Synthesis and Assembly of New Molecular Hosts: Solvation and the Energetics of Encapsulation

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Abstract: Experimental details are given for the preparation of "softballs", large self-complementary molecules capable of assembly into pseudo-spherical capsules. Evidence is presented for their existence as hydrogen bonded dimers in organic solvents, and binding affinities for the reversible encapsulation of smaller molecules of suitable size and shape are given. Studies at various temperatures result in calculated enthalpies and entropies of encapsulation that are **positive**; accordingly, the process is entropy driven. It is proposed that the hosts in their resting states contain two molecules of solvent such as benzene, and the encapsulation of a single large guest−the hostage−liberates the two solvents. The resulting increase in the number of free molecules gives rise to the increase in entropy observed for the exchange process. Experiments involving solvent mixtures are consistent with this rationale. Calculation of the capsule's interior volume and molecular dynamics simulations support the experimental observations, and hint at unexpected phenomena dealing with the occupancy factors of these systems.

Introduction

"Molecules within molecules"[1] is a phrase that characterizes an unusual, perhaps unique arrangement of matter. Introduced by Cram[2] and Collet[3] nearly a decade ago, these systems featured covalently assembled structures−carcerands and cryptophanes−with cavities capable of completely surrounding smaller molecules. The guest species could be found inside under two conditions: when they act as templates during the synthesis of the hosts,[4,5] or when they enter through openings created by structural distortions in the host molecules.[6] High activation barriers are generally associated with the latter process, a feature that permits the isolation of reactive molecules such as cyclobutadiene within the cavities.[7] A new form of stereoisomerism that arises from the restricted motion of encarcerated species has recently been discovered.[8]

With the premise that further new phenomena await the exploration of these systems, we have used weak intermolecular forces rather than covalent bonds as a means of assembling molecule within molecule complexes.[9,10] Our systems involve two identical self-complementary subunits that fit together as a dimer, in a way reminiscent of the way the two pieces of a tennis ball fit together into a hollow sphere. These dimers maintain the broad attributes of the carcerands and cryptophanes, but they are formed reversibly, and their dynamic qualities impart special merits. They form and dissipate on the time scale that varies from milliseconds to hours, intervals long enough for many types of interactions, even chemical reactions, to occur within them. We term the process encapsulation and describe here some unexpected behavior that is expressed when the larger host capsules take and exchange their hostages.[11]

Elsewhere we have dwelt on the virtues of hydrogen bonding as a vehicle for molecular recognition,[12] replication,[13] and self-assembly;[14] we have discussed in detail the application of the glycoluril module in the latter context: its advantages and limitations, the considerations of curvature, spacing, geometry, and solubility;[15] the failed early prototypes and the subsequent successes,[16] the spectroscopic characteristics of homodimeric and heterodimeric capsules in solution and the solid state,[15,17] and their ability to encapsulate smaller molecules.[18] We cannot repeat them here, rather, we proffer the picture of **1** and its dimeric form as a spur to the reader's attention.

The question−how to make a sizable capsule−finds an answer in the gentle curvature and reliable rigidity of the structure's 13 fused and 1 bridged ring systems, the four basic carbonyls of the centerpiece and their acidic glycoluril hydrogen

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(1) This phrase first appears as the title of a lecture by D. J. Cram at the C. David Gutsche Symposium, Washington University, St. Louis, Missouri, May 5, 1990; for examples, see: Cram, D. J. *Nature* **1992**, *356*, 29−36.

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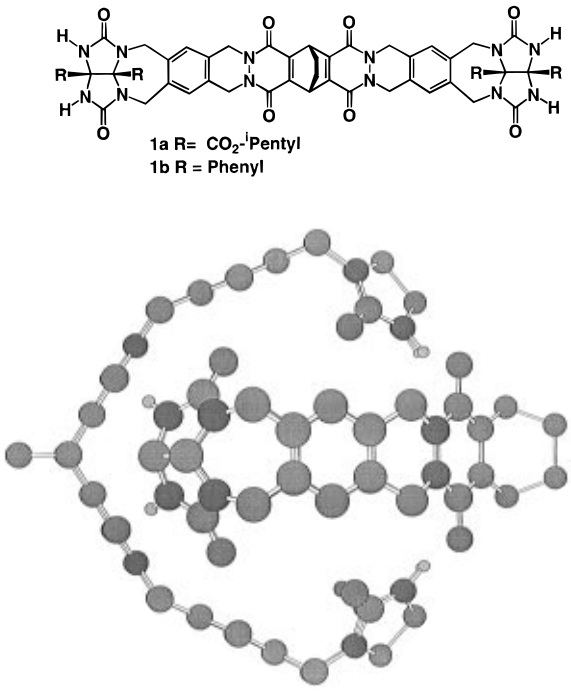


Figure 1. Structure of monomeric **1** and its energy minimized (MacroModel[20] 3.5X with MM2 force field) dimeric form. The peripheral R groups and some hydrogens have been omitted for viewing clarity.

complements on the molecule's ends, and the well-filled surface. The absence of large holes closes the avenues of escape of hostages from the dimeric, capsular host. Relative to the size of the original tennis ball, the structure becomes a notional "softball".[19]

Synthesis

The synthesis of the softball takes advantage of the same starting material used for the tennis ball—the tetrabromo durene **2** (Figure 2). This was used first to dialkylate a BOC-protected hydrazine derivative **3** to give structure **4**, then the remaining two halide sites were used to alkylate the appropriate glycouril **5** (R = CO_2-isopentyl). The resulting structure **6** represents the ends of the self-complementary pieces. Removal of the BOC groups gave the hydrazine salt **7**, the unstable free base of which was acylated by the centerpiece, the tetraacid chloride **8**, in good yield. The two other isomers were isolated by chromatography. These were identified by the (spectroscopically) different ends featured by the S-shaped isomer and the failure of the W-shaped isomer to assemble.

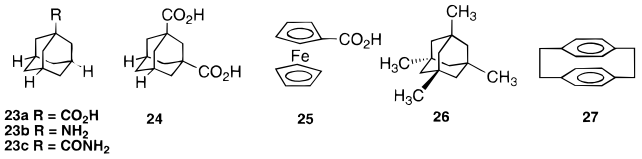
The synthesis of the centerpiece **8** (Figure 3) was somewhat more convoluted but followed a strategy developed earlier for such structures.[21] It involved a protected acetylene dicarboxylic acid **9** as the repeating module. Diels–Alder reaction with furan, then reduction and ether cleavage to afford the dihydrophthalate **10**, was followed by the second reaction with the acetylene derivative. The bicylic framework **11** was then deprotected and activated with oxalyl chloride to give the centerpiece module, the tetraacid chloride **8**.

Two versions of the softball were prepared. The one (**1b**) derived from diphenylglycouril was prepared as in Figure 4, followed by reaction of **22** with **8**. However, it showed limited solubility in organic media. The softball (**1a**) derived from the isopentyl ester of dihydroxy tartrate, as described earlier,[15] proved tractable in several solvents.

Characterization as Dimeric Structures

The proton NMR signals of molecule **1b** are sharp and well-defined in benzene-d_6, and considerable downfield shifts (δ > 8 ppm) were observed for the N-*H* resonances. This is characteristic of an ordered, extensively hydrogen bonded system (Figure 5A). However, in $CDCl_3$, the molecule dissolved with difficulty and formed a gel-like phase after a few minutes. The spectrum showed broad unresolved peaks (Figure 5B) and the suspension in the NMR tube could be turned upside down without loss of its contents. Evidently, in this solvent an aggregate of relatively low order was formed. The very same sample in a solvent such as benzene or toluene which, as we shall see, are good guests for the interior showed very different NMR spectra: the spectra of a well-filled dimeric capsule.

