Communication

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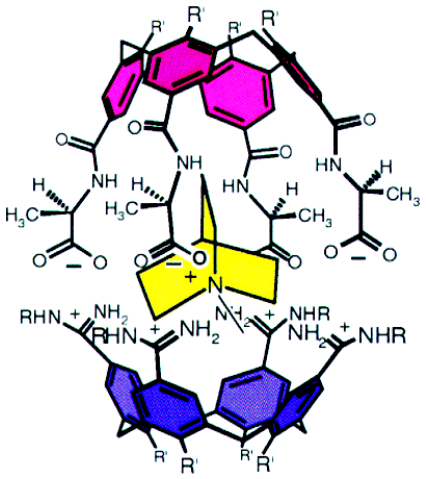

R= $CH_2CH_2CH_3$
R'= $OC_2H_4OC_2H_5$

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Guest Encapsulation in a Water-Soluble Molecular Capsule Based on Ionic Interactions

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The synthesis of molecular capsules using noncovalent interactions is currently a very attractive area in supramolecular chemistry.[1] The interest in the design and synthesis of molecules able to form confined spaces by self-assembly stems from their ability to stabilize reactive intermediates or geometries and to promote catalysis.[2] Because most biological processes take place in an aqueous environment, the synthesis of supramolecular containers for molecular recognition in water is a challenge. Hydrogen bonds have been widely used for the assembly of molecular capsules,[3] but the nature of this type of noncovalent interaction renders them not suitable for assembly in water.

So far, water solubility has been achieved for molecular capsules based on metal−ligand coordination. Among others, Fujita's cage complexes are formed by the assembly of planar organic components and metal ions, and they are able to reversibly bind or stabilize guest molecules and accelerate reactions in water.[4] Nevertheless, the rigidity provided by the metal−ligand coordination does not allow in some cases the encapsulation of guest molecules.[4g] Simple ionic interactions provide a powerful tool for building molecular capsules in polar solvents.[5] The ability to encapsulate guest molecules within these capsules in water would render these assemblies suitable for applications such as storage of molecules and drug delivery.

Recently, we have described[6] the first example of a capsule that is formed by the association between oppositely charged calix[4]arenes and binds charged guest molecules in methanol. In this Communication, we report that modification of one building block by introduction of amino acidic moieties results in the formation of the first molecular capsule (**1**·**2**) that is soluble in water and is able to encapsulate small molecules (Chart 1).

The formation of capsule **1**·**2** is the result of the electrostatic interactions between the negative carboxylate groups of calix[4]arene **1**, functionalized at the upper rim with L-alanine moieties, and the positively charged amidinium groups of calix[4]arene **2**. Compound **1** was synthesized starting from the tetrakis(ethoxyethyl) tetracarboxy calix[4]arene. After the formation of the corresponding tetraacyl chloride derivative, L-alanine methyl ester was added affording the calix[4]arene tetraester. Finally, the tetraester was hydrolyzed using LiOH.

The two building blocks are readily soluble in H_2O and, remarkably, unlike our previous experience,[6] the 1:1 mixture of **1** and **2** is completely soluble in H_2O buffered at pH 9. The ^{1}H NMR spectrum of the 1:1 mixture in buffered D_2O shows upfield shifts ($\Delta\delta_a = 0.22$ ppm, $\Delta\delta_b = 0.2$ ppm, $\Delta\delta_c = 0.25$ ppm) for the protons of the propyl amidinium chains of **2** (Figure 1). The shifts are the result of the shielding provided by the aromatic walls of the calix[4]arenes upon inclusion of the propyl side chains in the cavity of the capsule.[6] Additionally, there is a significant broadening of the propyl signals, most probably the result of the hindered rotation around the propyl C−N bond. In contrast, the signal of the aromatic protons of **2** undergoes a downfield shift and sharpens upon formation of the complex. An upfield shift is also observed for the α proton and the side chain protons of the alanine substituents of calix[4]arene **1** ($\Delta\delta_\alpha = 0.12$ ppm, $\Delta\delta_\beta = 0.08$ ppm). Addition of an excess of either calix[4]arene **1** or **2** to the 1:1 mixture resulted

