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Macrocycles within Macrocycles: Cyclen, Cyclam, and Their Transition Metal Complexes Encapsulated in Cucurbit[8]uril**

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Dedicated to Professor Eiichi Kimura
on the occassion of his retirement

Inclusion of a macrocycle in a macrocycle, reminiscent of Russian Matrioshka dolls, is a rare phenomenon, although inclusion of crown ethers, cryptands, and their alkali metal complexes inside the cavity of γ-cyclodextrin has been known for many years.[1] Recently, the encapsulation of cryptands, crown ethers, and their alkali metal complexes in supramolecular capsules and cages held together by hydrogen bonds and coordination bonds, respectively, has also been reported.[2, 3] However, few examples of the inclusion of transition metal macrocyclic complexes in synthetic molecular or supramolecular host systems are available in the literature[4] even though such systems are potentially useful as catalysts with high specificity as a result of the unique microenvironment around the transition metal ion which is reminiscent of metalloenzymes.

Cucurbituril (CB[6]), a macrocycle comprising six glycoluril units, forms stable host–guest complexes with small molecules, such as aliphatic and aromatic amines.[5] Our recent discovery[6] of new cucurbituril homologues, cucurbit[*n*]uril (CB[*n*]; $n = 5$, 7, and 8), containing five, seven, and eight glycoluril units has opened up new opportunities to expand the host–guest chemistry of cucurbituril. For example, the largest member of the cucurbituril family, CB[8], has a cavity comparable to that of γ-cyclodextrin and can accommodate two aromatic guest molecules to form 1:2 host–guest complexes,[6] or 1:1:1 ternary complexes.[7] The large cavity prompted us to explore the inclusion of macrocycles and their transition metal complexes in CB[8]. Of the many potential candidates for the guest macrocycles we chose tetraazamacrocycles, not only because they are effective hosts for transition metal ions[8] but also because their transition metal complexes exhibit catalytic activities in many reactions, such as epoxydation and DNA hydrolysis.[9] Here we present novel macrocycles within macrocycles, in which cyclen (1,4,7,10-tetraazacyclododecane), cyclam (1,4,8,11-tetraazacyclotetradecane), and their transition metal complexes are encapsulated in CB[8].[10]

Heating an aqueous solution of CB[8] and cyclen tetrahydrochloride at 100 °C for 2 h, followed by slow cooling to room temperature produces colorless crystals of complex **1a**. The ^{1}H NMR spectrum of **1a** in D_2O reveals a shift of the cyclen signal to higher field relative to that of free cyclen, which is consistent with the formation of a 1:1 host–guest complex of CB[8], and cyclen.[11] The X-ray crystal structure of **1a** (Figure 1) confirms the encapsulation of a fully protonated cyclen macrocycle in the cavity of CB[8] with four Cl^- counterions residing outside CB[8]. The inner macrocyle is significantly tilted with respect to the outer macrocyle: the angle between the average planes of the inner

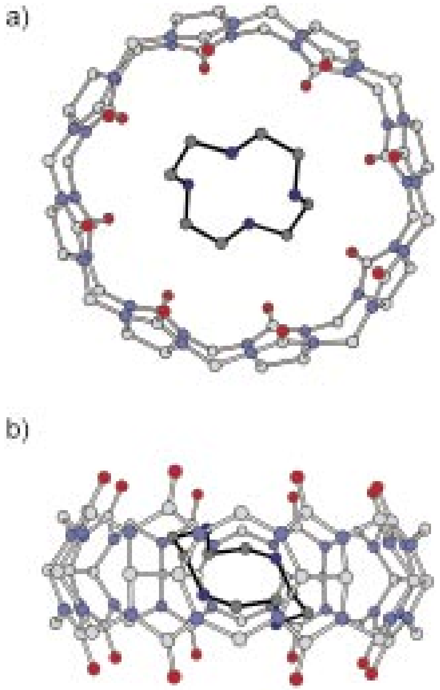

Figure 1. X-ray crystal structure of **1a**: a) top view and b) side view. Color code: oxygen: red, nitrogen: blue, carbon: gray. Hydrogen atoms, counterions (Cl^-), and solvent (H_2O) molecules are omitted for clarity.

