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Multicomponent, Hydrogen-Bonded Cylindrical Capsules

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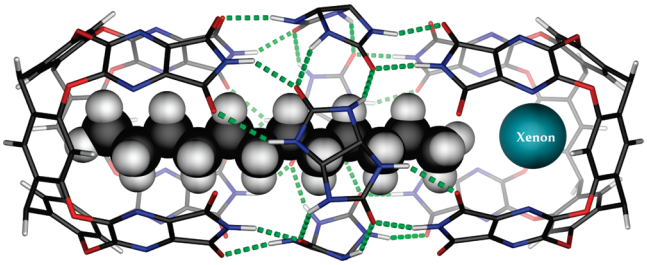

Self-assembled, hydrogen-bonded capsules emerge from synthetic resorcinarene-derived cavitands and soluble glycolurils when appropriate guest molecules are present. The assembly consists of 2 cavitands, 4 glycolurils and guest(s), and the arrangement of glycolurils leads to a chiral structure. The capsule features a space of ~620 Å^3 and accommodates narrow guests such as *n*-alkanes from C_{14} to C_{19}, or other molecules (e.g., capsaicin) and combinations of molecules of up to ~22 Å in length (e.g., two *p*-methylstyrene molecules). Positions of encapsulated nuclei can be predicted from NMR chemical shifts, with intense shielding of $\delta\Delta = -5$ ppm near the resorcinarene ends and mild deshielding of +0.5 to 1 ppm near the glycolurils at the capsule's center. Computational methods using nucleus independent chemical shifts (NICS) were used to map the induced magnetic shielding/deshielding for the inner space of the cavity. The asymmetric arrangement of the spacers creates a chiral steric and magnetic environment in the capsule and the geminal hydrogen atoms of encapsulated alkanes show diastereotopic proton signals. The two enantiomers interconvert (racemize) through an achiral intermediate involving a slight rotation of the spacers and lengthening of the cavity. Accordingly, longer, compressed alkanes accelerate the racemization by applying pressure from the inside on the capsule's ends. Guests that place hydrogen bond donors and acceptors near the glycolurils in the middle (e.g., *p*-isopropylbenzyl alcohol) also accelerate the racemization by facilitating the rotation of the glycolurils. Slow tumbling of guest on the NMR time scale inside the capsule leads to social isomerism of para-disubstituted benzenes such as *p*-methylstyrene. Flexible guests such as hexane tumble inside the cavity with an activation barrier of $\Delta G^{\ddagger} = 16.2$ kcal/mol. The middle of the extended capsule is narrow, but still accommodates phenyl groups such as those presented by *p*-quaterphenyl and alkylated biphenylcarbonitriles. The aromatic units in these guests report their positions by imparting magnetic anisotropy to the capsule components. Gases such as propane, butane, isobutane, propylene, 2-methylpropene, and 1,3-butadiene even xenon are coencapsulated with other guests and their motions inside are examined.

Introduction

The hydrogen-bonded dimeric capsule **1.1** (Figure 1) was introduced to surround and temporarily isolate guest molecules. The capsule defines a nanosized space of $\sim 4.2 \times 10^{-25}$ L (420 Å^3),[1−3] and molecules in this space enjoy a concentration of ~4 M. Like other reversibly formed capsules—whether

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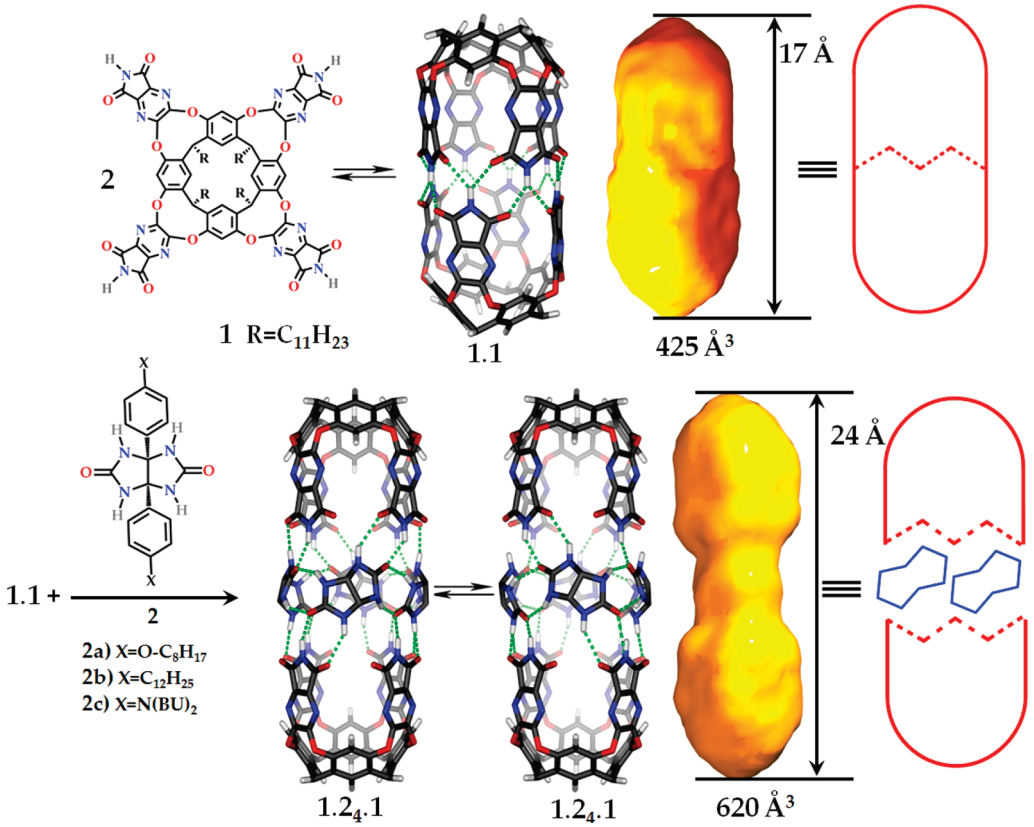

