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Template effects are an inevitable feature of supramolecular chemistry and were prominent in the discovery of crown ethers, carcerands and catenanes. Templates can act as guests or hosts, but in either role they must be structurally persistent – rigid or "hard" – on the timescale needed to form the final complexes. This report explores a peculiar effect encountered with self-assembled container molecules: soft templates. In these cases neither the guest nor the host has an independent existence, but they do coexist as complexes. The host and guest are prevented from collapsing into more familiar, stable structures by the forces that hold the complex together. The complexes represent emergent phenomena and offer a look at structures otherwise unknown in free solution.

Introduction

Template effects have a long history in supramolecular chemistry and self-assembly.[1] They are particularly effective in Dynamic Combinatorial Chemistry[2] (DCC) where spectacularly improbable host/guest complexes often emerge from simple components. From the discovery of crown ethers[3] to the characterization of mechanical bonds[4] and self-replicating systems,[5] templates deliver surprising structures and valuable lessons. No one could have predicted that the presence of acetylcholine as a template would weave the pseudodipeptide building block (Fig. 1) into a concatenated structure.[6] One interpretation of that outcome, which will be developed presently, is that the catenane host *didn't exist* before the template guest was introduced (in practice, it would be nearly impossible to synthesize this host without a suitable guest). The template is essential in DCC whether it plays the role of host or guest. And it must be a structurally stable species for long enough to let thermodynamic control do its magic.[7] Structural stability in the context of a template suggests rigidity, so what good is a "soft template" – a template able to assume many shapes?

The answer lies in the nature of the forces holding the assemblies together. Besides covalent DCC, there exists another type of self-assembly: Dynamic Noncovalent Chemistry (DNC or DNCC), and much of its activity involves container compounds held together by metal/ligand interactions.[8] These structures are usually predicted – even designed – and are stable in solvents (often water) that saturate their host spaces. A narrower subset of DNC involves containers held together by weaker intermolecular forces such as hydrogen bonds and hydrophobic interactions.[9] These containers, the cavitands and capsules, are subject to soft template effects and are the prime subjects of this review. The relatively feeble forces involved make for frail hosts that do not assemble in the absence of well-fitting guests. Frequently, solvents cannot fill their spaces properly, and in those solutions the container structures simply don't exist.[10] Now, rigid and "hard" templates are useful for assembling hydrogen-bonded capsules and often result in structures that are otherwise unknown in solution.[11] For example, the seemingly nondescript subunit structure **1** (Fig. 2) is perfectly stable as a monomer in

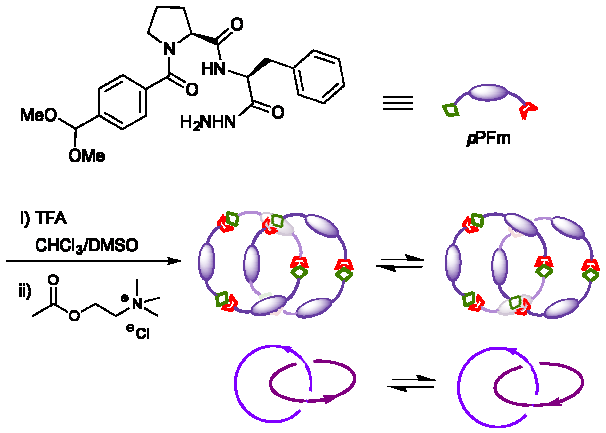

Fig. 1 Structures of the pseudo-dipeptide and acetylcholine. The two catenane products that emerge from the DCC reaction are shown in cartoon representations. From *Science* **2005,** *308*, 667-669. Reprinted with permission from AAAS.

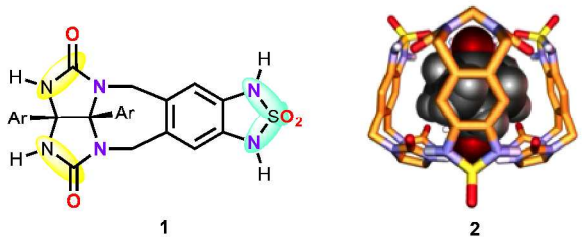

Fig. 2 A curved module with hydrogen bond donors and acceptors on both ends. Interaction of the strongest donors and acceptors occurs when four modules come together in a head-to-tail arrangement; the assembly is nucleated by adamantanedione.

solution, but in the presence of the rigid template adamantanedione, self-assembly takes place and a tetrameric capsule **2** emerges with a guest inside.[12] The complex persists in the solid phase.[13]

This report emphasizes the further attribute of self-assembled containers that is – as far as we can tell – unique in the DNC world: those cases where *neither the host nor the guest is a known stable structure.* They have no independent existence, but they coexist. These complexes emerge in a way that hasn't been seen before – and perhaps can't be exposed any other way. The prospect for novelty makes it worth pursuing these systems: how they assemble, what it's like inside and why host and guest adapt to each other in unexpected ways.

Covalent vs. Not

Some of the most dramatic template effects were encountered in the assembly of covalent hosts known as carcerands. For example, template effects varied over a range of 10^6 in the synthesis of a covalent capsule,[14] while the related noncovalent dimer showed a parallel trend toward guests.[15] As mentioned above, hydrogen-bonded capsules differ in a conceptual way from capsules held together by covalent bonds. The noncovalent host/guest complexes form through the spontaneous and more-or-less instantaneous process of self-assembly only when suitable guests are present.[16] This is a cooperative, all-or-nothing event guided by the curvature of the modules, the donor-acceptor patterns on their edges and the molecular recognition between the space of the host and the congruence of the guest – including just how much of the space is occupied.[17] We have yet to see an empty capsule, but filling of a capsule's space can sometimes be provided by properly-fitting solvent molecules.[18] The same is true for the capsules of Gibb,[19] held together by hydrophobic forces (about which more, later).

