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Carceplexes and Hemicarceplexes: Molecular Encapsulation–From Hours to Forever.

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1. Introduction

Nobel Laureate Donald J. Cram has been dazzling the scientific community for over a decade with accounts of his research on the encapsulation of molecules within molecules. Cram proposed the idea of a *carceplex* in a 1983 paper in *Science*[1] and reported the first example of a carceplex in 1985,[2] which was followed by the first fully characterized carceplex in 1989.[3] Since then, he has developed the field of

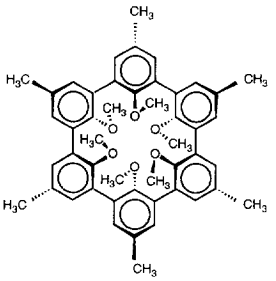
carceplexes and *hemicarceplexes*, and now laboratories worldwide are joining in the exploration of these fascinating compounds. Carceplexes and hemicarceplexes provide a unique perspective from which to study non-covalent interactions, which are important in molecular recognition,[4] supramolecular chemistry,[5] self-assembling structures,[6] templation[7] and molecular encapsulation.[8] Long range applications of carceplexes and hemicarceplexes include use in drug delivery, organ imaging and radiation therapy.

Cram presented discussions of the early work on carceplexes and hemicarceplexes in his book *From Design to Discovery* in 1990[9] and in *Nature* in 1992.[10] Professor and Mrs. Cram have published a new book entitled *Container Compounds and Their Guests*, which includes several chapters on carceplexes and hemicarceplexes.[11] Here, I present a chronological review of carceplexes and hemicarceplexes; the bulk of the work described was done in the laboratories of Professor Cram subsequent to his 1987 Nobel Prize in Chemistry.

The novelty and vividness of carceplexes and hemicarceplexes allow the research to sell itself. Nevertheless, to put the work in better context, I have tried to provide some perspective on how the field has evolved. As with many areas of research, carceplexes and hemicarceplexes went through an incubation period, during which formidable difficulties had to be overcome. The current explosion in new results, however, have more than compensated for the early troubles. I have tried to capture some of the serendipitous discoveries that helped this field along and hope the few anecdotes give the work a more tangible quality.

2. Definitions

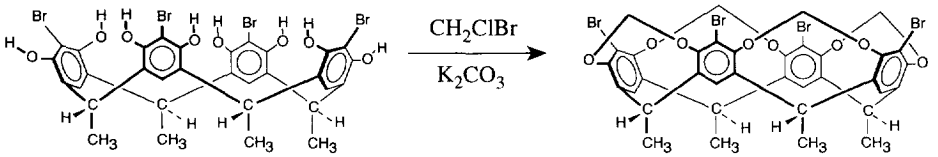
Carceplexes are closed surface compounds that permanently entrap guest molecules or ions within their shell, such that guest escape can only occur by rupture of covalent bonds.[2] *Hemicarceplexes* differ in that the shell's portals are large enough for egress of guest upon sufficient heat treatment. Hemicarceplexes must be kinetically stable and thus isolable without loss of guest.[12] This stability differentiates hemicarceplexes from most complexes, which undergo fast exchange on the human timescale (minutes to hours). Hemicarceplexes also differ from other complexes that undergo slow exchange. For example, clathrates[13] and other solid inclusion compounds[8] can retain guests within cavities formed in their crystal lattices, whereas hemicarceplexes are stable in solution. Zeolites can retain compounds via ion-dipole and other interactions, also in the solid state.[14] There are several other unusual systems that undergo slow guest exchange in solution such as a spherand (see below), which binds alkali metal cations.[15] By and large, hemicarceplexes contain neutral guest molecules that are retained in solution for hours or longer at room temperature by non-covalent, non-ionic forces. These closed surface compounds are called *carcerands* and *hemicarcerands* when no guest is present.



Spherand

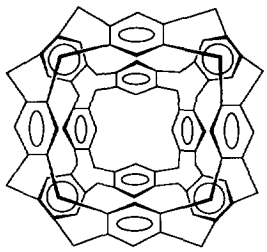
3. The First Carceplexes

In 1983, Cram proposed the permanent incarceration of molecules via the synthesis of a closed-surface spherical molecule.[1] The idea grew, in part, out of the success in creating a spherand, which has a nearly perfect, spherical binding cavity for Li^+.[15] Shortly thereafter, Cram had bridged the conformationally flexible bromo octol **1** with methylenes to give "bowl" **2**.[16] This "bowl" was very rigid and contained an enforced cavity. If a rigid molecular bowl could be synthesized, why not a sphere? If such a compound could be made, what would its properties be? More interestingly, what would the the properties of the entrapped species be? What would be the phase of an entrapped molecule? Phase being a macroscopic property, is this even a legitimate question to ask about an isolated molecule? How would the entrapped molecule move? Would it have a preferred orientation with respect to the shell? What would be the nature of the interactions of the entrapped molecule with the shell? Would the entrapped molecule be able to communicate with the external environment?



1 **2**

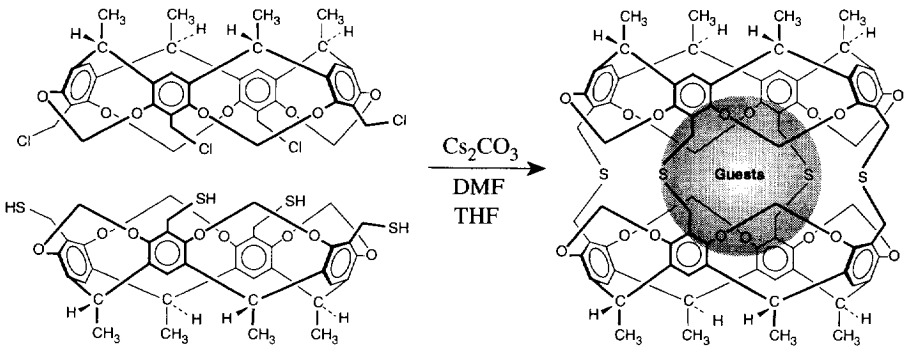
The first proposed structure for a carcerand, **3**, was based loosely upon the structure of bowl **2**.[1] The first carceplex to be synthesized, however, had the structure of **4** (**Scheme 1**).[2,17] Carcerand **3** and carceplex **4** both contain enforced cavities, according to CPK molecular models, that could accomodate molecules roughly the size of benzene. The reaction to form carceplex **4** led to a solid that was washed with water, ethyl acetate, ethanol, dichloromethane and chloroform and was insoluble in hot naphthalene, anisole, nitrobenzene, pyridine or xylene. This solid residue was characterized by elemental analysis and FAB mass spectrometry as a mixture of compounds with the shell of **4** (29% yield), but containing an assortment of entrapped species, including dimethylformamide, tetrahydrofuran, Cs^+ and even Ar. Further characterization by, for example, high resolution ^1H NMR required a substantial enhancement in solubility.



Carcerand 3

Incidentally, CPK models are invaluable for modelling the rigidity and cavity size and shape of compounds such as carceplexes and hemicarceplexes. Cram has reported the use of a plaster cast of the interior of carceplexes and hemicarceplexes as well as a silicon rubber mold of the casts. The mold and cast

allow for improved cavity analysis.[18] In addition to CPK models, plaster casts and rubber molds, computations are becoming increasingly important in enhancing our understanding of the non-covalent interactions in carceplexes and hemicarceplexes. An analysis of the change in free surface area of the host upon complexation has been used to model the close contacts formed between the host and guest.[19]



4

Scheme 1. Synthesis of carceplex **4**.

4. Soluble Carceplexes

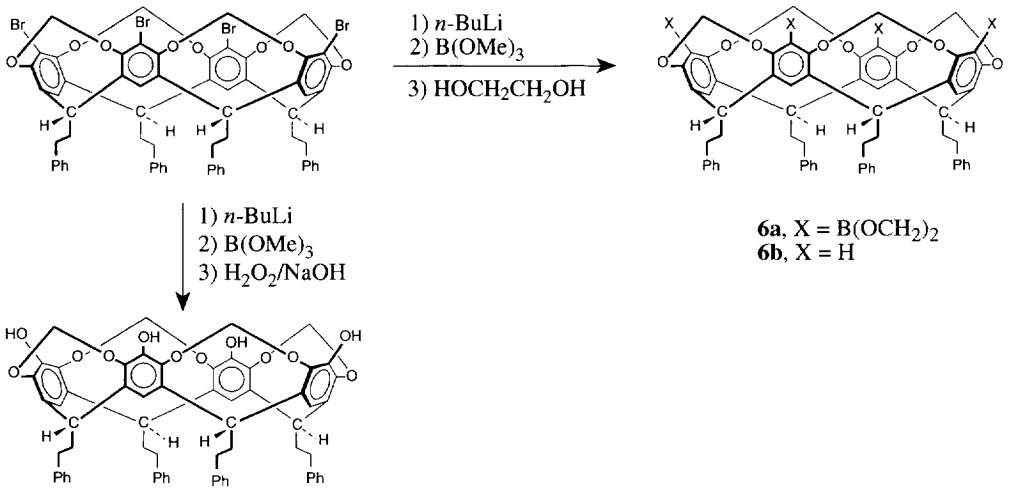
4.1 An Anecdote

By the mid 1980's, it was thought to be essential to incorporate lipophilic solubilizing groups into the building blocks for carceplexes.[20] In addition, the new bowl, tetrol **5**, functionalized with four phenolic groups between the bridges, was prepared.[3,21] The utility of tetrol **5** can be seen by the number of hemicarceplexes described in Section 5 whose syntheses were derived from tetrol **5**. Thus, a brief reflection on how this compound came to be is appropriate and provides an example of serendipity in science. Efforts to synthesize the tetra-boronic ester **6a** (**Scheme 2**) led to the isolation of tetra-protio bowl **6b**. To determine that the boronic esters were in fact formed and were undergoing proto-deboronation, the reaction mixture was subjected to H_2O_2/NaOH oxidation, which would result in the introduction of phenolic groups to the rim of the bowl. This reaction went smoothly, giving tetrol **5** in 53% yield, which is high considering three four-fold in situ transformations.[21] Thus, the boronic esters had been formed but were unstable.[21b,c] The foregoing results were of little help regarding the use of **6a** to build new macrocycles, yet the incidental synthesis of tetrol **5** has led to the design of a wide variety of macromolecules that are discussed in this review.

