Self-Assembling Supramolecular Complexes

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Contents

I. Introduction

The conventional fashion by which compounds are synthesized in the laboratory and, to a large extent, *in vivo* relies upon the stepwise formation of covalent bonds. However, such a process is burdened with several inherent limitations when applied to the construction of extremely large and complex biological molecules. For example, there would be tremendous difficulties associated with the synthesis of a cell if all the components of the cell were part of one giant molecule. Such difficulties would include the inordinate amount of time required to effect the synthesis of the end product. In addition, each synthetic step would have to proceed with absolute fidelity, since one mistake could jeopardize the functional integrity of the target species. Nature first encountered these limitations during protobiogenesis.[1] How were primordial cells created from relatively simple building blocks when these "cells" did not contain the necessary machinery, catalytic, genetic, or otherwise, to direct their own synthesis? Wald first raised the possibility that these building block molecules could spontaneously assemble into an intact cell.[2] In short, he proposed that each building block molecule contained all the necessary information to recognize and interact with other appropriate molecules. Self-assembly has now been recognized to be both a crucial component in the molecular events that comprised the evolution of life and an essential participant in the biosynthesis of contemporary biological systems.[3] Indeed, a wide variety of cellular constituents, such as ribosomes, mitochondria, and the multitude of smaller multicomponent enzyme complexes, are synthesized from comparatively simple subunits via noncovalent interactions. It is apparent that a process which constitutes such a pivotal role in biology must offer some advantages relative to the alternate approach: the synthesis of a single unitized supermolecule, a species maintained entirely by covalent bonds. These advantages include (1) a reduction in structural errors in the final product by rejection of defective subunits during self-assembly, (2) facile formation of the end product, facilitated by rapidly established noncovalent interactions, and (3) synthetic economy. The latter is true for two reasons. First, in biological systems, multiple copies of a single subunit are often employed in the synthesis of supramolecular complexes. This is economical in terms of genetic material, because a relatively short nucleic acid sequence can code for a larger than otherwise predicted protein. Second, the assembly process is a highly convergent synthetic protocol and therefore requires fewer steps to convert starting material to final product compared to that of a linear synthesis. In addition, since a convergent synthesis relies upon the construction of several individual subunits, such a strategy can simultaneously address a number of key, yet untested, synthetic transformations. In contrast, a linear synthesis devotes a relatively large proportion of time to the mundane process of transforming starting material into previously prepared synthetic intermediates.

What is self-assembly? Is there a simple definition? Unfortunately, it is not so easy to formulate a modest descriptive phrase that does justice to this wonderfully seductive phenomenon. In addition, the term "self-assembly" is liberally applied throughout the literature, which leaves one with the sense that a significant fraction of all chemical and biological processes fall within its realm. Perhaps the best place to start is with an analogy. The assembly line construction of a car bears more than just passing resemblance to the conventional covalent bond-driven approach by which compounds are typically synthesized in the laboratory. Both processes are performed in a stepwise manner. In both cases, the parameters (e.g. time and environmental conditions) associated with each discrete step are unique in order to maximize efficiency. Finally, the construction strategy in both instances typically tends to be highly linear (i.e. nonconvergent). In contrast, picture a process in which all of the components of the car have been magically endowed with the ability to seek out, recognize, and associate with their appropriate

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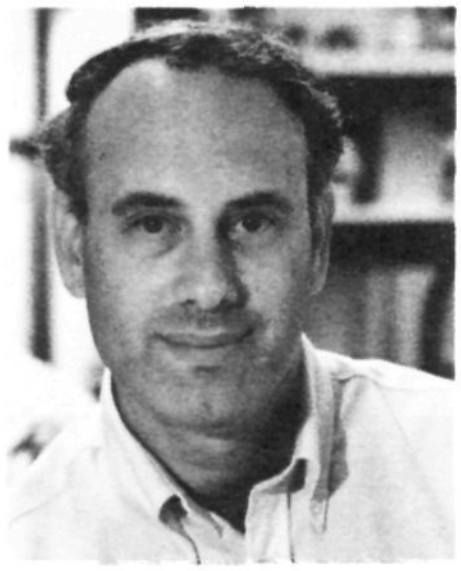
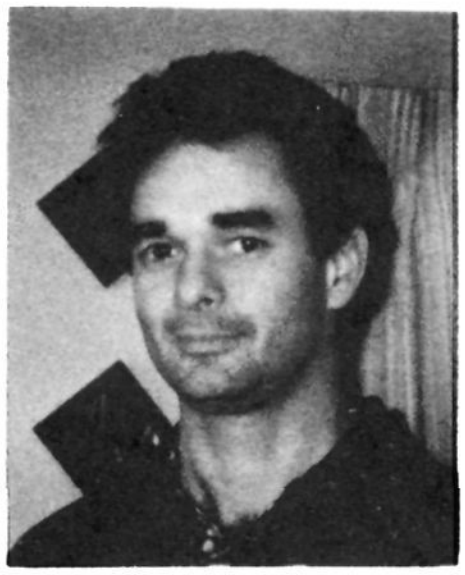


David S. Lawrence was born on the island of Manhattan in New York City. However, he spent his childhood playing in fields next to cow pastures in Orange County, California. He obtained his B.S. degree (summa cum laude and Phi Beta Kappa) in Biological Sciences from the University of California at Irvine. Late in his undergraduate career he was exposed to the wonders of organic chemistry in the laboratory of Professor Harold W. Moore. With a full year of sophomore organic chemistry under his belt, he entered graduate school in the Department of Chemistry at the University of California at Los Angeles and joined the research group of the late Professor Robert V. Stevens. Lawrence's thesis work dealt with the synthesis of steroids and vitamins. From his graduate student days he learned an important lesson that would serve him well in the future: *making covalent bonds is hard work.* He subsequently moved to the University of Chicago where he was an NIH postdoctoral fellow with the late Professor E. Thomas Kaiser. A short time later he, and the rest of the Kaiser team, moved to the Rockefeller University in New York City. In 1985, Lawrence was named an Assistant Professor of Chemistry at the State University of New York at Buffalo. He was promoted to Associate Professor in 1991 and Professor in 1995. In January of 1996 he will move back to the city of his birth as a Professor of Biochemistry at the Albert Einstein College of Medicine of Yeshiva University. He and his wife Heidi have three children, Nathan (6 years), Joshua (2 years), and Deborah (born 1995). Lawrence's research interests include self-assembling artificial enzymes and the chemistry and enzymology of signal transduction pathways.

Tao Jiang was born in 1963 in Jiangsu Province in the People's Republic of China. He received his B.S. degree in Chemistry from Fudan University in Shanghai. After five years as an assistant engineer at the research institute of Jinling Petrochemical Corporation in Najing, he entered graduate school at the State University of New York at Buffalo and joined the research group of Professor David S. Lawrence. He is currently a postdoctoral associate in the research group of Professor Roger Tsien at the University of California at San Diego. He is a member of the American Chemical Society. His research interests include the study of molecular interactions in both chemical and biological systems.

partners in the final product. Now imagine releasing these tens of thousands of individually animated pieces so that the car can instantaneously assemble itself. Of course, this analogy greatly oversimplifies the self-assembly phenomenon. In biological systems, self-assembly is often driven by a series of



Michael Levett was born in Buffalo, NY, in 1961. He earned his B.S. degree in Chemistry at the State University of New York at Albany in 1987. He is currently working on his Ph.D. in Chemistry at the State University of New York at Buffalo under the supervision of Professor David S. Lawrence. His main research interests lie in the synthesis of self-assembling complexes that mimic the activity of various enzymes.

discrete individual steps. Furthermore, in many instances, individual components do not contain all the information needed to associate with their prospective partners, but require guidance by "molecular chaperones" (however, such guidance may simply serve to preclude undesirable alternative pathways, such as aggregation).[4,5] In spite of these caveats, there is something wonderfully irresistible about a process that requires so little apparent effort on our part. We define self-assembly as a highly convergent synthesis protocol, one that is exclusively driven by noncovalent interactions. As a consequence, these same noncovalent interactions are wholly responsible for preserving the structural integrity of the end product.

Due to the restrictive nature of this definition, this review will focus on the synthesis of a relatively narrow range of supramolecular complexes (see refs 6–8 for earlier reviews). The complexes to be described herein all possess the following attributes: (1) *They are composed of a minimum of two subunits.* In short, phenomena analogous to protein folding, wherein a single molecule assumes a specific two- or three-dimensional structure, will not be covered. (2) *The molecular architecture of these complexes is maintained by noncovalent interactions.* Therefore the end product (although thermodynamically favored) is often in equilibrium with the component parts (however, *vide infra*). Lindsey has employed the term "strict self-assembly" to describe chemical reactions of this sort.[6] Since this limits our discussion to supramolecular entities whose structures are both driven and maintained by noncovalent interactions, those syntheses that utilize covalent bonds to preserve the structural attributes of the final product will not be covered. This excludes a large body of work, such as the syntheses of catenanes and rotaxanes by Gibson, Kaifer, Stoddardt, and others.[9] We have, however, made one exception to the exclusion of covalent bond-dependent syntheses by including multimeric complexes that employ coordinate covalent bonds ("dative" bonds), such as those present in tris(bipyridine)ruthenium. The dative bond is somewhat reminiscent of simple ionic interactions between metal ions and negatively charged ligands (i.e. a metal chelate). Therefore, as

a consequence of this resemblance, we have chosen to include syntheses that utilize this chemical interaction. (3) *The supramolecular complexes to be discussed exhibit a "utilitarian" property and/or structure that is not displayed by the subunits themselves.* Molecular recognition plays a crucial role in both host–guest chemistry and self-assembly, and indeed, it is not always easy to distinguish between these closely related processes. Nevertheless, once a host–guest complex has formed, the host is no longer "active", and the complex serves no additional role. This is in marked contrast to a self-assembly-driven synthesis, in which it is the supramolecular complex that exhibits some "active" property, such as a specific structure and/or function. However, this distinction is admittedly arbitrary and undoubtedly any reader, who so desires, will be able to find exceptions to and/or flaws in our reasoning. Nevertheless, it does allow us to exclude the huge literature devoted to host–guest chemistry. We will also not include any material related to liposomes or micelles for (what are hopefully) obvious reasons. Consequently, such interesting systems as Zasadzinski's "snap-together" vesicles will not be described.[10,11] We also note that there has been a recent flury of activity concerned with the self-assembly synthesis of compounds onto preexisting surfaces, such as monolayers. Multilayer formation based on the chemisorption of mercaptans, charged, and hydrophobic species is well known.[12–14] Particularly appealing, in this regard, is the recent monolayer/multilayer work of Ringsdorf and his colleagues.[15,16] However, we have decided not to include this important research area within the scope of this review. The restrictive nature of this article must be viewed as a necessity. Any presentation of such diverse topics as protein folding, host–guest chemistry, chemisorption, as well as all syntheses assisted by noncovalent interactions, would not only demand a Herculean effort, but would also require considerably more space than the editors of this Journal would be willing to provide. Finally, this review covers the literature through 1994. However, we have included some material that appeared in the early part of 1995 (particularly, in those cases that serve to clarify or significantly expand upon earlier work).

The self-organization of supramolecular entities is commonplace in vivo. In marked contrast, the design and synthesis of artificial self-assembling systems is a discipline still in its infancy. Indeed, synthetic supramolecular complexes that are functionally active remain a rarity. The reason for this is simple: those biological molecules that serve as subunits of multicomponent entities typically possess the ability to enter into literally thousands of precise noncovalent interactions with their nearest neighbors. These large number of interactions not only drive the self-assembly process but also maintain the structural integrity of the molecular assemblage. In contrast, at this point in time, the design of artificial self-assembling systems that can participate in a large number of precisely positioned noncovalent interactions represents a serious challenge. In order to fully appreciate the nature of this challenge, we will first describe two examples of self-assembling complexes found in biological systems.

II. Self-Assembling Biological Supramolecular Complexes

One of the best understood examples of a self-assembling protein-based complex is that of hemoglobin.[17] This oxygen-carrying entity is composed of four separate components; two α and two β subunits. Although each subunit is perfectly capable of reversibly binding oxygen, this ability is dramatically modified in the $\alpha_2\beta_2$ structure. Association of the first oxygen molecule with hemoglobin markedly enhances the affinity of hemoglobin for a second oxygen, which in turn promotes the binding of a third, and so on. This is a consequence of conformational changes that occur when oxygen binds to the individual subunits. The practical significance of this behavior is that the predominant *in vivo* forms of hemoglobin are the fully oxygenated and fully deoxygenated states. This provides for efficient oxygen binding in the lungs and complete oxygen release to the tissues. What is the nature of the interactions between the individual subunits in hemoglobin? The answer to this question is not all that surprising, especially when one compares the structures of the α and β subunits with that of myoglobin. The latter is the oxygen storage protein in muscle and is completely monomeric. Not unexpectedly, the gross structure of these proteins are very similar. However, there are some significant differences. Although there is little contact between the α and α, or β and β components, there are extensive noncovalent interactions between the α and β subunits in the hemoglobin tetramer. The so-called "packing contacts" between the α and β chains primarily involve the "B", "G", and "H" helices. Most of these contacts are hydrophobic in nature. In marked contrast, the corresponding residues in myoglobin are decidedly polar. Although the hydrophobic residues that line the interface between the α and β chains play a critical role in promoting the association of these hemoglobin subunits, the corresponding polar residues in myoglobin enable this monomeric protein to readily interact with a significantly more polar environment. There are also intersubunit contacts in hemoglobin that undergo changes upon oxygen binding (these constitute the conformational changes that control oxygen affinity described above). These noncovalent interactions are primarily hydrogen bonds and salt bridges and are termed "sliding contacts", since they differ in the oxygenated and deoxygenated forms. They involve the "C" and "G" helices as well as the corner region linking the "F" and "G" helices. Clearly, the multitude of precisely positioned noncovalent interactions that exist between the individual subunits in hemoglobin control both structure and function. Unfortunately, words alone do not do justice to the marvelous complexity associated with the manner by which the α and β subunits are united to produce the exquisitely fine-tuned oxygen-binding machine known as hemoglobin, a "simple" molecular assemblage. The interested reader is instead

referred to the beautifully illustrated monograph of Dickerson and Geis.[17] Nevertheless, it is possible to convey a sense of how influential noncovalent interactions are in producing a functionally active supramolecular complex by examining those situations where simple structural errors lead to terrible consequences. This is especially evident in the case of aberrant human hemoglobins.

Hemoglobin in patients suffering from sickel-cell anemia contains a valine at a position on the β chain normally reserved for glutamic acid. This has little effect on the structure of the oxygenated form of hemoglobin. However, the corresponding deoxyhemoglobin exhibits a profound tendency to aggregate, forming long fibers that deform the cell membrane (i.e. sickling). These aggregated hemoglobin mutants are but another example of self-assembly, albeit an inappropriate one. Erythrocytes containing these aggregates are not only deformed but are more rigid than their normal counterparts. As a consequence, they often get trapped in capillaries, resulting in both pain and inflammation. In addition, these sickled red blood cells are relatively fragile and must be replaced with greater frequency than healthy erythrocytes.

A somewhat different example of abnormal hemoglobin is produced in the disease state known as α-thalassemia. A shortage of α chains leads to the production of a tetrameric hemoglobin containing only β chains. Unforunately, this form of hemoglobin not only binds oxygen too tightly, but does so in a noncooperative fashion. In the most serious form of this disease, death occurs in the fetal stage just prior to birth. Once again, inappropriate self-assembly results in the formation of a defective product. In the case of both sickle-cell anemia and α-thalassemia, genetic abnormalities are responsible for the competing equilibria that lead to these aberrant protein assemblages.

The examples cited above illustrate the point that self-assembly is driven by weak, and therefore, reversible interactions. However, this apparent Achilles' heal in the self-assembly phenomenon can also be used to advantage. Imagine a situation in which a slight environmental change can lead to the rapid formation of a specific supramolecular complex or its equally speedy decomposition. If individual subunits were in equilibrium with some multicomponent assemblage, then a shift in that equilibrium would enable a cell or organism to respond with unusual dispatch to the ever-changing conditions of the surrounding environment. This is clearly one of the most powerful attributes of self-assembly. The assembly and disassembly of microtubules is an extraordinary example of this phenomenon.[18] Microtubules are protein fibers (along with actin microfilaments and intermediate filaments) that constitute the cytoskeleton of eukaryotic cells. They control the movement of subcellular structures: the separation of sister chromatids during mitosis, the transportation of proteins in neurons from the cell body down the axon to the synaptic region, and the conveyance of pigment granules in specialized cells in amphibians and fish to the cell surface (dark skin color) or interior (light skin color). In short, microtubules serve as subcellular "highways". However, these highways are remarkably dynamic! In nondividing cells, the cytoplasmic microtubule array extends from the center of the cell out to the plasma membrane. However, once the cell enters mitosis, this array is disassembled and the mitotic spindle assembled as the cell prepares itself for chromatid separation and subsequent division. These supramolecular microtubule complexes are composed of individual protein subunits known as tubulin (these subunits are themselves dimers, consisting of α- and β-tubulin). They are arranged in a cylindrical (as well as a helical) fashion to create a single microtubule (Figure 1). Microtubules exhibit a definite polarity, since individual subunits are preferentially added to one end ("+") and removed from the other ("−"). When the rate of addition exceeds the rate of removal, the microtubule is in the active state of assembly. In contrast, disassembly occurs if the removal rate predominates. Comparatively subtle changes in environmental conditions will influence the relative rates of these competing processes. For example, low temperatures or high pressures promote disassembly. Astonishingly, D_2O fosters assembly. Indeed, taxol promotes microtubule assembly to such an extreme extent that it interferes with the growth cycle. In contrast, colchicine enhances the rate of microtubule disassembly and thereby precludes the movement of chromosomes during mitosis.

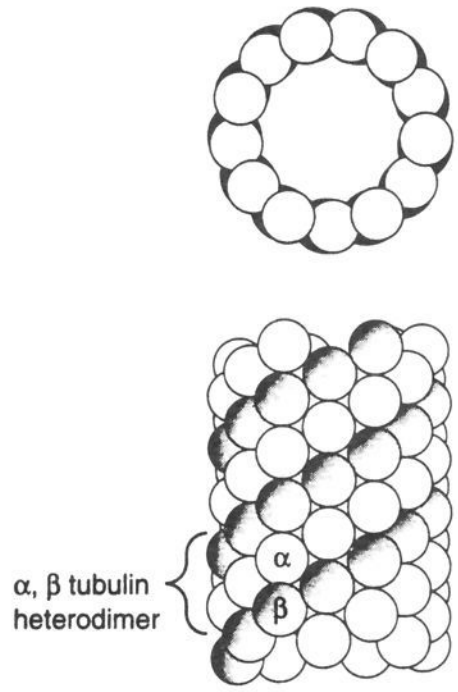


Figure 1. The assembled α,β-tubulin heterodimer. The top structure is a view of the microtubule from above, whereas the bottom structure is a view from the side.

III. Multiple Equilibria and Self-Assembly

Both the hemoglobin and microtubule examples cited above illustrate an important aspect of self-assembly that has a direct bearing on the design of synthetic molecular assemblages in the laboratory: the noncovalent interactions that drive self-assembly are weak compared to their covalent counterparts. As a consequence, supramolecular complexes can be in equilibrium, not only with their component parts, but with other undesirable complexes as well. In addition, subtle environmental factors can have a pronounced effect on the nature of the multiple equilibria that may be present in solution. In certain

instances, it may be desirable to have the coveted end product blink in and out of existence thousands of times per second. However, stable multimeric complexes are typically required. Nature has achieved this realization by reserving self-assembly for high molecular weight aggregates. Under these circumstances, there is the potential for a multitude of noncovalent interactions, which by sheer numbers can act to preserve the structural integrity of the final product. In spite of this, the elaborate molecular assemblages found in nature are not necessarily composed of structurally sophisticated individual subunits. Even functional group-deficient compounds, such as lipids, can form large, structurally well-defined aggregates (e.g. liposomes). Is it possible to drive the assembly of relatively small supramolecular complexes (e.g. <10 000 in molecular weight) in the absence of a legion of noncovalent interactions? Can this be realized in such a manner that the desired entity is the predominant species present?

