

Helical Folding of Alkanes in a Self-Assembled, Cylindrical Capsule

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Abstract: The reversible encapsulation of a series of normal alkane guests in a cylindrical host was studied by NMR methods. For small hydrocarbons such as *n*-pentane or *n*-hexane, two guests enter the host, and they move freely within. With *n*-heptane no encapsulation takes place. For longer alkanes such as *n*-decane, a single guest enters and the aromatic walls of the host are seen to twist to avoid empty spaces and increase favorable interactions with the hydrocarbon. The best guest (*n*-undecane) adopts a conformation with minimal gauche interactions. The longest alkane accommodated, *n*-tetradecane, adopts a helical conformation to fit in the cavity, a shape that maximizes CH/ π interactions with the aromatic walls of the receptor. These reciprocal conformational changes are discussed in terms of optimal host/guest interactions.

I. Introduction

Synthetic receptors in chemistry are used for the study of molecular recognition phenomena—how and why molecules fit together. Cavitands¹ and molecular capsules² are recent versions, and their relatively rigid structures as hosts present well-defined spaces to guests. Recognition then depends on the complementarity of size, shape, and chemical surface between host and guest and on entropic factors. Not surprisingly, rigid guests are studied the most: their interactions with the host are easily imagined, visualized, and even computed by modeling, and they give stable complexes since no internal rotations of the guest are restricted during complexation. When the guest is flexible and can assume many shapes, an ensemble of complexes may form between host and guest.³ Their relative stabilities are harder to predict as each complex has a different guest conformation and is inevitably destabilized by restricted internal rotations. We recently encountered these situations with guests bearing normal alkane chains too long to be accommodated in a rigid, cylindrical host.⁴ An entirely analogous situation was encountered by Gladysz⁵ with flexible alkanes surrounding a rigid polyacetylene. Here, we describe the details of the encapsulation

of normal alkanes (*n*-C₅H₁₂ to *n*-C₁₄H₃₀) in organic media within a self-assembled molecular capsule. Investigations using NMR spectroscopy helped evaluate kinetic and thermodynamic parameters of these complexes and demonstrated that the longer guests (*n*-C₁₂H₂₆ to *n*-C₁₄H₃₀) coiled to adopt helical conformations within the capsule. The unfavorable gauche interactions created were apparently compensated by the favorable CH/ π interactions with the fixed aromatic walls and the proper filling of the host. Deformation of the host during complexation was also detected through NMR temperature coefficients and molecular modeling.

II. General Methods

In purified mesitylene-*d*₁₂, resorcinarene-based tetraimide **1** (Figure 1) aggregates to undefined materials, which are mostly insoluble. The solvent mesitylene cannot fit inside. In the commercially available solvent (98% purity), impurities exist that allow self-assembly into molecular capsule **1**₂ to occur. The capsule is held together through a cyclic seam of eight bifurcated hydrogen bonds and whatever intermolecular forces exist between host and guest. Typically, the most abundant resting state in this solvent is a capsule with one molecule each of deuterated *p*-xylene and deuterated benzene inside—impurities of the commercial solvent. This varies from batch to batch, and since the capsule has a remarkable ability to encapsulate impurities that appropriately fill its space, other resting states can be present. Fortunately, the impurities, low concentrations (at 0.01% of the pure solvent, an impurity is typically at <1 mM) can be displaced by the intended guests (at millimolar or higher concentrations) in typical NMR experiments.⁶

The capacity defined by the internal aromatic surfaces is about 425 Å³, assuming that the capsule keeps its symmetry and shape during the encapsulation of guests. In general, the capsule binds

- (1) For reviews, see: (a) *Container Molecules and Their Guests*, Cram, D. J., Cram, J. M., Stoddart, F., Eds.; The Royal Society of Chemistry: London, 1994. (b) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663–2704. (c) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991–2005. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Saadioui, M., Eds.; Kluwer Academic Publishers: Dordrecht, Boston, London, 2001.
- (2) Conn, M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647–1668. Sherman, J. C. *Tetrahedron* **1995**, *51*, 3395–3422. Boehmer, V.; Vysotzky, M. O. *Aust. J. Chem.* **2001**, *54*, 671–677. Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488–1508.
- (3) For a recent example in water, see: Trembleau, L.; Rebek, J., Jr. *Science* **2003**, *301*, 1219–1220.
- (4) Hayashida, O.; Sebo, L.; Rebek, J., Jr. *J. Org. Chem.* **2002**, *67*, 8291–8298. Scarso, A.; Trembleau, L.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 5499–5502.
- (5) Stahl, J.; Bohling, J. C.; Bauer, E. B.; Peters, T. B.; Mohr, W.; Martín-Alvarez, J. M.; Hampel, F.; Galdysz, J. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1871–1876.

- (6) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **1998**, *394*, 764–766.

