Contortions of encapsulated alkyl groups

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Received (in Cambridge, UK) 1st December 2006, Accepted 31st January 2007
First published as an Advance Article on the web 20th March 2007
DOI: 10.1039/b617548a

Rotors are recalled as early molecular devices that transmit information through changes in conformation. Specific cases involve bipyridyls and biphenyls in which the biaryl bond acts as a fulcrum to relay applied stresses from one site to another. New types of molecular stress encountered by encapsulated molecules are identified—including bending, straightening, squeezing, grinding and compression. For flexible molecules in reversibly formed capsules a fluid model of recognition is proposed that is neither lock-and-key nor induced fit. Instead, the guest assumes the shape that best fills the available space, even if contortions to higher energy conformations are required. For encapsulated alkanes, a delicate balance of attraction and repulsion exists when the size of a guest molecule approaches the space available to it. The complexes are analyzed by both NMR and computational methods and detailed maps of the host–guest interfaces in solution are provided. The reversible transition of an encapsulated alkane between a compressed, coiled conformation and a relaxed, extended one is described. The system is a spring-loaded molecular device under the control of acids and bases that offers an alternative to the rotors of current molecular machinery.

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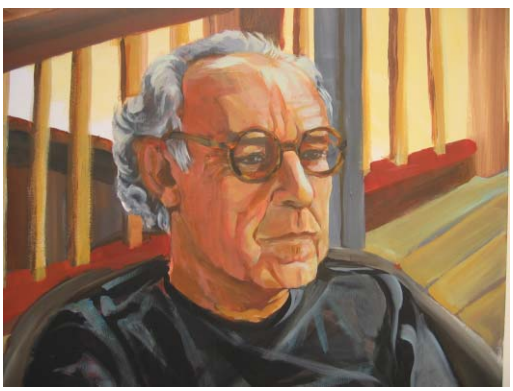


Julius Rebek, Jr.

Julius Rebek, Jr. was born in Hungary in 1944 and lived in Austria before arriving in the USA in 1949. He attended the University of Kansas and obtained the PhD degree from the Massachusetts Institute of Technology in 1970. He held appointments at the University of California at Los Angeles, the University of Pittsburgh and the Massachusetts Institute of Technology, then moved to The Scripps Research Institute in 1996 to become the Director of The Skaggs Institute for Chemical Biology. In the past he devised the three-phase test for reactive intermediates, developed cleft-like structures for studies in molecular recognition and introduced synthetic, self-replicating molecules. Currently his work involves biomimetic chemistry, self-assembling systems and reversible molecular encapsulation.

Introduction

Some 30 years ago, the Pauling principle of enzyme catalysis—maximum binding to the transition state—surfaced as a challenge to the biomimetic community: could the Pauling principle be reduced to practice in a synthetic system? The difficulty rested in the transition structures. At the time these structures were known for only the simplest of reactions: for example, the transition structure for the S_N2 reaction of chloride with methyl chloride had to feature D_{3h} symmetry. But how could a stress be applied to a methyl group that would contort it to that shape? A number of physical processes, such as bond rotations *did* have well-known transition structures, and it seemed likely that a binding force could be arranged to bear on a torsional transition structure. The binding of metals by 2,2′-bipyridyls shows maximum attraction between metal and ligand at the coplanar geometry of the chelate (Fig. 1). Accordingly, any groups on the 3,3′ positions are forced closer to each other in the chelate than they are in the free bipyridyl. In mechanical terms the biaryl bond is a notional fulcrum that transmits information of a binding event—metal chelation—to the 3,3′ sites on the bipyridyl in a predictable way.

The racemization of biaryls such as shown below is reasonably assumed to pass through a transition structure

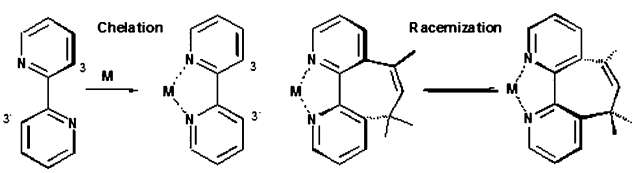


Fig. 1 Metal ion chelation and racemization of 2,2′ bipyridyls share the same geometry; as in the Pauling principle, maximum binding occurs in the transition state.

that features a coplanar geometry of the aryls. Could chelation of a metal by the two nitrogens induce a mechanical stress that flattens the molecule and forces it to racemize? That depends on how rigid the aryl groups are and if the biaryl bond really behaves like a fulcrum (we will soon raise the related question about a coiled alkane and a compressed spring). In the experiment,[1] metals did increase the racemization rate. The largest rate enhancement ($>10^6$) was found with the bipyridyl–crown ether[2] shown in Fig. 2.

The predictable structure changes induced by bipyridyl–metal chelation also provided a synthetic compound—a model—that showed allosteric effects in chemistry. In biology, small molecules often bind to macromolecules in a way that alters their behavior. This provides a means of signaling and regulation of affinities, selectivities, locations or activities. The binding of the small molecule (allosteric effector) is information; it is transmitted to a remote active site through conformational changes. The effector can bind weakly, through intermolecular forces or strongly through covalent bonds (methylation, acylation, phosphorylation, glycosylation) and the conformational changes can be subtle or profound, short- or long-lived. It is now generally accepted that the binding event causes motion, changes in molecular shape. We introduce these possibilities here because we will soon relate how a small molecule effector alters the size and shape of a synthetic receptor. For the moment, in the bipyridyl of Fig. 2 there are two sites for binding metals: bipyridyl and crown ether. When a transition metal binds to the bipyridyl function the shape and transport properties of the crown ether function are altered. A related biphenyl with two crown ether sites showed positive cooperativity in binding of covalent mercury compounds.[3] While we cannot dwell on the details here, the same "mechanism" operated in this system: binding at one site fixed the biaryl rotor and transmitted the conformational information to a remote, identical site.

I close the introduction with some generalizations. The first deals with molecular devices, and rather than recap them here, we refer readers to recent and comprehensive reviews on their history by Leigh *et al.*and Michl *et al.*[4] Since their introduction, the biaryl rotors as described above have been the starting point for almost all chemical expressions of allostery[5] and the majority of molecular machines.[6] That predeliction continues to this day,[7,8] but we will offer an alternative, later.

The second has to with dynamics. Synthetic receptors operate at equilibrium—that is the whole point of their existence, and it allows the experimenter to evaluate the free energies of the complexes and deduce the magnitudes of the attractive forces that hold them together. The complexes are dynamic; the motions of receptor and target are reciprocal and that behavior leads to entropy/enthalpy compensations. Recognition is the initial event in every bimolecular reaction but is often taken for granted. Inventors of modern asymmetric catalysts already incorporate features of recognition into their designs and when the reaction trajectories are better understood, dynamics will be considered and relegated a greater role than mere turnover. But these are future developments.

Fig. 2 Rate enhancements in racemization and allosteric effects in ion transport shown by a chemical system. Chelation of a transition metal at the bipyridyl site causes flattening and rapid racemization of the structure. The crown ether's geometry is altered and its selectivity for alkali metal transport changes. The system is a notional set of pliers.

The third has to do with vocabulary. How much, really, is a biaryl like a lever, or a coiled alkane like a compressed spring? The alternative to using words familiar to macroscopic mechanical phenomena—straightening, bending, friction, compression, *etc*—is to create a new vocabulary that is unique to molecular behavior and we shall not do so. Yes, steric effects are no more than electron–electron repulsions but anticipating molecular behavior and function in these terms is less than satisfying. Nature provides many behaviors such as allostery, replication, and supercoiling that have been discovered and biomimetic chemistry can offer model systems for them, but what about behaviors that are unknown in biology or elsewhere? Are these any less legitimate? Invention in chemistry is a larger enterprise. Neither asymmetric epoxidation nor olefin metathesis was bio-inspired and most of what follows here wasn't either.

Straightening

We first encountered the effects of a rigid microenvironment on a flexible target during the encapsulation of benzanilides in the dimer of **1**, the self-assembled capsule **1·1** (Fig. 3). While secondary anilides **2a** assume the s-*trans* or *Z* conformation favored by the typical peptide bond, the tertiary anilides prefer the s-*cis* or *E* conformation in solution (and solid state).[9] This preference lies at the heart of the application of multimeric

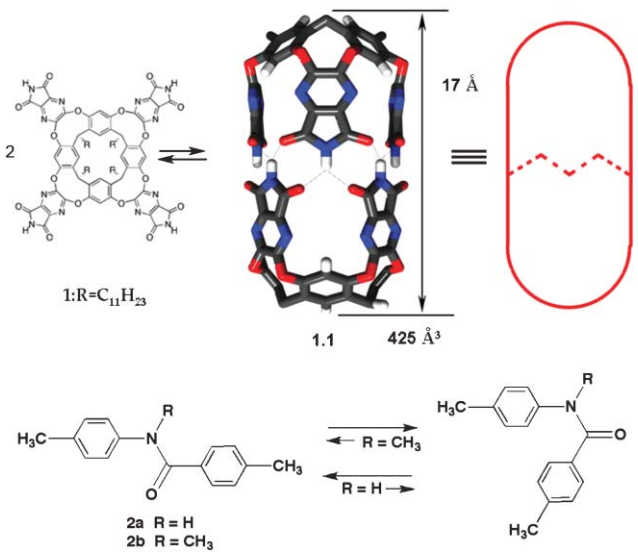


Fig. 3 Top: tetraimide cavitand **1**, the dimeric capsule **1·1** and its cartoon representation; peripheral alkyl groups have been deleted. Bottom: conformation preferences of secondary and tertiary benzanilides.[8] Only the extended conformation is encapsulated.

anilides as foldamer superstructures.[10] The encapsulation of either benzanilide proceeds smoothly and only the s-*trans* isomer fits in **1·1**.

