Host–Guest Systems

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Assembly of Hybrid Synthetic Capsules**

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Self-assembled capsules are nanoscale structures made up of modular subunits held together by weak intermolecular forces.[1] As in many assemblies in biology,[2] the subunits of the capsules are most often identical, self-complementary molecules. Capsules with two,[3] four,[4] six,[5] and more[6] modular components are now routinely available. In biology, heteromeric assemblies between different modules—hybrids—are also functional and give rise to new selectivities. In proteins they appear famously in hemoglobin, G protein coupled receptor heterooligomers,[7] and transcription factor heterodimers.[8]

We show herein that two distinct modules, each capable of forming homomeric capsules, also recognize each other to create a hybrid capsule. The binding selectivity of the hybrid differs from its parent capsules, and it emerges in response to small molecules that specifically template its assembly. The results point to some flexibility in the rules of self-assembly that allows new structures to arise spontaneously from seemingly unmatched modules.

Previous examples of hybrid capsules feature subunits with the same hydrogen-bonding patterns and similar shapes[9] but with different peripheral substituents.[10] A recent example is the hexameric capsule **1** (Figure 1). It exchanges its resorcinarene modules (different R′ groups) readily but does not exchange subunits with the closely related pyrogallolarenes **3** and their respective hexamers.[11] Other systems also exhibit "self-sorting".[12] In contrast, we describe here a hybrid capsule that forms from parent capsules of widely different size, shape, and hydrogen-bonding pattern.

Subunit **4** dimerizes through eight bifurcated hydrogen bonds[13] to give the cylindrical capsule **5**. Like other capsules, the assembly of **5** requires appropriate filling of the internal space. In chloroform ($CHCl_3$), three molecules of solvent perform this role as shown in Figure 1. This solvent also serves as a suitable guest for the hexameric capsule **1**, in which six $CHCl_3$ molecules fill the cavity.[14]

The addition of resorcinarene **2** to a solution of **4** in $CHCl_3$ exhibited the expected signals in the ^{1}H NMR spectrum for both capsule species **1** (Figure 2a) and **5** (Figure 2b), and signals for the formation of a new assembly were also present.

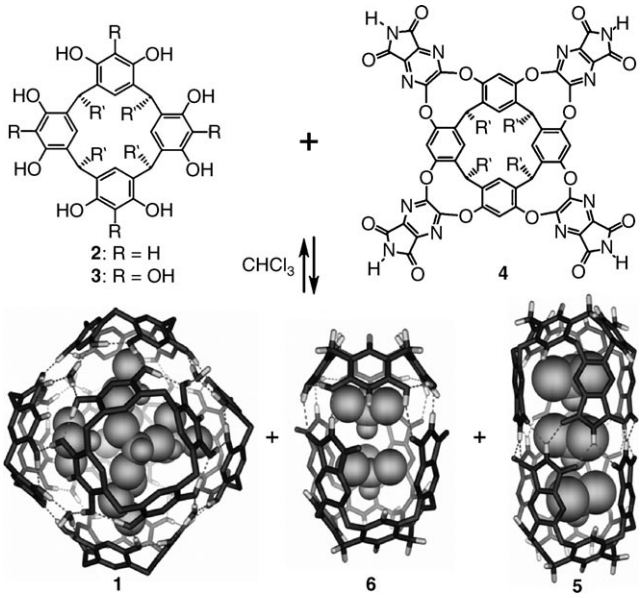

Figure 1. Chemical structures of resorcinarene **2**, pyrogallolarene **3**, and tetraimide cavitand **4** (R′ = $C_{11}H_{23}$), and models of hexameric capsule **1**, cylindrical capsule **5**, and the proposed structure of hybrid capsule **6** (stick representations) with six, three, and two $CHCl_3$ molecules (space-filling representation) inside, respectively. All three capsules coexist in $CHCl_3$. Peripheral alkyl groups and some hydrogen atoms have been removed for viewing clarity. Only one of several arrays of hydrogen bonds are shown for **1** and **6**.