The more soluble derivative **1a** showed a spectrum similar to that of **1b** in benzene-d_6, but in *p*-xylene-d_{10} produced broad signals in the NMR spectrum (Figure 6A). On the addition of suitable guests, e.g. excess [2.2] paracyclophane (**27**), sharp and clearly resolved spectra were obtained (Figure 6B).



Other sizable additives such as adamantane or ferrocene derivatives also led to the characteristic resonances of the capsule. Specifically, 1-adamantanecarboxylic acid (**23a**), the 1,3-dicarboxylic acid **24**, 1-adamantaneamine (**23b**), and the ferrocene acid **25** were able to induce this change in the spectrum, and even the nonpolar tetramethyladamantane **26**, when present in large excess, was able to generate the capsular form (the spectra are not shown here but appear in ref 11). In short, these guests **autoencapsulate** themselves, and in doing so, they become hostages, unable to leave until they are replaced. The autoencapsulation process results in the breakup of the rather loose aggregates and leads to the emergence of ordered, occupied capsular forms.

The ability of these guests to induce the capsular form at room temperature varied, and the values within this limited set are recorded in Table 1. Both adamantane and the ferrocenecarboxylic acids were suitable guests. For the adamantanes, signals appearing upfield of 0 ppm indicated that the guests were in an environment shielded by aromatic ring currents. For the ferrocene acid, the upfield shifts were comparable: 3.5 to 4.5 ppm free versus 2 to 2.5 ppm encapsulated. While it is barely conceivable that these changes in chemical shift involve some specific interactions between the solutes and the monomeric forms of **1** in an aromatic solvent, the facts leave little doubt that true encapsulation occurs.

Mere integration of the spectra established the stoichiometries of encapsuled guests in the softball. The apparent association constants are derived from the equation below and are only approximate, since the total concentration of the aggregate was involved in the calculations. Accordingly, the values are

(19) Garcias, X.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1225–1228.

(20) MacroModel V:5.5: Mohamadi, F.; Richards, N. G. J.; Guidia, W. C.; Liskamp, R.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467. Although appropriate force field parameters for all the functional groups in molecule **1** do not exist, we believe that the use of the force field Amber* of MacroModel 5.5 allows a reasonable approximation for the calculation and comparison of volumes.

(21) Beerli, R.; Rebek, J., Jr. *Tetrahedron Lett.* **1995**, *36*, 1813–1816.

(22) C. Wilcox, personal communication. We thank Prof. Wilcox for providing this information prior to publication.

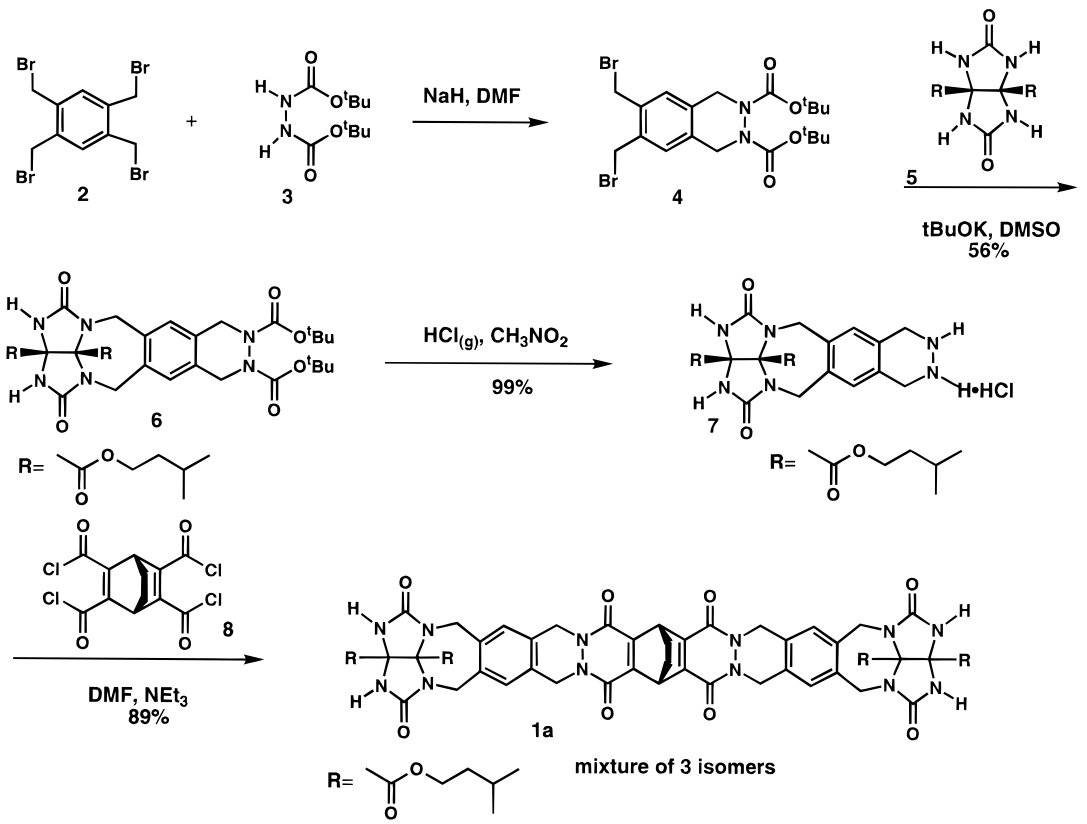


Figure 2. Synthesis of monomer 1a. Abbreviations: BOC = *tert*-butoxycarbonyl, DMF = *N*,*N*-dimethylformamide, ^{t}BuOK = potassium *tert*-butoxide, DMSO = dimethyl sulfoxide, NEt_3 = triethylamine.

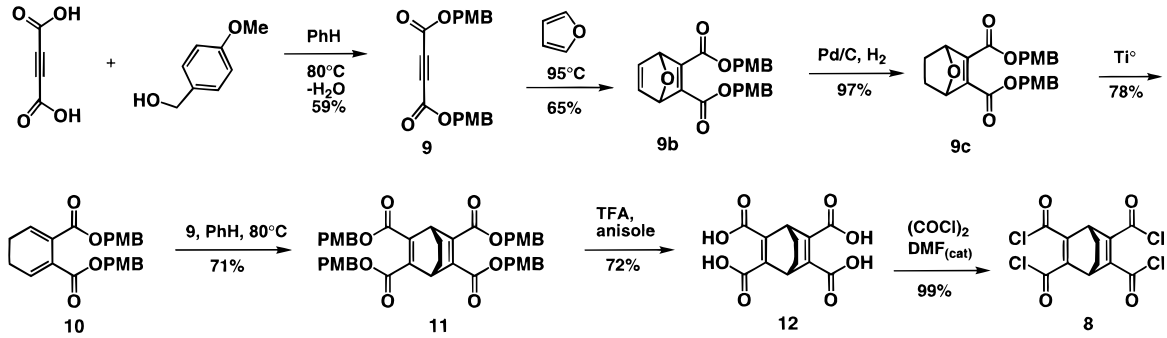


Figure 3. Synthesis of the central tetraacyl chloride. Abbreviations: TFA = trifluoroacetic acid, PMB = *p*-methoxybenzyl.

denoted as apparent association constants, K_a(app), because of the simplification of the several dynamic processes present into one represented by eq 1.

$$\mathbf{1b}_{(\text{aggregae})} + \text{guest} \rightleftharpoons \mathbf{1b}\cdot\text{guest}\cdot\mathbf{1b} \qquad (1)$$

$$K_{a(\text{app})} = \frac{[\mathbf{1b}\cdot\text{guest}\cdot\mathbf{1b}]}{[\mathbf{1b}_{(\text{aggregate})}][\text{guest}]}$$

In solvents that gave indications that the capsular form was the dominant species, it was possible to do more detailed studies. These were executed at various temperatures and some unusual results were encountered. For the specific case of 1-adamantanecarboxamide (**23a**) in toluene-d_8, the series of spectra are shown in Figure 7.

