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Chemistry

Synthesis and assembly of self-complementary calix[4]arenes

(self-assembly/encapsulation/molecular recognition/hydrogen bonding/urea)

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ABSTRACT **A calix[4]arene was designed to reversibly dimerize and form an egg-shaped enclosure. Adhesive interactions in the assembly were provided by four self-associating ureas, which form a cyclic array containing 16 hydrogen bonds. The synthesis was completed in four steps from the previously described *O,O′,O″,O‴*-tetrabenzylcalix[4]arene. Evidence for dimerization of the calixarene tetraurea was provided by ^{1}H NMR, mass spectrometry, and the observation of encapsulated molecules. The resulting cavity was of sufficient size to capture guests such as ethyl benzene and *p*-xylene.**

Synthetic self-assembly is a relatively new field that has become a current focus of molecular recognition research (1–3). In biological contexts, self-assembly is a ubiquitous organizational strategy where modular components are held together by noncovalent interactions. Complex structures such as membranes, ribosomes, and viral capsules attest to the importance and power of self-assembly. For the synthetic chemist, self-assembly holds a similar promise for the rapid construction of large and elaborate molecular architectures. In addition, these new assemblies often possess specific properties and abilities, which differ entirely from their smaller components. In this regard, we have recently introduced a molecule that dimerizes and forms a well-defined cavity capable of encapsulating small molecules (4, 5). We introduce here self-assembling calixarene **1**, which is easily synthesized and possesses a more sizable cavity. The resulting assembly **1.1** can encapsulate molecules such as toluene and chloroform. The synthesis, assembly, and encapsulation properties of tetraurea **1** are presented.

Like its predecessor, assembly **1.1** is a dimeric capsule held together by hydrogen bonds. The hydrogen bonds are provided by an unusual circular array of eight ureas, which "zippers" the two hemispheres together (Fig. 1) (6–9). Four of the interlocking ureas come from the top hemisphere, and four come from the bottom hemisphere. The ureas are held in place by a rigid calix[4]arene scaffold, which is locked in the "cone-conformation". This inviting bowl-like shape and their synthetic availability have made calixarenes attractive scaffolds for molecular recognition. Indeed, recent reviews of calixarene chemistry have been largely dedicated toward applications in supramolecular chemistry (10–12). Of note are calix[4]arene systems designed by van Loon *et al.* (13) and Kok *et al.* (14) to similarly assemble by hydrogen bonding.

Our inspiration for using ureas in self-assembly was drawn from urea itself, which can assemble in the solid state into cylinders, having an alkyl chain threaded through its center (15, 16). Furthermore, the hydrogen-bonding propensities of ureas have been extensively studied (17, 18). X-ray crystallography has shown that a "head-to-tail" topology, in which the carbonyl oxygen of one urea hydrogen bonds to both -NH groups of a neighboring urea, is the most common. For our purposes, this head-to-tail arrangement was particularly advantageous because the ureas do not all have to lie in the same plane and can act as hinges that allow a circular configuration and also can compensate for the splay of the dimerized calix[4]arenes.

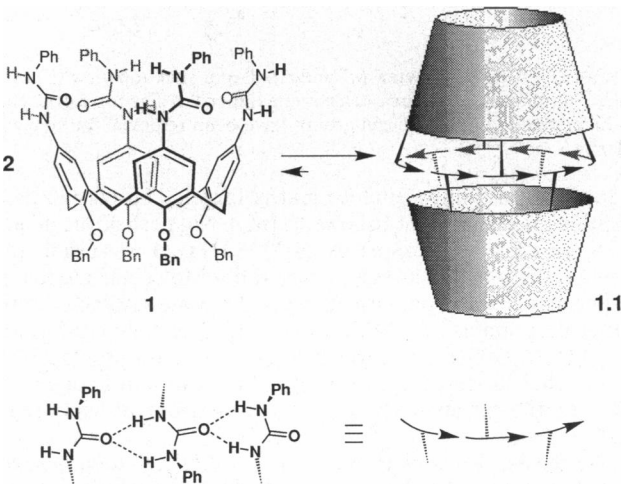

FIG. 1. Dimerization of calixarene **1**. The complex **1.1** is shown schematically with arrows representing ureas hydrogen-bonded in a head-to-tail topology. Bn, benzyl.