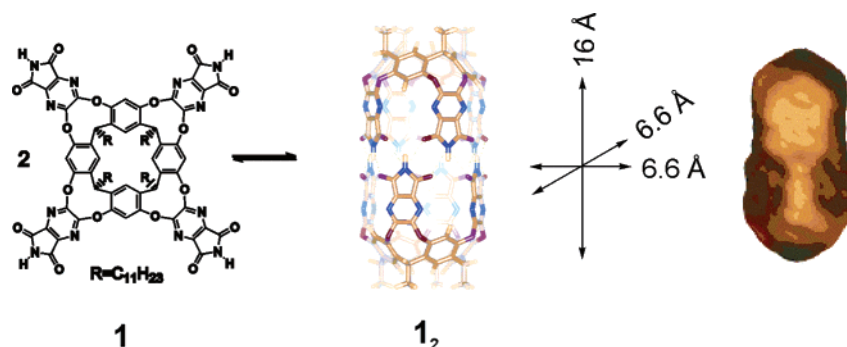


Figure 1. Line drawing of the synthetic receptor **1** (left) energy-minimized dimer **1₂** (center) and the size and shape of its cavity (right) using the program Swiss PDB viewer.

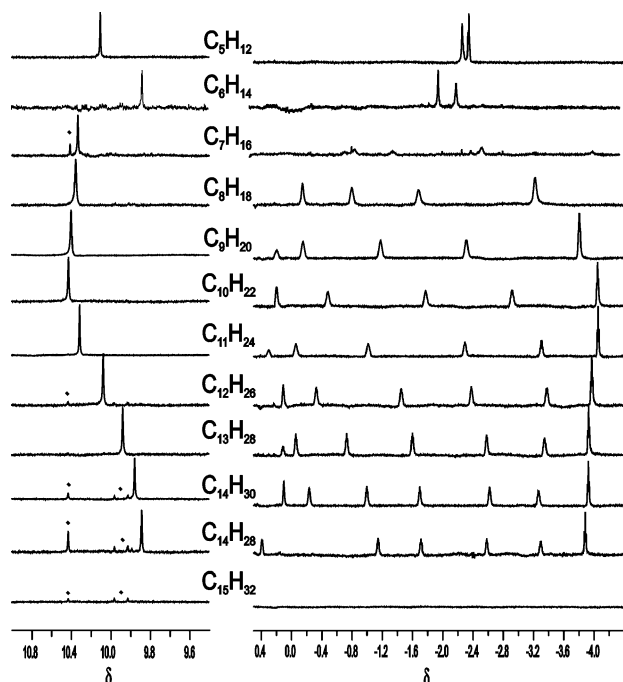


Figure 2. Upfield and downfield regions of the ¹H NMR spectra at 600 MHz in mesitylene-*d*₁₂ at 300 K of encapsulated alkanes (n -C₅H₁₂ to n -C₁₅H₃₂) @ **1₂** ([**1₂**] = 2 mM; [guests] = 100 mM). δ indicates complexes containing impurities from the deuterated solvent or from the commercial hydrocarbons.

guests that fill about 55% of the available volume.⁷ This is the appropriate packing coefficient (PC) in the liquid phase. Smaller guests interact weakly, and larger, rigid guests are rejected.⁸ Combinations of two or more different guests can also be encapsulated, a subject with consequences beyond the scope of the present work.⁹

III. Complexes with Alkanes

1. 1D NMR Results. Alkanes from n -C₅H₁₂ to n -C₁₄H₃₀ are generally encapsulated and form kinetically stable complexes on the chemical shift time scale (Figure 2).

Two molecules of n -C₅H₁₂ or n -C₆H₁₄ are incorporated in the capsule as revealed by integration of the signals. The spectra

Table 1. Dimension of Hydrocarbons and Computed Packing Coefficients (PC)

| guest | length (Å) | volume (Å ³) | cavity (Å ³) ^a | PC ^b (%) |
|---|------------|--------------------------|---------------------------------------|---------------------|
| 2 (n -C ₅ H ₁₂) | 2 × 8.7 | 2 × 85 | | – (40) |
| 2 (n -C ₆ H ₁₄) | 2 × 10.0 | 2 × 102 | | – (48) |
| n -C ₇ H ₁₆ | 11.2 | 117 | | – (28) |
| n -C ₈ H ₁₈ | 12.5 | 134 | | – (31) |
| n -C ₉ H ₂₀ | 13.7 | 151 | | – (36) |
| n -C ₁₀ H ₂₂ | 15.0 | 167 | 354 | 47 (39) |
| n -C ₁₁ H ₂₄ | 16.3 | 185 | 357 | 52 (44) |
| n -C ₁₂ H ₂₆ | 17.5 | 200 | | – (47) |
| n -C ₁₃ H ₂₈ | 18.8 | 222 | | – (52) |
| n -C ₁₄ H ₃₀ | 15.5 | 240 | 422 | 57 (56) |
| n -C ₁₄ H ₂₈ | 16.0 | 239 | | – (56) |
| n -C ₁₅ H ₃₂ | 16.3 | 258 | | |

^a Volume of the capsule's cavity after energy minimization of the structures. ^b Packing coefficients of alkanes in capsule **1₂** after energy minimization of the structures using nonhelical or fully helical conformations of the hydrocarbons according to NOESY data. Values in parentheses refer to packing coefficients calculated using a perfectly cylindrical capsule ($V_{\text{cavity}} = 425 \text{ Å}^3$).

of both encapsulated molecules show only two relatively sharp signals between -1.8 ppm and -2.4 ppm —one corresponding to the methylene protons and the protons of the terminal groups of the hydrocarbons—indicating that both hydrocarbons can tumble freely while within the capsule at room temperature. The maximal internal capacity of the cylindrical capsule (diameter of 6.6 Å, length of 16 Å) does not permit the tumbling of molecules longer than 6.6 Å. In their extended conformation, the length of n -pentane and n -hexane is about 8.7 and 10.0 Å, respectively (Table 1). These hydrocarbons must therefore fold in order to tumble rapidly on the chemical shift time scale in the capsule. Given the restricted elongated space available it is reasonable to presume that these two molecules adopt coiled conformations, although it is presently not possible to observe such structures experimentally. For the slightly longer n -heptane, no clear signals are observed in the upfield region, even if the NH resonances at 10.3 ppm are indicative of a capsular host.¹⁰ In this peculiar case, no clear encapsulation occurs because the cavity is too large to accept one molecule alone (small PC) but too small to accommodate two molecules (Table 1). Instead, impurities must occupy the capsule.

