Host–guest chemistry of calixarene capsules

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Reversible encapsulation is one of the more recent forms of molecular recognition. Small molecule targets are completely surrounded by larger molecular assemblies and steric barriers keep the guest from escaping the host. Calix[4]arenes make useful modules for capsule construction and the review traces their history. Applications in physical organic chemistry, materials science and spectroscopy are described.

Calixarenes are widely used modules in supramolecular chemistry but I was avoiding them. After all, there were (and still are) a good number of superbly capable research groups busy with these molecules. Their work has generated hundreds of original journal articles, extensive literature reviews and whole monographs; I did not intend to disappear in this avalanche of paper. But here I am, tossing another snowball on the heap, writing more about them. What changed my mind was the imagination and skill of a graduate student, Ken Shimizu. He presented me with an accomplished fact: a calixarene that formed an encapsulation complex. No one else could have arrived at the same molecules, we thought—but that was a colossal illusion.

Ken was working in aspects of molecular recognition chemistry involving cleft-like synthetic shapes and he possessed a keen eye for molecules with curvature. At that time more than half of the research group was involved in self-assembling systems, particularly hollow, pseudo-spherical structures, and he set out to invent his own version. Instead of carving up the sphere into a pattern of, say, a tennis ball, Ken felt that a simpler, hemispherical division would lead to a fertile formula for assembly. For this he needed a bowl-shaped molecule that could be usefully functionalized on its rim. He found it in calixarenes[1] when they are in the so-called 'cone' conformation (Fig. 1).

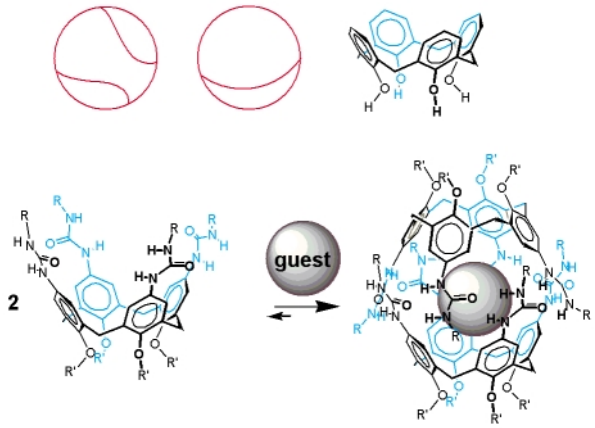

Fig. 1 *Top*. Ways of dividing a spherical surface and the curvature of a calix[4]arene in a cone conformation. *Bottom*. The calix[4]arene bearing ureas on the upper rim forms a dimeric capsule when an appropriate guest is present.

This conformation features a gentle curvature on its molecular surface that can be enforced and maintained by placing sizable groups on the lower rim, on the phenolic oxygens.[2] The cavity left by this shape is what matters; if the calixarene were constructed from CPK models then filled to the brim with, say, a quick-setting plaster,[3] then the hardened material, when removed, would resemble not so much a cone as it would (in miniature) the great pyramid at Giza. The cone descriptor was devised by Gutsche[1] whose heroic synthetic studies have resulted in calixarenes being articles of commerce. In addition, Böhmer,[4] Ungaro,[5] Shinkai,[6] de Mendoza[7] and others have worked out the synthetic protocols and the many conformational possibilities of calixarenes. I am grateful to the advantages their work gave us latecomers.

Shimizu's idea had been to bring two of these calixarenes together, rim-to-rim, and the enduring fashion in the group was to use hydrogen bonding patterns on self-complementary molecules to accomplish this. The moderate directionality and reversible formation of hydrogen bonds had been successful in other ongoing projects and Ken used the nature of ureas to nurture a seam of hydrogen bonds between the hemispheres. A circle of eight ureas, four from each hemisphere, assembled head-to-tail as shown in Fig. 1. This directionality leads to a reduction of symmetry (at least on the NMR timescale) and no planes of symmetry are present in the dimer: the two meta protons of the benzene units are now in different magnetic environments. It was the coupling constant between these protons that gave away the structure.

