Chapter One

Introduction to Supramolecular Chemistry

1 Overview

This thesis deals with the nature of fundamental intermolecular interactions and the ways in which they can be exploited using supramolecular chemistry. Three separate studies have been undertaken in order to explore and quantify different types of electrostatic interactions. Chapter 2 describes an investigation into the nature of hydrogen bonding interactions between charged species and well-defined neutral hosts, in order to quantify their hydrogen bonding strength on an already established scale. The importance of metal-ligand interactions in self-assembly is documented in Chapter 3, where the synthesis of functional supramolecules is described and their self-assembly in the presence of a bidentate ligand is investigated. Finally, Chapter 4 describes the use of calixarene-porphyrin conjugates in gas-sensing devices, showing how a handle on the design and synthesis of supramolecules and an understanding of their basic interactions can provide a useful application. The detailed background literature relating to the project will be described as an introduction to each chapter; this chapter provides a general introduction to the field of supramolecular chemistry and an overview of key advances that have been made since its inception.

1.1 Introduction to Supramolecular Chemistry

The field of supramolecular chemistry was first established in the late 1960s[1-3] and since then has enjoyed a huge interest from many research groups. It can be defined as the study of systems made up of a number of individual molecular components that are held together by weak, non-covalent interactions. These intermolecular bonds are reversible in nature and include electrostatic interactions, metal coordination, hydrogen bonding, π-π interactions, dispersion interactions and hydrophobic or solvophobic effects. The attraction of supramolecular chemistry is that it holds potential for synthesising nanoscale architectures that can mimic the functions of biological systems or act as molecular machines to carry out specific tasks. This 'bottom-up' approach is widely regarded to be the path to producing functional nanomachines in the future.

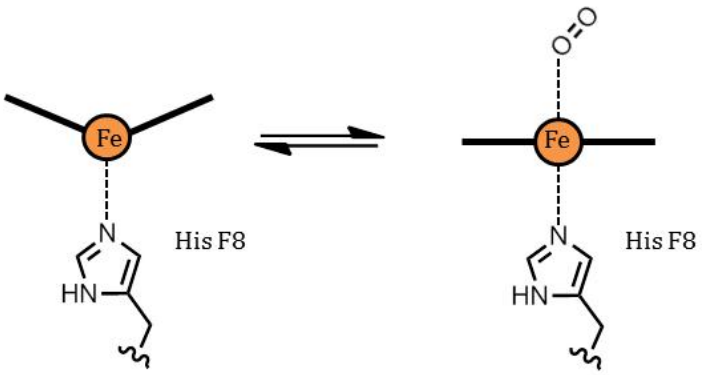


Figure 1.1. Binding of molecular oxygen to a heme fragment in haemoglobin induces conformational changes. The iron is pulled into the plane of the heme and the histidine fragment is pulled up with it. This induces conformational changes in the other heme fragments and enhances binding at the remaining sites.

1.2 Host-Guest Interactions

A molecule that is designed to selectively recognise and bind another species is called a 'host' molecule. The 'guest' species can be another molecule or metal ion. Host-guest systems are used in many applications such as analyte sensing, food additives, drug delivery, imaging, biological modelling and cosmetics.

1.2.1 Factors Affecting Host-Guest Interactions

In order for a host-guest complex to form in solution, certain factors need to be taken into account. Fisher introduced the 'lock and key' concept in 1894[4] through his work on the binding of substrates by enzymes. The substrate (key) has a complementary size and shape to the enzyme (lock). This approach is a little over-simplified as enzymes are very flexible and conformationally dynamic in solution. The induced-fit model takes this flexibility into account and proposes that binding is in fact a more interactive process; the enzyme changes shape during binding in order to better accommodate the guest. A wider description of this phenomenon is known as *complementarity*; in order for a host and guest to successfully bind, they must possess mutually complementary spatial and chemical binding sites.

Cooperativity is another important factor in determining the stability of a host-guest complex. It is used to describe the thermodynamic effect of making two or more non-covalent interactions in a multivalent system. Cooperativity can be positive or negative according to whether formation of the first intermolecular interaction favours or disfavours ensuing interactions. There are two types of cooperativity[5], known as allosteric and chelate. Allosteric cooperativity describes the binding of different monofunctional ligands to a multisite receptor. The classical example of this type of cooperativity is that of oxygen binding to haemoglobin[6-8] (Figure 1.1). The binding of the first molecule of oxygen to one of the four heme groups induces a conformational change in the protein quaternary structure which makes population of the other three binding sites more favourable.

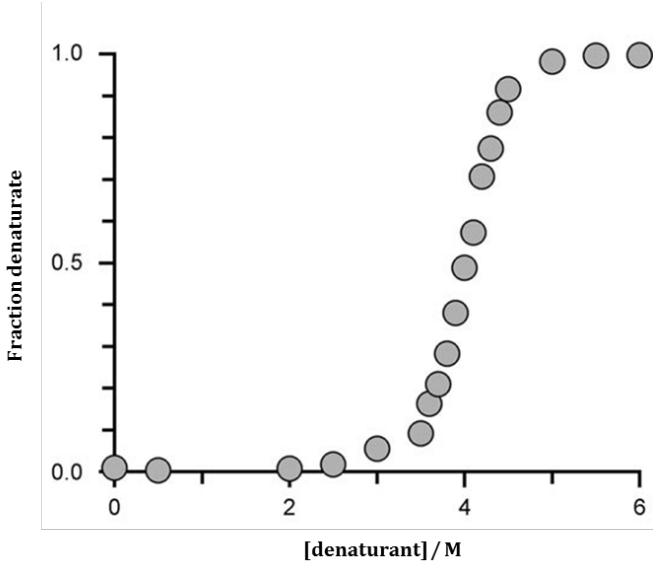
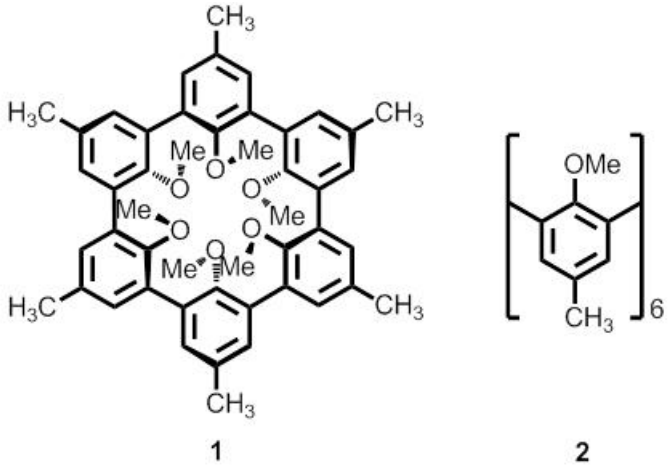


Figure 1.2. Example of the denaturation of a protein as a function of denaturant concentration. Figure reproduced with permission from the authors from C. A. Hunter and H. L. Anderson, *Angew. Chem. Int. Ed.*, 2009, **48**, 7488-7499.



