Extended Capsules

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Longer Guests Drive the Reversible Assembly of Hyperextended Capsules**

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Dedicated to Professor David N. Reinhoudt on the occasion of his 65th birthday

We recently reported that the cylindrical capsule host **1·1** incorporates glycoluril spacers **2a**,**b** when suitable guests are present to give an expanded assembly **1·2$_4$·1** (Figure 1).[1] Four glycoluril molecules are inserted, and they increase the cavity's length to accommodate longer alkanes and other molecules. With the weakly basic glycoluril **2c**, a spring-loaded system[2] was devised using external acids and bases to switch reversibly between the two expanded and original assemblies. The high solubility of **2c** allows access to larger ratios of spacer to cavitand, and we report herein the unexpected consequences. We find spontaneous assembly of new and even further expanded capsules in the presence of guests that are too long to fit within **1·2$_4$·1**. We propose structures for these encapsulation complexes in solution and some rationale for their emergent behavior.

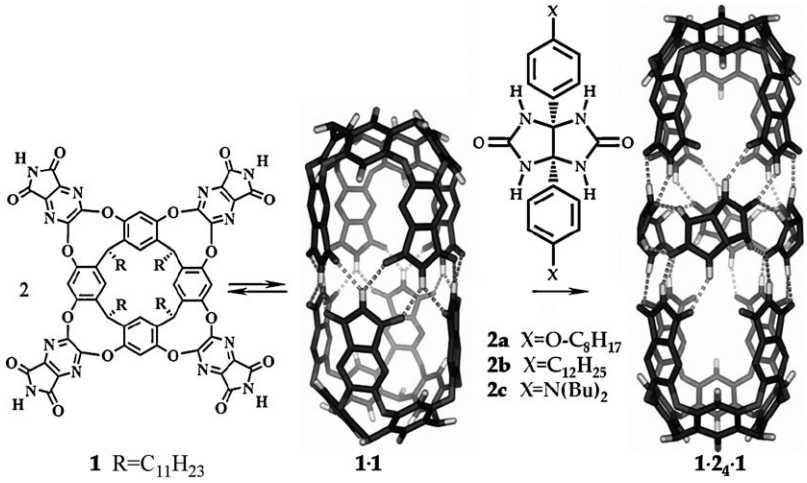

Figure 1. Structure of the original **1·1** capsule and the incorporation of four glycoluril spacers **2** to give the extended **1·2$_4$·1** capsule. Peripheral alkyl and aryl groups have been omitted for clarity, and only one enantiomer of the extended capsule is shown.

Many NMR spectroscopic studies have shown that the chemical shifts of encapsulated alkanes are related to their positions and conformations within the capsule **1·1**. Figure 2 shows the upfield regions of *n*-tetradecane (*n*-$C_{14}H_{30}$) encapsulated in **1·1** and in **1·2$_4$·1**. This alkane is coiled (compressed) in **1·1**, as shown by the close spacing of the signals (Figure 2a) and extended (relaxed) in **1·2$_4$·1**. In the latter, the spectrum (Figure 2b) reflects the downfield shifts of the methylene signals as they move away from the capsule's ends and toward the chiral microenvironment inside. At first glance, the asymmetric elements are far from the cavity's end, but the chiral arrangement of the glycoluril spacers at the center of the assembly shifts the eight walls in a manner that is transmitted effectively by the very rigidity of those walls.[3] NMR spectra of encapsulated *n*-alkanes often show hydrogen atoms on the penultimate carbon atoms to be diastereotopic. For example, the protons at both C2 and C4 (and, by symmetry, C13 and C11) of *n*-tetradecane inside **1·2$_4$·1** show this effect. At higher temperatures, the enantiomeric arrangements of the glycoluril molecules begin to interconvert, and the diastereotopic signals of the guest coalesce.

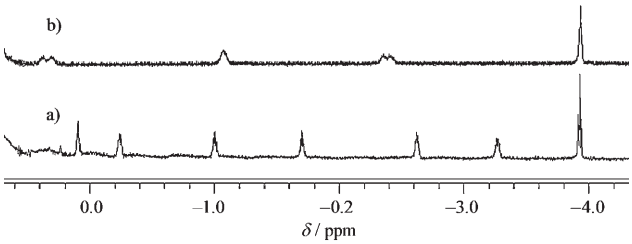

Figure 2. Upfield regions of the ^{1}H NMR spectra (600 MHz, [D_{12}]mesitylene) of tetradecane in solutions of **1·1** (a), and with excess added glycoluril **2c** (b).

