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Molecular Behavior in Small Spaces

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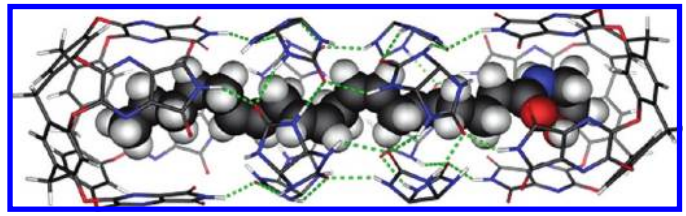

The study of physical organic chemistry in solution is a mature science, over a century old, but over the last 10 years or so, reversible encapsulation has changed the way researchers view molecular interactions. It is now clear that the behavior of molecules in dilute solution is really quite different from their behavior in capsules. Molecules isolated from bulk media in spaces barely large enough to accommodate them and a few neighbors show new phenomena: their activities resemble those of molecules inside biochemical structures—pockets of enzymes, interiors of chaperones, or the inner space of the ribosome—rather than conventional behavior in solution.

In this Account, we recount the behavior of molecules in these small spaces with emphasis on structures and reactivities that have not been, and perhaps cannot be, seen in conventional solution chemistry. The capsules self-assemble through a variety of forces, including hydrogen bonds, metal−ligand interactions, and hydrophobic effects. Their lifetimes range from milliseconds to hours, long enough for NMR spectroscopy to reveal what is going on inside. We describe one particular capsule, the elongated shape of which gives rise to many of the effects and unique phenomena. Molecular guests that are congruent to the space of the host can be tightly packed inside and show reduced mobilities such as rotation and translation within the capsule. These mobilities depend strongly on what else is encapsulated with them. We also relate how asymmetric spaces can be created inside the capsule by using a chiral guest. In contrast to the situation in dilute solution, where rapid exchange of solute partners and free molecular motion average out the steric and magnetic effects of chirality, the long lifetimes of the encounters in the capsules magnify the effects of an asymmetric environment. The capsule remains achiral, but the remaining space is chiral, and coencapsulated molecules respond in an amplified way.

We probe the various regions of the capsule with guests of different shape. Primary acetylenes, the narrowest of functional groups, can access the tapered ends of the capsule that exclude functions as small as methyl groups. The shape of the capsule also has consequences for aromatic guests, gently bending some and straightening out others. Flexible structures such as normal alkanes can be compressed to fit within the capsule and conform to its shape. We obtain a measure of the internal pressure caused by the compressed guests by determining its effect on the motion of the capsule's components. These forces can also drive a spring-loaded device under the control of external acids and bases. We show that spacer elements can be added to give self-assembled capsules of increased complexity, with 15 or more molecules spontaneously coming together in the assembly. In addition, we analyze the behavior of gases, including the breakdown of ideal gas behavior, inside these capsules.

The versatility of these capsule structures points to possible applications as nanoscale reaction chambers. The exploration of these confined spaces and of the molecules within them continues to open new frontiers.

The study of physical organic chemistry in solution is a mature science, over a century old, with many specialties: kinetics, thermodynamics, mechanisms of reactions, reactive intermediates, isotope effects, and intermolecular forces are generally well understood. In contrast, reversible

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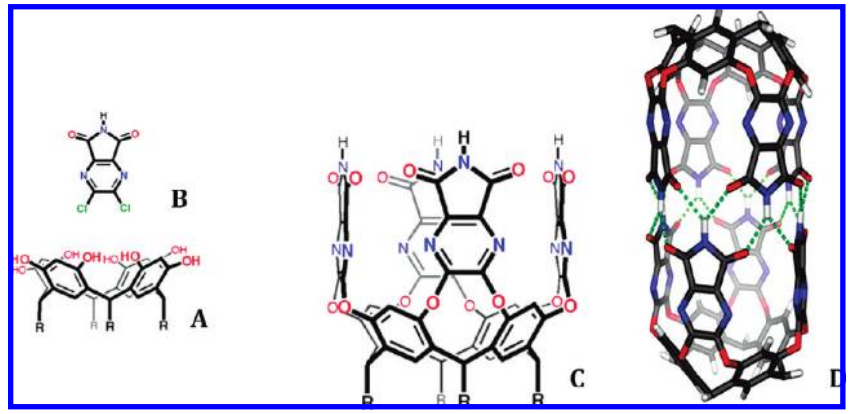


FIGURE 1. Synthesis and assembly of the capsule. The resorcinarene octol (A) and activated aromatic halides (B) combine to give the cavitand (C). The hydrogen-bonding sites on the upper rim allow dimerization in the presence of a suitable guest; (D) the cylindrical capsule is shown without peripheral groups, R, which are long chain alkyls.

