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Encapsulation Induces Helical Folding of Alkanes**

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Helical structures occur frequently in proteins and nucleic acids but are not encountered as conformations of naturally occurring hydrocarbons. In the gel state of membranes, for example, the long alkyl chain components of membranes adopt strain-free extended conformations. Folding to more compact forms reduces the hydrophobic surface but generates strain in the form of *gauche* interactions. We recently observed that the alkane chains of two common surfactants in aqueous solution are bound within an open-ended synthetic receptor by assuming helical coil conformations.[1] The formation of the complex buries the hydrophobic surfaces of both the surfactant and receptor. Here we show that complete encapsulation of long-chain, normal alkanes (C_{12}–C_{14}) in organic media also results in folding to helical structures. Molecular recognition occurs between the π lining of the rigid receptor and the C-H surface of the flexible alkane: the coiled alkane better complements the size, shape, and chemical surface of the receptor, even at the cost of $>6\,\mathrm{kcal\,mol^{-1}}$ in *gauche* strain. Shorter alkanes are encapsulated in more extended conformations.

The synthetic receptor $\mathbf{1}_2$ (Figure 1) offers an elongated cavity, lined with eight benzene rings and additional π surfaces. The calculated size of its cavity depends on the software

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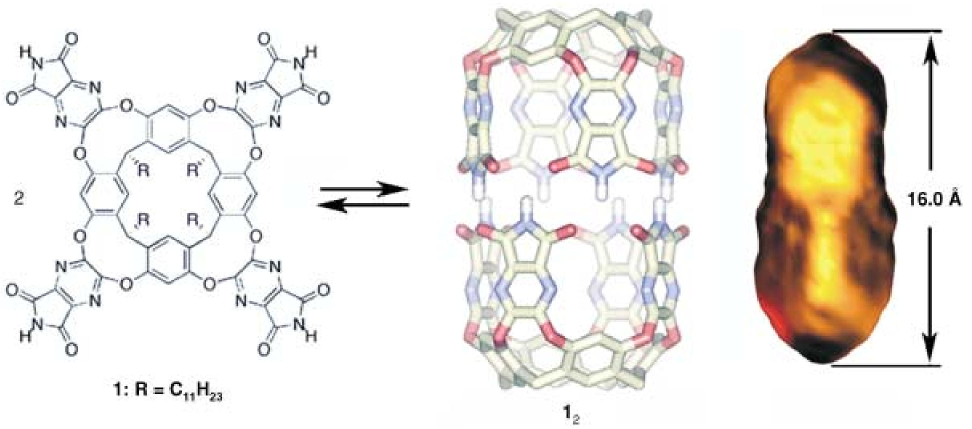
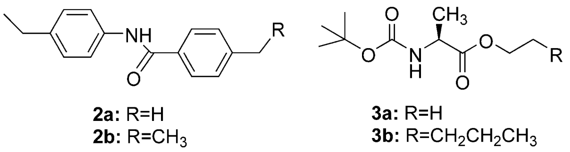


Figure 1. a) Schematic drawing of the synthetic receptor; b) the energy-minimized dimer; and c) the size and shape of its cavity.

used, for example, the Swiss PDB viewer gives a volume of 425 Å^3 and a length of approximately 16 Å, but the tapered ends can accommodate only the smallest of atoms. The capsule is a host to guests that fill about half of its volume. The binding of rigid guest structures is strictly limited by length: the anilide **2a** (Scheme 1) with a methyl group is encapsulated, but the slightly longer ethyl compound **2b** is not. Flexible guests are also accepted if they can assume complementary lengths.[2,3] The Boc-Ala-ethyl ester **3a** (Boc = *tert*-butoxycarbonyl) is a good guest, while its homologues, even up to the pentyl ester **3b**, are bound to some extent.[4] The longer esters must adopt nonlinear conformations to be accommodated. The capsules are held together through a cyclic seam of bifurcated hydrogen bonds (Figure 1) and guest exchange involves the rupture of the seam as well as a conformational change of the receptor. Activation barriers for the in/out exchange process in [D$_{12}$]mesitylene are in the range of about 20 kcal mol^{-1} for large guests,[5] and this process is slow on the NMR time scale: separate signals are seen in the spectra for the free and bound guest.



Scheme 1. Examples of common guests for 1_2.

Only undefined aggregates of the host with broad NMR signals are observed in distilled [D$_{12}$]mesitylene. The maximum number of hydrogen bonds per subunit are present only in the dimeric capsular form, but mesitylene cannot fit inside. Without an appropriate guest, the inner surfaces remain unsolvated and a vacuum would exist in the capsule since; this provides the driving force for the assembled complexes.

