FEATURE ARTICLE

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Molecules that can't resist templation

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The encapsulation of molecules or ions has captured the interest of a variety of researches, including those using zeolites, fullerenes, micelles, clathrates, and metal coordination complexes. Multiple hemispherical units have been used to create organic cages that can bind guests reversibly or irreversibly. Often such cages will only form in the presence of a guest, which acts as a template. This article summarizes some of the work in this field.

Introduction

Supramolecular chemistry is highly interdisciplinary and broad in scope. It spans physics to biology, the nano to mesoscopic scale, and it entails both basic and applied research. Some of the phenomena that fall within the purview of supramolecular chemistry are self-assembly, templation, and molecular encapsulation. Examples include self-assembly of phospholipids into cell membranes, use of ammonium cations as templates to form zeolites, and drug delivery devices that encapsulate drug molecules.

Classic host–guest chemistry can be considered as a subset of supramolecular chemistry. It is focused on the development of synthetic hosts that are capable of binding guest ions or molecules. The field began with ionophores such as crowns, cryptands, and spherands, although these hosts were predated by cyclodextrins and cyclophanes (Fig. 1). Nobel Laureate D. J. Cram coined the name host–guest chemistry in the 1970s.[1] In the 1980s, about the time attention began to shift from binding ions (mostly alkali cations) to binding molecules, Cram began to develop cavitands.[2] These rigid bowl-shaped molecules derive from resorcinarenes, which are close cousins to calixarenes,[3] which were developed in the 1970s (Fig. 1). Cavitands have enforced cavities, which means they cannot collapse upon themselves. Such preorganization provides for strong binding and high selectivity, as Nature abhors a vacuum. That is, the filling of any cavity to optimize the van der Waals contacts between host and guest provide a sufficient driving force for some remarkable supramolecular chemistry.

Two or more hemispherical cavitands have been linked to form a family of spheroid compounds called carceplexes and hemicarceplexes.[4,5] Carceplexes entrap guests such that loss of guest is only possible *via* rupture of a covalent bond. Hemicarceplexes can lose guests given sufficient time and heat, but they are stable enough to be handled intact; for example, they survive chromatography. Any more kinetically facile loss of guest and the species would be considered a complex. Reversible encapsulating species, capsules, have been studied extensively by Rebek and others.[6] It should be noted that the first species topologically related to carceplexes, the cryptophanes, were reported by Collet;[7] these compounds were shown to encapsulate guests reversibly.[8]

Cram proposed the idea of a carceplex in 1983,[9] and it was such an unusual concept that many questions were raised. Could such a molecule even be made? If so, how? What would the properties of the entrapped molecule(s) and/or ions be? How could such species be characterized? Could they be made empty? Cram went on to create the field of carceplexes and hemicarceplexes, and he addressed many of these questions.[4] Reviews have surveyed the entirety of the field.[4,5] In this article, I summarize my own contributions to the field of carceplexes and hemicarceplexes, starting from the time I was a graduate student in the Cram group.

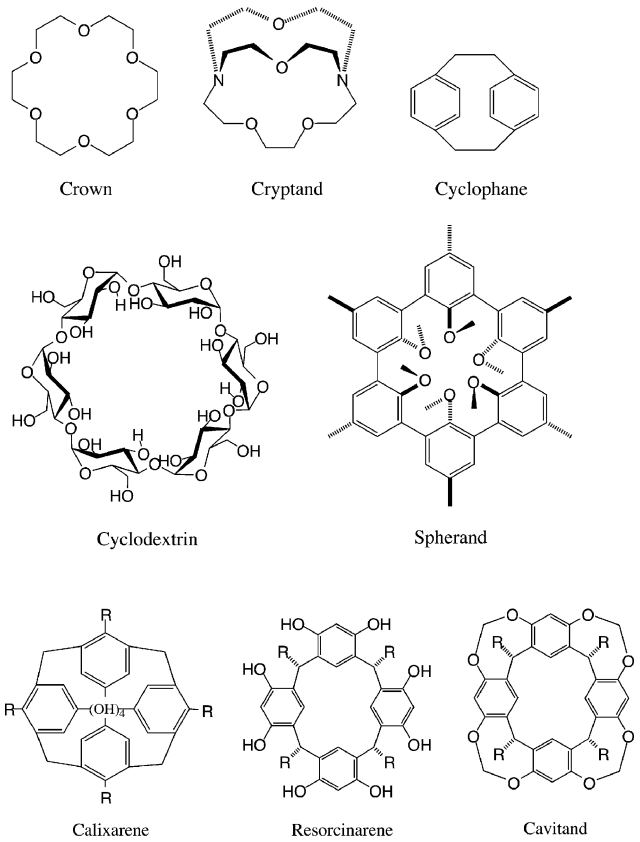

Fig. 1 Some common host molecules.

