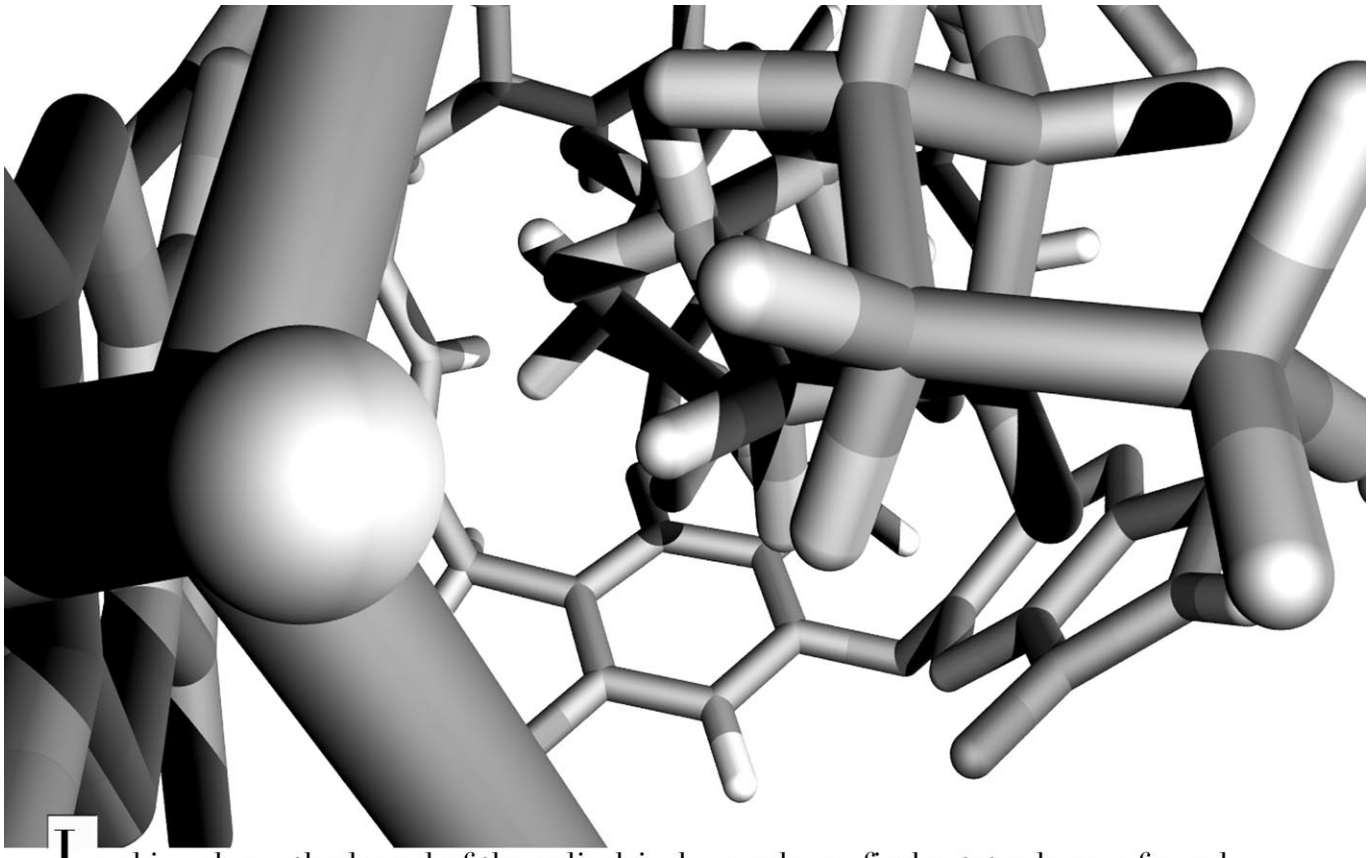
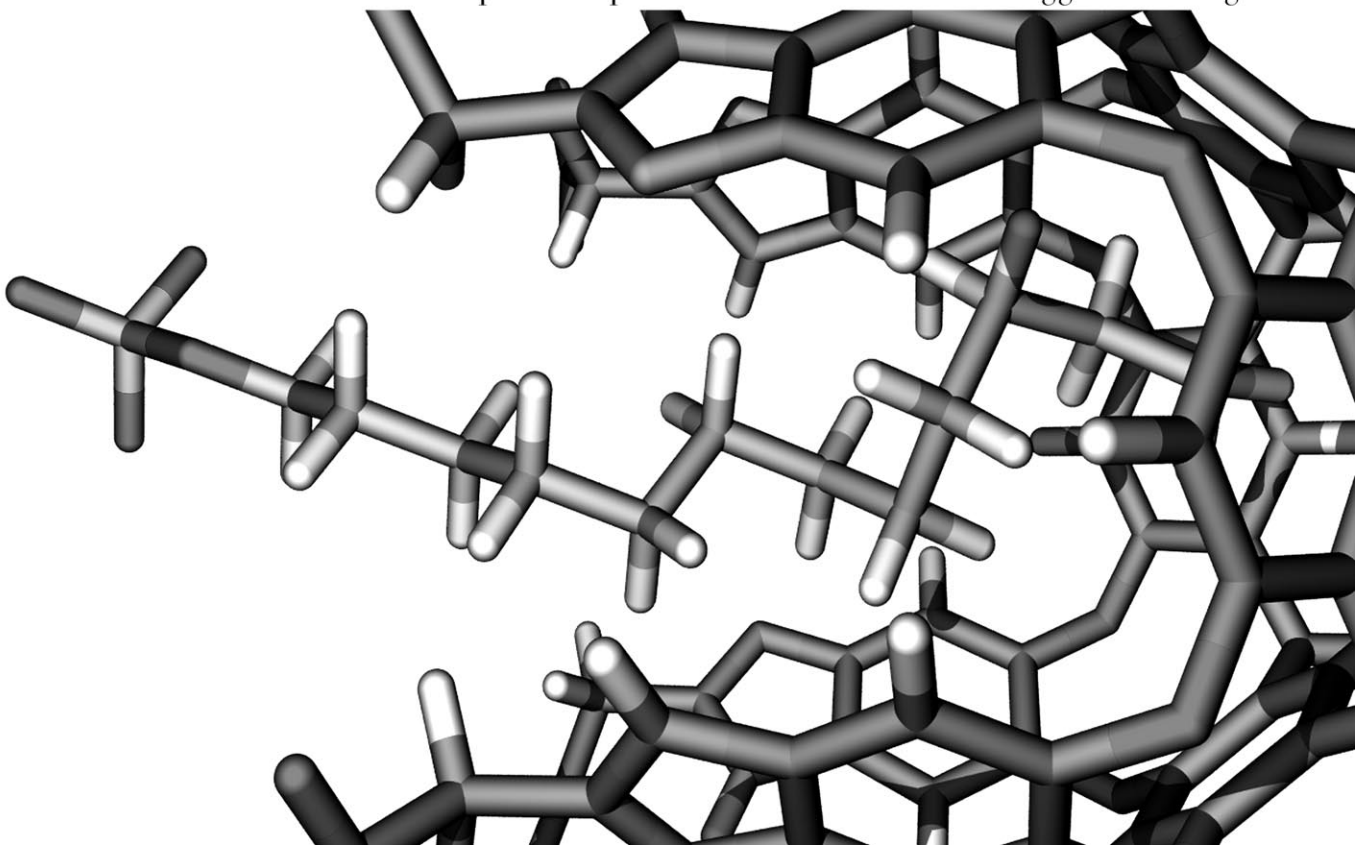