When I first lectured about this work at a conference in Jerusalem in the summer of 1995, I was disappointed to find that the calixarene capsule was greeted with some skepticism. Two other groups had already made molecules having all the functional aspects of Ken's, but had not recognized them to be dimeric capsules. Volker Böhmer proposed that we look for

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meta coupling in our systems, as predicted by a dimeric structure, and indeed, there was. Böhmer subsequently published his capsular system,[8] about which more later. David Reinhoudt favored a 'pinched cone' conformation but eventually described the cone conformation for anion detection with his urea and sulfonyl urea calixarenes.[9]

Even though the NMR spectra in solvents such as $CDCl_3$ were consistent with the formation of a dimeric capsule, it was not until Shimizu detected a guest inside the capsule that we were confident enough to publish this work.[10] First, it was necessary to solve the solvent problem and the solution was, well, in the solution. Still and Chapman[11] had shown that concave surfaces into which solvents do not fit tended to show high affinities for other small molecules that do. This scenario was staged by the use of solvents that are too large to be accommodated in the concavity, provided that they still dissolved the components of the system. These observations concerning solvent size *vs.* cavity size are generally applicable to encapsulation phenomena and we have used them extensively. For the case at hand, it meant that solvents such as $CDCl_3$ that are excellent guests for the cavities, are reluctant to leave the cavities to solutes. After all, the solvent at ~10 molar concentration has a seemingly insurmountable advantage. To make matters worse, trace impurities in the solvents can provide stoichiometric amounts of excellent guests. For example, a solvent like deuterated *p*-xylene, for which modeling suggested an uncomfortably tight fit, was easily displaced by simple aromatics. Benzene, for example, fits well and when it is added to such a solution a new resonance in the NMR spectrum appears, a sharp singlet at *ca.* 4 ppm. The benzene oozes into the cavity over the course of about an hour. But when the deuterated xylene solvent is subjected to fractional distillation to remove deuterated benzene contaminants, the added benzene guest enters rapidly.

A different approach to the dimeric nature of the capsule was provided by Böhmer. He showed that mixing two very similar calixarene dimers gave a heterodimeric system.[8] Shortly thereafter, Böhmer took all of the doubt out of things by providing an X-ray crystal structure[12] with the hydrogen bonds of the capsule clearly defined, and a benzene guest inside the capsule to boot.

Solubility is an ever-present issue for our self-assembling systems. For the calixarenes we enhanced it by attaching large groups, such as benzylic groups, to the lower rim and alkyl-substituted aromatics along the ureas of the upper rim. Nowadays, we use *p*-*n*-heptylphenyl, but in the early days the best peripherals were tolyl or even normal alkyl chains. Even with these appendages low solubility in our favorite (large) deuterated solvent, *p*-xylene and the pricey (largest) mesitylene often thwarted our encapsulation attempts. To this very day we suffer the neglect of commercial concerns for our need of larger, deuterated solvents.

Our studies centered around what types of guests could be ushered in. Because of the unusual shape of the cavity (two square pyramids rotated at 45° from each other) we tried some correspondingly exotic shapes (Fig. 2). Phil Eaton provided us with a generous sample of cubane and it proved to be an excellent guest. Halobenzenes, especially fluorobenzenes were also readily encapsulated and gave us some information about their orientation when trapped within. For example, in fluorobenzene the chemical shifts of the *ortho*, *meta* and *para* protons suggest a positioning in which the C–F bond and the *para* proton are along the equator (a polar microenvironment), directed at the seam of hydrogen bonds.[13] A semantically challenging situation arises in the description of these capsules since the 'poles' are not polar but the equator is! The resonance of the *para* proton of C_6H_5F was shifted only moderately upfield in the NMR spectrum, while the *ortho* and *meta* protons, directed at the eight aromatic faces in the poles of the cavity, experience the largest upfield shifts. Blake Hamann found that even the floppy pentane is encapsulated.[14] Its terminal methyl groups appear at higher field than −2 ppm. In any of these cases, it was possible to 'denature' the system, that is, by flooding the solution with competing ureas the hydrogen bonds were disrupted and the guest was liberated. Of course, the same result can be reached by adding a solvent such as DMSO that competes for the hydrogen bond acceptors. We will discuss those experiments in due course.

During this time, Christoph Schalley and Gary Siuzdak were intent on characterizing the capsules in the gas phase. Historically, it has not been easy to get evidence for hydrogen bonded assemblies through mass spectrometry, since the protic solvents required for protonation tend to disrupt the very hydrogen bonded aggregates that one wishes to detect. A number of static tactics have been used to overcome this problem: labeling with alkali ions by covalently attached crown ethers,[15] cation–π complexes with silver ions and suitably arranged aromatics,[16] and even anions[17] appended to the assemblies have been useful. Schalley tested various organic cations and found that the *N*-methylquinuclidinium ion was an excellent guest for the calixarene capsules, both in solution and in the gas phase. This ion acts simultaneously as a guest and an ion label. Moreover, this guest is one of the best for the calixarenes, it even competes with solvent chloroform for the interior of the capsule.[18] Cation–π interactions provide the driving force. Schalley used this ion in a number of contexts including heterodimerization experiments[19] and with a covalently bound capsule, discussed below.

