Assembly and Encapsulation with Self-complementary Molecules

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1 Introduction

Molecular recognition is a branch of chemistry that is concerned with complementarity. By this term is meant complementarity of size, and shape and chemical surfaces: the 'goodness of fit' between two molecules like the fit between a foot and a hand-made shoe. Molecular recognition defines this goodness of fit, and explores the intermolecular forces, the weak attractions that act over short distances between molecules. These forces – hydrogen bonds, aromatic stacking, polar and van der Waal's interactions – are the ones that bring molecules together into complexes. Such complexes are temporarily and weakly held groups of two or more molecules. More complicated complexes – assemblies – are also possible. These structures may be made up of complementary molecules or multiple copies of a self-complementary molecule. They form and dissipate on a timescale that varies from microseconds to hours: time intervals long enough for many types of chemistry to occur between them.

Assemblies have captured the attention of many research groups involved in molecular recognition because new phenomena frequently emerge whenever more than one copy of an entity is present. It is often as impossible to predict what emerges as it is to predict the hexagonal shape of a honeycomb from the study of a single bee. Biochemistry abounds with examples: allosteric enzymes, channel-forming peptides and viral coat proteins are all assemblies of multiple copies of a molecule that give rise to superstructures with functions that are unique to their assembled states: functions such as regulation, transport, replication and encapsulation. But simpler molecules, available through chemical synthesis, are also able to exhibit unique behaviour through assembly. This review is concerned with such molecules and is limited in its scope to systems that show sharply defined features of size and shape in solution. Specifically excluded are aggregates such as micelles, liquid crystals and the like as well as assemblies that emerge primarily in the solid state.

A two-dimensional system of three molecules illustrates some of the features of self-complementarity involved in assembly. The structure designed and synthesized by Zimmerman (Fig. 1)[1] presents a pattern of hydrogen bond donors and acceptors on one edge that is complementary to the pattern on the other functioning edge. Accordingly, assembly at one level can be predicted. The orientation in space of the atoms capable of hydrogen bonding at the two edges of the molecule is fixed at almost exactly 120 °C by the rigidity of the aromatic centrepiece of the structure. The information, the **code**, for the assembly is written into the hydrogen bond patterns of the edges and their angular orientations with respect to each other. In solution a trimer is formed, and assembly takes place in the manner expected. But entropy also has its say: linear aggregates intrude on the well-ordered cyclic trimer.

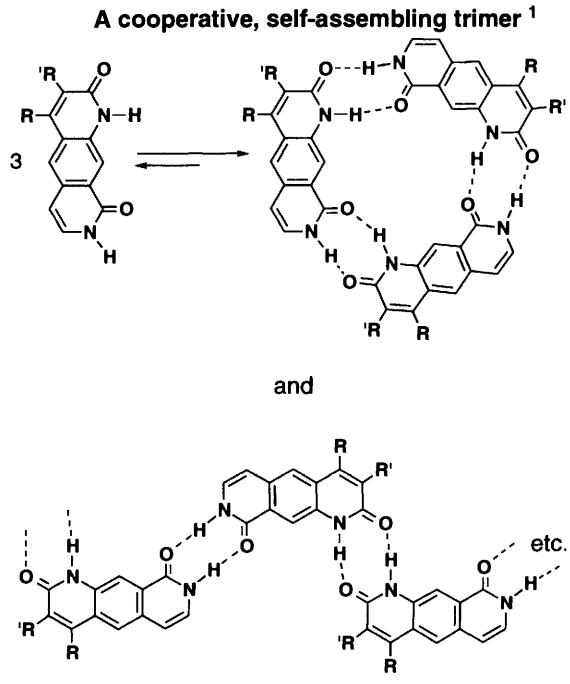

Figure 1 Self-complementary hydrogen bonding sites lead to trimers and oligomers

Two-dimensional hydrogen bonded arrays are enormously popular in supramolecular chemistry.[2] For the most part, the systems use rigid, flat, heterocyclic compounds. The resulting assemblies resemble practically infinite sheets;[3] crinkled tapes;[4] twisted ribbons;[5] ingenious rosettes,[6] to name just a few.

The principles of molecular recognition can also be used to assemble three-dimensional structures, but additional structural requirements must be met. The most important is curvature. This is beautifully illustrated with the constructs of Ghadiri.[7] These structures take the self-complementary hydrogen bonding patterns featured by peptide β sheets and wrap them into a macrocyclic format (Fig. 2). The resulting assembly is a hollow cylinder, a peptide nanotube, and is an early example of an assembly that actually shows **function**. Transport of glucose through the nanotube and across a lipid bilayer membrane was demonstrated.

The systems we have worked with at MIT are literally minimalistic: they involve only **two** copies of the same molecule. But it is the single molecule that holds the key, loaded with the information and what it promises for assembly. Rene Wyler synthesized the first

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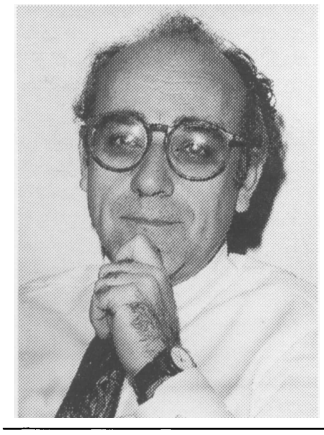


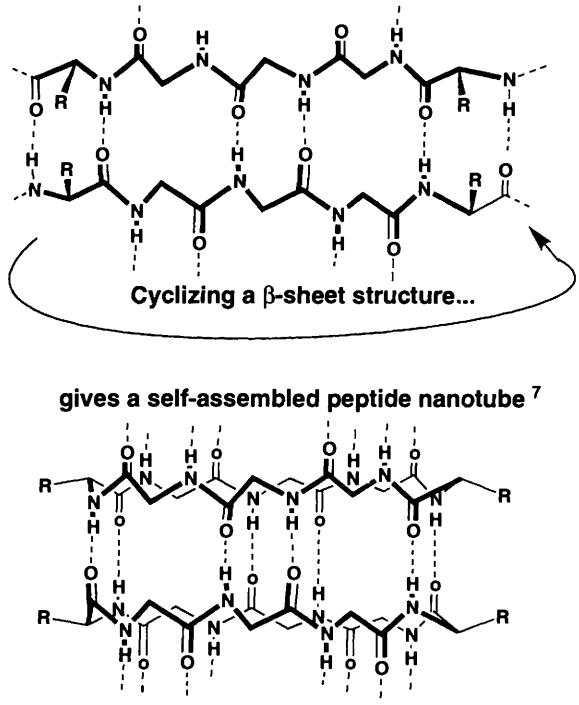


Figure 2 Curvature increases the complexity of self-complementary assemblies

such molecule **1a** from diphenylglycoluril and tetrabromodurene.[8] The *cis*-fusion of the two five-membered rings of the glycoluril forces a fold at either end of the molecule. Curvature along the length of the skeleton is caused by seven-membered rings on either side of the central benzene unit. When all of the glycoluril substituents appear on the same face of the molecule, a low energy conformation that features self-complementarity can be obtained. Specifically, the O–O distance indicated is appropriate for two hydrogen bonds to form to the ends of another molecule. The stereochemical features impart the necessary curvature for the dimeric assembly, while the hydrogen bonds provide the cohesive force, just as the stitching along the seam of a baseball holds the two pieces together.

