Molecular capsule constructed by multiple hydrogen bonds: self-assembly of cavitand tetracarboxylic acid with 2-aminopyrimidine

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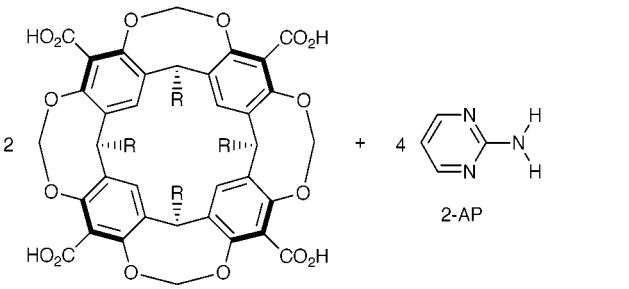
Two molecules of cavitand tetracarboxylic acid and four molecules of 2-aminopyrimidine assemble into a capsule *via* 16 hydrogen bonds, as shown by ^{1}H NMR titration and X-ray crystallographic analysis; in the solid state, two molecules of nitrobenzene are encapsulated in the capsule.

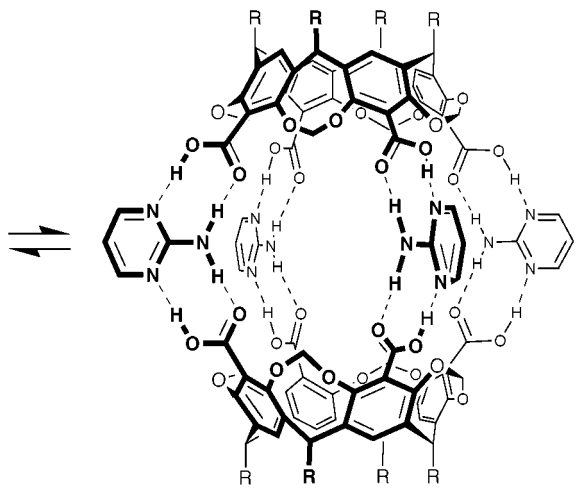
Error correction through thermodynamic equilibration, minimization of synthetic effort by use of modular subunits and control of assembly processes through subunit design are characteristic of supramolecular approaches to self-assembly.[1,2] Carcerands, in which two calix[4]resorcinarene cavitands are held together by four covalent linkages, have been synthesized and well-characterized by Cram and others, and have attracted considerable attention from the viewpoint of stabilization of reactive intermediates and microvesicles for drug delivery by confinement of guest molecules inside the capsules away from bulk phases.[3] Recently, the field of molecular capsules has advanced to a stage where self-assembly through noncovalent interactions such as hydrogen bonds and metal coordination has proved to be a reliable tool.[4,5] Based on hydrogen bonds, homodimers of functionalized cavitands in solution[6,7] and multicomponent assemblies of calix[4]resorcinarenes with solvent water or alcohol molecules as linkers in the solid state[8,9] have been reported. Metal-bridged assemblies of functionalized cavitands have also proved to be a viable alternative.[10] We have chosen the cavitand tetracarboxylic acid **1** as a concave subunit[11] and 2-aminopyrimidine (2-AP) as a hydrogen-bonded linker subunit. Our strategy for capsule formation is based on the combination of carboxylic acids with 2-AP to form a 2:1 hydrogen-bonded complex in the solid state.[12] Herein we report the construction of capsule **2** from six components *via* 16 hydrogen bonds: two molecules of **1** are indirectly held together in a rim-to-rim fashion by hydrogen bonding bridges involving four molecules of 2-AP (Scheme 1).

The cavitand **1** alone has a low solubility in $CHCl_3$ at room temperature { < 5 mM for **1a** [R = $(CH_2)_6CH_3$] and < 1 mM for **1b** [R = $(CH_2)_2Ph$]}. On the other hand, in the presence of 2 equiv. of 2-AP, **1** becomes very soluble in $CHCl_3$ (> 100 mM). The titration of a suspension of **1a** in $CDCl_3$ at 25 °C with aliquots of 2-AP was monitored by ^{1}H NMR spectroscopy. Fig. 1 shows the chemical shift changes for the NH_2 protons of 2-AP and the inward and outward methylene protons at the rim of **1a** as a function of 2-AP/**1a**.† Below the 2:1 ratio of 2-AP/**1a**, the NH_2 protons of 2-AP apparently give a saturated downfield shift ($\Delta\delta_{obs}$ = 2.95 ppm), independent of 2-AP/**1a**, while the methylene protons of **1a** are increasingly shifted downfield upon addition of 2-AP. At the 2:1 stoichiometry of 2-AP/**1a**, the mixture becomes completely homogeneous.† Beyond the 2:1 ratio, the former chemical shift changes decrease due to the average of signals between the free and complex 2-AP, whereas the latter ones remain unchanged. The fact that both titration curves have an inflection point at the 2:1 stoichiometry of 2-AP/**1a** indicates that an *n*:2*n* complex of **1a** with 2-AP is formed *via* hydrogen bonds and that this formation may be a cooperative process. The cavitand **1a** and 2-AP possess four and two hydrogen bonding sites, respectively. In principle, 1:2 and/or 1:4 complexes of **1a** with 2-AP may be conceivable. In such complexes, however, half of the hydrogen bonding sites still remain intact. The titration data obtained here suggests the formation of a capsule **2a** in solution from two molecules of **1a** and four molecules of 2-AP (Scheme 1).‡ The capsule **2a** in $CDCl_3$ was disrupted upon addition of DMSO-d_6 as a cosolvent.