The assembly of a capsule is in itself an emergent phenomenon, and there is always something inside. Naturally, we intended the molecules to assemble, but what we did not predict was how the intended guests would adjust to fill the limited space and how the host would adjust to surround the shape of the guest. The shape of the space also played a part in our selection of guest templates: the long narrow spaces of the cylindrical capsules begged for normal alkanes of various lengths, and their willingness to assume contorted conformations have made them probes of choice in our research, for binding behavior in small spaces. Flexible alkanes are ideal soft templates.

Normal hydrocarbons have also been featured in Gibb's systems studied in water,[20] where hydrophobic forces are regarded as the biggest force for assembly.[21] But we work in mostly organic solvents so many of the phenomena that we see have nothing to do with hydrophobic forces. The more general solvophobic forces, on the other hand, are involved to a great degree in our work.

The initial observation had to do with the nucleation of a cylindrical capsule by a series of hydrocarbons. With normal tetradecane (C_{14}), a guest that is unable to fit within the capsule in its fully extended conformation, we found that the alkane coils into a helix (Fig. 3).[22]

A large energetic price is paid for this compression, as each of the *gauche* interactions along the chain contributes to a destabilization of the complex. This is reflected in the relative affinities[23] of various alkanes for the space shown in Table 1.

Direct observation of the coiled conformation was made by two-dimensional NMR spectra that showed the NOE crosspeaks between hydrogens on C1 and C5, C2 and C6 and so on, up the chain of the alkane that are characteristic of a

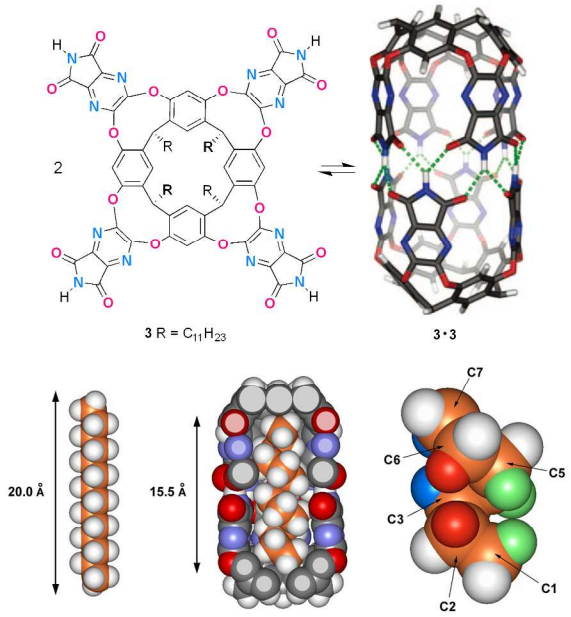

Fig. 3 Structure of the cavitand and its dimerization to form the cylindrical capsule. Models of C_{14} extended and compressed inside the capsule are shown. The NOE's observed in the 2-D NMR spectra are color-coded and indicate a helically coiled alkane inside. Originally published in *Nature Chem.* **2009,** *1*, 87-90.

helix. Table 1 shows the price paid for this coiling as determined by pairwise competition between various alkanes. The optimal guest C_{11} can be accommodated in its fully extended conformation, and coiling begins with C_{12} (4 *gauche*); C_{13} (8 *gauche*) and ends at C_{14} (11 *gauche*). The compressed alkanes are at uneasy equilibria inside: overall each *gauche* interaction – in this context – is destabilizing by 0.47 kcal/mol, but there are compensating C-H/π attractions that complicate this calculation. There was no evidence for encapsulation of C_{15}; nothing that molecule can do would make it fit into that space.

The studies might have ended there, with the characterization of the unprecedented (imaginary) helical conformation of an alkane. It did occur to us that the coiled alkane was exerting pressure to the ends of the capsule, but how to measure it?

There is a pattern of hydrogen bond donors and acceptors on a glycouril that is complementary to that presented by adjacent walls of the capsule, the pattern of the imides. It seemed possible that glycolurils could insert between the two halves of the capsule to give an extended structure, if entropy would not forbid it. In the experiment, the glycourils inserted quite readily and in an entirely unexpected manner (Fig. 4).[24] For starters, *four* of them slipped in. And they did so in an arrangement that gave a chiral assembly.[25]

Now this host was unexpected and, without the guest, was an unknown (imaginary) capsule. The glycolurils increase the capsule's length by nearly 7 Å and its volume by about 200 Å^3, creating a space big enough to accommodate C_{14} in its fully extended, relaxed conformation. Fig. 4 shows the NMR spectra of C_{14} in both the shorter and the lengthened capsules, corresponding to the compressed and extended C_{14}, respectively.

Table 1 Relative affinities of the *n*-alkanes for the capsule **3•3** as determined by competition experiments. The number of gauche conformations and the Packing Coefficients (P.C.'s) were calculated.