Looking down the barrel of the cylindrical capsule we find *n*-tetradecane forced into a coiled conformation.

In another instance, the water soluble cavitand entices the encapsulated portion of SDS into a non-staggered arrangement.



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Moving Targets: Recognition of Alkyl Groups

Michael P. Schramm and Julius Rebek, Jr.*[a]

Abstract: Alkyl chains can adopt seemingly unusual conformations, such as helices, when bound to natural and synthetic hydrophobic receptors. This plasticity allows the alkanes to assume shapes that are congruent to the receptor's space and fill that space properly. We describe here the use of cavitands and capsules as tools that expose the forces involved in the molecular recognition of hydrocarbons. Studies using NMR spectroscopy reveal how attractive interactions and solvophobic forces are maximized in solution through unprecedented contortions of alkanes and hint at a new generation of nanoscale mechanical devices.

Keywords: alkanes · encapsulation · molecular devices · molecular recognition · nanostructures · supramolecular chemistry

Introduction

Molecular recognition—the science of chemical complementarity—has been inspired by two dominant themes: Fischer's lock-and-key model[1] and Koshland's induced fit model.[2] The lock-and-key model pursues an idealized perfect fit between a rigid receptor and its rigid target. With maximum rigidity in both, the selectivity is unique and high affinity interactions are usually predictable. The disadvantages include demanding syntheses and high energetic barriers to complexation, that is, low on/off rates. An ultimate example of a lock and key, or in later terms "pre-organization," utilizing a synthetic receptor is provided by the spherands of Cram. In these molecules the oxygen ligands are rigidly pre-organized, fixed in an array optimal to fit a well-defined metal-ion sphere.[3] In the induced fit model, the receptor adapts and changes shape to accommodate the target. The synthesis of a flexible receptor is easier to conceive and execute, but the selection of one shape for the complex out of several for the receptor exacts an entropic penalty. This reduces affinity to the target, but the complexation dynamics are generally faster. Accordingly, most researchers use rigid targets so that the entropic penalty is not imposed twice.[4,5] We discuss here several situations that do not fall squarely into either of these two models. They involve dynamic alkyl group targets for which a number of conformations of comparable energy are possible, paired with relatively rigid, container-like receptors. We find that the receptor cavity molds the flexible target; a congruent shape is imposed on the alkyl group to maximize attractive interactions, even at the cost of internal strains along the alkyl chain.

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Examples from Nature

Nonspecific lipid-transfer proteins (nsLTPs) are a class of proteins found in plants and are involved in the transfer of fatty acids and other hydrophobics between membranes. The structural basis of nonspecific alkyl-chain binding to the maize nsLTP was recently disclosed.[6] A series of fatty acids from C10 to C18 in length were crystallized with the maize nsLTP, giving a detailed description of the different conformations that long alkyl chains adopt in a nonspecific pocket. The binding site consists of a hollow, curved, hydrophobic channel, which varies in volume from 550 to 620 Å, depending on the bound species. The cavity volume was shown to increase as a general function of length of the associated fatty acid. Oleic acid ($CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$) was found to complex with maize nsLTP in two different arrangements. In one of these complexes oleic acid adopts a partially coiled and partially staggered conformation to maximize van der Waals interactions with the nonspecific host (Figure 1). In contrast, when stearic acid ($C_{17}H_{35}COOH$) bound in the cavity, it was forced to adopt a structure with a partial coil and a partial "S-shape."

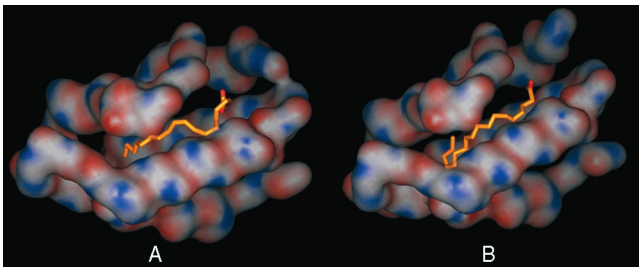

Figure 1. Maize nsLTP with bound oleate (A), and stearate (B).

The otherwise unfavorable interactions associated with alkane coiling are overcome in these complexes by maximization of contact with the somewhat pliable cavity. The cavity can change shape by rotations of the amino acid side chains, but the empty volume changes by less than 15% in the crystal structures.

A survey of the X-ray data shows unique conformations for each of the long fatty acid alkyl chains. In general it is observed that increasing the length of the alkyl chain causes an increase in the number of bends and kinks (dihedral angles of approximately $\pm 90°$) in the alkyl chain as well as the number of *gauche* interactions. In certain cases enough of these conformational distortions at adjacent centers impart coiled, or rather helical subdomains on the bound alkyl chain, as seen in Figure 1. Additionally, these interactions do not seem to correlate across homologous regions of different alkyl chains. Put differently, each guest adopts a seemingly unique conformation across its entire length.