encapsulation is little more than a decade old but has already had an impact in all these areas. It is now clear that the behavior of molecules in dilute solution is really quite different from their behavior in capsules. Molecules isolated from bulk media in spaces barely large enough to accommodate them and confronted for protracted times with one or two others show new phenomena; their activities resemble those of molecules inside biochemical structures—pockets of enzymes, interiors of chaperones, or the inner space of the ribosome—rather than conventional behavior in solution. Model systems for these biological systems have been popular in the past and include cyclodextrins,[1] which resemble nucleases;[2] polyethers, which resemble proteases;[3] cyclophanes, which resemble vitamins;[4] and cryptands,[5] carcerands,[6] and cryptophanes,[7] which resemble not at all their sinister macroscale namesakes. Beside these, there exist synthetic receptors with concave surfaces that bring components together that are too numerous to include here. But it is reasonable to question what relevance the open-ended containers operating in dilute solution have to biological macromolecules in which solvent is excluded and substrates surrounded are then confronted with functional groups in very small spaces. Accordingly, molecular behavior inside capsules can offer new perspectives on biological phenomena, but this is not the only, or even the primary reason to study them. I have a genuine curiosity about them, and as one of the architects of these systems, I feel obligated to explore them. A timely and comprehensive review of their use as reaction flasks has just appeared,[8] and here I emphasize their physical properties and how the mechanical boundaries of the capsules dictate the behavior of molecules inside. Some phenomena that are fleeting and barely observable in solution emerge, are amplified, and dominate activities in the nanometric space of the capsules. The molecular encounters of diffusion complexes in solution that last nanoseconds are lengthened to seconds in these capsules, and various interactions are intensified inside. The frequent exchange of collision partners in solution is replaced by a ferociously faithful one-on-one interaction inside. Moreover, the small spaces translate into very high concentrations of molecules inside, typically 4 M, and the shape of the space can impose specific conformations, confrontations, and constellations that can magnify their reactivity. In this Account, I limit the discussion to a single type of capsule even though the phenomena are common to other capsules, whether hydrogen-bonded[9−15] or held together by metal/ligand interactions,[16,17] hydrophobic effects,[18] or even covalent bonds.[19]

Some 10 years ago, the cylindrical capsule shown in Figure 1 was introduced.[20] This is a structure in which a resorcinarene provides the overall molecular curvature, four flat imide walls lend the depth, and self-complementary hydrogen bonding sites offer the recognition. The synthesis followed the well-trodden paths opened by Cram[21] and Dalcanale[22] to the cavitand structure. The resorcinarene itself is available thanks to Sverker Högberg[23,24] who refined its synthesis on a large scale nearly 30 years ago (some resorcinarenes are commercial products). It was expected that the cavitands could be in dynamic equilibrium between kite and vase forms, as established by earlier NMR studies, but the prospect of making a maximum number of hydrogen bonds would bring two of these together, concave face to concave face, to give a dimeric capsule.

That expectation was met: the NMR spectrum of the assembly featured sharp signals when some suitable guests (about which, more later) were dissolved with the capsule in deuterated mesitylene. This was the largest deuterated NMR solvent available at the time (perhaps it still is), and its dimensions are not accommodated by the capsule. Accordingly, intended guests that are at millimolar concentrations in

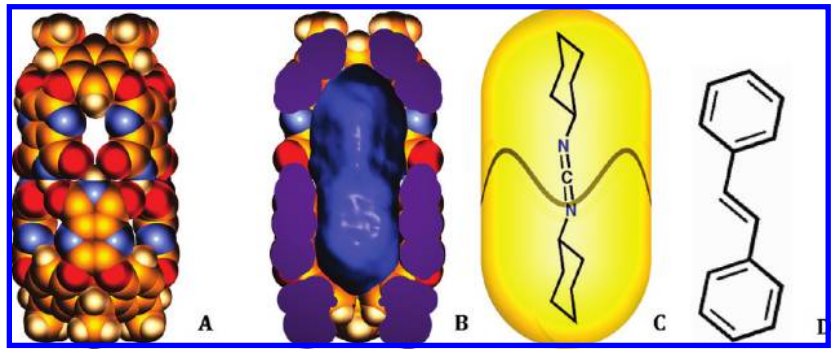


FIGURE 2. Renderings of the host capsule and guests. (A) The space-filling rendition of the capsule shows that the "holes" are too small to allow entry and departure of guests. (B) The cross-section of the capsule reveals the shape of the space (blue) inside. It consists of two square pyramids twisted 45° with respect to one another in the center. (C) The structure of dicyclohexylcarbodiimide in a cartoon representation of the capsule. (D) The structure of *trans*-stilbene, another guest.

this solvent (the solvent is at roughly 10 M concentration) can successfully compete for the interior of the space. There are impurities such as deuterated benzene and deuterated *p*-xylene in the NMR solvent. Their concentrations are typically 1 mM or less, so they do not compete effectively for the capsule, and it is generally possible to drive the intended guests in rather than the solvent impurities.

