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Carceplexes and Hemicarceplexes†

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Contents

† Dedicated to D. J. Cram on the occasion of his 80th birthday.

I. Introduction

Molecular recognition and self-assembly are an intrinsic feature of numerous biological processes in living cells. Examples include the highly specific substrate recognition by enzymes, the pairing of complementary nucleoside bases to form the double helix tertiary structure of DNA, and the formation of membranes and ribosomes. Undoubtedly, both molecular recognition and self-assembly played a fundamental role in the early stages of evolution of primordial living cells from the relatively simple molecular building blocks available in the pre-biotic "soup". It is clearly a remarkable feat that these basic building blocks were able to self-assemble spontaneously into complex defined molecular entities. Amazingly, each of these simple molecular constituents contains the requisite information to recognize and interact with other complementary molecules.[1] These interactions are largely composed of noncovalent interactions such as hydrogen bonding. The efficiency and precision at which nature exploits these noncovalent interactions to generate complex nanoscale structures has continually intrigued scientists for centuries. Indeed, efforts to understand the driving forces for these fundamental biological processes has led to the development of a new genre of chemical research collectively termed supramolecular chemistry.[2]

Supramolecular chemistry generally encompasses chemistry of the noncovalent bond for the assembly of large "supermolecules" from smaller molecular subunits,[2−4] and as such it relies heavily on weak intermolecular forces such as hydrogen bonding, aromatic $\pi-\pi$ stacking, and polar and van der Waals interactions. Additionally, the resultant macromolecules possess structural features and chemical properties that are distinct from the original constituents from which they were constructed.[5] Molecular recognition and self-assembly are the two integral features of supramolecular chemistry. These, however, are not two independent processes but rather are interdependent on each other. In order for a

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Ayub Jasat was born in Francistown, Botswana, in 1969. He was educated in Zimbabwe and England, and he obtained a B.Sc. (Hons) degree in 1992 from the University of Salford. In 1995, he received his M.Sc. degree from the University of British Columbia under the guidance of Prof. David Dolphin, with research directed toward the synthesis of expanded porphyrins. He subsequently joined Prof. John Sherman's group and is currently in the final stages of a Ph.D. program, studying the templation effects in cavitand-based macrocycles as a potential route toward the synthesis of self-assembling supramolecular arrays.

John Sherman is originally from New York and obtained a B.A. in chemistry from Haverford College (PA) in 1983 and a Ph.D. from UCLA in 1988, working with D. J. Cram. He spent one year as a postdoctoral associate in the lab of the late E. T. Kaiser at The Rockefeller University, working with J. W. Taylor. He then spent two years as an NIH postdoctoral fellow in the lab of N. R. Kallenbach at New York University. In 1991 he began as an Assistant Professor in the Department of Chemistry at UBC and is currently an Associate Professor. His research interests include the investigation of molecular encapsulation and the design, synthesis, and characterization of de novo proteins.

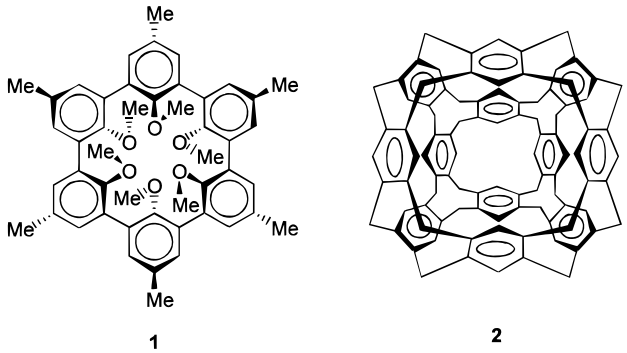
group of molecules to self-assemble, they must first aggregate. This occurs through molecular recognition, i.e., the process by which molecules selectively bind to form well-defined structures held together by intermolecular forces. Molecular recognition itself relies on complementarity of shape, size, and chemical functionalities. Self-assembly goes further and describes the spontaneous construction of defined structural noncovalent arrays from smaller engineered building blocks. The virtues of self-assembly were originally established from studying biological systems, namely the tobacco mosaic virus and ribonuclease enzyme.[6] This work carried out some three decades ago showed self-assembly to be a highly efficient, precise, and cooperative process, and as such was an extremely attractive new synthetic strategy for chemists. Indeed, there has been a plethora of research in this area recently,[6,7] largely driven by the need to access nanoscale devices for potential application as memory storage devices and molecular computers for the electronics industry.

Perhaps, some of the more interesting work to emerge from this research is the field of host−guest chemistry, wherein a host compound spatially accommodates a guest molecule or ion. Crown ethers are a classical example of hosts that are capable of incorporating guest molecules or ions within their confines.[8] More recent efforts in this area have focused on creating macromolecular capsules, which can totally encapsulate guest molecules both reversibly and irreversibly.[4b,7a,9] Supramolecules of this type have obvious potential as delivery devices, or miniature reaction vessels, for example.[10−15,16a,d] Numerous examples of structurally defined, container-like molecules with interesting host−guest binding properties have been reported in the past decade. These include Rebek's glycouril-based spheres,[16] cavitands,[9b,17,18] dimeric cyclocholates,[19] cucurbituril,[20] cyclodextrins,[21] and calixarenes-based dimers and oligomers.[22,23]

This review is on total molecular encapsulation of organic guest molecules by rigid macrocyclic host compounds with enforced cavities. Particular emphasis will be placed on carceplexes and hemicarceplexes, with attention to the more recent developments in this field. Finally, a brief overview of current directions in this field of host−guest chemistry will be presented.

II. Historical Perspective

In the early 1980s, Nobel Laureate Donald J. Cram proposed the formulation of carcerands as a potential enzyme mimic.[18a] The concept of molecular encapsulation within the confines of a rigid host grew in part from the Cram group's earlier successes with the spherands (e.g., **1**, Figure 1),[9b] and a general scientific



1 2

Figure 1.

curiosity as to what type of properties such container compounds and their imprisoned guests would possess. Spherands, as the name implies, are rigid polyaromatic macrocycles with an enforced, spherical cavity. Due to the rigidity of the aromatic backbone and the spatial requirements of the methoxy groups, the six oxygen atoms are fixed in an octahedral arrangement with their 24 lone pairs lining the cavity. Thus, spherand **1** displays a high degree of recogni-

tion toward the most complementary alkali metal cations. For instance, **1** strongly binds Li^+ and Na^+ cations only, and it has no affinity for K^{2+}, Mg^{2+}, or Ca^{2+}.[24] Through extensive examinations of molecular models loosely based on the spherand cast, Cram eventually proposed the egg-shaped prototype **2**.[18a] These novel hosts were christened *carcerands* and were defined as closed-surface, globe-shaped molecules with an enforced internal cavity within which small molecules, ions, or both could be incarcerated. *Carceplexes* are carcerands that contain permanently entrapped guest molecules or ions within their confines. Guest escape from a carceplex is thus only possible through breaking of the covalent bonds that link the atoms which form the walls of the molecular shell.

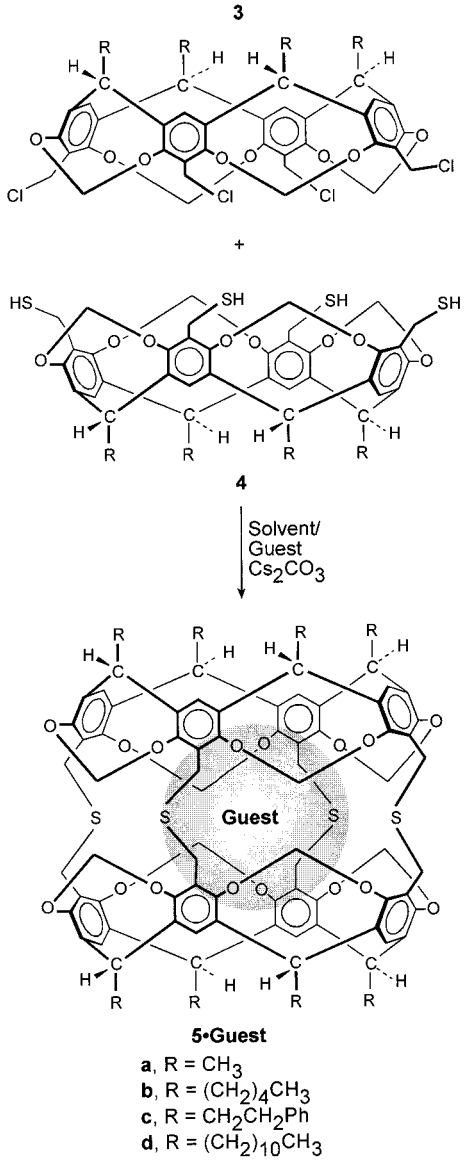
III. Carceplexes

A. Synthesis

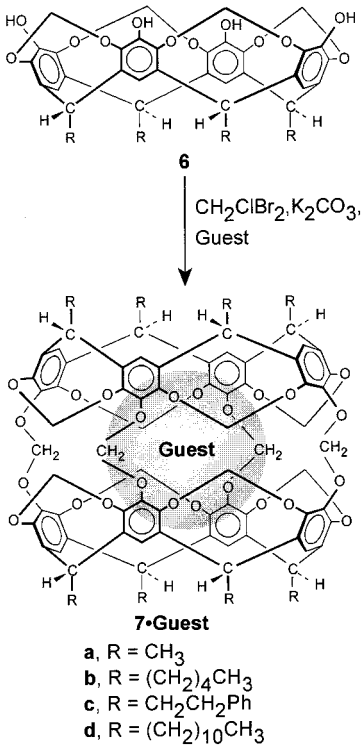
Shortly after proposing the concept of molecular incarceration, Cram's group reported the first true carceplex, **5a**.[25] Synthetically, this was achieved by coupling two bowl-shaped cavitands (i.e., macrocyclic molecules with an enforced internal cavity, such as tetrabenzyl chloride bowl **3** and tetrabenzyl thiol bowl **4**) in DMF in the presence of Cs_2CO_3 as base (Scheme 1). The poor solubility of this carceplex precluded full characterization. Nevertheless, using this same sequence, the more soluble carceplexes **5b**−**d** were later isolated with incarcerated methanol, ethanol, acetonitrile, DMF, *N*,*N*-dimethylacetamide (DMA), butanone, and pentan-3-one, in yields as high as 32%.[26] ^1H NMR spectra of these carceplexes, wherein the signals for the incorporated solvent as guest were shifted upfield due to the shielding effect of the aromatic rings, provided conclusive evidence for the entrapped guests.

In a related fashion, acetal-bridged carceplexes (**7**) were prepared in remarkably high yields (up to 87%) from tetrol **6**, by bridging the two bowls with bromochloromethane in the presence of a suitable guest (Scheme 2).[27−29] The astonishing efficiency of this reaction is particularly noteworthy, given that this bridging step involves the assembly of seven molecules! Indeed, this alone has led to the successful encapsulation of a multitude of small organic molecules by our group[29] and to the direct synthesis of the related octathiacarceplex **9**·DMA by Paek et al. albeit in 5% yield form tetrathiol bowl **8**.[30] The latter carceplex was originally synthesized independently by Cram in 22% yield via a two-step procedure involving isolation of the intermediate chloromethyl sulfide derivative **10** (Scheme 3).[31] More recently, the basic one-step reaction sequence provided four newer

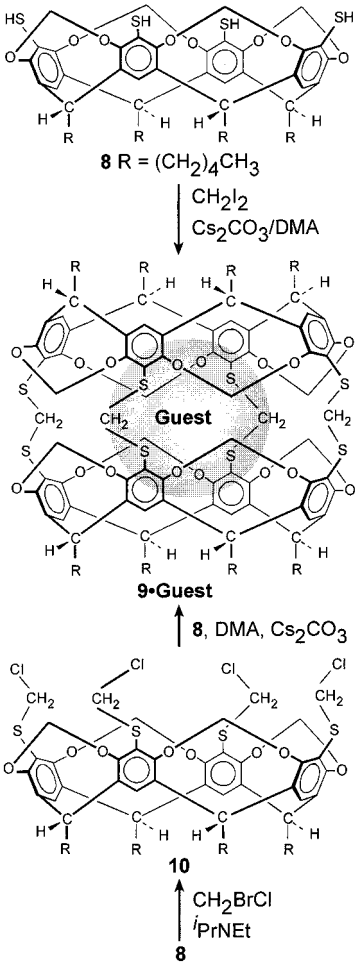
Scheme 1



Scheme 2

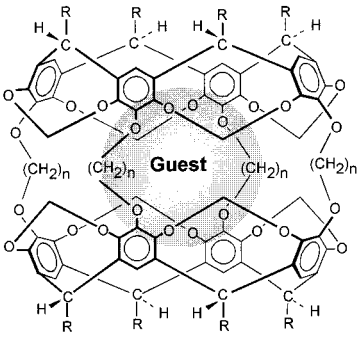


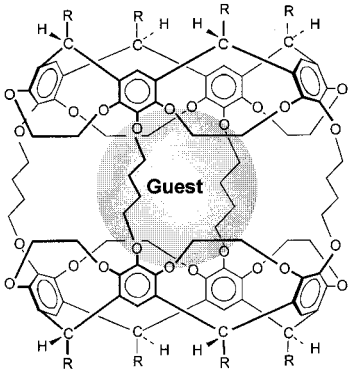
Scheme 3



carceplexes, **11**·DMA,[28a,32] **12**·DMA,[28a,32] **12**·NMP,[32] and **13**·DMSO[32] in 29, 20, 15, and 9% yield, respectively.

^{1}H NMR spectra of these carceplexes serve as a particularly useful diagnostic tool. Typically, the chemical shifts of the protons of the encapsulated species are shifted considerably upfield (between 2 and 4.5 ppm) from their normal resonance frequency when free in solution (in $CDCl_3$, for example) due to the shielding effects of the aromatic rings lining the cavity. In addition to providing evidence for an incarcerated species, the extent of this shift provides an insight into the orientation of the guest within the cavity: the deeper into the arene-rich polar regions of the cavity that the guest's parts penetrate, the larger the $\Delta\delta$ ($\delta_{free} - \delta_{entrapped}$) of the protons of the corresponding parts. The infrared spectra of these carceplexes were used to address the nature of the internal cavity. For example, the carbonyl stretching frequencies of DMA and DMF encapsulated as carceplex **7**·guest were found to be intermediate between that observed in the liquid and gas phases of these molecules.[27a] The energy barrier to the amide C−N bond rotation of encapsulated DMF and DMA further supported this notion of the carceplex's inner phase being intermediate between a liquid and a gas.[27a]





B. Templation Effects in Carceplex Formation

1. Acetal-Bridged Carceplexes

The presence of a suitable template (guest) in the reaction mixture during the formation of all carceplexes is a critical prerequisite.[26,27] In the absence of an appropriate template or in solvents that are too large to fit into the internal cavity, no carceplexes have been isolated. More importantly, the shell-closure process exhibits a high degree of selectivity when given a choice between two or more templates in the case of carceplex **7**·guest. This template effect was first recognized in the Cram group[26,27] and elucidated in detail more recently in our laboratories.[29] We determined the magnitude of this template effect as template ratios, i.e., the templating ability of one guest over another, for a range of small organic molecules in the formation of carceplex **7**·guest to be 1 million (Table 1).[29] Experimentally this was achieved by carrying out the reaction in *N*-methyl-2-pyrrolidinone (NMP—which is a poor template for this reaction) doped with two competing guests. Integration of the unique host and guest signals in the ^{1}H NMR spectra of the isolated product mixture subsequently provided the template ratio for these two guests, which were finally normalized to the poorest template molecule measurable (NMP). This 10^6-fold range in template ratios from the best guest (pyrazine) to the worst (NMP) represents the relative rates of the guest-determining step (GDS). The GDS is the step in the reaction beyond which all guest exchange ceases. The ratio of guests ultimately incarcerated in the carceplex is determined solely by their competition in the transition state of the GDS. Therefore,

Table 1. Selected Template Ratios for Carceplex 7c·Guest and K_{rel}'s of Complex 17·Guest

guest	template ratio for **7c**·guest[29]	K_{rel} of complex **17**·guest in nitrobenzene-d_5[37]
pyrazine	1 000 000	980 000
methyl acetate	470 000	420 000
1,4-dioxane	290 000	240 000
DMSO	70 000	58 000
pyridine	34 000	7100
acetone	6700	1300
benzene	2400	540
1,3-dioxane	200	140
DMA	20	8.9
NMP	1	1

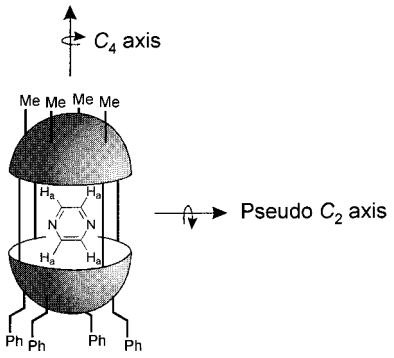
by analogy, just as a product ratio reflects the relative rate of the product-determining step, template ratios represent the relative rate of the GDS for two different guest molecules. In the case of **7**·guest, the GDS has recently been determined to be the formation of the second interbowl acetal linkage, either adjacent to (A,B) or opposite to (A,C) the initially formed interbowl bridge.[33] Pyrazine, for instance, lowers the transition state of the GDS by 8.3 kcal mol^{-1} compared to NMP at 300 K.[33] Additionally, these template ratios correlate to a certain extent with the product yields, as is exemplified with pyrazine: a 75% yield of carceplex **2c**·pyrazine was isolated as the sole carceplex from a reaction containing only a stoichiometric amount of pyrazine in NMP as bulk solvent (i.e., with a 10^4-fold excess of NMP).[29] However, this is not a general trend, as several notable deviations were observed in some guest's templating ability and the isolated yield of the corresponding pure carceplex.[29] Moreover, this templating effect is not limited to carceplex **7**·guest; recent preliminary work by our group has found that carceplex **5**·guest also exhibits a large template effect with a range of small organic molecules.[34]

Naturally, these results peaked our interest and numerous new questions arose, the most obvious being what drives this spontaneous assembly of seven individual molecules in such an efficient manner? Why do these bowls exhibit such a pronounced degree of molecular recognition? A total of 70 potential templates were examined, half of which were found to be suitable templates.[29,33] As anticipated, the guest size and shape played a significant role. More interesting, however, were the large changes in these template ratios brought on by subtle changes in guest structure. For example, the template ratio of 1,4-dioxane is approximately 1500 times greater than that of 1,3-dioxane.[29]

Collectively these results strongly suggest that noncovalent interactions between the walls of the forming cavity and guest are largely responsible for the large template effects observed. Thus, guests that can achieve the maximum number of van der Waals interactions and minimal steric interactions with the cavity wall should exhibit the most pronounced template ratio. Indeed, evidence for this was gleaned from a comparison of the X-ray crystal structures of carceplexes **7a**·pyrazine[35] and **7c**·DMA.[27a] The most notable feature of the crystal structure of **7a**·pyrazine is that the two bowls are twisted 21° with respect to each other and are virtually parallel (the two planes defined by the two sets of four interbowl oxygens of each hemisphere are 0.3° from a parallel arrangement).[35] This arrangement enables the interbowl oxygens to fully conjugate with the aromatic rings thereby imparting an additional 16−24 kcal mol^{-1} stabilization energy. In **7c**·DMA, on the other hand, these planes are distorted by 5.2° from a parallel arrangement, obviously due to the steric bulk of the larger DMA guest molecule compared to pyrazine.[27a] The net result is a partial disruption of this conjugation in **7c**·DMA, and hence the loss of substantial stabilization energy. This is consistent with the templating abilities of these two guests (Table 1): DMA is 140 000 times worse than pyrazine. Interestingly, an X-ray crystal structure of the octathiacarceplex **9**·DMA revealed that the two bowls are not twisted with respect to each other,[31] which precludes conjugation of the sulfur lone pairs with the aromatic rings. Presumably, the energy gain by the n-π^* conjugation is minimal for aryl sulfides compared to that for aryl ethers.

Crystal structures of carceplexes **12**·guest (guest = DMA and NMP) and **13**·DMSO have been reprorted.[32] The X-ray crystal structure of carceplex **12**·DMA revealed that in this molecule the two bowls are perfectly aligned, with the interbowl bridging carbon atoms forced outward and the electron pairs of their terminal oxygen groups facing inward,[32] thus enabling conjugation between these bridgehead phenolic groups and the aryl π-system. The crystal structure of the expanded carceplex **13**·DMSO, interestingly, indicates that expansion of both the intrabowl bridges and the interbowl linkers produces a more spherical cavity.[32] The carbon atoms of the intrabowl ethylene linkers are pushed upward and into the cavity, while the interbowl linkers are pushed outward from the cavity thereby rendering a near C_2 axis on this host.

Pyrazine's orientation and dynamic behavior inside carceplex **7** further exemplify the extent of its complementarity to the cavity of carceplex **7**. Guests generally rotate rapidly about the host's C_4 axis, whereas rotation about the C_2 axis is slow on the ^{1}H NMR time scale. For example, benzene and acetonitrile have been shown to reorient rapidly about the host's C_4 axis,[36] with a rate ($\sim 10^6$−10^7 s^{-1} for benzene, at $T = 310$−400 K) that is intermediate on the ^{2}H NMR time scale. The energy barrier for pyrazine rotation about the host's C_2 axis in asymmetric carceplex **14**·pyrazine was determined to be 19 kcal mol^{-1}.[35] Moreover, due to the asymmetry of **14**·pyrazine, the protons of incarcerated pyrazine are nonequivalent, hence two guest signals were observed in the ^{1}H NMR spectrum. Each signal was in turn split into a doublet ($J = 1.2$ Hz) indicative of *meta*-coupling, thereby suggesting that pyrazine is orientated with its two nitrogens located at the equator of the host (Figure 2). In this orientation, the narrow cross-section of pyrazine and the narrow equator of the host are aligned, which optimizes the noncovalent interactions between the host's cavity walls and the guest. This orientation of pyrazine concurs with that observed in the X-ray crystal



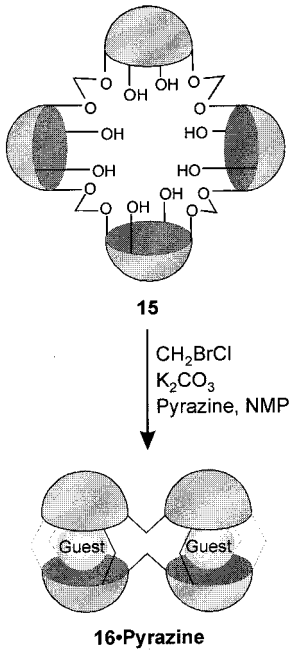
14•Pyrazine

Figure 2. Schematic representation of asymmetric carceplex **14**·pyrazine.

structure of **7a**·pyrazine.[35,37] Indeed, from the crystal structure of **7a**·pyrazine it is apparent that in this orientation, pyrazine can form (1) weak hydrogen bonds between its nitrogens and half of the intrabowl methylene bridges; (2) CH$-\pi$ hydrogen bonds between the interbowl methylene bridge hydrogens and the pyrazine π-system; and finally, (3) CH$-\pi$ interactions between the host cavity's aromatic π-system and the hydrogens of pyrazine itself.