Fatty acid binding proteins (FABPs), which play a role in fatty acid transport and metabolism in vertebrates and invertebrates present additional examples of bound alkyl chains in nonstaggered arrangements.[7]

Synthetic Receptors

Rotaxanes: The ability of hydrocarbons to adopt higher-energy coiled conformations imparts upon the hydrocarbon the properties of a notional molecular spring. The potential energy of such a spring is the difference in energy between the high- and low-energy states. The higher states involve more compression and are shorter, while the lower states involve more dihedral angles of 180° and are longer. An initial report demonstrated that when two vitamin B_{12} units are tethered at their metal centers with a tetramethylene unit, the C_2–$C_{2'}$ dihedral angle was 50(2)° as determined by X-ray diffraction analysis.[8] This *gauche* interaction creates a strain of approximately 0.8 kcal mol^{-1}, which could easily be overcome by the forces of the hydrophobic effect and the favorable associations (e.g., van der Waals interactions) of the two B_{12} units (Figure 2).

Continuing this theme, a later report in which the alkyl bridge was expanded from four carbon atoms to twelve allowed for the "threading" of α-cyclodextrin (α-CD) onto the dodecane thread to form a vitamin B_{12}–rotaxane dimer

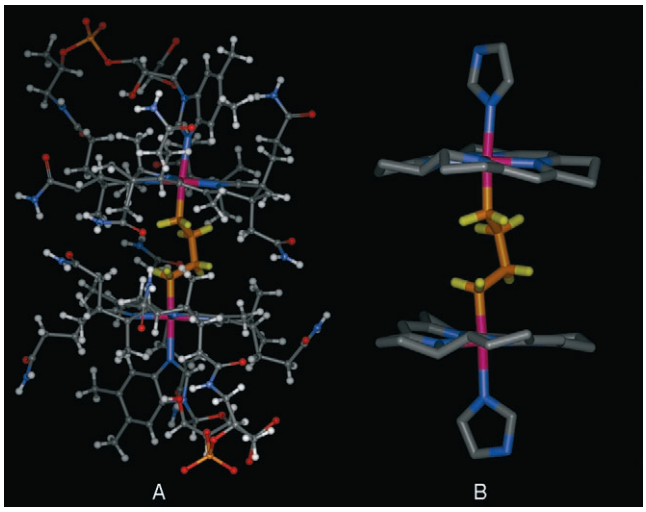

Figure 2. X-ray structure of two vitamin B_{12} units linked by a butylene bridge (shown in orange and yellow), full structure (A), and truncated structure (B) showing acute dihedral angle.

(Figure 3).[9] In the B_{12}–dimer (**1**), *gauche* conformations were indicated by NMR spectroscopy in D_2O at four sites. In water the hydrophobic chain contracts so as to minimize the solvent-exposed surface at the expense of about 3 kcal mol^{-1} of *gauche* strain. The threading of α-CD onto the dodecane shields a large portion of the chain from exposure to water. This in turn allows the alkyl chain to relax into a more staggered conformation, which represents a relaxed molecular spring (**2**).

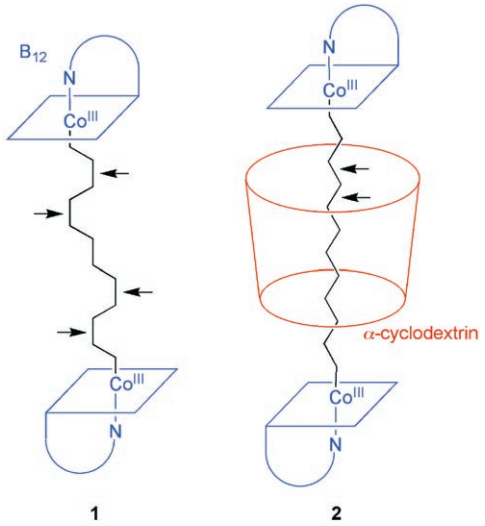

Figure 3. Solution structures in D_2O of the dodecane-linked B_{12} dimer (**1**), and its α-cyclodextrin rotaxane (**2**). Arrows indicate the locations of four *gauche* dihedral angles in structure **1**; on the other hand only one *gauche* dihedral angle is implicated by NMR spectroscopy at one of the two arrows in structure **2**.

Water-soluble cavitands: As seen in the previous section, alkyl chains adopt nonstaggered conformations in water to reduce the amount of surface exposed to the solvent, in spite of *gauche* interactions. This feature of alkanes manifests itself under other circumstances as well. Two long-chain surfactants, dodecylphosphocholine (DPC) and sodium dodecylsulphate (SDS), were found to adopt helical conformations when bound inside the hydrophobic cavity of a water-soluble cavitand.[10,11] When either DPC (**3**) or SDS (**4**) were in the presence of cavitand **5** in D_2O, the NMR signals of eight carbon atoms of both surfactants showed upfield shifts, indicating that these atoms must be inside the magnetically shielding region of the aromatic cavitand (Figure 4). It would be highly unlikely for the anionic water-soluble portion of **3** or **4** to be taken up by the interior of the electron-rich cavity leaving the hydrophobic alkyl chain exposed to the bulk D_2O, although these cavitands have affinity for tetraalkylammonium "knobs".[12]

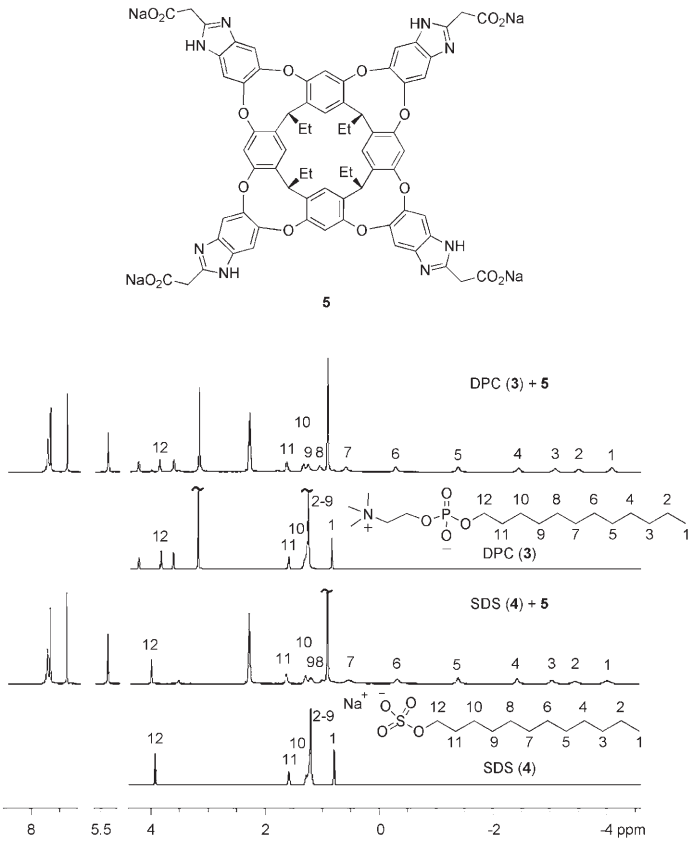

Figure 4. Binding of long-chain surfactants in the water-soluble cavitand **5**.

