

New supramolecular trigonal prisms from zinc(II)–1,4,7,10-tetraazacyclododecane (cyclen) complexes and trithiocyanurate in aqueous solution

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The multiple bonding between multinuclear zinc(II)–1,4,7,10-tetraazacyclododecane (cyclen, a 12-membered tetraamine) complexes and multidentate ligands is an effective method for constructing supramolecular complexes having well defined and distinct structures in aqueous solution. Herein we present examples of supramolecular D_{3h} prisms formed by self-assembly of linearly dimeric or trimeric zinc(II)–cyclen complexes with a potentially trianionic C_3 subunit trithiocyanuric acid (TCA^{3-}), wherein $Zn^{2+}-S^-$ or $Zn^{2+}-N^-$ coordination bonds and hydrogen bonds are responsible for the multicomponent architectures in aqueous solution at neutral pH.

Artificial supramolecular hosts with stable and well defined structures formed by spontaneous self-assembly of molecular building blocks in organic solvents have shown great potential for inclusion phenomena, molecular recognition, or catalysis (1–12). However, supramolecular complexes that operate in aqueous solution are rare (10–14). While working on molecular recognition of imide functions by zinc(II) complexes of 12-membered tetraamine [Zn^{2+} –1,4,7,10-tetraazacyclododecane (cyclen)] in aqueous solution (15–28), we tested interaction of cyanuric acid (CA) containing C_3 -symmetric three-imide functions with a C_3 -symmetric trinuclear zinc(II)–cyclen, $Tris(Zn^{2+}$ –cyclen) **1** [Zn_3L^1 ; $L^1 = 1,3,5$ - $Tris(1,4,7,10$ -tetraazacyclododecan-1-ylmethyl)benzene]. We have discovered quantitative formation of a 2:3 1–dianionic CA (CA^{2-}) complex at neutral pH that is represented schematically as a trigonal prism **2** (Fig. 1; ref. 29). More interestingly, we accidentally isolated a 4:4 assembly [$(Zn_3L^1)_4-(CA^{3-})_4$] from basic aqueous solution. The x-ray crystal structure showed four sets of completely deprotonated CA (CA^{3-}) binding to three Zn^{2+} –cyclen units from three different Zn_3L^1 at each N^- rim (29). Its outer shape may be viewed as a cuboctahedron **3a** with 12 vertices occupied by Zn^{2+} and its inner shell as a truncated tetrahedron **4a**. It was unfortunate, however, to find that this 4:4 cuboctahedral complex collapsed in neutral H_2O , possibly because of the extremely high pK_a value of the third imide proton of CA. More recently (30), this problem was overcome by replacing CA for TCA, the thioimide functions of which possess lower pK_a values [5.12 (pK_1), 8.24 (pK_2), and 11.69 (pK_3)] than those of CA [6.85 (pK_1), 10.91 (pK_2), and >12 (pK_3)]. As anticipated, TCA acted as a tridentate donor for three Zn_3L^1 at neutral pH to yield a similar type of the 4:4 self-assembling supercomplex **3b**, in which the deprotonated TCA^{3-} in an aromatic 1,3,5-triazine bound to **1** through $Zn^{2+}-S^-$ (exocyclic) coordination bonds, and thus the 4:4 assembly is a chiral, twisted cuboctahedron. More interestingly, **3b** [$(Zn_3L^1)_4-(TCA^{3-})_4$] encapsulates various size-matched and hydrophobic guest molecules such as adamantane in its inner cavity, which is represented as a twisted, truncated tetrahedron **4b**. Thus, we discovered an approach to design various supramolecular structures in aqueous solution.

Meanwhile, we had designed a linearly trimeric zinc(II) complex **8** (abbreviated here as p,p - Zn_3L^4), which has three (Zn^{2+} –cyclen) units connected by two p -xylyl units, to examine selective

and efficient recognition of three linear imide functions, i.e., thymidyl(3′-5′)thymidyl(3′-5′)thymidine [$d(TpTpT)^{2-}$] (Fig. 2; ref. 31). As anticipated, extremely efficient association was found with the dissociation constant (K_d) of 0.8 nM for p,p - Zn_3L^4 – $[d(TpTpT)^{5-}]$ complex **9** in aqueous solution at neutral pH, which was 1,000 times smaller than that (0.6 μ M) for a dimeric Zn^{2+} –cyclen **5**– $[d(TpT)^{3-}]$ complex **7** (31–33).

In the present work, we extended our previous principles to construct spherical supermolecules having a distinct structure by using TCA and various linear multi(Zn^{2+} –cyclen) complexes as building blocks. We have succeeded in synthesizing supramolecular trigonal prisms **10a** and **10b** from Zn_2L^2 **5** and Zn_2L^3 **6**, and another prism **11** from p,p - Zn_3L^4 **8** with TCA^{3-} in aqueous solution at neutral pH (Fig. 3).

Materials and Methods

All aqueous solutions were prepared by using deionized and redistilled water. Complexes **5** and **8** were prepared according to our previous papers (28, 31, 32). The Hepes {2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid, $pK_a = 7.6$ at 25°C} buffer was purchased from Dojindo Laboratories (Kumamoto, Japan) and used without further purification. Melting points were measured on Yanaco Melting Point apparatus and listed without correlation. IR spectra were recorded on a Horiba Fourier transform infrared spectrometer FT-710. 1H and ^{13}C NMR spectra were recorded on a JEOL Alpha 400-MHz or Lambda 500-MHz spectrometer. 3-(Trimethylsilyl)propionic-2,2,3,3- d_4 acid sodium salt (TSP) in D_2O or 1,4-dioxane were used as external references of 1H NMR and ^{13}C NMR experiments, respectively. The pD values in D_2O were corrected for a deuterium isotope effect by using $pD = (pH - \text{meter reading}) + 0.40$. Elemental analysis was performed on a Perkin-Elmer CHN Analyzer 2400.

