

that a large accumulation of albumin had taken place (Figure 5c). Peroxidase and vitamin B2 have also been successfully encapsulated by employing this method.

It has been shown that many water-soluble substances such as rhodamine, PAH, and dextran can spontaneously accumulate in the interior of the aged polyelectrolyte capsules templated on MF particles, forming filled capsules under ordinary conditions. The driving force for this phenomenon is attributed to the existence of a negatively charged complex (PSS/MF) within the capsule interior. The deposited material is in an aggregated or complexed form, rather than existing in its free state, which constrains the system so that the real concentration of the deposited substance within the interior of the capsule remains lower than in the bulk. By utilizing this effect, biomolecules such as albumin have been successfully encapsulated in large quantity by simple alteration of the pH value. In conclusion, we have shown herein that spontaneous and quantitative encapsulation of a drug can occur by deposition within the interior of a macromolecule, which specifically binds to it and initiates its precipitation. This process might in turn be useful in controlling the sustained release of water-soluble agents.

### Experimental Section

The sources of the chemicals employed in this study were as follows: PSS ( $M_w = 70$  kD), PAH ( $M_w = 15$  kD), and PDADMAC ( $M_w = 200$ – $350$  kD, 20% w/w in water, Aldrich; FITC-albumin (12:1 FITC:albumin molar ratio), FITC-Dextran ( $M_w = 77$  kD), TRITC-dextran ( $M_w = 65$  kD) and Rd6G, Sigma; MF particles, Microparticles GmbH, Berlin, Germany. All chemicals were used as received. TRITC-PAH was prepared by the literature route.<sup>19</sup> The water used in all experiments was prepared in a three-stage Millipore Milli-Q Plus 185 purification system and had a resistivity higher than 18.2 M $\Omega$  cm.

Membrane filtration was employed to consecutively adsorb PSS and PAH onto MF particles.<sup>10</sup> The adsorption of polyelectrolyte (1 mg mL<sup>-1</sup>) was conducted in 0.5 M NaCl solution for 5 min followed by three washings in H<sub>2</sub>O. After the desired number of oppositely charged layers had been adsorbed, the coated particles were added to 0.1 M HCl solution, in order to decompose the MF cores. The decomposition products and any excess HCl were then removed in H<sub>2</sub>O by filtration with gentle agitation until pH neutrality was established. The model PSS/MF complex was prepared by dropping the core decomposition solution into a stirred 0.25 mg mL<sup>-1</sup> PSS solution, followed by sufficient washing and filtration to remove the excess PSS or MF decomposition products.

Equal amounts of capsule suspension (aged for at least one month) and Rd6G, TRITC-PAH, TRITC-dextran, FITC-dextran, or FITC-albumin solution (2 mg mL<sup>-1</sup>) were mixed together and stored for several minutes at room temperature to obtain the filled capsules. The solutions were then directly observed using CLSM.

CLSM images were taken with a Leica TCS NT inverted confocal system (Leica, Germany) equipped with a 100 $\times$  oil immersion objective. The images of capsules in aqueous solution were acquired immediately, whereas images of species out of solution were taken after any residual water had evaporated. The marked spots in FITC-dextran filled capsules were bleached for 1 sec at maximum laser output at 488 nm. The recovery images were recorded and the relative fluorescence intensity was calculated automatically by using Leica TCS NT software.

SFM images were recorded in air at room temperature (20–25 °C) using a Nanoscope III Multimode SFM (Digital Instrument Inc., Santa Barbara, CA). The samples were prepared by applying a drop of the capsule solution onto freshly cleaved mica.

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## Solid-State and Solution Studies of a Tetrameric Capsule and Its Guests\*\*

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Synthetic capsules, assembled and even self-assembled from their many components, are host structures available in variety. Whether held together with hydrogen bonds or metal–ligand interactions, their reversible encapsulation of guests provides a modern vehicle for physical organic chemistry. Molecular recognition, stabilization of reactive

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intermediates,<sup>[1–3]</sup> and control of reactivity<sup>[4–9]</sup> and of the assembly process itself are amenable to study within capsules.<sup>[10–13]</sup> Like many of their biological counterparts,<sup>[14]</sup> these assemblies do not form in the absence of suitable guests.<sup>[15,16]</sup> Accordingly, there are intermolecular forces (in addition to mechanical ones) holding the guest within the host. Shape complementarity and the proper filling of space<sup>[17]</sup> play roles, but the attractions of host and guest, at least in neutral capsules, lack detail. We report here on some of these interactions through crystallographic and complementary solution-phase studies of an assembly consisting of four host subunits and a nucleating guest (Figure 1 a). The studies reveal a remarkable hydrogen-bonding motif: Each carbonyl oxygen atom of the diketone guest accepts hydrogen bonds from four identical N–H donors of the host.