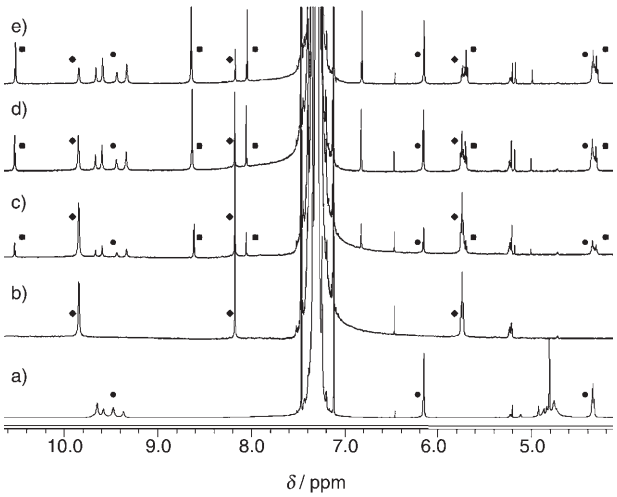

Figure 2. ^{1}H NMR spectra showing that two components lead to three distinct capsules in $CHCl_3$. a) A solution of **2** (2 mM) in $CHCl_3$ leads to the formation of hexamer **1** (●) with six encapsulated solvent molecules. b) A solution of **4** (4 mM) in $CHCl_3$ yields the cylindrical capsule **5** (◆) with three encapsulated solvent molecules. c–e) Titration of **4** (4 mM) with **2** (1.5 mM (c), 3.0 mM (d), and 4.5 mM (e)) generates varying amounts of each capsule, **1** (●), **5** (◆), and **6** (■). ($CDCl_3$ was used as internal standard, T = 300 K, 600 MHz).

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The new signals (Figure 2c) showed chemical shifts and integrations consistent with a hybrid assembly **6**. Further addition of **2** to the solution resulted in a decrease in signals for **5** and an increase in signal for **1** and the new species (Figure 2d,e).

We screened guests that favored the assembly of the hybrid capsule, especially those not readily encapsulated by either **1** or **5**. Midsize guests (such as diethylbenzene, **7**) require a small co-guest to be encapsulated within **5** (e.g. CH_2Cl_2, C_6H_6, $CHCl_3$), but **7** by itself proved an amicable guest for the smaller hybrid **6** (Figure 3a); furthermore, capsules **1** and **5** were not observed. The upfield region of the spectrum shows the encapsulated ethyl groups have different chemical shifts due to the anisotropy of the unsymmetrical capsule, and the downfield region is consistent with this assignment.

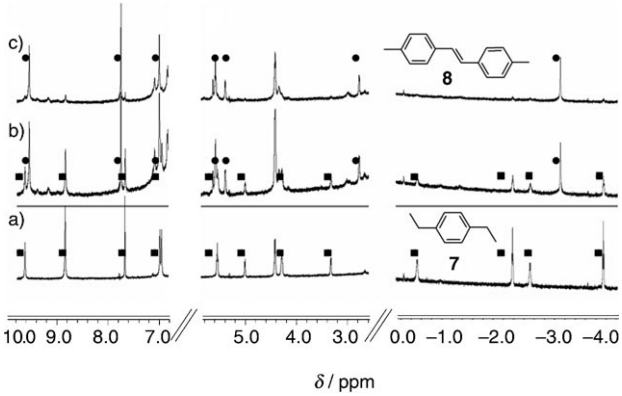

Figure 3. Reversible encapsulation as observed by ^{1}H NMR spectroscopy ([D_{12}]mesitylene, $T = 300$ K, 600 MHz). a) 1,4-Diethylbenzene (**7**, 20 mM) was mixed with **4** (4 mM) and **2** (2 mM), resulting in clean formation of **7** in **6** (■). b) Titration of the assembly (**7** in **6**) with 4,4′-dimethyl-*trans*-stilbene (**8**; 15 mM) shows the partitioning of the capsular components so that **8** may be encapsulated in **5** (●). c) Addition of 30 mM (total) of **8** drives the equilibrium away from formation of the hybrid capsule. The small peaks that appear at $\delta = 9$–10 ppm correspond to capsule **1** and module **2**.

The dynamic nature of the hybrid system was revealed through titration of the new capsular assembly (**7** in **6**) with 4,4′-dimethyl-*trans*-stilbene (**8**), a known guest for capsule **5**. Guest **8** proved to be a better guest for **5** than **7** was for **6**, and a shift in the equilibrium was observed to reflect these preferences (Figure 3b,c).