Isolation of 10a·6NO₃·6H₂O. **5**·4(NO_3^-)·2 H_2O (124 mg, 0.14 mmol; refs. 26 and 30), TCA (18 mg, 0.10 mmol), and $NaNO_3$ (0.84 g, 9.9 mmol) were dissolved in H_2O (50 ml), and the pH was adjusted to 8.0 ± 0.1 by the addition of aqueous NaOH. The whole mixture was filtered and concentrated slowly *in vacuo* for 1 week, and colorless prisms of **10a**·6(NO_3^-)·6 H_2O (80 mg, 67% yield) were obtained. mp $> 250^\circ C$. IR (KBr): 3,450, 3,234, 2,924, 2,876, 2,361, 1,652, 1,428, 1,384, 1,230, 1,093, 970, 844 cm^{-1} . 1H NMR (400 MHz, D_2O /external TSP): δ 3.03–3.07 (96H, m, CH_2 of cyclen), 3.55 (12H, brs, Ar CH_2), 6.82 (12H, brs, ArH). ^{13}C NMR (100 MHz, D_2O): δ 42.00, 43.60, 44.08, 48.24, 54.41,

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Abbreviations: cyclen, 1,4,7,10-tetraazacyclododecane; CA, cyanuric acid; TCA, trithiocyanuric acid; TSP, 3-(trimethylsilyl)propionic-2,2,3,3- d_4 acid sodium salt; ESI, electrospray ionization.

Data deposition: The atomic coordinates have been deposited in the Cambridge Structural Database, Cambridge Crystallographic Data Centre, Cambridge CB2 1EZ, United Kingdom (CSD reference no. 174993).

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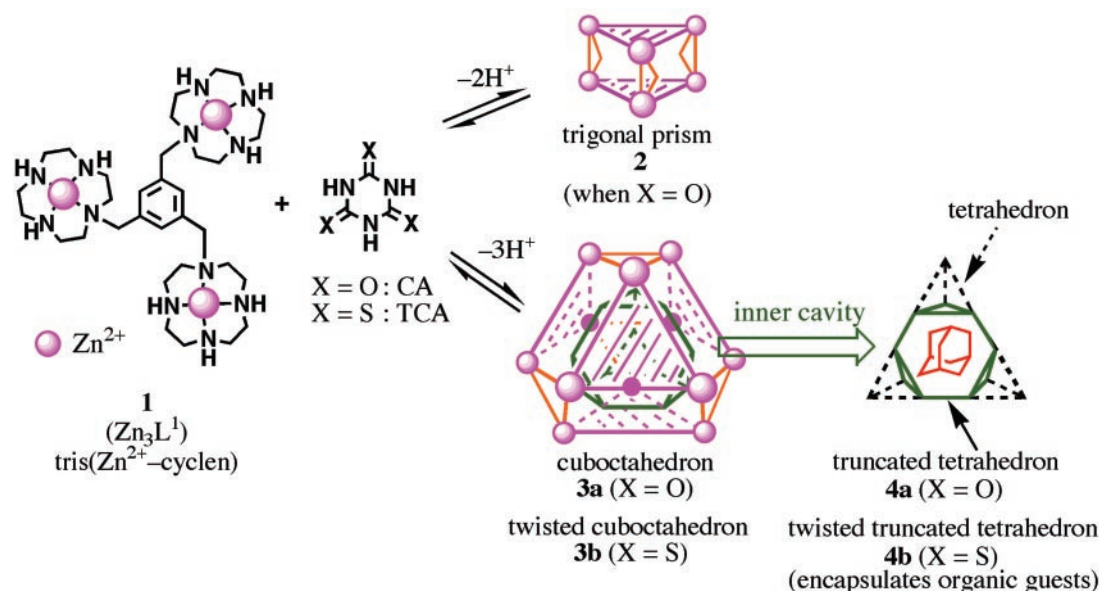


Fig. 1. Supramolecular self-assemblies to trigonal prism and cuboctahedral complexes from $\text{Tris}(\text{Zn}^{2+}\text{-cyclen})$ **1** and CA and trithiocyanuric acid (TCA) in aqueous solution.

130.23, 130.69, 183.36. Elemental analysis: calculated for $\text{C}_{78}\text{H}_{150}\text{N}_{36}\text{O}_{24}\text{S}_6\text{Zn}_6$, C, 36.58; H, 5.90; N, 19.69; Found: C, 36.86; H, 5.84; N, 19.53.

Isolation of $\mathbf{10b} \cdot 6\text{NO}_3 \cdot 10\text{H}_2\text{O}$. $6 \cdot 2(\text{SO}_4^{2-}) \cdot 4\text{H}_2\text{O}$ (123 mg, 0.13 mmol, for synthesis, see *Synthesis of $6 \cdot 2(\text{SO}_4^{2-}) \cdot 4\text{H}_2\text{O}$* , which is published as supporting information on the PNAS web site, www.pnas.org), TCA (16 mg, 0.09 mmol), and NaNO_3 (0.11 g, 1.29 mmol) were dissolved in H_2O (50 ml), and the pH was adjusted to 8.0 ± 0.1 by the addition of aqueous NaOH. The whole mixture was filtered and concentrated slowly *in vacuo* for 1 week, and colorless powders of $\mathbf{10b} \cdot 6(\text{NO}_3^-) \cdot 10\text{H}_2\text{O}$ (110 mg, 86% yield) were obtained. mp $> 250^\circ\text{C}$. IR (KBr): 3,432, 3,220, 2,922, 2,875, 1,628, 1,429, 1,383, 1,231, 1,092, 968 cm^{-1} . ^1H NMR (400 MHz, D_2O /external TSP): δ 2.65–2.74 (12H, m, CH_2 of cyclen), 2.76–2.98 (48H, m, CH_2 of cyclen), 3.04–3.17 (24H, m, CH_2 of cyclen), 3.23–3.36 (12H, m, CH_2 of cyclen), 3.88 (12H, brs, ArCH_2), 6.89 (12H, d, $J = 8.4$ Hz, ArH), 7.04 (12H, d, $J = 8.4$ Hz, ArH). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): δ 46.11, 17.79, 48.05, 52.31, 58.90, 129.88, 134.53, 134.82, 142.53, 187.56. Elemental analysis: calculated for $\text{C}_96\text{H}_{170}\text{N}_{36}\text{O}_{28}\text{S}_6\text{Zn}_6$, C, 40.60; H, 5.99; N, 17.62; Found: C, 40.59; H, 5.81; N, 17.56.