The curvature and chemical surfaces of monomer **1** encode information that permits 24 hydrogen bonds to form when a tetrameric capsule assembles around a guest. The specific interactions between the guest molecule 2,6-adamantane-dione (**3**) and host (**1**)<sub>4</sub> that ultimately drive capsule assembly were elucidated by X-ray diffraction analysis.<sup>[18]</sup> The four subunits of **3**⊂(**1**)<sub>4</sub> are held in a head-to-tail arrangement of

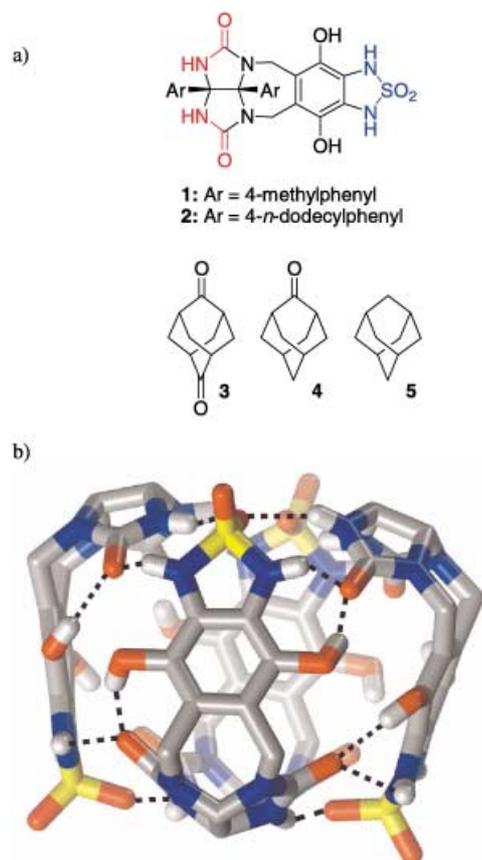


Figure 1. Summary of the monomers, guests, and capsules described herein: a) molecular structures of the monomers (**1** and **2**) and guests (**3–5**) used in this study. The glycoluril hydrogen bonding functionality is shown in red and the sulfamide group in blue; b) wireframe representation of the single-crystal X-ray structure of tetrameric capsule (**1**)<sub>4</sub>. The guest, along with the glycoluril phenyl rings of the host and the hydrogen atoms not participating in hydrogen bonding have been omitted for clarity. Nitrogen atoms are shown in blue, oxygen atoms in red, sulfur atoms are depicted in yellow, and carbon atoms are shown in gray.

glycoluril (urea) and sulfamide functionalities (Figure 1 b).<sup>[19]</sup> Compared to an earlier generation of tetrameric capsules,<sup>[13]</sup> this new capsule has an additional belt of eight phenolic hydrogen bonds around its equator that further stabilizes the assembly. The hydroxy groups on opposing sides of each monomer donate hydrogen bonds to different acceptors—one intermolecular and one intramolecular. The result is an alternating hydrogen-bonding motif that breaks the mirror symmetry of the monomer, leading to a chiral twist in the overall tetrameric capsule (Figure 1 b). The tetramer crystallizes as a racemate with no symmetry, although the structure has very nearly *D*<sub>2</sub> symmetry.

The width of the capsule, measured between opposing aromatic walls, is approximately 10 Å in the solid state, and approximately 8 Å separates the two glycoluril/sulfamide hydrogen-bonding seams. Coupled with the curvature of the monomer, these dimensions provide a host cavity with an interior volume of 184 Å<sup>3</sup>.<sup>[20]</sup> Cross-sectional views of the capsule depict the environment inside the cavity occupied by **3** (Figure 2). A perfect symmetry match for the cavity, guest **3** forms numerous CH–π interactions and van der Waals con-

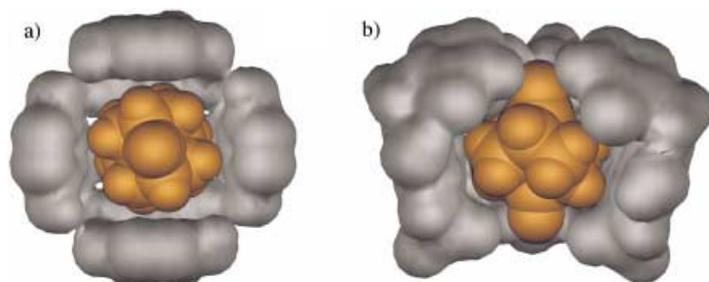


Figure 2. Space-filling views of **3**⊂(**1**)<sub>4</sub> from the single-crystal structure highlighting the orientation of the guest inside the host: a) cross-section of the structure of tetramer (**1**)<sub>4</sub> showing the close packing of the guest (**3**, brown space-filling spheres) inside the host (shown as a gray van der Waals surface); b) view showing the orientation of the guest (**3**) within the capsule. One of the four host monomers has been removed for clarity.

tacts with the electron-rich aromatic wall of the host. The guest is not disordered about any of the three pseudo-twofold axes of the capsule. Rather, its position within the host is well-defined and exposes the multiple intermolecular forces—including an intimate network of hydrogen bonds—that wedge the guest tightly into the capsule.

