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Review Article

Molecular Recognition and Assembly*

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The synthesis and characterization of a series of self-assembling capsules is described. Assembly takes place as a result of the self-complementary hydrogen bonding patterns on the subunit pieces and dimerization occurs in such a manner that the concave surfaces of the two subunits are directed at one another. This feature gives rise to close-shelled capsules which are shown to encapsulate smaller guest species. Selectivity is shown for guests ranging in size from methane to adamantane derivatives. Shape selectivity is shown in special capsules capable of recognizing disc-like molecules such as benzene and cyclohexane. Disproportionation reactions are shown to exist between capsules of slightly different sizes, and these are shown to be controlled by the nature of the guest species. The use of these capsules as reaction chambers is proposed.

The new science of complexity warns us about what can happen when more than one copy of an entity is present. New things emerge. It also teaches that studying the single entity is no more likely to predict what emerges than studying a single wasp can predict the structure of a wasp's nest. The only sure method to find out is to experiment. What then does complexity say about behavior at the molecular level? Can studying a chemical structure predict smectic phases? Crystal lattices? Melting points? Molecular assemblies may provide answers, and we give here an account of our recent experiments with minimalistic models for complexity.

For inspiration chemists need look no farther away than the sister science of molecular biology: allosteric enzymes, channel-forming peptides and viral coat proteins are all cases where multiple copies of a molecule give rise to superstructures with functions that are unique to their assembled states. The weak intermolecular forces – hydrogen bonds, salt bridges and hydrophobic effects – that hold them together endow their multimeric forms with dynamic, temporary and self-correcting qualities, loaded with information and promise. But even a simple two-dimensional system can illustrate the uncertainties involved in predicting the emergent assembly. Take the structure of the purine nucleus of guanine (Fig. 1). The hydrogen bond donors on the Watson–Crick edge of the purine are complementary to the hydrogen bond acceptors on its Hoogsteen edge, so predicting some assembly is easy. What is less obvious – at least in most renditions – is that the orientation in space of the atoms capable of base-pairing at the two edges of the purine is fixed at almost exactly 90°. The information in this pattern is there for all to see. What happens when the experiment is run? Potassium ions gather the oxygen atoms in a convergent manner, that is, provide a focus for the oxygens, and force guanine monophosphates into a cyclic, planar tetramer **1** in solution.[1] The assembly – a G quartet – is similiar to the assemblies found at the telomeric ends of nucleic acids. This nucleating event – the chelation of a potassium ion by the oxygen atoms – *leaves no choice but to assemble as a tetramer*! The latent information for the assembly is written into the hydrogen bond patterns of the edges of the purine and their angular orientations with respect to each other.

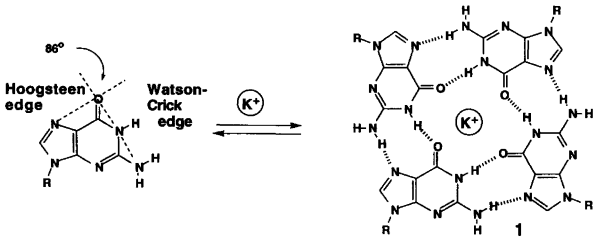

Fig. 1.

* Contribution presented at the Nobel Symposium on *Catalytic Asymmetric Synthesis*, September 3–7, 1995 at Tammsvik, Bro, Sweden.

Such two-dimensional hydrogen bond arrays are plentiful in supramolecular chemistry. Spectacular, practically infinite sheets, tapes and ribbons, as well as ingenious rosettes, tubules and other designed assemblies have been generated in many laboratories.[2] For the most part, the systems have been two-dimensional in nature, using hydrogen bonding patterns of rigid, flat, heterocyclic compounds as the information source for the assembly.

Minimalist assembly

Our intent has been to use principles of molecular recognition and the moderately directional and predictable characteristics of hydrogen bonds to assemble three-dimensional structures. The first of these stemmed from a collaborative effort with J. de Mendoza who designed structure **2** below (Fig. 2). In it the bisimide function provides hydrogen bond donors on the oxygens at the center of the molecule that are properly spaced to find their complements of hydrogen bond acceptors on the nitrogens of the glycoluril heterocycles at the ends of the molecule. Two of these were expected to come together in a manner where the ends of one bind to the middle of the other. This arrangement could be possible only if the stereochemistry of the centers are all *cis*, as shown.

In particular the *cis* fusion of the two five-membered rings of the glycoluril forces a fold in the end of the molecule. Another bend in the skeleton caused by the arrangement of rings in the middle of the structure and at the carbon attaching the middle to the indane spacers provides additional curvature along the length of the molecule. The upshot of these features is the dimer shown in Fig. 2 above, which was intended to resemble – notionally if not structurally – a 'softball'. The stereochemical features would impart the necessary curvature for the dimeric assembly while the hydrogen bonds would provide the stitching along the seam. The experimental work was begun in our labs by R. Wyler, who *in* the middle of the thing, suggested that the *entire* middle of the thing could be discarded. That is, the roles of the imide oxygens could be assumed by the oxygens of the glycoluril if an appropriate spacer (specifically, durene) was used in the center. This would reduce the dimensions of the dimer to that, say, of a baseball (similar in size to a tennis ball). Modeling further suggested that the new O–O distance in such a monomer would nicely complement the fixed H–H distance of the ends of the structure.