Spectroscopic studies in $CDCl_3$ indicated that a single species was present in solution which showed extensive hydrogen bonding. We were fortunate that this solvent (the industrial standard for studies in molecular recognition) was a poor fit for the interior of the capsule, as most of the encapsulation phenomena described in this review owe their very existence to two characteristics of a solvent. Foremost, it must dissolve reasonable concentrations of the assembly's components. Secondly, it must compete so poorly for the interior of the capsule that the encapsulation of solute guest molecules can be observed. In other words, the solvent's superior concentration – relative to an intended guest's – must be overcome by the goodness of fit. This observation was made earlier by Still and used with tremendous success by Cram in his incarceration of 'convicts' in covalently bound capsules.[9]

The ^1H NMR spectrum of this 'baseball' (**1a**—**1a**) in $CDCl_3$ saturated with methane is shown in Fig. 4 to illustrate some of the advantages of NMR for the study of assembly and encapsulation. The spectrum displays a sharp singlet at the unusual chemical shift of δ −0.9 representing encapsulated CH_4,[10] in addition to the resonance for free methane at δ 0.2 (the ethane signal at δ 0.82 and the characteristic pattern of propane at δ 0.9 and 1.3 are a measure of the purity of natural gas 'on line' at MIT). The separation of the free and bound signals for both host and guest places limits on the rates of exchange into and out of the capsule: the rates are slow on the NMR timescale but fast on the human timescale.

The crystal structure of dimeric **1c** was solved by Toledo,[11] and it is shown, shorn of its ethyl esters in Fig. 5. The crystal of **1·1** appears to contain a disordered guest species in its cavity, although it was not possible to determine unambiguously the identity of the

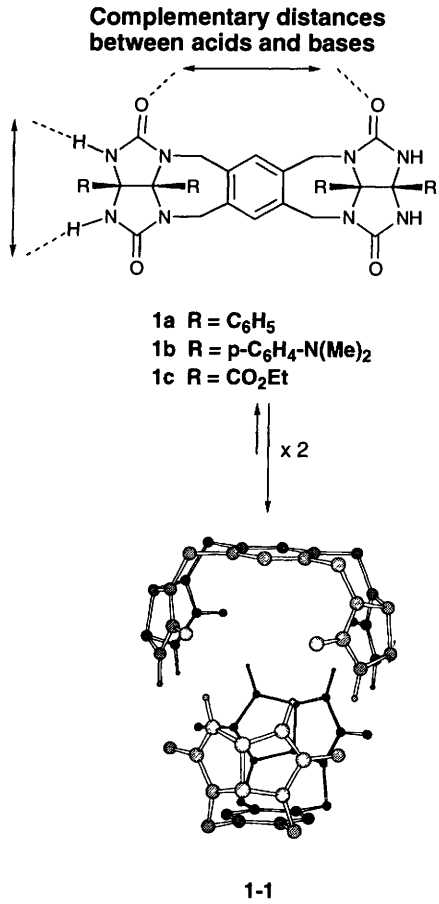


Figure 3 Two identical molecules give a closed-shell 'baseball'

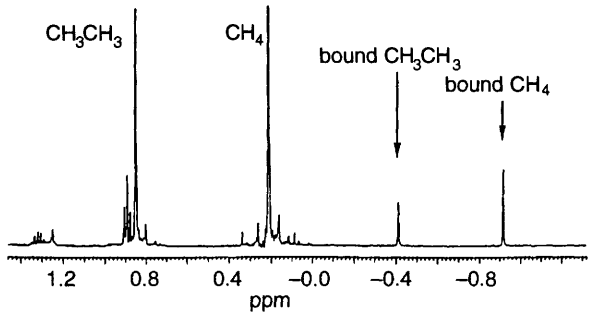


Figure 4 Unusual chemical shifts are observed for encapsulated small molecules

guest. It was possible, however, to locate and refine a carbon atom at two positions with assigned occupancy factors of 0.55 and 0.45. This leads us to believe that this guest species is a methanol molecule with a highly disordered oxygen atom. There are eight (carbonyl oxygen) good hydrogen bond acceptors along the seam of the capsule, and it is possible that the hydroxy group of methanol is disordered about eight positions.

It was desirable to find more soluble versions of the glycoluril subunit and the family of esters available from dihydroxytartaric acid were settled on. Their enhanced solubility in organic media and the possibility of functional group manipulations (*e.g.* hydrazinolysis) to water-soluble glycolurils are promising. The *p*-dimethylamino-diphenylglycoluril derivative **1b** and the capsule derived from it offer control of the assembly process by events that take place on the periphery of the structure rather than on the inside. Encapsulation of xenon in dimethyl formamide (DMF) solution can be directly observed in the ^{129}Xe NMR spectrum.[12] Neil Branda showed that the presence of xenon actually causes nucleation, the formation of the capsule. The basic sites of the dimethylamino function are subject to

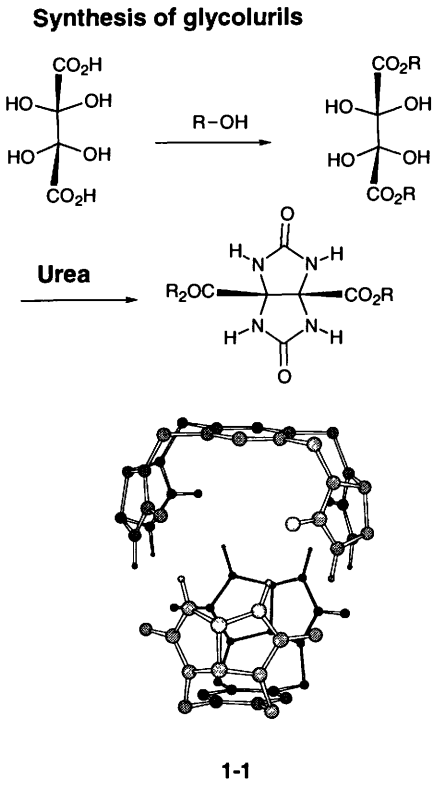


Figure 5 Synthesis of soluble glycolurils and the methane-selective capsule

protonation with strong acids, and at high acidities the guest is released. Neutralization with bases reverses the processes: the guest is again encapsulated (Fig. 6). The simplest interpretation (though still unproved) is that the multiple positive charges that build up on protonation of the periphery force the two halves of the capsule apart through coulombic repulsion. The influence of acidity on dimerization suggests that it may be possible to make multicomponent systems in which assembly is fine-tuned to subtle changes in pH.