The new signal for the encapsulated adamantane derivative appears upfield from 0 ppm and two different softball resonances can be observed between 7.8 and 8 ppm. Their ratios change as the temperature changes. Specifically, with approximately 3 equiv of **23a** at 45 °C, 47% of the dimeric hosts were occupied by the hostage (Figure 7B) but when the temperature is raised to 60 °C, 59% is occupied. *Encapsulation increases with increasing temperature*. Figure 8 shows the van't Hoff plot for the encapsulation, the most important feature of which is the uncharacteristic downward slope. The usual treatment of the data gives $\Delta S = 35 \pm 1.7$ eu and $\Delta H = 7.3 \pm 0.4$ kcal. As both enthalpy and entropy are positive for the process, it must be an entropy-driven process.

How can the phenomena be interpreted? The hydrophobic effect is the classical example, but in studies in organic solvents, this type of behavior is rarely seen. But why not? As two molecules come together to form a noncovalent complex, the liberation of solvent is a universal feature of molecular recognition phenomena and generally more than one solvent molecule is released. For example, the "activated water"[23] molecules inside cyclodextrins are displaced by organic guests, but conventional thermodynamics (enthalpy driven and entropy resisted) are, nonetheless, observed. Wilcox[22] has observed this behavior in water using macrocyclic hosts and organic guests.

(23) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344−362 and references therein.

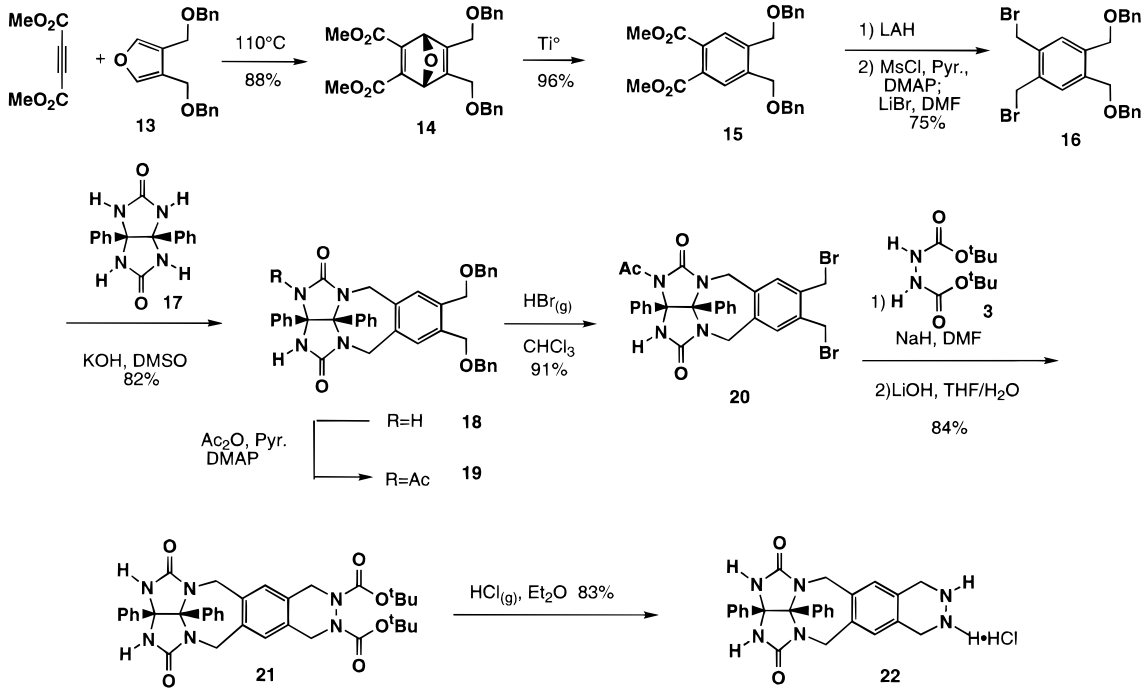


Figure 4. Synthesis of components for monomer **1b**.

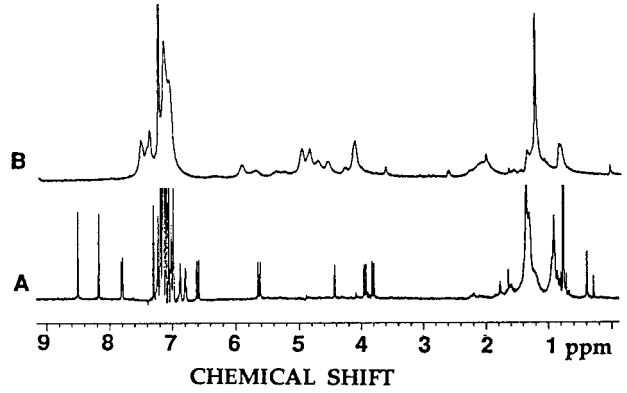


Figure 5. ^{1}H NMR spectra of **1b**. (A) Benzene-d_6 solvent; signals between 7.2 and 7.0 ppm and between 2.2 and 0 ppm are from the solvent and its impurities. (B) Chloroform-*d* solvent; the single peak at 7.26 ppm is from the solvent.

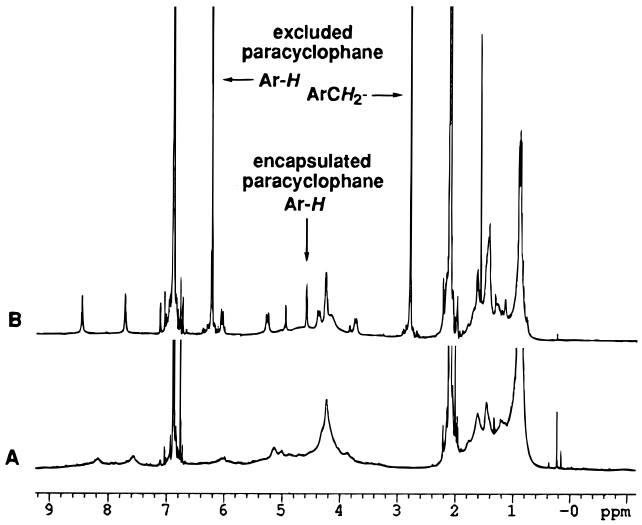


Figure 6. ^{1}H NMR spectra of **1a**. (A) Compound **1a** in 8.84 mM *p*-xylene-d_{10} solvent at 25 C; signals between 0.1 and 0.3 and 7.1 and 6.6 ppm, and 2.3 and 1.8 ppm are from the solvent and its impurities. (B) As in part A with 19.2 mM [2.2]paracyclophane (**27**) added. The signals of the included and free **27** are designated.

The velcrands described by Cram[24] show unprecedented (and unpredictable) ranges of ΔH from +6 to −8 kcal/mol and ΔS from-6 to +40 eu in organic media. There must be something special about the guest solvent in these capsules. Compared to the loosely bound surface solvents that are featured in most cases, the encapsulated solvents must enjoy less freedom.

