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Supramolecular chemistry: from complexes to complexity

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This review looks back to the birth of modern supramolecular chemistry with the formation of simple crown ether–alkali metal complexes through to more recent self-assembling molecular systems. The final section of this review speculates on what the future may hold for supramolecular assemblies. This includes new catalysts, self-replicating molecular systems, complexes that might be used for data storage, and the creation of molecular motors.

Keywords: supramolecular chemistry; macrocycles; cation recognition; anion recognition; self-assembly; molecular machinery

1. Introduction

Molecules that can recognize other molecules or ions, mixtures of molecules that can self-assemble into racks, rosettes or ribbons, molecular machinery, and molecules that can mimic life by self-replicating may sound like science fiction, but are actually examples of the progress made in the area of supramolecular chemistry in the last 30 years. Familiar molecules such as methane (CH_4) and carbon dioxide (CO_2) are made up of atoms joined together by strong chemical interactions called covalent bonds. Molecular chemistry is concerned with making and breaking covalent bonds to form new molecules. Supramolecular chemistry is different because it deals with synthetic molecular systems that are held together by weaker *non-covalent* interactions, such as electrostatic forces, hydrogen bonds, π–π stacking interactions, van der Waals forces, or hydrophobic effects. These non-covalent interactions taken individually are weak, but when several are used together, very stable molecular ensembles or *complexes* may result.‡ Jean-Marie Lehn encapsulated these ideas succinctly when he described supramolecular chemistry as 'chemistry beyond the molecule'.

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‡ Throughout this review, we will be considering the strengths of particular complexes. These are expressed as stability constants (K) which are the equilibrium constants for the formation of the complexes from their component parts; thus, the larger the magnitude of the stability constant, the stronger the complex:

$$\text{host} + \text{guest} \overset{K}{\rightleftharpoons} \text{complex}, \qquad K = [\text{complex}]/[\text{host}][\text{guest}].$$

They are frequently quoted as $\log K$ values, which are proportional to the free energy change for the complexation process. Solvent molecules play an important role in this process. Consequently, stability constants will vary from solvent to solvent for the same complex. Therefore, whenever a stability constant is quoted, the solvent in which it was measured is also mentioned.

Early work concentrated on *molecular recognition*, which is the selective binding of a particular substrate (or guest) by a receptor molecule (or host) using non-covalent interactions. This can be achieved by the careful design and synthesis of the receptor molecule so that it is complementary to the desired guest. For example, a problem in environmental chemistry might be the removal of pollutant metal ions from a river. A supramolecular coordination chemist may be able to design a receptor that is complementary to the metal ion, i.e. its size and the position of its binding sites matches the binding requirements of the metal-ion guest. The receptor may then form a strong complex with the metal ion, removing it from the environment.

Some interactions, such as hydrogen bonds and metal–ligand coordinate bonds, are directional. Chemists have learned how to use these interactions to 'programme' information into molecular subunits so that they *self-assemble* into potentially useful supramolecular superstructures. This self-assembly process, when combined with traditional synthetic covalent modification, gives us access to new molecules (e.g. molecular knots and chains) that previously could not be made.

This short review article will look back to the birth of modern supramolecular chemistry with the formation of simple crown ether–alkali metal complexes through to more recent self-assembling molecular systems. Finally, we will look at some fascinating work that is likely to attract increasing research activity in the new century.

2. Molecular recognition

The birth of supramolecular chemistry can be traced back to the pioneering work of Charles Pedersen, an industrial chemist who worked for DuPont. Pedersen was interested in finding ways to prevent the oxidative degradation of petroleum products and rubber, which is caused by trace amounts of metal-ion impurities, such as copper and vanadium. To do this, he developed a series of compounds known as 'metal deactivators'. These molecules bind the metal ions, converting them into inactive complexes. The catalytic activity of the metal ions is therefore suppressed. In 1960, while attempting to synthesize one of these compounds, he isolated some white crystals in very low yield. His curiosity was piqued by the fibrous, silky quality of the crystals. Even more interestingly, they were soluble in alcohols when sodium cations were present but insoluble in their absence. Elemental analysis and mass spectrometry showed that the crystals were a cyclic polyether **1** (figure 1*a*) that had formed due to the presence of a small amount of catechol (figure 1*b*) impurity in his reaction mixture (Pedersen 1967).

Pedersen observed from a space filling model that a sodium ion is held in the cavity of this macrocycle by attractive electrostatic ion–dipole interactions between the cation and the six oxygen atoms in the polyether ring. This binding mode accounted for the interesting solubility properties of the compound. It was later found that the metal ion acts as a template during the formation of the macrocycle by causing the reactants to wrap around it and orienting them in a favourable way to form the 18-membered ring, **1**.

Because the model of compound **1** looked like a crown, Pedersen called this class of compound the 'crown ethers'. This particular compound was named dibenzo-[18]crown-6. The [18] refers to the number of atoms in the macrocycle and 6 to the number of oxygen atoms in the ring. This is much easier to remember than the

systematic name of compound **1** which is 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadecane.

Many different sizes of crown ether have now been synthesized and coordination studies have shown that a relationship exists between the cavity size, cationic radius and stability of the resulting complex. In short, the better the fit of the cation into the crown, the stronger the complex formed. This phenomenon is referred to as *optimal spatial fit*. For example, [18]crown-6 (**2**, figure 1*c*) forms complexes with sodium, potassium and caesium cations in methanol with stability constant ($\log K$) values of 4.32, 6.10 and 4.62, respectively (Frensdorff 1971). The crystal structure of the potassium complex of [18]crown-6 (Seiler *et al*. (1974); see also figure 1*e*) shows that the cation fits snugly in the middle of the crown ether. Smaller cations, such as sodium, cause the crown ether to distort (Dobler *et al*. (1974); see also figure 1*d*), by wrapping itself around the metal to maximize the electrostatic interactions, which increases the strain in the molecule. Larger cations such as caesium must perch over one face of the macrocycle because they are too large to fit into the cavity (figure 1*f*; see also Dobler & Phizackerley (1974)).

Although Pedersen's discovery was serendipitous (Pedersen 1988), it demonstrated that selectivity could be introduced into synthetic receptors by making them complementary to the desired guest.

In 1969, improving on the cation binding ability of the crown ethers, Lehn and his co-workers at the Université Louis Pasteur in Strasbourg reported a new class of 'three-dimensional' cation receptors called cryptands (Dietrich *et al*. 1969, 1973*a*, *b*). These materials are cage-like bicyclic molecules that contain three polyether strands strung between two nitrogen bridgehead atoms (figure 1*g*). The cryptands have been found to complex group 1 and 2 metal cations with stability constants much higher than those of analogous crown ethers. For example, in methanol, [2.2.2]cryptand (**5**) is selective for potassium cations (with a diameter of 2.66 Å), binding them with a stability constant ($\log K$) of 10.4, which is over four orders of magnitude higher than [18]crown-6. The crystal structure of this complex is shown in figure 1*h*. By changing the length and number of oxygen atoms in each polyether strand, Lehn found that he could tune the receptor to be selective for smaller cations. For example, [2.1.1]cryptand (**3**) is selective for lithium cations (with a diameter of 1.36 Å) and [2.2.1]cryptand (**4**) is selective for sodium (with a diameter of 1.94 Å).

Both the crown ethers and the cryptands require some degree of rearrangement in order to form a complex with a metal cation. Recognizing this, Donald Cram reasoned that rigid receptors with binding sites fixed in an octahedral arrangement around an enforced cavity would show enhanced binding over flexible receptors. With the help of molecular models, he designed a new class of receptor, the spherands, that contains an enforced spherical cavity (compound **6** in figure 1*i*). Spherands bind sodium and lithium cations very strongly (compound **6** forms complexes with sodium with a stability constant $K = 1.2 \times 10^{14}\ \mathrm{M}^{-1}$ in chloroform-*d* saturated with water). Cram formalized these observations with the principle of *preorganization*, which states 'the more highly hosts and guests are organized for binding and low solvation prior to their complexation, the more stable will be their complexes' (Cram 1988).