Xavier Garcias showed it was also possible to alter the environment *inside* the cavity. The hydroquinone **2** and quinone **3** spacers present either electron rich or electron deficient surfaces to encapsulated guests (Fig. 7). The affinity of some small molecules to the capsules derived from these, compared to the original capsule, are given in Table 1.[13] The studies of the fluorinated methanes were inspired by recent calculations by Kollman[14] that predicted CF_4 to be an appropriate guest for these capsules, but experiment and computation for the affinity of CF_4 have yet to be reconciled. Qualitative evidence for the encapsulation of nitric oxides in **3**—**3** was also obtained.

2 Other Shapes and Sizes

In molecules **1**, **2** and **3**, the glycoluril functions at the end of the molecule and the connecting spacer elements, which determine the dimensions and the overall shape of the dimer, remain constant. It was not unexpected to find that heterodimers formed readily when

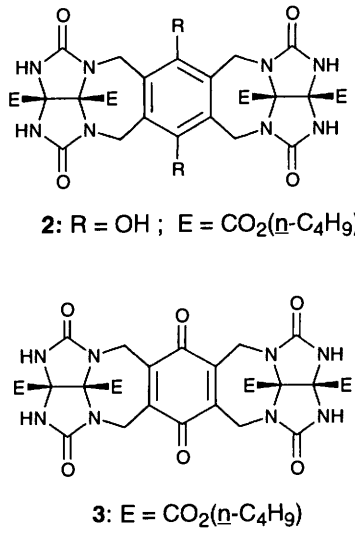


Figure 7 Electron rich and electron poor capsules show altered selectivities

Table 1 Association constants K_a/mol^{-1} l, (298 K), for encapsulation of guests in dimers **1c**—**1c**, **2**—**2**, and **3**—**3** (K_{a298} = [N–guest–N]/[N–N] × [free guest]).

Host / Guest	1c—1c	2—2	3—3
CH_4	33	70	10
C_2H_6	51	51	13
CH_3F	1.0	17	<0.3
CF_4	0.7	0.6	<0.2

the various components were present in the same solution. Can dimerization still take place if the spacers are varied? The monomers **4**, **5** and **6** contains ethylene, naphthalene and a bridged anthracene, respectively, as their spacer elements. If good hydrogen bonds are to be formed in the dimers, the 'length' of the spacer should complement the 'width' of the glycoluril. The energy-minimized structures of the corresponding dimers, as generated by an MM2 forcefield,[15] are provided in Fig. 8, and the calculated O–O distances of the monomers are shown.[11] The dimerization leads to unusual pseudo-spherical structures with cavities smaller or larger than that of **1·1**.

Obviously, **4·4** is smaller than **1·1**; calculations indicate that the cavity formed by **4·4** (41 Å^3) is approximately 18% smaller than that of **1·1** (50 Å^3). Carlos Valdés showed that dimer **4·4** does bind small molecules, and displays a remarkable selectivity: ethane, which binds to **1·1**, was not measurably encapsulated by **4·4**. However, a price is paid for the discrimination: the affinity of methane for **4·4** is approximately 70 times lower than for **1·1**.

What are the consequences for 'miscegenation'? Molecular models indicate that three heterodimeric combinations are especially likely to form: hybrid structures **1·4**, **1·6** and **5·6**.[16] The energy-minimized heterodimers are shown in Fig. 9. In the experiment, Urs Spitz observed heterodimers when two different

