Molecular Container Assembly Capable of Controlling Binding and Release of Its Guest Molecules: Reversible Encapsulation of Organic Molecules in Sodium Ion Complexed Cucurbituril

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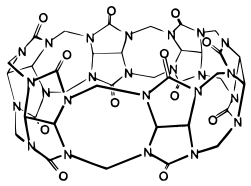
Molecular containers,[1] rigid hollow organic host compounds whose interior cavities are large enough to accommodate small guest molecules, are one of the fascinating developments in supramolecular chemistry. They usually have macrocyclic structures with openings of various sizes that permit entrance and exit of the guest. Recent elegant work[2] by Rebek and coworkers demonstrated that self-complementary molecules can dimerize to form spherical capsules in which small molecules or atoms are encapsulated. Moreover, the encapsulation and release of the guest can be controlled by change in the acidity of the medium.[2c] However, no other container molecules have demonstrated such reversible encapsulation and release of their guest molecules at ambient temperatures, which will be an important virtue of molecular containers when they are used in controlled release of drugs. To this goal one can envision the binding and release of guest molecules being controlled by blocking and unblocking an entrance of a molecular container, through which guest molecules go in and out. Here we present the first example of molecular container assemblies capable of controlling the binding and release of its guest molecules by this principle.

Cucurbituril (**1**) has a rigid structure with a hollow core of ∼5.5 Å diameter, which is accessible from the exterior by two carbonyl-fringed portals.[3] Its easy synthesis, rigid structure, and



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capability of holding guest molecules in the cavity make cucurbituril very attractive as a synthetic receptor. One severe drawback of cucurbituril as a synthetic receptor is, however, its extremely poor solubility in virtually any solvents except strongly acidic aqueous solution. Its host−guest chemistry has been, therefore, studied only in strongly acidic solutions. Also, most work has been done with aliphatic and aromatic ammonium ions which show exceptional affinity toward the receptor primarily due to strong electrostatic interactions between the ammonium ions and the carbonyl oxygen atoms at the portal of **1**.[4] Few substrates without ammonium functionality are known to be included in the cavity of **1**. Although the carbonyl groups at the portal of cucurbituril should provide metal ion binding sites, there are few detailed studies on the interactions of cucurbituril with metal ions.[5]

We recently observed that cucurbituril dissolves appreciably in aqueous solution of alkaline metal salts,[6] in particular, sodium sulfate solution (∼6.6×10^{-2} mol in 1.0 L of 0.2 M Na_2SO_4 solution). The markedly increased solubility of **1** in neutral aqueous solutions in the presence of metal ions suggests strong interaction or coordination of the metal ions to the carbonyl groups at the portal of **1**. We therefore decided to investigate this phenomenon in detail. Slow diffusion of diethyl ether into cucurbituril dissolved in 0.2 M sodium sulfate solution resulted in the formation of crystals of **2**. The X-ray crystal structure of **2** (Figure S1)[7,8] reveals that the molecule has a center of symmetry and two sodium ions are coordinated to each portal of cucurbituril. Interestingly, the two sodium ions and five water molecules bound to the metal ions effectively cover each portal of cucurbituril like a "lid" on a "barrel". Three water molecules reside in the cavity of the sodium ion "lidded" cucurbituril. This observation immediately prompted us to study inclusion phenomena of small molecules without ammonium functionality in the sodium ion "lidded" cucurbituril.

When THF is added to the cucurbituril in 0.2 M Na_2SO_4 solution,[9] inclusion of a THF molecule inside the sodium ion "lidded" cucurbituril occurs as evidenced by its ^{1}H NMR spectra. The formation constant of the inclusion complex is estimated to be 5.1×10^2 M^{-1} at room temperature.[10] Thermodynamic parameters associated with the inclusion phenomenon were obtained from the temperature dependence of the formation constant between 24 and 64 °C: $\Delta H° = -5.8$ kcal mol^{-1} and $\Delta S° = -7.4$ esu. The inclusion of a THF molecule was also confirmed by X-ray structural analysis[8] of the crystal **3** formed from the above-mentioned solution. The structure of **3** is nearly identical to that of **2** except for a disordered THF molecule sitting inside the sodium ion "lidded" cucurbituril in **3** (Figure 1). In particular, the structures of the "lids" in **2** and **3** are

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(2) (a) Wyler, R.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699. (b) Branda, N.; Wyler, R.; Valdes, C.; Rebek, J., Jr. *Science* **1994**, *263*, 1267. (c) Branda, N.; Grotzfeld, R. D.; Valdes, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 85.