FIGURE 1. Top left: Chemical structure of the cavitand component and calculated structure of the capsule **1.1** with peripheral alkyl groups removed. Top right: The shape of the space inside **1.1** and its cartoon representation. Bottom left: Incorporation of 4 glycoluril spacers **2** to give the chiral extended **1.2$_4$.1**. Peripheral alkyl and aryl groups have been removed; both enantiomers of the extended capsule are shown. Bottom right: The shape of the space inside **1.2$_4$.1** and its cartoon representation.

hydrogen bonded[4−11] or held together by metal/ligand interactions,[12,13] hydrophobic effects,[14] or even covalent bonds[15]—it can accommodate more than one small guest. But unlike spherical capsules,[16,17] its cylindrical shape channels their contacts along predictable orientations, rather than the random intermolecular encounters found in bulk solution. Combinations of different encapsulated guests[18] inside **1.1** have allowed its use as a reaction chamber,[19] chiral receptor,[20] and a space where single-molecule solvation can be observed.[21] Attempts to expand the capsule's cavity by replacing the imide walls with elongated panels proved insuperable; solubility problems were consistently encountered, resulting in the inevitable collapse of the large aromatic surfaces onto each other. An indirect approach succeeded, involving the use of external spacer elements with the appropriate curvature, size, and hydrogen bonding patterns to insert into the polar middle of the capsule. Specifically, the notoriously insoluble glycolurils **2**,[22] bearing peripheral, alkylated phenyl groups, were found to be compatible with the imides of the cavitand **1**. The concave face of the glycoluril is congruent with the resorcinarene and the convex face is coated with bulky groups that prevent stacking and enhance solubility. Accordingly, NMR studies showed a new extended capsule (**1.2$_4$.1**) was generated with these glycolurils and **1** in deuterated mesitylene when, and only when, appropriate guests are present. Previously we have communicated the composition and structure, its application as a spring-loaded device,[23] gas encapsulation,[24] and social isomerization[25] within. In this article we provide experimental details on the properties

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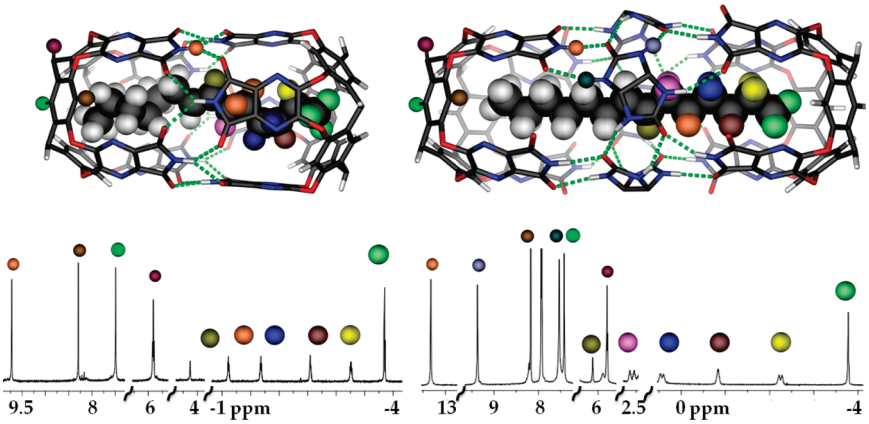

FIGURE 2. Top: Models of encapsulated *7*-tetradecene in both original capsule **1.1** and the expanded version **1.2$_4$.1** (peripheral groups omitted for clarity). Bottom: The ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) of *trans*-7-tetradecene (5 mM) in **1.1** (1 mM) or **1.2$_4$.1** (1 mM). The assignments are color coded.

of this extended capsule and the behavior of a range of organic compounds inside its elongated cavity.

Results and Discussion

Constitution. The *cis* fusion of the five-membered rings, the rich array of hydrogen bonds and the octyloxyphenyl, dodecylphenyl, or dibutylaniline on their convex faces provide glycolurils **2** with the appropriate curvature, adhesion, and solubility to complement the corresponding features of capsule **1.1**. Mere addition of the glycoluril **2** to a deuterated mesitylene solution of *trans*-7-tetradecene encapsulated in **1.1**, under ambient conditions, results in the appearance of the new signals within seconds in the NMR spectrum (Figure 2).[26] Integration of proton signals indicates that 4 molecules of glycoluril are present in the new assembly and the changes in chemical shifts of the guest reveals it to be in a larger space in the extended capsule. All of these capsules feature aromatic walls with polarizable π surfaces that impart an intense magnetic anisotropy to their cavities. The resulting upfield shifts of the NMR signals of encapsulated species are used to identify guests and monitor their positions. Furthest upfield shifts correspond to nuclei closest to the resorcinarene ends and to the capsule's aromatic walls. *trans*-*7*-Tetradecene is the longest alkene known to fit inside capsule **1.1**, but even it is some 4 Å longer, in a fully extended conformation, than the space on offer in the cavity. This alkene compresses itself by adopting a coiled shape inside the cavity through 8 *gauche* conformations. The coiled alkane is shorter and thicker; the stabilization through attractive C−H/π interactions with the cavity's aromatic lining compensates for the repulsive *gauche* interactions along the chain. Longer alkenes such as pentadecene simply cannot fit inside **1.1**. Comparison of the signals of *trans*-7-tetradecene in the two capsules shows that the hydrogen atoms on C_2/C_{13}, C_3/C_{12}, and C_4/C_{11} of this guest have moved away from the walls and the ends of the new capsule: they are in an extended rather than coiled conformation. In addition, the doubling of the signals on C_2/C_{13} and C_4/C_{11} in the longer capsule indicates that these hydrogen atoms experience an asymmetric magnetic environment—they are diastereotopic.

