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Molecular assembly and encapsulation

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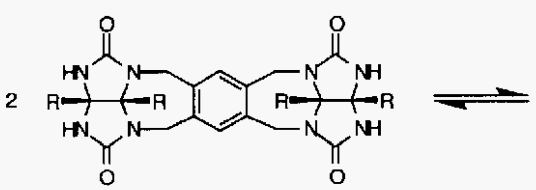
Abstract

Assemblies can emerge whenever more than one copy of a molecule is present and it is frequently difficult to predict what will emerge without experimentation. Multiple copies of complementary molecules can give rise to superstructures with functions that are unique to the assembled states. The weak intermolecular forces that hold assemblies together endow them with dynamic, temporary and even self-correcting qualities.[1] We give here an account of our recent experiments with minimalistic models for molecular assemblies.

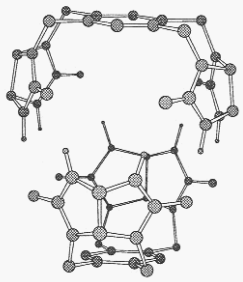
BASEBALLS

Since two-dimensional hydrogen bond arrays are plentiful in supramolecular chemistry, and even more elaborate assemblies have been characterized,[2] our intent was to use the principles of molecular recognition and the moderately directional characteristics of hydrogen bonds to assemble three-dimensional structures that may be said to have a function. These were intended to form closed shells that could encapsulate smaller molecules. The first of these are reported elsewhere[3] and involved a collaboration with Javier de Mendoza in Madrid.

Fig.1



1a R = C_6H_5
1b R = p-C_6H_4-N(Me)$_2$
1c R = CO_2Et



1-1

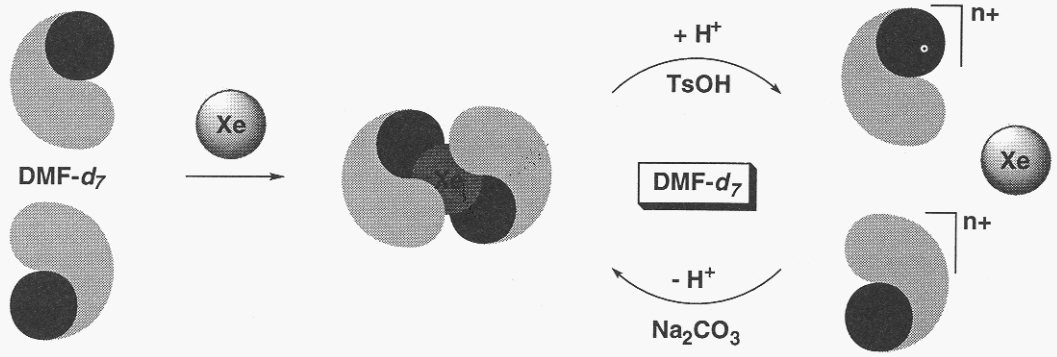
The experimental work was begun by Dr. René Wyler, who designed and synthesized the molecule **1a** in two steps.[4] It had low solubility in chloroform, but the NH signals in the NMR spectrum recorded in this solvent showed extensive, ordered hydrogen bonding (the signals appeared at 9.4 ppm!). Crystals were grown, and a partial structure was obtained by Bill Davis at M.I.T. and Carolyn Knobler at UCLA. The structure, which shows considerable disorder, has been refined to R = 0.17. The dimer **1-1** is shown without the phenyl groups in Fig. 1.

Beyond the fact of assembly, the molecule showed function. Neil Branda used NMR to study the encapsulation of smaller molecules by the baseball in solution. Slow exchange of guests into and out of the capsule was observed. For instance, the ^{1}H-NMR spectrum of **1a** in $CDCl_3$ saturated with methane displays a strong singlet at -1.51 ppm in addition to the signal for free methane at 0.22 ppm.[5]

Neil Branda and Robert Grotzfeld also studied means by which the assembly might be controlled. For example, the baseball derived from the p-dimethylamino diphenyl glycoluril **1b** in DMF-*d7* exists entirely as a monomeric species as judged by the NMR spectra. However, dimerization can be induced by a number of small molecule guests: for example, when methane ethylene or xenon is bubbled into the solution, new signals emerge that represent the dimer encapsulating the small guest molecule.[5] That encapsulation of the xenon occurs was directly observed in the ^{129}Xe spectrum. This was possible through a synthetic procedure of Dr. Carlos Valdes who made the more soluble **1c**.