Isolation of $\mathbf{11} \cdot 9\text{NO}_3 \cdot 21.5\text{H}_2\text{O}$. $8 \cdot 6(\text{NO}_3^-) \cdot 6\text{H}_2\text{O}$ (68 mg, 0.05 mmol; ref. 29), TCA (9 mg, 0.05 mmol), and NaNO_3 (0.38 g, 4.4 mmol) were dissolved in H_2O (50 ml), and the pH was adjusted to 8.0 ± 0.1 by the addition of aqueous NaOH. The whole mixture was filtered and concentrated slowly *in vacuo* for 1 week, and colorless prisms of $\mathbf{11} \cdot 9(\text{NO}_3^-) \cdot 21.5\text{H}_2\text{O}$ (42 mg, 60% yield) were obtained. mp $> 250^\circ\text{C}$. IR (KBr): 2,924, 2,876, 1,456, 1,433, 1,384, 1,231, 1,094 cm^{-1} . ^1H NMR (400 MHz, D_2O /external TSP): δ 2.60–2.95 (36H, m, CH_2 of cyclen), 3.05–3.41 (108H, m, CH_2 of cyclen), 3.72 (12H, brs, ArCH_2), 3.88 (12H, brs, ArCH_2), 6.91 (12H, d, $J = 8.0$ Hz, ArH), 7.02 (12H, d, $J = 8.0$ Hz, ArH). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6/\text{D}_2\text{O}$): δ 42.73, 43.03, 43.58, 44.37, 44.47, 45.08, 49.39, 49.61, 55.41, 56.02, 129.21, 130.74, 131.39, 131.87, 132.64, 184.44, 184.90. Elemental analysis: calculated for $\text{C}_{129}\text{H}_{259}\text{N}_{54}\text{O}_{48.5}\text{S}_9\text{Zn}_9$, C, 36.72; H, 6.19; N, 17.92; Found: C, 36.81; H, 6.00; N, 17.65.

Selected X-Ray Structural Analysis Data for $\mathbf{11} \cdot 9\text{NO}_3 \cdot 21.5\text{H}_2\text{O}$. Formula $\text{C}_{129}\text{H}_{259}\text{N}_{54}\text{O}_{48.5}\text{S}_9\text{Zn}_9$, molecular weight = 4,219.76, crystal dimension $0.30 \times 0.20 \times 0.15$, space group P1 (No. 2), $a = 15.465(2)$ Å, $b = 21.438(2)$ Å, $c = 29.380(3)$ Å, $\alpha = 92.417(2)^\circ$, $\beta = 94.281(1)^\circ$, $\gamma = 95.367(3)^\circ$, $V = 9,659(2)$ Å³, $Z = 2$, $D_{\text{calcd}} = 1.45$ g·cm⁻³, $\mu(\text{Mo K}\alpha) = 15.41$ cm⁻¹, $\lambda(\text{Mo K}\alpha) = 0.71069$ Å; unique reflection collected (completeness = 0.83) on a Rigaku RAXIS-RAPID imaging plate diffractometer at 123.2 K; $2\theta_{\text{min}} = 10.0^\circ$, $2\theta_{\text{max}} = 51.0^\circ$, $R = 0.14$ for reflections with $I > 2\sigma(I)$, $R = 0.22$ for all reflections; number of variables, 1,369. For CIF1 for $\mathbf{11} \cdot 9\text{NO}_3 \cdot 21.5\text{H}_2\text{O}$, see Table 1, which is published as supporting information on the PNAS web site. Crystallographic data (excluding structure factors) for $\mathbf{11} \cdot 9\text{NO}_3 \cdot 21.5\text{H}_2\text{O}$ have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-174993 (copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, U.K.).

Potentiometric pH Titrations. Potentiometric pH titrations were carried out with $I = 0.10$ (NaNO_3) at $25.0 \pm 0.1^\circ\text{C}$ (0.1 N NaOH was used as a base) as described earlier (19–26, 28–32), and at least two independent titrations were performed. Deprotonation constants of Zn^{2+} -bound water K^2 ($= [\text{HO}^- \text{-bound species}][\text{H}^+]/[\text{H}_2\text{O-bound species}]$) and apparent affinity constants K_{app} (defined by Eqs. 1–4 were determined by means of the program BEST (34). The species distribution values (%) against pH ($= -\log[\text{H}^+] + 0.084$) were obtained by using the program SPE (34).

UV Spectrophotometric Titrations and Fluorescence Titrations. UV spectra and fluorescence (excitation and emission) spectra were recorded on a Hitachi U-3500 spectrophotometer and a Hitachi F-4500 fluorescence spectrophotometer, respectively, at $25.0 \pm 0.1^\circ\text{C}$. The obtained data of UV titrations (decreases in ϵ values at a given wavelength) and fluorescence titrations (decreases in fluorescence emission intensity at a given wavelength) were analyzed for apparent complexation constants, K_{app} , by using the program BIND WORKS (Calorimetry Sciences, Provo, UT). Quantum yield (Φ) of fluorescence was determined by comparison of the integrated corrected emission spectrum of a standard an-