Molecular modeling studies suggested that a calix[4]arene in the cone-conformation would provide an optimal scaffold to position four ureas in the desired self-complementary manner. In the MM2 (MacroModel) minimized structure (19), the two calixarenes are twisted by 45°, resulting in an interleaved dimer that seals the resulting cavity (Fig. 2*a*). The symmetry of dimer **1.1** can be seen from a top view, in which the ureas that circle the equator of the assembly are particularly visible (Fig. 2*b*). All eight ureas are turned in the same direction and hydrogen-bonded to their neighbors, forming a total of 16 hydrogen bonds.

MATERIALS AND METHODS

General. Throughout, reagent-grade solvents were used except where noted. Chloroform and methylene chloride were dried over molecular sieves. Melting points were measured on an Electrothermal (Southend, England) model 9100 melting point apparatus. NMR spectra were taken on a Varian model XL-300 (300 MHz) and a Bruker (Billerica, MA) model WM-250 (250 MHz) spectrometer. ^{19}F NMR spectra were reported as positive values corresponding to an upfield shift from CCl_3F (0.00 ppm). IR spectra were obtained on a Perkin–Elmer model 1600 Fourier-transform IR spectrometer. High-resolution mass spectra were obtained on a Finnigan–MAT (San Jose, CA) model 8200 instrument. Plasma desorption mass spectra were obtained on a BioIon (Applied Biosystems) model 20 instrument with a ^{252}Cf source. Samples were prepared by dissolution of **1** in the specified solvents and

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Abbreviations: DMSO, dimethyl sulfoxide; FAB, fast atom bombardment; HRMS, high-resolution mass spectrometry; Ph, phenyl; Bn, benzyl; CPK, Corey–Pauling–Koltun (models).

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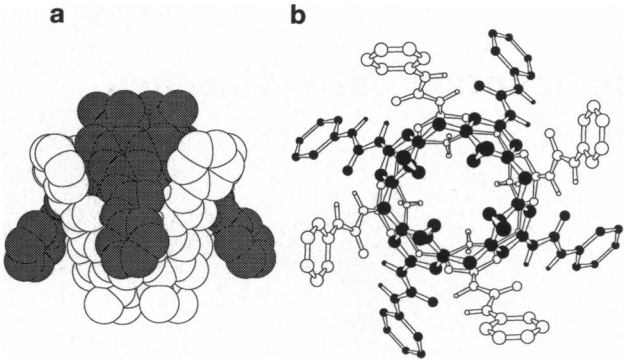


FIG. 2. A CPK side view (*a*) and a ball-and-stick top view (*b*) of a MM2-minimized structure of calixarene dimer **1.1**. The top calixarene is highlighted, and the benzyl groups have been removed for viewing clarity.

deposited on a nitrocellulose matrix target. The plasma desorption mass spectra of **1** showed a [M + Na] peak as the major peak for all calixarene species. A [M + H] peak was visible for some species but in a much lower ratio. Molecular modeling experiments were performed with the MACROMODEL computer program using a MM2 force field. The cone-conformer of *O,O',O'',O'''*-tetrabenzylcalix[4]arene (**2**) was synthesized from the de-tertbutylation of the cone-conformer of *O,O',O'',O'''*-tetrabenzyl-4,4',4'',4'''-tetratertbutylcalix[4]arene (20).