The knowledge garnered from these template ratios ultimately led to the recent synthesis of a bis-carceplex (Scheme 4).[38] The key shell closure was

Scheme 4

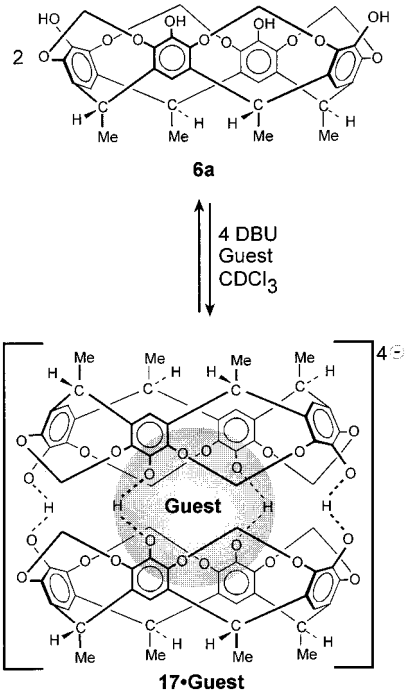


effected in 74% yield by treating cyclic tetramer **15** (derived from tetrol **6c**) with CH_2BrCl in NMP in the presence of pyrazine and K_2CO_3. ^{1}H NMR spectroscopy, elemental analysis, and MALDI-TOF mass spectrometry confirmed the presence of two pyrazine molecules per host molecule. The exclusive formation of bis-carceplex **16**·2pyrazine is noteworthy, as there has been no apparent evidence for the formation of the corresponding carceplex derived from the dimerization of two molecules of **15**. This ultimately arises from the flexibility of the interbowl acetyl bridges in tetramer **15**. However, as we shall see shortly, the formation of this species as the sole carceplex also results (to a significant extent) from the formation of a highly preorganized charged hydrogen-bonded complex under these reaction conditions. MM2 calculations on **16**·2pyrazine predict that each capsule is twisted by 90° with respect to the other.

2. Transition State Models

Subsequent work in our group led to the discovery of a novel ternary complex, **17**·pyrazine (Scheme 5).[37,39] Evidence for the formation of this complex was

Scheme 5



initially obtained from ^{1}H NMR spectroscopic experiments. Thus, titrating a solution of tetrol **6a** and pyrazine in $CDCl_3$ with DBU resulted in the appearance of a new set of host and guest signals in the ^{1}H NMR spectrum. Particularly obvious was the appearance of a singlet at δ 4.3 ppm, which is ascribable to encapsulated pyrazine in complex **17**·pyrazine. This complex is held together by four charged hydrogen bonds, further evidence for which was also obtained from the ^{1}H NMR spectrum of the tetrabutylammonium salt of **17**·pyrazine in acetone-d_6, where the hydrogen-bonded protons appeared as a singlet at 15.6 ppm at 200 K. Furthermore, formation **17**·pyrazine is reversible. Thus, addition of acid breaks up the complex giving tetrol cavitand **6a** and free pyrazine, and subsequent addition of DBU regenerates the complex. An X-ray crystal structure of this complex unequivocally proved the incarceration of pyrazine[37] and bears remarkable resemblance to that of carceplex **7a**·pyrazine.[35] Moreover, the guest's mobility and orientation are virtually identical within complex **17**·pyrazine and carceplex **7a**·pyrazine; the energy barrier to rotation of pyrazine about the psuedo-C_2 axis of the asymmetric complex analogous to **14** was determined by variable temperature NMR spectroscopy to be 18 kcal mol^{-1} (cf. 19 kcal mol^{-1} for carceplex **14**·pyrazine).

The relative stabilities (K_{rel}) of a series of complexes (**17**·guest) in both $CDCl_3$ and nitrobenzene-d_6 have been reported.[37,39] The K_{rel}'s for complexes **17**·guest in nitrobenzene-d_6 are summarized in Table 1. These values clearly indicate that, like carceplex **7**·guest, this complex is highly guest selective. More importantly, the selectivity observed for this complex correlates well with the template ratios previously reported for carceplex **7**·guest. This suggests that the guest molecules impart very similar stabilizing (or destabilizing) effects on the relative free energies of these complexes as they do on the relative activation energies for the GDS in the formation of carceplex **7**·guest. This implies that the factors governing both the formation of carceplexes **7**·guest and complexes **17**·guest are similar in nature. Hence, these complexes serve as ideal models for the transition state of the GDS in carceplex formation. Indeed, extensive examination of the thermodynamics of these complexes has provided a more detailed description of the forces driving the formation of complex **17**·guest and hence carceplex **7**·guest. From these data, it was concluded that for guest molecules that form the most van der Waals interactions the self-assembly of the two bowls is enhanced enthalpically, while for smaller guests the process is enhanced entropically. These findings fit well with computational simulations on a model dimer based on **17**·pyrazine but with no charged hydrogen bonds.[40]

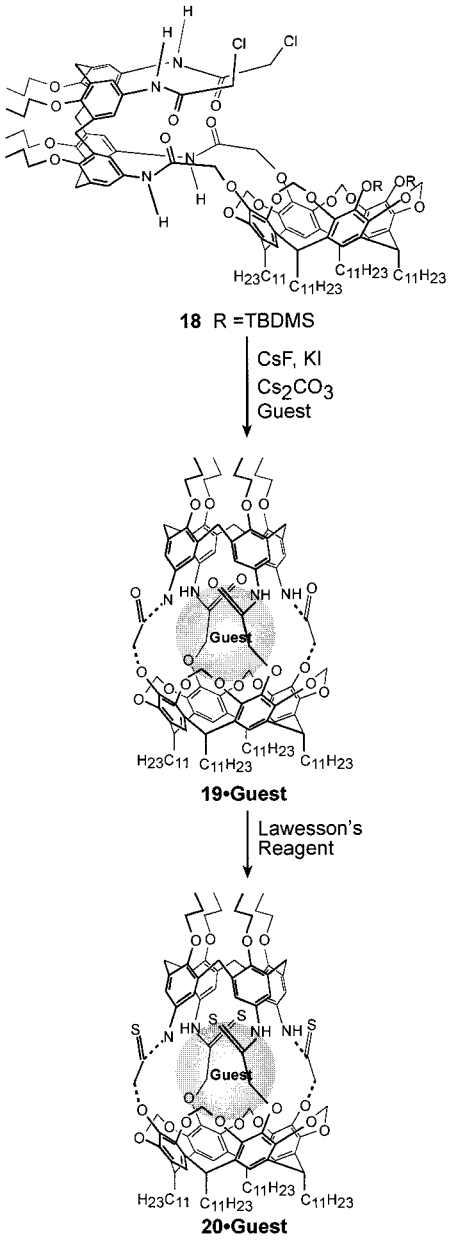
Complexes **17**·guest have undoubtedly provided a wealth of information regarding the mechanism for the formation of carceplex **7**·guest. Clearly, these complexes play a significant role in carceplex formation, since the observed template ratios are inherited from the high degree of guest selectivity dictated by this complex. Formation of this complex itself is driven by the formation of charged hydrogen bonds between the two bowls and the maximum possible favorable van der Waals interactions between the forming host's cavity and the guest molecule. Thus, under the reaction conditions employed, complex **17**·guest is indeed initially formed. Consequently, this self-assembled structure preorganizes the bowls for subsequent bridging by bromochloromethane. However, it is only after the second bridge is formed that the guest molecules are permanently incarcerated. Although the guests are in fast exchange until the formation of this second interbowl bridge, the host species formed during the transition state of this step is structurally well-defined, and selectively binds the most complementary guest. This generates the most stable complex, which then rapidly undergoes the second bridging step, thereby entrapping more of the superior guest. Subsequent bridging eventually leads to the product ratios observed. The significance of this complex during carceplex formation is further manifested in the formation of bis-carceplex **16**·2pyrazine. Undoubtedly, under the reaction conditions employed, the formation of an analogous hydrogen-bonded bis-complex initially occurs, thus resulting in the isolation of the bis-carceplex and not the dimeric carceplex **15**·**15**·4pyrazine as the sole carceplex. Indeed, we have observed the formation of such a bis-complex by ^{1}H NMR spectroscopy.[41] Clearly, it is the formation of these charged hydrogen-bonded complexes with both tetramer **15** and two molecules of tetrol **6** in the presence of a suitable template that drives the formation of these bis-carceplexes and carceplexes based on these tetraphenolic derivatized cavitands such as tetrol **6**.

C. Other Carceplexes

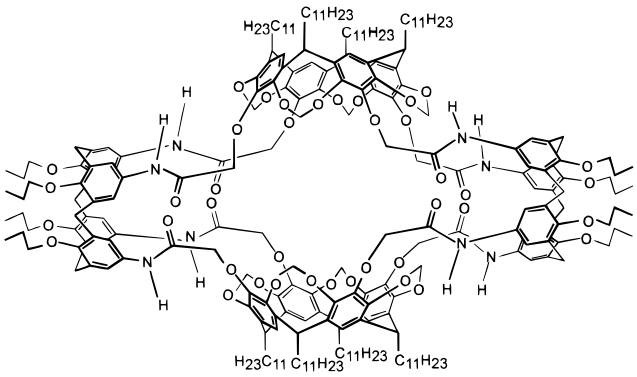
1. Calix[4]arene–Cavitand Hybrid Carceplexes

Since Cram's synthesis of prototypical carceplexes **5**·guest and **7**·guest, there have been very few variations on this basic carceplex structure, with the exception of thiacarceplex **9**·DMA. However, fairly recently David Reinhoudt and co-workers isolated asymmetric carceplex **19**·DMF based on a combination of resorcinarenes and calixarenes (Scheme 6),[42]

Scheme 6



albeit in 27% yield, initially as a byproduct in their synthesis of holand **21**. Nevertheless, effecting the



21

in situ desilylation and concomitant shell closure via slow addition of **18** to a mixture of CsF, KI, and Cs_2CO_3 in DMA at 80 °C afforded **19**·DMA in quantitative yield.[43] Using this standard procedure, carceplexes **19**·guest with entrapped DMF, DMSO, and ethyl methyl sulfoxide were also obtained in essentially quantitative yields.[43a,b] However, as the size of the guest increased, the yields of the resultant carceplex significantly decreased. Thus, carceplexes with NMP,[43a,c] thiolane-1-oxide,[43a,b] and 1,5-dimethyl-2-pyrrolidinone (DNMP)[43a,b] were isolated in 50, 16, and <5% yield, respectively. Using the doped inclusion method (i.e., addition of 5−15 vol % of cosolvent to the bulk reaction solvent) in DNMP further expanded the scope of this carceplex.[43a,b] Thus, these researchers were now able to screen a range of potential guest molecules, of which, 3-sulfolene, butanone, DMF-d_7, and DMSO-d_6 were successfully incorporated. This sequence also enabled these researchers to determine the templating ability of the successful guests. For the series of guests used in the formation of **19**·guest, a template ratio of 3.7:1 for DMA:butanone was obtained. This reaction appears to work best in polar solvents, since, for example, in neat butanone no carceplex was isolated. This preference was rationalized as follows: in order for the two bowls to align prior to the shell closure of **18**, hydrogen bonds between the NH atoms of the bridging amide group and the oxygens of the adjacent acetal bridges of the resorcinarene half must be disrupted. Additionally, molecular models indicate that the NH groups must point into the cavity of the forming carcerand during the shell closure, a process facilitated only by hydrogen-bond-accepting solvents. The apparent shifts in the signals of these NH groups in the ^{1}H NMR spectra of **19**·guest increase with increasing solvent polarity,[43a] thereby corroborating these inferences. Chemical modification of the amide bridges in **19**·guest with Lawesson's reagent proceeded smoothly affording the corresponding thioamide bridged carceplexes **20**·guest in excellent yield.[43a,b] Incidentally, this conversion nicely demonstrates the effective shielding ability of the host toward its imprisoned guests from external influences since amides, sulfoxides, and ketones readily react with Lawesson's reagent. Under electron impact mass spectrometry conditions, carceplex **20**·3-sulfolene undergoes SO_2 and butadiene extrusion at a probe temperature range of between 170 and 215 °C.[43a] In solution and solid phase experiments, however, **20**·3-sulfolene exhibited high thermal stability at temperatures up to 200 °C over 16 h when compared to neat sulfolene. Reinhoudt et al. have expanded their work with these carceplexes further, with the synthesis of monolayers of **20**·DMF on gold.[44]

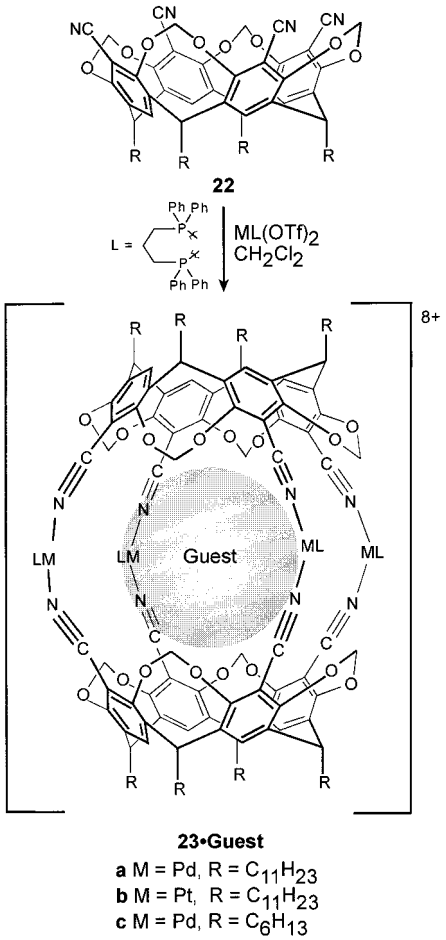
Due to the inherent asymmetry of **19**·guest and the hindered rotation of the encapsulated guests about the psuedo-C_2 axis, these carceplexes exhibit a new type of isomerism relating to the orientation of the guest molecule with respect to the calix[4]arene and resorcinarene halves of the molecule.[43] Reinhoudt proposed the term carceroisomerism (carcerism) for this type of stereoisomerism. Carcerism is, as expected, only evident with larger guests such as DMA, ethyl methyl sulfoxide (for **20**·guest only), and NMP, where the energy barrier to interconversion in these carceplexes (**19**·guest) and thiacarceplexes (**20**·guest) are in the 12.7−17.5 kcal mol^{-1} range.[43a,b] With relatively smaller guests, such as DMF, butanone, ethyl methyl sulfoxide (for **19**·guest only), and the larger DNMP, only one isomer was observed in the experimental temperature range (−50 to 120 °C). Conversion of the amide functionalities of **19** to thioamides increased the activation energy for interconversion between the different carcermers, presumably due a decrease in the cavity volume (as implied by molecular modeling calculations), and increased hydrogen bonding with the thioamide moieties. Computational analysis of this series of carceplexes revealed good correlation between the experimentally determined activation energies for guest rotation about the psuedo-C_2 axis and the calculated values.

2. Metal-Bridged Carceplexes

Traditionally, carceplexes and related compounds have been synthesized through covalent bonding and, more recently with charged hydrogen bonds, between the two hemispheres that form the vessels. Enrico Dalcanale's group, at the University of Parma in Italy, devised a rather intriguing method for inducing the self-assembly of a carceplex.[45] Thus, borrowing from the realms of inorganic supramolecular chemistry, wherein metal-induced self-assembly is commonplace in the formation of multicomponent, multidimensional architectures,[7d,46] the Parma group used square-planar palladium(II) and platinum(II) complexes to bridge two bowls together, with concomitant incarceration of a guest molecule. As summarized in Scheme 7, simply mixing tetracyano bowl **22** with [Pd(dppp)$(CF_3SO_3)_2$][47] or [Pt(dppp)$(CF_3SO_3)_2$][47] in acetone, chloroform, or dichloromethane at ambient temperature in a 1:2 molar ratio resulted in the spontaneous self-assembly of carceplex **23**·guest in quantitative yield.

Multinuclear NMR spectroscopy (^{1}H, ^{13}C, ^{31}P, and ^{19}F), ESI-MS, and vapor phase osmometry (VPO) confirmed the 2:1 structure of the carceplex. Additionally, the simplicity of the ^{1}H and ^{31}P NMR spectra was in accord with the highly symmetric D_{4h} structure. Evidence for an entrapped guest was gleaned from the ^{19}F NMR spectra of **23**. Here, two different fluorine signals were observed at δ −81 and −75 ppm in a ratio of 1:7, indicating that one of the triflate counteranions had indeed been encapsulated. The entrapment of charged species during carceplex

Scheme 7

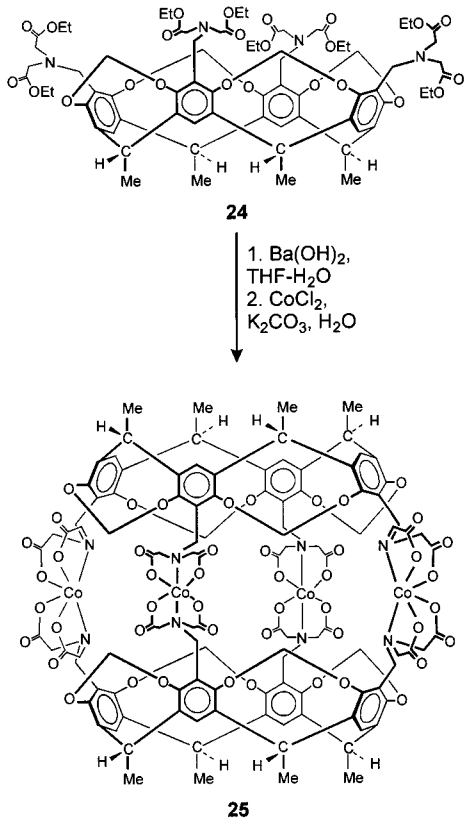


formation is particularly unusual, given the apolar nature of cavity walls. For example, as will be discussed in the following section, hemicarceplexes containing entrapped diethylamine and butylamine readily undergo decomplexation upon protonation of the amine.[48] Undoubtedly, for carceplexes **23**, the highly polarized cyano groups and the presence of the transition metal centers facilitate the encapsulation of an anion. Thus, it is highly likely that the entrapped triflate anion is located in the equatorial region of this carceplex, where maximum stabilization of the charge is possible.

The good thermal stability of **23**·$CF_3SO_3^-$ confirms their nature as true carceplexes. More interestingly, however, the self-assembly of **23**·$CF_3SO_3^-$ was shown to be a completely reversible process through simple metal−ligand exchange: addition of a competing ligand such as triethylamine (8 equiv) to a solution of **23b**·$CF_3SO_3^-$ resulted in complete dissociation of the carceplex into cavitand **22** (R = $C_{11}H_{23}$) and Pt complex [Pt(dppp)(Et_3N)$_2CF_3SO_3$)$_2$]. Subsequent addition of triflic acid (8 equiv) spontaneously regenerated the carceplex, once again in quantitative yield. The remarkable efficiency of this self-assembly process certainly represents a pinnacle in carceplex synthesis.

Very recent work by Roger Harrison and coworkers yielded the water-soluble metal-bridged carcerand **25** (Scheme 8).[49] Synthesis of the latter entails hydrolysis of the ester groups on the upper rim of cavitand **24**, followed by treating the resultant water-

Scheme 8



soluble octaacid derivative with cobalt(II) chloride and potassium carbonate at pH 6. An X-ray crystal structure of **25** confirmed the presence of the two resorcinarene cavitands held together by four divalent cobalt ions, imparting an overall D_{4h} symmetry to the molecule with a distorted octahedral geometry about the cobalt centers. Like the previous example, the self-assembly of **25** is a reversible process simply dependent on pH. Thus, gradually increasing the pD of a solution of the acid derivative of **24** and cobalt(II) chloride in D_2O from pD 1.0 to pD 6 results in significant broadening and isotropic shifting of the proton NMR resonance signals in the NMR spectrum of the ligand brought on by the paramagnetic Co(II) ions. Subsequent acidification with triflic acid regenerates the free diamagnetic species in solution. More intriguing, however, is the fact that both the X-ray crystallographic analysis and ^1H NMR spectroscopy provide no evidence for the presence of an entrapped guest molecule in **25**. The self-assembly of **25** is indeed a remarkable feat since, as we have just seen and will see later (section Va,b), the generation of related reversible capsular assemblies proceeds only in the presence of a suitable template.[7a,37,39,45] Thus, the self-assembly of this water-soluble carcerand (i.e., **25**) is driven by either the formation of a stable cobalt−ligand complex or the hydrophobic nature of the internal cavity of cavitand **24** or a combination of the two. Generation of the carcerand more efficiently shields the internal cavity from the polar surroundings, compared to the free cavitands.

This work clearly demonstrates that with appropriate choice of bridging groups and functional groups on the cavitands one can essentially design a highly efficient molecular switch. Indeed, as we unravel

more of the principles governing these self-assembling processes, one can anticipate the design of more intricate molecular architectures and eventual real-world applications in the not too distant future.

IV. Hemicarceplexes

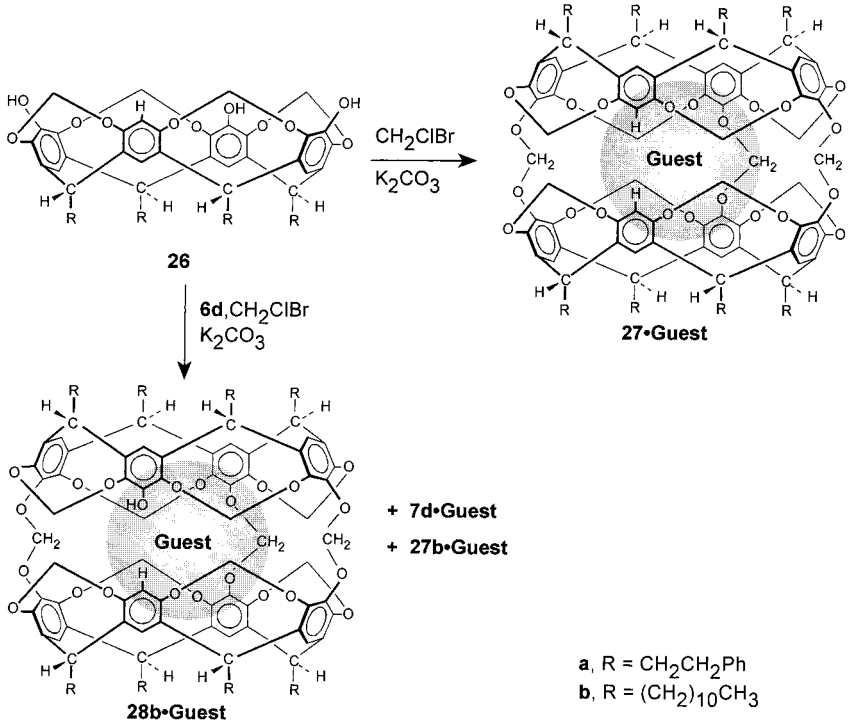
Hemicarceplexes are like carceplexes but contain small portals in their shells through which guests can enter and depart the inner cavity upon sufficient heating, without breaking any covalent bonds. By definition, hemicarceplexes must be kinetically stable to allow their synthesis, isolation, and characterization at normal temperatures. It is this feature that differentiates hemicarceplexes from the vast number of known complexes that rapidly undergo exchange on the human time scale. Unlike clathrates,[50] zeolites,[51] and other solid state inclusion compounds that accommodate guest (and/or solvent) molecules within the interstitial voids of the packed crystal,[52] hemicarceplexes are both soluble and stable in solution. Additionally, clathrate lattices generally tend to decompose upon removal of the guest, whereas empty hemicarceplexes (i.e., hemicarcerands) retain their molecular superstructure. Zeolites represent another class of solid state compounds that are also capable of binding small molecules and ions within their superstructures.[51] However, unlike all the hemicarceplexes known to date that contain a single defined internal cavity, zeolites characteristically contain tunnels of interconnected cavities. Furthermore, these cavities can be linked in multidirections to afford fibrous (one), lammellar (two), or complex three-dimensional (three) structures. Since the inception of this field of host−guest chemistry by Cram, hemicarceplexes have so far been the most widely studied of the broader carcerand family. This most likely results from their facile variability in size and the ability for one to perform reactions on the contained guests.