4.2 The First Soluble Carceplex

Tetrol **5** was prepared in four steps from the inexpensive compounds resorcinol and dihydrocinnamaldehyde in an overall yield of 11%. In light of the success in bridging octols such as **1** with bromochloromethane to produce rigid bowls, tetrol **5** was subjected to the same conditions in an attempt to form inter-bowl methylene bridges. The result was the first soluble carceplex **7**.[3,21] Phenethyls were chosen as the pendant groups for their lipophilicity and floppiness, which were deemed necessary to impart solubility

to the compounds. Carceplex **7** was indeed soluble in chlorofom and was fully characterized. Space-filling representations of the shell of carceplex **7** (where the pendant groups are methyls), with no guest, are shown in **Figure 1**.[23] One can see the largest portal at the "poles" of the shell. These holes are about 2 Å wide including van der Waals distances of the opposing and adjacent hydrogens that line the portal. The entrapped guests described below, cannot escape through these portals, even upon prolonged heating in solution. Thus, compound **7** is truly a carceplex.



Scheme 2. Synthesis of tetrol **5** and attempted synthesis of boronic ester **6a**.

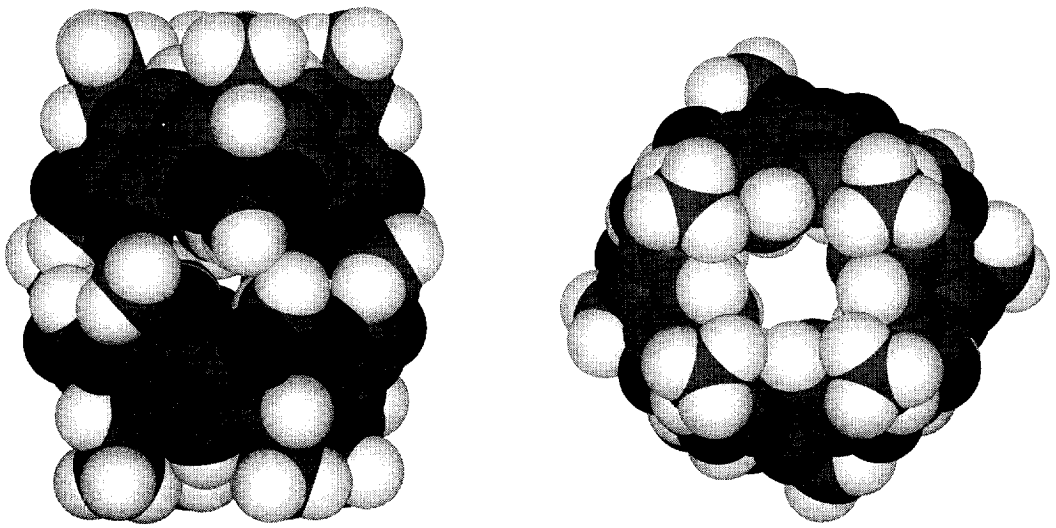
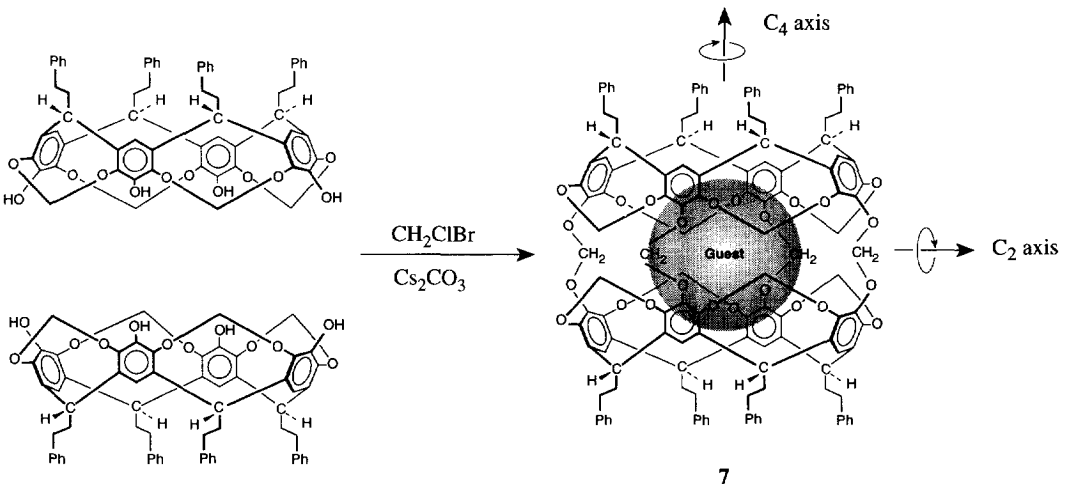


Figure 1. Side view and top view of empty carcerand **7**, where the eight phenethyl groups have been replaced by methyls.



7

The reactions to form carceplex **7** were run in dimethylacetamide (DMA), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) as solvents and gave carceplexes **7**•DMA, **7**•DMF and **7**•DMSO in 54, 49 and 61% yields, respectively. These yields are remarkably high, considering seven molecules are brought together (including guest) by the formation of eight new covalent bonds. No carceplex was isolated when the reaction was run in the bulky solvent *N*-formylpipyridine (NFP), but **7**•DMA was obtained in 10% yield when the reaction was conducted in NFP with 0.5 mole % DMA. Thus, the reaction requires a template molecule; this template effect is discussed further in Section 7. As is typical of the carceplexes and hemicarceplexes discussed in Sections 4 & 5, the chemical shifts of the hydrogens of the incarcerated guests were shifted upfield (2-4.5 ppm from their normal shifts) due to the shielding effect of the π electrons that line the walls of the cavity. Each of the three entrapped guest molecules was determined to have a preferred orientation with respect to the walls of the shell according to their ^{1}H NMR spectra, which agreed with structures predicted by MM2 calculations and with the crystal structure of **7**•DMA. All three guests were found to rotate quickly about the C_4 axis of the shell, on the ^{1}H NMR timescale down to -38 °C. With respect to the C_2 axes, DMF rotates quickly down to -38°C, whereas DMA rotates slowly up to 175°C; thus, the energy barrier for guest rotation about the host's C_2 axes could not be measured for these guests. For DMSO, rotation about the host's C_2 axes is slow below 2°C; the energy barrier for rotation of DMSO about the host's C_2 axes was determined to be about 13 kcal/mol.

The infrared spectra of **7**•DMF and **7**•DMA show carbonyl stretching bands that are intermediate between the gas and liquid phases for these molecules, and thus address the question of the effective phase of the entrapped guest molecules. Furthermore, the energy barriers to rotation about the C–N amide bonds of DMF and DMA are intermediate between the barriers for these molecules in normal gas and liquid phases.

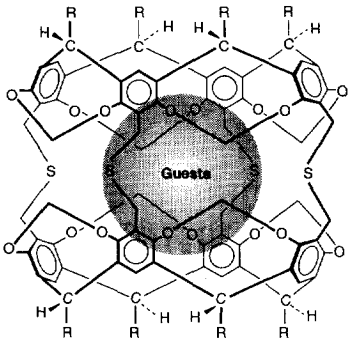
The chemical shifts of the hydrogens of entrapped DMA are sensitive to solvent and demonstrate that the inmates can communicate with the environment external to the carceplex. Furthermore, **7**•DMA was chromatographically separable from **7**•DMF. This behavior again suggests that the entrapped molecules can interact with the milieu that is external to the carceplex. Lastly, in the crystal structure of **7**•DMA, the guest

was observed in only two degenerate orientations, where four equivalent arrangements are possible. This finding indicates that, in the solid state, the guests can communicate with each other through the shells.

4.3 Soluble Sulfur-Bridged Carceplexes

With the success in characterization of carceplex **7**, the $-CH_2SCH_2-$ bridged carceplex **4** was reinvestigated, with phenethyl and pentyl groups as the solubilizing pendant groups.[24] Phenethyl units were chosen for their superior crystallinity, while pentyl groups impart better solubility to carceplexes and hemicarceplexes.