The stability of **2a** was evaluated by the dilution method in $CDCl_3$ at 25 °C using ^{1}H NMR, where the ratio of 2-AP/**1a** is maintained at 2:1. The chemical shift changes for the NH_2 protons of 2-AP decreased at less than 10 mM of 2-AP. The association constant for the formation of **2a** calculated from a nonlinear curve fitting was estimated to be $K_a = 3.7 \times 10^{19}$ M^{-5} in $CDCl_3$ at 25 °C with $\Delta\delta_{sat}$ = 2.96 ppm and a correlation



1a R = $(CH_2)_6CH_3$
1b R = $(CH_2)_2Ph$



2a R = $(CH_2)_6CH_3$
2b R = $(CH_2)_2Ph$

Scheme 1

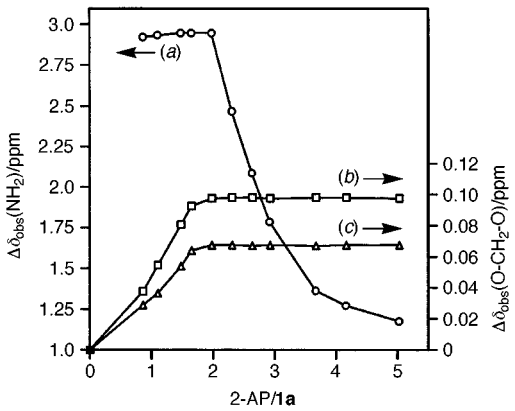


Fig. 1 Chemical shift changes for (*a*) the NH_2 protons of 2-AP and (*b*) the inward and (*c*) outward methylene protons at the rim of **1a** as a function of 2-AP/**1a** in $CDCl_3$ at 25 °C.

coefficient r = 0.99.§ This corresponds to an average $\Delta G°$ = −1.6 kcal mol^{-1} per hydrogen bond.[13]

Recrystallization of a mixture of **1** and 2-AP from various solvents such as *p*-xylene, anisole–$CHCl_3$ and nitrobenzene–$CHCl_3$ gave co-crystals composed of **1**:2-AP = 1:2 without exception. The IR spectra showed a shift (10 cm^{-1}) to lower wavenumbers of the $\nu_{C=O}$ for **1** upon adduct formation. The O–H stretching bands appeared at 2500 and 1900 cm^{-1}, which are characteristic of a carboxylic acid hydrogen bonded to an aromatic ring nitrogen.[12] When pyridine was used in place of 2-AP, co-crystals of **1**:pyridine = 1:4 were obtained. These results support the formation of **2** from **1** and 2-AP in the solid state.

Single crystals suitable for X-ray diffraction analysis were grown by allowing a hot solution of **1b** and 2-AP in nitrobenzene to slowly cool to room temperature.¶ As shown in Fig. 2, the molecular structure after symmetry operations unambiguously reveals the capsule **2b** in which two molecules of the hemispherical cavitand **1b** associate indirectly in a rim-to-rim fashion by hydrogen bonding bridges involving four molecules of 2-AP located on an equatorial position. The NH_2 protons and aromatic ring nitrogens of 2-AP form hydrogen bonds with the acid carbonyl oxygens and OH protons of **1b**, respectively. The hydrogen bonding distances of N(H)···O are 2.866(7), 2.841(7), 2.897(7) and 2.872(7) Å, and those of N···(H)O are 2.770(7), 2.604(7), 2.711(6) and 2.718(6) Å. Thus, the capsule **2b** is constructed *via* 16 hydrogen bonds between two molecules of **1b** and four molecules of 2-AP. The