A. Synthesis

1. Hemicarceplexes Containing Distinct Portals

The isolation of significant quantities of triol **26**[27a] as a byproduct in the synthesis of tetrol **6** inevitably led to the synthesis of the prototypical hemicarceplex **27**.[48,53] Thus, using the now standard shell-closure procedure summarized in Scheme 9, hemicarceplexes containing DMF, DMA, and DMSO were obtained in 20, 42, and 51% yields, respectively. More recent efforts by Kyungsoo Paek's group provided the more soluble undecyl-footed homologue **27b**·DMA (18%) and the asymmetric monool derivative **28b**·DMA (6%), in addition to carceplex **7d**·DMA (14%) in a one-pot reaction between triol **26b** and tetrol **6d**.[28] Other recent variations on this basic theme include the direct synthesis of the pincer-like A,B-bis-bridged species **29a** (Figure 3) independently by Reinhoudt's[54] and Cram's[55] groups, various tris-bridged derivatives (e.g., compounds **30a**−**c**) and A,C-bis-bridged hemicarceplexes **31a**−**c**[56] and **32a**[48,55] by Cram's group, and our isolation of the entire range of possible intermediate products (i.e., the mono-bridged species **33**,[33] A,B-bis-bridged species **29b**, A,C-bis-bridged **32b**, and tris-bridged hemicarceplex **30d**) in carceplex formation and various methylated derivatives (e.g., **29c** and **33b**).[57] The A,B-bis-bridged **29** and the mono-bridged species **33** were isolated with no guests, and therefore, as such are not hemicarceplexes but more correctly hemicarcerands, A,B-bis-bridged **29b** is capable of binding guest molecules, but guest exchange for this compound is reportedly fairly rapid (i.e., a few minutes) at ambient temperature in the absence of base.[33,55] This undoubtedly results from the high degree of flexibility inherent in these hosts[54a] and analogously the mono-bridged species, **33**. Interestingly, **33a** exhibited a templating effect identi-

Scheme 9



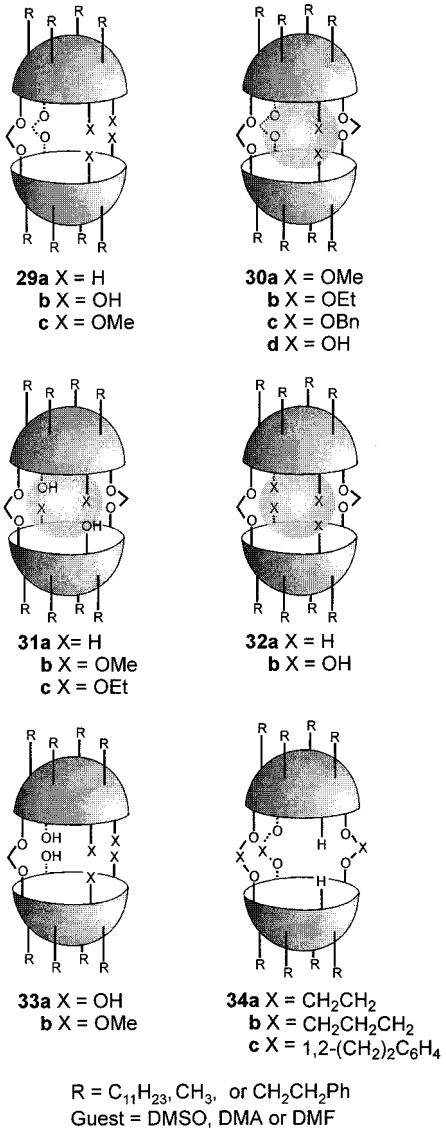


Figure 3. Schematic representations of some recent variations on hemicarceplex **27**.

cal to that of tetrol **6**[33] when subjected to the same competition experiments employed in determining the templating effects in the formation of carceplex **7**·guest from **6**.

The high yields obtained in the syntheses of hemicarceplex **27**·guest are particularly striking, considering that they surpass the statistically predicted yields. Moreover, despite the presence of a portal, the templating effects in the formation of hemicarceplex **27**·guest were found to correlate with those for the formation of carceplexes **7**·guest.[58] Thus, the same forces that drive the formation **7**·guest are at play in the transition states of the GDS in the formation of hemicarceplex **27**·guest. Independent work by Cram has shown that subjecting triol **26** and a series of mono protected triols to the standard shell-closure conditions predominantly furnished the corresponding hemicarceplexes (i.e., **27**·guest and **30**·guest, respectively).[56] The misaligned hemicarceplexes **31**, on the other hand, were only formed (in 5−11% yield) in DMSO, a solvent known to disrupt hydrogen bonding. The latter results coupled with the high yields obtained further underscore the significance of charged hydrogen-bonded dimers (such as **17**·guest) in the formation of these macromolecules, since, for hemicarceplex **27**·guest in particular, higher than statistically predicted yields are only possible if the two hemispheres are properly aligned. Furthermore, Paek et al. have shown that increasing the length of the interbowl linkers dramatically reduces the yields of the corresponding hemicarcerand. Thus, hosts **34a**−**c** were isolated in 25, 26, and 10% yields, respectively,[28a] which are more in accordance with the statistically predicted yield of 28%.[58] In the latter examples, due to the lengths of the linkers, the charged hydrogen-bonded complex is not expected to be terribly significant to the reaction transition state of the GDSs. Alternatively, the low yields may result from DMA (i.e., the template used in the reaction) simply being a poor template in the formation of these hosts.

Guest exchange was achieved by initially refluxing solutions of hemicarceplexes **27a**·DMA, **27a**·DMF, and **27a**·DMSO in mesitylene or 1,2,4-trichlorobenzene and then exposing the resultant hemicarcerand to an appropriate guest.[48,53] Complexes with a range of small molecules were thus obtained, the most notable being **27**·α-pyrone, **27a**·Et_2NH, **27a**·$BuNH_2$, **27a**·Xe, **27a**·H_2O, **27a**·N_2, **27a**·O_2, and **27a**·CO_2. However, the last four complexes were only stable for observation by NMR spectroscopy. Addition of TFA-d_1 to chloroform solutions of **27a**·Et_2NH and **27a**·$BuNH_2$ resulted in decomplexation of the putative charged complexes.[48] Apparently, separation of the charged ammonium anion from its counterion destabilizes these complexes. The slower rate of decomplexation observed for **27a**·$BuND_3^+$ than that for **27a**·$Et_2ND_2^+$ probably reflects the fact that in the latter complex the charge resides near the portal, whereas in the former case the charge is more likely situated at the polar regions. Thus, the butylammonium molecule has to undergo a high-energy reorientation in order to exit charge-first. Although the majority of host−guest chemistry of hemicarceplexes has been conducted in solution, Charles Wilkins' group has shown that in the gas phase hemicarcerands **27a** and **32a** (R = CH_2CH_2Ph) exhibit the same binding properties as in solution.[59]

2. Small Hemicarceplexes Containing Four Slotted Portals

An alternative and more widely adopted approach to hemicarceplexes relies on expanding the distance between the two bowls by varying the interhemispheric linkers of a carceplex (Scheme 10). This

Scheme 10

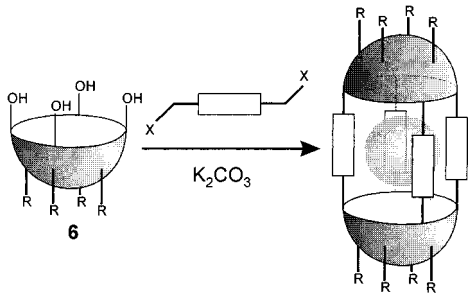
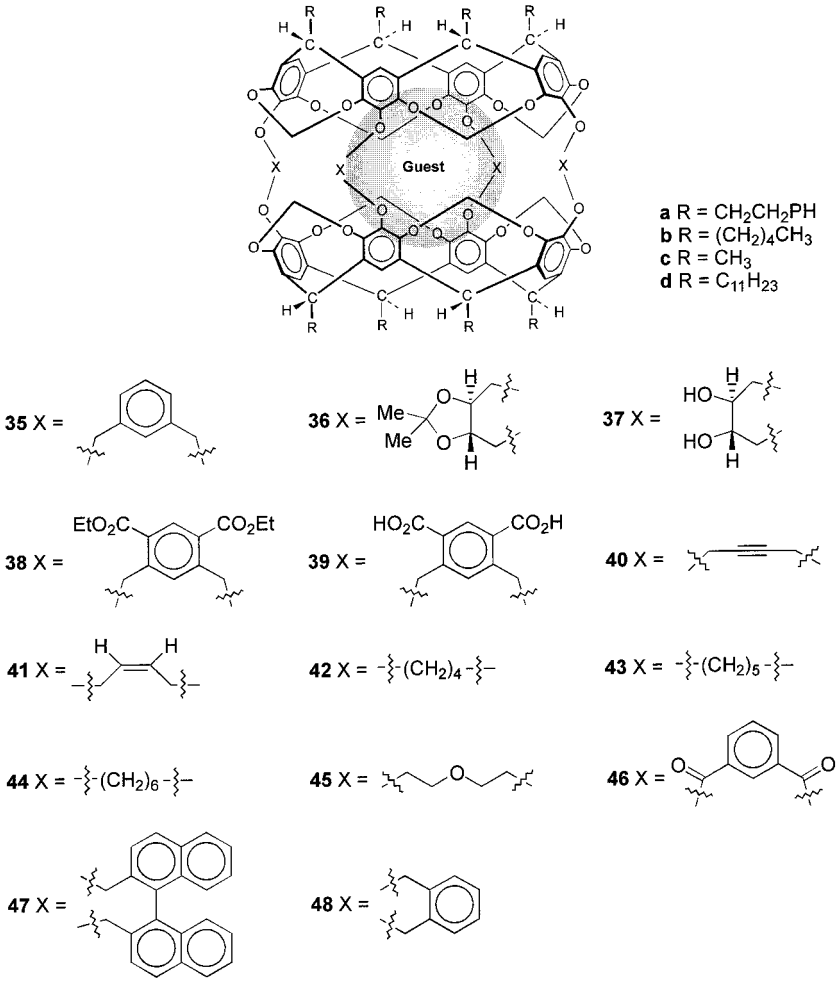
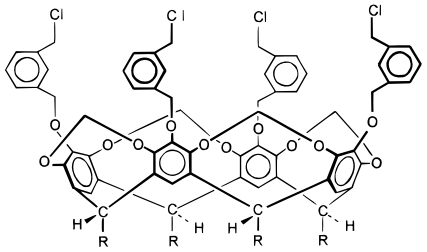


Chart 1



essentially creates a slot-type structure with four portals equally spaced throughout the longitudinal axis of the shell. The cavity shape and size is unique to each hemicarceplex, depending on the bridging units. The basic synthetic strategy (i.e., a "2 bowl + 4 linker" approach) is the same as that used for carceplex **7**·guest, as tetrol **6** served as the basic building block for **7**·guest as well as for a large number of hemicarceplexes. Thus, the versatility of this approach is evident by the large variations in hemicarceplexes and hemicarcerands (i.e., **35**−**48**) reported to date,[32,60−71] as summarized in Chart 1.

With α,α′-dichloro-*m*-xylene and tetrol **6b**, in NMP, hemicarcerand **35b** was isolated in 50% yield.[32] Alternatively, effecting the shell closure in a two-step sequence by initially converting tetrol **6b** to its tetra(chloroxylyl) derivative **49** and subsequent reaction between the latter and **6b** resulted in only a 2.2% yield of hemicarcerand **35b**. Thus, it appears that NMP does indeed template the direct formation of **35b** from tetrol **6b** but escapes during workup. The initially formed complex **17**·NMP preorganizes the two bowls for subsequent bridging in this instance. In the stepwise approach, on the other hand, formation of this complex reduces the concentration of free tetrol, thereby inhibiting shell closure with **49**. Conceivably, reaction between this complex (**17**·NMP) and **49** leads to an intermediate that is poised for oligomerization.



49 R = $(CH_2)_4CH_3$

A 1:2.33 mixture of **35b**·Ph_2O:free **35b** was obtained when the shell closure was performed in the presence of 5% (v/v) diphenyl ether.[60] Alternatively, heating free **35b** in a 1:1 mixture of coumarin and diphenyl ether at 165 °C over 48 h furnished a 60% yield of a 3:1 mixture of the free host:**35b**·Ph_2O. Nevertheless, the pure complex was successfully isolated by complexing the residual free host with 2,3-dimethyl-2,3-dihydroxybutane and subsequent purification by preparative TLC.[60] Hemicarceplex **35b**·Ph_2O is unique in that, unlike all known carceplexes and hemicarceplexes to date, the guest molecule does not rotate rapidly about any host axis on the NMR spectroscopic time scale. The restricted mobility of diphenyl ether obviously arises from the noncomplementarity of the inner phase of host **35** and diphenyl ether. Stable complexes with six other guest molecules (1,1,2,2-tetrabromoethane, pinacol, pinacolone,

tert-butylbenzene, 3,4,5-trimethoxyphenol, and 1,2,3-trimethoxybenzene) were also successfully isolated and characterized. In addition, fleeting evidence for complexes with toluene, acetophenone, *o*-dimethoxybenzene, *p*-dimethoxybenzene, and 4-methylanisole was obtained by ^{1}H NMR spectroscopy.[60]

Very recently, chiral hemicarceplexes (*S*,*S*)$_4$-**36a**·guest were prepared by Cram et al. with DMSO (16%), DMF (20%), and DMA (22%) incorporated.[61] Subsequent cleavage of the acetonide functionality of (*S*,*S*)$_4$-**36a**·DMA in refluxing THF containing a catalytic amount of concentrated HCl furnished (*S*,*S*)$_4$-**37a**·DMF in 80%. However, under the same conditions with (*S*,*S*)$_4$-**37a**·DMSO and (*S*,*S*)$_4$-**37a**·DMF the deprotection proceeded with concomitant decomplexation. The ^{1}H NMR spectrum of (*S*,*S*)$_4$-**36a**·DMSO exhibited two temperature independent (from −80 to 180 °C) singlets for the two methyl groups at δ −0.91 and −1.03 ppm in $CDCl_3$, thereby reflecting their diastereotopic nature in the asymmetric environment of the chiral host. Similarly, the ^{i}PrOH complex (*S*,*S*)$_4$-**36a**·^{i}PrOH exhibited two sets of signals for the two diastereotopically related methyl groups. Preliminary complexation experiments revealed that free host (*S*,*S*)$_4$-**36a** demonstrates chiral recognition toward asymmetric guests. For instance, heating (*S*,*S*)$_4$-**36a** in a 1:4 (v/v) mixture of Ph_2O and (±)-2-BuOH furnished a 2:1 ratio of diastereomeric complexes, which incidentally are separable by preparative TLC.

Hydrolysis of the ester moieties of hemicarcerand **38c** provided the first reported example of a water-soluble hemicarcerand (**39c**).[62] Ocatacid host **39c** complexes water-soluble organic molecules within minutes at ambient temperature in buffered (pH 9) D_2O. These guests ranged in polarity from the highly polar DMSO, DMA, NMP, and 4-methyl-5-(2-hydroxy-ethyl)thiazole to the moderately polar diethylamine, 2-butanol, and *p*-toluidine and the relatively apolar *p*-xylene, 1,4-dimethoxybenzene, and 1,3-dimethoxybenzene. Guests that have low solubility in water such as naphthalene required up to 12 h for complete complexation. Interestingly, complexes **35**·*p*-xylene and **35**·1,4-dimethoxybenzene rapidly decomplex at ambient temperatures in $CDCl_3$ with respect to the ^{1}H NMR time scale, thus inhibiting NMR spectroscopic characterization.[62] In contrast, host **39c** with analogously sized bridges forms stable complexes with both these guests in D_2O. This, however, is not too surprising since hydrophobic effects are expected to contribute more to the stability of **39**·guest in D_2O than solvophobic effects do to **35**·guest in $CDCl_3$.

Hemicarcerand **40a** was synthesized in 6.5% yield from 1,4-(ditosyloxy)-2-butyne and tetrol **6c**.[63] Analogously, hemicarceplex **41a** was obtained in 25% yield as a mixture of **41a**·DMA and **41a**·$CHCl_3$ (20:1) from **6c** and *cis*-dichloro-2-butene,[63] guest exchange for the latter having occurred during isolation. Apparently, chloroform and dichloromethane enter and depart the cavity of **40a** rapidly on the human time scale, but slowly on the ^{1}H NMR time scale. Complexes of **40a** with $CHCl_3$, $CF_3OC_6H_5$, $CF_3C_6H_5$, *p*-xylene, $CHCl_2$-$CHCl_2$, and (*S*)-(+)-1-bromo-2-methyl-butane and for **41a** with DMA, ethyl acetate, toluene, and *p*-xylene were successfully prepared. Catalytic hydrogenation of hemicarceplexes **40a**·*p*-xylene and **40a**·$CHCl_2$-$CHCl_2$ over Pd/C yielded the corresponding hemicarceplexes **42a**·guest without loss of the guest. Attempts to directly prepare **42a**·$CHCl_2CHCl_2$ from hemicarcerand **42a** were unsuccessful.[64]

Hemicarceplex **42a**·DMA and the pentyl-footed analogue **42b**·DMSO were also directly synthesized from tetrol **6** and $TsO(CH_2)_4OTs$ in much improved yields (40% and 18%, respectively).[64] Likewise, by successively increasing the length of the linker by one and two more methylenes (respectively), the pentamethylene and hexamethylene bridged hemicarcerands **43a** and **44a** were obtained in ca. 20% yields.[65] Markedly improved yields of both these hemicarcerands were obtained (51% and 27%) when the reaction was templated with veratrole. Preliminary work by our group clearly indicates that the formation of hemicarceplex **42a**·guest from tetrol **6c** is a highly template-directed process, analogous to that of carceplex **7**.[66] Cram et al. reported the final variation on this basic theme in 1995. Here, shell closure of tetrol **6c** with diethylene glycol ditosylate afforded hemicarcerand **45a** in 40−47% yields.[67] This series of hemicarcerands (i.e., **42**−**45**) differ only in the lengths of their interbowl linkers, and therefore they allow for an interesting comparison of the effects of such increments in cavity size on the complexation properties. Not surprisingly, the two penta-atom-bridged hemicarcerands, **43**[65] and **45**,[67] display virtually identical complexation properties. These hosts formed stable complexes with larger straight-chain guests such as $CHCl_2CHCl_2$ and (±)-MeCHBrCH-BrMe, cyclic species such as 12-crown-4, *ortho*- and *para*-disubstituted (halo and methoxy) benzenes, trisubstituted benzenes (e.g., 1,2,3-trimethoxybenzene, 1,2,3-tribromobenzene, and 4-bromoveratrole), monohalo- and 1,2-dibromo-substituted cylcohexanes, and various bicylic, tricyclic, and quadracylcic compounds (e.g., naphthalene, 2,5-norbonandiene, norbonene, *exo*-norborneol, 2-norbornanone, norbornane, *exo*-2,3-epoxynorbornane, 7-oxabicyclo[2.2.1]heptane, and quadricyclane).[65,67]

Tetramethylene-bridged hemicarcerand **42** has so far proved to be the most versatile of this group.[11b,14,15,64,68] To date, a large number of complexes have been reported with guests ranging from acyclic molecules, such as DMSO, DMA, ethyl acetate, iodoethane, and acetone, to cyclic five-membered rings, such as cyclopentanone, 2-cyclopenten-1-one, γ-butyrolactone, and γ-butyrolactam, bicyclic systems (e.g., naphthalene), and a series of mono, *ortho*-, *meta*-, and *para*-disubstituted and 1,2,3-trisubstituted benzene rings. Of these, host **42** was found to exhibit some degree of structural recognition with a strong preference for complexation of *p*-disubstituted benzene molecules over equivalently substituted *o*- and *m*-disubstituted benzene rings.[64] Moreover, X-ray structural data of free host **42** and that of the *p*-diodobenzene, *p*-xylene, nitrobenzene, DMA, and 2-bromophenol complexes indicate that this host can adjust its cavity size to maximize the host−guest interactions. Notably, in free host **42a**, the polar caps are twisted with respect to each other by 15° about

the polar axis.[64] Consequently, this arrangement brings the rims of the two polar caps into contact with each other, thereby maximizing the number of stabilizing hydrogen-bonding interactions. On the other hand, in all hemicarceplexes **42**·guest the polar caps are essentially collinear, as demonstrated by their X-ray crystal structures.[64] This generates the maximum cavity size by forcing the bridging methylenes away from the central cubed cavity defined by the eight oxygens attached to these groups. It also enables the lone pairs of electrons of the oxygens at the termini of the interhemispheric bridges to point into the cavity, thus compensating for the dipoles created by the two outwardly oriented flanking oxygens of the intrahemispheric bridges. In contrast to the solid state structures of **42**·guest, in hemicarceplexes **43**·$4CH_3CN$ and **45**·$(2CH_2Cl_2,2H_2O)$ one pair of the eight oxygens (i.e., the interbowl bridgehead phenyl oxygens) defining the cuboidal cavity in each hemisphere has its lone pair directed away from the internal cavity.[65,67] Thus, the interbowl linkers are partially directed inward, toward the central cavity, thereby increasing the interbowl bridge lengths. Consequently, the two near square planes defined by these four bridgehead phenyl oxygens within each hemisphere are displaced by 3.02 and 2.67 Å in **43**[65] and **45**[67] (respectively) from possessing a common perpendicular axis. In both complexes, however, the two hemispheres are not rotated with respect to each other.

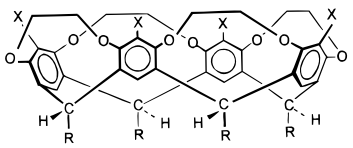
As expected, the larger hexamethylene derivative **44a** only formed stable, isolable hemicarceplexes with fairly large guests such as 2-adamantanone, 12-crown-4, and 15-crown-5.[65] Nonetheless, the large range of guests that were both successfully and unsuccessfully complexed with this series of hosts (i.e., **42**−**45**) nicely demonstrates that as the interhemispheric bridges get longer, the resultant host becomes more adaptable to guest entry and departure. Tetramethylene-bridged host **42** forms the most kinetically stable hemicarceplexes (in solution) in this series.[64,65,67]

Treating tetrol **6b** with isophthaloyl dichloride and Cs_2CO_3 at 65 °C in DMA provided the octalactone hemicarceplex **46a**·CH_2Cl_2 in rather poor yield (5%).[69] This hemicarceplex readily undergoes guest exchange between 110 and 125 °C with 1,1,2,2-tetrachloroethane, *o*-dichlorobenzene, and acetylmorpholine. An X-ray crystal structure of **46a**·$Cl_2CHCHCl_2$ revealed that each of the lactone bridging groups have one carbonyl group pointing into the cavity and the other directed outward.[69] Within each hemisphere, these carbonyls are arranged in an *in-in-out-out* manner. At ambient temperature, hemicarceplex **46a**·$Cl_2CHCHCl_2$ adopts the same conformation as in the solid state, as was implied by the ^{1}H NMR spectra in $CDCl_3$. Upon warming (in $Cl_2CDCDCl_2$), a more symmetrical time-averaged spectrum results, with a $\Delta G^{\ddagger}$ of 18 kcal mol^{-1}.