Based on the depth of the cavity, one could only expect six carbon atoms of either DPC or SDS to experience the induced magnetic field of the cavity if in an extended (staggered) conformation (Figure 5). Several factors can be attributed to the attractive forces that impart helicity on a long alkyl chain under these circumstances. Most notably

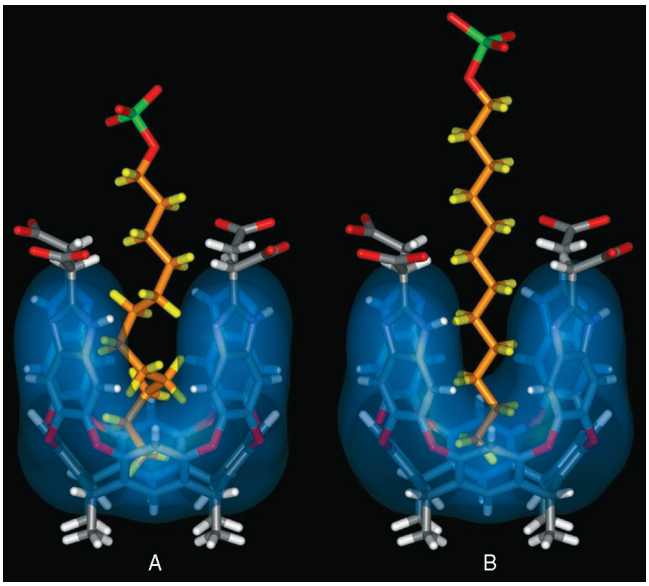

Figure 5. Molecular models showing the contracted accommodation of eight carbon atoms with five gauche conformations within the cavity (A) and extended conformation (B) of bound SDS inside water soluble cavitand **5**. The blue "cloud" indicates the highest aromatic atom on the rim of the cavity. Atoms above this level are not expected to show strong upfield shifts in their NMR signals.

was the realization that taking on a conformation with 2–3 kcal mol^{-1} of *gauche* strain allows more of the alkyl chain inside the cavitand and results in a packing coefficient of 56%. This value is very near the ideal for liquids and has been demonstrated in numerous host–guest systems to be an optimized value for recognition.[13]

The ability of the alkanes to overcome 2–3 kcal mol^{-1} of strain introduced from their unusual conformation stands as a testament to the complementary and dynamic nature of this cavitand–alkane host–guest system.

Surfactants were perfectly suited as guests for a hydrophobic cavitand in an aqueous environment: the polar group was located above the rim of the cavitand exposed to water, while the alkyl chain was bound deep in the cavity with its hydrophobic surface hidden from water. As *n*-alkanes do not have this bias, their behavior toward the cavity became intriguing; would they go in and how? The resting state of the cavitand has a single molecule of THF inside, an artifact of the final saponification reaction. When an aqueous solution of the cavitand was sonicated briefly with an alkane, the latter was extracted into the cavitand as a stoichiometric complex observed by NMR spectroscopy (no free guest could be detected). The alkanes, like surfactants, coiled to present a more complementary shape to the cavitand and to hide more of their surface from the aqueous medium.[14] In addition to coiling, *the alkanes were found to tumble rapidly on the NMR timescale*. A comparison of the spectra of *n*-C_5H_{12} to *n*-$C_{11}H_{24}$ with SDS shows few similarities. SDS buries its terminal methyl group in the base of the cavitand at −4.0 ppm. In none of the other cases is a methyl signal in this region. Instead, broad and in some cases un-

symmetric peaks are observed and their chemical shifts are clustered. The clusters move gradually downfield with increasing chain length. These features result from end-over-end tumbling of the guest on the NMR timescale. Averaging of the magnetic environments of the two ends occurs and only half the expected signals appear.

Tumbling on the one hand is quite easy to decipher, but on the other hand only close inspection revealed that the encapsulated alkanes were in fact coiled. By using the resonances of SDS as a reference for a coiled alkane conformation, average chemical shifts were calculated for the α and ω methyl moeties, the α+1 and ω−1 methylenes, and so on. The shifts calculated in this way were in nearly perfect agreement with those observed in the NMR spectrum of *n*-octane in the cavitand (Figure 6). Accordingly, the alkane

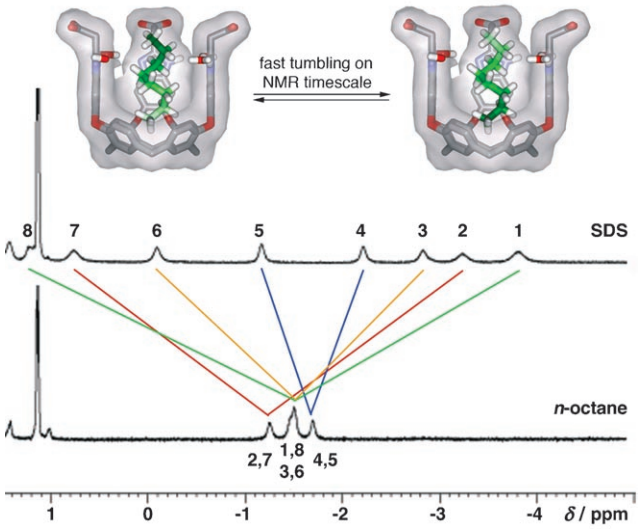

Figure 6. Observed chemical shifts for *n*-octane in the water-soluble cavitand **5** were in excellent agreement with the calculated means from equivalent nuclei of SDS.

must be in a compact, coiled conformation in its resting state between tumbles.

These results reaffirm the initial studies on the surfactants DPC and SDS: extended conformations of alkanes offer poor shape complementarity with cavitand **5**, but this is readily overcome by the alkane adopting a coiled shape. Despite unfavorable interactions introduced into the alkane in a nonstaggered conformation, the overall energetics of the host–guest system demand that such an unfavorable structure is adopted.