A recently discovered effect, but one that seems related to the straightening of anilides may be responsible for the altered equilibria shown by reversible ring–chain isomerization reactions within **1·1**. For the imine–oxazine interconversion, (**3** and **4**, Fig. 4) the capsule amplifies the cyclic isomer compared with its equilibrium concentration in solution because it would appear to be a better fit. Put alternatively, the open-chain imine must assume fewer and likely less stable shapes in the "straight jacket" imposed by the capsule. This effect becomes extreme in the case of the salicylaldehyde derivative **5**: outside the capsule in mesitylene solution *only the imine can be detected*, but inside the capsule the heterocycle can be observed. Because the appearance of the heterocycle in the capsule (<3 min) is much faster than the exchange rate of a guest this size, quite likely the reaction takes place within the capsule. The equilibrium between the encapsulated species is unaltered over a large temperature range, an unusual feature that suggests that entropic, rather than enthalpic factors are responsible. Whatever the cause, this is the first example of a reversible reaction to occur within an encapsulation complex. Other capsules, assembled through metal–ligand interactions have shown stabilization of unknown species in solution such as siloxanes[11] and phosphine–acetone adducts.[12] The earliest example is that of cyclobutadiene, stabilized in a covalent carceplex.[13] Reversible encapsulation offers alternatives to kinetic methods and qualitative methods that detect reaction intermediates that cannot be directly observed free, in solution.[14]

Not all encapsulations give stability to higher energy species. Encapsulation of cyclohexane in a flattened spherical capsule measurably reduced the ring inversion rate but it was not due

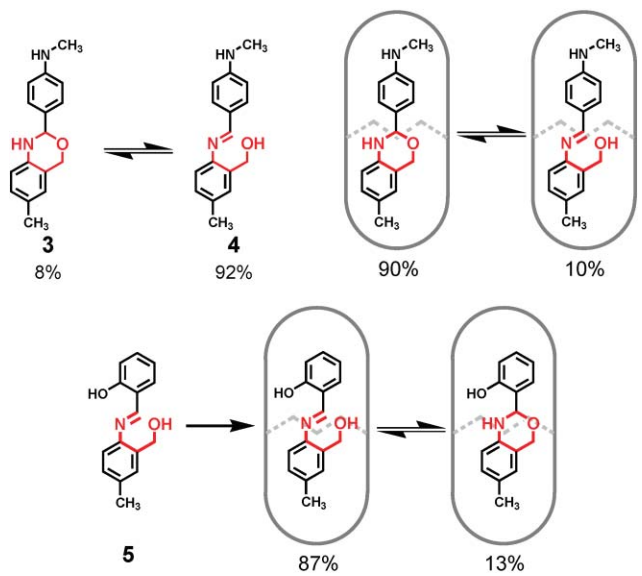


Fig. 4 Top: interconversion of cyclic and open chain species in solution favors the imine at equilibrium, but encapsulation in **1·1** favors the cyclic form. Bottom: the salicyl aldehyde derivative **5** is the *only* isomer observed in solution yet the cyclic isomer can be detected inside the capsule.

to the contortion of the guest. Rather, the stabilization of the resting state through C–H···π interactions was proposed.[15] Some straightening of encapsulated oligoethylene glycols must also take place on encapsulation in **1·1** since the native conformation of these guests has too great a helical diameter to be accommodated.[16]

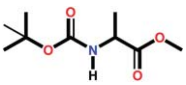
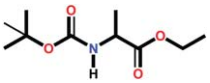
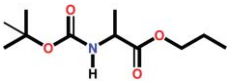
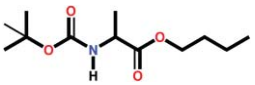
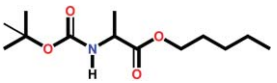
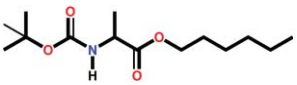
Bending

The lowest energy conformation of normal alkanes is a fully extended (*anti*) one and any bend (*gauche conformation*) creates steric repulsions between hydrogens on the C_i and C_{i+3} and even C_{i+4} carbons. The energetic cost is relatively small, as each bend increases the energy by only $\sim$0.55 kcal mol^{-1} in the liquid state. Accordingly, a number of conformations can be accessed under ambient conditions: *n*-heptane, for example, has 13 rapidly interconverting conformers at equilibrium in solution at room temperature.[17] In the solid state many folded or bent shapes are observed for alkyl chains when bound in protein interiors.[18,19] In these, alkyl groups of fatty acids conform to fill the space available to them. Crystal structures of alkyls and alkanes in synthetic host molecules[20,21] also show bent and twisted shapes while those of urea complexes show extended conformations.[22]

(1) In the capsule 1·1. We initially encountered the bending of alkyl groups during solution studies of encapsulation of N-protected amino acid esters in **1·1**.[23] A series of Boc-Ala-esters **6** and Boc-β-Ala-esters **7** were used as "rulers" to probe the effective dimensions of the space inside, with the premise that the blunt *t*-butyl group could not penetrate the tapered ends of the capsule and the atoms in the backbone, while connected by only single bonds, had little choice but to assume a fully extended conformation. This was a reasonable assumption in the Ala series for the chain of atoms from the *t*-butyl to the ester oxygen. The next atom—the first carbon of the ester alkyl—has a choice, but given the preference for an s-*trans* or *Z* conformation, its distance from the *t*-butyl methyls is also fixed.

The propyl ester in the **6** series is a good guest and modeling indicated that it can fit when fully extended, but its homologs, even up to the pentyl ester show some, albeit monotonically diminished binding (Table 1).[23] These must adopt a non-extended conformation to be accommodated, and this is reflected in their affinities for the capsule. The binding of the pentyl ester is modeled in Fig. 5 and its affinity is reduced about a thousand-fold with respect to the propyl ester. This corresponds to a factor of more than 4 kcal mol^{-1} in $\Delta\Delta G$, which would implicate 6 *gauche* interactions for the longer ester. As there are only 3 *gauche* conformations possible, clearly other factors must be at work, to wit, packing coefficients (PC's). The PC's increase with ester length as do the buried surface areas but the energetics of these factors are presently not readily estimated. In the β-Ala series **7** the ethyl ester is the best guest (it has the same PC as the propyl ester of the Ala series). The experimental and calculated relative binding affinities in this series were well-correlated and this trend is encouraging for predicting affinities of molecules within molecules.

Table 1 Guest volume (V), packing coefficients (PC) and relative binding affinities of *N*-protected Alanine esters for capsule **1**·**1**

	V/Å^3	P.C. (%)	K_{Rel}
	181	43	—
	199	47	0.03
	215	51	1.00
	231	55	0.24
	246	58	0.001
	262	62	—

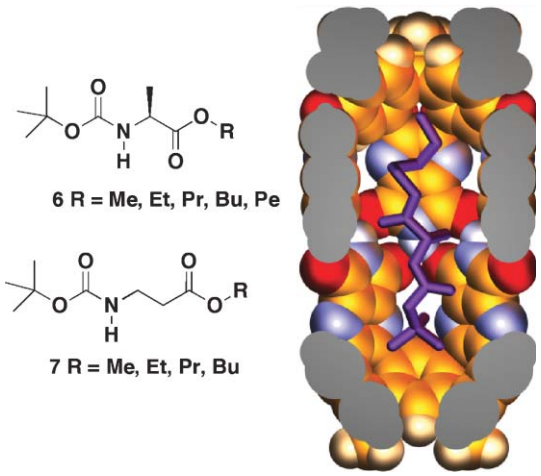


Fig. 5 Left: protected derivatives of alanine and β-alanine used for encapsulation studies with **1**·**1**. Right: energy minimized structure of pentyl ester of Boc-alanine showing the coiling of the ester alkyl groups.

(2) In resorcinarene hexamers. The bending of alkyl groups was encountered even in larger capsules such as **8**$_6$ (Fig. 6).[24] These assemblies form spontaneously in wet C_6D_6 or $CDCl_3$[25,26] solutions of appropriate guests. Avram and Cohen[27] deduced a hexameric assembly in the latter solvent alone, using diffusion NMR methods (DOSY). The NMR spectra of some tetra-alkyl ammonium salts **9**–**11** in the hexameric capsule is shown. These complexes are stabilized by cation–π interactions.[28,29] For smaller ions, encapsulation in extended conformations is possible and COSY spectra reveal a steady increase of induced chemical shift along the aliphatic chain, with the methyl groups nearest the resorcinarene "bowls". For example, in the hexyl case **9** the methyl group is shifted furthest upfield (Fig. 6a). In the tetraheptyl **10** and

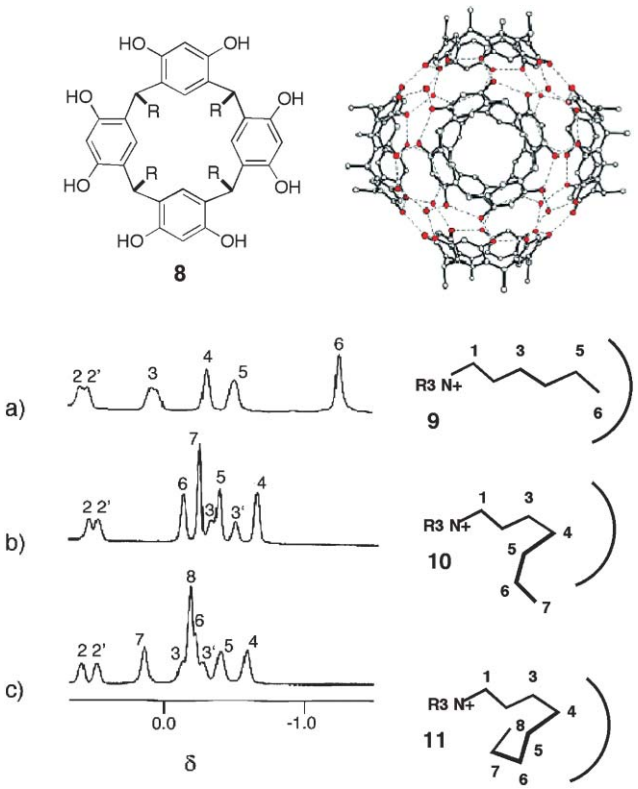


Fig. 6 Top: resorcinarenes have shallow, bowl-like conformations and assemble into hexameric capsules on exposure to wet organic solvents. The hexamer resembles a cube with one resorcinarene at each side and one water molecule at each corner. Bottom: NMR traces of the alkyl groups inside the hexameric capsule. In the hexyl derivative **9**, the methyl group is shifted furthest upfield (a) whereas bending in **10** (b) and **11** (c) leave the C_4 methylene closest to the resorcinarene "bowls" (curved line).

tetraoctylammonium **11** cations the most upfield signals are the resonances of the fourth methylene groups from the N^+ (Fig. 6b,c),and the methyl groups experience much less shielding. The bending of the heptyl and octyl chains also influences the protons of the third and fifth methylene groups, which become diastereotopic. The gauche conformations along the 3–4 and 4–5 bonds are probably responsible for the large difference in chemical shift of the diastereotopic hydrogens of the these methylene groups. The larger ions show lowered affinity for the capsule.

