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Templation and Encapsulation in Supramolecular Chemistry

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Contents

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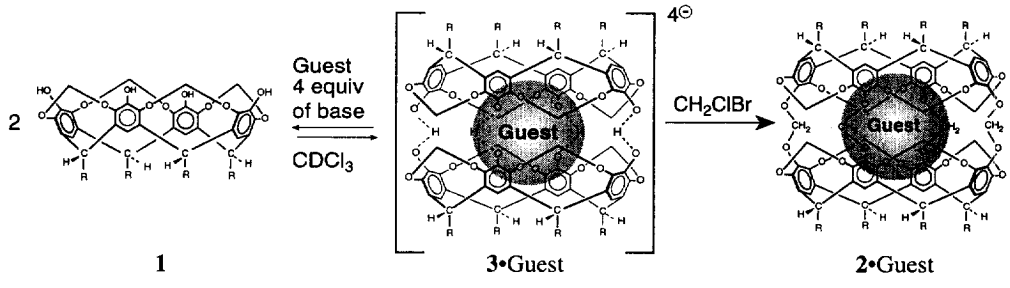
1. Introduction

Templation is integral to manifold processes from replication of DNA to the formation of zeolites. Furthermore, as the cornerstone of crown-ether synthesis, templation provided the underpinnings for the creation of the field of host-guest chemistry.[1] Such importance and ubiquity have led to numerous reviews on templation, many of which have focused on the use of metal ions as templates.[2] In this report we discuss how organic molecules and ions have been used as templates to generate whole new classes of supramolecular assemblies. We emphasize the evolution of chemists' understanding of noncovalent interactions and how this information has been used to design a variety of structurally disparate assemblies. In doing so we hope to demonstrate the common features of supramolecular assemblies which create a rich context for this widespread field.

The organization of this report is as follows. After an introduction to terms, a variety of salient examples of templation in supramolecular chemistry is presented, with particular emphasis on rotaxanes, catenanes, and self-replicating systems. A short section on templates used to make materials such as zeolites follows. We then present a review of a fast-growing field involving reversible encapsulating species. In some of these systems, the encapsulated species can act as a template and lead to permanent entrapment as in a *carceplex*, which is the subject of the final section.



1 **3**•Guest **2**•Guest

Scheme 1. Formation of Complex **3**•Guest and Carceplex **2**•Guest from Tetrol **1**. R = CH_3 or $PhCH_2CH_2$.

Recent work in our labs has focused on the mechanism of formation of carceplex **2**•guest (**Scheme 1**).[3,4] Such studies provide a confluence of the processes presented in this review including self-assembly, molecular recognition, and templation. Like catenanes and rotaxanes, carceplexes are known for their ability to mechanically ensnare molecules. The ensnared molecules act as sacrificial **templates** as they are integral to the formation of the carceplexes and they give up their independence in so doing. The formation process is highly sensitive to the template molecule, as demonstrated by a million-fold range in templating abilities; thus, carceplex formation provides a dramatic example of **molecular recognition**. Carceplex formation is preceded by the **self-assembly** of the precursors such that two molecules of tetrol **1** encapsulate one molecule of guest in the presence of base. This report will flesh out the above terms, illustrate each by example from the recent literature, and finally tie them all together in the discussion of the formation of carceplexes.

2. Supramolecular Chemistry, Molecular Recognition, Self-Assembly, and Templation: Definitions and Background

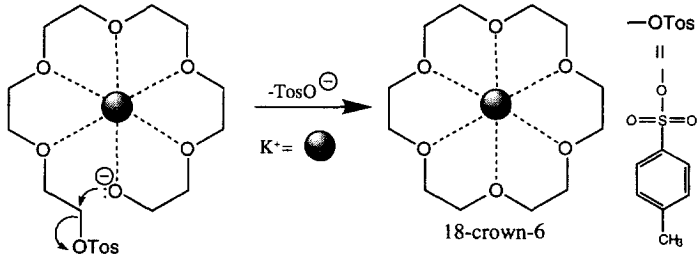
Advancements in synthetic chemistry over the past century have demonstrated an ever increasing mastery over the formation of covalent bonds to build molecules.[5] The techniques developed by synthetic chemists to construct covalent bonds have culminated in the total synthesis of highly sophisticated molecules such as vitamin B_{12}[6] and palytoxin.[7] In the 1970's, the traditional boundaries of synthetic chemistry were crossed as chemists began to extend their efforts from connectivity using the covalent bond, to organization of molecules using noncovalent interactions to form complexes or "supermolecules". The use of noncovalent interactions to form supermolecules created a new field called **supramolecular chemistry**, a term that was coined and defined by Jean-Marie Lehn to describe "chemistry beyond the molecule, referring to the organized entities of higher complexity which result from the association of two or more chemical species held together by intermolecular forces".[8] Supermolecules or Ümbermoleküle[9] is a term used to describe these entities of higher organization resulting from the association of multiple chemical species via noncovalent interactions.[8b] The structure and properties of the supermolecule are distinct from the properties of the chemical species or subunits of which it is composed.[10] Therefore, the development of supramolecular chemistry holds promise for the discovery of new and exciting supermolecules with correspondingly new and exciting properties.

The construction of a supermolecule involves two important and nearly synonymous processes: **molecular recognition** and **self-assembly**. **Molecular recognition** is the process by which some molecules select and bind other molecules in a structurally well defined pattern of intermolecular forces.[8b] For example, a substrate is selectively recognized by an enzyme and is bound in a specific orientation in the enzyme's active site. Likewise, cytosine recognizes guanine in duplex DNA. The functionality of one molecule complements the functionality of the other and the two molecules associate or bind with one another by sharing their noncovalent information. Often, one of the molecules has a convergent binding site (the host or receptor) and the other a divergent binding site (the guest or substrate) but by no means is molecular recognition limited to such host-guest or receptor-substrate systems. The concept of molecular recognition was described as early as 1894 by Emil Fischer in his lock-and-key theory.[11] According to Fischer's original idea, molecular recognition is similar to the complementarity of a lock and a key. The lock is the molecular receptor and the key is the substrate being recognized to form a receptor-substrate complex. Although this idea simplifies molecular recognition, it vividly emphasizes the complementarity necessary between the two chemical species involved in the recognition process. Over 100 years later, research in molecular recognition remains at the forefront of scientific thinking.

The second process that is integral to the construction of the supermolecule is **self-assembly**. The term self-assembly occurs frequently in the literature, and it has been the subject of numerous reviews.[12] Although many definitions exist for self-assembly,[13] the definition by Whitesides is the most appropriate for this report. Whitesides defines self-assembly as "the spontaneous assembly of molecules into structured, stable, noncovalently joined aggregates."[12c] The structural integrity of the self-assembled aggregate is maintained after its formation because it represents the thermodynamically most stable structure. There are four properties of self-assembling structures that are important: (1) The properties of the self-assembled aggregate are unique from

the properties of the subunits from which it is composed. (2) The reversibility of the self-assembly allows improperly formed assemblies or mismatched subunits to be eliminated from the final structure (a type of error checking). (3) All the information necessary for forming a self-assembled structure is contained in the individual subunits. (4) The subunits bind cooperatively to form the most stable structure. **Self-assembly** is inextricably linked to **molecular recognition** because the recognition of the individual components of the aggregate by each other guide the construction of the supermolecule, or self-assembling structure.[14]

Directed self-assembly is a type of self-assembly defined by Lindsey as "the case where a temporary scaffolding agent, jig, or **template**, participates as a structural element in the assembly process but does not itself appear in the final product."[12b] The external element may play a thermodynamic role by stabilizing the association of subunits or destabilizing an undesirable aggregate. It also can play a kinetic role by directing the association of subunits along a specific reaction pathway.[12b] As will be seen later, several assemblies are constructed via directed self-assembly where the template molecule does in fact become part of the product due to mechanical entrapment.



Scheme 2. Formation of 18-crown-6 Via Metal Templation.

Templation is an integral part of supramolecular chemistry as it often aids in the construction of complex molecular structures. Indeed, the prototypical example of a template in nature is DNA, which functions as its own template. The word template has been defined by Busch:[15] "a chemical **template** organizes an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of the atoms. Templates are distinguished from reagents because they effect the macroscopic geometry of the reaction and not the intrinsic chemistry".[15] The formation of a crown ether serves as an excellent illustration of the action of a template.[1] As shown in **Scheme 2**, the potassium ion acts as the template for the formation of 18-crown-6 by binding to the precursor acyclic polyether thereby organizing the reactive ends of the molecule in a conformation that allows for efficient covalent bond formation. Therefore, a chemical template manipulates a reaction pathway in order to achieve a particular linking of atoms, a process that is often referred to as a **template effect**.

Busch classified templates as either thermodynamic or kinetic.[15] A **thermodynamic template** shifts the equilibrium of a reversible reaction by binding to one of the products formed in a reaction, thereby shifting the equilibrium in favor of this product. The reversibility of the reaction can often lead to high chemical yields. On the other hand, kinetic templates operate in irreversible reactions. A **kinetic template** organizes the reactive groups of the forming structure with respect to geometry and orientation, facilitating the formation of a

predominant product.[15] The irreversible nature of the reaction requires the kinetic template to stabilize the transition state of the rate determining step of the reaction.

There are numerous examples of the use of templates in synthesis.[2, 12a, 12b, 15] There is a large body of work on the use of metal ions as templates especially for the synthesis of ligands and macrocycles such as the crown ethers.[2c] In the 1980's, the first examples of non-metal ions as templates for the synthesis of supramolecular structures appeared in the literature.[15] This report will focus on the more recent examples of organic molecules and ions as templates for the formation of supramolecular structures. But first, a classic example of a biological system that illustrates molecular recognition, self-assembly, and templation will be presented.

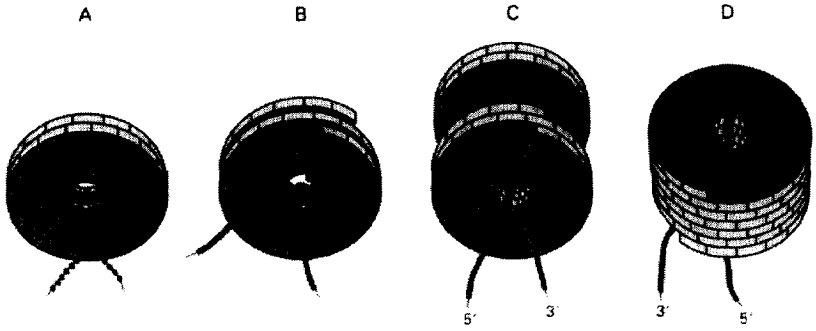


Figure 1. Model for the self-assembly of Tobacco Mosaic Virus (TMV): (A) initiation of self-assembly, RNA threads into the central hole of the protein disc and transforms it into (B) the helical lock-washer form; (C) self-assembly of additional discs; (D) one of the RNA tails is continually pulled through the central hole to aid in self-assemble of further discs. Adapted from reference 16.

Molecular recognition, self-assembly, and templation are the cornerstone of supramolecular chemistry. The formation of the tobacco mosaic virus (TMV) is a good example of a biomolecule that encompasses these components of supramolecular chemistry and is illustrated in **Figure 1**.[16] The TMV is composed of a 6400 base strand of RNA enclosed in a protein sheath that is made up of 2130 identical wedge-shaped protein subunits. Nature's use of multiple copies of the same building block reduces the amount of information necessary to create a self-assembling structure such as the TMV. If the components of the TMV are separated, they can be spontaneously reassembled *in vitro* to regenerate the active virus. The process of reformation of the active virus involves the *self-assembly* of the 2130 protein subunits around the strand of RNA, which acts as a *template*. *Molecular recognition* between protein subunits causes their self-assembly with each other and with the strand of RNA, which is necessary for the formation of the virus. Imperfectly formed subunits are excluded from the final structure as a result of the reversible nature of this self-assembly process.

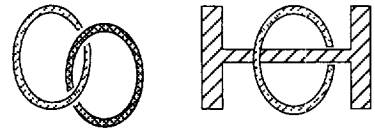
Chemists have gained a wealth of information about the self-assembly and molecular recognition processes that are at work in nature by studying biological systems such as the TMV. The beauty of such processes inspires us to learn more. Presently, we can embark on an iterative process of trying to devise nonnatural assemblies with low complexity (relative to nature), delineate the noncovalent interactions that govern their formation, and redesign the system using the newly found knowledge to create even more advanced

assemblies. During this process, we continue to re-check nature's examples, both to help in our design and to help understand nature as our science becomes more sophisticated.

3. Templation in the Formation of Supramolecules

3.1 Catenanes and Rotaxanes

Mechanically joined molecules such as catenanes (**4**) and rotaxanes (**5**) provide challenging syntheses for supramolecular chemists. The name "catenane" was derived from Latin "catena" meaning chain[17] due to their topological resemblance (**Figure 2**). For the n-catenanes, the n macrocycles are mechanically joined to each other but are not covalently bound. The prefix indicates the number of rings involved in the catenane; i.e., catenane **4** is a 2-catenane. Rotaxanes resemble catenanes as two or more molecules are mechanically linked but are not covalently bound. The name "rotaxane" was derived from Latin "rota" meaning wheel and "axis" meaning axle.[17] In rotaxane **5**, a dumbbell-shaped component is encircled by a macrocyclic component; the escape of the macrocyclic component is prevented by the bulky groups at the ends of the dumbbell-shaped component (**Figure 2**). If the bulky groups are small enough to allow the cyclic molecule to escape, the prefix pseudo is added to give pseudorotaxanes. Multiple rings threaded onto a single axle are referred to as a polyrotaxane. A variety of template studies have been performed recently with catenanes and rotaxanes and some of this work is presented below. The world of supramolecular chemistry can appear to be a small one, as both the mechanical confinement of their components and the templation involved in their formation make catenanes and rotaxanes highly relevant to carceplexes, which otherwise bear little resemblance to such species.