Structure. The new capsule's structure can be deduced from NMR evidence. The 4 added glycolurils form hydrogen bonds with each half of the original capsule and with each other. In the model proposed in Figure 1, each glycoluril has four hydrogen bonds with cavitands: two strong hydrogen bonds between the imide NH of the cavitand (the best hydrogen bond donor) and the ureido carbonyl of the glycoluril (the best hydrogen bond acceptor). This results in the 3 ppm downfield shift of the imide hydrogen to 13 ppm, as may be expected for an exceptionally strong hydrogen bond. The other two hydrogen bonds between spacer and cavitand are somewhat weak. These are between the ureido NH of the glycoluril (a good donor) and the imide carbonyl of the cavitand (the weakest acceptor). This signal appears at about 7 ppm in the NMR spectra. Each spacer unit also has four good hydrogen bonds with its adjacent spacers that further stabilize the assembly. These signals are located at ~9 ppm and reflect the involvement of good donors with good acceptors. The tilted (with respect to the long axis of the assembly) arrangement of the spacer elements in the middle of the capsule produces a chiral structure, and the two enantiomers are shown in Figure 1. This is a rare example of chiral assembly that arises from only achiral subunits.[27] Overall, 24 hydrogen bonds hold the new assembly together; the spacer elements increase the length of the capsule by 7 Å and its accessible volume by ~200 Å^3.

The Inner Space. The increased dimensions of **1.2$_4$.1** allow its encapsulation of *n*-alkanes from C_{14} to C_{19}.[27] The inner space of **1.2$_4$.1** is distinctively anisotropic and is apparent in the NMR spectra of encapsulated guests. The two resorcinarene ends of this capsule induce a magnetic anisotropy and intense shielding to the protons located in the inner space, as they are positioned near the π faces of the aromatic panels. The middle of the capsule has an opposite effect and provides moderate deshielding to the guest protons in the space defined by the 4 glycolurils. The nuclei in this area are exposed to the edges of the aromatic units on the convex surface of the glycolurils of the capsule. These effects are consistent with earlier experiences with aromatic

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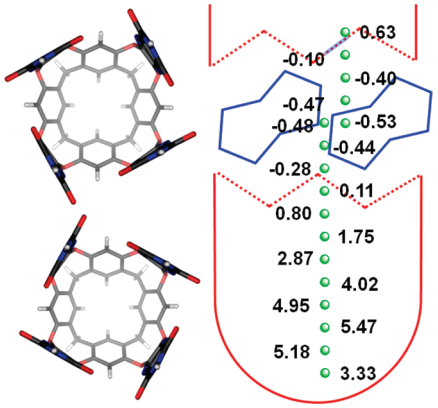

FIGURE 3. Left: A top view of the cavitand part of **1.2$_4$.1** enantiomers minimized at B3LYP/3-21G. The walls of the capsule are twisted and create an asymmetric magnetic environment. Right: Calculated NICS values for the space inside using B3LYP/6-31G*.

glycoluril-based capsules,[28] and those involving asymmetric elements *outside* capsules.[29] The NMR spectrum of *trans*-7-tetradecene (Figure 2) shows only 4 upfield shifted signals; only 4 carbon atoms of this alkene can fit in the aromatic envelope in an extended conformation. The methyl groups are positioned at the tapered ends of the capsule where the highest upfield shifts occur: $\Delta\delta$ is nearly -4.7 ppm! In contrast, the vinyl hydrogen signals located near the center of cavity are shifted downfield by 0.72 ppm.

Computational methods were applied to further explore the induced magnetic shielding regions of the cavity. A map of the induced magnetic shielding/deshielding for the inner space was prepared by using nucleus independent chemical shift (NICS)[30] calculations at the B3LYP/6-31G* level of density functional theory.[31] These values are shown in Figure 3 for coordinates along the central axis of **1.2$_4$.1** with spacing distances of 1 Å. The calculated values are in good agreement with the experimental results; the map can be used to locate and monitor the position of a guest nucleus inside the cavity.

The evidence of the capsule's chirality is reflected in the diastereotopic geminal hydrogen atoms of the encapsulated guest, but how is the chirality in the middle of the capsule transmitted to the aromatic subunits near the ends? The answer lies in the hydrogen-bonding patterns of the spacers with the imide walls. A carbonyl group of each imide wall is left without a hydrogen bond donor. This asymmetric arrangement causes a twist in the array of the imide walls that changes the symmetry of the cavitands from C_{4v} to C_4, and creates a chiral space, as shown in Figure 3. This twist is most pronounced at the narrower middle of the extended capsule to relieve the steric clashes of the unpaired carbonyl groups with the adjacent imide panels.