For the alkanes n -C₈H₁₈ to n -C₁₄H₃₀, single molecules were found in the capsule. In these cases, separate signals are observed for each methylene and for the terminal methyl groups. The magnetic shielding provided by the aromatic rings of the hosts gradually increases from the middle of the capsule to its

(10) The upfield signals observed could be accounted for by co-encapsulation of commercial n -heptane with low molecular weight impurities.

(7) Mecozzi, S.; Rebek, J., Jr. *Chem. Eur. J.* **1998**, *4*, 1016–1022.
 (8) Körner, S. K.; Tucci, F. C.; Rudkevich, D. M.; Heinz, T.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 187–195.
 (9) For leading references, see: (a) Shivanyuk, A.; Rebek, J., Jr. *Chem. Commun.* **2002**, *20*, 2326–2327. (b) Shivanyuk, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 684–686. (c) Scarso, A.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 13981–13983. Yamanaka, M.; Shivanyuk, A.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 2669–2672.

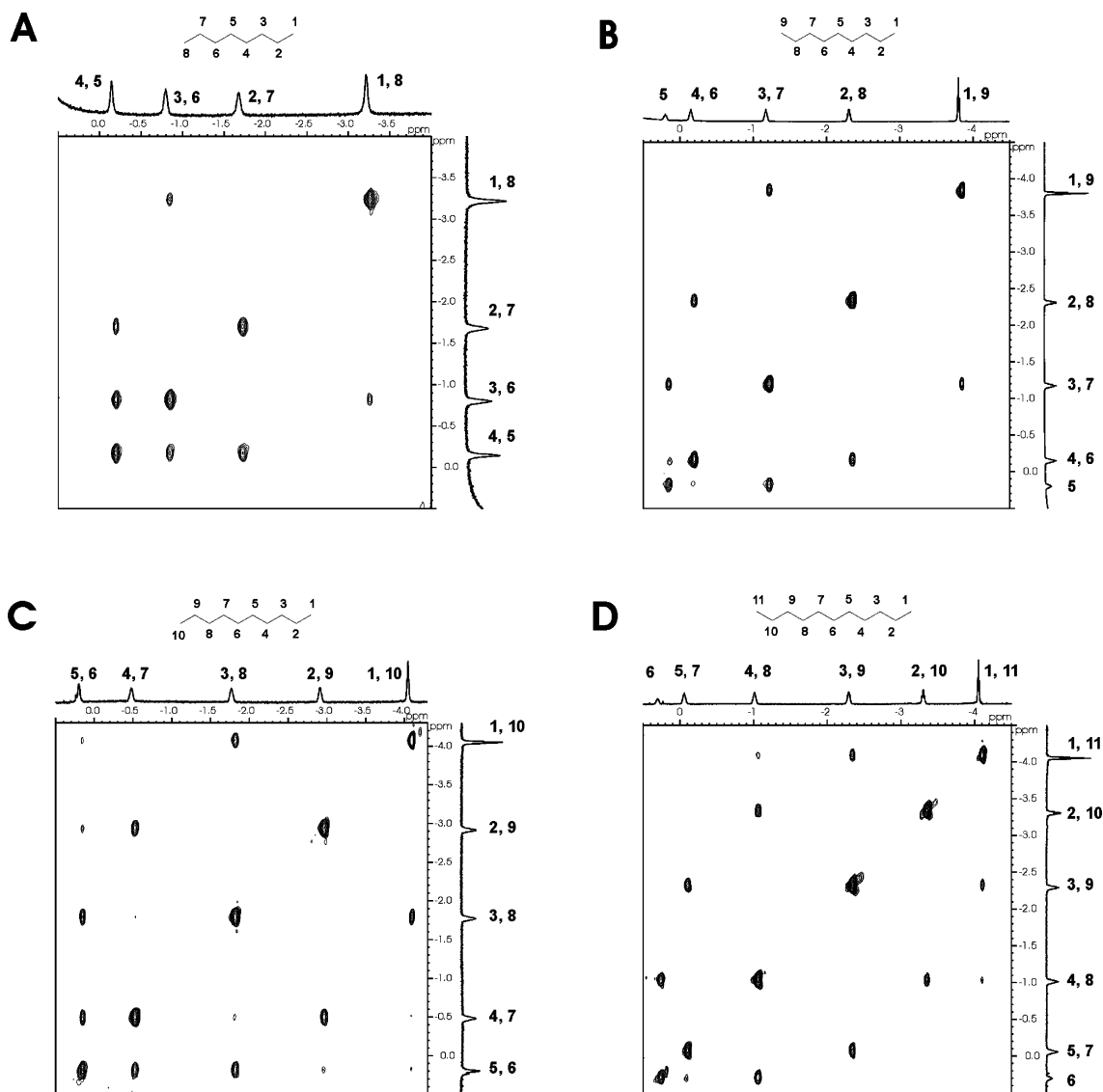


Figure 3. Upfield portion of the 2D NOESY spectrum at 600 MHz in mesitylene- d_{12} at 300 K of the encapsulation complexes of I_2 (2 mM) with (a) n - C_8H_{18} (100 mM), (b) n - C_9H_{20} (100 mM), (c) n - $C_{10}H_{22}$ (100 mM), and (d) n - $C_{11}H_{24}$ (100 mM).