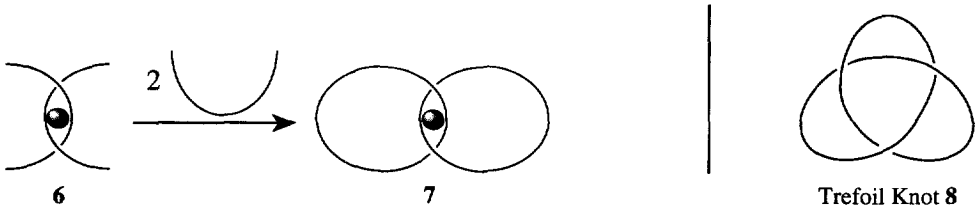


2-Catenane **4** Rotaxane **5**

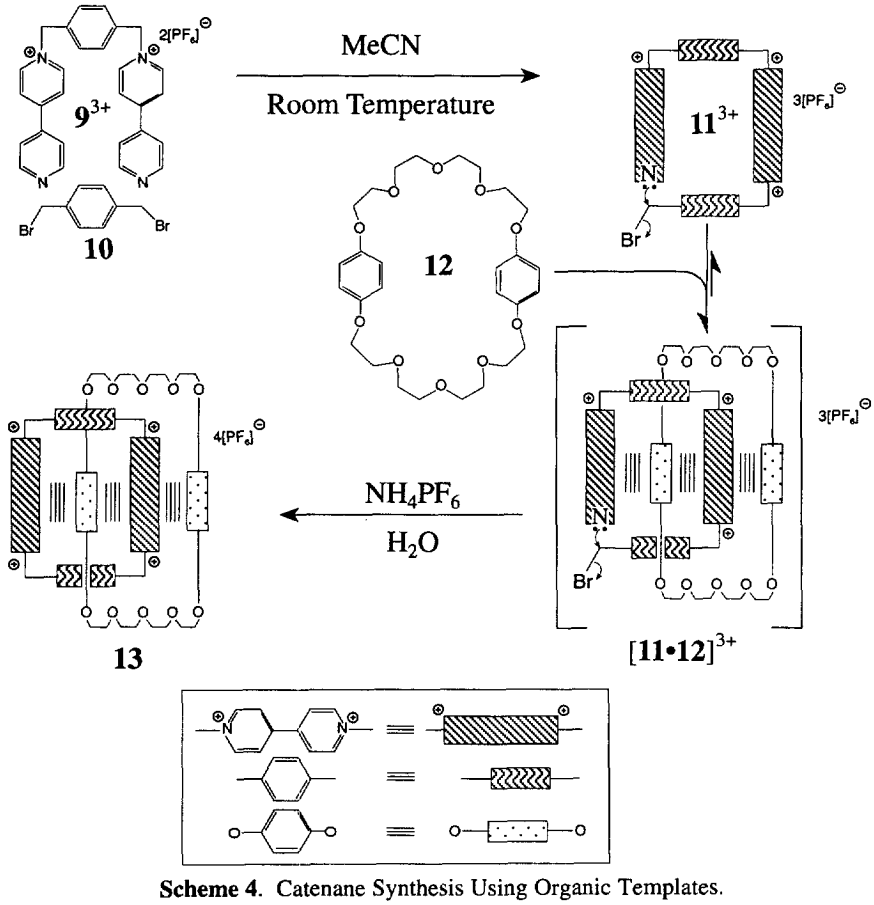
Figure 2. Catenane and Rotaxane.

3.2 Template Formation of Catenanes

Catenanes can be prepared using either metal ion templates or organic templates. The first efficient synthesis of a 2-catenane (**7**) was done by Sauvage et al. who used the tetrahedral coordination properties of Cu(I) to form an ordered molecular assembly of ligands around the Cu(I) template to give assembly **6** (schematically represented in **Scheme 3**).[18] Here, the Cu(I) holds two rigid aromatic ligands in an interwoven conformation (**6**) while macrocyclization of one or both of the ligands occurs. The Cu(I) template is then removed to give the free 2-catenane. The Cu(I) can be considered as a kinetic template as it enhances the irreversible reaction to form 2-catenane **7** over the irreversible reaction to form other products, e.g., polymer. Sauvage later used this strategy to produce a trefoil knot (**8**)[18] (**Scheme 3**) as well as 3-catenanes.[19]



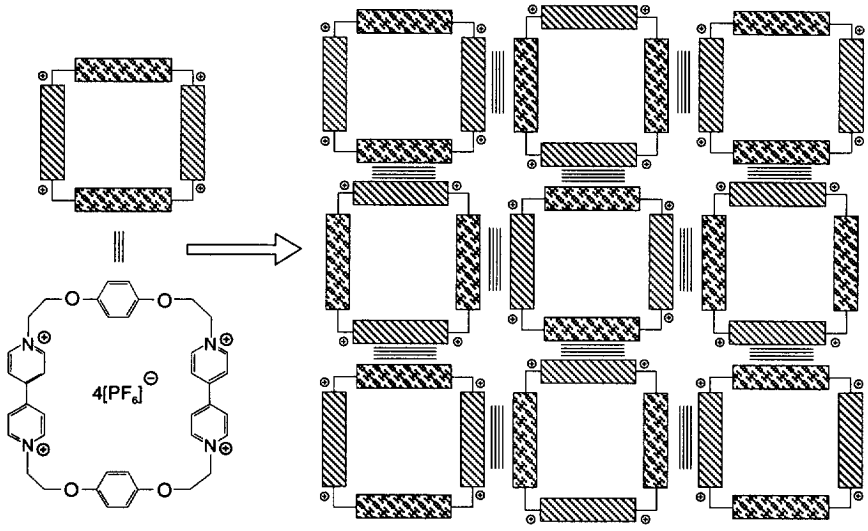
Scheme 3. Metal Templated Catenane Synthesis.



Scheme 4. Catenane Synthesis Using Organic Templates.

Stoddart and coworkers have developed efficient procedures for the preparation of a large variety of catenanes and rotaxanes by using a non-metal template.[12a] Stoddart's synthesis of 2-catenane **13** involved the use of macrocyclic polyethers that contain π-electron–rich aromatics as the templates for the formation of

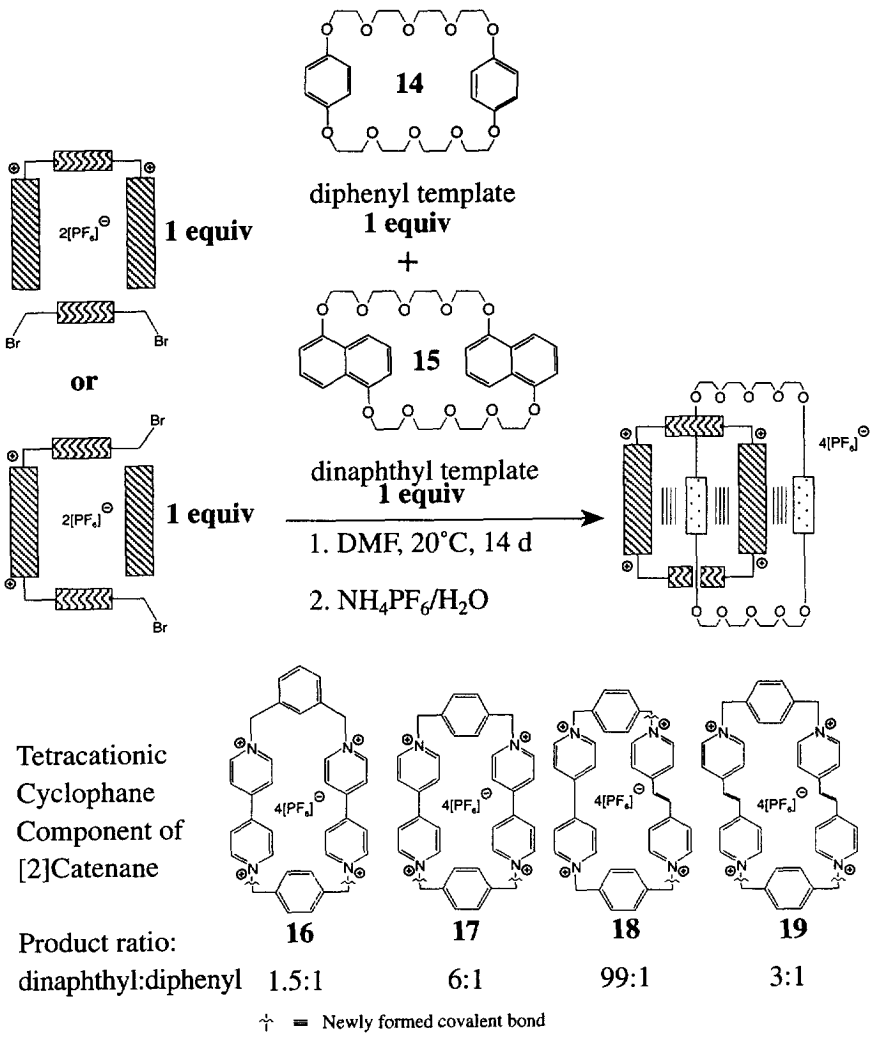
tetracationic cyclophanes that contain π-electron-deficient aromatic units (**Scheme 4**). The favorable π-π interactions between the electron rich aromatic template molecule (**12**) and the electron poor aromatic rings of the cyclophane precursors (**11** and/or **9**) promote an interwoven complex ([**11**•**12**][PF_4]$_3$) that cyclizes to form 2-catenane **13** in 70% yield.[20] In this synthesis, template molecule **12** becomes part of the product catenane. Similar templation procedures using π-π interactions were used to construct rotaxanes,[21] switchable pseudorotaxanes,[22] pseudopolyrotaxanes,[23] and self-assembled macrocycles forming a molecular mosaic pattern (**Scheme 5**).[24]



Scheme 5. Molecular Mosaic Pattern of a Self-Complementary Cyclophane.

3.3 Template Effects in the Formation of 2-Catenanes

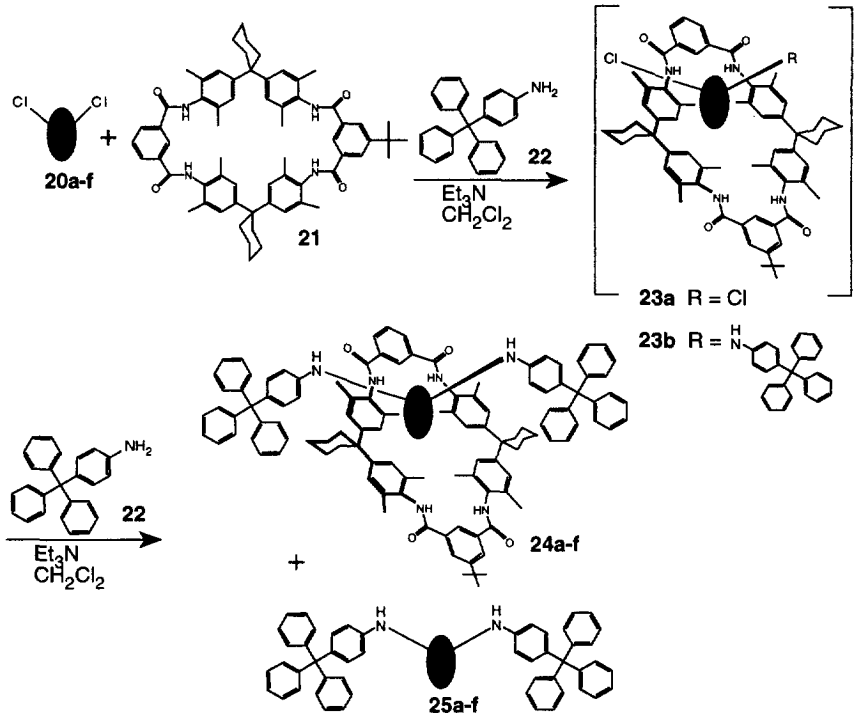
Stoddart has investigated the templation effect in the formation of four tetracationic cyclophanes (**16-19**) with two different template molecules (**Scheme 6**).[25] To determine the relative preference for one template molecule over another, competition experiments were carried out under identical conditions with equimolar amounts of diphenyl template **14** and dinaphthyl template **15** as well as the macrocyclic components of either **16**, **17**, **18** or **19** (**Scheme 6**). The product ratios of the isolated 2-catenanes were determined by ^{1}H NMR. They found that dinaphthyl template **15** was preferred over diphenyl template **14** in all cases and the magnitude of this selectivity depended upon which tetracationic cyclophane (**16-19**) was being cyclized. The greatest selectivity was 99:1 for dinaphthyl template **15** over diphenyl template **14** in the template formation of tetracationic cyclophane **18**.[25]

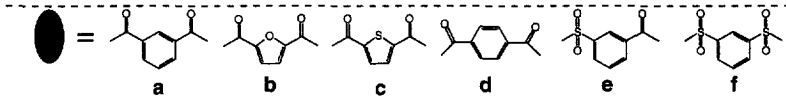


Scheme 6. Catenane Synthesis.

Further studies suggested that the selectivity for 2-catenane formation was under kinetic control. After the initial covalent bond is formed to produce the tricationic intermediates, self-assembly of these tricationic species with each of diphenyl template **14** and dinapthyl template **15** then occurs. The presence of complexes between the tricationic intermediate precursor to **16** and both diphenyl template **14** and dinapthyl template **15** were detected by FAB mass spectrometry as well as by ^{1}H NMR. The binding of the tricationic intermediate with either diphenyl template **14** or dinaphthyl template **15** is followed by the final irreversible covalent bond formation. Assuming the complexation and decomplexation rates for these complexes are fast, the relative rate

of the closure reaction with the two templates determines the final product ratio of the 2-catenanes. Stoddart et al. expected that the same transition state stabilization would exist in the formation of catenanes containing tetracationic cyclophanes **17** and **18**. They suggested further that the different rates of formation of the final covalent bond in the presence of two different templates is likely to be a result of different rate constants for these processes and not due to different stabilities of the two precursor complexes.[25]





	a	b	c	d	e	f
% Yield of Rotaxane **24**	11	19	6	7	41	4
% Yield of "Axle" **25**	83	44	85	39	10	17

Scheme 7. Amide Rotaxane Synthesis.

