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# Bent Alkanes in a New Thiourea-Containing Capsule

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Supporting Information

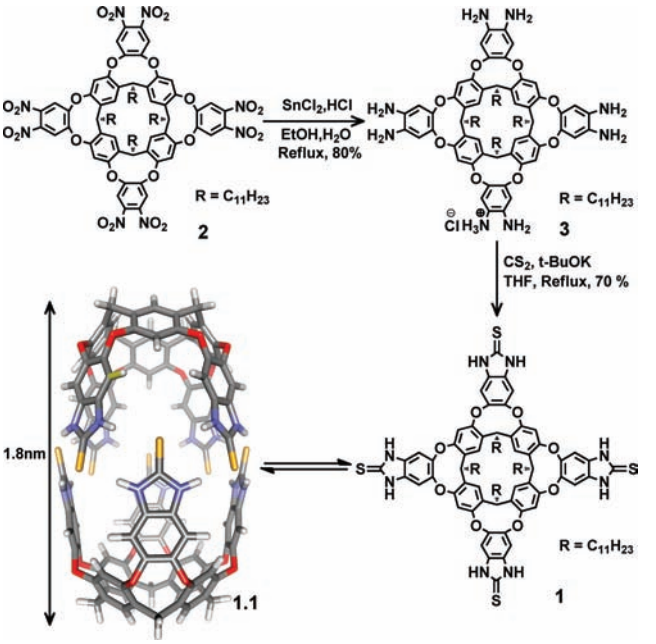
**ABSTRACT:** The synthesis of a cavitand featuring thiourea hydrogen bonding sites and its dimerization in the presence of suitable guests are reported. Dimerization creates a capsule host wider than the corresponding urea or imide structures, and longer alkanes can be accommodated. Specifically, *n*-$C_{15}H_{32}$ is encapsulated, but this guest appears folded inside as deduced from NMR studies. Apparently, the plasticity of hydrogen bonds between thiourea groups allows a stable encapsulation complex to persist in solution even though the guest is contorted.

Understanding molecular behavior in small spaces is of intrinsic interest in chemistry and, because the vast majority of medicines are synthetic molecules that fit into small spaces of proteins and nucleic acids, is relevant to human health. It has emerged that severely confined molecules behave quite differently than those in dilute solution. Reversible encapsulation is one method of isolating molecules and examining them in very small spaces of the capsules. This has led to some understanding of how molecules get in and out:[1] the amplified chemical interactions,[2] the stabilization of reactive intermediates,[3] and the facilitation of unusual reaction pathways[4] in the limited spaces. We describe here an unprecedented contortion[5] of *n*-alkanes in the limited space of a capsule. The adaptation of guest to host appears to be driven by the proper filling of the space and its shape.[6]

Hydrogen bonding is one means to program the self-assembly of complementary molecules into a variety of molecular capsules: spherical,[7] cylindrical,[8] and other shapes.[9] Ureas[10] and cyclic ureas (imidazolones[11,12] and glycolurils[13,14]) are particularly useful in this regard. At the same time, thiourea derivatives are much-admired in organocatalysis:[15,16] the enhanced acidity ($pK_a$ thiourea = 21.0 vs $pK_a$ urea = 26.9)[17] translates into better hydrogen-bond donors, and the lower electronegativity of sulfur vs oxygen (2.58 vs 3.88 on the Pauling Scale)[18] reduces its interference as an acceptor. To our knowledge, the thiourea has not been used in capsules but the corresponding urea has been described.[11,12] We report here the synthesis and unexpected behavior of guests in a thiourea-resorcinarene host.

The synthesis of **1** (Scheme 1) was accomplished from the known octanitro cavitand **2**[19] based on the methods originally established by Cram.[20] Reduction of **2** with $SnCl_2$ in EtOH/HCl afforded octaamino cavitand **3** (~80% yield). The condensation reaction of this amine salt with excess carbon disulfide in dry THF in the presence of potassium *tert*-butoxide at reflux generated the corresponding thiourea-containing calix[4] resorcinarene **1** in 70% yield.

**Scheme 1. Synthesis and Structure of Thiourea-Containing Cavitand 1 and Its Self-Assembly via H-Bonding into a Cylindrical Capsule 1.1**[a]




[a] The DFT-minimized (B3LYP/6-31G*) representation of the capsule **1.1** is shown; the long alkyl chains are omitted for simplicity.

