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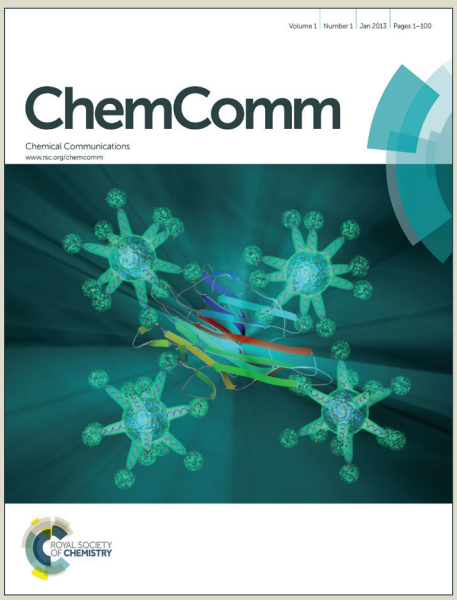

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Influence of Imperfect Walls on the Guest Binding Properties of Hydrogen-Bonded Capsules

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Three classes of hydrogen-bonded capsules with imperfect walls have been prepared and characterized. The defects reduce the symmetry of the capsules, leading to rich isomerism. The missing hydrogen bonds provide additional flexibility to the capsules and exert influence on their guest binding properties in different assemblies.

Reversible encapsulation[1] allows temporary isolation of guest molecules from the bulk solvent, resulting in special physical properties [2] including altered chemical reactivity. [3] The reversibility of hydrogen bonds is often harnessed to construct dynamic capsules that typically self-assemble from multiple identical modules. [4] This process affords highly symmetric structures with the added appeal of synthetic economy. For example, the cylindrical capsule **1.1**[5] is readily self-assembled from cavitand **1** (Fig. 1), in the presence of appropriate guests. The space in the capsule permits its use as a reaction chamber[6] with fixed solvation,[7] and more generally as a tool to study intermolecular forces.[8]

Hydrogen-bonded capsules self-assembled from less symmetric modules are relatively rare. [9] Reduction of the symmetry of modules inevitably causes complex isomerism. But it creates new possibilities: it provides an irregular binding pocket, with increased guest selectivity and it may allow modification of the capsular cavity with the introduction of functional groups bearing on the cavity. Earlier we reported a hydrogen-bonded capsule **2.2** self-assembled from cavitand **2**

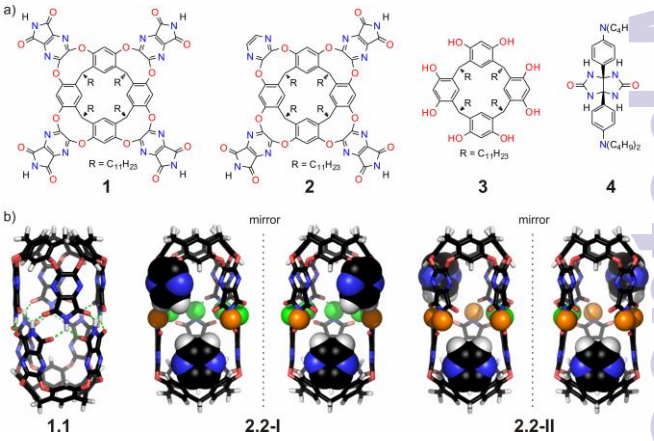

Fig. 1 (a) Chemical structures of cavitands **1** and **2**, resorcinarene **3**, and glycouril **4**, and (b) models of the dimeric capsule **1.1** and the two constitutional isomers of the capsule **2.2** and their enantiomeric pairs. The short walls are rendered as space-filling models and the imide N-H hydrogens of **2.2** are shown as colored balls to represent different hydrogen bonding types: green, bifurcated hydrogen bonds; orange, two-center hydrogen bonds. Peripheral groups are omitted for viewing clarity.

(Fig. 1).[10] Here, we report the influence of imperfect walls on molecular recognition properties in settings of extended capsules and hybrid capsules.