Introverted ester cavitands: An introverted acid[15,16] (that is, an acid with an "inwardly" directed OH bond) gave us an opportunity to explore the behavior of alkyl chains forced into the confined environment of cavitands. In cavitand **6**-R (Figure 7)[17] the acidic O–H bond (when R = H) is directed toward the bottom of the cavity. Esterification through the appropriate diazoalkanes allowed the facile attachment of

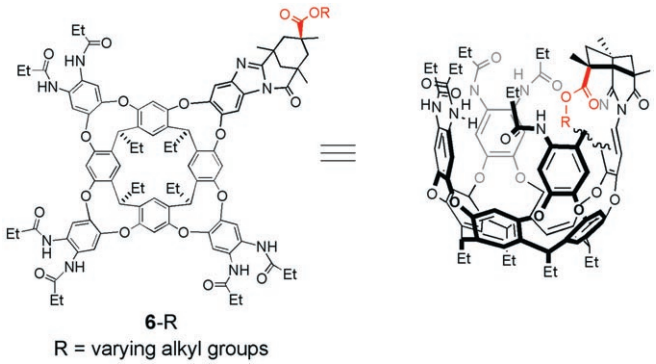

Figure 7. Cavitand **6** with introverted alkyl chains.

alkyl chains of varying length. The C–O bonds of the esters are likewise directed inwardly into a controlled environment, which could be systematically probed by a homologous series of alkyl chains.

A combination of NMR spectroscopy and molecular modeling studies revealed the nature of alkane contortions in this system (Figure 8). In the case of **6**-Me, the methyl group is obscured by other peaks around 1.8 ppm. Further extension of the alkyl chain reveals upfield signals as in the cases of **6**-Et, **6**-Pr, and **6**-Bu. The chiral nature of the cavitand affords diastereotopic methylene hydrogen atoms that are apparent in these cases. Cavitand **6**-Pr has the longest alkyl chain that can fit inside the cavity in a staggered conformation. This may explain the downfield shift of the terminal methyl group seen in **6**-Bu; the alkyl chain in this case could very well begin to adopt *gauche* conformations, leading to contraction of the alkyl chain and a downfield shift of the terminal methyl group. On the other hand, it is also possible that the methyl group is pushed *deeper* into the cavitand, where it has been shown that placement of nuclei can result in downfield shifts as the magnetic gradient of the cavitand inverts.[18]

The introverted heptyl ester (**6**-heptyl) exhibited the sharpest spectrum and was examined in detail by COSY and NOESY spectroscopy. These experiments revealed, quite unequivocally, the coiled nature of this long-chain alkane in a confined space. Stronger NOE signals near the terminal end of the chain were observed between C_i and C_{i+3} relative to those observed for C_i and C_{i+2}. Additionally, small C_i to C_{i+4} signals were observed. The combination of these results is consistent with *gauche* interactions resulting in a coiled conformation along the heptyl chain. While longer chains still exhibit resolved NMR signals, a marked decrease in resolution is evident and can be attributed dynamic processes involving deformations in the shape of the cavitand or slowed interconversions of various alkyl conformations. This is most evident in the case of **6**-decyl, for which no signals could be resolved, even as a function of varying temperature. At this extreme the cavitand is no longer able to retain a vase conformation on the NMR timescale (as evident from its downfield resonances) and the alkyl chain may no

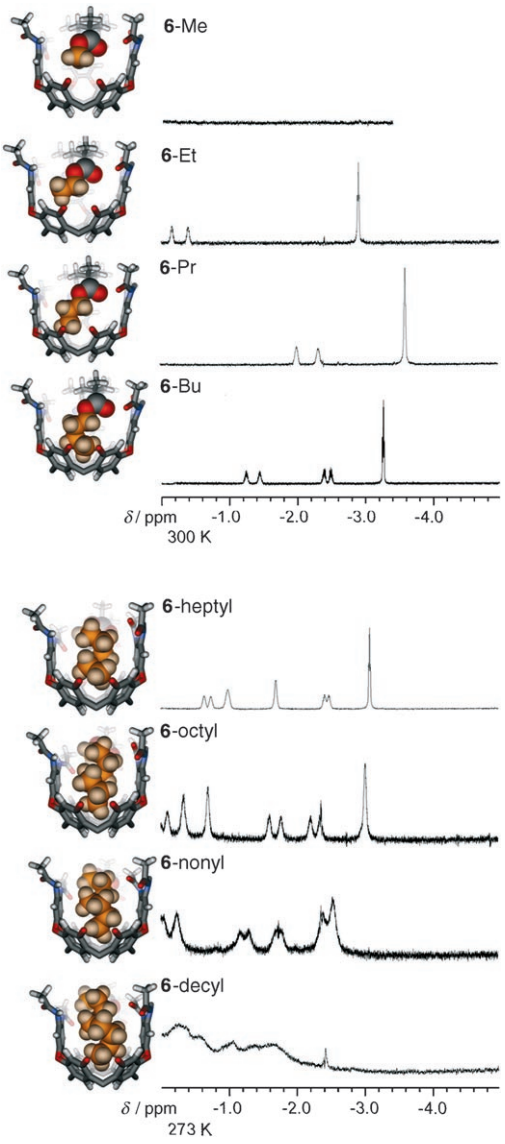

Figure 8. ^{1}H NMR ([D_{12}]Mes, 600 MHz) spectra of varying alkyl ester cavitands accompanied with model structures (AMBER; Maestro).

longer be required to compact itself into a coiled conformation.

Calixarenes: The study of alkane conformation in confined spaces has been carried out in *tert*-butylcalix[4]arenes.[19] A series of alkanes, alkyl halides, and terminal alcohols were crystallized as 2:1 calixarene-(host)–alkane(guest) complexes. Analysis of X-ray data in these examples provided the added challenge that the guest molecules were disordered over symmetry related locations, but the authors were able to conclude that "well-defined positions for all guest atoms can be found." Examination of the data reveals an increase in the number of bends and amount of coiling of alkanes as a function of length. Additionally, larger guests caused an increase in the disorder of the host, as has been demonstrated in other solution-based examples.

n-Hexane, 1,4-dichlorobutane, and 1-pentanol adopt nearly all-*trans* conformations. An increase in size to 1-heptanol and 1-octanol introduces an S-shape to the alkyl guest and when dodecane is inserted a tightly coiled helical conformation is achieved (Figure 9).