Wyler synthesized the molecule in two steps. The condensation of urea with benzil gave the notoriously insoluble diphenylglycoluril, which was alkylated with the commercially available tetrabromodurene in hot DMSO using potassium hydroxide as a base. After work-up, a modest (15–30%) yield of a single soluble compound, **3a** (Fig. 3) remained that had the appropriate stereochemistry.[3] It had low solubility in chloroform, but the NH signals in the NMR spectrum recorded in this solvent showed that extensive, ordered hydrogen bonding was involved (the signals appeared at 9.4 ppm!). Good crystals were obtained, and a partial structure was obtained by B. Davis and C. Knobler. It is shown as **3–3** in Fig. 3, and has been refined to $R=0.07$. NMR spectroscopy could also be used to study the encapsulation of smaller molecules by this 'baseball' in solution. For instance, the ^{1}H NMR spectrum of **3a** in $CDCl_3$ saturated with methane displays a strong singlet at -1.51 ppm.[4]

We also expended some effort in studying the dimerization phenomenon itself and our ability to control it. For example, the *p*-dimethylaminodiphenylglycoluril derivative **3b** and the baseball derived from it showed good solublility in DMF-d_7. In this solvent it exists entirely as a monomeric species as judged from the NMR spectra. However, nucleation can be induced by a number of small molecule guests: for example, when methane or ethylene is bubbled into the solution, new signals emerge that represent the dimer encapsulating the small guest molecule. Somewhat surprisingly, xenon turned out to be the most effective guest at nucleation.[5] Because of its size or polarizability, it seems to prefer the inside of the capsule and drives the dimerization nearly to completion. That encapsulation of the xenon occurs can be directly observed in the ^{129}Xe NMR spectrum. It shows the characteristic new signal shifted upfield as would be expected for a nucleus sandwiched between the two aromatic spacers of the capsule.

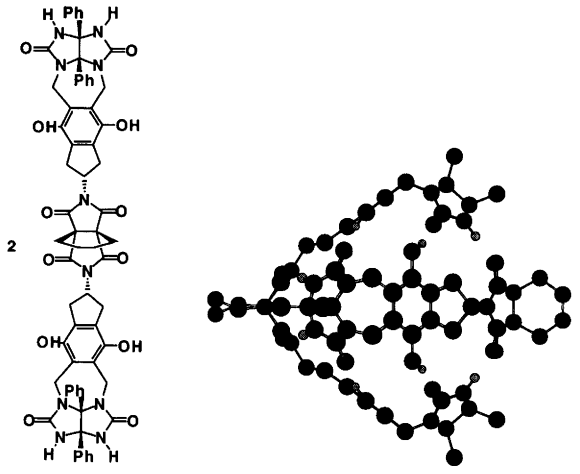

Fig. 2.

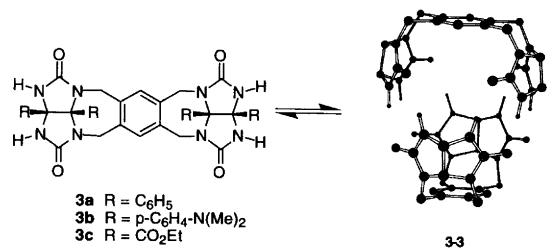

Fig. 3.

The basic sites on the *p*-dimethylamino groups provide an opportunity to use 'pH' to control the assembly. Specifically, it was our intent to protonate these sites (of which there are eight in the capsule) to such an extent that the positive charge that builds up on the periphery would force the two halves of the capsule apart. This is shown schematically in Fig. 4.

The experiment proved successful. A DMF solution under xenon was treated with incremental amounts of *p*-toluenesulfonic acid. When a large excess (90 equiv.) was added, the spectrum of the protonated monomer was obtained. Subsequently, neutralization of the positive charge was used to drive the formation of the capsule around its guests in the reverse direction. On addition of solid bicarbonate to the solution, the process was reversed and the spectrum of the encapsulated xenon returned. Control of the assembly can be exerted by the external influence of acidity. There are many examples of biological assemblies that are fine-tuned to subtle changes in pH, viral capsids being the most notorious, but many factors might be used to control assembly. For example, nucleation might be coaxed by high, external pressures of a guest species. 'Salting in' effects could also be used and even such mundane influences as temperature or irradiation can be considered as potential sources of control. In the meantime, we are exploring the synthesis of self-complementary structures in which the recognition surfaces diverge. These should permit the assembly of linear (one-dimensional) polymers as suggested in Fig. 5 below.