The cylindrical capsule **1.1** features a long and narrow cavity space, which can accommodate congruent guests. The arrangement of imides forms a cyclic seam of hydrogen bonds in the middle of the capsule, imparting positive cooperativity to the bonding array. The capsule **1.1** has S_8 symmetry, but reducing the symmetry of the cavitand as in **2** (having a single plane of symmetry) leads to dimeric capsules with two constitutional isomers, each of which is chiral. Unexpectedly, the two isomers were differentiated by the guests: flexible or short guests template **2.2-I**, while long and rigid guests template **2.2-II**.[10] The hydrogen bonding seam is not completely cyclic in **2.2**, and the cooperativity among these hydrogen bonds is attenuated. Accordingly, the stability of the assembly is weakened, and only the best guests for **1.1** can template the formation of **2.2**. Besides a narrower guest scope,

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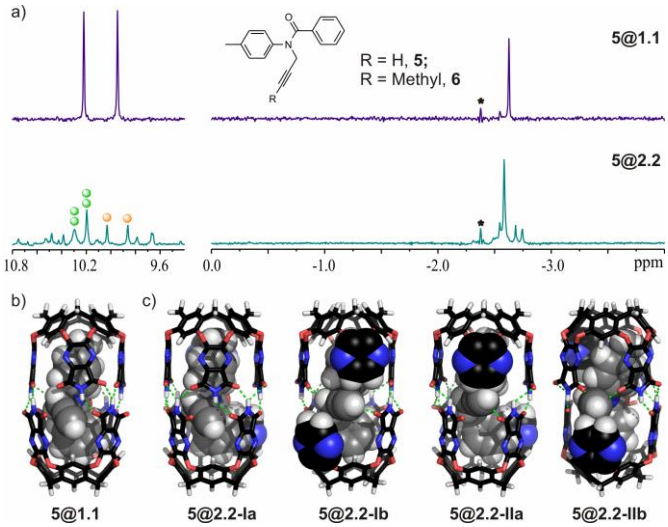

Fig. 2 a) Chemical structures of guests **5** and **6** and partial ^{1}H NMR spectra (600 MHz, Mesitylene-d_{12}, 300 K) of the solution of guest **5** in the presence of cavitands **1** and **2**. The imide N-H signals of **2.2** are labeled with colored balls: green, bifurcated hydrogen bonds; orange, two-center hydrogen bonds. Numbers of the colored balls represent the ratio of the corresponding peaks. Asterisk = NMR Noise. Energy-minimized structures of (b) **5@1.1** and (c) **5@2.2**.

how do the more flexible walls influence the guest binding properties?

In the isomer **2.2-I**, the two shortened walls without imide groups are proximal, and there is a hole in the surface of the capsule. We wondered whether this isomer can accommodate T-shaped guests with one arm "dangling" out of the hole. This behaviour had earlier been observed with more robust capsules held together by metal/ligand interactions. [11] Molecular modelling suggested an alkyne group could protrude from the hole in **2.2-I**, and we prepared two guests **5** and **6**. They are derivatives of benzoyl-*p*-toluidine, known to be a good template for isomer **I**.

We first tested the encapsulation of guest **5** and **6** in **1.1**. Guest **5** was completely encapsulated, a surprising result, since its N-propargyl side chain is scarcely smaller than an N-propyl side chain – which was not accommodated by **1.1** in a nearly identical setting. [12] No encapsulated species were detected using the homolog **6**, which is apparently too large for the cavity of **1.1**. Modelling of guest **5** in **1.1** indicates disruption of hydrogen bonds of the capsule near the alkyne group (Fig. 2b). But the guest obviously undergoes fast rotation in the cavity: all the walls exchange their position quickly on the NMR timescale, and only two single peaks were observed for NH protons.

Notwithstanding the modelling, guest **5** was a good template for the capsule **2.2**: the methyl signal of the guest in the NMR spectrum was shifted upfield to ca. -2.6 ppm (Fig. 2c), clearly indicating encapsulation and the imide proton signals appeared at ca. 10 ppm, which indicates their formation of hydrogen bonds. However, there were too many peaks for imide NH protons expected for a single assembly. One set of signals was identified. Based on the integration on the imide NH protons, the major species of the complex can again be