Under similar conditions, the enantiomerically pure hemicarceplexes $(R)_4$-**47a**·$CHCl_3$ (12%) and $(S)_4$-**47a**·$CHCl_3$ (13%) were subsequently prepared by Cram and Judice.[70] These hemicarceplexes readily undergo guest exchange when heated in the presence of *p*-xylene, 2-iodobutane, 2-butanol, or 1-bromo-2-methylpropane. More interestingly, both these hemicarceplexes exhibit chiral recognition toward racemic 1,2-dibromobutane, furnishing a 2:1 ratio of diastereomeric complexes. The chiral discrimination factors determined for these hemicarceplexes ($(S)_4$-**47a**·$CHCl_3$ and $(R)_4$-**47a**·$CHCl_3$) with 1,2-dibromobutane are of similar magnitude to that of free (*S*,*S*)-**36a** and racemic 2-butanol. The smaller *o*-xylyl-bridged hemicarceplex **48a**·DMA has also been prepared by Cram et al., using the basic strategy outlined in Scheme 9.[71] Guest incorporation in this hemicarceplex was effected by heating either the preformed hemicarcerand **48a** or the hemicarceplex **48a**·DMA in an appropriate solvent (guest). However, monitoring the guest exchange in **48a**·DMA by ^{1}H NMR spectroscopy indicates that this substitution proceeds via a two-step mechanism in which the empty hemicarcerand is initially formed followed by complexation of the second guest. Twelve new complexes were thus obtained. Of these, the largest guests incorporated were ethylbenzene, *p*-xylene, and 1,1,2,2-tetrachloroethane. Furthermore, hemicarcerand **48a** exhibited exclusive binding toward *p*-xylene over *o*- and *m*-xylene, a feature reminiscent of the tetramethylene-bridged hemicarcerands **42** described above. This shape selectivity obviously attests to the slot-shape portals of these hemicarcerands. In this regard, the X-ray crystal structure of **48a**·DMA revealed that the two polar caps are rotated by 21° with respect to each other.[71] This twist effectively closes the portals while simultaneously increasing the number of close contacts between the atoms at the rims of the hemispheres and those of the interbowl bridges. In addition to various other common organic solvents (e.g., THF, acetonitrile, DMF, ethyl acetate, chloroform, butanol, 2-butanone, toluene, and 1,1,2,2-tetrachloroethane), smaller homonuclear diatomic molecules (O_2 and N_2) were also complexed. Not surprisingly, these much smaller molecules are only weakly bound.

3. One-Step versus Two-Step Syntheses of Hemicarceplexes

The wide range of guests incorporated in hosts **35**, **42**−**45**, and **48** undoubtedly prompted Cram's group



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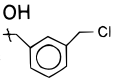
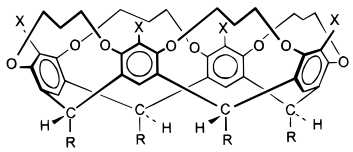
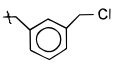
51 X = 

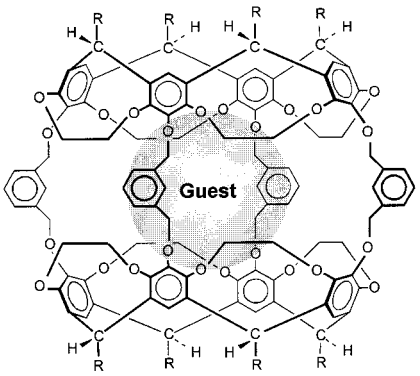


52 X = OH

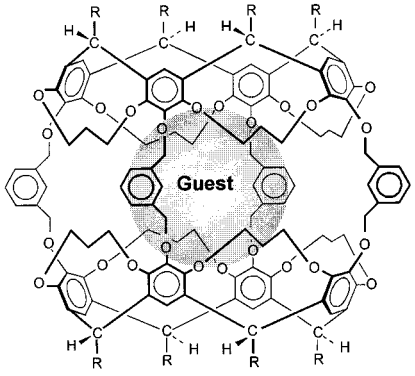
53 X = 

R = $(CH_2)_4CH_3$

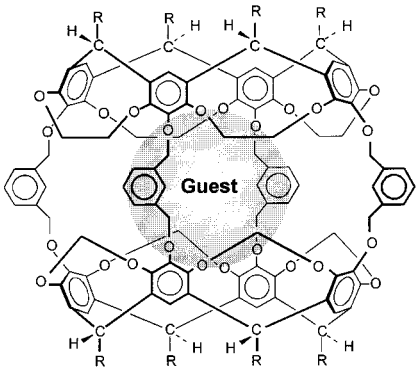
Chart 2



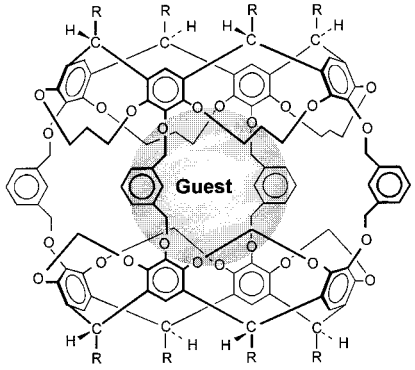
54



55



56



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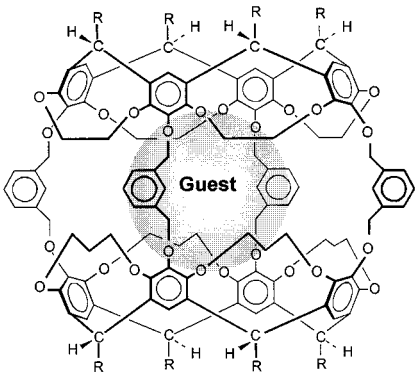


58

$R = (CH_2)_4CH_3$

to extend their investigation to a series of hosts in which the cavity shape could be altered.[32] Synthetically, this was achieved using ethylene- and propylene-bridged tetrol cavitands **50** and **52** and their tetraalkylated derivatives **51** and **53**. The shell-closure reactions of these two tetrols (i.e., **50** and **52**) with α,α′-dichloro-*m*-xylene in NMP revealed some interesting results. For instance, an 8% yield of hemicarcerand **54** (Chart 2) was obtained by treating tetrol **50** with α,α′-dichloro-*m*-xylene, but under the same conditions tetrol **52** failed to yield the corresponding hemicarcerand **55**. The latter hemicarcerand was finally isolated in 6% by shell closure involving the sequential construction of four bonds by reacting tetrol **52** with its tetrachloride derivative **53**; however, the reaction was successful only in the presence of 5% (w/w) 1,2,3-trimethoxybenzene. When this "1 + 1" approach was applied to tetrol **50** and tetrachloride **51**, the yield of hemicarcerand **54** improved dramatically (to 43%) over that via the "2 + 4" route described above. Molecular models of tetrols **50** and **52** (based on the conformations determined by X-ray crystallography of **50** and the tetrabromide cavitand precursor to **52**)[32] indicate that these cavitands are inadequately preorganized for the simultaneous 4-fold hydrogen bonding which we have shown predisposes tetrol **6** to subsequent shell closure. This notion is further supported by the synthesis of asymmetric hemicarcerand **56** and hemicarceplex **57**·1,2,3-trimethoxybenzene. Here, higher yields of **56** and **57**·1,2,3-trimethoxybenzene were obtained via this "1 + 1" strategy when tetrols **50** and **52** were reacted with tetrachloride **49** than when tetrol **6b** was reacted with tetrachlorides **51** or **53** (cf. 21 and 1.8% versus 2 and 0%), respectively. Undoubtedly, in the latter cases, tetrol **6b** most probably exists as its ternary complex **17**·NMP under these reaction conditions, thus lowering the concentration of free **6b**

available for reaction with **51** or **53**. Consistent with this interpretation, treating tetrol **52** with **51** or tetrol **50** with **53** furnished hemicarceplex **58** in 30 and 20% yield, respectively.

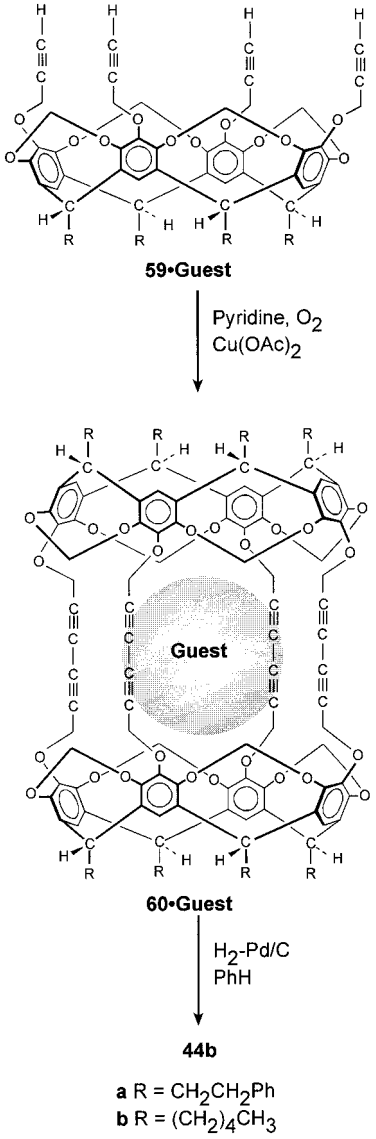
The complexation properties of these hosts have very recently been extensively studied by Cram and Helgeson.[60] Generally, hemicarcerands **54** and **58** display similar binding affinities for mono- and disubstituted benzenes (such as toluene, acetophenone, *tert*-butylbenzene, xylenes, 1,2-dimethoxybenzene, 2-methylanisole, 2-haloacetophenones, etc.), 1,2,3-trimethoxybenzene, and coumarin. Unfortunately, due to the poor yields of hemicarcerands **55**, **56**, and **57**, complexation has thus far been limited to *tert*-butylbenzene and 1,2,3-trimethoxybenzene with these hosts. Hemicarcerand **54** reportedly displays a high degree of structural recognition toward isomeric guests. For instance, complexation with 98% *tert*-butylbenzene (containing ~2% *sec*-butylbenzene) resulted in a 2:1 ratio of **54**·*tert*-butylbenzene to **54**·*sec*-butylbenzene. Furthermore, these hosts generally strongly favor binding of 1,2-disubstituted benzenes over 1,3- and 1,4-disubstituted benzene isomers.

X-ray crystal structures of **54**·4-MeC_6H_4OMe, **56**·4-MeC_6H_4OMe, **58**·4-MeC_6H_4OMe, and **58**·1,2-$(MeO)_2$-C_6H_4 have been reported.[60] The exact orientation of the disymmetric 4-MeC_6H_4OMe with respect to the two different bowls in hosts **56** and **58** could not be determined. Nevertheless, the crystal structures provided a quantitative measure of the effects of the intrabowl linkages on cavity size. Thus, the distance between the two polar axes (i.e., the distance between the four aryl carbon atoms at the northernmost and southernmost regions of the hemicarcerand) successively decreases in going from bowls with ethylene intrabowl linkages to those with propylene linkages (**56**·4-MeC_6H_4OMe (11.66 Å) > **54**·4-MeC_6H_4OMe (11.30 Å) > **58**·4-MeC_6H_4OMe (10.85 Å)). On the other hand, as expected, the equatorial axes increase in length in going from **58** (9.58 Å) to **56** (10.34 Å). Extrapolating this to the all-propylene-bridged complex **55**·4-MeC_6H_4OMe indicates by computational analysis that, in this host, the equatorial axis length (10.73 Å) exceeds the polar axis length (10.40 Å). Thus, in this host the guest can potentially lie across the equatorial region of the cavity, without deeply penetrating the polar caps.

4. Hemicarceplexes with Significantly Large Cavities

The hemicarcerands discussed to this point generally exhibit strong binding affinities toward relatively small guests, with a strong preference for polysubstituted benzene rings. Although fairly large polycyclic guests such as nobornene, *exo*-2,3-epoxynorbornane, 2-adamantanone, and quadricyclane, have been successfully encapsulated in the pentamethylene- (**43**),[65] hexamethylene- (**44**),[65] and diethylene glycol-bridged (**45**)[67] hemicarcerands, the flexibility of these bridges renders a vast majority of these complexes with poor kinetic stability. This instability is more pronounced in the hexamethylene-bridged derivative **44**,[65] as is evident by the limited number of hemicarceplexes (**44**·guest) isolated with this host. In an effort to address these limitations, Cram's group embarked on

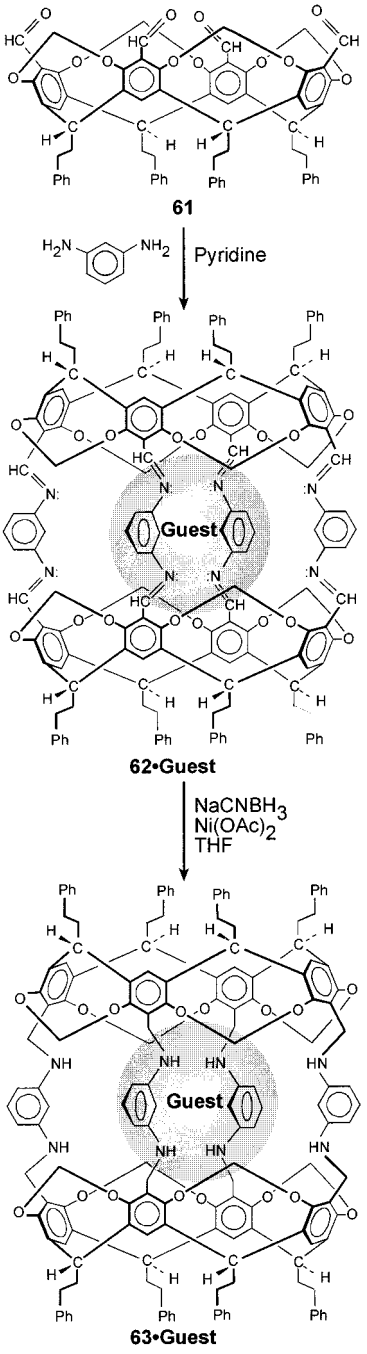
Scheme 11



the syntheses of a series of hosts with substantially larger cavities but with more rigid interbowl bridges.

Oxidative coupling of the tetraacetylenic ethers **59a** and **59b** (Scheme 11) provided bisacetylene-bridged hemicarcerands **60a** and **60b** in rather low yields (8 and 5.6%, respectively).[72] The low yields obtained here undoubtedly result from the lack of an appropriate template to direct the exclusive formation of the dimeric capsule. Despite this, these researchers isolated sufficient quantities of these hosts to further investigate their complexation properties. The larger cavity size and rectangular shape of the portals is evident in the shape and size of guests complexed. Generally, bulky trisubstituted benzenes (e.g., 1,3,5-triethylbenzene and 1,3,5-triisopropylbenzene), 1,3-dimethyladamantane, and a range of [*m*,*n*]paracylclophanes (such as [2,2]-, [2,3]-, and [3,3]paracyclophane, di- and tetradehydro[2,2]paracyclophane, and 4,12-dihdyroxy[2,2]paracyclophane, for example) formed stable, isolable complexes.[72] Catalytic hydrogenation over Pd at 10 psi cleanly provided the hexamethylene-bridged hemicarcerand, **44b**. It should be noted, however, that the phenethyl-footed analogue (**44a**) of the latter hemicarcerand has since been directly

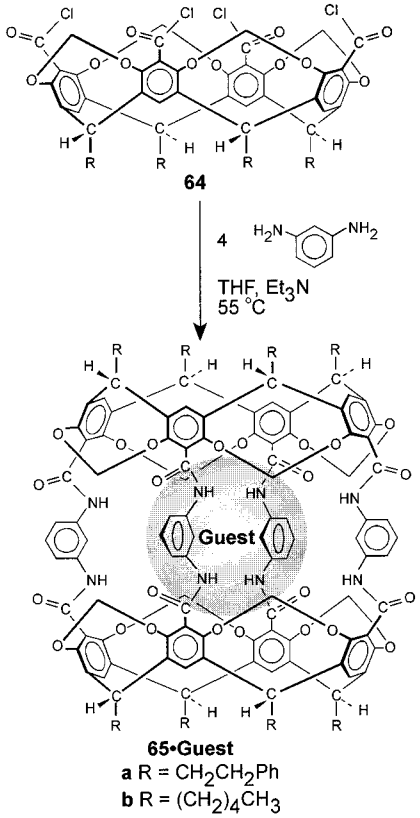
Scheme 12



synthesized by Cram et al. in higher overall yield from tetrol **6b**.[65]

The octaimine hemicarcerand **62** was prepared by a 4-fold shell closure of the tetraformyl bowl **61** with 1,3-phenylenediamine in average yield (45%).[73] As with the previous example, this hemicarcerand possesses a substantial internal cavity. Thus, fairly large guest molecules such as [2,2]paracyclophane, ferrocene, ruthenocene, camphor, amantadine, menthol, anthraquinone, and 9-cyanoanthracene readily form stable complexes.[73,74] A single-crystal X-ray structure of the pentyl-footed derivative of **62**·ferrocene has been determined.[75] In this solid state structure, all the imino groups have their two attached aryl groups arranged anti to one another, with the four bridging 1,3-diiminobenzene moieties dispersed perpendicularly outward from the central cavity akin to a paddle

Scheme 13



wheel. Reduction (Scheme 12) of free host **62** or **62**·[2,2]paracyclophane with $Na(CN)BH_3/Ni(OAc)_2$ in THF provided the corresponding amino-bridged hemicarcerand **63** and hemicarceplex **63**·[2,2]paracyclophane.[76] In a feature reminiscent of these researchers' experience with hemicarcerands **41a** and **42a**,[64] hemicarcerand **63** failed to bind [2.2]paracyclophane under conditions identical to those employed in the preparation of **62**·[2,2]paracyclophane. Clearly, reduction of the imine groups reduces the overall portal size thereby hindering complexation.[76] If the opposite were true, one would expect reduction of **62**·[2,2]-paracyclophane to proceed with concomitant decomplexation.

Despite the large cavity size of **62**, which endows this hemicarcerand with interesting binding properties, both this hemicarcerand and the octalactone derivative **46a**·$Cl_2CHCHCl_2$ are readily susceptible to hydrolysis. Consequently, Cram and co-workers synthesized the more stable octamide derivatives **65a**,**b** in rather poor yield (7%), as reviewed in Scheme 13.[77] Unfortunately, **65a**·1,4-diacetoxybenzene proved to be the only stable, isolable hemicarceplex of these hosts, with a range of potential guests including aspirin, adamantane, 1,4-diisopropylbenzene, menthol, azulene, bromobenzene, 3-brormotoluene, 4-methylanisole, tetrachloroethane, 1,4-dibromobenzene, and *N*,*N*′-tetramethylterephthalic diamide. In the X-ray crystal structure of the free host **65a**, the cavity was found to contain seven water molecules. The formation of a hydrogen-bonded network between the host and guests and among the guest molecules themselves undoubtedly stabilizes this complex. Another noteworthy feature gleaned from this crystal structure was that the two bowls are displaced by ap-

proximately 1.9 Å with respect to each other, thereby giving the hemicarceplex the skewed conformation depicted in Figure 4.

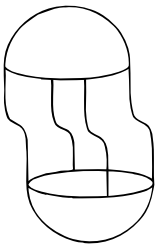
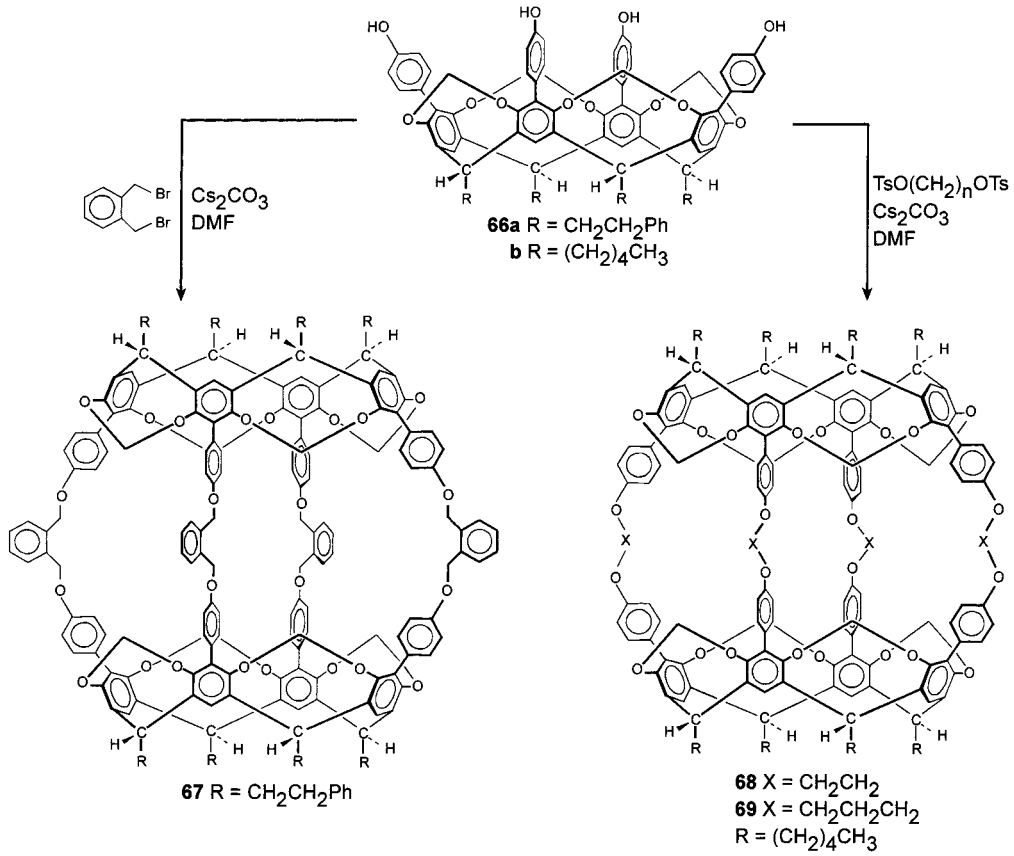


Figure 4. Skewed topology of **65a**.