As in conventional architecture, much of the business of this capsule is about the space it encloses rather than the structure itself. The space inside is 4.2×10^{-25} L, or about 420 Å^3, and its shape is neither spherical nor cube-like but long, twisted, and tapered, as shown in Figure 2. The space is two square prisms rotated 45° with respect to one another and capped by the square pyramidal shapes of the resorcinarene, again rotated by 45°, at either end. The figure also shows a cross-section where two benzene subunits of one resorcinarene end (at the top of the figure) are cut through their *para* positions, and the blue shape is the modeled space inside. Also on the left is shown a CPK version of the capsule that gives an idea of what "holes" are present at either end or in the walls. These holes are too small to allow the passage of any guests in and out. Calculations by Houk[25] on structurally related covalent carcerands indicate that the holes at either end (at the bottom of the resorcinarenes) cannot permit the passage of even a methyl group without a huge (>45 kcal/mol) energetic barrier.

The larger guests that find their way into this host generally have an orientation that aligns with the long axis of the structure. Some of the earliest guests to be encapsulated are also shown in Figure 2.[26] Dicyclohexylcarbodiimide (DCC) is nicely taken up and can fit only as shown, but its reactivity is turned off while in the capsule. Carboxylic acids, for example, do not have access to it. Once DCC escapes the capsule, it is free to react as a dehydrating agent, and the resulting urea can re-enter the capsule as even a better guest.[27] The

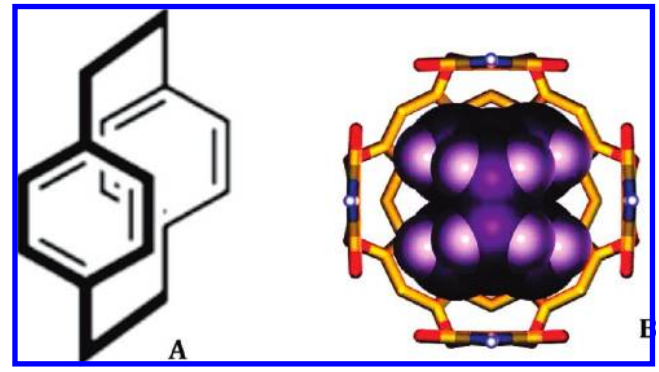


FIGURE 3. A square peg in a square hole. (A) The solid guest, 2,2-paracyclophane. (B) A model of the complex with 2,2-paracyclophane, which fits snugly in one half of the capsule.

carbonyl and NH of the urea provide additional hydrogen bonding complements to the polar seam of donors and acceptors that holds the capsule together. This gives rise to unprecedented chain reaction kinetics when encapsulated DCC is used as a dehydrating agent for the formation of certain benzanilides.[28] Other molecules such as terphenyl and *trans*-stilbene (about which, also more later) but not *cis*-stilbene are encapsulated.

One of the other features that gives rise to the unique behavior described here is that this capsule will assemble around *two different guests that together fill the appropriate amount of space.* For example, in a mixture of benzene and *p*-xylene, a single capsule structure is assembled in which one molecule of each solvent is found inside. This combination fills a little more than half the space, and we have discussed elsewhere why this is such a good fit in the liquid phase.[29] Briefly, it reflects the amount of space occupied in typical organic solvents, such as methanol, benzene, chloroform, or acetonitrile. About 55% of the space is occupied by molecules in these solvents. But it is possible to pack this space more densely with larger molecules. Figure 3 shows 2,2-paracyclophane inside the capsule. This compound does not go in alone because one

TABLE 1. Characteristics of Guests Coencapsulated with 2,2-Paracyclophane

	vol (Å^3)	PC (%)	k (min^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta\delta$ (ppm)
CH_3CH_3	42	62	178	14.8	4.43
$(CH_2)_3$	52	64	257	14.6	4.45
$(CH_3)_2CO$	60	66	297	14.5	4.44
$CHCl_3$	75	69	127	15.0	4.48
$(CH_3)_2CHCl$	76	70	76	15.2	4.49
$(CH_3)_2CHBr$	84	72	75	15.2	4.47
CCl_4	91	73	65	15.3	4.49
$CHBr_3$	99	75	36	15.6	4.52
C_6H_{12}	97	75	23	15.9	4.57
CCl_3Br	114	79	46	15.5	4.51

molecule does not fill enough space and two fill too much, but it is readily coencapsulated with any number of guests. On the right is shown the cavitand with 2,2-paracyclophane inside, a notional square peg in a square hole. Now it would seem that if the guest were to rotate along the axis of the capsule, something must give, and because of the rigidity of 2,2-paracyclophane, it is unlikely to distort, even though it is the guest that wants the freedom to rotate while inside. Instead, the capsule undergoes breathing motions that distort its hydrogen bonds. This breathing motion allows the 2,2-paracyclophane enough room to rotate without undue "friction" since hydrogen bonds are fairly forgiving when diversions from the ideal geometries are imposed.

