SUPRAMOLECULAR CHEMISTRY

1. Concept

It is almost impossible to exactly define the scope and limitations of supramolecular chemistry. Christoph A. Schalley (1)

The term "supramolecular" was first used in the context of biological interactions, especially between large molecules that bind to each other to perform a particular function. Examples of this type of behavior include the aggregation of amphotericin to form transmembrane channels and the convergence of the copper-containing protein plastocyanin with reaction partners to transfer electrons in photosystem I. Supramolecular chemistry has its origins in the supermolecule, a term widely used by Lehn from the early 1970s when referring to a well-defined chemical species comprising several components (2). In turn, Lehn cites the earlier use of *übermoleküle* to describe such species (3). The realization that supermolecules could in turn form larger molecular assemblies led to the shift in emphasis from super- to supramolecular in the literature to more accurately describe the complexity of systems involved. At this point in the field's evolution, the focus was on cyclic and encapsulating molecules ("hosts") and their interactions with small molecules or ions ("guests"). Representative host compounds include the crown ethers, cryptands, calixarenes, cyclotriveratrylenes, phthalocyanines, cyclodextrins, and spherands (Fig. 1). Spectroscopic and crystallographic data were often able to confirm the existence of complexes formed from small metal cation guests and encircling organic host molecules (Fig. 2). Furthermore, it was also possible to determine the level of selectivity that generally increased when the dimensions of a host's cavity most closely matched those of the guest. This finding led directly to the concept of "host-guest" chemistry, itself an extension of Fischer's enzymatic lock-and-key mechanism first proposed in 1894 (4). Today it is understood that supramolecular chemistry has advanced to include complexes between molecules with complementary binding sites ("molecular recognition"), multicomponent complexes ("supramolecular assemblies"), the programmed interactions between large molecular assemblies ("molecular tectonics"), and even the directed assembly of three-dimensional solids ("crystal engineering").

Although an implicit understanding of what "supramolecular" meant in a chemical context had existed for some time, it was through the award of the 1987 Nobel Prize in chemistry to Cram, Lehn, and Pedersen for "their development and use of molecules with structure-specific interactions of high selectivity" that the concept was presented to a wider scientific audience. The interactions in question are noncovalent: Permanent bonds are not formed in a supramolecular complex, and weaker attractions are relied on to hold the components together. Thus, electrostatics, hydrogen bonding, π-π stacking, and London forces are the all-important driving forces behind supramolecular chemistry. Individually they may be quite weak, but as they often act in concert, cumulative effects are great enough to stabilize supramolecule formation. In his Nobel Lecture, Lehn refined his concept of supramolecular chemistry as "the chemistry beyond the molecule bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces"

(5). This definition encapsulates three scales of molecular complexity: guest recognition based on careful *a priori* design of the host molecule, self-assembly or self-organization to produce molecular assemblies, and evolution at the molecular assembly scale through kinetic interplay between supramolecular components. Recently Lehn has stressed this latter point, stating that "supramolecular chemistry is a dynamic chemistry due to the reversibility of non-covalent interactions" (6). Inherent in this remark is that supramolecular chemistry should be reversible; indeed, this has become a key concept. The reversibility of interactions that aid in the formation of supramolecular species is essential if self-correction is to occur. Without self-correction the sheer complexity of most supramolecular assemblies would militate against their reproducibility. Fortunately many aspects of supramolecule formation can be directed. Complementary hydrogen bond motifs are one such mechanism; another is the use of reversible coordinate bonds between metals and ligands to control initial geometries. The latter are of clear importance in the template synthesis of macrocycles. However, some systems, widely believed to be supramolecular in nature, do not conform. Perhaps the most obvious example is a catenane in which two or more cyclic molecules interpenetrate each other (Fig. 3). Unless covalent bonds are broken the molecules cannot be separated, and given this irreversibility, the interlinked species should not be classed as truly supramolecular by this narrow definition. However, it is worth considering the synthetic processes that are necessary to form catenanes. Most syntheses start with a preformed macrocycle through which a second, linear molecule is threaded. Once this molecular entanglement (known as a rotaxane) occurs, the ends of the thread are induced to form an irreversible covalent link by one of many methods. Crucially the thread must be held in place by noncovalent forces (metal-ligand interactions, π-π stacking, hydrogen bonding, etc) for this step to occur. The synthetic process therefore must involve the formation of a supramolecular complex, if only as an intermediate; thus, the catenane may be considered as a supramolecular entity. To avoid contentious issues such as this it is worth bearing in mind Menger's assertion that "supramolecular chemistry, broadly speaking, entails the study of intermolecular bonding" and consider any complex chemical species where noncovalent interactions play a major role in their synthesis, or subsequent stability, to be a supramolecular entity (7).

2. Objectives

Supramolecular chemistry aims at developing highly complex chemical systems from components interacting by noncovalent intermolecular forces. Jean-Marie Lehn (8)

Once the processes behind the synthesis of molecular hosts and formation of supramolecular complexes had become better understood and predictable, the objective of supramolecular chemistry started to focus on the utilization of these molecules for highly specialized tasks. Much of the work in this field from the late twentieth century onward has attempted to harness highly specific supramolecular interactions between a carefully designed molecular host and an analyte of interest. To be of real value the interaction must give an observable

signal. This signal can be achieved in several ways, but the most common approach has been to couple the host to a chemical group that responds to the binding event through a change in fluorescence, color, or electrochemical properties as the cartoon in Fig. 4 illustrates (9). In this way the binding event becomes the input and the signal modulation the output. Some researchers have used this approach to construct extremely simple, but effective, molecular logic gates (10), and more recently, Stoddart has demonstrated the potential of rotaxanes to act as voltage-sensitive addressable bits of information as part of a drive toward molecular level computing (11).

A second theme in contemporary supramolecular chemistry is biomimicry. For example, there is a great similarity between [18]crown-6 and the natural antibiotic, valinomycin. Both are specific for the potassium cation in aqueous solution, and both are cyclic molecules comprising regular repeat units (ethers and amino acids, respectively) that direct six oxygen atoms toward the center of the macrocyclic cavity (Fig. 5). In a more intricate example, the calixarene motif has been used as a scaffold to bind zinc complexes, thus acting as a model enzyme (12). At the highest level of complexity, supramolecular principles have been used to guide the syntheses of self-replicating molecules and self-assembling nanospheres that mimic capsid viruses (13). One issue is clear: There has to be an implicit act of design in the formation of supramolecular complexes. The objective of the supramolecular chemist must be to prepare functionalized molecules with the specific intention that they act as components of a more complex system in a preordained fashion. This goal is as applicable to single molecule sensing, where the binding of one component could be signaled by a distinct wavelength shift or fluorescence enhancement upon supramolecule formation, as it is to solid state chemistry, where a novel material with particular bulk properties is created through the aggregation of molecular assemblies.

The formation of supramolecules and supramolecular assemblies relies on the favorable interactions between the components involved. These are, by definition, non-covalent intermolecular and interatomic forces: Their relative energies are given in Table 1. In designing components of supramolecular complexes, it is important to analyze the types and strengths of forces that could be employed to yield the specifically desired effect. For example, hydrogen bonds play an irreplaceable role in protein chemistry. To prepare a sensor that detects particular terminal amino acids on small proteins, it would be wise to consider incorporating functional groups that generate complementary hydrogen bonding to that exhibited by the amino acid of interest. The relative weakness of a single hydrogen bond is compensated for by the number, and preorganization, of sites in the sensor. The strength of interaction can be increased through careful substitution of the sensor molecule; for example, introduction of an electron donating group on a carbon atom next to a pyridine nitrogen will enhance hydrogen bonding to the latter.

Most supramolecular assembly occurs in solution, and the effect of the solvent must be considered. For example, if both host and guest are solvated, both must be partially or completely desolvated before complexation and resolvated afterward. Differences in solubility between the supramolecular complex and its components give rise to precipitation and crystallization, where the complex has low solubility, and solublization of one component (usually the guest) when

the complex is highly soluble. The affinity between components is also affected by the nature of the solvent. Polar solvents, such as water and tetrahydrofuran, that can also accept hydrogen bonds readily will solvate cations and compete with hosts containing electron donating groups. Electrostatically driven complexation will also be disfavored by these solvents. Where the solvent can form hydrogen bonds, as occurs in simple alcohols and water due to the hydrogen–oxygen dipole, anion solvation is enhanced. The amphoteric nature of water makes it a particularly competitive solvent for both cations and anions. Solvents that interact with either electron pair donors or hydrogen bond donors will also disrupt hydrogen bond formation and have a major impact on complexes or assemblies that use this phenomenon in their formation. Not all solvents are polar or can become involved in hydrogen bond formation. Some, hexane or toluene for example, are hydrophobic but will disolve a range of compounds. This result is relevant when macrocycles have nonpolar exteriors and polar interiors. When crown ethers bind cations, they adopt a conformation with electron pair donating oxygen atoms around the charged metal and the ethylene bridges on the exterior. This process allows the complex to pass from polar solvents into those that are largely hydrophobic while encapsulating a charged guest. Once the complex returns to a polar solvent, there is a change in conformation, due to a change in solvation, and the guest is released. The medium in which the supramolecular system operates is therefore a major influence on complex, or assembly, formation.

3. Early Developments and Their Contemporary Resonances

Although the concept of supramolecular chemistry is a relatively recent development, many ideas and compounds in use have much earlier origins. Most of the initial discoveries in the field have resulted from chance observations involving unusual behavior, often due to by-products, of a well-established industrial process. The late nineteenth century saw the first appearance of synthetic cyclic molecules capable of encapsulating guests (“macrocycles”). These molecules had been prepared as a direct consequence of increasing interest in organic synthesis and among them were the condensation products of phenols and aldehydes that led to the discovery of calixarenes, resorcinarenes, and pyrogallolarenes that are still in constant use today (14,15). Calixarenes are cyclic compounds comprising phenols linked to each other through the 2 and 6 positions by methylene spacers. Alongside crown ethers and industrially important cyclodextrins they are perhaps the most important compounds in contemporary supramolecular chemistry. The name was coined by Gutsche who noted the similarity of the cone-shaped compounds to that of a Greek vase known as the calix crater (16). The literature on calixarenes is vast with well over 2000 papers relating to the synthesis or properties of calix[4]arenes appearing in the past 25 years. Several excellent reviews and books have been published that chart the development of this class of macrocycles to which the reader is referred for further details (17). The renewed interest in these macrocycles during the twentieth century led to several synthetic approaches being taken to improve the yields or number of derivatives of the compounds (Fig. 6). The first approach involves

the reaction of phenols with formaldehyde under carefully controlled conditions, as exemplified by Gutsche's approach; the second is a stepwise construction of a linear polymer that is cyclized in the final stage, as reported by Hayes and Hunter (18). Böhmer and colleagues' "fragment" method contains aspects of both approaches (19). Recently an alternate strategy was reported by Gopalsamuthiram and Wulff who synthesized alternative aromatic rings through an elegant Fischer carbene reaction (20). The phenols can be further functionalized in the 4-position ("upper rim") and extended through the formation of phenolic ethers ("lower rim"). So far many calixarenes are known, starting with the easily prepared tetramer, calix[4]arene, and extending to useful quantities of calix[12]-arene and beyond. The synthesis of calix[3]arene has been claimed but never reproduced (21). Syntheses of the more obscure odd-numbered calix[5]- and calix[7]arenes have been optimized providing routes to these more unusual compounds (22,23). Several derivatives are also known (Fig. 7). Substituting sulfur for the methylene bridge generates the thiacalixarenes (24) and replacement of the bridge with $-CH_2OCH_2-$ or $-CH_2N(R)CH_2-$ yields the oxa-and azacalixarenes (25,26). Reaction of pyrroles with aldehydes generated calixpyrroles (27) and later formed the basis of synthetic porphyrin chemistry (28).

Not all developments of macrocycles came from experiments in polymer formation. In the early twentieth century, an observation by Dandridge led to the isolation of iron phthalocyanine. This finding became a valuable addition to the range of synthetic dyestuffs, but his employer soon discovered (and marketed) the much more stable copper complex (29). The compounds were initially discovered through the chance examination of a blue residue that appeared on the iron vessels used to prepare phthalimide from phthalic anhydride. It was determined that four equivalents of phthalimide had bound to the metal and then cyclized to form the thermally stable, and highly colored, macrocyclic iron complex. Similarly, Pedersen's discovery of crown ethers was notable because he proceeded to investigate their specificity as alkali metal extraction agents (30). Once supramolecular chemistry had been established as an identifiable theme, it was often through reinvestigation of this earlier work that more accessible and reproducible routes to these classic host molecules appeared. Cyclotriveratrylenes, the condensation product of veratrole with formaldehyde, were a curiosity when they were first prepared by Robinson in 1915 (31) but are now used by supramolecular chemists both for their inclusion properties (32) and for their ability to form supramolecular networks (33).