Template effect in forming carceplex 5·guest

By the mid-1980s Cram had made sulfide-bridged carceplex **3**·guest from cavitands **1** and **2** (Fig. 2).[10] The product was insoluble in the multitude of solvents with which it was washed. Characterization of this material was limited to crude mass spectrometry, elemental analysis, and other more esoteric methods. The routine tool of the organic chemist, solution NMR, was not possible, and the material was deemed to be a mixture of carceplexes containing many different ions and molecules; attendant polymer could not be discounted. Feeling that the small methyl feet in the cavitands were the culprit for the insolubility, efforts were made to incorporate larger, flexible

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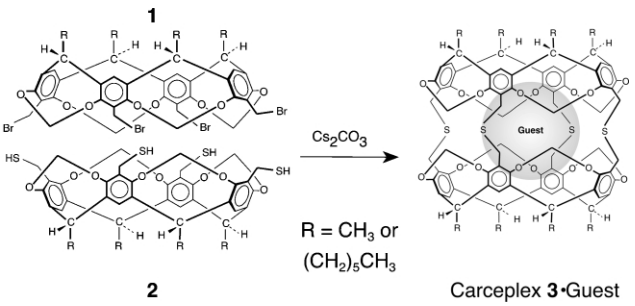

Fig. 2 Synthesis of carceplex **3**·guest.

solubilizing groups into the feet of the resorcinarenes,[11] and subsequently into the cavitands and carceplexes. Tetrol **4** was obtained by the author, and with it the bridging reaction routinely used to take resorcinarenes on to cavitands was attempted to incorporate linkages *between* two cavitands. Thus tetrol **4** was subjected to CH_2BrCl and base in a dipolar aprotic solvent. The reaction was successful and the first soluble, homogeneous, and fully characterizable carceplex, **5**·guest, was in hand (Fig. 3).[12,13] Subsequently, solubilizing groups were incorporated into cavitands **1** and **2**, and soluble versions of carceplex **3** were obtained.[14] Interestingly, the incorporation of methyl *versus* phenethyl groups into the feet of **5** have little effect on solubility,[15] whereas it is imperative to use flexible groups to solubilize **3**.[14]

As a graduate student in the Cram group, I found that dimethylacetamide (DMA) was a slightly better template for forming carceplex **5**·guest than was dimethylformamide (DMF).[13] Neither carceplex **5**·guest nor carcerand **5** could be obtained without a suitable template.[13] My research group at UBC has investigated the assembly process in forming carceplex **5**·guest in more detail. The reaction to form carceplex **5**·guest can be run in a variety of solvents, including those that make for poor templates.[16,17] Thus, template molecules can be screened using such solvents, and competition experiments can be run by pitting guest **A** against guest **B**. Relative templating abilities can be obtained *via* integration of the unique ^{1}H NMR signals of the resulting mixture of two species; no separation of carceplex products is necessary. By performing a series of such experiments, a table of *template ratios* was obtained. Template ratios represent the relative rates of the guest-determining step (GDS), the step past which no guest exchange is observed. The range in template ratios measured for **5**·guest is one million. This is a very sensitive system when one considers that it involves no ion–ion interactions, ion–dipole interactions, metal coordination, or even hydrogen bonds between host and guest. Only very weak van der Waals interactions are involved. Some striking examples from the data are: methyl acetate is 10 000 times better than ethyl acetate; 1,4-dioxane is 1400 times better than 1,3-dioxane; the best template, pyrazine, gives a 75% yield of the carceplex when present in only stoichiometric amounts (*i.e.*, 1 : 2 ratio of pyrazine:tetrol **4**) and in the presence of 10 000-fold excess *N*-methylpyrrolidinone, a poor, but suitable template.[17]