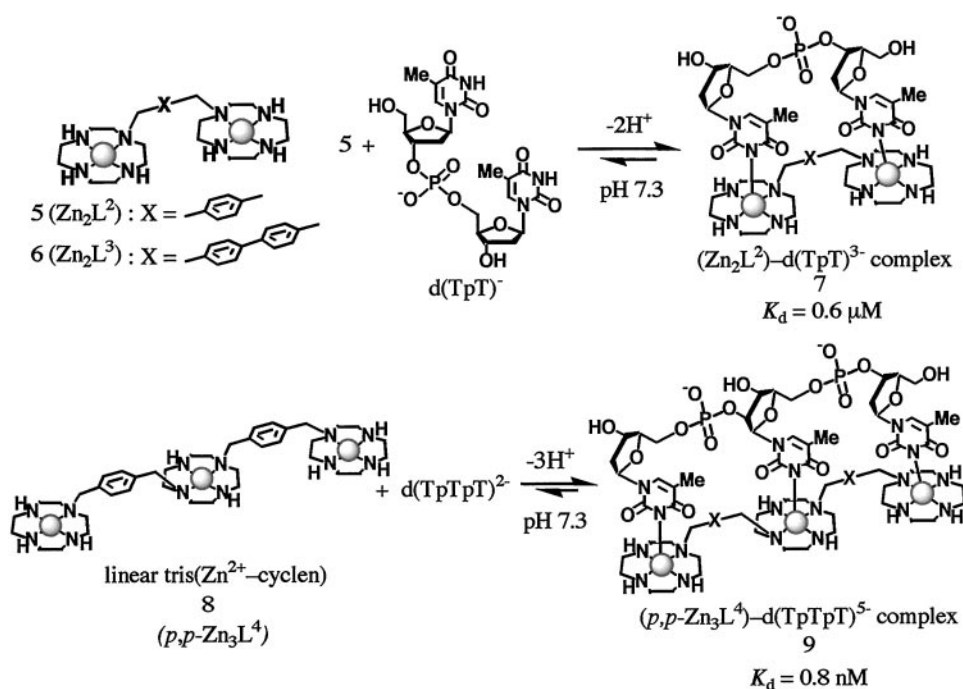


Fig. 2. Selective and efficient recognition of d(TpT) and d(TpTpT) by bis(Zn^{2+} -cyclen) **5** and linear Tris(Zn^{2+} -cyclen) **8** in aqueous solution at neutral pH.

thracene, the quantum yield of which in EtOH was assumed to be 0.30 ([anthracene] = 10 μM , excitation at 260 nm; ref. 35).

Electrospray Ionization (ESI) MS of 10a, 10b, and 11 Complexes. ESI mass spectra were recorded on an LCT (reflectron time-of-flight MS) mass spectrometer (Micromass, Manchester, U.K.). Aqueous solutions (100–200 ng/ μl) of given complexes were analyzed by direct infusion at 10 $\mu\text{l}/\text{min}$. In the positive-ion mode the following conditions were used: ES capillary, 2.8 kV; cone, 10–15 V; flight time, 55 μsec ; source block temperature, 20°C; desolvation temperature, 40°C. Mass spectra were scanned in the m/z range of 100–2,000 at 1 sec/scan with an interscan delay of 0.1 sec. Data were processed by using the spectrometer software (MASSLYNX). Theoretical distribution for the 2+ to 6+ species for **10** and 3+ to 9+ species for **11** with mass-to-charge ratios (m/z) were calculated by using the program MASSLYNX.

Results and Discussion

Isolation of Supramolecular Trigonal Prisms. Mixing Zn_2L (**5** or **6**) and TCA in a 3:2 ratio at pH 8.0 in aqueous solution and slow

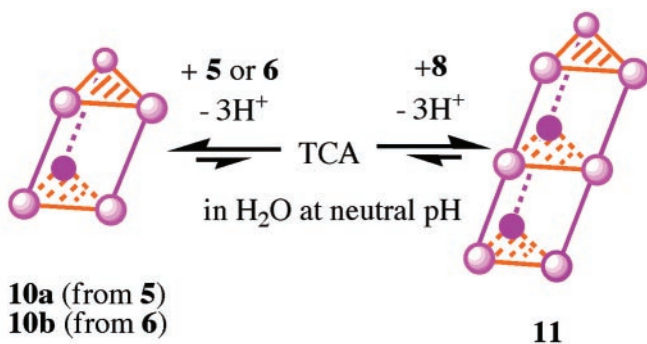


Fig. 3. Schematic presentation of trigonal prisms (D_{3h}) **10** and **11** formed by self-assembly of TCA with a bis(Zn^{2+} -cyclen) (**5** or **6**) and a linear Tris(Zn^{2+} -cyclen) **8** in aqueous solution at neutral pH.

evaporation yielded colorless prisms. Their elemental analyses (C, H, N) were consistent with a formula $[\text{Zn}_2\text{L}^2 \text{ (or } \text{Zn}_2\text{L}^3)]_3\text{-}(\text{TCA}^{3-})_2$, **10**. From a 1:1 mixture of $p,p\text{-Zn}_3\text{L}^4$ (**8**) and TCA, fine colorless crystals of a 3:3 complex, $(p,p\text{-Zn}_3\text{L}^4)_3\text{-}(\text{TCA}^{3-})_3$, **11** were isolated. The 3:3 structure of **11** was identified by x-ray crystallographic analysis (Fig. 4). Crystal data are presented in *Materials and Methods*. In Fig. 4A (top view) and 4B (side view), three molecules of **8** are colored in green-blue, green, and blue, and three TCA units are colored in orange with yellow sulfur atoms. Its exterior may be represented schematically as a trigonal prism **11** as shown in Fig. 3, the total prism length of which is ≈ 2.9 nm. The distance between two adjacent TCA^{3-} is ≈ 1.2 nm. Of the three TCA^{3-} units, the two terminal TCA^{3-} units bind all to Zn^{2+} ions through $\text{S}^- \text{—Zn}^{2+}$ coordination bonds (2.31 Å in average), whereby the TCA^{3-} takes an aromatic triazine form (Fig. 4C). Very interestingly, the central TCA^{3-} unit has a lesser aromatic structure with the anion localizing more on the imide Ns, which are major donors to Zn^{2+} ($\text{Zn}^{2+}\text{—N}^-$ distance is 2.07 Å in average) and supplementary $\text{Zn}^{2+}\text{—S}$ coordination (2.88 Å in average) bonds (ref. 36; Fig. 4D). As shown in Fig. 4E, three phenyl groups from three molecules of **8** are assembled very closely to each other. We assign the $\text{Zn}^{2+}\text{—S}^-$ binding structures to the first trigonal prisms **10**, as studied by the UV spectrophotometric titrations (*vide infra*).