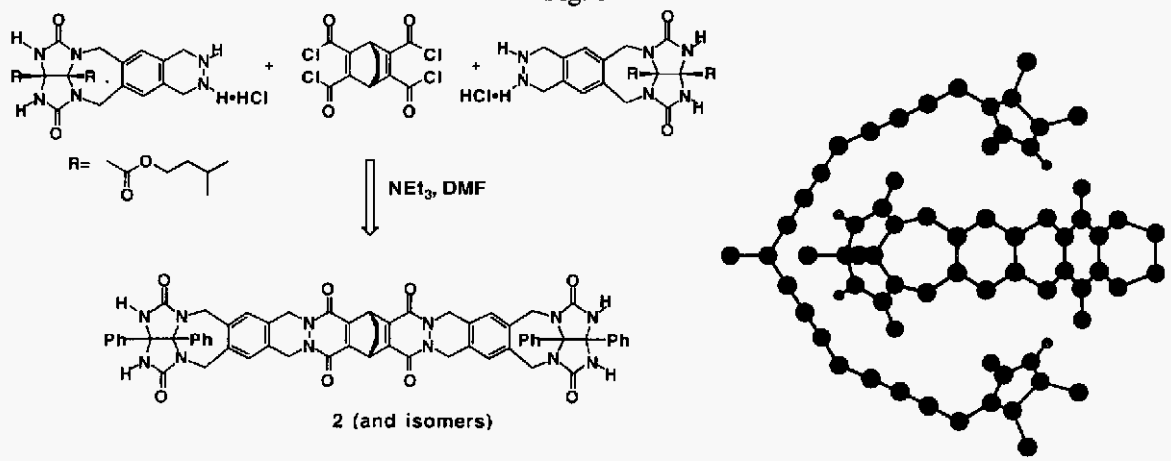
The basic sites on the p-dimethyl amino groups provided an opportunity to use "pH" to control the assembly. A DMF solution under xenon was treated with incremental amounts of p-toluene sulfonic acid. When a large excess (90 equivalents) was added, the spectrum of the protonated monomer was obtained. This is shown schematically in Fig. 2

Fig. 2



Dr. Rob Meissner and Jongmin Kang initiated work on a larger "softball" design shown as **2** in Fig.3 (this structure is similar to one independently suggested by Javier de Mendoza). The design involves a tape-like structure of 13 fused rings of which only two are benzenes; the other ring fusions provide the necessary, gentle curvature required for the assembly.

Fig. 3



Meissner synthesized the structure rapidly, and the fully deprotected molecule did show the NMR spectroscopic features expected 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 complement functional groups on guests. Specifically, adamantamine and adamantane dicarboxylic acid each bind strongly within this capsule.

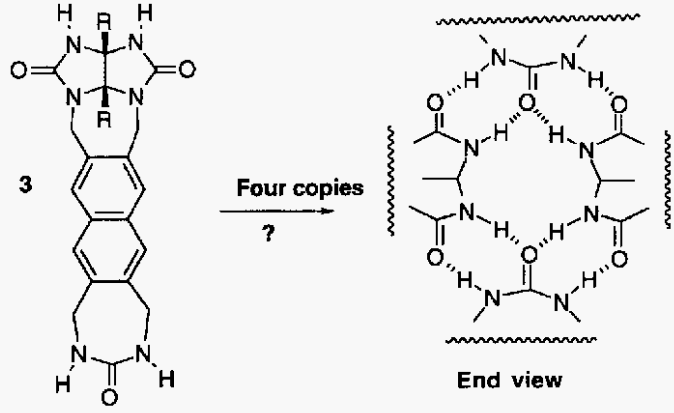
However, in chloroform the molecule dissolves with difficulty, and produces after a few minutes such a gel-like phase that the NMR tube can be turned upside down without loss of its contents. Apparently, a *polymeric* assembly takes place which shows incomprehensibly broad NMR signals. Hydrogen bonding 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 arrangment, but one that might be of interest to materials scientists. We are currently trying to unravel the mysteries of this superstructure.