Larger volumes

Meanwhile, R. Meissner had taken over the softball project with the help of J. Kang. I will not dwell here on the details of the synthesis, but those who are knowledgeable in these arts will recognize that the center was made from a Diels–Alder adduct of tetracyanoethylene, whereas the ends required numerous synthetic steps before the glycoluril could be fused to an appropriate indane. The synthesis concluded with a double Mitsunobu reaction, then deprotection (Fig. 6).

The spectroscopic characteristics of the product molecule **2** showed,however, that something had gone wrong. Specifically, the NMR spectrum revealed that there was a *dissymmetric* element in the structure. We concluded that these features could be accommodated by the collapse of the molecule in an intramolecular manner. Our proposed structure is shown below (Fig. 7) in which it is seen that the intramolecular hydrogen bonds between the ends of the structure are permitted by the bends along its length. Specifically, the sharp angles provided by the bisimide in the center and the angles where the exocyclic bond meets the five-membered ring of the indane permit the molecule to scrunch down on itself in a smug, self-sufficient manner.

This taught us the usual lesson in modeling and collaboration: who gets the credit, and who takes the blame? R. Meissner moved quickly to repair the defects of the molecule in a new design shown as **4** in Fig. 8, a design that was also independently suggested by J. de Mendoza. The design involves a tape-like structure of 13 fused and one bridged ring systems, of which only two are benzenes; the other ring fusions provide the necessary, gentler curvature required for the assembly. When viewed on edge, as shown in the figure, the somewhat exaggerated curvature of the structure can be seen. Compared with the original softball the angle in the center has been increased and the offending flexibility, imparted by the

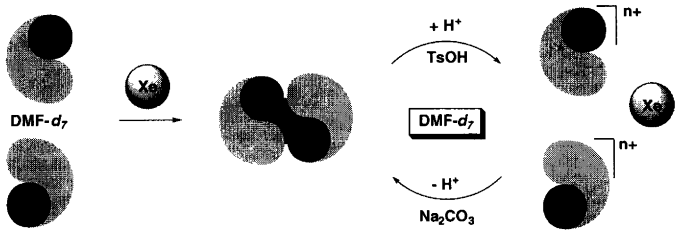

Fig. 4.

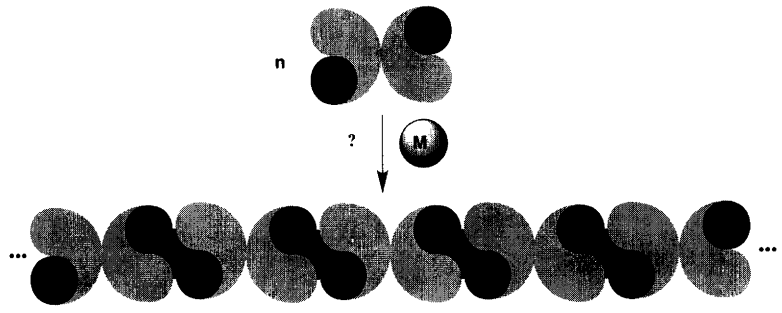

Fig. 5.

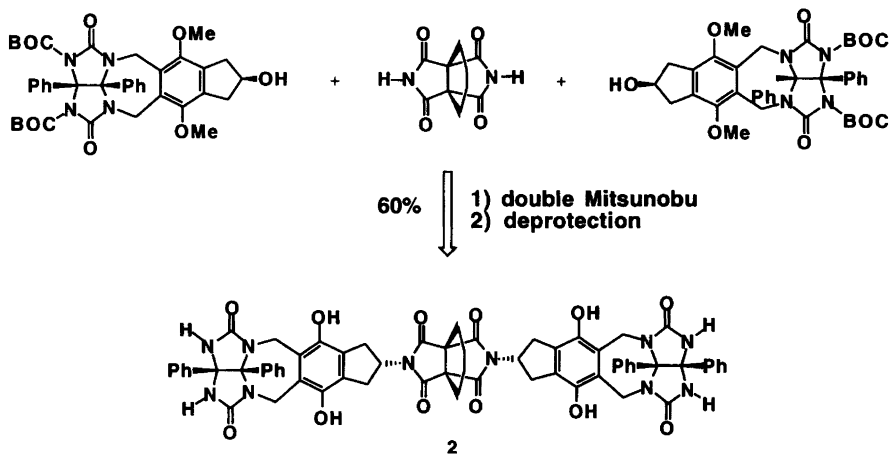

Fig. 6.