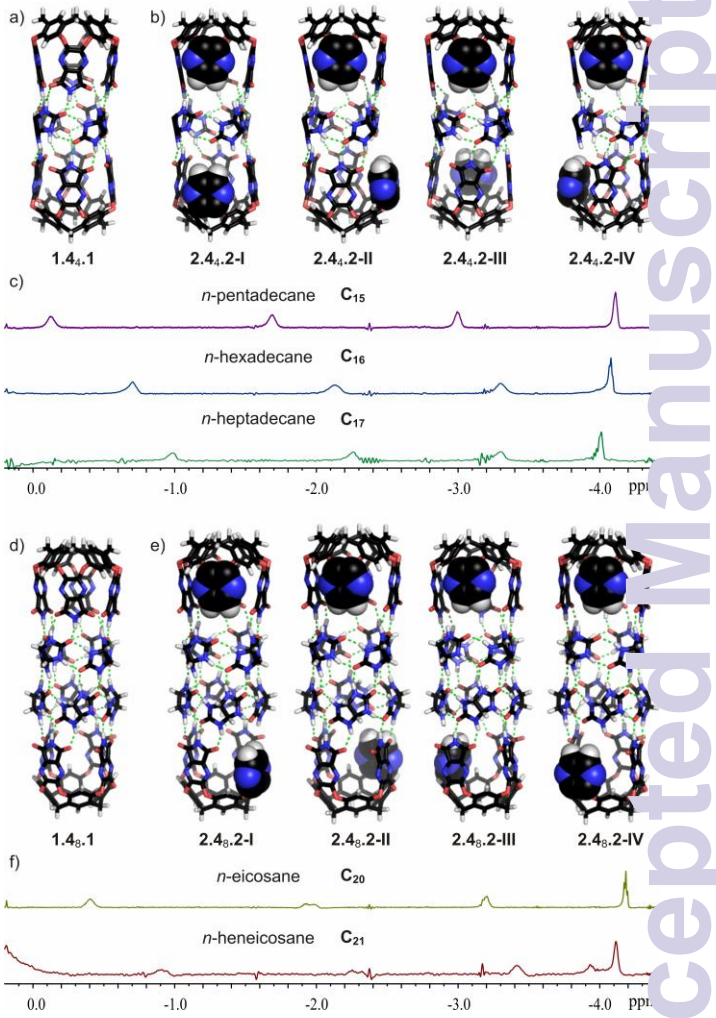

Fig. 3 Molecular modes of only one enantiomer of the extended capsules (a) **1.4$_4$.1**, (b) **2.4$_4$.2**, (d) **1.4$_8$.1**, and (e) **2.4$_8$.2**, and partial ^{1}H NMR spectra of (c) **C$_{15}$**, **C$_{16}$**, or **C$_{17}$** encapsulated in (f) **2.4$_4$.2** and **C$_{20}$** or **C$_{21}$** encapsulated in **2.4$_8$.2**. The short walls are rendered as space-filling models and peripheral groups are omitted for view clarity.

assigned to isomer **2.2-I**. [10] Other small peaks for imide N protons are too complex to assign. But it is much simpler an more revealing for the encapsulated methyl protons: four se of signals suggest that the guest sits at four different capsul environments which undergo slow exchange at the NM timescale. There are only two capsule isomers for **2.2**. How ca we have four different capsule environments? After carefully checking the molecular models (Fig. 2c), we found that in eac capsule isomer the guest may have two different orientations. Therefore, there are four isomeric complexes for **5@2.2**. ne first one (**5@2.2-Ia**) is like **5@1.1**: the alkyne of the guest r locate away from the imperfect walls. The other three hav the alkyne poke into the hole. In this way, the alkyne acts as brake to slow down the exchange of the two complexes in th same capsule isomer on the NMR timescale. From modelling, the guest seems to be more comfortable when the alkyn pokes into the hole, since additional hydrogen bonds between the guest and the capsule exist (Fig. 2c). Therefore, the majo species may be further assigned to **5@2.2-Ib**. Guest **5**

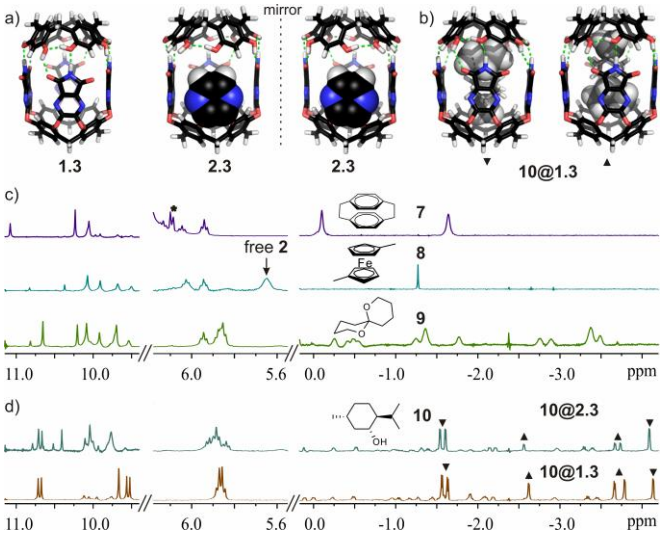

Fig. 4 (a) Molecular models of hybrid capsules **1.3** and **2.3**. The short walls are shown as space-filling models and peripheral groups omitted for viewing clarity. (b) Energy-minimized structures of two carceroisomers of **10@1.3**. The isopropyl and methyl groups of the guest are rendered as space-filling models to show the carceroisomerism. Partial ^{1}H NMR spectra (600 MHz, Mesitylene-d_{12}, 300 K) of the solution of (c) guests **7**, **8**, or **9** encapsulated in **2.3** and (d) **10** encapsulated in **2.3** or **1.3**. The assignments of the NMR peaks of the carceroisomers are according to the literatures.[14]

templated the less robust capsules with incomplete hydrogen binding seams. The imperfect walls generally help accommodate the N-propargyl group on **5**. Apparently, the missing hydrogen bonds provide additional flexibility and room that accommodates the guest with the N-substitution. However, guest **6** with a bulkier alkyne cannot template the capsule **2.2**, presumably due to the steric hindrance of the terminal methyl group on the alkyne.