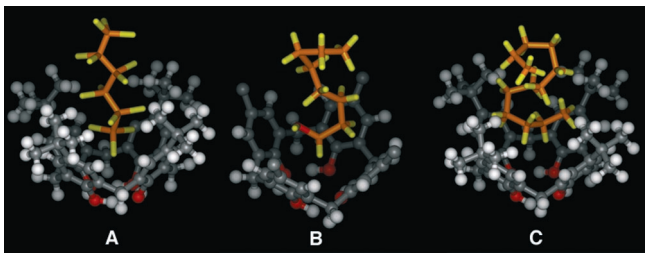

Figure 9. X-ray crystal structures revealing staggered *n*-hexane (A), "S"-shaped 1-octanol (B), and helical *n*-dodecane (C) conformations inside a *tert*-butylcalix[4]arene (top half of calixarene cage not shown). Some additional atoms omitted for clarity due to disorder.

Functionalized calixarenes bearing metal ions as binding sites for alcohols and amines also reveal bends in the alkyl groups of their guests as the space in the host widens.[20]

Capsules: Unlike the water-soluble cavitand **5** in which *n*-alkanes were shown to coil and tumble on the NMR timescale, the introverted ester cavitands **6**-R presented a system that forced long alkane chains permanently into a confined environment. Capsules are molecular assemblies that recognize appropriately sized guests and assemble around them. In the case of cylindrical capsule **8** (Figure 10),[21,22] a seam of hydrogen bonds joins the two halves (**7**) and confines encapsulated guests for an extended period of time.[23] This complements the open-ended cavitands, which do not have the ability to fully surround guests. This architecture allows guests more structured and long-lived interactions than cavi-

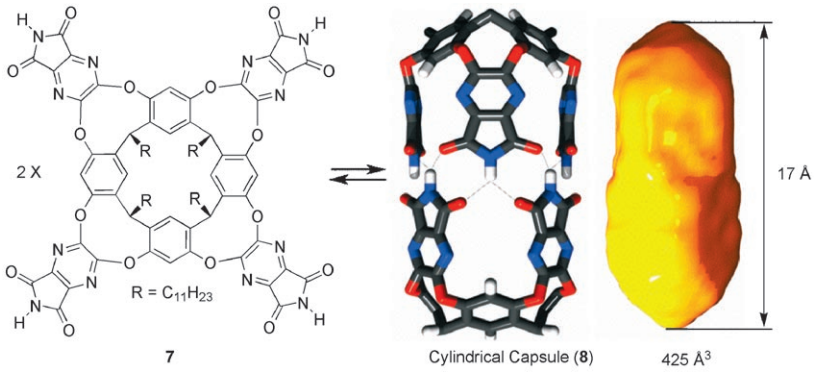

Figure 10. Chemical and structural representations of cylindrical capsule **8**.

tands, yet still allows exchange processes relative to the fixed introverted ester cavitand **6**-R.

An initial report indicated that alkyl groups could compact in length when placed inside the cylindrical capsule.[24] Long-chain *n*-alkanes (C_8–C_{14}) were shown to be fully encapsulated by capsule **8** in organic media.[25,26] As mentioned earlier in this review, increasing the length of an alkyl guest can (and often does) result in the alkane adopting a strained conformation, so as to maximize attractive contacts to its receptor. As seen in the upfield region of the ^{1}H NMR spectrum (Figure 11) encapsulation of C_8–C_{14} is apparent. The

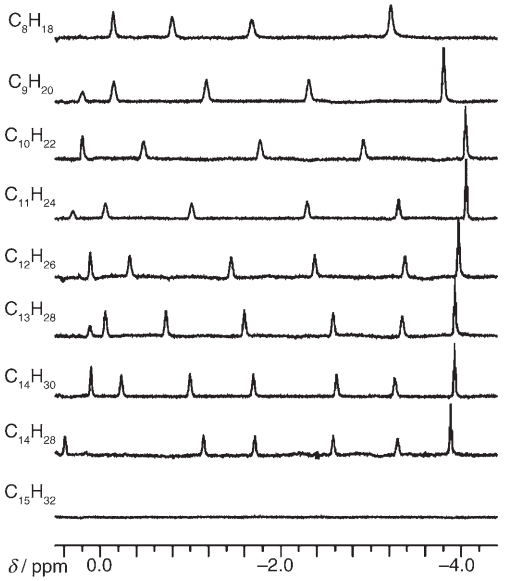

Figure 11. ^{1}H NMR of *n*-alkanes inside capsule **8**.

symmetry of the capsule dictates that half of the nuclei are observed. For shorter alkanes, such as C_8–C_{10}, it was predicted based on maximization of packing coefficients that they should exist in an extended, uncoiled conformation.

The NMR spectra confirm this prediction. For these guests, decreasing chemical shifts of the methyl groups (farthest upfield) is a function of forcing them deeper into the base of the capsule for which magnetic anisotropy is the greatest. For short alkanes, 2D NOESY reveals that cross peaks are only observed between the hydrogen atoms at C_i and C_{i+2} along the hydrocarbon chain. This is an indication that these encapsulated alkanes are in extended staggered conformations. For the longer alkanes, molecular modeling indicated that they could not fit inside the capsule in extended conformations. Clearly, from the NMR data encapsulation occurs by adopting a coiled, helical conformation. Longer *n*-alkanes decrease their overall length, while simultaneously increasing favorable contacts with the inside walls of the capsule. The first guest that exhibited evidence of *gauche* interactions was $C_{11}H_{24}$. NOESY spectroscopy showed cross peaks between C_1 and C_3 as well as C_1 and C_4, whereas C_2 was only in contact with C_4, C_3 with C_5, and C_4 with C_6 (Figure 12). The data indicates the presence of a