Guest encapsulation studies of capsule **1.1** were performed in mesitylene-$d_{12}$. Initially, we observed that tetra-thiourea capsule **1.1** can accommodate both 4-methyl-*N*-*p*-tolylbenzamide **5** and 4,4′-dimethyl-*trans*-stilbene **6** (see Supporting Information (SI)). The complexes were prepared by heating a mixture of **1** and guest (1 mM:2 mM, respectively) in mesitylene-$d_{12}$ using a heat gun or oil bath (10 min, 200 °C). Strongly shielded methyl signals for **6** (−2.5 ppm) and for **5** (−2.5 and −2.4 ppm) confirmed the formation of the corresponding encapsulation complexes. For the asymmetric guest, two sets of signals were detected for CH-methine (6.14 and 6.14 ppm) and the N−H's (11.9 and 12 ppm) of **1.1**.

We also examined the encapsulation of a series of normal alkane guests as reported earlier for a related tetra-imide capsule **4.4**. (Figure 1).[21] The longest alkane that can fit inside **4.4** is *n*-tetradecane, but it requires a change in shape to be

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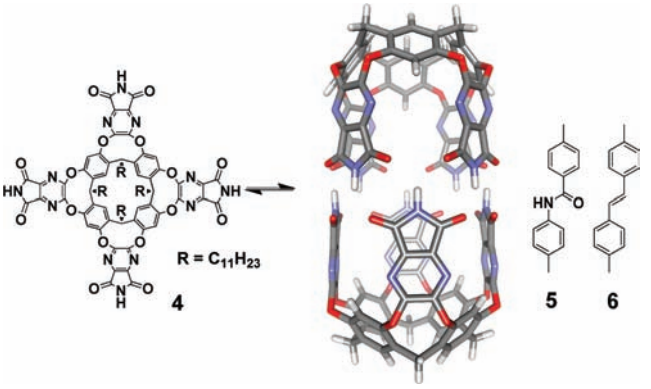


**Figure 1.** Energy-minimized representation of the corresponding tetraimide capsule[21] **4.4** and the structures of 4-methyl-*N*-*p*-tolylbenzamide **5** and 4,4′-dimethyl-*trans*-stilbene **6**.

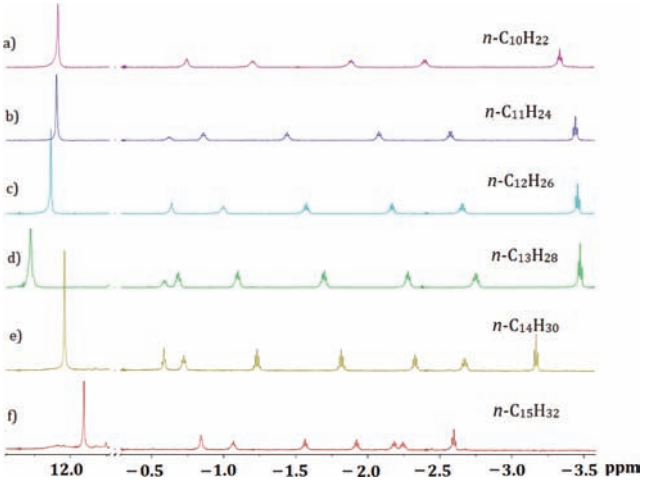


**Figure 2.** Upfield regions of the $^1$H NMR spectra (600 MHz, mesitylene-$d_{12}$, 300 K) of encapsulated alkanes (*n*-$C_{10}H_{22}$ to *n*-$C_{15}H_{32}$) in **1.1**.

accommodated: the alkane coils into a helical conformation that shortens its length and permits attractive C−H/$\pi$ interactions between guest and host. The energetics of encapsulation compensate for the *gauche* interactions created along the chain by coiling. All attempts to encapsulate *n*-pentadecane in **4.4** met with failure.

A parallel study was performed using **1.1** (Scheme 1) with a series of normal alkanes in mesitylene-$d_{12}$ at 300 K, and the spectra are shown in Figure 2. Encapsulation was observed at either room or elevated temperatures, and no changes were observed in the chemical shifts in the temperature range 25−70 °C. As expected, *n*-$C_{10}H_{22}$ to *n*-$C_{13}H_{28}$ are encapsulated in **1.1** and the spectroscopic trends are similar to those of capsule **4.4**.

Likewise, *n*-$C_{14}H_{30}$ is taken up, but the NMR spectrum (Figure 2e) indicates a change of guest shape. Unaccountably, *n*-$C_{15}H_{32}$ is also encapsulated (Figure 2f); this appears to be a behavior unique to this capsule. For the alkanes *n*-$C_9H_{20}$ to *n*-$C_{15}H_{32}$, single molecules are found in the capsule, and DOSY spectroscopy showed only one capsule species is present in the solution (see SI).

Previous experience with alkanes in **4.4** indicated that *n*-undecane is accommodated in its fully extended conformation.