(3) Pyrogallolarenes. We have examined normal alkanes in several well-defined (fixed volume) hosts in solution, and of these, the largest volume is offered by the hexameric pyrogallolarene cubes (Fig. 7).[30] Like the resorcinarenes, these macrocycles **12** self-assemble as capsules (**12**$_6$) in the crystalline state,[31,32] but no water is required for the hydrogen bond network that holds it together. Accordingly, there was reason to expect that **12** bearing long, hydrocarbon peripheral groups would form capsules in neat alkanes, and this turned out to be the case. Encapsulation occurred with liquid n-alkanes from C_5H_{12} to $C_{20}H_{42}$ (Fig. 7).

For the smaller alkanes (C_5H_{12}–C_8H_{18}) the most upfield-shifted signals are again the terminal methyls, which place

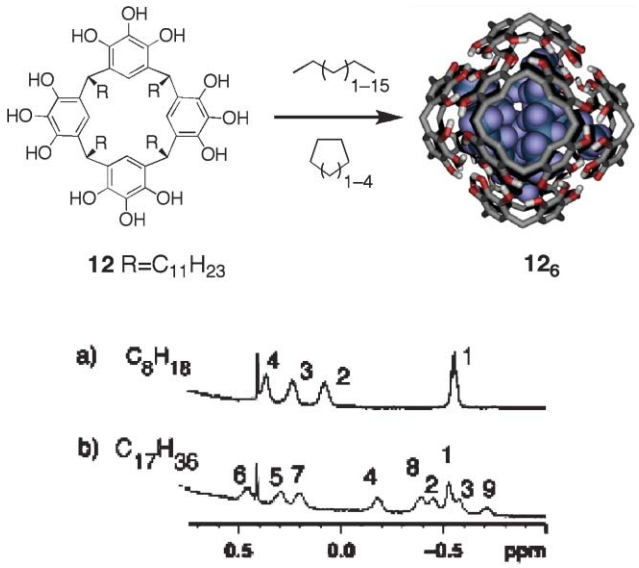


Fig. 7 Top: the pyrogallolarene **12** and the hexameric assembly $\mathbf{12}_6$ modeled with 6 n-octane guests inside. Bottom a: the upfield region and assignments of the NMR spectrum of (a) octane and (b) $C_{17}H_{36}$ in $\mathbf{12}_6$.

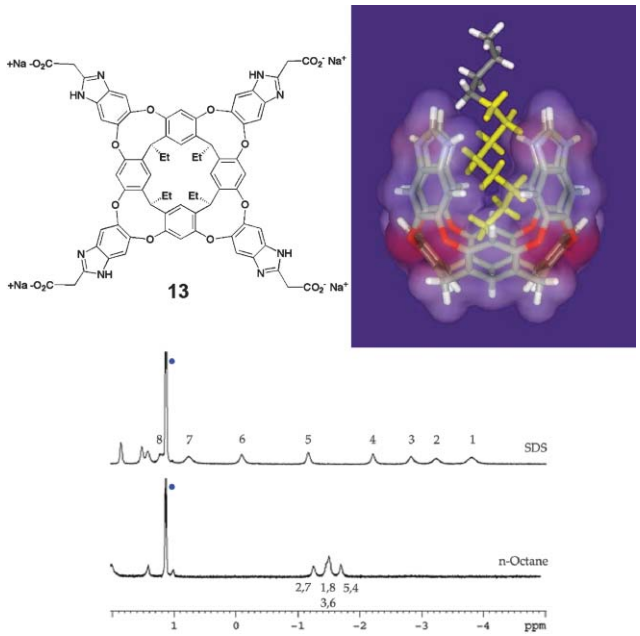


Fig. 8 Top: structure of a water-soluble cavitand and a computer modeled alkane inside. The alkane is coiled into a helical shape that allows good C–H···π contacts between host and guest. Bottom: eight carbons are seen to be within the envelope of the cavitand when the guest is in a coiled conformation. Accordingly, signals for the hydrogens of the methyl and 7 methylenes are shifted upfield in the NMR spectra. Octane within the cavitand tumbles rapidly and the signals for the hydrogens are averaged as shown.

them in close proximity to the aromatics of the host's "bowls". This would be expected for an extended conformation. The longer alkanes (C_9H_{20}–$C_{12}H_{26}$), show their methyl signals *less* upfield shifted and the methylenes are nearer the pyrogallols; these chains must be *folded*. The assignment of encapsulated guest protons for $C_{17}H_{36}$ was supported by 2D COSY experiments but the spectra of the higher alkanes were more complicated. The longer alkanes ($C_{18}H_{38}$ and above) are solids at room temperature and while the intensity of encapsulated peaks decreased, these alkanes clearly found their way inside.

What is the driving force here? Water is not involved so it cannot be hydrophobic. Moreover, as the solvent is the neat alkane, it can hardly be self-loathing, or solvophobic. The maximum hydrogen bonds per subunit are probably made with the capsular structure and reinforced by cooperativity, so enthalpy plays a role. The capsule cannot be empty, so the filling of space by the guest is an additonal consideration. Straight-chain alkanes have been largely ignored as targets of the molecular recognition community, with good reason. No improvements have been scored since the solid-state inclusion complexes of urea were described. They lack functional groups and, after all, what else can you bind to? Their shapes are dynamic and present moving targets but there is a chance to complement their sizes, or more specifically, their volumes, as described below.

Coiling

We encountered alkyl groups as unexpected guests in deep, water-soluble cavitands **13** in the presence of typical surfactants (Fig. 8).[33] These studies were reviewed recently[34] so we recap only the essentials here. Cavitands are synthetic receptacles that fold around solvents or other small molecules that fill an appropriate fraction of the space inside. They more or less surround their targets but feature one open end. The coiled alkanes are able to fill the cavitand and present its concave lining of aromatics with a convex surface of C–H bonds. They are more complementary to the cavity and bury more hydrophobic surfaces from the aqueous medium than do their extended conformations.

Additional experiments in water suggest that coiling may be a general feature of normal alkanes in not only the structured synthetic environments, but even in biological receptors. Brief sonication of octane, for example, with **13** in D_2O gave a stoichiometric complex but one featuring a very different NMR spectrum than the SDS complex (Fig. 8).[35] The alkane signals are compressed into a narrow range, corresponding to chemical shifts expected for the middle of the cavitand. The observed chemical shifts are appropriate for a coiled octane that is tumbling rapidly in the cavity on the NMR timescale. The methyls and methylenes of the octane show an averaged chemical shift of two magnetic environments. A number of alkanes showed this type of behavior in **13**, but only 8 carbons can be buried in a helical conformation, and as the alkanes get larger than C_8, they can no longer fit completely inside the cavity. Less than stoichiometric amounts of the longer alkanes are extracted into the cavitand as the hydrophobic driving force is diminished. The cavity also adapts and must widen to allow tumbling.

Organic solvents

The alkanes described above chose to enter the cavity on sonication in D_2O; they adopted the best conformation available that was compatible with the presumed driving

force—the burial of hydrophobic surfaces. The normal alkanes appear adept at filling spaces; we have seen that they *contort* to be accommodated. This behavior fits neither Fischer's[12] lock-and-key model[36] nor the Koshland[13] induced-fit model.[37] Instead, we suggest a fluid model: the alkane assumes the size, shape and chemical surface that is proper to fill the space on offer, just as a liquid can flow to fill any number of container shapes.

But what if the hydrophobic effect is not available as a driving force? Will alkanes contort to fill spaces in organic solvents to get away from a hostile interface? To approach these questions we looked closer at the experience with capsules.

Nowhere do we have more information on the encapsulation of smaller molecules in organic solvents than with the hydrogen-bonded cylindrical capsule **1·1** (Fig. 1).[38] The cavity features two square prisms, (the pyrazinimides) held together by a seam of 8 bifurcated hydrogen bonds. The two halves are rotated 45° with respect to each other at the center. The space is tapered at each end where two square pyramids (the resorcinarenes) are present and also rotated at 45° with respect to the prisms. The dimensions and space are inevitably a function of the software used; for the Swiss PDB viewer these are ~16 long by 6.6 Å wide at the center, but the tapered ends can accommodate only the smallest of atoms or the narrowest of functional groups (Fig. 9). The volume of the cavity is ~420 Å^3. The most hydrogen bonds per subunit are present in the dimeric capsular form, but a solvent that does not fit in the capsule would leave the inner surfaces unsolvated, creating an abhorrent vacuum. We use mesitylene-d_{12} to provide a medium that does not compete with intended guests.[39] In distilled mesitylene-d_{12} only undefined aggregates with broad, uninterpretale NMR signals are observed. In the commercial solvent, traces of benzene d_6 and *p*-xylene d_{10} are coencapsulated, but can be displaced by the higher concentrations of intended guest. It encapsulates complementary structures[40] of appropriate dimensions, and shows strict selectivity with rigid guests and some surprising promiscuity with flexible ones.[41]