The encapsulation of the C_{15} chain and normal alkanes up to C_{18} are seen in the new assembly, **1·2$_4$·1**, and we reported even longer molecular guests inside.[1] The case of $C_{19}H_{40}$ was puzzling, as the alkane is too long to fit within **1·2$_4$·1** in an extended conformation (Table 1). Yet the upfield region of

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Table 1: Relevant data for alkane dimensions and their packing coefficients (PCs). Alkanes that occupy two different capsules are shown in boldface.

Guest	Volume [Å^3]	Length [Å]		PC [%]	PC [%]	PC [%]	PC [%]
		Extended	Coiled	in **1**·**1**	in **1**·**2**$_4$·**1**	in **1**·**2**$_8$·**1**	in **1**·**2**$_{12}$·**1**
n-$C_{13}H_{28}$	230	17.3	13.7	54	37		
n-$C_{14}H_{30}$	247	18.6	14.8	**58**	**40**		
n-$C_{15}H_{32}$	264	19.8	15.7	62	42		
n-$C_{16}H_{34}$	281	21.1	16.8		45		
n-$C_{17}H_{36}$	297	22.3	17.6		48		
n-$C_{18}H_{38}$	314	23.6	18.5		51	39	
n-$C_{19}H_{40}$	331	24.8	19.2		**53**	**41**	
n-$C_{20}H_{42}$	348	26.1	20.1		56	43	
n-$C_{21}H_{44}$	364	27.3	20.9			45	
n-$C_{22}H_{46}$	381	28.6	22.1			47	
n-$C_{23}H_{48}$	399	29.8	23.0			49	41
n-$C_{24}H_{50}$	417	31.1	24.1			**51**	**43**
n-$C_{25}H_{52}$	434	32.3	24.8			54	44
n-$C_{26}H_{54}$	450	33.6	25.9				46

the NMR spectrum showed no evidence of coiling (nor did that of encapsulated $C_{21}H_{44}$). We mistakenly assumed that these guests were in capsule **1**·**2**$_4$·**1**, but, as we show below, they are in the doubly extended capsule **1**·**2**$_8$·**1**.

The spectrum of *n*-nonadecane (*n*-$C_{19}H_{40}$) under these conditions (Figure 3b) shows that two encapsulation complexes are present. In **1**·**2**$_4$·**1** coiling of the guest is apparent, while in the other complex, a relaxed, extended conformation is seen. The population of the latter complex increases at the expense of the former as more glycoluril **2c** is added (Figure 3c–e). The downfield region showed an increase in the number of resonances. These new resonances are from glycoluril NH groups, and their integrals indicate a ratio of glycoluril **2c** to cavitand **1** of 4:1, or a capsule formulated as **1**·**2**$_8$·**1**. The two extended capsules can coexist; in Figure 3, the alkane guest can be seen in both coiled and relaxed conformations.

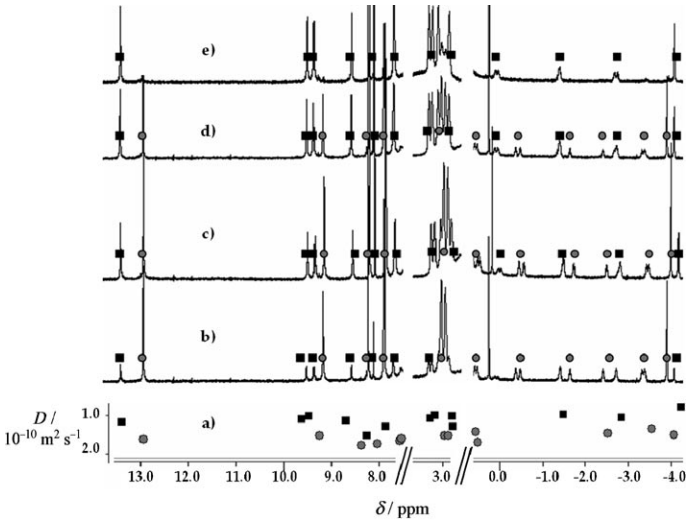

Figure 3. a) DOSY ^{1}H NMR spectrum (600 MHz, [D_{12}]mesitylene, *D* is the diffusion coefficient) of nonadecane (20 mM) in a 2 mM solution of **1**. b) ^{1}H NMR spectrum as in (a) with 3 mM added glycoluril **2c**; c) 5 mM **2c**; d) 7 mM **2c**; e) 10 mM **2c**. Resonances from the coiled guest and the extended capsule **1**·**2**$_4$·**1** are marked with circles; resonances from the relaxed guest and the doubly extended capsule **1**·**2**$_8$·**1** are marked with squares.