Synthesis. *Cone-conformer of* O,O',O'',O'''*-tetrabenzyl-4,4',4'',4'''-tetraiodocalix[4]arene (3).* Silver trifluoroacetate (1.20 g, 6.37 mmol) was heated under reflux for 15 min in 100 ml of dry $CHCl_3$ under argon. The cone-conformer of *O,O',O'',O'''*-tetrabenzylcalix[4]arene (**2**) (1.00 g, 1.24 mmol) in 30 ml of $CHCl_3$ was added dropwise, and the solution was heated under reflux for an additional 15 min. Iodine (1.62 g, 6.37 mmol) was placed in the elbow of a Y-tube, and the vapor was passed over it, slowly delivering I_2 into the reaction flask. After 30 min, addition was complete, and the reaction mixture was bright purple. The solution was washed with 1.0 M sodium thiolsulfate (100 ml twice) and brine (100 ml once), dried over $MgSO_4$, and concentrated *in vacuo* to a white solid (1.63 g, 100%): mp = 285–286°C; IR (KBr) 3028, 2913, 1561, 1456, 1191, 980, 862, 834, 746, 697 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.10 (m, 20 H, Ph), 6.91 (s, 8 H, Ar), 4.88 (s, 8 H, -CH_2Ph), 3.91 (d, 4 H, J = 13.6 Hz, -CH_2-), 2.70 (d, 4 H, J = 13.6 Hz, -CH_2-); high-resolution mass spectroscopy (HRMS) [fast atom bombardment (FAB), nitrobenzyl alcohol] calcd for $C_{56}H_{45}I_4O_4$ (M + H), 1288.949693; found, 1288.94845 (where Ph is phenyl).

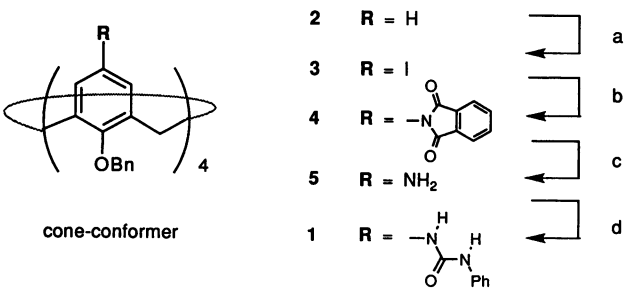
*Cone-conformer of 4,4',4'',4'''-tetraamino-*O,O',O'',O'''*-tetrabenzylcalix[4]arene (5).* Tetraiodocalixarene **3** (623 mg, 0.484 mmol), phthalimide (569 mg, 3.87 mmol), and Cu_2O (830 mg, 5.80 mmol) were heated in 2 ml of *N*-methyl-2-pyrrolidinone at 200°C for 16 hr. The solution was cooled, diluted with 150 ml of CH_2Cl_2, and filtered. The filtrate was concentrated to an oil (mostly *N*-methyl-2-pyrrolidinone) by rotary evaporation and then triturated with 1.0 M HCl solution (300 ml). The suspension was sonicated, and the crude product **4** was collected as a brown solid containing some excess phthalimide (Phth): ^1H NMR (250 MHz, $CDCl_3$) δ 7.60–7.10 (m, 36 H, Ph and Phth), 6.88 (s, 8 H, Ar), 5.00 (s, 8 H, -CH_2Ph), 4.30 (d, 4 H, J = 13.4 Hz, -CH_2-), 3.08 (d, 4 H, J = 13.5 Hz, -CH_2-).