For example, *n*-alkanes such as decane that are shorter than the cavity of the cylinder are bound in an extended conformation; if the alkanes are slightly too long, they adopt a compact helical conformation with several *gauche* configurations. We will examine these cases shortly. In the meantime, consider the reasons for alkane affinity for this capsule. What is the attraction of any alkane chain for the capsule? Consider first the resting states of the components. The hydrocarbon guest in solution gathers a number of mesitylene solvents around it to maximize the attractions between its CH bonds and[42] the aromatic surfaces of the solvent. How many solvents are held in place at any given time is not known as it depends on the length and conformation of the alkane. For the longer alkanes in an extended conformation at least 6 and as many as 8 mesitylenes could form a loosely-held and very temporary cage around a solute alkane. The capsule **1·1** can be considered *organized solvent*, 8 benzene surfaces are presented to the interior, the fixed structure of which is bought by the covalent bonds of the synthesis. This space is not empty and it is filled with the rather more tightly held resident guests (the solvent impurities). When the alkane enters, the solvent impurities are

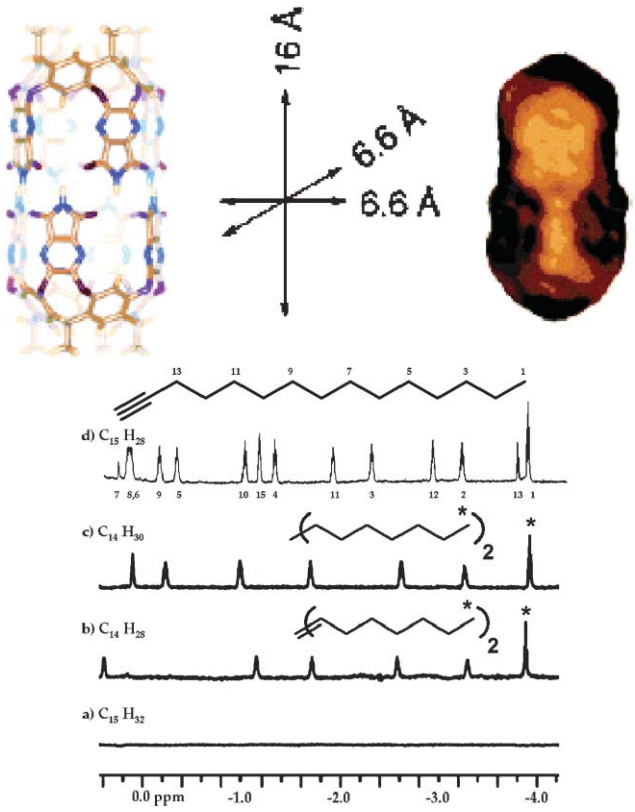


Fig. 9 Top: dimensions of the cylindrical capsule **1·1** and the shape of the space inside. Bottom: NMR spectra of encapsulated guests: (a) $C_{15}H_{32}$ is not encapsulated at all but 7-*trans*-tetradecene (b) and tetradecane (c) are well-encapsulated. The terminal alkyne pentadecyne (d) is also encapsulated and all of the hydrogens show separate signals. The narrow C–H of the acetylene penetrates the tapered ends of the capsule.

liberated in a classic solvophobic effect. While every recognition event involves release of solvents, the release of the resident guests has a large entropic advantage.[43]

Second, consider the chemical complementarity of the component surfaces. The helical conformation of the alkane provides the best shape for its CH bonds to contact[44] the fixed π surfaces of the cavity. Recall the diameter of the helix is about 5.5 Å and the compact coil can make simultaneous contact with a larger fraction of the cavity's inner surfaces at the ends of the capsule than the extended one can. Third, consider size complementarity. The volume of the cavity is ~420 A^3 while that of the *helical* alkane is 247 Å^3. The packing coefficient within this space is 0.58, near the ideal for the liquid state. These forces overcome the discomfort experienced by the *gauche* butane conformations that exist many times along the coiled chain.

The shape and dimensions of the space inside the capsule are shown in Fig. 9 and 10. The calculated values are, inevitably, a function of the graphics software used and we show results obtained by GRASP.[45] A cross-section of the capsule appears in Fig. 10, and the section goes through the para positions of two of the benzene rings that make up the tapered ends at the right side of the figure. These ends are hollow square pyramids and the standard probe indicates a space ~16 Å long from the

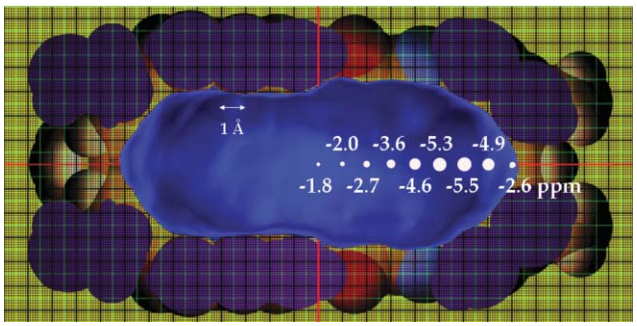


Fig. 10 Cross section of the capsule and B3LYP/6-31G* calculated NICS values along the center of the cavity. The four aryls at each of the resorcinarene ends impart an intense magnetic anisotropy: proton nuclei held near these ends show upfield shifts of up to 5 ppm in their NMR signals.

centroids of the benzenes from one end to the other. But what can fit into these tapered ends? A hydrogen atom of terminal acetylene is the smallest and narrowest organic substructure we could imagine so it was selected as a slim probe for the steric and electronic properties of this space.

We explored the inner space of the cavity both experimentally and computationally. The nucleus independent chemical shifts (NICS)[46] were calculated for the magnetically shielded regions of **1·1** at the B3LYP/6-31G* level of DFT.[45] These values are shown in Fig. 10 for coordinates along the central axis of **1·1** with a spacing distance of 1 Å. Along this axis the maximum effect, (−5.5 ppm) is at the uppermost carbon of the resorcinarene. From there a steep drop of the NICS is calculated as the cavity narrows and the "hole" in the end of the capsule is reached. This region is obviously not accessible to groups the size of methyl and larger. A calculation by Nakamura and Houk puts the activation energy for a methyl group to pass through this hole at $\sim$46 kcal mol^{-1}.[47]

The methyl groups of tetradecane are positioned in the area of the capsule that produces the highest upfield shifts; $\Delta\delta$ is approximately −4.8 ppm. The alkene 7-*trans*-tetradecene is also encapsulated with comparable chemical shifts for the nonallylic methylenes (Fig. 9b) but n-pentadecane is not encapsulated at all (Fig. 9a). Even in its most compressed form this alkane does not fit, but the methyl groups at each end are—relative to the tapered ends of the capsule—blunt instruments. When the methyl group is whittled down to a sharp point, accommodation is possible. The terminal alkyne 1-pentadecyne is encapsulated (Fig. 9d) and each of the proton resonances can be assigned; the acetylenic hydrogen is found at −1.2 ppm ($\Delta\delta$ 2.9 ppm), a value unexpectedly small for a nucleus so deep in the cavity's end. By way of contrast, the hydrogens of the methyl at the other end (C_{15}) shows $\Delta\delta$ −4.7 ppm and even the C_3 methylene shows $\Delta\delta > 5$ ppm, (the highest upfield shift ever observed in this capsule).

A series of biphenyl alkynes **14a–f** were prepared to probe the magnetic environment in the tapered end of the cavity. The biaryl is relatively rigid and bears the sharpened acetylenic tip, while the alkyl groups at the other end provide the "pressure". The relevant parts of the NMR spectra are shown in Fig. 11. The shortest guest is **14a**, and it can move freely to its optimal position in the capsule. It showed the methyne signal the

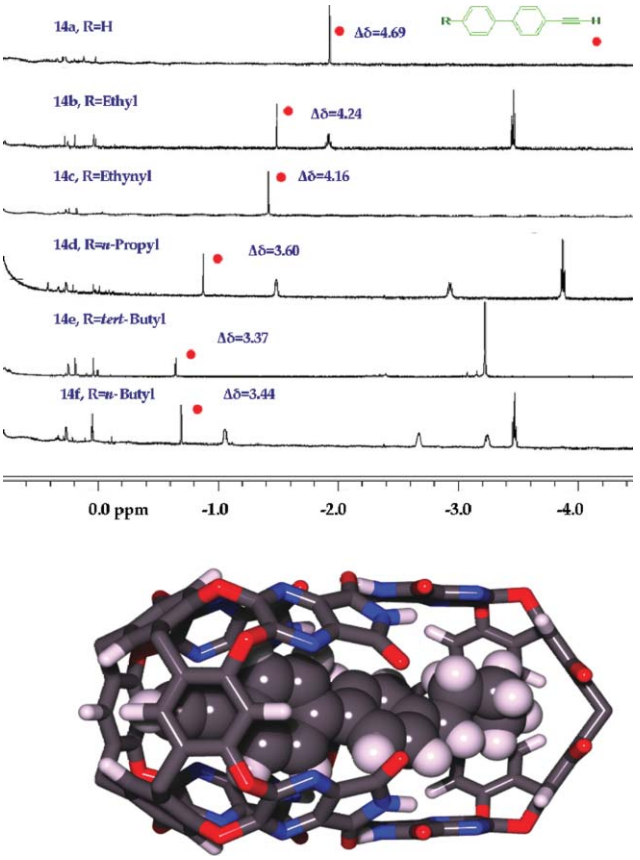


Fig. 11 (Top) Upfield regions of ^{1}H NMR spectra (600 MHz, mesitylene-d_{12}) of **1·1** (2 mM) with **14a–f** (10 mM); bottom) Modeled encapsulation of 4-ethynyl-4′-n-butylbiphenyl in **1·1**. The butyl adopts a gauche conformation and forces the acetylic hydrogen at the other end of the guest deep into the tapered end of the cavity. (Some groups omitted for clarity).

furthest upfield, at $\Delta\delta$ 4.7 ppm! As the remote alkyl increases in effective length, the pointed terminal acetylene is forced deeper into the cavitand, and the methyne hydrogen signal moves *downfield*: the magnetic environment it experiences is *less* shielding.