ends. Methyl groups are subjected to maximal upfield shifts with a $\Delta\delta$ up to -4.95 ppm. The chemical shifts of each methylene were determined by 2D-COSY experiments. Tumbling of these longer alkanes is improbable, but they are expected to rotate freely about the longitudinal axis of the capsule.

2. Conformations of Alkanes by 2D NOESY Experiments.

For all the complexes, NOE cross-peaks were observed between methyl groups of the guests and only the signal for the aromatic CH between the resorcinarene oxygens. Several cross-peaks were also detected between the imide NH of the capsule and methylene groups positioned in the middle of the hydrocarbon chain. This confirmed that included hydrocarbons are lying in an elongated manner within the cavity, with methyl groups positioned close to the ends. Alkanes longer than n - $C_{14}H_{30}$ are not encapsulated at all, even if employed in large excesses. In their extended conformations, alkanes from n - C_8H_{18} to n - $C_{10}H_{22}$ have lengths compatible with the capsule dimensions (Table 1). The conformations of included guests were further determined using 2D-NOESY experiments (Figures 3 and 4). Only cross-peaks between the hydrogen atoms at C_i and C_{i+2} were

observed all along the carbon chain, showing that these alkanes adopt extended conformations while inside the capsule. Accordingly, chemical shifts of the terminal methyl groups decrease from extended n - C_8H_{18} to extended n - $C_{10}H_{22}$ in accord with increased shielding at the ends of the cavity.

Two encapsulated molecules of n -hexane must adopt tightly coiled conformations in order to fit in the capsule. Molecular modeling clearly shows that hydrocarbons longer than n - $C_{10}H_{22}$ are also too long to be encapsulated in the cavity in their fully extended conformations (Table 1). Yet, all of them are encapsulated as shown by the 1H NMR spectra. Coiling into a helix is one way for the hydrocarbon chain to decrease its length in a restricted, cylindrical space. Examination of the complexes by 2D-NOESY showed that coiling starts at the alkyl chain extremities. For example, the complex with n - $C_{11}H_{24}$ shows NOE cross-peaks between the hydrogens at C_1 and C_3 and at C_1 and C_4 . But C_2 is in NOE contact only with C_4 , C_3 with C_5 , and C_4 with C_6 . This demonstrates the presence of gauche conformations of four carbon atoms at the extremities and an extended chain of carbon atoms in the middle. With only one more methylene (n - $C_{12}H_{26}$) the guest assumes a more helical