The incorporation of a belt of four glycoluril molecules into the assembly increases the dimensions of the capsule by 7 Å, or the length of about four extended C–C bonds. We expected capsule **1**·**2**$_8$·**1** to take hydrocarbons with lengths up to that of tetracosane. Normal alkanes C_{21}–C_{23} (Figure 4) are indeed encapsulated, but the incremental effects of compression are evident in the gradual upfield shifts of the methylene proton signals.

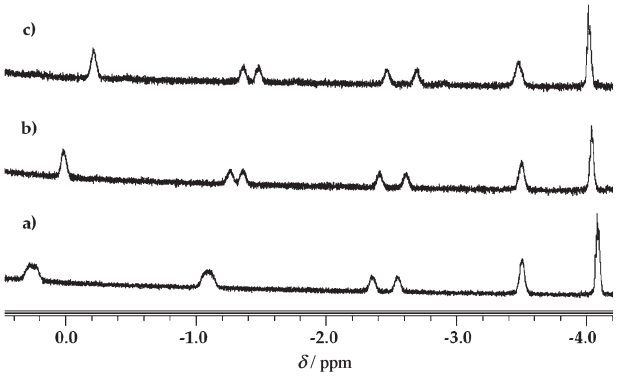

Figure 4. Upfield regions of the ^{1}H NMR spectra (600 MHz, [D_{12}]mesitylene) of *n*-alkanes (20 mM) in solutions of **1** (2 mM) with added glycoluril **2c** (10 mM). a) $C_{21}H_{44}$, b) $C_{22}H_{46}$, c) $C_{23}H_{48}$. The compression of the upfield signals reflects coiling of the guests in the capsule **1**·**2**$_8$·**1**. The hydrogen atoms on C3 (and some on C4) of the alkanes inside **1**·**2**$_8$·**1** give diastereotopic signals in the NMR spectra.

Yet a new species appears in the presence of $C_{24}H_{50}$. The downfield region reveals additional NH signals, and we formulate the new hyperextended capsule as **1**·**2**$_{12}$·**1** (Figure 5).

Additional support for the structural assignments of complexes involving the capsules **1**·**2**$_8$·**1** and **1**·**2**$_{12}$·**1** came from diffusion spectroscopy (DOSY)[4] and NOESY experiments. In the former, each assembly showed a different diffusion constant, but in a given assembly the same diffusion constant was seen for the glycoluril and cavitand units of the host and for the guest. The case of $C_{19}H_{40}$ is instructive, as this alkane is present in two different capsules in the same solution (Figure 3c). The DOSY spectra shown in Figure 3a give two different diffusion constants for the two capsular assemblies. The NOESY spectra (see the Supporting Information) showed the expected contacts between guest and cavitand, but the signals from the methylene protons near the glycoluril spacers at the center of the capsule could not be resolved and assigned.

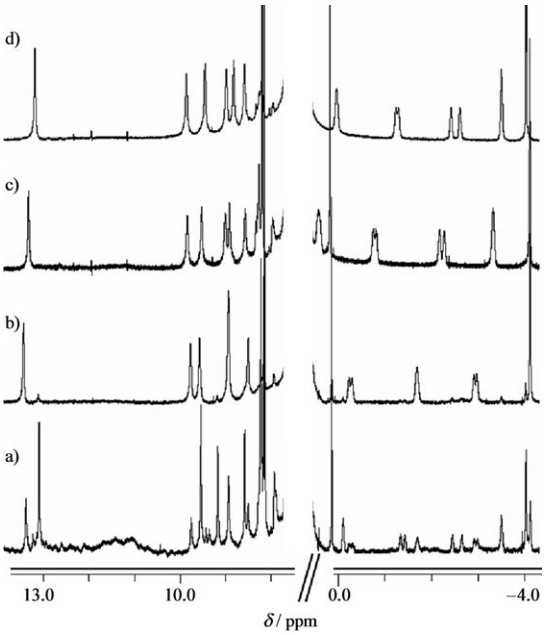

Figure 5. ^{1}H NMR spectra (600 MHz, [D_{12}]mesitylene) of *n*-alkanes in solutions of **1** (2 mM) with a) **2c** (7 mM) and $C_{24}H_{50}$ (20 mM); b) **2c** (14 mM) and $C_{24}H_{50}$ (20 mM); c) **2c** (14 mM) and $C_{25}H_{52}$ (20 mM); d) **2c** (14 mM) and $C_{26}H_{54}$ (20 mM).