Indeed, much has been written about the compensating effects of entropy and enthalpy in complex formation,[25−27] but for the softball the inclusion of guests involves an enthalpic *cost* compensated by a larger entropic *gain*. This behavior 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 behavior is rarely encountered and generally unpredictable.[24,28]

Table 1. Apparent Association Constants Derived from Eq 1)

guest	$K_{a(app)}$ $(M^{-1})^b$
1,3,5,7-tetramethyladamantane (**26**)	6.7
adamantaneamine (**23b**)	190
1-adamantanecarboxamide (**23c**)	310
1-adamantanecarboxylic acid (**23a**)	780
1,3-adamantanedicarboxylic acid (**24**)	*a*
1-ferrocenecarboxylic acid (**25**)	280

[a] Value not calculated due to the insolubility of the free guest.

Schematically, Figure 9 shows the case if *two* molecules of solvent occupy the interior of the softball in its resting state in benzene. The left hand side of the equation involves two particles but the liberation of the encapsulated solvent molecules

(24) Cram, D. J.; Choi, H-J.; Bryant, J. A.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7748−7765. Cram, D. J.; Blanda, M. T.; Paek, K.; Knobler, C. B. *J. Am. Chem. Soc* **1992**, *114*, 7765−7773.

(25) For a recent discussion with leading references, see: Dunitz, J. D. *Chem. Biol.* **1995**, *2*, 709−712.

(26) Peterson, B. R.; Wallimann, P.; Carcanague, D. R.; Diederich, F. *Tetrahedron* **1995**, *51*, 401−421.

(27) Searle, M. S.; Westwell, M. S.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 141−151.

(28) Canceill, J.; Cesario, M.; Collet, A.; Guilhem, J.; Lacombe, L.; Lozach, B.; Pascard, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1246−1248.

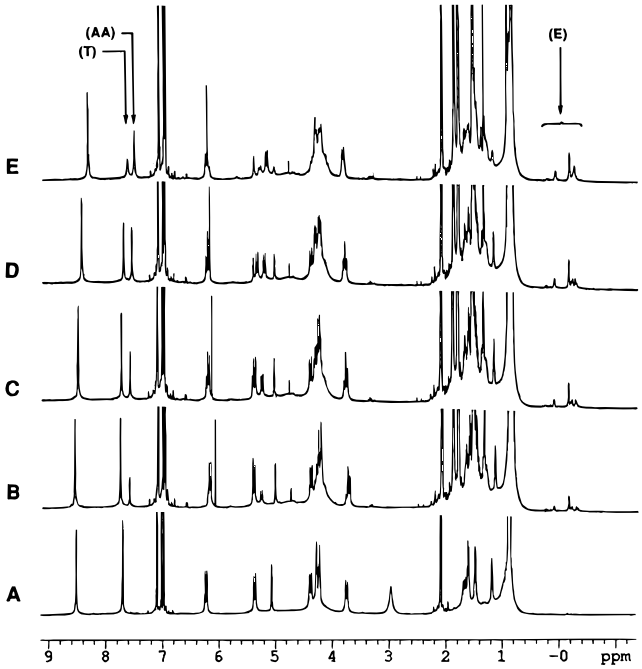


Figure 7. ^{1}H NMR spectra of **1a** in *p*-xylene-d_{10} solvent with **23a** as a function of temperature. Solvent resonances occur between 2.0 and 2.2 ppm and between 6.8 and 7.2 ppm. In spectra B through E, resonances for the encapsulated portion of **23a** occur between 0.2 and −0.4 ppm, and those for chloroform as a singlet which moves between 6.0 and 6.2 ppm. The resonance of the Ar-H protons are labeled with (T) for the host dimer assembly containing toluene-d_8 and with (AA) for that containing **23a**; these peaks are the best resolved for the two species, and were integrated for measurement of K_{eq}. The resonances for the encapsulated guest are labeled (E). (A) Toluene-d_8 solvent; 9.9 mM in **1a**, temperature = 25 °C. (B) 7.3 mM in **1a**, 20 mM in 1-adamantanecarboxylic acid (**23a**), temperature = 25 °C. (C) as in part B, temperature = 35 °C; (D) as in part B, temperature = 45 °C; (E) as in part B, temperature = 60 °C.

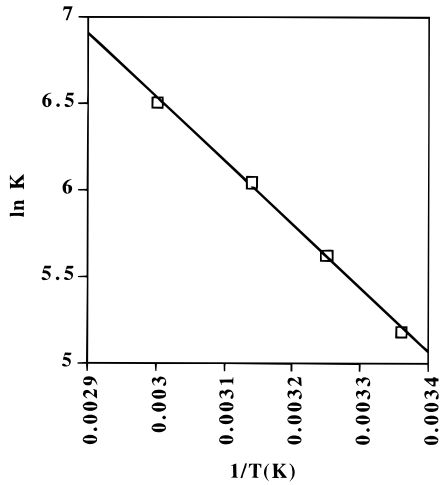


Figure 8. van't Hoff plot of data from Figure 7.

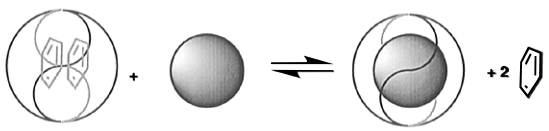


Figure 9.

leads to three particles on the right hand side. For the host, the process involves a hostage upgrade. Any solvent on the surface of the guest is also freed to the medium as encapsulation occurs. This should be an entropy driven process.

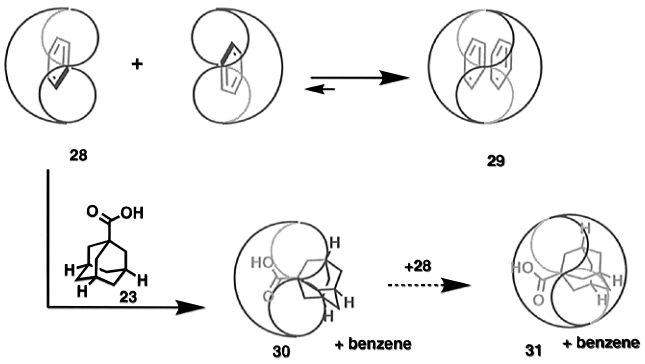


Figure 10.

A simple model for the encapsulation of two molecules of solvent can be constructed by considering that two solvated hemispheres come together to form a well-filled capsule. The microscopic reverse of the process, the separation of the fully-loaded softball into its halves, is also straightforward: as the seam of hydrogen bonds unravels, the two solvents need only to be positioned in a way that one solvent remains in the concave cavity of each subunit (Figure 10). This may be likened to the ease of evenly dividing a peach when the pit has already separated in the plane of the knife cut: little vacuum is created as the halves are pulled apart. It would appear, then, that two solvent guests are encapsulated smoothly since the softball is, after all, a dimer. For a larger solvent as xylene, the hemispheres should still be well solvated but as they come together the capsule is destabilized. Calculations reported elsewhere indicate that a constellation of two xylenes can be best accommodated inside when they are forced to a face-to-face distance of <3.3 Å.

How only one large guest becomes encapsulated is somewhat more complicated, but Figure10 provides a schematic proposal which is scarcely more than a restatement of the facts: the guest sequentially replaces solvent within each hemisphere.

We were able to find some confirmation, albeit indirect, of the occupancy of the softball by benzene through a two solvent experiment. In either deuterated benzene or deuterated fluorobenzene, sharply defined NMR signals are observed for the softball with the characteristic downfield shifts that indicate its assembly (Figure 11). When a *mixture* of the two solvents was used, the spectrum becomes somewhat broadened, but cooling the sample led to an increased resolution in which *three* species of the capsule can be observed. In changing the relative amounts of the two solvents, the corresponding redistribution of the three signals occurs. If indeed two molecules of solvent occupy each capsule, then the predicted result would be three different species.