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and outer ones is about 38°. The crystal structure indicates that the van der Waals interactions between the inner macrocyle and the inside wall of the outer macrocyles are mostly responsible for the stability of complex **1a**. A 1:1 inclusion complex of cyclam in CB[8] (**1b**) was also obtained by the same procedure and fully characterized. The X-ray crystal structure of **1b** (see Supporting Information) reveals that the encapsulated cyclam is even more tilted with respect to CB[8] with an angle between the average planes of the inner and outer macrocycles of approximately 59°. Presumably, the larger ring size of cyclam forces it to adopt the more titled orientation in the cavity of CB[8] in complex **1b**.

The inner macrocycles in **1a** and **1b** can be metalated. For example, heating an aqueous solution of **1a** (or **1b**) with an excess of $Cu(NO_3)_2$ at 100 °C for 2 h, followed by slow cooling to room temperature produces deep blue crystals of complex **2a** (or purple crystals of complex **2b**) in which a Cu^{II} ion is coordinated by cyclen (or cyclam) encapsulated in CB[8]. Similarly, a Zn^{II} ion can be introduced into the inner macrocycles. The structure of **2a** was determined by X-ray crystallography (Figure 2) and confirms the presence of $[Cu(cyclen)(H_2O)]^{2+}$ in the cavity of CB[8]. The crystallographic inversion center at the middle of the CB[8] host results in the encapsulated metal complex being disordered over two sites. The complex contains a five-coordinate Cu^{II} ion in a square-pyramidal environment, with the Cu ion being 0.652(10) Å above the average plane of the four N atoms of cyclen, and with the Cu–N bond lengths ranging from 2.040(2) to 2.220(2) Å. A water molecule is bound to the axial position of the copper ion (Cu–O bond length: 2.010(8) Å) while slightly tilted toward one side of the portal of CB[8]. In contrast to **1a**, the inner macrocycle in **2a** is almost parallel to the outer macrocycle, with an angle between their average planes of about 4°. It is interesting to note that attempts to introduce [M(cyclen)] (M = Cu^{II} or Zn^{II}) into CB[8] have failed even under forcing conditions. Presumably, the increased conformational rigidity of the macrocycle upon metalation hinders its inclusion in the cavity of CB[8].

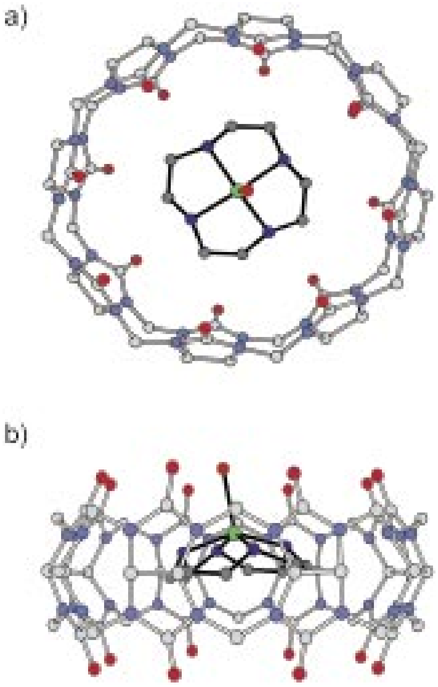

Figure 2. X-ray crystal structure of **2a**: a) top view and b) side view. Color code: copper: green, oxygen: red, nitrogen: blue, carbon: gray. Hydrogen atoms, counterions (NO_3^-), and solvent (H_2O) molecules are omitted for clarity. The $[Cu(cyclen)(H_2O)]$ unit is disordered over two sites as a result of a crystallographic inversion center at the middle of the CB[8] host. Only one orientation is depicted.