1 **2**

- ΔG (**1**.Li$^+$) > 23 kcal mol^{-1} - ΔG (**2**.Li$^+$) < 6 kcal mol^{-1}

Figure 1.4. Preorganisation is a central determinant to binding power. Cyclic polyether **1** undergoes less conformational change upon binding to alkali metal cations and consequently has a much stronger interaction with Li$^+$ than acyclic analogue **2**.[9]

Chelate cooperativity or multivalency is observed in the folding of biopolymers such as proteins, DNA and RNA. Such systems exhibit "all or nothing" behaviour whereby intermediate states are not populated and small changes in reaction conditions (concentration, pH, pressure, temperature, addition of denaturants) lead to total transition from free to fully bound states. Sharp melting curves are characteristic of this type of cooperativity (Figure 1.2).[10-15] The chelate effect is a classical example in coordination chemistry of how multidentate ligands (and by extension, hosts with multiple binding sites) result in more stable complexes than systems containing only monodentate ligands.[16] For example, ethylenediamine can form a complex with nickel that is 10^8 times more stable than the corresponding hexadentate ammonia complex (Figure 1.3).

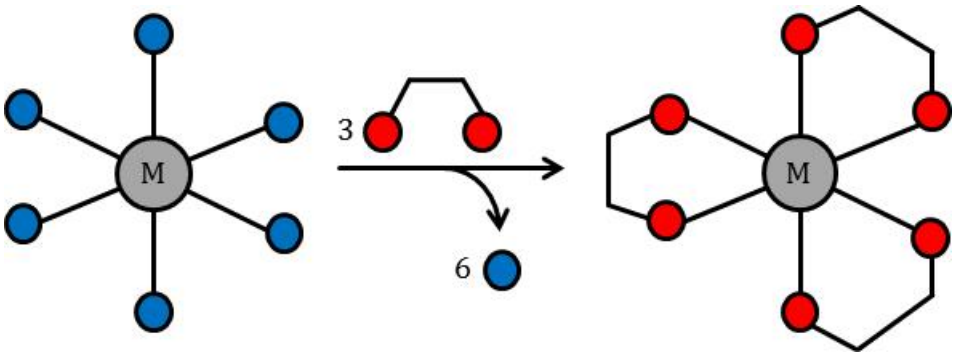


Figure 1.3. Schematic illustration of the chelate effect. The metal centre shown is nickel (II), which can either coordinate to 6 monodentate ammonia ligands (blue) or 3 bidentate ethylenediamine ligands (red). The ethylenediamine complex is 10^8 times more stable than the ammonia complex.

A significant energetic cost that has to be taken into account when considering host-guest binding is that of the conformational change involved. In order to minimise this cost, conformationally rigid hosts with a pre-formed cavity suitable for guest encapsulation can be synthesised. This approach is known as *preorganisation* and was elegantly used by Cram *et al.* to synthesise a macrocyclic polyether that can bind Li^+ with a free energy of > 17 kcal mol^{-1} larger than the corresponding acyclic system (Figure 1.4).[9]

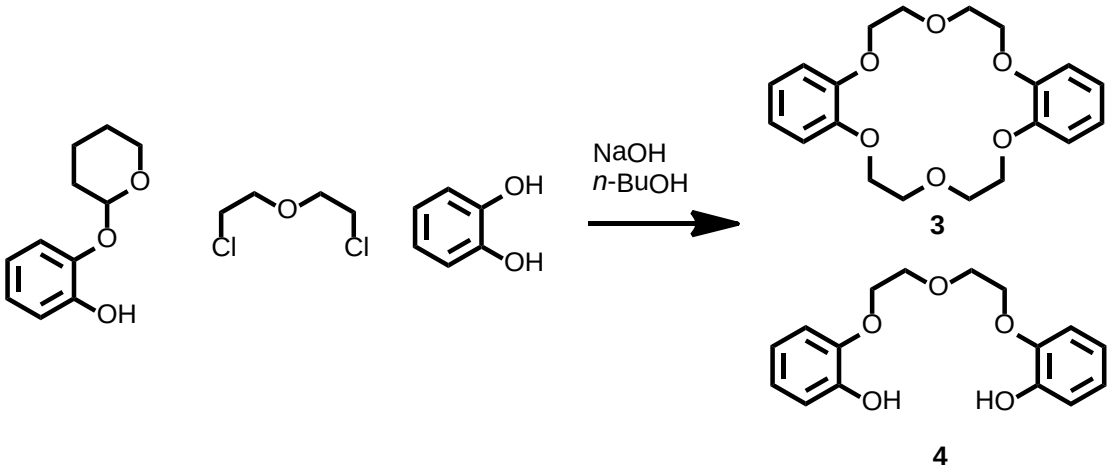
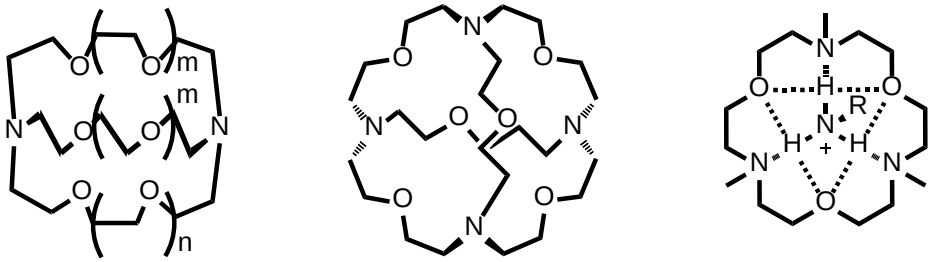


Figure 1.5. Pedersen's discovery of dibenzo[18]crown-6.[1] **3** was a minor product.



5a m=0, n=1
5b m=1, n=0
5c m=n=1

6 **7**

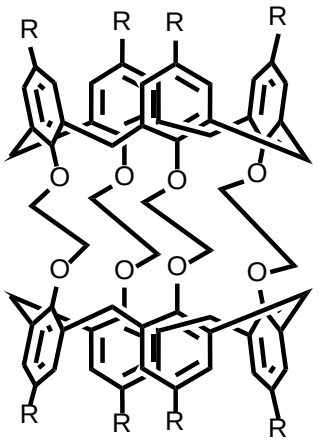
Figure 1.6. Lehn's macrocycles **5, 6** and **7** can selectively bind alkali metal cations, anions and primary ammonium cations respectively.

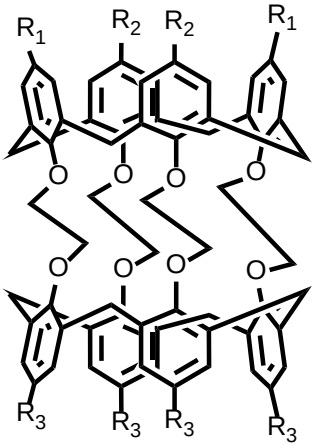
1.2.2 The Birth of Supramolecular Chemistry

In 1967, Pedersen discovered a new cyclic polyether (**3**) which was isolated as a side product during the preparation of a bisphenol derivative **4** (Figure 1.5).[1] He named it dibenzo[18]crown-6 as it comprises an 18 member ring with 6 oxygen donor atoms. The presence of sodium cations in the reaction medium had templated the formation of the cyclic product and this phenomenon indicated that the class of crown ethers, which he named *corands*, were capable of binding alkali metal cations. Pedersen went on to synthesise many crown ethers, including amine derivatives, which showed good binding with a variety of metal and alkylammonium cations.[17]

Jean-Marie Lehn elaborated on the structure of Pedersen's crown ethers and synthesised a family of macropolycyclic systems known as the *cryptands.* Lehn also coined the phrase defining supramolecular chemistry as "chemistry beyond the molecule"; making supermolecules of higher complexity from discrete molecular species held together by intermolecular forces.[2] By varying the size of the spherical cavity and the atoms incorporated into the macrocycles, Lehn showed that it was possible to design molecular receptors that could rival biological receptors in their recognition of alkali metal cations, alkaline earth cations, biologically relevant anions and ammonium cations (Figure 1.6).[18-27]

In 1988, Charles Pedersen and Jean-Marie Lehn were awarded the Nobel Prize for Chemistry for their contributions to the field of supramolecular chemistry. The third recipient of the prize was Donald J. Cram, who synthesised a range of ligands which already had an enforced cavity for binding which he called *spherands*.[3, 9, 28-30] In comparison to the corands and cryptands, the spherands did not have to undergo significant conformational change or desolvation upon binding and consequently were shown to be excellent receptors for metal cations. Furthermore, the controllable size of the cavity meant that the spherands could distinguish between medically important cations such as Li^+, Na^+ and K^+.