Carceplexes **8a** and **8b** were soluble and were fully characterized. Yields up to 32% were obtained, and various reaction solvent molecules were entrapped including DMA, DMF, butanone, ethanol, 3-pentanone, two molecules of acetontrile and two molecules of methanol. The latter two carceplexes are particularly striking since two molecules occupy the small confines of the carceplex cavity. Moreover, **8**•$2CH_3CN$ was unstable: loss of one molecule of acetonitrile was proposed to occur via a "billiard ball mechanism" whereby one acetonitrile collides with the other, transfers energy and allows the energized acetonitrile to depart through one of the small portals of the carceplex. The activation energy for this decomplexation was estimated to be 20 kcal/mol. Strictly speaking, **8**•$2CH_3CN$ is a hemicarceplex, whereas **8**•CH_3CN is a carceplex.



8a, R = CH_2CH_2Ph
8b, R = $(CH_2)_4CH_3$

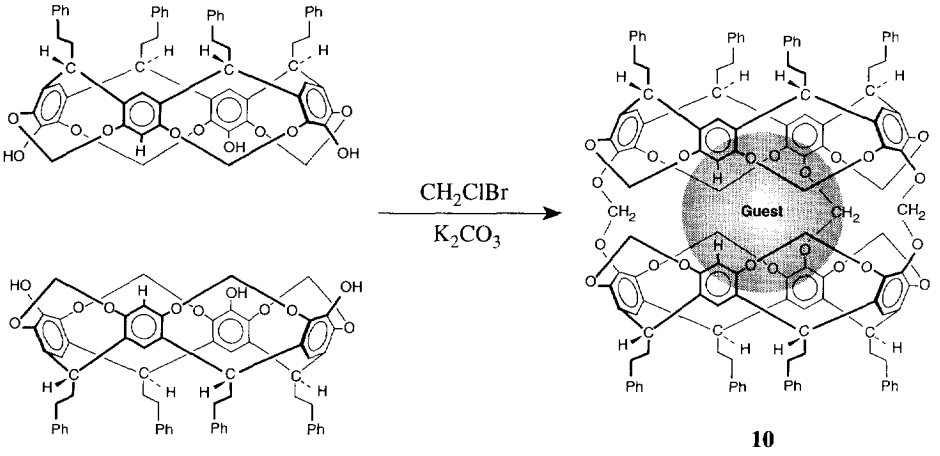
For carceplex **8**, the question arises: why were no carceplexes formed with guests such as Cs^+, as was the case with the methyl-footed analog **4**? It was suggested that any carceplexes containing charged ions were left on the silica gel column during purification (since **4** was insoluble, it was not chromatographed). The solubility difference between methyl- and phenethyl-footed carceplexes is discussed further in Section 7.

5. Hemicarceplexes

5.1 The First Hemicarceplex

Triol **9** was a side-product[21] in the synthesis of tetrol **5** and led to the design and synthesis of the first hemicarceplex, **10**. The researchers prepared **10** by bridging triol **9** with bromochloromethane to give **10**•DMA in 42% yield, **10**•DMF in 20% yield and **10**•DMSO in 51% yield when the reaction was run in the

solvents DMA, DMF or DMSO, respectively.[12,25] The 42 and 51% yields surpass that expected based upon statistical analysis of the reaction.



9 **10**

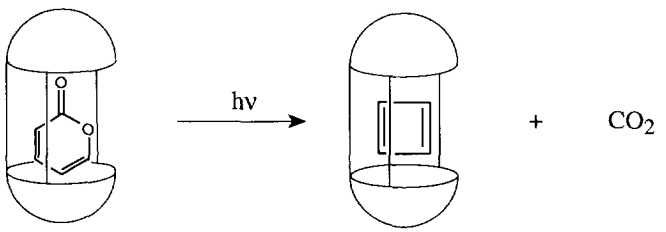
Hemicarceplex **10** contains a portal where carceplex **7** had a fourth $-OCH_2O-$ bridge. A crystal structure of **10**•DMF showed the guest's carbonyl pointing toward the portal of the host. The guests were expelled from the complex by extensive heat treatment in solvents that are too large to fit inside. This procedure was used to form many of the other hemicarcerands discussed in Section 5. Half-lives for decomplexation measured in 1,3,5-trichlorobenzene at 140°C were 14 h and 34 h for DMF and DMA, respectively, and 24 h at 195°C for DMSO. DMSO has the slowest decomplexation rate owing to its tetrahedral shape, which yields a cross section that is not complementary to the portal of the shell.

New complexes were formed by mixture of the empty hemicarcerand with suitable guests such as benzene, tetrahydrofuran, pyridine, diethylamine, *n*-butylamine, acetonitrile, carbon disulfide, dichloromethane, dibromomethane, α-pyrone, xenon, water, CO_2, O_2 and N_2, although the last four complexes were not stable enough for isolation. Heat was required to form some of the complexes; this inducement is typical in formation of many of the hemicarceplexes discussed below. The energy barrier for decomplexation of **10**•N_2 and **10**•O_2 were estimated to be 15 and 14 kcal/mol, respectively. Binding of paramagnetic O_2 resulted in the broadening and shifting of the ^1H NMR signals of the host to the extent that assignments could not be made. Like carceplex **8**, hemicarceplex **10** encapsulated two molecules of acetonitrile; it lost one of the two with a half-life of 20 minutes at 22°C (E_a ca. 21 kcal/mol), whereas the second molecule was stable indefintely at ambient temperature. An association constant of 200 M^{-1} was determined for Xe, and the half-life for decomplexation was 47 h at 22°C (ca. 24 kcal/mol). *Constrictive binding* was used to "describe the steric forces that must be overcome for decomplexation of hemicarceplexes whose guest cross sectional sizes exceed those of the host portals."[25]

Addition of trifluoroacetic acid to a chloroform solution of **10**•diethylamine resulted in instantaneous decomplexation, whereas addition of acetic acid resulted in proton exchange only. Addition of trifluoroacetic acid to **10**•*n*-butylamine resulted in comparatively slow decomplexation, with a half-life of 22 minutes at 22°C.

Diethylammonium and *n*-butylammonium are similar in size, shape and charge, but differ in that they are secondary versus primary ammoniums and in the location of the charges. Despite *n*-butylammonium having a more "bare" charge, which would be less favorable in the apolar cavity, it decomplexes more slowly. The charge most likely resides near the polar regions of **10** and may be stabilized by the π-electrons. Decomplexation might also be slowed by an interaction of the ammonium with its counterion through the polar portal. Alternatively, diethylammonium may depart charge-first, like an arrow, through the portal, whereas *n*-butylammonium may have to swing its ammonium end down from the poles of the shell to the portal at the shell's equator. Thus, the decomplexation of hemicarceplex **10**•*n*-butylammonium may be an example of a molecule that has trouble getting out of its own way.

Perhaps the most exciting carceplex/hemicarceplex experiment to date was the room temperature stabilization of cyclobutadiene in the shell of hemicarceplex **10**.[26] The instability of cyclobutadiene has been the subject of much theoretical and experimental research. The antiaromaticity of the four π-electron system renders cyclobutadiene both a reactive diene and dieneophile. The stability of cyclobutadiene in the gas phase and in a solid argon matrix at 8 K and its instability in solution suggest that the molecule itself is stable if intermolecular reactions are precluded. The interior of hemicarceplex **10** would provide just such an inert environment, but how could such a reactive molecule be encapsulated? Cyclobutadiene was generated inside hemicarceplex **10** by photolysis of encapsulated α-pyrone as illustatrated in **Scheme 3**. This was the first reaction to be conducted within the confines of a hemicarceplex. Carbon dioxide was also generated, but it quickly escaped though the portal. Encapsulated cyclobutadiene was shown to exist in the singlet ground state. Another example of the protective effect of hemicarceplex **10** is that **10**•dibromomethane was stable to the presence of 100 equivalents of *n*-butyllithium for one minute at 25°C.[25] Compounds **11**•DMF, **12**•DMSO and **13**•DMSO were prepared, but no guest exchange experiments were reported.[25]



Scheme 3. Photolysis of **10**•α-pyrone to give **10**•cyclobutadiene.

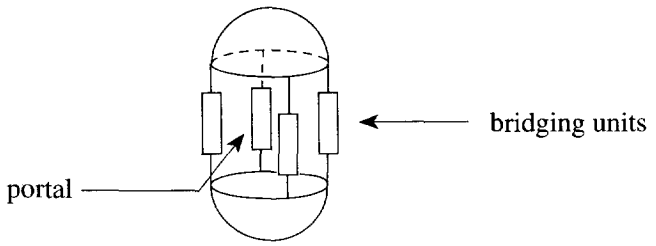
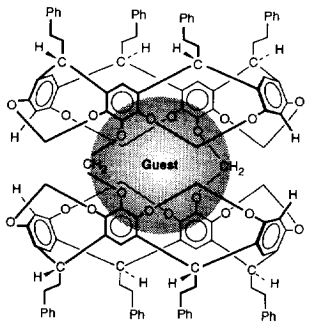


Figure 2. Schematic representation of hemicarceplexes containing four bridges and slotted portals.

All subsequent hemicarceplexes have been constructed with four larger bridges between two bowls and have pores that correspond to four equivalent slots as represented in **Figure 2**. Each hemicarceplex has a unique cavity size and shape as dictated by the bridging unit. Accordingly, a variety of guest molecules with a broad range of sizes and shapes have been encapsulated.