3.4 Template Effects in the Formation of a Rotaxane

The synthesis of rotaxanes that differ in their central axle component was the subject of a recent template effect study by Vögtle and coworkers.[26] In this reaction (**Scheme 7**), a cycloamide-based cyclophane template (**20**) is believed to bind an axle component (**20**) which then reacts with a primary amine blocking group (**22**) to

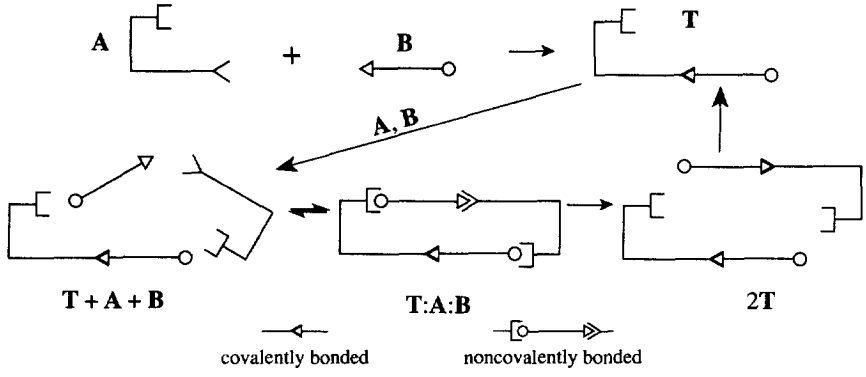
form complex **23b**. The formation of complex **23b** is designed to be stabilized by N-H to carbonyl hydrogen bonding and by π-π interactions between the macrocyclic template (**21**) and the axle molecules (**20a-f**). Reaction of complex **23b** with another equivalent of amine **22** produces rotaxanes **24a-f** while reaction of the unthreaded axle leads to compounds **25a-f**. A range of axle components **20a-f** that vary in their types of hydrogen bond donor abilities (carbonyls versus sulfones), shape selectivity (*meta* versus *para*-phenylene units), and size of the aromatic ring (six versus five-membered) were chosen in order to optimize the yield for rotaxane formation. Stronger noncovalent interactions as described above should lead to a greater formation of complex **23b** and result in higher yields of rotaxane **24** versus production of the undesired dumbbell molecule (**25**). As shown in **Scheme 7**, the formation of rotaxane **24e** proceeded with the highest yield over the five other axle molecules, and it also gave the lowest yield for the formation of dumbbell-shaped molecule **25e**. The authors concluded that the formation of rotaxane **24** is tolerant to a variety of axle molecules, which greatly expands the variations of linking molecules that can be used to create rotaxanes.[26]

In the above examples of catenane and rotaxane formation, the template molecule becomes mechanically entwined in the product. An intriguing question arises as to whether these molecules are really templates. This really depends on one's definition of a template. The fact that these putative template molecules are entwined in the product does not itself preclude them from being considered a template. The question is whether these molecules promote the formation of one product over another with respect to the same reaction run in the absence of the putative template molecule. Clearly new products are produced in the above reactions as a catenane is different from a single macrocycle, and a rotaxane is different from a single dumbbell-shaped molecule. By this simple definition, these molecules are certainly templates. However, other criteria can be used to designate a molecule as a template. For example, as these are examples of kinetic templates, one can ask if the catenane and rotaxane products form more quickly than the simple macrocycle or the dumbbell-shaped molecules. This would distinguish a molecule that acts as a kinetic template from one that merely goes along for the ride during the key covalent bond-forming reaction. In the case of the rotaxanes above, at least some of the examples produce higher yields of the dumbbell-shaped molecule with respect to the rotaxane. In these examples, it appears that the "template molecule" is fortuitously binding to the axle component while the reaction with the amine occurs to form the rotaxane. That is, the "template molecule" does not appear to enhance the rate of reaction with the amine and in that sense it would not be considered a template.

3.5 Self-Replicating Systems

Self-replicating and autocatalytic systems are other important areas of supramolecular chemistry that have received much attention due to their sweeping implications about the origin of life.[27] Replication is often thought of as a biological event whereby one generation passes on its hereditary information to the next. The seminal work of von Kiedrowski has furthered our knowledge of the processes that control replicating systems.[28] Chemists have recently developed a number of simple chemical models that are capable of self-replication.[29] In a schematic example of a self-replicating system (**Scheme 8**),[29d] molecule **A** reacts with molecule **B**, due to their complementarity, to form the template molecule **T**. The self-complementarity of template molecule **T** to **A** and **B** leads to formation of termolecular complex **T**:**A**:**B**. Complex **T**:**A**:**B** changes the reaction between **A** and **B** from intermolecular to essentially intramolecular and generally increases the rate at which **A** and **B** react to

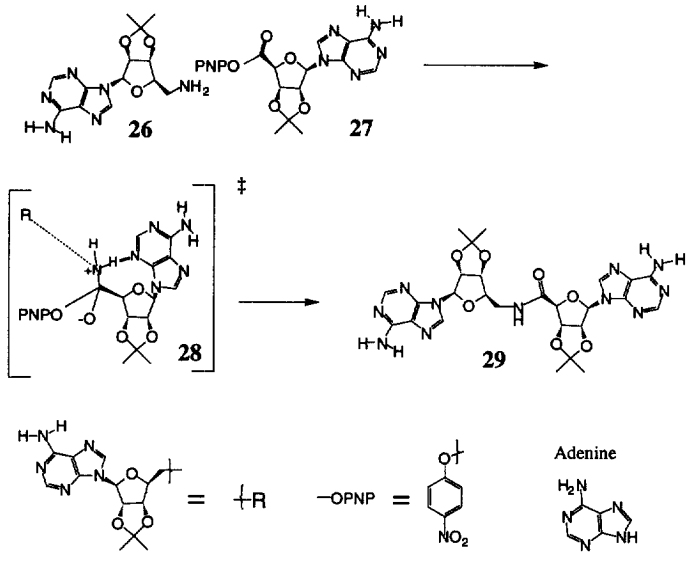
form complex 2T. Complex 2T then dissociates to form two molecules of template T and the cycle repeats itself.[29d]



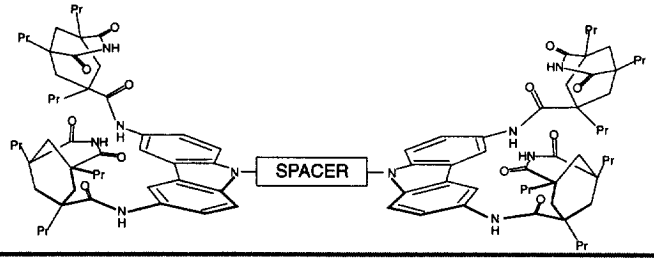
Scheme 8. Schematic Representation of Self-Complementary Template-Based Autocatalysis.

3.6 Template Effects in a Self-Replicating System

Rebek and coworkers have created a number of self-replicating systems based on adenine recognition of an imide derivative of Kemp's triacid.[29c, 29d, 30] In one example, they looked at the template-accelerated formation of adduct **29** from an adenine derivative (**26**) containing a primary amine group and a second adenine derivative (**27**) containing an activated ester (**Scheme 9**).[30b] The seven different template molecules (**30-36**, **Table 1**) all contained two recognition sites for adenine but these binding sites were separated by a different spacer located between the carbazole units of each template molecule. Spacers were chosen that varied the distance, geometry and rigidity of the template molecule. The use of these template molecules resulted in rate accelerations ranging from one to 160-fold for the coupling reaction between **26** and **27** to produce **29**. Generally, the high effective molarities of the activated ester and the amine groups when held in close proximity in the termolecular complex with the template resulted in faster reactions. Rebek and coworkers concluded that the most effective template molecule was better able to stabilize the tetrahedral intermediate (**28**). Templates **34** and **35** have the most complementary surface (distance and rigidity) that allows for stabilization of the transition state leading to **29** and therefore leads to the fastest rate enhancements. The other templates (**30-33** and **36**) did not cause large accelerations in the rate of reaction because they lacked either the proper distance or rigidity to stabilize the transition state leading to **29**. In another study, Rebek and coworkers showed that the rate of a reaction could be impeded by recognition of the reactants to form a complex. The complex formed in this example did not have the suitable geometry or distance to allow the reactive ends of the reactants to reach each other and undergo reaction.[30c] In the self-replicating systems studied by Rebek and others, effective turnover by the catalyst is often impeded by product inhibition. The design of template molecules that are only complementary to the transition state of these reactions and not the product would prevent such product inhibition. Indeed, the actual role of the template in these systems has created considerable controversy.[31]



Scheme 9. Reaction to Form Compound **29**.

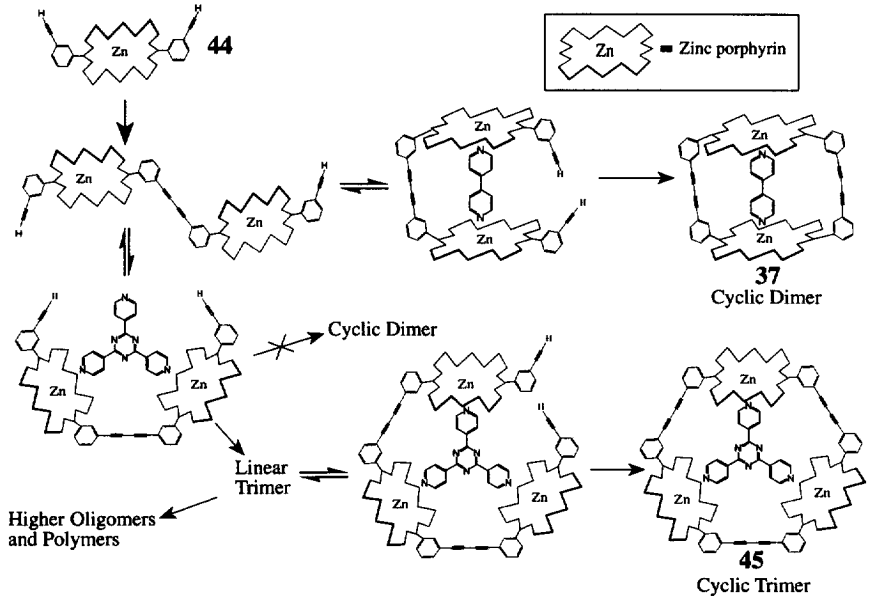


Compound	SPACER	Observed Acceleration
30		1.0
31		1.2
32		5.4
33		10
34		116
35		160
36		31

Table 1. Effect of Template Spacer on Reaction Rate.

3.7 "Positive" and "Negative" Templates

Sanders and coworkers have developed efficient syntheses for the formation of a series of cyclic porphyrin oligomers using a variety of pyridine-based template molecules.[32] They used the template formation of cyclic porphyrins to further classify template molecules as either "positive" or "negative". A **positive template** directs a reaction to form a particular product while a **negative template** will disfavor the formation of a particular product.[2b] A negative template can be considered as a type of inhibitor. In one experiment, a series of six template molecules (**38-43**) that range in size, shape and zinc binding sites (**Table 2**) were used to probe the product distribution of cyclic dimer **37** versus cyclic trimer **45** (**Scheme 10**).[32d] They found that the use of a noncomplementary template molecule such as pyridine (**38**) led to formation of both the cyclic dimer and cyclic trimer in approximately equal amounts. When bipy (**39**) was used as a template molecule there was an overall increase in yield with a large preference for dimeric host **37** to which bipy template **39** is complementary. Both templates **41** and **42** increased the yield of cyclic trimer **45** relative to pyridine (**38**) but also substantially decreased the yield of cyclic dimer **37**. The highly complementary template **43** increased the yield of cyclic trimer **45** and decreased the yield of cyclic dimer **37** to the greatest extent within this series of templates, but it was only slightly better than the bifunctional templates, **41** and **42**. As templates **41** and **42** are not complementary to trimer **45**, the selective formation of cyclic trimer **45** with the templates **41** and **42** is largely the result of these templates inhibiting the formation of cyclic dimer **37** (**Scheme 10**). Using Occam's Razor, template **43** is also likely to operate largely as a negative template for the formation of dimer **37**.



Scheme 10. Formation of Cyclic Dimers and Trimers of Porphyrins.

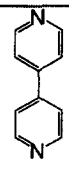
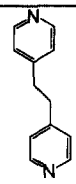
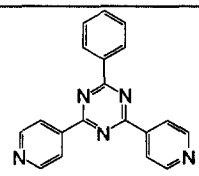
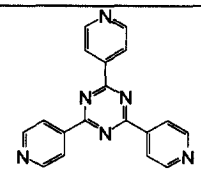
Template						
	38	**39**	**40**	**41**	**42**	**43**
% Yield Cyclic Dimer **37**	23	72	27	7	8	6
% Yield Cyclic Trimer **45**	34	4	34	43	44	52

Table 2. Template Effects on Cyclic Porphyrin Oligomers.