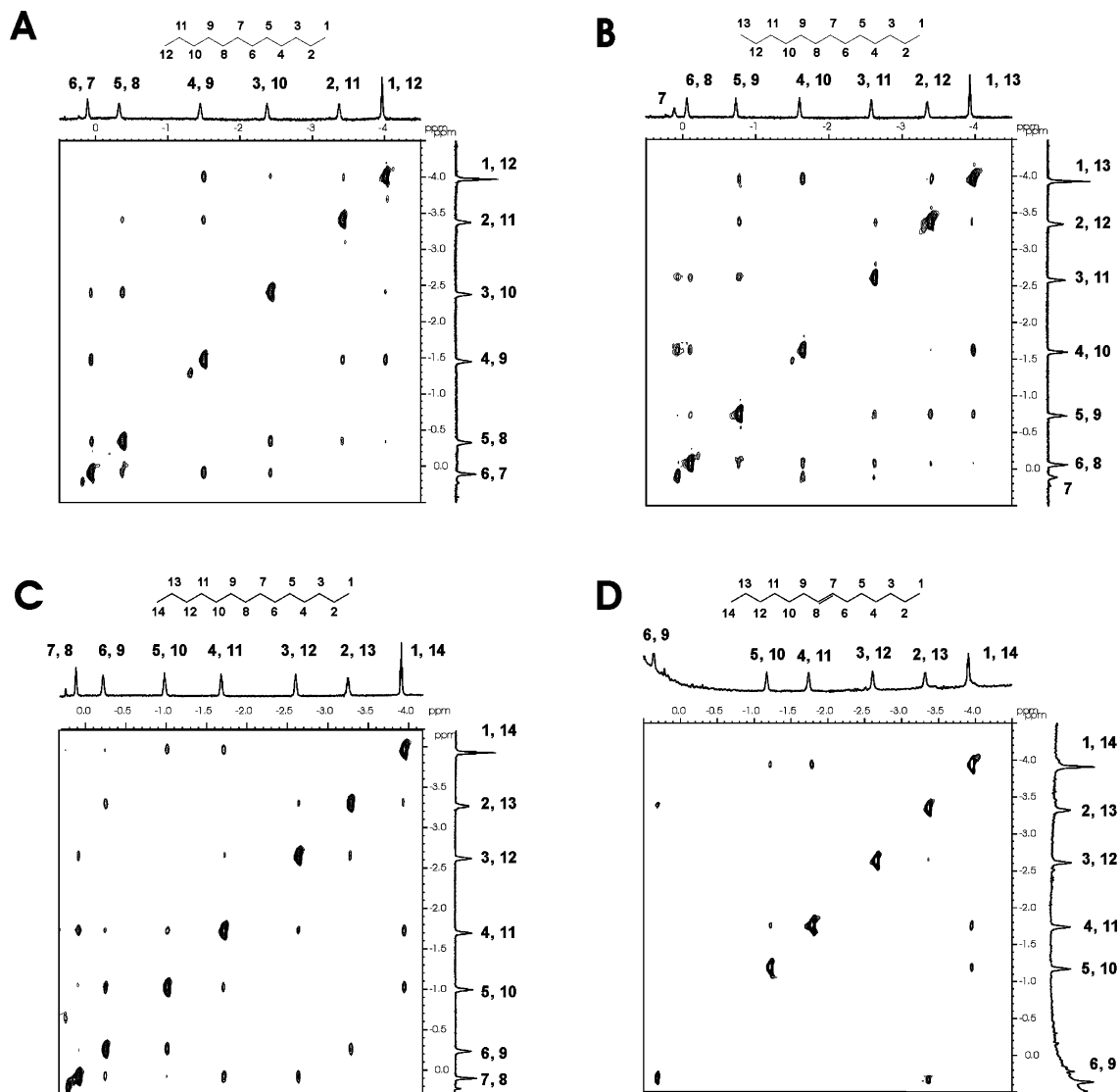


Figure 4. Upfield portion of the 2D NOESY spectrum at 600 MHz in mesitylene- d_{12} at 300 K of the encapsulation complexes of I_2 (2 mM) with (a) $n\text{-C}_{12}\text{H}_{26}$ (100 mM), (b) $n\text{-C}_{13}\text{H}_{28}$ (100 mM), (c) $n\text{-C}_{14}\text{H}_{30}$ (100 mM), and (d) $n\text{-C}_{14}\text{H}_{28}$ *trans*-7-tetradecane (100 mM).

conformation as demonstrated by the presence of $C_i\text{--}C_{i+2}$ and $C_i\text{--}C_{i+3}$ NOE interactions all along the chain. With $n\text{-C}_{14}\text{H}_{30}$, gauche conformations are predominant as indicated by NOE cross-peaks between hydrogens at C_i and C_{i+3} , and C_i and C_{i+4} indicative of a tightly coiled conformation.

In the ^1H NMR spectra, chemical shifts of the terminal methyl groups increase with gradually longer and consequently more coiled alkanes. In other words, coiling into helical conformations causes the terminal methyl groups to move slightly away from the tapered ends of the cavity.

3. Dynamics of Coiling. Useful indications about the dynamics of the system are given by signal's multiplicity in the ^1H NMR spectra. For hydrocarbons that fit in a strictly extended conformation ($n\text{-C}_8\text{H}_{18}$ to $n\text{-C}_{10}\text{H}_{22}$), the broadness of the signals observed is indicative of a process with a rate that, at the temperature employed for the experiments, is still lower but not very different to the ^1H NMR chemical shift time scale (600 MHz). This can be due to the relatively small size of these guests and the low complementarity with the capsule that increases the in-out exchange rates, leading to broader signals. For $n\text{-C}_{11}\text{H}_{24}$ and $n\text{-C}_{12}\text{H}_{26}$ the in/out exchange rates are likely to decrease. Signals are still slightly broad, possibly because

coiling can occur in an unsymmetrical manner at the extremities of the chain. For $n\text{-C}_{13}\text{H}_{28}$ and $n\text{-C}_{14}\text{H}_{30}$ the signals are increasingly sharp: a sextet and a triplet can be readily distinguished for the terminal methylene and methyl, respectively. This is expected for rapid rotation around the $C_1\text{--}C_2$ and $C_2\text{--}C_3$ bonds. Additionally, these two guests possess slightly sharper signals for the central methylene groups: this could be related to steric interactions of the extremities with the capsule's concave surfaces (Figure 2).

Helices are chiral structures, and the hydrogens at each methylene are therefore diastereotopic. This should result in geminal coupling but no such splitting is seen in the ^1H NMR spectrum of the encapsulated $n\text{-C}_{14}\text{H}_{30}$. Rather, a sharp sextet ($J^3 = 7.48$ and 6.78 Hz) is present for the penultimate methylenes. We presume that helix-helix interconversions (racemization) occur rapidly on the chemical shift time scale. There is not enough space in the capsule for this process to take place within the cavity through a fully extended conformation. A dynamic undulation of short extended conformations traveling up and down the chain via *anti* transition states is the most probable mechanism. Some evidence of this is provided by the olefin *trans*-7-tetradecene. It is a suitable guest as