Other properties of carceplex 5·guest

The high selectivity reflected by the template ratios for carceplex **5**·guest is a manifestation of the rigidity of the cavitands. They are unforgiving to small changes in guest, which result in significant deviations from the optimal quality and quantity of van der Waals surface contacts. For example, small guests such as acetonitrile are poor templates largely because of reduced van der Waals contacts compared to (larger) superior guests. Large guests such as *N*-methylpyrrolidinone are poor due to the steric strain induced in the host upon shell closure. The potentially snug fit of large and/or ideal guests is also demonstrated by the mobility of the entrapped guests. Entrapped pyrazine has a 19 kcal mol^{-1} energy barrier to rotation about its pseudo-C_6-axis (Fig. 4).[15] This is a large barrier considering the small change in going from having the guest's nitrogens reside at the equator of the host to having its CHs at the equator. Another example is the conformational constraint put on 1,4-thioxane *via* entrapment: the energy barrier for ring-flipping in thioxane is 1.8 kcal mol^{-1} greater when incarcerated in **5** than when free in solution (Fig. 5).[18] Interestingly, this measurement is very difficult to make for species such as thioxane when free in solution because the chemical shifts of its axial and equatorial hydrogens are essentially coincident.[19] In contrast, such measurements are facilitated by incarceration because the anisotropy induced by the host creates significant dispersion in the chemical shifts of the entrapped guest. The host acts as a shift reagent and the well resolved guest signals can easily be used as handles for probing dynamic processes.

As stated earlier, the creation of an unusual compound like a carceplex raises the possibility for unusual properties, some of which were described in the preceding paragraph. Others will be discussed later after more compounds have been presented. One more novel property is mentioned here, as it pertains to carceplex **5**·guest. It was found the two cavitands that comprise the carceplex are twisted with respect to each other (Fig. 6).[20] That is, the opposing phenolic oxygens are not aligned, but are out of register about the equator by 20°. The ensuing "twistomers" are chiral as a result of their helical twist. Twistomers containing chiral guests could be distinguished by ^{1}H NMR, as entrapment of enantiomeric guests leads to diastereomeric carceplexes when the twistomers are frozen out by ^{1}H NMR at low temperature. Likewise, in frozen twistomers enantiotopic guest protons are rendered diastereotopic.[20] The energy barrier for interconversion of twistomers was found to be 12.6–16.5 kcal mol^{-1}, depending on the guest.[18] No significant diastereoselective binding was observed.

Template effect in related systems

The template effect that occurs during the assembly process to form carceplex **5**·guest was explored by looking into other systems. One was the formation of hemicarceplex **7**·guest from triol **6** (Fig. 7).[21] The template effect in forming **7** mirrored that found in forming **5**, in terms of the template ratios of the guests. Thus, the same forces are at play in forming each compound; the transition states must manifest very similar host–guest interactions. The only difference in the two species is that **7** lacks one OCH_2O linkage. The effects of this change, lower symmetry and the creation of a hole, are not important to the assembly process. The nature of the transition state was explored further as described next.

A model for the transition state of the GDS in the formation of **5**·guest (or **7**·guest) was sought. The simplest place to start

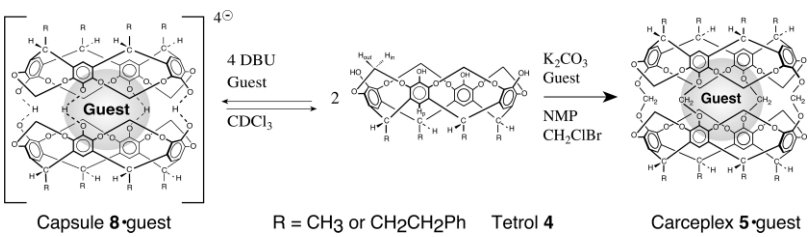

Fig. 3 Preparation of carceplex **5**·guest and capsule **8**·guest from tetrol **4**.

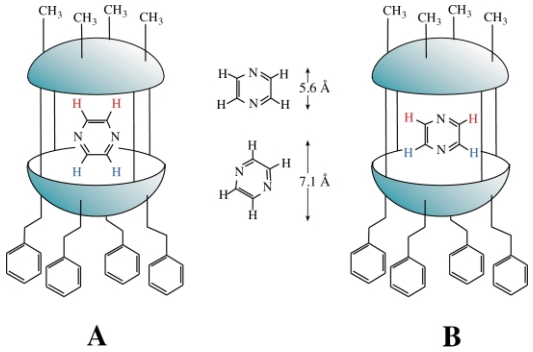

Fig. 4 Rotation of pyrazine in **5**·guest and **8**·guest. **A** is the ground state and **B** approximates the transition state.

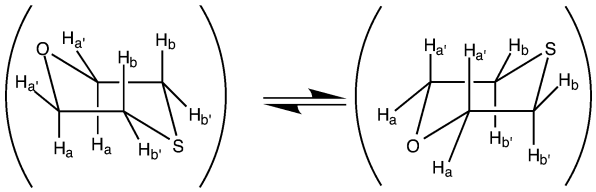

Fig. 5 Ring-flipping of incarcerated thioxane.