The pioneering work of Pedersen (1988), Lehn (1988) and Cram (1988) ignited interest in supramolecular chemistry and was recognized with the award of the 1987 Nobel prize for chemistry. Since then, the field of molecular recognition has grown

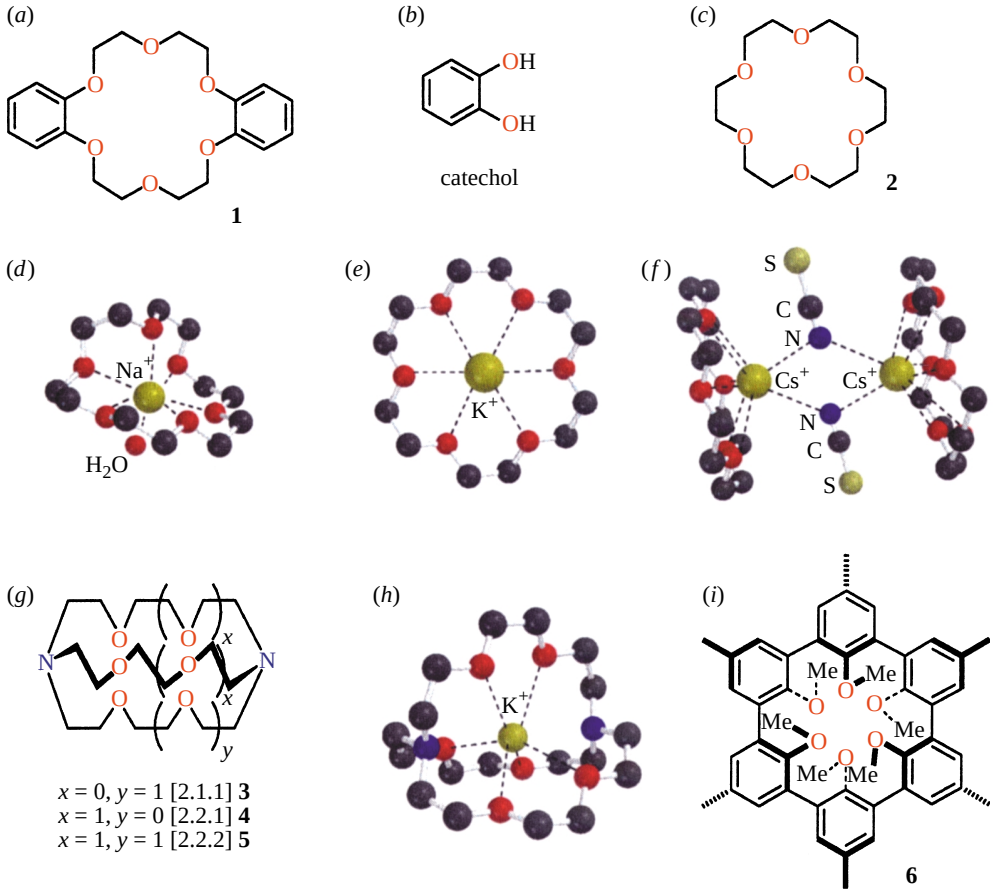


Figure 1. The chemical structures of the cation binding agents (*a*) dibenzo[18]crown-6 **1** and (*b*) 18-crown-6 **2**, with the crystal structures of the sodium (*c*), potassium (*d*) and caesium (*e*) cation complexes of [18]crown-6. The chemical structure of [2.1.1], [2.2.1] and [2.2.2]cryptands (**3**, **4** and **5**, respectively) is shown in (*f*) with the crystal structure of the potassium complex of [2.2.2]cryptand (*g*), and (*h*) spherand **6**. Cations are yellow, oxygen is red and nitrogen is blue.

with the development of receptors for a wide range of cationic, anionic and neutral guests as well as for more complex biomolecules.

The coordination chemistry of negatively charged ions (anions) has only recently attracted the attention of chemists, although the first example of a synthetic receptor was reported in 1968 by Park & Simmons (1968). Anions are ubiquitous throughout biological systems. They carry genetic information (DNA is a poly-anion) and the majority of enzyme substrates and co-factors are anionic (Lang *et al*. 1974). Chemists are, therefore, very interested in making molecules that can recognize particular anions.

Franz Schmidtchen has produced a series of macrotricyclic receptors that use electrostatic ion–ion interactions *alone* to coordinate to anions. For example, receptor **7** (figure 2*a*) contains four positively charged quaternary ammonium groups surrounding a central cavity (Schmidtchen 1980, 1981). Halide anions can be bound within the cavity with stability constants up to 500 M^{-1} for iodide binding in water.

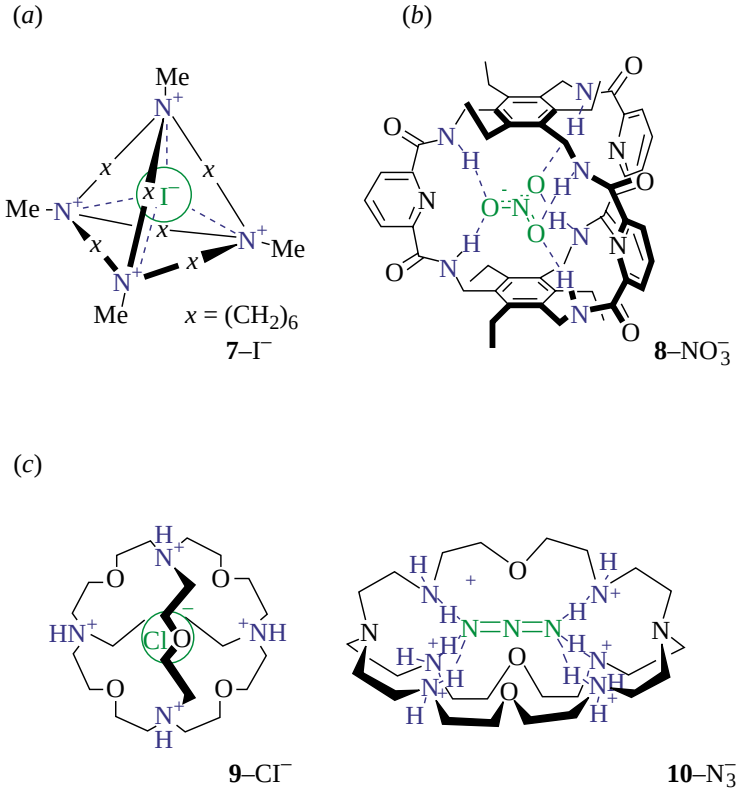


Figure 2. The chemical structures of anion binding agents: (*a*) cage complex, **7**, which uses electrostatic interactions to coordinate to anions; (*b*) a trigonal amidic box **8** that uses hydrogen bonds to coordinate to anions; and (*c*) ammonium cryptand molecules, **9** and **10**, that use electrostatic and hydrogen bonds to coordinate to anions. Anions are green and anion binding groups are blue.

Hydrogen bonds are directional, allowing the possibility of designing receptors with *specific shapes* that are capable of differentiating between anionic guests with different geometries or hydrogen bonding requirements. An excellent example of this is the trigonal box **8** (figure 2*b*), which was synthesized by Anslyn and co-workers (Bisson *et al*. 1997). This receptor forms strong complexes with complementary trigonal nitrate anions (stability constant with NO_3^- anions is $300\,M^{-1}$ in acetonitrile-d_3–dichloromethane-d_2 3:1), while other anions such as chloride or dihydrogen phosphate have stability constants with compound **8** of less than $50\,M^{-1}$.

Hydrogen bonds and electrostatic interactions can be used together to produce very effective receptors for anions. In the 1970s, Lehn's research group reported that the protonated cryptand molecules **9** and **10** (figure 2*c*) bind anions selectively via a combination of electrostatic interactions and hydrogen bonds. Receptor **9** is selective on the basis of *size*, binding chloride anions with a stability constant ($\log K$) of more than 4 in aqueous solution, while the much larger iodide anion is too big to fit into the cavity and is, therefore, bound only weakly (Graf & Lehn 1976). On the other hand, receptor **10** is ellipsoidal and, therefore, is selective for anions such as azide (N_3^-) that are complementary to the *shape* of the cavity (Lehn *et al*. 1978).

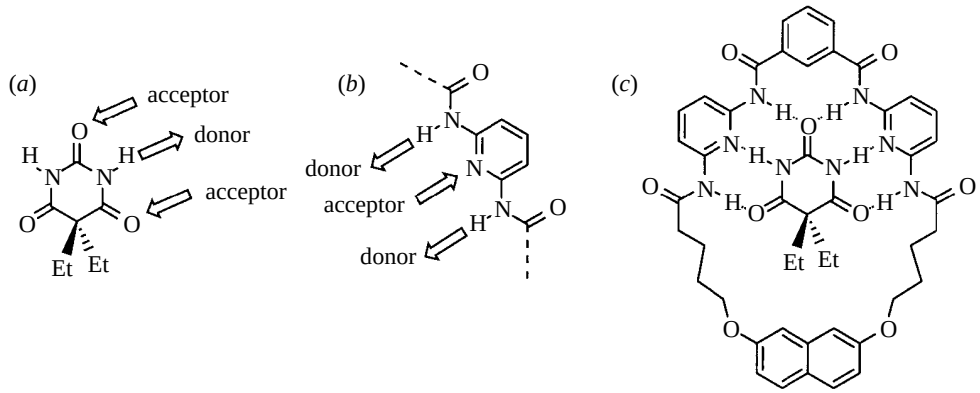
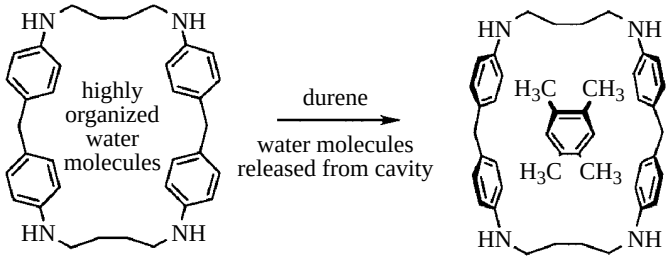


Figure 3. Hydrogen bonding arrays present in (*a*) barbiturate and (*b*) diamidopyridine, together with (*c*) barbiturate complex of receptor **11**. The barbiturate guest is held by six hydrogen bonds from the host molecule.