The positive enthalpy observed for encapsulation does not give a comparably simple or satisfying picture. Adamantanecarboxylic acid alone in a nonpolar solvent such as toulene is expected to be largely in the form of a hydrogen bonded dimer. In the presence of the softball, groups rich in hydrogen bond donors and acceptors abound and the carboxylic acid must be hydrogen bonded to the outer surface. We cannot predict how the enthalpy of those hydrogen bonds, many of which are of the bifurcated sort, are changed on the adamantane's moving to the interior. Nor can we predict whether the van der Waal's contacts between encapsulated solvents and the concave surface of the capsule are more or less favorable than those interactions of the hydrocarbon portion of the adamantane guest. We know that aromatics such as benzene or *p*-xylene are less polarizable, along the axis going through the centroid of the molecule, than

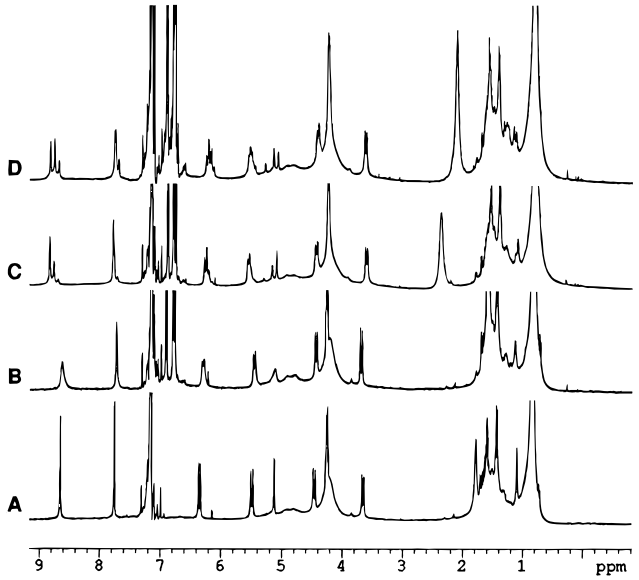


Figure 11. ^{1}H NMR spectra of compound **1a**: encapsulation of benzene-d_6 and fluorobenzene-d_5. The resonances of the *N*-H protons for the dimeric host assemblies occur between 8.6 and 8.8 ppm; these peaks are among the best resolved, clearly showing that three species are present. Incompletely deuterated benzene-d_6 resonances occur between 6.8 and 7.2 ppm. (A) Benzene-d_6 solvent (400 μL); 15.8 mM in **1a**, temperature = 25 °C; (B) benzene-d_6 solvent (400 μL) + fluorobenzene-d_5 (100 μL), 12.6 mM in **1a**, temperature = 25 °C; (C) as in part B at temperature = 0 °C; (D) benzene-d_6 solvent (400 μL) + fluorobenzene-d_5 (200 μL); 10.5 mM in **1a**, temperature = 0 °C.

saturated hydrocarbons such as cyclohexane.[29,30] However, it is uncertain how these molecules can fit into the cavity and there is no reliable way of predicting what the enthalpy of the overall process depicted in the equation should be.

What is the relationship of the two encapsulated species to each other? Confined at such close quarters, are their rotational motions restricted? A clue is given by the behavior of asymmetric guests within. To date, we have yet to observe a loss of symmetry in the capsule's NMR spectra even when, for example, asymmetric guests or two different guests are inside. Accordingly, the guests must be rotating rapidly within. For the two guests encapsulated in the softball, the motion might be similar to a binary star system, a microconstellation inside a cavity that defines their universe. This is not the case in the covalent systems of Reinhoudt,[8] who discovered a new form of stereoisomerism caused by restricted rotation of a guest inside a carcerand. Even constrained internal rotations, such as the increased barrier for rotation around the amide bond of encarcerated dimethylacetamide have been observed.[31] Whether such phenomena can be detected in a capsule held together with easily deformable hydrogen bonds remains to be seen, but there is cause for optimism. Relevant to the case at hand is the observation reported by Sherman.[32] In a (heterodimeric) capsule held together by only four hydrogen bonds, a desymmetrization in the NMR spectrum of encapsulated pyrazine was interpreted in terms of the guest's restricted rotation.

Additional insights can be gained by a quantitative evaluation of the volume of the interior cavity of **1**. In order to estimate this volume in the most precise way, we first optimized the conformation of the softball in the gas phase by using the force field Amber* of MacroModel 5.5.[20] Next a molecular dynamics simulation[33] in chloroform was run using the same force field. The resulting averaged structure was then analyzed with the program GRASP.[34] A molecular surface was built using a spherical probe of 1.4 Å radius, in such a way that open surface areas were artificially closed to allow measurement of the internal volume.[35] We calculated an average internal volume of 300 Å^3, and used the same program to calculate the guest volumes (Table 2).

Table 2. Molecular Volumes and Occupancy Factors for Some Guests in the Softball **1b**

guest	molecular vol (Å^3)	occupancy factor
23a	155	0.52
24	185	0.62
23b	137	0.46
26	181	0.60
27	188	0.63
23c	157	0.52
benzene	77	0.26
p-xylene	105	0.35

It can be seen that the occupancy factor[36] of the relevant guests ranges from 0.26 for one molecule of benzene to 0.63 for the biggest guest, [2.2] paracyclophane. The latter value corresponds to the occupancy factor of a typical solid. For benzene, two molecules inside correspond to a concentration of about 10 M, approximately the value in pure benzene (11 M). Alternatively stated, the occupancy, 0.52, for two benzenes inside is also close to the value (0.58) calculated for pure benzene. It should be possible to select solute combinations merely on the basis of occupancy for encapsulation in dilute solutions, and pseudoconcentrate them to high effective molarities within these capsules. For the case at hand, a combination of, say, C_4 with C_8 should better fill the capsule at ~5 M each inside than two molecules each of C_4 or C_8.

In order to evaluate how the size and shape of the cavity is affected by a bound guest we ran a similar molecular dynamics simulation[37] on the complex between molecule **1b** and the diacid **24**. We chose this large guest in order to maximize the effect of a massive, asymmetric, and polar guest on the cavity. One can imagine this guest molecule, inside the softball, as a lumpy sphere that frequently collides with the cavity walls. After the simulation, the guest was removed and the volume of the cavity was recalculated. It amounted to 290 Å^3. Apparently, the presence of this guest inside the ball does not substantially modify its internal volume, but some distortion of the cavity occurs. It is clear that among guests **23**−**27**, only one guest molecule at a time can be encapsulated. What can be said about smaller guests such as benzene and *p*-xylene? We ran molecular dynamics simulations[37] for these guests, and we encountered two completely different situations. In the case of benzene, two molecules can fit into the cavity and the simulation gave

(29) Craven, I. E.; Hesling, M. R.; Laver, D. R.; Lukins, P. B.; Ritchie, G. L. D.; Vrbancich, J. *J. Phys. Chem.* **1989**, *93*, 627.
(30) Gentle, I. R.; Ritchie, G. L. D. *J. Phys. Chem.* **1989**, *93*, 7740.
(31) Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. B.; Cram, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5590−5604.
(32) Chapman, R. G.; Sherman J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081−9082.
(33) Temperature was kept constant at 300 K during the whole simulation. Total time = 100 ps, time steps = 1 fs. GB/SA chloroform solvation was used.
(34) Nicholls, A.; Sharp, K. A., Honig, B. *Proteins* **1991**, *11*, 281.
(35) This task is automatically accomplished by GRASP. During the triangulation of the surfaces of the two softball halves for the calculation of the interior volume, the program calculates the average position of all the triangles at the edges of these surfaces. Joining of these edges generates the surface of the internal cavity.
(36) The occupancy factor of a guest molecule in the cavity of a host is usually defined as the ratio of the van der Waals radius of the guest to the volume of the cavity calculated on the van der Waals interior surface of the host. We calculated this factor based on the volumes generated by the program GRASP.
(37) T = 300 K, total time = 150 ps, time step = 1fs. GB/SA chloroform solvation was used.