There are a number of ways to promote the formation of small self-assembling complexes:

(1) *The strength of the noncovalent interactions that are responsible for maintaining the structural integrity of the complex can be enhanced.* This can be achieved by conducting the assembly process in an appropriate solvent. For example, if two or more species are designed to interact via hydrophobic interactions, then self-assembly is best conducted under aqueous conditions. In contrast, hydrogen bonds and electrostatic interactions are strongest in apolar aprotic solvents. Obviously, the magnitude of a particular interaction is not only dependent upon environmental conditions. For example, hydrogen-bond strengths are directly related to the structure of both the hydrogen-bond donor and acceptor, as well as the relative orientation of these species.[19] Consequently, subunit design is an especially important factor in ensuring that the individual components that comprise the molecular assemblage are firmly coordinated to one another.

(2) *The supramolecular complex can be selectively sequestered from solution in order to prevent dissociation of the complex back to its component parts.* Since the molecular assembage is isolated in this approach, characterization should be somewhat more tractable than with an equilibrium mixture of complexes. Although this approach does have its advantages in terms of characterization, it should be noted that if the isolated end product is almost completely dissociated in solution, then its usefulness as a functionally active entity is questionable.

(3) *Finally, a large excess of one of the components can be employed to drive the self-assembly process to completion.* This approach has some restrictions as well. Notably, although the molecular assemblage may be the predominant complex in solution under these conditions, it will still be in equilibrium with its component parts. Therefore, it is critical that the free subunits do not disrupt or otherwise disturb the ability of the desired complex to perform the task for which is was designed.

The goal of each of the possibilities outlined above is to shift the equilibrium in favor of the desired product. Unfortunately, the mere presence of an equilibrium mixture of product(s) and starting component(s) creates an obstacle of such magnitude that it often overshadows all other difficulties that the practitioners of this science must confront. The nature of this impediment and the difficulties that it engenders are described below.

IV. The Characterization Problem

Although self-assembly may predate the beginning of life, from the point of view of the contemporary organic chemist, it remains an emerging discipline. This is due to the fact that the study of complexes stabilized by reversible interactions poses a unique challenge, namely structural characterization.

Consider a hypothetical complex, composed of two separate subunits (Figure 2). The stoichiometry of

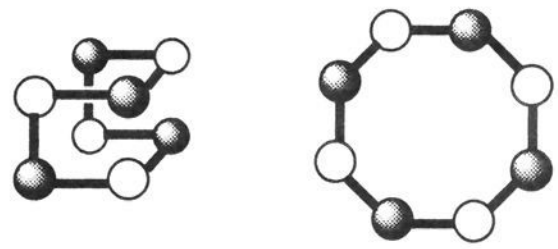


Figure 2. Two hypothetical complexes, each containing a 4:4 stoichiometry of two different subunits.

the individual subunits in the final product is 4:4. As with many of the low molecular weight complexes to be described herein, assume that this species is in equilibrium with its component parts. Structural information can be readily obtained if the desired complex is not only isolable, but yields X-ray quality crystals upon purification. Otherwise, characterization will be difficult. First, relative and absolute stoichiometry must be gauged. The former can be estimated by employing various titration methods, assuming that the components in the complex exhibit some measurable physical characteristics that are distinct from those features associated with the uncomplexed subunits. One common approach is the method of continuous variations.[20] Unfortunately, there is a critical restriction associated with this procedure, one which limits its application to the simplest of equilibria: relative stoichiometry can be readily estimated only if each component is present in a maximum of two different states in solution. In short, the method of continuous variations is virtually impossible to apply to systems in which three or more species (containing different subunit stoichiometries) are in equilibrium.

Assuming that it is possible to obtain the relative ratio of the individual components, then an assessment of absolute stoichiometry must be made. Obviously, this will be clear from the molecular weight of the complex. The latter is readily obtained via mass spectrometry if the complex is stable enough to provide a molecular ion. Unfortunately, mass spectrometry is unlikely to be generally applicable to loosely coordinated multicomponent species. Vapor pressure osmometry, a low-resolution solution phase method, has been extensively employed to assess the molecular weight of such species. This method has the advantage that it can be applied to complexes in organic solvents. Other methods, based

on such colligative properties as freezing point depression and boiling point elevation, can be used to gauge molecular weight as well. However, care must be taken with boiling point measurements to maintain a constant barometric pressure. A key limitation with both freezing point depression and boiling point elevation measurements is that high molecular weight complexes may produce effects that are too small to be accurately measured (due to the fact that a relatively small number of molecules are present under these circumstances). Finally the cryoscopic and ebullioscopic constants (i.e. the temperature change due to 1 mol of solute particles dissolved in 1 kg of solvent) for water are relatively small, necessitating extremely precise temperature measurements. However, some organic solvents are characterized by more manageable constants (e.g. cyclohexane). Light scattering measurements, which are performed at wavelengths that are of comparable size to the molecular dimensions of the solute, have also been employed for an assessment of molecular weight. Other techniques, such as sedimentation velocity and equilibrium methods, gel filtration, small-angle X-ray scattering, and gel electrophoresis, are commonly applied to biological molecules. The interested reader is referred to the monographs of Cantor and Schimmel[21] and Bell and Bell[22] for an in-depth survey of the analytical methods described above.

Unfortunately, in spite of the difficulties inherent in obtaining an assessment of molecular weight and relative subunit stoichiometry, this information is likely to be much more readily acquired than that of the actual structure of the complex in solution. For example, how would the cube-like species in Figure 2 be distinguished from its planar counterpart? The greater the number of different components in the complex under study, the more likely the issue of solution structure can be addressed in a meaningful fashion. At first glance, such a statement may appear to be preposterous. However, if there are many different types of subunits present, then nuclear Overhauser experiments should allow one to decipher the relative position of the individual subunits, information that may provide the critical data to determine the overall molecular architecture. In contrast, the applicability of this method will be severely curtailed if multiple copies of only a single component are contained within the supramolecular complex under evaluation. In short, there are obvious limitations associated with the use of NMR methods for determining the relative orientation of identical nearest neighbors. Consequently, the characterization of small self-assembling molecules, particularly those containing several copies of a single subunit, represents a major challenge that has yet to be resolved in a general fashion. In spite of the difficulties associated with structure characterization, most of the focus in the field of artificial self-assembling molecules has centered on the creation of structurally well-defined supramolecular complexes. Therefore, we have organized this review to emphasize the structural attributes of spontaneously organized multicomponent complexes.

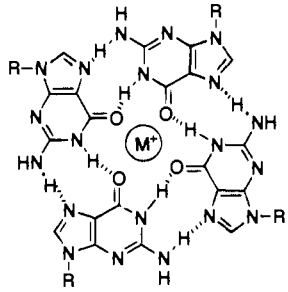
V. Self-Assembling Supramolecular Complexes

A. Cyclic Arrays

In many of the examples to be described in this section, the individual subunits have the opportunity to assemble into either a cyclic or linear array. Since cyclic structures generally exhibit more order than their linear counterparts, entropy should favor the formation of the latter. In contrast, since there will be a greater number of noncovalent interactions per subunit in a cyclic species, compared to that of a linear complex, the former will be favored from the enthalpic point of view. Consider a hypothetical species that self-associates to form a cyclic complex composed of three identical subunits, one in which each subunit is hydrogen bonded to the other two subunits. In this case, there is an average of 1.0 hydrogen bond per monomer. However, this drops to 0.67 for the corresponding linear trimer. In absolute terms, this advantage is even greater when there are two (2.0 versus 1.33) or three hydrogen bonds (3.0 versus 2.0) between subunits. Under these circumstances (and neglecting entropic factors), one might predict that the cyclic species would be favored. Nevertheless, the enthalpic advantage is dramatically diminished in large multicomponent aggegates [e.g. a 20-mer composed of one hydrogen bond between monomers: cyclic (1.0 bonds/monomer), linear (0.95 bonds/monomer].

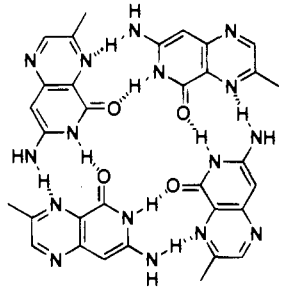
The enthalpy and entropy of complex formation has been used to distinguish between the formation of linear and cyclic aggregates.[23-25] For example, the enthalpy and entropy associated with the tetramerization of aniline has been interpreted to be most consistent with that of a cyclic structure.[23,25] In general, however, thermodynamic data is typically not employed to differentiate between the cyclic and linear alternatives. Obviously, the best way to address this issue is via structural information (e.g. X-ray crystallography). However, the anticipated behavior of the complex has also been employed as a basis for structure evaluation. For example, if an internal cavity is generated in a cyclic complex, then this could serve as a simple binding site for guest compounds. Consequently, if a multicomponent complex is able to transport guest compounds from one solvent to another, then this can also be taken as evidence that a cyclic species has formed.

Perhaps it is fitting that one of the first compounds recognized to assemble into a cyclic supramolecular complex is a species found *in vivo*. In the presence of metal ions (e.g. potassium), guanosine monophosphate spontaneously assembles to produce planar rings ("G-quartets") which are themselves stacked in a cylindrical fashion.[26] Each planar subunit is composed of four guanine bases hydrogen bonded as shown in **1**. This structure has been confirmed by a variety of techniques, including X-ray diffraction studies. Interestingly, the G-quartet is thought to have biological significance as well. For example, guanosine-based tetramers appear to play an important structural role in the formation of telomeres,[27] the assembly of a deoxynucleotide aptamer that inhibits thrombin,[28] and the formation of a phosphorothioate nucleotide that inhibits herpes simplex virus.[29]



1

Based upon certain structural similarities between guanine and folic acid, Ciuchi et al. examined whether the latter could also spontaneously assemble to produce higher order aggregates in solution.[30] Indeed, columnar arrays were observed in aqueous solution that proved to resemble to those formed by guanosine monophosphate. Based upon this analogy, the hydrogen-bonding scheme in **2** was proposed.



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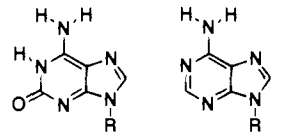
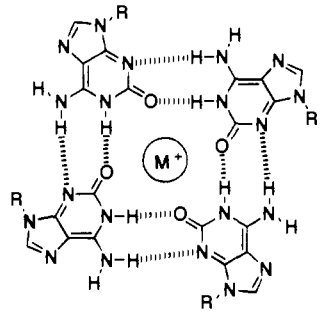
Davis and his colleagues have recently demonstrated that isoguanosine (**3**) forms tetramers in organic solvents.[31] Interestingly, these investigators



3 4

found that the formation of the tetramer **5** is an enthalpy driven process ($\Delta H = -40$ kcal/mol) that exhibits an almost negligible entropic component.

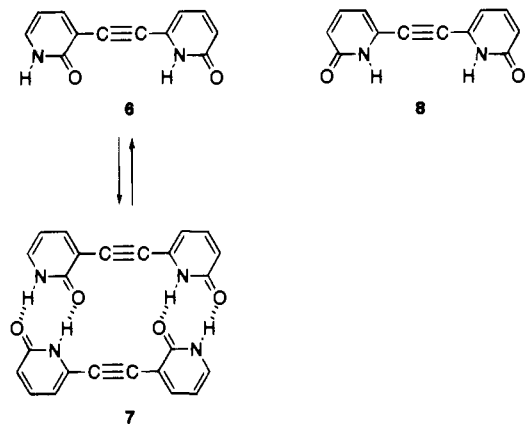


5

Although the tetramer is strongly favored in the presence of K^+, the monomer is the predominant species with Na^+ and Li^+. MM2 calculations suggest that the size of the central cavity of the tetramer is ideal for K^+ coordination. In contrast, adenosine (**4**), which lacks the C-2 carbonyl, is a monomeric species under identical conditions. K^+ not only induces the tetramerization of **4**, but it also drives the formation of higher order structures. NMR titration experiments suggest that a complex containing a 1:8 ratio of K^+/isoguanosine is generated under these circumstances. Davis and his colleagues propose that a sandwich complex has formed, one in which two tetramers are stacked about a single K^+ ion.

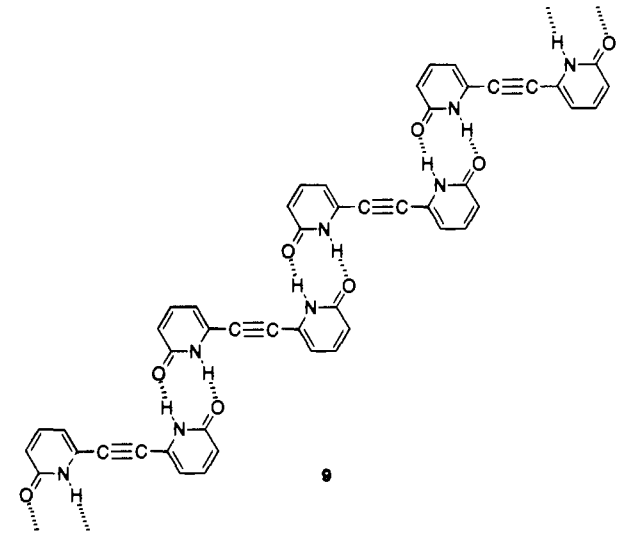
In the examples cited above, it is evident that the lactam functionality is absolutely critical for self-recognition. Obviously, an amide moiety can serve as both a hydrogen-bond donor and acceptor. Consequently, it is not too surprising that several groups have utilized the lactam motif to create compounds that can spontaneously assemble into multimeric complexes.

Wuest and his colleagues have synthesized dipyridones that are linked by different types of spacer units.[32,33] For example, compound **6** was designed to produce the dimer **7**.[32] In contrast, since **8** is not



6 8 7

"self-complementary", it should polymerize to a high molecular weight species instead (**9**). Vapor pressure



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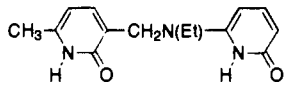
osmometry was employed to investigate the aggregation behavior of these compounds in solution. Since hydrogen bonds are the key elements responsible for association, it is reasonable to expect that any solvent that disrupts these interactions should likewise disrupt the ability of either **6** or **8** to aggregate. Indeed, both **6** and **8** exist only as monomers in the protic solvent methanol. In contrast, **6** produces the dimeric species in $CHCl_3$ (>90% dimeric in the submillimolar range). Interestingly, even at 1 mM,

compound **8** is predominantly monomeric. X-ray crystallographic studies were also performed on compounds **6** and **8**. As predicted, **6** forms a discrete dimer (**7**), whereas **8** produces a planar polymer (**9**). Clearly, in both the solid state as well as in solution, minor differences in subunit structure can have a profound effect on aggregation behavior. More recently, these investigators have shown that analogous behavior is observed with a dipyridone that contains an amine linkage, a functional group significantly more flexible than the acetylenic moiety.[33] In the case of a saturated $CHCl_3$ solution of the self-complementary dipyridone **10**, vapor pressure osmometry experiments demonstrate that this species is predominantly dimeric. In addition, NMR experiments reveal an nOe though-space interaction between the methyl group at C-6 and the proton at C-3. This implies that the dimer has formed in an antiparallel fashion and exists as structure **12** and/or **13** *in solution*. In contrast to the solution behavior of **10**, **11** apparently produces the expected short linear oligomers.



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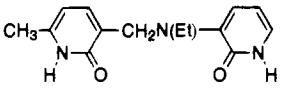

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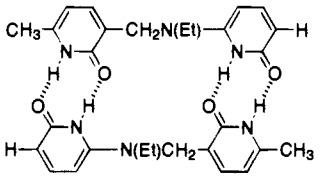

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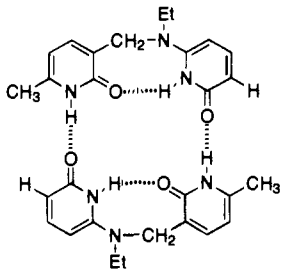
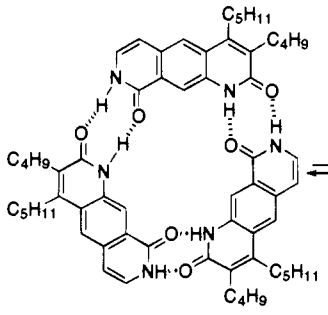


13

Zimmerman and his colleagues have also employed the amide functional group to create cyclic aggregates.[34] In this case, they designed the quinoline **14** to trimerize to the circular array **15**. The ability of **14** to aggregate was investigated via vapor pressure osmometry and ^1H NMR. The molecular weight of the complex in solution was found to be 942 ± 80 g/mol, which is consistent for a trimeric species.



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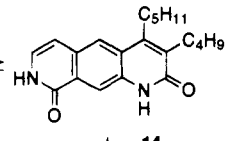

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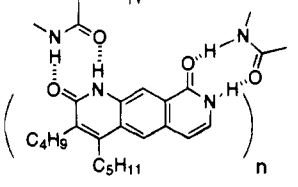
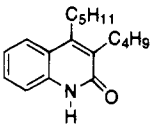


16

However, this result does not discriminate between a cyclic array and a mixture of linear aggregates (**16**). Additional support for the cyclic trimeric species was obtained from an NMR titration study. The resultant data was fit to various models (i.e. dimer, trimer, tetramer) via the Saunders–Hyne method[35] and appears to be most consistent with the presence of an aggregate composed of three subunits. The trimerization constant for **14** is 20 000 M^{-2}. In addition, compounds **17** and **18** were examined for their ability to self-associate. In contrast to **14**, the aggregation constants for **17** and **18** are negligible.



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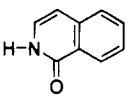
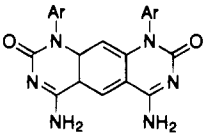


18

Although **14** can self-associate in a cooperative fashion to form the cyclic species, **17** and **18** cannot. These results, taken together, imply the formation of the circular array **15**. This study very clearly illustrates the problems associated with solution structure determination of self-assembling complexes. Although organic chemists will continue to be confronted with these difficulties for the foreseeable future, these investigators have shown that alternate solution structures can be ruled out through the use of "impaired" subunits, species that can participate in some, but not all, of the desired interactions.

In keeping with the amide functionality motif, Lehn and his colleagues have synthesized the heterocycles **19** (hydrogen bond **a**cceptor/**a**cceptor/**d**onor) and **20** (hydrogen bond **d**onor/**d**onor/**a**cceptor).[36] Both species contain identical hydrogen-bonding arrays of opposite sides of the molecule. Although self-assembly studies have not yet been reported, the authors propose that an equimolar mixture of these compounds should assemble to form the disk-like structure **21**.



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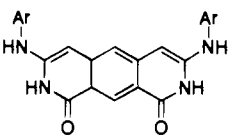

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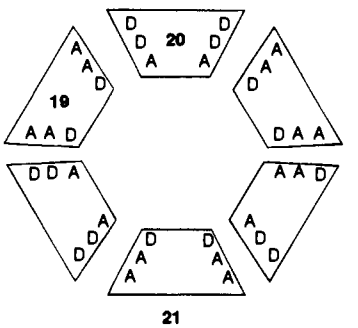
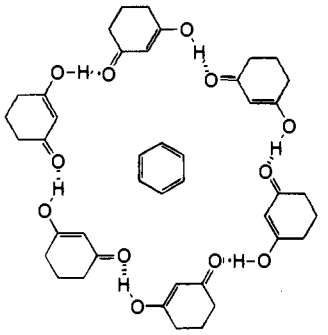


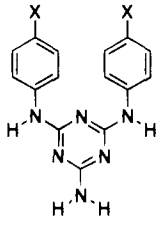
21

Etter and her colleagues have shown that the relatively simple compound, 1,3-hexanedione, forms a cyclic hexamer (**22**) host–guest complex with benzene (in the solid state).[37] X-ray crystallography revealed that the hydrogen-bond stereochemistry is syn–anti.