12

Figure 4. Koga's cyclophane **12** binds neutral molecules such as durene by using the hydrophobic effect.

Neutral guest binding is especially challenging. Receptors must rely less on electrostatic interactions and more on complementary hydrogen bonding arrays, π–π stacking interactions, charge transfer interactions, and hydrophobic effects. Hamilton and co-workers have produced a series of receptors, including compound **11**, that use complementary arrays of hydrogen bonds to bind barbiturates, a class of compound used as sedative and anti-convulsant drugs (Chang & Hamilton 1988; Hamilton 1990). Receptor **11** contains two 2,5-diamidopyridine units that are each complementary to one face of the barbiturate guest. The receptor forms six hydrogen bonds (donating four and accepting two) to give a very stable complex ($K = 1.35 \times 10^5\ \mathrm{M}^{-1}$ in chloroform-*d*; see figure 3).

The other main approach to the complexation of neutral species uses the hydrophobic effect to drive guest binding in receptors containing apolar cavities. In aqueous solution, these cavities are filled with water molecules that form ordered arrays of hydrogen bonds. The degree of order in a chemical system is measured by its entropy. Entropy and enthalpy (a measure of the heat stored in chemical bonds) are the two factors governing whether a chemical transformation (such as complexation) will occur. An increase in entropy (disorder) makes a complexation process more likely to occur. When a neutral hydrophobic guest is available to bind in the cavity, it dis-

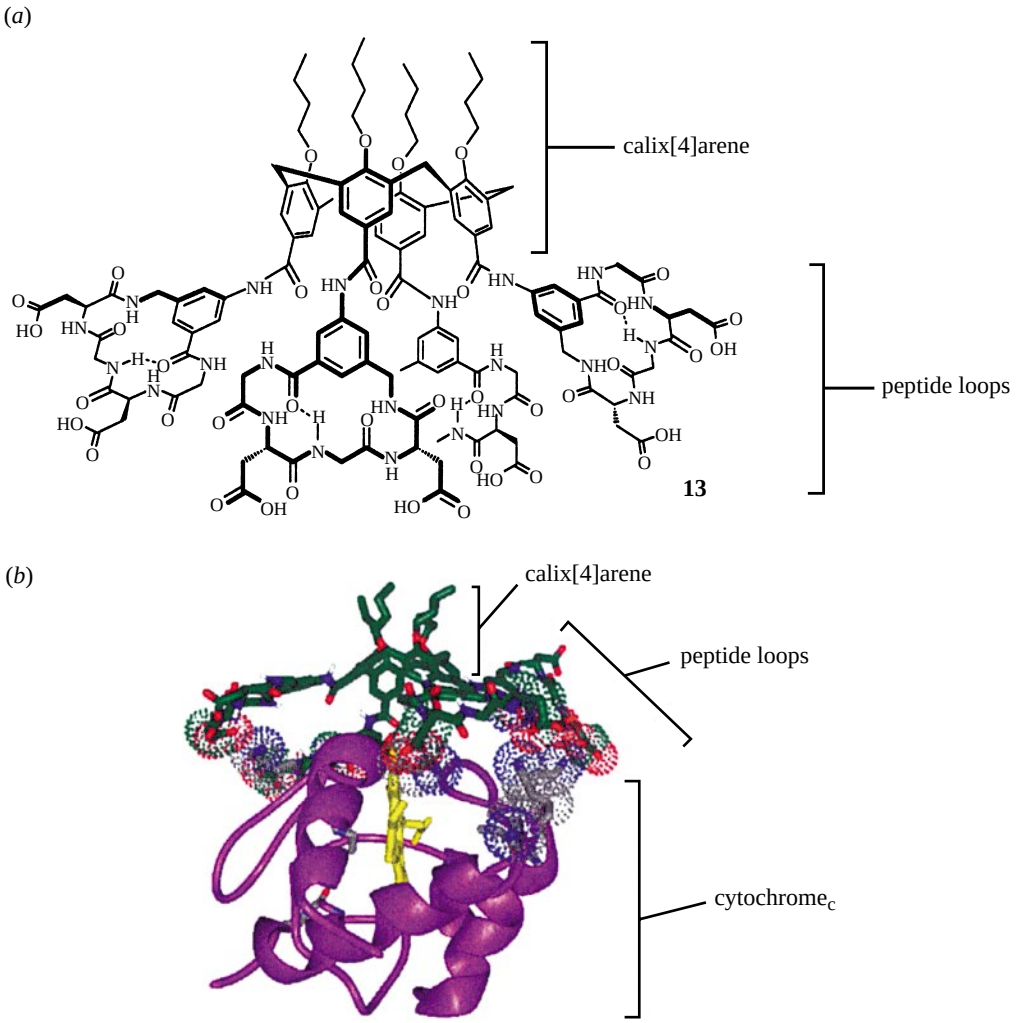


Figure 5. (*a*) The chemical structure of receptor **13**; and (*b*) its proposed complex with cytochrome *c*. (Reproduced with permission from Hamuro *et al*. (1997), © 1997, Wiley-VCH.)

places the ordered water molecules and increases overall entropy. In addition, there is an enthalpic driving force for complex formation because the cavity-bound water molecules may form more hydrogen bonds when released from the hydrophobic cavity than they could inside it. In 1980, Koga and co-workers reported that compound **12**, a cyclophane containing four aromatic rings linked by aliphatic chains, binds aromatic guests such as durene (figure 4; see also Odashima *et al*. (1980)). Acyclic analogues of **12** showed no affinity for potential aromatic guests.

Molecular recognition has advanced to the point where the complexation of complex biomolecules is now possible. Hamilton has attached four peptide loops to the upper rim of a calix[4]arene (a bucket-shaped molecule that, in this case, is being used as a piece of molecular scaffolding holding the four peptide loops close together in space; see Hamuro *et al*. (1997)). Similar peptide loops are present in fragment

antigen binding regions of antibodies. X-ray analysis of antibody–protein complexes has shown that binding occurs by the formation of a large and open interfacial surface composed of residues capable of non-covalent binding interactions with the antibody. In the majority of cases, the antibody contacts the antigen via at least four peptide loops. In Hamilton's synthetic antibody **13** (figure 5*a*), the rigid cone-like calixarene acts as a molecular scaffold holding the peptide loops in an arrangement that defines a peptide binding domain.

The peptide loops present in **13** contain the negatively charged Gly–Asp–Gly–Asp sequence. Hamilton decided to study the interaction of **13** with cytochrome *c* (cyt *c*), a protein that carries a number of positively charged groups on its surface. This was achieved using a technique called affinity chromatography. It was shown that **13** binds cyt *c* strongly, with a binding constant similar to that of the natural cytochrome *c* oxidase–cyt *c* complex. Nuclear magnetic resonance studies indicate that it is likely that the calixarene binds to cyt *c* in a region close to the heme edge. This is a part of the protein that contains an iron (III) metal ion bound in a heme group. Figure 5*b* shows a model of the calixarene docked with the crystal structure of the protein. This demonstrates that the receptor can interact with four of the five available positively charged lysine residues and cover a large portion of the protein surface. It was found that the rate of reduction of the heme group in the calixarene–cyt *c* complex in the presence of excess ascorbate was considerably slower than that observed for the free protein. This is further evidence that the calixarene binds at the heme edge of the protein, and thus hinders the approach of the reducing agent to the heme group. Hamilton has succeeded in disrupting the properties of a protein with a synthetic receptor molecule. This work may pave the way for the production of new pharmaceutical agents designed to modify or disrupt the properties of proteins involved with particular diseases, providing therapeutic benefit to the patient.

Whereas Hamilton has succeeded in binding a biological guest with a synthetic host, Douglas & Young (1998) adapted the protein coat of a virus to act as a host for anionic polyoxometalate species. The protein coat of cowpea chlorotic mottle virus (CCMV) consists of 180 identical protein subunits. Even in the absence of the RNA contents, this structure will spontaneously self-assemble from the constituent protein subunits to form a capsule with an internal diameter of 150 Å. At pH higher than 6.5, the viral coat swells, opening up 60 separate portals, each with a diameter of *ca.* 20 Å (figure 6*b*). This allows the exchange of molecular species between the virus interior and the bulk medium. At pH lower than 6.5 (i.e. more acidic conditions), the virus contracts, closing the portals and trapping any material that is inside (figure 6*a*).

Douglas & Young (1998) took empty virons and incubated them at pH higher than 6.5 with WO_4^{2-} ions. These ions oligomerize under acidic conditions to form paratungstate ($H_2W_{12}O_{42}^{10-}$) polyanionic clusters. When the pH was lowered, the protein coats contracted, resulting in the spatially selective entrapment of paratungstate clusters within the viruses.

Transmission electron microscopy was used to image the mineralized virus particles (figure 6*c*). These images indicate that the paratungstate anions crystallized within the cavity, as their diameter of 150 Å matches the internal cavity size of the virus. A negative stain of the mineralized virus particles revealed the intact viral coats surrounding the paratungstate core (figure 6*d*).