We examined the encapsulation of straight-chain alkanes C_{10} to C_{15}. At first glance, the hydrocarbons are ill fits as they are too narrow to complement the cavity of the capsule. A summary of the relevant properties of the guests, including their dimensions, surface areas, and volumes in both the extended and entirely helical conformations are given in Table 1. Even tightly coiled, alkane C_{15} is seen to exceed the capsule's length, but alkane C_{10} can fit in a fully extended conformation. The hydrocarbons C_{10} to C_{14} were found by experiment to be encapsulated in 1_2, but C_{15} was not. The NMR spectra (Figure 2) showed separate signals for each encapsulated methylene and methyl group; the latter appeared at −4 ppm. This chemical shift ($\Delta\delta \sim 5$ ppm) is associated with a methyl group positioned at the very end of the cavity; the magnetic environment changes gradually as the guest moves toward the center of the capsule, where $\Delta\delta$ changes of approximately 1 ppm is typically observed.[6]

Table 1: Dimensions of the hydrocarbons.

Alkane[a]	Length [Å]	Surface area [Å^2]	Volume [Å^3]	PC[b] [%]	$K_{rel.}$[c]
$C_{10}H_{22}$ extended	15.0	196	167	39	1.00
$C_{12}H_{26}$ extended	17.5	230	200	47	1.35
$C_{12}H_{26}$ coiled	13.6	207	206	48	
$C_{14}H_{30}$ extended	20.0	264	235	–	0.80
$C_{14}H_{30}$ coiled	15.5	235	240	56	
$C_{14}H_{28}$ coiled	16.0	239	239	56	0.32
$C_{15}H_{32}$ coiled	16.3	251	258	–	

[a] $C_{10}H_{22}$: *n*-decane; $C_{12}H_{26}$: *n*-dodecane; $C_{14}H_{30}$: *n*-tetradecane; $C_{14}H_{28}$: *trans*-7-tetradecene; $C_{15}H_{32}$: *n*-pentadecane. [b] Packing coefficients of alkanes in capsule 1_2 were calculated using Grasp[13] (1.5 Å probe) after energy minimization of the structures. [c] Relative association constants K_{rel} were determined by NMR spectroscopy at 300 K by direct competition experiments.

Since no more than 10 carbon atoms can be accommodated in a fully extended conformation, folding must occur during the encapsulation of the longer alkanes. The conformation of the longest alkane guest (C_{14}) was determined through nuclear Overhauser enhancement (NOE) experiments. Cross-peaks between the hydrogen atoms on C1 and C4, and C1 and C5 were observed, and in accord with *gauche* interactions at the carbon atoms at the ends of the chain (Figure 3). The hydrogen atoms on C2 showed cross-peaks

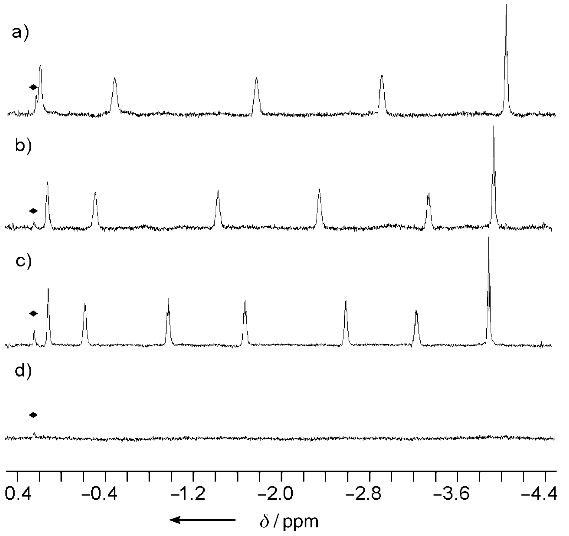


Figure 2. ^{1}H NMR spectra at 600 MHz in [D$_{12}$]mesitylene at 300 K of $\mathbf{1}_2$ (2 mM) with a) n-$C_{10}H_{22}$ (100 mM); b) n-$C_{12}H_{26}$ (100 mM); c) n-$C_{14}H_{30}$ (100 mM); d) n-$C_{15}H_{32}$ (100 mM). ◆indicates an impurity from the deuterated solvent.