A number of other functional groups were attached to the upper rims of the calixarenes then screened for capsule formation. One of these led to a discovery that had far-reaching consequences for our program. Ron Castellano and Professor Byeang Hyean Kim made a sulfonyl urea derivative,[20] similar to one earlier reported by Reinhoudt.[9] It was characterized as a capsule, but in the presence of a aryl urea capsule, disproportionation took place in an exclusive manner: only the heterodimeric system was observed by NMR! Probably the superior acidity of the sulfonyl urea finds its counterpart in the

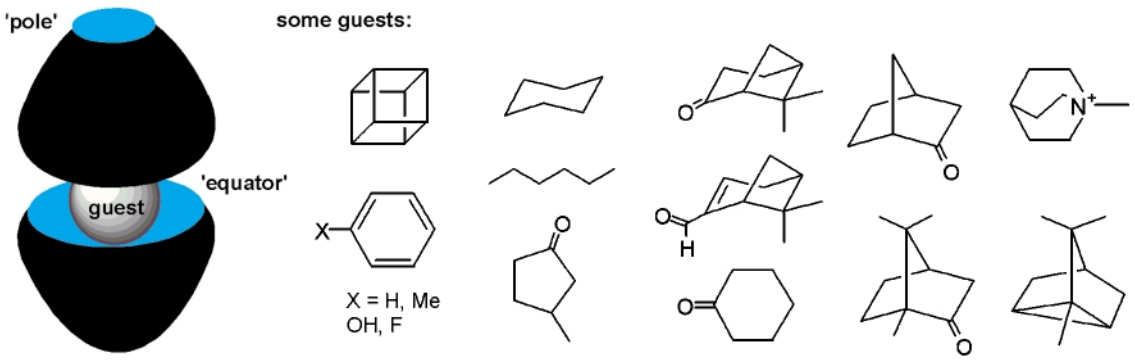

Fig. 2 *Left.* Cartoon representation of the calixarene capsules used elsewhere in this review. *Right*. Some of the many guests encapsulated by these dimers.

basicity of the aryl urea, but there must be other intermolecular forces involved since simple alkyl ureas do not show the same tendency to heterodimerize. Whatever the cause, this phenomenon helped us characterize a number of systems of increasing complexity (Fig. 3). For example, using a 1,3,5-trisubstituted aromatic spacer, we were able to observe an assembly in solution that was capped by three sulfonyl ureas.[21] This is one of the most complicated assemblies we have prepared to date; it consists of seven molecules – the centerpiece, three caps and three guests. It maintains its structure in solution and in the gas phase when quinuclidinium is the guest.

The calixarenes also allowed us to explore the practical differences between covalently bound molecules-within-molecules, carcerands[22] and reversibly formed capsules.[23] Independently, Sherman was pursuing this very line of inquiry using resorcinarene-based systems.[24] The question dealt with whether or not we could combine the best aspects of assembly—reversibility and stability—but side-step the worst aspects—lengthy syntheses and solubility problems—with capsules that were hybrids. In both approaches, the tactic was the same; to covalently attach two of the bowl-shaped molecules at their upper rims in such a way that they would still form a capsule. For the calixarenes, a tether was needed that was long enough to reverse the seemingly divergent directions, and yet short enough to minimize the problems posed by entropy. Marcus Brody arrived at the hexyl tether since it modeled well and provided the distance needed to span the two hemispheres without causing an undue amount of entropy loss from the methylenes of the chain. The synthesis was uneventful, following well-trodden paths.[25] Happily, he found enhanced stability for the new molecule (Fig. 4). It was loathe to miscengenate with other aryl substituted ureas at comparable concentrations; it neither dimerized nor polymerized, but it could be forced to heterodimerize with excess sulfonyl ureas. The product favored at equilibrium was a dumbbell-shaped assembly that featured five molecules. Again, it was characterized both in solution and in the gas phase as its quinuclidinium complex.

The capsule exists as a pair of enantiomers but we expected very little in the way of entantioselective recognition from such a system. After all, the chirality exists in the lining, in the seam of the hydrogen bonds, as a clockwise or counter-clockwise arrangement with respect to the tether. The tether is largely external and cannot reasonably be expected to influence binding events inside. The longer-term significance of this molecule is that the tether also provides a place for covalent attachment of an entire capsule-forming unit on, say, a solid surface. We have aims on a sensing device for appropriate guests, but this has not yet been brought to practice.