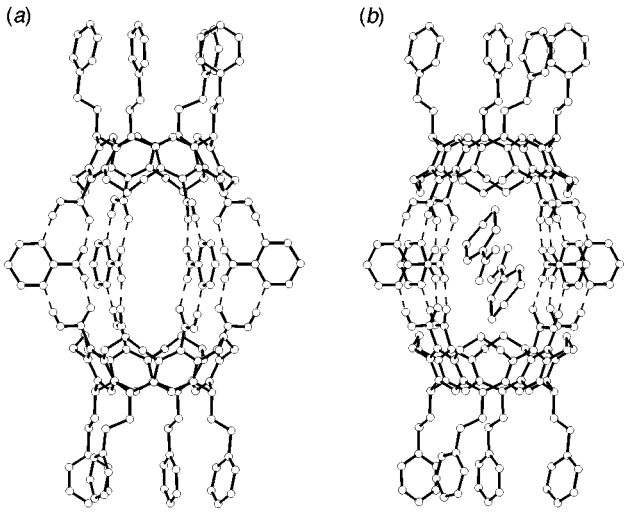


Fig. 2 Molecular structure of capsule **2b** (*a*) without and (*b*) with encapsulated nitrobenzenes. Nitrobenzenes which are not located inside the cavity and hydrogen atoms except for NH_2 protons of 2-AP and acid protons of **1b** are omitted for clarity. Dashed lines represent intermolecular hydrogen bonds.

dihedral angles between the carboxylic acid groups and the resorcinol rings of **1b** are almost perpendicular (83.5, 85.7, 105.9 and 80.2°), probably due to the electronic repulsion between the oxygen atoms of their moieties. This orientation plays an important role in the formation of the capsule. The capsule **2b** features dimensions of *ca.* 9 × 15 Å. Two molecules of nitrobenzene are encapsulated in the cavity of **2b** in an antiparallel fashion with an inter-ring distance of *ca.* 3.3 Å. They are oriented with the nitro groups towards the equatorial windows of **2b**.

In summary, we have demonstrated the capsule **2**, composed of two molecules of the cavitand tetracarboxylic acid **1** and four molecules of 2-aminopyrimidine, as a hydrogen-bonded linker. Exploration of linkers such as bipyridine derivatives and transition metals in order to control the cavity size of the capsules is currently underway in our laboratory.

Notes and references

† The concentration of **1a** is 20 mM if completely soluble in $CDCl_3$. The equilibrium is reached immediately. At the 2:1 stoichiometry of 2-AP/**1a**, the signal of the acid protons of **1a** was observed at δ 16.00 at −30 °C. Irradiation of the C(4,6) hydrogens of 2-AP showed a 3% NOE at the acid protons of **1a** at −30 °C.

‡ No evidence for the encapsulation of guests into **2a** in $CDCl_3$ is available, probably due to favorable accommodation of $CDCl_3$ as a bulk phase in **2a**.

§ A constant ratio [2-AP]:[**1a**] = 2:1, and the assumption that free **1a**, free 2-AP and capsule **2a** are the only components present, give eqn. (1),

$$[\text{2-AP}] = \{(\Delta\delta_{obs}/\Delta\delta_{sat})/[K_a(1 - (\Delta\delta_{obs}/\Delta\delta_{sat}))^6]\}^{0.2} \quad (1)$$

where $\Delta\delta_{obs} = \delta_{obs} - \delta_{free}$ and $\Delta\delta_{sat} = \delta_{sat} - \delta_{free}$ are the observed and saturated chemical shift changes of the NH_2 protons of 2-AP, respectively.

¶ *Crystal data* for **1b**·2(2-AP)·6($PhNO_2$): $C_{112}H_{96}N_{12}O_{28}$, M = 2058.05, crystal size 0.52 × 0.45 × 0.40 mm, triclinic, space group $P\bar{1}$, a = 17.79(2), b = 19.78(1), c = 15.047(5) Å, α = 107.32(4), β = 96.18(3), γ = 79.05(5)°, U = 4955(6) Å^3, Z = 2, D_c = 1.379 g cm^{-3}, μ(Mo-Kα) = 1.00 cm^{-1}, $2\theta_{max}$ = 50.2°. Intensity data (11593) were measured on a Rigaku RAXIS-II diffractometer at 120 K. The final least-squares refinement based on F for 8815 unique reflections [with $I > 3.0\sigma(I)$] and 1396 parameters converged with R = 0.110 and R_w = 0.124. CCDC 182/1489. See http://www.rsc.org/suppdata/cc/a9/a908315d/ for crystallographic data in .cif format.

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