force field are bond stretch (E_{bs}), bond angle (E_{ba}), dihedral angle (E_{da}), improper torsion (E_{it}), van der Waals (E_{vdw}), electrostatic (E_e), and hydrogen bond (E_{hb}): E_{total} = −151.3 kJ mol^{-1} for **15** (E_{bs} = 46.3, E_{ba} = 286.1, E_{da} = 34.7, E_{it} = 0.5, E_{vdw} = 18.9, E_e = −528.2, and E_{hb} = −9.6); E_{total} = −376.5 kJ mol^{-1} for **16** (E_{bs} = 96.8, H_{ba} = 515.0, H_{da} = 84.7, H_{it} = 0.3, H_{vdw} = −16.3, H_e = −1040.0, and H_{hb} = −17.0).

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