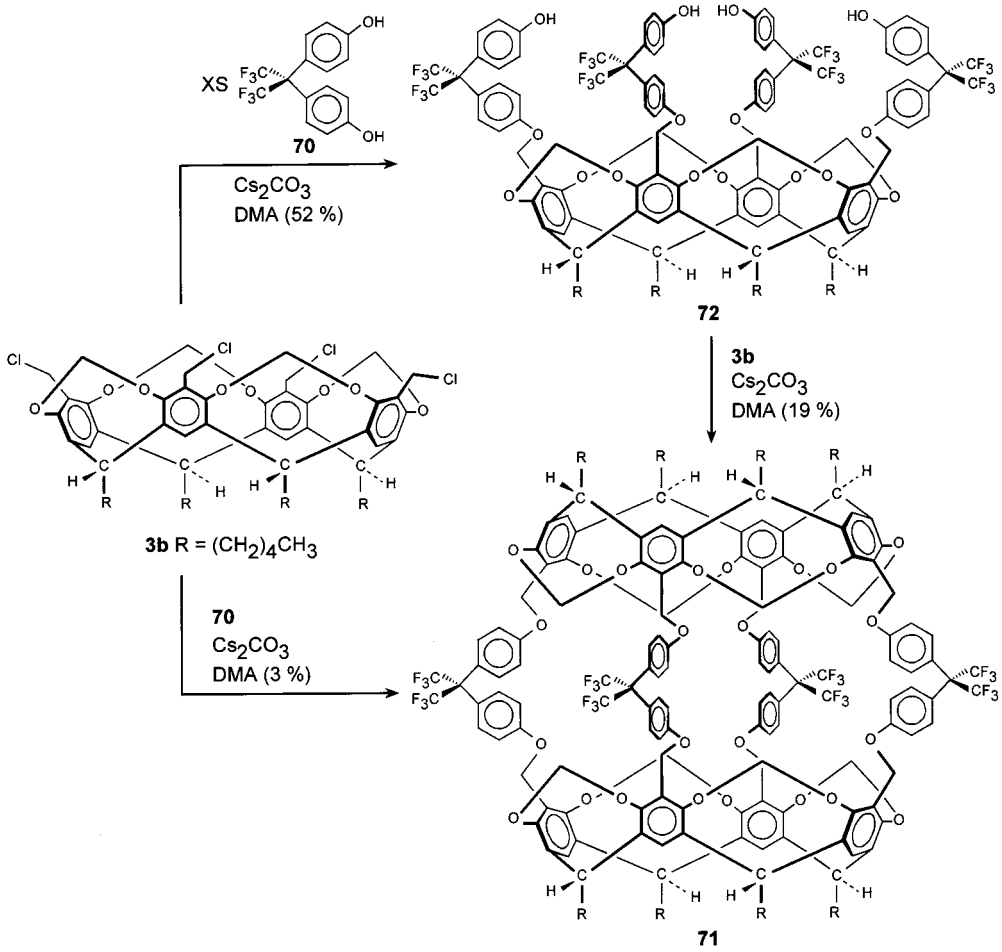
Continuing on their work in this area, a series of even larger macrocyclic hosts based on the extended cavitands **66a**,**b** were isolated (Scheme 14).[78] Thus, the macrocyclization of tetrol **66a** with α,α′-dibromo-*o*-xylene in DMF furnished the first member (**67**, 17%) in this series of large hosts. Analogously, treating **66b** with ethyleneditosylate and propyleneditosylate provided macrocyclic hosts **68** and **69** (respectively, in 30−32% yield). No guests have been successfully complexed within these hosts to date, and therefore, these compounds cannot be considered as true hemicarcerands. While CPK models and MM2 force field calculations predict that large guests such as C_{60} and tetraphenylporhyrin (TPP) are ideally suited for the internal cavity of **67**, attempts to incarcerate these guests met with little success. The failure to encapsulate C_{60} and TPP was rationalized on account of the large activation energy barrier for complexation of these two guests by **67**. Interestingly, the X-ray crystal structure of **67** provides evidence for the presence of an encapsulated guest molecule. However, the exact nature of this guest could not be determined due to the high degree of its disorder in the crystal structure.

Treating tetrabenzyl chloride bowl **3b** with diol **70** in the presence of Cs_2CO_3 gave hemicarcerand **71** in very low yield (3%).[78] Alternatively, better yields resulted when tetraalkylated bowl **72** was capped with the tetrabenzyl chloride **3b** (Scheme 15). The observed increase in yield using this "1 + 1" approach clearly attests to the role of preorganization in the product yields in these shell-closure reactions forming the corresponding hemicarcerands. Indeed, Cram et al. have successfully exploited this effect in their syntheses of hemicarcerands **54**−**58**.[32] No complexation studies of hemicarcerand **71** have been reported to date. Paek's group treated benzylthiol bowl **4** with 1,2,4,5-tetrakis(bromomethyl)benzene and Cs_2CO_3 in DMA, furnishing **73** in 15% yield (Scheme 16).[79] The NOESY spectrum of **73** and MM+ force field calculations indicate that **73** exists in a closed conformation, in which the two bridging aromatic rings are held parallel to each other within the cavity by weak $\pi-\pi$ interactions (as depicted schematically in Figure 5). Consequently, this hemicarcerand is not expected to display interesting binding properties, since this conformational arrangement divides the central cavity into two smaller ones. This alignment of the aromatic bridging units undoubtedly provides some conformational stability to **73**. Indeed, variable temperature ^{1}H NMR spectroscopy (−40 to 150 °C) indicates that **73** is conformationally locked. The high

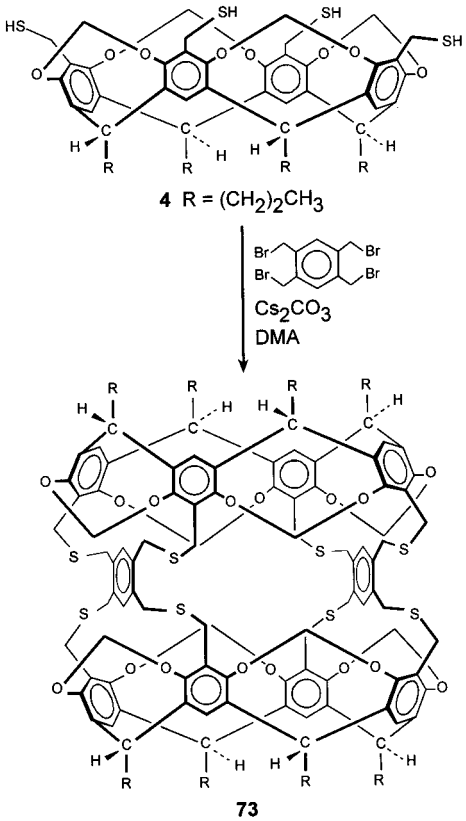
Scheme 14



Scheme 15



Scheme 16



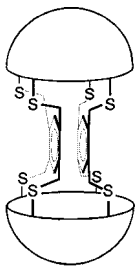


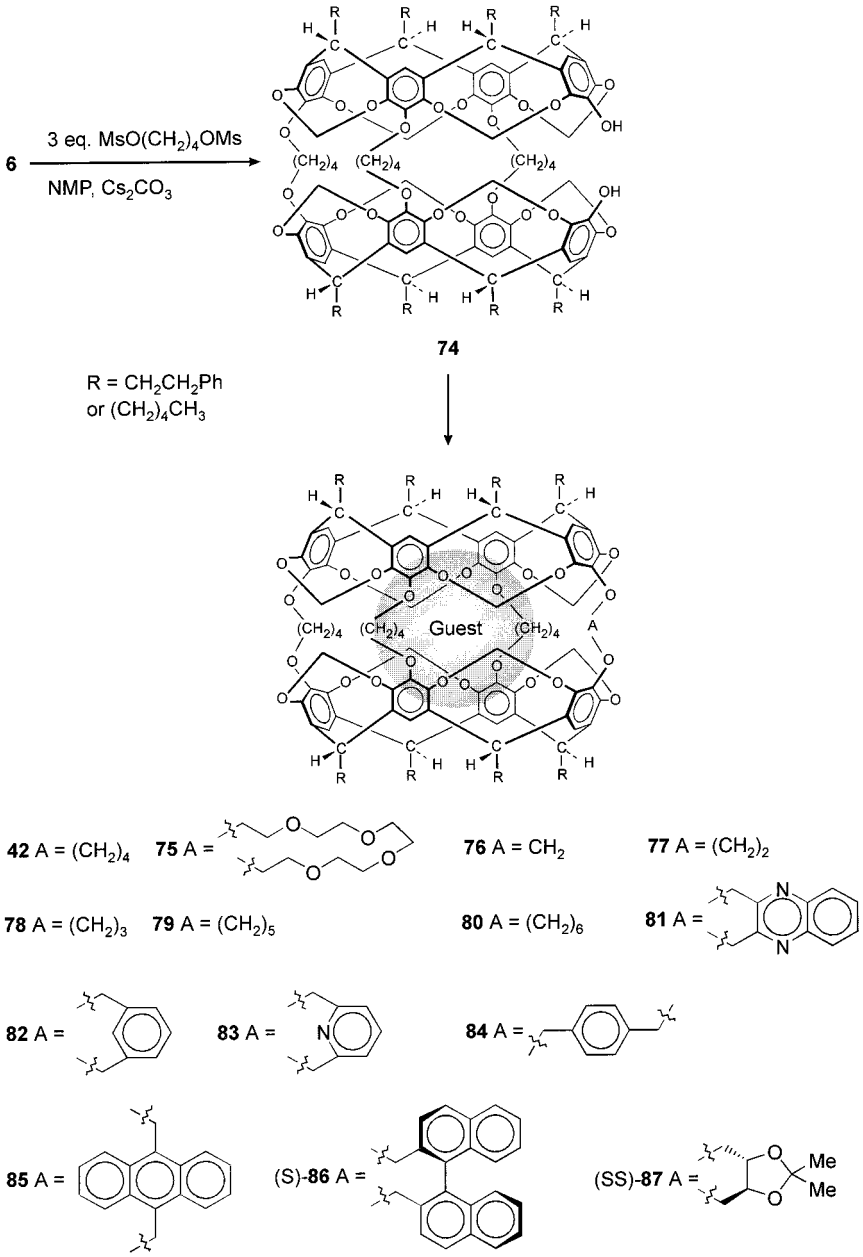
Figure 5. Schematic representation of the conformation of **73**.

rotational barrier around the thia ether moieties must also lend additional stability to this conformation. Moreover, the $\pi-\pi$ interactions that bring these two aryl units into the cavity may also enable the phenyl groups to template the formation of **73**.

5. Dissymmetric Hemicarcerands

Exploiting the fact that formation of the fourth bridge is usually the slowest step in the syntheses of many of the container molecules discussed this far,[48] Cram's group prepared a series of dissymmetric hemicarceplexes, **75**−**87** (Scheme 17).[15,80−82] The key intermediate, diol **74**, was readily available in moderate yield (30−40%, Scheme 17).[15,80] Subsequent shell closure with an appropriate alkylating agent in NMP, DMSO, DMF, DMA, or HMPA either in the presence or in the absence of another suitable guest

Scheme 17



molecule provided the corresponding hemicarceplexes or hemicarcerands shown. Other complexes were prepared via the now standard thermally induced guest exchange procedure. These include complexes with naphthalene, various 1,2-, 1,3-, and 1,4-disubstituted benzenes (e.g., *p*-xylene, 1,2-, 1,3-, and 1,4-dimethoxybenzene, 4-methylanisole, and *o*-cresol), and the bulky 1,2,3-trimethoxybenzene.[80,82] Initially, this stepwise route was utilized as a means for isolating complexes of hemicarcerand **42** with guests that were either too large to pass through this host's portals or too thermally unstable to undergo thermally activated complexation. Indeed, using this approach, guests such as NMP, *N*-formylmorpholine, and 1,4-benzoquinone were successfully complexed with **42** via shell closure of **74** with either tetramethyleneditosylate or tetramethylenedimesylate at ambient temperature.[15]

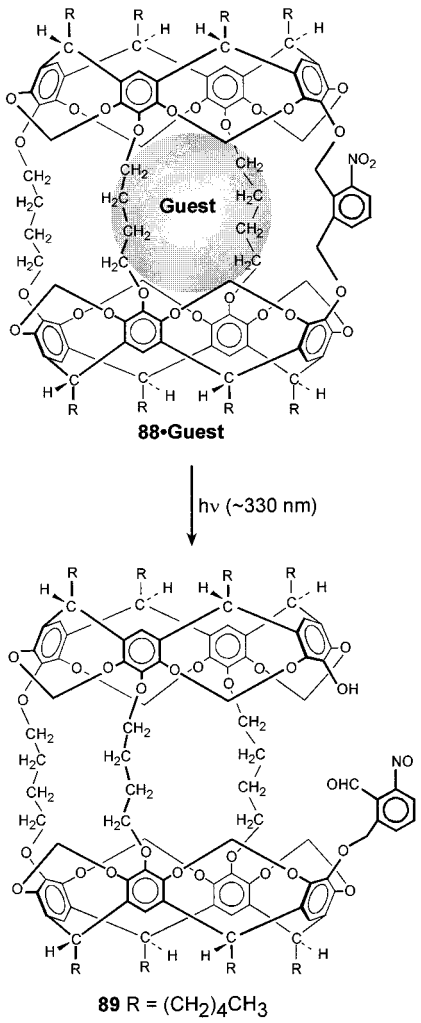
Undoubtedly, dissymmetric hemicarcerands **75**−**87** are among the more interesting hemicarcerands reported by Cram since they may exhibit unusual complexing properties. Additionally, they enable one to probe the effects of variations in linkers on the overall cavity size. Not surprisingly, for the homologous series of hemicarceplexes, **76**·NMP−**79**·NMP, wherein the unique interbowl linker is successively increased by a methylene group, the polar axis of the internal cavity of the resulting hemicarceplex increases with increasing methylene units, although there is very little difference in cavity size between trimethylene-bridged host **78** and tetramethylene-bridged compound **42**. This is consistent with the effective shielding patterns observed for the N−Me group's protons of NMP (which are certainly located in the polar arene-rich regions of the cavity) in the ^{1}H NMR spectra and with force field calculated

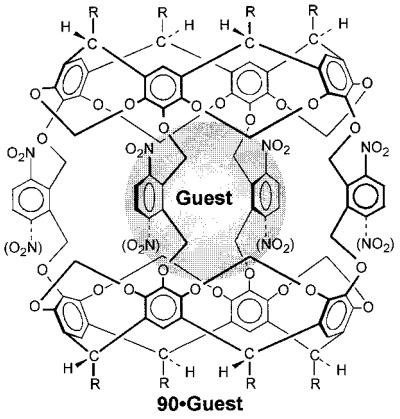
structures of these hemicarceplexes (i.e., **76**·NMP−**78**·NMP).[80] These large shielding effects are more pronounced in hemicarceplexes with more tightly bound larger guests (e.g., NMP) than those with the smaller guests (such as DMSO, for example). Accordingly, in **81**·NMP, the $\Delta\delta$ of the guest protons are surprisingly large. This was explained by the steric requirements of the four-atom 2,3-dimethylenequinoxline bridge of hemicarceplex **81**·NMP which effectively reduces the cavity length of host **81**.

X-ray crystal structures of **79**·4-MeC_6H_4OMe, **82**·$CHCl_3$,[80] and **84**·$PhNO_2$[82] have been determined. Addition of a single methylene group to one of the tetramethylene bridges of **42** has little effect on the topology of the resulting hemicarceplex (i.e., **79**). Thus, the crystal structure of hemicarceplex **79**·4-MeC_6H_4OMe is essentially isostructural to those of the tetramethylene-bridged hemicarceplexes **42**·guest reported to date;[64] incorporation of an *m*-xylyl group rotates the two hemispheres slightly from a perfectly parallel alignment with respect to one another.[80] Additionally, the average distance between the two planes defined by the four bridgehead oxygens in each hemisphere is virtually identical in hemicarceplexes **79**·4-MeC_6H_4OMe (4.10 Å) and **82**·$CHCl_3$ (4.03 Å).[80] The slight variation in this interhemispheric distance between these two hemicarceplexes most likely results from guest effects. However, the two portals flanking the unique *m*-xylyl bridge in this hemicarcerand (i.e., **82**) are, as anticipated, larger than those flanked by the $O(CH_2)_5O$ bridge of **79**. On the other hand, the somewhat more rigid *p*-xylyl group in **84** has an even more dramatic effect on the structure of the resultant hemicarceplex (**84**·$PhNO_2$).[82] Thus, to accommodate this bridging unit, one of the two $O(CH_2)_4O$ bridges adjacent to this xylyl bridge is increased in length (7.98 Å) compared to the other two $O(CH_2)_4O$ bridges (cf. 6.51 and 6.82 Å). Moreover, the two hemispheres are twisted with respect to each other from a parallel arrangement. Consequently, the methylene groups of this long $O(CH_2)_4O$ bridge are turned toward the central cavity, and the lone pair of the corresponding bridgehead oxygen face outward. Collectively, this structural arrangement increases the axial cavity length in **79**·$PhNO_2$ compared to **42**·$PhNO_2$ (cf. 12.15 and 11.28 Å, respectively).

Cram's foray into these dissymmetric hemicarceplexes inevitably led to the synthesis of chiral hemicarcerands (*S*)-**86** and (*S*,*S*)-**87**.[81] Treating diol **74** with excess (*S*)-(−)-2,2′-bis(bromomethyl)-1,1′-binaphthyl in DMA containing Cs_2CO_3 gave (*S*)-**86**·$CHCl_3$ (79%). Similarly, (*S*,*S*)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol and **74** in DMF gave empty **87** (56%). Hemicarceplexes **87**·guest (where guest = DMA, NMP, or DMSO) were subsequently isolated in 55−60% yield when the shell closure was effected in DMA, NMP, or DMSO. Complexes of both these hosts with a series of racemic guests were prepared thermally either from the free hosts or during the final shell-closure step. The diastereomeric ratio of complexes thus obtained with hemicarcerand (*S*)-**86** ranged from >20(*R*):1(*S*) for (*S*)-**86**·(methyl *p*-tolyl sulfoxide), through 2.5(*S*):1(*R*) with **86**·$C_6H_5CH(OH)CH_3$ and 1.6(*R*):1(*S*) **86**·(phenyl methyl sulfoxide), to 1:1 for (*S*)-**86**·2-methyl-1-butanol, (*S*)-**86**·1,2-dichloropropane, and (*S*)-**86**·5-methyl-2-hexanol. Thus, the calculated differences in free energies between the two diastereomeric complexes (*S*)-**86**·(*R*)-4-MeC_6H_4S(O)Me and (*S*)-**86**·(*S*)-4-MeC_6H_4S(O)Me were >2.4 kcal mol^{-1}.[81] The chiral recognition factors of hemicarcerand (*S*,*S*)-**87** were generally less pronounced than those of host (*S*)-**86**, ranging from a high of 1.4(*R*):1(*S*) for (*S*,*S*)-**87**·2-butanol to 1:1 for complexes (*S*,*S*)-**87**·guest with methyl phenyl sulfoxide, 1,2-dihydroxypropane, and 2-methyl-1-butanol.[81] Furthermore, the diastereomeric ratios obtained from hemicarcerands prepared via the thermal route were slightly higher than those obtained from complexes accessed via the "sealed in" strategy. Under thermal conditions the diastereomeric ratios represent a thermodynamic equilibration whereas under those of the low temperature (40 °C) "sealed in" approach represent the relative rates of template-driven encapsulation. The differences in chiral recognition between these two hosts likely results from the greater flexibility of the chiral bismethylene-binaphthyl bridge of (*S*)-**86** compared to the tetramethylene and threitol acetonide bridges, as inferred from CPK models. Experimentally, this view is supported by the observation that the two diastereomeric complexes (*S*)-**86**·(*R*)-PhS(O)Me and (*S*)-**86**·(*S*)-PhS(O)Me have differ-

Scheme 18



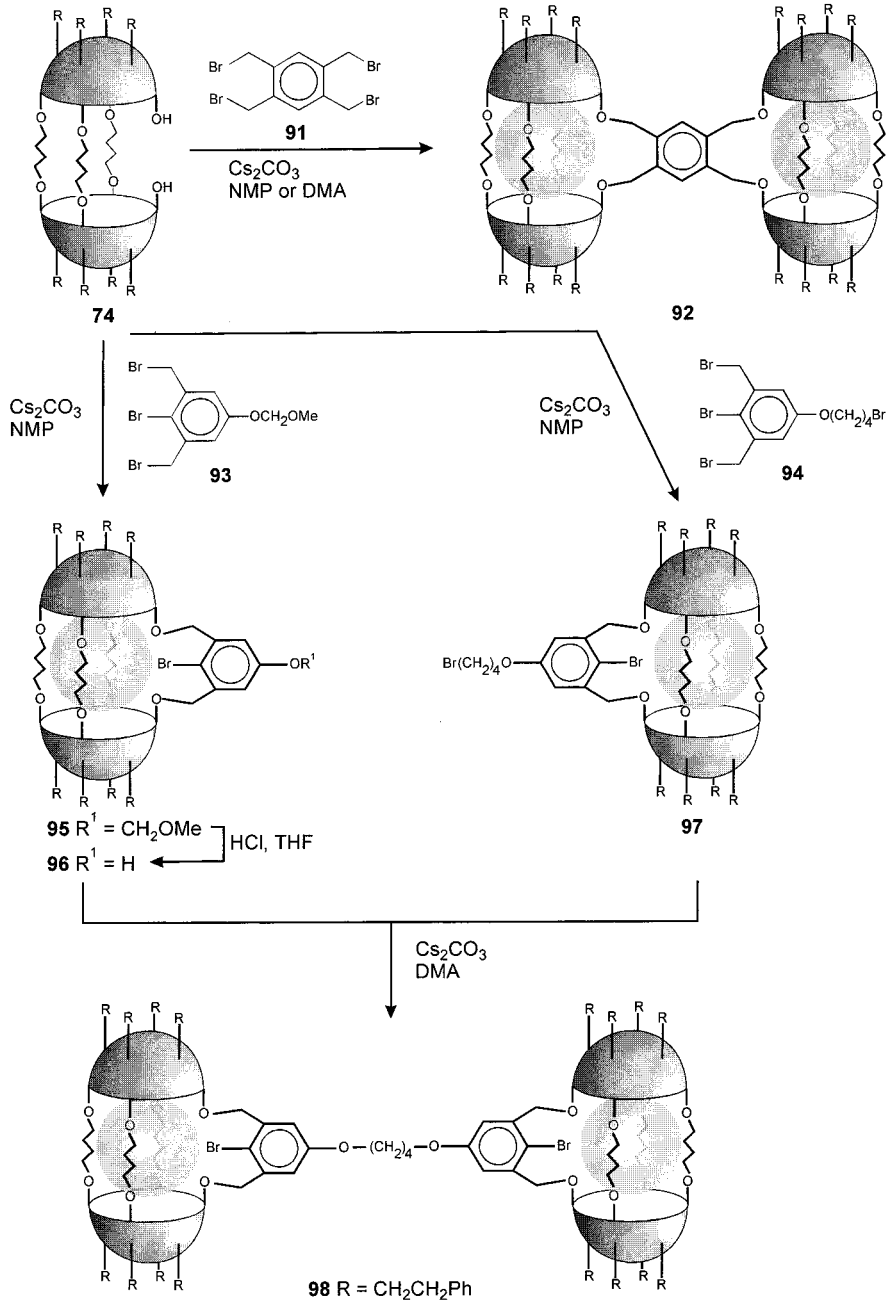


90•Guest

ent R_f values on TLC silica gel plates, whereas complexes (*S*,*S*)-**87**•(*R*)-PhS(O)Me and (*S*,*S*)-**87**•(*S*)-PhS(O)Me are inseparable. Thus, it is clearly apparent that host (*S*)-**86** can modify its structure to complement the incarcerated guest by changing the naphthyl−naphthyl dihedral angles. In contrast, the rigidity of the threitol acetonide bridge of (*S*,*S*)-**87** prevents any change to the overall shape of the host's shell.