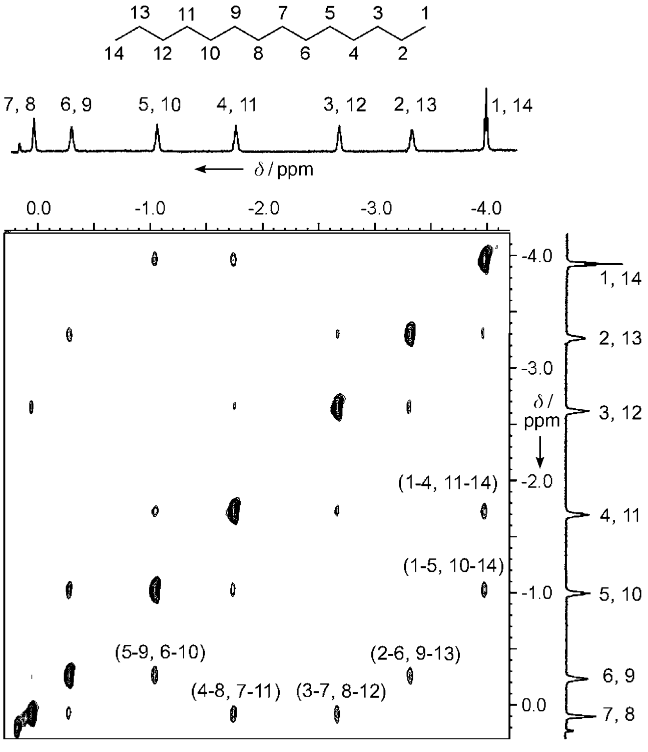


Figure 3. Upfield portion of the 2D NOESY spectrum of the encapsulation complex of $\mathbf{1}_2$ [2 mM] with n-$C_{14}H_{30}$ [100 mM] (600 MHz; 300 K in [D$_{12}$]mesitylene; mixing time of 300 ms).

with C6 and those on C3 with C7—in general, Ci interacted with C$i+4$ ($i=2$ to 6)—thus indicating a tightly coiled helical structure. At least five *gauche* interactions exist at both ends of the C_{14} alkane chain, each at an energy cost of 0.5–0.6 kcal mol^{-1} in the liquid phase.[7,8] Direct competition experiments gave the relative binding affinities reported in Table 1 and revealed that the rate of equilibration in mesitylene is very slow at 300 K: more than 20 days was required to reach equilibrium in some cases. Dodecane ($C_{12}H_{26}$) was bound the strongest and reflects the balance of forces involved in encapsulation: as the chain length increases so do the unfavorable *gauche* interactions, but better packing coefficients and more favorable CH/π interactions[9,10] result between the guest and host (Figure 4). Accordingly, the binding affinity of the C_{14} alkane for the capsule is reduced by only a factor of 0.6. Liberation of the mesitylene solvent in contact with the alkanes outside the capsule undoubtedly provides an entropic benefit to offset the limitations of the guest inside the organized walls of the capsule. Size complementarity also exists: the volume of the cavity is about 425 Å^3 while that of the helical alkane is approximately 240 Å^3. The packing coefficient for the C_{14} alkane within this space is 56%, which is near the ideal value for the liquid state.[11]

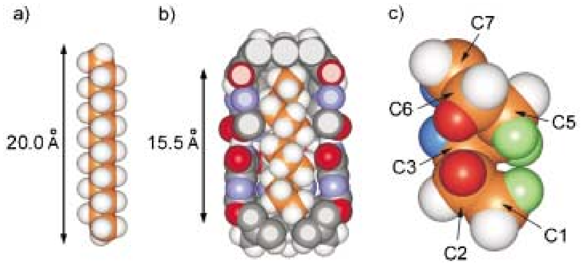


Figure 4. Energy-minimized structures of $C_{14}H_{30}$@$\mathbf{1}_2$ complex:[12] a) extended conformation of tetradecane ($C_{14}H_{30}$); b) space-filling model and cross-section of the cavity showing C-H/π contacts; c) the origins of the intramolecular NOE interactions between hydrogen atoms at C1 and C4/C5, Ci and C$i+4$ ($i=2$ to 6).

The signals in the ^{1}H NMR spectrum corresponding to the methylene groups of alkane C_{10} are shifted downfield in accord with positions nearer the center of the capsule (Figure 2 a,c) and its NOE patterns correspond to those of a fully extended conformation (see Supplementary Information). Both conformations were present with alkane C_{12} as a guest: the ends showed the characteristics of a coil and the central segment those of an extended conformation.

Finally, there are the motions of the alkanes while inside the capsule. The resting state of encapsulated alkane C_{14} is helical, but the system is dynamic. Helices are, of course, chiral and the hydrogen atoms on C2 (and C3, etc) are then diastereotopic. Yet in the ^{1}H NMR spectrum C2 appears as a fairly sharp hextet pattern, as would be expected of rapid rotation about the C2–C3 bond. A frozen helical conformation would generate signals of higher multiplicity than those actually observed (Figure 2 c). Consequently, the enantiomeric helical forms must interconvert rapidly (racemize) on the NMR time scale while within the capsule. The eclipsed transition states for rotation about each *gauche* bond contribute only a barrier of about 2.7 kcal mol^{-1}, and rapid racemization seems energetically quite reasonable. There is not enough room in the capsule for this interconversion to take place through a fully extended conformation, but crankshaft motions of a few carbon atoms up and down the chain are a likely mechanism for the interconversion, and some evidence of this is provided by the olefin *trans*-7-tetradecene. This alkene has its central four carbon atoms fixed in an extended conformation and is encapsulated almost as well as the C_{14} alkane: direct competition experiments with the C_{14} alkene and alkane showed the alkane is favored by only a factor of 2.5. In other words, the energetic cost of an extended conformation for four carbon atoms of the C_{14} alkane is less than 0.5 kcal mol^{-1}.

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