THE FOOTBALL

Can we force more than two self- complementary molecules to assemble in a controlled way? Clearly, the work accomplished elsewhere[2] demonstrates that it is possible; there are no prohibitive entropic barriers. But we have not yet succeeded in our attempts to make larger capsules as assemblies of, say, 4 subunits, but we have tried. For example, the structure **3** is one of a family of self-complementary molecules that could fit together head-to-tail to generate an (American style) football-shaped tetramer (Fig. 4) . Dr. Javier Garcias

synthesized it, but it showed little evidence of assembly in solution. The structure in the crystalline state was solved by Dr. Leticia Toledo and revealed a crinkled, tape-like array, rather than a closed shell superstructure. 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.

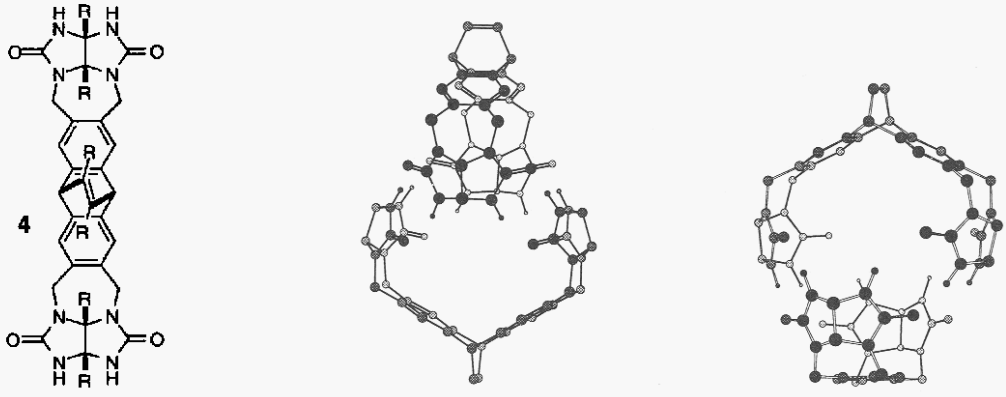
Fig. 4



RECOMBINATION AND NUCLEATION

We have also explored variations on the original baseball structure. Drs. Stefan Kubik, Carlos Valdés and Urs Spitz developed an efficent synthesis of the bridged anthracene derivative **4**, and showed that indeed it does assemble quite nicely.[7] The dimer is now egg-shaped and shows strong hydrogen bonding even though modeling shows nonlinear and nonplanar arrays for the hydrogen bond geometries (Fig. 5). The holes in structure are quite large; it leaks. Smaller molecules can enter and depart quite rapidly, but we have indirect evidence for their presence within the capsule.

Fig. 5



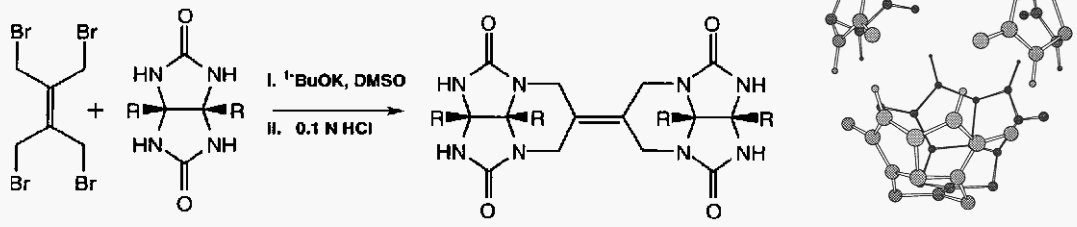
What we were unprepared for emerged when the anthracene **4** and benzene derived molecules **1** were both in the same solution. They formed a *heterodimeric structure!*
The hydrogen bonding patterns of this structure, **1-4** depicted above (Fig. 5), lead to a pear-shaped dimer, to continue our size, if not sport analogies. Modeling shows that not all eight hydrogen bonds can be strong: four hydrogen bonds can be short, but the other four are long. This is reflected in the NMR spectrum, which shows 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.[8] 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. In chloroform the equilibrium constant is 12 in favor of the heterodimer, but the distribution of species can be shifted dramatically in the other direction by using slightly larger solvents. 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 only feel