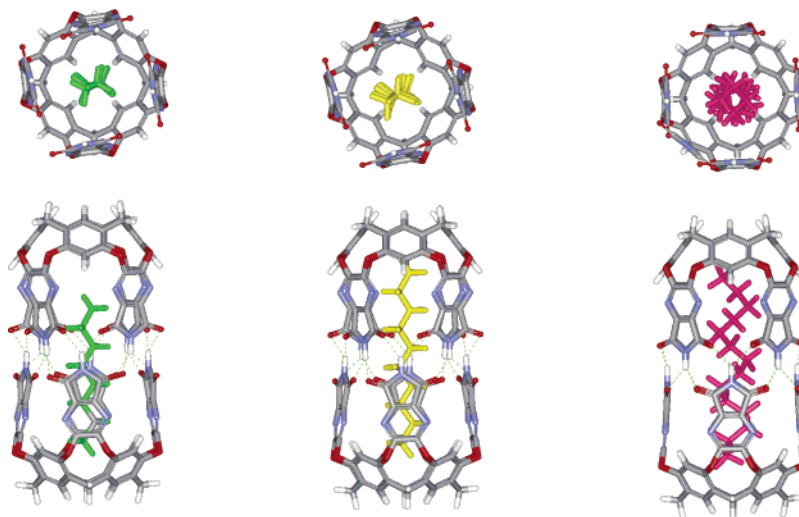


Figure 5. Top and front views of the minimized structures for the complexes $n\text{-C}_8\text{H}_{18}@12$ (left), $n\text{-C}_{10}\text{H}_{22}@12$ (middle), $n\text{-C}_{14}\text{H}_{30}@12$ (right) (molecular mechanics AMBER* force field with the program Maestro using the dielectric constant for benzene). Alkyl chains of the cavitands have been omitted for clarity as well as one-half of the capsule for views from the top.

Table 2. Imide Proton Chemical Shifts in Mesitylene- d_{12} at 300 K and Temperature Coefficients

| guest | NH (ppm) | TC (ppb/K) | guest | NH (ppm) | TC (ppb/K) |
|--------------------------------|----------|------------|--------------------------------|----------|------------|
| $2(n\text{-C}_5\text{H}_{12})$ | 10.10 | -7.0 | $n\text{-C}_{11}\text{H}_{24}$ | 10.31 | -5.9 |
| $2(n\text{-C}_6\text{H}_{14})$ | 9.68 | -4.3 | $n\text{-C}_{12}\text{H}_{26}$ | 9.88 | -5.8 |
| $n\text{-C}_8\text{H}_{18}$ | 10.35 | -6.4 | $n\text{-C}_{13}\text{H}_{28}$ | 9.87 | -4.9 |
| $n\text{-C}_9\text{H}_{20}$ | 10.40 | -5.8 | $n\text{-C}_{14}\text{H}_{30}$ | 9.75 | -3.6 |
| $n\text{-C}_{10}\text{H}_{22}$ | 10.43 | -5.8 | $n\text{-C}_{14}\text{H}_{28}$ | 9.69 | -2.9 |

observed from Figure 2; its affinity for the capsule is diminished, but only by a factor of 2.8 compared with $n\text{-C}_{14}\text{H}_{30}$. The presence of the four central atoms in a rigid *trans* geometry resembles the *anti* transition state as proposed for racemization within the capsule.

IV. Capsule Deformation to Accommodate the Guest

Alkanes encapsulated in their fully extended conformations seem too narrow to complement properly the cylindrical cavity of the capsule, and light variations of its shape might occur upon binding, in response to the size of the guests. The NH chemical shift is a parameter that gives a good indication of the hydrogen bond strength that is responsible for dimerization of the capsule. From $n\text{-C}_8\text{H}_{18}$ to $n\text{-C}_{10}\text{H}_{22}$ (Figure 2 and Table 2), the NH's chemical shift is almost unchanged, while with longer guests there is an inverse trend that correlates this shift with the packing coefficient and indicates the increasing difficulty to keep the capsule assembled.

Molecular modeling of the complexes (Figure 5) combined with the experimental temperature coefficients associated with the imide NH signals for each guest were explored. Temperature coefficients are parameters extracted from chemical shift measurements used to characterize conformations and aggregation status of peptides and proteins in solution.¹¹ They reflect the temperature dependence of ^1H chemical shifts of NH amide hydrogens, either involved or not involved in hydrogen bonding. Values are sensitive to the solvent used and the state of the

hydrogen under observation over a certain range of temperatures. In an apolar solvent like CDCl_3 , Stevens and Toniolo¹² showed (1) that the temperature dependence of NH chemical shifts are small for NH protons exposed to the solvent and for NH protons that are shielded (hydrogen bonded or buried) over the course of temperature variation and (2) that the dependence is significantly larger for NH protons initially buried but transferred to a more solvated environment during the course of temperature variation. For the capsular system under investigation changes in guests conformation and more likely in/out exchange could also affect this parameter, especially for guests smaller than $n\text{-C}_{10}\text{H}_{22}$. Nevertheless, we anticipated that only a small temperature dependence of NH chemical shifts of imides participating in the capsule's hydrogen bond network would be observed for a perfectly cylindrical capsule. In the case of inward deformations of the imide aromatic walls, larger variations would be expected, as hydrogen bonds would move to a more buried position. Therefore, we employed temperature coefficients as a tool to investigate conformational changes of the receptor and variations of the NH's chemical shift to probe the strength of the hydrogen bond network.

In the case of complexes with $(n\text{-C}_6\text{H}_{14})_2$ and $n\text{-C}_{14}\text{H}_{30}$, the calculated packing coefficients are maximal. As a result, a more cylindrical shape of the capsule is expected. In agreement with this hypothesis, low absolute temperature coefficients (4.3 and 3.6 ppb/K, respectively) and a relatively weak hydrogen bond network was observed as testified by a minimal chemical shift of the imide NHs (Table 2).