Guest	K_{rel} (C_9D_{12})	ΔΔ G°, 300 K, kcal mol^{-1} (# *gauche*)	P.C.
n-C_9H_{20}	0.3	0.72	43
n-$C_{10}H_{22}$	16.9	-1.70	48
n-$C_{11}H_{24}$	100	-2.75 (0)	52
n-$C_{12}H_{26}$	24.4	-1.91 (4)	54
n-$C_{13}H_{28}$	1.0	0.00 (8)	55
n-$C_{14}H_{30}$	0.008	2.87 (11)	58

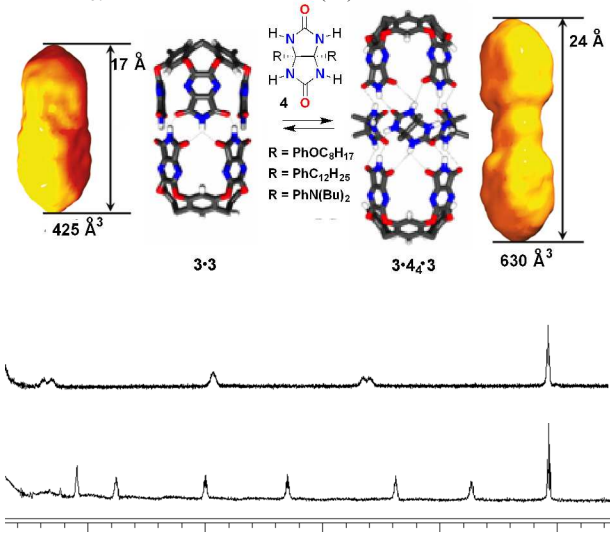

Fig. 4 Structure of the glycoluril spacer and the expansion of the cylindrical capsule. A chiral arrangement is assembled and only one enantiomer is shown. The shapes of the spaces inside and their dimensions are also modeled. The NMR spectra shown are of C_{14} as the extended conformation in **3•4$_4$•3** (top) and coiled in **3•3** (bottom). Adapted with permission from *J. Am. Chem. Soc.* **2009**, *74* 6584-6591. Copyright 2009 American Chemical Society.

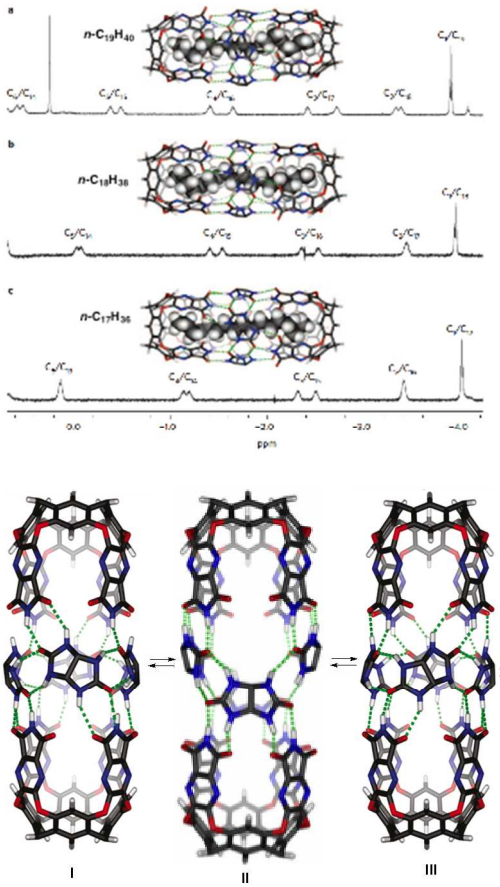

Fig. 5 The effects of coiled guests on racemization of the extended capsule are shown. Racemization of the capsule proceeds through an achiral intermediate that is slightly longer than either enantiomer. Increasingly compressed guests exert more pressure on the inside of the assembly and lower the energetic barrier to racemization. Both host and guests are soft templates; they conform to each other but have no independent existence. Originally published in *Nature Chem.* **2009,** *1*, 87-90.

Also, normal alkanes C_{15} to C_{19} are accommodated in the extended capsule, but the chemical shifts of the longer alkanes show evidence of coiling, even in the lengthened space (Fig. 5).[26] We were able to use the pressure of the coiled C_{14} for a spring-loaded molecular device under the control of acid and base chemistry.[27] But the soft template story lies in the extended capsules with the coiled alkanes inside – real complexes comprising imaginary host and guest. These are fragile, 6-component capsules with uneasy, compressed guests inside.

The assemblies reflect the compromises made by the alkanes involving the destabilizing compression and the stabilizing van der Waals attractions. Both extended capsules and compressed guests are soft, and the complexes arise from mutual induced fit. We were able to assess the amount of internal pressure exerted on the extended capsule by the longer alkanes through studying the racemization rates of their complexes (Fig. 5).[26] As revealed in Table 2, each *gauche* interaction contributes to the destabilization of the assemblies. The kinetic data from the racemization of the extended capsules suggest *gauche* interactions are only worth about 0.1 to 0.25 kcal/mol. The value recommended by Eliel[28] for *gauche* interactions in the liquid state is 0.55 kcal/mol, which is quite different from that in use by many physical organic chemists (0.9 kcal/mol) in conformational analysis. In the capsule, the coiling moves the C-H bonds closer to the capsule's walls: there the attractive C-H/π interactions compensate for the *gauche* repulsions,[29] and the increased P.C.'s stabilize the assemblies.

But this account is less about these applications than about the phenomena of emergence. Who could have guessed that C_{20}, in the presence of the glycoluril and the cavitand, would have made yet another new and hyperextended capsule?[30] Or that anandamide, an endogenous cannabinoid receptor ligand, would also assemble such a capsule. These feature 10 molecules that define the chiral host with two "belts" of glycolurils and one guest inside (Fig. 6).