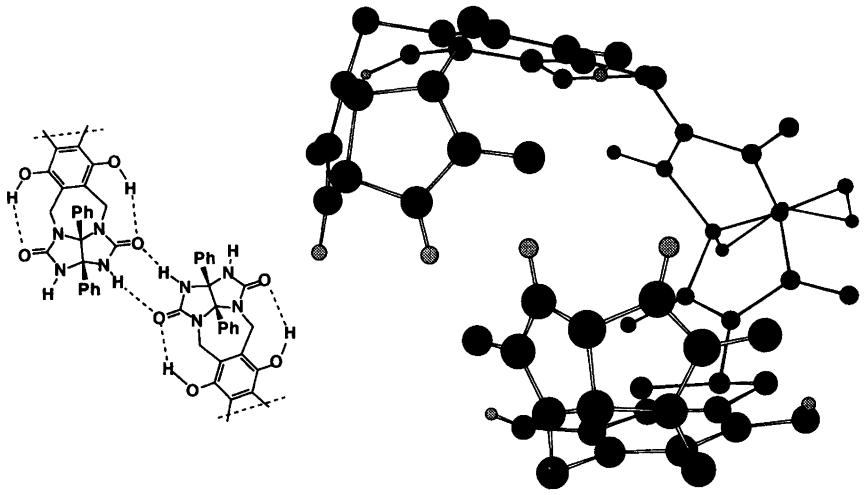

Fig. 7.

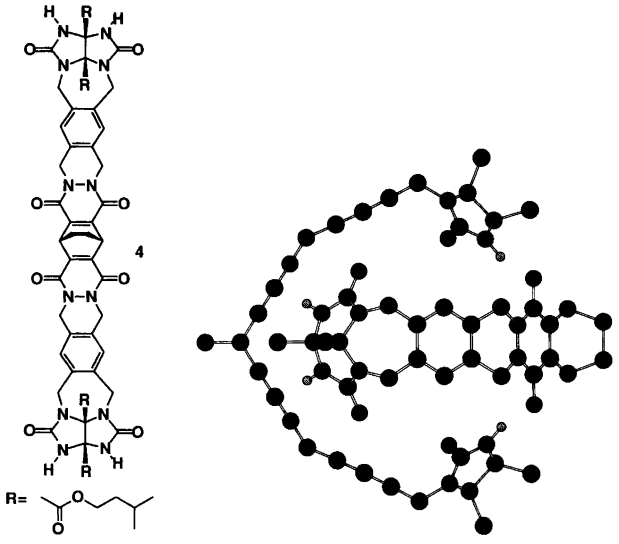

Fig. 8.

rotations around single bonds in the earlier design, has been removed.

Meissner assembled the structure rapidly in the method shown schematically in Fig. 9. The fully deprotected molecule did show the expected NMR spectroscopic earmarks of a dimer in aromatic solvents.[6] Sharp signals and downfield N–H resonances were observed for the molecule, and we have been able to drive guests of suitable size and shape into this modified softball. Adamantane is a particularly welcome guest – a diamond in rough company! Even tetramethyladamantane fits inside. The numerous polar and polarizable atoms that line the inner surface of the softball have also been recruited to stabilize complementary functional groups on guests. Specifically, adamantanamine and adamantanedicarboxylic acid are each bound strongly within the capsule.

But, as I warned, interesting things emerge from multiple copies. In chloroform the molecule dissolves with difficulty, and produces after a few minutes such a gel-like phase that the NMR tube can be turned upside

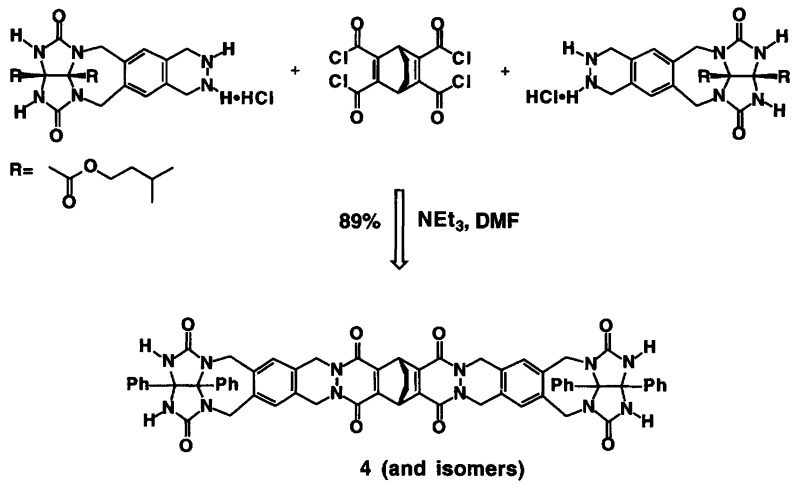

Fig. 9.