The long axis of the guest is oriented along the short axis of the host cavity. The orientation of the guest is determined by an unusual array of hydrogen bonds bridging the host and guest (Figure 3). The ketone oxygen atoms of the guest are fixed at each end of the cavity by polar interactions with the glycoluril/sulfamide hydrogen-bonding seam. The distances between each ketone oxygen atom of the guest and the four proximal urea nitrogen atoms, as well as the corresponding N–H⋯O angles all fall within the permissible ranges for hydrogen bonds in the solid state.<sup>[21]</sup> This pattern represents an exceptional mode of hydrogen bonding: each ketone carbonyl group accepts hydrogen bonds from four identical donor atoms. These multiple attractive interactions between the guest and the host (a total of eight bifurcated hydrogen

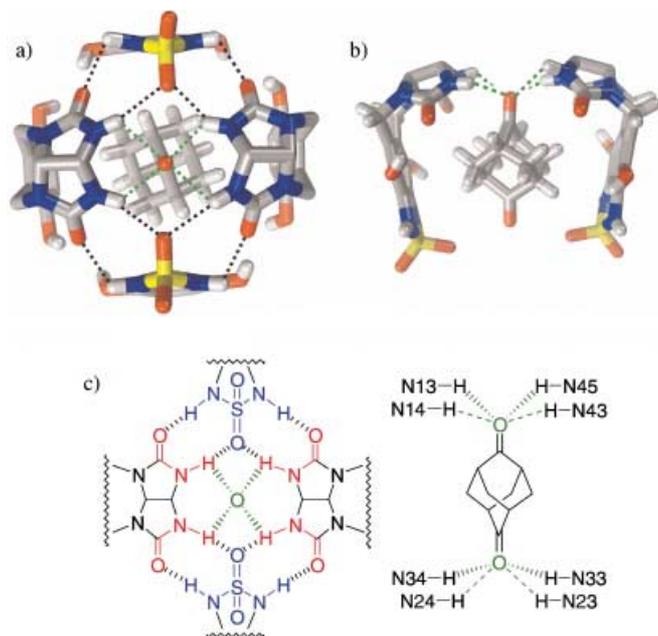


Figure 3. Detailed views of the hydrogen-bonding schemes between the guest and the tetrameric capsule shell: a) view down the axis of **(1)**<sub>4</sub> coincident with the oxygen–oxygen axis of **3**, which shows the hydrogen bonding between the urea groups and the guest ketone groups; b) side view of the same hydrogen-bonding interaction with two monomers of **(1)**<sub>4</sub> removed for clarity. The same color scheme as in Figure 1 has been used, and hydrogen bonds between the guest and host are shown as green dashed lines; c) left: a representation showing the hydrogen-bonding interactions between glycoluril functionalities (red), sulfamide groups (blue) and the ketone groups (green) of the guest, showing how the capsule is stitched together and the role the guest plays, right: the hydrogen-bonding interactions between the eight urea hydrogen atoms and the two ketone oxygen atoms. Selected hydrogen-bond lengths [Å] and N–H···O angles [°]: N13–O200 2.98, N14–O200 2.99, N43–O200 2.98, N45–O200 2.87, N23–O201 3.11, N24–H201 2.92, N33–O201 2.87, N34–O201 3.04; N13–O200 111, N14–O200 122, N43–O200 98, N45–O200 129, N23–O201 105, N24–H201 125, N33–O201 130, N34–O201 97.

bonds and at least four CH– $\pi$  interactions) result in the guest filling approximately 72% of the available space in the capsule cavity. This cavity packing coefficient was compared to several nanoscale capsules<sup>[22–27]</sup> found in the Cambridge Structure Database (CSD). Our survey revealed that between 40% and 65% volume of the capsule cavities is typically filled by guests in the solid state; the structure of **3C(1)**<sub>4</sub> is unique in this regard.<sup>[20]</sup>

When one equivalent of a suitable guest such as 2,6-adamantanedione (**3**), 2-adamantanone (**4**), or adamantane (**5**) is added to a CD<sub>2</sub>Cl<sub>2</sub> solution of **2**, the <sup>1</sup>H NMR spectrum indicates the formation of a discrete assembly.<sup>[13,28]</sup> Sharp, concentration-independent signals emerge, including singlets at approximately 10.6 ppm and 6.2 ppm, which correspond to the sulfamide N–H and glycoluril N–H protons, respectively (see Supporting Information). Upfield-shifted resonances appear for the bound guest; their 1:4 ratio relative to the host provides unambiguous evidence for the existence of a tetrameric assembly encapsulating one equivalent of guest in solution. Unlike the solid-state tetramer, the solution assembly exhibits overall *D*<sub>2d</sub> symmetry, perhaps as a result of fast exchange between the two slightly twisted *D*<sub>2</sub>-symmetric enantiomers.

