Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Expanding capsules

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To cite this Article Ajami, Dariush and Rebek Jr., Julius(2009) 'Expanding capsules', Supramolecular Chemistry, 21: 1, 103 — 106
To link to this Article: DOI: 10.1080/10610270802549691
URL: http://dx.doi.org/10.1080/10610270802549691

Supramolecular Chemistry
Vol. 21, Nos. 1–2, January–March 2009, 103–106

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Expanding capsules

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(*Received 10 July 2008; final version received 13 October 2008*)

A self-assembled capsule held together by hydrogen bonding incorporates spacer modules that extend the capsule's length and increase its capacity. The modules are glycoluril derivatives that provide appropriate molecular curvature and complementary hydrogen bonding surfaces. Four glycoluril modules insert into the capsule in a chiral arrangement and allow encapsulation of longer guests. Specifically, *n*-tetradecane is the longest guest accommodated by the original capsule, but normal alkanes C_{15}–C_{19} fit into the extended capsule. The hydrogen bonded, dimeric capsule can be expanded with 4, 8 or 12 glycoluril spacers that increase the cavity's volume by up to 530 $Å^3$ and length by ~21 Å. The extended assemblies are chiral and encapsulate a variety of longer normal alkanes.

Keywords: molecular recognition; multi-component assembly; spring-loaded device; molecular capsules

Hydrogen bonded capsules come in many shapes (*1*) and sizes (*2, 3*) with spaces enough to accommodate more than one guest (*4*). The cylindrical capsule **1.1** (Figure 1), for example, can take up to three guests the size of $CHCl_3$ (*5*). For larger, multiple guest assemblies, it is desirable to expand the size of the cavity but attempts to use aromatic panels with increased surface areas failed. Desultory attempts with added spacers were frustrated by solubility problems – not to mention entropic resistance to bringing more molecules together. Self-complementary modules have been the standard for hydrogen bonded dimers, tetramers and hexamers, but two-component systems, such as those devised by Kobayashi (*6*) and Reinhoudt (*7*), inspired us to look further for such a solution.

Glycolurils **2**, of great versatility in other settings (*8*), offered curvature as well as solubility, and the deformability of hydrogen bonds suggested their insertion between the imides of the capsule could be achieved. It appeared likely that two glycolurils would fit, as shown in Figure 2.

Addition of glycoluril **2** to *n*-tetradecane encapsulated in **1.1** did indeed give new signals in the NMR spectrum consistent with a new capsular assembly (*9*). The *downfield* shifts of the guest's methylene signals indicate that these hydrogens have moved away from the walls and towards the centre of a new capsule (Figure 3). However, the splitting of the geminal CH_2 signals, as most clearly seen for C_2 and C_4, is inconsistent with the expected, symmetrical structure above. Instead, a chiral magnetic environment is indicated; moreover, NMR integration showed that *four* glycolurils, not two, were incorporated.

Tetradecane is known to assume a helical shape (*10*) in **1.1** (*11*) (Figure 4(a)) since its fully extended conformation is too long to fit into the capsule. The chirality of the helix creates an asymmetric environment, but the spectrum shows the geminal hydrogens to be equivalent. Accordingly, the helical conformation of encapsulated C_{14} racemises rapidly on the NMR time scale. In a longer space, this alkane should racemise even more rapidly; so the diastereotopic signals for the geminal hydrogens of the C_{14} in the new assembly must arise from a chiral arrangement of the glycolurils. The proposed enantiomeric arrays are shown in Figure 4(b). The glycoluril units in the new assembly can rotate and are not static on the NMR time scale. The rearrangements lead to racemisation of the extended capsule.

The increased length of $\mathbf{1.2_4.1}$ allows the encapsulation of *n*-alkanes from C_{15} to C_{19} (*12*), but compression of the alkane sets in with the longer guests. As the alkane coils, it applies pressure to the ends of the assembly. The diastereotopic geminal signals of the assemblies containing C_{16}–C_{19} coalesce as a function of temperature and provide a way to measure the pressures guests apply to the inside of the capsules. The *gauche* conformations of a compressed alkane create H—H repulsions that tend to extend the chain, but the hydrogen bonds resist this motion. The encapsulation complexes exist under an uneasy balance of forces: the H—H repulsions are compensated somewhat by the better C—H/π attractions offered by a shorter, but thicker, guest; a longer, but narrower, unwound alkane creates vacuums in the form of unsolvated surfaces of host and guest. Direct competition