^1H NMR Spectral Changes in Formation of the Supramolecular Complexes in D_2O at pH 7.0. We followed the binding of **5**, **6**, and **8** with TCA by ^1H NMR spectral changes in D_2O at pH 7.0 ± 0.2 and 35°C. Fig. 5A shows a broad singlet of aromatic protons of **5** (all equivalent; 3 mM) at δ 7.44 against an external reference, TSP. As we added TCA (1 and 2 mM) to **5**, Fig. 5B and C were obtained. The final broad singlet appearing at δ 6.82 indicates that a single product species is formed by assembly of **5** with TCA in a 3:2 ratio to yield **10a** in D_2O . A fact that two independent signals are observed for **5** and the **5**-TCA complex indicates that the **5**-TCA complex is not only thermodynamically but also kinetically stable on the NMR time scale (28–32). Similarly, another Zn_2L^3 (**6** (1.5 mM) with two doublets at δ 7.48 and 7.72

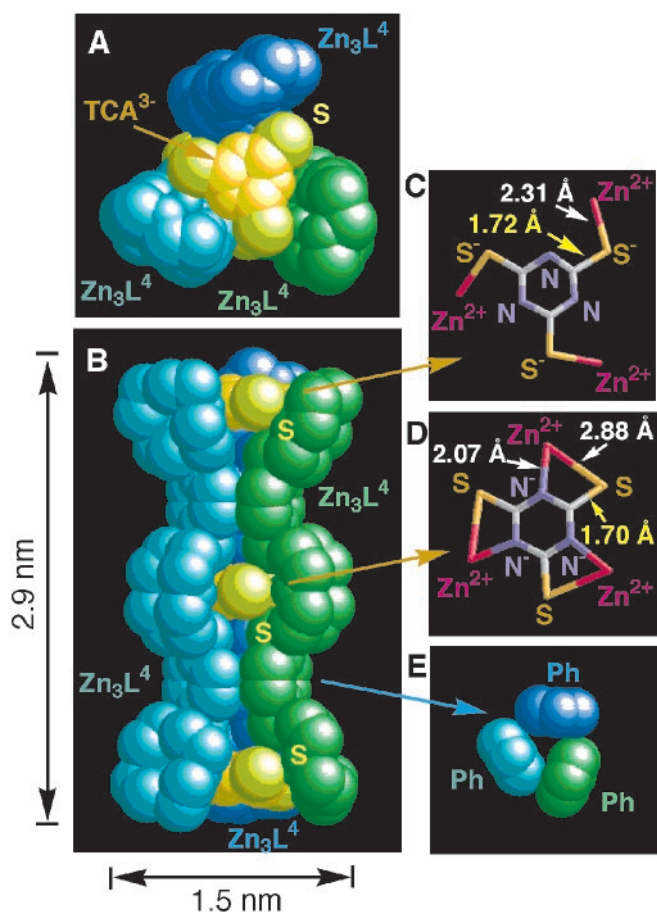


Fig. 4. X-Ray crystal structure of $11 \cdot 9\text{NO}_3 \cdot 21.5\text{H}_2\text{O}$ (A, top view; B, side view). Nitrate anions and water molecules are omitted. Three molecules of **8** are colored in green, blue-green, and blue. TCA^{3-} units are orange, and sulfur atoms are yellow. (C) Two TCA^{3-} parts at edges bind to **8** through $\text{Zn}^{2+}-\text{S}^-$ (2.31 Å in average) coordination bonds. (D) The TCA^{3-} part at the middle bind to **8** through $\text{Zn}^{2+}-\text{N}^-$ (2.07 Å in average) and $\text{Zn}^{2+}-\text{S}^-$ (2.88 Å in average) coordination bonds. (E) Three phenyl groups from three **8** units.

showed upfield shifts to δ 6.89 and 7.04 after mixing with TCA (1.0 mM) under the same conditions (Fig. 5D and E), indicating the formation of a similar 3:2 supramolecular prism **10b**.

When *p,p*- Zn_3L^4 **8** (2 mM) with a broad singlet at δ 7.44 (Fig. 5F) was mixed with TCA (2 mM), two distinct doublets at δ 6.91 and 7.02 replaced them, as shown in Fig. 5G. This fact supports the structure of the 3:3 supramolecular complex **11**, in which the benzene protons near the middle TCA and terminal TCA are in a different environment because of the different TCA— Zn^{2+} binding modes (Fig. 4). The addition of 10–50 equivalents of F^- , Cl^- , Br^- , I^- , ClO_4^- , N_3^- , and SO_4^{2-} caused negligible change of the ^1H NMR spectra of **11** (PF_6^- caused precipitation).

Potentiometric pH Titrations for the 3:3 (8/TCA) and 3:2 (5/TCA) Assemblies in Aqueous Solution. Fig. 6A shows typical pH titration curves for 0.5 mM **8** (curve a, pKa values of three Zn^{2+} -bound waters of **8** are 6.98, 7.41, and 8.02; ref. 31), 0.5 mM TCA (curve b), and 0.5 mM **8** + 0.5 mM TCA (curve c). The curve c with a distinct break at $\text{eq}(\text{OH}^-) = 3$ supports that the three protons of all TCA are deprotonated to bind with all the Zn^{2+} -cyclen units under pH 6.5. Analysis of the pH titration curves by the program BEST (34) was in good agreement with the formation of a 3:3 complex **11**. Fig. 6B is a speciation diagram of seven possible species, *p,p*- $\text{Zn}_3\text{L}^4(\text{H}_2\text{O})_3$, *p,p*- $\text{Zn}_3\text{L}^4(\text{OH}^-)_3$, TCA, TCA^- , TCA^{2-} , TCA^{3-} , and [*p,p*- Zn_3L^4] $_{3-}(\text{TCA}^{3-})_3$ (**11**), for the 0.5