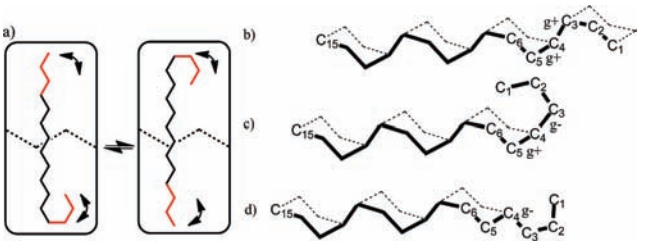


**Figure 3.** (a) The schematic representation of the folding mechanism of *n*-$C_{15}H_{32}$ in **1.1** is shown. (b) Line drawing of a helical pentadecane with all *gauche* + conformations along the backbone; the cyclohexanes are added merely to guide the eye. (c) Rotation about the $C_{3-4}$ bond to the *gauche* − conformation creates steric clashes like those of 1,3 diaxially substituted cyclohexane. (d) The clashes are relieved when the conformation of the $C_{4-5}$ bond is *anti*. Rotations about the $C_{2-3}$ bond do not change the overall length of the alkane.

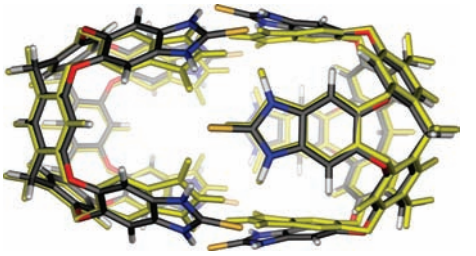

**Figure 4.** Superimposed capsule **1.1** and **4.4** (yellow).

The methyl groups of this guest are as far as they can reach in the tapered ends of the capsule where they experience the maximum upfield shift. As the guest length increases, *gauche* interactions set in and each of these shortens the length by some 0.32 Å. This compression moves the methylenes (on average) closer to the walls and to the ends of the capsule and results in upfield shifts of the hydrogens as they experience the intense anisotropy of the aromatic panels of the host. Simultaneously, the signals for the capsule's imide N−H's move upfield as stress is applied by the compressed guest that lengthens the hydrogen bonds. The behavior observed for *n*-$C_{11}H_{20}$ to *n*-$C_{13}H_{28}$ encapsulated in **1.1** follows this analysis, but *n*-$C_{14}H_{30}$ and *n*-$C_{15}H_{32}$ represent discontinuities: their methyl ends are, on average, in a different magnetic environment. The unusual chemical shifts observed can be reconciled if these alkanes adopt a conformation where one end is bent or folded in the resting state (Figure 3a).

This shortens the guest enough to fit inside the capsule. Exchange between the two ends occurs rapidly on the NMR time scale: the methyl signals and every methylene signal of the alkane are an averaged chemical shift of two magnetic environments. A tumbling of the guest could also exchange the magnetic environments of the two ends of the capsule and guest, but this is unlikely: a closely related hydrocarbon 1-pentadecyne as guest showed the two ends of the capsule remained different on the NMR time scale (see SI). Likewise, with the unsymmetrical guest anilide **5** in the capsule the spectra showed two N−H signals and two triplets for the methine C−H signals. While details of the folded conformation are impossible to deduce from the spectra, one mechanism for folding a helically coiled alkane is shown schematically in Figure 3 (the cyclohexyls provide a simple mnemonic for an all *gauche* + helix). A *gauche* + to *gauche* − change at one bond


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and a compensating *gauche* + to *anti* change at an adjacent bond creates a kink in the hydrocarbon's conformation. The kink can move rapidly up and down the chain on the NMR time scale.

What causes the different accommodations in the capsules **1.1** and **4.4**? A superimposition of the two host structures at one end (resorcinarene) shows the thiourea **4.4** to be marginally shorter (0.35 Å) but some 2.2 Å wider (Figure 4) at the capsule's middle. The increased width allows a kink in the alkane guest to move along the chain.

In summary, the new thiourea cavitand **1** has been synthesized and it dimerizes to a H-bonded capsule **1.1** that can encapsulate lengthier alkanes such as *n*-$C_{15}H_{32}$. This system can be used to accommodate inconveniently shaped longer and bent guests. Apparently, the thiourea H-bonding interaction keeps the **1.1** capsule intact while encapsulated species suffer unusual contortions.[22]

## ■ ASSOCIATED CONTENT

**Supporting Information.** Synthetic procedures, characterization data for **1**, $^1$H NMR spectra encapsulated alkanes (*n*-$C_{10}H_{22}$ to *n*-$C_{15}H_{32}$) in **1.1** capsule, DOSY spectra, NICS values, and molecular dynamics simulation data. This material is available free of charge via the Internet at http://pubs.acs.org.

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