Why do the geminal hydrogen signals of C_2 and C_4 in the aliphatic guest show pronounced diastereotopic signals? The methyl group of the alkane is positioned in the center of the resorcinarene at the end of the capsule. Consequently, in extended conformation C_2 is closer to the aromatic walls where the best CH$-\pi$ interactions are possible. The next carbon atom, C_3, is located nearer the central axis and C_4 is again nearer the walls. In an extended conformation only these last four carbon atoms are affected; C_5 is in the region of the electron-poor imide walls. The longer guests, *n*-alkanes from C_{15} to C_{19}, must undergo increasing compression to fit within **1.2$_4$.1**.[26,27] As the alkane coils, the number of methylene groups that fit into the aromatic zone increases and gauche conformations force all protons near the twisted walls. There they experience the chiral environment; for example, encapsulated *n*-nonadecane shows six upfield shifted signals and all five sets of the geminal hydrogens are diastereotopic.

Energetics. There are long-standing problems posed by these reversible encapsulation complexes that can be traced to the historical fact that we have never seen an empty capsule. If there are no suitable guests to occupy the space, the capsule simply does not assemble. Instead, some other undefined aggregates are present that show broad, uninterpretable NMR spectra. The glycoluril itself in bulk mesitylene solution is also loosely organized in some hydrogen-bonded arrays, again shown by a broad cluster of resonances. Consequently, although it is possible to get relative association constants through direct competition between guests and derive thermodynamic parameters for guest exchange from these experiments, the absolute values are not accessible: the resting state of the capsule alone is not known. The energetic forces that drive the formation of the extended assembly are not measured. The contributions that can be identified must include the enthalpic benefits of a complete set of hydrogen bonds to the components, including those between the best donors (cavitand) and acceptors (glycolurils). In the extended capsule the glycourils can have the maximum number of hydrogen bonds with the minimum number of partners. Another enthalpic benefit is the relaxation of the coiled guest to its extended conformation that relieves *gauche* interactions. But during the unwinding of an alkane guest, the C$-$H/π interactions within the aromatic inner space must decrease and this desolvation of surfaces creates a vacuum—clearly enthalpic liabilities. In the context of proteins, this corresponds to ~1.1 kcal/mol in free energy for the creation of a cavity the size of a methylene group.[32] The flexibility of the capsule's hydrogen-bonded parts allows some collapse around guests, so the empty space is not easily estimated. From an entropic perspective, the first interpretation of the formation of this ordered, 6-component + guest assembly should be that it is extremely unfavorable. But on reflection, any assembly (and even any molecular recognition event) liberates solvent molecules from the surfaces of the solutes that become engaged. This is an entropic benefit, but the number of such solvent molecules released in the assembly process is difficult to even estimate, let alone determine for organic solvents. (Again, there are figures available for water, where the burial of hydrophobic, solvent-accessible surface[33] is ~25 cal/mol for each Å^2.) The guest molecules in mesitylene have the same C$-$H/π and

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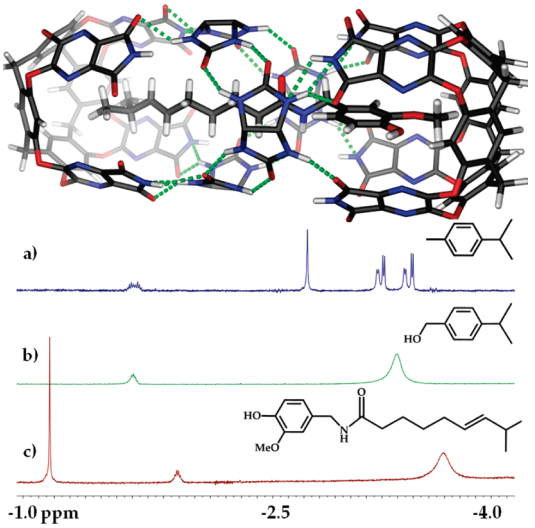

FIGURE 4. Top: Model of encapsulated capsaicin in the proposed (achiral) intermediate structure of the capsule (peripheral groups omitted for clarity). Bottom: The upfield region of the ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) of **1.2$_4$.1** (1 mM) with (a) *p*-cymene (5 mM), (b) 4-isopropylbenzyl alcohol (5 mM), and (c) capsaicin (5 mM).

van der Waals interactions available, inside or outside the capsule, but the potential guest must organize a large number of the solvent molecules around itself to experience the same level of attraction it can achieve with the walls of the capsule. In other words, the capsule acts as an organized solvent offering 16 fixed aromatic rings and the entropic penalty for its organization has already been paid through the synthesis of cavitand **1**.

Dynamics. Previously, we showed that coiled alkanes apply pressure on the inside of capsule **1.2$_4$.1**, and facilitate racemization—the interconversion of enantiomeric capsules.[34] We proposed formation of an achiral and slightly longer intermediate in the racemization process. This intermediate likely forms by the concerted ~30° rotation of all glycolurils in one direction, in a process that creates new hydrogen bonds as the old ones are broken. For longer alkanes such as *n*-C_{18} and *n*-C_{19} this process was slow at room temperature and we could measure the rate of interconversion and the racemization activation energy at the coalescence temperature by heating. The racemization rates increased with increased length of the guests: the longer, more compressed guests applied more pressure to the interior of the assembly and forced it toward the racemization transition structure. Surprisingly, some guests are capable of accelerating the racemization of the chiral capsule, in a manner unrelated to "pressure". In the extreme cases the racemization is so fast that the encapsulated guest experiences an average achiral environment at room temperature. Both capsaicin (Figure 4c) and *p*-isopropylbenzyl alcohol (as a dimer) show broadened NMR signals for their terminal isopropyl groups (Figure 4b). These guests present hydrogen bond donor and acceptor groups to the middle of the assembly that apparently catalyze the rotation of the glycolurils and accelerate racemization of their complexes.

