Acc. Chem. Res. **1999,** *32,* 278−286

Reversible Encapsulation and Its Consequences in Solution

JULIUS REBEK, JR.

Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received October 7, 1997

Much has been written about the biological inspiration for molecular assemblies, the many macromolecular systems held together by weak intermolecular forces. In this Account we shall emphasize chemistry—inventing new molecules rather than uncovering the behaviors of naturally occurring ones. Our initial ideas came from sports equipment, and we will borrow terms from the sports world because the language of chemistry is limited: no words exist that adequately describe some of these stuctures and phenomena, and why should there be? The molecular structures speak for themselves, and do so far more eloquently than we can. Their emphasis is graphic, and as a result, the illustrations exceed the recommended limits for this journal. As a recent review[1] covers the work of our group and other groups through 1996, the emphasis here will be on what was accomplished in 1997 and on the experiments being done in the laboratory today.

The notional tennis ball became the target to answer the question, Can a pseudospherical structure be made by the reversible dimerization of two copies of the same molecule? The information necessary for assembly is written in the convex and the concave edges of the molecule and in its shape in the third dimension: its *curvature* (Figure 1). When binding forces such as hydrogen bonds are picketed along the edges in a self-complementary manner, they can hold the two units together, much as the stitches along the seam hold a baseball together. A tennis ball has the same appearance on the outside but is held together by an altogether different seam on the inside (as only cutting one open will show). Nevertheless, the stiffness of the tennis ball and its hollow interior provide apt analogies for the curvature and the cavity featured in the molecular dimer. These aspects are discussed in what follows.

Sources of molecular curvature for hollow, pseudospherical assemblies can be found loitering unrecognized in many places. Originally prepared for one purpose but then abandoned, they have been resurrected for use in wider applications. Examples include Kemp's[2] triacid, Högberg's resorcinarenes,[3] and Gutsche's calixarenes,[4] which emerged as modules of seemingly inexhaustible repertoires, numbing performances, and interminable encores in roles of what is now, but was not at the time of their "design", known as supramolecular chemistry. The word "design" appears much too frequently in current studies of molecular recognition. The more familiar experience—at least in our group—is that synthetic accessibility and luck determine what molecules come to hand. A process akin to random screening then identifies the molecule's ability to interact with others, its *function*.

For the tennis ball, the curvature came from Rene Wyler's fusion of a glycoluril with an aromatic spacer: the glycoluril was prepared from urea and benzil and then alkylated with a limited amount of tetrabromodurene with KOH in hot DMSO (Figure 1).[5] As this is also a recipe for a polymer, some considerable amount (about 75%) of insoluble material was formed, but the $CHCl_3$-soluble fraction eventually proved to be almost entirely the tennis ball dimer (a small amount of a 2:2 macrocyclic condensation product was also identified). The solubility of these hydrogen-bonded dimers has repeatedly helped us separate the desired products from the notoriously insoluble glycolurils. The same richness of hydrogen-bonding sites of the glycoluril that lead to dimerization when the molecular curvature is right results in precipitation of stonelike oligomers when the curvature is wrong. For example, the eight hydrogen bonds along the seam of the dimer shown in the figure satisfy the acidic and basic sites of the monomers as well as can be imagined, and its solubility, as the dimer, is mostly determined by the groups on its periphery.

Eventually a crystal was obtained, and with the help of Dr. Carolyn Knobler at UCLA and Leticia Toledo, the crystallography reached a level of refinement that revealed the expected dimer in the solid state,[6] but it was not until we observed encapsulated methane by NMR in solution that we were confident enough to publish. The problem was that the molecules making up the tennis ball are identical. New spectroscopic features emerge when two different molecules are involved in an assembly since they interact when they are present in the same solution. But when there is only one component, to what can the spectra be compared? The sharp, widely separated signals for free and encapsulated methane in the NMR spectrum provided a suggestion of the size of the energy barriers that separate inside and outside, and the characteristic

Julius Rebek, Jr., was born in Hungary and emigrated to the United States in 1949. He is a graduate of the University of Kansas and the Massachusetts Institute of Technology. He has held faculty positions at UCLA, the University of Pittsburgh, and MIT. His research has involved the "three-phase test" for reactive intermediates, cleftlike structures for molecular recognition, synthetic, self-replicating molecules, solution phase combinatorial chemistry, and self-assembling systems. In July of 1996, he moved his research group to The Scripps Research Institute, where he is the Director of the Skaggs Institute for Chemical Biology.