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ISSN 1061-0278 print/ISSN 1029-0478 online

DOI: 10.1080/10610270802549691
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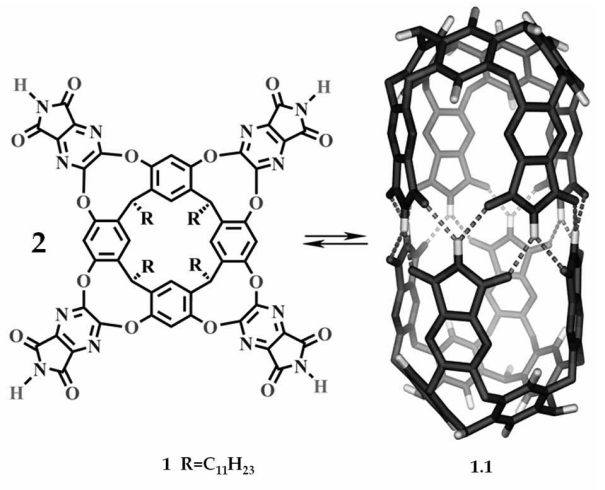

Figure 1. The resorcinarene subunit **1** and a model of its dimeric capsule **1.1**. The capsules are shown without peripheral alkyl and aryl groups.

experiments showed that increasingly compressed guests were less likely to be taken up by the capsules.

Compressed alkanes in capsules are notional spring-loaded devices, and we used an acid/base cycle to switch between their expanded and contracted states. The remote, weakly basic sites of **2** (*13*) can be protonated by HCl and the hydrochloride salt of the glycoluril precipitates in the non-polar solvent. Accordingly, the spectrum of coiled C_{14} in the original capsule **1.1** was again observed (Figure 3(a)). Addition of Me_3N to the NMR tube then deprotonates the glycoluril, which redissolves and regenerates the capsule with extended C_{14} inside (Figure 3(b)). The cycles are summarised in Figure 5.

The term 'spring loaded' has been broadly interpreted at the molecular level as well. Examples comprise diiron-oxo bisporphyrins (*14*), cis/trans isomerisation of retinal (*15*), interconversion of peptide helices (*16*), motions in block copolymers (*17*) and the shape of inclusion compounds in the solid state (*18*). The behaviour

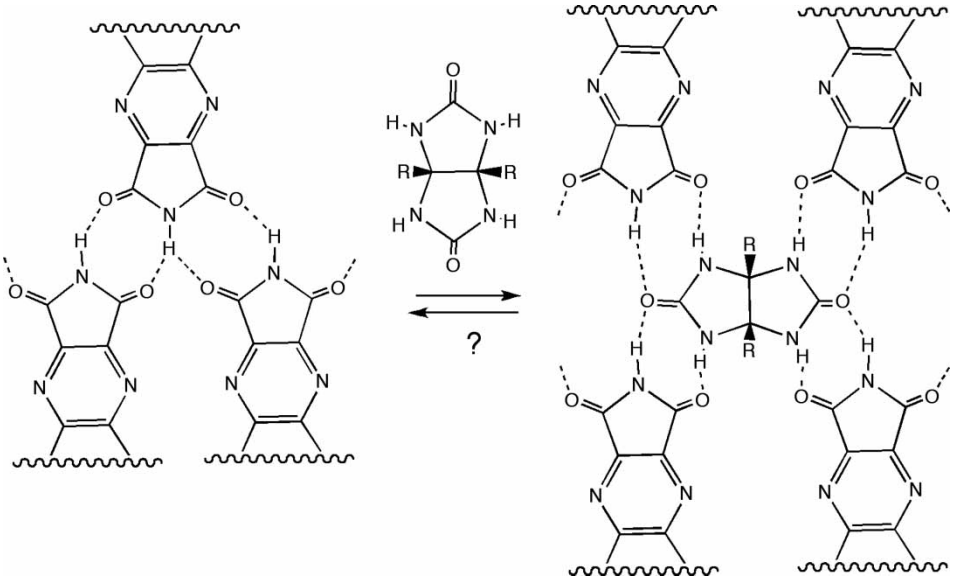

Figure 2. Structure expected through insertion of two glycolurils **2** between the halves of **1.1**.