We can anticipate the use of engineered viral protein coats as drug delivery agents capable of transporting a drug and releasing it in a particular part of the body (for

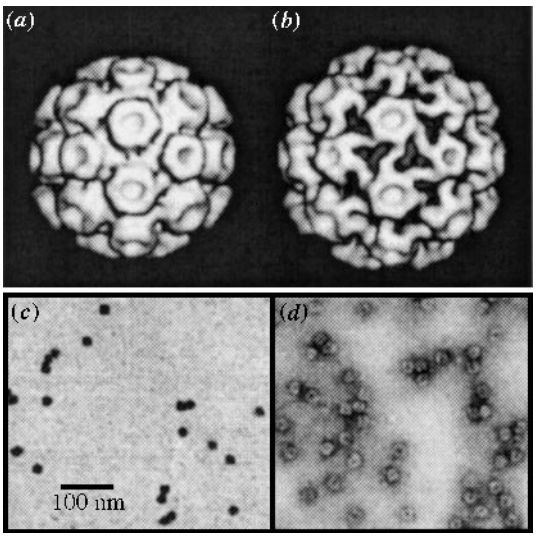


Figure 6. Cryo-electron microscopy and image reconstruction of the CCMV. In (*a*), an unswollen condition is induced by low pH. In (*b*), a swollen condition is induced by high pH. Swelling results in the opening of 60 portals in the virus coat. Transmission electron microscopy images of paratungstate-mineralized virus particles. In (*c*), the electron-dense paratungstate cores may be observed. In (*d*), a negatively stained sample reveals the intact virus protein coats surrounding each core. (Reproduced with permission from Douglas & Young (1998), © 1998, Macmillan Magazines Ltd.)

example, in a cell interior or within the brain; see Smith (1995)). We could also envision the use of these capsules as molecular reaction vessels. The use of synthetic capsules to do this is discussed in the next section of this review.

3. Self-assembly

The CCMV is just one of many self-assembling biological systems. The formation of the DNA double helix from two complementary deoxyribonucleic acid strands is another particularly striking example. The thermodynamically stable double helical structure forms spontaneously and reversibly as the strands are mixed together under the right conditions and hydrogen bonds form between complementary base pairs. The rapid reversibility of the process ensures that any errors that may have occurred during assembly can be corrected.

Chemists can use self-assembly to access new non-covalently linked molecular architectures by combining appropriately designed yet simple subunits. These molecular components contain within them the information required to construct the self-assembled architecture in terms of the position and directionality of their binding sites, the distribution of electron density over their surfaces, or their oxidation states. This information is accessed when the components are mixed together and 'read out' as the self-assembled structure.

Hydrogen bonds have been used to direct the assembly of many different types of non-covalently linked molecular architectures. One early example is the formation of a 'rosette-like' insoluble complex **14** between melamine and cyanuric acid discovered by Whitesides and co-workers (Mathias *et al*. 1994). Melamine can be regarded as

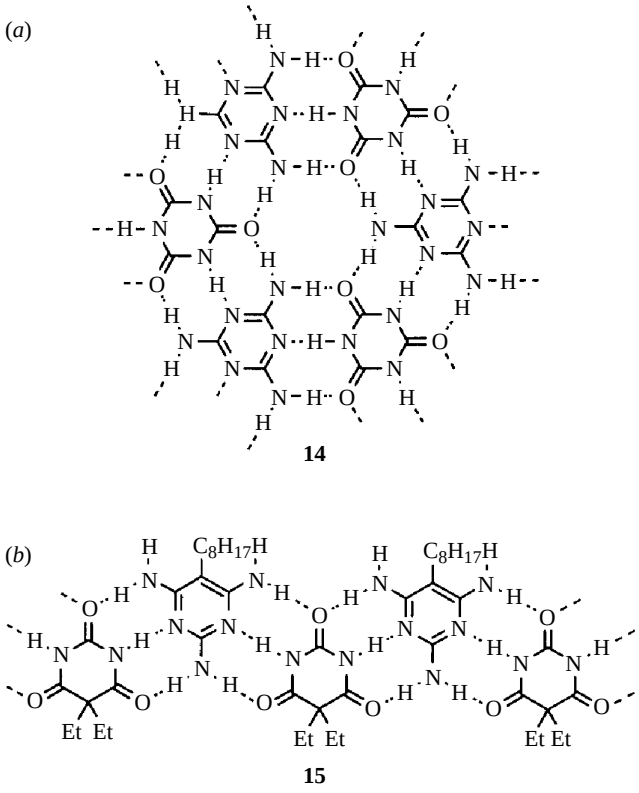


Figure 7. Melamine and cyanuric acid form an insoluble 'rosette-like' complex **14** (*a*), whereas sterically hindered analogues form a molecular ribbon **15** (*b*).

having three faces, each of which can donate two hydrogen bonds from the amine groups and accept one from the aromatic nitrogen atom. In contrast, cyanuric acid can accept two hydrogen bonds and donate one from each of its 'faces'. When mixed together, the two compounds form an insoluble hexagonal network resembling a rosette, as shown in figure 7*a*.

Lehn and co-workers adapted this hydrogen-bonding motif by blocking one face of each of the subunits with alkyl chains (Lehn *et al*. 1990). Steric interactions cause these compounds to form a linear molecular ribbon **15**, which is a non-covalently linked polymer (figure 7*b*).

Self-assembled molecular arrays that contain large interior cavities have the potential to bind large guest species or act as 'molecular reaction vessels' in which reactions may be catalysed by increasing the effective concentration of the reactants. The molecular subunits required to construct these cavities need not be complex. Indeed, MacGillivray & Atwood (1997) have recently shown that six molecules of commercially available (and easy to make) *C*-methylcalix[4]resorcinarene (**16**) self-assemble with eight water molecules to form a chiral spherical molecular assembly held together by 60 hydrogen bonds (**17**). This remarkable structure contains an internal cavity of *ca.* 1375 $Å^3$ (a side view of the capsule is shown in figure 8). The chirality of this assembly arises from the complex network of hydrogen bonds holding it together. Molecular-modelling studies suggest that **17** is large enough to encapsulate

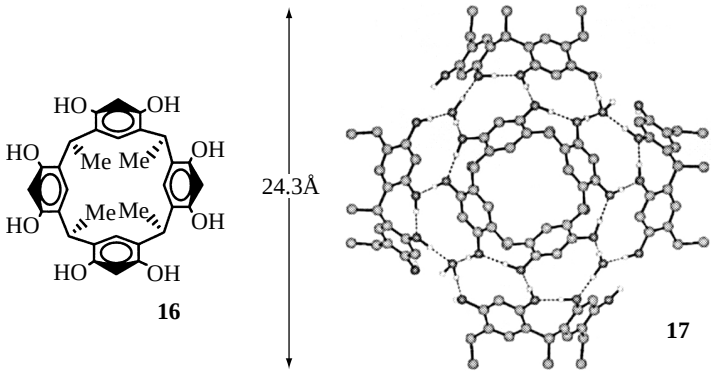


Figure 8. (*a*) The cross-sectional view of the self-assembled capsule **17** showing part of the hydrogen-bond network that holds this complex together. (Reproduced with permission from MacGillivray & Atwood (1997), © 1997, Macmillan Magazines Ltd.)

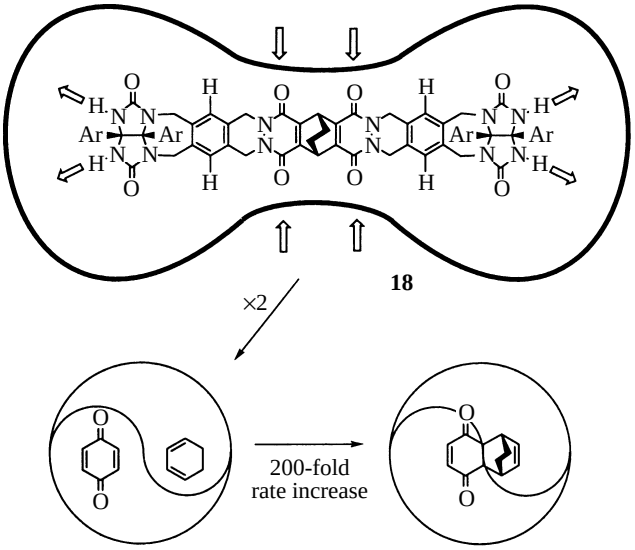


Figure 9. The curved molecule **18** dimerizes to form a molecular tennis ball. This self-assembled sphere can be used as a molecular reaction vessel, catalysing Diels–Alder reactions by up to 200-fold.

coordination compounds (ML-octahedra) or fullerenes. Nuclear magnetic resonance experiments in benzene-d_6 suggest that the cage structure persists in solution. This introduces the exciting possibility of using these *C*-methylcalix[4]resorcinarene cages as chiral catalysts.