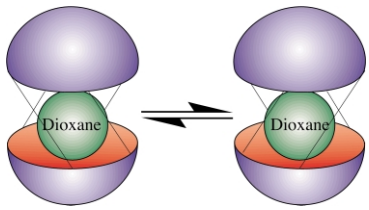

Fig. 6 Interconversion of twistomers.

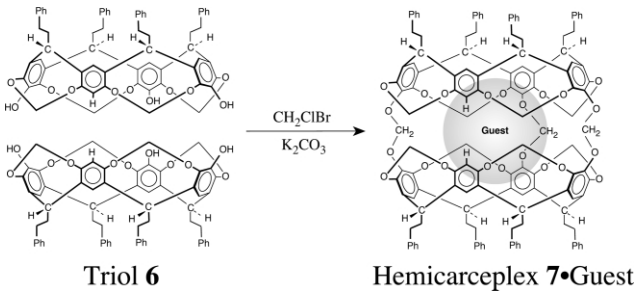

Fig. 7 Formation of hemicarceplex **7**·guest from triol **6**.

was with tetrol **4**, and indeed, complexes (**8**·guest) between tetrol **4** and guests formed in the presence of base.[22] The complexes (or capsules) formed reversibly in solution, were readily characterized by ^{1}H NMR spectroscopy, and the thermodynamic guest binding selectivities mirrored the kinetic template ratios found with carceplex **5** and hemicarceplex **7**. The capsular complexes (**8**·guest) are composed of two molecules of tetrol **4** surrounding one molecule of guest, where the two tetrols have collectively lost four protons and are thus linked to each other *via* charged hydrogen bonds. These complexes serve as simple transition state models for the formation of **5** (and **7**).[23] It turns out that a series of related complexes form, including the one based on two molecules of triol **6**, that vary in the number of charged hydrogen bonds and covalent linkages.[24] Each of these complexes can be considered a transition state model for the assembly process as each demonstrates similar guest selectivity. Our overall conclusion was that the common guest selection requires two or more charged hydrogen bonds or covalent linkages between the bowls. The assembly process is driven largely by ground state effects, meaning that binding of guest to the forming host is key, while the rate constants for the GDS are largely independent of the guest. This conclusion is based upon the similarity in the (kinetic) template ratios in forming **5** (or **7**) to the (thermodynamic) relative binding affinities in forming **8**·guest and its relations.

Since complex **8**·guest appeared to be such a good general model for assembly of two cavitands, we wondered if it would be relevant to the formation of any hemicarceplex based on tetrol **4**. For example, how about the larger tetramethylene-bridged hemicarceplex **9**·guest (Fig. 8), which forms from tetrol

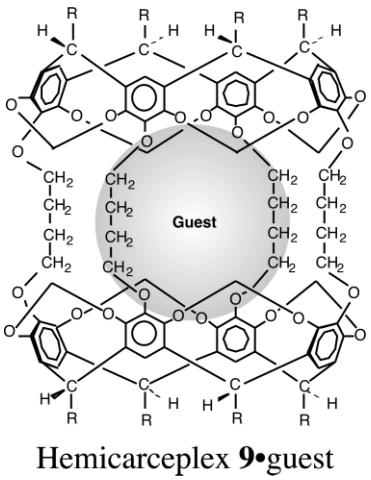

Fig. 8 Tetramethylene-bridged hemicarceplex **9**·guest.

4 and butaneditosylate? If the GDS to form **9**·guest is early, then **8**·guest should be a good transition state model. However, if the GDS is, for example, formation of the fourth bridge, then the cavity at that point would not resemble that of **8**. We screened suitable guests/templates for formation of **9** and determined their template ratios. There was no correlation between the template ratios for **9** and those for **5** (or the guest binding selectivities of **8**).[25] Thus, the GDS in forming **9** is indeed late, and not surprisingly complex **8** is not a good model for all assembly processes involving tetrol **4**. Examination of CPK models suggests that the GDS in forming **9** is indeed the final bridging, as the remaining hole is rather large. Preliminary data from our lab confirms this experimentally.[26] A final comment on yields in forming **9**·guest is worth mentioning. The yields in forming carceplex **5**·guest are very high, often over 50%. The yields in forming hemicarceplex **7**·guest are higher than expected statistically. Yet the yields in forming hemicarceplex **9**·guest are very low, often $< 10\%$.[25] This is because the assembly processes to form **5** and **7** start at once, before any bridges are formed (Fig. 9). The hosts are preorganized by the