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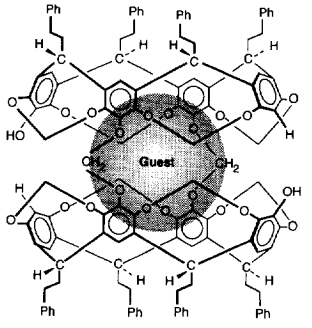

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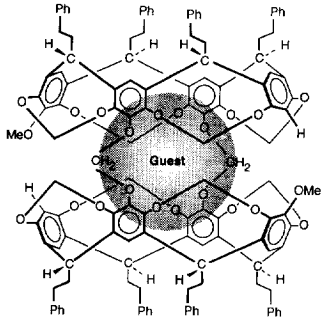

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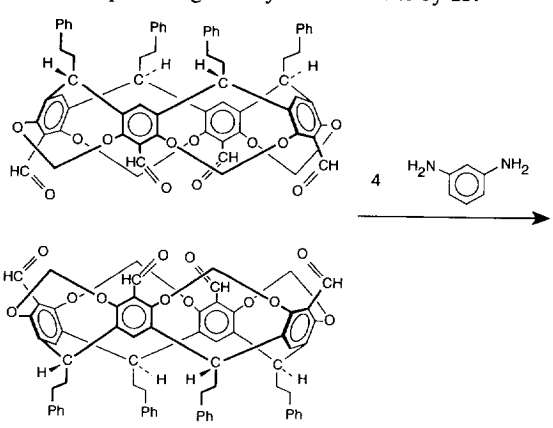
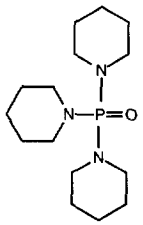
5.2 Imine Bridges

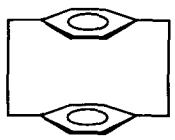
Hemicarcerand **15** was prepared in 45% yield from the condensation of tetraldehyde **14** with 1,3-diaminobenzene.[27] Complexes of **15**•guest were obtained when the empty hemicarcerand was heated in guest as solvent or in bulky high boiling solvents such as tripiperidylphosphine oxide in the presence of suitable guests. Fourteen guests including [2.2]paracyclophane and adamantadine were encapsulated. Adamantadine is the only drug to be encapsulated by a hemicarceplex. Decomplexation half-lives for the complexes ranged from 3.2 h at 25 °C for **15**•hexachlorobutadiene to 19.6 h at 112 °C for **15**•ferrocene. Activation energies for dissociation as high as 28 kcal/mol were determined. A crystal structure of **15**•ferrocene was determined.[28a] The photolysis of **15**•9-cyanoanthracene has been investigated recently.[28b] Time-resolved examination of the emission and absorbtion properties of **15**•9-cyanoanthracene showed modified behavior that was attributed to electron transfer quenching of 9-cyanoanthracene by **15**.



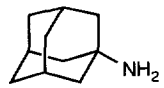
14 **15**



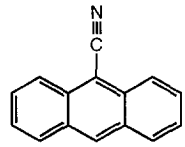
tripiperidylphosphine oxide



[2.2]paracyclophane



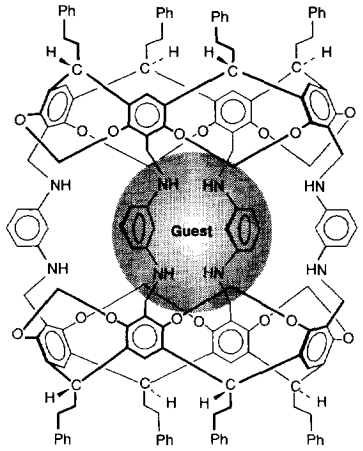
adamantadine



9-cyanoanthracene

5.3 Amine Bridges

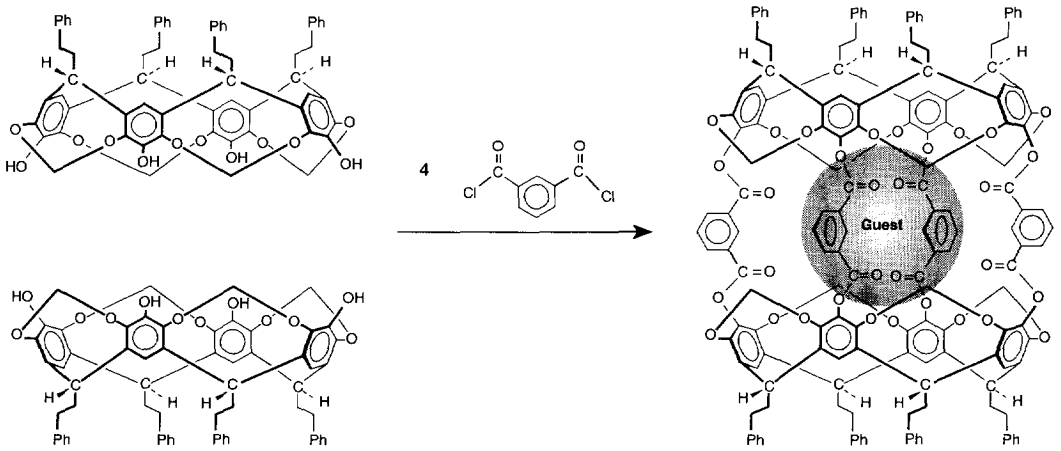
Hemicarceplex **15**•[2.2]paracyclophane was reduced with THF-NaCN-Ni(AcAc) to **16**•[2.2]paracyclophane in 87% yield.[29] Although hemicarcerand **15** formed a complex with [2.2]paracyclophane, hemicarcerand **16** did not form such a complex under similar thermal treatment in the presence of an excess of [2.2]paracyclophane. Nevertheless, reduction of **15**•[2.2]paracyclophane to **16**•[2.2]paracyclophane went smoothly, with no loss of guest nor inhibition of product formation. No decomplexation studies of **16**•[2.2]paracyclophane were reported.



16

5.4 Lactone Bridges

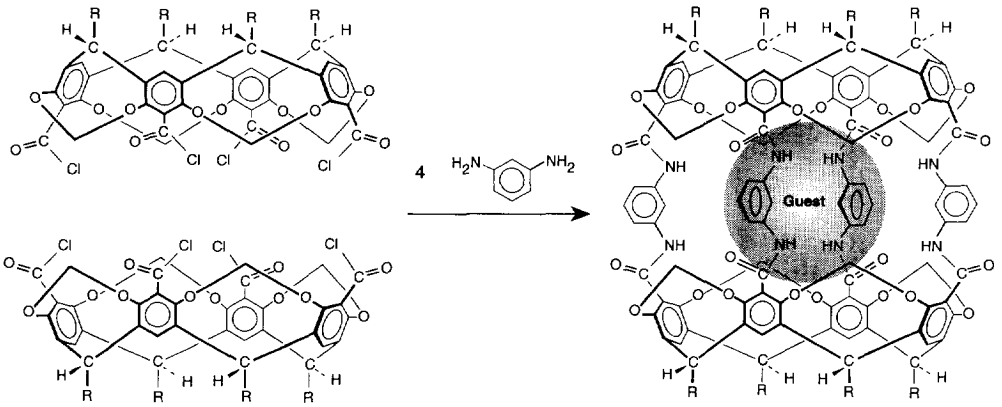
Hemicarceplex **17**•CH_2Cl_2 was prepared in 5% yield by treatment of tetrol **5** with isophthaloyl chloride in DMA with Cs_2CO_3 as base and was purified by chromatography with dichloromethane as the eluent.[30] Hemicarceplex **17**•$CHCl_2CHCl_2$ was prepared by guest exchange in $CHCl_2CHCl_2$ at 110°C for 12 h and was crystallized from nitrobenzene. A crystal structure showed that some of the carbonyls stick into the cavity while others project out of the cavity. The activation energy for decomplexation of **17**•$CHCl_2CHCl_2$ is 25 kcal/mol with a half-life of 18 h at 25 °C.



17

5.5 Lactam Bridges

Hemicarcerands **19a** and **19b** were prepared in 7% yield from the reaction of tetra-acid chlorides **18a** and **18b**, respectively, with 1,3-phenylene-diamine.[31] A crystal structure of **19a**[31,32] showed seven water molecules in the cavity each within 3 Å of one of the nitrogens. The two bowls are displaced with respect to each other by 1.9 Å, which gives the hemicarceplex the unusual topology represented schematically in **Figure 3**. Four carbonyls point into the cavity and four point out. Twelve guests failed to form complexes, but 1,4-diacetoxybenzene formed a stable complex.



18a, R = CH_2CH_2Ph
18b, R = $(CH_2)_4CH_3$

19a, R = CH_2CH_2Ph
19b, R = $(CH_2)_4CH_3$

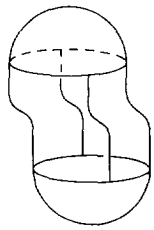
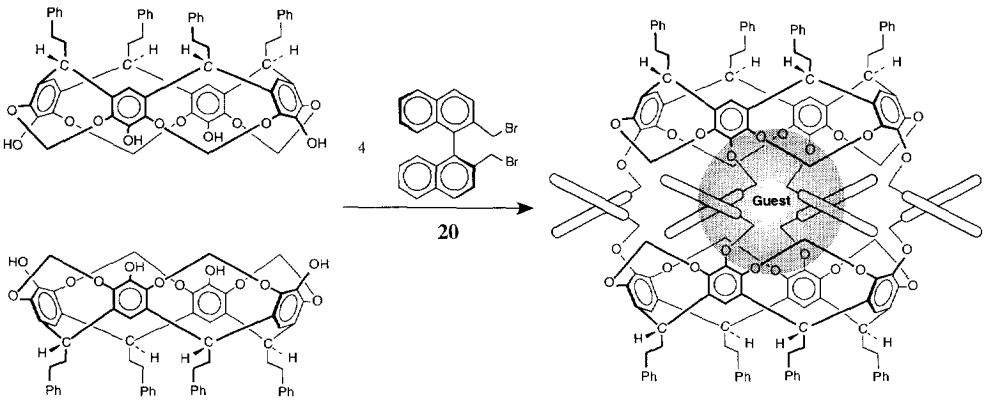


Figure 3. Topology of the crystal structure of **19a**•7H_2O.