Semi-empirical energy minimized (AM1) structures of the encapsulation complexes showed the variation of the positioning of the acetylenic tips given in Fig. 5. The 1-pentadecyne and the *p*-butyl biphenyl acetylene **14f** are seen to be deepest within the cavitand with the hydrogen approaching but not protruding from the small opening, much like the tip of a retracted ball-point pen. For 1-pentadecyne, this places the C_3 methylene in the highest shift region with $\Delta\delta$ = 5.6 ppm. These positions are in accordance with the calculated NICS $\Delta\delta$ values described above (Fig. 10). The NICS calculated shifts are absolute values while those of Fig. 4 represent the difference between the chemical shifts in aromatic solvents and inside the capsule. The general agreement with experiment confirms the less shielding environment at the deepest part of capsule. The aromatic rings of the guests have fewest steric clashes with the pyrazine walls if they are placed diagonally in the box defined by the pyrazines. With such a placement the ortho hydrogens of the proximal phenyl of the n-Bu derivative

are also well shielded and the calculated value is 4.4–3.5; the observed value is 3.3 ppm.

What price is paid for forcing the acetylene deeper into the cavity? Pairwise competition studies between the rigid guests established the affinity order Et (**14b**) 10× > Pr (**14c**) 9× > H (**14a**) ~ t-Bu (**14e**) 9× > n-Bu (**14f**). The range of affinities is less than 1000 fold or about 4 kcal mol^{-1}. Each change affects not only the positioning of the guest but also the packing coefficient and the conformation so interpretations are compromised. For example, the worst guest **14f** is nearly the deepest but must also adopt a gauche conformation along the butane chain to be encapsulated (Fig. 12). The shortest **14a** leaves empty space and is only a fair guest.

Grinding and friction

The tapered ends in the cylindrical capsule **1·1** have consequences for motion of encapsulated guests. The ends are in a covalent framework and are rather rigid, whereas the belt of weaker hydrogen bonds between the imides leaves region around the middle comparatively flexible. After many unsuccessful attempts using long molecules (such as the anilides **2**), we were finally able to observe hindered rotation, the spinning of guests along the long axis of the capsule with 2,2-paracyclophane **15**. This compound does not fill the capsule alone, even though it fills the requisite fraction of the space. It is so compact that alone it leaves sizable vacuum and is coencapsulated with other small molecules such as ethane, chloroform, carbon tetrachloride and cyclohexane. The snug fit of paracyclophane in one end of the capsule is shown in Fig. 13. It is clear from this that rotation would create steric clashes between host and guest, and given the rigidity of the latter, if anything gives it must be the former. We observed variable temperature NMR spectra for this capsule's signals when paracyclophane was inside; rotation of the guest took place on intermediate time scales and we were able to determine activation barriers for the rotation.

The next figure (Fig. 14) shows what must happen as the paracyclophane rotates: the walls of the capsule must lean outward, the capsule bulges at 45° of rotation where the transition state is reached, *i.e.*, all four walls have the same relationship to the guest. We found that the activation energy

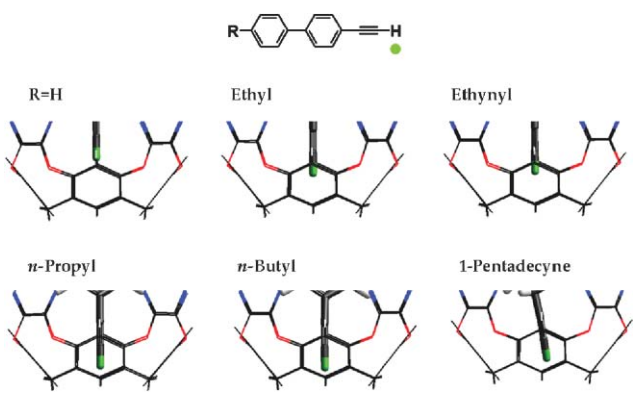


Fig. 12 Semi-empirical calculated (AM1) positions of the acetylenic hydrogens. The terminal acetylene C_{15} and the *t*-Bu biphenyl acetylene **14f** are seen to penetrate deepest into the tapered ends.

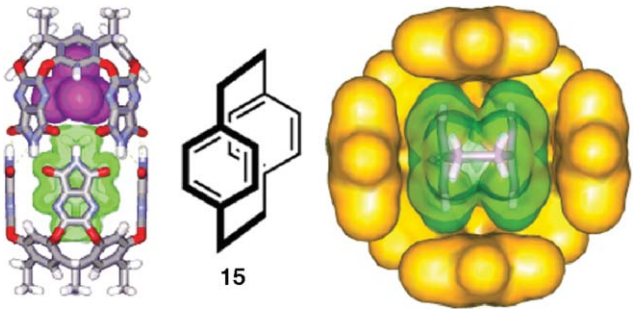


Fig. 13 Paracyclophane (center) is coencapsulated in **1·1** with carbon tetrachloride (left). The snug fit of paracyclophane in one end of the capsule is shown on the right.

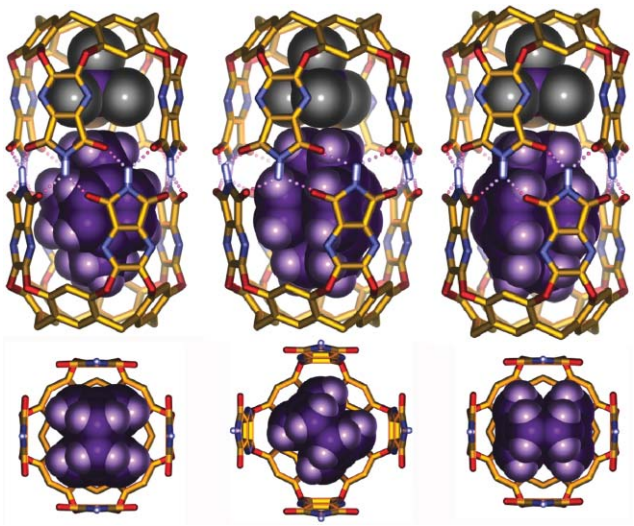


Fig. 14 Top: as paracyclophane spins along its axis with co-encapsulated C–C_{14} the capsule must breath as shown the center structure. Bottom: the rotation of paracyclophane in one end of the capsule causes the four walls to lean outward (center) at the transition state.

for this process depended on the co-encapsulated guest, specifically, on the "size" of that molecule. For small co-guests such as ethane the rotation of the paracyclophane was relatively rapid, whereas with the largest co-guest, cyclohexane, the rotation was quite slow. We propose that the larger structures compete for the space inside the capsule and force the paracyclophane down into the more rigid, tapered ends of the cavity where rotation experiences greater steric "friction". Smaller co-guests allow the paracyclophane more space near the center and the rotation is easier when the belt of hydrogen bonds expands. In short, the rotation rate becomes a measure of the effective volume of a molecule. This provides an alternative measure of size compared to those involving cyclohexyl *A* values or those based on substituents in hindered biaryl rotations.

Spring loading

We examined the encapsulation of straight-chain alkanes of C_{10} to C_{15}. At first glance these are ill fits. The hydrocarbons, linear (as we generally picture them) are long and too narrow

to complement the cavity of this capsule. Other self-assembled hosts, whether held together by hydrogen bonds,[48] salt bridges[49] or metal–ligand interactions,[50,51] are roughly spherical and this may be the reason that typical alkanes alone have not been encapsulated. But co-encapsulation of, for examples, pentane with *p*-ethyl-toluene[52] or ethane with anthracene[53] does occur. Unaccountably, long chain hydrocarbons, fluorocarbons and ethylene glycols are encapsulated in **1·1** (Fig. 15). The movement of the alkane in and out of the cavity is slow on the NMR timescale and separate signals are present for the free and bound guest. The exchange involves the rupture of the hydrogen bond seam as well as the conformational change of the receptor. Activation barriers for the in–out exchange process are in the range $\sim$20 kcal mole^{-1} for large guests.[54]

The conformation of the coiled part of the longest C_{14} guest was determined through NOE experiments. Cross-peaks between the hydrogens on C_1 and C_4, and C_1 and C_5 were observed in accord with a helical conformation with 2 gauche interactions along the first 5 carbons (Fig. 16). The hydrogens on C_2 showed crosspeaks with C_6 and C_3 with C_7 indicating the continued helical structure.

This information allows the assignment of the ends of the alkane as helical, but given the symmetry of the system, the dihedral angles around C_6–C_7, C_7–C_8 (the midpoint) and C_9–C_{10} are unknown. An entirely helical structure is shown but the disposition about any three contiguous bonds could be antiperiplanar. Some indirect evidence on this issue is provided by the *trans* olefin 7-tetradecene. It binds nearly as well as the tetradecane (direct competition showed a factor of 4 favoring the alkane). In any event, at least six gauche interactions exist along the chain (*ca.* 3.6 kcal mol^{-1}) and this higher energy would reduce binding affinity by a factor of a thousand.

Compression

Alkanes such as n-decane (C_{10}) are encapsulated in an extended conformation (Fig. 17) but the longer tetradecane (C_{14}) adopts a helical conformation.[55] This coiled conformation is shorter but thicker; it and allows the alkane to fit and to make attractive CH–π interactions with the aromatic surfaces of the capsule, but induces *gauche* configurations along the backbone. The encapsulated tetradecane is in an uneasy equilibrium: the CH–π interactions lower the energy but the gauche interactions raise the energy and exert pressure on the capsule as the alkane tries to uncoil. As described earlier, longer alkanes such as C_{15} and higher, are not encapsulated in **1·1**.

A newly discovered property of **1·1**, its ability to incorporate spacer elements, suggested its application as a notional spring-loaded device. Glycoluril structures **16a–b** (Fig. 18) can insert

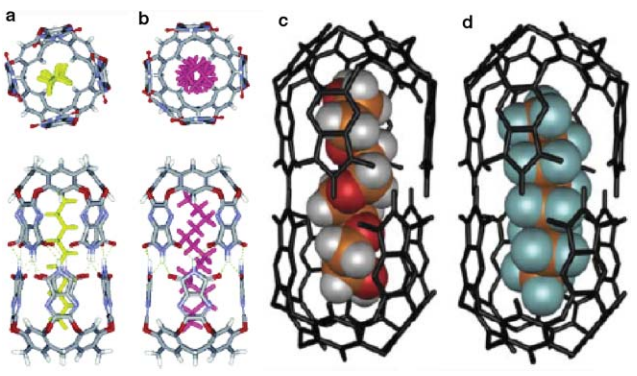


Fig. 15 Top and front views of the minimized structures for the complexes *n*-$C_{10}H_{22}$ (a), *n*-$C_{14}H_{30}$ (b), tetraethylene glycol (c), and perfluorooctane (d) in **1·1**. Alkyl chains of the cavitands have been omitted for clarity as well as one-half of the capsule for views from the top.