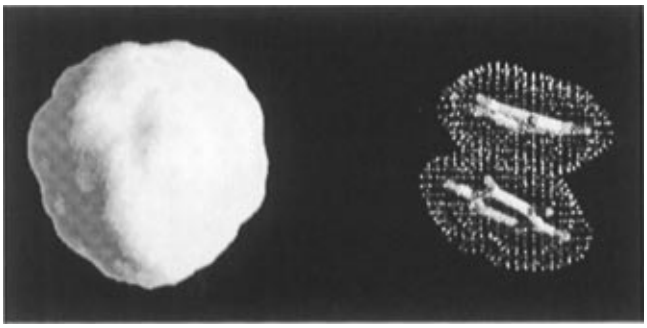


Figure 12. Size and shape of the cavity in the softball. The cavity inside the dimeric form of **1b**: (a) in the free capsule; (b) in the presence of **24**. Both structures originated by molecular dynamic simulations (see text for details).

an increased volume for the cavity (~330 Å^3), but the hydrogen-bonding network remains intact; the ball is not destabilized. The cavity shape after the simulation with two benzenes inside is nearly spherical (Figure 12, left), while the space occupied by the two benzenes is more elongated (shown on the right in Figure 12). In the case of *p*-xylene, two molecules can fit into the cavity only if the ball is deformed in such a way that at least two hydrogen bonds are destroyed. This means that a rupture is created in the softball and the assembly is destabilized. This result nicely fits the experimental observations of a broadened NMR spectrum in deuterated xylene.

The complex calculated between **1b** and two benzene molecules features the benzene molecules in parallel planes at an average distance of 3.4 Å. This is approximately the distance between layers in graphite. Accordingly, this system can be considered as a microenvironment where the guest molecules experience conditions that are more typical of the solid state. When proximity effects are also taken into account, it then becomes apparent that the interiors of these self-assembled balls represent very special chambers where reactions might take place. We will report on these developments in the sequel.

Finally, a word on vocabulary. Because there are not yet single words in the language precise enough to provide the images we intend to evoke, we have used—and unabashedly mixed—sports, fruits, political, and astrophysical metaphors. After all, reversible encapsulation is a recent concept and somewhat discontinuous with other recognition phenomena, and if the promise of discovery with these systems is fulfilled, new words may have to be added to an already jargon-ridden vocabulary.

Experimental Section

Hydrazide 4. A mixture of 2.61 g (11.24 mmol) of the hydrazide **3** and 15.16 g (33.7 mmol) of the tetrakis(bromomethyl)benzene **2** in 200 mL of DMF was heated to 65 °C. Then 1.35 g of NaH (60% in mineral oil) was added in 20 mL of DMF and the mixture was stirred for 20 min and then evaporated to dryness. The residue was slurried in 300 mL of ether, the solids were allowed to settle, and the supernatant was decanted. The supernatant was washed with water, dried over $MgSO_4$, and evaporated. The resulting residue was chromatographed on silica gel with 12% ethyl acetate/hexanes to give 2.40 g (41%) of the hydrazide as a colorless foam. ^{1}H NMR ($CDCl_3$, mixture of rotomers): δ 7.13 (s, 2H), 5.2−4.7 (m, 2H), 4.62 (s, 4H), 4.4−4.2 (m, 2H), 1.47 (s, 18H). HRMS (EI): calculated for $C_{20}H_{28}O_4N_2Br_2$, 518.0416; found 518.0413.

Glycoluril Hydrazide 6. To a solution of 17.05 g (46 mmol) of isopentyl ester glycouril **5** in 300 mL of DMSO at 50 °C was added 10.33 g (92.1 mmol) of KO^{t}Bu. After the mixture was stirred for 20 min, 2.395 g (4.6 mmol) of the dibromide in 10 mL of DMSO was added dropwise, the heating bath was removed, and the mixture was allowed to stir for 25 min. The reaction mixture was then poured into 1 L of water containing 15 mL of concentrated HCl. The mixture was then filtered and the solids washed with water. The solids were slurried in 300 mL of MeOH and filtered, which gave recovered excess glycoril as a white solid. The filtrate was evaporated, and the residue slurried in 200 mL of dichloromethane and filtered to give additional glycoluril. The filtrate was evaporated, and the residue was chromatographed on silica gel with 30% ethyl acetate/dichloromethane to give 1.87 g (56%) of the product as a colorless foam. ^{1}H NMR ($CDCl_3$, mixture of rotomers): δ 7.10 (br s, 2H), 5.80 (m, 2H), 5.18−4.75 (m, 4H), 4.50−4.18 (m, 8H), 1.40−1.72 (m, 24H), 0.92 (m, 12H).

Tetraacid Chloride 8. To a suspension of 0.100 g (0.354 mmol) of the tetraacid **12** (see below) in 1 mL of dichloromethane was added 1 mL of oxalyl chloride and 1 drop of a 10% v/v mixture of DMF in dichloromethane. The mixture was stirred for 3 h or until complete dissolution occured, then diluted with benzene and evaporated to give 0.120 g (96%) of the tetraacid chloride as a light brown solid. ^{1}H NMR ($CDCl_3$): δ 4.77 (s, 4H), 1.92 (s, 4H).

Acetylenic Ester 9. To a mixture of 1.0 g (8.77 mmol) of acetylene dicarboxylic acid in 30 mL of benzene at reflux was added 2.8 mL (21.2 mmol) of 4-methoxybenzyl alcohol in 4 portions over 15 min. The solution was then heated at reflux for 3 h with Dean-Stark removal of water. Following evaporation of the benzene, the residue was chromatographed on silica gel with 15% ethyl acetate/hexane to give 1.89 g (61%) of the ester as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.30 (d, 4H, J = 8.7 Hz), 6.88 (d, 4H, J = 8.6 Hz), 5.17 (s, 4H), 3.81 (s, 6H). HRMS (EI): calculated for $C_{20}H_{18}O_6$, 354.1103; found 354.1100.

Diester 9b. A mixture of 3.0 g (8.47 mmol) of the ester and 5 mL of furan was heated in a sealed tube placed in an 85 °C oil bath for 4 h. Following evaporation of the furan, the residue was chromatographed on silica gel with 30% ethyl acetate/hexane to give 2.33 g (65%) of the ester as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.31 (d, 4H, J = 8.4 Hz), 7.26 (s, 2H), 6.93 (d, 4H, J = 8.6 Hz), 5.73 (s, 2H), 5.16 (dd, 4H, J = 14.2, 26.5 Hz), 3.87 (s, 6H). HRMS (EI): calculated for $C_{24}H_{22}O_7$, 422.1366; found 422.1369.

Dihydro Diester 9a. A vigorously stirred mixture of 4.5 g (10.7 mmol) of the diene and ~0.5 g of 5% Pd/C in 60 mL of ethyl acetate was hydrogenated at ambient pressure until 260 mL of hydrogen had been consumed. Additional hydrogen was introduced until ^{1}H NMR analysis showed that the diene was consumed. The mixture was then filtered and the solvent evaporated to give 4.39 g (97%) of the cyclohexene as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.21 (d, 4H, J = 9.0 Hz), 6.82 (d, 4H, J = 9.0 Hz), 5.2 (m, 2H), 5.04 (dd, 4H, J = 13.5, 22.0 Hz), 3.76 (s, 6H), 1.80 (m, 2H), 1.42 (m, 2H). HRMS (EI): calculated for $C_{24}H_{24}O_7$, 424.1522; found 424.1517.