5.6 Binaphthyl Bridges

Reaction of tetrol **5** with enantiomerically pure *R*-**20** or *S*-**20** gave enantiomerically pure hemicarceplexes (*R*)$_4$-**21**•chloroform and (*S*)$_4$-**21**•chloroform in 12-13% yields.[33] Dissolution of these hemicarceplexes in *p*-xylene, 2-iodobutane or $BrCH_2CH(CH_3)_2$ resulted in guest exchange. Dissociation half-lives for these hemicarceplexes at 23°C ranged from 0.3 h to ~50,000 h. Diastereomeric complexes (*R*)$_4$-1-(*S*)-$BrCH_2CH(CH_3)CH_2CH_3$ and (*S*)$_4$-1-(*S*)-$BrCH_2CH(CH_3)CH_2CH_3$ had first-order rate constants for guest release of 4.4 x 10^{-2} h^{-1} and 6.2 x 10^{-3} h^{-1}, respectively. The $\Delta\Delta G°$ for the diastereomeric complexes for **21**•(*R*)-$BrCH_2CH_2CHBrCH_3$ and **21**•(*S*)-$BrCH_2CH_2CHBrCH_3$ was 0.3 kcal/mol at 100°C.

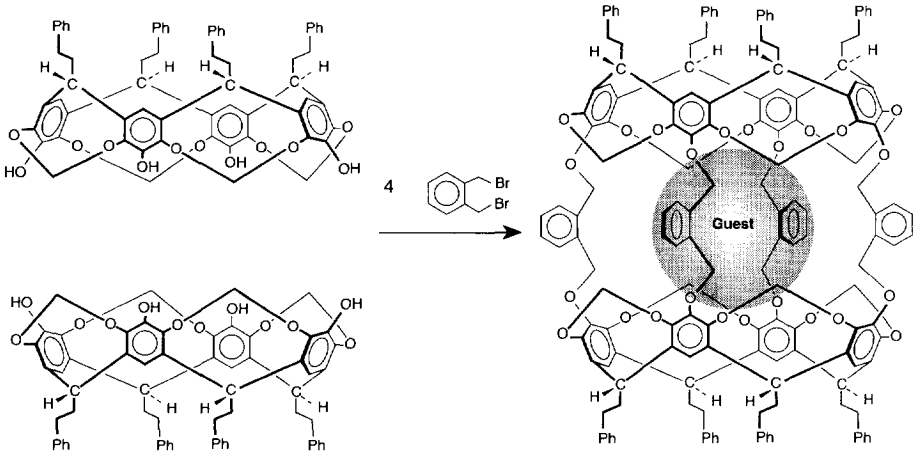


21

5.7 *o*-Xylyl Bridges

The reaction of tetrol **5** and 1,2-$(BrCH_2)_2C_6H_4$ in DMA with cesium carbonate as base gave hemicarceplex **22**•DMA in 23% yield.[34] A crystal structure showed the top and bottom bowls to be rotated with respect to each other by 21°, which is typical of the tetrol-derived carceplexes and hemicarceplexes. Twelve guests were incorporated into hemicarceplex **22**. Half-lives for dissociation of the complexes ranged from 38 to 409 minutes at 100°C in $CDCl_2CDCl_2$. Decomplexation rates were dependent on solvent; this behavior implies that solvent is important in the stabilization of the transition state of guest exchange. In all cases where the solvent molecules were suitable guests, there was some buildup of empty hemicarcerand **22**, so egress is a two step process. The values $\Delta G°$, $\Delta H°$ and $\Delta S°$ for association and $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for association and dissociation were determined for complexes of **22** with ethyl acetate, toluene, butanone and DMA. *Constrictive binding* free energy was defined as $\Delta G^{\ddagger}_{dissoc.} - (\Delta G°) = \Delta G^{\ddagger}_{assoc.}$, where $\Delta G°$ is the

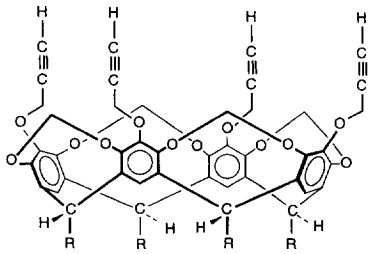
intrinsic binding free energy and $\Delta G^{\ddagger}_{assoc.}$ is the activation free energy of binding or the constrictive binding free energy. It was concluded that complexation of ethyl acetate, butanone and DMA is driven by both enthalpy and entropy, whereas complexation of toluene is driven by entropy and opposed by enthalpy. The entropic driving force was explained by: 1) a solvophobic effect, where expulsion of guest from solvent frees up solvent molecules to bulk solvent; and 2) the large empty space in the hemicarcerand, which is broken down into many smaller empty spaces that are distributed about the solvent upon complexation. The unfavorable enthalpy upon binding toluene was explained by the poor interactions of the flat guest with the concave walls lining the interior of **22**.



22

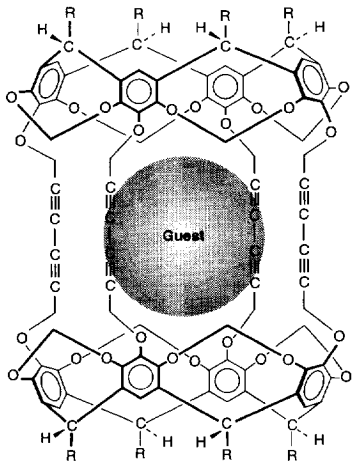
5.8 Bis-Acetylene Bridges

Hemicarcerands **24a** and **24b** were prepared in 5-8% yields by oxidative coupling of **23** (derived from tetrol **5**) in pyridine-O_2-$Cu(OAc)_2$.[35] Twelve guests were complexed and had decomplexation half-lives ranging from 0.5 h for [2.2]paracyclophane to 1608 h for 1,3,5-(i-Pr)$_3$C$_6$H$_3$ at 25°C in $CDCl_3$. The decomplexation rates depended on guest shape as well as size. The rectangular portals allow relatively easy egress of rectangular guests such as paracyclophanes, while egress of square-shaped guests such as trisubstituted benzenes are much slower. [2.3]Paracyclophane decomplexes over ten times faster than [2.2]paracyclophane or [3.3]paracyclophane. This difference was explained by the asymmetry of [2.3]paracyclophane, which gives it a screwlike structure that complements the transition state for decomplexation; thus "[2.3]paracyclophane can worm its way into [or out of] the cavity."[35] Reduction (H_2, PdC) of **24b** gave **25** in 91% yield; no complexation studies for **25** were reported.

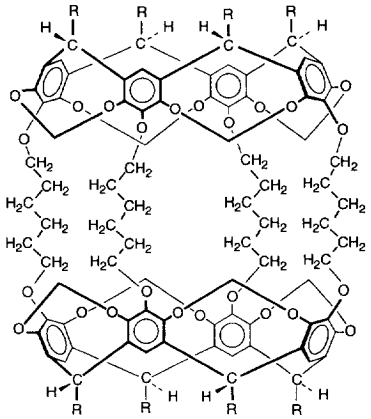


23a, R = CH_2CH_2Ph
23b, R = $(CH_2)_4CH_3$

pyridine
O_2
$Cu(OAc)_2$



24a, R = CH_2CH_2Ph
24b, R = $(CH_2)_4CH_3$

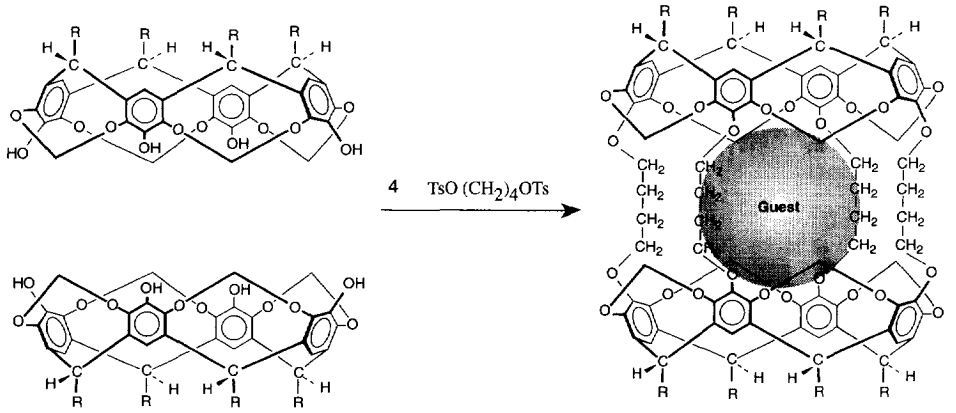


25, R = $(CH_2)_4CH_3$

5.9 Tetramethylene Bridges

Hemicarceplex **26a**•DMA was synthesized in 30-40% yield by bridging tetrol **5** with $TsO(CH_2)_4OTs$ in DMA with Cs_2CO_3 as base.[36,37] Hemicarceplex **26b**•DMSO was obtained in a similar manner in 15-20% yield with DMSO as the solvent. Thirty guests were incorporated into hemicarceplex **26a** and six crystal structures were determined. A crystal structure of **26a**•$6H_2O$ shows that the six water molecules fill the cavity in an approximate octahedral arrangement, similar to the eight polymorphs of ice. Of the other five crystal structures, the bowl-to-bowl distance was found to be guest dependent and to decrease in the following order of guests: 1,4-diiodobenzene > *p*-xylene > nitrobenzene > *o*-bromophenol > DMA. This trend demonstrates that the shell of hemicarceplex **26a**•guest can adjust its cavity size and shape to optimize its van der Waals

contacts with the guests. Moreover, strong binding was evident by the relatively large M•guest signals in the FAB mass spectra, which usually causes ejection of guests from hemicarceplexes (see Section 6). The energy barrier for decomplexation of DMA was 23.5 kcal/mol, which corresponds to half-lives for decomplexation of 223 minutes at 140°C and 30 minutes at 170°C. According to Cram, "this host is the strongest and most versatile hemicarcerand yet prepared."