Cyclophanes represent yet another class of simple compounds with cyclic structures with applications in supramolecular chemistry. As their name implies, they consist of aromatic rings linked by short bridges (34). Although the compounds are relatively inert, rarely incorporating functional groups, a recent development in templated synthesis has shown that they can be coupled in an elegant manner to form two-dimensional sheets (35). The original cyclophane, reported in 1899, consists of two benzene rings linked through the 1,3-positions by ethyl bridges and is named, according to cyclophane terminology, [2.2]metacyclophane (36). It took 50 years for rational synthesis to appear with Brown and Farthing isolating small amounts of [2,2]paracyclophane (where the rings are linked in the 1,4-positions) in 1949 (37). This procedure was followed in 1951 by Cram and Steinberg's [2,2]paracyclophane synthesis, which ushered in a

new era for this class of compounds (38). Several methods can now be used to prepare cyclophanes including sulfur extrusion [aromatic groups are linked through thioether bridges that are later pyrolyzed (39)] and Wurtz coupling (40).

Alongside the production of macrocycles, the nineteenth century saw the development of theories of molecular interactions that would influence supramolecular chemists. Foremost among these was Fischer's "lock and key" hypothesis to explain enzyme specificity (4). This fundamental leap in understanding noncovalent interactions has been expanded on significantly in the intervening time but remains at the heart of supramolecular chemistry. The origins of coordination chemistry also stem from this period with Werner postulating this original concept in his thesis of 1890. There is an interesting parallel between the development of both coordination and supramolecular chemistry, separated as their origins are by some 80 years. Both are concerned with potentially reversible chemical interactions: between transition metals and ligating donor atoms, in the case of the former, and molecular complementarity, in the case of the latter. The importance of metal chelation and selectivity can be observed in both fields. Coordination chemistry has had a particular influence on supramolecular chemistry where it is concerned with the relative stabilities of metal–ligand complexes. It can be shown that bidentate ligands bind to transition metals far better than unidentate ligands that contain the same donor groups. For example, the reaction of aqueous nickel with ammonia results in the formation of the hexaamminenickel(II) species and a log K value (where K is the overall binding constant) of 8.6. The analogous reaction with bidentate ethylenediamine yields tris(ethylenediamine)nickel(II) and a log K of 18.3 (41). The metal is six-coordinate in both cases, so the only explanation for the enhanced binding is that the bifunctional ligand is better disposed to interact with the metal than two molecules of ammonia. The ligand is thus preorganized to fit around the metal lowering the enthalpic barrier to coordination. As only three ethylenediamine molecules, rather than six ammonia molecules, are required to fill the metal's primary coordination shell, entropic factors are also favorable even though the conformational rearrangement necessary to preorganize flexible ethylenediamine molecules reduces this benefit slightly. Binding constants for linear polyamine complexes of nickel (diethylenetriamine, triethylenetetramine, tetraethylenepentamine, and pentaethylenehexamine) also increase as the number of ethylenediamine units increases [log K values increase steadily from 7.35 to 19.1 (42), Fig. 8]. The favorable combination of entropic and enthalpic contributions provided by a flexible multidonor ligand over several smaller, unorganized ligands is known as the "chelate effect." If several donor atoms can be linked together, with the correct geometry, in a multidentate ligand, then the chelate effect is enhanced. Once one donor atom has bound, it becomes increasingly easier for subsequent coordinate bonds to form, making additional enthalpic terms increasingly favorable. In a natural extension of this principle, it is possible to encircle a guest with donor groups linked together in a macrocycle. The enhanced stability that results comes from the "macrocyclic effect" as shown by the data for some alkali metals in Table 2 (43). Note that the anomalously high binding constant for potassium with [15]crown-5 is due to a 2:1 crown:metal complex. With the exception of this result, the correlation between guest size to the crown cavity size is remarkable. Unsurprisingly, complete

encapsulation of a guest, by a cryptate or sepulchrate, leads to even higher binding constants, sometimes ascribed to the "macrobicyclic effect." Again the fit between guest and host is as predicted, although this time without the potassium anomaly as only 1:1 complexes can form for steric reasons. In highly preorganized ligands, such as cryptands (44) spherands (45), and torands (46), the cavity sizes and donor atom geometries are rigidly defined. Ultimately these high degrees of complementarity leads to unusually high binding constants with specific guests.

4. Synthesis and Structures of Supramolecular Synthons

If an old man can get ideas, you should let him try them.

Charles J. Pedersen, on the discovery of crown ethers shortly before his retirement from Du Pont (47)

Supramolecular assemblies form between molecules with complementary functionality or through the mutually beneficial interactions between hosts and guests. The former case covers a broad range of complexes from capsules formed by self-complementary macrocycles to self-assembled stacks of abiotic cyclopeptides. Here, one or more of the components may also have been designed to elicit specific supramolecular interactions. In the latter case, it is typical for the host to have been designed with a particular intent. By analogy to traditional synthetic chemistry, where the components of the target molecule are known as "synthons," the components of a supramolecule have been termed "supramolecular synthons." Incorporation of functional groups that induce ion–dipole and hydrogen–bonding interactions is the predominant design strategy for host molecules as these forces can interact in a complementary fashion with guests. Given the relative strength of hydrogen–bond donor/acceptor interactions with ions and ion–dipole interactions, it is no surprise that most hosts have been designed with ionic guests in mind. Hosts for neutral molecules rely on hydrogen-bonding, π-π stacking, and hydrophobic interactions. Due to the relative weakness of these interactions, designing hosts for neutral guests is far more challenging.

5. Cation Binding

5.1. Alkali Metals, Alkaline Earths, and the Lanthanides. One classic discovery in supramolecular chemistry was the accidental preparation of dibenzo[18]crown-6 by Pedersen. Fortunately Pedersen was already aware of cyclic compounds reported by Luttringhaus and Ziegler (48) and others (49) and realized that cyclic polyethers, with several donor atoms, had the potential to bind cations. Quick to capitalize on the methodology, he prepared over 30 crown ether derivatives, investigated their cation-binding abilities, and published the results in 1967 (30). Pedersen struggled with the IUPAC nomenclature for his compounds (dibenzo[18]crown-6 was named 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene in the 1967 paper) and resorted to the trivial nomenclature still in use today. In most cases, the rings comprise

ethyleneoxy units ($-CH_2CH_2O-$) where the oxygens are envisaged as the points on a crown. In this article, the following nomenclature will be used: The number of atoms in the ring is given first, in square brackets, followed by "crown" and the number of non-carbon atoms in the ring. Thus, a cyclic polyether with 15 atoms in the macrocycle, 5 of which are oxygen, would be [15]crown-5. Variations in the basic structure can be denoted within this nomenclature. For example, in aza[18]crown-6 nitrogen substitutes for one of the ethereal oxygens, dibenzo[18]-crown-6 contains two benzene groups, and in hexathia[18]crown-6, all oxygen atoms have been replaced by sulfurs (Fig. 9). Although the oxygen-containing crown ethers had no affinity for transition metals, they appeared to bind alkali and alkaline earth cations with a selectivity that was directly related to the size of the macrocyclic cavity. Size specificity has since been used to direct the template synthesis of the crown ethers. Template synthesis, where metal coordination holds ligand components in close proximity to each other to maximize the possibility for reactive centers to meet, was particularly valuable in the formation of [18]crown-6. This archetypal crown ether was isolated in less than 2% yield by Pedersen, but later, templated, methods increased this to more than 30% (50) and gave access to azacrowns (51). Many crown ethers are now known, from sulfur derivatives such as trithia[9]crown-3 (often called [9]aneS_3) that can bind to transition metals (52), to azacrowns with extended *N*-substituents that form artificial ion channels (53).

At the same time that Pedersen's crowns were being investigated more thoroughly, two other routes to cation complexation were being pursued. Vögtle and Weber prepared acyclic podands, by adding chelating groups to the termini of polyethers, and were able to bind several simple cations (54). Within two years of Pedersen's paper on crown ethers, Lehn and colleagues synthesized encapsulating cryptands from diazacrown ethers and were later able to demonstrate that the addition of a chelating arm increased binding constants by several orders of magnitude (44). Gokel and colleagues later took Greene's aza[18]crown-6 and introduced sidechains appended from the nitrogen, thereby introducing the supramolecular world to lariat ethers (55). These derivatives can combine the host function of a crown ether and functional sidechains that can interact to generate unusual structures such as the linear polymer formed by *N*-allylaza[15]-crown-5 with silver and the "scorpionate" complex formed by silver and *N*-3-butenylaza[18]crown-6 (56). Polyethers and crown ethers can also bind lanthanide cations, in addition to group 1 and 2 metal cations, due to similarities in both size and binding preferences between the lanthanides and the lighter *s*-block elements. These structural similarities extend to the solid state complexes as exemplified by the work of Rogers and colleagues (57).

Related to the azacrowns, another group of macrocycles has been used to great effect to bind lanthanide, and some *p*-block, metals. The tris- and tetra(acetic acid) derivatives of triazacyclononane, cyclen and cyclam, are easy to prepare from the parent compounds and are particularly suited to encapsulate lanthanides (Fig. 10). The complexes can be designed to have magnetic, luminescent, or radioactive properties, depending on the metal chosen, and then appended to an antibody or similar substrate-specific species. Once administered, the magnetic and luminescent species give diagnostic information on the individual's health and the radioactive species can be used therapeutically (58).

5.2. Transition Metals. Outside the main group metals, and those like the lanthanides that have similar nondirectional binding preferences, the predominant targets are transition metals. Supramolecular complexing agents for transition metals tend to have their origins in classic coordination chemistry. For example, ammonia often ligates to metals such as cobalt. Polyamines and cyclic amines have therefore been used to incorporate cobalt into supramolecular systems. Polyamines have also successfully been cyclized to form cyclam and related species that are predisposed to bind to transition metals, particularly those for which a square planar geometry predominates such as nickel(II) (59). In a similar manner, iron, which does not bind to conventional crown ethers containing oxygen, can form complexes with thiacrowns due to the metal's affinity for sulfur. In this way, an octahedral iron species can be capped by two trithia[9]-crown-3 ligands in a facial manner that satisfies its preferred geometry (60).

Transition metals may be incorporated into supramolecular chemistry through complexation by planar macrocycles with convergent binding sites, such as cyclams, porphyrins, or phthalocyanines, or encapsulation within preorganized cavities as found in azacryptands (61) and sepulchrates (62) (Fig. 11). The extensive application of Schiff base chemistry to macrocycle formation is also of great importance. The addition of diamines to dialdehydes led to the early discoveries of Curtis (63) and Busch and colleagues (64) that has in turn greatly expanded the number of cyclic ligands capable of binding transition metals. One other motif that has received considerable interest of late has been the use of transition metals as structural elements in supramolecular architecture. Thus, octahedral species with one capped face, leaving three orthogonal coordination sites, can form the corner of a cube (65). Tetrahedral centers can template the formation of chiral helices from achiral ligands, and other, angled, Schiff-base ligands can be induced to form triple helices in the presence of octahedral metal centers (66). Other forms of architecture can be generated by these principles. Silver has been used to direct flexible ligands into interlocked linear, sheet-like, and three-dimensional lattices (67). In a particularly fascinating development, transition metals have been used to hold ligating structural elements in place while further reactions pin them into interlocking Borromean molecular entanglements (68).

5.3. Organic Cations. The organic cation that has attracted the greatest interest as a target for supramolecular recognition is the ammonium ion. It is bound by [18]crown-6 and its derivatives through the excellent fit between the relative positions of crown ether oxygens and the tripodal symmetry of the cation. Further use has been made of this phenomenon: It is possible to incorporate the binding motif into bifunctional sensors that detect specific amino acids (69). Larger crown ethers, although more flexible and therefore less preorganized for guest recognition, can be used as a basis for cation recognition. It was shown that the guanidinium cation could template the formation of [27]crown-9 due to the complementary symmetry of the planar guanidinium cation (70). This inclusion property later formed the basis of a guanidinium-selective electrode (71). It is also possible to use preorganized molecular clefts to bind organic guanidinium cations. The hexagonal lattice approach, initiated by Zimmerman and colleagues (72) and used to great effect by Bell and colleagues (73), has shown how an *N*-alkyl guanidinium guest can be bound by a rigid complementary hydrogen

bond array (74). In a related approach, the macrocycle dibenzo[30]crown-10 is flexible enough to allow its benzene rings to stack and form a cleft suitable for planar, positively charged guests and derivatives of this crown have been shown to bind to diquat cations (75).

6. Anion Binding

Anions are harder species to complex than cations. Simple anions, such as the halides, are relatively large compared with other spherical species and require large cyclic or encapsulating ligands for strong and specific binding. To make a large cavity available, large macrocycles must have either high conformational mobility (to encapsulate the large anion) or, conversely, a very rigid structure (to keep the large cavity accessible). In the first case, the ligand will lack specificity; in the second, there is the possibility of competitive binding by other, smaller species. Of course not all anions are spherical and the design of ligands for other species needs to consider directionality as well as size and charge: It should be possible to discriminate between carbonate and nitrate based on charge and size, although not on geometry. A similar argument may be extended to the tetrahedral phosphate and sulfate anions (Fig. 12). Specific binding of other tetrahedral species such as pertechnetate, chromate, molybdate, and permanganate is a greater challenge.