Encapsulated guests $n\text{-C}_8\text{H}_{18}$ to $n\text{-C}_{12}\text{H}_{26}$ possess extended chains in the middle region, and coaxial to the imide hydrogen bond network considerable free space would remain unfilled if the capsule would keep its cylindrical shape. Higher values of the absolute temperature coefficients (6.4–5.8 ppb/K) and a stronger downfield shift of the NHs were observed, revealing that the capsule adopts a different conformation with a stronger hydrogen bond network. In agreement, computational modeling of the complexes showed that the twisting of the imide walls should occur, filling empty spaces, and maximizing interactions

(11) (a) Baxter, N. J.; Williamson, M. P. *J. Biomol. NMR* **1997**, *9*, 359–369. (b) Stevens, E. S.; Sugawara, N.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048–7050. (c) Das, C.; Shankaramma, S. C.; Balaram, P. *Chem. Eur. J.* **2001**, *7*, 840–847.

(12) Stevens, E. S.; Sugawara, N.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048–7050.

Table 3. Relative Affinities of Capsule **1**₂ for Hydrocarbons *n*-C₉H₂₀ to *n*-C₁₄H₃₀ in Deuterated Mesitylene and Chloroform at 300 K

| guest | $K_{\text{rel}}(\text{C}_6\text{D}_{12})$ | $K_{\text{rel}}(\text{CDCl}_3)$ |
|---|---|---------------------------------|
| <i>n</i> -C ₉ H ₂₀ | 0.3 | |
| <i>n</i> -C ₁₀ H ₂₂ | 16.9 | 17.8 |
| <i>n</i> -C ₁₁ H ₂₄ | 100 | 100 |
| <i>n</i> -C ₁₂ H ₂₆ | 24.4 | 20.3 |
| <i>n</i> -C ₁₃ H ₂₈ | 1.0 | |
| <i>n</i> -C ₁₄ H ₃₀ | 13.2 | |
| <i>n</i> -C ₁₄ H ₂₈ | 4.7 | |

with the guest (Figure 5). For instance, the internal volume of the capsule minimized with *n*-C₁₀H₂₂ decreases from 425 to about 354 Å³ and the PC for the hydrocarbon increases from about 39 to 47%. In other words, this conformational change reciprocates the solvation of the capsule's aromatic surfaces by the guest and vice versa. A similar trend is observed for *n*-C₁₀H₂₂, *n*-C₁₁H₂₄ and *n*-C₁₂H₂₆ in the more polar chloroform-*d*₁, but with magnitude about half of that observed in mesitylene-*d*₁₂. This is probably due to the higher polarity of the chlorinated solvent and to the consequent higher exposure of the NHs to the external environment ($\delta_{\text{NH}} = 9.80$ ppm).

V. Relative Affinities and Driving Forces Involved in Complexation

Relative binding constants were determined by competitive experiments using ¹H NMR spectroscopy. In the experiments, the host **1**₂ was offered large excesses (overall more than 200 equiv) of the two competitive guests and the system was left at room temperature until the equilibrium was reached. Integration of the NH signals for the different complexes allowed the calculation of the relative affinities. In mesitylene-*d*₁₂, sometimes up to 12 weeks was required to reach the equilibrium because of an exceedingly slow in/out exchange rate (see the Supporting Information). Apparently, long hydrocarbon guests require the capsule to completely disassemble in this solvent before the incoming guest can occupy the cavity. Typically for rigid guests of the size of benzene, in/out exchange processes go through activation barriers of approximately 20 kcal/mol.¹³ In mesitylene, the solvent is too large to participate in the process; the transition state is expected to involve partially unfilled cavities and should be of relatively high energy. In deuterated chloroform, equilibrium was reached immediately on mixing the components. This smaller solvent is known to be encapsulated and can play a part in the exchange process,⁹ filling space as required. Consequently, only the best guests—namely *n*-C₁₀H₂₂, *n*-C₁₁H₂₄, and *n*-C₁₂H₂₆—were detected in the capsule in CDCl₃ solvent.

The results of the determination of the relative binding constants are reported in Table 3. The relative affinities were found to be similar for both solvents. The nature of the external environment appears to have negligible effects on the interactions at work within the capsule. Several parameters influence the free energies of the complexes; in particular, entropic factors related to these adaptation processes between capsular host and guest are indubitably involved, but because of the slow kinetic characteristic of some equilibration experiments, the temperature effect on binding constants was not investigated. These are the subjects of ongoing experiments.

(13) Craig, S. L.; Lin, S.; Chen, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 8780–8781.

Small, extended guests force the capsule to adopt energetically demanding twisted conformations of the walls. On the other hand, folding of long guests into helical conformations increases the energy due to the presence of several unfavorable gauche interactions, each at an energy cost of 0.5–0.6 kcal/mol in the liquid phase.¹⁴ Hydrogen bond strength is not directly correlated to the relative binding affinity of guests, indicating that for the preferred guest *n*-C₁₁H₂₄ a delicate balance of entropic and enthalpic contributions is involved. It was no surprise that binding affinities increased from *n*-C₈H₁₈ to *n*-C₁₀H₂₂ since packing coefficients rise toward an ideal value and NH's packing coefficients rise toward an ideal value and NH's conformational shift is not affected by the size of these guests. From *n*-C₁₁H₂₄ to *n*-C₁₃H₂₈, the favorable CH/ π contacts and the relaxation of the formerly twisted walls do not entirely compensate the energetic cost of coiling and concomitant weakening of hydrogen bonds. These lead to a decrease in the relative binding affinity. Remarkably, the binding of the cylindrical capsule for the fully coiled *n*-C₁₄H₃₀ is about 13 times ($\Delta\Delta G = -1.5$ kcal/mol) higher than for *n*-C₁₃H₂₈. Apparently, the tightly coiled alkane forces the capsule to adopt the ideal cylindrical shape—minimizing torsions of the imide aromatic walls—providing better size and shape complementarity (PC of 56%) and stronger CH/ π interactions^{15–17} with the aromatic walls of the capsule. Finally, the binding affinity is reduced by a factor of 2.8 for the longer *trans*-7-tetradecane (*n*-C₁₄H₂₈); its length approaches the limit accepted by the cavity.