10.1021/ar970201g CCC: $18.00
Published on Web 12/10/1998

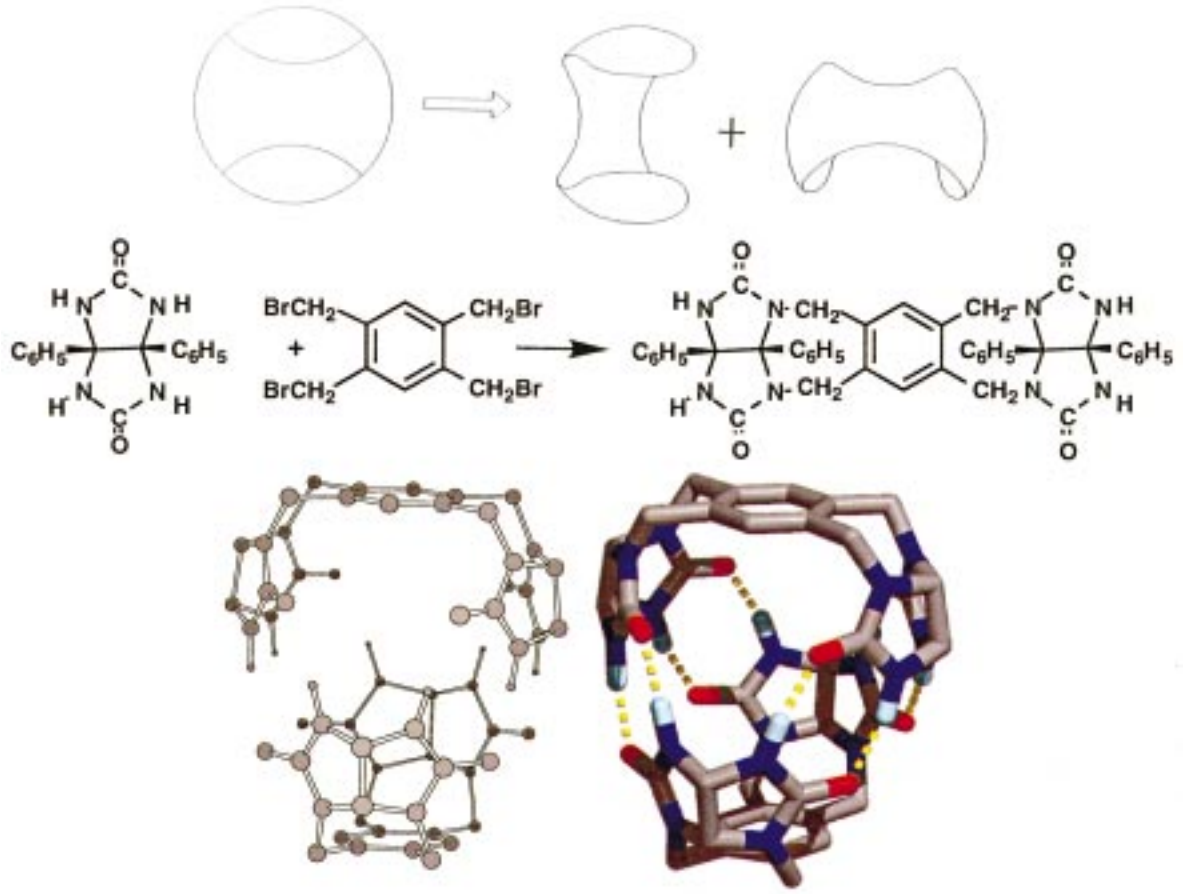

FIGURE 1. Schematic of the tennis ball assembly (top), the synthesis (middle), and depictions of the dimeric form (bottom). The peripheral groups have been removed from the dimeric forms, and the hydrogen-bonded seam is highlighted in yellow.

upfield shifts induced by the anisotropy of the aromatic spacers reported on the peculiar microenvironment inside the capsule.[7] The exchange of methane is fast on the human time scale (< seconds) but slow on the NMR time scale, and its fit (about which more, later) is shown in Figure 2.

The glycoluril nucleus has served us well: the hydrogen-bonding possibilities, the curvature imparted by the cis fusion of the five-membered rings and the solublizing functions that can be presented on the convex, outer surface, and the number of compatible spacers that can provide the basic architecture for dimerization paid greater dividends than we deserved for our initial investment. For example, an ethylene spacer put in place by Carlos Valdés gave the smallest dimer.[6] This "hackeysack" version binds methane but excludes the longer ethane and has peripheral esters that result in good solubility in organic solvents. The saponification of these esters gives a system freely soluble in water. Another example involves the triphenylene spacer. Neil Branda noticed the self-complementarity can be maintained because expanding the molecules' dimensions in one direction of the skeleton could be accommodated by making compensatory changes in another direction. The 120° bend in the middle of the aromatic framework and the placement of *three* glycolurils on that framework recovers the proper O−O distance for bridging the N−H bonds of a second molecule (Figure 3).

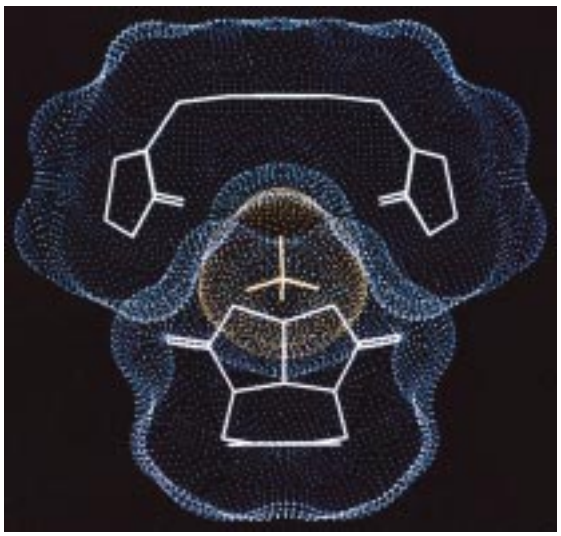

FIGURE 2. Solvent-accessible surfaces of the tennis ball (blue) with encapsulated methane (gold). The peripheral groups on the outer surfaces of the glycolurils have been removed.

The triphenylene's dimer is a flattened sphere resembling (on a table with the tennis ball) a jelly doughnut.[8] For those unfamiliar with this foodstuff, it is similar to a berliner, but choice of the description has to do with size and shape as compared to a tennis ball. The 12 nearly ideal hydrogen bonds along its equator slow its uptake

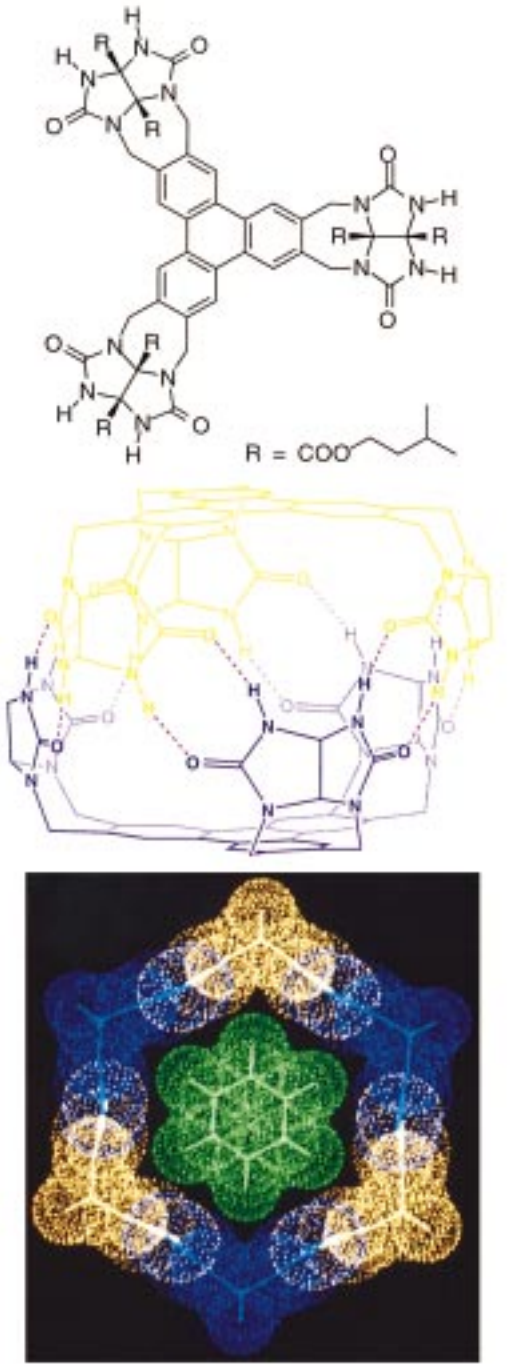

FIGURE 3. The structures of the triphenylene subunit of the jelly doughnut (top) and the assembled dimer (middle). The van der Waals surfaces of the two interlocking subunits are shown in blue and gold (bottom), and that of encapsulated cyclohexane is shown in green.

and release of occupants to a time scale of hours, particularly when disk-shaped molecules are the guests.

