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Expanded Calix[4]arene Tetraurea Capsules

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Since their invention 5 years ago, calix[4]arene tetraureas **1·1** have become the most extensively studied molecular capsules.[1] Their architecture comprises the bowl-shaped curvature of the calixarene **1** in the cone conformation (Figure 1) and the four self-complementary ureas on the upper rim. Their hydrogen bond donors and acceptors allow a dimeric assembly to form, in the manner of two hemispheres, giving a capsule **1·1** held together by a seam of 16, intermolecular $C{=}O\cdots H{-}N$ hydrogen bonds around the equator. The capsule features a well-defined, roughly spherical cavity of $\sim$7 Å diameter, with an internal volume of $\sim$200 Å^3, and accommodates benzene- or chloroform-sized molecules and even some terpenes such as camphor. The exchange rate of guests is slow on the NMR time scale (at ambient temperatures), and separate, sharp signals are seen in the NMR spectra for free and encapsulated guest.[2] More recently, examples of heirarchical assembly,[3] polymerization,[4] and chiral recognition[5] were all revealed through reversible self-assembly of **1·1**. Here we relate our initial experiences with a second generation of these calixarene tetraureas, those intended to offer expanded cavities for guest encapsulation.

The synthesis of the new structures began with the tetrabromo tetrabenzyloxy calix[4]arene **3** prepared earlier by Gutsche.[6] The depth of the cavity was increased by Suzuki reaction with *p*-nitrophenyl boronic acid, Pd(PPh$_3$)$_4$, and Na$_2$CO$_3$ in a mixture of toluene and water (Scheme 1). The benzylic protection was then removed with AlCl$_3$ to afford tetranitrocalixarene **4** in 61% overall yield (Scheme 1). The phenols of **4** were alkylated with ClCH$_2$C(O)NEt$_2$ (Na$_2$CO$_3$, MeCN, 83%), and the nitro groups were reduced (H$_2$, Raney/Ni, 58%). Finally, acylation of the resulting amino groups with the appropriate isocyanates gave the ureas **2a,b** in 60−83% yields. These are tan-colored solids; tetraurea **2b** is soluble in most chlorinated solvents but the solubility of tetraurea **2a** was disappointingly limited.

Solutions of **2b** in apolar solvents (CDCl$_3$, CD$_2$Cl$_2$) show well-resolved ^{1}H NMR spectra, featuring two unusually downfield urea C(O)−NH singlets of equal intensity between 9 and 8.5 ppm (Figure 2a and Supporting Information). These resonances are concentration (0.1−20 mM) and temperature (250−310 K) independent. These downfield signals are characteristic of capsule formation and this was confirmed through heterodimerization experiments: the downfield shifts of the urea NH for **2a** and **2b** are different, but mixing their solutions in a 1:1 ratio in CD$_2$Cl$_2$ gave rise to yet another set of NH resonances. These reflect the slow (on the NMR time scale) formation of a mixed dimer. Further, from a NOESY experiment with tetraurea **2b** (CD$_2$Cl$_2$), NOE contacts were detected that are possible *only* in a dimer rather than in a monomer (see Supporting Information).

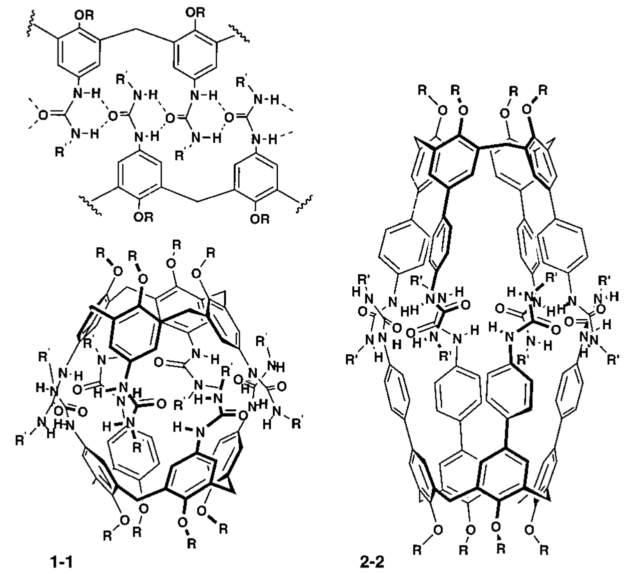


Figure 1. Calix[4]arene based capsules **1·1** and **2·2** assembled through hydrogen bonding. Top left: Schematic representation of hydrogen bonding in dimer **1·1**.