Polycaps

Self-complementary structures have fascinated us for some time as there is a certain economy, even dignity, in a molecule that recognizes itself in a predictable way. By predictable I include the contributions of crystal engineering,[26] but any molecule that enjoys a liquid or solid state does express some self-complementarity, intended or not. When the recognition surfaces are arranged in a way that all sites find their complements in a dimer, then additional possibilities arise: these self-complementary structures can give rise to the simplest molecular replicators.[27] Experiments in the Ghadiri lab have recently shown that trimeric peptide helix bundles are also capable of replication,[28] and there is no reason to exclude tetramers or higher order aggregates, even if no specific cases exist at this writing. What is certain is that recognition surfaces that diverge on self-complementary molecules lead to open-ended systems such as polymers. For some years we had been trying to realize this in the context of the capsular structures, and the calixarenes gave us the opening we were looking for.

Professor Dmitry Rudkevich and Ron Castellano used literature precedents to synthesize a calixarene tetraurea bearing

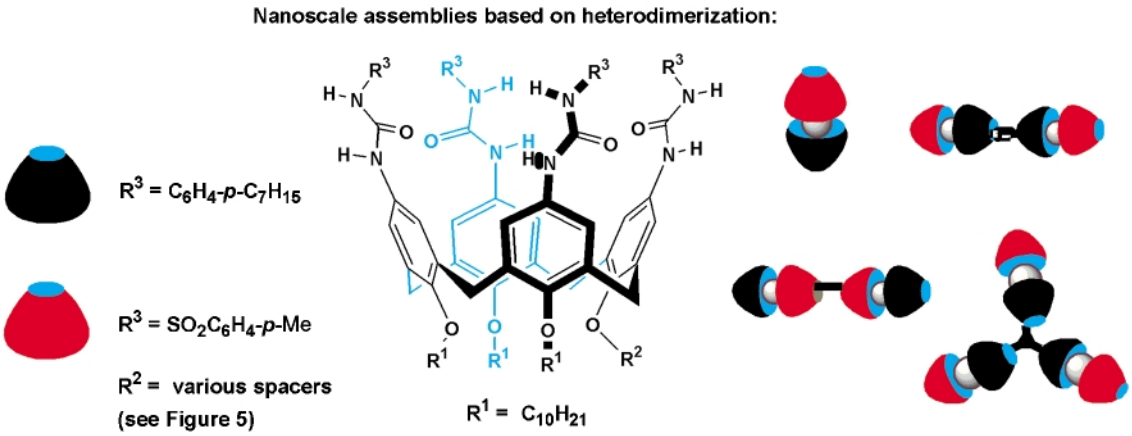

Fig. 3 Aryl and sulfonyl ureas further functionalized on their lower rims are converted into modules. Heterodimerization takes place exclusively to give predictable nanoscale assemblies.

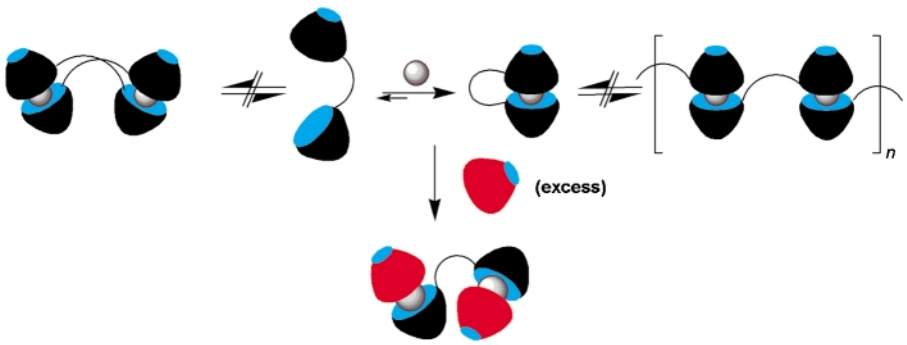

Fig. 4 Covalent connection of the two hemispheres at their upper rims now leads to capsules in an intramolecular sense. Neither 2+2 dimers (top left) nor polymers (top right) are formed. However, with excess sulfonyl functionalized calixarenes a dumbbell-like shape is favored (bottom).

a unique site for functionalization on the lower rim. This had already been accomplished elsewhere[29] to anchor alkali and alkaline earth ions to a calixarene platform. Dimerization of this molecule was as expected but gave us a taste of the complex flavors of isomerism that lay ahead. For example, two regioisomers of the capsules exist and there are unique environments for all 8 (downfield) N–H resonances in each! Nonetheless, they are not very different; these 16 urea resonances appear within 0.1 ppm of each other in the NMR spectrum. Two of the monomeric calixarenes were duly linked through amide bonds to relatively short spacers (Fig. 5).[30]