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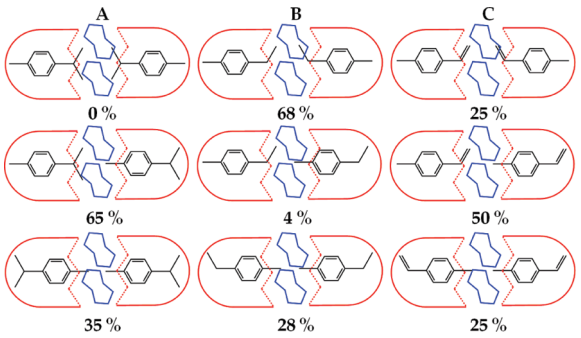

FIGURE 5. Cartoon representation of the social isomers of (A) *p*-cymene, (B) *p*-ethyltoluene, and (C) *p*-methylstyrene inside **1.2$_4$.1**.

Multiple Guests. The size of **1.1** has given rise to several phenomena including coencapsulation,[19] a situation that arises when one molecule of a potential guest does not fill enough space but two molecules cannot fit. The capsule then selects combinations of two *different* molecules that together fill the right amount of space. The increased dimensions of extended capsule **1.2$_4$.1** now allow two long molecules (or several short ones) to be observed inside. Take, for example, *p*-cymene. Two molecules are inside but the spectrum shows two arrangements in the space—a symmetrical one and one with two different ends (Figure 4 trace a, and Figure 5). These are social isomers.[35] They arise from restricted motion in the confined space and give rise to supramolecular diastereomers. The guests are too thick to slip past each other and too long to tumble rapidly (on the NMR time scale) inside the cavity, thus separate sets of signals appear in the NMR spectrum for each arrangement. Long molecules (e.g., *p*-disubstituted benzene derivatives) generally show this behavior and the orientation of one guest depends on the presence and nature of the other. Three different arrangements are possible for guests with two different substituents such as *p*-cymene or *p*-ethyltoluene (Figure 5). For the former, only two are formed, the isomer with 2 isopropyl groups in the narrower center of the assembly is missing. In the case of the *p*-ethyltoluene, the most favored isomer places the methyl of the tolyl group in the tapering ends of the capsule where it can achieve close C−H/π interactions with the aromatic surface of the resorcinarene. Although the unsymmetrical isomer is statistically favored, it represents only 4% of the total isomers and must be the highest energy form of three arrangements. The energetic differences between the social isomers reflect not only the better "fit" in the space but also the interactions between the coencapsulated molecules. Surprisingly, *p*-methylstyrene behaves much differently than *p*-ethyltoluene although they are closely related. All three social isomers of *p*-methylstyrene in **1.2$_4$.1** coexist in the capsules in their statistically predicted populations: the unsymmetrical isomer (which was very underrepresented in the case of *p*-ethyltoluene) is now 50% of the population!

What governs this behavior? There is some tumbling inside the cavity of **1.2$_4$.1**: 2D ROESY spectroscopy shows exchange cross peaks and the three social isomers can interconvert at room temperature, but this tumbling is slow

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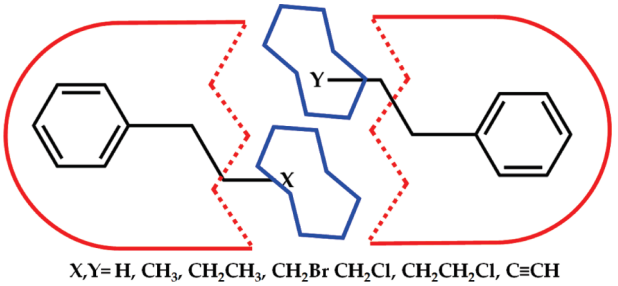

FIGURE 6. Cartoon representation of the bimolecular encapsulation of guests as a single social isomer inside **1.2$_4$.1**.

on the NMR time scale, and separate sets of signals appear in the spectrum for each arrangement. Similar observations have been reported for *p*-methylstyrene in a water-soluble capsule, although that capsule is much wider than **1.2$_4$.1**.[36] (The exchange and NOE cross-peaks are not defined in this publication.) For *p*-methylstyrene to tumble inside **1.2$_4$.1** some large breathing motions of the capsule walls must take place. The social isomers could, in principle, interconvert also by disassembly/reassembly of the encapsulation complex but this is unlikely to be the case: the chance that the same guest molecule is released and again re-encapsulated is spectacularly improbable. The time scale of the assembly/dissipation of this capsule must await kinetic studies using fluorescence at nanomolar concentrations.[37−39]

Two molecules of monosubstituted phenyls such as ethyl-, propyl-, and butylbenzene are also accommodated inside **1.2$_4$.1**. Their NMR spectra are consistent with the existence of only one social isomer, the one with the phenyl groups located at the aromatic ends of the capsule and the alkyl groups positioned in the (more polar) middle. Apparently, two thin, flexible alkyl chains can better fit the narrower middle region of the capsule than two stacked, rigid phenyl groups (Figure 6). London dispersion forces are presumably the only attraction between these guests. Other functionalized guests such as 1-chloro-3-phenylpropane, 1-chloro-4-phenylbutane, or 4-phenyl-1-butyne behave similarly and only assemble as one social isomer with the phenyl groups at the ends and substituted groups toward the middle. This tendency provides an opportunity to perform reactions inside this confined space,[40] and we are pursuing this line of research.