Anions range in character from hydrophilic fluoride and hydroxide to hydrophobic perchlorate, so the effects of solvent must be taken into account when designing suitable ligands. The effect of pH is also a major influence on anion binding with many species stable only within particular pH ranges. This effect can be illustrated by the anionic species resulting from the ionization of phosphoric acid (H_3PO_4) to dihydrogen phosphate ($H_2PO_4^-$) and hydrogen phosphate (HPO_4^{2-}). In aqueous solution, dihydrogen phosphate is formed at approximately pH 4.5 and hydrogen phosphate at pH 9.5. Thus, the pH of the solution must be adjusted depending on which anion is the target. Similar considerations must be made for sulfates, carboxylates, and amines.

The earliest anion binding ligands to be prepared were those of Park and Simmonds (76,77) whose katapinands were similar to Lehn's cryptands, prepared a decade later, but lacked coordinating oxygen atoms in the linkages connecting the nitrogen atoms. In the diprotonated form, this ligand could encapsulate chloride as shown by the x-ray structure of the complex. Graf and Lehn later reported that the tetraprotonated form of a tricyclic encapsulating ligand could bind both fluoride and chloride (78). Similar compounds have been used to complex ATP through recognition of the polyphosphate residue by protonated regions in mixed oxa- and azacrown ethers. These crowns additionally incorporate a pendent acridine group that is believed to π-stack with adenosine, thus enhancing binding strength and specificity (79). Many polyammonium-containing ligands, mostly macrocycles, have since been prepared. A particular design twist was incorporated by Schmidtchen who prepared molecular tetrahedra that contained quaternary ammonium groups at the vertices (80).

One approach to partially encapsulate anions, pioneered by Steed and colleagues (81), is to prepare organometallic derivatives of calixarenes and cyclotriveratrylenes. Here the aromatic rings form part of an organometallic bis(arene) where the metal and second aromatic group lie outside the macrocyclic cavity. When iron and ruthenium are used in this context, they reduce the electron density of the macrocyclic aromatic rings, attracting anions to the electron deficient cavity. A similar philosophy underlies the use of rigid tripodal ligands derived from 1,3,5-triethyl-2,4,6-tribromomethylbenzene (Fig. 13). Formation of quaternary ammonium derivatives through reaction of functionalized pyridines yields a permanently charged, rigid recognition site for anions (82). A permanent positive charge can also be achieved by incorporating metal-binding substituents to a macrocyclic framework. This approach has been successfully used to prepare calix[4]arene-zinc complexes that bind phosphate though direct coordination of the anion to the metal (12). Combining amines with redox active metal centers, as in the work of Astruc and colleagues (83) and Beer and Keefe (84), enhances the acidity of the anion binding site while allowing the binding to be measured electrochemically.

Extensive work by Gale and colleagues (85) on calixpyrroles has shown that their proton-rich central cavity makes them ideal hosts for anions. A particularly useful result is that anion competition can be used to give a colorimetric response in acetonitrile or dichloromethane. In those solvents, the 4-nitrophenolate complex with calix[4]pyrrole is colorless, but when the guest is displaced by a competing anion, the free nitrophenolate turns the solution yellow (Fig. 14). The increasing intensity of the absorbance at 432 nm gives a direct measure of anion displacement (86). Macrocycles are not the only platforms for colorimetric detection of guest anions. Podands, such as Steel's tripodal coelenterands (87), have been used to bind a variety of cationic species but can be modified to complex anions. Anslyn and colleagues showed that 2,4,6- triethylbenzene with guanidinium substituents in the alternating positions is perfectly matched to citrate and used this complementarity to demonstrate the compound's potential as a citrate chemosensor. Initially a complex with carboxyfluorescein is formed and the concentration of citrate is determined through its displacement of the fluorescent dye (88). Anslyn and colleagues' chemosensor used fluorescence absorption and emission to give results that were comparable to gravimetric and nuclear magnetic resonance determinations of citrate in a range of beverages ranging from pure orange juice to carbonated drinks. A related compound, where one "arm" is replaced by an arylboronic acid group, can be used to sense tartrate through a similar displacement method, although this time alizarin is used to give a colorimetric response (89). The use of guanidinium groups or derivatives to induce anion complexation is not surprising: The common motif for biological anion binding is the arginine residue that contains a terminal guanidinium group. It can remain protonated over a wide pH range and therefore provides an ideal monodentate or bidentate anion binding site, particularly if it is to be incorporated into a diagnostic sensor with potential clinical use. Other supramolecular guanidinium-based receptors using this principle have been prepared by several groups, most notably those of Lehn and colleagues (90,91) and Schmidtchen and colleagues (92).

A further approach to anion binding is to design a proton-rich cavity that is flexible yet predisposed to bind a specific guest. Examples of this type include the metal-containing polyazacryptands reported by Jazwinski and colleagues (93) and Arthurs and colleagues (94) that encapsulate succinate and nitrate. A more flexible approach has been taken by Valiyayeettil and colleagues (95), Beer and colleagues (96), and Danby and colleagues (97) who have used tris(aminoethyl)amine, *tren*, as the basis for preorganized anion binding (Fig. 15). Most recently, this theme has been extended to include *tren*-derived, Schiff base podands that have subsequently been reduced to form triamines capable of binding anions, from phosphate to bromide, with a range of specificities (98). The copper complex of a more complex reduced *tren*-derivative, incorporating benzylamine termini, has been shown to bind a variety of anionic guests (99). Inspiration for anion complexation has also been drawn from nature: Davis and colleagues have used derivatives of cholic acid, a bile acid, as a neutral, and highly effective, lipophilic transporter for chloride (100). The compounds have anion-binding pockets comprising amide links to the cholic acid framework, which allows anions to be encapsulated within a lipophilic environment. Proof of the compounds' ability to transport chloride across artificial vesicle membranes was demonstrated by the changes in fluorescence in vesicle-encapsulated dyes.

7. Binding Neutral Molecules

Without the use of charge complementarity as a driving force to induce guest binding, other forces must be considered when designing hosts for neutral molecules. If the guest has well-defined hydrogen-bond donor or acceptor groups that are easily accessible, then it is possible to design a host with complementary groups that will promote complexation. Examples of this type include barbiturate receptors derived from crown ethers (101) and hexagonal lattice receptors for creatinine (102) and guanine derivatives (74). Some aromatic molecules can be bound through π-π stacking interactions (103), and others can use this effect to augment weak hydrogen-bonding (104,105). Natural systems make extensive use of chiral discrimination, but although this can be a very powerful method, the biological receptor (or supramolecular host) must use chirality in conjunction with other forces such as hydrogen-bonding that orient the guest in the correct manner. Many metal-containing biomolecules, including enzymes, use the Lewis acidity of the bound metal to attract polarizable neutral molecules. This approach is the driving force behind dioxygen binding by iron in hemoglobin and many zinc-mediated enzymic reactions. Calixarenes have been made that incorporate three pendent imidazole substituents to mimic a common biological binding site for zinc. The zinc-calixarene complexes have been shown to bind a wide variety of small organic molecules with variable efficacy (106).

If none of these interactions is strong enough to bind the desired molecules, then the hydrophobic effect is worth considering. Many potential host molecules have hydrophilic and hydrophobic regions. Flexible molecules, the crown ethers, for instance, can change conformation to present an exterior surface that matches the solvent in which they are dissolved and can thus transport guests between organic and aqueous phases. Rigid cyclic molecules with well-defined

internal and external faces, of which the cyclodextrins are an excellent example, cannot do so and thus have a more limited solubility range. This result can, however, be an advantage. Cyclodextrins are cyclic sugars that have many outward-facing alcohol groups giving a hydrophilic, water-soluble exterior. By contrast, their interiors are hydrophobic and present an ideal environment for small molecules that have limited, or no, solubility in water. The inclusion of these guests within the macrocyclic cavity is an example of the hydrophobic effect. Cyclodextrins were originally observed by Villiers, who in 1891 noticed that a small amount of a crystalline product formed after the degradation of starch by *Bacillus amylobacter* (107). Schardinger later found that the action of *Bacillus macerans* on mixtures of starch-containing plants and sugar generated crystalline products in 30% yield. These were later identified as cyclodextrins containing six (α), seven (β), and eight (γ) linked D-glucopyranoside units. It has since been determined that the enzyme *cyclodextrin glucanotransferase* catalyses the cyclization and the compounds are now produced on an industrial scale. A wide variety of guests, from volatile gases to steroids, can be accommodated by cyclodextrins, although they are necessarily related to the cavity size. All members of the class are about 0.78 nm in depth, but the internal cavity sizes increase with the number of dextrin units. α-Cyclodextrin has a cavity size of 0.5 nm, β-cyclodextrin of 0.65 nm, and γ-cyclodextrin of 0.8 nm. When crystalline the complexes tend to form stacked channels, face-to-face dimers, cages, or layers depending on the size of the included guest molecule.

Using weak forces to bind neutral molecules presents many problems, but careful design of molecular capsules can lead to size-based guest selection. Molecular capsules are of two types, those that are essentially extended macrocycles and those that form through self-complementary dimerization. The former group includes covalently linked resorcinarene dimers, carceplexes (Latin: *carcer*, prison), first prepared by Cram and colleagues (108) and subsequently advanced by Sherman and colleagues (109) and Gibb and colleagues (110) (Fig. 16). The latter extends to urea-appended calixarenes (111,112), "soccer balls" formed from self-complementary diphenylglycoluril units (113) and calix[4]resorcinarenes (114,115). The power of molecular encapsulation was demonstrated by Cram and colleagues who showed that a hemicarcerand could act as a molecular reaction vessel. They encapsulated a lactam guest then, by irradiation, formed the highly unstable (and usually unobservable) cyclobutadiene, which dimerized to cyclooctatetraene before escaping from the host (116).

8. Synthesis and Structures of Supramolecular Assemblies

Several classes of supramolecular assemblies have emerged over the past few decades. Some take their inspiration from biological processes and attempt to replicate effects such as self-assembly and self-replication, enzyme mimicry, biomineralization, and ion transport across cell membranes. Other classes seek to fabricate "smart" or multifunctional materials using alternative methods to conventional chemistry. Yet others are more abstract, often extending the boundaries of current supramolecular chemistry to generate, for example, unprecedented molecular architectures or binding motifs.

9. Self-Assembly and Self-Replication

The two related themes of self-assembly and self-replication rely on accurate molecular recognition between components of supramolecules, in the first case, or between a molecular template and reactive precursors that combine to reproduce the original template, in the second. In both cases, supramolecular chemists base their approaches on those found in nature (Fig. 17). There are many examples of biological self-assembly by identical, or very similar, subunits: the most widely cited being the icosahedral structures of viral capsids and tubular structures such as those formed by tobacco mosaic virus. Atwood and colleagues showed that 4-sulfonatocalixarenes, long known to form bilayers, could also self-assemble into icosahedral supramolecules in the presence of pyridine *N*-oxide as a templating species (117). The phenomenon is not confined to this amphiphilic class of macrocycles; spherical arrays of resorcinarenes had been held together by extensive hydrogen bonding (118). Others have since expanded the scope of this behavior (119). Just as these abiotic systems mimic viral encapsulation, examples of self-replication often attempt to mimic the complementary hydrogen bonding observed in duplex DNA. Rebek and colleagues have been particularly active in the field of artificial self-replication (120), which has proven to be a controversial area (121).

10. Molecular Entanglements

Many compounds encountered in supramolecular chemistry are conformationally mobile and may incorporate potential donor or acceptor groups. This combination of functionality and flexibility can give rise to some surprising behavior, notably, molecular entanglements. One of the earliest examples can be traced back to Wasserman in 1960 (122) who reported the preparation of interlocked organic rings and coined the term "catenane."

Catenanes are interlinked systems in which one cyclic molecule penetrates another and has its origins in topology (123). This concept has been applied to chemical entities by Sauvage and Stoddart, both of whom used large polyether rings for one or more components. The approach taken by Sauvage (124) used tetrahedral copper(I) centers to initiate the formation of interlocked rings. Derivatives of 1,10-phenanthroline bind to copper(I) in a 2:1 stoichiometry. The divergent termini of these ligands then react, under high dilution conditions, with diiodopolyethers to give the catenate in 42% yield. The result is an interlocked pair of macrocycles in which both phenanthrolines remain bound to the copper center. Treatment with cyanide removes the copper and gives rise to a conformational rearrangement in which the phenanthrolines move as far apart as possible. Sauvage introduced a double twist by linking two 1,10-phenanthroline derivatives in sequence. Once this unwound, after the removal of copper, a molecular trefoil knot was formed (125). The principle can be used to form even more exotic species as shown by Lehn's bipyridyl trimers that spontaneously formed double helical complexes in the presence of copper(I) salts (126). Stoddart's extensive work on catenanes used dibenzocrown ethers with two binding sites,

a polyether electron-donor region and an electron-rich region with π-stacking potential. The aromatic regions hold a 4,4′-bipyridinium-based molecular clip in place while 1,4-di(bromomethyl)benzene reacts to form a macrocycle (127). The bipyridinium "train" travels around the polyether thread and has an affinity for the aromatic "stations" through π-π-interactions between the pyridinium groups in the train and the electron-rich aromatic stations (Fig. 18). The shuttle also spins around the thread under a secondary process. The same synthetic strategy has been used to create larger polyethers containing more stations, the most spectacular example of which is undoubtedly the [5]catenane, Olympiadane (128).