We encountered another expression of pressure inside the small spaces and again, NMR chemical shifts gave the key measurements. Carboxylic acid hydrogen-bonded dimers are well known in non-competing media, but they are ephemeral: the acid components are constantly and rapidly exchanging partners, and other oligomeric states are present. So a time-averaged signal is usually observed in solution and it is difficult to get a snapshot of a discrete dimer. Limbach has devised probes for NMR spectrometers that operate under tremendous pressures and has analyzed the effects of pressure on the hydrogen-bonded dimers in non-competitive media.[31] The signals of the acid hydrogens are forced further and further downfield in the spectra by the externally applied pressure.

We re-assembled the extended capsule around dimeric benzoic acid structures and found that increasing length of the guest also forced the acid hydrogen signals further downfield. By using isotopic substitution as described by Limbach, we were able to correlate the pressures inside the capsule with those that had been determined outside (Fig. 7). In short, the confined space has the same effect on the hydrogen bonds as a pressure of several thousand bars.[32] Just as the coiled alkanes apply pressure to the inside of the capsule, the capsule applies pressure to the hydrogen bonds of the guest carboxylic acids inside.

Table 2 Activation energies for racemization of the extended capsule **3•4$_4$•3** with *n*-alkanes guests as determined by NMR coalescence experiments. The number of gauche conformations and the Packing Coefficients (P.C.'s) were calculated.

Guest	Δ G*, kcal/mol (# *gauche*)	P.C.
n-$C_{19}H_{40}$	15.7 (12)	53
n-$C_{18}H_{38}$	16.7 (8)	51
n-$C_{17}H_{36}$	17.2 (4)	48
n-$C_{16}H_{34}$	> 20 (0)	45

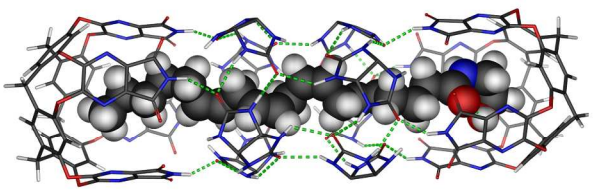

Fig. 6 Anandamide, the ethanolamide of arachidonic acid, nucleates the assembly of a doubly-extended capsule **3•4$_8$•3**.

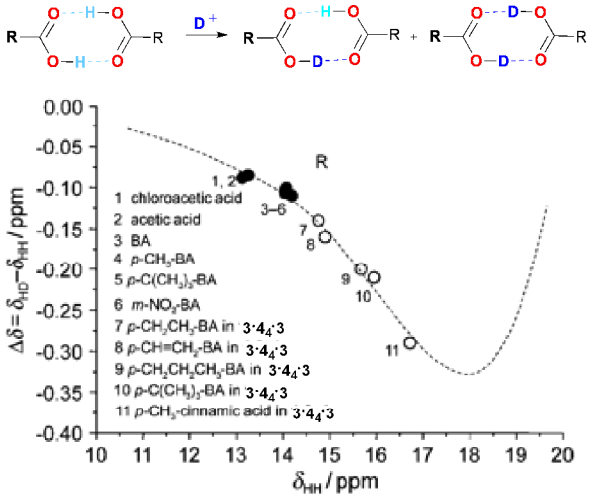

Fig. 7 The effects of compressing dimeric carboxylic acids guests in the extended capsule **3•4$_4$•3** are shown. The hydrogen bonds are shortened as measured by isotopic substitution; that is, the encapsulated acids behave as though they were under a pressure of many kilobars. (BA = benzoic acid)

The discrete pair-wise hydrogen bonded systems that could be accessed in this extended capsule suggested an application to the disproportionation equilibria between carboxylic acid and primary amide hydrogen-bonded dimers. In solution, averaged spectra are observed since the components exchange partners very rapidly (at least on the NMR timescale) and larger aggregates also exist. However, in the extended capsules we could access discrete assemblies that consisted of the acid dimer, the amide dimer, and the acid-amide heterodimer. These could be observed and directly quantified by conventional NMR methods (Fig. 8). It should be emphasized that such discrete encapsulation assemblies exist under conditions of ambient temperature and pressure and in the liquid phase.[33] While these conditions are arbitrary, they are convenient for the experimenter when exchange rates are slow on the NMR scale. Discrete assemblies can be observed independently and isolated from each other by the barriers imposed by the capsule's walls. Examples are shown in Fig. 8.

Table 3 shows how disproportionation occurs between the various components.[34] The disproportionation constant K_d depends on the nature of the R group: with benzoic acid and amide, it is only 0.4 while with the cyclohexanecarboxylic acid and amide, it is 18. The purely statistical value is 4, but this number is approached only when benzamide was paired with the cyclohexyl carboxylic acid. These numbers could be accessed for the first time and our collaborators in Greece used computational methods put the values on a theoretical basis.[35]

The helical alkanes inside the capsule can exist in enantiomeric forms and our measurements indicated that these interconvert

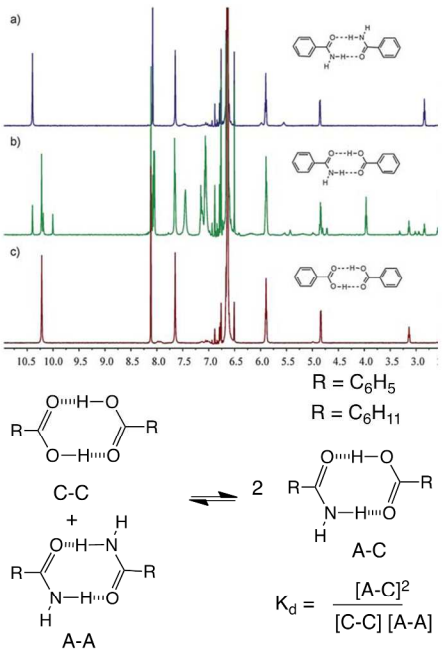

Fig. 8 Disproportionation of homodimers of carboxylic acids and amides in the capsule **3•4₄•3**.