The color figure shows the beautiful fit of cyclohexane. It touches the ceiling and floor of the cavity, and, as detected by Brendan O'Leary and Robert Grotzfeld, there is a reduced rate for the ring inversion of cyclohexane-d_{11} inside.[9] This was interpreted as the result of a C−H to π binding affinity of a few hundred calories per mole, comparable in size to that measured by Wilcox's ingenious torsion balance.[10] The axial C−H bonds of the cyclohexane make attractive contacts with the π system of the triphenylene. Any attempts to decrease these contacts as the molecule contorts to the half-chair transition state for ring inversion are resisted. The anisotropy provided by the triphenylene above and below has an additional effect on cyclohexane-d_{11}. The chemical shift differences ($\delta\nu$) between axial and equatorial environments are typically ~0.5 ppm, but inside the jelly doughnut this is magnified to 1 ppm.

Related behavior had already been observed in "container" molecules—those held together by covalent bonds. Restricted tumbling of dimethylacetamide bound within an asymmetric carceplex leads to diastereomers that were separated in Reinhoudt's group,[11] and even the internal rotations of such amides could be slowed by Cram in the cramped quarters.[12,13] Assemblies held together by only hydrogen bonds would appear, at first glance, less rigid since the disortion of hydrogen bonds from their ideal geometries and distances is accompanied by small changes in energy, but a study by Sherman[14] concludes that rotation of pyrazine within an unsymmetrical capsule is constrained and is slow on the NMR time scale. It seems reasonable that motions which disrupt favorable contacts of encapsulated species with the surrounding structured environments will be resisted. After all, it is just these contacts that contribute to the encapsulation process. In special cases, nearby heteroatoms can provide polarized microenvironments that are magnified by the rigidity of the organized surroundings. Such should be the case in the contacts between the polarized C−H bonds of pyrazine and the electron-rich phenoxide surfaces in Sherman's capsule.[14] It is possible to make further distinctions between steric and attractive effects—even at the subkilocalorie level—and address the related question of how much space is ideally filled in molecule-within-molecule complexes. This is a subject to which we return after some other capsules are introduced.

Consider calixarenes[4]—cyclic oligomers of four to eight phenols condensed with as many formaldehydes, U-turns on the road to Bakelite (Figure 4) but with suitable, solublizing lower rim attachments, existing in a number of conformations from among which a (time-averaged) cone conformation, *providing the curvature*, can be isolated. Or consider their resorcinarene cousins—more rigid and wider of mouth. Any two of these subunits can be forged together with covalent linkages, creating internal cavities capable of ingesting, if not digesting (but give it time), smaller molecules. These led to the original "molecules within molecules"[15]—Cram's carcerands[3,16] and Collet's cryptophanes.[17] Both calixarenes and resorcinarenes are—on the table with the jelly doughnut—cones about the size of the business end of a martini glass. When Ken Shimizu[18] outfitted their rims with urea functions, the two glasses were held together rim-to-rim by a circle of hydrogen bonds. The cavity inside was a bit less symmetrical, actually two square pyramids offset by 45°, but the notion rather than reality is what matters. What, then, fits inside? Blake Hamann's competition studies[18] showed that it is most appropriate for simple benzene derivatives—

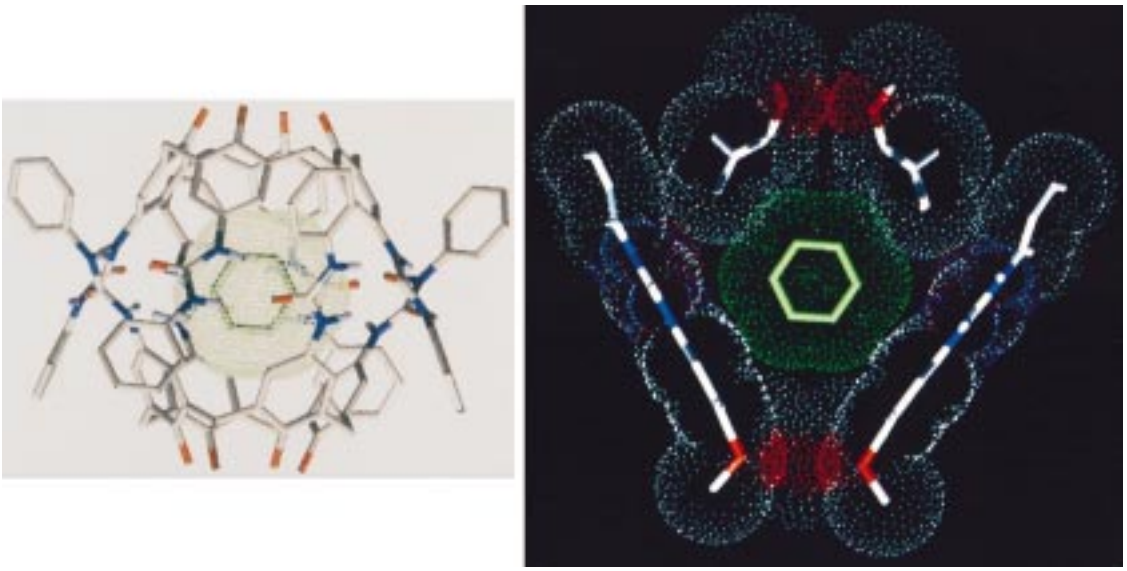

FIGURE 4. The calixarene dimer is held together by a circle of hydrogen-bonded ureas (left). The vertical section through the skeletal framework and the van der Waals surfaces (right) emphasizes the snug fit and orientation of benzene (green).