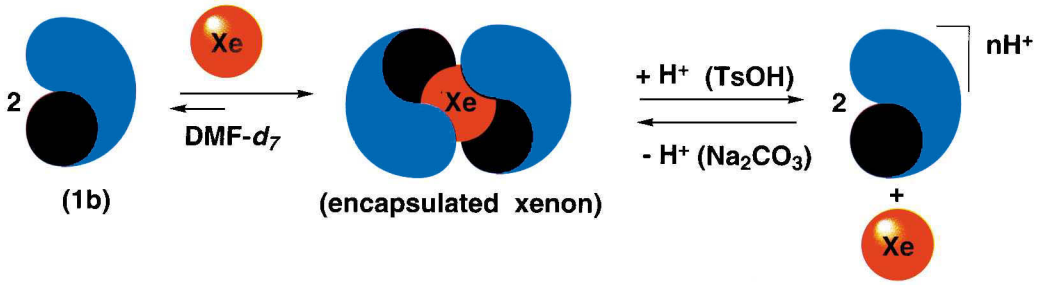


Figure 6 Control of encapsulation is possible with changes in acidity

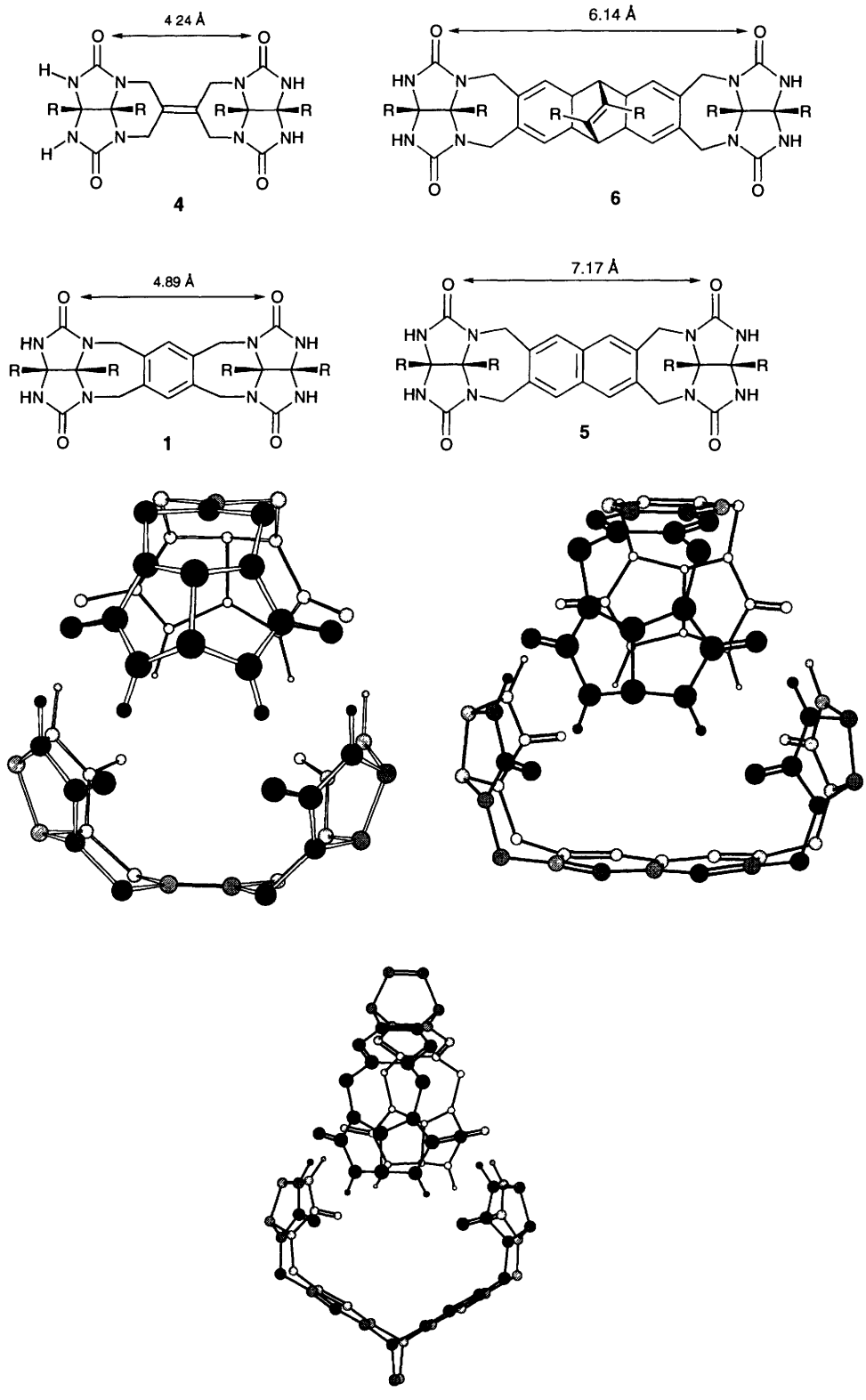


Figure 8 Dimensions and shapes of new capsules

dimers were present in the same solution. The formation of hybrid capsules showed that structurally related molecules that are self-complementary are often complementary to each other.

The 'recombination' of the homodimers to form hybrids is an equilibrium process, and opens access to new capsule shapes. The hydrogen bonds in the homodimers are expected to be superior to those of the heterodimers; the disproportionation observed must, to some extent, be driven by the entropy of mixing. The recombinations (disproportionation equilibria) of the dimers depended strongly on the solvent.[11] For example, in the case of **1** with **4**, the disproportionation constant $K_{1\cdot4}$ is large in $CDCl_3$, $CDBr_3$ and $Cl_2DCCDCl_2$ but is an order of magnitude smaller in CD_2Cl_2. The former three solvents are too large to fit the cavity of any of the three species present in the equilibrium, but CD_2Cl_2 is of appropriate size for **1·1**. The CD_2Cl_2 provides a motivation, the driving force, for the formation of **1·1**. The goodness of fit again determines the favoured species.

Of the various possible capsules, only **6·6** appears large enough to accommodate $Cl_2DCCDCl_2$. Accordingly, only traces of heterodimer **1·6** are present in solutions of this large solvent. The current

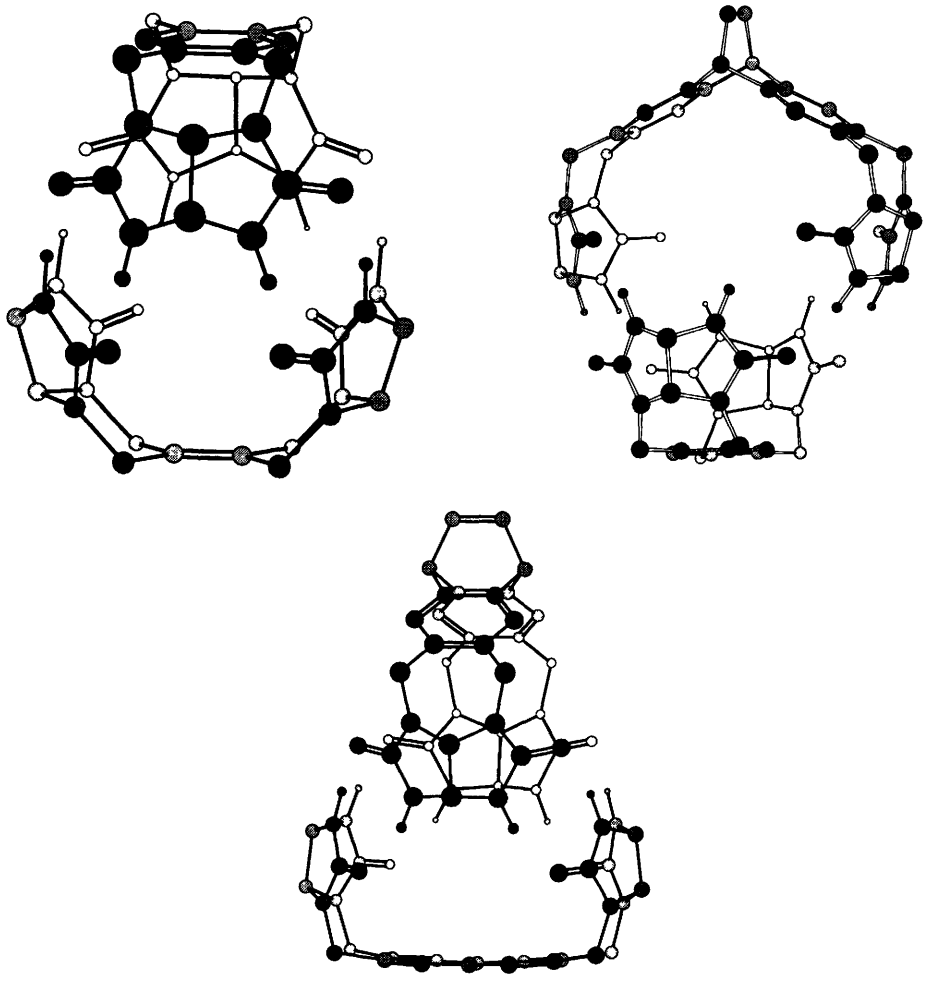


Figure 9 Hybrid or heterodimeric capsules form when exposed to complementary guest solvents