Table 3 Distributions and disproportionation constants, K_d (mesitylene-d_{12}, 300 K, [capsule] = 1.0 mM) of acid and amide homodimers and heterodimers in the capsule **3•4₄•3**. The guests are abbreviated as: benzamide = A_{ben}; benzoic acid = C_{ben}; cyclohexane carboxamide = A_{hex}; cyclohexane carboxylic acid = C_{hex}.

Pair	Distribution	Pair	Distribution	Pair	Distribution
A_{ben} A_{ben}	19%	A_{hex} A_{hex}	8%	A_{ben} A_{ben}	44%
A_{ben} C_{ben}	22%	A_{hex} C_{hex}	64%	A_{ben} C_{hex}	42%
C_{ben} C_{ben}	59%	C_{hex} C_{hex}	28%	C_{hex} C_{hex}	14%
K_d	0.4	K_d	18	K_d	2.9

(racemize) rapidly, presumably through a crank-shaft motion that moves up and down the alkane chain. The motion is suggested by encapsulation of a C_{14} bearing a *trans* double bond at C7 (at its middle). Presumably, a *trans* double bond – or the equivalent antiperiplanar arrangement of 4 methylenes – could be accommodated anywhere along the chain of this longest encapsulated guest. We propose such a crankshaft mechanism for the racemization of the helix in the capsule. By using a chiral guest, Waldvogel[36] was able to obtain evidence for a preference of one of the forms of the helix inside the capsule. Again, this is a structure that has not (and probably could have not) been observed by any other methods in solution.

An extreme example of soft template and assembly occurred when the cavitand, glycoluril and cyclopropane were combined to give the extended capsule with 4 cyclopropane guests inside. It is hard to even visualize a gas – fast-moving, fluid and compressible – as a template, yet the assembly forms spontaneously under ambient conditions. Moreover, the crosspeaks in the 2D NMR spectrum of the guests show that the cylopropanes can exchange positions inside; they are moving targets! But they are able to nucleate the assembly and act as the softest of templates (Fig. 9, top). Another case of 4 molecules providing the template is given with the example of γ-picoline trifluoroacetate (Fig. 9, bottom). In this assembly, the ion pairs are in the deepest part of the cavitand, an unlikely place for a CF_3 group. We had expected the CH_3 groups in that position since there are no apparent attractions and expected repulsion between the resorcinarene aromatics and the CF_3 group. Perhaps this is a default situation: the CF_3 groups are too large to fit in the narrow center of the assembly and the CH_3 groups appear there instead.

The expansion of the capsules with the glycolurils was a surprise. But a mere glance at the geometry of the capsule walls (at 90°) and the fold of glycoluril **4** (113°) suggested that the chiral arrangement and the four glycolurils spacers are a result of a mismatch of these angles. A propanediurea subunit **5** (Fig. 10) at 99° is a better match for insertion into the capsule, and a series of these were prepared and tested.

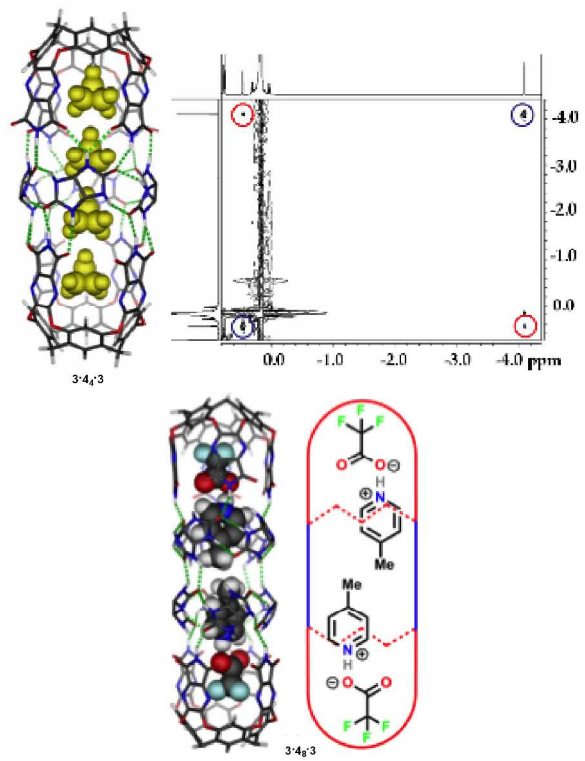

Fig. 9 Top: Cyclopropane in the extended capsule **3•4$_4$•3**. The guests are able to exchange positions slowly on the NMR timescale. The gas experiences a pressure of many atmospheres. Adapted with permission from *J. Am. Chem. Soc,* **2012**, *134*, 11971−11973. Copyright 2012 American Chemical Society. Bottom: The CF_3 groups of γ-picoline trifluoroacetate appear near the resorcinarene ends of the capsule while the narrower CH_3 groups appear near the center. Copyright © 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

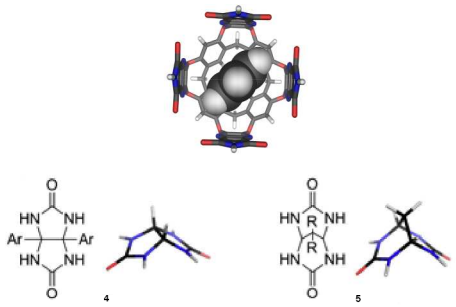

Fig. 10 The preferred orientation of aromatics in the capsule **3•4$_4$•3**. Geometries of glycolurils **4** and propanediureas **5** are shown