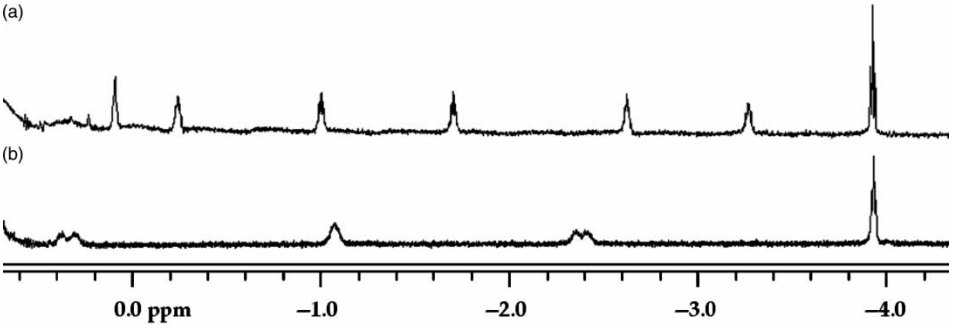

Figure 3. Upfield region of ^{1}H NMR spectra of the encapsulation complexes (600 MHz, in mesitylene-d_{12} solvent): (a) spectra of n-$C_{14}H_{30}$ (15 mM) encapsulated in **1.1** (2 mM) and (b) addition of **2** (5 mM) to (a). The downfield shifts of the methylenes in (b) indicate a longer capsule and the doubling of signals for the geminal hydrogens indicates a chiral environment.

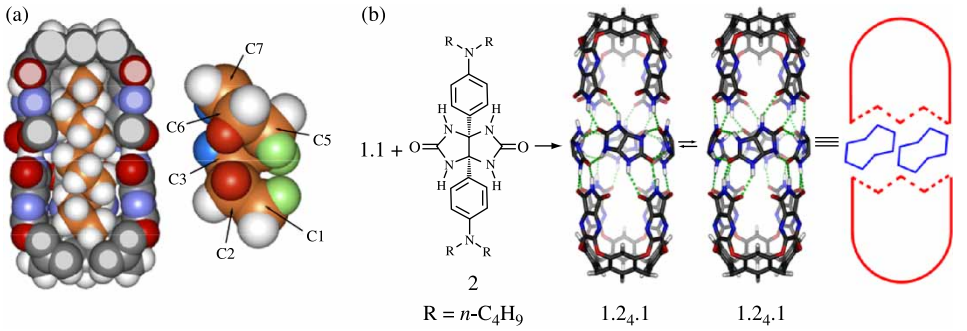

Figure 4. (a) A cross section of the assembly with encapsulated tetradecane, coiled in a helical conformation is shown as a space-filling model. (b) The glycoluril spacer **2** and the structure of the expanded capsule **1.2$_4$.1** are depicted. Both enantiomers are shown but peripheral alkyl and aryl groups have been removed for viewing clarity. The cartoon used elsewhere in the manuscript is shown on the right.

of a —$(CH_2)_{12}$— segment when threaded through a cyclodextrin is also related to the phenomenon at hand (*19*); it assumes multiple gauche conformations in water, but relaxes to an extended conformation in non-aqueous media.

The incorporation of glycoluril spacers does not end with **1.2$_4$.1**. The NMR spectra of guests too long to fit inside this lengthened capsule reveal signals for even further expanded capsules. In the downfield region, new N—H resonances appear and peak integrations formulate the new capsule as **1.2$_8$.1**. With even longer guests and excess glycoluril, **1.2$_{12}$.1** can be observed. Their relevant sizes and shapes are shown in Figure 6. In some ways, the capsule/glycoluril system resembles dynamic combinatorial systems (*20*) – they adjust to and assemble around whatever guests are on offer, but cannot be formed in the absence of guest. The diversity of capsules presented here indicates that increasingly complex molecular assemblies can emerge from only a few modules.