Julius Rebek Jr and co-workers have synthesized a series of self-assembled 'tennis balls' from curved molecular subunits (de Mendoza 1998). Compound **18** (figure 9) contains hydrogen-bond donating groups (blue) and hydrogen-bond accepting groups (red) that cause two of these molecules to wrap around each other and form a spherical complex with a large central cavity. This cavity contains solvent molecules that are released on guest binding, making guest binding an entropically favourable process.

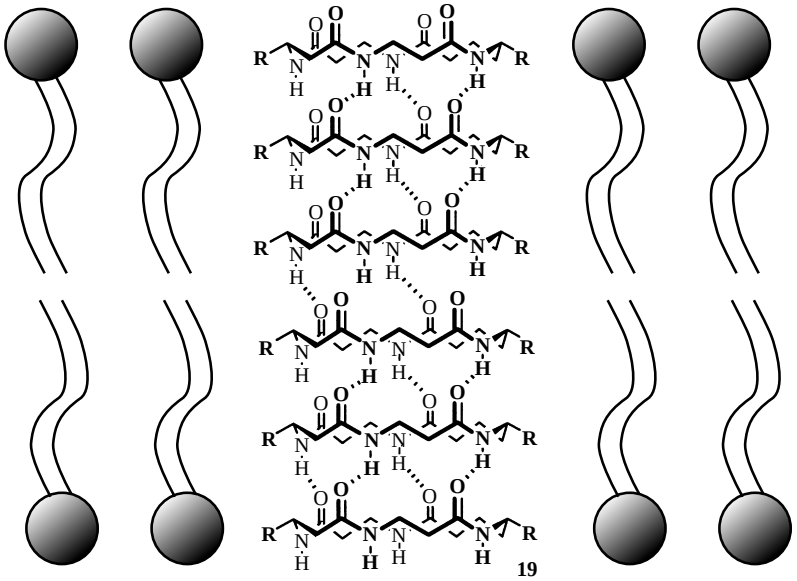


Figure 10. Schematic of a cyclic-peptide based, self-assembled transmembrane channel structure **19** embedded in a lipid bilayer membrane.

This particular tennis ball is capable of encapsulating *p*-quinone and cyclohexadiene simultaneously, and, by increasing their effective concentration, accelerating the reaction between them 200-fold (figure 9).

In cell membranes, proteins such as gramicidin A form channels that allow the passage of protons and alkali metal cations across the lipid bilayer. They do this by forming a β-helix (this type of helix contains a central channel) in which amide (N–H) groups from the peptide backbone alternatively point up and down, forming hydrogen bonds with amide carbonyl oxygen atoms. Two gramicidin A helices, assembled in a head-to-head arrangement, are required to span the membrane. A supramolecular approach to the formation of synthetic ion channels has been pioneered by Ghadiri and his research group at the Scripps Research Institute in California (Hartgerink *et al*. 1998). These researchers use cyclic β-peptides and cyclic D,L-α-peptides to form self-assembled peptide nanotubes. The cyclic peptides adopt conformations wherein the peptide NH and CO bonds point up and down in a similar fashion to the hydrogen bonds of the gramicidin A helix. This allows the formation of multiple hydrogen bonds between cyclic peptides and drives the formation of the peptide nanotube. One example is shown in figure 10. In this case, the cyclic β-peptides **19** have self-assembled into a nanotube within a lipid bilayer (Clark *et al*. 1998). The opening and closing of this channel can be monitored using K^+ single channel conductance techniques, which reveal sharp opening and closing corresponding to either conformational changes in the assembly or to a dynamic assembly–disassembly processes occurring in the membrane. Larger versions of these channels have been shown to transport bigger molecules, such as glucose, across membranes (Granja & Ghadiri 1994).

Transition metals can also be used to direct the assembly of non-covalently linked molecular ensembles. Although metal–ligand bonds are not non-covalent interac-

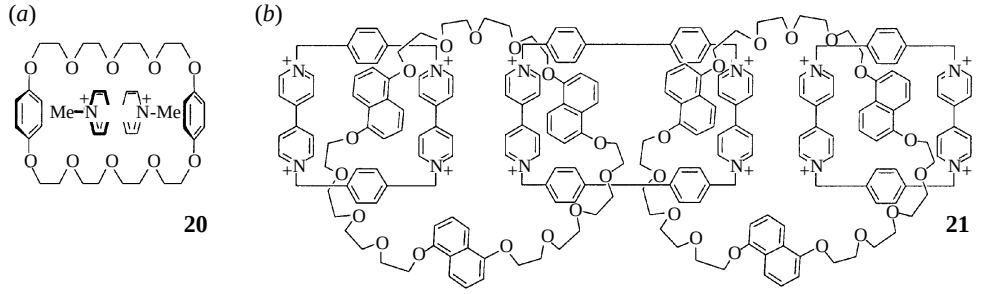


Figure 11. (*a*) A paraquat dication threaded through a bisparaphenylene-[34]crown-8 forming a charge transfer complex **20**; and (*b*) the chemical structure of the [5]catenane, olympiadane **21**.

tions, they are commonly used by supramolecular chemists because, although they are thermodynamically strong interactions, they have varying degrees of lability. This means that the bonds may persist for a long time or may be short lived, continuously breaking and remaking in a reversible, dynamic process. This reversibility allows a type of 'error checking' in the assembly process that will consistently lead to the thermodynamically most stable assembly. Additionally, due to ligand field effects, transition-metal ions often have very specific coordination geometry requirements, which afford very precise control of the structure of the molecular assembly. By changing the oxidation state of the transition metal in an assembly, it may be possible to alter its preferred coordination geometry and so electrochemically switch the assembly between two different states. The electrochemical control of assemblies will be discussed in the final section of this review.

4. Self-assembly with covalent modification

When a strategy of self-assembly is used in concert with covalent modifications, previously inaccessible molecular topologies may be obtained. Stoddart and coworkers have employed electron-rich and electron-poor aromatic components that self-assemble primarily via a charge-transfer interaction to produce a wide variety of self-assembled structures, including catenanes (molecular chains). This work stemmed from Stoddart's discovery that bisparaphenylene[34]crown-10 (an electron-rich crown ether) will bind the positively charged and electron-poor paraquat dication to form the charge-transfer complex **20** (figure 11*a*). Catenanes can be synthesized from precursors similar to this complex. One example, the [5]catenane **21** ([5] designates the number of interlocked rings) is shown in figure 11*b*. This compound is called 'Olympiadane' because of its similarity to the five interlinked Olympic rings (Amabilino *et al*. 1994, 1998).

Perhaps the most ambitious chemical goal that has been reached so far, using self-assembly techniques, is the synthesis of a molecular knot. Sauvage and his research team at the Université Louis Pasteur, Strasbourg, are pioneers in this area of chemistry (Dietrich-Buchecker *et al*. 1994). Sauvage used a transition metal (in this case copper (I), an ion that prefers to adopt a tetrahedral coordination environment) to direct the assembly of the double helical complex **22**. The ends of the helix were linked together covalently to form the metallated trefoil knot **23** and the metal ions removed to afford the metal-free knot **24** (figure 12). The knot is one continuous

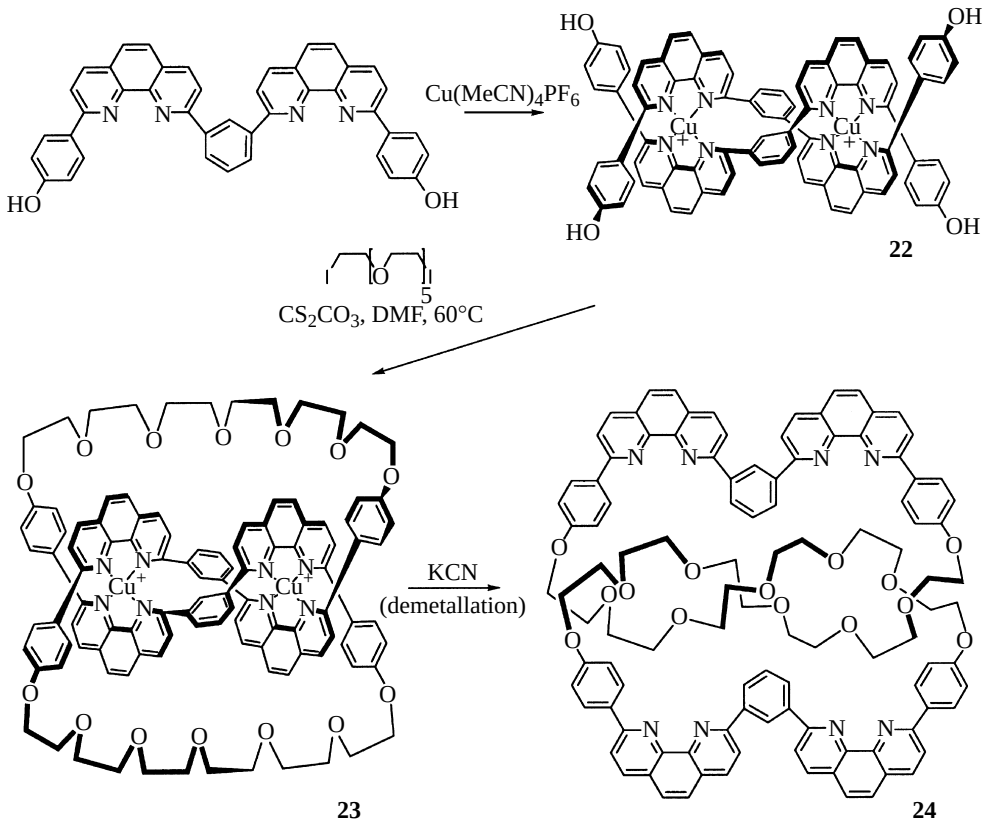


Figure 12. The metal-directed assembly of a trefoil knot **24**.

strand that crosses itself three times. Again, it should be emphasized that the synthesis of this remarkable material would be practically impossible without self-assembly strategies.