Related to the catenanes are the rotaxanes, molecules in which one linear molecule is threaded through a macrocycle and held in place by large "stoppers" at either end that are too large to fit through the macrocyclic "bead." Thus, a macrocycle with electron-deficient aromatic units, bipyridium for example, can form through a templated reaction around an electron-rich aromatic group such as a dihydroxybenzene spacer in a large polyether. Once "stoppers" are attached covalently to the termini of the polyether, the small cycle can shuttle along the "thread" without ever coming off (129). Sauvage accomplished this feat by attaching porphyrin rings to a 1,10-phenanthroline fragment threaded through a macrocycle and held in place by copper(I). The idea of threading one molecule through another has in fact been around since an early paper by Harrison and Harrison (130) but has reemerged as a goal in supramolecular chemistry. More recent work of Amabilino and Stoddart on "molecular meccano" has led to a reevaluation of these compounds (131). Rotaxane-forming systems have also been extensively studied by Leigh and colleagues (132,133) and Gibson and colleagues (134), and there is an interest in rotaxanes from cyclodextrin chemists to the extent that a review dedicated to this subclass has been published (135).

In an exciting extension of catenane chemistry, Stoddart and Atwood and colleagues reported the synthesis and crystal structure of a triply interlocked supramolecule that forms a Borromean link. The Borromean topology, known from ancient times through Norse and early Christian symbolism, takes its name from a design on the Borromeo family's coat of arms that first appeared in Milan during the fifteenth century (Fig. 19). It shows three rings that interpenetrate each other and cannot be separated unless one ring is broken; however, when one ring breaks, the remaining two also fall apart (136). Although known to occur as a structural motif in DNA (137), it is elusive in synthetic chemistry. In Stoddart's example, each ring is prepared by a zinc-templated cyclization of two 2,4-diformylpyridines and two diamines containing bipyridyl ligating sites. The interpenetrating nature of the rings was confirmed by x-ray crystallography (68). In a further example of interpenetrating systems, Böhmer and colleagues reported the synthesis and structure of an [8]catenane that forms when two calix[4]arenes self-assemble into a molecular capsule and are then locked in place through reactions of upper-rim substituents (138). Even compounds with remarkably simple structures can generate surprising interpenetrating supramolecular architectures. Hosseini and colleagues coupled hexaethyleneglycol, known to encapsulate alkali and alkaline earth cations, to isonicotinic acid at both ends. The resulting compound was found to loop around

one silver cation and to coordinate to two others in the axial positions (139). This result generated a linear entanglement of two parallel strands.

11. Current and Anticipated Applications

Supramolecular chemistry has been applied, knowingly or unknowingly, to many areas of contemporary science. In a few instances, this has already resulted in tangible benefits, but it is in the future that widespread applications are most likely to be observed. Research that is at the moment inchoate has, nevertheless, unrivalled promise in fields as diverse as materials science, diagnostic and therapeutic medicine, molecular-level computing, and nanotechnology.

12. Materials Science

In seeking to build complex nanoscale molecules from smaller precursors, it is necessary that the resulting species exhibit long-range order. It may take the form of crystalline lattices or more flexible structures that, nevertheless, have a regular and reproducible form. The former category includes much of what is now known as "crystal engineering" (140): This field extends from the many types of dendrimers (141) through functional polymeric materials (142), mineralized organic compounds (143), and molecular electronics (144) to the extensive and elegant work of Whitesides and colleagues on micron-sized self-assembling particles (145).

Crystal engineering is an attempt to direct the properties of solid materials by generating self-complementary interactions between multifunctional molecules or by developing mixtures of different molecules that assemble to give long-range structural order (146). One outcome has been the preparation of crystalline lattices containing extensive voids (147). These materials have the potential to absorb and store gases that can later be liberated by changes in pressure and temperature. Interest in these absorbent materials has grown of late through the twin developments of fuel cells and hydrogen power as a source of energy (148). Crystals of calixarenes grown by sublimation have been shown to absorb a variety of gases (149), including hydrogen (150), although, given the manufacturing costs of these macrocycles, it is unlikely that they will see large-scale use in hydrogen storage devices.

A more flexible approach to guest inclusion comes from the use of dendrimers. Dendimers are branched polymers with the potential to be further extended at the end of each branch. The dendrimer core may be a simple organic compound, such as 1,3,5-trifunctionalized benzene, or a macrocycle such as a calixarene (151). The core is referred to as "generation 0." It is treated with an excess of a bifunctional reagent that, in turn, grows two or more reactive branches from each point of attachment. Once all core sites have reacted, remaining reagents are washed off to leave a generation 1 dendrimer. Subsequent generations are formed by repeating this process, which leads to a rapid increase in the complexity and size of the dendrimer, changing the properties of each generation. Many groups may be incorporated within the structure

from those with simple chelating potential to fullerenes (152). Dendrimer properties, such as solubility, can be determined in advance and varied depending on the eventual use. It is possible to incorporate groups that use weak forces associated with supramolecular chemistry to bind particular guests and then let them dissociate at a known rate. This "controlled release" makes dendrimers good candidates as drug delivery agents (153).

Dendrimers are not the only method of introducing long-range order. Nature uses simple bifunctional molecules, phospholipids, from which to make cell membranes. Phospholipids comprise charged head groups attached to long alkyl chains, and the latter, in aqueous solution, interact due to their hydrophobic character. In an idealized case, this self-organizes to form a "bilayer" with a hydrophobic interior and hydrophilic exterior. As surface energy is lower for a sphere than a planar structure, the entire assembly adopts the lower energy form. The same phenomenon occurs with unnatural surfactants that have hydrophobic tails and hydrophilic (or charged) heads. At a certain point (the critical micelle concentration, or cmc), these compounds self assemble in aqueous solution to form spheres, or micelles, where the tails are at the center and the head groups on the exterior. As with natural phospholipids, it is also possible to form larger structures as a result of bilayer formation. The resulting structure has an aqueous interior and exterior and is termed a vesicle. Artificial vesicles comprising phospholipids are often used as simplified models for cells and, as with dendrimers, can be used as drug delivery systems (154).

Liquid crystals are another example where long-range order can occur through favorable intermolecular interactions. A variety of compounds ("mesogens") can give rise to liquid crystalline ("mesomorphic") behavior, exemplified by the formation of regular, crystalline phases within an amorphous whole, under the influence of temperature or solvent composition. Most mesogens are planar or rod-like and usually have subsitutents, such as alkyl chains, to enhance the mesomorphic phase.

Recently another intermediate structural motif, the gel, has been linked to supramolecular chemistry. Here complementry interactions between molecules ("gelators") stabilize long-range order to form a porous material that encapsulates a large volume of solvent. The gelators are often dendritic but contain groups with the potential to interact either with each other or with a second component. The interactions are those typical of supramolecular assemblies resulting from hydrogen bonding, π-π stacking, and hydrophobic efffects (155).

13. Medical Applications

13.1. Diagnostics. One of the most fundamental uses to which supramolecular chemistry has been put has been the fabrication of single molecule sensors. When a specific guest ion or molecule forms a supramolecular complex with a carefully designed host, the information can be relayed to an appended chemical group that has colorimetric, fluorescent, or electrochemical activity. Any change in the signaling response that occurs upon binding can be used to indicate the presence of the guest species. Thus, the binding event can be observed and the host molecule can be used as a sensor.

In the early 1990s, metal complexes of crown-like macrocyles called cyclams were found to be excellent DNA scission agents, oxidizing accessible guanine residues. More recently, bis(cyclam)s, in which two such molecules are joined together, have exhibited anti-HIV activity. They have been found to be antagonists for the CXCR4 receptor and thereby stop HIV cell entry, probably by blocking amino acids important for *in vivo* binding of the virus. Other cyclam-like macrocycles have been used as magnetic resonance imaging (MRI) contrast agents as they bind strongly to paramagnetic lanthanide ions to enhance the MRI imaging effect (156).

Many examples of diagnostic sensors that evolved from consideration of supramolecular interactions are based on the crown ether motif (Fig. 20). Gokel and colleagues reported an aza[15]crown-5 derivative that responded to Na^+ in methanol (157) that was subsequently improved on by Gunnlaugsson and colleagues, who incorporated a diazacoupled 4-nitrophenol group to enhance the colorimetric response, so that it could detect Na^+ in blood (158). Incorporation of a fluorescent anthracene spacer between the crown and the secondary binding site enables sensitive fluorimetric detection methods to be used. This motif can be found in the extensive work of de Silva. In a classic example, an aza[18]crown-6 was linked to a guanidinium group yielding a fluorescent photoinduced electron transfer (PET) sensor for the brain neurotransmitter GABA (γ-aminobutyric acid) (159). In its zwitterionic form, the ammonium group of GABA binds to the sensor's azacrown ether, whereas the carboxylate terminus binds to the guanidinium group: The binding sites in the sensor are the correct distance apart to select GABA over simple amino acids as the latter cannot span between the two. Shortly after this sensor was reported, Cooper and James used the same crown-anthracene unit, but introduced an aryl boronic acid group, to detect D-glucosamine hydrochloride (160). Still using the azacrown structure, but this time with an azatetrathia[15]crown-5 linked directly to fluorescein, Chang and colleagues have been able to detect mercury under physiological conditions in edible fish (161). Using a similar approach, Odashima and colleagues reported that derivatives of oxacalixarenes, molecules having properties of crown ethers and calixarenes, show promise as detectors for dopamine (162).

Not all detection systems designed using supramolecular concepts require analytes to fit inside cavities within cyclic molecules. Determination of creatinine levels in blood is possible by monitoring the color change of a "hexagonal lattice receptor" when it binds specifically to that analyte (163). Recently it has been shown that calixarenes incorporating peptide loops on their upper rims can recognize specific proteins and disrupt protein–protein complex formation (164), and thus they may find use in the rapidly expanding field of diagnostic proteomics (165).

Although these examples are potential diagnostics, it is important to note that there are also examples where the supramolecular principle has been put into practice. The commercial OPTI Critical Care Analyzer (Osmetech Inc.) measures so-called "critical care analytes" in blood (oxygen, carbon dioxide, pH, key cations and anions, and specific metabolites) using optical sensors. The sensors for Na^+, K^+, and Ca^{2+} are based on a crown ether, cryptand, and podand, respectively (166). Each sensor is located on a separate disk on a disposable cassette. The ligands are attached to a polymer via a 4-aminonaphthalimide linker: As the

concentration of the cations increases, so does the fluorescence of the fluoroionophores. The sensor works on optical, rather than electrical, principles and is thus termed an optode. In a similar approach, ionophores derived from cryptaspherands with chromogenic substituents have been developed to detect alkali metals in blood serum (167). Recent advances in this field have been published in a theme issue of the *Journal of Materials Chemistry* to which the reader is referred (168).

13.2. Therapeutics. The porphyrin motif found throughout nature also has the potential to be used in several different therapeutic strategies. Often insight comes from harnessing the effects of naturally destructive compounds and applying them where they can have a beneficial effect. For example, the disease porphyria arises through the accumulation of porphyrins in the skin, which renders the individual highly sensitive to light. Once the cause of this disease had been determined, the effects could be replicated by simple model compounds leading to the concept of photodynamic therapy (PDT). PDT has its origins in the work of Finsen, toward the close of the nineteenth century, but was first demonstrated successfully using haematoporphyrin in 1961 (169). Other porphyrin derivatives and phthalocyanines, which share a similar structural motif, have since been shown to act as photosensitizing agents (170). PDT uses the metal-free macrocycles to target tumor cells, for which they have some selectivity. With these compounds *in situ*, the affected area (usually the skin) is irradiated with red light to promote the molecules into an excited state that reacts with dioxygen to return to the ground state and, in doing so, form highly reactive singlet oxygen. This approach in turn generates a cascade of cytotoxic free radicals that damage DNA leading to destruction of the targeted cell. As the light source can be a laser, it is possible to use this therapy in a highly accurate manner. Unfortunately, the macrocycles are not entirely specific to cancer cells and can circulate throughout the body until destroyed by natural processes and excreted. It means that for some time after therapy, the patient remains highly sensitive to light, including wavelengths in sunlight's broad spectrum.