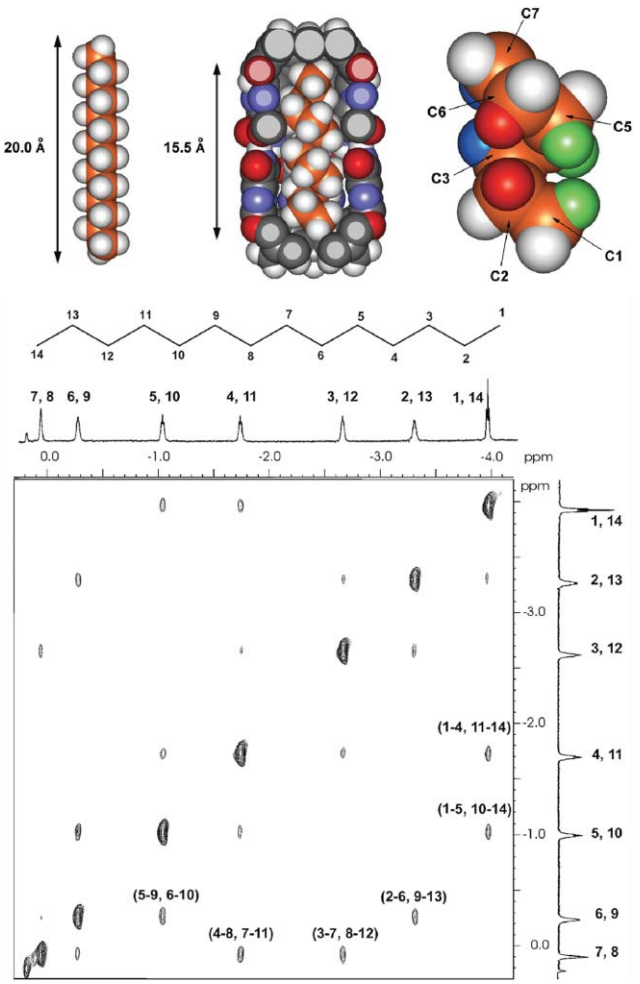


Fig. 16 Top: tetradecane in an extended conformation is too long to fit in the capsule but in a coiled conformation, the space is properly filled. The helical coiling puts hydrogens on C_1 (green) next to those on C_5 and those C_2 (red) next to those on C_6, *etc*. Bottom: cross peaks are observed between C_1 and C_5, C_2 and C_6, and C_3 and C_7 in the 2D NOESY spectrum of encapsulated tetradecane.

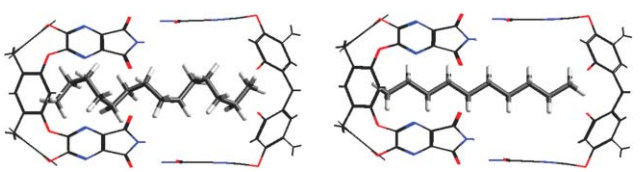


Fig. 17 Two views of **1·1** with alkanes inside: (left) tetradecane coils into a helical conformation, while decane is accommodated in its fully extended, anti conformation; (right). Peripheral alkyl groups and some capsule "walls" have been removed for viewing clarity.

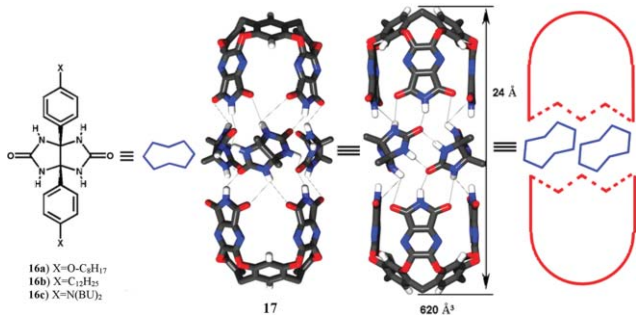


Fig. 18 Proposed structure for the expanded capsule **17** and its cartoon representation. Peripheral alkyl groups and some capsule "walls" have been removed for viewing clarity.

between the halves of the capsule, much like added leaves can be inserted to extend a dining table. An analogy from biology is allosteric behavior where a small molecule can regulate the receptivity and activity of a large enzyme. While glycoluril is not a conventional complement to imides[56] four glycolurils insinuate themselves and the capsule's length increases to allow the accommodation of longer guests.[57] The new assembly is chiral and racemic.

We prepared **16c**, a glycoluril with remote, weakly basic sites that can be protonated by strong acids. Addition of **16c** to the capsule **1·1** containing the coiled guest C_{14} causes changes in the NMR spectrum (Fig. 19). *The alkane relaxes to an extended conformation in a new host capsule*. The guest's methylene signals move downfield, indicating that the corresponding carbons move away from the ends of the capsule as would be

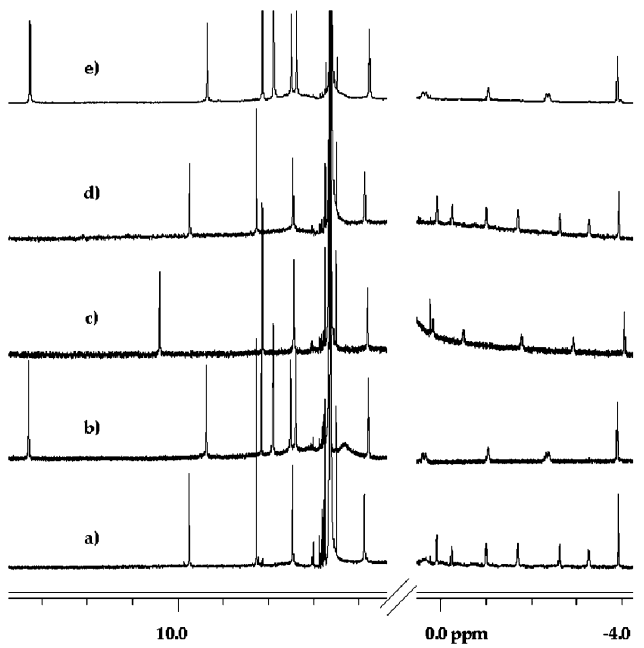


Fig. 19 Proton NMR spectra of the encapsulation complexes (600 MHz, in mesitylene – d_{12} solvent): Furthest upfield resonances are guest hydrogens nearest the ends of the capsule. (a) C_{14} and **1·1**; (b) C_{14} and **1·1** with **16c**; (c) C_{10} and **1·1** with or without **16c**; (d) solution (b) treated with HCl gas; (e) suspension obtained from (d) with added Me_3N.

expected for an extended conformation. In such a conformation the C–H bonds, on average, must move away from the walls of the capsule since not all these bonds can be touching the walls simultaneously. This positioning also results in downfield shifts of the signals. When the coil unwinds it becomes thinner. The doubling of the signals indicates the geminal hydrogens of the CH_2 groups at C_2 and C_{13} are diastereotopic, and places them near an asymmetric magnetic environment. Most informatively, addition of **16c** to the capsule **1·1** containing the extended guest C_{10} shows no changes in the spectrum.

Addition of HCl gas to the solution of C_{14} in the extended capsule caused the precipitation of **16c** as its hydrochloride salt and regenerated the spectrum of coiled C_{14} in the original capsule **1·1** (Fig. 19d). Next, the addition of Me_3N to the precipitated suspension liberated **16c** into solution and regenerated the spectrum of extended C_{14} in the extended capsule **17**. The coiling–extension cycles were repeated at least 6 times before the build-up of Me_3NHCl salt began to interfere with the spectroscopy. These cycles are summarized in Fig. 20.

The term "spring-loaded" evokes a range of macroscopic phenomena from the connection of the ornament to the hood of a Mercedes-Benz to the mechanism of an automatic gun. It has been broadly interpreted at the molecular level as well—to name a few: the behavior of diironoxo bisporphyrins,[58] *cis–trans* isomerization of retinal,[59] interconversion of peptide helices,[60] motions in block copolymers[61] and of inclusion compounds in the solid state.[62] More relevant is the behavior of a $-(CH_2)_{12}-$ segment; it assumes multiple gauche conformations which shrink its hydrophobic surface in water but relaxes to an extended conformation when threaded through a cyclodextrin.[63] But to what extent is a coiled alkane the

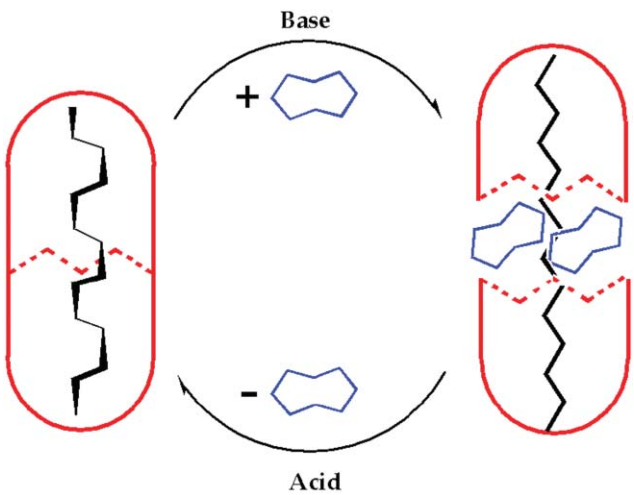


Fig. 20 Schematic representation of the coiling–uncoiling cycles of tetradecane, $C_{14}H_{30}$. The C_{14} is encapsulated as a helical coil in **1·1**. Addition of spacer **16c** to the solution generates the longer assembly **17** and the C_{14} guest relaxes to an extended conformation. Addition of HCl to **3** protonates the aniline sites of the spacer and causes precipitation of **16c** as its dihydrochloride salt; the system reverts to coiled C_{14} in the original capsule **1·1**. Addition of trimethyl amine to the mixture releases the spacer into solution where it inserts and generates the longer assembly with extended C_{14} inside.

driving force—the compressed spring—given the other forces involved in the reversibly formed assemblies at hand?