The entire sample of tetraphthalimidocalixarene (**4**) was suspended in 20 ml of EtOH and 4.5 ml of hydrazine hydrate. The solution was refluxed for 3 hr and then diluted with H_2O. The mixture was extracted repeatedly with CH_2Cl_2 (100 ml four times). The organic layers were combined, dried over Na_2CO_3, and concentrated *in vacuo* to a brown solid (409 mg, 100% from the tetraiodocalixarene **3**): mp = 148°C; IR (KBr) 3405, 3345, 3038, 1608 (br), 1473, 1212, 992, 756, 868 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.00 (m, 20 H, Ph), 5.98 (s, 8 H, Ar), 4.83 (s, 8 H, -CH_2Ph), 4.05 (d, 4 H, J = 13.5 Hz, -CH_2-), 3.05 (s, 8 H, -NH_2), 2.70 (d, 4 H, J = 13.5 Hz, -CH_2-); HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{56}H_{53}N_4O_4$ (M + H), 845.406681; found, 845.40740.

*Cone-conformer of 4,4',4'',4'''-tetrakis(phenyl urea)-*O,O',O'',O'''*-tetrabenzylcalix[4]arene (1).* Phenyl isocyanate (150 μl) and tetraaminocalixarene (**5**) (95 mg, 0.122 mmol) were dissolved in 15 ml of CH_2Cl_2 and stirred for 1 hr. The solution was concentrated *in vacuo* to a beige solid. Chromatography on silica gel (13%–15%, EtOAc/CH_2Cl_2) gave a white solid. The product was taken up in toluene and reconcentrated *in vacuo* to remove EtOAc and CH_2Cl_2 (99 mg, 67%): mp = 195–196°C (decomposed); IR (KBr) 3383, 3033, 2928, 1670, 1598, 1566, 1542, 1498, 1473, 1442, 1315, 1206, 750, 696 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.34 (s, 4 H, -NH), 7.79 (d, 8 H, J = 6.9 Hz, *o*-Ph), 7.59 (d, 4 H, J = 3.0 Hz, Ar), 7.40–7.00 (m, 36 H, Ph and -NH), 5.73 (d, 4 H, J = 3.0 Hz, Ar), 4.74 (d, 4 H, J = 12.6 Hz, -CH_2Ph), 4.39 (d, 4 H, J = 12.6 Hz, -CH_2Ph), 3.57 (d, 4 H, J = 12.3, -CH_2-), 2.26 (d, 4 H, J = 12.6, -CH_2-); HRMS (FAB, nitrobenzyl alcohol) calcd for $C_{84}H_{73}N_8O_8$ (M + H), 1321.55514; found, 1321.55323.

RESULTS

Synthesis. The cone-conformer of tetrabenzylcalixarene (**2**) was synthesized as described (20). The benzyl groups prevent internal rotations of the calix[4]arene macrocycle and permanently fixed its conformation. Of the three possible isomers, the cone-conformer was selectively synthesized. Functionalization proceeded smoothly, using similar examples from the literature (10–12). The synthetic route is outlined in Scheme I. Conditions



Scheme I

were as follows: for a—I_2, CF_3CO_2·Ag, $CHCl_3$, reflux; for b—phthalimide, Cu_2O, *N*-methylpyrrolidinone at 200°C for 12 hr; for c—H_2NNH_2, EtOH, reflux for 3 hr; and for d—PhNCO, CH_2Cl_2. In this manner, the three-step procedure of iodination, Ullmann coupling, and hydrazinolysis efficiently introduced four *p*-amino groups into calixarene *2* (21). Subsequent reaction of tetraamine *5* with phenyl isocyanate gave the desired tetraurea **1** in an excellent overall yield (67%).

Assembly. Evidence for the assembly of calixarene **1** was provided by a combination of ^1H NMR spectroscopy, mass spectrometry, and, most importantly, the detection of molecules in the resulting cavity. The first indication that calixarene tetraurea **1** was assembling was provided by its ^1H NMR spectra. In all nonpolar solvents examined so far, the ^1H NMR spectra of **1** displayed an unusual symmetry (Fig. 3). The spectra were unlike any of the nonassembling synthetic precursors of **1** and even differed from the ^1H NMR spectra of calixarene **1** polar solvents such as dimethyl sulfoxide (DMSO)-d_6 (Fig. 3). The unusual ^1H NMR spectra of **1.1** was attributed to the differing symmetries of the dimeric complex versus the unassociated calixarene. Typically, calix[4]arenes that are fixed in the cone-conformation