Dihydrophthalate 10. To a solution of 15.31 mL (140 mmol) of $TiCl_4$ in 30 mL of hexane at OC was added 125 mL of THF over 20 min. A slurry of 1.87 g (49.4 mmol) of LAH in 15 mL of THF was then added over 10 min. The mixture was then heated at reflux for 30 min and cooled to room temperature, and a solution of 5.70 g (13.4 mmol) of the cyclohexene in 15 mL of THF was added over 5 min. After 2 h, the mixture was poured into 1 L of 10% K_2CO_3(aq). The mixture was extracted with ether and the organic extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel with 25% ethyl acetate/hexane to give 4.32 g (79%) of the diene as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.23 (d, 4H, J = 9.1 Hz), 6.85 (d, 4H, J = 8.7 Hz), 5.02 (s, 4H), 3.79 (s, 6H), 2.25 (m, 4H). HRMS (EI): calculated for $C_{24}H_{24}O_6$, 408.1573; found 408.1567.

Bridged Tetraester 11. A mixture of 1.75 g (4.28 mmol) of the diene and 1.98 g (5.57 mmol) of the acetylene in 10 mL of benzene was heated at reflux for 40 h. Following evaporation of the benzene, the residue was chromatographed on silica gel with 35% ethyl acetate/hexane to give 2.46 g (61%) of a mixture of the starting components and 1.06 g (33%) of the product tetraester as a colorless oil. Resubjection of the recovered starting components to heating and chromatography gave an additional 2.37 g (41%) of the product after two additional cycles, for a total of 2.43 g (74%). ^{1}H NMR ($CDCl_3$): δ 7.17 (d, 8H, J = 8.5 Hz), 6.84 (d, 8H, J = 8.5 Hz), 4.97 (s, 8H), 4.42 (s, 2H), 3.79 (s, 12H), 1.58 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 164.6, 159.6, 140.8, 130.1, 127.3, 113.8, 66.9, 55.2, 40.8, 24.4. HRMS (FAB): calculated for $C_{44}H_{42}O_{12} - C_2H_4 + H^+ = C_{42}H_{39}O_{12}$, 737.2598; found 737.2611.

Centerpiece Tetraacid 12. To a solution of 1.33 g (1.74 mmol) of

the tetraester in 3 mL of dichloromethane and 3 mL of anisole was added 25 mL of TFA in one portion. After being stirred for 15 min, the mixture was diluted with benzene and evaporated. The residue was then diluted with ether and filtered to give 0.355 g (72%) of the tetraacid as a white powder. ^{1}H NMR (DMSO-d_6): δ 4.27 (s, 2H), 1.45 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 166.2, 140.8, 40.7, 24.1. HRMS (FAB): calculated for $C_{12}H_{10}O_8$, 282.0376; found 282.0371.

Synthesis of Furan 13. To a solution of 10.0 g (47.1 mmol) of 3,4-bis(acetoxymethyl)furan in 200 mL of methanol was added 7 mL of a saturated solution of K_2CO_3 in methanol. The flask was placed on a rotory evaporator with a bath temperature of about 50 °C, and the flask was rotated with heating but no vacuum for 15 min. The vacuum was then applied, and half the methanol was evaporated to drive out the methyl acetate byproduct. Following the addition of 100 mL of methanol, the procedure was repeated, and the solution fully evaporated. Two sequential additions and evaporations of 100 mL of benzene each were used to remove any residual methanol. The resulting residue was dissolved in 80 mL of DMF and cooled to 0 °C, and 4.51 g (60% in oil, 113 mmol, 2.4 eq) of NaH was added in 3 portions over 10 min. After 15 min, 12.35 mL (103 mmol, 2.2 equiv) of benzyl bromide was added over 1 h. The mixture was then allowed to warm to room temperature and stirred for 15 h, poured into 500 mL of water, and extracted with ether. The organic extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel with 8% ethyl acetate/hexanes to give 12.7 g (88%) of the dibenzyl ether as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.41 (s, 2H), 7.3−7.2 (m, 10H), 4.52 (s, 4H), 4.47 (s, 4H). HRMS (EI): calculated for $C_{20}H_{20}O_3$, 308.1412; found 308.1414.

Bridged Diester 14. A mixture of 14.33 g (46.6 mmol) of the dibenzylfuran and 6.93 g (48.7 mmol, 1.05 equiv) of dimethyl acetylenedicarboxylate was heated to 110 °C for 1 h, then cooled to room temperature. The residue was chromatographed on silica gel with 30% ethyl acetate/hexanes to give 18.69 g (89%) of the oxa-diene as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.4−7.2 (m, 10H), 5.69 (s, 2H), 4.45 (dd, 4H, J = 12.0 Hz), 4.28 (dd, 4H, J = 12.5 Hz), 3.73 (s, 6H). HRMS (EI): calculated for $C_{26}H_{26}O_7$, 450.1678; found 450.1683.

Durene Diol 15. To 200 mL of vigorously stirring THF at 0 °C was added 29.73 mL (269 mmol) of $TiCl_4$ dropwise over 20 min. A suspension of 3.64 g (95.2 mmol) of LAH in 100 mL of THF was then added in 3 portions over 10 min. The mixture was then heated at reflux for 30 min and cooled to room temperature, and a solution of 18.69 g (41.4 mmol) of the oxadiene in 40 mL of THF was added over 5 min. After 15 min, the mixture was poured into 1.4 L of 10% K_2CO_3 in water, and filtered. The blue gelatinous residue was extracted with THF, and the THF washes were dried over $MgSO_4$ and evaporated. The oily residue (17.0 g) was dissolved in 150 mL of THF, and 1.92 g (538 mmol) of LAH was added in 4 portions over 5 min. After the mixture was stirred for 15 min, 4 g of ice was added cautiously, then 5 mL of 15% NaOH, then 7 mL of water, then 30 g of $MgSO_4$. Filtration and evaporation afforded an oily residue which was chromatographed on silica gel with 70% ethyl acetate/hexanes to give 14.14 g (90%) of the diol as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.41 (s, 2H), 7.4−7.1 (m, 10H), 4.65 (s, 4H), 4.46 (s, 4H), 4.41 (s, 4H). HRMS (EI): calculated for $C_{24}H_{26}O_4$, 378.1831; found 378.1830.

Durene Dihalide 16. To a mixture of 17.4 mL (149 mmol) of 2,6-lutidine, 8.65 mL (112 mmol) of methanesulfonyl chloride, and ∼0.5 g of DMAP in 90 mL of DMF at 0 °C was added a solution of 14.1 g (37.3 mmol) of the diol in 40 mL of DMF over 10 min. The mixture was then allowed to warm to room temperature and stirred for 15 h. Then 20 g of LiBr was added in 50 mL of THF, and the mixture was stirred for 1 h, then poured into 500 mL of 1.5 N HCl and extracted with ether. The organic extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel with 12% ethyl acetate/hexanes to give 14.37 g (76%) of the dibromide as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.43 (s, 2H), 7.4−7.2 (m, 10H), 4.70 (s, 4H), 4.52 (s, 4H), 4.49 (s, 4H). HRMS (EI): calculated for $C_{24}H_{24}Br_2O_2$, 502.0144; found 502.0139.