22

Three approaches have been utilized to construct cyclic aggregates that employ, as one of the components, barbituric acid (or the closely related cyanuric acid). Whitesides and his colleagues have reported that derivatives of barbituric acid/cyanuric acid and melamine will assemble into an astonishing variety of structural motifs.[38] Specifically, these investigators have proposed that the solid-state structure of an aggregate of **23** and **24** is dependent



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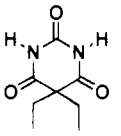
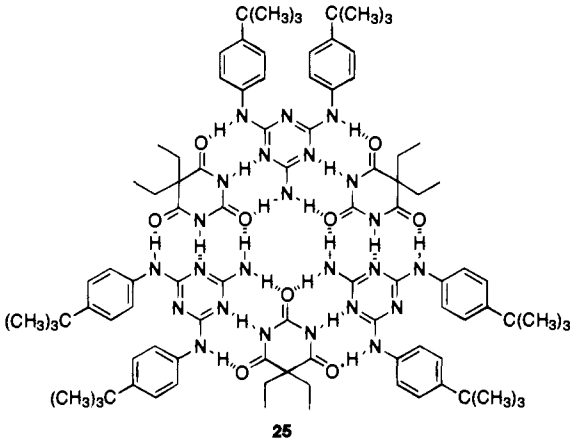


24

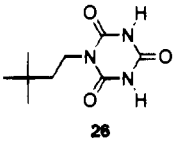
upon steric interactions. For example, a cyclic hexamer **25** is formed in the case where the para substituent is a *tert*-butyl group (i.e. X = *tert*-butyl in **23**). Substituents smaller than the *tert*-butyl



25

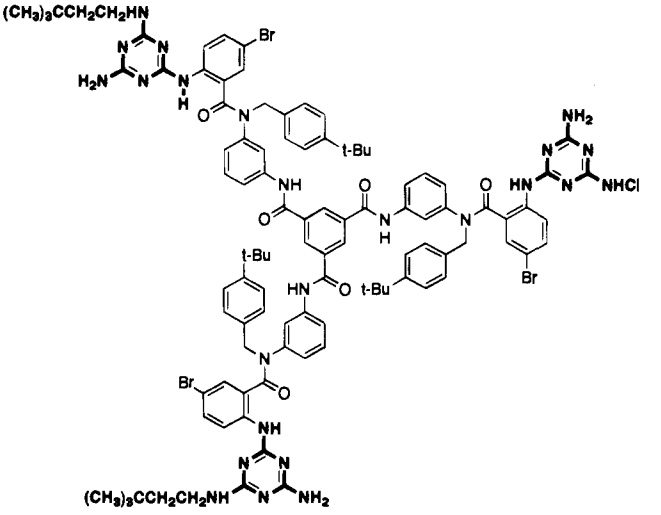
moiety lead to two-dimensional infinite arrays, such as linear and crinkled tapes. These species will be described in section V.B. For the present, it is simply important to note that minor variations in monomer structure can have a profound effect on the architecture of self-assembling systems.

Whitesides and his colleagues developed a second approach to construct cyclic arrays, one which employs the barbituric acid analog **26** (i.e. cyanuric acid). However, this strategy differs from that described above in that its relies upon the concept of preorganization.[39-45] Seto and Whitesides prepared



26

27, which contains three subunits of melamine that are covalently attached to a central hub.[39,41] Since



27

these melamine subunits are held in close proximity to one another and their geometrical relationship is cyclic in nature, it is easy to see how the formation of a cyclic array will be favored upon introduction of **26**. The anticipated interaction between these subunits is shown in a schematic fashion in Figure 3.

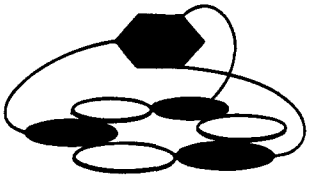


Figure 3. A preorganized cyclic array. Adapted from ref 39.

This complex was found to exhibit a 1:3 stoichiometry via NMR titration and the overall structure proved to be consistent with the results of NOESY experiments. Vapor pressure osmometry reveals a molecular weight also consistent with the proposed structure. Interestingly, the complex is stable enough to be chromatographed (reverse-phase TLC; 5% isopropyl alcohol in CH_2Cl_2). Seto and Whitesides have also prepared doubly (shown schematically in Figure 4 as a 2 + 3 complex)[40,42-44] and triply (shown

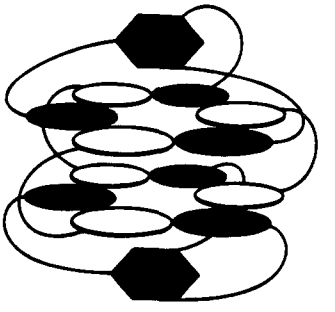


Figure 4. A preorganized doubly stacked cyclic array. Adapted from ref 40.

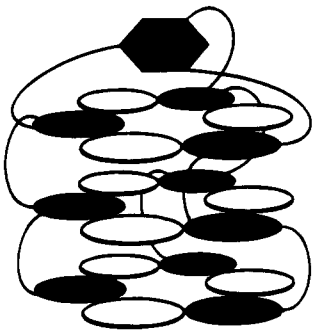
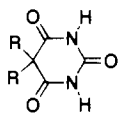


Figure 5. A preorganized triply stacked cyclic array. Adapted from ref 45.

in Figure 5, one of 16 possible conformational isomers)[45] stacked cyclic arrays.

In contrast to the steric bulk and preorganization approach to generate cyclic complexes, Lehn and his co-workers designed a set of subunits that were predicted to assemble in a 3:3 hexagonal fashion.[46] The idea is based upon early work performed with subunits **28** and **29**.[47] At the time, it seemed likely



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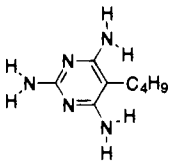
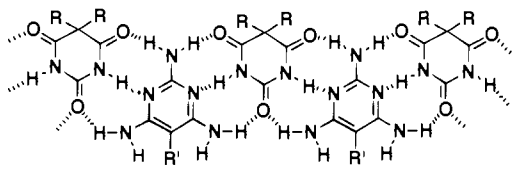


29

that these species could interact to generate one or both of two structural forms: the infinite linear ribbon **30** or the cyclic hexamer **31**. X-ray crystal-



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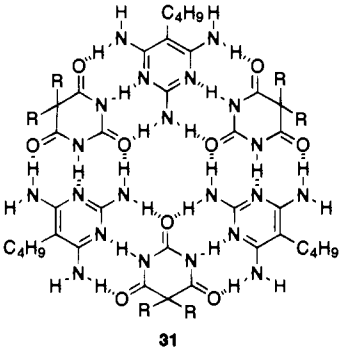
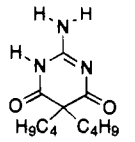


31

lography reveals that the former structure is generated. In this case, each subunit is engaged in a total of six hydrogen bonds. This result is intriguing in light of the close structural resemblance between the characterized cyclic array **25** of Whitesides[38] and the hypothetical species **31**. The subunits contained within these structures do differ in one tantalizing sense, namely the butyl groups of **31** are replaced by sterically demanding *tert*-butyl aryl groups in **25**. Is this dissimilarity the critical molecular feature responsible for the tendency to form cyclic versus linear aggregates? Interestingly, Whitesides has proposed that it is the steric bulk associated with **25** that disrupts linear structures and, as a consequence, favors the cyclic species.

Lehn and his co-workers subsequently employed a dramatically different approach to create cyclic arrays.[46] Although not yet successful (due to unanticipated difficulties described below), the strategy is especially clever. These investigators have noted that both subunits **28** and **29** have two faces that can engage in hydrogen bonding. These faces are symmetric. In the case of **28**, a symmetrical hydrogen bonding acceptor–donor–acceptor pattern is evident. For **29**, it is the equally symmetric donor–acceptor–donor pattern. In short, **28** and **29** can associate with each other from two faces, one of which leads to a linear structure (**30**) and the other to the hypothetical cyclic species (**31**). In contrast, this symmetry is destroyed in subunits **32** and **33**. Con-



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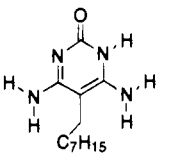
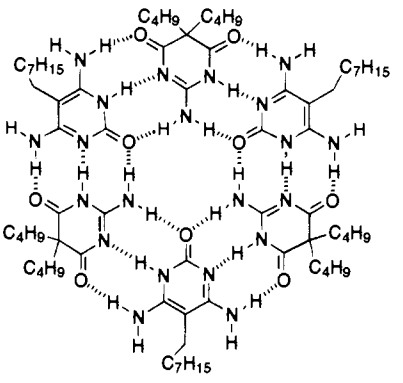


33

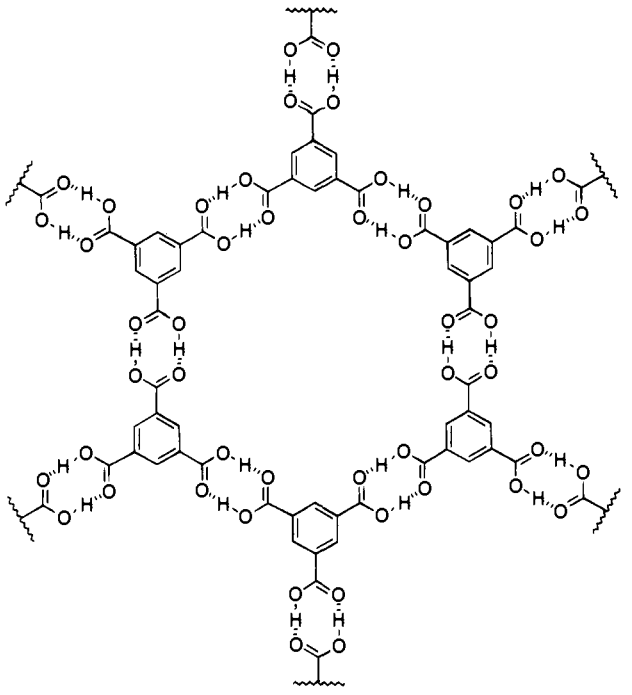
sequently, these species should only associate in an unambiguous fashion to generate the cyclic complex **34**. Unfortunately, when a DMF solution of these



34

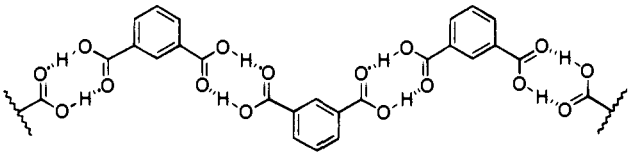
two compounds was heated and subsequently cooled, only crystals containing the less soluble compound **33** were formed. The structure of the complex containing only **33** will be described in the section devoted to two-dimensional infinite arrays.

Like their amide counterparts, carboxylic acids exhibit a strong propensity for dimer formation in aprotic solvents. Consequently, it is not at all surprising that the carboxylic acid functional group has also been employed to drive the assembly of various supramolecular complexes. Indeed, Duchamp and Marsh demonstrated in 1969 that trimesic acid (1,3,5-benzenetricarboxylic acid) self-assembles into a hydrogen-bonded sheet composed of repeating hexagonal arrays.[48] The cyclic motif **35** is plainly evident within this array. Indeed, one might anticipate that isophthalic acid would generate a cyclic hexameric species. However, X-ray crystal-



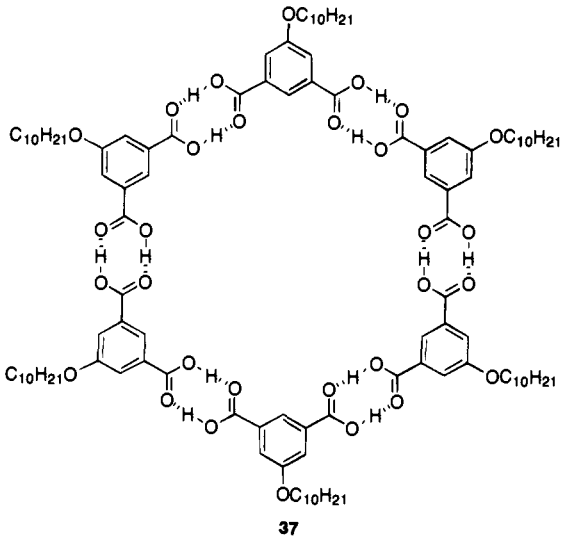
35

lographic analysis revealed only a ribbonlike structure **36** in the solid state.[49]



36

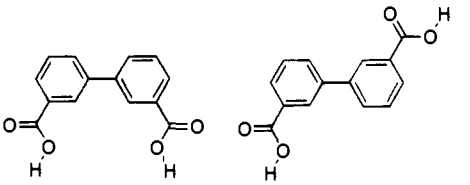
Since these initial observations, Hamilton and his colleagues have found that an appropriately modified isophthalic acid subunit can be induced to form a cyclic array.[50] These investigators reasoned that a bulky substituent at C-5 of isophthalic acid might disrupt the linear packing motif in the solid state. Indeed, X-ray structural analysis confirm the formation of the desired species **37**. In addition,



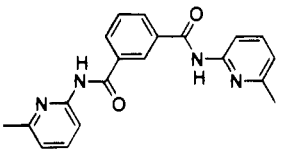
37

vapor pressure osmometry experiments establish the presence of this hexameric aggregate in solution as well.

Hamilton has also employed a hydrogen bond-driven approach to create a cyclic aggregate whose structure is somewhat reminiscent of a figure eight.[51] Biphenyl-3,3'-dicarboxylic acid can exist in two discrete conformational states, the syn (**38**) and anti (**39**) forms. The syn confomer and the diamide **40** should initially generate species **41**. Since the



38 39



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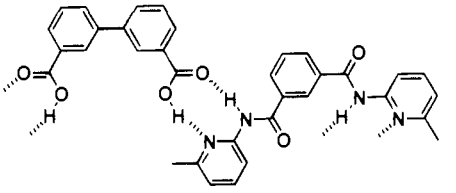
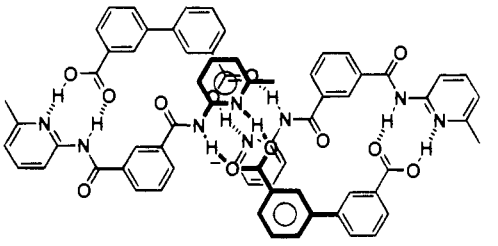


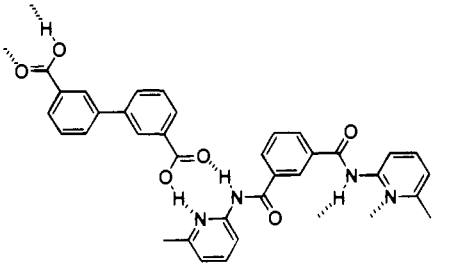
41

carboxylic acid moiety and *N*-pyridyl amide moiety are both oriented in the same direction, this 1:1 complex should subsequently dimerize to the cyclic species **42**. Both solution (vapor pressure osmom-



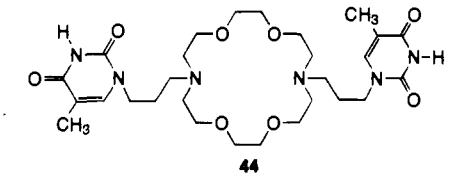
42

etry, chromatography, and NMR) and solid-state (X-ray crystallography) experiments establish the structure of the predicted 2 + 2 complex. The anti conformer **39** can also interact with **40** via hydrogen bonding, but in this case the carboxylic acid and *N*-pyridyl amide functionalities are not arranged in the same direction. Under these circumstances, one might expect the formation of a polymeric aggregate (**43**).



43

The circular arrays described to this point are relatively flat, disk-like structures. However, it is also possible to envision a molecule, or molecules, that cyclize to generate complexes with interior cavities. One of the earliest examples of this type of supramolecular complex was reported by Gokel and his colleagues.[52,53] These investigators found that the crown ethers **44** and **45** base pair in $CHCl_3$ to create a molecular box (**46**; $K_a = 885\ M^{-1}$). NMR chemical



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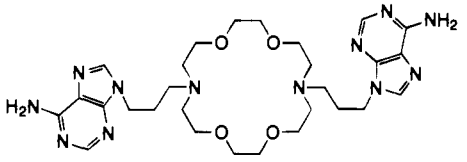

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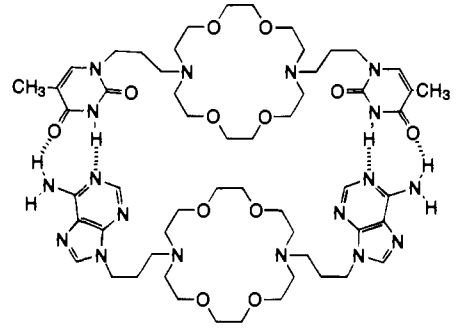
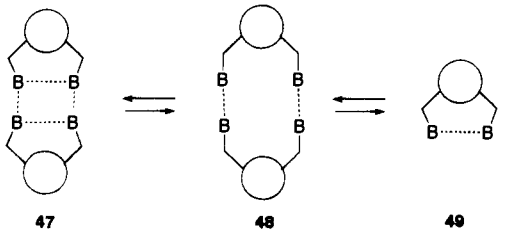


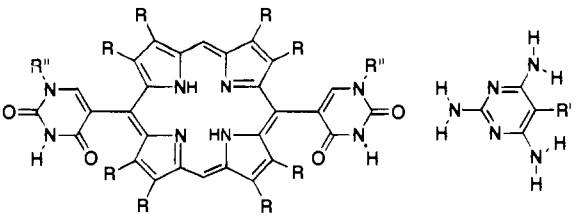
46

shift data reveal that both Watson–Crick and Hoogsteen hydrogen bonding patterns are present. In addition, the broadened NMR signals were interpreted to be indicative of the presence of more than one aggregate form. A few of these possibilities are illustrated below (**47**–**49**):



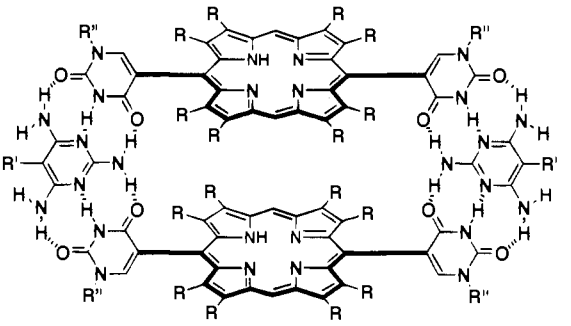
47 **48** **49**

Lehn and his colleagues have described the assembly of a bisporphyrin-containing supramolecular cage.[54] The porphyrin subunit contains two alkyluracil groups (**50**). These uracil groups possess a hydrogen-bond acceptor–donor–acceptor motif designed to coordinate the triaminopyrimidine derivative **51**, which is a hydrogen-bond donor–acceptor–donor. However, since there are two possible atropisomers of the porphyrin, there are two possible structures that can be generated upon addition of the pyrimidine component. Although the syn species should furnish a cagelike complex **52**, the

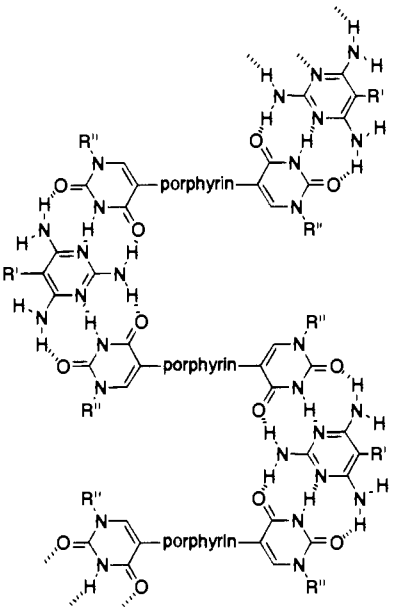


50 **51**

corresponding anti isomer should produce an infinite array (**53**). As expected, the NMR spectrum (in



52

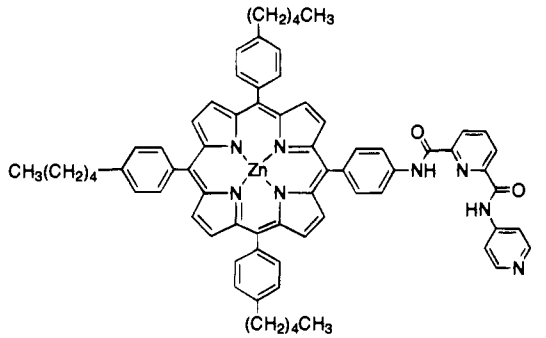


53

CD_2Cl_2) of **50** is consistent with a mixture of the syn and anti atropisomers. Upon addition of the pyrimidine, a shift in the NH signal associated with the uracil moiety occurred, which is indicative of hydrogen bonding. Interestingly, after 3 days, the anti isomer decreased to less than 20% of the total, suggesting that the assembly of the cage may be responsible for shifting the syn–anti equilibrium. Indeed, electrospray mass spectrometry reveals the presence of an ion whose mass-to-charge ratio is consistent with **52**. Vapor pressure osmometry experiments (CH_2Cl_2) provide additional support for the presence of the 2:2 cage complex. In addition, apparently only uncomplexed components are present under solvent conditions (i.e. 10% ethanol/0.1% HCl in CH_2Cl_2 or DMF at 90 °C) that should disrupt the

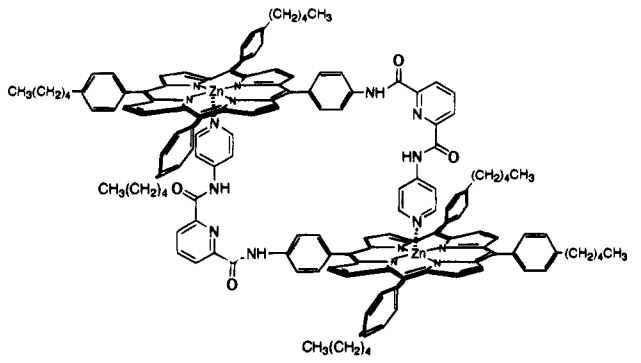
proposed hydrogen-bonding pattern. The latter is a particularly useful control, because it demonstrates that the proposed key noncovalent interactions are, in fact, critical for self-assembly. Finally, two additional sets of experiments were performed that helped to establish the three-dimensional structure of **52**. First, fluorescence studies suggest that the two porphyrin components are arranged in a cofacial fashion, the expected result for the cage-like structure **52**. Second, 4,4′-bipyridine was found to coordinate more strongly to the Zn−porphyrin supramolecular complex than to simple Zn−porphyrins alone. This implies that the two metalloporphyrin subunits are not only oriented in a cofacial fashion, but the distance between these subunits is appropriate for coordination of bipyridine.