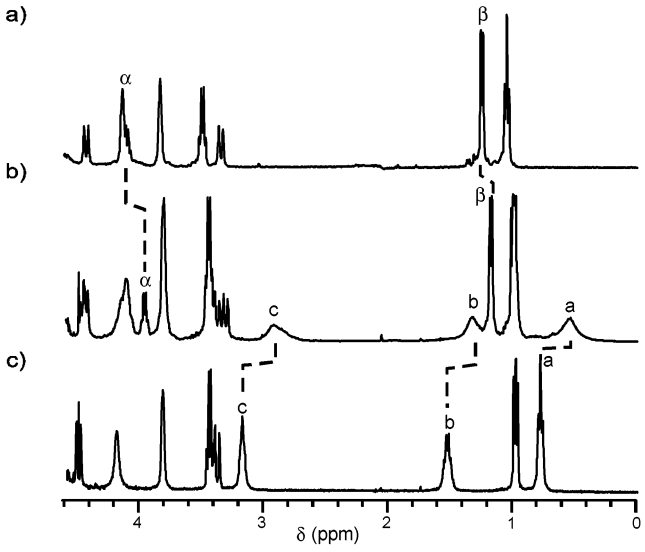
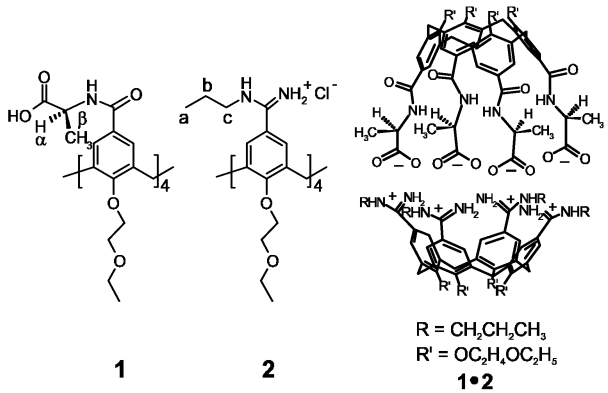


Figure 1. Portion of the ^{1}H NMR spectra ($Na_2B_4O_7 \cdot H_2O$, D_2O, 298 K) for (a) **1**, (b) **1**·**2**, and (c) **2**. For the assignment of the protons, see Chart 1.

Chart 1. Molecular Building Blocks and Resulting Molecular Capsule



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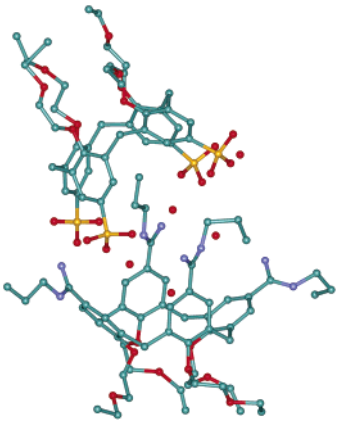

Figure 2. X-ray structure of the capsule **2**·tetrasulfonate calix[4]arene.

in averaged signals for the free and complexed components. This indicates that the assembly formation is fast on the NMR time scale.

While this work was in progress, we obtained the X-ray structure of a previously reported capsule[6] which represents the first crystal structure of a complex formed by self-assembly of oppositely charged calix[4]arenes.[7] This stable and water-insoluble complex is based on the ionic interactions between the sulfonate groups of a calix[4]arene tetrasulfonate and the amidinium moieties of **2**. This solid-state structure is direct evidence of the structure of these ionic calixarene assemblies, and it indisputably proves that, in absence of guest encapsulation, only one of the propyl side chains of **2** is included inside the cavity of the capsule pointing toward the aromatic walls of the anionic calix[4]arene (Figure 2).

Complex **1·2** has been also characterized by ESI-TOF-MS spectrometry. The spectrum of an equimolar mixture of **1** and **2** in buffered H_2O shows a peak at *m*/*z* 1134 of the capsule $[\mathbf{1}\cdot\mathbf{2} + 2\mathrm{Na}]^{2+}$ together with two other major peaks, one at *m*/*z* 1049 and the other at *m*/*z* 620 corresponding to $[\mathbf{2} - 4\mathrm{HCl} + \mathrm{H}]^{+}$ and $[(\mathbf{1} - \mathrm{H} + \mathrm{Na}) + 2\mathrm{Na}]^{2+}$, respectively (cf., Supporting Information).