Do the host–guest contacts observed represent attractive interactions or do they exist only to minimize repulsions in the solid state? In solution, adamantane (**5**) is a sufficient guest to drive capsule assembly, presumably because of its ability to form CH– $\pi$  interactions with the aromatic walls of the host, similar to those observed in the structure of **3C(1)**<sub>4</sub>. <sup>1</sup>H NMR spectroscopic competition experiments show that 2-adamantanone (**4**) and 2,6-adamantanedione (**3**) are bound more favorably than adamantane by  $\approx 0.7$  kcal mol<sup>–1</sup> and  $\approx 1.8$  kcal mol<sup>–1</sup>, respectively. These differences can only be attributed to the stabilizing influence of hydrogen bonds between the guest carbonyl groups and the urea hydrogen atoms of the capsule. Although each individual hydrogen bond to the guest must be quite weak (ca. 0.2 kcal mol<sup>–1</sup>), the solution and solid-state studies show that host–guest hydrogen bonding is not only an important driving force for capsule formation, but also dictates the guest binding selectivity.

As more complicated receptors capable of enclosing larger “empty” spaces are elaborated, the importance of solvent and other guests filling these spaces is appreciated. Other X-ray structures of multimeric hydrogen-bonded capsules are all the more spectacular given the larger number of components involved,<sup>[29,30]</sup> with only one example reporting the presence and positions of the multiple solvent molecules occupying the capsule.<sup>[31]</sup> Here, studying the lone guest within a constrained environment reveals two features: 1) the guest fills an inordinately large amount of space inside the capsule, and 2) the guest experiences a unique mode of hydrogen bonding for a carbonyl group. This novel binding motif<sup>[32]</sup> may have implications in the activation of carbonyl compounds by multiple Lewis acids or in the binding of compounds in biological settings.

### Experimental Section

General: The synthesis and characterization of all compounds, as well as a description of the procedure used to determine solution guest binding constants, are in the Supporting Information.

X-ray diffraction study of **3C(1)**<sub>4</sub>·3CH<sub>2</sub>Cl<sub>2</sub>·2C<sub>5</sub>H<sub>12</sub>: A general crystallographic experimental is in the supporting information. CCDC-183906 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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## The Supercritical Fluid Antisolvent Synthesis of C<sub>60</sub>(C<sub>2</sub>H<sub>x</sub>) (x = 4 or 6); The Crystal Structures of Two Materials Which Were Thought Unlikely to Exist\*\*

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Synthetic routes to C<sub>60</sub>(gas) intercalation compounds have reached the point where the intercalation of molecules larger than CO<sub>2</sub> has appeared impossible.<sup>[1]</sup> We report the synthesis of the intercalation compounds of C<sub>60</sub> with C<sub>2</sub>H<sub>4</sub> and C<sub>2</sub>H<sub>6</sub>, by using supercritical fluid (SCF) antisolvents to grow single crystals from C<sub>60</sub> dissolved in 1,2-dichlorobenzene.

Interest in C<sub>60</sub>(gas) intercalation compounds remains high. Their use as gas storage media has been suggested, with approximately 40 bar of intercalated gas able to be held at atmospheric pressure, with the possibility of controlled release.<sup>[1,2]</sup> More recently, superconducting properties have been reported in these materials by hole and electron doping.<sup>[3,4]</sup>

The lattice compressibility studies of Morosin and co-workers led to the discovery of the intercalating behavior of He and Ne into C<sub>60</sub>.<sup>[5]</sup> The field was expanded by Gadd et al., who introduced hot isostatic pressing (HIP, greater than 1.5 GPa and above 500°C) to open thermally the fullerene lattice and facilitate diffusion.<sup>[1,2]</sup> In 1999, this work culminated in a review of all gas-intercalated species. There was no clear evidence for the intercalation of hydrocarbons larger than CH<sub>4</sub> because the forcing conditions of HIP appear to promote polymerization.<sup>[1]</sup> It was concluded that true intercalation of hydrocarbons larger than CH<sub>4</sub> was unlikely.

In contrast, fullerene(solvent) intercalation compounds are known for a wide range of hydrocarbon solvents.<sup>[6,7]</sup> These are related to the C<sub>60</sub>(gas) materials, although they have several solvent molecules per C<sub>60</sub> unit, with a complete rearrange-

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