A second dimeric porphyrin-containing species has been prepared via self-assembly, but in a fashion that is decidedly different from that described above.[55] Hunter and Sarson constructed a cyclic host by taking advantage of the natural tendency of pyridine to form complexes with the metal ion of metalloporphyrins. Zinc−porphyrins, such as **54**, can coordinate a single pyridine ligand to furnish a five-coordinate species. Spectroscopic data are concen-



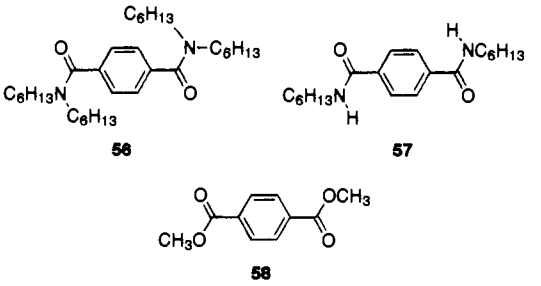
54

tration independent in the range from 10^{-7} to 10^{-2} M, implying no change in aggregation state in this concentration range. In addition, vapor pressure osmometry indicates that **54** exists as a dimer (**55**).



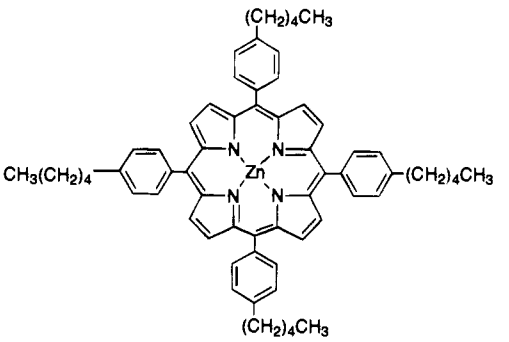
55

The latter was found to bind the guest compounds **56** (1400 M^{-1}), **57** (>1400 M^{-1}), and **58** (40 M^{-1}) in $CHCl_3$. These investigators point out that the four amide moieties of **55** can be directed into the host's



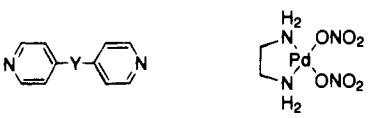
56 **57** **58**

cavity. Upon guest complexation, the amide proton signals are shifted downfield, implying that the amide functionalities are involved in hydrogen-bonding interactions, possibly with the carbonyl groups of the guest. In contrast to these observations, little binding was noted with the Zn−porphyrin **59**, a species that cannot dimerize.



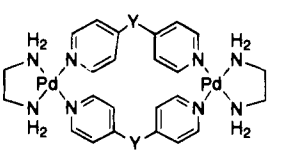
59

Fujita, Ogura, and their colleagues have described the palladium (and platinum)-assisted assembly of binding sites.[56-58] The bipyridine species **60**, in the presence of the ethylenediamine−palladium complex **61**, is rapidly converted to the cyclophanes **62**−**64**.



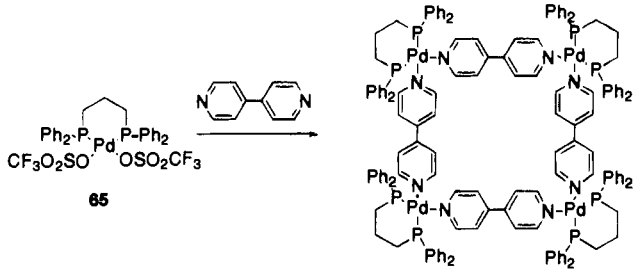
60 **61**

The structure of these compounds was confirmed by NMR, elemental analysis, mass spectrometry, and crystallographic analysis (crystal structure for **63**, but not for **62** or **64**). **62** and **64** have been found to bind a variety of aromatic guests in aqueous solution. Interestingly, the tetrafluorobenzene-containing host (**64**) exhibits a selectivity for electron-rich guests.



	Y
62	
63	- CH_2CH_2 -
64	- CH_2 - (para)C_6F_4 - CH_2 -

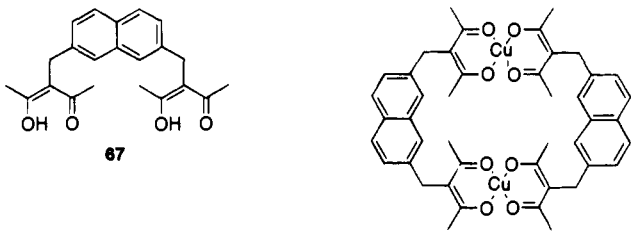
Recently, Stang and Cao have described an intriguing variation on the Fujita−Ogura protocol.[59] The Utah group employed the metal complex **65** to drive the self-assembly of **66**. The lipophilic bisphosphine ligand generates the desired cyclophane in CH_2Cl_2. However, this species (unlike those of the



65 66

Japanese group) is soluble in solvents such as CH_2Cl_2 and $CHCl_3$. Stang and his colleagues have recently utilized several different organic ligands to generate a wide variety of structurally dissimilar molecular boxes, including a species that contains a deeper cavity than that of **66**.[60] Furthermore, these investigators have shown that, in addition to 4:4 complexes, 2:2 macrocyclic squares can be generated as well.[61,62]

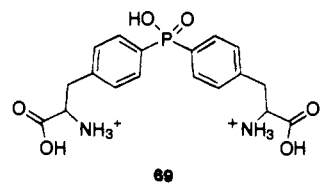
Maverick and his colleagues have also employed a metal ion-assisted approach to create hydrophobic binding sites, but in a fashion that markedly differs from the bipyridine-based system of Fujita, Ogura, and Stang.[63-65] Treatment of the bis-dione **67** with an excess of $Cu(NH_3)_4^{2+}$ in $CHCl_3$ furnished the Cu-containing complex **68**. This species is soluble in



67 68

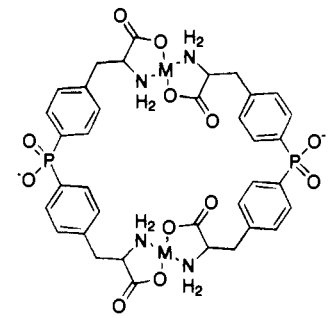
$CHCl_3$ and has been shown to bind such guest molecules as Dabco and 2,5-dimethylpyrazine. Binding constants for a variety of guests have been determined, but are generally less than 1 M^{-1} [with the exception of Dabco (220 M^{-1}) and 2-aminopyrazine (93 M^{-1})]. The mode of binding is apparently via coordination of the amine site on the guest with one or both of the copper moieties of the host.

Schwabacher and co-workers have likewise generated cyclic hosts via a metal ion-assisted approach.[66] These investigators positioned a phosphinic acid functionality outside of the nascent hydrophobic binding site to render the complex water-soluble. Indeed, the phosphinic acid-containing species **69**, in the presence of Co(II) or Ni(II), was found to transport pyrene from one isooctane layer, through water, into a second isooctane layer [i.e. a U-tube experiment, see ref 67]. A Job plot demonstrates that



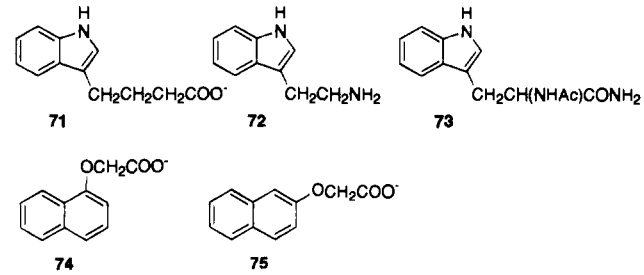
69

the species responsible for pyrene transport is a 1:1 ratio of metal ion and phosphinic acid. In addition, as one might anticipate for a cavity of a specific size and shape, not all aromatic species are transported with equal efficacy. For example, pyrene is transported an order of magnitude more rapidly than biphenyl or *p*-iodotoluene. On the basis of these observations, Schwabacher proposes that it is the 2:2 species **70** that is responsible for active transport of various aromatic guest compounds.



70

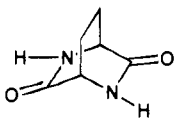
More recently, Lee and Schwabacher found that the hydrophobic pocket and the diacid-bound metal ion can act in concert to coordinate guests.[66] In spite of the anionic nature of the receptor, these investigators observed enhanced binding of appropriately substituted, *negatively charged*, aromatic compounds. For instance, **70** binds the indole **71** (645 M^{-1}) an order of magnitude more strongly than either **72** or **73**. The geometry of the guest is apparently important as well, since the cavity-containing species **70** coordinates **74** (6060 M^{-1}) 67 times more tightly than its isomeric counterpart **75**. These investigators



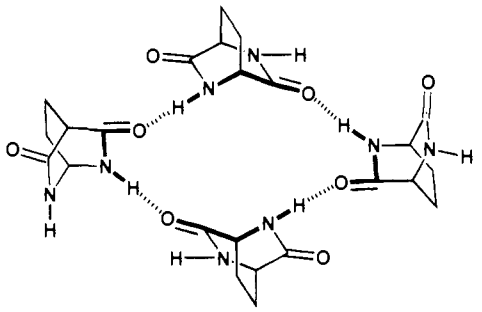
71 72 73 74 75

propose that the hydrophobic portion of the guest compound is bound to the lipophilic cavity of the host while, simultaneously, the negatively charged carboxylate interacts with one of the two coordinated metal ions. NMR data is offered in support of their model.

The Lehn group has recently shown that the enantiomeric purity of monomeric subunits can have a profound influence on the type of supramolecular architecture generated.[69] The bis-lactam **76** was prepared as a racemic mixture and then subsequently resolved into the individual enantiomers. The (−) isomer produces the tetrameric species **77**. Interestingly, these investigators had initially

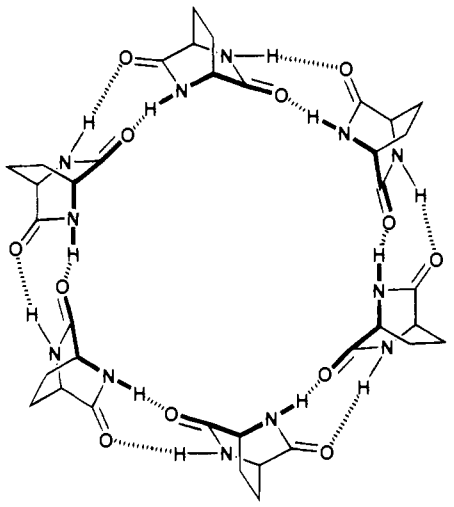


76



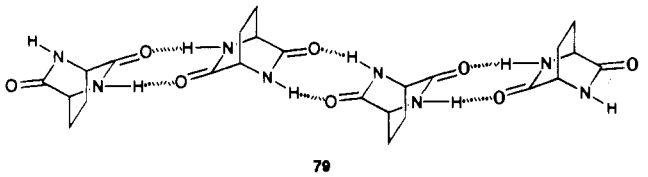
77

predicted that enantiomerically pure bis-lactam should produce the hexameric complex **78**. The racemate,



78

in contrast, was found to assemble into a sinuous string of alternating (+) and (−) subunits held in place via hydrogen bonds (**79**). The solid-state structure of this complex was elucidated by X-ray crystallography. As will be noted in the subsequent section, these results highlight a recurring theme. Namely, minor differences in subunit structure can have dramatic architectual consequences for the final product.

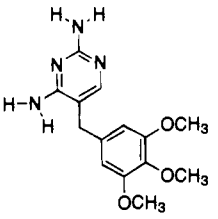


79

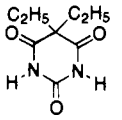
B. Infinite Two-Dimensional Arrays

A variety of planar supramolecular complexes have been reported that lack defined boundaries. These species have been described as tapes, chains, ribbons, strands, and sheets. Several complexes that adhere to this structural motif have been previously alluded to (i.e. **9**, **30**, **36**, **43**, **53**, and **79**). In these instances, slight variations in subunit structure have a profound impact on whether the final complex will assume an infinite two-dimensional array or a cyclic structure. Several additional examples of the former are presented in this section.

A short note appeared in 1982 that described the X-ray elucidated structure of a complex containing the diaminopyrimidine **80** and diethylbarbituric acid (**81**).[70] Clearly, the barbituric acid derivative can

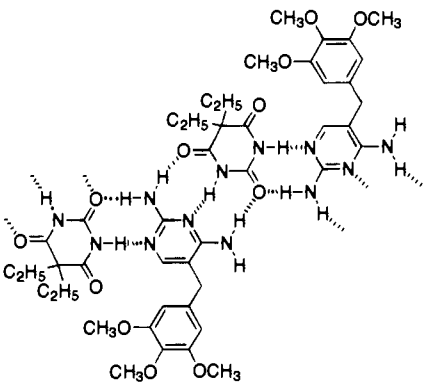


80



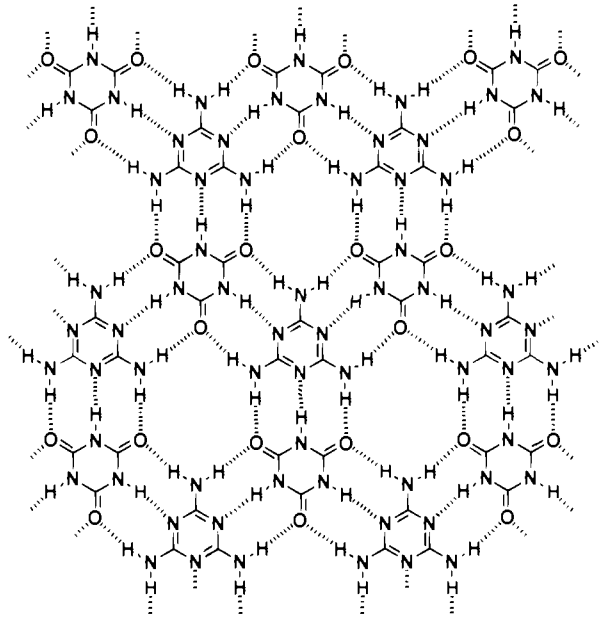
81

serve as a hydrogen-bond acceptor−donor−acceptor on both faces and the pyrimidine can act as the complementary donor−acceptor−donor on one face and as a donor−acceptor on the other. These two species have the potential to not only interact with one another, but to do so to form an infinite chain. Indeed, the polymeric complex **82** forms in the presence of **80** and **81**. Although this study is particularly noteworthy, due to its relevance to the subsequent work of Whitesides and Lehn, it is important to note that it is by no means the first example of an infinite two-dimensional array containing two different subunits. The interested reader is referred to a 1972 paper by Voet and the references cited therein.[71]



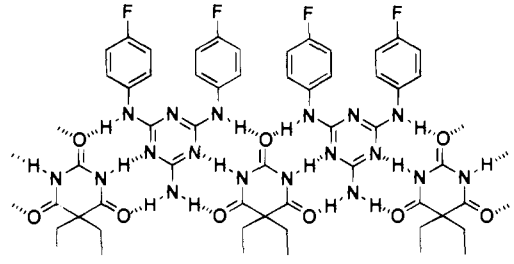
82

As noted in section V.A, Whitesides and his colleagues have employed melamine and cyanuric acid (or barbituric acid) to create a number of different supramolecular structures.[38-45,72-76] The hydrogen-bond network that is present in the melamine/cyanuric acid complex is delineated in **83**.[77] These subunits generate a flat lattice in organic solvents (e.g. $CHCl_3$) in which each component participates in a total of nine hydrogen bonds. One can readily detect, within this planar sheet, a cyclic array. Indeed, appropriately derivatized subunits generate the cyclic species **25**. One can also easily discern both linear and crinkled tapes buried within **83**. Once again, carefully designed monomers have been prepared that specifically lead to the formation of an undulating string of alternating subunits. Whitesides and his colleagues have argued that it is possible to direct the synthesis of any one of these three structural motifs via steric control. For



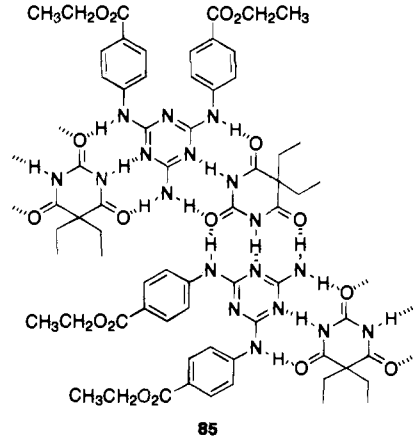
83

example, melamine derivatives containing relatively small para substituents (X = F, Cl, Br, I, CH_3), generate a linear tape (**84**).[73] In contrast, when the



84

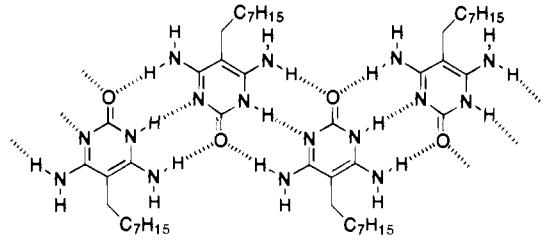
substituent is an ethyl ester, the product assumes a crinkled tape structure (**85**).[38] This may be due to



85

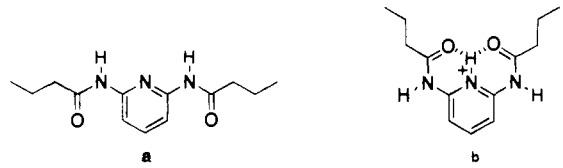
steric interactions between the ethyl ester moieties on adjacent melamines in the linear structure, interactions that are apparently alleviated in the crinkled motif.

Almost simultaneously, Lehn and his colleagues described a self-assembling system closely related to that of the Whitesides group.[47] In this case, the barbituric acid **28** was employed to coordinate the triaminopyrimidine derivative **29** (instead of melamine). These species interact to generate the linear entity **30**. In an attempt to create a cyclic species, subunits **32** and **33** were prepared. Unfortunately, only crystals containing compound **33** were obtained. The hydrogen-bonded ribbon-like species **86** is produced by **33**.



86

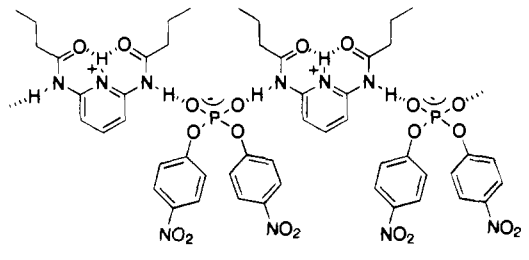
The relationship between functional group orientation in the monomer and the structure of the multicomponent complex has been investigated with the deceptively simple compound **87**.[78] In the conformation exhibited in **a**, the hydrogen bond-accepting pyridine nitrogen and the hydrogen bond-donating amide NH groups are all oriented in the same direction. This is the conformation that species



a **b**

87

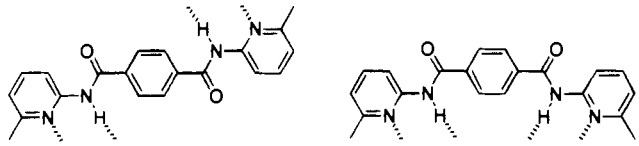
structurally related to **87** occupy in the solid state.[79-83] In contrast, Hamilton predicted that protonation of the ring nitrogen might induce **87** to assume the conformation illustrated in **b**. This subtle shift in structure should control how the pyridine diamide interacts with other compounds. In the case of **a**, the orientation of the hydrogen-bond donor/acceptor groups should limit complex formation, with suitably functionalized guests, to a 1:1 stoichiometry (i.e. **87a** is essentially a simple receptor). In contrast, under acidic conditions the NH groups in **b** should be oriented outward and away from each other, (i.e. **87b** is a self-assembling subunit). Indeed, upon introduction of bis(4-nitrophenyl) hydrogen phosphate to a CH_2Cl_2 solution of 2,6-dibutyramidopyridine, a supramolecular complex is formed (**88**). The resulting ribbon-like species is composed of a 1:1 mixture of alternating anionic and cationic subunits.