In the medical diagnostics field, a group of compounds called texaphyrins, artificial expanded porphyrin-type compounds first prepared by Sessler and colleagues (171) based on the porphyrin structures observed at the core of hemoglobin and other bioinorganic complexes, have been developed and marketed. Their greater size allows them to form complexes with metals such as gadolinium so that they can be used as MRI contrast agents. More importantly, texaphyrins have also been shown to have therapeutic effects (Fig. 21). One compound, motexafin lutetium, has been used to destroy vascular plaque in animal models for atherosclerosis through the light initiated production of singlet oxygen and thus has promise in PDT. The gadolinium analog, motexafin gadolinium, enhances the efficacy of treatment for certain brain tumors through redox cycling that generates free radicals (172).

Other therapeutic agents developed from well-known supramolecular synthons include carboxylic acid functionalized derivatives of triazacyclononane and tetraazacyclododecane that have been linked to monoclonal antibodies. These compounds can bind a range of cations including those with potential for diagnostic imaging (^{111}In and ^{67}Ga) or therapeutic β^--decay (^{90}Y). Once administered the conjugated metal complex is concentrated at the site complementary to the

attached antibody where the diagnostic or therapeutic effect then occurs (58,173). The valuable aspect of this "magic bullet" approach is that the therapy can be tailored to individuals using their own antibodies.

Cyclodextrins are particularly attractive as drug delivery agents due to their wide availability and low toxicity. These macrocycles are water soluble but can encapsulate a range of hydrophobic drugs for slow release through the skin or routes where there is a high degree of hydration, such as the nasal passage. One area in which they are particularly effecatious is as steroid delivery agents (174).

14. Biological Interface

Biological systems have inspired supramolecular chemists for decades, so it is no surprise that the interface between supramolecular chemistry and biology is particularly important. Indeed, calixarenes have had biological applications even before their structures were fully understood. Cornforth reported as early as 1955 that lipophilic calixarenes had antitubercular effects (175), and calix[4]sulfonates are now known to have antimicrobial properties (176), presumably through blocking endogenous transmembrane anion channels (177). Hamilton and colleagues have shown that calix[4]arene with appended cyclopeptides can recognize and bind to basic residues on the surface of α-chymotrypsin, a digestive enzyme found in the small intestine (178). Subsequently calixarenes have been used as the scaffold from which combinatorial libraries of polypeptides can be appended (179).

There has been a sustained interest in applying the concepts and methods of supramolecular chemistry to model biological phenomena at the molecular level and nowhere more so than in the synthesis of compounds that can act as artificial ion channels (180). From a synthetic standpoint, they represent a great challenge due to the complexity and size of molecules required to successfully form channels across biological membranes. Nevertheless, the insights that these compounds give to our understanding of natural channel function, and the potential to develop novel therapeutic strategies, have led many supramolecular chemists to investigate ways of preparing ion channel models (Fig. 22). Given the changes in charge and lipophilicity encountered as a cell membrane is traversed, most researchers start with molecules that can interact favorably with guests in aqueous, lipid-rich, and polarized environments. Polyethers, and more specifically, the crown ethers are ideal candidates in this regard. Many examples of crown ethers are being incorporated into membrane-spanning molecules including Lehn's "chundles" (181), Fyles' synthetic transporter (182), Gokel's hydraphiles (53), Matile's aza[18]crown-6 appended α-helical "barrels" and "rods" (183), and Voyer's helical polypeptide incorporating benzo[21]crown-7 (184). Lehn extended a crown ether derivative with polyamide groups terminating in polyethers to span a lipid bilayer but no transport data were determined. Fyles used [18]crown-6 di-, tetra- or hexaacids derivatized with cyclic tetraesters that terminated in acid, alcohol, or glucose groups, all of which have the necessary hydrophilic character to intercalate into the polar surfaces of lipid bilayers. The crown ether arms alternated to span a membrane in a symmetrical and

amphiphilic manner, and although some compounds showed simple ionophore-type behavior, several showed transmembrane channel properties. These complicated molecules used a modular approach to solving the problem of ion transport. Each section relies on a particular physical property (hydrophobicity, size, dipole, etc), often encountered in selective supramolecular synthons, but brings them together covalently in a logical manner to create an effective biomimetic entity. Gokel's hydraphiles are simpler versions of these compounds. They are composed of crown ethers linked by alkyl chains that can insert through a phospholipids bilayer and guide alkali metals through. Interestingly the hydraphiles based on [18]crown-6 transport Na^+ better than K^+ despite the better size complementarity with the latter. Both can be bound by [18]crown-6 in aqueous solution, but the selectivity (based on relative binding constants) for K^+ is 18 times that for Na^+. The selectivity is in fact derived from two components, the rate of binding and the rate of release, which is 10 times greater for Na^+ than K^+. These compounds therefore transport Na^+ preferentially because K^+ is released more slowly.

Two, more rigid, channel-forming systems also make use of crown ethers. Matile's "push–pull" rods and barrels comprise a 1,4-linked polyphenyl skeleton with aza[18]crown-6 sidechains that emerge in alternating directions. The crown ethers interdigitate to form tetramers and hexamers that self-assemble in polarized membranes. In a similar approach, Voyer has used a sequence of 21 amino acids prepared from alanine and benzo[21]crown-7, inserted as a phenylalanine derivative as every third or fourth residue, to increase Na^+ conductivity across planar lipid bilayers. The resulting compound resembles a peptide α-helix with a series of stacked crown ethers emanating from the external surface. Bilayer experiments indicated that Na^+ conductance could be reduced temporarily by guanidinium or Cs^+. Other macrocycles have been developed to span a biological membrane alone or as interlocking dimers through incorporation of long sidechains. Obvious candidates come from the calixarene family (185), although combinations of amino acids and bifunctional molecules such as aminobenzoic acids have also been shown to form artificial ion channels (186).

Supramolecular chemists do not restrict their choices of synthon to unnatural macrocycles but also use more well-known molecules. Peptides naturally adopt hydrogen-bonded structures and self-assemble in various fashions with the α-helix and β-sheet motifs being the best known. Careful choice of amino acid sequences can be used to prepare unnatural cyclic compounds that then interact cooperatively. Ghadiri and colleagues (187,188), and Inoue and colleagues (189), have explored the potential for cyclic peptides to self-assemble into hydrogen bonded tubes. This approach removes the necessity for long sequences of peptides with carefully tailored helical properties. Indeed, compounds as simple as cyclic tripeptides with an internal diameter of about 0.4 nm have been shown to be permeable to K^+.

Ghadiri and colleagues used alternating sequences of D- and L-amino acids to form structures such as *cyclo*[(L-arg-D-leu)$_4$-] and *cyclo*[(L-glu-D-leu)$_4$-] with inner diameters of 0.75 nm. Initial experiments showed that these cyclic peptides could lodge in a constriction inside transmembrane porin channels reducing the innate Cl^- flux and allowing K^+ to pass through (187). The structures of the cyclic peptides have since been varied to give differential effects in cell membranes.

Specifically, they have antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli*. The peptides self-assemble through complementary hydrogen bonding patterns and then insert, stack, and tilt at about 70° to the bacterial membrane. The insertion compromises the membrane structure and leads to species-dependent cell destruction (188). Inoue and colleagues have reported a similar series of cyclic compounds comprising three to five dipeptide units alternating between natural and rigid, unnatural, amino acids (189). These compounds showed greater permeation to K^+ than Na^+ and were blocked by Ca^{2+} in a voltage-dependent fashion. Interestingly, even simple cyclic compounds containing complementary hydrogen-bond donors and acceptors can form columnar tubes. Shimizu and colleagues prepared a macrocycle that incorporated two urea groups that formed tubes upon crystallization (190). Cyclopeptides comprising "unnatural" amino acid analogs hydroxyproline and 6-aminopicolininc acid have been prepared by Kubiak and Goddard and bind anions, even in aqueous solution (191). Other derivatives exhibit enantioselectivity toward chiral quaternary ammonium ions (192).

Much of supramolecular chemistry draws its inspiration from biological structures. Although most of these structures are organic, some relate to the inorganic architecture found in mineralization. One outstanding example is the artificial synthesis of structures inspired by coccolith exoskeletons. Coccoliths are single-cell organisms that biosynthesize sections of their calcium carbonate shells internally before arranging them on their outer surface through the process of exocytosis. It is possible to mimic the process and form hollow inorganic spheres similar to calcium carbonate exoskeletons (193). Through their preparation, these model compounds give an insight into the natural processes that must occur in their biosynthesis and, once prepared, can be filled with other materials to act as time-release capsules (194).

15. Molecular Computers

The need to store more data in smaller and smaller devices will eventually outstrip the physical capacity for conventional solid-state data storage methods. Several molecular scale possibilities have been advanced in recent years to circumvent this problem, including systems based on quantum mechanics. One potential solution that uses supramolecular chemistry has come from Stoddart and colleagues (11,195). Rotaxanes incorporating electrostatically driven shuttles are tethered to a surface and then a change in potential moves each shuttle from the surface to the rotaxane stopper thereby functioning as an ON/OFF, or 0/1, binary switch. By preparing a small array of these rotaxanes the reliability of the switch can be improved so that only a majority of shuttles need move to signal a change in state. Although this currently represents an expensive solution to increasing chip capacity, it nevertheless illustrates the validity of the molecular computer concept.

16. Bottom-Up Nanoscale Fabrication

With the ever-increasing use of nanoscale components in engineering and elsewhere, there is a concomitant need for manufacturing techniques that produce these components with dimensions between 10^{-10} and 10^{-7} m. Classic lithography methods, augmented by laser technology, can make large numbers of complex objects to 70-nm resolution. This approach makes fabrication at the upper end of the nanoscale possible, but definition is lost as the features become smaller. Conversely, traditional synthetic chemistry can be used to "grow" structures from the atomic scale upward. This approach borders on the lower end of the nanoscale but loses accurate reproducibility as the molecules grow larger. A supramolecular approach assembles molecules using a variety of noncovalent forces, relying on thermodynamic control to give greater accuracy while building up each phase of the material. It is possible to covalently link a monolayer of a bifunctional compound to a surface and then add a second compound that uses supramolecular interactions to align and bind to the first monolayer. The process can be repeated to generate functionalized surfaces several nanometres thick. The reproducibility and specificity can be extremely high as defects are corrected by Lehn's "dynamic reversibility of noncovalent interactions" (5) that ensure the correct fit is achieved between adjacent molecular monolayers. The dynamic, self-correcting process is also at the heart of many biological processes such as self-replication, peptide synthesis, and phospholipid membrane formation. Considering how well this method of synthesis suits biological systems it is perhaps the most useful approach currently available to accurately prepare nanoscale devices and functional materials.

As a starting point from which to prepare nanoscale materials, many groups have coupled conventional coordination chemistry with self-assembly (196). Metal ions that generally adopt octahedral geometries are predisposed to form bonds at 90° to each other and, when linked by bifunctional ligands, can become the basis for molecular boxes. Other geometric arrangements arise from tetrahedral or square planar metal centers capped in particular positions. For example, Thomas and colleagues prepared discrete cubes from the reaction of a trithia[9]crown-3 ruthenium complex and excess 4,4-bipyridine (65) and Fujita and colleagues have shown that careful choice of ligands can generate small molecular tetrahedra (197) or large spherical coordination networks (198). Raymond and colleagues have demonstrated that chiral supramolecular clusters can be formed from achiral bifunctional ligands that bind octahedral metals at the corners of tetrahedra (199) and act as supramolecular catalysts (200). Other advances in this field have come from Champness and colleagues, who have prepared honeycomb arrays from melamine and perylenetetracarboxylic acid. These arrays can be used to entrap fullerenes or be manipulated by atomic force microscopy (201).

17. Nanomachines

The ultimate objective of nanotechnology is the production of complex multifunctional systems on the nanoscale. These entities, may be free-standing such as "smart" pills that detect when and where an individual requires medication and then delivers it accurately, or incorporated into materials, for example, in detecting and evening out strain experienced by different cable strands. Supramolecular chemistry is very much a part of this endeavor. Currently, much activity has been to prepare small molecules that act as gears (202) or electrochemical switches (203). Combinations of supramolecular components have been used to make nanoscale models of conventionally engineered components such as a "nanocar" (204) that can be driven across a gold surface on its fullerene wheels (Fig. 23). It is unlikely in the near future that nanomachines will become as complex as envisaged by Drexler (205); however, a deep understanding of the forces driving supramolecular chemistry will surely be required if nanoscale engineering components are ever to be realized.

18. Conclusions

This article can only serve as a brief introduction to the extensive and fascinating field of supramolecular chemistry. The growth of the field over the past 20 or 30 years has been sustained and shows no sign of slowing down. Perhaps the most valuable feature of supramolecular chemistry is its multidisciplinarity, which becomes apparent through the breadth of research papers using "supramolecular" as a keyword. Since the term was first coined by Lehn, over 14,000 papers have appeared on the subject and it has been the subject of introductory and advanced textbooks (206,207) , practical guides (208), book series (209), and encyclopedias (210). Indeed, it is almost impossible to read the tables of contents for leading chemical journals without coming across at least one paper with "supramolecular" in the title; there are even journals dedicated entirely to the subject (211). The reader is referred to these sources for further information.