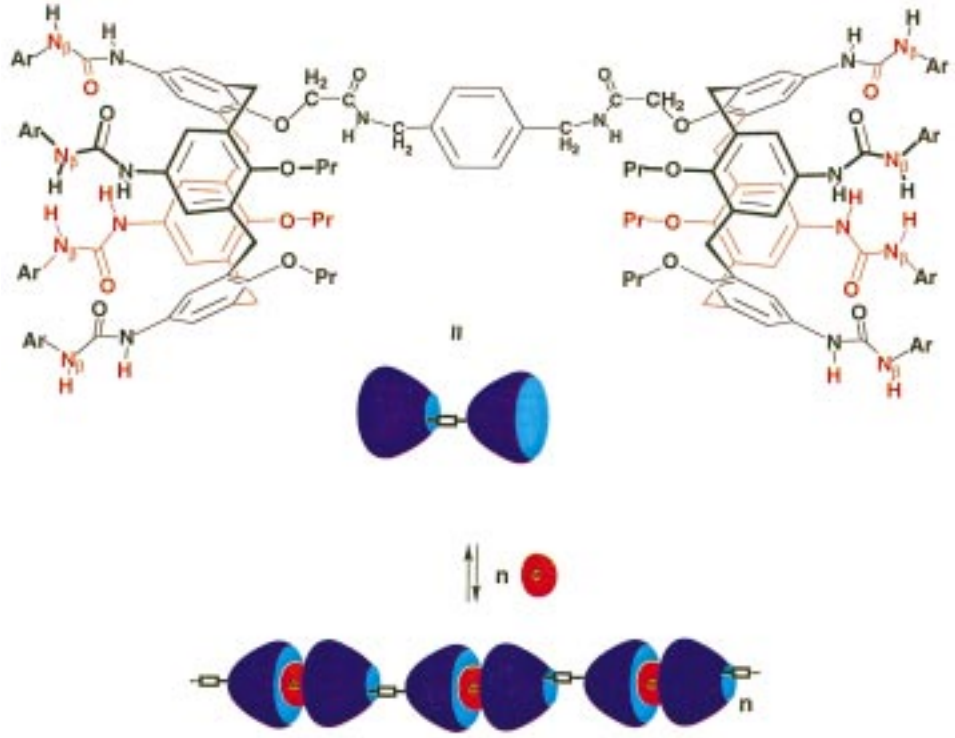

FIGURE 5. Two calixarene units are covalently bonded through an aromatic spacer (top). Assembly through hydrogen bonds and encapsulation of guests (G), leads to linear oligomers "polycaps" (bottom).

a finding that may offer some comfort to purveyors of contaminated mineral waters. How many can fit? The NMR spectra show only one encapsulated species, a result supported by a recent crystal structure,[19] and molecules as diverse as *n*-pentane and camphor can be encapsulated in solution. Think of it—a linear, flexible alkane *or* a spherical, rigid natural product. What are the rules that govern these encapsulations?

The functions on the lower rim found a use in the synthesis of "polycaps": polymeric capsules.[20] Two calixarene units were covalently attached to a spacer by Ron Castellano in such a way that their recognition surfaces—the ureas—were oriented in opposite directions (Figure 5). The "dimerization" led to linear polymers that formed reversibly, and we have observed encapsulation of benzene and toluene derivatives in the polycaps by NMR. Gel permeation chromatography, accomplished in Andy Hamilton's laboratory,[21] is consistent with an average molecular weight approaching one million or about 250 subunits. The polymeric assembly is reversible in another less common sense: upon addition of an excess of a simple calixarene dimer, capping of the free ends of the polycaps occurs and leads ultimately to a dumbbell-shaped heterosystem, an assembly composed of five molecules.

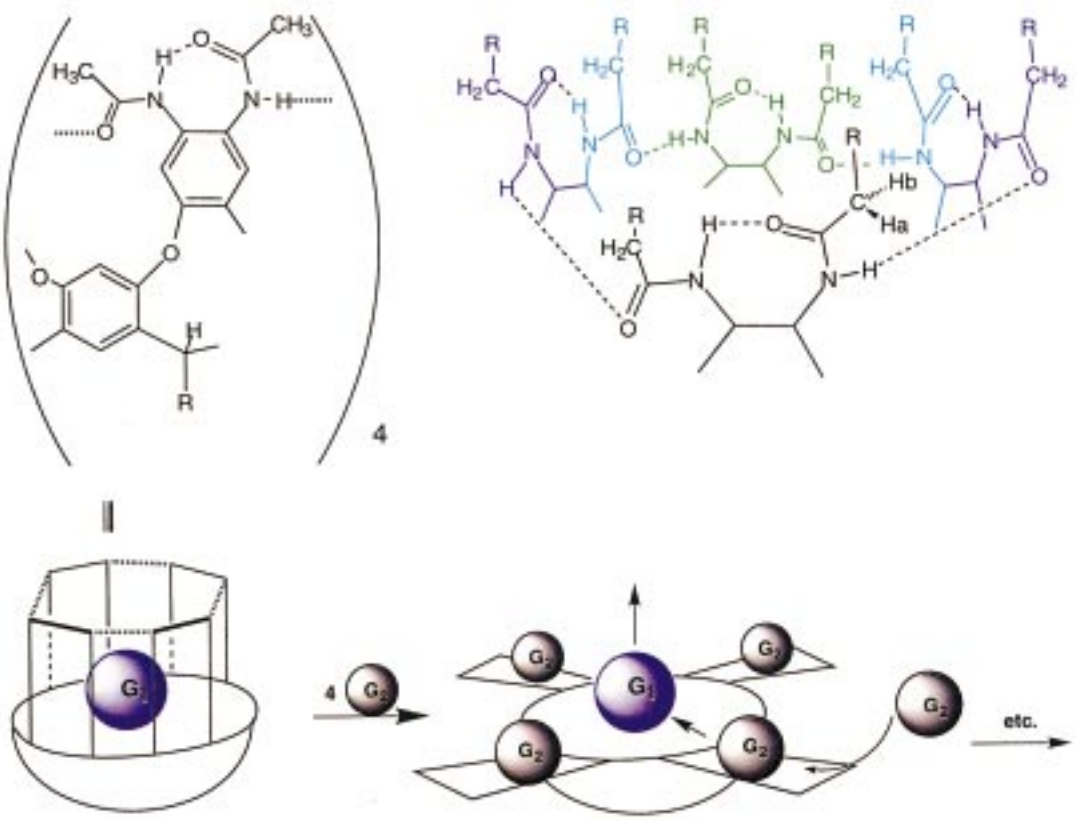

FIGURE 6. A circle of alternating inter- and intra-ring hydrogen bonds holds the sides of a vase-shaped resorcinarene together (top). Unfolding the structure to the "kite" conformation (bottom) allows the orderly exchange of solvents or other captives (H_1, H_2) to occur through a series of displacements.