This rotation is easily monitored by dynamic NMR techniques, which show coalescence of the signal for the four walls. Table 1 gives the activation parameters for this process.[30] What emerges is that the rates of rotation depend on the coguest: they are slowest for the largest, such as cyclohexane, and fastest for the smallest, such as ethane. This measures, then, the effective "size" of a molecule. Both guests are coping with the limited space, and the larger cyclohexane is able to better force the cyclophane into the tapered end of the capsule, where more friction takes place. This is quite a different measure than the *A* values of cyclohexane and those determined from the hindered rotation of substituted biaryls. Again, the shape of the space gives rise to this intermolecular phenomenon since spherical capsules cannot show this behavior.[31]

The intimacy shared by the coencapsulated guests has been reviewed,[32] but recent experiments with chiral sensitivity in the limited space merit mentioning. Consider the diol guest shown in Figure 4. Because of its length, it is unable to tumble freely in the capsule, and therefore it presents either one end or the other to the coguest isopropanol. Can the coguest "see" beyond the nearby asymmetric center and through the molecule to the far end where the second asymmetric center resides? That is, can the guest distinguish between *R* and *S* centers at the remote site? If these were in solution, the rapid tumbling and exchange processes would obliterate any differences. But in the capsule, where the assembly lifetime is on the order of seconds, the configuration of the remote center *does* effect the coguest.[33] Specifically, the NMR spectra of isopropanol coencapsulated with the *meso* compound and the homochiral compound are shown in the figure. The differences are not likely to be steric effects, and the capsule remains achiral (by CD spectra). Instead, magnetic effects propagated from the remote asymmetric center fixed in time and space are felt by the coguest.

Consider now a closer look at the tapered ends of the capsule. Figure 5 A shows that tetradecane is too long in its fully extended conformation to be accommodated. Its length is more than 20 Å, and therefore, it must be compressed, coiled in a helical conformation, to fit inside as in Figure 5B.[34] This coiling is not without cost because each *gauche* interaction emphasized in Figure 5C costs slightly more than half a kilocalorie in the liquid state,[35] but it also has its benefits. The alkane becomes shorter yet thicker, and now its CH bonds can come into gentle contact with the polarizable π surfaces that line the host cavity. The π electrons present a thin layer of negative charge on the inside of the host, and the CH bonds a thin layer of positive charge on the outside of the guest. The upshot is an ideal congruence and complementarity of chemical surfaces.[36] The precise dimensions of any molecule are a function of what software is used, but all software shows that the space inside is less than 17 Å long and less than 8 Å wide as shown in Figure 5D. The hole at the end, as we have said, is not accessible, but what is accessible to this space? The methyl group of tetradecane is in a position to fit as is shown on the spectra in Figure 5E. But experimentally the incrementally longer pentadecane does not fit inside (Figure 5F).

There is nothing C_{15} can do to make it short enough to fit, but the methyl groups at either end of pentadecane are relatively blunt instruments. What if they are sharpened to a narrower shape? We used the narrowest of functional groups, a primarily acetylene, and found that indeed it is encapsulated: 1-pentadecyne can access the tapered ends of the capsule, and a well-resolved, first-order NMR spectrum emerges as shown in Figure 5G.

We have further probed the dimensions using primary acetylenes placed on a rigid biaryl spacer with various alkanes at the far end providing the "pressure". With the considerable pressure provided by the *n*-butyl group,[37] the acetylenic hydrogen goes deepest into the tapered space of the cavitand. Curiously, at these depths, the cavitand's anisotropy shifts the signals in the NMR *downfield*, an experi-