26a, R = CH_2CH_2Ph
26b, R = $(CH_2)_4CH_3$

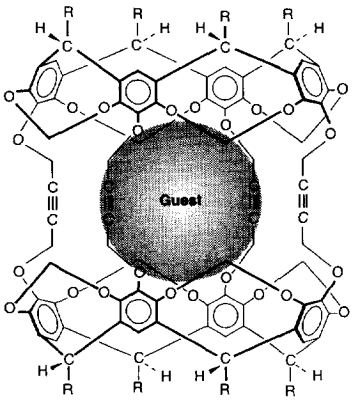
Hemicarceplex **26a** with nitrobenzene, para-hydroquinone, ortho-hydroquinone, 3,5-dihydroxytoluene and 3,4-dihydroxytoluene as guests were subjected to redox chemistry.[37] The four encapsulated hydroquinones were quantitatively converted to the corresponding quinones by use of either $Ce(NH_4)_2(NO_2)_6$-silica gel-CCl_4 at 25°C or $TlCO_2(CF_3)_3$-CCl_4 at reflux as the oxidizing agents. These quinones could not be incarcerated directly because of decomposition at the temperature needed for complexation. The incarcerated quinones were stable up to 100°C, reminiscent of the hemicarcerand-stabilized cyclobutadiene discussed in Section 5.1. It was concluded that "electrons, protons and water can be transferred into and out of the interior of hemicarceplex **26a**" and that "the inner phase of hemicarceplex **26a**, tailored to the dimensions of potential transition states, is a unique place to carry out highly specific reactions involving ordinarily unstable reactants."[37]

5.10 Mono-Acetylene Bridges

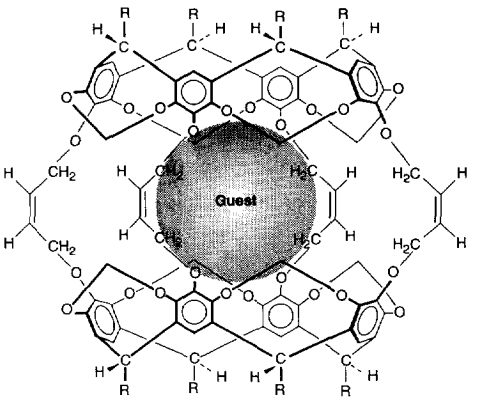
Hemicarcerand **27** was prepared in 6.5% yield from tetrol **5** and $TsOCH_2C{\equiv}CCH_2OTs$.[38] This compound formed complexes with $CHCl_3$, $CHCl_2CHCl_2$, $CF_3C_6H_5$, $CF_3OC_6H_5$, 1,4-$(CH_3)_2C_6H_4$ and (S)-(+)-1-bromo-2-methylbutane. The values $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for decomplexation were determined as well as half-lives for decomplexation, which were found to decrease in the order 1,4-$(CH_3)_2C_6H_4$ > $CF_3C_6H_5$ > $CF_3OC_6H_5$. The faster decomplexation rate with $CF_3OC_6H_5$ relative to $CF_3C_6H_5$ was said to be a result of the greater conformational adaptability of $CF_3OC_6H_5$. Hemicarceplex **27**•$CDCl_3$ exhibited a positive entropy of complexation similar to that observed with hemicarceplex **22**•toluene; this behavior was explained on similar grounds. A crystal structure of **27**•$CHCl_2CHCl_2$ showed that the two bowls are not twisted with respect to each other; thus constrictive binding is relatively small. Hemicarceplex **27**•$CHCl_2CHCl_2$ was reduced in 80%

yield to hemicarceplex **26**•$CHCl_2CHCl_2$; yet empty hemicarcerand **26** did not form a complex with $CHCl_2CHCl_2$ under conditions that were sufficient for the formation of **27**•$CHCl_2CHCl_2$.

A mixture of hemicarceplex **28**•$CHCl_3$ and **28**•$CH_3CO_2CH_2CH_3$ was prepared in 25% yield from tetrol **5** and *cis*-1,4-dichlorobutene.[38] Complexes were formed with DMA, $CH_3CO_2CH_2CH_3$, toluene, and 1,4-$(CH_3)_2C_6H_4$. Decomplexation rates were found to decrease with guest in the following order: toluene > 1,4-$(CH_3)_2C_6H_4$ > $CH_3CO_2CH_2CH_3$ > DMA. The decomplexation rate for hemicarceplex **28**•1,4-$(CH_3)_2C_6H_4$ was 36 times slower than for **27**•1,4-$(CH_3)_2C_6H_4$; this was explained by the extra C–H's in the bridges of **28**, which partially block the portals and hinder egress of guest.



27, R = CH_2CH_2Ph



28, R = CH_2CH_2Ph

6. Mass Spectrometry of Carceplexes and Hemicarceplexes

Most studies of carceplexes and hemicarceplexes have been done in solution, particularly by ^1H NMR, and several crystal structures have been determined. Mass spectral analysis represents the study of carceplexes and hemicarceplexes in the gas phase and completes the trinity of phases in which carceplexes and hemicarceplexes have been analyzed.

Several factors need to be considered in interpretation of mass spectra of carceplexes and hemicarceplexes. They are large (MW ca. 1500-2500 daltons), lipophilic compounds that contain guests and portals and may be strained. A substantial amount of energy is needed to volatilize these compounds and this energy may cause guest escape through portals or by rupture of covalent bonds. The degree of mildness of mass spectrometric techniques increases in the following order: LSIMS/FAB < DCI~LD < MALDI.[39] Carceplexes **7**[21] and **8**[24b] give intense empty signals by FAB, presumably via rupture of covalent bonds due to high strain in these compounds. The complexes with smaller guests produce larger signals for M•guest.[21] Reinhoudt's carceplex **29**•DMF, described in Section 8, has ample room for its guest and gives a large signal for M•DMF by FAB.[40] Hemicarceplex **10** lost most of its guest by DCI,[25] but gave prominent M•guest signals by MALDI.[41] Hemicarceplex **26a** gave unusually large signals for M•guest by FAB, suggesting that the guest is bound tightly with a high energy barrier to decomplexation and that the overall complex has little

strain.[37] This is perhaps the best illustration of constrictive binding where the host can clamp down tightly on the guest but remains nearly free of strain.

7. Mechanism for the Formation of Carceplexes and Hemicarceplexes

Recently, interest in the reaction to form carceplex **7** was rekindled in my laboratory.[42] Knowing that the formation of carceplex **7** required the presence of a template molecule, we conducted the reactions in the solvent *N*-methyl-2-pyrrolidinone (NMP), which is a poor template, and added of a variety of molecules to screen suitable templates. Twenty four molecules were found to be suitable, while 24 were unsuitable. The suitable template molecules were pitted against each other in competition reactions where a pair of starting templates would yield a mixture of carceplexes, the ratio of which was measured by integration of the host and guest signals in the ^{1}H NMR spectra of the mixtures. The ratios for all the template molecules were tabulated and referenced to the poorest template, NMP, which was assigned a value of one. Pyrazine turned out to be the best template with a *template ratio* of one million! This superiority was evident from a 75% yield of **7**•pyrazine when the reaction was run at 1 mM concentration of tetrol **5** and a *stoichiometric* amount of pyrazine. That is, in the presence of 10,000 fold excess of NMP, a poor but suitable template, no **7**•NMP was observed to form. The template ratios represent the relative rates of the guest-determining step (GDS), which is the step beyond which no guest exchange occurs. Thus, based on the size and shape complementarity of the host and guest, one important component of the driving force for templation is van der Waals interactions of the template molecule with the walls of the forming cavity in the transition state of the GDS.

