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Selective Stabilization of Self-Assembled Hydrogen-Bonded Molecular Capsules Through $\pi-\pi$ Interactions

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Supporting Information

ABSTRACT: Subtle noncovalent forces such as $\pi-\pi$ interactions play an import role in the folding of biological macromolecules such as DNA and proteins. We describe here a system where such interactions on the outside of a molecular capsule trigger a selective change of its structure as a self-assembled receptor.

Noncovalent interactions of aromatic rings play an important role in biological systems: They stabilize the structure of biomolecules such as DNA and proteins and also play a crucial role in protein–ligand binding.[1] Although individual $\pi-\pi$ interactions are weak, they are typically numerous in protein interiors and contribute in sum to protein folding and thermal stability. We sought to engineer such stabilizing aromatic $\pi-\pi$ interactions into hydrogen-bonded molecular capsules and report here that a number of these weak interactions impart selectively on the self-assembly process.

A multitude of capsules have been devised over the last two decades, held together mainly either via covalent bonds,[2] hydrogen bonds,[3] metals, and ligands,[4] or simple hydrophobic effects.[5] Inside these capsules a molecule's behavior is quite different than it is in bulk solvent; interactions are amplified,[6] reactive intermediates are stabilized,[4b,f,g,7] reactions are accelerated[8] and even catalyzed,[4c,9] unusual reaction pathways are facilitated,[10] and new types of stereochemistry emerge.[11] Hydrogen-bonded capsules have been extended with spacer modules,[12] and we recently reported the extension of the dimeric host capsule **1.1** (Figure 1a) with propanediurea (PD) units **2** (Figure 1b) through self-assembly in the presence of suitable *n*-alkane guests.[13] The shorter *n*-alkane guests (*n*-tetradecane to *n*-hexadecane) induced the formation of the isomeric assemblies **I** and **II**. Assembly **I** (Figure 1c) features a chiral arrangement of four PD units in a "twisted belt" orientation; assembly **II** (Figure 1d) features a plane of symmetry as two of the PD units are in a "horizontal" orientation (Figure 1d). At equilibrium, mixtures of **I** and **II** are formed for these guests, with ratios ranging from 2:1 to 1:5 for *n*-tetradecane and *n*-hexadecane, respectively (Table 1). The preference follows considerations of length (**I** is slightly shorter than **II**). Accordingly, assembly **I** favors the shorter guests, *n*-tetradecane and *n*-pentadecane, while host **II** favors the longer *n*-hexadecane and *n*-heptadecane. Size also bears on the corresponding packing coefficients (PCs) and the extent to which the longer guests must assume *gauche* conformations to fit inside. These assemblies prefer a PC of slightly above 50%,[14] but the existence

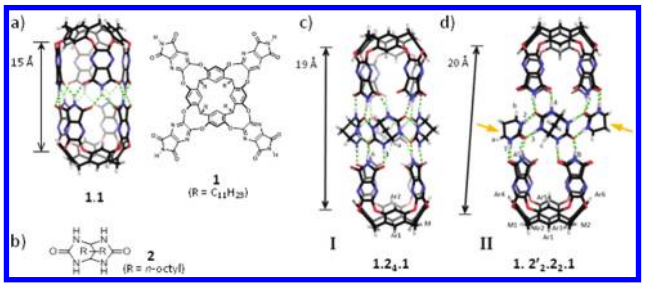

Figure 1. (a) Molecular model of dimeric capsule **1.1**, its approximate accessible cavity length and structure of cavitand unit **1**. (b) Structure of propanediurea spacer unit **2**. (c) Molecular model of extended capsule **I** consisting of two cavitand units **1** and four PD spacer units **2**, which are arranged in a "twisted-belt" fashion. (d) Molecular model of an isomeric capsule **II** again with two cavitands and four spacer units; In this case two PD units are oriented in a twisted fashion, while the remaining two PD units (marked by orange arrows) are bound horizontally with respect to the cavitand. (Peripheral alkyl groups have been deleted for easier viewing.).

Table 1. Distribution of Assemblies I and II formed with Guests *n*-Tetradecane to *n*-Heptadecane and Corresponding Packing Coefficients (PC)

guest	formation of I (%)	PC in I	formation of II (%)	PC in II
n-tetradecane	67	50	33	47
n-pentadecane	67	53	33	50
n-hexadecane	17	55	83	53
n-heptadecane	–	56	100	53

of mixtures indicates that assemblies **I** and **II** are very close in free energy. This thermodynamic balance suggested the system could be a measure of $\pi-\pi$ interactions, as even small contributions from these subtle attractive forces could tip the balance for formation of one assembly over the other. This turned out to be the case.