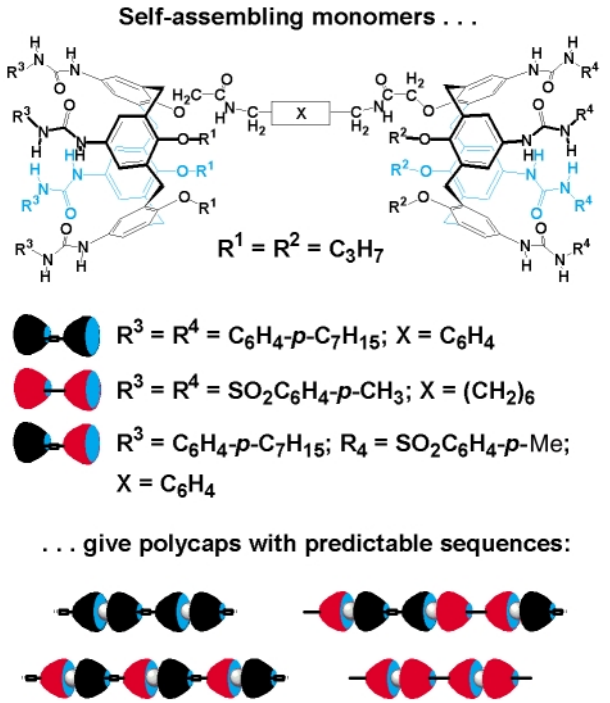

Fig. 5 Heterodimerization preferences lead to predictable polymer sequences from either complementary or self-complementary subunits.

Consider, now, the assembly of such a unit in a linear polymeric array. Capsules appear like beads on a string, and each site is at a characteristic distance from the end of the polymer. At first glance, one might think there is symmetry about the center of the supermolecule, but the two halves of each capsule are different, each cavity is chiral, that is, the head-to-tail arrangement of ureas is either clockwise or counterclockwise at each capsule. For a string of, say, 100 units the number of isomers due to chirality and regiochemistry approaches 4^{100}. This figure is many times greater than the total number of molecules in the sample (or on earth, for that matter). The symmetry must be broken as described by Eschenmoser.[31] That we were able to observe and interpret the signals for the polycaps and their encapsulated guests was a triumph of high resolution NMR.

The polymeric assemblies do show broadened NMR spectra but the positions of the resonances matched very closely those of simpler model (dimeric) capsules. Addition of guests resulted in the emergence of new signals, and the encapsulated species showed up right where we expected them. The reversibility of the polymerization was readily established: for example, a few % DMSO added to the $CDCl_3$ solvent gave a system that contained roughly equal amounts of monomer and polycap. When a good guest like *p*-difluorobenzene was then added, the growth of a new polycap species was evident at the expense of both the monomer and the original (solvent-filled) polycap.

A linear polymeric capsule can be of any length and we attempted to determine the length with size exclusion or gel-permeation chromatography. The polycaps proved to be at the limits of the sensitivity of our columns, and the technique, but we have been fortunate to recruit Professor George Benedek and Aleksey Lomakin to address some physical aspects of these systems. They are presently unraveling the complex questions regarding polymer length, individual association constants of the polycaps and their effect on reptation, that is, the entanglements often encountered in covalently bound polymers. The reversible formation of the polycaps may allow ideal, untangled arrangements to form. In the meantime, we note that there are not many examples of reversibly-formed, hydrogen bonded polymers.[32] The uniqueness of the systems at hand have to do with their ability to function as capsules as well as polymers.

The formation of heterodimeric systems was likewise explored by 'end capping' experiments. Specifically, the polycap rapidly broke down to a dumbbell-shaped assembly when treated with an excess of the simple dimeric capsule. The dumbbell featured a sharply resolved NMR spectrum that showed all of the expected resonances. A version capable of cross-linking was also prepared. This was based on a spacer derived from a symmetrical 1,3,5-trisubstituted benzene to which three of the monofunctionalized calixarenes described earlier[21] were attached. The polycap here was insoluble in all of the solvents in which it assembled, but the monomer proved useful in nucleating other complex assemblies.

Let me now describe the long-range order of these polycaps. Colin Nuckolls and Ron Castellano felt confident that the polycaps could be forced into increasing order, for example, into liquid crystalline phases, if the appropriate modifications were made on the surface of the structures. Accordingly, the monomers were outfitted with long alkyl chains that provided a liquid-like sheath around the polymer chains; this helps fill the space between the chains. The resulting polycaps (at high concentrations) showed birefringence patterns when viewed between crossed polarizers and gave typical Schlieren textures.[33] These textures reflect the morphology of the liquid crystals and were found to be a function of what guest was inside. Lyotropic, nematic liquid crystalline phases were generally observed with the polycaps. The characterization was done by our collaborators: Holger Eichhorn in Timothy Swager's lab at M.I.T. and Andrew Lovinger at the Bell Labs. Typically, molecules like difluorobenzene and nopinone were readily encapsulated in these liquid crystalline phases. Further characterization by X-ray diffraction patterns showed peaks at 2.4 and 1.6 nm that match well the repeat distances and the dimensions of the polycaps (Fig. 6).