comfortable in the largest cavity, shifts the equilibrium back to the homodimers.[8] These notions are fragile; they have been deduced from the current experimental observations and are subject to reinterpretations in the future.

In the meantime, what about other sizes? For example, compare the ethylene spacer in **5** (Fig. 6) with the benzene spacer in **1**. The small difference in O-O distances,(~0.6A) could be compensated by a flattening of the two rings connecting the ethylene spacer and glycolurils. The shortening of the spacer was contemplated by Dr. Carlos Valdes who then prepared this "hackeysack" version **5-5**.

Fig. 6

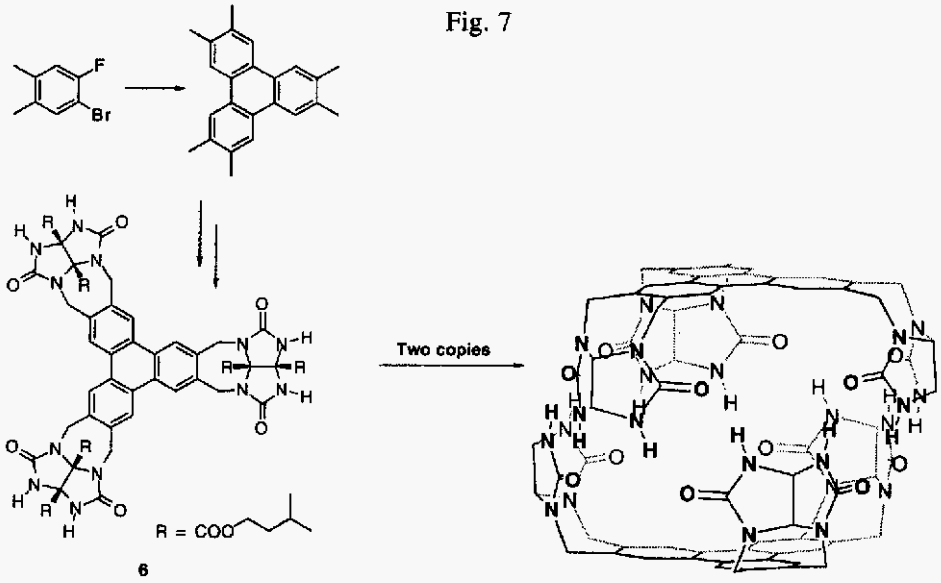


The cavity of the hackeysack **5-5** is smaller than that of **1-1**, too small to accommodate CD_2Cl_2. Even so, dimer **5-5** can bind small molecules, such as methane. Drs Urs Spitz and Leticia Toledo were able to show that the smaller **5-5** could exclude ethane from its cavity, but at a price: the affinity of methane for the hackeysack is about 70 times lower than that found for the phenylglycoluril analog of **1-1**.[9] We estimate that the cavity formed is approximately 20% smaller that the one of **1-1** (50 $Å^3$). Dr. Leticia Toledo has grown crystals of the hackeysack and has refined the x-ray data to $R_W = 0.071$ and $R = 0.098$ (Fig. 6).