In other work done in my laboratory recently,[43] a crystal structure of carceplex **7**•pyrazine (where the pendant groups are methyls) was determined and shows a more symmetric, less distorted structure in the shell of the carceplex than does the crystal structure of **7**•DMA.[21a] It turns out that DMA is a 50,000 times poorer template than pyrazine.[42] The complementarity of host and guest in the crystal structure of **7**•pyrazine is consistent with the better template molecule having superior van der Waals interactions with the walls of the shell while imparting minimum steric strain to the system. These interpretations suggest that the complementarity of the guest with the product host may have relevance to the transition state of the GDS. We also synthesized an asymmetric carceplex containing four phenethyl pendant groups on one bowl and four methyl pendant groups on the other bowl, and this tactic enabled us to determine the energy barrier for rotation of pyrazine within the shell. The barrier of 19 kcal/mol demonstrates the remarkable complementarity of host and guest, as this barrier represents the energy needed for the narrow equator of the shell to accommodate the 7.1 versus 5.6 Å wide cross section of pyrazine.[43]

In work to be reported shortly, we have found that the starting tetrol **5** forms a ternary complex with the template molecules in the presence of base.[44] The binding affinities correlate with the template ratios of the carceplex reaction and imply that the ground state of the starting material can be used to model the transition state of the GDS for carceplex formation and help to explain the better than statistical yields found for hemicarceplex **10**[25,41] and carceplex **7**.[42]

We have also conducted competition reactions using triol **9** and generated a table of template ratios for the formation of hemicarceplex **10**.[41] These template ratios correlate with the template ratios obtained with carceplex **7**. Thus, there are similar driving forces at play in the transition states of the GDS's in the formation

of carceplex **7**and hemicarceplex **10**. These forces include favorable van der Waals interactions as well as hydrogen bonds.

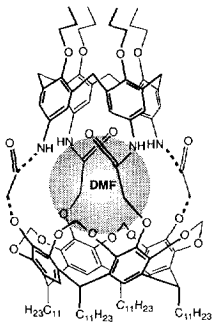
Interestingly, the carceplex **7** used in the crystal structure of **7**•pyrazine[43] contained pendant methyl groups! The compound is soluble in chloroform and forms stable crystals, whereas the carceplexes and hemicarceplexes containing phenethyl or pentyl groups give rise to highly unstable crystals, which turn to powder upon removal from their mother liquor. Furthermore, with phenethyls or pentyls as pendant groups, the interstices of the crystals are filled with loosely held solvent molecules that are often disordered. These problems are solved by the use of methyl groups, but the question is raised: Why was carceplex **4** insoluble? A high percentage of these molecules was reported to contain ions,[17] and a large lipophilic molecule encapsulating a charge may have low solubility in all solvents.[24]

8. Related Compounds

8.1 Catenanes, Rotaxanes and Fullerenes

Compounds such as rotaxanes[45] and catenanes[46] entail two or more molecules that are physically, but non-covalently linked, such that the structures are stable permanently or at least long enough for isolation. Rotaxanes are like beads on a string with the ends capped, whereas catenanes are two or more intertwined molecular loops. No guest binding is involved with these compounds.

There has been increasing interest in the use of fullerenes for the encapsulation of metals.[47-49] Fullerenes are carcerands with no pores at all and should be able to encapsulate single atoms, very small molecules or ions. When a guest is entrapped, the complex is called an endohedral complex. Recently a crystal structure of an endohedral complex was obtained.[49h] However, it has generally been very difficult to obtain pure samples of endohedral complexes. Large carbon nanotubes have been filled with metal, but no solution characterization of homogeneous materials has been achieved.[50]



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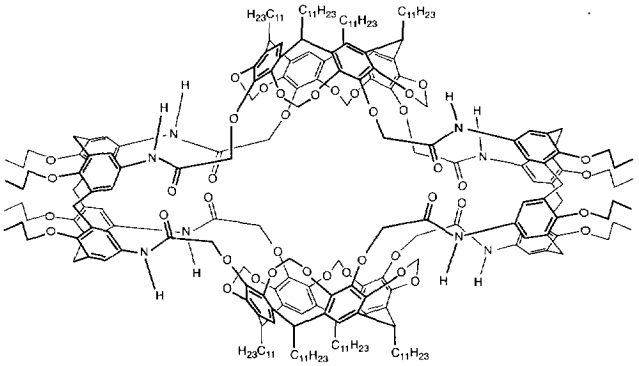
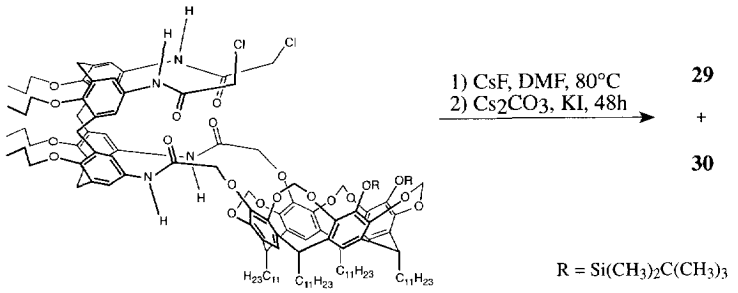


30

8.2 Calixarenes

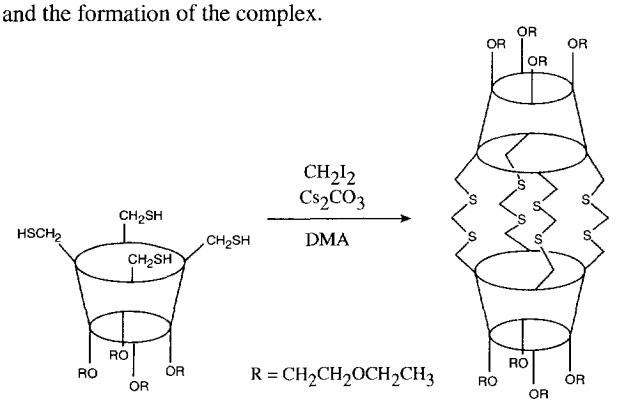
According to Shinkai, the family of macrocycles called calixarenes represents the third generation of supramolecules, after cyclodextrins and crown ethers.[51] Effort has recently turned toward the use of calixarenes to synthesize carceplexes and hemicarceplexes as outlined below.

Reinhoudt has reported the synthesis of carceplex **29** (28% yield), which is composed of tetrol **5** and a calix[4]arene linked by amides.[40] The synthesis, shown in **Scheme 4**, also gave compound **30** (26% yield), which was named holand because of the large hole through the center of the molecule. Carceplex **29** was characterized by FAB MS and ^{1}H NMR, where no guest exchange occurred in DMF-d_7 at 100°C for 1 h.



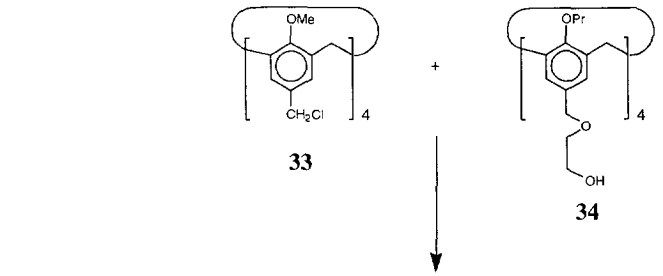
Scheme 4. Synthesis of carceplex **29** and "holand" **30**.

Blanda has synthesized head-to-head (the head is the end opposite the phenolic groups) bis-calix[4]arene **32** in 25-30% yield by bridging calixarene **31** with diiodomethane as shown here schematically.[52] Although compound **32** was synthesized using DMA as the solvent, the product isolated was free of DMA. However, they prepared complexes by heating **32** in neat guests including toluene, ethylbenzene, *p*-xylene, *p*-chlorotoluene, *p*-diethylbenzene and *p*-methylanisole. Although decomplexation studies have not been reported, at least the *p*-xylene complex gave ^{1}H NMR spectra that demonstrated the encapsulation of guest and the formation of the complex.

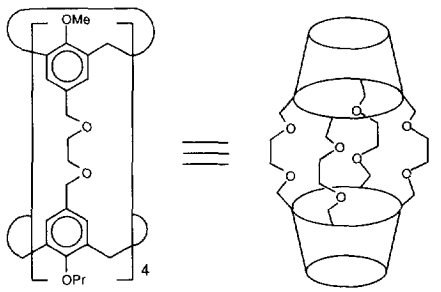


31 **32**

Shinkai has synthesized the head-to-head biscalix[4]arene **35** in 12% yield by reaction of calix[4]arenes **33** and **34** in tetrahydrofuran in the presence of NaH under high dilution.[53] Preliminary ^{1}H NMR studies indicate that inclusion of guests such as quaternary ammonium species is possible. Head-to-head tetra-bridged bis-calix[4]arene **36** was synthesized by Böhmer in low yield; no binding studies were reported.[54]



33 34



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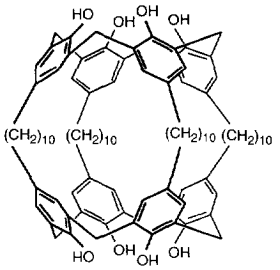

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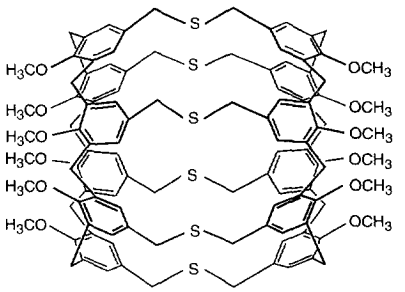
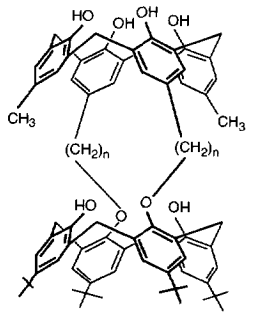
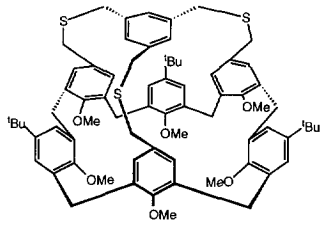


37

Others have linked calix]4]arenes head-to-head using two instead of four linker groups to give compounds with large holes.[54,55] Shinkai synthesized head-to-head bis-calix[6]arene **37**, which was shown to contain 10 mol% *N*-methylformanilide according to elemental analysis.[56] Unfortunately, the signals in the ^{1}H NMR spectra were very broad. Calixarenes have also been linked tail-to-tail by use of metallo bridges such as Si,[57] Al,[58] Nb[59] and Ti[60] or organic bridging groups such as benzophenone derivatives[61] and other groups.[61,62] These compounds do not encapsulate guest molecules. Böhmer has synthesized head-to-tail bis-calix[4]arenes **38a** and **38b**, but no guest binding studies have been reported.[63] Shinkai prepared capped calix[6]arene **39**, which forms a complex with $[PhNMe_3I]^+$ via π-cation interactions.[64] The complex undergoes slow exchange on the NMR timescale.