Although the extended capsule models as having a narrow middle, it does accommodate phenyl groups: *p*-quaterphenyl and substituted biphenyls are taken in. The rigid *p*-quaterphenyl is poorly soluble in mesitytlene but **1.2$_4$.1** absorbs it very effectively to form a stable complex. The pattern of magnetic anisotropy in this host−guest system is dramatic; while the hydrogen atoms at the two ends of the guest (the CH's at the *para* positions of the terminal benzene rings) shift *upfield* 3.6 ppm, the hydrogen atoms of the central aromatics experience a *downfield* shift of around 1.5 ppm (see the SI).

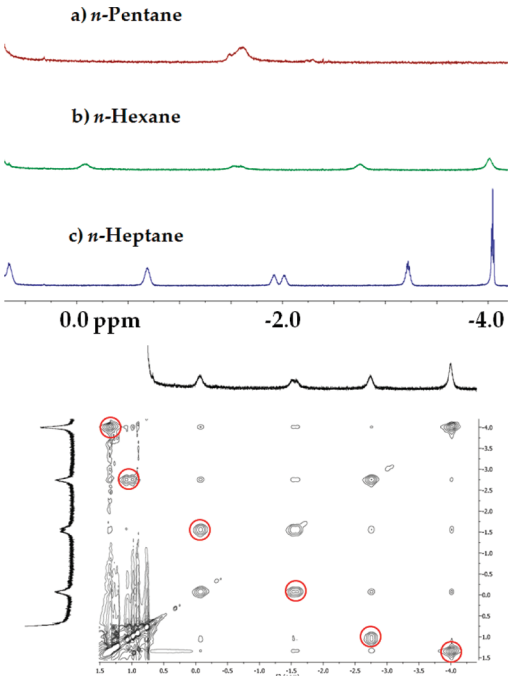

FIGURE 7. Top: The upfield region of the ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) of **1.2$_4$.1** (1 mM) with (a) *n*-pentane (5 mM), (b) *n*-hexane (5 mM), and (c) *n*-heptane (5 mM). Bottom: 2D ROESY spectrum of *n*-hexane in **1.2$_4$.1**, the exchange cross peaks have been circled.

Smaller Guests. Three pentane molecules fit inside the capsule **1.2$_4$.1** and they tumble freely but do not exchange positions while inside the cavity. Accordingly, a single average (broadened) proton signal is observed for the guests in the cavitands (Figure 7a), but signals due to the central pentane are obscured by signals from the cavitands' alkyl groups. Two heptane molecules, however, do not tumble rapidly inside the cavity at room temperature (on the NMR time scale). The spectrum features sharp signals for the heptanes (Figure 7c) and no cross-peaks are observed in the 2D ROESY spectra. The behavior of *n*-hexane is somewhere in between. Four broadened, upfield shifted signals are observed for its methyl and methylene protons (Figure 7b) and 2D ROESY spectroscopy shows that the proton signals are in slow exchange at room temperature. The activation barrier for the hexane tumbling inside was calculated as 16.2 kcal/mol, using magnetization exchange rate constants. The mechanism of this tumbling is revealed by NOE cross peaks of the alkane with fixed protons of the capsule. The methyl group of hexane *outside* the cavitand exchanges with the methyl group inside. Both methyl and methylene signals of guest hexane show NOE cross peaks with the imide hydrogens of the capsule but only the methyls have NOE cross peaks with aromatic signals at the ends of the capsule (see the SI). The two different N−H signals of the glycoluril also exchange slowly in the complex of pentane and hexane with **1.2$_4$.1** at room temperature. The third molecule of these guests probably facilitates the racemization process as the intermediate is longer. Cyclic alkanes such as cyclopentane and cyclohexane also fit and tumble freely inside the cavity (see the SI).

Nematic liquid crystal components such as alkylated biphenylcarbonitriles were also examined in the confined

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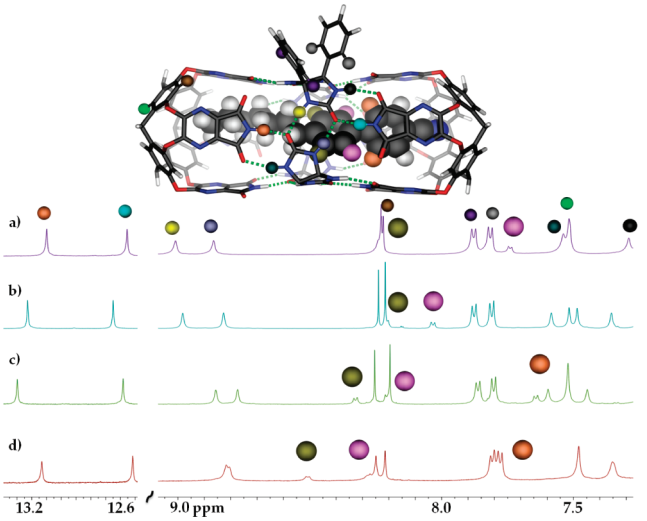

FIGURE 8. Top: Model of encapsulated 4-heptylbiphenyl carbonitrile inside **1.2$_4$.1** (peripheral groups omitted for clarity). Bottom: The ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) of **1.2$_4$.1** (1 mM) with (a) 4-octylbiphenyl (5 mM), (b) 4-heptylbiphenyl (5 mM), (c) 4-hexylbiphenyl (5 mM), and (d) 4-pentylbiphenyl (5 mM). Assignments are color coded.