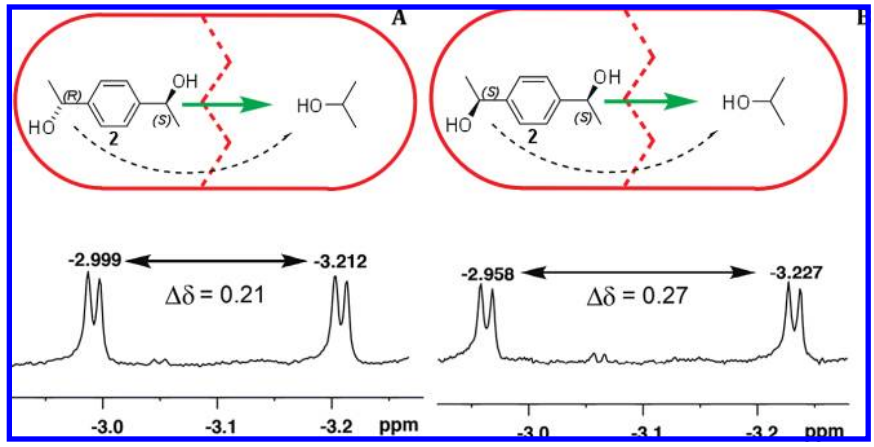


FIGURE 4. Effects of remote asymmetric centers. (A) Coencapsulation of isopropanol with a *meso* diol gives diastereotopic signals for the methyl groups of isopropanol in the NMR spectra shown. (B) The same guest coencapsulated with the homochiral diol shows different signals. The isopropanol "sees" beyond the nearby asymmetric center to the remote center. The capsule itself is achiral.

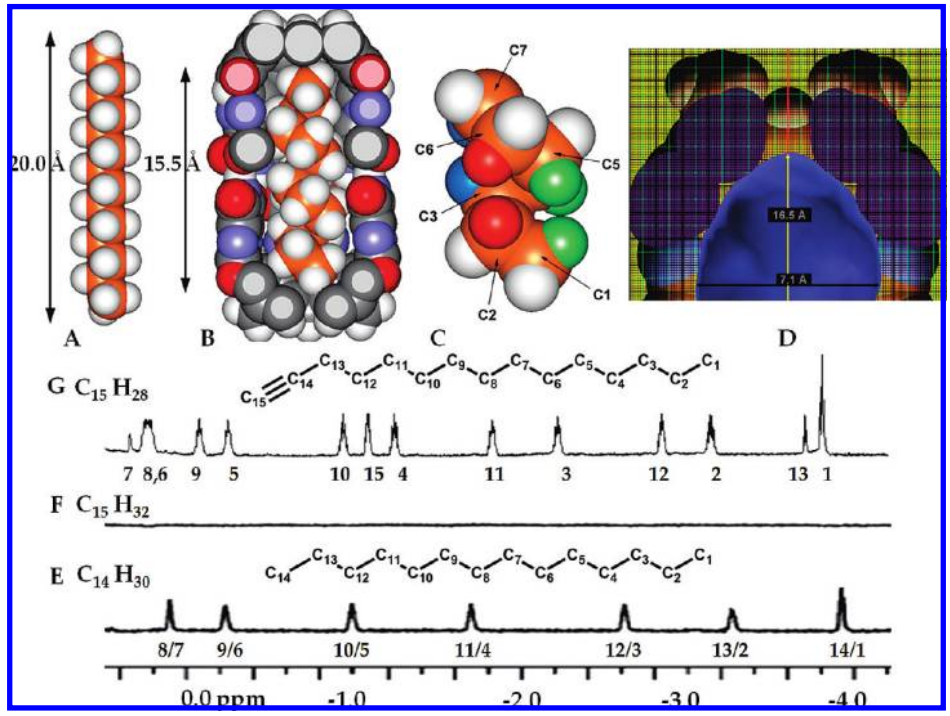
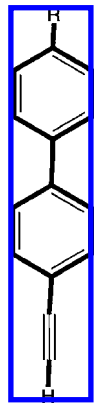


FIGURE 5. Complexes with long chain hydrocarbons. (A) A space-filling model of tetradecane in its fully extended conformation. (B) A cross-section of the capsule with tetradecane inside: the guest is coiled in a helical conformation that allows it to fit and make CH$-\pi$ contacts with the inner lining of the capsule. (C) A detail of the helix in which hydrogens on C_1 are near those on C_5 (green); the hydrogens on C_2 are near those on C_6 (red), and so on. These *gauche* interactions can be seen as the cross peaks in the 2-D NMR spectra. (D) A close-up of the cross-section of the tapered ends of the capsule through two benzene rings (purple). The larger black squares represent 1 Å^2. (E) The NMR spectrum of encapsulated C_{14}, shows first-order features. (F) No upfield signals are seen with C_{15} because it does not fit. (G) The corresponding spectrum of the primary acetylene, pentadecyne. It can fit because the narrow, primary acetylenic hydrogen can access the tapered end of the capsule.

mental result that confirms the predictions of the nucleus-independent chemical shifts developed by Schleyer.[38] This trend is shown in Table 2.