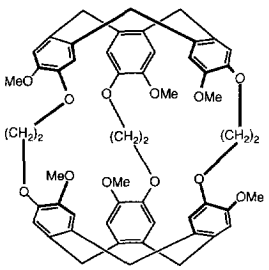
38a, n = 3
38b, n = 4



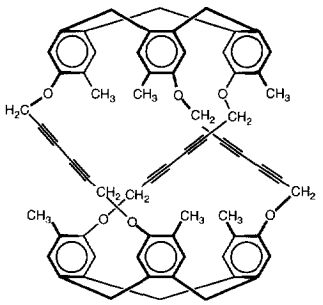
39

8.3 Cryptophanes

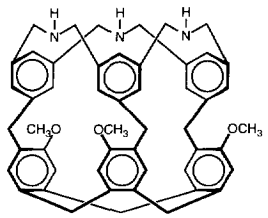
Many cyclotriveratrylene-based cryptophanes have been synthesized that encapsulate a variety of guests. Collet has done the bulk of the work on cryptophanes[65a] such as **40**, which has an energy barrier to decomplexation of chloroform of 14.7 kcal/mol.[65b] Collet provided an intriguing analysis of the *occupancy factors* for complexes of **40**. These factors reflect the ratio of the van der Waals volume of the guest to the van der Waals volume of the cavity. For **40**•chloroform the occupancy factor is 0.886, which corresponds to a very closely packed crystal. For methane, which undergoes fast exchange at ambient temperature on the ^1H NMR timescale, the occupancy factor is 0.348, which corresponds to a supercritical fluid and would translate to a pressure of 610 atm at 298 K. A similar cryptophane to **40**, where the three methoxyl groups of one cyclotriveratrylene unit are replaced by hydrogens, showed enantioselective complexation with bromochlorofluoromethane;[65c] the selectivity was comparable to that observed with hemicarceplex **21**•$BrCH_2CH_2CHBrCH_3$.[33]



40



(±) **41**

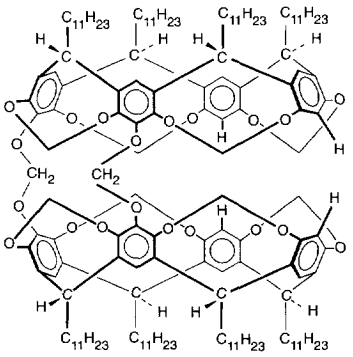


42

Cryptophane ±**41** binds chloroform, cubane, benzene, $CHCl_2CHCl_2$ and *t*-butyl alcohol and has energy barriers for decomplexation of 13-14 kcal/mol, which corresponds to exchange rates of sub-seconds at room temperature.[66] Compound **42** binds O_2, N_2, H_2O, CH_3CN and CH_3OH in rapid exchange, whereas the complex **42**•CH_3CH_2OH decomplexes with a half-life of 40 minutes at 22°C.[67]

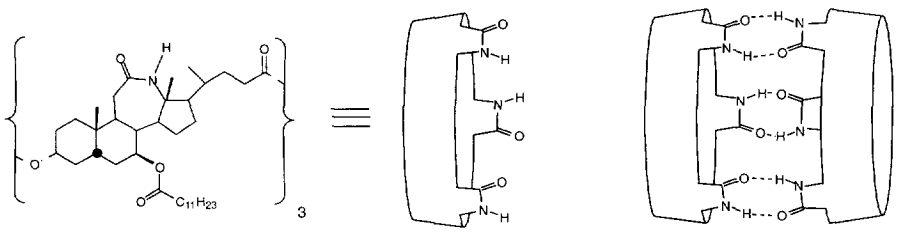
8.4 Other Related Compounds

Compound **43** was synthesized by Reinhoudt in 71% yield by bridging the corresponding diol with bromochloromethane.[68] No binding studies were reported.



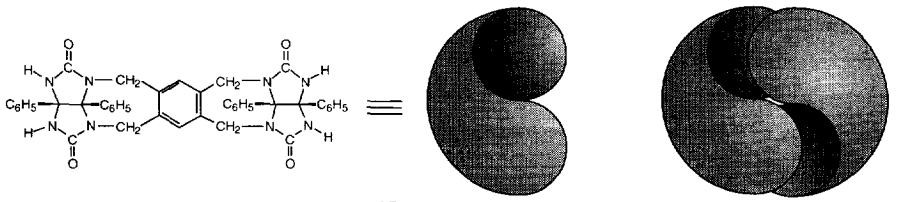
43

Cyclocholates such as **44** have been shown to self-assemble to produce a closed surface dimer.[69] No guest binding was reported.



44 **44 · 44**

Rebek reported the self-assembly of two molecules of **45** in which guests such as methane and chloroform can be encapsulated.[70] Guest exchange is slow on the ^{1}H NMR timescale.



45 **45 · 45**

Vögtle has reviewed the inclusion phenomena of a large family of compounds that contain two spacer units linked by three long bridges as depicted in **Fig. 4**.[71] These hosts contain the topological elements of a hemicarceplex, but the portals are large and exchange rates greatly exceed those of hemicarceplexes.

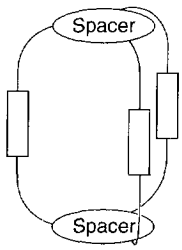
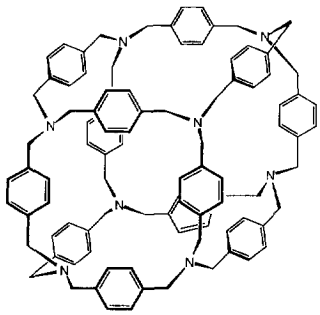


Figure 4. Schematic representation of Vögtle's compounds.[71]

Murakami has synthesized a series of cyclophanes such as **46** that he calls kyuphanes.[72] These compounds form complexes with a variety of large guests; the complexes undergo fast exchange on the NMR timescale.



46

9. Conclusions and Future Prospects

Carceplexes and hemicarceplexes are well-defined, complex molecules that can be efficiently prepared from simple and inexpensive starting materials such as resorcinol and acetaldehyde. These compounds have a combination of properties (solubility, crystallinity and small number of conformational minima) that facilitate their characterization by routine methods, particularly solution NMR spectroscopy and X-ray crystallography. Philosophical questions have been raised with respect to the effective phase of an isolated molecule. New concepts have been introduced, such as *constrictive binding*. Difficult feats have been achieved, such as the room temperature stabilization of cyclobutadiene. A novel perspective on reaction mechanisms and non-covalent interactions has revealed a one-million-fold range in template effects during the formation of a carceplex.

The immediate future promises further exploration of larger vessels that can contain larger guests, including important drugs. Several research groups have developed interest in performing reactions inside the confines of hemicarceplexes. My group is continuing to explore the template effects on the formation of

carceplexes and hemicarceplexes, and we are now developing a new series of self-assembling structures that have grown out of the templation study.

There are many potential long-range uses for carceplexes and hemicarceplexes. Drug encapsulation is one currently being pursued (and has been achieved with adamantadine). If the shells could be appropriately functionalized, drugs might be delivered specifically to cancer cells. Release of the drugs could be by slow diffusion or by an engineered release mechanism, such as hydrolysis of ester linkages of a lactone-bridged hemicarceplex.[17] On a similar vein, permanent encapsulation of radioactive metals could lead to agents for targetted radiation therapy or organ imaging. Another possible use for these compounds is as solar cells. There are now several examples of photolytic reactions inside hemicarceplexes. Compounds such as the norbornadiene family that abosrb light (to form quadricyclane) and thermally degrade would be ideal guests for a hemicarceplex solar cell, as the shell would keep the photoactive guests from polymerizing. A possible long-range application for carceplexes and hemicarceplexes is as memory storage devices. It has been shown that the encapsulated DMA molecules in **7**•DMA have some orientational preference with respect to each other in the crystal structure. If the guest molecules could be switched "up" versus "down" while the shell is in the solid state, a binary code would be created. The outcome would be memory storage on the molecular scale so that today's microchips could be tomorrow's nanochips.

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