LARGER CAVITIES

One other compensating geometric change 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. This structure **6** was designed by Dr. Neil Branda, and resembles a jelly doughnut (to continue our food analogies). It was recently synthesized by Robert Grotzfeld (Fig. 7). The synthesis involves the formal trimerization of the dimethyl benzyne as shown to give a hexamethyltriphenylene. This compound was brominated, then used to alkylate soluble versions of the glycoluril (usually branched-chain alkyl esters). The desired product was obtained in low (single digit) yield.[10]

Fig. 7



6

The dimeric species **6-6** is organic soluble, and a depth-shaded view of it is shown above. The model involving benzene nested inside is quite provocative. Indeed, we have used ^{13}C NMR spectroscopy to show that benzene is encapsulated in the assembly in chloroform. If the primary solvent is larger than the cavity can comfortably accommodate, suitable guests are pulled in. This tactic was introduced for binding in carcerands[11] and other synthetic receptors,[12] and we were able to observe the encapsulation of cyclohexane in p-xylene..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, **6-6** takes hours to equilibrate. This was observed with

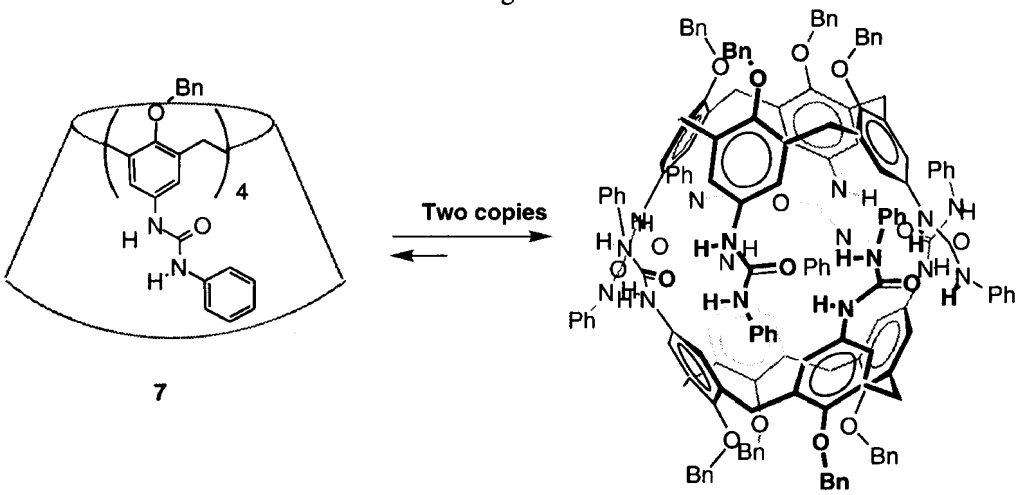
cyclohexane, a guest that probably requires a large fraction of the host's hydrogen bonds to break before passage into and out of the cavity is permitted. Slow exchange is one of the characteristic features of binding by covalent assemblies[13] The beautiful fit of cyclohexane suggests the use of this 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 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 are the calix[4]arenes devised by Shinkai[15], which were similarly designed to assemble by hydrogen-bonding.

In contrast to these systems, Ken Shimizu designed the self-complementary calixarene **7** to form a completely 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. 8). Each hemisphere is a calix[4]arene locked in a cone-shape[16, 17] and functionalized with phenyl ureas 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 -NH's of the preceding urea. All eight ureas may be fixed in same direction forming up to 16 hydrogen-bonds.

Fig. 8



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NMR experiments in the presence of likely guest species show the expected features: downfield-shifted urea hydrogens, *meta* coupling of the calixarene protons, diastereotopic benzyl hydrogens, and slow exchange between complexes. The hydrogen-bonding slows rotation about the calixarene-urea bond resulting in an isomer of S8 symmetry. The interleaved geometry of the assembly seals off holes and prevents visiting guests from leaving or entering quickly.

In conclusion, we are learning that the behavior and functions of molecular assemblies can, to some extent, be controlled. Perhaps assembly is too sophisticated a term for the simple dimerizations presented in this account, but a phenomenological pattern is emerging for the behavior of these systems. Solvation effects and nucleation by guests-a process for which "autoencapsulation" may be an appropriate description-appear to be strong determinants. In the future we will be evaluating the catalytic potential of the interiors presented by these capsules. For the moment we are satisfied by the new light they shed on the dynamics of intermolecular forces.

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