5. Into the 21st century

This final section of this review speculates on what the future may hold for supramolecular assemblies. This includes new catalysts, self-replicating molecular systems, complexes that might be used for data storage, and even the creation of molecular motors.

In the coming years, we can expect to see the use of custom-designed supramolecular catalysts that solve specific problems in mainstream organic synthesis. We have already seen that self-assembled structures can enhance the rate of a chemical reaction by increasing the effective concentration of the reactants. A more controlled approach to catalysis is to stabilize the transition state of the reaction product relative to the starting materials, which thus enhances the forward reaction rate (Sanders 1998). Sanders and co-workers have synthesized porphyrin trimer molecules that are capable of coordinating to pyridine-containing reactants via the porphyrin-bound zinc metal ions, and then catalysing the reaction between them (a single zinc–porphyrin molecule coordinated to a pyridine ring is shown in figure 13). Subtle

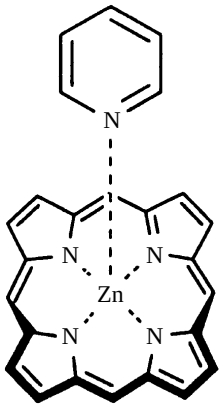


Figure 13. A zinc–porphyrin molecule coordinated to a pyridine molecule.

changes in the structure of their porphyrin trimer molecules have been found to redirect the course of reactions (Clyde-Watson *et al*. 1998). For example, the 2,2,2-trimer **25** catalyses the formation of an *exo*-adduct, while the smaller 1,1,2-trimer **26** catalyses the formation of the *endo*-product (figure 14). Sanders found that neither the 1,1,2- nor the 2,2,2-trimer has the ideal geometry to bind the *exo*-transition state. However, at 30 °C the greater flexibility of the larger host molecule allows for a more complete accommodation of the geometrical requirements of the *exo*-transition state.

The development of chemical systems that can self-replicate by catalysing their own formation may, in the future, provide us with insights into how our own ecosystem arose from the pre-biotic chemical soups on the early Earth (Rebek 1994). The first of a number of self-replicating systems developed by Rebek and his research group is shown in figure 15. The reaction between an adenosine amine molecule **27** and a Kemp's tri-acid-derived ester **28** forms the amide product **29**. This product contains two hydrogen-bonding arrays that are complementary to both **27** and **28**. Compound **29** binds **27** and **28** to give complex **30**, which holds the amine and ester groups in close proximity. This leads to an enhanced reaction rate for the formation of the amide bond between **27** and **28**. Compound **29**, therefore, autocatalyses its own formation. Self-replicating systems developed over the last few years have increased in complexity. Recently, in an important paper (Lee *et al*. 1996), Ghadiri and co-workers have shown that peptides can self-replicate. Unlike simple nucleic acid base pairing interactions that provide a clear basis for establishing complementary molecular recognition and, therefore, the transfer of genetic information, polypeptide–polypeptide interactions are much more complex. Nevertheless, these workers have shown that certain α-helical peptides are capable of self-replication and have, therefore, demonstrated that peptide self-replication may have been involved in the early evolution of life (Lee *et al*. 1997).

Lehn has suggested that spectacular complexes such his 3×3 molecular grid **32** may be used in the future for the storage of information. The grid self-assembles when six equivalents of the linear ligand **31**, which contains three binding sites, are mixed with nine silver (I) metal ions (figure 16*a*; see Baxter *et al*. (1994)). One could imagine that each metal ion corresponds to a 'bit' of information, with one oxidation state corresponding to a 1 and another to a 0. Such arrays would allow the storage of very large amounts of information at the molecular level, in very

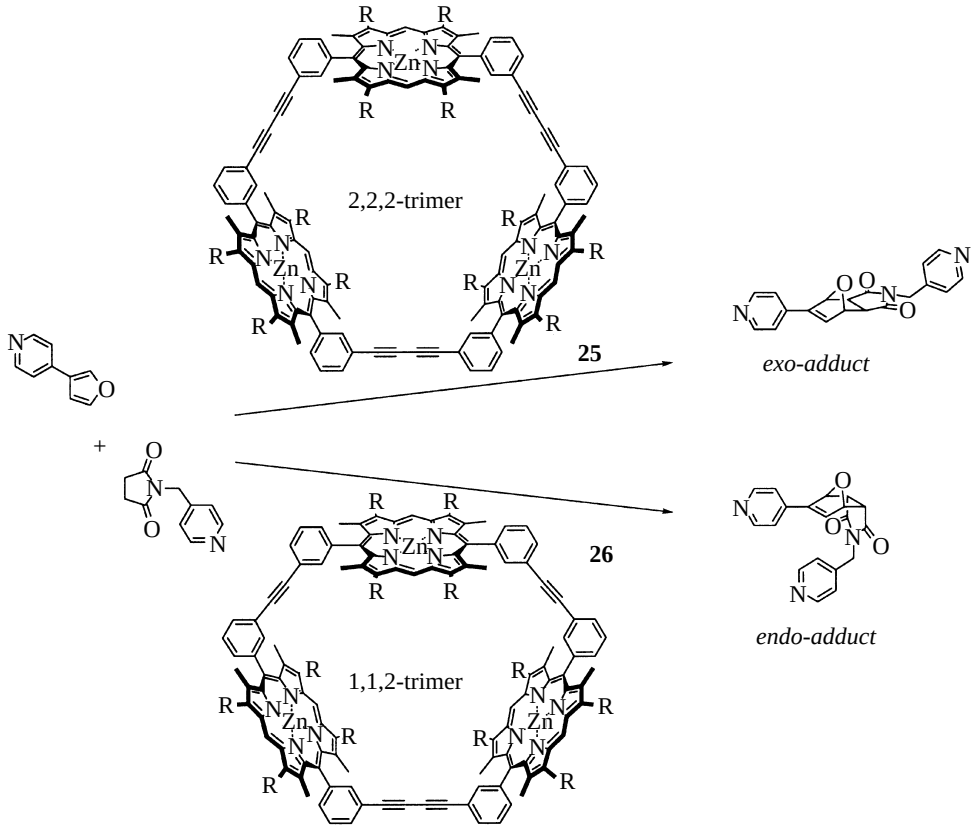


Figure 14. Porphyrin trimer complexes **25** and **26** catalyse the Diels–Alder reaction between pyridine-containing reactants forming the *exo*- and *endo*-adducts, respectively.

small volumes of material. Of course, we will need to find a way to read and write information to and from the individual metal ions first! An alternative way of storing information in a read-only format would be to produce grids that contain different metals in different positions, where the information is stored as the identity of the metal. In fact, Lehn has recently reported the synthesis of 2×2 molecular grids in which the identity of the metals at each position in the grid can be controlled during the stepwise synthesis process (Bassani *et al*. 1998). One corner of the grid **34** is produced first (figure 16*b*) by blocking one binding site in the linear ligand strand **33** with a protecting group and then metallating it. The protecting group is subsequently removed and the resulting corner is mixed with a second metal ion that drives the assembly of the 2×2 heterometallic grid **35**. By mixing corners containing two different metal ions with a third metal ion, a grid containing three different metals, such as **36**, may be isolated (figure 16*c*).