4. Templates Used to Make Materials

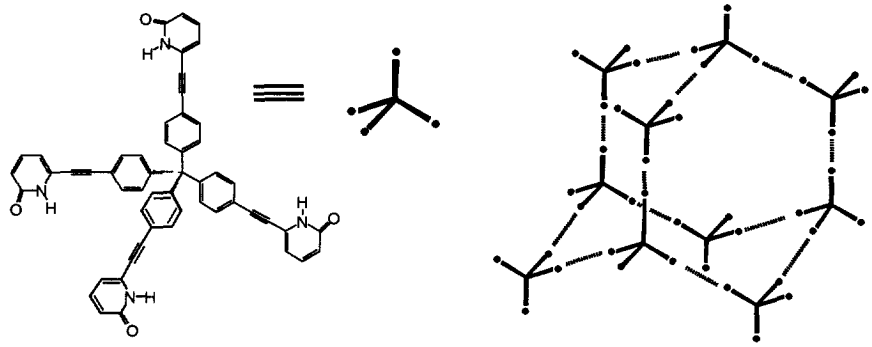
4.1 Molecularly Imprinted Polymers

The use of templates to create molecular imprints in polymers is another active area of supramolecular chemistry.[33] The preparation of a molecularly imprinted polymer involves the formation of a cross-linked polymer around a template molecule. After removal of the template, a functionalized cavity remains that is complementary to the template molecule used in its synthesis. This cavity is capable of selectively recognizing the template molecule and even capable of resolving enantiomers of chiral templates. The process of creating the molecularly imprinted polymer resembles the production of antibodies in biological systems. As in antibodies, the shape of the cavity, the spatial arrangement of functional groups, and the flexibility of the binding site all contribute to the molecular recognition. The transfer of molecular recognition information from the template to the polymer is a quick and efficient means of creating a selective molecular host without the laborious task of synthesizing a host in a step-wise manner as is done in many supramolecular systems.[34] The disadvantage of imprinted polymers is that they are difficult to characterize because they lack homogeneity within their binding cavities. Molecular imprinting has been done on surfaces such as silica gel[35] and monolayers on gold.[36] Imprinted polymers have found uses in resolution of enantiomers,[37] asymmetric catalysis,[38] mimicry of antibodies,[39] and selective transport across membranes.[40]

4.2 Templates in Crystal Engineering

As illustrated by imprinted polymers above, molecular recognition between molecules is far from restricted to solution chemistry. Another example of molecular recognition in the solid state is crystal engineering, which seeks to create solid state structures with useful functions. As with supramolecular chemistry in solution, the noncovalent interactions and molecular recognition between molecules during crystal packing are not well understood.[10] Often the growth of a crystal will lead to the inclusion of a guest molecule within the interstitial space of the packed crystal. Such inclusion of a guest molecule is often called **enclathration**, and the solid state structure is described as an **inclusion compound**.[41] Wuest et al. have

developed structure-directing molecules know as **tectons** such as **46** to aid in the self-assembly of three-dimensional networks that form large chambers.[42] The tecton is designed with directional hydrogen bonding sites that direct their aggregation to form predictable structures. The use of tecton **46** led to the formation of a diamondoid network (**47**) in the presence of a suitable enclathrate or template molecule (**Figure 3**). When the crystal was grown with tecton **46** from CH_3CH_2COOH/hexane/MeOH or CH_3COOH/hexane/MeOH, a non-diamondoid network was formed due to the competitive hydrogen bonding of the acid molecule with tecton **46**. The use of larger acid molecules in the solvent mixture as in ($CH_3(CH_2)_2COOH$/hexane/MeOH) or ($CH_3(CH_2)_3COOH$ /hexane/MeOH) led to the predicted diamondoid crystal structure, **47**. Although the crystallization was performed in a mixed solvent, only the acid molecules were incorporated into the cavity, demonstrating that the self-assembly of tectons are template-dependent.[42] Wuest has also used a similar approach to create a porous material whose pores remain largely intact even upon removal of guests.[43] There are many potential applications for such materials. For example, Aoyama has generated organic solids that catalyze a Diels-Alder reaction.[44]



Tecton **46** Diamondoid Network **47**

Figure 3. Tecton Assembly.

4.3 Template Molecules Used to Create Zeolites

Zeolites, especially silica-based zeolites, are another type of material whose structure is highly dependent on the structure-directing agents, or template molecules, used in their synthesis.[45] The use of a variety of rigid polycyclic template molecules[45] and liquid crystals as template assemblies have expanded the types of zeolite structures that can be made. The applications of zeolites in applied chemistry and engineering disciplines are continually expanding from the traditional catalysis and adsorbent technology to more recent micro-reaction chambers.[46] Templation will play a key role in the development of such new molecular sieve lattices. Presently it is difficult to predict what structure of zeolite would be produced from a given template molecule. The prediction of the final structure of the zeolite, however, may be aided by computational approaches. Lewis et al. have developed a program for the *de novo* design of template molecules that are "computationally grown" in the desired inorganic framework.[47] They have successfully worked backwards from known zeolite structures to create the template molecules that were shown experimentally to form these structures. In the future, such computations may vastly expand our knowledge about the templation of zeolites.

4.4 Template Formation of Tubules

Electronically conductive polymer nanostructures such as fibrils and tubules have been successfully synthesized within the pores of nanoporous membranes.[48a] The nanoporous membrane acts as a mold or template for the formation of the nanostructure. After its formation, the nanostructure can be separated from the nanoporous template. The nature of the nanostructure is dependent upon chemical make up and size of the nanoporous membrane employed in the synthesis. These structures have applications in bioencapsulation and biosensors.[48] Others have created nanotubes via self-assembly of cyclodextrins[48b, 48c] or cyclic peptides.[48d]

5. Molecular Encapsulation

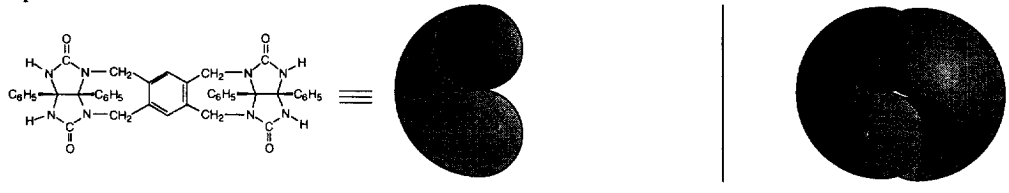
5.1 Self-Assembly of Cavities Capable of Molecular Encapsulation

The phenomenon of self-assembly is important to biological and materials sciences alike because of its widespread use in the formation of structures such as cell membranes and monolayers. The driving forces for the formation of a self-assembling structure are a multitude of noncovalent interactions, such as hydrogen bonds, van der Waals, electrostatic, and π-π interactions, that bring the molecules together in a defined aggregate. Numerous one dimensional and two dimensional self-assembled systems are known,[12c, 49] but relatively few self-assembling structures are known to form in three dimensions and create cavities capable of encapsulating guest molecules, which in some cases can act as templates. Here, we examine a number of self-assembling structures that demonstrate the formation of internal cavities capable of recognizing guest molecules.

The design of self-assembling structures that contain a cavity capable of encapsulating one or more guest molecules has attracted great attention recently because of their novelty and because of potential applications, including use as drug delivery devices or as miniature reaction chambers.[50] The construction of traditional molecular hosts used for molecular recognition has generated sophisticated compounds such as spherands,[50b] cryptophanes,[51] and modified cyclodextrins[52] that are capable of binding ions or molecules of various sizes. These systems often require multistep syntheses and also require an opening that will allow for guest entrance and egress. A more appealing and economic method of creating a host-guest system would be to self-assemble the host around the guest molecule. The encapsulated molecule could act as a template by aiding in this self-assembly of molecular components. The result is a well-defined three dimensional spherically-shaped aggregate. Here the word template is used in the formation of a noncovalent and reversible assembly of molecules instead of in the formation of a covalently assembled product. Such flexibility was left in Busch's definition[15] of the word "template" which stated: "a template organizes an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of the atoms". The word "linking" can be extended to both covalent and noncovalent bonds. The discovery in our labs of complex **3**•guest (**Scheme 1**)[4] represents one of the few self-assembling structures that is capable of selective, reversible molecular encapsulation, and is discussed in the final section of this report. A number of researchers are actively exploring related types of self-assembling structures and they are reviewed here.

5.2 Rebek's Tennis Ball

Rebek and coworkers have created a number of self-assembling systems that form cavities which are capable of binding neutral molecules that vary in size from methane to substituted adamantanes.[53] A common design feature of Rebek's self-assembling structures is the use of two di-substituted glycoluril substituents connected by a rigid spacer such as durene, as shown in structure **48** (**Figure 4**).[53f] The concave nature of compound **48** allows for its self recognition to form a reversible dimeric capsule that encapsulates a guest molecule within its interior to yield complex **48•48•**guest (**Figure 4**), which has the same shape and symmetry as the cover of a tennis ball. Complexes such as **48•48•**guest are amenable to NMR characterization where the decomplexation rates are manifested by slow exchange on the ^{1}H NMR timescale, and thus signals for bound guest are distinguishable from free guest. Moreover, integration of the ^{1}H NMR gives the stoichiometry of the complex, the N-H signals are shifted downfield indicating hydrogen bonding, and the encapsulated guest molecules have large upfield shifts due to the shielding by the aromatic host. Rebek et al. have used X-ray crystallography and mass spectrometry to further characterize their complexes. The ^{1}H NMR spectrum of compound **48** in $CDCl_3$ shows two sets of host signals in the presence of a suitable guest such as methane. One set of signals is due to complex **48•48•**CH_4 while the other set of signals is thought to correspond to the empty dimer. The possibility that the empty species contains water or dissolved gases in the cavity could not be excluded.[53f] Binding constants ([**48•48•**guest]/([free guest][free **48•48**]) for complex **48•48•**guest were determined: $CHCl_3$ (0.04 M^{-1}), CH_2Cl_2 (4 M^{-1}), ethylene (280 M^{-1}), and CH_4 (300 M^{-1}) in $CDCl_3$; complex **48•48•**Xe was also shown to form in the presence of the noble gas Xe in $CDCl_3$ but no binding constant was reported.[53e]



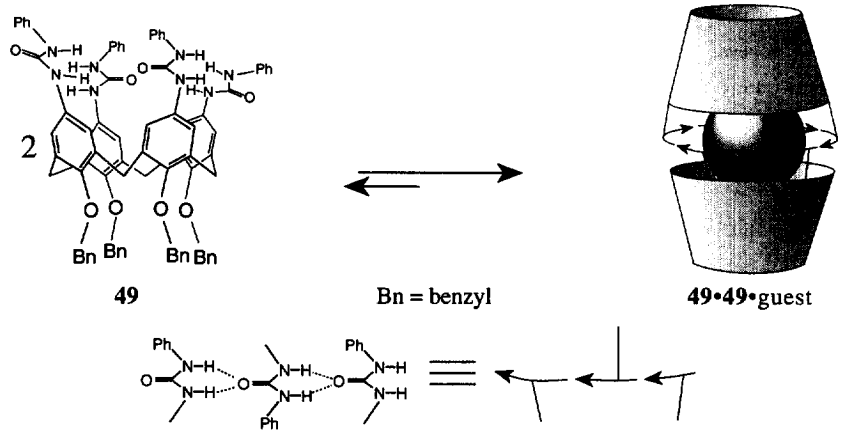
48 **48•48**

Figure 4. Rebek's Tennis Ball.

Derivatives of compound **48** that are large enough to encapsulate substituted adamantanes, ferrocenes and two molecules of benzene derivatives have been synthesized by this group.[53c] The incorporation of two molecules in Rebek's larger self-assembled host molecules provides the opportunity to perform bimolecular reactions within complex interiors.[54] In some of the larger complexes, the host alone yields a broad NMR spectrum, whereas the addition of guest sharpens the spectrum significantly. This implies that the guest induces the formation of a well-defined capsule from an undefined aggregate. In this regard, the guest can be considered as a kind of template. In a related system created by Fujita,[55] a tris-paladium-hexapyridyl complex forms in low yield in the absence of guest, but in high yield in the presence of guest. The guest can be encapsulated in the host, and the reaction to form the host is reversible. Again, the encapsulation of the guest can be viewed as a templation process.

5.3 Urea-Based Calixarene Dimer

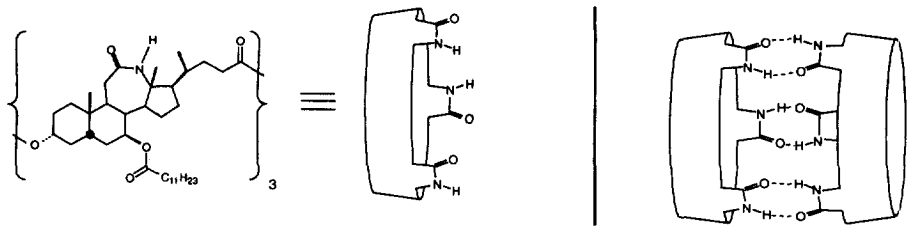
Rebek and coworkers have recently described the dimerization of self-complementary calix[4]arenes, such as **49**, through intermolecular hydrogen bonding of the urea functionalities incorporated into the upper rim of the calix[4]arene.[56] The urea moieties form hydrogen bonds in a directional cyclic array as shown in **Scheme 11**. The resulting complex (**49•49•**guest) was found to selectively bind the following molecules in order of increasing binding constants: ethylbenzene < *p*-xylene < *o*-xylene < toluene < chloroform ≅ benzene (the binding constant of benzene was reported as 2.3 x 10^2 M^{-1} in *p*-xylene-d_{10}). Desorption mass spectrometry gave molecular ion peaks for the complexes with the same relative intensities as that found in solution.[56c] A series of related calix[4]arene dimers were studied in a variety of solvents by Böhmer and coworkers but no evidence of molecular encapsulation of guest molecules within the cavities of the dimers was reported in solution, although a disordered benzene was found to be encapsulated in the solid state.[57] Instead, Böhmer and coworkers focused on the formation of heterodimers that resulted when calixarenes that differ in the urea groups at the upper rim were mixed together in solution. These studies found that a more or less statistical equilibrium controlled the dimerization process. Similarly, Reinhoudt studied the dimerization of two bis-functionalized calixarenes.[58]



Scheme 11. Urea-Based Capsule.