8 R = *t*-Bu
9 R = *t*-Oct
10 R = H

11 R_1= R_2 = H, R_3 = *t*-Bu
12 R_1= R_2 = *t*-Oct, R_3 = *t*-Bu
13 R_1= R_2 = isopropyl, R_3 = *t*-Bu
14 R_1= R_2 = phenyl, R_3 = *t*-Bu
15 R_1= R_2 = *t*-Oct, R_3 = H
16 R_1= R_3 = *t*-Bu, R_2 = H

Figure 1.7. Symmetric and asymmetric calixtubes synthesised by Beer *et al.* capable of acting as selective potassium ion receptors.[31]

The highest selectivity obtained was a factor of $>10^{10}$ for Na^+/K^+ using **1** (Figure 1.4). Cram and co-workers also synthesised the first *carcerand*, a closed-surface host formed by the shell closure of two bowl-shaped cavitands based on a calixarene scaffold.[32] The insoluble product formed was shown by FT-IR, elemental and FAB-MS analysis to have incarcerated various reagents and solvents involved in the synthesis within its walls.

1.2.3 Applications of Host-Guest Chemistry

An increasing understanding of non-covalent interactions and biological processes, coupled with sophisticated synthetic techniques, mean that recently many examples of using supramolecular chemistry to mimic biological processes and carry out other useful functions have emerged. Calixarenes and resorcarenes have proven to be excellent scaffolds for receptors due to their rigidity, ease of derivatization and availability of oxygen donor atoms that surround the cavity.[33]

There has been significant interest in the selective recognition and extraction of alkali metal cations[34-36] in recent years. Beer and co-workers have synthesised a range of potassium-selective ionophores based on a bis calix[4]arene scaffold (Figure 1.7).[31] The calixtube receptors proved to be highly selective for the potassium ion over all group I metal cations and barium. The complexation rates of the spherand-like molecules could be tuned by altering the substituents on the calix[4]arene upper rim and this led to the hypothesis that the potassium ions entered the receptor *via* an axial route.

A calixarene modified with four peptide loops on the upper rim has been used as an antibody mimic to recognise cytochrome c.[37] The incorporation of the peptide motif was used to mimic natural antibodies, which all have six loops arrayed around a central binding site that interacts with the antigen.[38-40] The binding power of the synthetic receptor with cytochrome c was tested by affinity chromatography and gel permeation chromatography. A particular aim of the work was to use the antibody mimic to disrupt normal protein function.

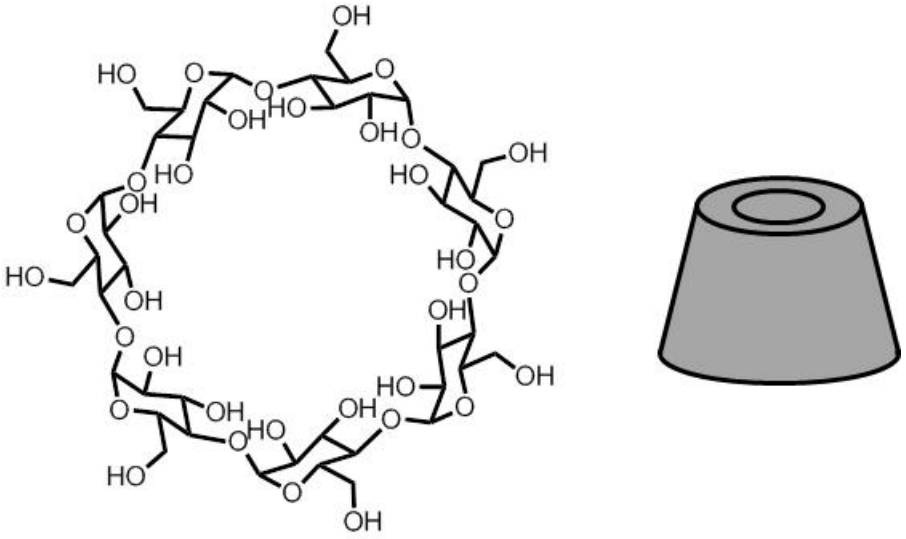


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Figure 1.8. *β*-cyclodextrin **17** is composed of 7 α-(1,4) linked glucopyranose units. Cyclodextrins have a rigid structure with a well-definined hydrophobic cavity.

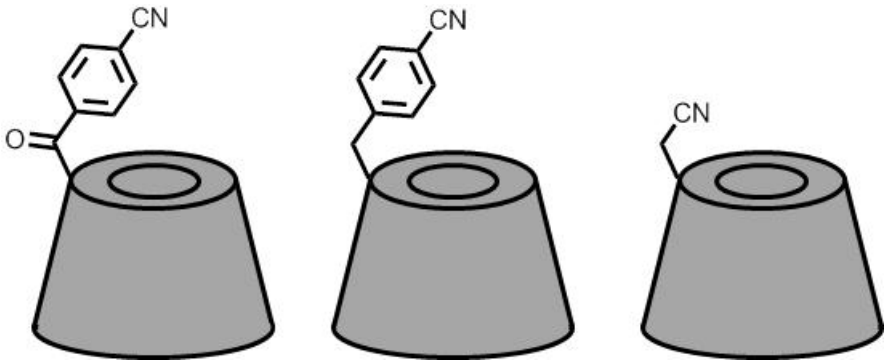

Figure 1.9. Cyclodextrins were functionalised with nitrile moieties to improve yield and selectivity in the Wacker oxidation of higher alkenes.[41]

In the presence of the calixarene receptor, the rate of reduction of Fe(III) cyt-c by ascorbate was diminished 10-fold. A similar effect is seen with the cytochrome c/cytochrome c peroxidase complex, indicating that the calixarene antibody mimic is likely to interact with cytochrome c in a similar fashion to cytochrome c peroxidase.

The cyclodextrin family is an important class of molecular hosts due to their wide use in industrial applications.[42] Cyclodextrins are cyclic oligosaccharides composed of 6 (α-cyclodextrin), 7 (β-cyclodextrin) or 8 (γ-cyclodextrin) α-(1,4) linked glucopyranose units (Figure 1.8). They were discovered in 1891 and are produced from the enzymatic conversion of starch. Their wide availability, low toxicity, solubility in water and cage-like supramolecular structure make them ideal carrier molecules and they are used throughout the pharmaceutical, cosmetic, food, agricultural and chemical industries. The hydrophobic effect is responsible for driving the equilibrium towards complexation with guest molecules: the reduction in the number of repelling interactions between water molecules and the cyclodextrin cavity and the corresponding increase in the number of hydrophobic interactions between the cyclodextrin and a guest molecule mean that complexation is highly favourable.