Rotaxanes are composed of a macrocyclic ring through which an axle is threaded. The ends of the axle are blocked by bulky groups that prevent the macrocycle from slipping off. These systems also have potential uses for the storage of information. Sauvage and co-workers have recently produced the rotaxane **37** (figure 17), which acts as an abacus-like molecular shuttle (Gavina & Sauvage 1997). The complex

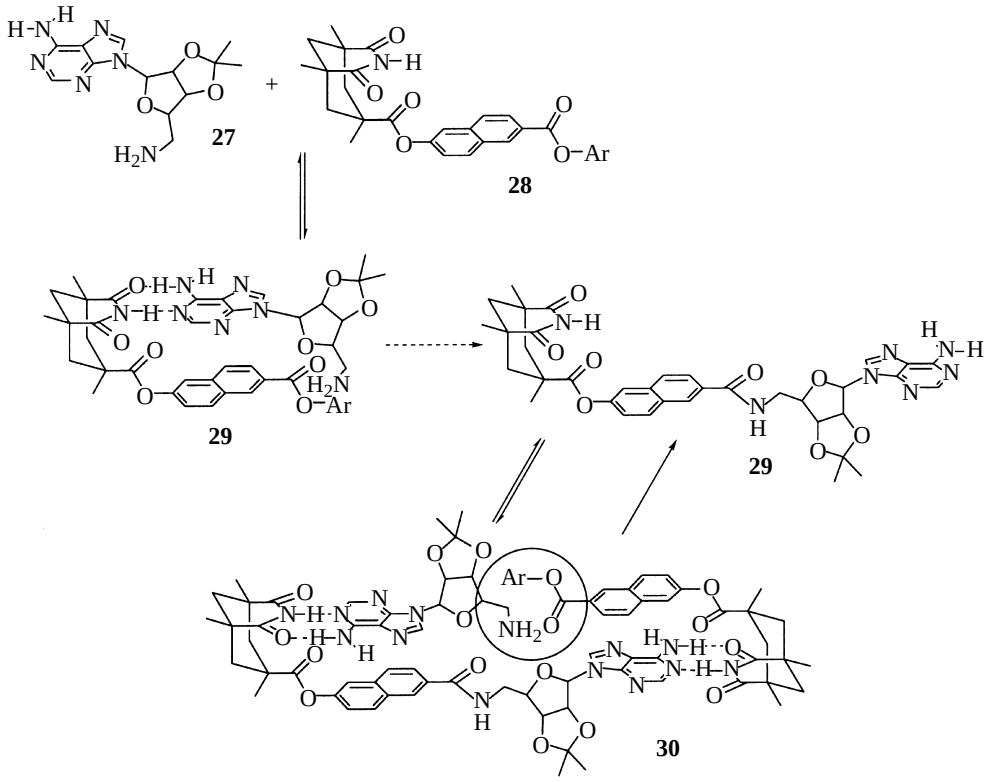


Figure 15. Reaction of molecules **27** and **2** produces a template molecule **29** that can catalyse its own formation through the formation of complex **30** (see text).

was produced using transition-metal-directed self-assembly to thread the macrocycle onto the axle with subsequent covalent modification of the axle by the introduction of blocking groups. The axle contains a 1,10-phenanthroline moiety containing two nitrogen atoms and a terpyridine group containing three nitrogen atoms. The macrocycle also contains a 1,10-phenanthroline group, and, in the presence of copper (I), the metal ion coordinates to both the phenanthroline groups (complex **37** in figure 17). Copper (II) requires a higher number of coordinated groups than copper (I). When the copper ion is oxidized to +2 oxidation state, it jumps to the 3-coordinate terpyridine group, so increasing its coordination sphere to five, forming complex **38** (figure 17). The position of the macrocycle is, therefore, dependent on the oxidation state of the copper ion.

The synthesis of the molecular shuttle **37**/**38**, and others like it, may come to be viewed as the genesis of molecular machinery, i.e. the generation of molecular-sized devices such as gears, switches and motors built by chemical and supramolecular chemical techniques from the ground up (Chambron & Sauvage 1998; Sauvage 1998). The alternative approach of miniaturizing our macroscopic world to produce machinery in the micrometre-size range can be achieved through the use of silicon micromechanics (Howe *et al*. 1990). However, this technique produces machines that have a limited lifespan and that are orders of magnitude larger than the molecular devices that are currently emerging from supramolecular chemistry.

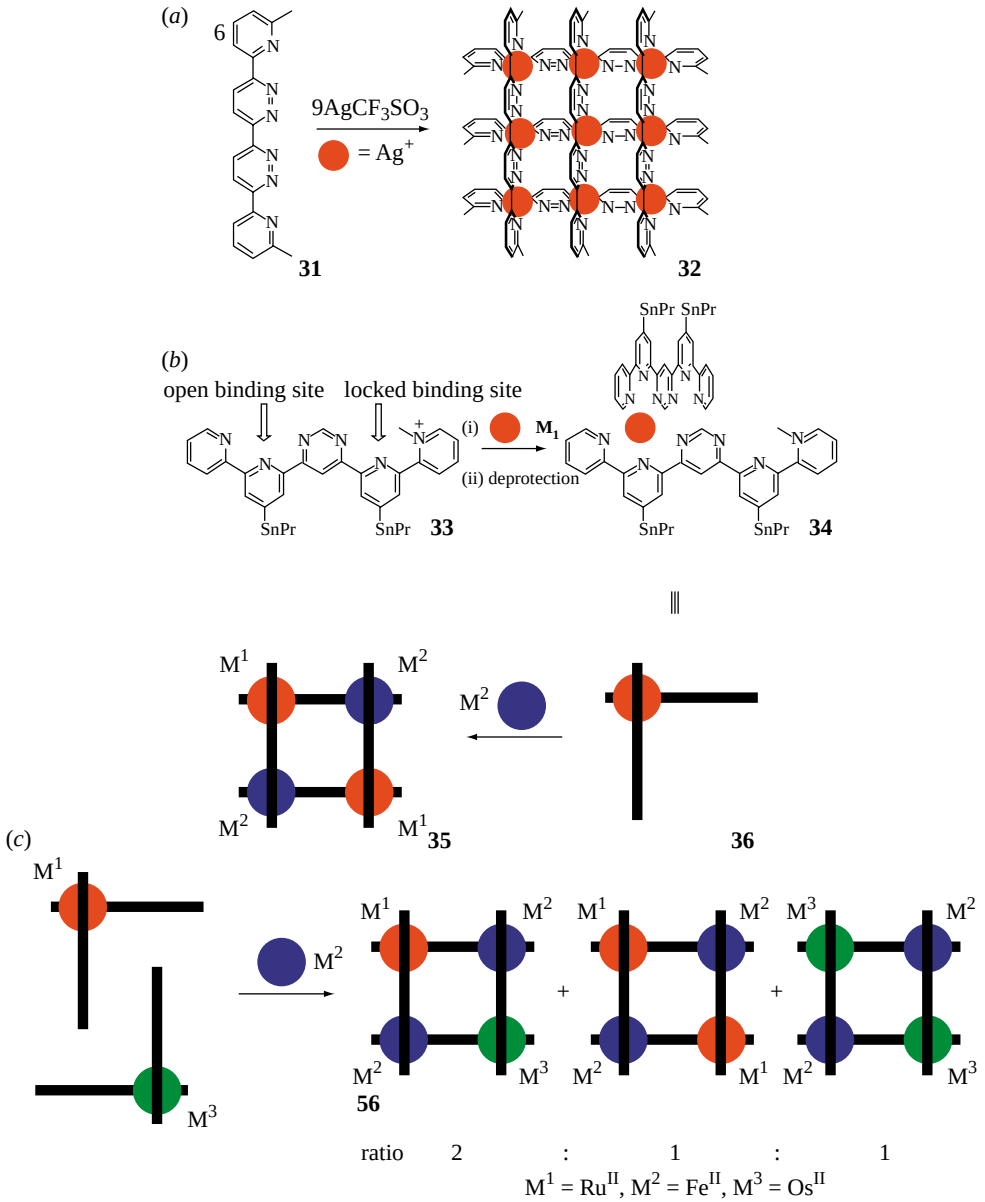


Figure 16. (*a*) Six equivalents of compound **31** and nine silver (I) cations self-assemble to form a 3 × 3 molecular grid **32**; and (*b*), (*c*) assembly of 2 × 2 molecular grid complexes containing up to three different metal ions.

One system that may be a progenitor of a synthetic molecular motor has recently been constructed by Gimzewski *et al*. (1998). Gimzewski's group studied the motion of propeller-shaped hexa-*t*-butyldecacyclene (HBDC) molecules (**39**) (figure 18) on atomically clean copper surfaces. When the copper surface is totally covered with a single layer of the molecules (a monolayer), scanning tunnelling microscopy (STM) reveals that the molecules are immobilized, presumably by intermolecular steric inter-

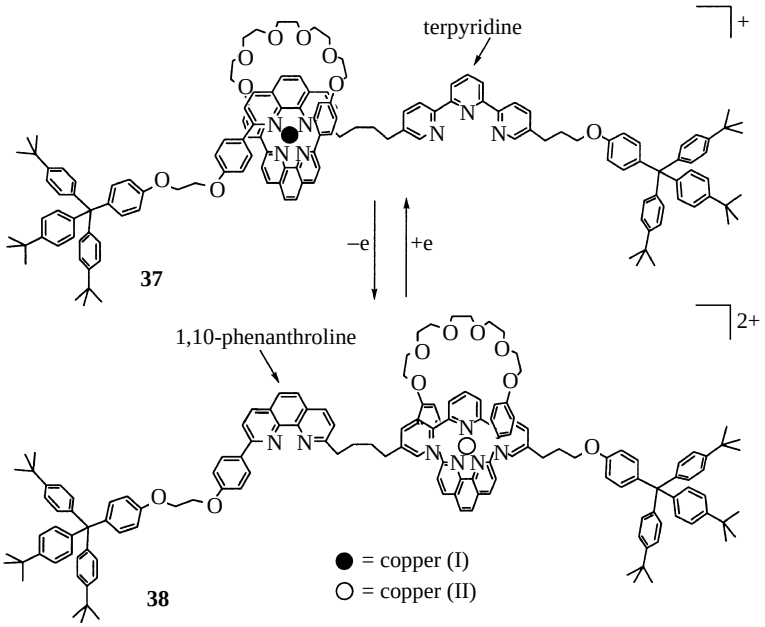


Figure 17. An electrochemically controlled molecular shuttle **37**/**38**.