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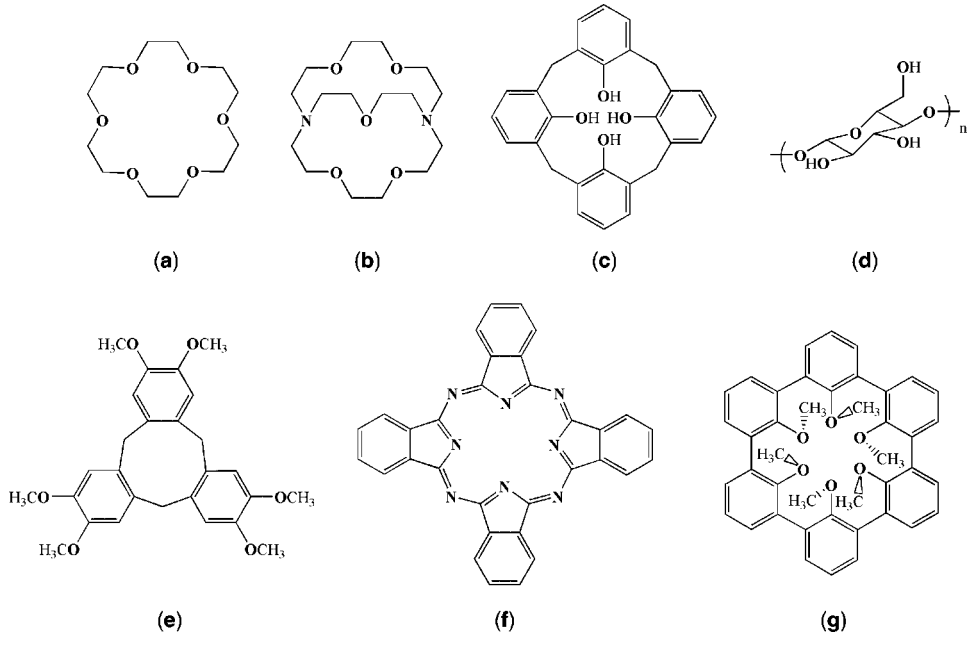

Fig. 1. Representative molecular host molecules: (**a**) crown ether, (**b**) cryptand, (**c**) calixarene, (**d**) cyclodextrin, (**e**) cyclotriveratrylene, (**f**) phthalocyanine, and (**g**) spherand.

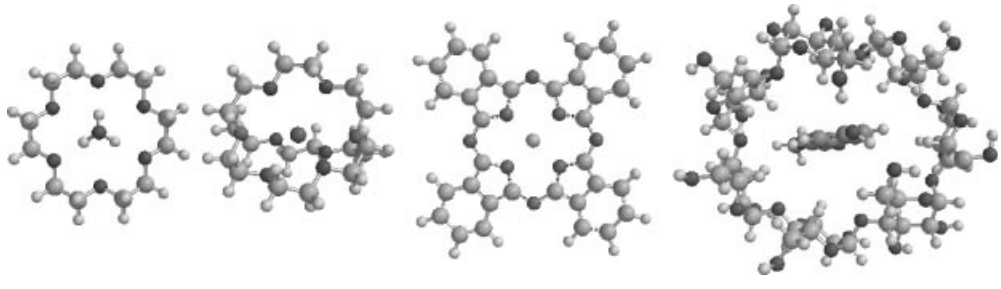

Fig. 2. Host–guest complexes (from left): [18]crown-6·H_3O^+, [2.2.2]cryptand·K^+, phthalocyanine·Cu^{2+}, and β-cyclodextrin·methyl 4-hydroxybenzoate.

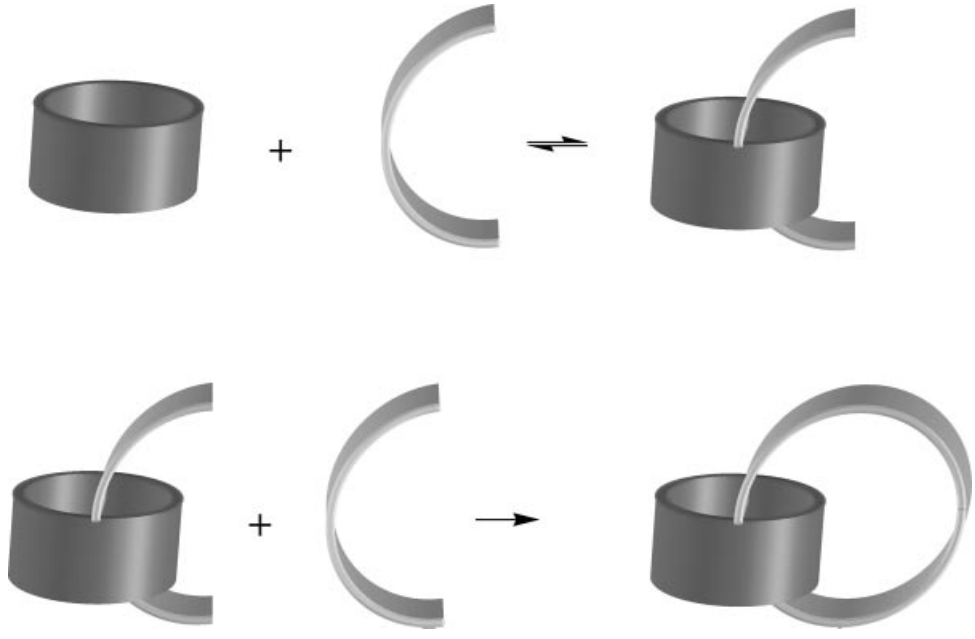

Fig. 3. Catenane formation: The first step is dynamic and reversible; the second involves the formation of irreversible covalent bonds.

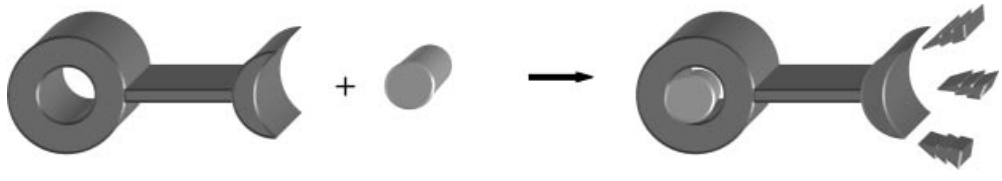

Fig. 4. A sensor based on supramolecular principles: The receptor is connected to a reporting unit by a linker, and when a guest binds, the event is signaled by a response from the reporting unit.

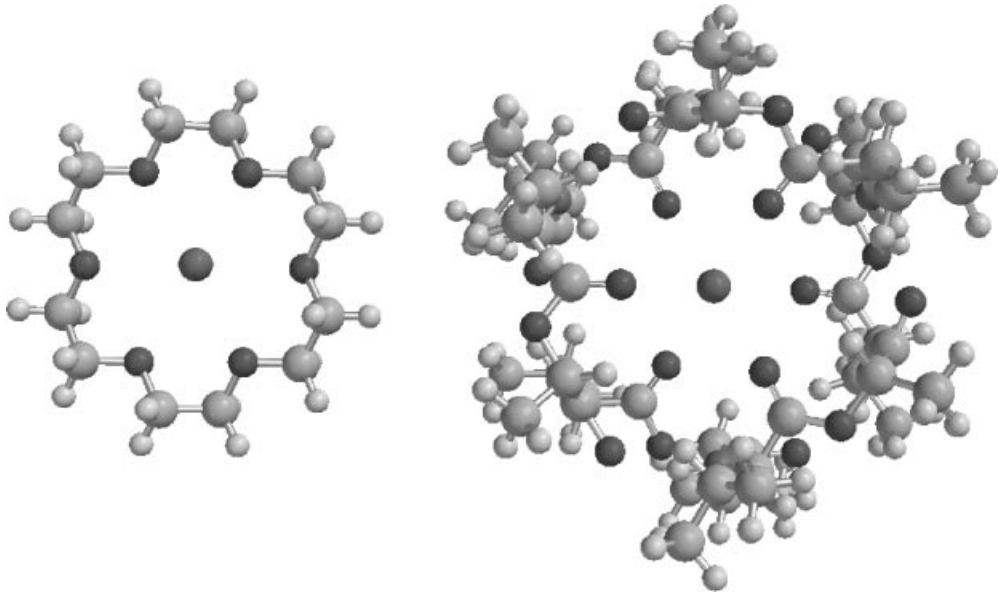

Fig. 5. Potassium binding by [18]crown-6 (left) and valinomycin (right).

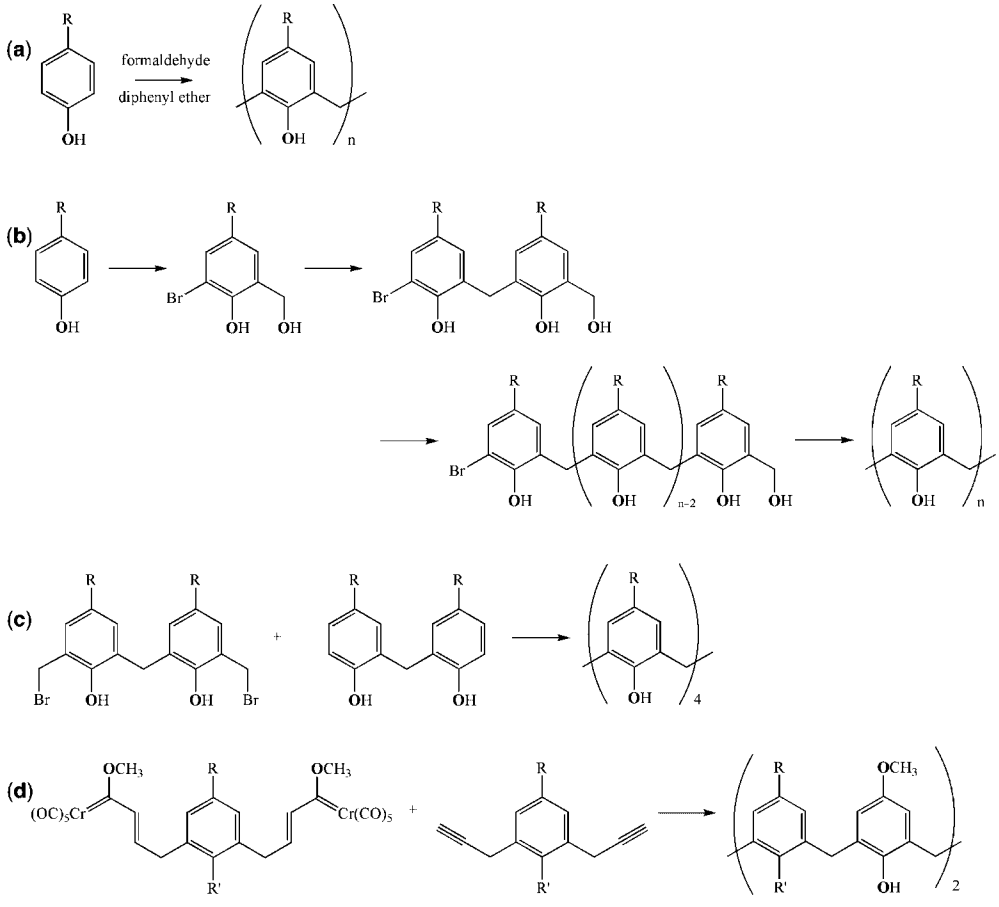

Fig. 6. Approaches to calixarene synthesis: (**a**) Gutsche's one-pot method, (**b**) Hayes' and Hunter's linear synthesis, (**c**) Böhmer's convergent method, and (**d**) Wulff's method, employing Grubbs' catalyst to cyclize the calixarene.

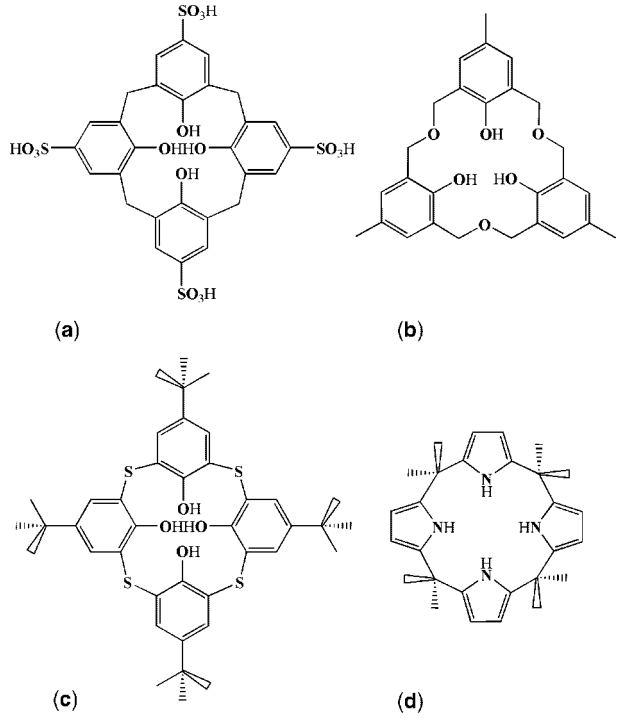

Fig. 7. Calixarene derivatives: (**a**) water-soluble calix[4]sulfonate, (**b**) oxacalix[3]arene, (**c**) tetrathiacalix[4]arene, and (**d**) calix[4]pyrrole.