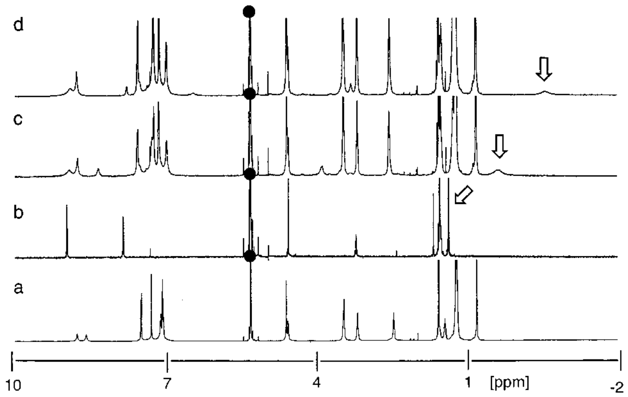
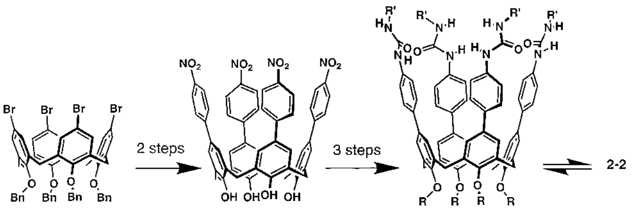


Figure 2. ^{1}H NMR spectra in CD$_2$Cl$_2$ (600 MHz, 295 K) of (a) capsule **2b·2b**, (b) guest **10**, (c) **10** + **2b**, 1:0.5, and (d) **10** + **2b**, 1:1. Further addition (>2 equiv) of **2b** does not change the spectrum. The guest *i*-Pr group is indicated by an arrow.

Scheme 1



2a R = CH$_2$C(O)NEt$_2$, R' = *p*-tolyl
2b R = CH$_2$C(O)NEt$_2$, R' = *p*-(*n*-hexyl)phenyl

When a CH$_2$Cl$_2$ solution of **2a** with **2b** was analyzed by electrospray mass spectrometry (ESI-MS), three dimeric species **2a·2a·**2Na$^+$, **2b·2b·**2Na$^+$, and **2a·2b·**2Na$^+$ were clearly observed at 1797, 2077, and 1937 daltons, respectively. These results show that extended calix[4]arene tetraureas **2a,b** self-assemble into

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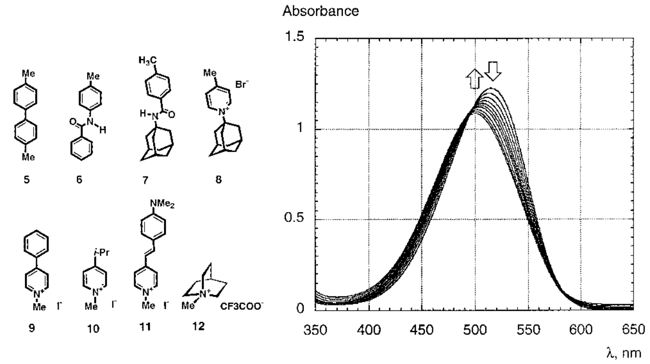

Figure 3. (a) Guests **5**−**12**. (b) Portion of the UV/vis titration with dye **11** in CH_2Cl_2 (295 K). The band at λ_{max} = 518 nm for free **11** shifts toward λ_{max} = 497 nm upon addition of capsule **2b·2b**. [**11**] = 25 μM; [**2b**] up to 0.5 mM.

dimers in apolar solution. As with capsule **1·1**, a seam of 16 C═O···H−N intermolecular hydrogen bonds at the upper rim is formed; the dimerization constant value is apparently beyond the NMR limits ($>10^5$ M^{-1}). The egg-shaped cavity that results has a volume estimated at ∼400 Å^3, the largest volume for a calix[4]arene based capsule synthesized to date.[7] According to molecular modeling, the interiors can accommodate at least two benzene- or chloroform-sized guest molecules.

The main features of the newly prepared capsules are the following.