It has also been possible to use a spacer with three calixarenes in fixed orientations; we suspect that the system assembles to make cross-linked polycaps, but solubility problems have thwarted attempts at its characterization in noncompeting organic solvents.[22] These molecular arrays start to resemble the three-dimensional hydrogen-bonded dendrimers of Zimmerman[23] but lack their closed-shell long-range structure.

Now, it came as a surprise that a completely closed surface is not necessary for the "slow" exchange of guests. We thought the high energetic barriers involved in pulling dimers apart kept the process slow, but limited access—one door to the chamber—can also slow things down. The resorcinarene base of Figure 6 is rigid, but bridging adjacent resorcinols with aromatic rings creates nine-membered rings and introduces some flexibility. The conformational dynamics of such molecules have been thoroughly described by Cram.[24] The molecules flutter between C_{4v} and C_{2v} symmetries; the former which presents all four catechol sides up is called vaselike. In comparison to the martini glass, its shape and larger size approximate a tumbler for scotch on the rocks. The latter, called kitelike, has sides flipped out and resembles an ashtray. Dmitry Rudkevich added a circle of hydrogen bonds along the upper rim of the structure to stabilize the tumbler conformation. This was accomplished by attaching the eight amides as shown.[25] They present hydrogen bonds that can bridge adjacent rings (interannular stitches) in addition to those on the same rings that form seven-membered intraannular stitches (Figure 6). The result is a much deeper cavity and one that resists opening to the C_{2v} ashtray.

Addition of excess adamantane to a solution of these tumblers in *p*-xylene-d_{10} gives rise to a new signal in the NMR spectrum (at −1 ppm), a feature characteristic of inclusion in a magnetically shielded environment. The sharp, separate signals for free and bound adamantanes indicate that exchange of adamantane in and out of the tumbler is slow on the NMR time scale at room temperature. Why so? The open end of the tumbler is seemingly unobstructed and adamantane's dimensions are easily accommodated. The problem is in solvation. The deepest part of the cavity is undoubtedly occupied by solvent in its resting state. Obviously, this solvent must be gone by the time the adamantane takes residence, but with only one opening, how does it get out? Intuitively, pulling the solvent out directly would seem prohibitive in energy—the interior would become desolvated, and as the structure is too rigid to collapse on itself, an (abhorrent) vacuum would be created. Squeezing two molecules past each other in opposite directions inside the tumbler is also unlikely: there is not enough room. This leaves no alternative but to deform—temporarily—the structure. This breaks the interannular hydrogen bonds as the conformation changes to the ashtray. Dynamic NMR measurements by Göran Hilmersson showed the energetic price for this change is approximately 17 kcal/mol.[25] The changes are likely to be those shown in the bottom of Figure 6 (only

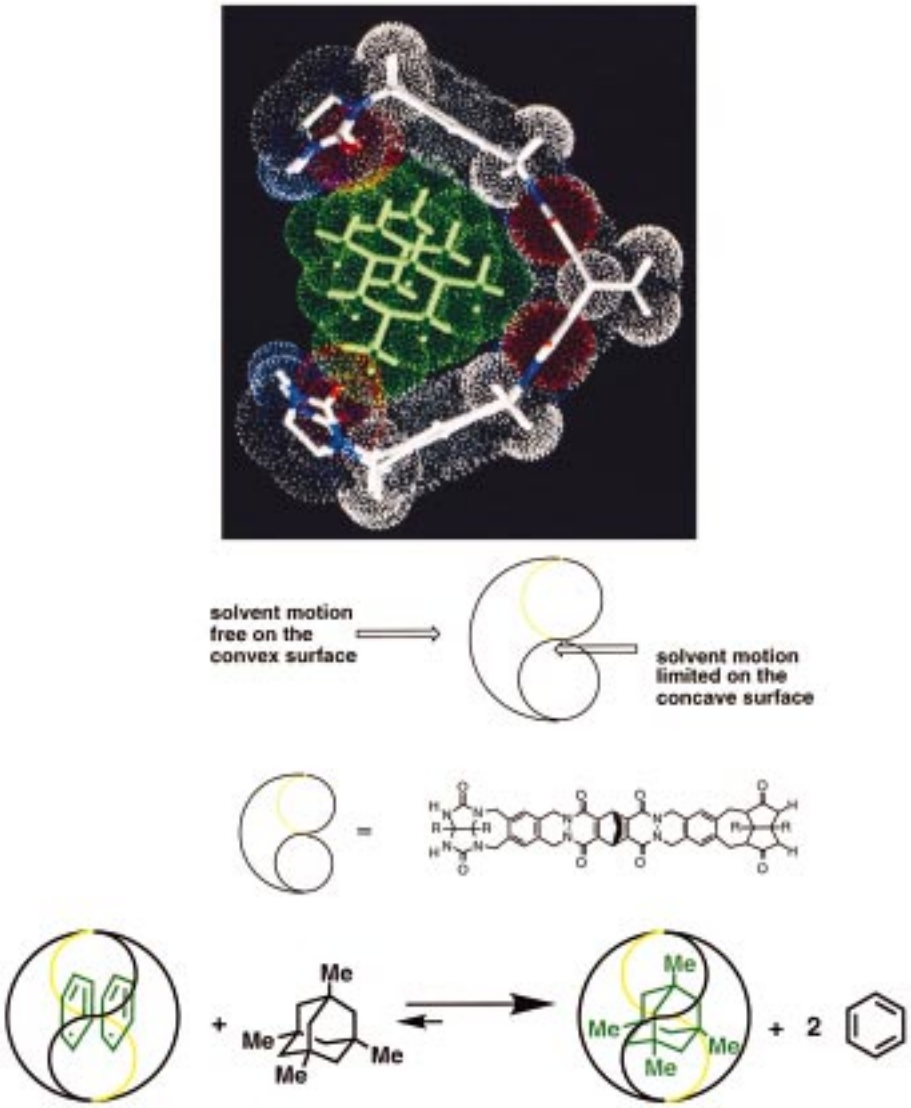

FIGURE 7. Top: Tetramethyladamantane (green) is nestled in the concave surface of the softball subunit. The van der Waals surfaces of both are modeled. Middle: Relative restraints of solvents on the surfaces of curved molecules, such as the softball's monomer. Bottom: The release of two benzene solvent molecules from the softball by one large guest increases the number of free particles in solution; the encapsulation is entropy driven.

the changes in solvation of the concave surfaces are outlined). As a new solvent species comes in, the exchange can take place in an orderly fashion of *displacement*. The process is depicted as exchange from the periphery toward the center of the assembly, but the flow in the opposite direction or direct substitution at the center of the ashtray is just as likely. The sequence may be considered as the supramolecular version of the familiar S_N2 reaction. Refolding of the system completes the exchange process. This is the minimalist mechanism, but we dwell on the sequence because even such a minimal exchange is far from simple. The process is much more complicated in biological macromolecules, but the same considerations apply to, say, the motions that the flaps of HIV protease undergo as it releases products and binds fresh substrate.