88

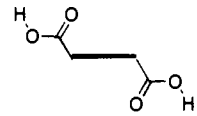
In the majority of complexes described to date, those groups that serve as hydrogen-bond donors are

easily differentiated from those that act as hydrogen-bond acceptors. In instances where a particular functional group (e.g. an amide or carboxylic acid) can act as both, the nature of the supramolecular complex is such that there is no room for structural ambiguity. In contrast, Hamilton and co-workers have investigated the assembly of a complex containing the subunits **89** and **90**.[84] Several bis(aminopyridines) (**89**) were prepared, including species that contained phenyl, naphthyl, biphenyl, and terphenyl spacer units (shown schematically as elipsoids in **91**). In addition, straight chain diacids (**90**) containing four, eight, and 12 carbon spacers were employed in this study as well. Both the bis(aminopyridines) and



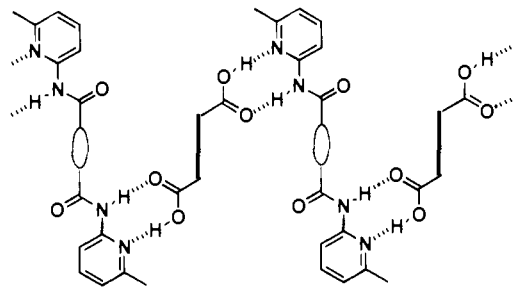
a b

89



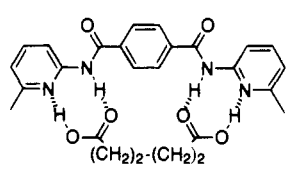
90

the diacids can interact in a homomolecular fashion. However, invoking the premise that the strongest hydrogen-bond donor (i.e. carboxylic acid) should preferentially coordinate to the strongest hydrogen-bond acceptor[85] (i.e. amide), these investigators anticipated the formation of a heteromolecular array in which the subunits are present in a 1:1 stoichiometry (**91**). In addition, it is important to



91

note that the diamide **89** can exist in two possible conformations (anti **a** and syn **b** forms). The consequences are reminiscent of previous work by these investigators; namely, whereas **89a** can serve as a self-assembling subunit, the role of **89b** is limited to that of a mere receptor. With this in mind, X-ray crystallography reveals that a simple dimer (**92**) is generated in the presence of adipic acid and the bis(amidopyridine) **90** (where the linkage group is *p*-phenyl). In this case, the distance between the



92

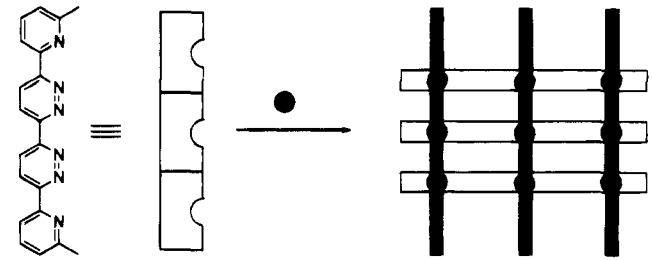


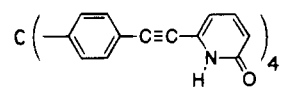
Figure 6. Self-assembly of a 3 × 3 molecular grid. Adapted from ref 87.

amide nitrogen groups in **89b** and the carboxylic acid moieties in adipic acid are comparable. In contrast, 1,12-dodecanedicarboxylic acid produces an infinite sheet of alternating diacid/diamide subunits (**91**). The hydrogen-bond network illustrated in **91** is analogous to that previously observed for homomolecular complexes of secondary diamides.[86] In addition, Hamilton and his colleagues subsequently exploited the preference of carboxylic acids for amides to generate the previously discussed complex **42**.

In contrast to all of the complexes described in this section, Lehn and his colleagues have created a two-dimensional array that contains well-defined borders.[87] 3,6-Di-2-pyridylpyridazine generates a 3 × 3 grid in the presence of Ag(I) ions (Figure 6). The structure of the complex was elucidated by X-ray crystallography.

C. Cylindrical Arrays

We previously noted that guanosine monophosphate forms a tetrameric cyclic array in the presence of metal ions (section V.A).[26] However, these flat disks subsequently associate to form a columnar mesophase. Indeed, an analogous assembly process is observed with folic acid salts as well.[30] There are many reports of cylindrical channel-like architectures generated from relatively simple compounds. Recent examples include complexes derived from crown ether-[88-93] and porphyrin-based subunits.[94] In addition, channel-like networks have been generated with the tetrahedral subunit **93**.[95-96]

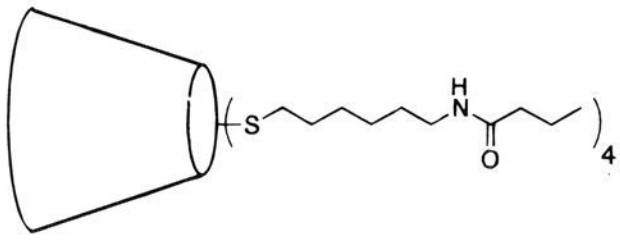


93

However, in this section we will focus on supramolecular complexes that contain an inner channel, one which can actively participate in ion and molecular transport. These species have been designed with function in mind. Gramacidin A is a naturally occurring example of a self-assembling ion channel.[97] The individual subunits of this dimer species are helical in nature. However, the gross structure is that of a tube-like material through which ions can be transported from one end to the other. Several complexes have been designed based upon this structure/function premise.

One of the earliest example of a self-assembling ion channel was reported by Tabushi and his colleagues in 1982.[98] These investigators prepared a β-cyclodextrin derivative containing four lipophilic arms

(this species is illustrated in a schematic fashion in **94**). This compound enhances the rate (by an order



94

of magnitude) of Co^{2+} transport into the interior of an egg lecithin-based liposome compared to that of 18-azacrown-6. The rate of Co^{2+} transport exhibits second-order kinetics with respect to the membrane concentration of **94**. Consequently, a model was proposed in which the two subunits of **94** dimerize to produce a species that can span the length of the lecithin bilayer (Figure 7).

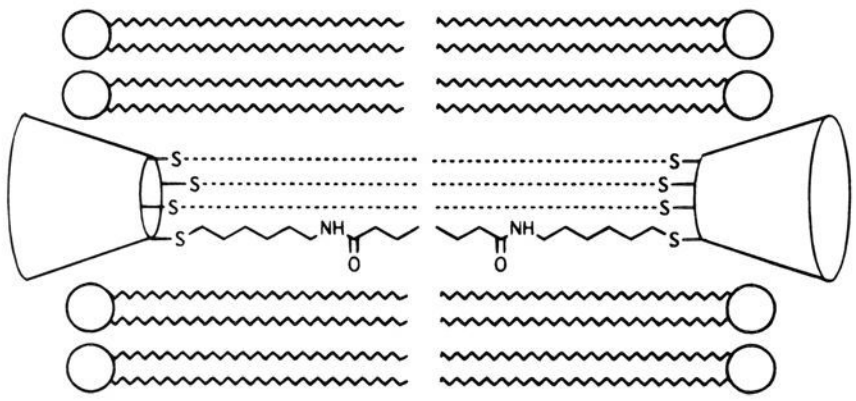
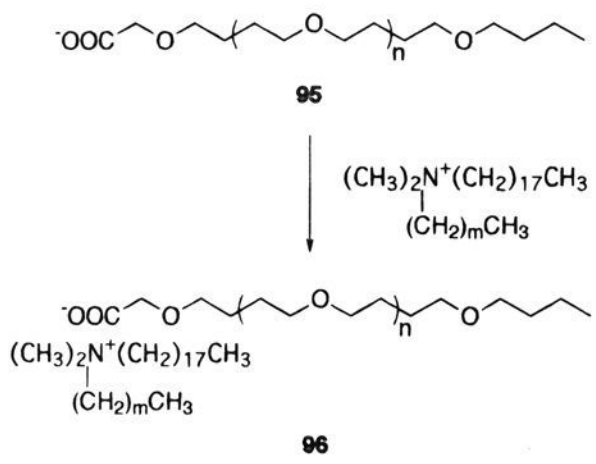


Figure 7. Self-assembly of a cyclodextrin-based ion channel. Adapted from ref 98.

Kobuke et al. have described amphiphilic molecules that, upon insertion into a lipid bilayer, are thought to assemble into a channel-containing species.[99] The polyether **95** was converted to the ammonium carboxylate **96**. The additional hydrophobic alkyl



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96

chains (on the amine) are present in order to promote incorporation of **96** into the lipid membrane. Upon membrane insertion of **96**, stable conductance levels were observed (10−1000 pS) and the channels were found to be cation selective. Perhaps the most intriguing aspect of this work, in terms of self-assembly, is the proposed mechanism by which the synthetic channel is though to form. The following sequence of events are suggested: (a) amphiphile **96** is inserted into the membrane, (b) the individual components in each portion of the bilayer associate, (c) the channels are connected, and (d) ion transport occurs (Figure 8).

A particularly ingenious approach to the creation of ion and molecular channels is based upon cyclic peptide subunits. De Santis and co-workers reasoned

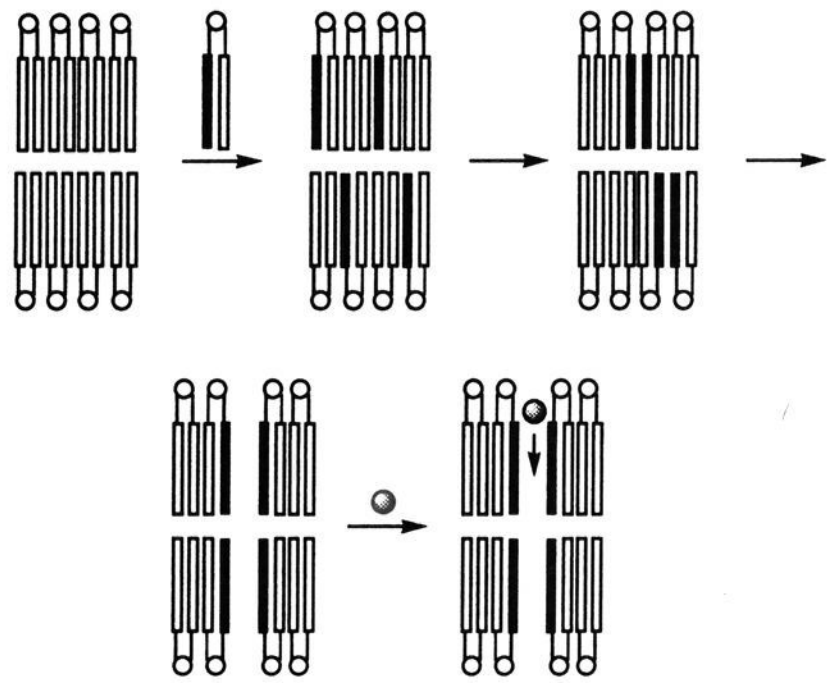


Figure 8. Self-assembly of an ion channel. Adapted from ref 99.

that a cyclic peptide, composed of alternating D- and L-amino acids, would assume a roughly planar structure.[100] In this conformation, the backbone amide groups are expected to adopt an orientation that is approximately orthogonal to the plane of the macrocyclic ring. Furthermore, whereas the carbonyl oxygen on one residue may be "up", the carbonyl functional on the adjacent residues should occupy the opposite orientation (the same analysis applies to the amide NH groups as well). In short, the carboxamide moieties are ideally positioned to favor the formation of an intermolecular hydrogen bonding network between stacked rings (Figure 9). One of the most intriguing aspects of the alternating D/L structural

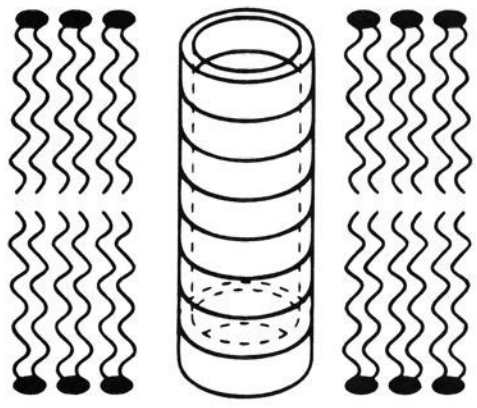


Figure 9. Self-assembly of a peptide-based ion channel. Adapted from ref 105.

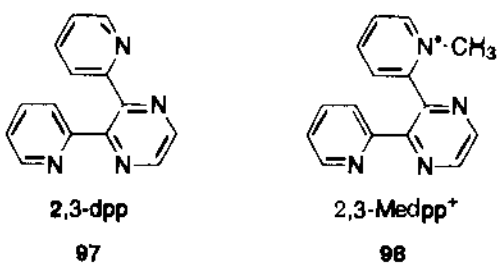
motif is that the side chains are oriented away from the periphery of the ring, thereby establishing a hollow core. As a consequence, pore size is directly related to the number of residues contained within the ring. On the basis of the De Santis model, Tomasic and Lorenzi prepared *cyclo*[-(D-Val-L-Val)2,4], as well as several related species.[101] Unfortunately, these peptides proved to be insoluble in a variety of organic solvents (conditions which would favor ring stacking). One possible explanation for this behavior is that extensive peptide aggregation (in the form of long tubular structures) has already taken place in the solid state. In order to prevent the latter from occuring, the Lorenzi group subsequently prepared the partially N-methylated peptide *cyclo*[-(D-Leu-L-MeLeu-D-Leu-L-MeLeu-D-Leu-L-MeLeu)-].[102] In this case, only one face of the cyclic peptide is available for a hydrogen-bonding interaction with a second peptide. In short, such species should generate

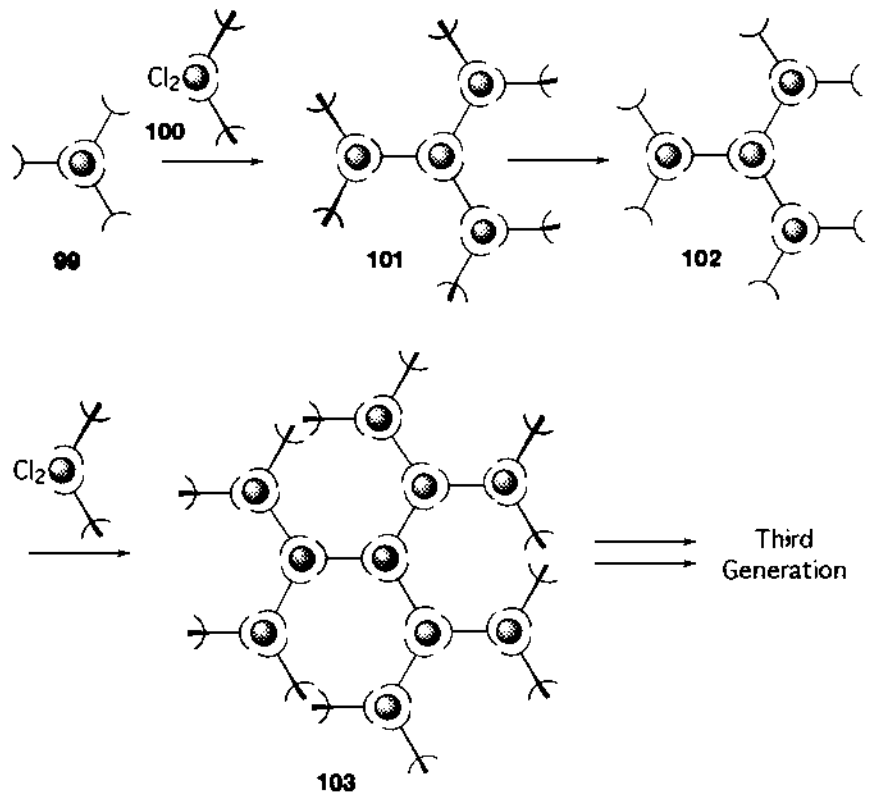
dimeric complexes. Indeed, in CCl_4 as well as CCl_4/C_6D_{12}, dimer formation and ring stacking is observed (vapor pressure osmometry, IR, NMR, and X-ray crystallography[103]).

Just prior to Lorenzi's work with N-methylated cyclic peptides, Ghadiri and his colleagues initiated a research program that has lead to the creation of functioning ion channels.[104] These investigators prepared *cyclo*[-(D-Ala-Glu-D-Ala-Gln)$_2$-]. The glutamic acid was envisioned to play a key role in controlling self-assembly. At neutral pH, this negatively charged residue should electrostatically disfavor self-assembly. Upon acidification, a tubular-like structure should result. Indeed, transmission electron microscopy reveals the formation of closely associated "nanotubes". Electron diffraction patterns are consistent with the presence of stacked rings and infrared spectroscopy supports the involvement of intermolecular hydrogen bonds. One of the most satisfying aspects of this work is that these peptide-based nanotubes actually serve as ion channels.[105] The octapeptide *cyclo*[-(Trp-D-Leu-Trp-D-Leu-Trp-D-Leu-Gln-D-Leu)$_2$-] should contain an inner diameter pore size of 7.5 Å. Not only is the proton transport activity of the assembled cyclic peptides similar to that exhibited by gramacidin A and amphotericin B, but in addition, this synthetic ion channel transports cations three times more rapidly than gramacidin A. In addition, the 7.5 Å diameter channel exhibits a modest selectivity for K^+ (65 pS at 500 mM KCl) versus that of Na^+ (50 pS at 500 mM NaCl). More recently, Ghadiri has demonstrated that a 12-residue cyclic peptide, which should possess a 12 Å pore diameter, also assembles to create nanotubes.[106] Furthermore, a cyclic decapeptide, with a 10 Å internal diameter, is capable of glucose transport, whereas a corresponding octapeptide is not.[107]

D. Dendrimeric Arrays

To the best of our knowledge, there is only one example of a self-assembling dendrimer.[108] Serroni and his colleagues have mixed the elements of conventional synthesis with that of self-assembly to perform an elegant stepwise preparation of redox active dendrimers. Dendrimers, which are also known as cascade molecules or arborols, are commonly synthesized in a stepwise fashion, but through the use standard covalent bonds.[109] As with the preparation of all dendrimers, these investigators initiated their synthesis at what ultimately will be the center of the cascade complex. $[Ru(2,3\text{-dpp})_3]^{2+}$ (**99**) contains three separate sites that can complex the building block compound $[Ru(2,3\text{-Medpp})_2Cl_2]^{2+}$ (**100**). The interaction of these two subunits furnishes a first-generation tetranuclear metal complex (**101**; which is not a planar species, but is shown as such for ease of visualization). This species is incapable of further ruthenium coordination due to the presence of the methylated ring nitrogen. However, upon removal of these methyl groups (Dabco in refluxing DMF), **102** is now able to react with $[Ru(2,3\text{-Medpp})_2Cl_2]^{2+}$ to afford a second-generation dendrimer (**103**). Ultimately, these investigators prepared a complex containing 22 metal ions, with a molecular weight of 10 890 and a predicted size of 5 nm. Compounds **101** and **102** were characterized by NMR, IR, elemental analysis, UV−vis, and luminescence spectroscopy. In addition, electrochemical oxidation of of the third-generation complex yields a peak corresponding to 12 electrons (there are 12 equivalent subunits that lie on the periphery of the complex).



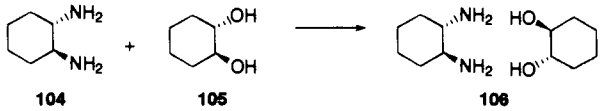


E. Helical Arrays

The self-assembly of helical arrays has attracted a great deal of attention. The DNA double helix has clearly served as an inspiration in this regard. In this case, hydrogen bonds between the individual DNA strands play a key role in maintaining the structural integrity of the dimer. Although hydrogen bonds have been employed in an analogous fashion in the synthetic systems to be described in this section, hydrophobic interactions and metal ion assistance have been extensively utilized to promote the assembly of helical arrays as well.