We engineered additional stabilization into the self-assembling systems **I**/**II** through $\pi-\pi$ interactions *on the outside of the assembly*. Specifically, aromatic panels were installed on the propanediurea units that could fold onto the outer surface of the capsule. Direct connection of phenyl groups to the propanediurea framework (PD **3**) results in rigid aromatic units directed away from assembly **I** (**1.3$_4$.1**, Figure 2a), but connection through the flexible benzyl groups permits the

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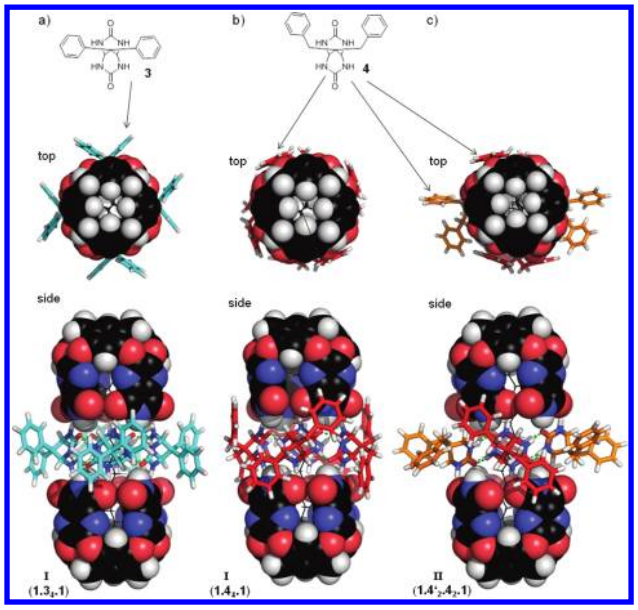

Figure 2. (a) Molecular models of assemblies **I** incorporating phenyl-PD **3** (cyan) units; (b) Model of assemblies **I** incorporating benzyl-PD **4** (red); (c) Model of assemblies **II** incorporating benzyl-PD **4** (marked red if oriented in a "twisted" fashion or marked orange if bound "horizontally" to the cavitand). The benzylic side chains of the PD **4** units bound in a "twisted" fashion (marked red) can fold back onto the surface of the capsule and give rise to potentially stabilizing $\pi-\pi$ interactions with the assembly's hydrogen-bonding array. (Peripheral alkyl groups have been deleted for easier viewing.)

aromatic panels to fold back on the outer surface of capsule **I** (**1.4$_4$.1**) and offer stabilizing $\pi-\pi$ interactions to the assembly's hydrogen-bonding array (Figure 2b). The molecular models indicated that the distance of the benzylic side chains to the hydrogen-bonding array is approximately 3.5 Å, a value that is in good agreement with literature distances for $\pi-\pi$ interactions of hydrogen-bonded arrays to aromatics.[1a,b] In the case of **1.4$_4$.1**, eight benzene rings (two on each of the four PD units) could form such interactions. However, the same components assembled as capsule **II** (**1. 4'$_2$.4$_2$.1**) lose half of these interactions, since the "horizontally" bound PD units (highlighted in orange in Figure 2c) present the benzylic functions in a way that prevents stacking on the capsular surface.

Encapsulation studies with these systems were performed in mesitylene-d_{12}, which, due to its size and inconvenient shape, does not compete for the capsules with the intended guest molecules. This solvent required that a soluble (lipophilic) derivative of PD **4** be synthesized. Earlier experiments with related glycoluril spacer units[12a] suggested the attachment of remote dibutylamino groups onto the aromatic side chains (PD **5**, Figure 3) and PD **5** was synthesized in nine steps and 7%

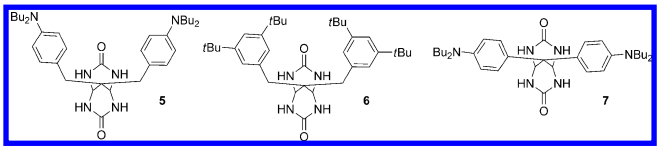

Figure 3. Structures of the investigated propanediurea spacers.

overall yield (see SI for details). Its assembling properties with cavitand **1** in the presence of *n*-alkanes were compared with those of dioctyl-PD **2**. Using **5**, the shorter guests (*n*-$C_{14}H_{30}$ to *n*-$C_{17}H_{36}$) were *exclusively encapsulated in assembly I* (Figure 4).