Acylated Glycoluril 19. To a solution of 11.67 g (39.7 mmol) of diphenylglycouril in 280 mL of DMSO was added 4.45 g (79.3 mmol) of powdered KOH. The mixture was heated to 50 °C, and after 10 min, 2.0 g (3.97 mmol) of the dibromide was added in 50 mL of DMSO. The solution was stirred at 50 °C for 10 min, then poured into 1.2 L of water and filtered. The solid residue was extracted with THF, and the THF was dried over $MgSO_4$ and evaporated. The resulting residue was slurried in 30 mL of pyridine, 3 mL of acetic anhydride was added, and the mixture was heated at reflux for 2 h, during which time the residue dissolved. The mixture was then evaporated and the residue chromatographed on silica gel with 40% ethyl acetate/dichloromethane to give 2.60 g (96%) of the monoacetate as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.49 (s, 1H), 7.47 (s, 1H), 7.4−6.9 (m, 10H), 6.34 (s, 1H), 4.96 (d, 2H, J = 20.0 Hz), 4.85 (d, 2H, J = 18.5 Hz), 4.6−4.5 (m, 8H), 4.29 (d, 2H, J = 19 Hz), 4.18 (d, 2H, J = 20.0 Hz), 2.52 (s, 3H). HRMS (EI): calculated for $C_{42}H_{38}N_4O_5$, 678.2842; found 678.2846.

Protected Dihalide 20. A stream of HBr(g) was bubbled through a solution of 2 g (2.95 mmol) of the monoacetate in 100 mL of $CHCl_3$ for 8 min. The flask was then capped, and the solution was stirred for 3.5 h. Benzene was then added and the solution evaporated. The residue was chromatographed on silica gel with 7.5% ethyl acetate/dichloromethane to give 1.64 g (91%) of the dibromide as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.4−6.8 (m, 12H), 6.28 (s, 1H), 4.93 (d, 1H, J = 15.6 Hz), 4.81 (d, 1H, J = 15.9 Hz), 4.62 (s, 2H), 4.60 (s, 2H), 4.27 (d, 1H, J = 15.0 Hz), 4.14 (d, 1H, J = 15.6 Hz), 2.51 (s, 3H). HRMS (EI): calculated for $C_{28}H_{24}N_4O_3Br_2$, 622.0216; found 622.0215.

Glycoluril Hydrazide 21. A mixture of 1.70 g (7.32 mmol) of the hydrazide and 0.35 g (14.6 mmol) of NaH in 20 mL of DMF was stirred for 15 min. The dibromide was then added as a solid, and the mixture was then stirred 20 min and poured into 300 mL of water. The mixture was extracted with ether and the organic extracts were dried over $MgSO_4$ and evaporated. The resulting residue was dissolved in 30 mL of THF and 6 mL of MeOH, and 5 drops of saturated LiOH-(aq) was added. After 30 min, the mixture was evaporated to one-fourth the original volume, diluted with dichloromethane, dried over $MgSO_4$, and evaporated. The resulting residue was chromatographed on silica gel with 50% ethyl acetate/dichloromethane to give 1.46 g (84%) of the hydrazide as a colorless oil. ^{1}H NMR ($CDCl_3$, mixture of rotamers): δ 7.3−7.0 (m, 12H), 5.1−4.7 (m, 4H), 4.4−4.0 (m, 4H), 1.5−1.3 (m, 18H). HRMS (EI): calculated for $C_{36}H_{40}N_6O_6$, 652.3009; found 652.3011.

Glycoluril Amine 22. A stream of HCl(g) was bubbled through a solution of 0.060 g (0.0919 mmol) of the monoacetate in 3 mL of nitromethane and 1 mL of $CHCl_3$ for 1 min. The solvents were then evaporated to give 0.044 g (98%) of the hydrochloride as a white powder. ^{1}H NMR (DMSO-d_6): δ 9.9 (br s, 3H), 8.18 (s, 2H), 7.3−7.1 (m, 10H), 4.79 (d, 2H, J = 11 Hz), 4.38 (s, 4H), 4.18 (d, 2H, J = 12 Hz). HRMS (EI): calculated for $C_{36}H_{40}N_6O_6$, 652.3009; found 652.3011.

Softball 1a (R = Phenyl). To a mixture of 0.10 g (0.205 mmol) of the tetrahydrophthalazine hydrochloride in 2 mL of DMF was added 0.143 mL (1.02 mmol) of NEt_3, and the mixture was stirred to effect dissolution. After cooling to 0 °C, a solution of 0.0364 g (0.102 mmol) of the tetraacid chloride in 0.4 mL of $CHCl_3$ was added dropwise. The mixture was allowed to warm to room temperature, stirred for 14 h, then evaporated to dryness. The residue was slurried in 2 mL of MeOH, then 5 mL of water was added, the mixture was filtered, and the solids were washed with water. Drying of the solids under vacuum gave 0.101 g (89%) of the crude isomer mixture as a white solid. The residue was chromatographed on silica gel with 10−30% MeOH/chloroform to give the C-shaped isomer (middle fraction) as a colorless oil. ^{1}H NMR (DMSO-d_6): δ 8.17 (s, 4H), 7.46 (s, 4H), 7.18−7.0 (m, 20H), 5.33 (d, 4H, J = 15.6 Hz), 5.07 (d, 4H, J = 15.9 Hz), 4.98 (s, 2H), 4.68 (d, 4H, J = 11.6 Hz), 4.06 (d, 4H, J = 15.9 Hz), 1.44 (s, 4H). HRMS (CI): calculated for $C_{64}H_{50}N_{12}O_8$, 1114.3874; found 1114.3872.

Softball 1b. Through a solution of 1.0 g (1.37 mmol) of the hydrazide in 50 mL of nitromethane and 10 mL of chloroform was bubbled a gentle stream of HCl(g) with a pasteur pipet for 30 s. After the mixture was stirred for 1 min, the solution was purged with argon for 3 min, which caused a white precipitate to form. The solvent was evaporated, and the residue was subjected to high vacuum, producing 0.734 g (95%) of the hydrazine hydrochloride as an off-white foam. To a solution of this foam in 8 mL of DMF was added a trace of DMAP and 0.956 mL (6.50 mmol) of NEt_3, and the solution was cooled to 0 °C. A solution of 0.231 g (0.650 mmol) of the acid chloride in 2 mL of chloroform was added dropwise, and then the solution was allowed to warm to room temperature and stirred for 14 h. The solvents were

then evaporated to give a moist residue, which was dissolved in 4 mL of MeOH and added to 30 mL of water. The mixture was filtered, and the solids washed with water. To the solids were added 40 mL of benzene, and the mixture was vigorously stirred for 15 min. Filtration and evaporation of the filtrate gave a tan solid which was about 75% pure C-shaped isomer by NMR. Chromatograph of this residue on silica gel with 10% MeOH/25% ethyl acetate/65% chloroform gave 0.071 g (9%) of the product as an off-white glassy solid. Additional C-shaped isomer can be obtained from chromatography of the remaining crude residue. ^{1}H NMR (DMSO-d_6): δ 8.45 (s, 4H), 7.43 (s, 3H), 5.25 (d, 4H, J = 16.8 Hz), 5.09 (d, 4H, J = 16.9 Hz), 4.97 (s, 2H), 4.60 (d, 4H, J = 15.0 Hz), 4.45 (d, 4H, J = 15.0 Hz), 4.19 (t, 4H, J = 6.6 Hz), 4.08 (t, 4H, J = 6.6 Hz), 1.7−1.4 (m, 16H), 0.88 (d, 12H, J = 4.5 Hz), 0.86 (d, 12H, J = 4.8 Hz). ^{13}C NMR (benzene-d_6): δ 167.6, 167.2, 157.9, 153.6, 144.0, 139.2, 129.8, 129.6, 126.0, 83.7, 74.9, 65.8, 65.5, 46.0, 45.1, 37.8, 37.6, 25.7, 25.5, 23.0, 22.9. HRMS (FAB): calculated for $C_{64}H_{74}O_{16}N_{12}$, 1266.5346; found 1266.5334.

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