The results revealed an astonishing array of extended capsules,

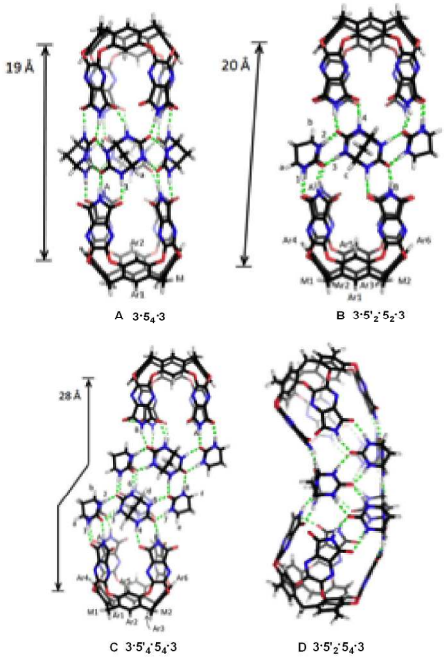

Fig. 11 The effects of inserting propanediureas into the capsule. Kinked and banana-shaped capsules form to accommodate increasingly long *n*-alkane templates. Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

even beyond those that arose from the glycolurils. New geometric patterns emerged from the mixtures (Fig. 11). The counterpart of the familiar glycoluril extended capsule appeared as **A** as did its unfamiliar isomer **B**. The most bizarre was an assembly that emerged having 6 propanediureas inserted between the two halves of the capsule. The only way that this number can be accommodated is through a bent, or a banana-shaped capsule **C**. This structure is proposed below and is supported by NMR assignments.[37] The kinked structure **D** adds to the unexpected gallery and was also characterized.

There is also support for this that is functional: curved or bent molecules are good guests, while rigid and rectilinear structures are not. That is, the various structures can be elicited with harder (less flexible) templates. The alkane guests tolerate, fit in and conform to almost any of the shapes;[38] they flow easily into the kinked, banana shaped and linear assemblies derived from the propanediurea spacers. They are the universal guests, unlike the rigid heterocycles that dominated earlier molecular recognition studies.[39]

In the world of self-assembly, nothing came as a bigger surprise than the spontaneous assembly of the simple resorcinarenes. But it took a long time to realize what was happening. In 1980, Högberg described a synthesis of resorcinarenes easily performed on multi-gram scales (from which most of the compounds in this review are derived).[40] Atwood solved a spectacular solid-state structure in 1997,[41] consisting of 6 resorcinarenes and 8 water molecules. Even earlier, Aoyama characterized 1:1 complexes of resorcinarenes with a variety of organic molecules in solution.[42] These are now known to be 6:6

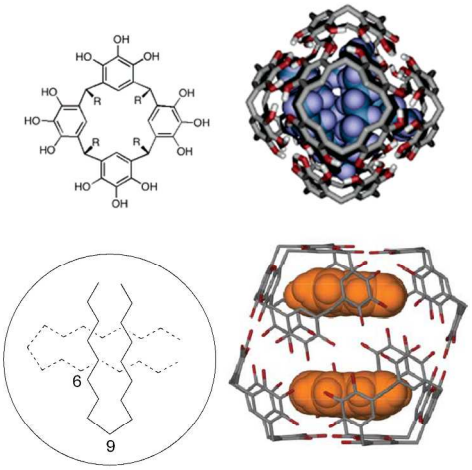

Fig. 12 Top: The pyrogallolarene monomer and its modeled capsule with 5 octanes inside the hexameric assembly. From *Org Lett.* **2005**, 7, 787-789. Copyright 2005 American Chemical Society. Bottom: Cartoon of the capsule with two *n*-C_{17} guest folded inside; C9 is nearest the pyrogallolarene. A solid state structure[48] with 2 pyrene derivatives stacked near the walls of the capsule is also shown. Adapted from *Science* **2005**, *309*, 2037-2039. Reprinted with permission from AAAS.

complexes that involve encapsulation.[43] The resorcinarenes assemble around one large guest such as *tetra*-hexyl ammonium ion in organic solvents,[44] but even wet solvents such as chloroform and benzene[45] are capable of inducing the assembly. Therefore, it is likely that Högberg had encountered the hexameric resorcinarene capsules in solution in 1980, and since he was using a procedure introduced much earlier by von Bayer, perhaps hydrogen bonded capsules existed even 100 years ago.

Another unanticipated example was in the roughly spherical space of a hexameric pyrogallolarene capsule.[46] This was known to assemble around sizable guests, but on treating it with a series of hydrocarbons, a curious discontinuity was observed in the NMR chemical shifts of guests. As the alkanes became longer and reached a point where they could not fit inside in their extended conformations, they *folded in half*.[47] For example, 2D COSY NMR experiments showed that with C_{17} inside the capsule, the center CH_2 of the guest molecule (on carbon 9) showed the furthest upfield ^1H chemical shift. The CH_2 groups of carbons 5, 6 and 7 were the least affected by the shielding of the aromatic panels and are therefore near the center of the capsule. As shown in cartoon form below, there are two of the C_{17} guests inside, based on packing coefficients. Atwood[48] found 2 pyrene butyric acids, which are relatively hard templates, nestled within the same capsule (Fig. 12). With EtOAc, six guests and a water molecule were encapsulated, and the orientations of the softer EtOAc guests depend on the environment outside the capsule.[49]