Cyclodextrins have also been widely used in catalytic applications.[16, 41] The hydrophobic cavity can complex a substrate and stabilise the transition state whilst the outer rim of the cyclodextrin can be functionalised to coordinate to metal centres in catalysts, thereby bringing the catalyst into close proximity with the substrate. One important example is the Wacker process, where ethene is oxidised to ethanal. Oxidation of higher alkenes to the corresponding ketones using traditional conditions is problematic as selectivity is low. β-cyclodextrin was derivatised with a nitrile group (Figure 1.9) that can coordinate to the Pd (II) centre of the catalyst. The use of the cyano-derivatised cyclodextrin allowed the conversion of 1-octene to 2-octanone in 2-4 h whereas traditional conditions required a significantly longer reaction time and more Pd (II) in the cycle.

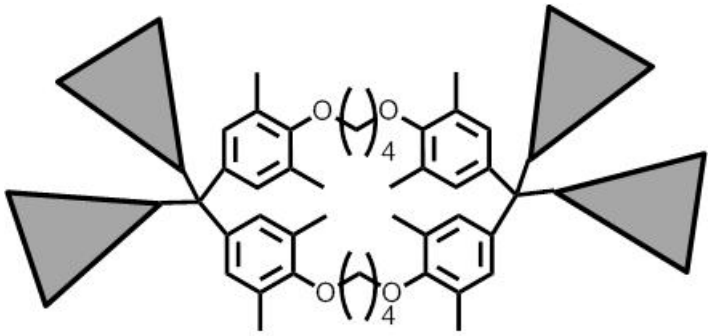

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Figure 1.10. An example of a dendritic cyclophane as synthesised by Diederich *et al*. The wedges represent polyamide dendrons.[43]

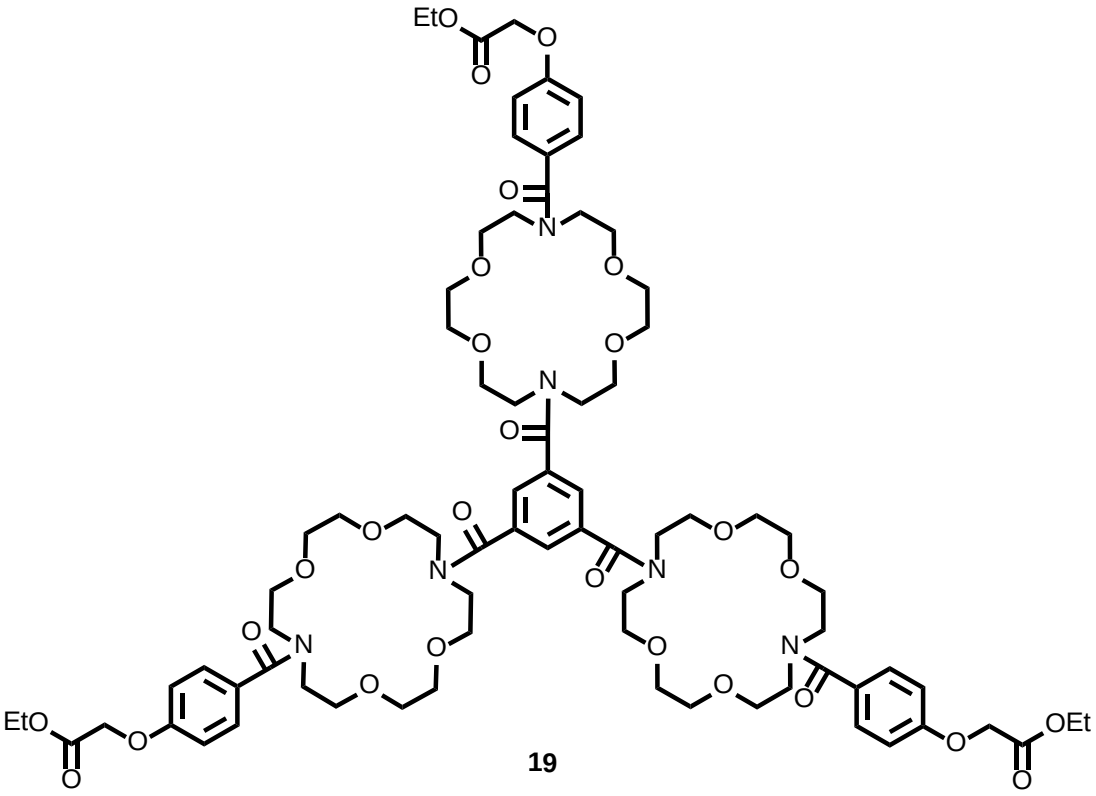

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Figure 1.11. Shinkai *et al*. have synthesised dendritic aza crown ethers for use as alkali metal cation extraction agents. [44, 45]

Dendrimers have also played an important role in host-guest chemistry applications. They are branch-like polymers that can contain a wide variety of functionalities at the core. Their ability to bind and shield substrates from external media has made them useful in the fields of medicinal applications, catalysis and substrate extraction.[46-52]

The encapsulation of dyes by dendrimers has been widely studied, particularly for Rose Bengal.[53] As a free molecule in solution, Rose Bengal is an achiral molecule that shows no fluorescence in the 600 nm region. When it is encapsulated within a dendrimer, it has a CD spectrum similar to its UV spectrum and a strong fluorescence band at 600 nm.[54] Dendrimers functionalised with palmitoyl chains on the periphery can act as inverted unimolecular micelles in organic solvents and can extract several anionic xanthene-based dyes from water to dichloromethane and toluene.[55]

Diederich *et al*. have synthesised dendrimers with a cyclophane core that can act as models for globular proteins that have buried apolar binding sites (Figure 1.10).[43, 56, 57] These molecules can selectively bind flat arenes or steroids. Spectroscopic studies in water and aqueous methanol showed the guests to be exclusively bound to the dendritic host and that the presence of the dendritic branches had little effect on the selectivity of binding. Dendritic aza crown ether arborols as synthesised by Shinkai *et al*. (Figure 1.11) have been shown to be efficient receptors for alkali metal cations and can transfer them from water to dichloromethane.[44, 45] The lowest-generation aza crown ether dendrimers can solubilise myoglobin in dimethylformamide *via* interactions of the carboxylate and ammonium functions on the peptide with the aza crown ether cores.

1.3 Self-Assembly

The term 'self-assembly' is used to describe the "spontaneous and reversible association of molecular species to form larger, more complex supramolecular entities according to the intrinsic information contained in the components".[16] Nature itself uses self-assembly in protein folding, viral assembly and the formation of the DNA double helix, where two complementary strands are entwined *via* hydrogen bonds and π-π stacking.