The system is dynamic and adjusts to the guests that are available.[5] Our experience is that encapsulation complexes form when, and only when, suitable guests are present.[6] The guests may be solvent molecules; if the solvent is too large to fit inside the capsule, other molecules or ensembles of molecules[7] that fill the appropriate amount of space are taken in. The relevant dimensions of the various capsules are shown in Figure 6, and the lengths of the fully extended hydrocarbons are given in Table 1. The tapered ends of the capsules are able to accommodate only the narrowest of functional groups, such as terminal acetylenes.[8] For the blunt end of an alkane (the methyl group), the effective length is somewhat shorter, so the dimensions given are those of a "methyl accessible" surface.

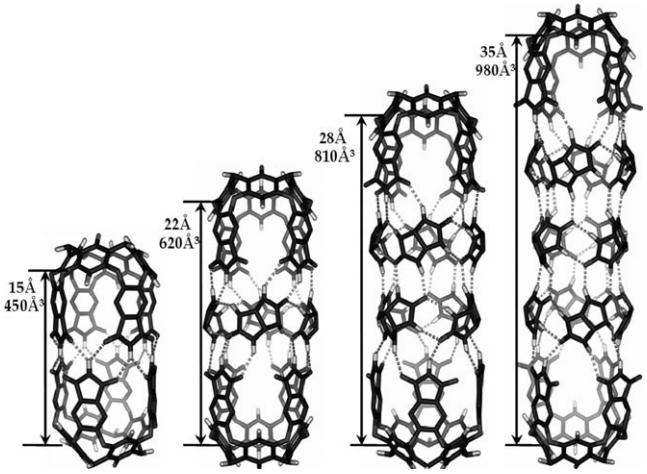

Figure 6. Dimensions and inner spaces of the original capsule **1**·**1** and of those incorporating four, eight, and twelve glycoluril spacers. All structures were minimized with semiempirical methods. Peripheral alkyl and aryl groups have been omitted for clarity, and only one enantiomeric arrangement of the glycoluril spacers is shown.

What provides the driving force? In solution, the alkane has the same C–H–π interactions available but must organize a large number of solvent (mesitylene) molecules to experience them. Release of these molecules to the bulk solvent (solvophobic forces) must be a factor. Glycoluril molecules alone are also loosely organized in this solvent (as shown by a broad cluster of resonances in its NMR spectrum) and further organization into the "belts" of the capsule should not be entropically expensive. In other words, most of the entropic penalty has been paid through the synthesis of cavitand **1**; it provides a fixed cage of solvent molecules. In addition, the maximum number of hydrogen bonds is present in the belted arrays, so an enthalpic component is also involved. The alkane guests fill the narrow space created by the glycoluril belts quite appropriately. The belt of glycoluril molecules resembles the environment presented by the interior of the cucurbiturils, which are cylindrical synthetic receptors known to sequester linear alkanes.[9] The resorcinarene cavitands of the assemblies permit stronger C–H–π interactions[10] with the terminal methyl groups. The capsules surround the extended conformations of the alkanes but add spacers (Figure 5) when these cannot be comfortably accommodated.

These results indicate that increasingly complex molecular assemblies can emerge from only two modules. Combinations of different guests inside the original capsule **1**·**1** have allowed its use as a reaction chamber,[11] a chiral receptor,[12] and a space where single-molecule solvation can be observed.[13] New forms of stereochemistry have also arisen from co-encapsulation studies,[14] and hybrid capsules form readily.[15] Elsewhere, related capsules have been used to stabilize reactive intermediates[17] and even transition states.[18] There are biological precedents for the behavior at hand; for example, some viral capsids can incorporate additional protein subunits to accommodate larger genomes.[16] The assembly of these extended capsules is an emergent phenomenon that is driven by molecular recognition coupled with the proper filling of space.[19]

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