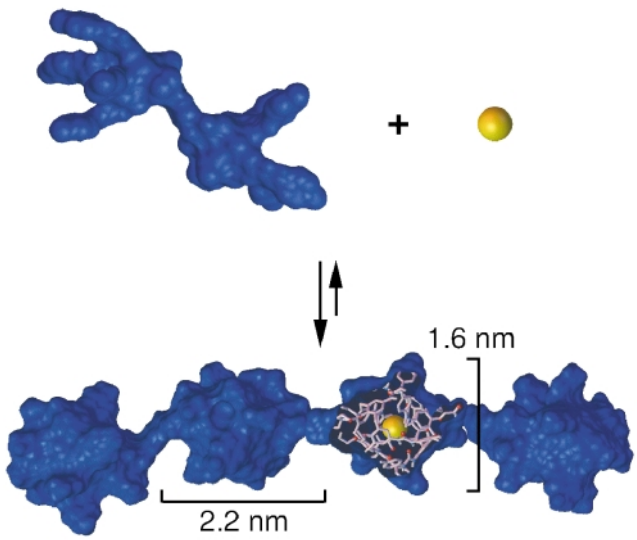

Fig. 6 Covalently-linked calixarenes form polycaps in the presence of a suitable guest.

It was also possible to show that external, mechanical forces can be used to further organize the liquid crystalline phases. For example, shearing gave fibers that showed a uniform width of about 6 μm when viewed through a confocal microscope. Macroscopic samples were also prepared. Specifically, fibers from liquid crystalline samples could be pulled to cm lengths. This ability to draw fiber structures from polymeric liquid crystals is also characteristic of other hydrogen bonded polymers.[34] In short, a hierarchical ordering of the molecules that ranges from the Å to the cm scale is at hand. Whether we are able to find applications for these liquid crystals that have encapsulated guests is not yet clear. After all, liquid crystals are a dime a dozen (or worse, a dime a pound) and our polymeric capsules cost a bit more.

While we started this discussion praising the virtues of self-complementarity, the heterodimerization that we discussed between the sulfonyl ureas and the aryl ureas took us a long way in ordering assemblies. There is another way heterodimerization became an advantage and that dealt with chiral derivatives. The calixarene tetraureas derived from norleucine in its optically active form showed a very high preference for forming heterodimers with the parent aryl urea. Within these the head-to-tail arrangement of the eight ureas appeared entirely to be oriented in one direction. In other words, the peripheral point chirality of the amino acid was being transmitted to the capsule's lining (Fig. 7). This heterodimerization was shown to

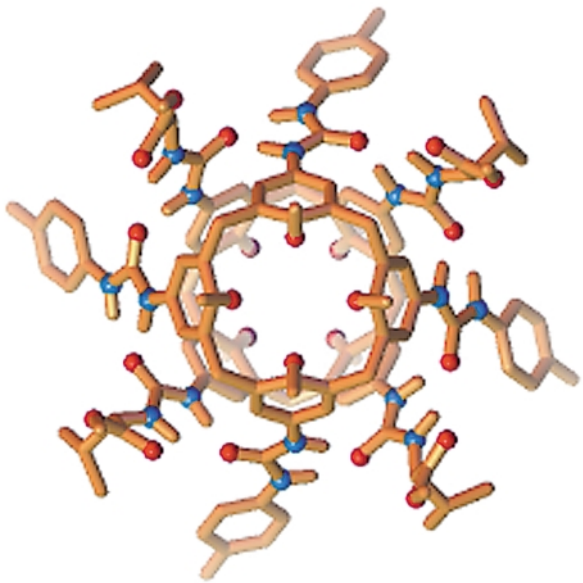

Fig. 7 The heterodimer formed between a tolyl urea and a chiral urea (L-valine) as viewed from one of its poles.

be exclusive with other amino acids that have β-branched side chains, like isoleucine and valine.[35] Circular dichroic spectroscopy was used to assign the absolute configuration of these capsules. The side chains of the amino acids provide contacts that are vital in the dimeric assembly and eventually lead to instruction of the clockwise or counter-clockwise arrangement of the ureas.