In our attempts to find a larger cavity, while staying within sports analogies, the "softball" came to mind and—thanks to Rob Meissner and Javier de Mendoza—into existence. This structure features one bridged ring and 13 fused ring systems that provide essential information: *curvature and rigidity*. Here the centerpiece carbonyls provide the hydrogen bond acceptors for the familiar N−H donors at the ends of glycolurils (Figure 7). With the benzene spacer shown, a pseudospherical structure is generated mostly, but not exclusively.[26] At high concentrations and in solvents that do not fill the space well, oligomers are observed and their NMR spectra are incomprehensibly broadened. Even gels form, and though we have no structural evidence, a chainlike oligomer with the convex face of one molecule bound to the concave face of another seems probable. In solvents that do fill the appropriate fraction of the cavity (computed by Sandro Mecozzi to be about 55% of the volume), sharp NMR spectra are seen and the dimeric softball is the exclusive form. The softball offers a volume of about 300 Å^3 inside, space enough for more than one captive at a time. It is an ordinary calculation but one that has an extraordinary result: that two identical molecules in that

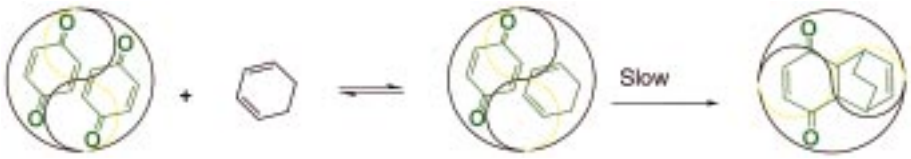

FIGURE 8. The 2:1 complex of the softball with quinone equilibrates with free cyclohexadiene to give a "Michaelis" complex. The adduct is formed inside the capsule, but turnover is a problem.

volume are at a concentration of about 10 M! That this concentration could be attained was revealed in an indirect manner by Xavier Garcias' idea to use two solvents of similar sizes, C_6D_6 and C_6D_5F. When either solvent alone was present, NMR showed only one softball species in solution, but when a mixture of the two solvents was used, three different softballs were observed.[27] This result requires that two solvent molecules, rather than one, be confined inside. For the one containing two deuterated benzenes, the concentration of solvent inside is comparable to its concentration outside, about 10 M. *The sociology of two benzenes inside is, to a reasonable approximation, that of the pure liquid*. In pure benzene, about 55% of the volume is occupied and 45% is empty, and many other common organic solvents share these numbers. These values are easily obtained from a given molecule's volume (although the value for a molecule's volume depends very much on the program used) and its density. The occupancy or packing factors represent a compromise between the cohesive forces among ever-shifting neighbors and the need for mobility experienced by a molecule: in short, what it means to be a liquid rather than a gas or a solid. Competition experiments showed that those molecules or combinations of molecules that fill about 55% of the softball's volume bind with highest affinity. To be sure, when additional attractive interactions such as hydrogen bonds are involved, even higher affinity and higher occupancy can be seen. But the tradeoff is between the entropic freedom of the molecules and the enthalpic comforts of rubbing against their friends. There might even be a message to the broader molecular recognition community in general: First fill 55% of the space to appease the dynamic issue; then build in specific attractive contacts for higher affinity and selectivity.

The presence of two solvents inside the resting state of the softball has some unusual consequences for the thermodynamics of encapsulation. When a large single molecule such as adamantane is encapsulated, two molecules of the solvent are released and the overall entropy of the system increases. Now, solvent release must be a universal feature of molecular recognition, but only rarely does the entropy term dominate the free energy and equilibria in organic solvents. In general, binding is driven by enthalpic gains that overcome the entropic costs of bringing the components together. Accordingly, lower temperatures favor association. For the softball case, the opposite is observed: more adamantane goes inside as the temperature is increased.[29] A graphical restatement of the situation is given in Figure 7.

The softball also offers structural diversity, but its analogues are generated with a different algorithm than was used for congeners of the tennis ball. Tomas Martin and José Rivera-Ortiz noticed that if the hydrogen bonds between the centerpiece and ends can be maintained, the structure can be shortened or elongated at the sides without much effect on self-complementarity. Ethylene, for example, inserted in place of benzene as a spacer gives a dimer of intermediate size between a baseball and softball (a "wiffle ball" for the American reader) of 245 Å^3 capacity that captures camphor.[30] On the other hand, anthracene as a spacer gives a dimer of rugby ball-like shape (so far only in silico, rather than in vitro) with an interior volume calculated to be large enough to accommodate some steroids.

Probably the most unique consequence of the encapsulation of two different molecules is the possibility of bimolecular reactions inside the softball. As reaction chambers these capsules show promise: they offer high concentrations of reactants inside, provide shape and size selectivity, and prevent rapid diffusion. Typical solvent cages last for nanoseconds or less, but encapsulation holds complexes together for intervals that are millions of times longer. Readers familiar with penitentiaries will appreciate the intensity of behavior that develops when two entities are confined in a small volume of space. Initially, Jongmin Kang[31] allowed the components of a Diels–Alder reaction, cyclohexadiene and *p*-benzoquinone, to find their way inside the softball (Figure 8). The transition state geometry of this reaction (leading to the endo product) is reminiscent in size and shape of two encapsulated benzene molecules positioned in a face-to-face manner. The accommodation of that Diels–Alder reaction inside the softball is a reasonable expectation. In the experiment, an acceleration of 180-fold resulted with the softball, and Javier Santamaria has observed other Diels–Alder reactions taking place inside.[32] Control experiments ruled out other known types of catalysis, and the other characteristics, including size selectivity, saturation kinetics, and competitive inhibition, all indicate that the reaction occurs within the softball. Product inhibition, however, prevents the system from showing true catalysis: the adduct is a very good guest, and the system does not turn over.

The corresponding reaction of 2,5-dimethylthiophene dioxide and *p*-benzoquinone does turn over, although the rate enhancements are quite modest (single digits).[33] But we have cause for optimism. The use of these cages as catalysts is expected to be favorable for certain dissociative processes in which, say, two product molecules are formed from a single starting material. Turnover should be driven by the entropic considerations discussed above.