When appropriate guests are available, glycourils such as **4** can insert into the middle of the capsule **1.1** and form extended capsules **1.4$_4$.1** (Fig. 3a) and **1.4$_8$.1** (Fig. 3d).[13] We tested the behaviour of cavitand **2** in this setting. As shown in Fig. 3b and 3e, four constitutional isomers may exist for the extended capsule **2.4$_4$.2** or **2.4$_8$.2** due to the relative arrangement of two cavitands in the assembly. Each of the isomers is chiral and has enantiomers, but only one enantiomer is shown in the figure. As was the case for capsule **2.2**, only the best guests for **1.4$_4$.1** and **1.4$_8$.1** could template the formation of the extended capsules (Fig. 3c and 3f). The alkane guests are quantized in their ability to generate capsules. Specifically, **C$_{11}$**~**C$_{12}$** template **2.2**;[10] *n*-Pentadecane (**C$_{15}$**), *n*-hexadecane (**C$_{16}$**), *n*-heptadecane (**C$_{17}$**), were guests of the extended capsules **2.4$_4$.2** while *n*-eicosane (**C$_{20}$**), and *n*-heneicosane (**C$_{21}$**) were guests of **2.4$_8$.2**. The assignments of the extended capsules are based on their size matching with the corresponding alkanes in analogy to **1.4$_4$.1** and **1.4$_8$.1**.[13] As discussed above, there are four constitutional isomers for each extended capsule. These isomers have very similar capsular spaces, and thus the alkane should see no difference in their spaces. Indeed, only one set of slightly broadened signals for the encapsulated alkanes are observed. The coexistence of the constitutional isomers is supported by the complex spectra in the downfield region (NH protons of the capsules, see Fig. S8).

Cavitand **1** also forms a hybrid capsule **1.3** (Fig. 4a) with resorcinarene **3**.[14] The hybrid can readily take up some small guests, such as paracyclophane, ferrocene, and solvent molecules. We expected cavitand **2** to also form a similar hybrid capsule **2.3** (Fig. 4a). Again, only a limited set of guests were used to template the formation of hybrid capsule **2.3**. Some guests of **1.3**, such as *p*-ethyltoluene, *p*-diethylbenzene, were not guests for **2.3**. However, guests such as *p*-cyclophane (**7**), 1,1'-dimethylferrocene (**8**), and 1,7-dioxaspiro[5,5]undecane (**9**), were good guests for **2.3** (Fig. 4c). Although the capsule **2.3** is chiral (as is the capsule **1.3**) due to the arrangement of hydrogen bonds, the fast rearrangement of these bond results in fast racemization and diastereotopic guest signals were not observed.

The guest **10** ((1R,2S,5R)-(-)-menthol), which has low symmetry proved more revealing. This guest had not been tested in the capsule **1.3**. The different "ends" of the guest menthol allow two possible orientations in the capsule **1.3** (Fig. 4b and S11): one with the methyl group of the guest placed into the cavitand **1** (▼) and the other one with the isopropyl group of the guest in the cavitand **1** (▲). These are two carceroisomers[15] and both are present in approximately equal amounts (ca. 1:1, Fig. 4d and S11). This indicates that the two ends of the cavity in the capsule **1.3** are not very different (sterically) and that the guest tumbles slowly on the NMR timescale. In contrast, the ratio of the two carceroisomers (▲ : ▼) in **2.3** is 1:3. The missing hydrogen-bonding wall in **2.3** creates room in the "upper" space (the end where resorcinarene **3** is located), and the bulky isopropyl group is more comfortable when positioned there.

In summary, we examined the influence of the imperfect walls on the three classes of capsules. In general, the missing hydrogen bonds weakened the stability of these capsules, and only the best guests drove the formation of these assemblies; a much narrower guest scope was observed. For the *n*-alkane guests, encapsulation with spacer elements was a linear and predictable function of guest length. Present research is directed at tailoring the capsule's cavity with catalytic functional groups.

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