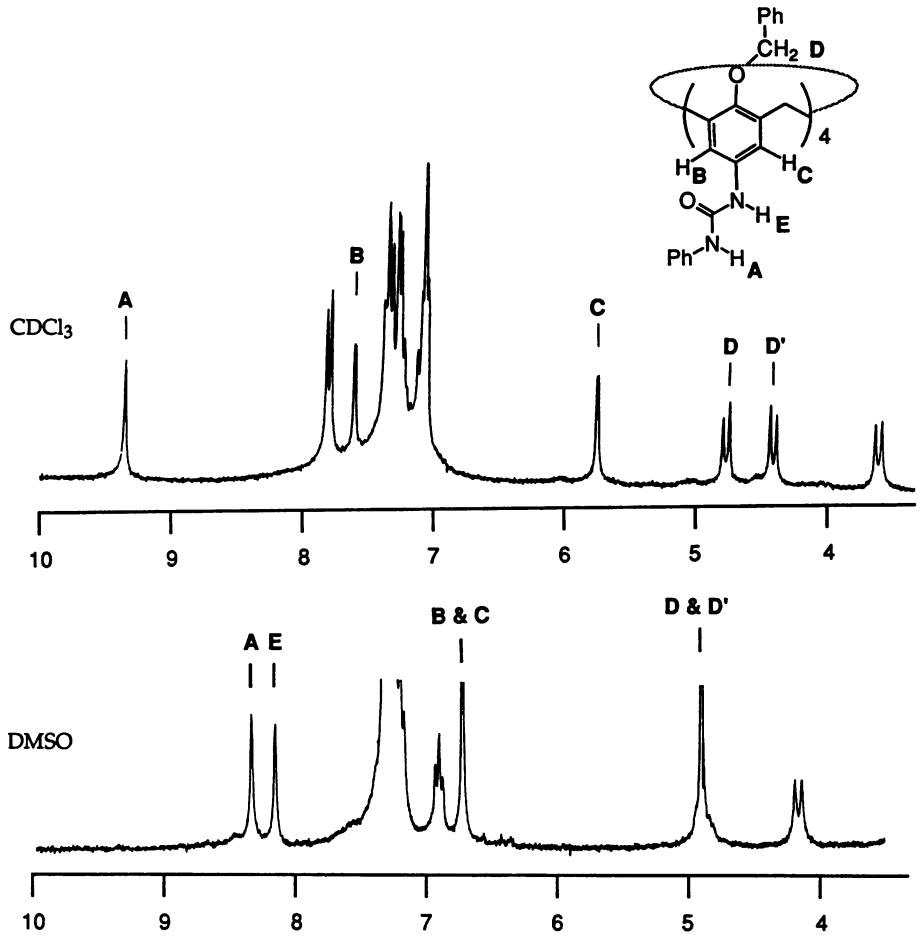


FIG. 3. ^{1}H NMR spectra of **1.1** in $CDCl_3$ and DMSO-d_6.

have an apparent C_4 symmetry, so that every aryl ring is chemically equivalent. In contrast, the octaurea dimer **1.1** possesses an S_8 symmetry in which each individual calixarene is chiral, although the overall assembly is meso and therefore achiral.

The asymmetry of calixarene **1** in nonpolar solvents correlated well with that anticipated for the desired assembly (**1.1**). Most striking was the desymmetrization of the calixarene aryl (H_B and H_C) and benzyl protons (H_D and $H_{D'}$) in the ^{1}H NMR spectra, which in previous derivatives had been singlets. For example in $CDCl_3$, protons H_B and H_C of dimer **1.1** were at 7.59 ppm and 5.73 ppm, respectively, and these assignments were verified by their *meta*-coupling of 3.0 Hz. Likewise, the benzyl protons H_D and $H_{D'}$ became diastereotopic and exhibited large geminal coupling constants of 12.6 Hz. Otherwise, the ^{1}H NMR spectra of **1.1** was consistent with that of previous cone-shaped calix[4]arene derivatives. In particular, the bridging methylenes ($-CH_2-$) remained a simple AB quartet with a δ_ν characteristic of the cone-conformation (22, 23).