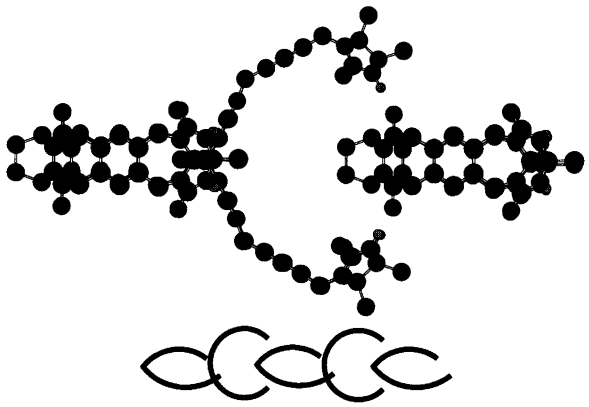

Fig. 10.

down without loss of its contents! Apparently, a *polymeric* assembly takes place which shows incomprehensibly broad NMR signals. Our present view of the general features of this assembly is given below (Fig. 10). Hydrogen bonding does take place between the ends of one molecule and the middle of another, but it does so in a chain-like manner. The molecule expresses its self-complementarity in an unexpected arrangement, but one like that of Fig. 5 that is of interest to materials scientists. We are currently trying to unravel the mysteries of this superstructure.

The rugby ball

Can we force more than two self complementary molecules to assemble in a controlled way? Clearly, the work done elsewhere[2] demonstrates that it is possible; there are no prohibitive entropic barriers. We have not yet succeeded in our attempts to make larger capsules as assemblies of, say, four subunits, but we have tried. For example, the structure **5** is one of a family of self-complementary molecules that could fit together head to tail to generate a rugby ball shaped tetramer (Fig. 11). X. Garcias synthesized it, but it showed little evidence of assembly in solution. The structure in the crystalline state was solved by L. Toledo and revealed a tape like array.[7] Perhaps what is needed in solution is just the right guest, to initiate, nucleate or coax the subunits to wrap around it and stabilize the assembled tetramer.

Recombination and nucleation

We have also explored variations on the original baseball structure. It is clear from its two-dimensional depiction below that extending the aromatic spacer will move the two oxygens involved too apart far to bridge the hydrogens of the end of the structure unless some additional, compensating changes are made in another spatial direction. This can be accomplished by folding the structure in the center as is shown below for the bridged anthracene derivative **6**. S. Kubik, C. Valdés and U. Spitz developed an efficent synthesis of this structure, and showed that indeed it does assemble quite nicely.[8] The dimer is now egg-shaped and shows strong hydrogen bonding even though modeling shows non-linear and non-planar arrays for the hydrogen bond geometries (Fig. 12). However, the holes in structure are quite large; it is leaky. Smaller molecules can enter and depart quite rapidly, but we have indirect evidence for their presence within the capsule.

What we were unprepared for emerged when the anthracene **6** and benzene-derived molecules **3** were both in the same solution. They formed a *heterodimeric* structure!

Again, interesting things emerged. The hydrogen bonds of this structure, **3–6** depicted above (Fig. 13), lead to a pear-shaped dimer. The hydrogen bonds are quite bent and not at all in the cosmetic arrays that we expected in most of the symmetrical dimers. Moreover, modeling shows that not all eight hydrogen bonds can be good. In fact, four hydrogen bonds can be most excellent, but the other four are only mediocre. This is reflected in the

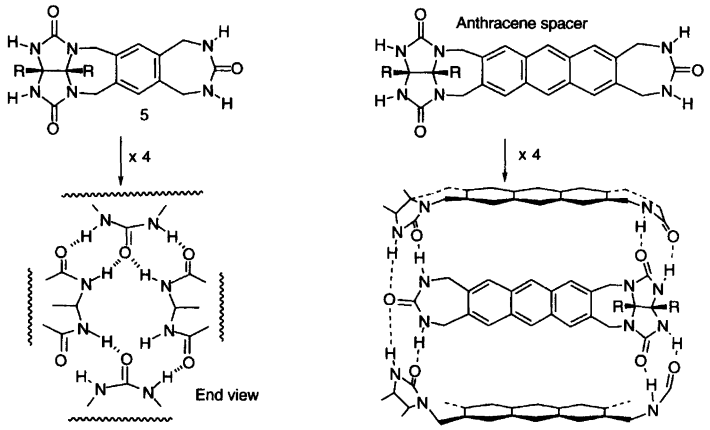

Fig. 11.

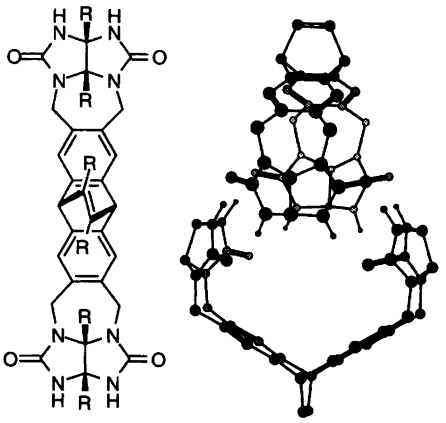

Fig. 12.