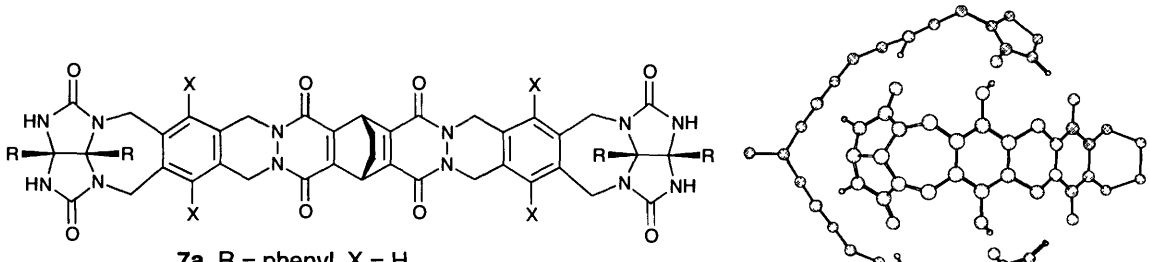
state of predictions regarding the energetics and geometry of hydrogen bonds is far from ideal, and to predict the magnitude and the sign of the thermodynamic parameters for hybrids **1·6** and **5·6** without knowledge of the number of species being encapsulated or released is tenuous.

3 Larger Volumes

Robert Meissner and Jongmin Kang, with the collaboration of Javier de Mendoza developed a new system shown as **7** in Fig. 10.[17] The overall architecture involves a tape-like structure of 13 fused and one bridged ring systems. The ring fusions provide the gentle curvature required for the pseudo-spherical assembly. When viewed on edge, as shown in the Fig. 10, the somewhat exaggerated curvature of the structure can be seen. Compared to the 'baseball' the new system is a larger 'softball'. The compound did show the expected NMR spectroscopic earmarks of a dimer in some aromatic solvents. But in chloroform the molecule produces a gel-like phase. Apparently, a *polymeric* assembly takes place; the molecule expresses its self-complementarity in an unexpected arrangement.

The large solvent [$^2H_{10}$]-*p*-xylene permitted the encapsulation of guests of considerable size and shape in the dimeric form. Adamantane is a particularly good fit and even tetramethyladamantane can be accommodated. Again, the widely separated and relatively sharp signals for free and encapsulated guest in the NMR spectra indicate that exchange of guests in and out of the capsule is slow on the NMR timescale. The numerous polar and polarizable atoms that line the inner surface can also stabilize complementary functional groups on guests, such as those on adamantaneamine and adamantanedicarboxylic acid. These proved to be the most tightly bound guests.

Because higher order aggregates were also observed with **7a**, it was necessary to find modifications by which the assembly process



7a R = phenyl, X = H
7b R = CO_2-i-pentyl, X = H
7c R = 4-n-heptylphenyl, X = OH

Figure 10 Self-complementary 'softballs' feature up to sixteen hydrogen bonds

could be better controlled. For example, in **7c** additional hydrogen bonding sites are provided by the phenolic functions. As these sites are positioned along the seam and can provide up to eight additional hydrogen bonds to stabilize the capsule, dimerization is favoured over other processes.[18] The encapsulation behaviour of this system proved surprising. The data for adamantane and ferrocene with **7c·7c** in [$^2H_{10}$]-*p*-xylene are given in Table 2.

Table 2 Thermodynamic parameters for guest encapsulation by the **7c·7c** dimer in [$^2H_{10}$]-*p*-xylene. The temperature range was from 298 to 343 K (K = association constant as defined in ref. 18; 1 cal = 4.184 J).

Guest	K_{298}	ΔG/kcal mol^{-1}	ΔH/kcal mol^{-1}	ΔS/cal mol^{-1} K^{-1}
Adamantane	$1.7 \times 10^3 \pm 90$	-4.6 ± 0.2	2.2 ± 0.1	22.6 ± 1.1
Ferrocene	$3.3 \times 10^3 \pm 170$	-5.0 ± 0.3	2.3 ± 0.1	24.4 ± 1.2

The most significant observation is that guest encapsulation *increases* with temperature. Now, most processes involving host–guest association are entropically unfavourable but enthalpically favourable, and much has been written about the compensating effects of entropy and enthalpy in complex formation.[19] For **7c·7c** the inclusion of guests involves an enthalpic *cost* compensated by a larger entropic *gain*. Such entropy-driven binding is reminiscent of the classical hydrophobic effect, wherein release of bound water to the bulk solvent compensates for the association of solutes In organic media such behaviour is not frequently detected,[18] even though liberation of solvent must be a universal feature of molecular recognition phenomena. How can this anomalous behaviour be interpreted?

A single solvent molecule appears too small to fill the cavity of the capsule **7c · 7c**; more than one $CDCl_3$ or *p*-xylene is required to maximise the intermolecular forces – the van der Waal's interactions – between the convex surfaces of the guests and the concave surface of the host's interior. The answer came from a simple set of experiments. In either [$^2H_6$]benzene or fluoro[$^2H_5$]benzene the NMR spectra of compound **7b** are characteristic of a single dimeric species. When the spectra was recorded in a *mixture* of the two solvents it became clear that three species were present.[20] The most economical interpretation is that the third species is the capsular form that contains one of each solvent molecule (Fig. 11).

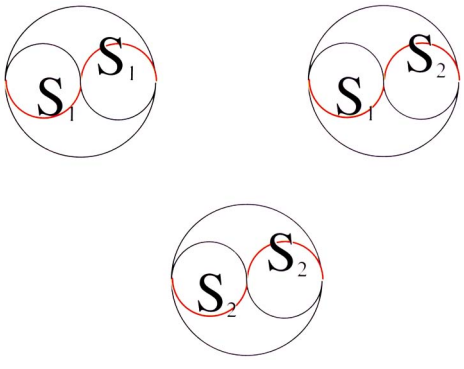


Figure 11 Three distinct softballs are observed in a mixture of two solvents

It is reasonable that single molecular guests which fill the cavity and offer chemical and structural complementarity are preferred to multiple solvent molecules; one guest releases the two solvent molecules inside the capsule (as well as the retinue of solvents associated with the guest outside). Consequently, the encapsulation of adamantanes or ferrocenes by **7c·7c** increases entropy, since more than one encapsulated solvent is released to the bulk solution (Fig. 12).