The source of the asymmetry in dimer **1.1** is apparently the slowed rotation about the aryl-urea bond. We propose that the circular hydrogen-bond array of the dimer forces all eight ureas to point in the same direction. This restricted rotation also explains the large downfield shift of aryl proton H_B and the upfield shift of H_C from the constant proximity of the urea carbonyl and -NH, respectively. By contrast, highly competitive solvents such as DMSO caused the collapse of protons H_B and H_C into a singlet at an intermediate value of 6.79 ppm, apparently from the disruption of the hydrogen-bonding array.

Although the assembly had a more complex symmetry than its corresponding monomer **1**, the ^{1}H NMR spectra of dimer **1.1** was still highly symmetrical and fairly well-resolved; this gave additional support for the formation of a highly ordered and well-defined assembly. In fact, the retention of C_4 symmetry upon assembly was consistent only with the desired dimer **1.1**, in which all four ureas point in the same direction. Any other rotational isomer would have led to a considerably more complex ^{1}H NMR spectra.

The ^{1}H NMR also indicated a high degree of hydrogen bonding in the complex. In nonpolar solvents, the urea protons of **1.1** were shifted significantly downfield in comparison to diphenyl urea (≈6.2 ppm). Amazingly, the urea proton H_A of dimer **1.1** shifted even further downfield than the corresponding proton of the monomer in the strongly hydrogen-bonding solvent DMSO-d_6. For example in $CDCl_3$, H_A was at 9.34 ppm, a full 1.0 ppm further downfield than in DMSO (Fig. 3). The urea protons of **1.1** also remained downfield, even when diluted to the limits of the NMR spectrometer used (≈1 mM). In contrast, the spectra of most ureas, such as diphenyl urea, are highly concentration dependent. The second urea proton H_E of **1.1** was also shifted downfield but to a lesser extent and in $CDCl_3$ was buried in the 7.40- to 7.00-ppm multiplet. The large 2.0-ppm difference between urea protons H_A and H_E showed that they were in very different environments in the assembly. Molecular modeling of the dimer suggests two explanations for the smaller downfield shifts of H_E. In the model, the "inner" urea proton H_E comes in close contact with a phenyl ring of the opposing calixarene. The close contacts of the phenyl group may also explain the large upfield shifts of the nearby calixarene aryl proton H_C in the assembly. Second, modeling also predicts that the urea -NH groups will be

