

Li⁺ Selective Encapsulation through the Intramolecular Hydrogen-Bonding Gate

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Abstract: We developed a self-organized monomeric molecular container **3** based on two pairs of intramolecular hydrogen bonds between adjacent carboxylic acid moieties on the upper rim of the cavitand **1**. The formation of the molecular container was confirmed by inclusion phenomena of Li⁺ in a mixture of CDCl₃ and C₆D₆. The lid formed by two pairs of intramolecular hydrogen bonds can be opened in polar solvents such as CD₃CN and the encapsulated guest was subsequently released. All these phenomena were elucidated by ¹H NMR spectroscopy, MALDI mass spectrometry, vapor pressure osmometry, and molecular modelling studies. © 1997 Elsevier Science Ltd.

Container molecules which could be used as drug delivery vehicles, sensors of small molecules, or catalysts can be obtained either by the traditional chemical-bond synthesis^{1,2} or by the noncovalent assembly of preformed monomeric subunits.^{3,4} Hemicarcerands formed as single, covalently linked molecules are hosts that can form reversible complexes with a range of guest molecules by adjusting the size of the portal through a conformational process called gating, resulting from heating.³ Rebek's self-assembled molecular containers are capable of controlling reversible inclusion and release of the guests by pH adjustment.⁴ Recently, Kim and coworkers demonstrated that reversible encapsulation and release of guest molecules can be achieved by pH-controlled complexation and decomplexation of metal ions at the portals of the host molecule.⁵ Here we describe a new monomeric molecular container assembly for the selective encapsulation of Li⁺ through intramolecular hydrogen bonding gate on the upper rim of the cavitand **3**⁶ and solvent polarity-controlled unblocking of the portal and subsequent release of the guest.

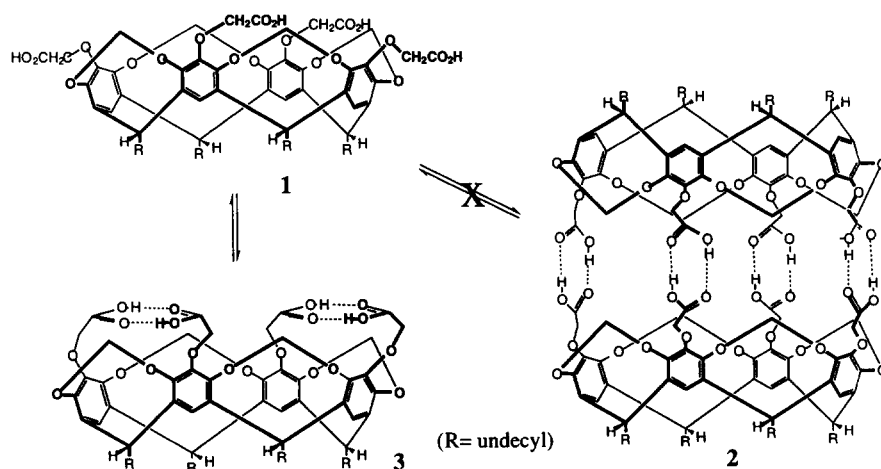


Figure 1

Since the bowl-shaped cavita nd monomer **1** has four carboxylic acid functional groups on the upper rim that would recognize each other, the homodimeric supermolecule **2** assembled noncovalently from two monomers should result in a molecular capsule which can encapsulate suitable molecules of complementary size and shape.⁸ Evidence against formation of the dimeric capsule **2** came from the fact that neutral guests such as CHCl_3 , CH_2Cl_2 , benzene, and *p*-xylene suitable for the dimeric cavity of **2** were not included judging from ^1H NMR spectra. This should result from entropic disadvantage in the formation of the dimeric molecular capsule **2**. Vapor pressure osmometry (VPO) measurement suggested formation of the monomeric molecular container **3** instead of the homodimer **2**.⁹