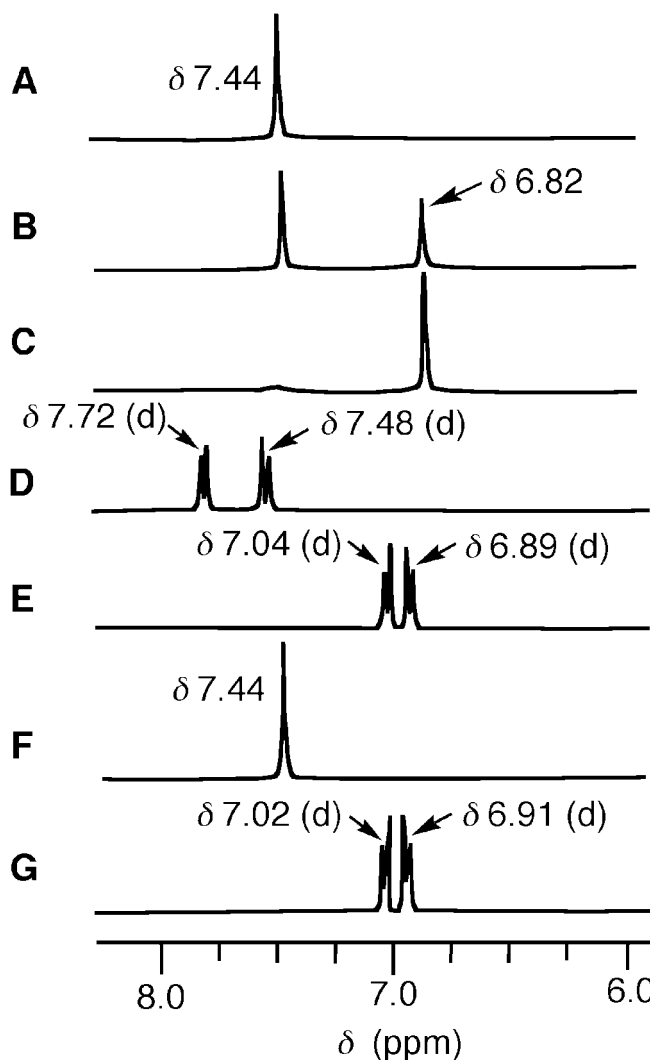


Fig. 5. The ^1H NMR spectral change of **5**, **6**, and **8** (aromatic regions) after the addition of TCA in D_2O at $\text{pD } 7.0 \pm 0.2$ and 35°C : A, 3.0 mM **5**; B, 3.0 mM **5** + 1.0 mM TCA; C, 3.0 mM **5** + 2.0 mM TCA; D, 0.5 mM **6**; E, 0.6 mM **6** + 0.4 mM TCA; F, 0.5 mM **8**; and G, 0.5 mM **8** + 0.5 mM TCA.

mM **8** + 0.5 mM TCA mixture as a function of pH at 25°C with $I = 0.1$ (NaNO_3). The nearly quantitative population of the 3:3 complex **11** is apparent at $6.4 < \text{pH} < 8.8$. The apparent 3:3 complexation constant for **11**, $\log K_{\text{app}}$ (defined by Eqs. 1–3 at pH 7.0) was calculated to be 30.6 ± 2.0 . A similar potentiometric pH titration of 0.75 mM **5** + 0.5 mM TCA gave the apparent 3:2 complexation constant for **10a**, $\log K_{\text{app}}$ (defined by Eq. 4) of 26.3 ± 1.0 at pH 8.0 and a similar speciation diagram showing $>95\%$ formation of **10a** at $7.2 < \text{pH} < 8.2$.

$$K_{\text{app}} = [\mathbf{11}]/[\text{uncomplexed } \mathbf{8}]^3[\text{uncomplexed TCA}]^3 \text{ (M}^{-5}\text{)} \quad [1]$$

$$[\text{uncomplexed } \mathbf{8}] = [\mathbf{8} \cdot (\text{H}_2\text{O})_3]_{\text{free}} + [\mathbf{8} \cdot (\text{H}_2\text{O})_2(\text{HO}^-)]_{\text{free}} + [\mathbf{8} \cdot (\text{H}_2\text{O})(\text{HO}^-)_2]_{\text{free}} + [\mathbf{8} \cdot (\text{HO}^-)_3]_{\text{free}} \quad [2]$$

$$[\text{uncomplexed TCA}] = [\text{TCA}]_{\text{free}} + [\text{TCA}^-]_{\text{free}} + [\text{TCA}^{2-}]_{\text{free}} + [\text{TCA}^{3-}]_{\text{free}} \quad [3]$$

$$K_{\text{app}} = [\mathbf{10a}]/[\text{uncomplexed } \mathbf{5}]^3[\text{uncomplexed TCA}]^2 \text{ (M}^{-4}\text{)} \quad [4]$$