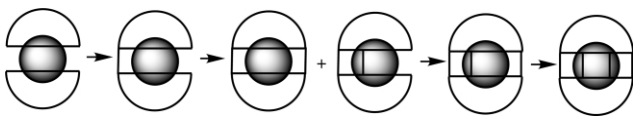

Fig. 9 Preorganization in the formation of **5**·guest and **7**·guest.

guests for appropriate bridge formation from the beginning. For **9**, the template effect doesn't kick in until the third bridge is formed (Fig. 10). Thus, polymerization runs rampant. In this

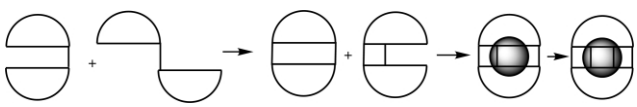

Fig. 10 Lack of preorganization in the formation of **9**·guest.

regard, the assembly process to form **9** is much less impressive than that in forming **5** and its ilk.

The high efficiency in forming carceplex **5**·guest led us to pursue the formation of higher order assemblies. Thus, bis-

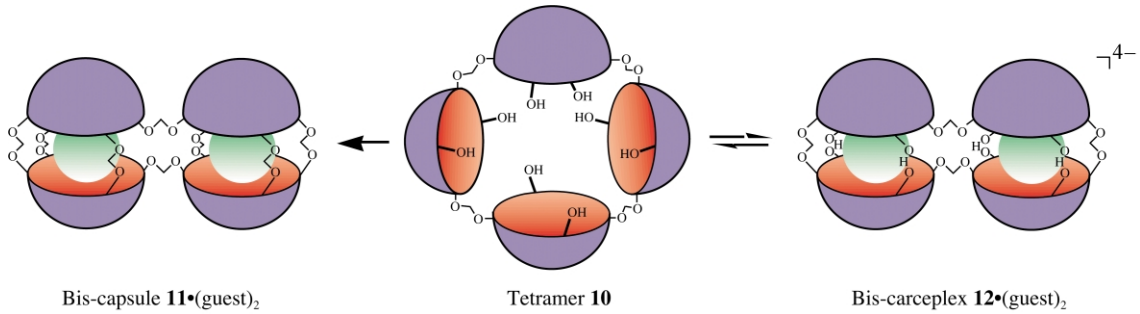

Fig. 11 Formation of bis-capsule **11**·(guest)$_2$ and bis-carceplex **12**·(guest)$_2$ from tetramer **10**.

carceplex **11**·(guest)$_2$ and bis-capsule **12**·(guest)$_2$ were generated from tetramer of cavitands **10** (Fig. 11). Formation of **11**·(pyrazine)$_2$ proceeded in 74% yield.[27] Formation of **12**·(guest)$_2$ was found to be cooperative, as only tetramer **10** and bis-capsule **12**·(guest)$_2$ were observed when a limiting amount of guest was present; no intermediates containing only one guest were observed.[28] Recently, we reported the production of tris-carceplex **14**·(methyl acetate)$_3$ and tris-capsule **15**·(methyl acetate)$_3$ from hexamer of cavitands **13** (Fig. 12).[29] Formation of the tris-capsule was again cooperative, and formation of the tris-carceplex proceeded in 37% yield. Such yields are quite high when one considers the number of "wrong" bonds that can form that would lead to misaligned cavitands. Thus, the organization of the host by the guests is substantial, and the efficiency of the assembly process allows a large (*e.g.*, the MW of **14**·(methyl acetate)$_3$ is 6479) and complex molecule to be made in relatively high yield.

Larger carceplexes

In ours and related systems[30] there is a current interest in making larger encapsulating species. Driving forces for such endeavours are manifold. The challenge of making larger and more complex assemblies is itself seductive. In addition, such species may find application as delivery devices or as catalysts. As well, the collection of several molecules within a cage opens the door to more novel inquiries such as probing guest–guest interactions between two or more entrapped guests. These and other issues are raised in this section.