We will begin our discussion with an inorganic double helix that is so unusual that it bears no resemblance to any of the other complexes described thus far.[110] Zubieta and co-workers found that a mixture of KVO_3, V, H_3PO_4, $CH_3PO(OH)_2$, $(CH_3)_2NH$, and H_2O generates an extraordinary species composed of pentameric vanadium building blocks. The structure of these subunits was determined by single-crystal X-ray diffraction. The building blocks are arranged in a spiral fashion, with four pentamers per spiral. The spirals themselves are intertwined to produce the two strands of the double helix. Even these strands are arranged in an unusual fashion. Loops are formed that protrude from the double helix, and these in turn interweave with other helices to generate the overall three-dimensional structure. The interested reader is referred to the primary reference.[110]

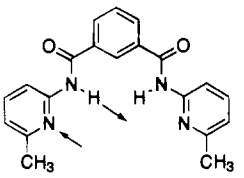
Another unprecedented species has been described by Hanessian and co-workers.[111] *RR*- or *SS-trans*-1,2-diaminocyclohexanes (**104**), when melted with an equimolar amount of *SS-trans*-1,2-cyclohexanediol (**105**), produce two discrete supramolecular complexes. X-ray structure analysis confirms a 1:1



104 105 106

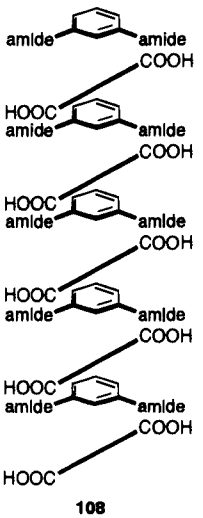
stoichiometry. The diamine and dialcohol interact as shown in **106**. The *SS* diamine produces a 1:1 homochiral complex, whereas its *RR* counterpart generates a heterochiral species. In both cases, these diastereomeric complexes produce supramolecular entities containing an overall triple helical structural motif. The *SS* diamine furnishes a left-handed helix, whereas the *RR* isomer generates a right-handed species. Once again, the interested reader should refer to the original report.[111]

Hamilton and his colleagues have also employed hydrogen bonds to to produce a self-assembling double helical entity.[112] The bispyridine-based compound **107** forms a 1:1 complex with heptanedioic



107

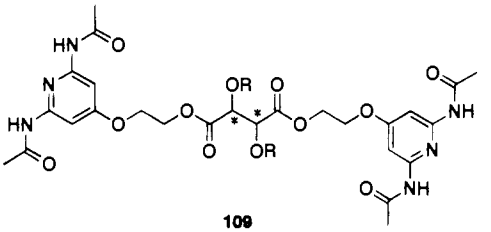
acid. The three-dimensional structure (**108**) was elucidated by X-ray crystallography. The aminopy-



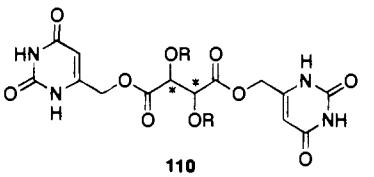
108

ridine units in each monomer (**107**) do not occupy the same plane. One lies 20.5° above the isophthalate ring and the other 9.4° below. Amazingly, these hydrogen bond-linked helices come in pairs, one of which is right handed and the other left handed. NMR solution studies are consistent with the solid-state structure. The pyridine NH protons are shifted downfield, suggesting that they are engaged in hydrogen bonding. Nuclear Overhauser interactions between the β- and γ-CH_2 of the diacid and the aromatic protons of the pyridine unit are present as well. Interestingly, a shorter diacid (glutaric) generates a less-extended helix.

Lehn and his colleagues prepared the tartaric acid-based hydrogen-bond donor–acceptor–donor **109** and acceptor–donor–acceptor **110**.[113] These strands

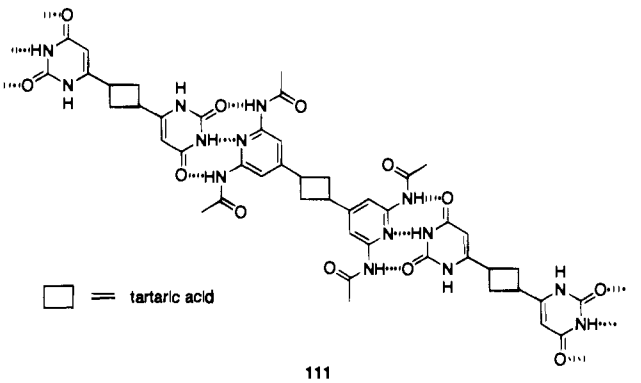


109



110

interact, via complementary uracil/pyridine base pairs,to furnish a helical superstructure (**111**).



111

Equimolar mixtures of the L-tartaric acid-based species **109** and **110** generate right-handed helices, as demonstrated by electron microscopy. The corresponding D-tartaric acid-containing compounds produce left-handed helices. In addition, a mixture of the D isomer of **109** and the L isomer of **110** generates a right-handed helical structure, whereas L-**109** and D-**110** provides a left-handed superstructure. In contrast, no helicity is observed with compounds containing *meso*-tartaric acid. Clearly, the helical chirality is dictated by the tartaric acid component in the uracil-based species **110**. Perhaps, most fascinating, is the structure of the complexes that result when all four D and L compounds are allowed to interact in one flask. These species generate both right- (L,L) and left-handed (D,D) superhelices. Apparently, only configurationally compatible subunits are added to the growing chiral helices. In short, chiral resolution has occurred during the self-assembly process!

A large number of metal ion-promoted helical arrays have been described. Lehn and his colleagues demonstrated that treatment of the quaterpyridine ligand **112** with Cu(I) produces a complex of a 2:2 stoichiometry (Figure 10).[114] In this tetramer, two quaterpyridine units are twisted about each other as a consequence of coordination to the two Cu(I) ions.

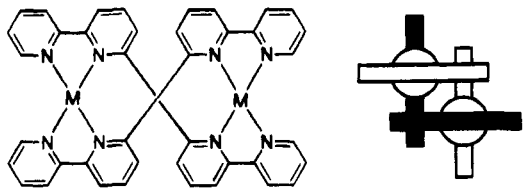
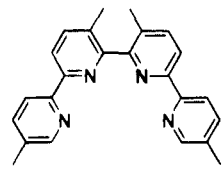
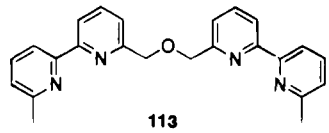


Figure 10. The Cu(II)-driven association of two quaterpyridine units. A schematic is provided on the right. Adapted from ref 114.

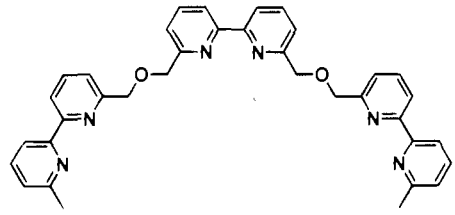


112

In short, the origin of a double helix is latent within the structural framework of the organic ligand. The oligobipyridine moieties **113** and **114** were subsequently prepared.[115] These species possess a $-CH_2-$



113



114

$O-CH_2-$ linkage, a structural feature which was anticipated to provide strain-free coordination of Cu(I) ions. In the presence of Cu(I), **113** and **114** produce the dinuclear $[Cu_2(BP_2)]^{2+}$ and trinuclear $[Cu_3(BP_3)]^{3+}$ complexes, respectively. An X-ray crystal structure analysis of the trinuclear species confirms the formation of the double helix (schematically shown in Figure 11). Solution structure

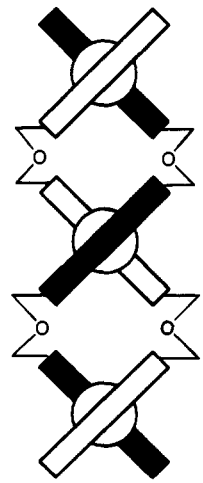
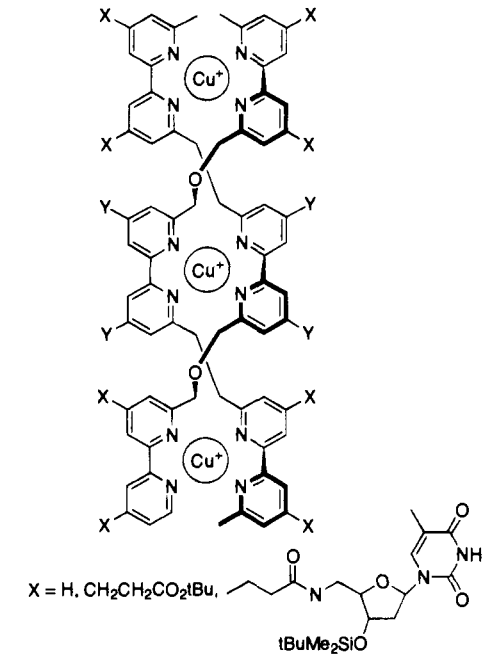


Figure 11. The Cu(II)-driven association of two equivalents of **114**. Adapted from ref 115.

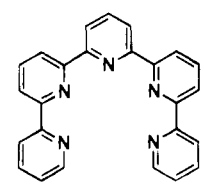
analysis (NMR and UV–visible) of the dinuclear and trinuclear complexes are also consistent with the solid state structure. These investigators have extended this work to include tetra- and pentacopper(I) complexes of poly(bipyridine) strands.[116] In addition, they have recently prepared the corresponding Ag(I) helicates as well.[117] Finally, Lehn and his colleagues have also utilized the helix as a molecular scaffold, upon which substituents can be attached at the periphery (**115**).[118] In this specific



115

case, the thymidine substituents should be able to hydrogen bond to appropriate target compounds. An amusing feature of **115** is that the charged moieties are positioned within the interior of the double helix, whereas the hydrogen bonding species (i.e. the thymine) are located on the periphery of the helix. This structural pattern is reminiscent of Pauling's erroneous structural model for DNA.[119]

Constable and his co-workers have also utilized metal ions to generate double helical complexes of oligopyridines. These investigators have found that two molecules of quinquepyridine **116**, upon exposure to various metal ions, intertwine to produce a double helix.[120–125] They subsequently found that sexi-



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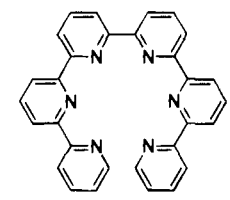
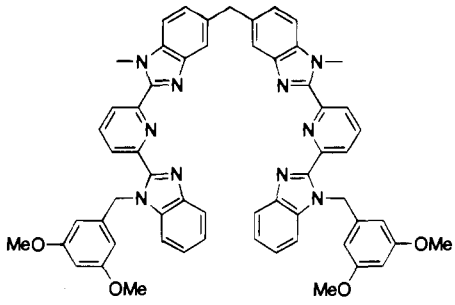


117

pyridine **117** and second-row (as well as third-row) transition metals combine to form double helices.[126] Both Constable[121] and Potts[127–130] have independently demonstrated that mixed-valence dinuclear complexes can be prepared from quinquepyridine as well.

Williams and co-workers have shown that the bis(bidentate) ligand **118** will form a triple helical structure when coordinated to an octahedral



118

metal.[131-134] X-ray crystallographic analysis reveals that three molecules (shown as strands A, B, and C) of **118** are twisted around a helical axis that contains two lanthanide cations (Figure 12). In addition,

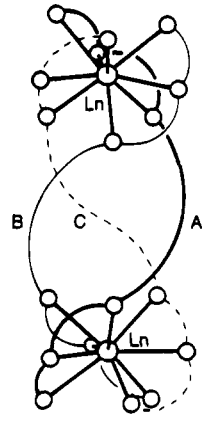
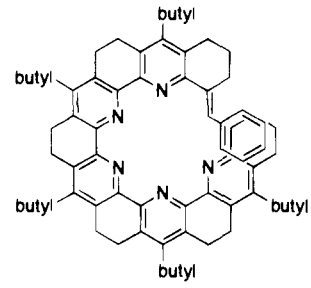


Figure 12. The lanthanide-assisted assembly of a triple helix. Compound **119** is shown schematically as strands (A, B, and C). Adapted from ref 131.

these investigators demonstrated that electrospray mass spectrometry provides an assessment of the absolute stoichiometry of these supramolecular complexes in solution. The molecular ion $[(Ln)_2(X)_3]^{6+}$ was observed for all of the lanthanides (La, Eu, Gd, Tb, and Lu) investigated in this study. Furthermore, peak intensity was found to be a reflection of the distribution of these species in solution. For example, NMR experiments reveal that complexes containing the heavy lanthanides (Tb and Lu) are less stable than their ligher counterparts. The ES–MS results are consistent with this observation since the molecular ion peak intensities decrease from La to Lu. Additional characterization studies of the complexes in solution were informative as well. Spectrophotometric titrations of the ligand with the various lanthanides reveals a precise end point at a Ln/ligand ratio of 1:0.65. In addition, the presence of only two species in solution is implied since isosbestic points were observed during all of the titrations. These apparently are the free ligand and the metal-ligated triple-helix assemblage. Finally, ^{1}H NMR experiments demonstrate that two of the protons on the pyridine moiety in the ligand are dramatically shifted upfield upon lanthanide coordination. These results are expected, since the crystal structure reveals that these protons lie in the shielding region of the aromatic benzimidazole rings in the triple helix. In addition, the NMR data indicates that the three ligands lie in magnetically equivalent environments. Taken together, the solution studies are consistent with the X-ray structure obtained for the dinuclear triple-helical complex. Finally, we note that the interest in these complexes arises from the possibility that related species may be useful as light-conversion molecular devices. In order for such compounds to be of general utility, (1) the lanthanide ion must be protected from the solvent in order to reduce quenching; (2) there should be multiple light-absorbing groups positioned near the ion that are suitable for efficient energy transfer; and (3) the complex should be thermodynamically stable and kinetically inert. In terms of thermodynamics, these investigators have estimated the formation constant for the complex to be greater than 10^{20} (where Ln = La and Eu).

As nicely illustrated by Williams and his colleagues,[131-134] the final structure of the helical complex (i.e. double versus triple helix) is strongly influenced by the geometry of ligand coordination about the transition metal ion,[135] a structural feature largely controlled by the metal ion itself. In contrast, Bell and Jousselin have utilized a decidedly different strategy, by emphasizing the geometrical preference of the ligand (as opposed to the metal ion).[136] These investigators employed the heterohelicene **119**, which

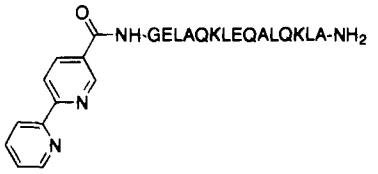


119

is even more rigid than oligopyridines **116** and **117**. The additional ethylene bridge produces a slight twist between pyridine rings, which is ultimately responsible for generating a preorganized helical shape. In the presence of sodium triflate (methanol) a 2:2 **119**/Na complex is formed bearing an overall double helical shape (mass spectrometry, NMR). The investigators propose that longer molecular coils might assemble to produce a double helical form even in the absence of metal ions.

In recent years, chemists have launched a methodical assault on the challenges associated with protein design. In this regard, the amphiphilic α-helix proved to be one of the earliest successes. In particular, Kaiser and his colleagues utilized this structural motif to generate synthetic analogs of a variety of peptide hormones, such as calcitonin and β-endorphin.[137] As one might expect from a structural form that is hydrophobic on one face and hydrophilic on the other, there can, in some instances, be a tendency toward aggregation.[138] Recently, Ghadiri[139] and Sasaki[140] independently demonstrated an intriguing approach to limit the extent of peptide aggregation, one which relies upon metal ion participation. Ghadiri has noted that the general strategy associated with this approach stems from three specific design principles: (1) each individual α-helical peptide must contribute at least one ligand to a metal ion organizing site; (2) the structural attributes of this site must be such that

undesired structural arrangements are disfavored; and (3) the metal ligand complex must be both thermodynamically and kinetically stable.[139] With these features in mind, Ghadiri prepared peptide **120**, which contains a bipyridine moiety at the N-terminus. The five different amino acids contained



120

within this peptide are known to strongly support helix formation. The helical wheel diagram (Figure 13) illustrates the fact that the hydrophilic and

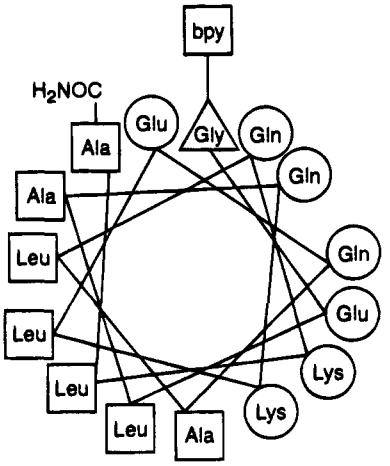


Figure 13. A helical wheel diagram of **120**. The helical peptide is viewed from above, down the axis of the helix. The hydrophobic amino acids leucine (Leu) and alanine (Ala) are segregated on one face of the helix from the polar glutamine (Gln) and the charged glutamic acid (Glu) and lysine (Lys) residues. The bipyridine (bpy) is attached to the N-terminal glycine (Gly). The C-terminus is amide-capped. Adapted from ref 139.

hydrophobic residues are segregated to specific halves of the helical surface. In the absence of any other factors, one might expect that **120** would exist in solution as a monomer in equilibrium with a variety of multimeric aggregates. However, in the presence of transition metal ions, such as Ni^{2+}, Co^{2+}, or Ru^{2+}, aggregation is limited to the trimeric species by virtue of the bidentate bipyridine ligand. Evidence for the three helix topology (Figure 14) is as follows:

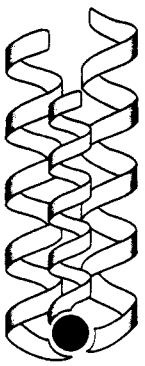
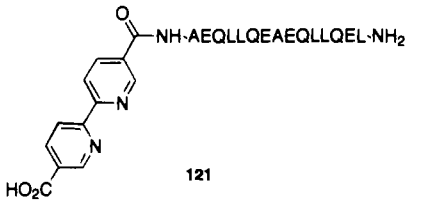


Figure 14. The transition metal ion-assisted assembly of **120** into a three helix bundle. Adapted from ref 139.

(1) molecular mass analysis by mass spectrometry, (2) an increase in α-helical content [30% to >70% as assessed by circular dichroism (CD)] of the peptide in the presence of Ni^{2+} or Co^{2+}, and (3) [Co(bpy-peptide)]$^{2+}$ CD spectrum independence as a function of metallopeptide concentration. The three-helix bundle lacks a solvent-exposed hydrophobic surface. Consequently, one might expect that this structural form would not be prone to further aggregation; an expectation borne out by observation 3. In contrast, in the absence of a transition metal ion, the ellipticity of the peptide at 222 nm is remarkably dependent upon metallopeptide concentration. Under these conditions, it is evident that the monomeric peptide does exhibit a marked tendency to aggregate.

Lieberman and Sasaki reported the metal ion-induced assembly of an analogous three-helix bundle.[140] These investigators found that Fe^{2+} promotes a sharp increase in the α-helical content associated with **121**. In addition, a peptide that lacks the bidentate ligand moiety was also prepared (**122**).



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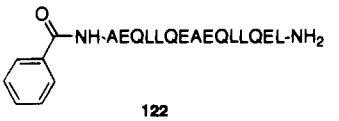
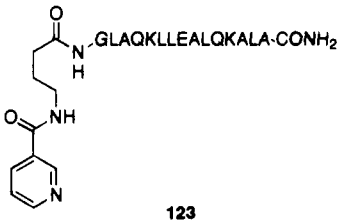


122

As expected, Fe(II) failed to produce any change in the percent helical content of the latter species. As we saw earlier in the work of Zimmerman and Duerr,[34] monomeric units that are unable to participate in the assembly process represent a useful control. They allow one to assess the validity of the basic design features associated with the formation of the desired supramolecular complex.