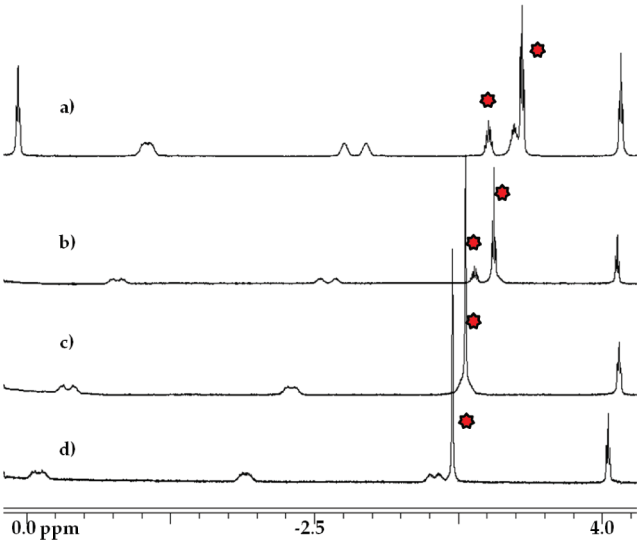

FIGURE 9. The upfield region of the ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) of **1.2$_4$.1** (1 mM) with propane gas coencapsulated with (a) *n*-dodecane (5 mM), (b) *n*-undecane (5 mM), (c) *n*-decane (5 mM), and (d) *n*-nonane (5 mM) . The peaks of propane have been marked with red stars.

space and they revealed additional information about the structure of the assembly. The phenyl rings of the guest can impart magnetic anisotropy to the capsule's protons and cause them to shift upfield as well. The 4-pentylbiphenylcarbonitrile fills about of 42% of the space and is fully extended inside the cavity. It has a slight translational movement (Figure 8d) that results in an average upfield shift of the spacers' NH proton signals. Through elongating the alkyl group—hexyl, heptyl, and octyl—of the biphenyl carbonitrile, the biphenyl core is forced toward one end of the capsule. As a result, the different NHs of the glycolurils are exposed to different degrees of magnetic shielding and they show separate signals. The phenyl group of the guest can also shield the spacer's protons by as much as 0.25 ppm. The groups on the convex face of the glycoluril (outside) are also affected by the magnetic environment provided by nearby phenyl groups on the inside (Figure 8).

Both **1.1** and **1.2$_4$.1** are capable of encapsulating gases and we have reported[25] that 3 molecules of cyclopropane occupy 39% of the inner space of **1.1** and 4 fill 36% of the extended capsule's cavity. 2D ROESY[41,42] spectroscopy confirmed that encapsulated cyclopropanes move past each other at measurable rates (on the NMR time scale) as they exchange their positions while within the capsule. This phenomenon has not been observed for liquid or solid guests in these cylindrical capsules. Although **1.1** has a higher packing coefficient with cyclopropane, it shows a slightly lower activation barrier for the exchanging of positions (17.5 kcal/mol) than extended capsule **1.2$_4$.1** (18.5 kcal/mol). This probably reflects the constricted middle region of the extended capsule **1.2$_4$.1**.

A wide variety of other gases such as propane, butane, isobutane, propylene, 2-methylpropene, and 1,3-butadiene also fit inside the extended capsule with packing coefficients between 36% and 40%. A symmetrical capsule is observed for encapsulated cyclopropane, *n*-butane, isobutane, and 1,3-butadiene, but the other gases mentioned also show *asymmetric* capsules that are likely due to the coencapsulation of atmospheric gases such as nitrogen or oxygen. Coencapsulation of a gas molecule with other guests is well-known: those gases that alone are not a good fit for **1.2$_4$.1** such as methane, ethane, xenon, or carbon dioxide can be captured and studied by using a matching coguest.[43] The NMR spectrum of coencapsulated propane and nonane in **1.2$_4$.1** is shown in Figure 9. The propane occupies almost one-third of the inner space and it tumbles freely; the propane's protons experience similar magnetic environment and they no longer show coupling, resulting in a broad NMR signal (Figure 9c,d). The 2D ROESY spectrum showed that the two guests do not slip past each other and nonane does not tumble inside the cavity (see the SI). Elongation of the coguest puts pressure on the propane and pushes it further into the tapered end of the capsule. Replacing nonane with dodecane increases the packing coefficient of propane from 30% to 60% and well-resolved signals can be observed for methyl and methylene of the gas (Figure 9a). One methyl group of the dodecane is at the tapered end while the other methyl reaches into the opposite cavitand (near the propane) where it experiences magnetic shielding and appears at 0.2 ppm.

Simple ideal gas calculations give a pressure of 387 atm for propane encapsulated with dodecane and 196 atm for coencapsulation with nonane. Does this compression convert the gaseous propane to liquid or solid propane? The calculated pressures are hardly valid since these gases are far from ideal. The gases are neither point masses nor are their collisions with the walls elastic. Rather, there exist CH/π interactions between the gases and the aromatic panels of the capsules

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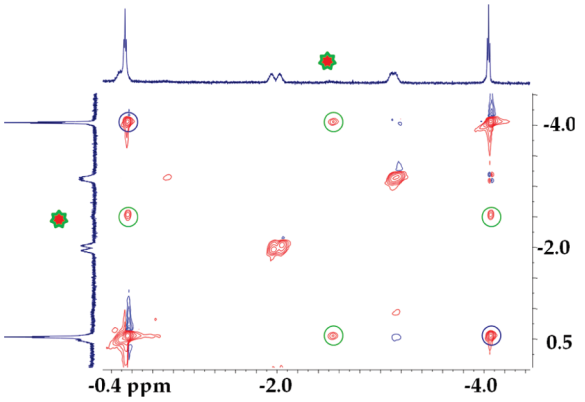

FIGURE 10. The upfield region of the 2D ROESY spectrum of *n*-dodecane coencapsulated with Xenon in **1.2$_4$.1** at 340 K. The exchange cross peaks are circled. The broadened methyl peak of the singly encapsulated dodecane intermediate is marked with a star.

and these favorable attractions lower the potential energy and thereby permit the "high pressures".