Do these asymmetric microenvironments distinguish between enantiomeric guests? They do, but to date only modestly. For example, with norcamphor as a racemic guest, the heterodimer shows two sets of assemblies and there is about a 15% excess of one diastereomeric complex. With smaller guests such as 3-methylcyclopentanone encapsulation occurs, but no enantioselective binding is observed. So the many asymmetric centers in these molecules do not necessarily translate into an outrageously chiral space. Rather, as is the case with cyclodextrins, the bumps and dimples of the lining of these capsules are smoothed over by the large number of their subunits. On the positive side, the heterodimerization systems that have emerged out of the studies of sulfonylureas and β-branched chiral ureas represent forms of molecular instruction. They have parallels in base pairing in double-stranded DNA. All of the bases can—and to some extent, do—homodimerize, but the appropriate heterodimers are far more stable.[36]

Polymeric systems based on heterodimerization capabilities of the capsules were also explored by Ron Castellano. For example, the alternating urea/sulfonyl urea polycap was made as was the system in which each subunit had one urea and one sulfonyl urea at each end. Both of these systems gave nearly the same NMR spectrum. The instructions for heterodimerization represent a vehicle for information in these systems, and it becomes possible to consider an informational polymer based on these molecules. For example, consider a backbone along which the calixarenes may be appended. One of the simplest constructs is an amino acid that has the calixarene as the side chain. Such a system was duly made[37] and is recognizable as a quite large amino acid (Fig. 8). The intent was to build a ladder-like polypeptide molecule capable of pairing, wherein the sequence of ureas and aryl ureas could be read by an opposite strand, very much like a sequence of a nucleic acid is read by the complementary strand. Would such a system show pairing? Our early characterization of the molecule answers this question in the affirmative. Specifically, the dipeptide analog was prepared and characterized as a self-complementary dimer, but the molecules have become so large that their characterization, even for the simplest cases, has become unmanageable by the conventional techniques we have at hand.

A third and independent means of establishing heterodimerization comes from Ron Castellano, Colin Nuckolls, and Stephen Craig's recent experiments with fluorescence resonance energy transfer, or FRET (Fig. 9). Two different dyes are placed on each of the lower rims of two different calixarenes and only when they are held in a heterodimeric capsule are the dyes close enough together to permit energy transfer.[38] Excitation of the donor ($h\nu$) results in two colors of emitted light: one fluorescence band at the donor emission wavelength ($h\nu'$), and a second at the acceptor emission wavelength ($h\nu''$) that signals the noncovalent union of three species—donor, acceptor and guest. By monitoring these wavelengths, assembly and dissociation processes can be observed in real time.

The FRET process allows for much more than just *detection* of the heterodimer; the kinetics and thermodynamics of the assembly can also be determined. We knew that a donor sulfonyl urea **1D** would heterodimerize exclusively with an acceptor aryl urea **2A** to give a predominance of the desired complex, **1D·2A**, capable of FRET. When these species are combined, the heterodimer **1D·2A** duly forms, FRET occurs, and the acceptor emission increases until essentially quantitative energy transfer is observed. By using different stoichiometries of donor and acceptor, as well as untagged derivatives, we were able to determine association and dissociation rates under pseudo first-order conditions. The corresponding K_A's are, as expected, high—just shy of 10^9 M^{-1} for **1D·2A** in benzene. By titrating these dimer solutions with a solvent that can effectively compete for the hydrogen bonds, such as DMSO, the assembly process can be reversed, and the donor emission is restored. We believe that energy transfer fluorescence techniques may be a general means to investigate the solution behavior of related assemblies wherein association constants are high and compound availability is low.

The assembly process shown in Fig. 9 can only occur in the presence of a suitable guest molecule. In our work published to date that role is played by the solvent itself, but when the solvent is not a viable guest, then the FRET system may be a sensitive method for small molecule detection. The analytes remain chemically unmodified because they are held in capsules by mechanical as well as intermolecular forces. In the sytem with heterodimers of calixarenes functionalized with aryl ureas and amino acid-derived ureas, our initial results are promising;