Very recently, Deshayes' group prepared the mono-3-nitro-*o*-xyly-bridged hemicarceplexes **88**•NMP and **88**•DMA from diol **72** (Scheme 18).[83] The unique feature of these two hemicarceplexes over the myriad of examples reported by Cram is their ability to undergo bond cleavage at the adjacent benzylic position upon irradiation with UV light. Indeed, these researchers elegantly demonstrated that irradiation of chloroform solutions of **88**•NMP or **88**•DMA proceeds with photocleavage of the unique 3-nitro-*o*-xyly bridge and concomitant guest release, furnishing the tris-bridged adduct **89** (Scheme 18). The rate of guest

Scheme 19



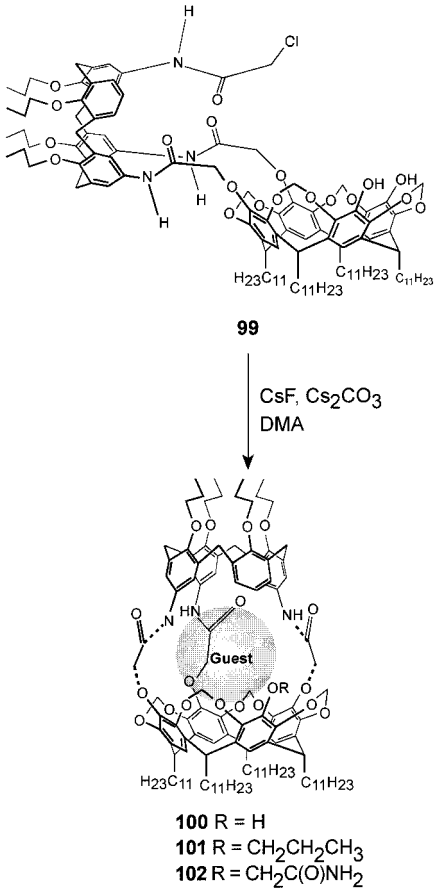
release for both complexes is linearly dependent on light intensity. Moreover, the progress of this photocleavage can be monitored by the appearance of the formyl proton signal in the ^{1}H NMR spectrum, which also corresponds to the rate of guest release. Encouraged by these results, this group consequently prepared tetra(3-nitro-*o*-xyly)-bridged hemicarceplex **90**·DMA, which was isolated as an inseparable mixture of isomers differing only in the relative position of the nitro group.[83] Expectedly, the incorporation of additional photoactive bridging units into the shell of **88** increases the probability of a photochemical reaction in the resultant hemicarceplex (i.e., **90**·DMA). Hence, **90**·DMA releases its guest 3.2 times faster than **88**·guest. Furthermore, the rate of DMA release from **90**·DMA increases linearly with light intensity, thereby indicating that this is a single-photon process, and henceforth guest release results from a single-bond cleavage only.

The successful isolation of diol **74**, and subsequently the series of asymmetric hemicarceplexes **75**−**85**, inevitably led to the synthesis of the first bis-hemicarceplexes **92**·2guest and **98**·2guest by Yoon and Cram.[84] Thus, as outlined in Scheme 19, treating diol **74** with the 1,2,4,5-tetrakis(bromomethyl)benzene (**91**) and Cs_2CO_3 in NMP or DMA exclusively gave hemicarceplexes **92**·2NMP and **92**·DMA as the sole dimeric species, with no evidence for the bis-hemicarceplexes derived from the alternative *m*-xylyl-type intercapsular-bridging. Hemicarceplex **98**·2guest, on the other hand, was synthesized in a stepwise fashion from **74**, involving initial shell closure of diol **74** in NMP with bis(bromomethyl) derivatives **93** and **94** in NMP to give hemicarceplexes **95**·$CHCl_3$ and **97**·$CHCl_3$, respectively (guest exchange, i.e., NMP with $CHCl_3$, apparently occurs during isolation). Deprotection of the phenolic group of **95** and subsequent coupling of the resultant alcohol **96**·$CHCl_3$ with bromide **97**·$CHCl_3$ provided bis-hemicarceplex **98**·$6H_2O$ in 82% yield. Once again, guest exchange of the initially encapsulated $CHCl_3$ molecules with CH_2Cl_2 readily occurs during purification. The latter guests are subsequently lost during drying and replaced by atmospheric moisture in the final product. The absorption of atmospheric H_2O within the apolar cavities of **98** is particularly sticking, given that the formation of host **25** in aqueous media does not proceed with concomitant encapsulation of water molecules within the cavity,[49] despite the presence of polar bridging groups. These bis-hemicarceplexes are topologically related to our recently reported bis-carceplex **16**·2pyrazine,[38] differing only in the inter-bowl and intercapsular linkers. Perhaps future work on these dimeric capsular molecules may provide detailed insight into the effects of the entrapped guests on the host's macroscopic properties, such as the electrical properties, for example, which may ultimately lead to the design of robust, conducting polymers based on these systems.

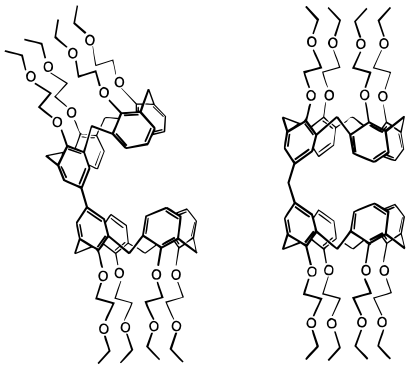
6. Calix[4]arene-Derived Hosts

David Reinhoudt's interest in molecular switches ultimately led to the synthesis of calix[4]arene-based host **100**.[43a] The final shell closure in this sequence

Scheme 20



hinged on an intramolecular coupling between the chloromethyl functionality of the third bridge attached to the calix[4]arene half of dimer **99** with the directly opposing free phenolic group of the cavitand half (Scheme 20). Subsequent O-alkylation of the free hydroxyl group of **100** quantitatively provided the *n*-propyl and acetamido hosts, **101** and **102**. Unfortunately, due to the inherent flexibility of the calix[4]arene subunit, hosts **100**−**102** displayed no binding properties toward potential guest molecules. Indeed, dynamic NMR spectroscopic experiments revealed that the "free" aromatic moiety of the calix[4]arene is in a flattened orientation. The diametrically bridged aromatic units of the calix[4]arene, in contrast, are arranged in a cone-like fashion. Consequently, all these hosts possess a cleft-like cavity as opposed to an enforced cavity typical of hemicarcerands. Furthermore, derivatization of the free phenolic group (as in **101** and **102**) has no effect on the binding properties of the resultant macromolecule since these groups freely rotate away from the cavity. Very recent preliminary work emerging from Placido Neri's group indicates that 5,5′-biscalix[4]arene **103** binds *N*-methylpyridinium iodide in solution[85] with an affinity constant of ∼153 M^{-1}. Moreover, the X-ray crystal structure revealed that in the solid state this centrosymmetric macromolecule adopts an anti conformation and forms a stacked array with an opposite facing calix[4]arene bowl of a second molecule. Within each of the pseudo capsules thus created lies a single chloroform molecule. Shinkai's group had shown earlier that the larger methylene-



103 104

bridged bis-calix[4]arene **104** also has a strong propensity to bind cationic guest molecules such as *N*-methylpyridinium iodide ($K_{assoc} \approx 480$ dm^3 mol^{-1}), 1,4-dimethylpyridinium iodide (36), 1,3,5-trimethylpyridinium iodide (2.0), and *N*-methylquinolinium iodide (97) in this cooperative manner.[86] This inclusion of charged guests within these calix[4]arene dimers is in marked contrast to charged complexes **27a**·$Et_2ND_2^+$ and **27a**·$BuND_3^+$, which are highly unstable apparently due to separation of the cation from its counteranion.[48] Clearly, the larger portals and adaptability of the cavity of **103** and **104** compared to **27a**·$Et_2ND_2^+$ and **27a**·$BuND_3^+$ prevent this destabilizing charge separation in these dimeric calix[4]arene complexes.

B. Decomplexation

A critical feature of all hemicarceplexes is their ability to undergo guest exchange without significantly disrupting the structural integrity of the shell. The resulting complexes are kinetically stable at ambient temperatures, which allows their isolation and characterization. The enhanced stability of these compounds further enables chemical modification of the host without undue effects to the guest and, as we shall see shortly, the alternative modification of the encapsulated guests without affecting the host. The decomplexation rates of a vast number of the hemicarceplexes prepared to date have been determined. As one would expect, the larger and more rigid the guest the slower the rate of decomplexation. Furthermore, the spatial distribution of the guest relative to the portal's shape is also a significant factor in the decomplexation rates. Generally, guests that spatially extend into all three dimensions form the most kinetically stable complexes with these hosts. Cram consequently introduced the concept of *constrictive binding* to describe the activation energy barrier to decomplexation of hemicarceplexes imposed by guests with larger cross-sectional areas than that of the host's portals.[48] Quantitatively, constrictive binding simply represents the difference between the activation energy of dissociation and the intrinsic binding free energy of the two complexing components.[71] By definition, "hemicarceplexes" with very small guests (such as those of **27** with N_2, O_2, CO_2, and H_2O[48] and **48a** with N_2 and O_2,[71] for example), which are in rapid exchange at ambient temperatures on the ^{1}H NMR time scale, are more correctly classified as complexes rather than true hemicarceplexes.

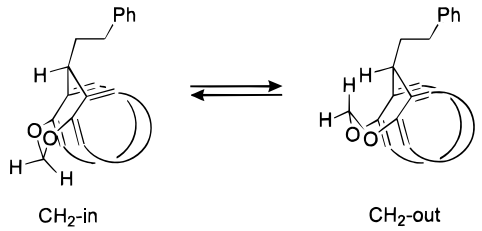


Figure 6. Chair-to-boat interconversion of the dioxacyclooctane rings in gating.

Carceplex **5c**·2CH_3CN, unlike all other traditional carceplexes, is thermally unstable and thus readily loses one acetonitrile molecule.[26a] The resultant complex **5c**·CH_3CN, in contrast, is indefinitely stable. Strictly speaking, the former complex is a hemicarceplex, whereas the latter is indeed a true carceplex. Kinetic studies on the bis-acetonitrile complex gave an activation energy for decomplexation of 20 kcal mol^{-1}.[26a] Ken Houk's group has shown by computational analyses that at elevated temperatures (viz. 110 °C reported experimentally),[26a] a pair of adjacent intrabowl acetal groups of **5c** undergo a conformational flip from an inward to an outward position,[87,88] i.e., a chair-to-boat interconversion of the dioxacyclooctane rings of each bowl (Figure 6). Consequently, this increases the side-portal size, thereby enabling one of the two acetonitrile molecules to exit the cavity of **5c**·2CH_3CN. The calculated activation energy (cf. 22 kcal mol^{-1}) for this mode of escape is consistent with that measured experimentally by Cram. Furthermore, these computational models predict that expulsion of the second acetonitrile molecule (i.e., from **5c**·CH_3CN) from the cavity is energetically unfavorable.[87] These authors have referred to these conformational changes which alter the portal's size as gating. The actual size of the portal is thus controlled by motions related to either "French doors" or "sliding doors" (Figure 7).

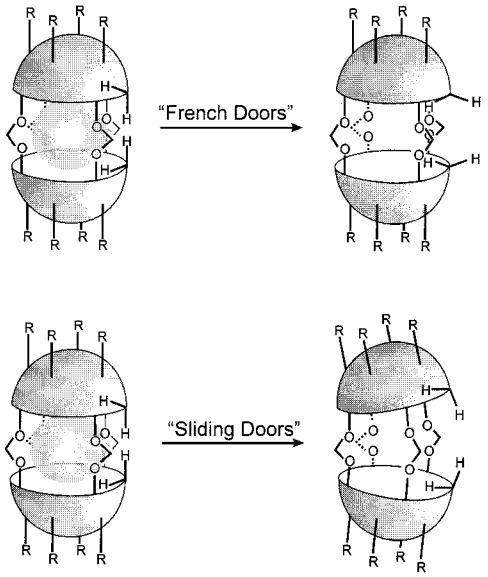


Figure 7. The French door and sliding door gating mechanism in hemicarceplexes.

At 140 °C, the half-lives ($t_{1/2}$) for decomplexation of prototypical hemicarceplexes **27**·DMF and **27**·

DMA were calculated to be 14 and 34 h.[48] The differences in rates observed here obviously arise from the difference in relative size of these two guests. Hemicarceplex **27**·DMSO, on the other hand, has an even higher energy barrier to decomplexation (t = 24 h at 195 °C), compared to the former two hemicarceplexes. This clearly can be attributed to the poor complementarity between the tetrahedral-shaped guest molecule and the more semitubular host portal. Interestingly, the congeneric hemicarceplexes **27**·guest and **32a**·guest (guest = DMF, DMA) have identical decomplexation kinetics.[48,55] The activation energies measured for decomplexation of DMA from host **27** and **32a** are lower than that for DMF (cf. ~23.9 vs 20−22 kcal mol^{-1}).[55] Clearly the shear bulk of DMA compared to DMF destabilizes the corresponding hemicarcerands **27**·DMA and **32a**·DMA relative to **27**·DMF and **32a**·DMF.

The importance of guest and portal shape complementarity on decomplexation is beautifully demonstrated by hemicarceplexes **60**·guest.[72] Here, the t for **60**·1,3,5-$Et_3C_6H_3$ ($t_{1/2}$ = 960 h, in $CDCl_3$ at 25 °C) is approximately 1000-fold greater than that with the slightly larger 2,9-dioxa[2.2]paracyclophane ($t_{1/2}$ = 1 h). This large difference in decomplexation rates reflects the complementarity of the hemicarceplex's portals to the rectangular cross-section of 2,9-dioxa-[2.2]paracyclophane versus the square cross-sectional area of 1,3,5-triethylbenzene. More intriguing was the observation that [2,3]paracyclophane ($t_{1/2}$ = 0.5 h, in $CDCl_3$ at 25 °C) is expelled from the internal cavity of **60** at a rate approximately 10 times faster than [2,2]paracyclophane (t = 5 h) or [3,3]paracyclophane ($t_{1/2}$ = 13 h).[72] This anomaly was rationalized on the asymmetry of [2,3]paracyclophane, which imparts the molecule with the ideal "screw-like" geometry required by the transition state for decomplexation. Similarly, the conformational flexibility of the guest also plays a part in the decomplexation rates. For instance, $CF_3OC_6H_5$, despite being larger than $CF_3C_6H_5$, exits the cavity of host **40a** at a faster rate (cf. $t_{1/2}$ = 1.62 vs 2.46 min, at 45 °C, in $CDCl_3$), simply on account of $CF_3OC_6H_5$ being conformationally more adaptable.[63] Likewise, host **62**·adamantane has a higher kinetic stability than **62**·$(PrO)_3PO$, simply due to the conformational flexibility of tripropyl phosphate over the rigidity of admantane.[73] The activation energies for the decomplexation of **62**·adamantane and **62**·ruthenocene have been determined to be 19 and 28 kcal mol^{-1}.[73]

The first-order rate constants for decomplexation of **48**·guest ranged from 0.28 × 10^4 s^{-1} for ethyl acetate to 3.0 × 10^4 s^{-1} for acetonitrile (at 100 °C in $CDCl_2CDCl_2$) which are in accord with a guest's shape, size, and conformational flexibility and the electronic character of the attached functional groups. Evaluation of the thermodynamic parameters for complexation with host **48** indicates that for guests such as DMA, ethyl acetate, and butanone binding is both entropically (due to a combination of solvophobic effects and dispersion of the inner phase into smaller voids about the solvent upon complexation) and enthalpically driven. With toluene, on the other hand, due to the poor shape complementarity between this planar guest and the concave cavity walls, complexation is entropically driven and opposed by enthalpy. A similar rationalization was invoked by Cram to explain the binding of $CDCl_3$ by hemicarcerand **40a**.[63]

Acetylene-bridged hemicarceplex **40a**·*p*-xylene decomplexes 36 times faster than ethylene-bridged hemicarceplex **41a**·*p*-xylene.[63] This difference was explained in terms of the extra C−H bonds in **41** effectively blocking off the portals. Octalactone hemicarceplex **46**·$Cl_2HCCHCl_2$ has a $t_{1/2}$ of 18 h at 100 °C.[69] Diastereomeric complexes $(R)_4$-**47**·(*S*)-$BrCH_2CH(CH_3)CH_2CH_3$ and $(S)_4$-**47**·(*S*)-$BrCH_2CH(CH_3)CH_2CH_3$ had first-order rate constants for decomplexation of 4.4 × 10^{-2} and 6.2 × 10^{-3} h^{-1}, respectively.[70] The decomplexation kinetics of equilibrated diastereomeric mixtures of the complexes of host $(S)_4$-**47** with racemic 1,3-dibromobutane and 1,2-dibromobutane displayed chiral selectivity factors (i.e., k_{fast}/k_{slow} for the two diastereomers) of 5 and 9, respectively (at 23 °C, in $CDCl_3$). In these instances, the observed chiral selectivity most probably results from differences in steric repulsions and dipole−dipole alignments in the diastereomeric transition states. In comparison, chiral hemicarceplex (*S*)-**86**·1,3-dibromobutane, with a single bismethylenebinaphyl bridge, was indefinitely stable under the same conditions.[81] However, with smaller guests such as 1,2-dibromo- and 1,2-dichloropropane, chiral decomplexation rate factors of ~3 and 1.6 were obtained at 25 °C in $CDCl_3$. The more closely related acetonide-bridged hemicarceplex $(S,S)_4$-**36**·DMA and its acyclic-bridged derivative **37**·DMA reportedly have $t_{1/2}$ values of ~113 and 4.5 h at 150 °C in $CDCl_2CDCl_2$.[61] Apparently, the rigidity of the acetonide bridges hinders the egress of DMA from $(S,S)_4$-**36**, since with the smaller DMF molecule as guest the half-life for decomplexation of $(S,S)_4$-**36**·DMF was ca. 1.5 h at 138 °C in the same solvent.

Hosts **35** and **54**−**58**,[32,60] containing *m*-xylyl interbowl linkers and varying intrabowl linkers (i.e., methylene, ethylene, and propylene), provide a nice series of hemicarceplexes to evaluate the effects of subtle changes in hosts (such as cavity shape and size and flexibility) on the decomplexation properties. The half-lives (at ambient temperature in $CDCl_3$) for this series ranged from a few minutes to several months.[60] For instance, the half-lives of **58**·acetophenone and **54**·acetophenone were 0.33 and 48 h, respectively. In contrast, the acetophenone complexes of **35** and **55** were highly unstable. Expectedly, changes in guest structure also have an effect on the kinetic stabilities of these complexes, as is evident by the vastly improved stability (at 25 °C) of complex **54**·*o*-xylene (10% decomplexed after 30 days) over **54**·*p*-xylene ($t_{1/2}$ = 13 days) and **54**·*m*-xylene ($t \approx$ 3 h).[60]

The high activation energy for the decomplexation of **42**·DMA (23.5 kcal mol^{-1}) indicates that a large portion of this energy barrier results from constrictive binding,[64] which when coupled with the intrinsic binding imparts substantial stability to the hemicarceplex. At ambient temperature, in $CDCl_3$, the decomplexation half-lives for hemicarceplexes **42**·guest, **79**·guest, and **82**·guest (with 4-methylanisole, 1,4-

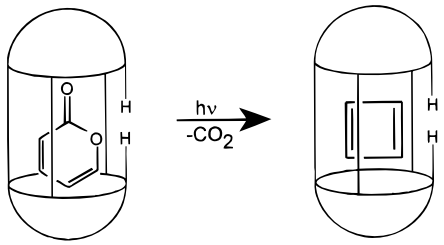
and 1,3-dimethoxybenzene) decreased in the following order: **42**·guest > **79**·guest ≫ **82**·guest.[80] In striking similarity to **48**·guest,[71] the decomplexation rate of **82**·4-$MeOC_6H_4OMe$ varied with solvent.[89] The decomplexation half-life for this hemicarceplex is ~800 times longer in $CDCl_2CDCl_2$ than in $CDCl_3$ (at 35 °C), with a corresponding increase in activation energy of 4.1 kcal mol^{-1}, which suggests that the transition state structure resembles the dissociated rather than the starting complex. More specifically, steric inhibition for effective solvation of the transition state for decomplexation by the larger 1,1,2,2-tetrachloroethane-d_2 solvent molecules brings about this large solvent effect. The decomplexation rate constants and activation free energies for a series of related dissymmetric hosts·4-$MeOC_6H_4OMe$ (namely with hosts **79**, **80**, **82**, **84**, and **85**) have also been reported.[89] The activation free energies for this series ranged from 22.0 kcal mol^{-1} for **80**·4-$MeOC_6H_4OMe$ to >27 kcal mol^{-1} for **85**·4-$MeOC_6H_4OMe$. Typically, these values progressively increase as the portal size decreases (cf. **79**·4-$MeOC_6H_4OMe$ $\Delta G^{\ddagger} = 25.2$ kcal mol^{-1}), or as the steric bulk of the unique bridge is increased (e.g., **84**·4-$MeOC_6H_4OMe$ ($\Delta G^{\ddagger} = 23.4$ kcal mol^{-1}) and **82**·4-$MeOC_6H_4OMe$ ($\Delta G^{\ddagger} = 23.7$ kcal mol^{-1})), in comparison to the more flexible hexamethylene derivative **80**. Collectively, since all these hosts have very similar cavities, the intrinsic binding energies of these complexes must therefore be very close to one another. Consequently, the activation energies reported here provide a reasonable estimation of the relative constrictive binding energies of the complexes. In collaboration with Ken Houk's group, Cram et al. concluded that the methylene gating phenomena vide supra plays a smaller role in guest release in these hemicarceplexes.

The more flexible diethylene glycol-bridged hemicarcerand **45** formed kinetically stable complexes only with guests such as norbornane, norbornylene, etc., with half-lives ranging from minutes to several days in $CDCl_3$.[67] Moreover, the decomplexation rates were solvent dependent. For example, at 60 °C in $CDCl_3$ the half-life of **45**·norbornylene was 11 h, while in nitrobenzene-d_5 at 100 °C, there was no apparent decomplexation over several days. The solvent dependencies of the rate constants were attributed to the differences in solvation free energies of the transition states for complexation−decomplexation and of the fully complexed and noncomplexed states. In contrast, with cyclic guests such as monosubstituted cyclohexanes and disubstituted benzenes, the resulting complexes **45**·guest readily decomplex at room temperature in $CDCl_3$. Molecular mechanics and computational thermodynamic studies on this host revealed that gating contributed significantly to the constrictive binding energies of complexes **45**·guest[90] and hence to the rates of decomplexation.