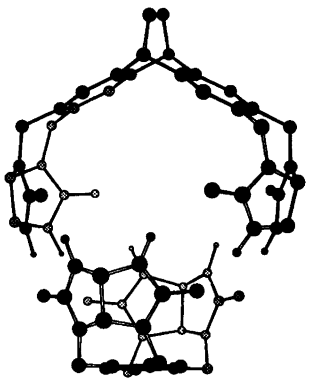

Fig. 13.

NMR spectrum with two different chemical shifts for the NH signals, separated by more than 2 ppm.

We were puzzled by the presence of this heterodimer, and have studied the motivations for its formation. We can control its appearance in competition with its homodimeric forms by providing solvent guests of appropriate molecular size. Perhaps, mere entropy of mixing or the reduction of symmetry causes the heterodimer to form in the first place. For example in chloroform the equilibrium constant is 12 in favor of the heterodimer. Now, chloroform is a very poor guest for the baseball but, apparently of a reasonable size for inclusion in the heterodimer. However, when a few percent of dichloromethane are added to the chloroform solution, the equilibrium distribution of species shifts to the homodimers. Dichloromethane is quite a good guest for the baseball, and most small solvents appear to be capable of leaking in and out of the large, egg-shaped structure. The distribution of species can be shifted dramatically in the other direction by using solvents with slightly larger molecules (Table 1). Molecules of the size that favor residence in the heterodimer – e.g., bromoform – drive the equilibrium constant to 40 in that direction. The largest solvent, $CHCl_2CHCl_2$, which can fit only in the largest cavity, shifts the equilibrium in the other direction to the homodimers.[8,9]

What about other sizes? For example, compare the ethylene spacer in **7** with the benzene spacer in **3** (Fig. 14). The small difference in O–O distances, (~0.6 Å) could be compensated by a flattening of the two rings connecting the ethylene spacer and glycolurils. The shortening of the spacer was contemplated by C. Valdes who then prepared the 'hackeysack' version.

The cavity of **7–7** is smaller than that of **3–3** and too small to accommodate CD_2Cl_2. Even so, dimer **7–7** can bind small molecules, such as methane. U. Spitz was able to show that unlike **3–3**, the smaller **7–7** was able to exclude ethane from its cavity.[10] The affinity of methane for **7–7** is considerably less than for **1–1**. A binding constant $K^{273}=4.2\ M^{-1}$ was measured for **7–7**, a value that is about 70 times lower than that found for the diphenylglycoluril analog of **3–3**.[3a] We estimate that

Table 1. Equilibrium distributions in the dimerization of **3** and **6** with different guest species.

Solvent	Guest	Favored species **3-3**+**6-6**=2 **3-6**
$CDCl_3$	CD_2Cl_2	←
$CDBr_3$	CD_2Cl_2	←
$CDCl_2CDCl_2$	$CDCl_3$, $CDBr_3$	→

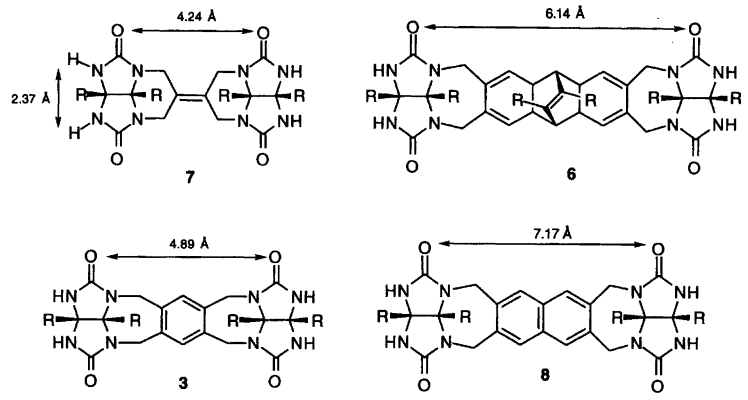

Fig. 14.

the cavity formed by **7–7** is approximately 20% smaller that the one of **3–3** (50 Å^3). L. Toledo has grown crystals of **7–7** and has refined the X-ray data to $R=0.10$.

The obstacles to self-assembly of naphthalene derivative **8** appear less surmountable.[9] The increase in O–O distances is >2 Å, and, if all eight possible hydrogen bonds were to be formed with reasonable geometries in **8–8**, the π-surface of the naphthalene would have to fold (or at least bend) at a considerable energetic cost. Little driving force for dimerization could be expected.

Accordingly, in the NMR spectra of **8–8** the chemical shift of the NH protons strongly correlates with the size of the solvent used to record the spectrum. The signal moves downfield with decreasing size of the solvent molecules. It appears that CD_2Cl_2 nucleates the formation of the dimeric **8–8** structure, although we are unable to provide any more direct evidence. Molecular models and IR spectra suggest that because the shape complementarity of the hydrogen binding sites in dimer **3–3** is poor, it can be stabilized by only four simultaneous hydrogen bonds. It is likely that the dimerization–dissociation processes involved in this case are fast since a dimer with only four hydrogen bonds should be labile. At any rate we were unable to find two separate sets of NMR signals corresponding to 'full' and 'empty' **8–8**.