Tetramer **10** and hexamer **13**, mentioned earlier, were prepared from a macrocyclization of macrocycles (cavitands).[27] From the same preparation, trimer of cavitands **16** could be obtained.[27] Tetramer **10** and hexamer **13** are flexible and contain an even number of cavitands. They can readily complex two and three guests in two and three chambers, respectively.[27,29] In contrast, trimer **16** contains an odd number of cavitands and is far more rigid than **10** or **13**. No two of its cavitands can close upon one another, and the six phenolic groups are held rigidly apart. Thus, trimer **16** is preorganized in a different manner than **10** and **13**. It is predisposed for capping rather than for bridging. Capping of **16** can lead to a single large enforced cavity that is sealed off. In this vein, trimer **16** was capped with tris-bromomethylmesitylene in DMF to give trimer carceplex **17**·(DMF)$_3$ in 36% yield (Fig. 13).[31]

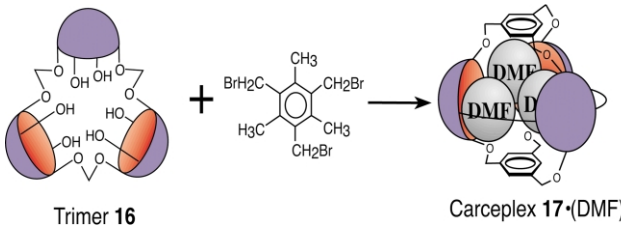

Fig. 13 Formation of trimer carceplex **17**·(DMF)$_3$. Methyls left off caps of **17** for clarity.

A common mass spectrometric method for characterization of carceplexes and hemicarceplexes is MALDI-TOF. This method is relatively mild, so it is effective at volatilizing such large non-polar molecules without substantive disruption of covalent bonds. Still, some rupture is observed on occasion and empty species can be observed. TOF allows determination of high *m/z* of singly charged species. Thus, MALDI-TOF of **17**·(DMF)$_3$ gave a signal of 3641; **17**·(DMF)$_3$·Na$^+$ weighs 3642.[31] The Na$^+$ and/or K$^+$ adducts of carceplexes are commonly observed as these cations are ubiquitous (*i.e.*, they are present in the target, glassware, fingertips, *etc.*); they are not entrapped, nor are they complexed to any significant extent in solution.

Carceplex **17**·(DMF)$_3$ appears to be sealed off according to examination of CPK models. No loss of guess was observed after six hours at 160 °C in nitrobenzene.[31] Even more rigorous treatment can be applied to test the constriction of guest binding, but this is sufficient to call the compound a carceplex, as it would be impractical at best to attempt to remove the contents without breaking covalent bonds. Recent work in our group suggests that water can enter the cavity of **17**, and this makes for some unusual chemistry, which will be reported shortly.[32] In this regard, the designation of a particular compound as a carceplex or a hemicarceplex is dependent on a number of factors including the size and shape of the guest.[5]

The occupation of space within a carceplex is on par with that found with most complexes as well as liquids; the molecular

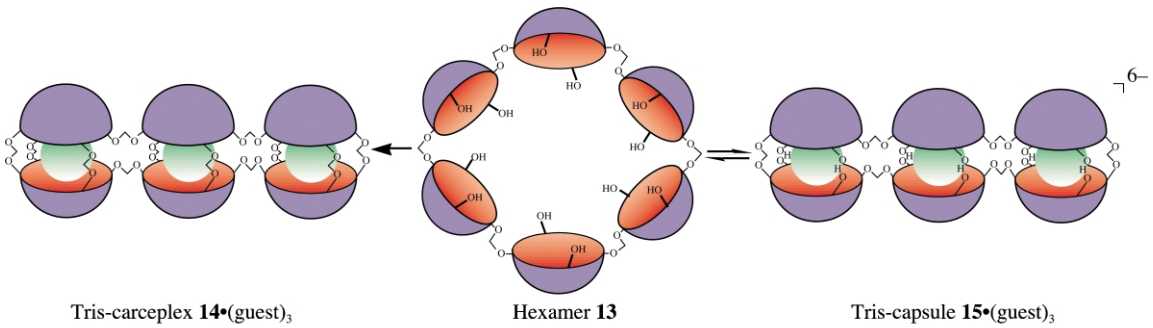

Fig. 12 Formation of tris-capsule **15**·(guest)$_2$ and tris-carceplex **14**·(guest)$_2$ from hexamer **13**.

volume occupies about 55–60% of the space. This is true for **17**·(DMF)$_3$. Since this carceplex is larger than the ones described above, the guests reside farther from the arenes of the bowls on average. This is demonstrated by a smaller change in the chemical shift ($\Delta\delta$) with respect to the free species in solution: 2.97 and 1.94 ppm for the *N*-methyls in **17**·(DMF)$_3$[31] versus 4.00 and 2.90 ppm for the corresponding methyls in **5**·DMF. The *N*-methyls of entrapped DMF spend less of their time jammed into the arenes of the bowl in **17** than in **5**. Note that in both cases, the *N*-methyls are non-equivalent. One of the methyls prefers to reside in the cavity of the bowls. At low temperature, the methyls of the DMFs in **17**·(DMF)$_3$ split out further, into three sets (six signals in all) of equal intensity. It appears that the three guests reside in non-equivalent orientations within the cage. At room temperature, the mobility of the guests renders an average set of guest signals.[31]