C. Reactions inside Hemicarceplexes

The internal cavity of hemicarceplexes represents a unique microchamber within which novel chemical reactions may be explored. Unfortunately, due to the highly effective shielding ability of the shell's superstructure, the chemistry inside this chamber has largely been relegated to photochemical processes and reactions with small reactants that can readily traverse the portals. Perhaps the most elegant display to date of this effect was Cram and co-workers' room-temperature stabilization of cyclobutadiene in solution, within hemicarceplex **27a**.[10] Photolysis of the readily available hemicarceplex **27a**·α-pyrone in $CDCl_3$ generated hemicarceplex **27a**·cylobutadiene (Scheme 21). The resulting entrapped product (i.e., cyclobutadiene) was sufficiently stable to enable spectroscopic characterization and was shown to exist in a singlet ground state. Further irradiation provided the free host and acetylene. Additionally, upon thermal guest exchange with THF, the liberated cyclobutadiene spontaneously dimerized.

Scheme 21



27a·α-pyrone

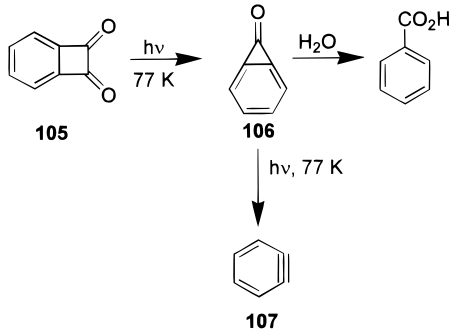
Pina et al. exploited the shielding effect of hemicarceplex **48a**·2,3-butanedione's shell to stabilize the long-lived T_1 excited state of incarcerated 2,3-butandione from energy quenching by molecular oxygen. Moreover, the absorption, fluorescence, and phosphorescence maxima of the imprisoned guest were all red-shifted compared to the values obtained for the free species in solution.[91] Subsequently, these researchers and Deshayes group independently showed that triplet energy transfer between the excited guest molecules in **48a**·2,3-butanedione[92,93] and **48a**·acetophenone[68] and external quenchers such as aromatic amines (e.g., diphenylamine, 1-naphthylamine, and benzidine) or triplet energy acceptors (e.g., phenanthrene, naphthalene, pyrene, and piperylene) does indeed occur. However, as expected, the electronic interactions between the excited guest molecules and the external quenchers are fairly weak, as evidenced by the decrease in rate constants for quenching by the excited encapsulated guests compared to that of the free excited species. Nonetheless, quenching of the excited guests is proposed to occur through electron- or energy-transfer processes mediated by the hemicarceplex's walls. In stark contrast, the excited state of 9-cyanoanthracene in hemicarceplex **62**·9-cyanoanthracene has a shorter lifetime ($\tau = 350$ ps) than that of the corresponding free 9-cyanoanthracene ($\tau = 15$ ns).[74] Additionally, the quantum yield of the fluorescence of the entrapped species is approximately 50 times less than that of the free species. An electron-transfer quenching process between the imine bridging groups and the excited guest is envisaged to provide the pathway for energy dissipation in **62**·9-cyanoanthracene* since, energy-transfer quenching between the aromatic-

lined walls of the cavity and excited guests is energetically not possible.[74]

Robbins and Cram have successfully oxidized hydroquinone guests in hemicarceplexes **42**·1,4-$(HO)_2C_6H_4$, **42**·1,2-$(HO)_2C_6H_4$, **42**·2-Me-1,4-$(HO)_2C_6H_3$, and **42**·4-Me-1,2-$(HO)_2C_6H_3$ to yield the corresponding encapsulated benzoquinones,[14] with either ceric ammonium nitrate−silica gel in CCl_4 at room temperature or in refluxing CCl_4 with thallic trifluoracetate. Incidentally, this represents the only method of incorporating these thermally labile quinones, particularly the *o*-quinones. Exposing these novel quinone-containing hemicarceplexes **42**·quinone to samarium iodide in refluxing THF cleanly gave back the hydroquinone complexes. Furthermore, under the same conditions, hemicarceplex **42**·$PhNO_2$ was reduced to **42**·PhNHOH in high yield. Collectively, these experiments demonstrate that electrons, protons, and small molecules such as water readily transfer into and out of the central cavity. In some more recent work, Cram's group has shown that it is possible to methylate (MeI, NaH, THF, or HMPA) the hydroxyl groups only at *ortho* and *meta* positions of encapsulated disubstituted benzene rings encapsulated within hemicarceplex **75**.[15] For encapsulated disubstituted benzene rings containing the hydroxyl group in a *para* position (e.g., hemicarceplex **75**·4-HOC_6H_4OMe), the guest remained unchanged. The selectivity observed for *ortho*- and *meta*-disubstituted benzene derivatives over their *para*-disubstituted counterparts is believed to arise from the orientation of the guests within the shells: while the *para* substituents are relegated to the polar regions of the cavity, the *ortho* and *meta* substituents partially extend beyond the host's cavity into the equatorially located portals of the host.

In an ongoing effort to "tame" highly reactive molecules in the Cram laboratories, Warmuth recently reported the isolation of hemicarceplex **42**·*o*-benzyne, albeit at −75 °C.[11b] Scheme 22 summarizes

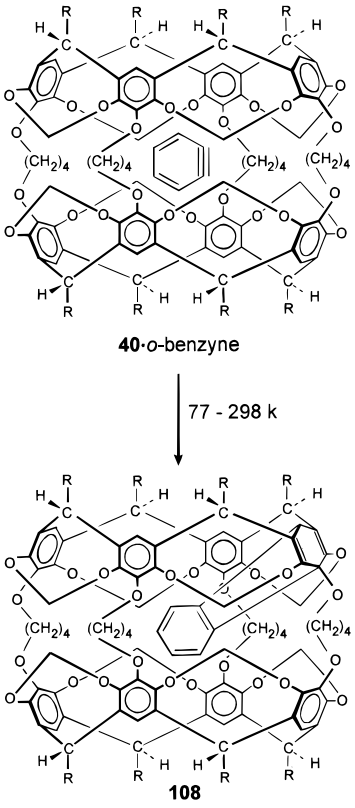
Scheme 22



the transformations carried out within the cavity to give **42**·*o*-benzyne. Heating empty host **42** in molten benzocyclobutenedione (**105**) provided the corresponding hemicarceplex **42**·**105** (30−35%); subsequent photolysis in $CDCl_3$ at 77 K furnished the benzocyclopropenone (**106**) complex **42**·**106**. The formation of this complex was supported by NMR spectroscopic data and a single-crystal X-ray structure—details of which have not yet been published.[11b] Nevertheless, at ambient temperature in the presence of water, the guest is slowly converted to benzoic acid, thus giving **42**·benzoic acid. Further irradiation (280 nm) of **42**·**106** in THF-d_8 at 77 K provided **42**·*o*-benzyne.

Evidence for the formation of *o*-benzyne (**107**) within the host's cavity was gleaned from ^1H and ^{13}C NMR spectra of the resultant complex at −75 and −98 °C, respectively.[11b] The proton signals for the two sets of protons of *o*-benzyne were observed at δ 4.99 and 4.31 ppm. However, excessive line broadening precluded determination of the fine structure of these resonance signals. More interestingly, upon warming up to ambient temperature in solution, the encapsulated *o*-benzyne (**107**) molecule undergoes a Diels−Alder reaction with one of the arene rings lining the cavity wall of **42**, furnishing the endohedral compound **108** (Scheme 23).[11a] Further variable temper-

Scheme 23



ature ^1H NMR spectroscopic studies indicate that the *o*-benzyne sits in the host cavity with its C_2 axis parallel to the polar axis of **42**, thus explaining the observed reactivity with a polar aromatic moiety and not with residual water in the bulk solvent. This Diels−Alder reaction was shown to follow first-order kinetics, and thus it is more like an intramolecular reaction than a traditional bimolecular, intermolecular reaction.

V. Related Compounds

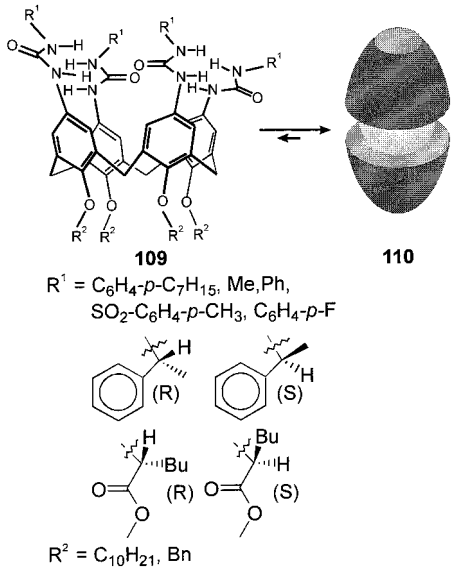
A variety of species that are topologically related to carceplexes and hemicarceplexes have been reported in the last two decades. Some relevant examples are presented in the following sections, with emphasis on very recent work. An in-depth account of this area is beyond the scope of this review; however the

interested reader is directed to some recent more specific reviews on these capsular compouds.[4b,7a,23]

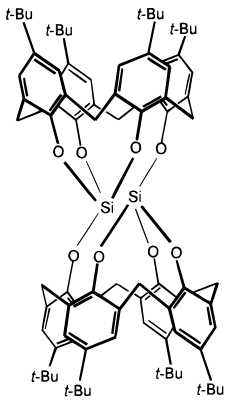
A. Molecular Capsules Derived from Calix[4]-arenes

Calix[4]arenes are basket-shaped molecules that have attracted widespread interest in the last two decades,[22] chiefly for probing molecular recognition and metal binding. Recently, Rebek's and Böhmer's groups have independently exploited the aryl- and sulfonyltetraurea-functionalized calix[4]arenes **109** to probe self-assembly and molecular encapsulation (Scheme 24).[7a,23,94,95] In apolar solvents, these self-

Scheme 24



complementary molecules dimerize to form hydrogen-bonded capsule **110**. This intermolecular hydrogen bonding locks the two normally flexible calix[4]arene subunits into a rigid cone conformation, which consequently engenders the resultant dimer with an enforced internal cavity.[94d] These dimeric capsules reversibly encapsulate small organic molecules (such as chloroform, benzene, *p*-xylene, and pyrazine) on a slower exchange rate than that of the ^{1}H NMR time frame. Thus, unlike the hemicarceplexes which retain their container-like superstructures upon thermal decomplexation, these dimeric capsules do not exist in the absence of an appropriate guest and, as such, they bear strong resemblance to the ternary complex **17**·guest discussed previously. Additionally, dimer **110** displayed competitive binding toward a series of aromatic guests, with a relative binding affinity of $\sim$ 60:1 between *p*-difluorobenzene and toluene.[94e] An X-ray crystal structure of capsule **110**·C_6H_6 (R^1 = *p*-tolyl, $R^2 = CH_2CO_2Et$) irrefutably confirmed the structure of these capsules.[96] Although the homodimers of **110** are achiral (with S_8 symmetry), encapsulation of chiral polycyclic guests (e.g., (1*R*)-(+)-camphor) reduced the symmetry of the two hemispheres.[94b] Evidently, due to the restricted rotation and preferred orientation of the guest within the cavity, these complexes with chiral guests provide unequal mixtures of diastereomers. Thus, like Reinhoudt's carceroisomerism with calix[4]arene-based carceplexes **19** and **20**,[43] these capsules display a similar type of stereoisomerism. These researchers have subsequently extended this work to optically active capsules by incorporating chiral substituents on the urea headgroups of the calix[4]arenes. As anticipated, preferred guest orientation within these optically active heterodimers was evident.[94b] More recent work in this direction by Rebek's group has focused on self-assembling tetramolecular and polymeric rods in solution based on this reversible dimerization process, by covalently linking two or more of these tetraurea calix[4]arenes **109** via their lower rims.[94a,c] Hosseini et al. have similarly synthesized tail-to-tail calix[4]arene dimers, by linking the free phenolic groups of two *p*-*tert*-butylcalix[4]arene molecules with tetrachlorosilane,[97] which they have christened koil-

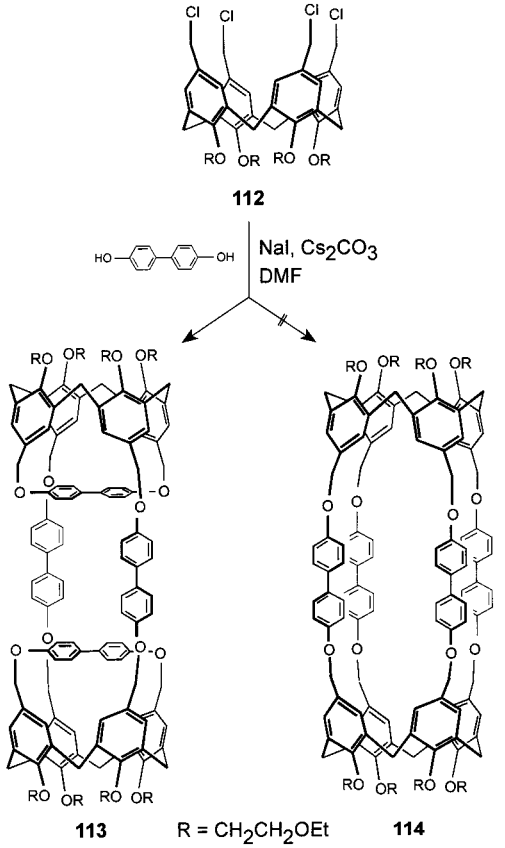


ands (**111**). They have since shown that in the solid state these dimers self-assemble in a head-to-head fashion forming a linear polymeric array, with a molecule of *p*-xylene partially encapsulated within the resulting pseudo capsule.[98] Shinkai and Reinhoudt have independently studied a similar head-to-head and head-to-tail dimerization of difunctionalized and tetrafunctionalized calix[4]arenes, containing complementary hydrogen-bonding groups.[99,100]

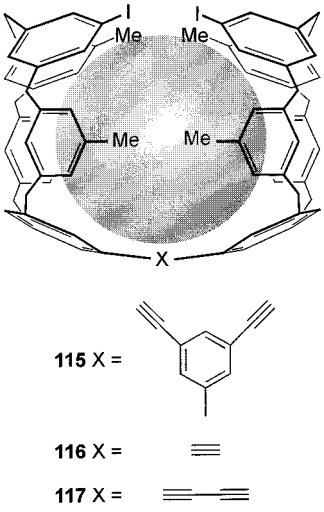
Continuing on their efforts toward the synthesis of cyclophane macromolecules containing large internal cavities,[101] Vögtle and co-workers reacted the tetrabenzyl chloride calix[4]arene **112** with 4,4′-biphenol in an attempt to isolate host **114** (Scheme 25).[102] However, only the cross-linked isomer **113** was isolated, with no evidence for the formation of the host **114**, in these attempts. Undoubtedly, the inherent flexibility of the calix[4]arene units plays a significant role in the outcome of this reaction. Perhaps, in the presence of suitable template or with a linker that cannot undergo intramolecular bridging, this goal will be achieved.

The design of a large molecular host that can encapsulate the fullerenes has been a common goal to numerous supramolecular chemists.[4b,22a,103] These efforts are largely geared toward discovering rapid, efficient methods for their purification. Numerous examples have appeared in the literature, but by and large, these are usually 1:1 or 2:1 fullerene:host complexes. Nevertheless, Yoshida et al. have reported a 1:2 complex between C_{60} and γ-cyclodextrin.[104] Fukazawa's group has also recently provided evi-

Scheme 25



dence for a solid state 1:2 C_{60}:calix[5]arene inclusion complex,[105] with an association constant of 2.1×10^3 $dm^3\ mol^{-1}$ in toluene.[106] Consequently, these workers prepared calix[5]arene dimers **115**−**117**,[107] with the hope of exploiting the preorganization of the host to bind C_{60} more efficiently in solution. Indeed, of these, host **115** showed a markedly improved association constant for C_{60} in toluene (cf. 7.65×10^3 $dm^3\ mol^{-1}$). Moreover, all three hosts exhibited specificity for C_{70} over C_{60}.



B. Resorcinarene-Based Molecular Assemblies

We have seen that resorcinarenes derivatives, wherein the phenolic hydroxyls are bridged, have served as the fundamental building blocks of a vast majority of the carcerands and hemicarcerands synthesized to date. In 1992, Aoyama and co-workers demonstrated that (unbridged) resorcinarene **118a** forms a hydrogen-bonded dimeric capsular assembly in apolar organic solvents, in the presence of β-methyl glucopyranoside.[108] Evidence for the encapsulated sugar molecule and the host:guest stoichiometry was derived from ^{1}H NMR spectroscopic and VPO measurements. Jerry Atwood's group has very recently provided more conclusive evidence for the formation of such hydrogen-bonded dimers[109] with their reported X-ray crystal structure of the corresponding phenethyl-footed resorcinarene dimer **118b·118b·** guest. Additionally, the X-ray crystal structure provided compelling evidence for intramolecular hydrogen-bonding between the hydroxyl groups of the resorcinarene and intermolecular hydrogen bonds between the phenolic moieties of the two resorcinarenes and eight 2-propanol solvent molecules. Collectively, this hydrogen bond network and the two tetraarene hemispheres define the internal cavity of the capsule. Although the identity of the guest could not be conclusively established, it is most likely a molecule of *o*-dichlorobenzene solvent. Moreover, in the solid state, these dimers are aligned in a columnar array via tail-to-tail interactions, with molecules of C_{60} (presumably added as a potential template in the crystallization solvent mixture) interspersed between each column. More astonishingly, these researchers discovered that **118b** self-assembles in nitrobenzene to form closed-surface spherical hexamer **119** (Figure 8).[110] An X-ray crystal structure of this supercapsular assembly unequivocally proved its formation. Structurally, this supercapsular assembly is composed of six resorcinarene molecules and eight water molecules held together by sixty O−H···O hydrogen bonds, arranged in an overall snub cubic geometry. Furthermore, ^{1}H NMR spectra of **118a** at high concentrations in benzene-d_6 strongly indicate that this supercapsular structure is indeed maintained in solution. This spontaneous self-assembly of six resorcinarene molecules to furnish the supramolecular spherical capsule **119** is indeed a remarkable feat, reminiscent of viral capsids. Most intriguing, however, is the fact that the formation of this spherical macromolecule does not appear to be template driven. Although there is significant electron density maxima within the internal cavity of this supramolecular assembly, the identity of the guest(s) has not been conclusively determined. Nevertheless, it is most likely filled with several solvent molecules.

In an effort to create self-assembling capsules with a large inner cavity, Rebek et al. have recently synthesized extended cavitands **120** containing self-complementary hydrogen bond donor and acceptor groups along the upper rim.[111] These cavitands were indeed found to dimerize in apolar organic solvents. Moreover, this dimerization ($K_D \sim 1700\ M^{-1}$) is a self-templated process, wherein one of the alkyl chains (R^1) attached to the amide group from each hemisphere is encapsulated within the cavity (Figure 9). The presence of broad multiplets at δ −1.02 and −1.78 ppm ascribable to the terminal methyl group

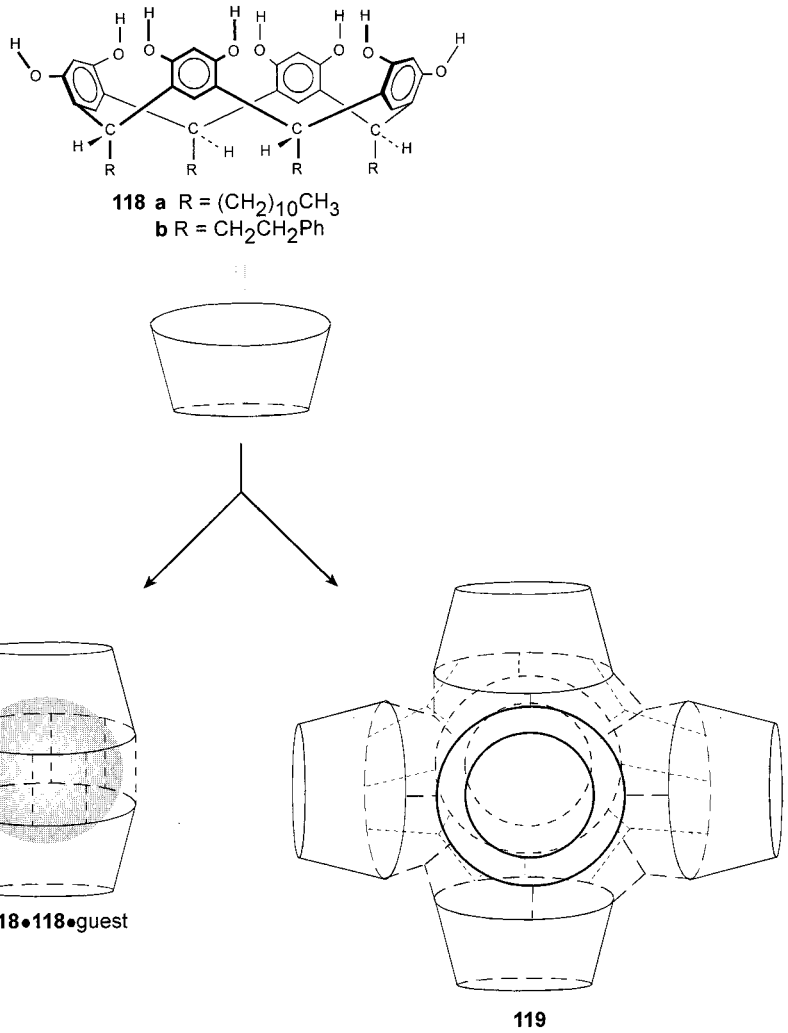


Figure 8. Two modes of self-assembly of resorcinarene **118**.

of the amide side chain in the ^{1}H NMR spectra of **120a** and **120b** (respectively) provided conclusive evidence for the encapsulation of these side chains. From the large upfield shifts, these methyl groups are obviously located deep in the cavity of each hemisphere. MALDI mass spectra and FTIR data further corroborate this dimeric structure. The exchange rate between the monomeric and the dimer species is slow, even on the ^{1}H NMR time scale. However, this process is, as expected, both concentration and temperature dependent. Attempts to encapsulate suitably sized guests such as adamantane, paracyclophane, ethylbenzene, and C_{70}, for example, in toluene-d_8 with **120a·120a** reportedly failed. Undoubtedly, the alkyl side chains replace the solvent molecules inside the cavity upon dimerization. Thus, it appears that this dimerization with self-inclusion is energetically favored. Evaluation of the thermodynamic parameters for the formation of **120a·120a** showed that this self-assembling process is enthalpically favored but highly unfavorable entropically. These researchers concluded that the deep cavity of these bowls might account for this self-inclusion dimerization, since dimerization only occurs when the cavity is completely filled. For instance, the shorter propionylamide and longer palmitoylamide derivatives of **120** exist exclusively as monomers in toluene-d_8, thus indicating the necessity for sufficiently large groups for self-templation. Cram et al. have also shown earlier that ester derivative **121** undergoes a similar self-inclusion driven dimerization in apolar solvents.[17d] However, in this case, the two bowls are staggered as depicted in Figure 9. Evidence for this structure was gleaned from the ^{1}H NMR spectra and more conclusively from a single-crystal X-ray structure.