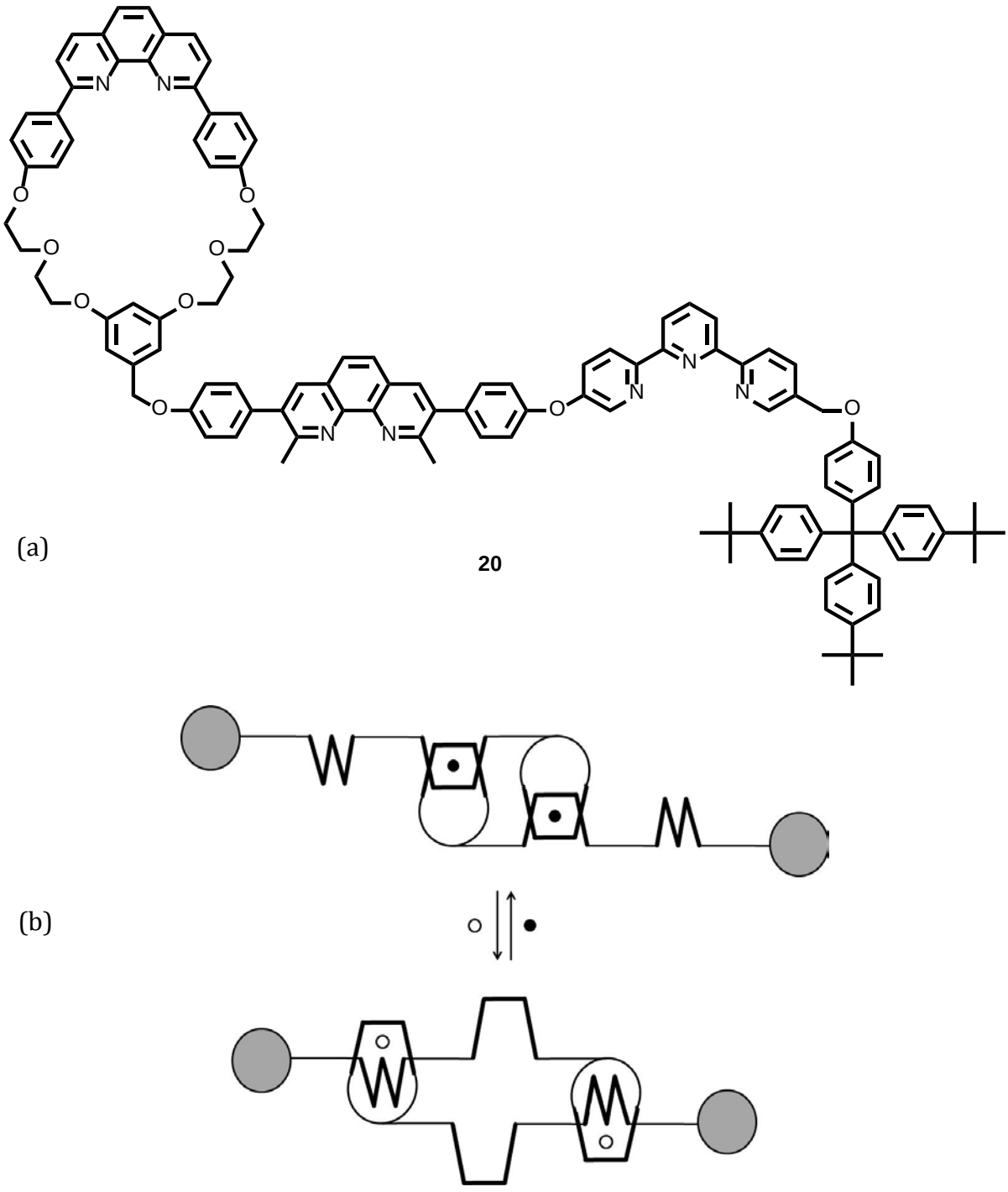

Figure 1.12. (a) The rotaxane synthesised by Sauvage *et al* that can act as a molecular muscle. (b) When copper (I) ions are present (black circles) the muscle is in the extended situation but when they are replaced by zinc (II) ions (white circles) the rotaxane dimer contracts.[58, 59]

For a system to be truly defined as self-assembled, the self-assembly process should be kinetically rapid and completely reversible and replicable. Furthermore, the discrete molecular entities should be held together by non-covalent interactions only. However, perhaps the most interesting and useful application of self-assembly is the production of interlocked species that can act as molecular switches or even nanoscale molecular machines. This often requires the self-assembled components to be modified post-assembly in order to ensure the topologically intertwined species cannot dissociate. Jean-Pierre Sauvage and others have made major inroads into this area and the following is a brief overview of the progress made up to the present day.

1.3.1 Rotaxanes and Catenanes

Rotaxanes are a class of supramolecular assembly that involve a linear molecule and one or more macrocycles that thread onto the linear entity and are held in place by intermolecular interactions. The macrocycles are prevented from slipping off by the addition of bulky 'stopper' groups after self-assembly has taken place. Without the stopper groups in place, the compounds are known as pseudorotaxanes.

In 2000, Sauvage *et al.* published the first 'molecular muscle' based on a rotaxane system.[58, 59] Synthetic systems representing the process of skeletal muscles expanding and contracting have long been a target[60, 61] and the rotaxane system was designed to mimic the process that takes place in the sarcomere, in which the thick myosin filament glides along the thinner actin filament. The rotaxane dimer was synthesised in more than 20 steps from commercially available starting materials and each filament contains a bidentate chelating ligand (phenanthroline) and a terdentate ligand (terpyridine) (Figure 1.12(a)). Copper (I) is the assembling and templating metal, but exchange of the four-coordinate copper ion for a five-coordinate zinc (II) ion causes the 'muscle' to go from the extended to the contracted conformation (Figure 1.12(b)). The reverse motion could easily be induced upon addition of excess $Cu(CH_3CN)_4.PF_6$.

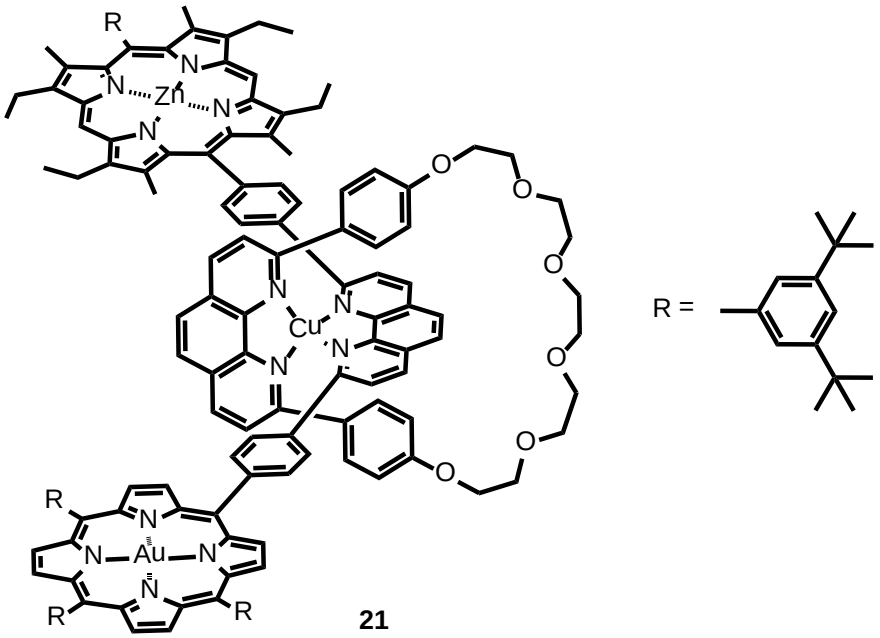

Figure 1.13. The porphyrin-stoppered rotaxane used by the Sauvage group to study photosynthetic processes. [62-67]