(3) (a) Behrend, R.; Meyer, E.; Rusche, F. *Libigs. Ann. Chem.* **1905**, *339*, 1. (b) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367.

(4) Reviews: (a) Mock, W. L. *Topics Curr. Chem.* **1995**, *175*, 1. (b) Cintas, P. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 205.

(5) The metal ion binding phenomenon of cucurbituril was mentioned even in the original report by Behrend *et al.*[3a] Buschmann *et al.* recently studied complexation of alkaline metal ions to cucurbituril by UV−vis spectroscopy (Buschmann, H.-J.; Cleve, E.; Schollmeyer, E. *Inorg. Chim. Acta* **1992**, *193*, 93). The complex formation constants were measured in the presence of metal salts in the range of 1×10^{-5} to 5×10^{-4} M. However, their analysis appears to be flawed as they assumed only one metal ion is bound to each portal of cucurbituril in all cases, which contradicts our current finding.

(6) Solubilities of cucurbituril (mol L^{-1}) in 0.2 M other alkaline or alkaline earth metal salts: LiCl, 9.4×10^{-4}; KCl, 3.7×10^{-2}; CsCl, 5.9×10^{-2}; $CaCl_2$, 7.0×10^{-2}.

(7) Supporting information.

(8) Crystal data of **2**: $[(C_{36}H_{36}N_{24}O_{12})Na_4(H_2O)_{10}\cdot 3(H_2O)](SO_4)_2\cdot 10H_2O$, fw = 1695.37, monoclinic, $P2_1/c$, $a = 12.566(4)$ Å, $b = 14.312(2)$ Å, $c = 19.365(5)$ Å, $\beta = 102.64(1)°$, $V = 3398(1)$ Å^3, $Z = 2$, $d_{calcd} = 1.657$ g cm^{-3}, $T = 296$ K, Enraf-Nonius CAD4 diffractometer, Mo Kα ($\lambda = 0.710\,73$), $\mu = 2.27$ cm^{-1}. The structure was solved by direct methods (SHELXS-86). All non-hydrogen atoms were refined anisotropically (SHELXL-93). Final full-matrix least-squares refinement on F^2 with all 4182 reflections and 582 variables converged to *R1* ($I > 2\sigma(I)$) = 0.065, *wR2* (all data) = 0.187 and GOF = 1.10. Crystal data of **3**: $[(C_{36}H_{36}N_{24}O_{12})Na_4(H_2O)_{10}\cdot C_4H_8O](SO_4)_2\cdot 10H_2O$, fw = 1713.41, monoclinic, $P2_1/c$, $a = 12.592(5)$ Å, $b = 14.268(1)$ Å, $c = 19.428(8)$ Å, $\beta = 102.60(2)°$, $V = 3406(2)$ Å^3, $Z = 2$, $d_{calcd} = 1.670$ g cm^{-3}, $T = 296$ K, Enraf-Nonius CAD4 diffractometer, Mo Kα ($\lambda = 0.710\,73$), $\mu = 2.26$ cm^{-1}. The structure was solved by direct methods, and all non-hydrogen atoms were refined anisotropically. Final full-matrix least-squares refinement on F^2 with all 4728 reflections and 609 variables converged to *R1* ($I > 2\sigma(I)$) = 0.066, *wR2* (all data) = 0.162 and GOF = 1.13.

(9) Like cucurbituril itself, **2** and **3** do not dissolve appreciably in water but do in the presence of excess sodium ions.