C. Cyclodextrins

Cyclodextrins (**122**) are naturally occurring cyclic oligosaccharides, composed of six (α), seven (β), and eight (γ) α-1,4-linked D-glucopyranose subunits. These torus-shaped molecules have long been of considerable interest on account of their ability to form inclusion compounds.[21] Typically, these complexes involve 1:1 host:guest stoichiometry, although examples of 2:1 cyclodextrin:guest complexes have recently been reviewed.[4b,7a] In order to achieve cooperative binding, numerous research groups have linked two or more cyclodextrin units covalently[7a,e,4b,112,113] and indeed have reported higher binding affinities with these

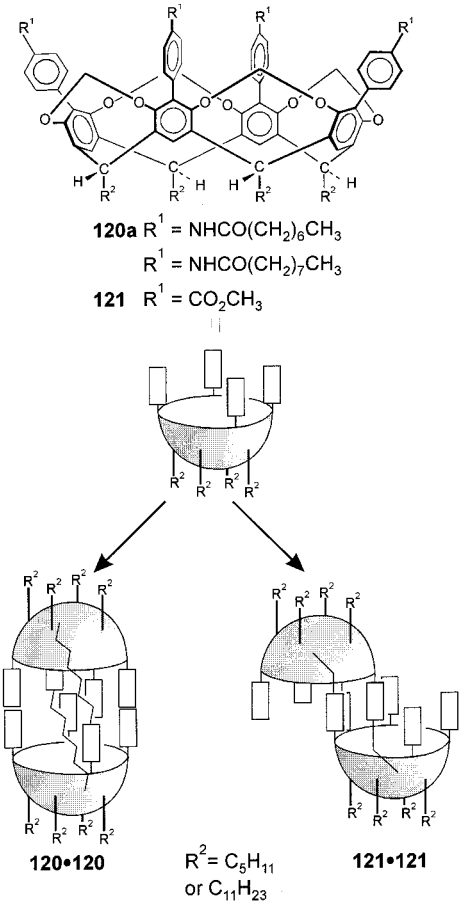
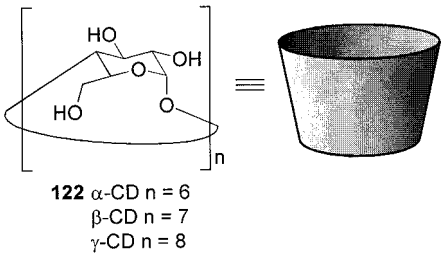


Figure 9. Self-assembly of deep-cavity cavitands.

systems. In addition, Douhal and co-workers have recently shown that β-cyclodextrin binds 2-(2′-hydroxyphenyl)imidazo[1,2-*a*]pyridine **123** in a 2:1 fashion with an apparent association constant of 10^5 M^{-2}.[114] This binding process was monitored by fluorescence spectroscopy in aqueous solutions with increasing cyclodextrin concentrations, and the dimerization was found to proceed via a stepwise mechanism outlined in Figure 10. Formation of the initial 1:1 inclusion complex **124** occurs rapidly (within seconds), whereas that of the 2:1 capsule **125** proceeds at a markedly slower rate (∼hours). Moreover, the formation of this ternary complex is dependent on relative concentrations and temperature. A recent X-ray crystal structure of the 2:1 β-cyclodextrin: pyrene complex **126** unequivocally supports this notion of β-cyclodextrin dimerization in the presence of suitable guests. Interestingly, in this solid state structure, the guest molecule (pyrene) was found to lie flat across the broad equatorial region of the cavity, between the two cyclodextrin molecules (as depicted in Figure 11). Thus, the guest does not penetrate the cavity at all, as has commonly been proposed in many solution models and in modeling calculations. The remaining empty space in each hemisphere of the dimer is filled by an octanol solvent molecule. This complementary space filling of the hydrophobic cavity in the dimer, by the guests, is believed to impart enhanced stability to the dimer in solution.[115]



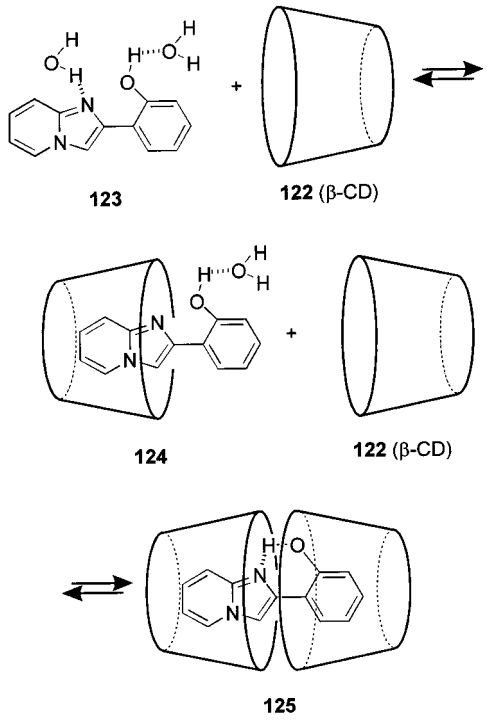


Figure 10.

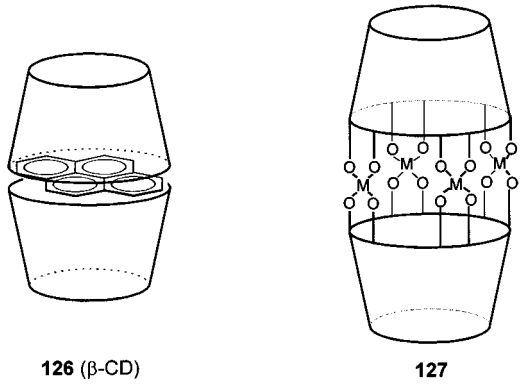


Figure 11.

While the majority of cyclodextrin complexes described above rely on extensive hydrogen bond networks for the formation of the capsular-type species, Peter Klüfers' group was the first to successfully use metal ions to bridge two cyclodextrin molecules with general structure **127** (Figure 11).[116] These researchers isolated cyclodextrin dimers from aqueous alkali solutions of α-CD[116a] and β-CD[116c] with copper and of γ-CD with lead,[116b] all of which were characterized by X-ray crystallography. The presence of an extensive network of metal−oxygen interactions was clearly evident in these solid state structures. For instance, in the γ-CD·γ-CD lead complex,[116b] the two cyclodextrins are held together by 16 lead atoms—each

cyclodextrin tori being deprotonated 8-fold, with each resulting alkoxide coordinated to two lead atoms. Similarly, in the β-CD dimeric copper complex the molecular shell is closed by 4 Cu(II) ions and 11 Li cations.[116c] Additionally, seven water molecules were encapsulated within the interior of the cavity of this dimeric host, each completing the tetrahedral coordination sphere of a lithium cation. These guest molecules are thus only located in the hydrophilic equatorial region of this molecular assembly. More recent work by this group with α-CD has revealed that the number of Cu(II) cations complexed between the two cyclodextrins depends on the counterions present.[116a] Thus, with lithium and sodium the trinuclear Cu(II) complexes $M_3[M_3Cu_3(\alpha\text{-}CDH_{-6})_2]^{6-}$ (M = Li or Na) were isolated, whereas with potassium and rubidium, only the dinuclear complexes $M_4[Cu_2(\alpha\text{-}CDH_{-4})_2]^{4-}$ (M = K or Rb) formed. Upon deprotonation and metal complexation, the hydrogen bond network of the cyclodextrin ring undergoes reorganization, i.e., a general decrease in length. Consequently, the resultant capsule takes on a more cylindrical shape. Additionally, the sodium complex, $Na_3[Na_3Cu_3(\alpha\text{-}CDH_{-6})_2]$, contains an intercalated acetone and two water molecules, while the potassium complex, $K_4[Cu_2(\alpha\text{-}CDH_{-4})_2]$, contains two acetone molecules only.[116a] Interestingly, in the structure of the sodium complex, one of the three sodium ions at the equatorial region of the capsule is forced away from the outer shell, toward the internal cavity. Thus, the intercalated acetone molecule and one of the water molecules in the complex $Na_3[Na_3Cu_3(\alpha\text{-}CDH_{-6})_2]$ are not held within the cavity by van der Waals interactions typical of the host−guest inclusion compounds described here, but they are instead fixed by well-defined Na−O contacts. This is believed to result from the geometric constraints imposed by the coordination requirements of the Cu(II) and Na ions and the extremely hydrophobic nature of the cavity. The latter feature is clearly apparent in the crystal structure of the complex with potassium ions as counterions. Here, the water ligands are exclusively located outside of the cylindrical shell, and the two acetone guest molecules are only loosely held by van der Waals interactions near the openings of each cylinder.

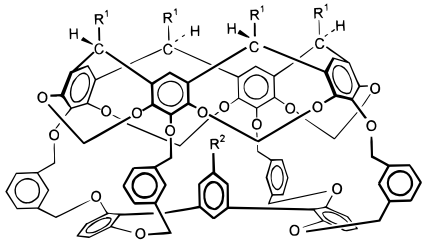
D. Endohedral Complexes

Since their discovery in 1985 by Sir Harold Kroto and Richard Smalley, the fullerenes have generated one of the most prolific areas of research in the past decade.[117] The fullerenes, like carcerands, are closed-surface spherical aromatic compounds, with an enforced internal cavity. Recently examples of endohedral fullerene complexes such as $M@C_{60}$, $M@C_{74}$, $M@C_{80}$, and $M@C_{82}$ (where M = Ln, Ca, Sr, Ba, Ce) have been reported in the literature.[118] Typically, these complexes are prepared by graphite evaporation techniques,[119] which is an inherently indiscriminate methodology. Consequently, a mixture of M@ fullerene complexes result, which have additionally proven difficult to separate, particularly those of C_{60}. Moreover, this technique is limited to the lanthanide, Ca, Sr, and barium metals. Nevertheless, a series of representative metallofullerenes of the larger fullerenes (C_{80}, C_{82}, C_{76}, C_{78}, and C_{84}) with these metals have indeed been successfully isolated and characterized by X-ray photoelectron, UV−vis−NIR, and mass spectroscopy and X-ray diffraction.[118,120] The difficulties in isolating these compounds has unquestionably hampered their investigation. Nonetheless, Kubozono and co-workers have more recently successfully purified a series of $M@C_{60}$ metallofullerenes, using aniline as solvent.[121] However, detailed characterization of these complexes have yet to be reported. Undoubtedly, this exciting development will spur further effort in this area. Despite the difficulties associated with their purification, Shiohara's group has successfully isolated and characterized (by UV−vis spectroscopy, LD-TOF and DCI mass spectroscopy) endohedral metallocomplexes of the two "missing" fullerenes C_{72} and C_{74},[122] i.e., $Ca@C_{72}$ and $Ca@C_{74}$. While both of the two parent fullerenes (i.e., C_{72} and C_{74}) have been known to exist, their isolation from soot produced by arc discharge has thus far remained elusive largely due to their high chemical reactivity and structural instability. Thus, it appears that inclusion of a calcium atom within the molecular cage significantly increases the stability of these two fullerenes. This increased stability largely results from intrafullerene electron transfers from the calcium atom to the fullerene cage which alter the electronic structures near the HOMO−LUMO levels. This notion is supported by the absorption bands in the UV−vis spectrum of $Ca@C_{72}$ and by ab initio calculations.[122]

The fullerenes have also been shown to encapsulate noble gas molecules, and this has been the subject of considerable theoretical discussion.[123] Evidence for this was initially obtained from mass spectroscopic collision experiments.[124] A more common approach currently employed involves heating the fullerene in a noble gas atmosphere,[125] preferably under high pressure (~40 000 psi).[126] Thus, through these experiments, He, Ne, Ar, Kr, and traces of Xe have been observed. Very recently a new class of endohedral fullerene complexes in which the guest is a highly reactive nonmetal has been reported.[127] Astonishingly, in the prototypical member, $N@C_{60}$, the incarcerated nitrogen atom was found (by ESR and electron nuclear double resonance (ENDOR) spectroscopy) to be in its atomic ground state ($^4S_{3/2}$) and not covalently bound to any of the carbon atoms lining the fullerene's internal cavity. This unprecedented observation inspired Hirsch's group to investigate the shape of the fullerene carbon network and its impact on its reactivity.[128] Indeed, these computational studies revealed that the rigidity, coupled with the concave shape of the internal cavity, imparts unprecedented inertness to the carbon skeleton lining the cavity toward the encapsulated nitrogen atoms. More specifically, due to significant pyramidalization of the carbon atoms, the electron charge density is higher on the exterior of the fullerenes than on the inside. Consequently, the orbital overlap between the fullerene's carbons and the encapsulated N atom is highly unfavorable. The estimated energy barrier for extrusion of N from

within the confines of C_{60} is calculated to be about 40 kcal mol^{-1}.[128]

Ozkazaki's group, at the University of Tokyo, has proposed an alternative approach to endohedral compounds.[129] In their molecular design, an appropriate functional group is attached onto the inner surface of the cavity wall of the capsular host molecule, such that it projects into the endohedral space of the host. This approach not only imparts another useful element of design to the resulting supramolecule but also shields the attached functional group from external forces, thus paving the way for some unusual endohedral chemistry. Synthetically, these lantern-shaped molecules (e.g., **128**)



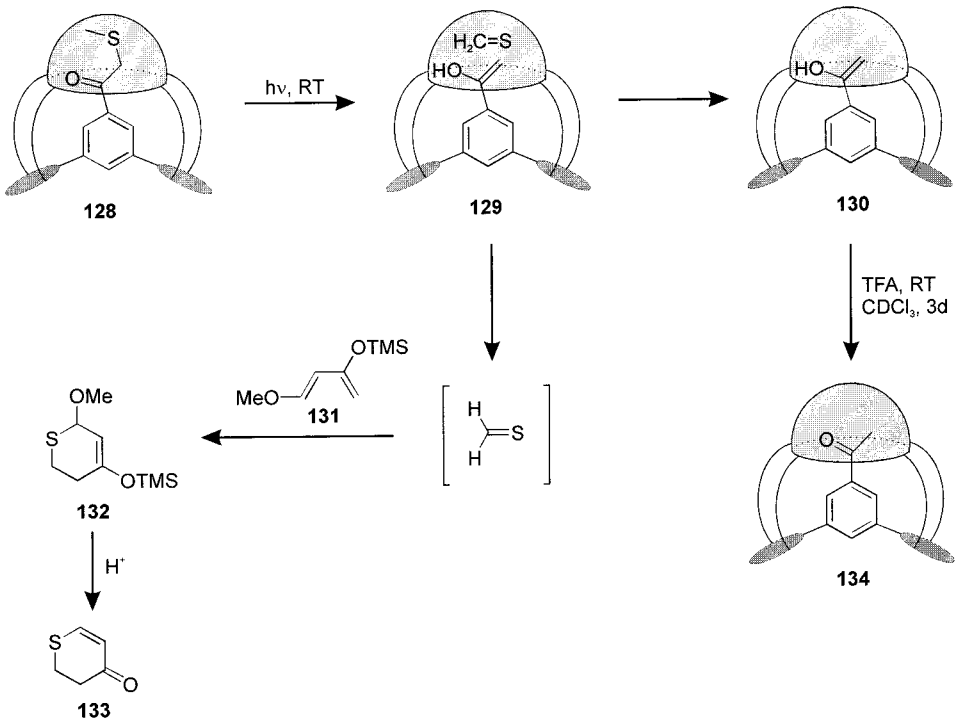
128 $R^1 = C_6H_{14}$
$R^2 = COCH_2SCH_3$

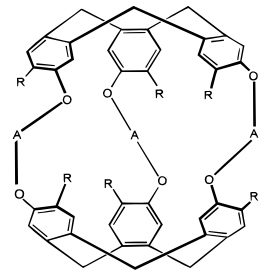
were obtained via a sequence that initially involves extending the cavity of tetrol **6b** with α,α′-dibromo-*m*-xylene to give the tetrabromo analogue of **49**[130] and subsequent capping with an *m*-terphenyl unit onto which the masked endohedral functionality is preattached. Using this approach these researchers isolated the methylthioacetyl-derivatized endohedral compound **128**.[130a] Subsequent photolysis of **128** in toulene-d_8, in the presence of Danishefsky's diene **131** as a trapping reagent, afforded the β-unsubstituted enol adduct **130** (Scheme 26). The thioformaldehyde byproduct was trapped as enone **133**, presumably after hydrolysis of the silyl ether **132**. Typically, β-unsubstituted enols are highly unstable species; however, in this instance, the enol adduct **130** proved to be remarkably stable in solution, even in the presence of TFA wherein ketonization to the acetyl derivative **134** occurred after 3 days at ambient temperature. Undoubtedly, this stability arises from the shielding nature of the upper resorcinarene cavity. Incidentally, these molecular lanterns are not true host−guest systems; thus Okazaki has proposed the term "mother molecular−daughter molecular" complexes.

E. Cryptophanes

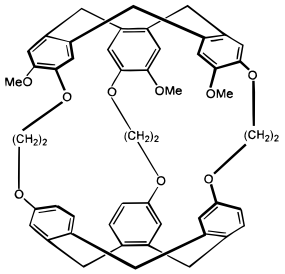
Cryptophanes are hollow macrocycles containing two cyclotriveratrylene (CTV) caps linked together by three bridges. The prototypical members in this series of rigid host molecules (e.g., compounds **135**−**139**) were reported in the mid-1980s by Collet and were shown to bind a variety of organic guests such as chloroform, methane, dichlorfluromethane, dichloromethane, etc.[131] The energy barriers for decomplexation of methane and chloroform from host **135** are 10.5 and 14.7 kcal mol^{-1}.[131a] Further investigation of the thermodynamic properties for binding revealed that for larger guests the complexation is driven by attractive host−guest interactions. On the other hand, for smaller guests the host−guest interactions do not play a significant role; instead, solvophobic effects contribute more to the enhanced stability of the complex.[131a,b] Water-soluble derivative **138** strongly binds chloroform and dichloromethane in D_2O.[131d] Interestingly, asymmetric cryptophane (−)-**139** enantioselectively bound bromochloroflouromethane, with a $\Delta\Delta G°$ of ∼260 cal mol^{-1}.[132] Very recently, these workers have applied molecular dynamic simulations to these diastereomeric complexes to determine the

Scheme 26

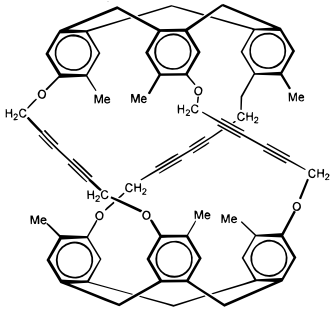




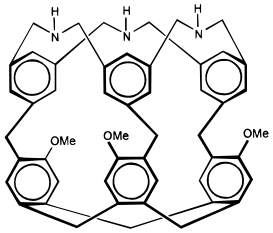
135 R = OMe, A = $(CH_2)_2$
136 R = OMe, A = $(CH_2)_3$
137 R = OMe, A = CH_2—≡—CH_2
138 R = CH_2CO_2H, A= $(CH_2)_2$



139



140



141

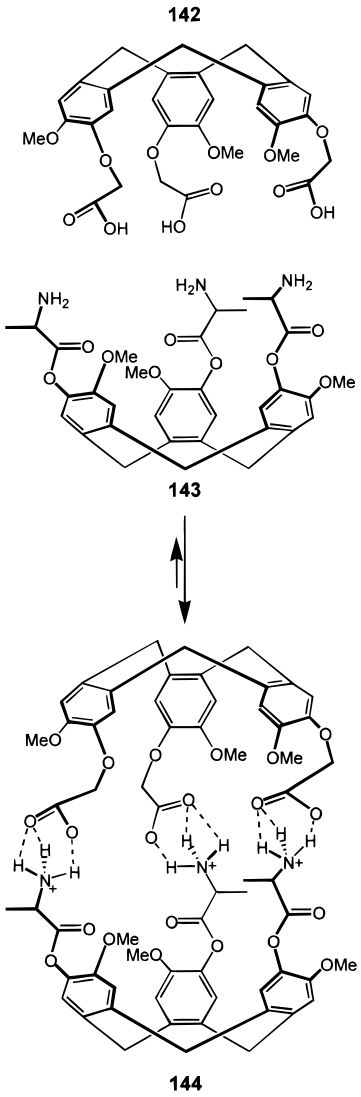
absolute configuration of the guest, a feat that attracted considerable attention for over half a century.[133] Surprisingly, these chiral hosts have attracted little attention in recent years.

Cram's contribution to this field includes the slightly larger bisacteylenic-bridged cryptophane (±)-**140**.[134] This cryptophane forms complexes with chloroform, cubane, propylene oxide, benzene, dichloromethane, and *tert*-butyl alcohol, with energy barriers to dissociation of 13−14 kcal mol^{-1}. The smaller chiral cryptophane (±)-**141**, in contrast, weakly binds N_2, O_2, water, methanol, and ethanol ($t_{1/2}$ = 40 min, at 25 °C).[135]

Lee and Hong have prepared the self-assembling heterodimer **144**[136] from the two complementary functionalized CTV subunits **142** and **143** (Figure 12). Heterodimer **144** was found to bind bromoform, chloroform, 1,1,1-trichloroethane, *tert*-butyl chloride, and tetramethylsilane with relative association constants ranging from 1 to 200, respectively. Moreover, this dimerization is reversible, thus addition of TFA to a solution of **144**·Me_4Si breaks up the ternary complex into its constituents. The formation of this hydrogen-bonded heterodimer in DMSO is particularly noteworthy, given this solvent's strong propensity to disrupt these types of complexes. Clearly, this complex owes its stability to the charged hydrogen bonds and the noncovalent interactions between the encapsulated guest molecule and the walls of the cavity.

VI. Future Outlook

Since their conceptualization by Cram and his subsequent pioneering synthesis of the first carceplexes, these container compounds have inspired a diverse field of research toward novel container



142

143

144

Figure 12.

compounds, as is evident by the work presented here. As more of the fundamental properties that drive these self-assembly processes are worked out, one can expect to see the development of more intricate systems even possibly approaching the efficiency and accuracy demonstrated by nature. Cram's recent work on hemicarceplexes, for example, demonstrates that there is indeed a fine balance between synthetic success, preorganization, and templation in synthesizing larger molecule assemblies. On the other hand, Atwood's discovery of the large hexameric resorcinarene array illustrates that chemistry can advance in surprisingly large steps. The current trend toward reversible assemblies is unquestionably a step in the right direction toward molecular delivery devices and switches and perhaps even molecular computers. Deshayes' recent synthesis of a photolyzable hemicarceplex provides strong evidence that our goal toward these molecular devices is surely just on the horizon.

Perhaps the most useful application to date of hemicarceplexes is their ability to function as unique microreaction chambers and in stabilizing highly reactive species. Indeed, Rebek's glycouril-based spheres have been shown to accelerate a Diels−Alder

reaction between *p*-quinone and cyclohexadiene.[7,12,16a,23] Moreover, the high degree of molecular recognition demonstrated by these molecules makes them ideal targets for synthetic enzymes. The endohedral molecular lanterns provide an excellent example of one strategy toward these artificial enzymes, as one can now introduce appropriate functionality within the internal cavity.

VII. Acknowledgments

We acknowledge all our colleagues whose continued contributions have led to the success of this field of chemistry and hopefully inspire further exciting developments. We warmly thank the University of British Columbia for providing a pleasant and stimulating environment for undertaking both scientific research and extracurricular activities and Shannon Salvador for proofreading this manuscript. We are indebted to the Natural Sciences and Engineering Research Council of Canada, the National Institutes of Health, and the donors of the Petroleum Research Fund for generous financial support of our research. A.J. thanks the University of British Columbia for a fellowship award.

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