What are the limits on the capacity, *i.e.* what fraction of the space in these capsules can be occupied? What is the volume? Using MACROMODEL[15] the capsule's volume is calculated to be about 400 Å^3, or 4×10^{-25} dm^3. Two benzenes or two toluenes can easily be accommodated in this space. This suggested that the cavity was

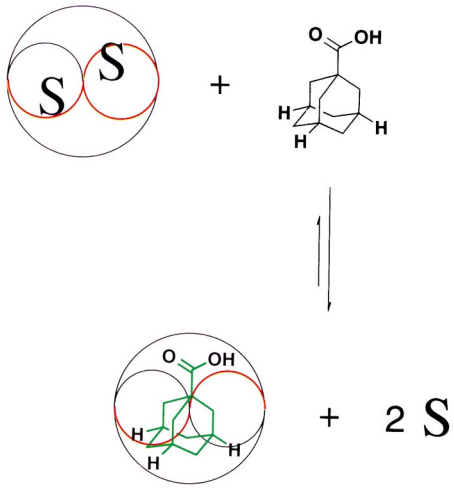


Figure 12 Encapsulation is entropy driven since two solvent molecules are liberated

roomy enough to accommodate the transition state geometry of a typical Diels–Alder reaction. When both *p*-quinone and cyclohexadiene are present in solution with **7a**, a single well-defined complex emerges in the NMR spectrum. Integration shows one molecule of quinone is present within this complex, but no signals unique to encapsulated cyclohexadiene can be assigned. Nonetheless it must also be present, since the encapsulated Diels–Alder adduct is observed by NMR within one day (Fig. 13).[21] The rate of this reaction in bulk solution is so slow at these concentrations that reaction must be taking place within the capsule. The effective molarity of the reactants inside is *ca.* 1 mol l^{-1}. This is a promising figure for the future use of capsules as reaction chambers for bimolecular processes.

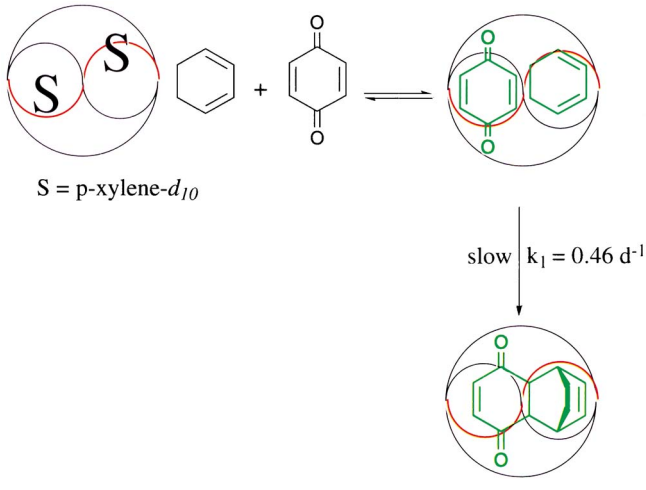
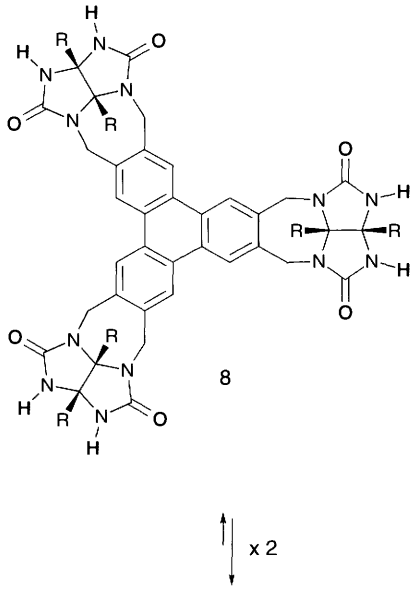


Figure 13 The softball as a reaction vessel for a Diels–Alder cycloaddition

4 Flattened Spheres

Other geometric changes that can be made on the original design involve higher symmetries and one such improvement was provided by a triphenylene spacer. This dimer features D_{3d} symmetry, but it resembles – in shape and size comparisons relative to the baseball and softball – a jam (jelly) doughnut. This structure **8** was synthesized by Robert Grotzfeld (Fig. 14).[22] The ceiling and floor of the assembled capsule consist of aromatic π-surfaces; 12 strong hydrogen bonds hold the two halves together. Titration experiments with benzene in $CDCl_3$ reveal a direct competition between benzene and $CDCl_3$ for the cavity of **8·8**. Titration in [$^2H_{10}$]-*p*-xylene solution (an uncomfortable guest for **8·8**) with cyclohexane revealed a new upfield (δ −0.87) signal in the 1H NMR spectrum for the encapsulated aliphatic guest.



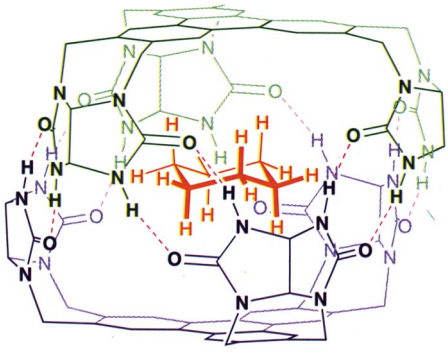


Figure 14 The 'jelly doughnut' **8·8** has an ideal cavity for cyclohexane encapsulation

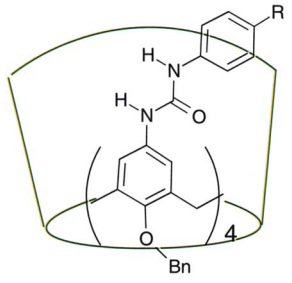
A depth-shaded view of the complex with cyclohexane reinforces the notional and functional aspects of the jam (jelly) doughnut description. Unlike the other capsules, which take up and release guests at a rate that is fast on the human timescale, **8·8** takes hours to equilibrate with cyclohexane. This guest probably requires a large fraction of the host's hydrogen bonds to break before passage into and out of the cavity is permitted.

5 Assembly with a Macrocycle

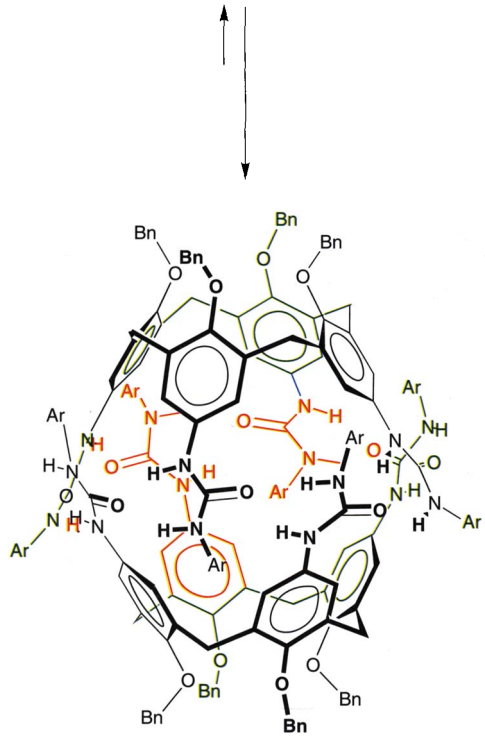
Ken Shimizu proposed and synthesized the self-complementary calixarene **9a**. It forms a dimeric capsule of yet another shape. The overall architecture of the assembly **9a·9a** is that of two hemispheres 'zippered' together along the equator by hydrogen-bonded ureas (Fig. 15).[23] This hydrogen-bonding pattern of ureas has been well established, particularly in the solid state, where X-ray crystallography has shown that the head-to-tail arrangement is a common geometry. Their inviting bowl-like shape and their synthetic availability have made calixarenes attractive scaffolds for applications in supramolecular chemistry.[24] The calix[4]arene systems synthesized in the research groups of Reinhoudt,[25] Ungaro[26] and Shinkai[27] to assemble by hydrogen bonding are particularly relevant.