Cyclic voltammetry was performed on free $[Cu(cyclen)(NO_3)_2]$ and **2a** in order to understand the effect of encapsulation in CB[8] on the redox properties of metal macrocyclic complexes. Free $[Cu(cyclen)(NO_3)_2]$ undergoes a reversible, one-electron reduction at −0.85 V (versus SCE), which corresponds to the reduction of Cu^{II} to Cu^{I}. For **2a**, however, the same redox couple is observed at −0.72 V (versus SCE) with a large separation (ca. 0.24 V) between the cathodic and anodic peaks. This result suggests that the encapsulation of [Cu(cyclen)] in CB[8] increases the stability of the Cu^{I} state, but considerably slows down the electron transfer between the electrode and the redox center. Similar behaviors have been observed in the direct electrochemistry of metalloproteins in which redox centers are embedded in protein coats.[12]

The aqua ligand in **2a** can be replaced by other ligands, such as ammonia and imidazole. For example, treatment of a solution containing **2a** with ammonia gas results in an instant color change of the solution: the absorption band corresponding to the d–d transition shifts from 600 to 650 nm. A similar change in the visible spectrum is observed when the solution is treated with excess imidazole. The spectral change is caused by the replacement of the aqua ligand with ammonia or immidazole; this has been confirmed by a preliminary X-ray diffraction study.[13] Further studies on the ligand exchange are in progress.

In summary, we have synthesized and fully characterized novel macrocycles within macrocycles. The host–guest chemistry presented here involves multiple complexation events: a macrocycle is first encapsulated by the CB[8] host, and a transition metal ion is subsequently introduced into the inner macrocycle. These transition metal macrocyclic complexes with the exchangeable axial ligand within CB[8] may serve as biomimetic systems for the binding, activation, and catalytic transformation of specific substrates.

Experimental Section

1a: CB[8] (100.0 mg, 59.4 μmol) and cyclen · 4HCl (120.0 mg, 6.3 equiv) were dissolved in distilled water (10.0 mL) and heated at 100 °C for 2 h. Slow cooling of the solution to room temperature produced colorless crystals of **1a** (82.0 mg, 73 %). ^1H NMR (500 MHz, D_2O): $\delta = 2.55$ (s, 16H), 4.31 (d, 16H), 5.62 (s, 16H), 5.82 (d, 16H); ^{13}C NMR (125 MHz, D_2O): $\delta = 43.92$, 54.20, 72.45, 157.20; ESI-MS: *m*/*z*: 751.31 $[M+2H]^{2+}$, 1501.42 $[M+H]^+$. Elemental analysis calcd for $[(C_{48}H_{48}N_{32}O_{16})(C_8H_{20}N_4)] \cdot 4HCl \cdot 13H_2O$: C 35.75, H 5.25, N 26.80; found: C 35.89, H 5.51, N 26.81.

2a: An aqueous solution of **1a** (30.0 mg, 15.9 μmol) and $Cu(NO_3)_2 \cdot 6H_2O$ (30.0 mg, 6.3 equiv) was heated at 100 °C for 2 h. Slow cooling of the mixture to room temperature produced deep blue crystals of **2a** (26.8 mg, 83 %). ESI-MS: *m*/*z*: 782.77 $[M-H_2O]^{2+}$. Elemental analysis calcd for $[(C_{48}H_{48}N_{32}O_{16})(CuC_8H_{20}N_4)(H_2O)] \cdot 2NO_3 \cdot 19H_2O$: C 33.11, H 5.26, N 26.20; found: C 32.98, H 5.00, N 25.99.