One of the consequences of the internal pressure was its effect on the expansion of the original capsule. We found that glycolurils would insinuate themselves between the two halves of the capsule to give a new extended version shown in Figure 6. Quite unexpectedly, four glycolurils were inserted.[39] Moreover, they were inserted in a manner that led to a chiral assembly. The increased dimensions of the assembly allowed tetradecane to be taken up in its fully extended or relaxed form, and even longer normal alkanes were encapsulated (C_{15}, C_{16}, C_{17}, C_{18}, and C_{19}). With the longer alkanes, the effect on the spectra included broadening of the signals indicative of a dynamic process taking place on the NMR time scale. The diastereotopic signals for the geminal methylene

TABLE 2. Chemical Shifts of Acetylenic Hydrogens for Encapsulated Biphenyl Structures



R	$-\Delta\delta$ (ppm)
H	4.7
C_2H_5	4.24
C≡CH	4.16
$CH_2CH_2CH_3$	3.6
$C(CH_3)_3$	3.37
$CH_2CH_2CH_2CH_3$	3.44

hydrogens coalesced as the samples were heated, and this can only be accomplished if the capsules are racemizing, that is, if the enantiomeric assemblies are interconverting. This gives a crude measure of the "pressure" inside the capsule.[40] The racemization is most easily accomplished if the rotation of all four glycolurils occurs in a more or less concerted fashion as implied in the figure (e.g., from panel B to panel C in Figure 6). This motion creates new hydrogen bonds as old ones are broken and is energetically less costly than a complete dissociation and reassembly of the extended capsule. The intermediate proposed in Figure 6C is achiral and *longer* than either enantiomer. Consistent with this interpretation, the larger and more compressed guests show faster racemization

TABLE 3. Energetics of Extended Capsule Racemization with Compressed Alkane Guests

alkane	$\triangle G^{\ddagger}$ (kcal/mol)	T_c (K)
$nC_{16}H_{34}$	>22	
$nC_{17}H_{36}$	17.2	365
$nC_{18}H_{38}$	16.7	350
$nC_{19}H_{40}$	15.7	330

of the capsule, since they force the assembly toward the achiral intermediate. The trend is shown in Table 3.

Can the extension of the capsule be reversed? A glycoluril was prepared bearing remote basic sites provided by the dibutyl aniline groups shown in Figure 6A. This glycoluril also assembled around tetradecane in its relaxed, extended conformation. When HCl was bubbled into the NMR sample, the anilines became protonated, the glycolurils precipitated, and the original cylindrical capsule was regenerated in the NMR tube. This, of course, encapsulates the coiled, compressed version of tetradecane. The same NMR tube can then be treated with trimethylamine: The glycolurils are deprotonated; they reenter the solution and insert into the capsule to give the extended capsule and fully relaxed tetradecane. The effects of the cycle are modeled in Figure 7. As many as six acid/base cycles could be completed in the same NMR tube before the buildup of solid trimethylamine hydrochloride deteriorated the resolution of the NMR spectra. The compressed alkane is a notional spring-loaded system that operates the under the control of acid−base chemistry.[41]

A curious observation led to the study of the other effects of the shape of the capsule on the guests. *trans*-Stilbenes are not highly fluorescent at the best of times but do show intense fluorescence in constrained environments provided by, for example, antibodies.[42] We found that *trans*-stilbene in the

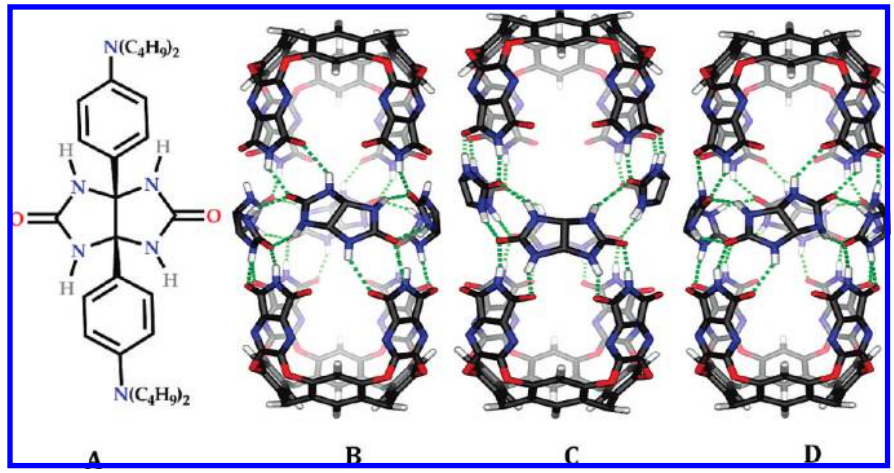


FIGURE 6. Extension of the capsule. (A) The glycoluril spacer bears remote, weakly basic nitrogens on the benzene rings. (B) Insertion of four glycolurils into the seam of hydrogen bonds gives a chiral assembly. (C) The slightly extended intermediate postulated in the racemization of the capsule is achiral. (D) This structure is the mirror image of the one in panel B. Compressed alkanes inside the capsule exert pressure and increase racemization rates. Peripheral groups have been removed for viewing clarity.