Almost everyone asks, What about chiral capsules? After all, a better device for enantioselection is difficult to

imagine. Well, how chiral should, or could, such a capsule be? There is some debate on this issue, but the experimental facts do not give cause for optimism. Consider cyclodextrins. Their dozens of asymmetric centers do not translate to efficient enantioselection.[34] The problem is that their interiors are still highly symmetrical, while what is desired is a blatant, flagrant, and overt *asymmetric cavity*. To place optically active groups on the exterior to make a "chiral" capsule is a parlor trick, and we have performed it. The magnetic properties of these capsules are not without interest, though the cavity itself lacks asymmetry.[35] Next, *racemic* dimers were prepared by Yuji Tokunaga[36] and Tomas Szabo,[37] and their interconversions permitted the first measures of the rates of dissociation and recombination of the capsules and provided evidence concerning the mechanism of guest exchange. It has been possible to introduce handedness to the *lining* of the cavity: the clockwise or anticlockwise arrangement of the head-to-tail ureas in the calixarene-based capsules emerge if the two subunits are different. Such heterodimers were prepared, and Byeang Hyean Kim established that they do show some diastereomeric encapsulation of chiral guests.[35] Finally, capsules with asymmetric cavities are in the hands of José Rivera-Ortiz and Tomas Martin; the capsules show modest enantioselectivity with terpenes, but it should be possible to "design" optimal guests for them in the future.

In the meantime, there is something about the curvature of molecules that intrigues us. Flat surfaces—aromatic structures and heterocyclics—are certainly easier to make, and their stacking and hydrogen-bonding tendencies can be used to prepare a seemingly endless array of self-assembled systems. The catenanes of Stoddart,[38] the rosettes, tapes, and sheets of Whitesides,[39] and the clusters of Reinhoudt[40] are particularly ingenious examples. These systems assemble *because they fill the available interior space*; their functional interactions with other molecules will likely be on their exterior surfaces. Curved molecules, however, can assemble to give accessible cavities; their structures have defined insides and outsides.

This Account is intended to show one of the newer faces of physical organic chemistry: intermolecular forces in the context of molecular recognition and assembly. The studies have, as usual, raised more questions than answers about information, dynamics, mechanism, and the very nature of liquids. We expect to be busy in the foreseeable future.

The research described here is due to the superb co-workers who have joined the molecular assembly project over the past few years, and I have referred to them by name in the narrative and in the literature cited. I am grateful to Chris Foote for this chance to write in a less formal manner—to make "forward-looking statements" about completed but yet unpublished experiments. For financial support, I am grateful to the NIH for initiating this project and to L. Sam Skaggs whose extraordinary generosity has removed limits on the scope of our research agenda.

References

(1) Rebek, J., Jr. Assembly and Encapsulation with Self-Complementary Molecules. *Chem. Soc. Rev.* **1996**, 255−264. For a broader coverage, see: Conn, M. M.; Rebek, J., Jr. Self-Assembling Capsules. *Chem. Rev.* **1997**, *97*, 1647−1668.

(2) Kemp, D. S.; Petrakis, K. S. Synthesis and Conformational Analysis of *cis,cis*-1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic Acid. *J. Org. Chem.* **1981**, *46*, 5140−5143. Other uses: Rebek, J., Jr. Molecular Recognition with Model Systems. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245−255. Kocis, P.; Issakova, O.; Sepetov, N. F.; Lebl, M. Kemp's Triacid Scaffolding for Synthesis of Combinatorial Nonpeptide Uncoded Libraries. *Tetrahedron Lett.* **1995**, *36*, 6623−6626.

(3) Högberg, A. G. S. Stereoselective Synthesis and DNMR Study of Two 1,8,15,22-Tetraphenyl[1_4]-metacyclophan-3,5,10,12,17,19,24,26-octols. *J. Am. Chem. Soc.* **1980**, *102*, 6046−50. Other uses: Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, U.K., 1994. Sherman, J. C. Carceplexes and Hemicarceplexes: Molecular Encapsulation—From Hours to Forever. *Tetrahedron* **1995**, *51*, 3395−3422.

(4) Gutsche, C. D.; Muthukrishnan, R. Association Phenomena. 5. Synthesis and Properties of 1,4-Dipolar Substituted Cyclohexenes. *J. Org. Chem.* **1978**, *43*, 4069−4075. Other uses: Böhmer, V. Calixarenes, Macrocycles with (Almost) Unlimited Possibilities. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745. Shinkai, S. Calixarenes—The Third Generation of Supramolecules. *Tetrahedron* **1993**, *49*, 8933−8968.

(5) Wyler, R.; de Mendoza, J.; Rebek, J., Jr. A Synthetic Cavity Assembles Through Self-Complementary Hydrogen Bonds. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699−1701.

(6) Valdés, C.; Spitz, U. P.; Toledo, L.; Kubik, S.; Rebek, J., Jr. Synthesis and Self-Assembly of Pseudo-Spherical Homo- and Heterodimeric Capsules. *J. Am. Chem. Soc.* **1995**, *117*, 12733−12745.

(7) Branda, N.; Wyler, R.; Rebek, J., Jr. Encapsulation of Methane and Other Small Molecules in a Self-Assembling Superstructure. *Science* **1994**, *263*, 1267−1268. For methane complexation inside a cryptophane: Garel, L.; Dutasta, J.-P.; Collet, A. Complexation of Methane and Chlorofluorohydrocarbons with Cryptophan A in Organic Solution. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1169.

(8) Grotzfeld, R. M.; Branda, N.; Rebek, J., Jr. Reversible Encapsulation of Disc-Shaped Guests by a Synthetic, Self-Assembled Host. *Science* **1996**, *271*, 487−489.

(9) O'Leary, B. M.; Grotzfeld, R. M.; Rebek, J., Jr. Ring Inversion Dynamics of Encapsulated Cyclohexane. *J. Am. Chem. Soc.* **1997**, *119*, 11701−11702.

(10) Paliwal, S.; Geib, S.; Wilcox, C. S. Molecular Torsion Balance for Weak Molecular Recognition Forces. Effects of "Tilted-T" Edge-to-Face Aromatic Interactions on Conformational Selection and Solid-State Structure. *J. Am. Chem. Soc.* **1994**, *116*, 4497−4498.