Ghadiri and his co-workers subsequently employed this strategy to create a four-helix bundle.[141] The pyridine-appended peptide **123** was treated $Ru_5Cl_{12}^{2-}$ in a 50% ethanol–water solution to afford the desired metallotetrapeptide [Ru(peptide)$_4$] in just under 70% yield (purified and isolated). Once again, mass



123

spectrometry and circular dichroism were employed to elucidate the structure of the end product. However, a chemical test was performed as well. As one might expect, high concentrations of guanidine hydrochloride denatures the four-helix bundle. The denaturation curve (from low to high concentrations of guanidinium) is independent of metallopeptide concentration. In contrast, denaturation of the free peptide (i.e. no ruthenium present) is strongly

dependent upon peptide concentration. These results indicate that, although the free peptide generates various intermolecular aggregates, the metalated peptide shows no tendency for this behavior. This is consistent with the notion that there are no solvent exposed hydrophobic surfaces in the tetrameric complex.

Ghadiri and Case have described the self-assembly of a peptide-based three-helix bundle containing both Ru(II) and Cu(II).[142] The design principles are analogous to those described above, except a histidine moiety is positioned at the C-terminus of the peptide. Upon introduction of ruthenium, three peptides assemble into a three-helix bundle as noted above. However, in this complex, the three histidines moieties are positioned within close proximity to one another, thereby providing a Cu(II) binding site.

The peptide-based entities discussed to this point have either utilized cyclic systems containing D-amino acid residues or peptides that have been modified with metal-coordinating ligands. What of simple linear peptides containing only L-amino acids? Can they be induced to assemble into structurally well-defined supramolecular complexes? The answer, of course, is a resounding yes. The work in this area is immense, in large part due to the many naturally occurring systems (or derivatives thereof). We have already noted the fashion by which gramacidin A assembles to create an ion channel.[97] Other examples include the assembly of alamethicin into α-helical rods.[143] Peptide self-assembly is not merely limited to "simple" helical systems. Fragments of SH2 domains self-assemble,[144] as do fragments from the proline-rich neutralization domain of the external glycoprotein of the feline leukemia virus.[145] Insulin dimerizes in neutral and acidic solutions, and forms hexamers in the presence of Zn(II).[146] The assembly of the β peptide, derived from amyloid precursor protein, into amyloid plaques, may play a key role in the progression of Alzheimer's disease.[147] Of course, we would be remiss if we failed to mention the double- (and triple!) helical structure assumed by DNA. In short, the assembly of peptides and oligonucleotides into structurally well-defined entities is a field of research that is simply too large to cover in an adequate fashion in this review. Consequently, what will follow are a few examples of purely peptidic supramolecular complexes that are helical in nature. These examples reflect our own personal bias and should not be taken as comprehensive.

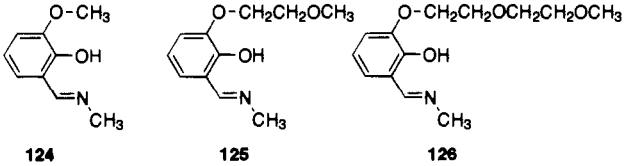
Multiple-helix bundles have been created utilizing peptides that contain only L-amino acids. Much of this work is an outgrowth of the recent interest in the *de novo* design of a four-helix bundle. The latter is a structural feature that is found in a number of different proteins.[148-149] One can envision several different design strategies for the construction of this helical system. For example, one obvious approach is to prepare a single peptide that contains four separate helical regions. These four covalently linked helical segments could then spontaneously interact to generate the desired helix bundle. Although the approach may be obvious, the design of a single polypeptide that could pack in such a predictable fashion is not straightforward. Instead, Ho and DeGrado employed an incremental strategy for the construction of this helical system.[150] They first designed a relatively short peptide (16 amino acids), with a strong helical propensity, that could tetramerize in solution. The peptide-based helix was predicted to exhibit an amphiphilic structure, namely a portion of the helical surface contains lipophilic residues that are segregated from the hydrophilic residues. The apolar side chains were designed so as to interdigitate with the adjacent helices in the four-helix bundle. Tetramer formation was demonstrated via size exclusion chromatography as well as by an analysis of the concentration dependence of the CD spectra. Interestingly, the CD spectra of the peptide, when extrapolated back to infinite dilution, revealed relatively low helical content. Under these conditions, the peptide is in the monomeric state. In contrast, a much higher helical content is found when the peptide is presented as a tetrameric species. In short, aggregation appears to stabilize the helical structure. DeGrado and his colleagues subsequently characterized the four-helix bundle by sedimentation equilibrium centrifugation (molecular weight determination), vacuum UV CD, pH studies, and two-dimensional NMR.[151] In addition, a peptide containing a helix–loop–helix motif has been shown to dimerize to a four-helix bundle.[150] Recently, the DeGrado group has employed this approach to create both Zn^{2+}- and heme-binding four-helix bundles.[152-153]

Yang and his colleagues have demonstrated that an appropriately designed peptide can aggregate to form a six-helix bundle.[154] Amphiphilic α-helical peptides were employed here as well. However, these peptides contain a wider hydrophobic face than those utilized by DeGrado and his collaborators. This greater proportion of hydrophobic to hydrophilic residues appears to be responsible for the higher order of aggregation. The hexameric species has been characterized by size exclusion chromatography, as well as CD and fluorescence[155] spectroscopy. In addition, NMR experiments reveal that this species binds an octyl-substituted aromatic guest. An X-ray crystallographic analysis has also been performed.[156]

F. Receptors

The superstructures described to this point have been discussed in the context of general structural motifs. With certain notable exceptions, we have emphasized structure rather than function. The complexes to be described in this section do not readily conform to a specific structural archetype, rather their design has focused on function; namely, they are to serve as receptors for a structurally diverse array of guests.

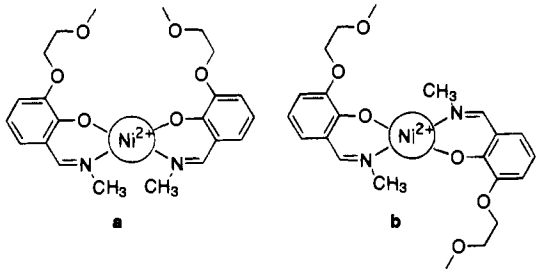
In 1989, Schepartz and McDevitt reported the self-assembly preparation of ionophores.[157] In the presence of $NiSO_4$, the aromatic imine **124** is able to extract alkali metal ion picrate salts from water into $CHCl_3$. The complex derived from **124** exhibits the



124 **125** **126**

extraction order: $Na^+ > Li^+ > K^+ \sim Rb^+ \sim Cs^+$. In contrast, aromatic imine **125**, in the presence of Ni^{2+},

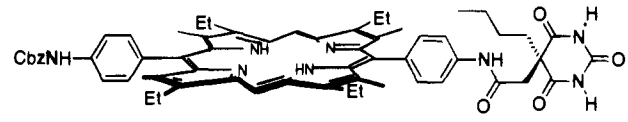
preferentially extracts Li^+ relative to the other metal ions. Furthermore, the Ni^{2+}/**126** complex extracts Na^+ and K^+ with nearly equal efficiency. The Ni^{2+} complexes (i.e. in the absence of the alkali metal ion) possess a 1:2 stoichiometry and a molecular weight, as determined by vapor pressure osmometry, that is consistent with either of the two structures in **127**.



127

It is tempting to assign structure **127a** to the ionophore since, in this orientation, the two polyether chains are adjacent to each other in space. This would presumably favor cation coordination. However, a subsequent analysis of the Ni^{2+}/**125** complex in the presence of sodium picrate by Atwood, Gokel, and their colleagues revealed a startling structural feature; namely, the complex actually contains two Ni^{2+} ions, four imine ligands, two Na^+ ions, and a picrate counterion (the latter appears to play a key role in Na^+ coordination).[158,159] Furthermore, in this complex (see ref 158, Figure 2), two of the methoxy arms bind one Na^+, a third is coordinated to Ni^{2+}, and the fourth is apparently free. The overall structure is somewhat reminiscent of a cage. Interestingly, a further analysis by Schepartz, Thorp, and their colleagues revealed that, although Ni^{2+}/**124** exists as the 1:2 complex in solution, addition of an alkali metal ion induces the formation of a 2:4 entity (as assessed by vapor pressure osmometry), in apparent agreement with the crystal structure data.[160] In addition, this Na^+-induced change in stoichiometry occurs in the presence of $NaClO_4$, indicating that cation binding can occur even in the absence of the picrate counterion (the picrate and perchlorate salts of Na^+ bind with equal affinity to the dinuclear complex of **124**). However, the actual structure of this ion-coordinating species, which lacks the picrate counterion, remains to be determined.[159]

The photosynthetic reaction center is a beautiful example of a naturally occurring, structurally well-defined supramolecular complex.[161] In this context, Hamilton and his co-workers have designed an artificial self-assembling energy-transfer system.[162] These investigators found that a 1:1 complex (as assessed by NMR titration) forms upon treatment of the barbituric acid-modified porphyrin **128** with the bis(diaminopyridine) **129**. This results in the quenching of the fluorescence of the dansyl moiety. The proposed 1:1 complex is illustrated in **130**. Hydrogen bonding appears to be an important factor here, since there is a significantly smaller reduction in the fluorescence emission when dansyl ethyl ether is employed. The ethyl ether is a species that cannot engage in hydrogen bonding with the barbituric acid appendage. In addition, these investigators have obtained preliminary evidence for the formation of the 2:1 complex **131** (Chart 1).



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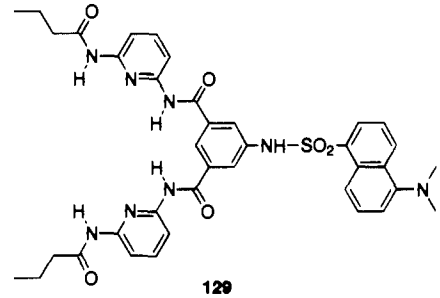

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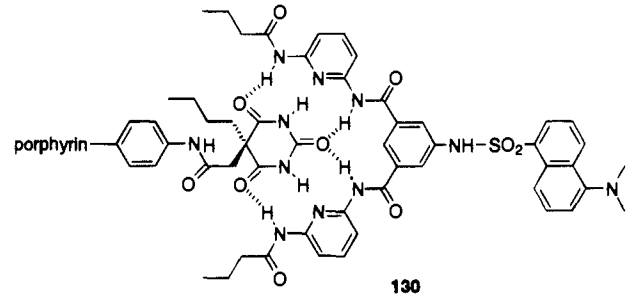
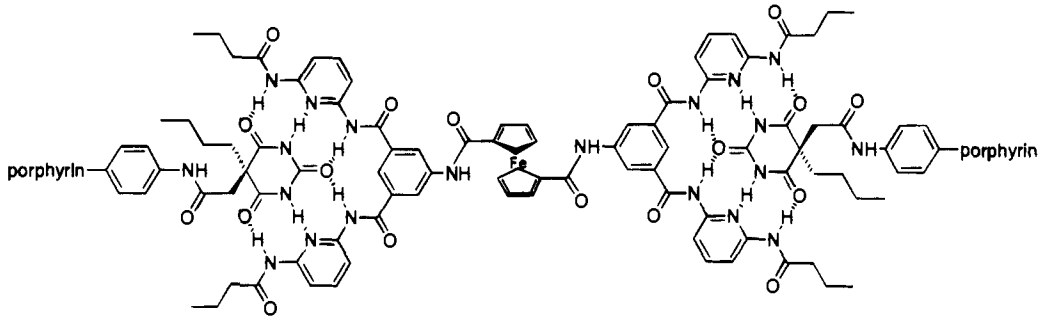


130

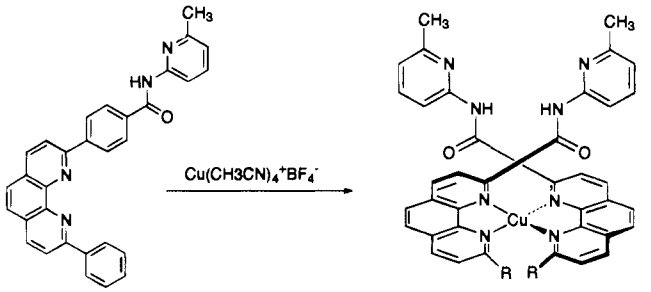
Hamilton has also recently reported a self-assembling receptor for dicarboxylic acids.[163] The synthetic strategy is reminiscent of one developed by Sauvage for the construction of catenanes and knots.[164] The phenanthroline complex **133** is obtained upon treatment of **132** with $Cu(CH_3CN)_4^+$ BF_4^- in CH_3CN/CH_2Cl_2. (Note: In the interest of clarity, the 1,4-disubstituted aromatic ring linking the phenanthro-

Chart 1



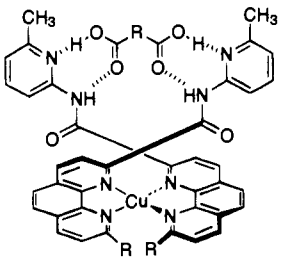
131

line and aminopyridine subunits in **132**, is not displayed in **133** and **134**.) The resultant product



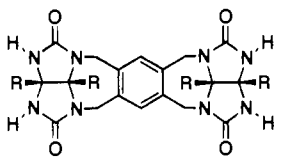
132 **133**

133 is stable and can be readily purified via chromatography. Species **133** is designed to bind dicarboxylic acids in the fashion shown in **134**. Binding constants for guests, such as glutaric and pimelic acids, are in the 10^4 M^{-1} range. The formation of a four hydrogen bonded complex (i.e. **134**) is consistent with the observation that glutaric acid binds to **134** more strongly than to **132**.



134

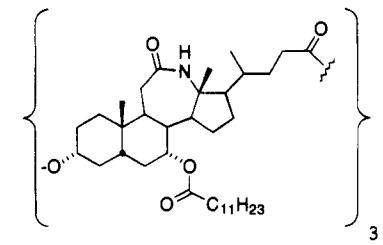
A self-assembling complex that contains an interior cavity has been described by Rebek and his colleagues.[165] Mass spectrometry and vapor pressure osmometry are consistent with the notion that the assembled species is a dimer composed of two identical subunits (**135**; where R = C_6H_5). The **135** subunit possesses both a convex and a concave face.



135

NMR analysis indicates that the molecule is engaged in hydrogen bonding. These results have lead to the suggestion that 2 equiv of **135** interact, via a molecular handshake, to create an interior void. These investigators have now shown that methane (300 M^{-1}), ethylene (280 M^{-1}), CH_2Cl_2 (4 M^{-1}), and $CHCl_3$ (0.04 M^{-1}) can be encapsulated by the dimer in $CDCl_3$.[166] The binding affinity of these guests appear to correlate well with the estimated cavity volume of the dimer (approximately 50 Å^3). As one might predict, the inclusion process is characterized by a loss in entropy that is compensated for by a gain in enthalpy. The most likely culprits responsible for the latter are van der Waals interactions between the guests and the assembled host. Two additional analogs of **135** have now been described [R = $-CO_2CH_2CH_3$ and $-p$-$C_6H_4N(CH_3)_2$].[167] The dimer of the former is extremely soluble in organic solvents, whereas dimer formation of the latter is acid dependent. Under acidic conditions (e.g. toluenesulfonic acid), the amine is protonated and the dimer undergoes decomposition to its component parts. Both dimeric entities bind xenon, a process that can be readily observed by ^{129}Xe NMR.

A second example of cavity-forming compounds has been reported by Bonar-Law and Sanders.[168] Cyclocholates are macrolides prepared via the condensation of multiple subunits of cholic acid derivatives. Compounds **136**–**138** are shown in schematized form in Figure 15. Dimer formation was



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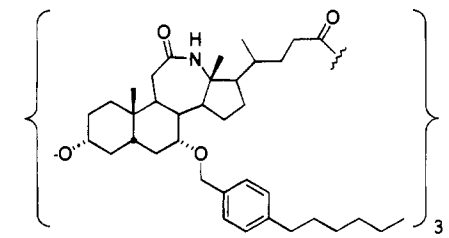

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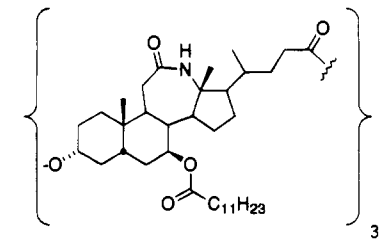


138

assessed by vapor pressure osmometry and freezing point depression measurements in benzene. Hydro-

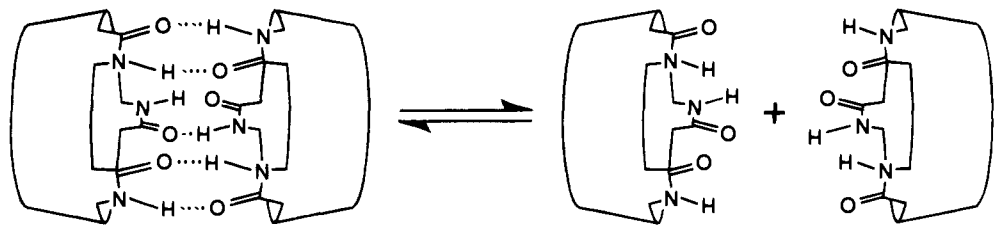


Figure 15. Dimerization of cyclocholates. Adapted from ref 168.

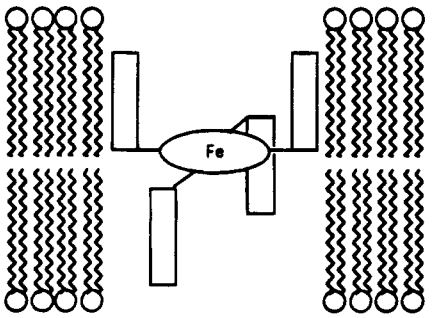
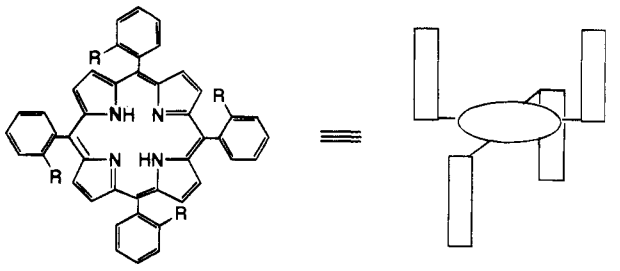


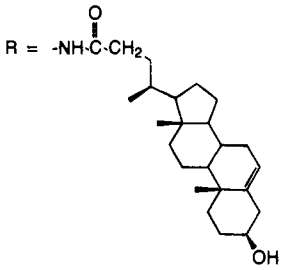
Figure 16. The phospholipid bilayer–Fe–porphyrin (**139**) assembly. Adapted from ref 169.

gen-bond formation was observed via both NMR and IR spectroscopy, thereby leading to the suggestion that the cyclocholates interact in a head-to-head fashion. Interestingly, the dimerization constants for both **136** ($3 \times 10^4\ M^{-1}$) and **138** ($2 \times 10^4\ M^{-1}$) are an order of magnitude larger than that obtained for **137** ($2 \times 10^3\ M^{-1}$). This has been ascribed to unfavorable steric interactions between the converging benzyl rings in the dimer of **137**.