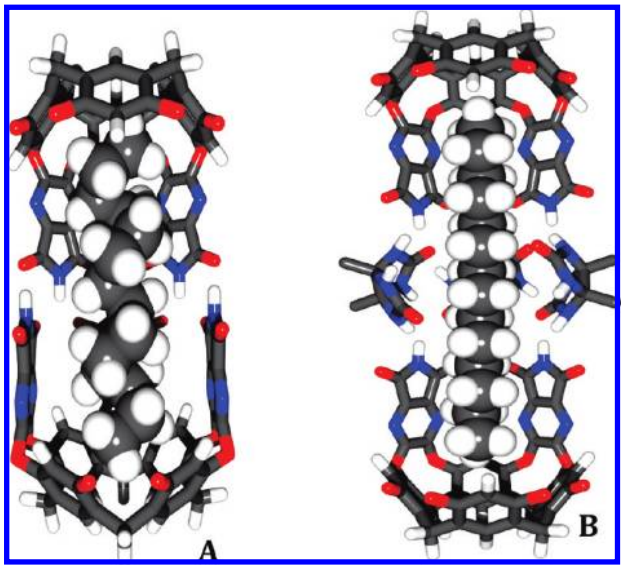


FIGURE 7. The two states of tetradecane in a spring-loaded device. (A) The compressed tetradecane is coiled in the original capsule. (B) The fully relaxed form of the guest exists in the extended capsule. The two states can be controlled by the addition of acids and bases. The acids protonate the glycolurils, which precipitate and generate the shorter capsule with the compressed C_{14} inside. Some capsule walls have been removed for viewing clarity.

cylindrical capsule showed quenched fluorescence, an outcome that was unexpected. A mere glance at Figure 8 suggests what may be the cause. Aromatics in either half of the capsule find their lowest energies when they are positioned diagonally in the square cross-section of the cavitands. As a result the two benzenes of the stilbene must be twisted some 45° in their ground states. Accordingly, if fluorescence needs to lead to a ground state, in this capsule it cannot lead to a fully coplanar ground state and is therefore quenched.[43]

As was seen in Figure 6, the extended capsule has the two square prisms of the cavitands back in register, that is, fully aligned. A guest such as stilbene inside can be either coplanar (where it is at lower energy due to resonance) or twisted at 90° in its ground state. With suitable substituted stilbenes that fill this space, it should be possible to recover the fluorescence in the extended capsule. As was the case with the alkane in the spring-loaded system, it may even be possible to turn the fluorescence of stilbenes on and off under the control of acids and bases.

At best, it is improper to mention "phase" when only a few molecules are involved, but the behavior of encapsulated liquid guests differs from that of solids or gases. Gases as guests within these capsules produce another kind of "pressure" that can be examined. When cyclopropane is bubbled into an NMR solution of the capsule in mesitylene, three guests are seen inside as in Figure 9. Moreover, because these are relatively small, some exchange of positions takes place on the NMR time scale.[44] Now, given the number of guests and the space, it is trivial to do a calculation of the pressure inside using the ideal gas law. This calculation gives some 270 atm, a ridiculous value given that the cyclopropane is merely bubbled into the solution at about 1 atm. Despite the absurdity, there is "pressure" involved because addition of the glycolurils allows the system to relax and now four cyclopropanes are taken up. The calculated pressures are still huge. Calculations using the van der Waals approximation give pressures that are even higher. Recall or be informed that this approximation takes into account the volume occupied by the gases whereas the ideal gas law treats them as point masses having elastic collisions with the walls. The ideal gas laws clearly do not apply here an because there are *attractive* forces between the gases and the walls. This is also the case with many metal−organic frameworks where the walls are made up of large panels of aromatic surfaces, and it is likely also to be the case if and

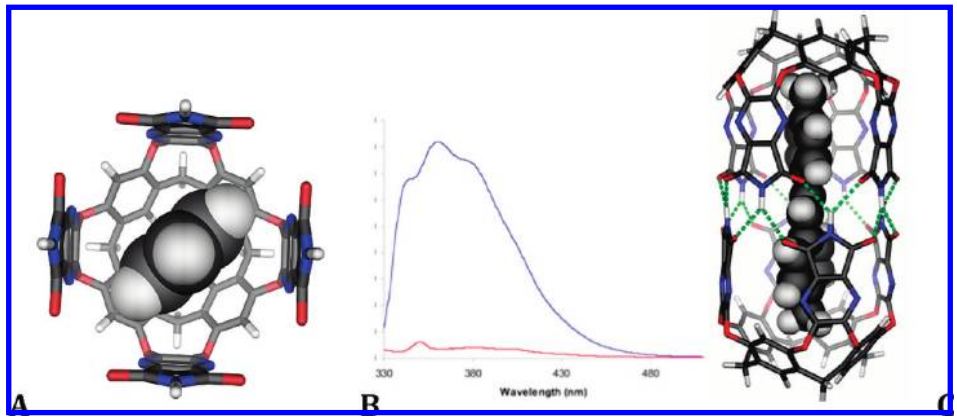


FIGURE 8. Photophysics of stilbenes in the capsule. (A) The lowest energy position of an aromatic such as benzene in one end of the capsule is along a diagonal. (B) The fluorescence spectrum of free stilbene in solution (blue trace) and stilbene inside the capsule (red trace). (C) A model of dimethyl stilbene in the capsule shows that the molecule is twisted in its ground state, with both benzenes arranged along diagonals. The noncoplanar conformation of the encapsulated stilbene may cause the quenching of its fluorescence.