In addition to the new opportunities offered by larger carceplexes, interest lies in making systems in which guest release can be controlled.[33] Such a carceplex would allow guest delivery. If it is reversible, it would allow a template effect to be investigated under both thermodynamic and kinetic conditions. To that end, we investigated a new approach to making larger cages, and that is by expanding the cavitand itself to contain five resorcinols. Thus, bridging of a [5]resorcinarene and subsequent functionalization gave the pentathiol [5]cavitand, **18**.[34] It should be noted that in addition to the novelty of this family (we have also characterized the [6] and [7]cavitands)[34] being non-[4]cavitands, they are the first with no "feet." Subjecting [5]cavitand **18** to air oxidation in DMF as solvent led to [5]carceplex **19**·(DMF)$_2$ (Fig. 14).[35] This is the first carceplex with a C_5-axis of symmetry, and it is the first disulfide-linked carceplex. Interestingly, the corresponding reaction starting from the [4]cavitand tetrathiol did not yield any carceplex in DMF. This may be due to DMF being an inappropriate template for the reaction as the corresponding [4]carceplex has a cavity that is the size of about 1.5 DMF molecules, according to CPK models. Once we have studied the reaction to form [5]carceplex **19**·(DMF)$_2$ in more detail, we will return to the [4]cavitand tetrathiol system. We hope to learn more about [5]carceplex **19**·guests by exploring the template effect for its formation under both thermodynamic and kinetic control. We have found that the DMFs reside parallel to each other in **19**·(DMF)$_2$, one just above and one just below the equator of the host.[35] This is quite different from the orientation found in the [4]carceplexes, where a methyl group of DMF always resides in a bowl. The [5]cavitand is much larger than a [4]cavitand, so it not surprising that a methyl group is just too small to have effective van der Waals contacts with a [5]bowl. Such a phenomenon may manifest itself by unusually high mobility of the guest within the cage.

Recently we have made use of 1D-NOESY (EXSY) experiments to obtain rates of exchange for a number of dynamic processes.[34] For example, the benzylic methylenes in the linkage between the bowls in [5]carceplex **19**·(DMF)$_2$ are non-equivalent (Fig. 15).[35] This is a result of the twists of the bowls with respect to each other, similar to the phenomenon observed with the tetrol system. Interconversion of the

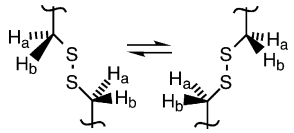

Fig. 15 Interconversion of diastereotopic protons *via* twisting of disulfides.

diastereotopic protons occurs with a $\Delta G\dagger$ of 14.4 ± 0.1 kcal mol^{-1}.[35] This is far greater than that found for unstrained disulfides, which cannot even be measured by NMR. The high energy barrier in **19**·(DMF)$_2$ is a result of the constraints put on the disulfides by the rigid bowls; in addition to being highly inflexible, all five disulfides must "flip" in concert.

Another dynamic experiment is the determination of the energy barrier for bond rotation of the C=N partial double bond of the amide of entrapped DMF (Fig. 16).[13] This has been

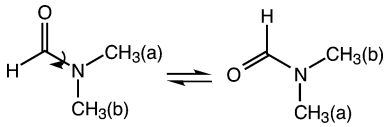

Fig. 16 Interconversion of syn and anti methyls of DMF.

measured in a number of carceplexes, usually by coalescence of the two *N*-methyls by ^{1}H NMR. To compare these systems on the same footing, and to get more precise data, we measured this barrier by 1D-EXSY for the following compounds: [5]carceplex **19**·(DMF)$_2$ (20.8 kcal mol^{-1}), **3**·DMF (20.5), **5**·DMF (19.1), and trimer carceplex **17**·(DMF)$_3$ (20.5). All measurements were done in nitrobenzene-d_5 at 77 °C. The corresponding value for free DMF under the same conditions (9% DMF in nitrobenzene-d_5) was 21.1 kcal mol^{-1}.[35] These results suggest that carceplex **5**·DMF is anomalous; the entrapped DMF must be in a more gas-phase like and/or more non-polar environment when in **5** than when in the other carceplexes or when free in solution. Free DMF in nitrobenzene-d_5 may indeed provide a more polar environment than inside **5**, and both [5]carceplex **19**·(DMF)$_2$ and **17**·(DMF)$_3$ contain multiple DMFs, which may produce micro-polar environments and/or micro-liquid environments. Sulfide-linked **3**·DMF may polarize the entrapped DMF with its bridging sulfur atoms.