This monomeric molecular container **3** involves two pairs of intramolecular hydrogen bonds to form a hemisphere that can trap proper-sized guests in its cavity through the intramolecular hydrogen bonding gate. In fact, the formation of a self-organized molecular container by two pairs of intramolecular hydrogen bonds between adjacent carboxylic acid moieties on the upper rim was confirmed by selective inclusion of Li^+ within the container (*vide infra*). The tetraacid **1** was solubilized in LiOTf -saturated CHCl_3 containing 10% CH_3CN and the volatiles were completely evaporated *in vacuo* and 2:1 (v/v) $\text{CDCl}_3/\text{C}_6\text{D}_6$ was added to the residue. The insoluble solid was filtered out and the NMR spectrum was obtained for the resulting solution. Figure 2(b) displayed two sets of host signals. This indicates that exchange of Li^+ in and out of the cavity is very slow at rt

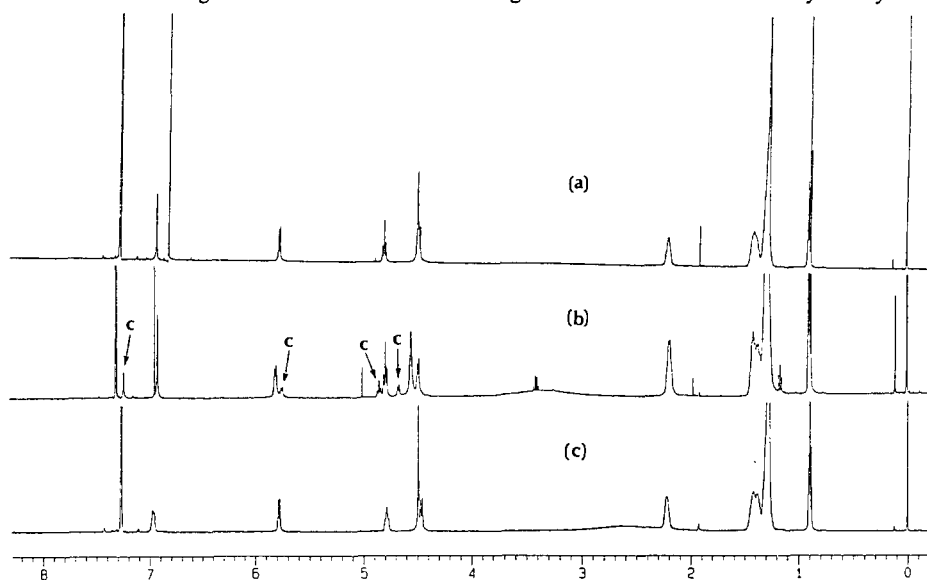


Figure 2. (a) ^1H NMR spectra of the free host **3** in a mixture of CDCl_3 and C_6D_6 (v/v 2:1, 1 mM); (b) after addition of lithium triflate; (c) after addition of 3 vol % of CD_3CN . Signals for the lithium-containing host are indicated in an arrow c.

on the NMR time scale. One corresponds to the Li^+ inclusion complex and the other corresponds to either the Li^+ -free host **3** or Li^+ binding to the carboxyl moieties outside the cavity. The NMR spectrum of a Li^+ inclusion complex shows the downfield shift of the aromatic protons, chiral methine protons, and methylene protons pointing toward the aromatic cavity, indicating the cation- π interaction inside the aromatic cavity.¹⁰ However, we believe that major intermolecular force within the cavity should come from the cation-carboxyl oxygen dipole interaction. Addition of CD_3CN (3 vol %) to the Li^+ inclusion complex in a mixture of CDCl_3 and C_6D_6 (v/v