The formation of new hydrogen bonds to the spacers is a principal driver of the molecular device from the compressed to the extended states. The glycolurils can make the maximum number of hydrogen bonds as shown in Fig. 18 and pair their best acceptors with the cavitand's superior donors. The capsule **1·1** can be considered an organized solvent, the fixed structure of which is bought by the rigors of synthesis. This space needs to be filled and to do it optimally, the C_{14} must contort itself and assume the size, shape and chemical surface that are proper to the fixed cavity. In bulk solution the alkane has the same C–H$\cdots\pi$ interactions to offer, but must organize the solvent (mesitylene) to experience them. Release of these molecules to the bulk solvent—solvophobic forces—are also in play. The coiling of C14 within **1·1** provides the spring-loading in the form of guest strain and the reversible lengthening of the space to **17** provides the relief. Removal of the spacers through precipitation by acid forces the recoiling of the alkane back into the original capsule. The encapsulated C_{10} has no driving force for change; the spacers can add hydrogen bonds but the longer capsule leads to a poorer fit with additional empty space—vacuum—in the complex.[64]

Reversible spring loading in synthetic capsules is unprecedented, but has counterparts in biology. The coiled nucleic acids in capsids of bacterial viruses are under pressure that is relieved through their injection into hosts.[65] Even the addition of spacers has analogues in those viral capsids that can incorporate additional protein subunits to accommodate larger genomes.[66] Recent descriptions of biological transcription machinery also use terms like compaction stress, compression stress and "scrunching" for DNA.[67] It may be possible to harness the molecular device described here to do work on other molecules[68] and we are pursuing this goal.

Conclusions

In conclusion, reversibly formed capsules,[69] are assemblies held together by weak intermolecular forces hydrogen bonds, CH–π interactions, van der Waals forces and even stronger metal–ligand binding.[70–73] The lifetimes of the complexes vary from milliseconds to days, a range that makes them useful as nanometric reaction chambers,[74] as means to stabilize reagents,[75] sources of "complexes within complexes," and as spaces where new forms of stereochemistry can emerge.[76,77] When encapsulated, guests are unreactive to dissolved reagents, since the capsule provides a mechanical barrier. Exchange between the environments inside and outside the capsule becomes a means of regulating reactivity.

The concave inner surface of the host capsule and the convex outer surface of the guest define the congruence necessary for molecular recognition but for encapsulation to occur, a good "fit" is required. The fit with respect to size usually involves filling just more than half of the space in the host in the liquid phase.[78] Complementary shapes are ideal, but this review brings forward those cases where guests contort themselves to higher energy conformations in order to better occupy the available space. With access to chiral capsules[79] and hybrids[80] the potential diversity of guest shapes imposed by hosts is huge. We are exploring this shape space.

Acknowledgements

I am deeply indebted to the generosity of the Skaggs family: they are ultimate examples of philanthropy. The National Institutes of Health (GM 50174, GM 29372) provided support and Drs L. Sebo and D. Ajami created the graphics. Dr M. Schramm helped greatly with the manuscript and designed the cover graphic and Anna Rebek painted the portrait. Finally, I am grateful to Sarah Thomas for this invitation to write for *Chemical Communications*.

References

1 (*a*) J. Rebek, Jr. and J. E. Trend, *J. Am. Chem. Soc.*, 1978, **100**, 4315; (*b*) J. Rebek, Jr., T. Costello and R. Wattley, *J. Am. Chem. Soc.*, 1985, **107**, 7487.
2 (*a*) J. Rebek, Jr., T. Costello and R. V. Wattley, *Tetrahedron Lett.*, 1980, 2379; (*b*) J. Rebek, Jr. and L. Marshall, *J. Am. Chem. Soc.*, 1983, **105**, 6668; (*c*) K. Onan, J. Rebek, Jr., T. Costello and L. Marshall, *J. Am. Chem. Soc.*, 1983, **105**, 6759; (*d*) J. Rebek, R. V. Wattley, S. Chakravorti and J. E. Trend, *J. Am. Chem. Soc.*, 1979, **101**, 4333.
3 (*a*) J. Rebek, Jr., R. V. Wattley, T. Costello, R. Gadwood and L. Marshall, *Angew. Chem., Int. Ed. Engl.*, 1981, **93**, 584; (*b*) J. Rebek and R. V. Wattley, *J. Heterocycl. Chem.*, 1980, **17**, 749; (*c*) J. Rebek and R. V. Wattley, *J. Am. Chem. Soc.*, 1980, **102**, 4853; (*d*) J. Rebek, Jr., R. V. Wattley, T. Costello, R. Gadwood and L. Marshall, *J. Am. Chem. Soc.*, 1980, **102**, 7398; (*e*) J. Rebek, Jr., T. Costello, L. Marshall, R. Wattley, R. Gadwood and K. Onan, *J. Am. Chem. Soc.*, 1985, **107**, 7481.
4 (*a*) E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2007, **46**, 72; (*b*) G. S. Kottas, L. I. Clarke, D. Horinek and J. Michl, *Chem. Rev.*, 2005, **105**, 1281–1376.
5 J. Rebek, Jr., *Acc. Chem. Res.*, 1984, **17**, 258.
6 V. Balzani, A. Credi and M. Venturi, in *Molecular Devices and Machines*, Wiley-VCH, Weinheim, Germany, 2003, chap. 12, pp 288–328.
7 J. Vicario, M. Walko, A. Meetsma and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 5127.
8 T. R. Kelly, H. De Silva and R. A. Silva, *Nature*, 1999, **401**, 150.
9 (*a*) A. Itai, Y. Toriumi, N. Tomioka, H. Kagechika, I. Azumaya and K. Shudo, *Tetrahedron Lett.*, 1989, **30**, 6177; (*b*) I. Azumaya, K. Yamaguchi, I. Okamoto, H. Kagechika and K. Shudo, *J. Am. Chem. Soc.*, 1995, **117**, 9083; (*c*) K. Yamaguchi, G. Matsumura, H. Kagechika, I. Azumaya, Y. Ito, A. Itai and K. Shudo, *J. Am. Chem. Soc.*, 1991, **113**, 5474; (*d*) I. Azumaya, H. Kagechika, K. Yamaguchi and K. Shudo, *Tetrahedron*, 1995, **51**, 5277.
10 M. Tominaga, H. Masu, K. Katagiri, T. Kato and I. Azumaya, *Org. Lett.*, 2005, **7**, 3785.
11 T. Kusukawa, M. Yoshizawa and M. Fujita, *Angew. Chem., Int. Ed.*, 2001, **40**, 1879.
12 M. Zeigler, J. L. Brumaghim and K. N. Raymond, *Angew. Chem., Int. Ed.*, 2000, **39**, 4119.
13 D. J. Cram, M. E. Tanner and R. Thomas, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1024.
14 (*a*) J. Rebek, Jr., *Tetrahedron*, 1979, **35**, 723; (*b*) J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 245.
15 (*a*) R. Grotzfeld, N. Branda and J. Rebek, Jr., *Science*, 1996, **271**, 487; (*b*) B. M. O'Leary, R. M. Grotzfeld and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1997, **119**, 11701.
16 B. Purse and J. Rebek, Jr., *Chem. Commun.*, 2005, 722–724.
17 E. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, chap. 10, pp 597–664.
18 G. Zanotti, G. Scapin, P. Spadon, J. Veerkamp and J. Sacchettini, *J. Biol. Chem.*, 1992, **267**, 18541.
19 G. W. Han, J. Y. Lee, H. K. Song, C. S. Chang, K. Min, J. Moon, D. H. Shin, M. L. Kopka, M. R. Sawaya, H. S. Yuan, T. D. Kim,