The association constant and the thermodynamic parameters for the complex formation were determined by isothermal titration calorimetry (ITC) measurements. Addition of increasing aliquots of compounds **2** (2 mM) to **1** (0.2 mM) in H_2O containing borate buffer revealed the formation of a 1:1 complex with an association constant K_a of 3.3×10^4 M^{-1} (cf., Supporting Information). Overall, the formation of the capsule **1·2** is exothermic ($\Delta H° = -3.3$ kcal mol^{-1}) as a result of the favorable assembly of the two oppositely charged building blocks. The positive change in entropy ($T\Delta S° =$ 2.9 kcal mol^{-1}) is most probably due to the liberation of solvent molecules from the binding sites upon complex formation.

The molecular mechanics calculation showed that the *N*-methylquinuclidinium cation (NMQ^+) exhibits a good fit for encapsulation in the assembly **1·2**. Encapsulation experiments were performed in water, and the propyl side chain, which is either in or out of the cavity of the capsule, was used as a probe to detect guest encapsulation.[8]

Changes in the chemical shifts of the signals of the protons of the amidinium side chains ($\Delta\delta_a = 0.17$ ppm, $\Delta\delta_b = 0.15$ ppm, $\Delta\delta_c = 0.17$ ppm) were observed upon addition of 30 equiv of guest to a 1.2 mM solution of **1·2**. A slight upfield shift was also observed for the α proton of compound **1** (cf., Supporting Information). The chemical shifts of the other protons, including the one of the guest, did not show significant changes. The fact that there is only one set of resonances of the guest indicates that the encapsulation is a fast process on the NMR time scale. Therefore, the chemical shifts are simply averaged signals between free and complexed *N*-methylquinuclidinium.[9] Guest encapsulation was supported by mass spectrometry. The ESI-MS spectrum of a water solution of **1·2** containing 30 equiv of NMQ chloride showed signals at 2222.6 and 2347.7 corresponding to $[\mathbf{1}\cdot\mathbf{2} + \mathrm{H}]^+$ and $[\mathbf{1}\cdot\mathbf{2} + \mathrm{NMQ}]^+$, respectively.[10]

This water-soluble capsule (**1·2**) opens new ways for the use of supramolecular structures as molecular receptors or drug delivery systems in physiological media. The encapsulation of different drugs as guest molecules is under investigation.

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Supporting Information Available: ^{1}H NMR of **1·2** upon addition of *N*-methylquinuclidinium, ITC titration for the formation of **1·2**, ESI-MS spectrum of **1·2**, synthesis of **1** and **2**. Crystallographic and experimental data for Figure 2 (PDF/CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Crystals of **2**·tetrasulfonate calix[4]arene were obtained by the hanging drops method adapted for supramolecular complexes (see also: Di Costanzo, L.; Geremia, S.; Randaccio, L.; Purrello, R.; Lauceri, R.; Sciotto, D.; Gulino, F. G.; Pavone, V. *Angew. Chem., Int. Ed.* **2001**, *40*, 4245−4247). Data collection was performed at the XRD1 beam-line of Elettra Synchroron, Trieste (Italy). Crystal structure data have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 202688.
(8) In methanol, the encapsulation of small charged guests into the capsule shifts the signals of the protons of the amidinium compound **2** downfield in the ^{1}H NMR because of the extrusion of the propyl side chain.[6]
(9) A calorimetric titration of **1** with **2** in the presence of a large excess (60 equiv) of NMQ chloride was performed. The experimental data were consistent with a 1:1 binding with a K_a in the same order of magnitude as that found in the absence of the salt which rules out the possibility that the charged guest could lead to the dissociation of the capsule (cf., Supporting Information).
(10) Analogous results were obtained using FAB-MS. Although the complex is not very strong, both spectra showed peaks (5% intensities) that were indisputably assigned to the ($\mathbf{1}\cdot\mathbf{2}$+$NMQ^+$) complex.

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