2:1) opened the lid of **3** and regenerated free LiOTf as illustrated in Figure 2(c). This clearly indicates that the cavity suitable for the Li⁺ inclusion was formed by two pairs of the intramolecular hydrogen bonds. This also demonstrates that formation of the bimolecular inclusion complex **3** + Li⁺ can be controlled by solvent polarity.^{4e,8} The ratio of the Li⁺ inclusion to the non-inclusion is about 1/3 from the NMR integration. In the case of complexation with NaOTf, KOTf, RbOTf, and CsOTf under the same condition, the NMR spectrum did not show any evidence for the metal ion encapsulation or cation- π interaction. These metal ions seemed to be too large to go into the cavity. However, this does not imply that alkali metal ions larger than Li⁺ can not interact with the host because these metal ions may bind to the carboxyl moieties outside the closed gate of the container **3**. MALDI mass spectrum of a mixture of **1** and alkali metal salts (LiOTf, NaOTf, KOTf, RbOTf, and CsOTf)¹¹ showed the formation of M⁺ + host adducts, indicating the presence of the intermolecular interaction between alkali metal ions and host **1**. Furthermore, as expected, **3** + Li⁺ gave the most intense signal, presumably indicating the strongest binding of Li⁺ inside the cavity than that of other alkali metal cations to the carboxyl moieties above the closed cavity.¹²

The minimum energy structure of **3** was obtained from the MC/SD conformational searching¹³ with MacroModel V5.5 utilizing the MM2* force field¹⁴ and the GB/SA solvation model for chloroform.¹⁵ Inspection of the computer-generated structure of **3** (Figure 3) indicates that Li⁺ can be imbedded within the container formed by the aromatic walls and the lid consisting of two pairs of intramolecular hydrogen bonds.

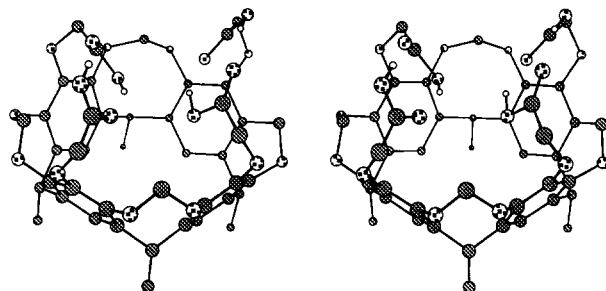


Figure 3. Energy-minimized structure of **3** shown in stereo. The undecyl group is modeled by a methyl group and hydrogens except those on the carboxylic acids have been omitted for clarity.

In conclusion, we have developed a self-organized monomeric molecular container **3** based on two pairs of intramolecular hydrogen bonds between adjacent carboxylic acid moieties of **1**. The formation of the molecular container was confirmed by the selective inclusion phenomena of Li⁺ in a mixture of CDCl₃ and C₆D₆. The lid formed by two pairs of intramolecular hydrogen bonds can be opened in polar solvents such as CD₃CN and the encapsulated guest was subsequently released.

Acknowledgement. This work was supported by the Basic Science Research Institute Program (BSRI-96-3416), OCRC and KOSEF (Grant No. 96-0501-08-01-3).

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 6. The tetrol precursor⁷ was treated with K₂CO₃ and ethyl bromoacetate in acetone to give the tetraester which was hydrolyzed with NaOH in a mixture of THF and H₂O to give rise to compound **1**. Spectral data for **1**: mp 215 °C; ¹H NMR (300 MHz, CDCl₃) δ 6.92 (s, 4 H, ArH), 5.77 (d, *J* = 7.5 Hz, 4 H, outer OCH₂), 4.80 (t, *J* = 8.0 Hz, 4 H, Ar-CH-Ar), 4.48 (br, 12 H, inner OCH₂, Ar-OCH₂-CO₂H), 2.2 (br, 8 H, -CHCH₂), 1.17 - 1.45 (m, 72 H, -CH₂-), 0.90 (t, *J* = 7.0 Hz, 12 H, CH₃); MS (FAB, NBA) *m/z* 1449 (M + H⁺).
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(Received in Japan 28 July 1997; revised 1 October 1997; accepted 3 October 1997)