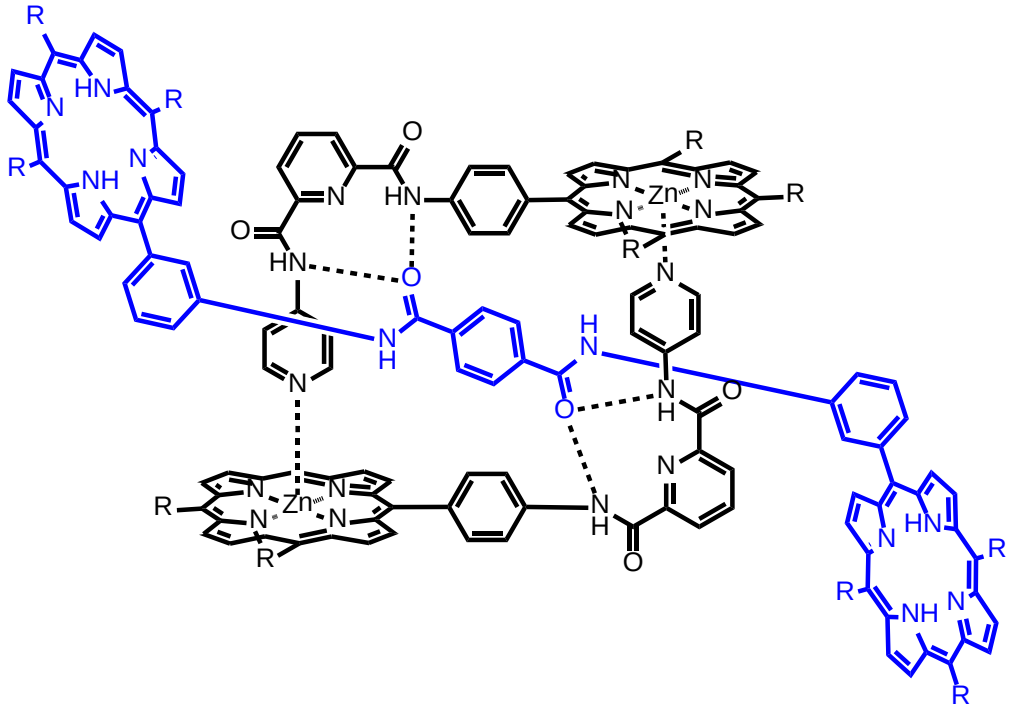

Figure 1.14. A self-assembled macrocycle (Zn**22**)$_2$ (black) held together by metal-ligand coordination can form a [2]rotaxane with porphyrin-stoppered guest H$_4$**23** (blue). [68]

The evidence for the contracting/stretching process was provided by large changes in chemical shift for selected protons in the ^{1}H NMR spectrum.

Another interesting example of a rotaxane system from the Sauvage group is an unsymmetrical porphyrin-stoppered [2]rotaxane.[62-67] Copper (I) is again used to template the formation of the rotaxane and the second zinc porphyrin stopper is formed using mild conditions after the formation of the pre-rotaxane. The use of the (PZn/PAu^{+}) porphyrin couple enabled the group to study photoinduced electron transfer between the two porphyrin centres and draw comparisons with photosynthetic processes (Figure 1.13). Upon photoexcitation, the Zn (II) porphyrin is able to transfer an electron to the Au(III) porphyrin at a rate of 1.7 ps. The presence of the copper (I) bisphenanthroline complex is thought to mediate efficient electron transfer between the two porphyrin moieties.

Hunter *et al.* have shown that porphyrin-stoppered [2]rotaxanes can be formed using two molecules that can dimerise in non-coordinating solvents and self-assemble around a third guest molecule (Figure 1.14).[68] Variable temperature NMR experiments showed that $(Zn\mathbf{22})_2 \cdot H_4\mathbf{23}$ had a larger barrier for the exchange of free and bound species than the corresponding complex containing a guest with the same backbone as **23** but no porphyrin stoppers. This led to the conclusion that $(Zn\mathbf{22})_2 \cdot H_4\mathbf{23}$ was a true rotaxane and that in order for the guest to leave the macrocycle, one of the metal-ligand coordination bonds first had to be broken, as shown in Figure 1.15.

Sauvage *et al*. have shown that copper complexed [2]catenanes can act as rotary motors under electrochemical control (Figure 1.16).[59, 69] A classical catenane containing a bidentate phenanthroline unit and a terdentate terpyridine unit similar to the rotaxane described in Figure 1.12(a) was synthesised using the usual copper (I) template method.[70] Copper (I) shows a strong preference for 4-coordinate conformations and therefore it is complexed to the two phenanthroline units.

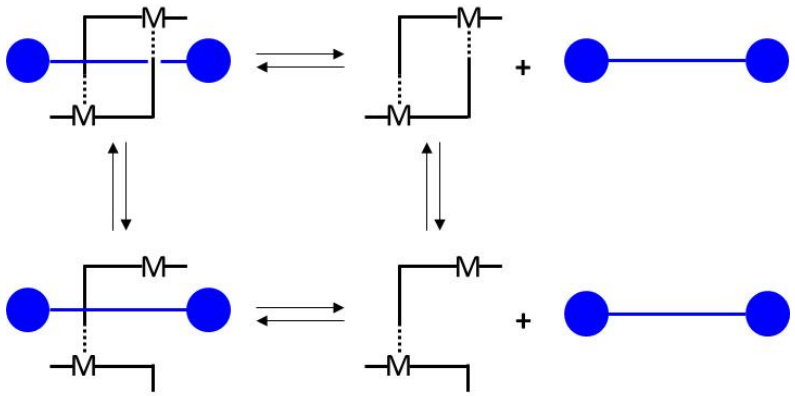

Figure 1.15. In order for the [2]rotaxane $(Zn\mathbf{22})_2 \cdot H_4\mathbf{23}$ to be disassembled, the metal-ligand coordination bonds in the macrocycle must first be broken.

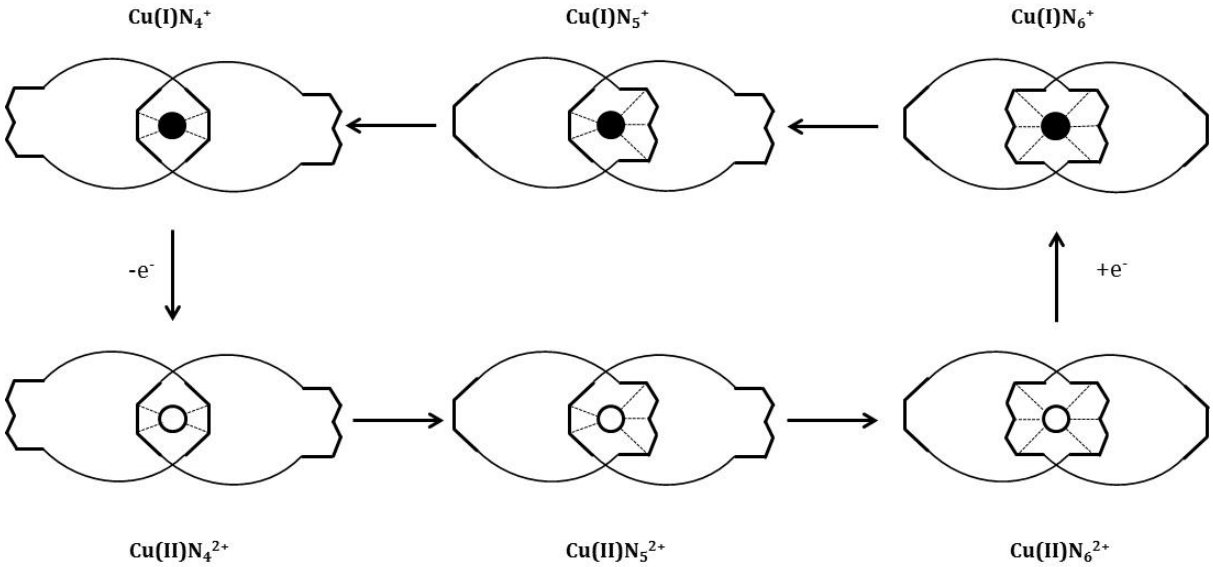

Figure 1.16. A [2]catenane that is capable of acting as a rotary motor under electrochemical control. Black circles represent copper (I) ions, white circles represent copper (II) ions. Terpyridine ligands are represented by a stylised 'W' and bidentate phenanthroline units are represented by a 'U' shape. Copper (I) is most stable in the 4-coordinate conformation whereas copper (II) shows a strong preference for a 6-coordinate arrangement.[59, 69]

However, upon oxidation to the divalent species, the interlocked rings rearrange so that the copper atom is complexed in its preferred hexadentate arrangement with the two terpyridine units. This process is entirely reversible upon reduction of the copper (II) species.