Flattened spheres

The other compensating geometric changes that can be made on extension of the baseball's dimensions are in-plane bends. For example, the triphenylene spacer allows the O–O distances to be quite nicely complementary to those of the H–H distances of a second copy. We have found no sports analogy for such a dimer which features D_{3d} symmetry, but it resembles, in shape and size comparisons, a jelly doughnut. This structure **9** was designed by N. Branda, and was recently synthesized by R. Grotzfeld (Fig. 15). The synthesis involves the formal trimerization of the dimethylbenzyne as shown to give a hexamethyltriphenylene. This was brominated and then used to alkylate soluble versions of the glycoluril (normally long-chain esters). The desired product was obtained in low (single digit) yield.[11]

The dimeric species **9–9** is soluble in organic solvents, and a depth-shaded view of it is shown below. The model involving cyclohexane nested inside reinforces the notional and functional aspects of the jelly doughnut description. Indeed, we have used ^{13}C NMR spectroscopy to show that benzene is encapsulated in the assembly in chloroform. Usually, the guest must be present in a large excess (practically as cosolvent) in order for the second species to be observable, since it often must compete with the primary solvent for the interior. If anything, these capsules are like trashcans, they ingest any nearby molecular debris – solvents, atmospheric gases – anything to avoid a void inside. This can be used to advantage; if the primary solvent is larger than the cavity can accommodate, suitable guests are pulled in. This was introduced for binding in carcerands and other synthetic receptors,[12] and we were able to observe the encapsulation of cyclohexane in *p*-xylene using this tactic. Unlike our other capsules, which take up and release guests at a rate that is slow on the NMR timescale but fast on the human timescale, **9–9** takes hours to equilibrate. This was observed with cyclohexane, a guest that probably requires a large fraction of the host's hydrogen bonds to break before passage into and out of the cavity is permitted. Strong hydrogen bonds are a recently observed feature in new self-assembling systems related to carciplexes.[13] The beautiful fit of cyclohexane is modeled in Fig. 16. It may be possible to use this capsule as a reaction chamber for, say, a Diels–Alder reaction of ethylene and butadiene.

Assembly with a macrocycle

The inviting concave shape of calixarenes and their synthetic – even commercial – availability have made them attractive scaffolds for molecular recognition. In fact, recent reviews of calixarene chemistry are dedicated almost entirely toward applications in supramolecular chemistry.[14] Of particular relevance to the issues at hand are the calix[4]arenes devised by Shinkai,[15] which were similarly designed to assemble by hydrogen-bonding.

In contrast to these systems, K. Shimizu designed the self-complementary calixarene **10** to form a completely

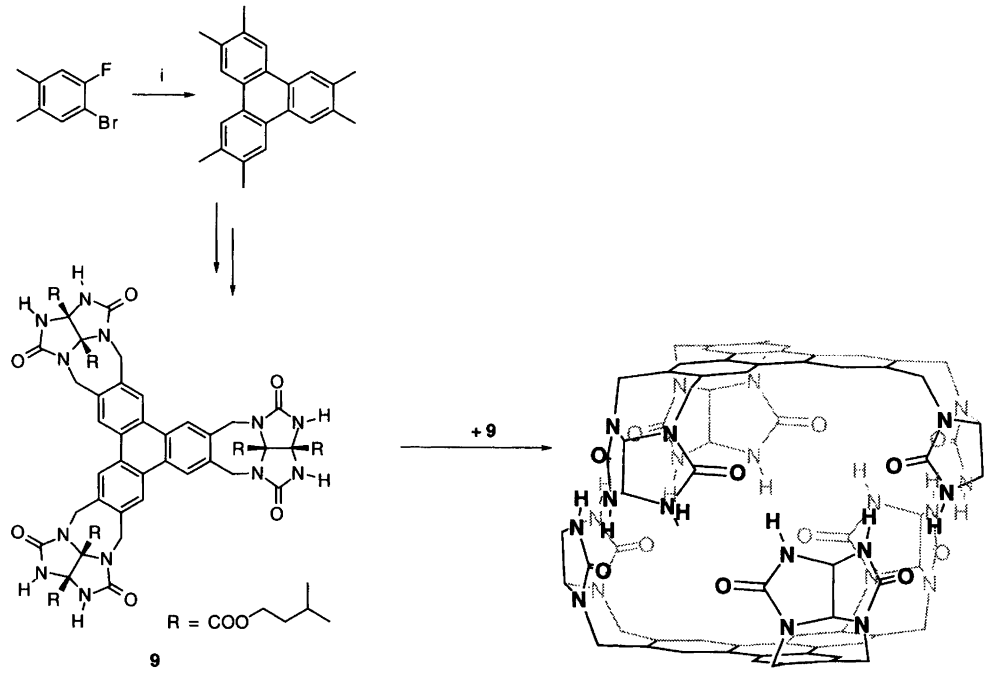

Fig. 15.