Xenon is also coencapsulted with *n*-alkanes from nonane through dodecane. Despite the spherical shape of xenon, it does not slip past the alkane inside the cavity at ambient tempertaure, as revealed by 2D spectroscopy. But at higher temperatures (340 K) encapsulated deodecane begins to exchange its position with xenon in the cavity and the two ends of the capsule exchange as well. Two different mechanisms could be in play for this observation: either dodecane and xenon slip past each other or xenon leaves the capsule and the returning xenon enters the opposite end (half of the time). The 2D ROESY spectrum (Figure 10) confirmed the existence of an intermediate in which dodecane is encapsulated alone! The peaks for the encapsuated alkane are very broad for this intermediate because the alkane can translate freely between two ends.

Conclusions

A range of guests—solids, liquids, and gases—can provide the appropriate size, shape, and chemical surfaces to be recognized by the extended capsule **1.2$_4$.1**. The inner space of the capsule has a capacity of around 600 Å^3, and there are few directional interactions between the host and the guest; instead London dispersion forces and C−H/π interactions dominate. The inner cavity with its polarizable π surface provides attraction to molecules bearing a thin layer of positive charge such as the C−H bonds of *n*-alkanes. Flexible guests show a variety of motions—coiling, sliding, tumbling, and even exchanging positions inside. The capsules provide a means to study single or multiple copies of a molecule isolated from the bulk solution. The reversible encapsulation complexes operate at equilibrium, under ambient conditions, and in the liquid phase. As modern tools of physical organic chemistry, they reveal the otherwise invisible behavior of molecules in small spaces.

Experimental Section

General Considerations. ^{1}H, 2D NOESY, and 2D ROESY NMR spectra were recorded on a 600 MHz spectrometer with a 5-mm QNP probe. Proton (1H) chemical shifts are reported in parts per million (δ) with respect to tetramethylsilane (TMS, δ = 0), and referenced internally with respect to the protio solvent impurity. All calculations were performed with Gaussian 03. Geometries of stationary points were fully optimized by using the B3LYP method and 3-21G basis set on a LINUX cluster. NICS calculations were executed with the B3LYP method and 6-31G* basis set. Cylindrical capsule subunit **1** and precursors were synthesized according to the literature procedure.[44]

Synthesis of Bis[(dibutylamino)phenyl]glycouril 2c. 4,4′-Bis-(dibuthylamino)benzil (4.6 g, 10 mmol), urea (1.3 g, 22 mmol), toluene (50 mL), and trifluoroacetic acid (2 mL) were combined in a flask equipped with a Dean−Stark trap. After overnight reflux, the mixture was cooled to room temperature. The mixture was filtered and the filter cake was washed with dichloromethane (50 mL) and methanol (50 mL) and air-dried. The residue was purified by column chromatography on silica gel, eluting with 50% ethyl acetate in hexane, to afford glycouril **2** (3.8 g, 6.9 mmol, 69%) as a white solid. ^{1}H NMR (600 MHz, acetone) δ 7.00 (d, J = 8.1 Hz, 4H), 6.47 (d, J = 8.4 Hz, 4H),, 3.24 (t, J = 7.4 Hz, 8H), 1.5 (p, J = 7.8 Hz, 8H), 1.35 (h, J = 7.6 Hz, 8H), 0.94 (t, J = 7.4 Hz, 12H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 160.7, 147.1, 127.9, 124.3, 110.3, 81.8, 49.7, 28.8, 19.7, 13.8. HRMS (MALDI-FTMS: MH$^+$) calcd for $C_{32}H_{49}N_6O_2^+$ 549.3911, found 549.3906.

Procedure for 2D NOESY and 2D ROESY Experiments. The 2D NOESY spectra of the assembly were recorded at 300 K at 600 MHz with the phase-sensitive NOESY pulse sequence. Each of the 512 F1 increments was the accumulation of 32 scans. Two-dimensional ROESY spectra were also taken to determine whether the cross-peaks observed derived from NOE enhancements or chemical exchange, and were recorded at 300 K at 600 MHz with the phase-sensitive ROESY pulse. Before Fourier transformation, the FIDs were multiplied by a 90° sine square function in both the F2 and the F1 domain. 1K × 1K real data points were used, with a resolution of 1 Hz/point. For EXSY, two NOESY spectra were taken sequentially, one with 300 ms mixing time and then with 0 ms mixing time. The rate constant k was calculated by using the EXSYCALC program (Mestrelab Research, Santiago de Compostela)[41] and is the sum of the two dependent magnetization-transfer rate constants obtained from the calculations, an approximation due to the system being in equilibrium.

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Supporting Information Available: ^{1}H NMR and 2D NOESY/ROESY spectra discussed but not present in the text, and also general procedures for samples preparation. This material is available free of charge via the Internet at http://pubs.acs.org.

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