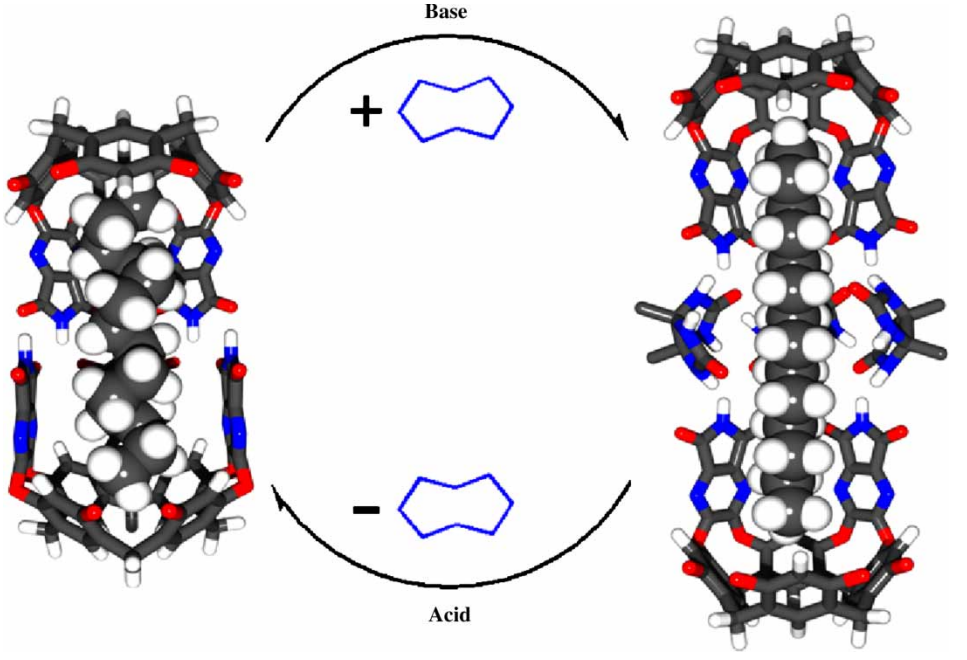

Figure 5. Schematic of the coiling/uncoiling cycles of encapsulated tetradecane, $C_{14}H_{30}$. The C_{14} assumes a helical coil conformation in **1.1**. Addition of spacer **2** to the solution generates the longer assembly **3** and the C_{14} guest relaxes to an extended conformation. Treatment with HCl protonates the spacer and causes precipitation of **2** as its dihydrochloride salt; the system reverts to coiled C_{14} in the original capsule **1.1**. Peripheral alkyl groups and some capsule 'walls' have been removed for viewing clarity.

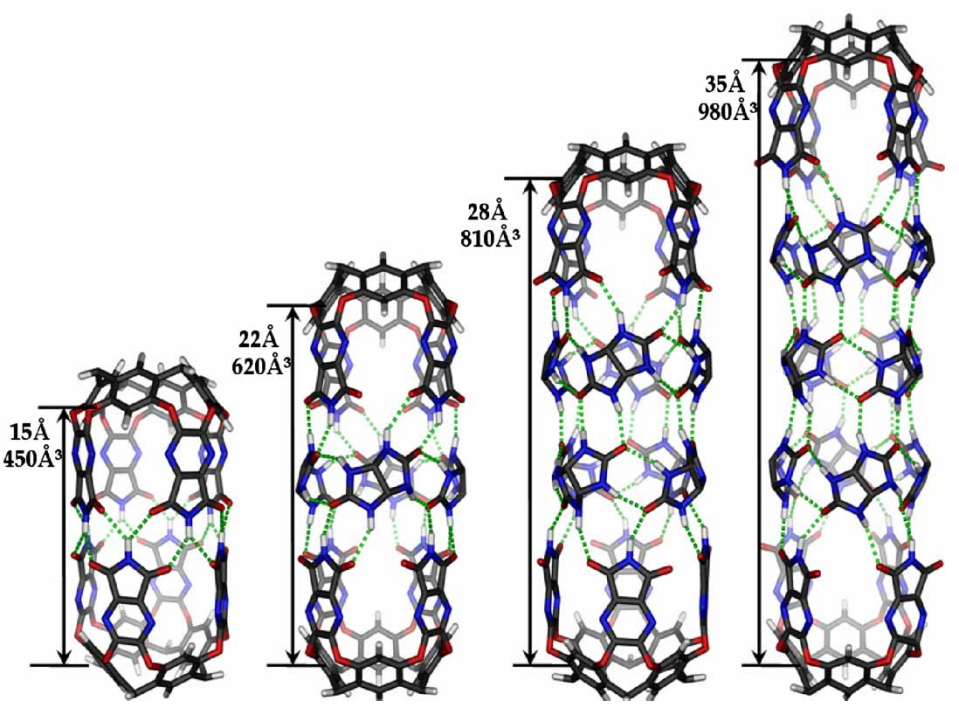

Figure 6. Dimensions and inner spaces of the original capsule, **1.1** and those incorporating 4, 8 and 12 glycoluril spacers are shown. The program Hyperchem was used to energy minimise the structures. Peripheral alkyl and aryl groups have been removed for viewing clarity.

Acknowledgements

We are grateful to the Skaggs Institute for Research for support. D.A. is a Skaggs postdoctoral fellow.

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