5.4 Cyclocholates

Bonar-Law and Sanders have reported a similar self-assembled structure to those discussed in the previous two sections. The dimerization of cyclocholate **50** via hydrogen bonding of amides groups in the C-ring of the steroid led to the formation of a capsule-like assembly, **50•50** (**Figure 5**).[59] Cyclocholates are rigid macrocycles formed by the condensation of multiple units of cholic acid. Dimerization of the cyclocholates was evident by the large downfield shifts of the N-H protons in the ^{1}H NMR spectra and the N-H and carbonyl stretching frequency in the IR spectra. Both vapor pressure osmometry (VPO) and freezing point depression experiments in benzene indicated molecular weights consistent with the proposed dimer **50•50**. No guest binding studies were reported but the dimerization constant for **50•50** was determined to be 3 x 10^4 M^{-1} in $CDCl_3$.[59a]

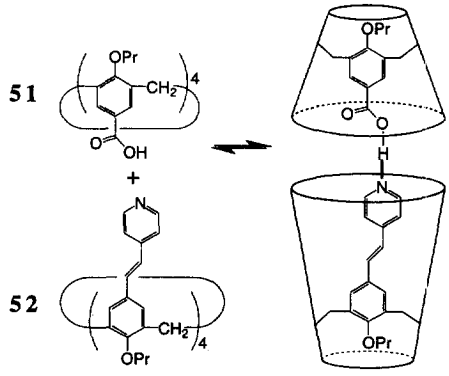


50 **50•50**

Figure 5. Cyclocholate Dimer.

5.5 Heterodimers

In addition to the calixarene heterodimer investigated by Böhmer,[57] Shinkai *et al.* reported the self-assembly of two calixarenes functionalized at their upper rims to form heterodimer **51•52** (**Scheme 12**).[60] The proposed structure of heterodimer **51•52** isbased on VPO measurements, fluorescence spectroscopy of the stilbazole unit of **52**, and the increased solubility of calixarene **51** in $CDCl_3$ when calixarene **52** is present. No guest binding studies were reported. Later, Reinhoudt et al. reported the formation of a similar heterodimer via the association of a calix[4]arene functionalized at the bottom rim with 4-pyridyls and another calix[4]arene functionalized at the upper rim with carboxylic acid groups.[61]



51•52

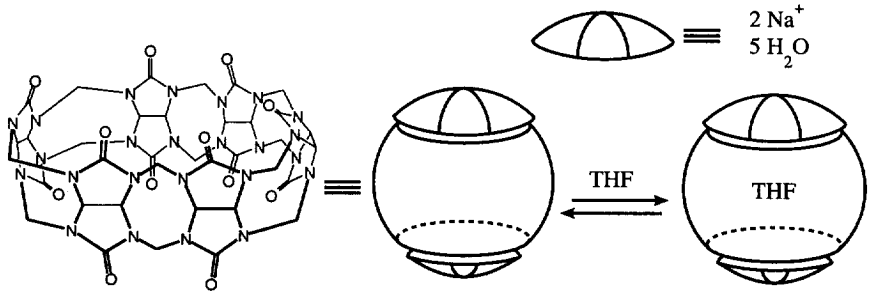
Scheme 12. Formation of Calixarene Heterodimer.

Heterodimers of cyclotriveratrylene (CTV) have been formed that are capable of encapsulating molecules such as chloroform and tetramethylsilane in DMSO as solvent.[62] The linkage between the CTV's is three salt bridges between carboxylates and ammoniums. Covalent dimers of CTV's have also been shown to encapsulate molecules such as CHBrClF.[62b] Unlike hemicarceplexes (see section 6.5), the guest-exchange rate for these dimers is fast. Interestingly, these compounds can resolve the enantiomers of CHBrClF.[62b]

5.6 Encapsulation in Cucurbituril

Recently, Kim et al. reported the switchable assembly of a molecular container capable of reversibly binding guests molecules such as THF.[63] They found the solubility of cucurbituril **53** increased dramatically in aqueous solutions of alkali metal salts such as sodium sulfate. They grew crystals from this solution and the X-ray crystal structure indicated that a rigid molecular container had formed whereby two molecules of Na^+ ions and five H_2O molecules formed a cap-like structure at the top and at the bottom of cucurbituril (**54**, **Scheme**

13). Addition of THF to a D_2O solution of cucurbituril and Na_2SO_4 resulted in the formation of a complex that was in slow exchange on the ^1H NMR timescale and had a formation constant (K_f) of 5.1 x 10^2 M^{-1}. An X-ray crystal structure of complex **54**•THF indicated that the host had the same shape and symmetry as it did in the absence of guest. Furthermore, complex **54**•THF was found to be "switchable" by altering the pH of the solution. Thus, addition of trifluoroacetic acid to a solution of complex **54**•THF results in decomplexation as indicated by the decrease in bound THF and the increase in uncomplexed THF. Addition of Na_2CO_3 to this sample regenerated complex **54**•THF. Similar binding experiments were performed with cyclopentanone (K_f = 2.2 x 10^3 M^{-1}), benzene (K_f = 2.7 x 10^1 M^{-1}) and furan (K_f = 7.1 x 10^3 M^{-1}). This study of the binding properties of cucurbituril expands the range of molecules that can be incorporated into its cavity from traditional ammonium-based guests[64] to neutral guests about the size of benzene.

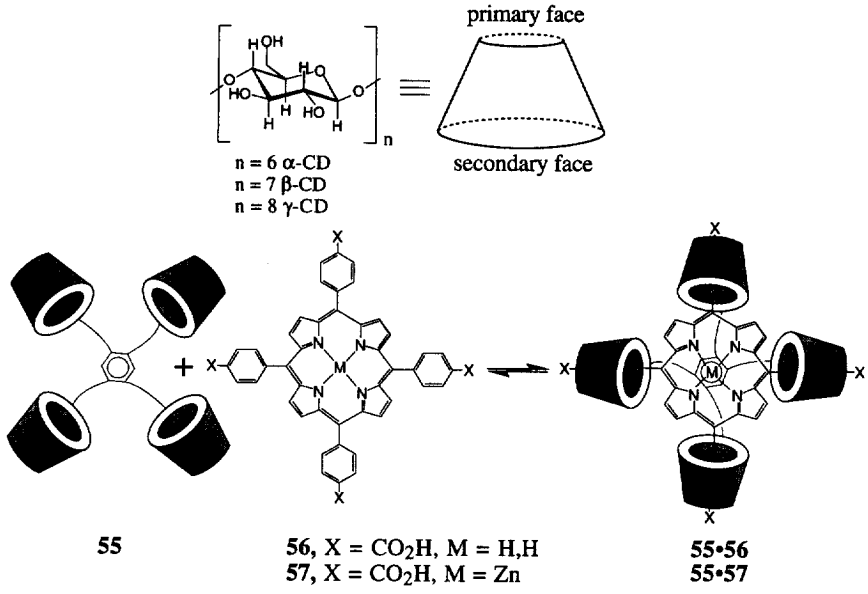


53 **54** **54**•THF

Scheme 13. Cucurbituril Complex.

5.7 Molecular Encapsulation in Cyclodextrins

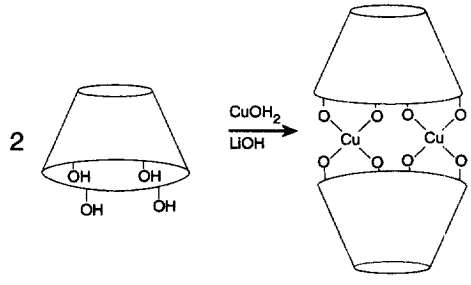
Cyclodextrins (CD's) are "lamp-shade" shaped cyclic oligomers of glucose.[65] They are soluble in water and contain a chiral hydrophobic cavity with openings at both ends. The size of the cavity and its openings depend upon the number of glucose subunits in the cyclodextrin; (denoted by the prefix α (6), β (7), and γ (8)) (**Scheme 14**). CD's bind a number of hydrophobic guest molecules in aqueous solution where the strength of binding is often determined by the hydrophobic effect. Thirty years of investigation into the binding properties have revealed a large variety of molecules that bind to CD's[52] and the search for new substrates still continues.[66] Porphyrins, especially metalloporphyrins, are important components of natural systems such as in cytochromes where they aid in electron transport. The versatility of porphyrins makes them interesting building blocks for the formation of supramolecular structures. The encapsulation of porphyrins in CD complexes has been studied by Lawrence,[67], Nolte,[68] and others.[52, 69] The binding constants of porphyrins to CD's was demonstrated to increase when multiple CD's are covalently linked together with an appropriate spacer. The use of a covalently linked tetramer of CD's (**55**), as illustrated schematically in **Scheme 14**, formed one of the strongest complexes with porphyrins. For example, both neutral porphyrin **56** and zinc porphyrin **57** form complexes **55**•**56** and **55**•**57** with binding constants (K_b) of ~ 10^8 M^{-1} in D_2O.[67b] Binding constants for dimers of CD's (two covalently linked CD's) with porphyrins are significantly smaller (e.g., K_b ~ 10^4 M^{-1}).[67b] The binding properties of porphyrins in CD's holds promise as new catalytic systems.



Scheme 14. Cyclodextrin/Porphyrin Complex.

5.8 Cyclodextrin Dimerization

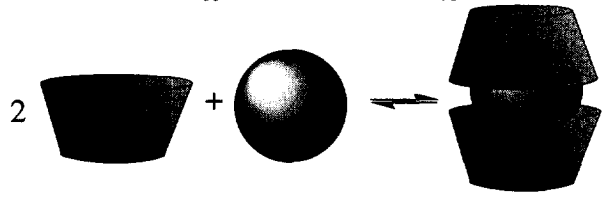
Klüfers et al. discovered that mixing ß-CD **58**, lithium hydroxide and a source of copper(II) ions in an aqueous solution resulted in the formation of blue crystals. X-ray crystallography showed that two ß-CD's are connected via metallic bridges to give a ß-CD dimer **58•58** that is schematically illustrated in **Scheme 15**.[70] ß-CD dimer **58•58** contained four copper(II) ions that connect the two CD's. In addition, a number of intramolecular and intermolecular lithium ion salt bridges and charged O^----H-O hydrogen bonds were found in the crystal structure. The charged hydrogen bond distances ranged from 2.46-2.60 Å indicating strong hydrogen bonds.[71] Seven molecules of water were encapsulated within the interior of the cavity of ß-CD dimer **58•58**, each of which completed the tetrahedral coordination sphere of a lithium ion. Diffusion of acetone vapor produced crystals that contain two acetone molecules within the cavity of the CD dimer.[70a] A similar γ-CD dimer structure was found to form in the presence of lead(II) ions; this dimer had a higher metal to CD ratio and represents the first lead(II) carbohydrate complex known to date.[72]



Scheme 15. CD Metallic Dimer.

5.9 Encapsulation of C_{60} by CD's and Calixarenes

Yoshida *et al.* discovered that an aqueous solution of γ-CD (**59**) could selectively extract C_{60} from a mixture of fullerenes in toluene.[73] Remarkably, only C_{60} (7 Å, spherically-shaped) and not C_{70} (7 Å by 8 Å oval-shaped) was extracted into an aqueous solution of γ-CD (there is a 9 Å circular opening at the secondary face). Both α-CD and β-CD failed to extract any fullerenes from the toluene solution. They found encapsulation of C_{60} involved two molecules of γ-CD; the corresponding complex, **59•59•**C_{60}, resulted in the solubilization of C_{60} into aqueous solution (**Scheme 16**). Furthermore, evidence for complex **59•59•**C_{60} included ^{13}C NMR chemical shifts and integration of host and guest, ^{1}H NMR chemical shifts of the γ-CD, and elemental analysis. Calix[5]arenes have also recently been shown to encapsulate C_{60} in a 2:1 fashion, with association constants as high as 2.1 X 10^3 M^{-1}.[74] Other researchers have developed means of purifying fullerenes by the aid of 1:1 binding in bowl-shaped compounds such as calix[8]arenes,[75] calix[6]arenes,[76] and cyclotriveratrylenes.[77] In the case of calix[8]arenes, a trimer of hosts forms that is capable of encapsulation of three molecules of C_{60} or two molecules of C_{60} and one molecule of C_{70}.[75]



γ-CD (**59**) C_{60} **59•59•**C_{60}

Scheme 16. γ-CD Dimer Encapsulating C_{60}.

5.10 Encapsulation of ß-Methyl Glucopyranoside

Aoyama et al. reported the encapsulation of a ß-methyl glucopyranoside between two molecules of octol **60**.[78] Here octol **60** extracts the normally insoluble ß-methyl glucopyranoside into $CDCl_3$ or CCl_4 from aqueous solution, to form complex **60•60•**ß-methyl glucopyranoside where there are two molecules of octol **60** to one ß-methyl glucopyranoside (**Figure 6**). The 2:1 stoichiometry was confirmed by VPO measurements. The ^{1}H NMR spectrum of complex **60•60•**ß-methyl glucopyranoside exhibited an upfield shift of 3.58 ppm for the methoxy group of ß-methyl glucopyranoside, indicating that it is strongly shielded by the aromatic host. A 3.58 ppm shift of the methoxy group of ß-methyl glucopyranoside indicates that it is most likely held very close to the aromatic rings of complex **60•60•**ß-methyl glucopyranoside and not at the equator of the molecule as the illustration in Aoyama's paper (and below) suggests. The ^{1}H NMR spectrum of complex **60•60•**ß-methyl glucopyranoside exhibited a complex spectrum with a multitude of peaks, indicating that the ß-methyl glucopyranoside guest manifests slow motion within the host on the ^{1}H NMR time scale. The octol dimer also showed remarkable selectivity for ß-methyl glucopyranoside over α-methyl glucopyranoside.