Current efforts in our research group are toward production of larger systems. Pioneering work to create large cages have been reported by Fujita, Atwood, Mattay, Rebek, and Stang.[30] These workers have used metal–ligand assemblies or have noncovalently linked multiple resorcinarenes to generate hosts in very high yield that can potentially encapsulate large or multiple guests. Most of these studies have been in the solid state, and the guests that have been bound can escape through portals in the hosts. One approach toward large cavitand-based cages that can contain their guests for long periods is to expand the cavitands via the bridging group as has been done by Rebek and Gibb to create deep cavity cavitands.[36,37] Our contributions to this approach has included incorporation of xylyl linkages within

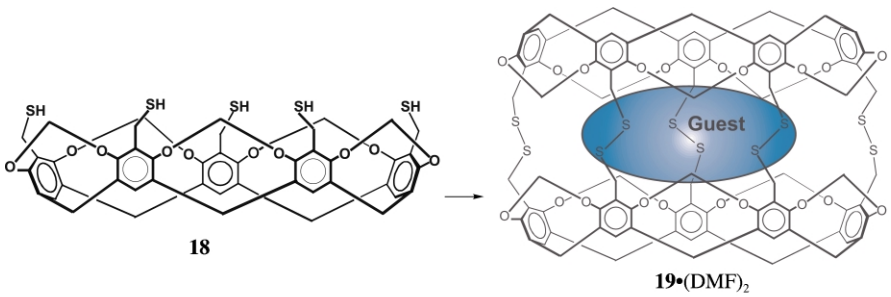

Fig. 14 Formation of [5]carceplex **19**·(DMF)$_2$ from [5]cavitand **18**.

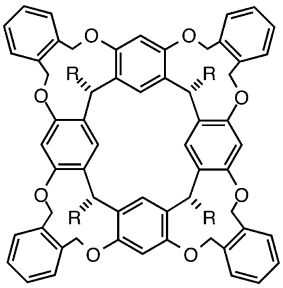

Fig. 17 Xylyl-bridged cavitand.

the cavitands (Fig. 17).[38] Another approach entails creation and use of larger cavitands (*e.g.*, [5]–[7]cavitands) to create larger cage structures as illustrated by **19**·$(DMF)_2$. A third approach is linkage of more than two cavitands to create carceplexes such as **17**·$(DMF)_3$. We now have preliminary data for linking more than three cavitands together to create a much larger carceplex; we will report on these results shortly.[32]

There are many potential applications for such large cage species. We have made some inroads toward getting our compounds into water, as have others.[39] Water solubility paves the way to biological applications. For example, we have another program that entails the investigation of protein structure using cavitands as scaffolds (Fig. 18).[40] Drug delivery is another possibility. With a disulfide linkage, release of guest is possible. Other release mechanisms have also been reported.[33] Entrapment of a useful drug and targeting to cells of interest are the current challenges here.

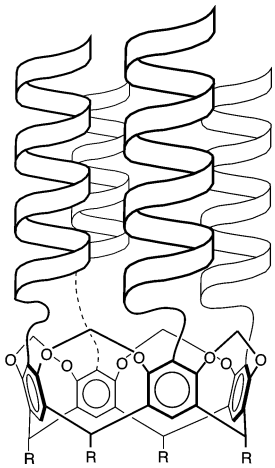

Fig. 18 A cavitein, or cavitand-based template-assembled synthetic protein.

Carceplexes and hemicarceplexes have been used to stabilize reactive intermediates, as beautifully exemplified by Warmuth using *o*-benzyne and cycloheptatetraene as the reactive species.[41] We have recently investigated the interaction of water with entrapped species, and will be reporting our results shortly.[32] We are also interested in investigating the role of large and, more interestingly, multiple molecules as templates. We may find that solvent effects and template effects meet and become one and the same once enough molecules are involved. Along these lines, we may be able to probe clusters of molecules as our systems get larger. NMR data already suggest that as multiple molecules are entrapped, properties (*e.g.*, chemical shifts) begin to move toward that of the bulk phase.

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