(10) The formation constant of the inclusion complex was estimated by the integration of the signals for the free and bound THF in ^{1}H NMR spectra of 0.2 M Na_2SO_4 solutions (in D_2O) containing cucubituril (2.8×10^{-2} M) and THF ($(1.8-3.7) \times 10^{-2}$ M).

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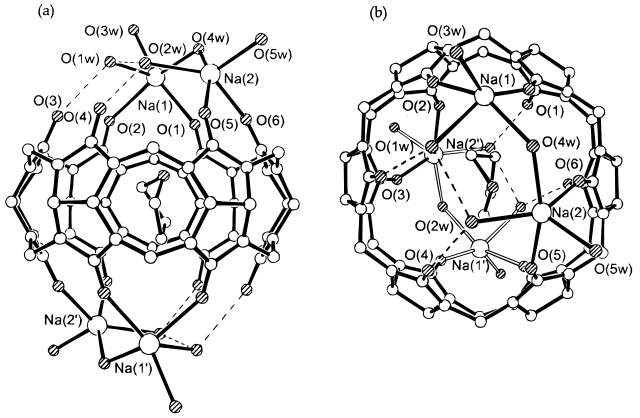


Figure 1. X-ray crystal structure of **3**: (a) side view; (b) top view. The included THF molecule is disordered over two sites; only one orientation is displayed. The broken lines indicate the possible hydrogen bondings. Selected interatomic distances (Å): Na(1)−O(1), 2.347(4); Na(1)−O(2), 2.461(4); Na(1)−O(1w), 2.396(5); Na(1)−O(3w), 2.374-(6); Na(1)−O(4w), 2.441(7); Na(2)−O(5), 2.375(4); Na(2)−O(6), 2.275(4); Na(2)−O(2w), 2.326(5); Na(2)−O(4w), 2.394(7); Na(2)−O(5w), 2.293(5); Na(1)···Na(2), 4.229(4); O(1w)···O(2w), 2.737(6); O(1w)···O(3), 2.856(5); O(2w)···O(4), 2.756(5).

essentially the same, i.e., each portal of cucurbituril in **3** is fully covered with two Na ions and five water molecules coordinated to the metal ions in the same manner as in **2**. Each sodium ion is coordinated by two neighboring portal oxygen atoms of cucurbituril and three water molecules in a distorted square pyramidal geometry. The two sodium ions are linked by a bridging water molecule (O(4w)). Two water molecules bound to the sodium ions (O(1w) and O(2w)) form strong hydrogen bonds to each other (O(1w)···O(2w), 2.737(6) Å) as well as to the portal oxygen atoms of cucurbituril (O(1w)···O(3), 2.856-(5) Å; O(2w)···O(4), 2.756(5) Å). Since the whole molecule **3** is sitting on an inversion center, the THF molecule in the cavity is disordered over two sites. The oxygen atom of the THF molecule points toward the portal; however, no interaction exists between the oxygen atom and the sodium ions. The nearly identical structures of the sodium ion "lids" covering the portals in **2** and **3** suggest that the "lids" are maintained in the solution. However, ^{23}Na NMR spectra of **2** or **3** in aqueous solutions in the presence of ∼10-fold excess of sodium ions[9] show only a single peak at room temperature, which indicates that the coordinated sodium ions are exchanging rapidly with those in solution on the NMR time scale.

When the pH of the solution containing the sodium ion "lidded" cucurbituril and THF is lowered by adding trifluoroacetic acid, the ^{1}H NMR signals for THF encapsulated in the cavity decrease while those for free THF increase (Figure 2b).[11] Addition of ∼300 equiv of trifluoroacetic acid makes the signals for the bound THF essentially disappear (Figure 2c). When the pH of the solution is raised again by adding Na_2CO_3, the signals for the encapsulated THF are almost fully restored (Figure 2d). A series of these observations suggests that the sodium ion "lids" are removed in strongly acidic solution due to the protonation of the carbonyl groups at the cucurbituril portals; consequently, the encapsulated THF molecule can escape from the cavity readily (Scheme 1). Raising the pH of the solution restores the sodium ion "lids" of cucurbituril and, therefore, the capability of encapsulating THF. A similar behavior is observed with other guest molecules such as