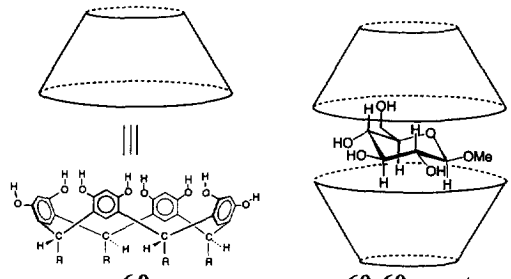


Figure 6. Encapsulation of β-Methylglucopyranoside. R = $(CH_2)_{10}CH_3$.

6. Carceplexes

6.1 Introduction

Mechanically joined supramolecular structures, which include both catenanes and rotaxanes, have attracted the attention of chemists for years because of their novel structures, challenging syntheses, and potentially useful properties. In 1983, Cram proposed another technique for mechanically joining molecules whereby a rigid closed surface spherical host such as **61** acts as a molecular prison for the entrapment of a guest molecule within its interior (**Figure 7**).[79] This type of highly preorganized compound had never been made before and would likely have interesting chemical and physical properties.

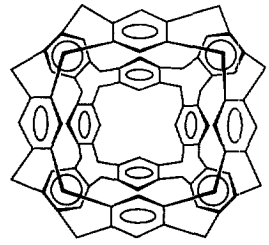


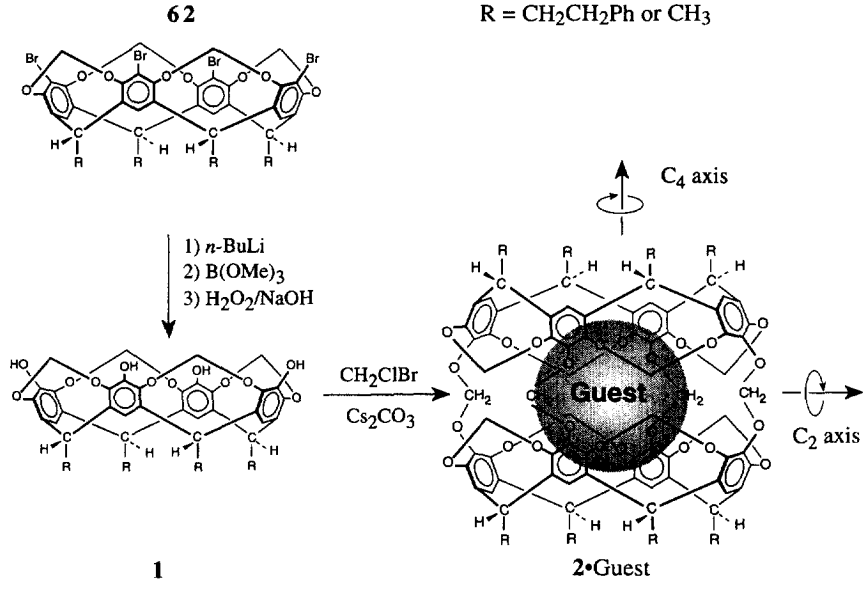
Figure 7. Molecular Prison **61**.

The preparation of such compounds was achieved via the synthesis of **cavitands**, which are rigid macrocyclic molecules that contain an enforced cavity.[80] Conformationally flexible resorcinarenes (e.g., octol **60**) can be rigidified by linkage of adjacent phenolic groups to yield cavitands. Thus, multigram quantities of cavitands such as **62** (**Scheme 17**) can be prepared. The methylene bridging of the phenols has been successfully applied to a diverse range of compounds that differ in their pendent group;[81] also, a variety of bridges can be introduced between the adjacent phenols.[80b] Furthermore, tetrabromo-bowl **62** can be further modified by conversion of the aryl bromide into a variety of functional groups, which makes cavitands attractive components for supramolecular synthesis. Cavitands provided the stepping stone into the synthesis of the first **carceplexes** where covalent linkage of two of these hemi-spherical molecules leads to a spherical molecule with a cavity large enough to entrap small molecules in its interior.[82] One such carceplex, **2**•guest, [83] has led to the discovery of an unusual template effect in the assembly process that is responsible for its formation.[3]

6.2 Template Effects in the Formation of Carceplex 2•Guest

Tetrol **1**, the starting material for formation of carceplex **2**•guest, was synthesized on a multi-gram scale from tetrabromo-bowl **62**.[83] The successful bridging of adjacent phenols to produce cavitands such as **62** led

to the idea to intermolecularly bridge the phenols of two molecules of tetrol **1** with bromochloromethane. Thus, the intermolecular bridging reaction between two molecules of tetrol **1** was attempted under high dilution conditions using bromochloromethane as the bridging material and cesium carbonate as the base (**Scheme 17**). The reaction, when performed in neat dimethylformamide (DMF), dimethylacetamide (DMA) and dimethyl sulfoxide (DMSO) gave carceplexes **2**•DMF, carceplexes **2**•DMA and carceplexes **2**•DMSO, in 49, 54 and 61% yields, respectively.[83] These yields are remarkably high for a reaction that joins seven molecules together and makes eight new carbon-oxygen bonds. Moreover, Cram and Sherman also discovered three interesting features of this reaction: (1) No carceplex was formed when the reaction was run in *N*-formylpiperidine (NFP), a molecule too big for the interior of carceplex **2**•guest. (2) A 10% yield of DMA carceplex was obtained when the reaction was run in a mixture of NFP and DMA (99.5/0.5 molar ratio) as solvent. (3) A 5:1 ratio of carceplex **2**•DMA and carceplex **2**•DMF resulted when the reaction was run in a mixture of DMA and DMF (50/50 v/v) as solvent.[83] Taken together, these three results suggested two things: (1) The reaction to form carceplex **2**•guest requires a template molecule because no carceplex was isolated without a guest. (2) The carceplex reaction demonstrates selectivity when given the choice of two suitable templates.



Scheme 17. Synthesis of Carceplex **2**•Guest.

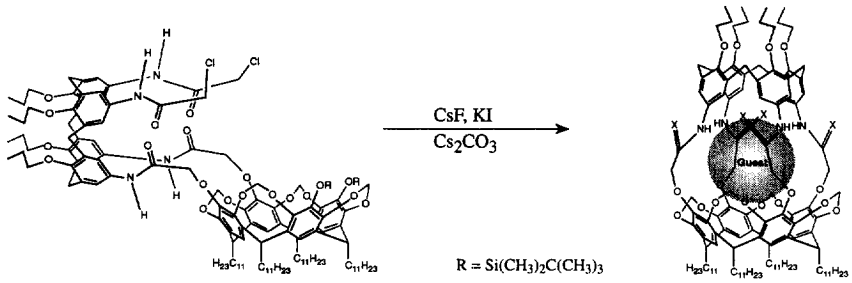
Further studies have shown that the template effect varies one million-fold, with pyrazine as the best template and *N*-methylpyrolidinone (NMP) as the poorest measurable template.[3] A complex (complex **3**•guest, see **Scheme 1**) was discovered where two molecules of tetrol **1** encapsulate a template molecule in the presence of base.[4] Complex **3**•guest manifests the same guest-selectivity as carceplex **2**•guest. Thus, complex **3**•guest is a good transition state model for the guest-determining step (GDS, the step beyond which guests no longer

exchange) in the formation of carceplex **2**•guest. Complex **3**•guest is reversible and is switchable by adjustment of pH, and thus represents a highly organized self-assembling structure in its own right.[4]

The template selectivity in the above system is unusually high. Beyond the million-fold overall range in template abilities, very small perturbations in the guest lead to large differences in template abilities. For example, the relative template abilities for pyrazine:pyridine:benzene are 420:14:1, and for 1,4-dioxane:1,3-dioxane, they are 1400:1.[3] This level of selectivity has led to a theoretical analysis of the driving forces for complexation in **3**•guest, and thus the template effect in the formation of carceplex **2**•guest.[84] Preliminary results suggest that the driving forces include favorable van der Waals interactions, CH-π interactions, and π-π interactions between the host and guest, while the conformation of the host, desolvation of the guest, and the entropy of complexation are clearly important as well. Thus, the formation of carceplex **2**•guest involves the highly selective molecular recognition and self-assembly of two cavitands about a guest, where the guest acts as a kinetic template. The guest allows the most stable complex to form, much like the encapsulating species in the preceding section. The most stable complex then affords the fastest guest-determining bridge formation, leaving the template molecule mechanically ensnared, much like the catenanes and rotaxanes described in Section 3.

6.3 Other Carceplexes

Very few true carceplexes have been synthesized to date. Of these, with the exception of carceplex **2**•guest, few details are available regarding the template effects that drive their assembly processes. Carceplex **2**•guest and an analogous carceplex,[82] where the inter-bowl linkage is $-CH_2SCH_2-$, represented the only carceplexes until 1993 when Müller synthesized polyoxyvandate compounds that incarcerated anions.[85] In 1994, Reinhoudt et al. synthesized carceplex **64**•guest via combination of a calix[4]arene and a cavitand (**Scheme 18**).[86c] They observed high yields for the shell closure of compound **63** in neat solvents to form carceplex **64**•guest where the guest was a molecule of solvent. Guests entrapped in carceplex **64**•guest included DMA, DMF and *N*-methyl-2-pyrrolidinone(NMP). These compounds did not exchange their guests molecules even under prolonged periods of heating, which confirms that they are indeed carceplexes. Later, in studies similar to those described above for carceplex **2**•guest, Reinhoudt et al. used a doping procedure whereby a guest molecule is added to a solvent (5-10 mol % based on solvent) which is itself a poor template for formation of carceplex **64**•guest, thereby facilitating the screening of various template molecules.[86b] The newly incarcerated guest molecules include: 1,5-dimethyl-2-pyrrolidinone, 2-butanone, ethylmethylsulfoxide, thiolane 1-oxide, and 3-sulfolene. Relative template abilities as high as 3.7:1 for DMA:butanone were determined.[86a] In other studies, chemical modification of carceplex **64**•guest to carceplex **65**•guest occurred without the loss of its guest molecule and was found to modify the orientation of the incarcerated guest molecule.[86b] The carceplexes created by Reinhoudt et al. show a unique type of stereoisomerism (named carcerism) due to the restricted internal rotation of the incarcerated guest molecule and the asymmetry of the host and guest.[86c] Reinhoudt's group has also created monolayers of their calix[4]arene-based carceplexes on a gold surface.[87]



63 **64**•Guest, X = O
65•Guest, X = S

Scheme 18. Synthesis of Calix[4]arene-Based Carceplex.

Anions have been used as templates for the synthesis of a variety of ion cages.[88] The organization of polyoxometalates of vanadium, molybdenum and tungsten around anions such as Cl^-, CO_3^{2-}, ClO_4^-, N_3^- and SO_4^{2-} to form host-guest structures that resemble the structures of carceplexes has been studied by Müller and coworkers.[85] Here the anionic guest is crucial to the formation of the caged structure. In the absence of the anionic template no such cages are formed. The structure of the cage was also found to be dependent upon the anionic template used. Similar investigations into the template effects of halide ions for the formation of macrocyclic mercury complexes were explored by Hawthorne et al.[89] Cavitands have also been bridged by Pd to produce dimeric species that encapsulate one of eight triflate counterions; conceivably, the triflate acts as a template for formation of this complex.[90]

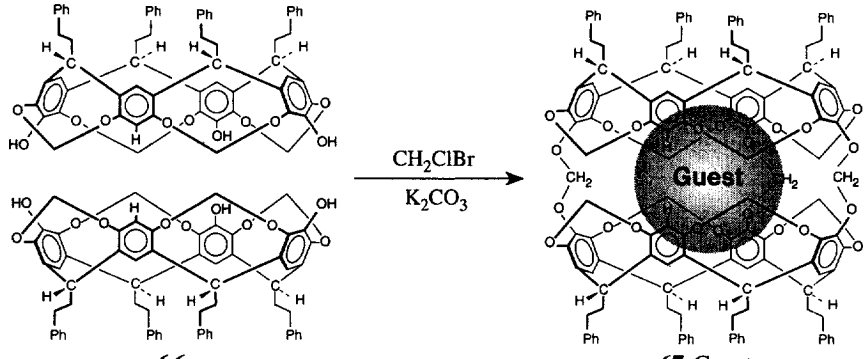
6.4 Endohedral Complexes of Fullerenes

Fullerenes are spherical closed surface aromatic carbon compounds discovered in 1985 whose prototypical member is C_{60}.[91] The founders of this new area of chemistry, Kroto, Smalley and Curl, were awarded the 1996 Nobel prize in chemistry. The fullerenes represent one of the most intensely studied compounds of the past decade.[91] Besides their promising applications as superconductors and semiconductors, fullerenes can encapsulate atoms such as noble gases[92] and a large variety of metal ions.[93] Difficulties in the extraction of these endohedral complexes of fullerenes and their subsequent purification have created problems with their isolation. The endohedral complexes of larger fullerenes such as M@C_{82}, M@C_{80}, and M@C_{74} traditionally are easier to isolate than their M@C_{60} counter parts, but recently the use of aniline as an extraction solvent led to successful isolation of significant quantities of M@C_{60}.[93a] The formation of endohedral complexes of fullerenes with noble gases is traditionally done by heating samples of the fullerene in the presence of a noble gas at high pressures (e.g., 600 °C, 2500 atm., 5 hours).[92a] Also, mass spectroscopic collision experiments have been used to form the endohedral complexes of fullerenes and noble gases.[92a] The formation of endohedral complexes of fullerenes and various metals can be prepared by arc-heating M_xO_y/graphite rods in a low pressure helium atmosphere.[93a] X-ray diffraction has been used to confirm that the metal is indeed inside the fullerene.[94] The interior of endohedral complexes of fullerenes are only large enough to entrap atoms or

small ions thus making them possibly the smallest carceplexes that can be formed. The promising properties of fullerenes will continue to keep them at the forefront of scientific research.