VI. Conclusions

Conformational changes during the binding of flexible molecules by natural receptors are frequently encountered in biological systems but more rarely seen with synthetic receptors. In this study, we showed that the intimate association of alkanes of different lengths with self-assembled capsule **1**₂ in mesitylene and chloroform results in conformational changes of both guests and host. These are driven by the combination of size and shape complementarity as well as chemical surface interactions between the two partners. Solvation of alkanes outside the capsule requires organization of several molecules of mesitylene; inside the capsule the walls are more or less fixed and the guest must conform to the presentation of the aromatic units.

VII. Experimental Section

1. General Methods. Deuterated solvents were used as purchased from Cambridge Isotope Laboratories. Hydrocarbons were obtained from Sigma-Aldrich or Acros Chemicals and used without further purification. Capsule **1**₂ was prepared and purified according to procedures previously described.¹⁸

2. NMR Spectroscopy Studies. 1D and 2D NMR data were recorded on a Bruker 600-DRX (600 MHz) spectrometer. Chemical shifts (δ) are expressed as parts per million (ppm) relative to the peak for SiMe₄ (TMS; $\delta = 0$ ppm) and referenced internally with respect to that for the protio solvent impurity. 2D-COSY and 2D-NOESY experiments were acquired with a spectrum width of 18 ppm, a relaxation delay *d*₁ of 2.5 s, using 1K data points in the *t*₂ dimension and 400 data points

(14) Eliel, E.; Wilen, S. H. *Stereochemistry of organic compounds*; Wiley: New York, 1994.

(15) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/ π interaction*; Wiley: New York, 1998.

(16) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545.

(17) Meyer, E. A.; Castellano R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.

(18) Hayashida, O.; Sebo, L.; Rebek, J., Jr. *J. Org. Chem.* **2002**, *67*, 8291–8298.

in the t_1 dimension, with subsequent weighting with the sine-bell function using 64 scans for each t_1 increment. The mixing time d_s employed was 0.3 s, and the spectra acquired with different values (in the range 0.15–0.45 s) showed comparable results.

For the mixing times employed, no in–out exchange cross-peaks between encapsulated and free guest in solution were observed. The temperature of the probe was calibrated prior of each experiment using a solution of 4% methanol in methanol- d_4 and applying the empirical equation that correlates the $\delta\Delta$ difference between the CH_3 and the OH resonance to the real temperature.¹⁹ The spectra were processed and analyzed with the program XWIN-NMR.²⁰

Temperature coefficients: imide NH chemical shifts were plotted versus temperatures in the range 240–320 K for each guest, and the corresponding temperature coefficients (ppb/K) were extracted from the slopes of the lines obtained (see the Supporting Information).

3. Preparation of the Samples. Solutions of the complexes were prepared by mixing mesitylene- d_{12} (or CDCl_3) solutions of capsule **1**₂ with mesitylene- d_{12} (or CDCl_3) solutions of the hydrocarbons. Typically, 400 μL of guest solution at 125 mM was added to 100 μL of a solution of **1**₂ at 10 mM concentration to give 500 μL of a solution of the capsule **1**₂ (2 mM) and the guest (100 mM). Competitive experiments were performed by addition of mixtures of two hydrocarbons at overall >500 mM concentrations in the deuterated solvent to a host solution. NMR data were recorded directly after mixing and at regular time intervals

(hours to weeks) until the thermodynamic equilibrium was reached (see the Supporting Information). The relative binding affinities of the guests to the capsule were determined by direct integration of the corresponding peaks of the encapsulated guests and/or integration of the NH signals.

4. Molecular Modeling. Structures of the cylindrical capsule **1**₂ and the hydrocarbons were built and minimized (AMBER* force field with a dielectric constant of 2.3 for benzene) using the program MacroModel or Maestro (Schroedinger, Inc.) on a Silicon Graphics Octane workstation. The inner space of the capsule was determined using the program GRASP²¹ (probe radius of 1.5 Å). The length of the capsule was measured as a distance between the centroids of methine carbons of the capsule. End-to-end lengths of the hydrocarbons were measured using the built-in tool provided by GRASP after generation of van der Waals surfaces.

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Supporting Information Available: Plots for the determination of temperature coefficients and kinetics of complexation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) Braun, S.; Kalinowski, H. O.; Berger, S. *150 and More Basic NMR Experiments*; Wiley-WCH: New York, 1998.

(20) Bruker BioSpin, GmbH.

(21) Nicholls, A.; Sharp, K.; Honig, B. *Proteins* **1991**, *11*, 281.