Wozniak and co-workers have reported the first heterodinuclear bismacrocyclic transition-metal complex that exhibits potential-driven intramolecular motion of the interlocked crown-ether unit (Figure 1.17).[71] Upon application of appropriate potentials either the copper or nickel centres (or both) can be reversibly oxidised to the +3 oxidation state, which favours an interaction of the oxidised metal centre with the π-electron rich benzene ring of the crown ether unit. The catenane is constructed in such a way that one benzene ring lies in between the two metal centres and the other one is outside the macrocyclic ring almost parallel to the first. The crown ether unit moves so that the best electron acceptor metal at the given potential is sandwiched between the two benzene rings (Figure 1.18).

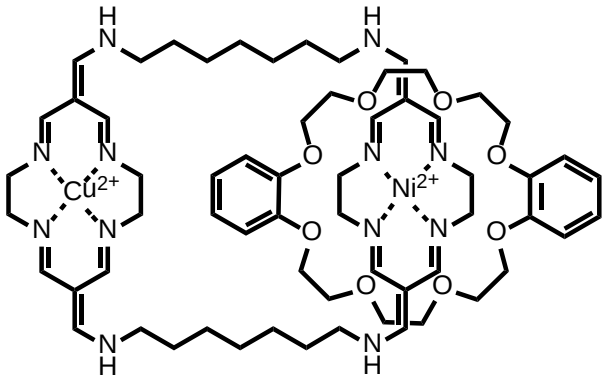

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Figure 1.17. A heterodinuclear bismacrocycle synthesised by Wozniak and coworkers.[71]

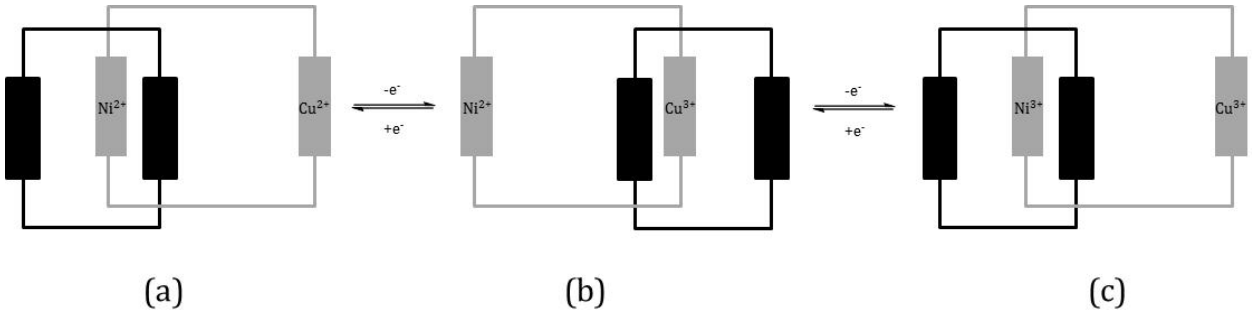

Figure 1.18. Schematic representation of an electrochemically controlled [2]catenane. The crown ether units (black rectangle) move to interact with the best electron acceptor metal.[71]

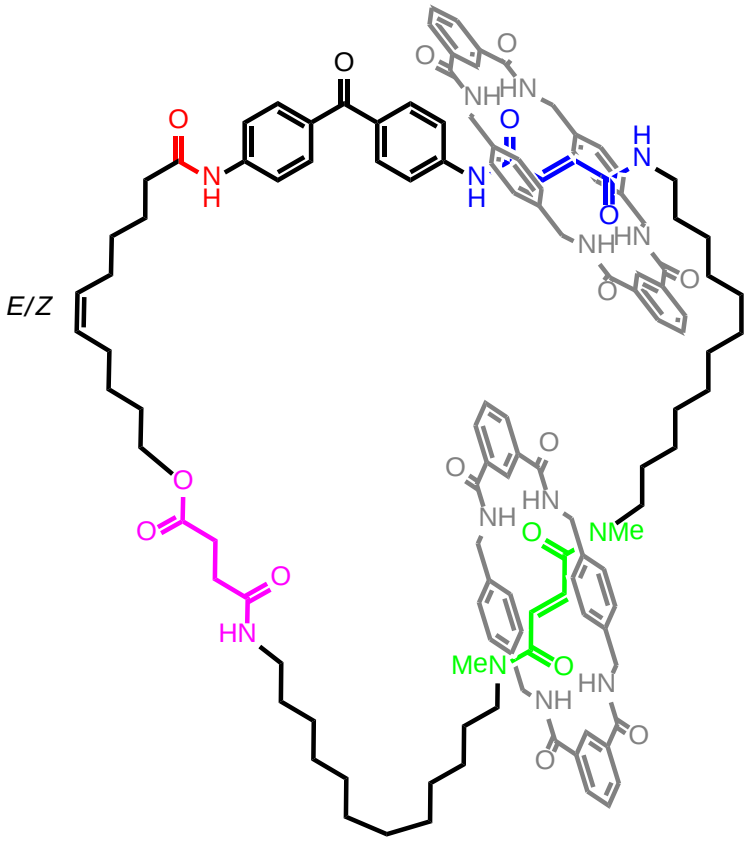

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Figure 1.19. A [3]catenane that can act as a unidirectional molecular rotor.[72] The larger macrocycle contains four binding sites A (blue), B (green), C (pink) and D (red). The smaller macrocycle (grey) shows preference for the binding sites in the order A>B>C>D. Isomerisation of sites A and B force the macrocycles onto the less preferred binding sites C and D. Isomerisation is fully reversible, enabling the system to complete an entire cycle.

1.3.2 Moving Towards Molecular Machines

The ultimate aim for the supramolecular chemist is to be able to design and synthesise molecular architectures that rival natural molecular machines such as proteins in their size, complexity and function. Few biological molecular motors are well understood due to such complexity but one particular example is that of ATP synthase, the mechanism of which was elucidated in the late 1990s.[73-80]

Many advances have been made in the field of individual molecular switches, but only a few systems fulfil the criteria to be called true nanoscale molecular machines.[72, 81-86] Stoddart proposed that in order for a system to be called a true molecular machine, it must be able to carry out useful work on its surroundings at nano-, micro- and macroscopic levels. In addition, systems should be coupled to the local environment and composed of individual molecular switches that work together in an organised, hierarchical fashion.[87] This proposal naturally leads into the field of solid-supported molecular machines but a few examples of primitive molecular machines that work in solution are described below.