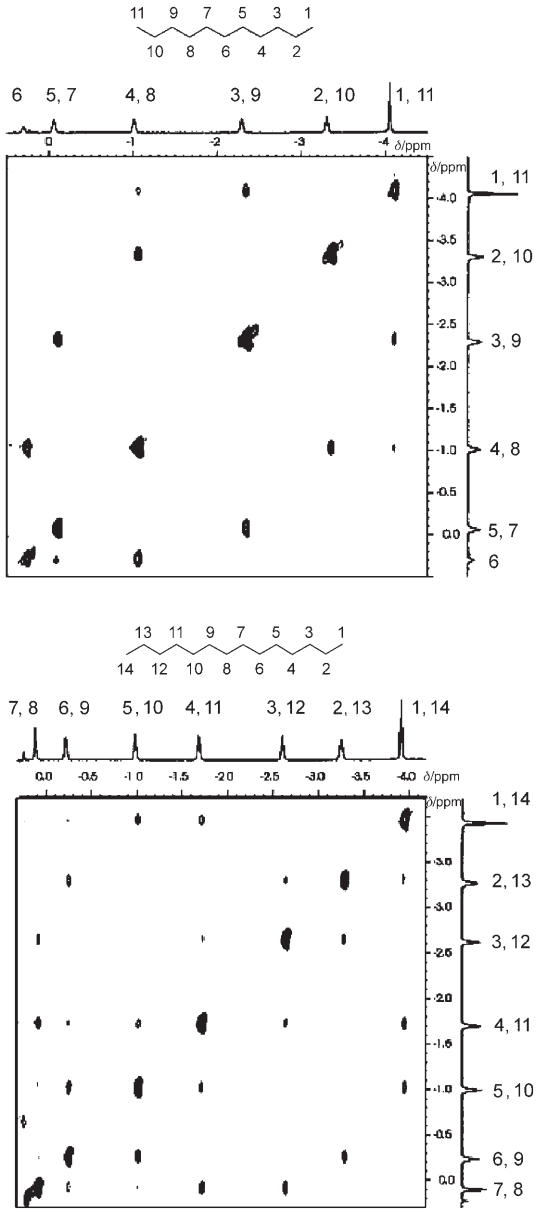

Figure 12. NOESY spectra for $C_{11}H_{24}$ and $C_{14}H_{30}$ inside cylindrical capsule **8**.

gauche conformation at the four carbon atoms at both ends of $C_{11}H_{24}$, and staggered conformation in the middle of the chain. This trend logically continues with $C_{12}H_{26}$ showing *gauche* interactions along the entire chain.

Upon examining the NOESY (Figure 12) spectra for $C_{14}H_{30}$ *gauche* conformations are predominant as indicated by cross peaks between C_i and C_{i+3}, and C_i and C_{i+4} ($i=2$–6). This result in conjunction with molecular modeling gives support for a tightly coiled conformation. The coiling of $C_{14}H_{30}$ can introduce $>6\,\mathrm{kcal\,mol^{-1}}$ of energy through *gauche* strain. The encapsulation of this molecule is a testament to the ability of alkanes to adapt in an effort to maximize contact with corresponding hosts. In addition to the ability of the alkane guests to adapt, evidence exists that the

seam of hydrogen bonds, which seal the capsule, changes in response to elongation of the guest.[25] The relative affinities of the alkane guests also shed light on the fine balance between optimization of packing and guest coiling. The optimal alkane $C_{11}H_{24}$ was the first to exhibit signs of coiling by NOESY yet is the most strongly bound (Table 1). The

Table 1. Relative affinities of capsule **8** for hydrocarbons in [D_{12}] mesitylene.

Guest	$K_{rel}(C_9D_{12})$	Guest	$K_{rel}(C_9D_{12})$
n-C_9H_{20}	0.3	*n*-$C_{12}H_{26}$	24.4
n-$C_{10}H_{22}$	16.9	*n*-$C_{13}H_{28}$	1
n-$C_{11}H_{24}$	100	*n*-$C_{14}H_{30}$	12.3

alkane $C_{10}H_{22}$ (extended) was found to have a very similar binding affinity compared to the tightly coiled $C_{14}H_{30}$, the longest and most strained in this study. This final result is the strongest affirmation that attractive host–guest interactions and the proper filling of space can overcome otherwise unfavorable interactions of alkanes when forced to adopt unusual conformations.

In addition to the *n*-alkane coiling inside the cylindrical capsule, analogous studies were performed on oligoethylene glycols (OEGs) and perfluoro-*n*-alkanes.[27] These two studies are complicated by divergent solution behavior with respect to *n*-alkanes: oligoethylenes natively adopt extended helical conformations with *gauche* dihedral angles about their C–C bonds and *trans* about their C–O bonds, while perfluoroalkanes adopt gently twisted but nearly staggered conformations with dihedral angles of about 167°. NMR studies demonstrated that the conformational flexibility of OEGs allowed for the encapsulation of chains with 12–16 carbon and oxygen centers, the optimal length being 12, one greater than for the *n*-alkanes. It should be noted that the binding affinities for *n*-alkanes (C_{10}-C_{12}) were far stronger than for any perfluoroalkanes or oligoethylene glycols. The presence of fluorine along the backbone of perfluoro-*n*-alkanes disfavors the chains from adopting a truly staggered conformation, as well as from adopting *gauche* dihedral angles. This constitution simultaneously increases the diameter so that van der Waals contact with the capsule wall can occur without additional coiling. These two parameters may support the findings that only the shorter C_8 and C_9 perfluoro-*n*-alkanes were well encapsulated. Taken as a whole these results show that OEGs and *n*-alkanes optimally fill the cavity by coiling to simultaneously shrink in length and maximize van der Waals contacts, while perfluoroalkanes seem unable to coil and are encapsulated in their native conformation.

Reversibly expanded capsules: The upper size limit of *n*-alkanes encapsulated in **8** was $C_{14}H_{30}$; the upfield region of the NMR spectrum in the presence of $C_{15}H_{32}$ remained featureless indicating no encapsulation (Figure 11). It was conceivable that the addition of another component (i.e. a spacer) would afford an expanded capsule which would incorporate larger guests. Indeed, when glycoluril **9** was added to cavitand **7** in the presence of *n*-pentadecane, the upfield region revealed that a new assembly had formed (Figure 13).[28] In addition to the encapsulation of $C_{15}H_{32}$, alkanes up to $C_{21}H_{44}$ were readily encapsulated (selected spectra shown) demonstrating that the addition of **9** expanded capsule **8** in length *significantly.*

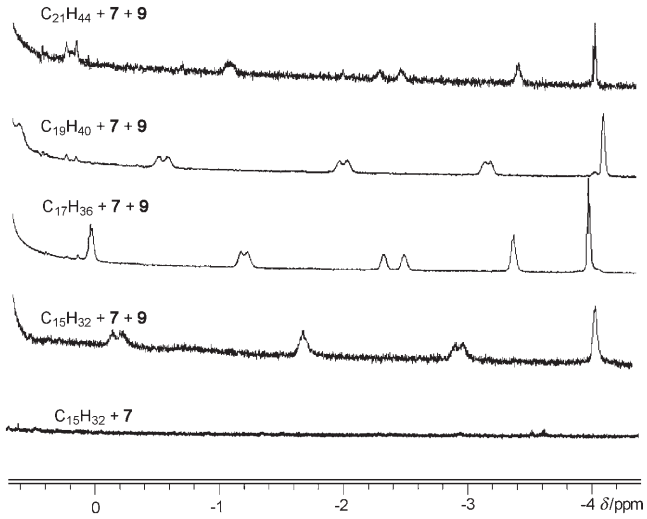

Figure 13. ^{1}H NMR of *n*-alkanes in an expanded capsule.