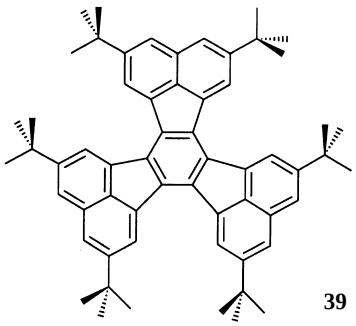


Figure 18. The structure of the propeller-like HBDC **39**.

actions, into a two-dimensional lattice. The molecules appear as immobilized hexagonal structures in the STM images. At surface coverages of slightly less than one monolayer, a random array of voids containing a number of possible sites for the HBDC molecule exist in the monolayer. One of these voids (described by Gimzewski as a 'supramolecular bearing') is shown by STM in figure 19. In some sites (A and C), where it appears as a hexagon, the molecule is 'engaged' and is prevented from rotating by non-covalent steric interactions with adjacent molecules in the layer. If the molecule is moved by 0.26 nm with the tip of the scanning tunnelling microscope, it now occupies a position in which it is free to convert thermal energy into rotational motion (B and D). The spinning molecule now appears as a torus in the image. This work serves to demonstrate that motion can now be controlled out of solution on a molecular level and is a first step on the road to constructing complex mechanical devices within monolayer structures.

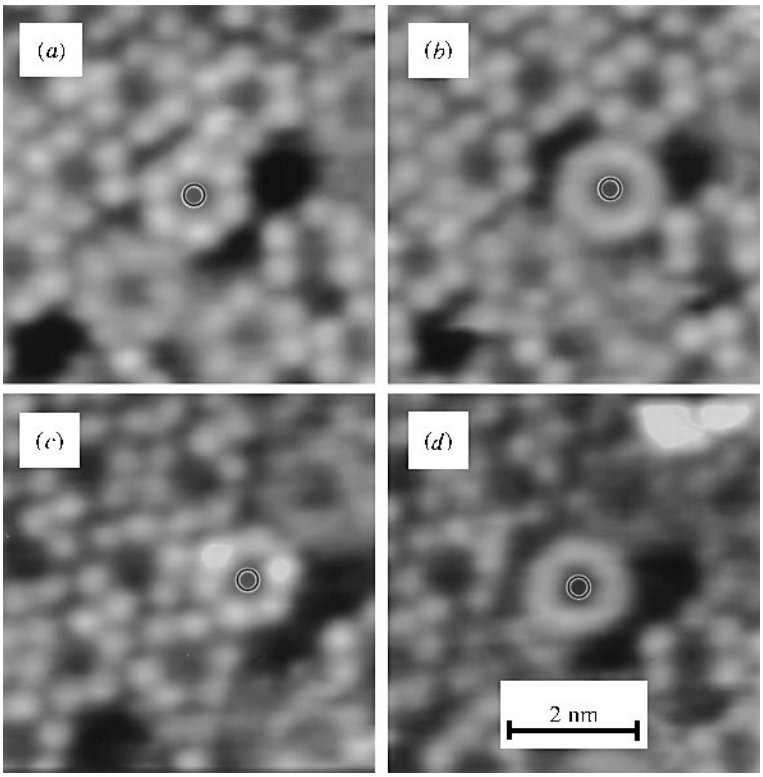


Figure 19. Sequence of STM images of an atomically clean Cu surface after exposure to just below one complete monolayer of HBDC measured in an ultra-high vacuum at room temperature. In (*b*) and (*d*), the molecule is imaged as a torus and is in a location where it is not in phase with the overall two-dimensional molecular overlayer (it is disengaged). In (*a*) and (*c*), the same molecule is moved by 0.26 nm and imaged as a six-lobed structure in registry with the surrounding monolayer. (Reprinted with permission from Gimzewski *et al*. (1998), © 1998, American Association for the Advancement of Science.)

de Silva and co-workers (de Silva *et al*. 1997) have developed a series of molecular switches and logic gates that could, in the future, be used as the basis for a molecular computer. For example, receptor **40** functions as an AND gate (figure 20). This receptor possesses two binding sites. One is an amine group that can bind protons and the other is a crown ether that can bind sodium ions. In the absence of either guest, photo-electron transfer (PET) can occur from both of these binding sites to the anthracene unit, quenching the fluorescence of this group. Only when a sodium cation binds to the crown and a proton binds to the amine are both PET pathways inhibited, switching the molecule to a fluorescent state. The action of this type of switch is reversed by adding a base to remove the protons and cryptands to scavenge the sodium ions from the switch.

6. Conclusion

This short review article has surveyed supramolecular chemistry from simple molecular recognition systems to the construction of functional supramolecular arrays

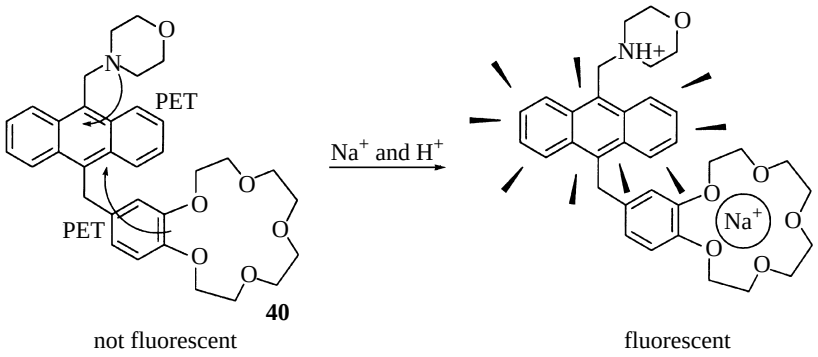


Figure 20. (*a*) A molecular AND switch **40**, in which the fluorescence is only turned on when both protons and sodium cations are present.

and prototypical molecular machines. The supramolecular systems described illustrate the great creativity of the researchers involved in this interdisciplinary area of science. As supramolecular chemistry moves into the third millennium, we can look forward with great excitement to the development of new supramolecular drug delivery systems, pharmaceuticals, smart materials, molecular machinery and logic gates, and catalysts. There can be no doubt that more esoteric complexes, with uses that can now only be dreamt of in the pages of science fiction novels, will emerge in the coming years.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

AUTHOR PROFILE

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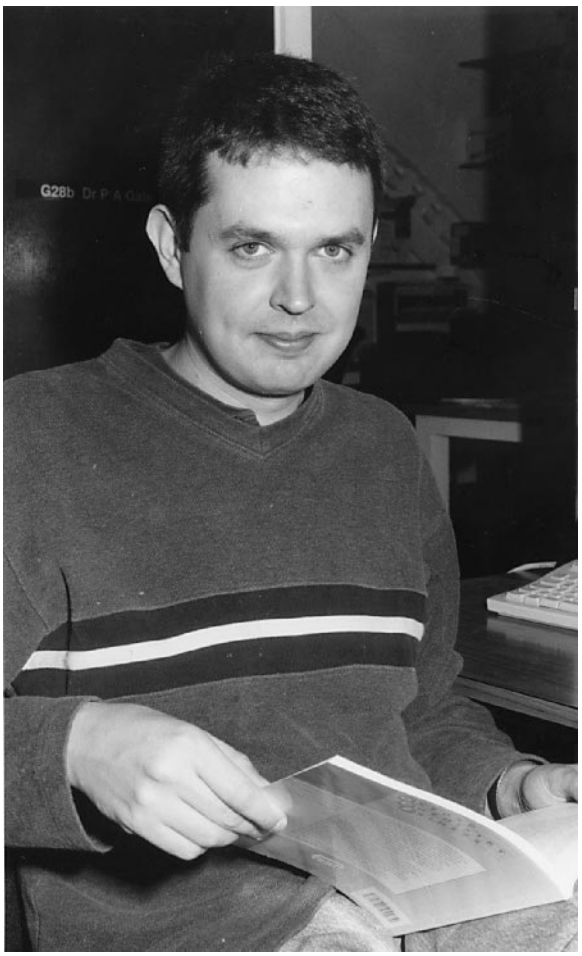
Philip A. Gale was born in Liverpool. He graduated with a BA (Hons) and MA in chemistry from Wadham College, Oxford, in 1992 and 1995, respectively, and a DPhil (for work conducted in Professor Paul Beer's research group) from Linacre College, Oxford, in 1995. In October 1995 he joined Professor Jonathan L. Sessler's group at the University of Texas at Austin as a Fulbright postdoctoral fellow where he studied the anion coordination properties of calixpyrrole macrocycles. In October 1997 he took up a Royal Society University Research Fellowship at the Inorganic Chemistry Laboratory, Oxford. Aged 30, he moved to his present position as Royal Society University Research Fellow and Lecturer at the University of Southampton in September 1999. His research interests include anion coordination and self-assembling molecular hosts.



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