Crystal data for **1a**: $[(C_{48}H_{48}N_{32}O_{16})(C_8H_{20}N_4)]\cdot 4\,HCl\cdot 19.67\,H_2O$, $M_r = 2001.50$, rhombohedral, space group $R\bar{3}$ (No. 148), $a = b = 29.1533(10)$, $c = 26.7471(13)$ Å, $V = 19\,687.1(14)$ Å^3, $Z = 9$, $\rho_{calcd} = 1.519\ g\,cm^{-3}$, $T = 188$ K, Siemens SMART CCD diffractometer, $Mo_{K\alpha}$ ($\lambda = 0.71073$), $\mu = 2.42\ cm^{-1}$. The structure was solved by the Patterson method (SHELXS-86). All non-hydrogen atoms were refined anisotropically (SHELXL-93). Final block-diagonal matrix least-squares refinement on F^2 with all 6967 reflections and 628 variables converged to $R1$ ($I > 2\sigma(I)$) $= 0.0923$, $wR2$ (all data) $= 0.2737$, and GOF $= 1.068$. Crystal data for **1b**: $[(C_{48}H_{48}N_{32}O_{16})$-$(C_{10}H_{24}N_4)]\cdot 4\,HCl\cdot 18\,H_2O$, $M_r = 1999.64$, rhombohedral, space group $R\bar{3}$ (No. 148), $a = b = 29.3372(7)$, $c = 26.6945(10)$ Å, $V = 19\,897.1(10)$ Å^3, $Z = 9$, $\rho_{calcd} = 1.502\ g\,cm^{-3}$, $T = 213$ K, $\mu = 2.38\ cm^{-1}$. $R1$ ($I > 2\sigma(I)$) $= 0.1005$, $wR2$ (all data) $= 0.2957$, and GOF $= 1.088$. Crystal data of **2a**: $[(C_{48}H_{48}N_{32}O_{16})$-$(CuC_8H_{20}N_4)(H_2O)]\cdot 2\,NO_3\cdot 16\,H_2O$, $M_r = 1995.30$, rhombohedral, space group $R\bar{3}$ (No. 148), $a = b = 29.8575(3)$, $c = 24.8758(4)$ Å, $V = 19\,205.0(4)$ Å^3, $Z = 9$, $\rho_{calcd} = 1.553\ g\,cm^{-3}$, $T = 188$ K, $\mu = 3.70\ cm^{-1}$. $R1$ ($I > 2\sigma(I)$) $= 0.1015$, $wR2$ (all data) $= 0.3134$, and GOF $= 1.063$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-156566 (**1a**), -156567 (**1b**), and -156568 (**2a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[13] A preliminary X-ray diffraction study has confirmed the replacement of the aqua ligand in **2a** with an imidazole ligand, but the structure refinement has been hampered by severe disorder of the solvent molecules.

A Perfluorinated Nanosphere: Synthesis and Structure of Perfluoro-deca-*B*-methyl-*para*-carborane[**]

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In the early stages of the chemistry of polyhedral boranes the direct, exhaustive halogenation of *closo*-boranes and carboranes was one of the first reactions studied in detail.[1] The most challenging endeavor in this context, their perfluorination, led to the synthesis of $B_{12}F_{12}^{2-}$,[2] 1,2-$(H)_2$-1,2-$C_2B_{10}F_{10}$,[3] 1,7-$C_2B_{10}F_{12}$,[3,4] and 1,12-$(H)_2$-1,12-$C_2B_{10}F_{10}$.[3] While the existence of $B_{12}F_{12}^{2-}$ was never confirmed,[5] all three carborane fluorides can be isolated and 1,12-$(H)_2$-1,12-$C_2B_{10}F_{10}$ can even be handled in the presence of moist air. In aqueous media however, they hydrolyze to form boric acid as the final product.[3] The recently reported anion 1-$HCB_{11}F_{11}^-$ has been shown to undergo the nucleophilic substitution at the B–F moieties by OH^- as well, but under basic aqueous conditions.[6]

History repeated itself with the discovery of C_{60}.[7] Shortly thereafter its exhaustive fluorination was intensively investigated[8] and it is now widely accepted that $C_{60}F_{48}$ is the most fluorine-rich fullerene which can be isolated.[9] However, $C_{60}F_{48}$ is metastable in solution, decomposing according to the reaction $C_{60}F_{48} \rightarrow C_{60}F_{36} + 6\,F_2$,[10] and hydrolyzing rapidly in aqueous media.[11] The idea of a chemically resistant "fluorinated ball" based on C_{60} was further pursued through its perfluoroalkylation.[12] Up to 14 perfluoroalkyl addends (R_f) ($R_f = CF_3$, C_2F_5, C_3F_7, C_6F_{15}) can be added to C_{60}, about half the number needed to achieve a perfluorinated surface. Solutions of the mixtures of $C_{60}(R_f)_nH_m$ have been shown to be resistant to acids and bases.[12]

The generation of a neutral perfluorinated nanosphere by replacement of all H atoms of per-*B*-methylated carboranes by fluorine appeared to us to be a feasible goal. Previously, the radical chlorination of 1,12-$(H)_2$-1,12-$C_2B_{10}Me_{10}$ (**1**), yielding 1,12-$(H)_2$-1,12-$C_2B_{10}(CHCl_2)_{10}$,[13] as well as the synthesis of the 1-hydroxymethyl-2-hydroxyimino derivative of **1**[14] demonstrated the viability of radical reactions to transform the methyl substituents of camouflaged species such as **1**, leaving

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