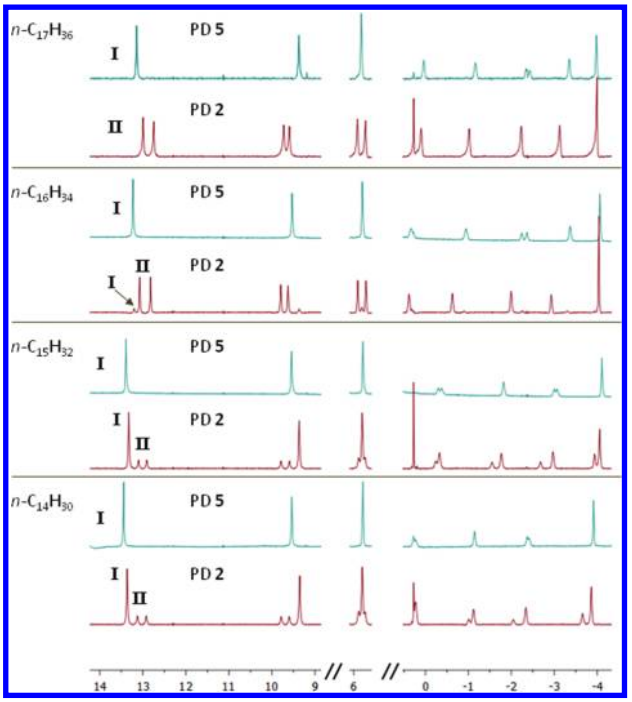

Figure 4. Comparison of the ^{1}H NMR spectra of assemblies containing either spacer unit **5** or unit **2**, formed in the presence of the guests *n*-tetradecane to *n*-heptadecane. The labels **I** or **II** refer to

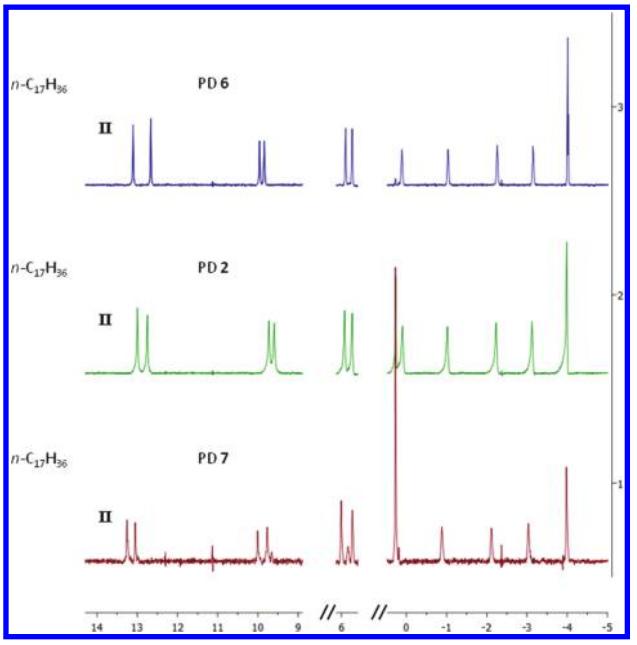

Figure 5. Comparison of the ^{1}H NMR spectra of assemblies containing either PD spacer unit **6**, **2**, or **7**. These PD-units lack the ability to stack to the outside of the capsule and all form assembly **II** in the presence of *n*-heptadecane as guest.

As described above, use of **2** gave mixtures of arrays **I** and **II** for guests *n*-$C_{14}H_{30}$ to *n*-$C_{16}H_{34}$ and **II** exclusively with *n*-$C_{17}H_{36}$.

A further test of the role $\pi-\pi$ stacking plays was provided by propanediurea derivative **6** (Figure 3) (synthesized in four steps, 47% overall yield; see SI). This also features benzylic side chains, but the two bulky *tert*-butyl groups on each benzene prevent efficient stacking onto the capsules surface. In the experiment, PD **6** behaves in the same manner as the original