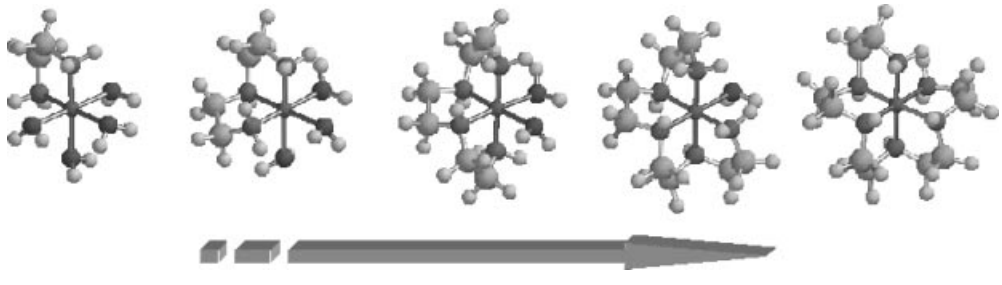

Fig. 8. The chelate effect: Cobalt–ligand complex stability increases from left (with ethylenediamine) to right (with pentaethylenehexamine).

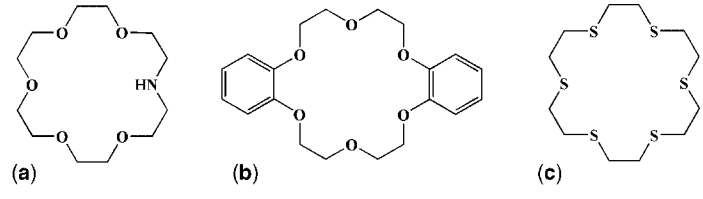

Fig. 9. Examples of crown ether derivatives: (**a**) aza[18]crown-6, (**b**) dibenzo[18]crown-6, and (**c**) hexathia[18]crown-6.

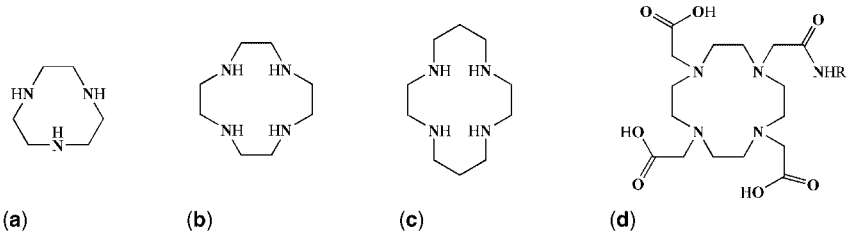

Fig. 10. Azamacrocycles: (**a**) 1,4,7-triazacyclononane, (**b**) 1,4,7,10-tetraazacyclododecane (cyclen), (**c**) 1,4,8,11-tetraazacyclotetradecane (cyclam), and (**d**) a "DO3A" derivative of cyclen.

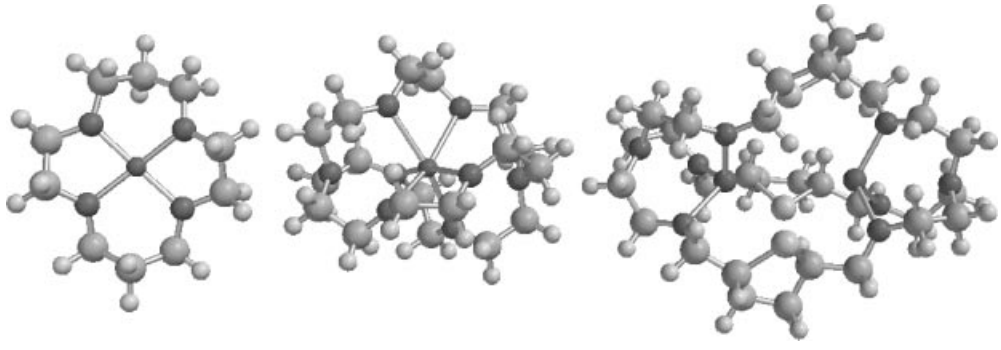

Fig. 11. Guest encapsulation by cyclam (left), sepulchrate (center), and azacryptand (right).

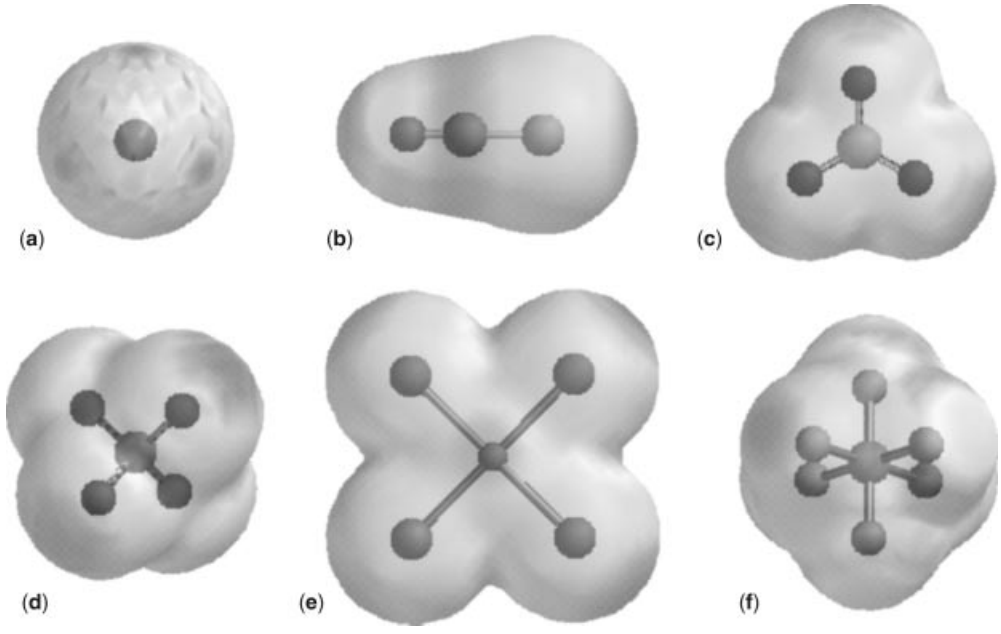

Fig. 12. Examples of anion geometries and relative sizes: (**a**) chloride (spherical), (**b**) thiocyanate (linear), (**c**) carbonate (trigonal planar), (**d**) sulfate (tetrahedral), (**e**) tetrachloroplatinate(II) (square planar), and (**f**) hexafluorophosphate (octahedral).

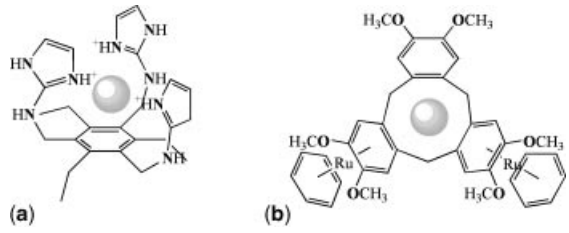

Fig. 13. Electrostatic approaches to anion binding: (**a**) podand containing quaternarized nitrogens, and (**b**) organometallic derivatives of macrocycles.

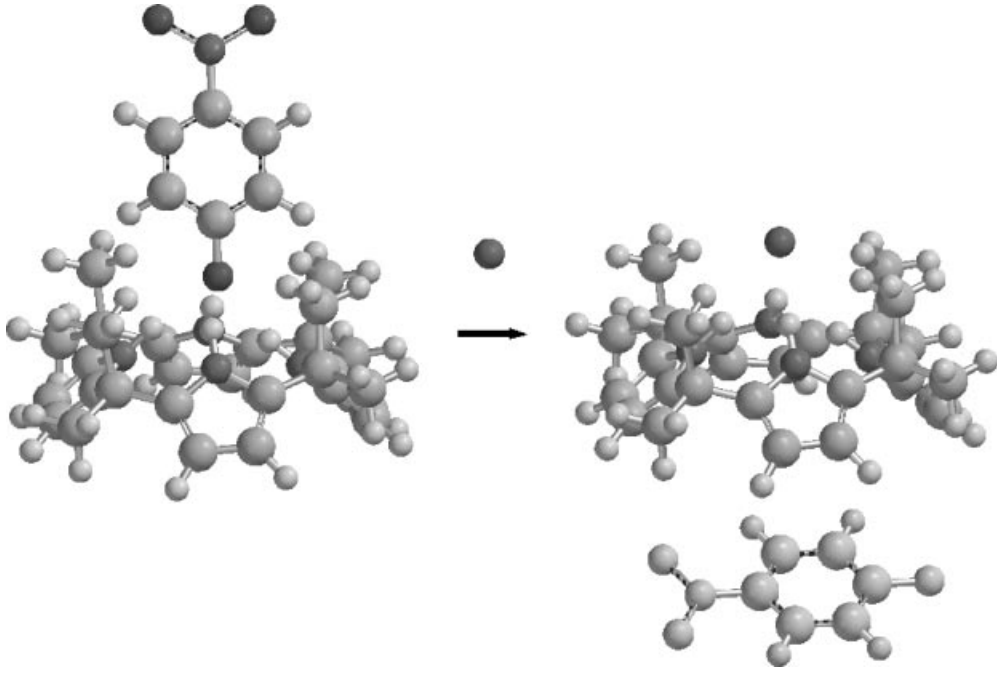

Fig. 14. Displacement assays using calixpyrrole: The complex (left) is colorless, but when fluoride is added, 4-nitrophenolate is released giving a characteristic yellow color (right).

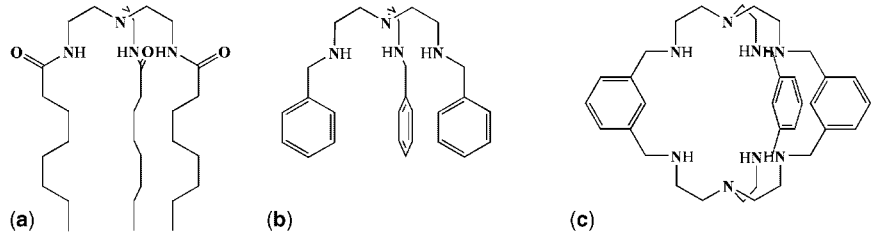

Fig. 15. *Tren*-derived anion binding systems: (**a**) amide derivative, (**b**) amine derivative, and (**c**) anion encapsulating derivative.

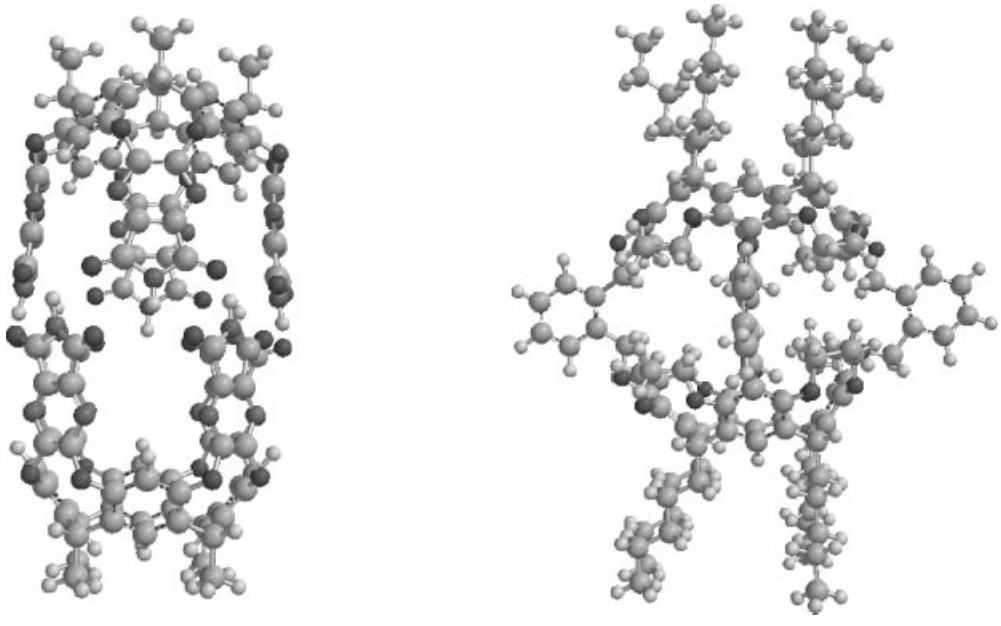

Fig. 16. Supramolecular capsules: Rebek's resorcinarene dimer (left) and Cram's hemicarceplex (right).