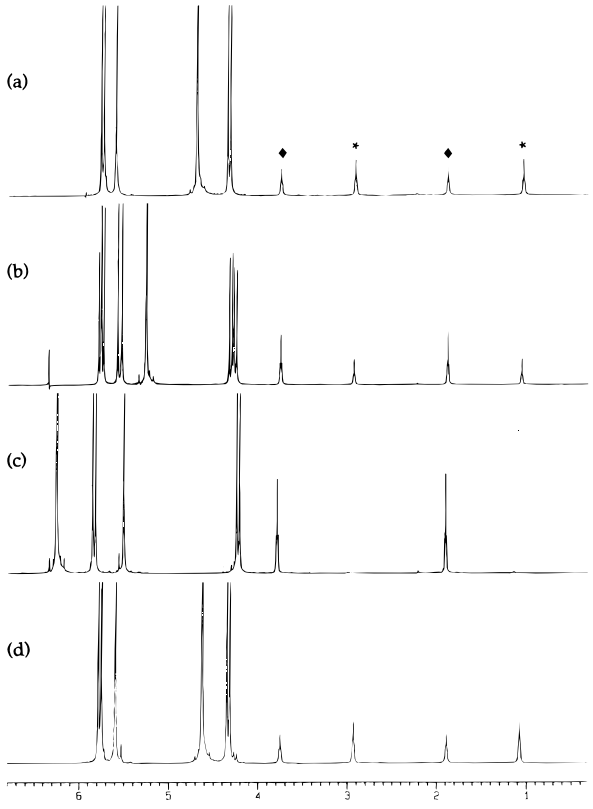
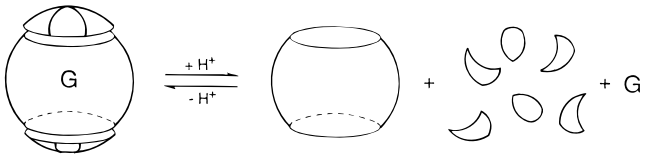


Figure 2. (a) ^{1}H NMR spectra of the sodium ion "lidded" cucurbituril (2.8×10^{-2} M) and THF (5.0×10^{-2} M) in 0.2 M Na_2SO_4 solution (D_2O); (b) after addition of ∼100 equiv of trifluoroacetic acid; (c) after addition of ∼300 equiv of trifluoroacetic acid; (d) after addition of excess Na_2CO_3 to the solution in c. Signals for the free THF (◆) and encapsulated THF (*) are highlighted.

Scheme 1



benzene, cyclopentanone, and furan.[12] Such reversible encapsulation of guest molecules controlled by complexation and decomplexation of metal ions at the portals of host molecules is unprecedented.

In conclusion, we present a novel molecular container assembly capable of controlling the binding and release of its guest molecules by complexation and decomplexation of metal ions at the portals of the host molecule. This principle may be applied to the design of new molecular containers for drug delivery. We are continuing to investigate the reversible encapsulation of guest molecules in this and other metal ion "lidded" cucurbiturils.

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Supporting Information Available: Experimental details of X-ray crystal structure determination of **2** and **3** including PLUTO diagrams with full atom labeling schemes as well as crystallographic tables and listing of atomic coordinates, thermal parameters, and bond distances and angles (27 pages). See any current masthead page for ordering and Internet access instructions.

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(11) A similar behavior was observed with addition of other acids such as HCO_2H and toluenesulfonic acid. Inclusion of trifluoroacetic acid in cucurbituril is negligible as indicated by ^{19}F NMR spectroscopy under these conditions. This observation excludes the possibility of simple exchange of the encapsulated THF with added trifluoroacetic acid.

(12) Formation constants of the inclusion complexes for benzene, cyclopentanone, and furan are estimated to be 2.7×10^1, 2.2×10^3, and 7.1×10^3 M^{-1}, respectively, at room temperature.