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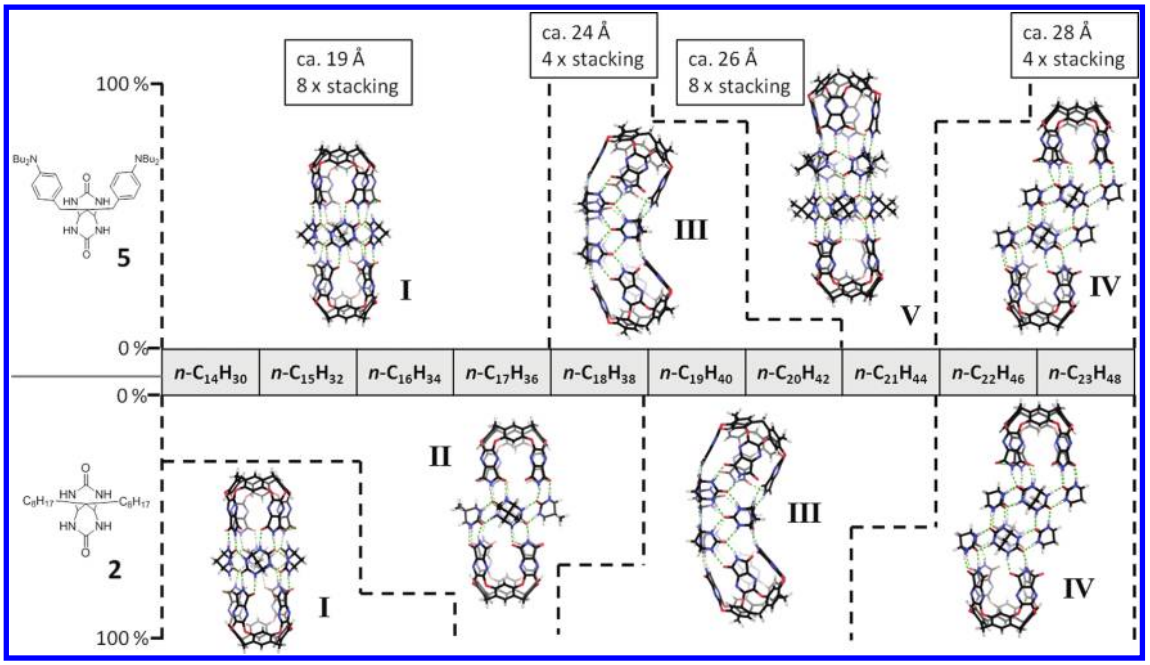

Figure 6. Overview of the self-assembled molecular capsules formed with PD **5** (top part) in the presence of an *n*-alkane guest, ranging from *n*-tetradecane to *n*-tricosane. For comparison the reported results[13] with PD **2** are displayed in the lower part. (Peripheral alkyl and aryl groups have been deleted for easier viewing.)

dioctyl-PD **2**; it gives assembly **II** exclusively with *n*-$C_{17}H_{36}$ (Figure 5: top). Additionally, a shortened relative of PD **5**, namely PD **7**, was synthesized (six steps, 8% overall yield; see SI). It lacks the flexibility of the benzylic side chains (cf. PD **3** in Figure 2a) so the phenyl groups of **7** cannot fold onto the capsule. Using **7** with these guests, we saw a behavior similar to that seen with **2** and **6** (Figure 5: bottom), further corroborating the role $\pi-\pi$ stacking plays in the case of PD **5**. The stacking interactions between the aromatic side chains in **5** and the hydrogen-bonding array are also revealed in the NMR spectra (see SI-Figure 7).

Additional consequences of the folded aromatics of spacer **5** (as compared to **2**) appeared when longer guests were encapsulated. With *n*-$C_{18}H_{38}$ and *n*-$C_{19}H_{40}$ a banana-shaped assembly **III** dominated (Figure 6) with results comparable to those with the original spacer **2**; however, starting with *n*-$C_{19}H_{40}$ a cylindrical, doubly extended assembly[12a] **V** was formed. Even longer guests (*n*-$C_{22}H_{46}$ and *n*-$C_{23}H_{48}$) were cleanly encapsulated as expected in the S-shaped assembly **IV**. How can these observations be rationalized? There are two main factors influencing these self-assemblies beyond guest size. (1) First, there is an intrinsic tendency for PD units to assemble in the fashion displayed by assemblies **II**, **III**, and **IV**, where the assemblies feature two "horizontal" and two "twisted" propanediurea units.[13] With the dioctyl-PD **2**, this preferred arrangement is abandoned only for the shortest guests, which enjoy a more favorable packing coefficient in the smaller host **I**. (2) Second, there are contributions from $\pi-\pi$ interactions (described in this communication) which favor assemblies **I** and **V** (with eight stacking interactions) over assemblies **II**, **III**, and **IV** (with four stacking interactions) (Figure 6).

What do the properties of spacer **5** teach us about self-assembly? Folding, when it can be arranged, minimizes unoccupied space (e.g., unsolvated surfaces), the characteristic of vacuums. Folding liberates solvent and increases overall intermolecular interactions that stabilize assemblies. The folding results in exclusive formation of host **I** for the shorter *n*-alkanes and the appearance of new host **V** for longer guests. These assemblies, which present their spacer units in a "twisted" fashion can most efficiently stack onto the hydrogen-bonding array of the capsule (as modeled in Figure 2b).

In conclusion, a propanediurea spacer unit was developed that features aromatic surfaces that interact with the hydrogen-bonding seams of a capsule on its outer surface. The intracomplex $\pi-\pi$ interactions increase the selectivity of the self-assembling process. While elegant devices can assess subtle forces in intramolecular settings,[15] this represents an example where a recognition event outside of the capsule triggers a change of its structure as a self-assembled receptor.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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