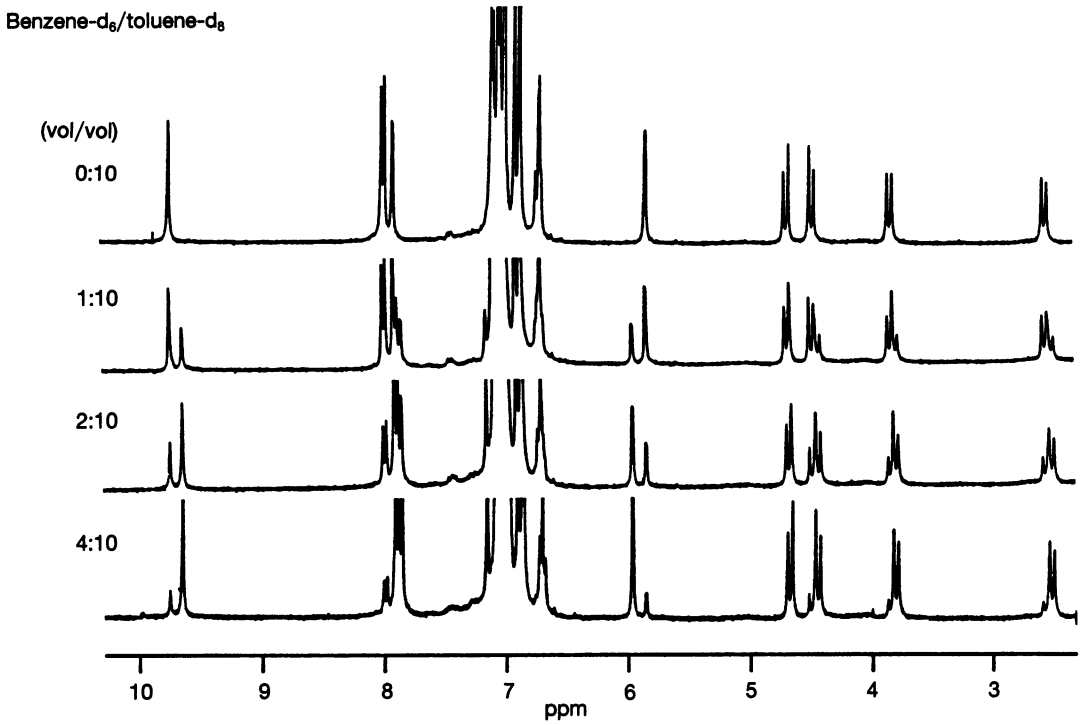


FIG. 4. The top ^{1}H NMR spectra shows dimer **1.1** in toluene-d_8. Subsequent spectra show the effects of adding increasing amounts of benzene-d_6. Solvent ratios represent volume measurements.

hydrogen-bonded at different angles to the C=O dipole, which could result in very different hydrogen bond strengths and chemical shifts.

The best evidence for the existence of calixarene **1** as a hydrogen-bonded dimer comes from the encapsulation of solvent molecules inside the assembled cavity. Inclusion was most apparent in mixed solvent systems, where two distinct calixarene assemblies were observed by ^{1}H NMR. For example, the sequential addition of benzene-d_6 to a solution of assembled dimer **1.1** in toluene-d_8 led to the appearance of a second calixarene species (Fig. 4). From the similar splitting patterns, it was evident that both calixarene species were still assembled, and we attributed the two different species to be assemblies containing benzene-d_6 and toluene-d_8, respectively. The addition of more benzene-d_6 shifted the equilibrium even further toward the benzene-d_6 encapsulated species until it became predominant. To date, no solvent has been found in which the dimer **1.1** appears to be empty.

Competition experiments gave the relative fit of different included guests. Measurements of their relative populations in an equimolar solvent mixture led to the following series: ethyl benzene < *p*-xylene < *o*-xylene < toluene < benzene ≃ chloroform. Chloroform and benzene were excellent guests, whereas ethyl benzene was the worst. The series roughly corresponds to the relative van der Waals volumes of the guests, with smaller molecules offering the better fit. Bucking the trend were ethyl benzene, *p*-xylene, and *o*-xylene, which all have nearly identical volumes. These three aromatic guests were apparently differentiated by shape.

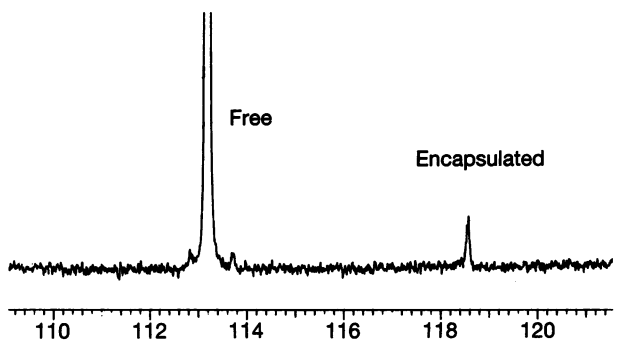


FIG. 5. ^{19}F NMR spectra of **1.1** in 1% (fluorobenzene/*p*-xylene-d_{10}), showing free and encapsulated fluorobenzene.