NMR integration supports a composition of two cavitand halves assembled with four glycolurils to form the new capsule **10** (Figure 14). Due to the nature of the assembly, two enantiomeric capsules are possible. EXSY spectroscopy revealed that the magnetically nonequivalent protons of the glycoluril are in chemical exchange on the NMR timescale. Accordingly, the two enantiomeric capsules readily interconvert. In addition to the encapsulation of larger alkanes, the presence of diastereotopic nuclei were observed in several cases employing capsule **10**. The longer alkanes inside capsule **8** are presumed to be in a helical conformation. This chiral structure renders the methylene groups diastereotopic, but it appears that on the NMR timescale interconversion of helixes is rapid. Heating *n*-heptadecane in **10** resulted in coalescence of the diastereotopic nuclei as would be expected if they were rapidly interconverting at the coalescence temperature. In the present case, a smaller internal volume at the seam of glycolurils as proposed in the structural model may slow the interconversion.

The addition of glycoluril **9** to a mixture of **7** and *n*-pentadecane readily demonstrated the dynamic nature of this system through the formation of a new assembly (Figure 14), but is the reverse possible? Tetradecane (**11**) was encapsulated in the expanded capsule and then the assembly was treated with 4,4′-dimethyl-*trans*-stilbene (**12**). The glycoluril capsule **10** partially disassembled, leading to

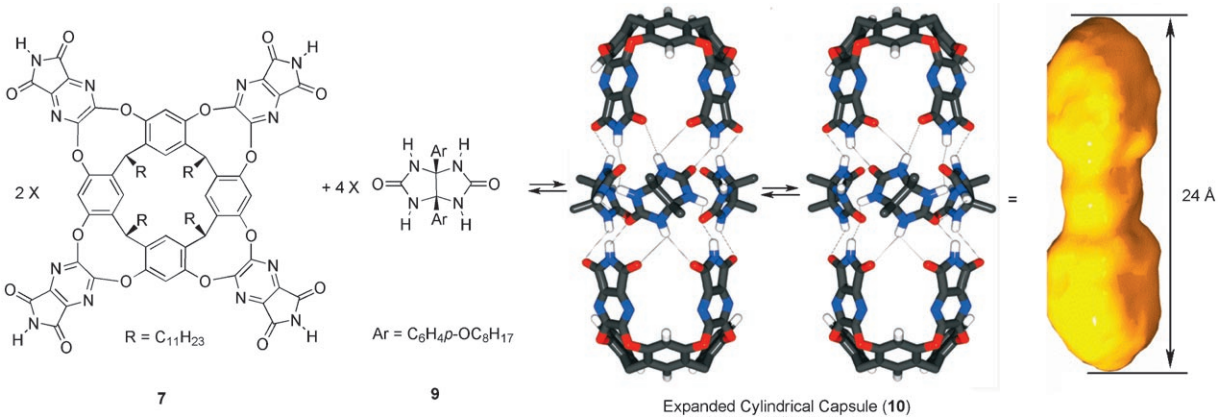

Figure 14. Structural proposal for expanded cylindrical capsule **10**.

the formation of the shorter capsule **8** containing one molecule of stilbene **12** as observed by NMR spectroscopy (Figure 15).

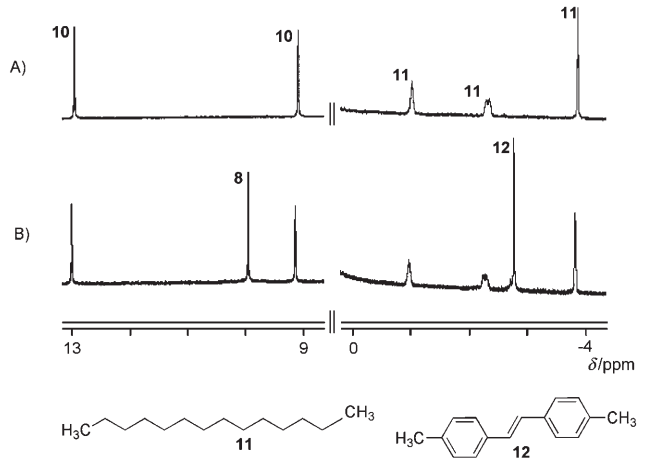

Figure 15. Reversible added spacers: encapsulation of *n*-tetradecane (**11**) in the extended molecular capsule **10** (A) and after addition of **12** (a good guest for capsule **8**) results in a "contraction" of the elongated capsule (B).

Conclusion and Outlook

This review has highlighted a collection of work demonstrating the ability of alkanes to adopt unusual conformations to maximize interaction with natural and synthetic hydrophobic cavities. In this regard the coiling of alkanes results in an increase in steric strain through the introduction of *gauche* conformations, but through mutual adaptation the union of host and guest overcomes these otherwise unfavorable interactions. Looking beyond the results presented, we envision that the behavior of alkanes in unusual conformations could define a new molecular machine: a molecular spring. To what extent is a helical alkane like a compressed spring? The coiling of an alkane within a capsule exerts stress on the surroundings: it is spring-loaded. The lengthening of the capsule through the incorporation of spacers provides relief of the strain as the guest relaxes to an extended conformation. This transformation is also reliant on the formation of more complementary hydrogen bonds provided by the glycoluril moieties; this too drives the molecular device from the coiled to extended state. Solvophobic forces are also in play: *the capsule is organized solvent*, the fixed structure of which is bought through synthesis. This fixed space demands to be filled, due to nature's resistance to vacuum. To accommodate this demand properly, the alkanes contort themselves to assume the size, shape, and chemical surface that are complementary to the fixed space. In bulk solution the alkane has the same C–H/π interactions to offer, but must organize the solvent (e.g. mesitylene) to experience them. Accordingly, the behavior of alkanes in both hydrophobic and hydrophilic environments can result in a change in their conformations. The examples presented in which alkane conformation can be tuned by environment as illustrated in Figures 3 and 15 suggest that the field is on the brink of new systems: molecular springs that coil and uncoil. The problem of control and reversibility thus become the new challenges to this emerging area of research.

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