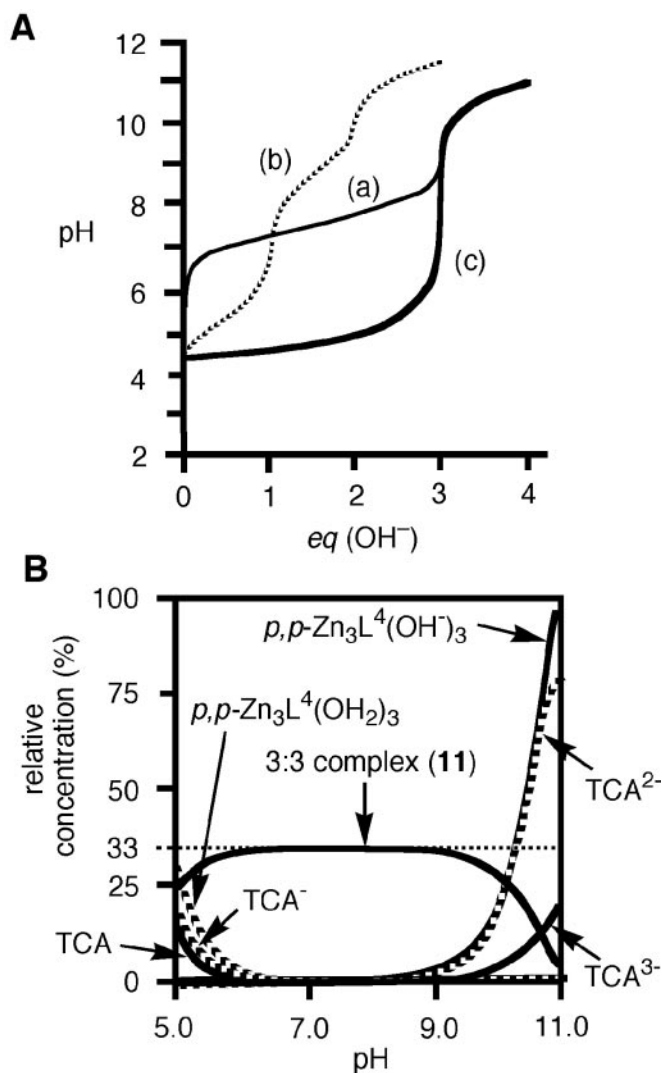


Fig. 6. (A) Typical pH titration curves of 0.5 mM **8** (a), 0.5 mM TCA (b), and 0.5 mM **8** + 0.5 mM TCA (c) in aqueous solution with $I = 0.1$ (NaNO₃) at 25°C, where $eq(OH^-)$ is the number of equivalents of base (NaOH) added. (B) Speciation diagram for the **8** and TCA species in a 0.5 mM **8**/0.5 mM TCA mixture as a function of pH at 25°C with $I = 0.10$ (NaNO₃). For clarity, the species less than 5% are omitted.

UV Spectrophotometric Titrations of the Supramolecular Complexes 10a and 11 and Fluorescence Titration of 10b. From UV spectrophotometric titration of TCA (30 μM) with **5** and **8** in 50 mM Hepes (pH 7.0) with $I = 0.1$ (NaNO₃; see Fig. 8, which is published as supporting information on the PNAS web site, www.pnas.org), almost quantitative 2:3 and 3:3 complexation to **10a** and **11**, respectively, has been established. Understanding from the result of the x-ray crystal structure analysis, considerable differences were observed for the UV spectra of TCAs in **10a** and **11**. The uncomplexed TCA has absorption maxima (λ_{max}) at 283 nm [$\epsilon 4.1 \times 10^4$ (M⁻¹·cm⁻¹)] and 323 nm [$\epsilon 2.8 \times 10^4$ (M⁻¹·cm⁻¹)] at pH 7.0 (where [TCA]:[TCA⁻]:[TCA²⁻]:[TCA³⁻] distribution is estimated to be 1:93:6:0). In the 2:3 complex **10a**, the two TCA took aromatic TCA³⁻ forms, and the UV absorption maximum shifted to λ_{max} at 268 nm with $\epsilon 4.1 \times 10^4$ (M⁻¹·cm⁻¹) per TCA unit, which was almost the same value as that [$\epsilon 4.1 \times 10^4$ (M⁻¹·cm⁻¹) at λ_{max} of 268 nm] for the aromatic TCA³⁻ moiety in the cuboctahedron **3b** (30). On the other hand, in the 3:3 complex **11** having the two

aromatic TCA³⁻ at terminals and the one less aromatic TCA³⁻ at the central prism, absorption maximum shifted to 278 nm with $\epsilon 3.1 \times 10^4$ (M⁻¹·cm⁻¹) per TCA, which corresponds to 76% of the ϵ_{268} value for the aromatic TCA³⁻ unit in **10a** (see Fig. 9, which is published as supporting information on the PNAS web site). This fact, although qualitative, supports that the middle TCA³⁻ in **11** indeed is not fully aromatic but rather in a thioketo form in aqueous solution.

The changes of fluorescence excitation and emission of **6** [10 μM; quantum yield (Φ) = 0.23] in interaction with TCA are noteworthy. Fluorescence emission of **6** was quenched quantitatively after the addition of 0.66 equivalents of TCA against **6** in 10 mM Hepes [pH 7.0 with $I = 0.1$ (NaNO₃) (emission at 260 nm)] at 25°C (see Fig. 10, which is published as supporting information on the PNAS web site), a fact suggesting that three biphenyl units may be assembled somewhat specifically in **10b**.

ESI MS of Supramolecular Assemblies. We measured ESI MS of **10a**, **10b**, and **11** in H₂O (pH 7.5 ± 0.1) to confirm the supramolecular 2:3 and 3:3 structures. The 2+, 3+, 4+, 5+, and 6+ species for **10a** and **10b** and 2+–9+ species for **11** with mass-to-charge ratios (m/z) were observed. Fig. 7A shows the ESI/time-of-flight mass spectra for **11** (0–2,000 m/z) along with observed peaks for 3+ species (Fig. 7B), which matched to the theoretical distribution (Fig. 7C). For the spectra for **10a** and **10b**, see Figs. 11 and 12, which are published as supporting information on the PNAS web site).

Conclusion

We have discovered a way of building supramolecular trigonal prisms, **10a**, **10b**, and **11**, by quantitative self-assembly of bis(Zn²⁺–cyclen)s, **5** and **6**, and linear Tris(Zn²⁺–cyclen) **8** with TCA. The supramolecular products were characterized by x-ray crystal analysis, potentiometric pH titrations, UV spectrophotometric titrations, fluorescence titrations, and ¹H NMR titrations, and ESI MS and were found to be stable thermodynamically and kinetically (on the NMR time scale) in aqueous solution at neutral pH. Their stability mostly comes from the stable Zn²⁺–S⁻ and Zn²⁺–N⁻ (imide) coordinations, presumably aided by hydrophobic and/or C–H– π interaction between three phenyl rings from the Zn²⁺–cyclen components. Although functions such as encapsulation of organic and inorganic guest

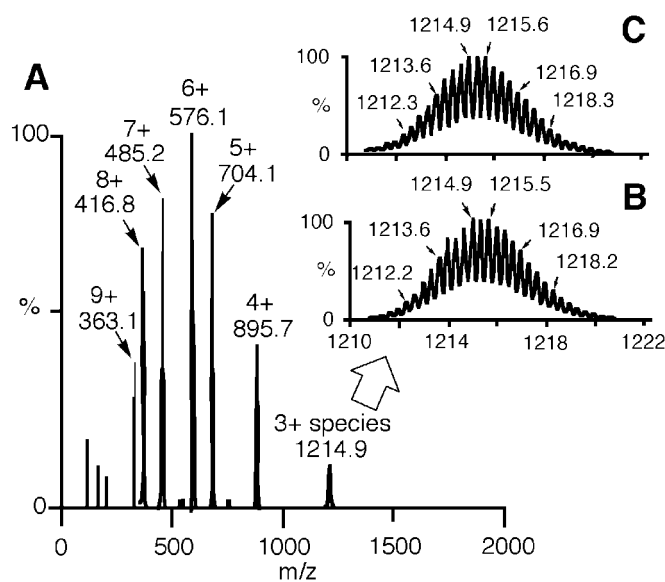


Fig. 7. (A) ESI mass spectra of **11**. Observed peaks (B) and theoretical distribution (C) for 3+ species of **11** ([11·6(NO₃)₃]³⁺) are shown.

molecules in **10** and **11** remain to be seen, these supramolecular motifs should set a design of new supramolecular complexes in aqueous solution and may have wide applications.