J. Choe, D. Lim, M. J. Moon and S. W. Suh, *J. Mol. Biol.*, 2001, **308**, 263.
20 O. Séneque, M.-N. Rager, M. Giorgi and O. Reinaud, *J. Am. Chem. Soc.*, 2000, **122**, 6183.
21 K. A. Udachin, G. D. Enright, E. B. Brouwer and J. A. Ripmeester, *J. Supramol. Chem.*, 2001, **1**, 97.
22 (*a*) M. D. Hollingsworth and K. D. M. Harris, in *Comprehensive Supramolecular Chemistry*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, Elsevier Science Ltd., Oxford, 1996, Vol. 6, pp 177–237; (*b*) M. E. Brown and M. D. Hollingsworth, *Nature*, 1995, **376**, 323.
23 O. Hayashida, L. Sebo and J. Rebek, Jr., *J. Org. Chem.*, 2002, **67**, 8291.
24 M. Yamanaka, A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 2939.
25 C. F. Wilson, M. P. Eastman and C. J. Hartzell, *J. Phys. Chem. B*, 1997, **101**, 9309.
26 (*a*) A. Shivanyuk and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 7662; (*b*) A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2003, **125**, 3432; (*c*) M. Yamanaka, A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 2939; (*d*) L. C. Palmer, A. Shivanyuk, M. Yamanka and J. Rebek, Jr., *Chem. Commun.*, 2005, 857.
27 (*a*) L. Avram and Y. Cohen, *Org. Lett.*, 2003, **5**, 1099; (*b*) L. Avram and Y. Cohen, *J. Am. Chem. Soc.*, 2004, **126**, 11556; (*c*) L. Avram and Y. Cohen, *J. Am. Chem. Soc.*, 2002, **124**, 15148.
28 M. A. Petti, T. J. Shepodd, R. E. Barrans, Jr. and D. A. Dougherty, *J. Am. Chem. Soc.*, 1988, **110**, 6825.
29 P. C. Kearney, L. S. Mizoue, R. A. Kumpf, J. E. Forman, A. McCurdy and D. A. Dougherty, *J. Am. Chem. Soc.*, 1993, **115**, 9907.
30 L. C. Palmer and J. Rebek, Jr., *Org. Lett.*, 2005, **7**, 787, the complete structural assignment for encapsulated C17 is given in this publication, not (as reported) C12.
31 T. Gerkensmeier, W. Iwanek, C. Agena, R. Fröhlich, S. Kotila, C. Näther and J. Mattay, *Eur. J. Org. Chem.*, 1999, 2257.
32 (*a*) J. L. Atwood, L. J. Barbour and A. Jerga, *Chem. Commun.*, 2001, 2376; (*b*) J. L. Atwood, L. J. Barbour and A. Jerga, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4837; (*c*) G. W. V. Cave, J. Antesberger, L. J. Barbour, R. M. McKinlay and J. L. Atwood, *Angew. Chem., Int. Ed.*, 2004, **43**, 5263.
33 L. Trembleau and J. Rebek, Jr., *Science*, 2003, **301**, 1219.
34 M. P. Schramm and J. Rebek, Jr., *Chem.–Eur. J.*, 2006, **12**, 5924.
35 R. J. Hooley, S. M. Biros and J. Rebek, Jr., *Chem. Commun.*, 2006, **5**, 509.
36 E. Fischer, *Ber. Dtsch. Chem. Ges.*, 1894, **27**, 2985.
37 J. A. Thoma and D. E. Koshland, Jr., *J. Am. Chem. Soc.*, 1960, **82**, 3329.
38 A. Scarso, L. Trembleau and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2003, **42**, 5499.
39 (*a*) K. T. Chapman and W. C. Still, *J. Am. Chem. Soc.*, 1989, **111**, 3075; (*b*) R. Meissner, X. Garcias, S. Mecozzi and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1997, **119**, 77.
40 (*a*) T. Heinz, D. M. Rudkevich and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 1999, **38**, 1136; (*b*) T. Heinz, D. M. Rudkevich and J. Rebek, Jr., *Nature*, 1998, **394**, 764.
41 (*a*) J. Chen, S. Körner, S. L. Craig, D. M. Rudkevich and J. Rebek, Jr., *Nature*, 2002, **415**, 385; (*b*) J. Chen, S. Körner, S. L. Craig, S. Lin, D. M. Rudkevich and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 2593.
42 (*a*) M. Nishio, M. Hirota and Y. Umezawa, in *The CH/Interaction*, (Wiley, New York, 1998); (*b*) W. Blokzijl and J. B. F. N. Engberts, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1545.
43 J. Kang and J. Rebek, Jr., *Nature*, 1996, **382**, 239.
44 (*a*) M. Nishio, M. Hirota and Y. Umezawa, *The CH/π Interaction*, Wiley, New York, 1998; (*b*) W. Blokzijl and J. B. F. N. Engberts, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1545.
45 A. Nicholls, K. Sharp and B. Honig, *Proteins: Struct., Funct., Genet.*, 1991, **11**(4), 281ff.
46 P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao and N. J. R. v. E. Hommes, *J. Am. Chem. Soc.*, 1996, **118**, 6317.
47 K. Nakamura and K. N. Houk, *J. Am. Chem. Soc.*, 1995, **117**, 1853.
48 (*a*) J. M. Rivera, T. Martin and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2001, **123**, 5213; (*b*) J. Tokunaga and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 66; (*c*) R. K. Castellano, C. Nuckolls and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 11156; (*d*) R. K. Castellano, B. H. Kim and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1997, **119**, 12671; (*e*) C. Nuckolls, F. Hof, T. Martin and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 10281; (*f*) R. Meissner, J. Rebek, Jr. and J. de Mendoza, *Science*, 1995, **270**, 1485; (*g*) C. Valdés, U. P. Spitz, S. W. Kubik and J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, 1995, 1885; (*h*) C. Valdés, U. P. Spitz, L. Toledo, S. Kubik and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1995, **117**, 12733.
49 (*a*) S. B. Lee and J. J. Hong, *Tetrahedron Lett.*, 1996, **37**, 8501; (*b*) F. Corbellini, L. Di Constanzo, M. Crego-Calama, S. Geremia and D. R. Reinhoudt, *J. Am. Chem. Soc.*, 2003, **125**, 9946.
50 (*a*) M. Fujita, K. Umemoto, M. Yoshizawa, N. Fujita, T. Kusukawa and K. Biradha, *Chem. Commun.*, 2001, 509; (*b*) S. Hirakoa and M. Fujita, *J. Am. Chem. Soc.*, 1999, **121**, 10239; (*c*) T. Kusukawa and M. Fujita, *J. Am. Chem. Soc.*, 2002, **124**, 13576.
51 D. L. Caulder and K. N. Raymond, *Acc. Chem. Res.*, 1999, **32**, 975.
52 A. Scarso, A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2003, **125**, 13981.
53 A. Shivanyuk, A. Scarso and J. Rebek, Jr., *Chem. Commun.*, 2003, 1230.
54 S. L. Craig, S. Lin, J. Chen and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 8780.
55 A. Scarso, L. Trembleau and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 13512.
56 (*a*) T. K. Park, J. Schroeder and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 5125; (*b*) J. S. Nowick, P. Ballester, F. Ebmeyer and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1990, **112**, 8902.
57 (*a*) D. Ajami and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2006, **128**, 5314; (*b*) D. Ajami and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2006, **128**, 15038.
58 J. M. Hodgkiss, C. J. Chang, B. J. Pistorio and D. G. Nocera, *Inorg. Chem.*, 2003, **42**, 8270(*a*) N. R. Branda, R. M. Grotzfeld, C. Valdés and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1995, **117**, 85.
59 U. F. Roehrig, L. Guidoni, A. Laio, I. Frank and U. Rothlisberger, *J. Am. Chem. Soc.*, 2004, **126**, 15328.
60 P. Pengo, L. Pasquato, S. Moro, A. Brigo, F. Fogolari, Q. B. Broxterman, B. Kaptein and P. Scrimin, *Angew. Chem., Int. Ed.*, 2003, **42**, 3388.
61 Y.-W. Chiang, R.-M. Ho, B.-T. Ko and C.-C. Lin, *Angew. Chem., Int. Ed.*, 2005, **44**, 7969.
62 M. D. Hollingsworth, U. Werner-Zwanziger, M. E. Brown, J. D. Chaney, J. C. Huffman, K. D. M. Harris and S. P. Smart, *J. Am. Chem. Soc.*, 1999, **121**, 9732.
63 R. B. Hannak, G. Färber, R. Konrat and B. Kräutler, *J. Am. Chem. Soc.*, 1997, **119**, 2313.
64 A. Scarso, H. Onagi and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 12728.
65 S. Tzlil, J. T. Kindt, W. M. Gelbart and A. Ben-Shaul, *Biophys. J.*, 2003, **84**, 1616.
66 B. J. M. Verduin and J. B. Bancroft, *Virology*, 1965, **37**, 501.
67 (*a*) A. Revyakin, R. H. Ebright and T. R. Strick, *Science*, 2006, **314**, 1139; (*b*) A. N. Kapanidis, E. Margeat, S. O. Ho, E. Kortkhonjia, S. Weiss and R. H. Ebright, *Science*, 2006, **314**, 1144.
68 T. Muraoka, K. Kinbara and T. Aida, *Nature*, 2006, **440**, 512.
69 (*a*) M. M. Conn and J. Rebek, Jr., *Chem. Rev.*, 1997, **97**, 1647; (*b*) J. Rebek, Jr., *Chem. Soc. Rev.*, 1996, 255; (*c*) J. Rebek, Jr., *Chem. Commun.*, 2000, **8**, 637; (*d*) J. Rebek, Jr., *Acc. Chem. Res.*, 1999, **32**, 278.
70 T. N. Parac, D. L. Caulder and K. N. Raymond, *J. Am. Chem. Soc.*, 1998, **120**, 8003.
71 D. L. Caulder and K. N. Raymond, *J. Chem. Soc., Dalton Trans.*, 1999, 1185.
72 K. Umemoto, K. Yamaguchi and J. Fujita, *J. Am. Chem. Soc.*, 2000, **122**, 7150.
73 M. Fujita, K. Umemoto, M. Yoshizawa, N. Fujita, T. Kusukawa and K. Biradha, *Chem. Commun.*, 2001, 509.
74 (*a*) J. Kang, J. Santamaria, G. Hilmersson and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 7389; (*b*) J. Kang, G. Hilmersson, J. Santamaria and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 3650; (*c*) J. Rebek, Jr., *Acc. Chem. Res.*, 1999, **32**, 278.
75 (*a*) J. Chen, S. Körner, S. L. Craig, S. Lin, D. M. Rudkevich and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**,

2593; (*b*) T. Iwasawa, E. Mann and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2006, **128**, 9308; (*c*) V. M. Dong, D. Fiedler, B. Carl, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2006, **128**, 14464.
76 R. G. Chapman and J. C. Sherman, *J. Am. Chem. Soc.*, 1995, **117**, 9081.
77 F. C. Tucci, D. M. Rudkevich and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 4928.
78 (*a*) S. Mecozzi and J. Rebek, Jr., *Chem.–Eur. J.*, 1998, **4**, 1016; (*b*) J. Kang and J. Rebek, Jr., *Nature*, 1996, **382**, 239.
79 (*a*) Y. Tokunaga and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1997, **120**, 66; (*b*) J. M. Rivera, T. Martin and J. Rebek, Jr., *Science*, 1998, **279**, 1021; (*c*) C. Nuckolls, F. Hof, T. Martín and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 10281; (*d*) J. M. Rivera and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2000, **122**, 7811; (*e*) A. Scarso, A. Shivanyuk, O. Hayashida and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2003, **125**, 6239.
80 (*a*) F. Hof, C. Nuckolls and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2000, **122**, 4251; (*b*) D. Ajami, M. P. Schramm, A. Volonterio and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2007, **46**, 242.