For the dimerization at hand, the ureas can be hydrogen-bonded in this fashion with the carbonyl oxygens buried into the NH's of the preceding urea. All eight ureas may be fixed in same direction forming up to 16 hydrogen bonds. The hydrogen-bonding slows rotation about the calixarene–urea bond resulting in an isomer of D_{4d} symmetry.

Evidence for the existence of calixarene as a hydrogen bonded dimer **9a·9a** comes from the encapsulation of solvent molecules inside the assembled cavity. Inclusion was initially apparent in mixed solvent systems where two distinct calixarene assemblies were observed by ^{1}H NMR. Direct observation of the encapsulated guests by ^{1}H NMR is also possible, given some time.[28] For example, when excess benzene is added to the solution of **9b·9b** in [$^2H_{10}$]-*p*-xylene, a new signal for encapsulated benzene appears at δ 4.02 and gradually grows in over the course of *ca.* 40 min. The interleaved geometry of the assembly prevents visiting guests from leaving or entering quickly.



9a R = H
9b R = F



9a-9a Ar = C_6H_5
9b-9b Ar = C_6H_4p-F

Figure 15 The head-to-tail ureas drive the formation of new capsules **9·9**

Other guests have also been directly observed, such as fluorobenzene, *p*-difluorobenzene and pyrazine. Blake Hamann observed remarkably different chemical shifts for encapsulated fluorobenzene; the *para* and *ortho* protons are separated by > 2 ppm, suggesting that a particular orientation is favoured by this guest within the cavity. The orientation shown in **10** (Fig. 16), where the *ortho* and *meta* hydrogens are directed at the π faces of the calixarene while the *para* hydrogen and the fluorine are directed at the belt of ureas, is consistent with the chemical shifts.

Competition studies of guests with benzene were undertaken and the affinity of the calixarene dimer for these, relative to benzene, is given in Table 3.

Addition of other ureas such as the phenyl–α-phenylethyl deriv-

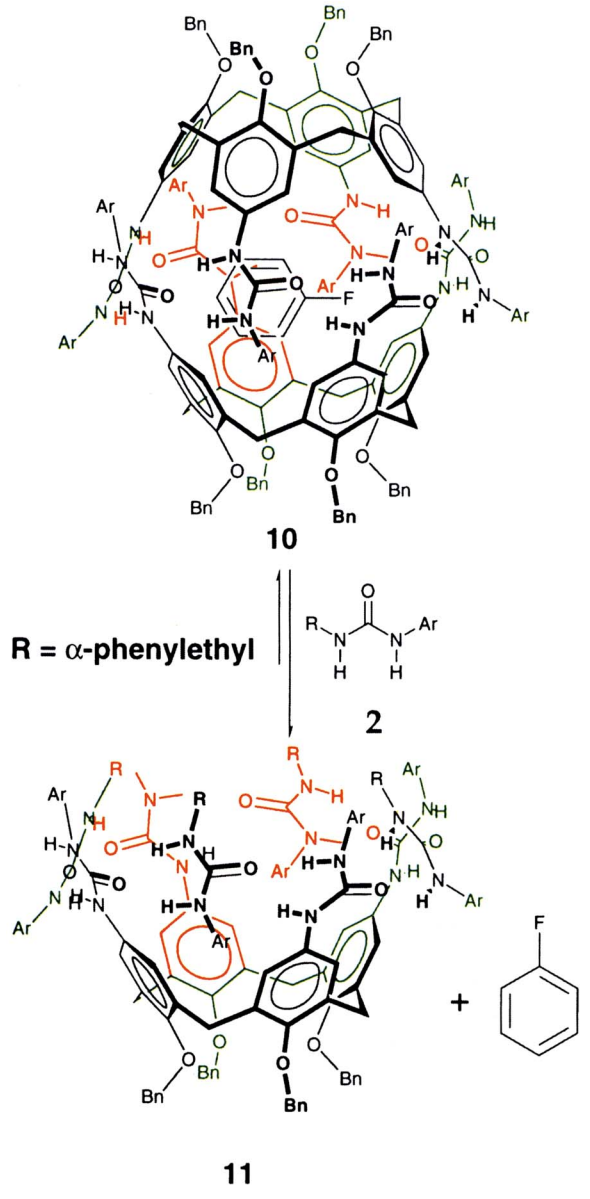


Figure 16 'Denaturation' of the capsule and liberation of *p*-fluorobenzene by competing urea functions

ative to the solution results in the liberation of guests and a new calixarene species **11** appears. This is most likely a result of the 'denaturation' of the calixarene dimer by the urea through competitive hydrogen bonding (Fig. 16), a process analogous to the denaturation of proteins with urea.

Table 3 Relative affinities of guests in competition experiments with benzene

Guest	Affinity (25 °C)	Guest	Affinity (25 °C)
C_6H_6	1.0	C_6H_5OH	0.83
C_6H_5F	2.6	$C_6H_5NH_2$	0.32
p-$C_6H_4F_2$	5.8	Pyrazine	3.2
C_6H_5Cl	0.30	Pyridine	1.2
$C_6H_5CH_3$	<0.1		

The high affinity observed for pyrazine is also suggestive of a conformation that directs the nitrogen lone pairs at the urea hydrogens within the complex. A recent study by Sherman[29] also finds pyrazine a favoured guest. The system involves a belt of strong hydrogen bonds (phenol with phenolate) and structures closely related to calixarenes (Fig. 17).