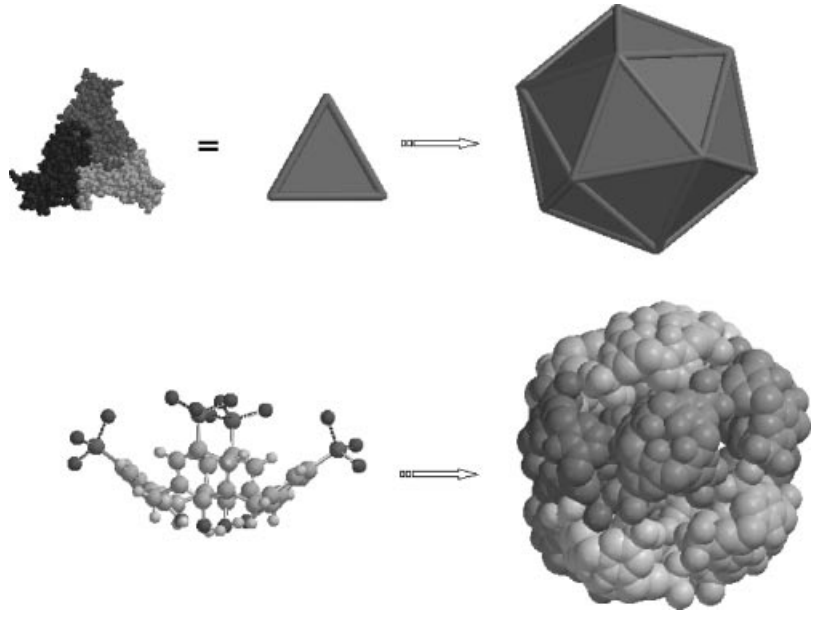

Fig. 17. Inspired by biology: Three subunits of turnip yellow mosaic virus interlock to form one face of the icosahedral capsule (top), and 12 calix[4]sulfate molecules interlock to mimic the same geometry.

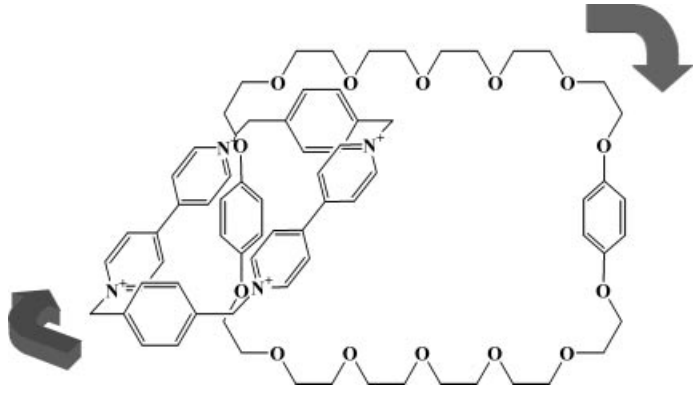

Fig. 18. A supramolecular train. The positively charged "train" rotates around the aromatic ether "station" and can move between electron-rich "stations" using polyether "rails."

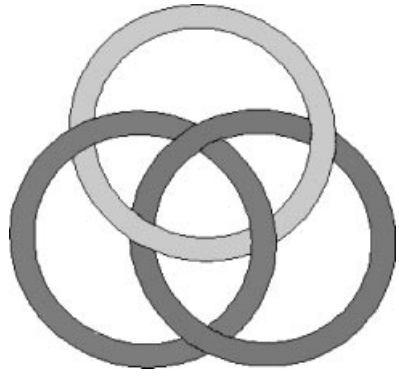

Fig. 19. Borromean topology: The rings are interlocked, but cutting any one also releases the other two.

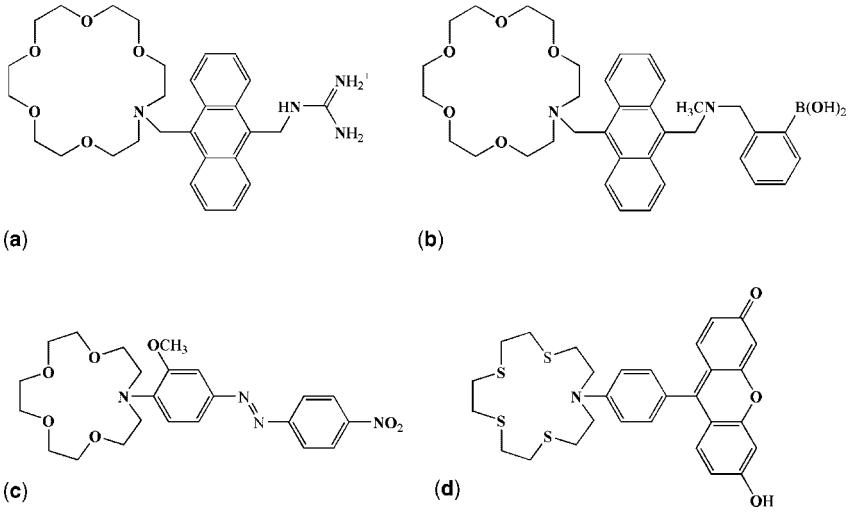

Fig. 20. Supramolecular diagnostics: Sensors for (**a**) GABA, (**b**) D-glucosamine, (**c**) Na^+, and (**d**) Hg^{2+}.

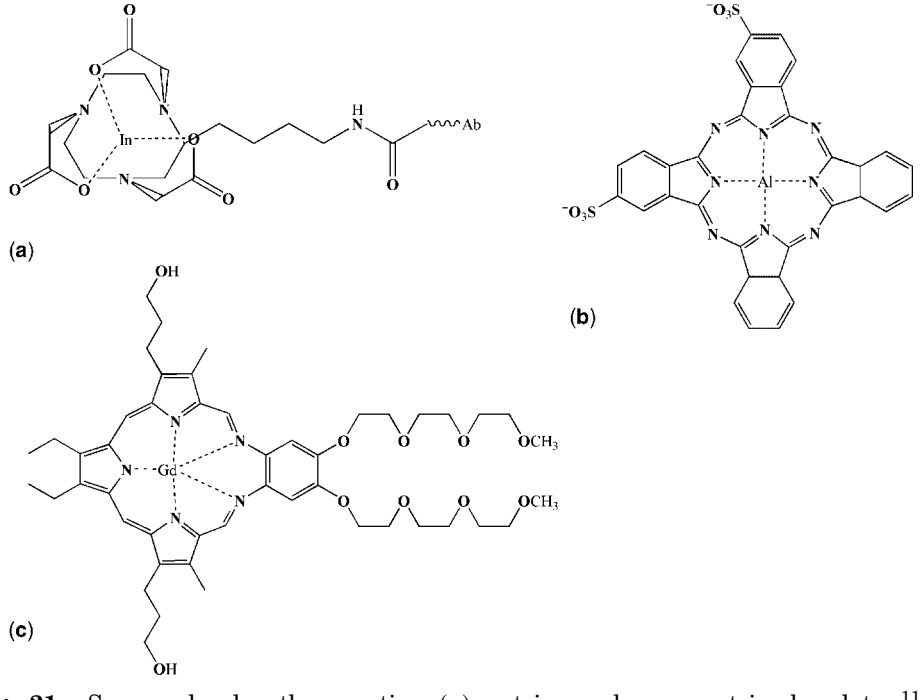

Fig. 21. Supramolecular therapeutics: (**a**) a triazacyclononane tricarboxylate–^{111}In complex coupled to an antibody (Ab) for radioimaging, (**b**) a disulfonated aluminium–phthalocyanine complex for photodynamic therapy, and (**c**) motexafin gadolinium, an anticancer agent in phase III clinical trials.

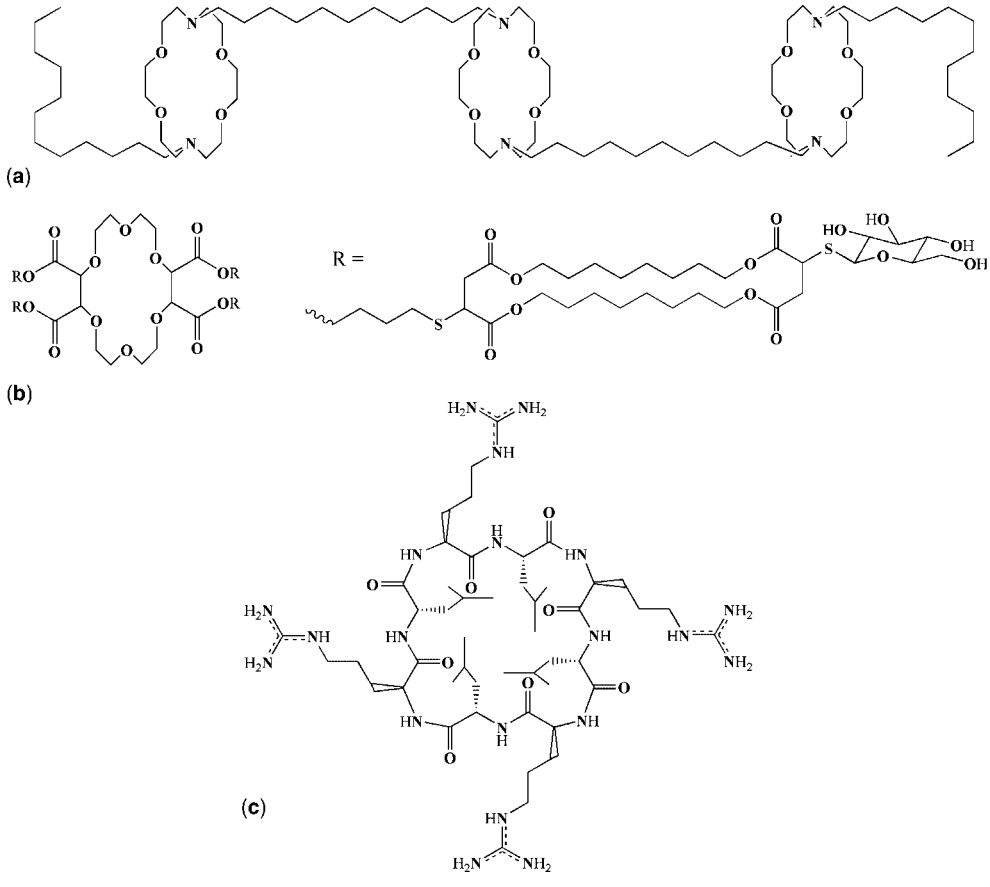

Fig. 22. Ion channel mimics: (**a**) Gokel's hydraphile, (**b**) Fyles' membrane-spanning crown ether, and (**c**) Ghaderi's self-stacking cyclopeptide.

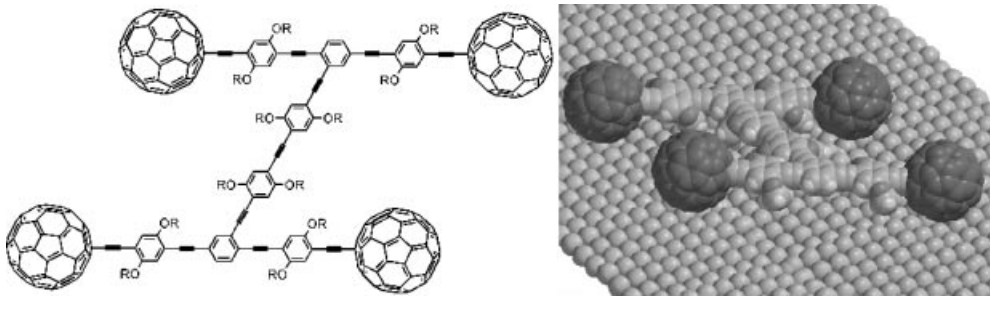

Fig. 23. A supramolecular nanocar: Chemical structure (left) and computational model of the nanocar driving over a gold surface (right).

Table 1. **Noncovalent Interactions of Note in Supramolecular Chemistry**

Interaction	Energy ($kJmol^{-1}$)	Example
Ion–ion	400–4000	Anion inclusion by ligands containing quaternary ammonium groups
Ion–dipole	50–500	Cation inclusion by neutral crown ethers
Dipole–dipole	5–25	Polar solvent inclusion by deep cavity macrocycles
Hydrogen bonds	10–200	Self-assembled capsules
π–π	0–50	Barbiturate recognition by macrocycles containing aromatic groups
van der Waals (hydrophobic)	0.05–40	Inclusion by cyclodextrins

Table 2. **Approximate Binding Constants for 1:1 Host–Guest Complexes of Alkali Metal Cations with Crown Ethers and Cryptands in Methanol**

	Li^+	Na^+	K^+
[12]Crown-4	500	100	10
[15]Crown-5	10	500	$4 \times 10^{3\dagger}$
[18]Crown-6	$1^{\ddagger}$	2×10^4	10^6
[2.1.1]Cryptand	8×10^7	4×10^6	100
[2.2.1]Cryptand	5×10^4	5×10^9	2×10^8
[2.2.2]Cryptand	450	6×10^7	3×10^{10}

†A highly stable 2:1 complex forms.
‡In methanol:benzene (8:2).