Deconstruction

Our experience with glycoluril extended capsules suggested that the mono-substituted glycolurils such as **6** (Fig. 13) could "deconstruct" the capsules and force them into deepened cavitands. The substituents on the glycoluril were intended to "short-circuit" the hydrogen bonds that we had seen in, for example, the doubly expanded capsules. Moreover, as these mono-substituted glycolurils would be chiral, it would be possible to consider their assembly in an enantioselective form, where only one enantiomer would be involved in a given assembly. Indeed, short chain hydrocarbons (C_{10}-C_{14}) in the presence of **3** and **6** gave a new deep cavitand **3•6$_4$** with the alkanes partially inside.[50] While this was expected and hardly emergent, the unexpected came with longer alkanes where the system assembles to give extended cavitands **3•6$_2$•6$_2$•3**. Two deepened cavitands come together and shed two glycolurils. The new capsular species with 6 components is held together by the single, long guest inside (Fig. 13). Apparently, alkanes minimize their exposure to the mesitylene solvent and maximize their occupancy of the organized solvation modules provided by the complex assemblies.

There are reports of nonlinear behavior of this sort with other

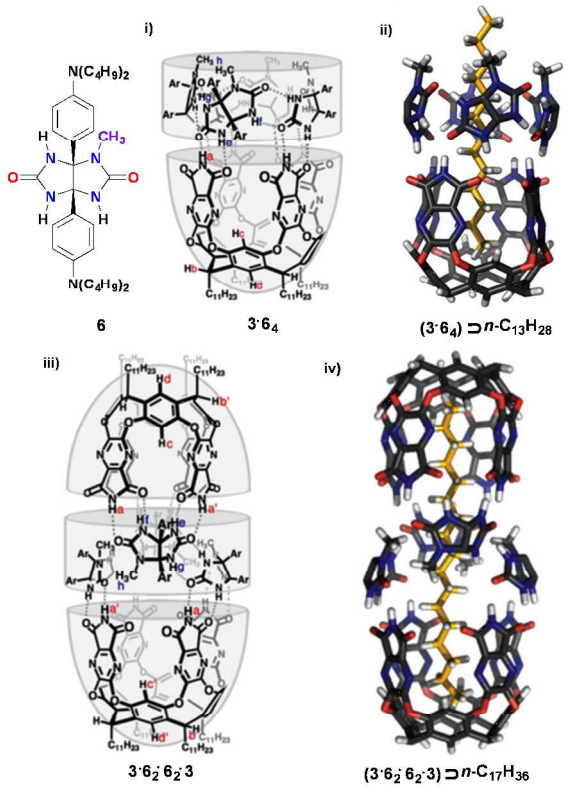

Fig. 13 The monosubstituted glycoluril **6** is chiral and 4 modules are taken up by the cavitand in i). Only one cycloenantiomeric array of the deepened cavitand assembles in response to shorter (C_{10}-C_{14}) alkane guests as in ii). Longer guests (C_{15}-C_{19}) induce the assembly of capsules as in iii) and iv). Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

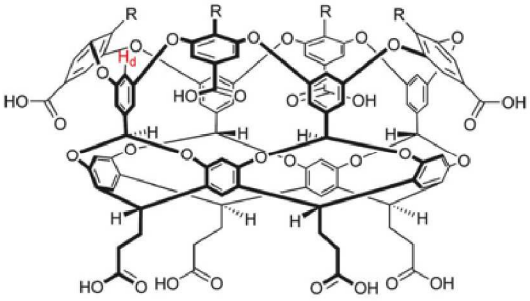

Fig. 14 Chemical structure of octaacid **7** and tetra-*endo*-methyl octaacid **8**.

self-assembling capsules.[51] A parallel and independent series of experiments were performed by Gibb,[52] who used a water-soluble cavitand bearing seemingly passive methyl groups, with a series of hydrocarbon guests (Fig. 14). With these he showed a non-monotonic assembly sequence in which small guests (methane and ethane) formed 1:1 complexes; larger guests (C_3 to C_6) formed mixtures of 1:1 and 2:2 host/guest complexes; even larger guests (C_7 and C_8) formed 1:1 complexes and finally the longest guests (C_9 to C_{14}) formed 2:1 complexes. The analysis involved the extensive application of DOSY experiments to establish the sizes of the complexes. This behavior was unpredicted as it was in stark contrast to that of the cavitand **7** missing the methyl groups on the rim. The latter showed the expected monotonic increases in complex sizes with guest sizes.

This series is illustrated in cartoon form in Fig. 15, where the cartoons represent the structures of the cavitands bearing methyl groups. The peripheral methyl groups of **8** have a defining role in the dimerization. Although at the time of this writing, there exists no structure for the dimeric capsule and the details of the interface between the cavitands are unknown, we propose a model (Fig. 15) shown with C_{12} inside.

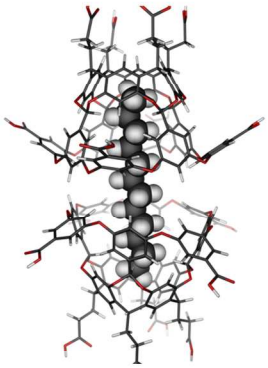

Fig. 15 Proposed model of the Gibb capsule with an extended C_{12} guest. The contacts at the interface between the two cavitands are unknown; the guest itself can be the cohesive force.