(11) Timmerman, P.; Verboom, W.; Veggel, F. C. J. M.; Duynhoven, J. P. M.; Reinhoudt, D. N. A Novel Type of Stereoisomerism in Calix[4]arene-Based Carceplexes. *Angew. Chem., Int. Ed. Engl.* **1994**, *34*, 2345−2348.

(12) Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. B.; Cram, D. J. Guest-Assisted and Guest-Inhibited Shell Closures Provide Differently Shaped Carceplexes and Hemicarceplexes. *J. Am. Chem. Soc.* **1996**, *118*, 5590−5604.
(13) van Wageningen, A. M. A.; Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. Calix[4]arene-based (Hemi)carcerands and Carceplexes: Synthesis, Functionalization and Molecular Modeling Study. *Chem.—Eur. J.* **1997**, *3*, 639−654.
(14) Chapman, R. G.; Sherman, J. C. Study of Templation and Molecular Encapsulation Using Highly Stable and Guest-Selective Self-Assembling Structures. *J. Am. Chem. Soc.* **1995**, *117*, 9081−9082.
(15) Cram, D. J. Lecture at the C. David Gutsche Symposium, Washington University, St. Louis, MO, May 5, 1990.
(16) Cram, D. J.; Karbach, S.; Kim, Y. H. Shell Closure of Two Cavitands Forms Carcerand Complexes with Components of the Medium as Permanent Guests. *J. Am. Chem. Soc.* **1985**, *107*, 2575−2576.
(17) Collet, A.; Dutasta, J. P.; Lozach, B.; Canceill, J. In *Chemistry I—Directed Synthesis and Molecular Recognition*; Weber, E., Ed.; Topics in Current Chemistry, Vol. 165; Springer-Verlag: Berlin, 1993; pp 104−129.
(18) Hamann, B. C.; Shimizu, K. D.; Rebek, J., Jr. Reversible Encapsulation of Guest Molecules in a Calixarene Dimer. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329.
(19) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. J. Hydrogen-bonded Dimers of Tetraurea Calix[4]arenes: Unambiguous Proof by Single-Crystal X-ray Analysis. *J. Chem. Soc., Chem. Commun.* **1996**, 2533−2534.
(20) Castellano, R K.; Rudkevich, D. M.; Rebek, J., Jr. Polycaps: Reversibly Formed Polymeric Capsules. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 7132−7137.
(21) We are grateful to Professor A. Hamilton and Abdullah Zafar for these measurements.
(22) Castellano, R. K.; Rebek, J., Jr. Formation of Discrete, Functional Assemblies and Informational Polymers through Hydrogen Bonding Preferences of Calixarene Aryl and Sulfonyl Tetraureas. *J. Am. Chem. Soc.* **1998**, *120*, 3657−3663.
(23) Zimmerman, S. C.; Zeng, F.; Reichert, D. E. C.; Kolotuchin, S. V. Self-Assembling Dendrimers. *Science* **1996**, *271*, 1095−1098.
(24) Cram, D. J.; Choi, H.-J.; Bryant, J. A.; Knobler, C. B. Solvophobic and Entropic Driving Forces for Forming Velcraplexes, Which are Four-Fold, Lock-Key Dimers in Organic Media. *J. Am. Chem. Soc.* **1992**, *114*, 7748−7765. Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. Vases and Kites as Cavitands. *J. Am. Chem. Soc.* **1991**, *113*, 5707−5714.
(25) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. Intramolecular Hydrogen Bonding Controls the Exchange Rates of Guests in a Cavitand. *J. Am. Chem. Soc.* **1997**, *41*, 9911−9912.
(26) Meissner, R.; de Mendoza, J.; Rebek, J., Jr. Autoencapsulation Through Intermolecular Forces: A Synthetic Self-Assembling Spherical Complex. *Science* **1995**, *270*, 1485−1488.
(27) Meissner, R.; Garcias, X.; Mecozzi, S.; Rebek, J., Jr. Synthesis and Assembly of New Molecular Hosts: Solvation and the Energetics of Encapsulation. *J. Am. Chem. Soc.* **1997**, *119*, 77−85.
(28) Mecozzi, S.; Rebek, J., Jr. The 55% Solution: A Formula for Molecular Recognition in the Liquid State. *Chem.—Eur J.* **1998**, *4*, 1016−1022.
(29) Kang, J.; Rebek, J., Jr. Entropically-Driven Binding in a Self-Assembling Molecular Capsule. *Nature* **1996**, *382*, 239−241.
(30) Rivera-Ortiz, J.; Martin, T.; Rebek, J., Jr. Chiral Spaces: Dissymmetric Capsules Through Self-Assembly. *Science* **1998**, *279*, 1021−1023.
(31) Kang, J.; Rebek, J., Jr. Acceleration of a Diels−Alder Reaction by a Self-Assembled Molecular Capsule. *Nature* **1997**, *385*, 50−52.
(32) Kang, J.; Hilmersson, G.; Santamaría, J.; Rebek, J., Jr. Diels−Alder Reactions through Reversible Encapsulation. *J. Am. Chem. Soc.* **1998**, *120*, 3650−3656.
(33) Kang, J.; Santamaria, J.; Hilmersson, G.; Rebek, J., Jr. Self-Assembled Molecular Capsule Catalyzes a Diels−Alder Reaction. *J. Am. Chem. Soc.* **1998**, *120*, 7389−7390.
(34) Easton, C. J.; Lincoln, S. F. Chiral Discrimination by Modified Cyclodextrins. *Chem. Soc. Rev.* **1996**, *25*, 163−170.
(35) Castellano, R.; Kim, B. H.; Rebek, J., Jr. Chiral Capsules: Asymmetric Binding in Calixarene-Based Dimers. *J. Am. Chem. Soc.* **1997**, *119*, 12671−12672.
(36) Tokunaga, Y.; Rebek, J., Jr. Chiral Capsules: Softballs with Asymmetric Surfaces Bind Camphor Derivatives. *J. Am. Chem. Soc.* **1998**, *120*, 66−69.
(37) Szabo, T.; Hilmersson, G.; Rebek, J., Jr. Dynamics of Assembly and Guest Exchange in the Tennis Ball. *J. Am. Chem. Soc.* **1998**, *120*, 6193−6194.
(38) Philp, D.; Stoddart, J. F. Self-Assembly in Natural and Unnatural Systems. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1155−1196.
(39) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. Molecular Self-Assembly and Nanochemistry: A Chemical Strategy for the Synthesis of Nanostructures. *Science* **1991**, *254*, 1312−1319.
(40) Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. M. Molecular Boxes Based on Calix[4]arene Double Rosettes. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1215−1218.

AR970201G