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1. Cram, D. J. & Cram, J. M. (1994) *Container Molecules and Their Guests* (R. Soc. Chem., Cambridge, U.K.).
2. Lehn, J.-M. (1995) *Supramolecular Chemistry: Concepts and Perspectives* (VCH, New York).
3. Whitesides, G. M., Shimanek, E. E., Mathias, J. P., Seto, C. T., Chin, D. N., Mammen, M. & Gordon, D. M. (1995) *Acc. Chem. Res.* **28**, 37–44.
4. Philip, D. & Stoddart, J. F. (1996) *Angew. Chem. Int. Ed. Engl.* **35**, 1155–1196.
5. Conn, M. M. & Rebek, J., Jr. (1997) *Chem. Rev. (Washington, D.C.)* **97**, 1647–1668.
6. Linton, B. & Hamilton, A. D. (1997) *Chem. Rev. (Washington, D.C.)* **97**, 1669–1680.
7. MacGillivray, L. R. & Awood, J. L. (1999) *Angew. Chem. Int. Ed. Engl.* **38**, 1018–1033.
8. Leininger, S., Olenyuk, B. & Stang, P. J. (2000) *Chem. Rev. (Washington, D.C.)* **100**, 853–908.
9. Greig, L. M. & Philip, D. (2001) *Chem. Soc. Rev.* **30**, 287–302.
10. Fujita, M. (2000) *Molecular Self-Assembly Organic Versus Inorganic Approaches* (Springer, Berlin).
11. Fujita, M., Umamoto, K., Yoshizawa, M., Fujita, N., Kusukawa, T. & Biradha, K. (2000) *J. Chem. Soc. Chem. Commun.* 509–518.
12. Caulder, D. L. & Raymond, K. N. (1999) *J. Chem. Soc. Dalton Trans.* 1185–1200.
13. Shivanyuk, A. & Rebek, J., Jr. (2001) *J. Chem. Soc. Chem. Commun.* 2374–2375.
14. Atwood, J. L., Barbour, L. J. & Jerga, A. (2001) *J. Chem. Soc. Chem. Commun.* 2376–2377.
15. Kimura, E. (1994) in *Progress in Inorganic Chemistry*, ed. Karlin, K. D. (Wiley, New York), Vol. 41, pp. 443–491.
16. Kimura, E., Koike, T. & Shionoya, M. (1997) in *Structure and Bonding: Metal Site in Proteins and Models*, ed. Sadler, P. J. (Springer, Berlin), Vol. 89, pp. 1–28.
17. Kimura, E. & Koike, T. (1998) *J. Chem. Soc. Chem. Commun.* 1495–1500.
18. Kimura, E. (2001) *Acc. Chem. Res.* **34**, 171–179.
19. Shionoya, M., Kimura, E. & Shiro, M. (1993) *J. Am. Chem. Soc.* **115**, 6730–6737.
20. Shionoya, M., Ikeda, T., Kimura, E. & Shiro, M. (1994) *J. Am. Chem. Soc.* **116**, 3848–3859.
21. Koike, T., Takashige, M., Kimura, E., Fujioka, H. & Shiro, M. (1996) *Chem. Eur. J.* **2**, 617–623.
22. Fujioka, H., Koike, T., Yamada, N. & Kimura, E. (1996) *Heterocycles* **42**, 775–787.
23. Kimura, E., Aoki, S., Koike, T. & Shiro, M. (1997) *J. Am. Chem. Soc.* **119**, 3068–3076.
24. Koike, T., Gotoh, T., Aoki, S. & Kimura, E. (1998) *Inorg. Chim. Acta* **270**, 424–432.
25. Kimura, E., Ikeda, T., Aoki, S. & Shionoya, M. (1998) *J. Biol. Inorg. Chem.* **3**, 259–267.
26. Aoki, S., Honda, Y. & Kimura, E. (1998) *J. Am. Chem. Soc.* **120**, 10018–10026.
27. Kikuta, E., Murata, M., Katsube, N., Koike, T. & Kimura, E. (1999) *J. Am. Chem. Soc.* **121**, 5426–5436.
28. Aoki, S. & Kimura, E. (2000) *J. Am. Chem. Soc.* **122**, 4542–4548.
29. Aoki, S., Shiro, M., Koike, T. & Kimura, E. (2000) *J. Am. Chem. Soc.* **122**, 576–584.
30. Aoki, S., Shiro, M. & Kimura, E. (2002) *Chem. Eur. J.* **8**, 929–939.
31. Kimura, E., Kikuchi, M., Kitamura, H. & Koike, T. (1999) *Chem. Eur. J.* **5**, 3113–3123.
32. Aoki, S., Sugimura, C. & Kimura, E. (1998) *J. Am. Chem. Soc.* **120**, 10094–10102.
33. Kikuta, E., Aoki, S. & Kimura, E. (2001) *J. Am. Chem. Soc.* **123**, 7911–7912.
34. Martell, A. E. & Motekaitis, R. J. (1992) *Determination and Use of Stability Constants* (VCH, New York), 2nd Ed.
35. Murov, S. L., Carmichael, I. & Hug, G. L. (1993) *Handbook of Photochemistry* (Dekker, New York), 2nd Ed.
36. Clegg, W., Davies, J. E., Elsegood, M. R. J., Lamb, E., Longridge, J. J., Rawson, J. J., Snaith, R. & Wheatley, A. E. H. (1998) *Inorg. Chem. Commun.* **1**, 58–60.