6.5 Related Compounds

Hemicarceplexes are worthy of mention here because of their similarity to carceplexes and because some studies into the template effect in their formation have been undertaken. Hemicarceplexes differ from carceplexes in that they can reorganize to create holes or portals which allows for egress of guests. By definition, hemicarceplexes must be kinetically stable at ambient temperatures to allow for their isolation and subsequent characterization. A large number of hemicarceplexes have been synthesized to date.[50] Tetrol **1** has been used to create a large portion of the known hemicarceplexes via the use of large inter-bowl bridges which include: o-xylene, naphthalene, hexamethylene, tetramethylene, and 2-butyne.[50] Activation energies for decomplexation have been calculated for a number of such hemicarceplexes.[50]



66 **67**•Guest

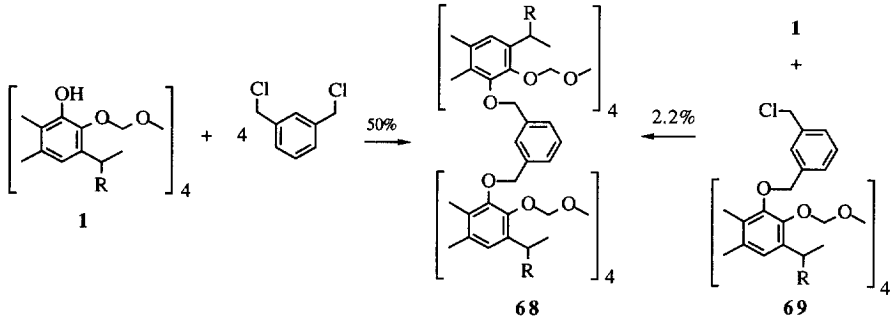
Scheme 19. Formation of Hemicarceplex **67**•Guest.

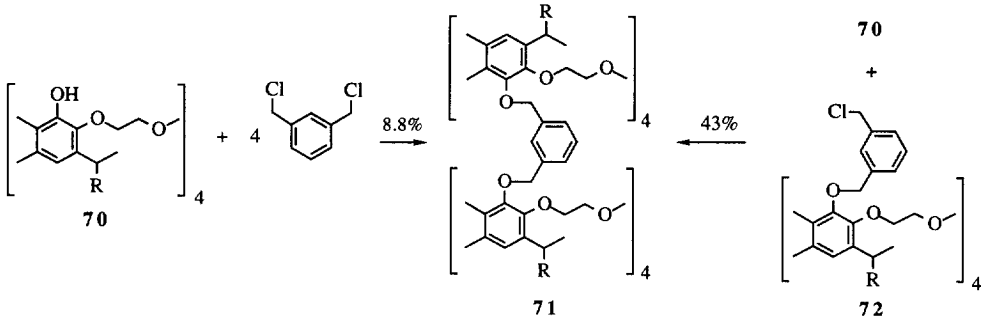
The template effect on the formation of hemicarceplex **67**•guest (**Scheme 19**) was investigated and followed the effects described for carceplex **2**•guest.[95] The guest-selectivity was very similar, and a complex between the two precursor triols (**66**) and guests has been observed.[96] The high yields obtained suggest that the two triols align non-randomly, as "proper" alignment would furnish the most stable maximum of three charged hydrogen bonds. Thus, the template affords alignment of the cavitands and optimizes hydrogen bonding, which facilitates the formation of hemicarceplex **67**•guest.

The interiors of hemicarceplexes allow for unique chemical reactions to occur where bulk solvent or external reagents cannot directly participate.[97] This environment has provided some unique chemistry, probably the most famous example being the room temperature stabilization of cyclobutadiene.[97f] The use of hemicarceplexes continues to provide exciting examples of unique chemistry.

In the case of carceplex **2**•guest the formation of the second covalent bridge is the GDS. It happens in this system (and in hemicarceplex **67**•guest) that there is a GDS; i.e., the guest is entrapped at some point. In a series of hemicarceplexes (including **68** and **71**, **Scheme 20**)) studied by Cram, it appears that guests can act as templates, but escape capture, as the portals of the products are large enough to allow egress of the guests;

thus, there is no GDS.[98] The formation of these compounds involve the use of templates in the purer sense that Busch defined, as the templates are regenerated and are not part of the product.





Scheme 20. Preparation of Hemicarceplexes **68** and **71**.

Closer analysis of the reactions to form hemicarceplexes **68** and **71** (if no guest is encapsulated, the host is properly called a **hemicarcerand**) reveals a sophisticated assembly process. The elucidation of this process allows significant improvement in yields to be gained and thus, may facilitate the design of yet more sophisticated assemblies. When tetrol **1** was reacted with α,α'-dichloro-*m*-xylene, a 50% yield of hemicarcerand **68** was obtained. In contrast, reaction of tetrol **1** with its tetra(chloroxylyl) derivative (**69**) gave hemicarcerand **68** in only 2.2% yield. The former reaction used NMP as a template, which escapes the hemicarceplex during workup.[98] Apparently, the complex of two molecules of tetrol **1** about NMP forms, and the corresponding singly- and doubly-bridged complexes may also form, maintaining preorganization for further bridging. This is not possible under the second reaction conditions as no intramolecular hydrogen bonding is possible after a bridge has formed. Furthermore, tetrol **1** is likely to form its NMP complex under these conditions, which effectively reduces the concentration of free tetrol available to react with the tetra(chloroxylyl) cavitand (**69**). (Alternatively, complex **3**•guest could react with cavitand **69**; this would be a sterically hindered reaction and would lead to an intermediate that is poised for polymerization.) One could consider NMP as a positive template under the first conditions as it enhances the formation of hemicarcerand **68**, but as a negative template under the second conditions as it inhibits formation of the very same hemicarcerand.

Analysis of one more experiment enhances the above interpretation. Tetrol **70** was bridged with α,α'-dichloro-*m*-xylene to give hemicarcerand **71** in 8.8% yield. Alternatively, tetrol **70** plus the corresponding tetra(chloroxylyl) cavitand (**72**) yields hemicarcerand **71** in 43% yield.[98] In this case, a complex of two molecules of tetrol **70** cannot form, according to CPK models, so preorganization for reaction with α,α-dichloroxylene is very low. On the other hand, under the second reaction conditions, since tetrol **70** is not tied up as a complex, it is free to react with the tetra(chloroxylyl) cavitand (**72**). Although this reaction does not appear to benefit from templation, the context of former experiments provides a rational explanation for, and a rational approach toward, the preparation of hemicarcerand **71**.

7. Conclusions

This report has illustrated that the formation of sophisticated supramolecular assemblies is often facilitated by maximizing favorable noncovalent interactions between the reactants; template molecules are often used for this purpose. It is important for chemists to learn as much as possible about these noncovalent interactions because they dominate the properties of many biological assemblies, including enzymes, cell membranes and viruses. A wealth of information about noncovalent interactions is presently available but even more is required in order for chemists to develop supramolecular assemblies that approach the complexity of those found in natural systems.

The study of self-assembling structures that can form cavities capable of molecular encapsulation is an expedient means of obtaining valuable information about the noncovalent interactions that governs self-assembly. The reversible nature of these systems allows examination of the thermodynamic properties of the system. Such information increases our knowledge of the importance of particular interactions such as hydrogen bonds, π-π interactions and van der Waals interactions. This information can then be used to develop more complex assemblies of molecules with useful properties, and it may also be used to refine the parameters used for noncovalent interactions in computer modeling programs, which iteratively enhances future designs.

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References

1. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017-7036.
2. (a) Busch, D. H.; Vance, A. L.; Kolchinski, A. G. Chapter 1; *Molecular Template Effect: Historical View, Principles, and Perspectives*; Gokel, G. W., Vol. Ed.; in the series *Comprehensive Supramolecular Chemistry*; Lehn, J.-M.; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Series Ed.; Pergamon: New York, 1996; Vol. 9, pp 1-42. (b) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469-475. (c) McMurray, T. J.; Raymond, K. N.; Smith, P. H. *Science* **1989**, *244*, 938-942.
3. Chapman, R. G.; Chopra, N.; Cochien, E. D.; Sherman, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 369-370.
4. Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 9081-9082.
5. (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996. (b) Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.

6. Woodward, R. B. *Pure Appl. Chem.* **1973**, *33*, 145-177.
7. Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.-I.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525-7530.
8. (a) Lehn, J.-M. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304-1319. (b) Lehn, J.-M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89-112. (c) Lehn, J.-M. *Science* **1985**, *227*, 849-856.
9. Wolf, K. L.; Frahm, H.; Harms, Z. *Phys. Chem. Abt. B.* **1937**, *36*, 17.
10. Desiraju, G. R. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311-2327.
11. (a) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2985-2993. For excellent reviews of molecular recognition in host-guest chemistry, see (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1995**, *95*, 2529-2586. (c) Izatt, R. M.; Bradshaw, J. S.; Pawlak, K.; Bruening, R. L.; Tarbet, B. J. *Chem. Rev.* **1992**, *92*, 1261-1354. (d) Schneider, H.-J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1417-1436.
12. (a) Philp, D.; Stoddart, J. F. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154-1196. (b) Lindsey, J. S. *New J. Chem.* **1991**, *15*, 153-180. (c) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312-1319.
13. Fredricks, J. R.; Hamiliton, A. D. Chapter 16; *Hydrogen Bonding Control of Molecular Self-assembly: Recent Advances in Design, Synthesis, and Analysis*, Gokel, G. W., Vol. Ed.; in the series *Comprehensive Supramolecular Chemistry*; Lehn, J.-M.; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Series Ed.; Pergamon: New York, 1996; Vol. 9, pp 565-594.
14. Bradley, D. *Chem. Soc. Rev.* **1995**, 379-382.
15. Busch, D. H. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *12*, 389-395.
16. Stryer, L. *Biochemistry*; 2nd ed.; W. H. Freeman: New York, 1988, pp 724-727.
17. (a) Schill, G. *Catenanes, Rotaxanes and Knots*; Acedemic: New York, 1971. (b) Jäger, R.; Vögtle, F. *Ang. Chem. Int. Ed. Engl.* **1997**, *36*, 930-944.
18. Chambron, J. C.; Dietrich-Buchecker, C. O.; Nierengarten, J. F.; Sauvage, J. P. *Pure Appl. Chem.* **1994**, *66*, 1543-1550, and references therein.
19. Kern, J.-M.; Sauvage, J.-P.; Weidmann, J.-L. *Tetrahedron* **1996**, *52*, 10921-10934.
20. Brown, C. L.; Philp, D.; Stoddart, J. F. *Synlett* **1991**, 462-464.
21. Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, M.; Gandolfi, M. T.; Philp, D.; Prodi, L.; Raymo, F. M.; Reddington, M. V.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 4931-4951.
22. Ballardini, R.; Balzani, V.; Credi, A.; Gandolfi, M. T.; Langford, S. J.; Menzer, S.; Prodi, L.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 978-981.
23. Zhu, S. S.; Carroll, P. J.; Swager, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 8713-8714.
24. Ashton, P. R.; Claessens, C. G.; Hayes, W.; Menzer, S.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1862-1865.
25. Amabilino, D. B.; Ashton, P. R.; Pérez-García, L.; Stoddart, J. F. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2378-2380.
26. Vögtle, F.; Jäger, R.; Händel, M.; Ottens-Hildebrandt, S.; Schmidt, W. *Synthesis* **1996**, 353-356.
27. Fox, S. W.; Dose, K. *Molecular Evolution and the Origin of Life*; Dekker: New York, 1977.
28. (a) Sieves, D.; von Kiedrowski, G. *Nature* **1994**, *369*, 221-224. (b) von Kiedrowski, G.; Wlotzka, B.; Helbing, J.; Matzen, M.; Jordan, S. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 423-426. (c) von Kiedrowski, G.; Wlotzka, B.; Helbing, J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1235-1237. (d) von Kiedrowski, G. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 932-935.
29. (a) Lee, D. H.; Granja, J. R.; Martinez, J. A.; Severin, K.; Ghadiri, M. R. *Nature* **1996**, *382*, 525-528. (b) Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1657-1659. (c) Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8877-8884. (d) Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *Acc. Chem. Res.* **1994**, *27*, 198-203. (e) Orgel, L. E. *Nature* **1992**, *358*, 203-209.
30. (a) Rebek, J., Jr. *Chem. Rev.* **1996**, *96*, 255-263. (b) Huc, I.; Pieters, R. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 10296-10297. (c) Conn, M. M.; Wintner, E. A.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1577-1579.
31. (a) Menger, F. M.; Eliseev, A. V.; Khanjin, N. A. *J. Am. Chem. Soc.* **1994**, *116*, 3613-3614. (b) Conn, M. M.; Wintner, E. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8823-8824. (c) Menger, F. M.; Eliseev, A. V.; Khanjin, N. A.; Sherrod, M. J. *J. Org. Chem.* **1995**, *60*, 2870-2878. (d) Reinhoudt, D. N.; Rudkevich, D. M.; de Jong, F. *J. Am. Chem. Soc.* **1996**, *118*, 6880-6889.