Encapsulation was particularly favorable in bulky solvents that provide poor competition for the cavity compared with smaller guest molecules (24, 25). For example, a solution of **1** in 1% (fluorobenzene/*p*-xylene-d_{10}) already showed equal populations of the two encapsulated species. In the case of fluorobenzene, the encapsulated guest was directly observable by ^{19}F NMR (Fig. 5). A new peak appeared 5.4 ppm upfield of the bulk fluorobenzene peak at 113.1 ppm; this new peak was not visible in the absence of **1.1**.

There are indications that calixarene **1** assembles and retains encapsulated guests even in the gas phase. The plasma desorption mass spectra showed the presence of a ternary complex in excellent agreement with the observed binding propensities of calixarene **1** in solution. The calixarene dimer peak [2M + Na] was visible in every plasma desorption mass spectra of **1**. In contrast, the presence of a ternary complex consisting of calixarene dimer plus guest [2M + guest + Na] depended upon the last solvent used. The inclusion complex was seen only for solvents that by modeling were small enough to fit inside—such as benzene (Fig. 6*a*), chloroform (Fig. 6*b*), and methylene chloride. Larger solvents such as *p*-xylene or ethyl benzene, which are poor guests, showed no measurable inclusion complex. While these observations are consistent with encapsulation inside the dimer, other structures are possible for the assembly in the gas phase.

In conclusion, we have prepared a highly self-complementary calix[4]arene **1**. The large size and ease of synthesis make **1** an attractive self-assembling system. In nonpolar solvents, calixarene **1** was observed to dimerize through a circular array of eight hydrogen-bonded ureas, and the resulting cavity was capable of capturing and holding guest molecules. Future applications for self-assembling capsules of this sort are the

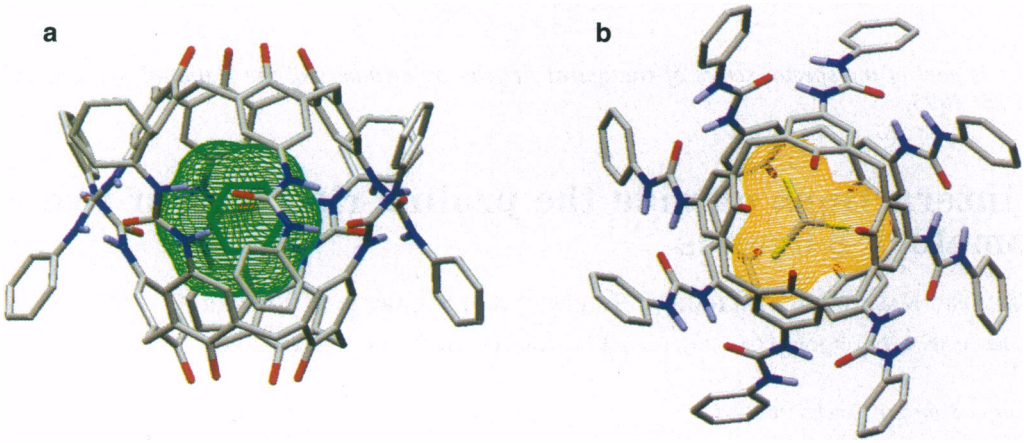


FIG. 6. (*a*) Side view of dimer **1.1** containing an encapsulated benzene guest. (*b*) Top view of dimer **1.1** containing a chloroform molecule. In each case, the encapsulated guests are shown with their respective van der Waals surfaces. The trimeric complexes were generated with the MACROMODEL program (19) and minimized using the MM2 force field.

transport of guests, stabilization of high-energy species (26), and as "high pressure" reaction chambers.

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