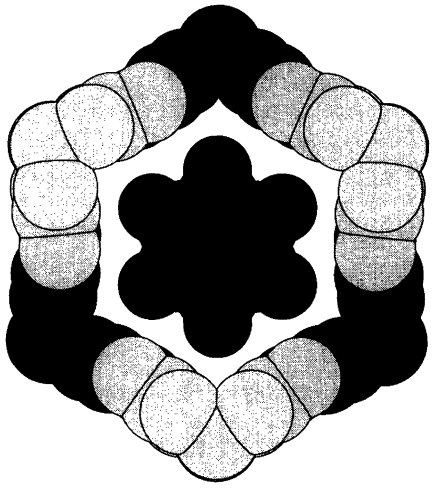

Fig. 16.

closed cavity by dimerization. The overall architecture of the assembly is that of two hemispheres 'zippered' together along the equator by hydrogen-bonded ureas (Fig. 17). Each hemisphere is a calix[4]arene locked in a cone-shape[16,17] and functionalized with phenylureas on the upper rim. 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 the most common geometry.[18] For the dimerization at hand, the ureas can be hydrogen-bonded in this fashion with the carbonyl oxygens buried into the NHs of the preceding urea. All eight ureas may be fixed in the same direction forming up to 16 hydrogen bonds. The hydrogen-bonding slows rotation about the calixarene–urea bond resulting in an isomer with an S_8 axis.

The synthesis was accomplished in short order (Fig. 18) and the interleaved geometry of the assembly effectively prevented visiting guests from leaving or entering quickly. NMR experiments in the presence of likely guest species showed the expected features: downfield-shifted urea hydrogens, *meta* coupling of the calixarene protons, diastereotopic benzyl hydrogens, and slow exchange between complexes.[19]

In conclusion, the behavior and functions of molecular assemblies can, to some extent, be controlled – either by solvation effects or nucleation by guests. The energetics for such complexes invariably pit favorable binding forces (enthalpy) against the decreased freedom of the included guest (entropy). For the cases at hand, the favorable forces are the van der Waals' interactions and hydrogen bonds between the contact areas – the exterior surface of the guest and the interior surface of the host. Accordingly, guests which more closely fit the host's cavity in size and shape and leave no abhorrant vacuous spaces are favored.[20] These time-honored considerations of host–guest complementarity and the sizable cavities of the dimeric structures described here suggest catalysis of reactions having transition states of the appropriate size, shape and functionality, a long-term goal of our efforts. In the meantime, we will continue to explore the unexpected things that emerge from molecular assemblies.

Acknowledgements. I am indebted to the members of my research group for their inspired designs and superbly executed experiments. Their names appear on the

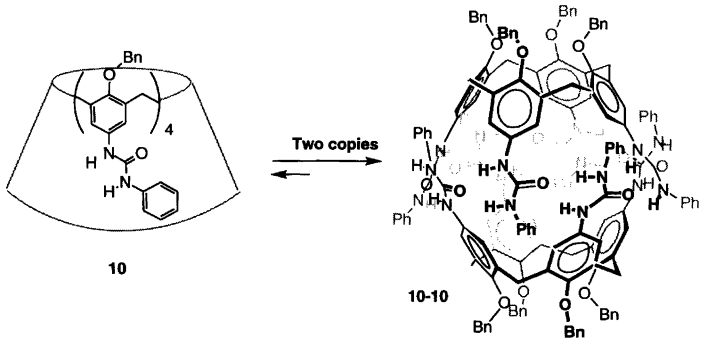

Fig. 17.

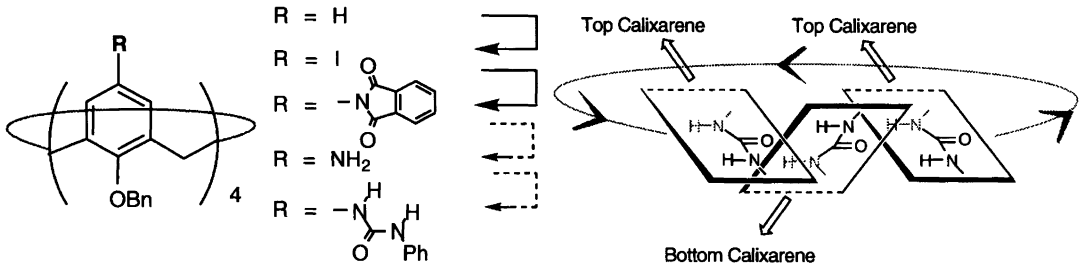

Fig. 18.

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