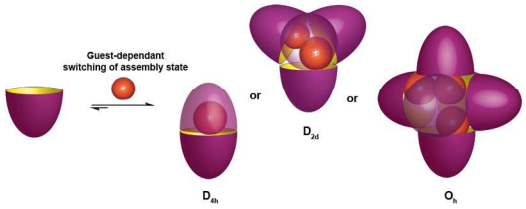

Fig. 16 Cartoons of assemblies involving cavitand **8** and long chain hydrocarbon guests.[53] All assemblies show 2 cavitands per guest but have different DOSY spectra.

The Gibb cavitands showed even more surprises with guests than could not be accommodated in the dimeric capsule – higher order assemblies emerged![53] These all showed a 2:1 ratio but appeared as multiples. For example, with C_{17} to C_{20} complexes emerge whose dimensions correspond to the tetrahedral assembly shown (Fig. 16) and indicate a 4:2 stoichiometry. A congruent single guest, the *tetra*-(*n*-hexyl)ether of pentaerythritol was also encapsulated in a 4:1 complex. With the longer guests C_{24} to C_{26} yet another assembly arises, corresponding to a spectacular octahedral complex of 6:3 stoichiometry. This series is illustrated in the figure where the cartoons represent the structures of the cavitand **8**. The dimensions were deduced from the large hydrodynamic volumes determined by the NMR experiments. It may be some time before the shapes of the hydrocarbons inside these assemblies are determined but they are unlikely to be familiar; the tetrahedral assembly cannot accommodate simple extended conformations and the noncovalent intersection of three alkanes lacks structural precedent.

Penultimately, we give an example of how the shape space affects photophysics in a confined environment. Stilbene has been a very welcome guest inside the cylindrical capsule **3•3** but showed an unexpected quenching of its fluorescence inside. Unexpected because stilbene inside the tight confines of an antibody showed extremely enhanced fluorescence,[54] and we thought this behavior would extend to other snug places. The quenching was finally understood through the orientation that

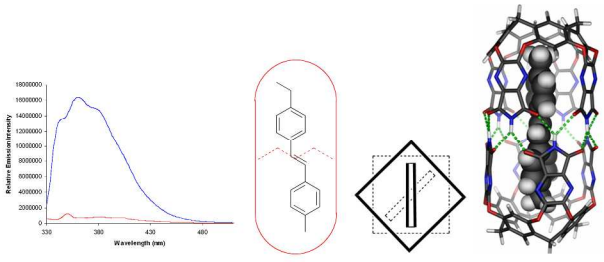

Fig. 17 Left: fluorescence spectra of a free stilbene (blue) and encapsulated stilbene (red). Center: a cartoon of the aryl dispositions in the capsule **3•3**. Right: an energy-minimized model of the stilbene complex.

the aromatics take inside the capsule. As shown earlier, aromatics tend to be diagonally disposed in the square cross-section of the capsule.[55] Because the shape of the space inside consists of two square prisms rotated 45° with respect to each other, it is impossible for stilbene to achieve a coplanar ground state: the twist between aryls is 45° optimally, but in energy-minimized models, appears more like 40°.[56] This is shown (Fig. 17) both schematically and as an energy-minimized model. Fluorescence requires that the excited state drops to the ground state, without change in geometry. A completely coplanar stilbene would be a *transition state* in the stilbene's spinning along the long axis within the capsule. It is clear then that fluorescence cannot occur. Instead, the excitation energy must be dissipated by some other way.

The linear growth of our capsules with inserts of spacers and the expansion in 3-dimensions recently reported by Gibb are also examples of emergence in supramolecular chemistry. The versatility of the alkane as soft templates was one of the drivers of the phenomena, and the various stoichiometries of the host components simply do not exist in the absence of the guest.[57] Perhaps a different medium would give another set of results.

One may well ask *why* molecules fit together. Molecular surfaces that maintain some contact with each other are shielded from outside chemicals – e.g., oxygen, acids/bases or water and dissolved reagents. Less than 200 years ago, when chemists began to synthesize new molecules, all existing organic compounds were products of biology and subject to Darwinian pressures; survival is the first requirement of living systems and their components had to avoid exposure to potential means of destruction.[58] Molecules that mutually adapt to each other – a fundamental feature of molecular recognition – can share an interface and force out solvents from between them. This protection of the interface enhances stability, or in prebiotic terms, promotes survival and provides a vehicle for molecular evolution.[59] Compartmentalization is an extreme tactic to minimize exposure and molecules completely surrounded by others enjoy the greatest protection.

Are there soft templates in Nature? Induced fit is a venerable concept that implies some softness in the shape of biological active sites and the newer "conformational selection" emphasizes dynamic ensembles of protein structure.[60] An increasing number of functional proteins are shapeless before they contact their targets.[61] That most famous of templates, DNA, is flexible but the more rigid transcriptional machinery that operates on it does allow for mutation slip-ups. But these are asides; the review has emphasized our fascination with emergence of those encapsulation complexes in which *neither* the host nor guest structure is stable alone, but together they provided us a look at something really new. Realizing the otherwise imaginary continues to sustain our interest in encapsulation phenomena.

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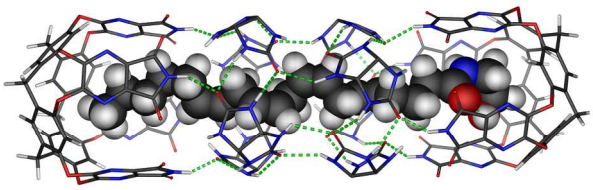

The ethanolamide of arachidonic acid (Anandamide) nucleates the assembly of a capsule incorporating 8 spacer units.