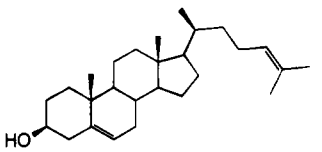
There are a number of investigators who have utilized the organization inherent within phospholipid bilayers to create species that exhibit biomimetic activity. We will highlight this very active area by focusing on recent work described by Groves and his colleagues.[169–172] These investigators prepared the phospholipid bilayer compatible porphyrin **139**.[169] The steroidal side chains of **139** are oriented in an $\alpha,\beta,\alpha,\beta$ conformation (Figure 16). Iron–porphyrin **139** exhibits pronounced regioselective epoxidation of steroids in the presence of a dimyristoylphosphocholine bilayer (and iodosylbenzene oxidant). For



139



example, epoxidation of desmosterol (**140**) occurs exclusively at the side-chain olefin. In contrast, the



140

ring olefin is the more reactive site when the oxidation reaction is performed in CH_2Cl_2 in the absence of the bilayer. These investigators have also linked the oxidation of ethylbenzene to the pyruvate oxidase-catalyzed decarboxylation of pyruvate to acetate (Figure 17).[171] In this case, oxidative decar-

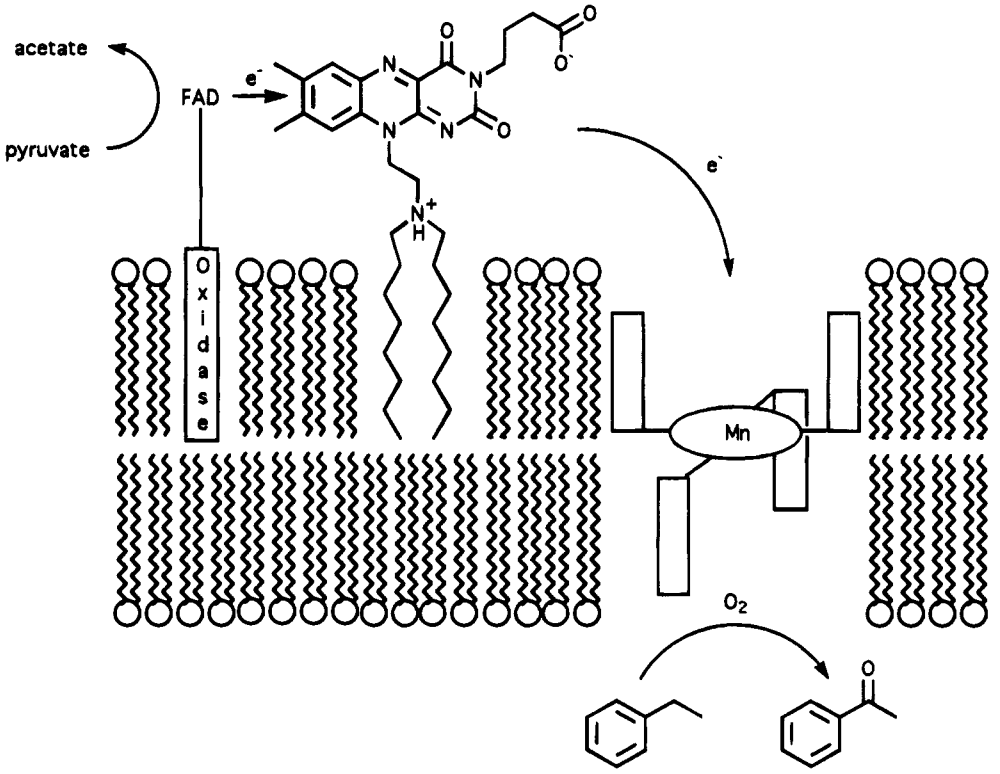


Figure 17. The pyruvate oxidase-initiated reductive activation of molecular oxygen by Mn–porphyrin (**139**). Adapted from ref 171.

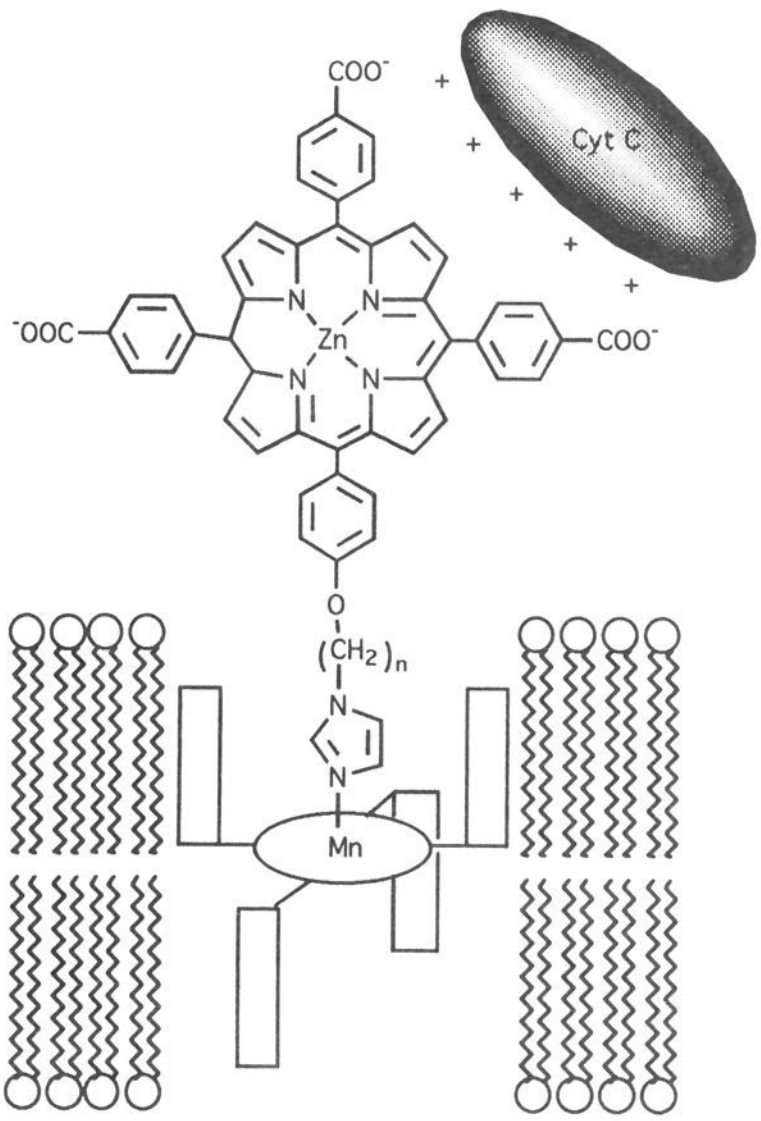


Figure 18. Assembly of a multicomponent electron-transfer system. Adapted from ref 172.

boxylation leads to the reduction of the FAD of pyruvate oxidase. An electron is subsequently transferred from $FADH_2$ to the Mn−porphyrin via the amphiphilic flavin shown in Figure 17. Reductive activation of molecular oxygen by the Mn−porphyrin leads to hydrocarbon oxidation. Finally, Groves and his colleagues have recently demonstrated that the bis-heme assembly illustrated in Figure 18 is able to recruit (via electrostatic interactions) cytochrome *c* to the surface of the phospholipid bilayer.[172] These investigators found that electron transfer occurs between the redox active centers of the protein and those embedded within the bilayer.

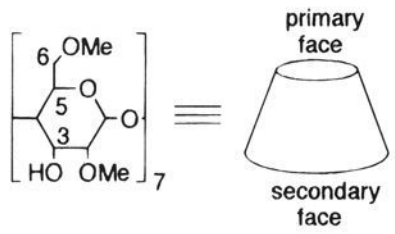
G. Catenanes and Rotaxanes

There have been a large number of reported syntheses and catenanes, many of which are prepared via self-assembly. Gibson has reviewed this area and the interested reader is referred to his extensive analysis of the recent literature.[6]

VI. Self-Assembly: A Narrative

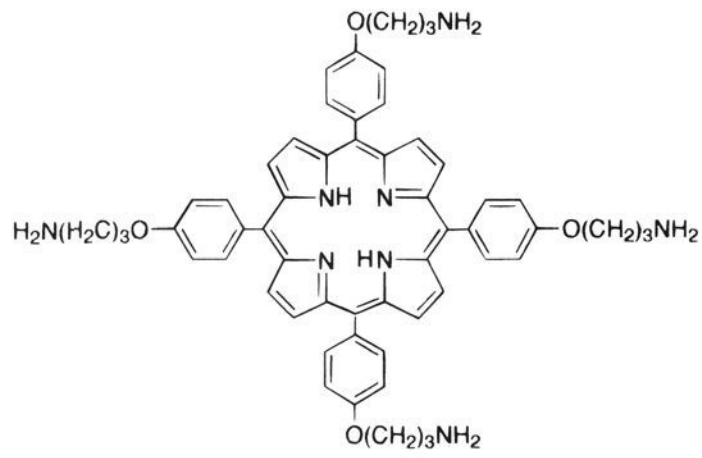
Solvent plays a critical role in self-assembly. Although hydrophobic interactions are strongest in a polar protic solvent (i.e. water), hydrogen bonds and electrostatic interactions are favored under nonpolar aprotic conditions. Unfortunately, if a particular self-assembly process is driven by both electrostatic and hydrophobic forces, one is immediately confronted with the impossible task of finding conditions that are favorable for both. Of course, this is not an especially difficult problem in nature, where relatively large components can generate their own nonpolar environments in aqueous solution. However, it is a significant issue with low molecular systems. How does one overcome the difficulty of simultaneously exploiting hydrogen bonding, electrostatic, and hydrophobic interactions in a nonparadoxical fashion? A few years ago, we were forced to address this question.

There are certain generic structural traits that are shared by many enzymes. One particularly pervasive property is the presence of a hydrophobic active site embedded within an otherwise, water-soluble protein. This is a particularly useful arrangement, since the inclusion of lipophilic compounds within the active site is strongly driven by the hydrophobic effect. Once properly positioned within the enzyme, the substrate is transformed to product by interaction with the catalytic apparatus of the active site. This "apparatus" may be entirely comprised of amino acid side chains or may also contain a nonproteinoid cofactor. From the point of view of biomimetic chemistry, the latter is particularly appealing since these species are often capable of acting as catalysts themselves, without requiring participation by exogenous functional groups. For example, the biomimetic chemistry of simple isolated heme units has been extensively examined.[173−175] With this background in mind, we wondered whether it was possible to create a water-soluble self-assembling species that possesses a catalytically active cofactor embedded within a hydrophobic pocket. We immediately recognized that since the self-assembly process would be conducted under aqueous conditions, it would be necessary to drive the assembly of this species via hydrophobic interactions. We chose to start with a porphyrin cofactor, since the chemistry of metalloporphyrins is particularly well-understood. A methylated cyclodextrin derivative (**141**) is the second component employed in this self-assembling system.[176]



141

Cyclodextrins are "lamp-shade"-shaped cyclic oligosaccharides of glucose.[177] These water-soluble compounds possess a hydrophobic interior that can bind a wide variety of lipophilic guests. The porphyrin **142**, with its hydrophobic aryl substituents, was expected to act as a template, guiding the association of two cyclodextrins about the porphyrin moiety. This creates a groove that circumscribes the



142

metal binding site of the porphyrin nucleus (Figure 19). This groove should be somewhat lipophilic in

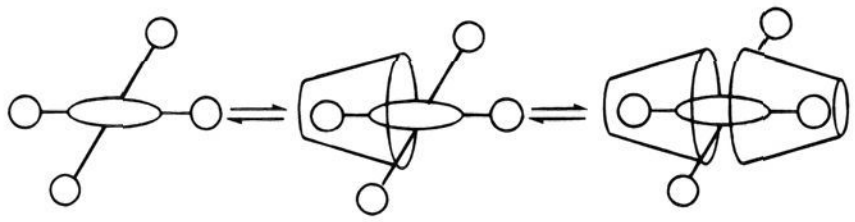
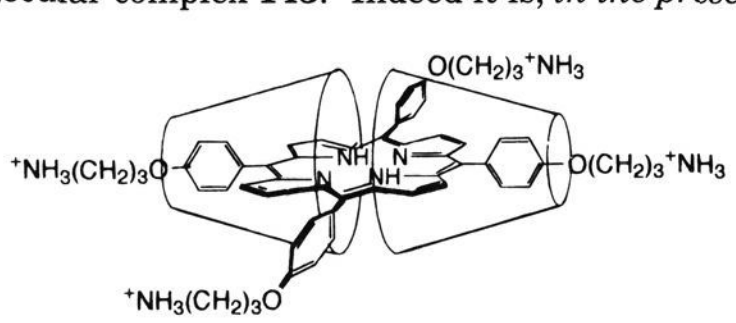


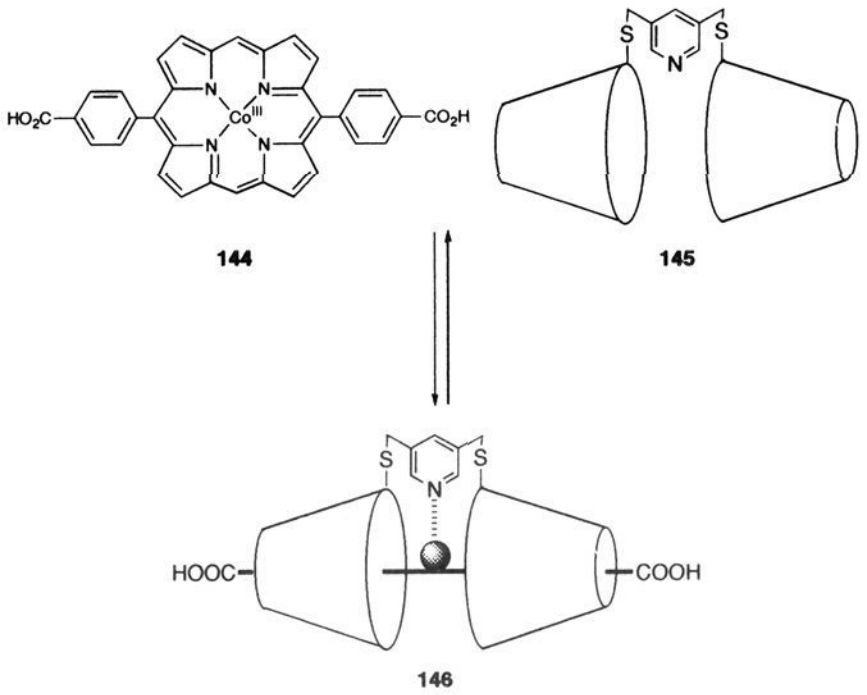
Figure 19. The template-driven assembly of a porphyrin-containing supramolecular complex. Adapted from ref 179.

character since the methyl substituents on the secondary face of the cyclodextrin line its rim. Clearly, this hydrophobic region has obvious implications in terms of substrate binding. In addition, it is important to recognize that the protein component of heme-containing proteins does more than simply provide a hydrophobic binding site for porphyrins. For example, most water-soluble porphyrins exhibit a marked tendency to aggregate in aqueous solution.[178] Indeed, simple Fe(II)–porphyrins, upon oxygenation, immediately oligomerize in nonaqueous solvents.[173] Such behavior dramatically interferes with the ability of these species to perform biologically relevant tasks. In heme-containing proteins, the protein sheath serves as a giant protecting group by imprisoning the heme, which precludes undesirable side reactions. In much the same way, one would expect this to be the case for the supramolecular complex **143**. Indeed it is, *in the presence*



143

of excess cyclodextrin.[179] Unfortunately, species **143** is in equilibrium with its component parts. Although we have found that complexes, such as **146**, can exhibit formation constants of greater than 10^8 M^{-1},[180] it is evident that the dissociation process must be shut down in order for the complex to retain its functional viability. As we noted earlier in this review, one way to eliminate the equilibrium between

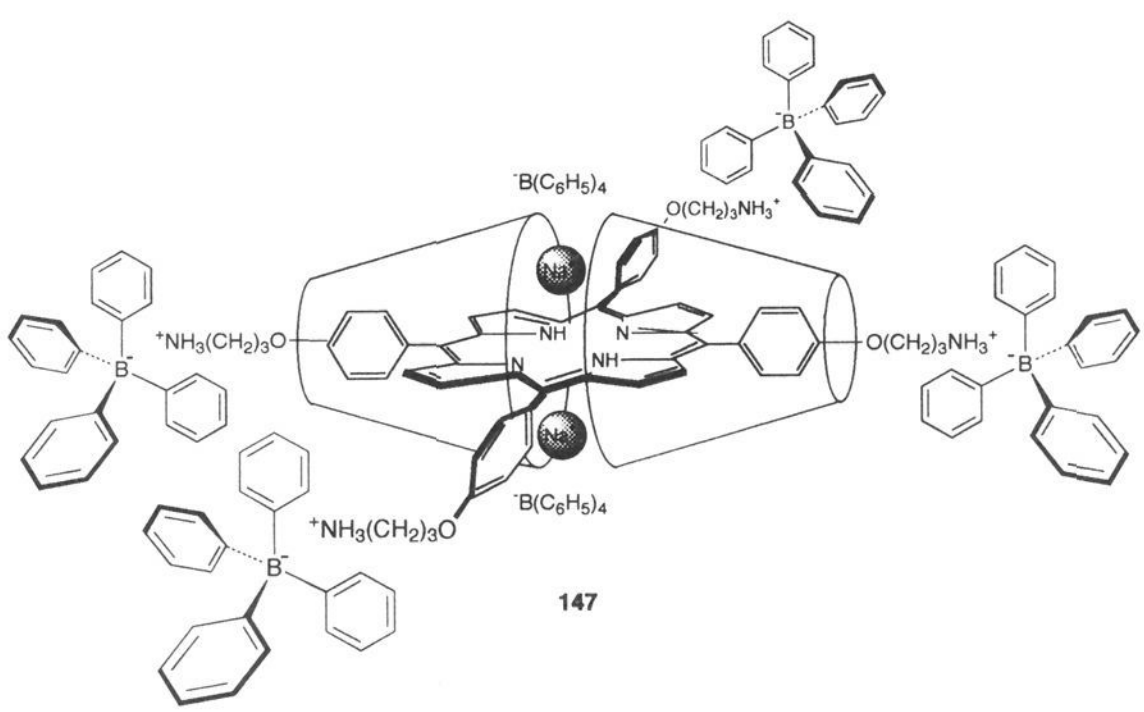


144 **145**

146

desired complex and component parts is to sequester the coveted species from solution. In keeping with the spirit of self-assembly, we attempted to achieve this goal via noncovalent interactions. The tetraammonium porphyrin–cyclodextrin complex **143** was prepared with this in mind.[181] We viewed the ammonium functionalities as the critical residues for isolating a relatively stable species. Crown ethers, especially 18-crown-6, have been commonly employed to precipitate a variety of ammonium salts out of aqueous solution in high yield. Consequently, we applied this strategy to an aqueous solution containing the species **143** (in the presence of a 10-fold excess cyclodextrin in order to ensure that the vast majority of porphyrin present in solution was bound by cyclodextrin moieties). Much to our chagrin, the resultant precipitate contained porphyrin and crown ether (as determined by NMR), but little cyclodextrin. We later discovered that 18-crown-6 forms a complex with the cyclodextrin derivative **141** in water. Presumably, the excess crown ether competes with the porphyrin for the cyclodextrin cavity. Ammonium salts in aqueous solution can also be precipitated by sodium tetraphenylboron. We felt that the structural attributes of the tetraphenylboron were such that it would not be tightly ensconced within the cyclodextrin cavity. Indeed, we isolated, in excellent yield, the desired species **147** (Chart 2). One might expect that **147** would be relatively stable in a nonaqueous solvent due to the large size of the tetraphenyl-

Chart 2



147

boron gegenion. That is, the cyclodextrin would be sterically unable to thread off the porphyrin core as a consequence of the bulk counterion. However, it is important to keep in mind that tetraphenylboron does not readily form tight ion pairs in solution. In other words, the tetraphenylboron would not be expected to be tightly associated with the ammonium functional groups. Nevertheless, the complex is stable in acetone (e.g. **147** was purified on a cellulose column using acetone/benzene as the eluent). Why? The key appears to be the ammonium functional groups. There is a definite energy barrier associated with the disruption of the complex to the individual components. Heating the complex to reflux in acetone results in decomposition. So does treatment with triethylamine. The later observation suggests that it is the solvation of the ammonium ions that maintains the structural integrity of this supramolecular complex in acetone. In short, although the self-assembly process was initiated in aqueous solution and driven by the hydrophobic effect, the final step, conducted in acetone, serves to stabilize the end product via solvation of the ammonium ion functionalities.

These results demonstrate two key points with respect to the design of self-assembling systems. First, it is possible to combine a variety of noncovalent interactions, in a productive fashion, to create stable supramolecular complexes. Second, solvent itself can serve as an essential participant in maintaining the structural integrity of the end product.

VII. Summary

As we noted in the introduction, self-assembly holds several advantages over covalent bond-driven organic synthesis. However, these advantages are more than offset by the often dynamic structural nature of the end product, as well as by the difficulties associated with characterization. In addition, a wide variety of compounds (steroids, alkaloids, etc.) are simply not amenable to this unconventional form of synthesis. Given these limitations, it is fair to ask "what is all the excitement about?" Certainly, from the intellectual (as well as emotional!) point of view, there is something irresistibly enchanting about an object that builds itself, be it a house, a car, or even a prosaic supramolecular complex. However, although it may be fun to watch a well-designed system perform magic tricks on the molecular level, it is important to keep in mind that these species have potential practical applications as well. For example, Ghadiri's self-assembling ion channels[104] or Rebek's pH sensitive host[167] may ultimately spawn a new generation of delivery systems for medicinally useful compounds. However, one must be cautious. If a structurally inert molecular species is required for a particular application, then the self-assembly approach may not make sense. Of course, this concern will be partially mitigated if the self-assembled species can be utilized in the solid state. However, as with the microtubule example described in section II, there will undoubtedly be instances in which a structurally dynamic entity will be of decided benefit. This is where self-assembly holds its greatest promise and, for the contemporary organic chemist, its greatest challenge.

VIII. Acknowledgments

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