Additional guests **9**–**14** were selectively encapsulated by hybrid **6**, as is evident from the upfield region of their ^{1}H NMR spectra (Figure 4a–d). The racemic spirocyclic compound 1,7-dioxaspiro[5.5]undecane **12** did not show evidence of diastereotopic differentiation when encapsulated (Figure 4d), although the capsule presents a chiral magnetic environment due to the directionality of hydrogen bonding at the seam. Encapsulated *p*-cymene (**13**) displayed the telltale signs of carceroisomerism, a form of stereoisomerism first reported by Reinhoudt and co-workers.[15] It involves an unsymmetrical host with an unsymmetrical guest that does not "tumble" freely within. In the case at hand, the major

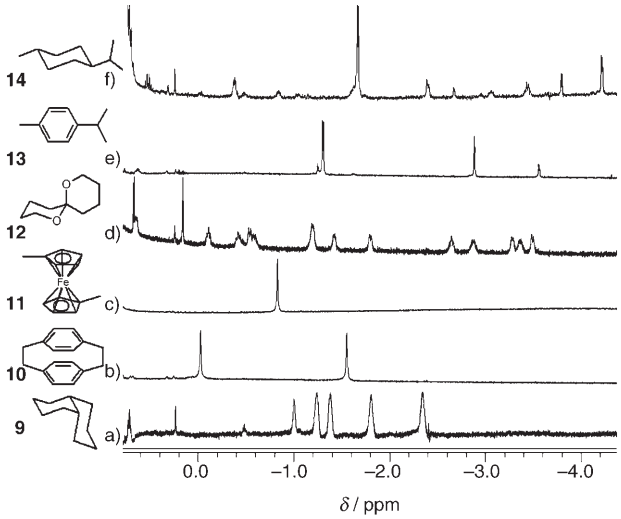

Figure 4. Upfield regions of ^{1}H NMR spectra show signals for the encapsulation of a) *cis*-decalin (**9**), b) *p*-cyclophane (**10**), c) 1,1′-dimethylferrocene (**11**), d) 1,7-dioxaspiro[5.5]undecane (**12**), e) *p*-cymene (**13**), and f) *trans*-1-isopropyl-4-methylcyclohexane (**14**) in the hybrid capsule **5** ([D_{12}]mesitylene, $T = 300$ K, 600 MHz). The minor peaks in parts (e) and (f) represent carceroisomers.[15]

isomer places its unique methyl group into the cavitand **4** while the isopropyl group resides near the seam of hydrogen bonds. The fully saturated analogue **14** also showed two orientations in **6** (Figure 4f).

Further structural confirmation of **6** was achieved through diffusion-ordered spectroscopy (DOSY).[16] The encapsulated guests (in slow exchange with the free guests) show the same diffusion coefficient as the capsule itself, as the assembly diffuses as a single supramolecular entity. The DOSY spectrum of the new assembly clearly confirmed encapsulation of *p*-cyclophane (**10**; Figure 5) and dimethylferrocene (**11**; Figure 6) inside **6**; their associated resonances showed the same diffusion coefficient. Additionally, the diffusion coefficient of **6** ($D = (1.714 \pm 0.007) \times 10^{-10}$ m^{2}s^{-1}) compared with that of **5** ($D = (1.456 \pm 0.009) \times 10^{-10}$ m^{2}s^{-1})[17] indicates that the molecular weight of **6** is lower than that of **5**.

^{1}H NMR spectra were recorded for a mixture of **11**, **2**, and **4** at three temperatures (Figure 6). At 270 K, all peaks are readily attributed to assembly **6**. At higher temperatures

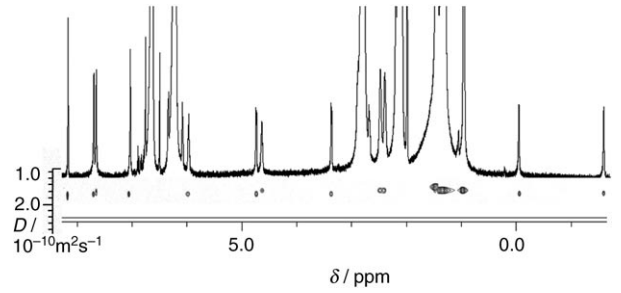

Figure 5. The DOSY spectrum ([D_{12}]mesitylene, $T = 300$ K, 400 MHz) of paracyclophane (**10**) in **6**. All the signals of the hybrid capsule and encapsulated paracyclophane have the same diffusion coefficient ($D = (1.714 \pm 0.007) \times 10^{-10}$ m^{2}s^{-1}).

evidence of other capsular species exist; at room temperature there is evidence for the coexistence of **1**. The broad, small peaks are indicative of ill-defined species. At 330 K these peaks are cleanly resolved, illustrating that both **1** and **6** are present.

In conclusion, we have found that a new hybrid capsule **6** emerges even in direct competition with their respective homomeric capsules.[18] The hybrid capsule achieves equilibrium concentrations under ambient conditions in solution within seconds and allows access to the direct spectroscopic observation of new encapsulated guests. Indeed, the hybrid forms in response to a guest that fills its space properly. Its formation is an exception to self-sorting and demonstrates flexibility in the rules of self-assembly phenomena.

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