1. Sodium complexes of **2a** and **2b** were readily prepared by solid−liquid extraction of sodium perchlorates and picrates into their CH_2Cl_2 solutions. In these, the sodium cation is tightly coordinated at the lower rim by the four carbonyl and four phenolic ether oxygens.[8] Solutions of these in apolar solvents ($CDCl_3$, CD_2Cl_2, etc.) also show self-assembly (^{1}H NMR, ESI MS). When Na^+-complexes of **2a** and **2b** are mixed in CD_2Cl_2, heterodimers are also formed (well-resolved NMR, ESI MS in Supporting Information).

2. The solvent exchange in and out of the cavities is fast, although dissociation of **2·2** is slow on the NMR time scale. For example, when **2·2** is placed in mixtures of two suitable deuterated solvents only a single species is observed. This contrasts with the behavior of capsule **1·1**, which shows the presence of two distinct species.[1,2] Apparently, the large holes in the skeleton of **2·2** permit the solvent molecules to pass rapidly in and out of the dimer. This has consequences for the guest encapsulation, since entropic gains of the solvent release are not favorable for **2·2**. Indeed, all attempts to encapsulate neutral guests of appropriate size and shape inside the capsule failed. Neither the flat and long 4,4′-dimethylbiphenyl **5** nor *N-(p*-tolyl)benzamide **6** nor even the bulkier adamantyl derivative **7** showed any spectroscopic signs of encapsulation.

3. The positively charged *N*-alkyl pyridinium derivatives **8**−**11** and *N*-methylquinuclidinium **12** are strongly complexed inside capsule **2b·2b** (Figure 3a), most probably due to the strong ion−dipole interactions. The guest exchange rate is *fast* on the NMR time scale.[9] Accordingly, only complexation induced shifts (CIS) of the guest's ^{1}H NMR signals (rather than separate signals for free and bound species) were detected in CD_2Cl_2 solution upon dilution of the guest with increasing amounts of **2b·2b** (Figure 2b−d). In particular, *o*- and *m*-pyridinium CH protons shift ∼1−2 ppm and *N*-CH_3 protons shift ∼1.5 ppm upfield (see Supporting Information). This indicates their location inside the shielded environment of **2b·2b**. The CIS data fit nicely into a complexation model with one guest in the capsule, and for complex [**2b·2b·9**] this stoichiometry was confirmed by a Job plot. From the ^{1}H NMR titrations in CD_2Cl_2, high association constant (K_{ass}) values in a range of 5.6×10^3 to 1.9×10^5 M^{-1} ($-\Delta G^{295} = 5.0-7.1$ kcal/mol) were obtained.

4. A solvent molecule may be present with the guest inside the capsule. Upon encapsulation of guests **8**−**12**, between 34 and 59% of the inner cavity **2·2** is filled (Table 1 in Supporting Information). A recent compilation of occupancy factors, or packing coefficients (PC) of molecule-within-molecule complexes in solution, indicates that an optimal PC value is ∼55% occupancy.[10] For 4-isopropyl-*N*-methyl pyridinium and *N*-methyl quinuclidinium complexes [**2b·2b·10**] and [**2b·2b·11**], the PC's are only 37 and 34%, respectively, but an additional solvent molecule would raise the figure to near optimal.

5. Complexation could additionally be followed by UV/vis spectroscopy. Titration of the deep-red dye *trans*-4-[4-(dimethylamino)styryl]-1-methyl-pyridinium iodide **11** resulted in a hypsochromic shift of the λ_{max} band from 518 to 497 nm (Figure 3b).[11]

6. Hybridization takes place between the original capsule and the newer, deeper version. When tetraureas **1** (R = $CH_2C(O)OEt$) and **2b** were mixed, a unique, nonsymmetrical capsule **1·2b** was formed (^{1}H NMR data in Supporting Information). It is present, along with the corresponding homodimers, in roughly statistical amounts and guarantees that the spacer of **2b** did not affect the energetics of the assembly into capsules. It may be possible to drive the equilibria to the hybrid with appropriate guests as has been shown with other capsules.[5a]

The features of capsules **2·2** (size, exchange rate, and hybridization) place it in a special category among nanoscale self-assembled cavities. They suggest uses as selective reaction chambers for chemical catalysis, and we are working toward this goal.

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Supporting Information Available: Experimental protocols for the synthesis of **2a,b** and **4**; molecular modeling; selected ^{1}H NMR, NOESY, and ESI-MS characterization data for assemblies **2·2**, their sodium complexes and heterodimers; and ^{1}H NMR titration data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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