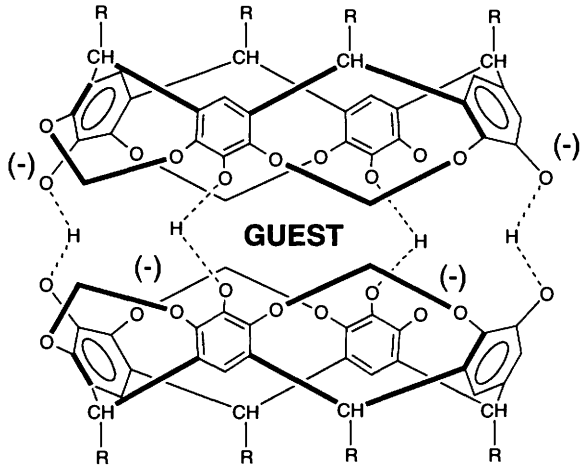


Figure 17 Hydrogen bonding holds hemispheres together for guest encapsulation

The volume of the cavity was estimated to be *ca.* 210 Å^3, and most guests appear to fill *ca.* 50% or less of the available space in the cavity. By comparison, in a typical liquid 70% of space is filled. The shape of the cavity within **9·9** is difficult to visualize, but a geometric simplification is shown in Fig. 18. Each calix[4]arene is represented by a square pyramid with its triangular facets corresponding to the outside of the aromatic surfaces. In the dimer, the pyramids are offset by 45°, and the corners are cut off to represent the eight interleaved ureas which encircle the equator.

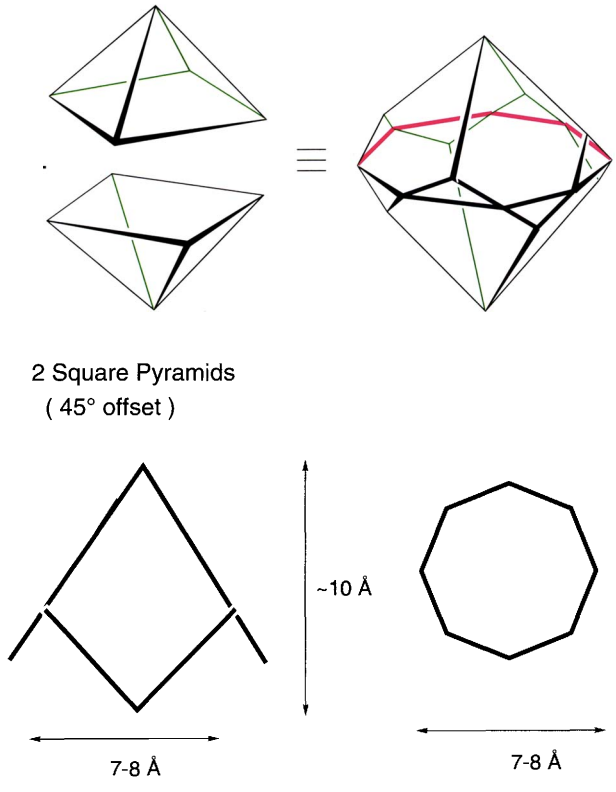


Figure 18 Schematic representations of the cavity formed by the dimerization of tetraureas **9**, and vertical and horizontal cross sections

Cross sections of the molecular model are in agreement with the gem-like geometric representation. A horizontal slice through the plane of the ureas yields an octagonal cavity, while a vertical slice gives a diamond-shaped cavity, having different angles and lengths for the top and bottom sections.

The representations shown in Fig. 18 suggest that cubane is a

reasonable three-dimensional complement for the cavity shape. The energy-minimized structures for the complexes with cubane are shown in Fig. 18, again with the cavity walls cut away for ease of visualization. In the experiment, cubane was added to a solution of **9b·9b** in [$^2H_{10}$]-*p*-xylene and the formation of a 1:1 complex was again observed by NMR.

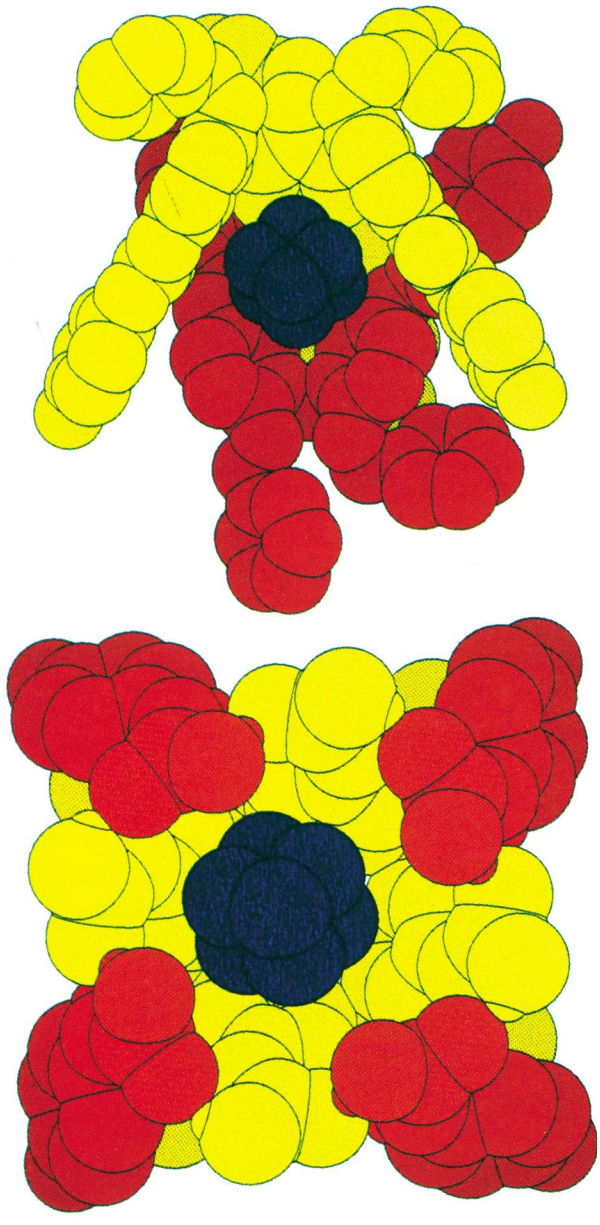


Figure 19 Cut-away views of CPK representations of the calixarene dimer with encapsulated cubane

In conclusion, the behaviour and functions of molecular assemblies can, to some extent, be controlled – either by solvation effects or by nucleation by guests. The energetics for such complexes invariably pit intermolecular forces against the decreased freedom of the included guest. These forces are the van der Waals' interactions and hydrogen bonds between the exterior surface of the guest and the interior surface of the host. In addition, special entropic effects can emerge when more than one solvent molecule is present in the capsules. Guests, or better, hostages, which more closely fit the host's cavity in size and shape and leave no empty space are favoured.[30] The acceleration of a Diels–Alder reaction augurs well for the long-term goal of using these capsules as reaction chambers. In the meantime, we continue to explore the behaviour of 'molecules within molecules.'[31]

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