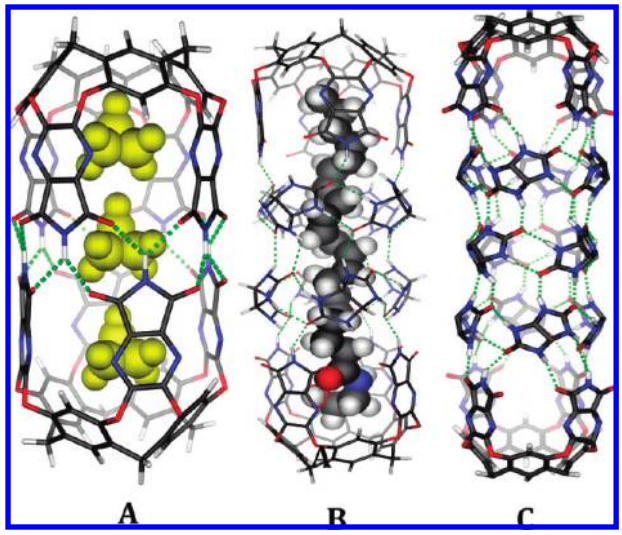


FIGURE 9. Three types of capsules. (A) The original capsule with three cyclopropanes inside. Ideal gas laws calculate a pressure of nearly 300 atm. (B) The ethanol amide of arachidonic acid (anandamide) is modeled inside a capsule with two belts of glycoluril spacers. (C) A hyperextended assembly with three belts of glycoluril spacers is generated when normal hydrocarbon guests longer than C_{24} are encapsulated. Host/guest attractions overcome the entropic penalties of bringing 15 molecules together.

when hydrocarbon gases are absorbed inside carbon nanotubes. The collisions of cyclopropane with these walls are hardly elastic; instead they are sticky. The attractive forces lower the energies and allow the seemingly high "pressures" to be achieved inside.

Internal pressure can also be applied by even longer alkane guests or with molecules such as anandamide when excess glycoluril is present in solution. A capsule is formed that has two belts of glycolurils insinuated between the two cavitands as in Figure 9.[45] Other longer alkanes and alkynes behave the same way.[46] Moreover, two shorter alkanes can also provide this result. However, eight glycolurils are not the limit; with alkanes larger than C_{24}, it is possible to characterize a capsule that has three belts of glycolurils, and with alkanes like C_{30}, we have evidence of four glycoluril belts in the capsule.[47]

What is the driving force for these complex assemblies? Why does an alkane prefer the inside of the capsule, and how does it pay the entropic price for gathering so many components, up to 15 and counting, into a single assembly? At least two processes can be identified. The closed capsule assembly leads to the maximum number of hydrogen bonds for the glycoluril and matches the best donors with the best acceptors, so an enthalpic contribution is present. For a long chain alkane to dissolve in mesitylene, many solvent molecules must surround the alkane with π surfaces and C−H bonds in close contact. These solvent molecules are released to the bulk medium when the alkane enters the capsule, so there can also be an entropic advantage. However, the analysis of the energetics awaits more direct measurements by, for example, calorimetric methods. For now, the exploration of shape space and the molecules that are confined in them continues to open new frontiers.[48]

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BIOGRAPHICAL INFORMATION

Julius Rebek, Jr., was born in Hungary in 1944 and lived in Austria from 1945 to 1949. He and his family then settled in the U.S.A. in Kansas. He received his undergraduate education at the University of Kansas in 1966 and obtained a Ph.D. degree from the Massachusetts Institute of Technology (1970) for studies in peptide chemistry with Professor D. S. Kemp. As an Assistant Professor at the University of California at Los Angeles (1970−1976), he developed the three-phase test for reactive intermediates. In 1976, he moved to the University of Pittsburgh where he rose to the rank of Professor of Chemistry and developed cleft-like structures for studies in molecular recognition. In 1989, he returned to the Massachusetts Institute of Technology, where he was the Camille Dreyfus Professor of Chemistry and devised synthetic self-replicating molecules. In July of 1996, he moved his research group to The Scripps Research Institute to become the Director of The Skaggs Institute for Chemical Biology, where he continues to work in molecular recognition and self-assembling systems.

FOOTNOTES

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