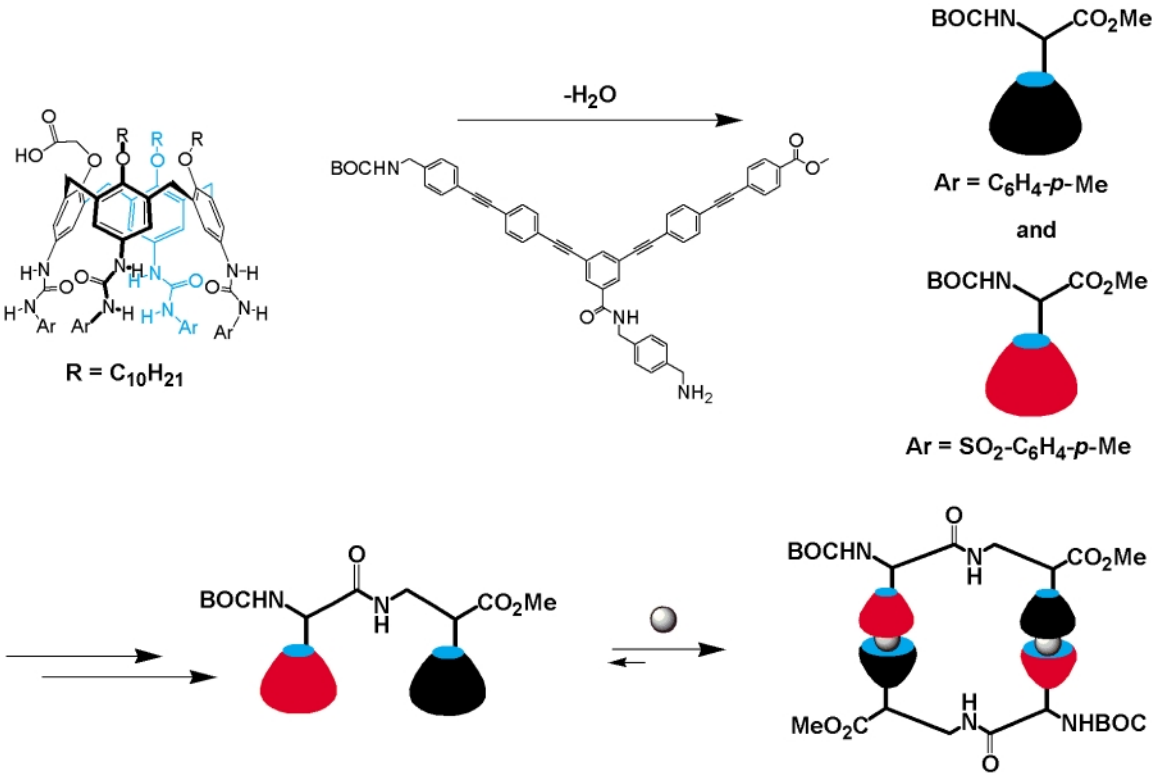

Fig. 8 A 'two bit' system. Hemispheres are placed on an extended amino acid. Heterodimerization preferences provide molecular instructions along the peptide backbone.

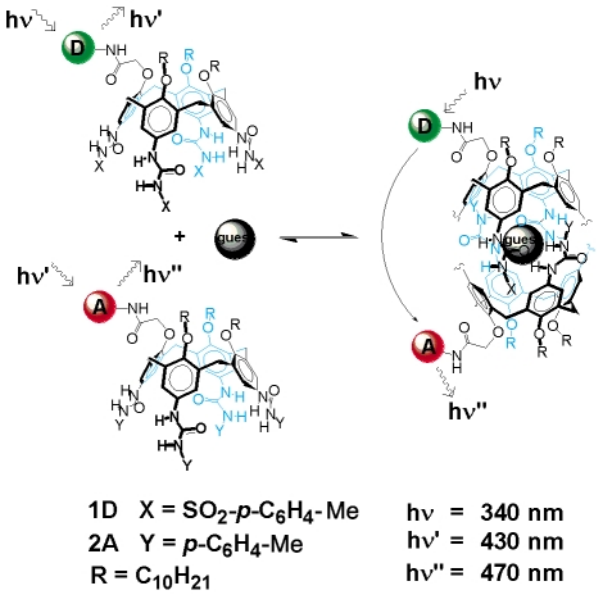

Fig. 9 The use of fluorescence resonance energy transfer (FRET) to monitor self-assembly. The two calixarene hemispheres are outfitted with energy transfer dyes; the presence of the guest nucleates the heterodimerization and allows the FRET to occur. Some ureas have been omitted for clarity.

energy transfer is observed only in the presence of the intended guest.

The molecular encounters described here are matters of timing and the timescales are huge. A normal diffusion complex lasts less than a billionth of a second, while molecules held within the carcerands[22] are confined for the lifetime of a covalent bond, typically a billion seconds. The reversible encapsulation complexes exist in the midrange of these extremes on a human-friendly timescale of 1 second, with three orders of magnitude on either side. Conventional kinetic studies concerning how guests get in and out of these capsules have been initiated and we have made some progress on the problem in the context of 'softballs'.[39] The calixarenes still pose a challenge that inspires our current efforts.

Acknowledgements

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