32. (a) Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *18*, 2223-2229. (b) Anderson, H. L.; Anderson, S.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *18*, 2231-2245. (c) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *18*, 2247-2254. (d) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *18*, 2255-2267. (e) Mackay, L. G.; Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, *18*, 2269-2273.
33. (a) Wulff, G. *Template Induced Control of Stereochemistry for the Synthesis of Polymers*; Wulff, G., Ed.; Kluwer Academic Publishers: Netherlands, 1995; Vol. 473, pp 13-19. (b) Spivak, D.; Gilmore, M. A.; Shea, K. J. *J. Am. Chem. Soc.* **1997**, *119*, 4388-4393. (c) Wulff, G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1812-1832.
34. Tanabe, K.; Takeuchi, T.; Matsui, J.; Ikebukuro, K.; Yano, K.; Karube, I. *J. Chem. Soc., Chem. Commun.* **1995**, 2303-2304.
35. Wulff, G.; Heide, B.; Helfmeier, G. *J. Am. Chem. Soc.* **1986**, *108*, 1089-1091.
36. (a) Chailapakul, O.; Crooks, R. M. *Langmuir* **1995**, *11*, 1329-1340. (b) Chailapakul, O.; Crooks, R. M. *Langmuir* **1993**, *9*, 884-888.
37. (a) Wulff, G. *Biorecognition in Molecular Imprinted Polymers: Concept, Chemistry and Applications*; Wulff, G., Ed.; Plenum: New York, 1993, pp 363-381. (b) Andersson, L. I.; Ekberg, B.; Mosbach, K. *Bioseparation and Catalysis in Molecular Imprinted Polymers*; Ngo, T. T., Ed.; Plenum: New York, 1993, pp 383-394.
38. Gamez, P.; Dunjic, B.; Pinel, C.; Lemaire, M. *Tetrahedron Lett.* **1995**, *36*, 8779-8782.
39. Hedborg, E.; Winquist, F.; Lundstrom, I.; Andersson, L. I.; Mosbach, K. *Sensors Actuators A* **1993**, *37-38*, 796-799.
40. Mathew-Krotz, J.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 8154-8155.
41. Bishop, R. *Chem. Soc. Rev.* **1996**, 311-319.
42. Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696-4698.
43. (a) Brunet, P.; Simard, M.; Wuest, J. D. *J. Am. Chem. Soc.* **1997**, *119*, 2737-2738. See also (b) Russell, V. A.; Evans, C. C.; Li, W.; Ward, M. D. *Science* **1997**, *276*, 575-579.
44. Endo, K.; Koike, T.; Sawaki, T.; Hayashida, O.; Masuda, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4117-4122.
45. Zones, S. I.; Nakagawa, Y.; Yuen, L. T.; Harris, T. V. *J. Am. Chem. Soc.* **1996**, *118*, 7558-7567.
46. (a) Pitchumani, K.; Corbin, D. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **1996**, *118*, 8152-8153. (b) Pitchumani, K.; Warrier, M.; Cui, C.; Weiss, R. G.; Ramamurthy, V. *Tetrahedron Lett.* **1996**, *37*, 6251-6254. (c) Xu, T.; Munson, E. J.; Haw, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 1962-1972.
47. Lewis, D. W.; Willock, D. J.; Catlow, C. R. A.; Thomas, J. M.; Hutchings, G. J. *Nature* **1996**, *382*, 604-606.
48. (a) Martin, C. R. *Acc. Chem. Res.* **1995**, *28*, 61-68. See also (b) Harada, A.; Li, J.; Kamachi, M. *Nature* **1994**, *370*, 126-128. (c) Wenz, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803-822. (d) Ghadiri, M. R.; Granja, J. R.; Buehler, L. K. *Nature* **1994**, *369*, 301-304.
49. (a) Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1215-1218. (b) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, *28*, 37-44. (c) Fan, E.; Yang, J.; Geib, S. J.; Vicent, C.; Garcia-Tellado, F.; Tecilla, P.; Hamilton, A. D. *Macromol. Symp.* **1994**, *77*, 209-217.
50. (a) Maverick, E.; Cram, D. J. Chapter 12; *Carcerands and Hemicarcerands: Hosts that Imprison Molecular Guests*; Vögtle, F. Vol. Ed.; in the series *Comprehensive Supramolecular Chemistry*; Lehn, J.-M.; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Ed.; Pergamon: New York, 1996; Vol. 2, pp 367-418. (b) Cram, D. J.; Cram, J. M. *Container Compounds and Their Guests*; The Royal Society of Chemistry: Cambridge, 1994; Vol. No. 4. (c) Sherman, J. C. In *Large Ring Molecules*; Semlyen, J. A., Ed.; J. Wiley & Sons: West Sussex, England, 1996; pp 507-524. (d) Sherman, J. C. *Tetrahedron* **1995**, *51*, 3395-3422.
51. Garel, L.; Dutasta, J.-P.; Collet, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1169-1171.
52. Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146-153.
53. (a) Meissner, R.; Garcias, X.; Mecozzi, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 77-85. (b) Rebek, J., Jr. *Pure Appl. Chem.* **1996**, *68*, 1261-1266. (c) Kang, J.; Rebek, J. J. *Nature* **1996**, *382*, 239-241. (d) Meissner, R. S.; Rebek, J. J.; de Mendoza, J. *Science* **1995**, *270*, 1485-1488. (e) Branda, N.; Grotzfeld, R. M.; Valdés, C.; Rebek, J. J. *J. Am. Chem. Soc.* **1995**, *117*, 85-88. (f) Branda, N.; Wyler, R.; Rebek, J. J. *Science* **1994**, *263*, 1267-1268.
54. Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50-52.

55. Fujita, M.; Nagao, S.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 1649-1650.
56. (a) Hamann, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1326-1329. (b) Castellano, R. K.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 10002-10003. (c) Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci.* **1995**, *92*, 12403-12407.
57. (a) Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, *52*, 8489-8496. (b) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thorndorf, I.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1996**, 2533-2534.
58. Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476-3481.
59. (a) Bonar-Law, R. P.; Sanders, J. K. M. *Tetrahedron Lett.* **1993**, *34*, 1677-1680. (b) Bonar-Law, R. P.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1995**, *117*, 259-271.
60. Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255-8258.
61. Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 4282-4288.
62. (a) Lee, S. B.; Hong, J.-I. *Tetrahedron Lett.* **1996**, *37*, 8501-8504. (b) Costante-Crassous, J.; Marrone, T. J.; Briggs, J. M.; McCammon, J. A.; Collet, A. *J. Am. Chem. Soc.* **1997**, *119*, 3818-3823.
63. Jeon, Y.-M.; Kim, J.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9970-9971.
64. Cintas, P. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 205-220.
65. Szejtli, J. *Cyclodextrins and Their Inclusion Complexes*; Akademiai Kiado: Budapest, 1982.
66. Maletic, M.; Wennemers, H.; MacDonald, D. Q.; Breslow, R.; Still, W. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1490-1492.
67. (a) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229-2260. (b) Jiang, T.; Li, M.; Lawrence, D. S. *J. Org. Chem.* **1995**, *60*, 7293-7297.
68. Venema, F.; Rowan, A. E.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1996**, *118*, 257-258.
69. (a) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1996**, *118*, 8495-8496. (b) Breslow, R.; Halfon, S.; Zhang, B. *Tetrahedron* **1995**, *51*, 377-388. (c) Wenz, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803-822. (d) Mosseri, S.; Mialocq, J. C.; Perly, B.; Hambright, P. *J. Phys. Chem.* **1991**, *95*, 4659-4663.
70. (a) Klüfers, P.; Piotrowski, H.; Uhlendorf, J. *Chem. Eur.* **1997**, *3*, 601-608. (b) Fuchs, R.; Habermann, N.; Klüfers, P. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 852-854.
71. (a) Hibbert, F.; Emsley, J. *Advances in Physical Organic Chemistry* **1990**, *26*, 255-379. (b) Emsley, J. *Chem. Soc. Rev.* **1980**, *9*, 91-124. (c) Novak, A. *Struct. Bonding* **1974**, *18*, 177-216.
72. Klüfers, P.; Schuhmacher, J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1863-1865.
73. Yoshida, Z.-I.; Takekuma, H.; Takekuma, S.-I.; Matsubara, Y. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1597-1599.
74. Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 259-260.
75. (a) Atwood, J. L.; Koutsantonis, G. A.; Raston, C. L. *Nature* **1994**, *368*, 229-231. (b) Raston, C. L.; Atwood, J. L.; Nichols, P. J.; Sudria, I. B. N. *J. Chem. Soc., Chem. Commun.* **1996**, 2615-2616.
76. Araki, K.; Akoa, K.; Ikeda, A.; Suzuki, T.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 73-76.
77. Steed, J. W.; Junk, P. C.; Atwood, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 10346-10347.
78. Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10302-10306.
79. Cram, D. J. *Science* **1983**, *219*, 1177-1183.
80. a) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826-5828. (b) Cram, D. J.; Karbach, S.; Kim, H. E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229-2237.
81. (a) Gibb, B. C.; Chapman, R. G.; Sherman, J. C. *J. Org. Chem.* **1996**, *61*, 1505-1509. (b) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663-2704.
82. (a) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167-2172. (b) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1403-1405.
83. (a) Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194-2204. (b) Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4527-4528.
84. Nakamura, K.; Sheu, C.; Keating, A. E.; Houk, K. N.; Sherman, J. C.; Chapman, R. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 4321-4322.
85. (a) Müller, A.; Krickemeyer, E.; Dillinger, S.; Bögge, H.; Stammler, A. *J. Chem. Soc., Chem. Commun.* **1994**, 2539-2540. (b) Müller, A.; Diemann, E.; Krickemeyer, E.; Che, S. *Naturwissenschaften* **1993**, *80*, 77-78.
86. (a) van Wageningen, A. M. A.; Timmerman, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Chem Eur.* **1997**, *3*, 639-654. (b) van Wageningen, A. M. A.; van Duynhoven, J. P. M.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 1941-

1942. (c) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2345-2348.
87. Huisman, B.-H.; Rudkevich, D. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, *118*, 3523-3524.
88. (a) Kaufmann, D. E.; Otten, A. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1832-1834. (b) Müller, A. *J. Mol. Struct.* **1994**, *325*, 13-35.
89. Zheng, Z.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1995**, *117*, 5105-5113.
90. Jacopozzi, P.; Dalcanale, E. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 613-615.
91. (a) Kroto, W. H.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature* **1985**, *318*, 162-163. (b) Goroff, N. *Acc. Chem. Res.* **1996**, *29*, 77-83. (c) Avent, A. G.; Birkett, P. R.; Christides, C.; Crane, J. D.; Darwish, A. D.; Hitchcock, P. B.; Kroto, H. W.; Meidine, M. F.; Prassides, K.; Taylor, R.; Walton, D. R. M. *J. Mol. Struct.* **1994**, *325*, 1-11.
92. (a) Patchkovskii, S.; Thiel, W. *J. Am. Chem. Soc.* **1996**, *118*, 7164-7172. (b) Saunders, M.; Jiménez-Vázquez, H. A.; Cross, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 2193-2194.
93. (a) Kubozono, Y.; Maeda, H.; Takabayashi, Y.; Hiraoka, K.; Nakai, T.; Kashino, S.; Emura, S.; Ukita, S.; Sogabe, T. *J. Am. Chem. Soc.* **1996**, *118*, 6998-6999. (b) Braun, T. *ACH - Models Chem.* **1995**, *132*, 245-263.
94. Takata, M.; Umeda, B.; Nishibori, E.; Sakata, M.; Saito, Y.; Ohno, M.; Shinohara, H. *Nature* **1995**, *377*, 46-48.
95. Chopra, N.; Sherman, J. C. *Supramol. Chem.* **1995**, *5*, 31-37.
96. Chapman, R. G.; Sherman, J. C., unpublished results.
97. (a) Farrán, A.; Deshayes, K. D. *J. Phys. Chem.* **1996**, *100*, 3305-3307. (b) Farrán, A.; Deshayes, K.; Matthews, C.; Balanescu, I. *J. Am. Chem. Soc.* **1995**, *117*, 9614-9615. (c) Pina, F.; Parola, A. J.; Ferreira, E.; Maestri, M.; Armaroli, N.; Ballardini, R.; Balzani, V. *J. Phys. Chem.* **1995**, *99*, 12701-12703. (d) Parola, A. J.; Pina, F.; Maestri, M.; Armaroli, N.; Balzani, V. *New J. Chem.* **1994**, *18*, 659-661. (e) Robbins, T. A.; Cram, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 12199. (f) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024-1027.
98. Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. E.; Cram. D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5590-5604.

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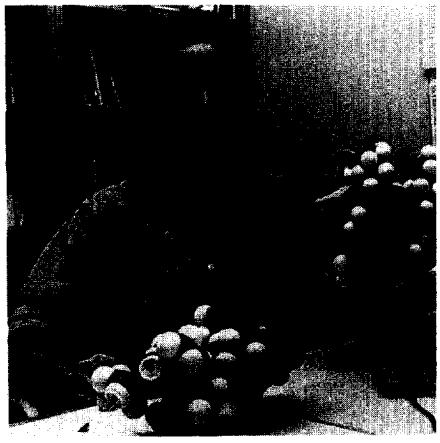
Biographical Sketch



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John Sherman is originally from New York, obtained a B.A. 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 became an Assistant Professor of Chemistry at UBC, and in 1996 he was promoted to Associate Professor. His research interests include the investigation of molecular encapsulation and the design, synthesis, and characterization of de novo proteins. When not supervising his research group or playing with his two young sons, he tries to sneak off to Whistler/Blackcomb for some skiing.

Bob Chapman is from Prince Edward Island, Canada. He obtained his B.Sc. from UPEI in 1991 and started graduate school at UBC in the same year. He completed his Ph.D. in March of 1997 with J.S. as his supervisor and held both NSERC and University Graduate Fellowships. He then moved to Harvard University where he is an NSERC PDF with G. M. Whitesides. His Ph.D. work involved the study of carceplex formation and revealed numerous self-assembling structures based on the resorcinarene "bowls". His current interests involve the use of self-assembled monolayers (SAMs) for studying molecular recognition phenomena on surfaces. He hopes to combine his experience in host-guest chemistry and materials science in an academic pursuit. Outside of lab, he enjoys hockey, mountain biking and skiing.