Leigh and co-workers described in 2003 a molecular rotor **25** that is capable of moving in a unidirectional manner according to an external photophysical stimulus.[72] The system comprises a large macrocycle with four binding sites A-D as depicted in Figure 1.19, and one or two smaller benzylic amide macrocycles threaded onto it to form [2]- or [3]catenanes. The binding sites differ in their power as intermolecular hydrogen bond acceptors: site A is a secondary amide fumaride group and in the *E* conformation and is almost ideally arranged for intercomponent hydrogen bonding. Site B is a tertiary amide fumaride and the extra bulk of the methyl groups make it less available for hydrogen bonding. Site C contains an ester group which is a poorer hydrogen bond acceptor, and site D is a simple amide.

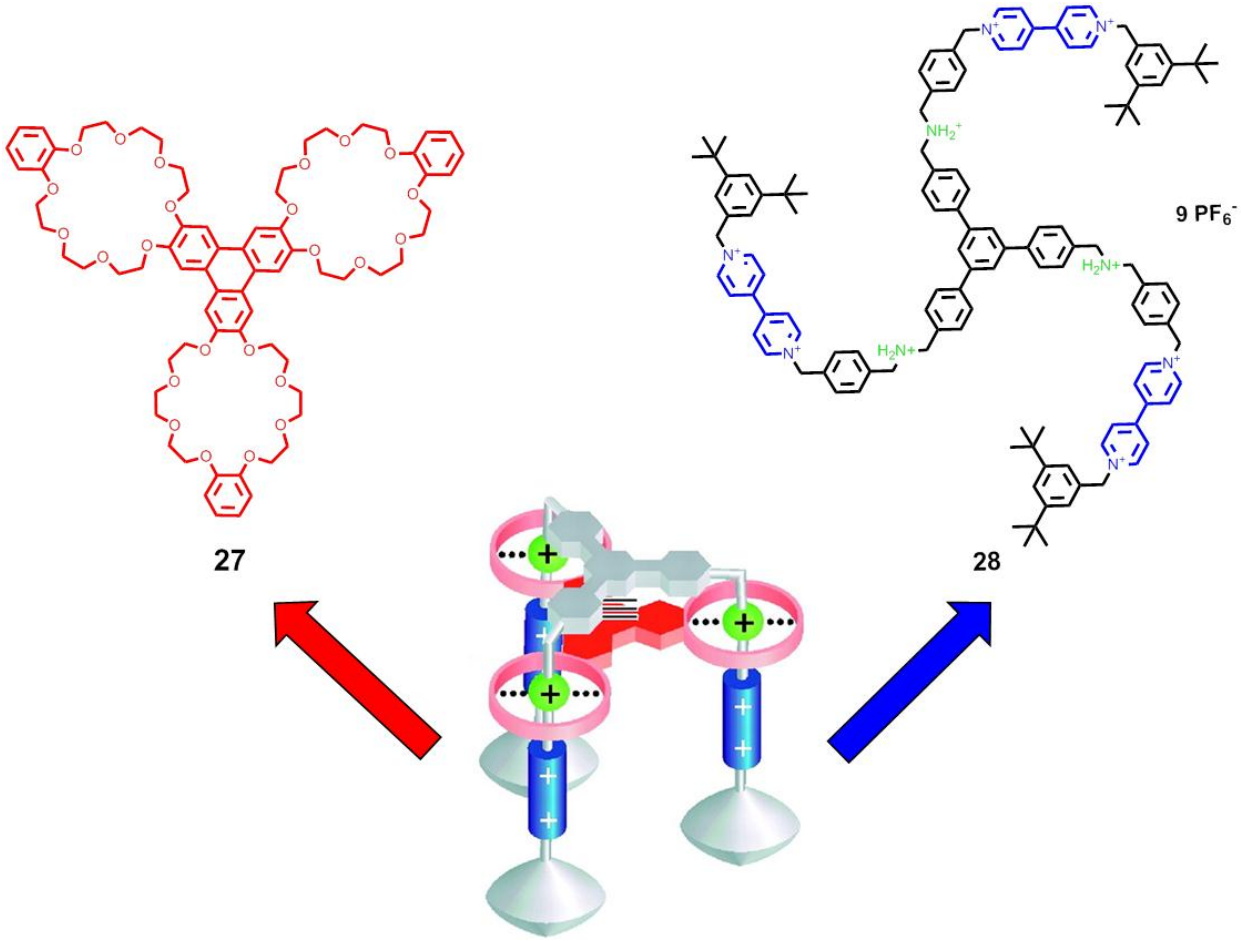

Figure 1.20. A molecular elevator synthesised by Stoddart and co-workers.[88] Adapted from J. D. Badjic, V. Balzani, A. Credi, S. Silvi and J. F. Stoddart, *Science*, **2004**, 303, 1845-1849. Reprinted with permission from AAAS.

The smaller benzylic amide macrocycles interact with these sites in the preferred sequence A>B>C>D; photoisomerisation of A and B forces the macrocycles onto C and D. As is a requirement for all molecular machines, this process is fully reversible and enables to system to complete an entire cycle. The benzophenone group attached to binding site A means that the secondary fumaride group is isomerised selectively at 350 nm, then a second photophysical stimulus isomerises binding site B. Movement of the smaller macrocycle around the [2]catenane is not unidirectional as the ring can travel either clockwise or anticlockwise to reach its preferred binding site, however the presence of two of the smaller rings in the [3]catenane means that Brownian motion is limited and the macrocycles can travel in one direction only.

J. Fraser Stoddart has been a pioneer in the field of molecular machines.[81, 82, 87-97] One recent example of his work is a molecular elevator[88] that is capable of moving from one station to another and in doing so generating a force of around 500 pN. The system is based on a trifurcated rig-like structure which contains two different binding sites (a protonated secondary amine and a protonated bipyridine unit) at different levels. A platform based on a tritopic crown ether is threaded onto the structure and the legs of the elevator are capped with bulky aromatic stopper groups (Figure 1.20). A ^{1}H NMR spectrum of the system in CD_3CN confirmed that the platform preferentially binds to the protonated secondary amine sites resulting in the elevator being in the 'up' position. Addition of a strong phosphazene base to the system results in deprotonation of the secondary amines and the platform moves to the 'down' position in order to bind to the protonated bipyridine units. The initial structure is regenerated when a small amount of trifluoroacetic acid is added.

1.4 Supramolecular Analytical Chemistry

Advances in supramolecular chemistry over the past forty years means that now we are equipped with the tools to create increasingly sophisticated supramolecular assemblies. The emerging field of supramolecular analytical chemistry[98, 99] utilises these synthetic capabilities but also draws inspiration from Nature and the way that our senses of taste and smell depend on arrays of different receptors. The problem with trying to design synthetic receptors for specific targets is that the receptors may have cross-reactivity with similar structures to the analyte. The field of differential sensing relies on this cross-reactivity to enable an array of receptors to produce a unique fingerprint for many different analytes, thus providing a simple way of sensing similar to the way our tongues and noses identify different smells and tastes.

Anslyn and co-workers have pioneered this new field of chemistry and have had considerable success with their approach to designing "electronic tongues" to distinguish various classes of interesting compounds. The first approach to designing the electronic tongue was to synthetically derivatize solid phase resin beads with various indicators sensitive to Ca^{2+}, Ce^{3+}, fructose and changes in pH.[100] These beads were immobilised on Si/SiN wafers and solutions containing various analytes were passed through the array using a fast protein liquid chromatograph. A charge coupled device (CCD) was used for image capture (red, blue and green light density) before and after exposure. Evaluation of the absorbance changes for each bead in the array for each solution containing the different metals at different pH values gave a distinctive colorimetric response to each solution. The sensor array was later refined by using a video capture card to monitor real-time colorimetric changes and hence evaluate the kinetics of binding.[101]

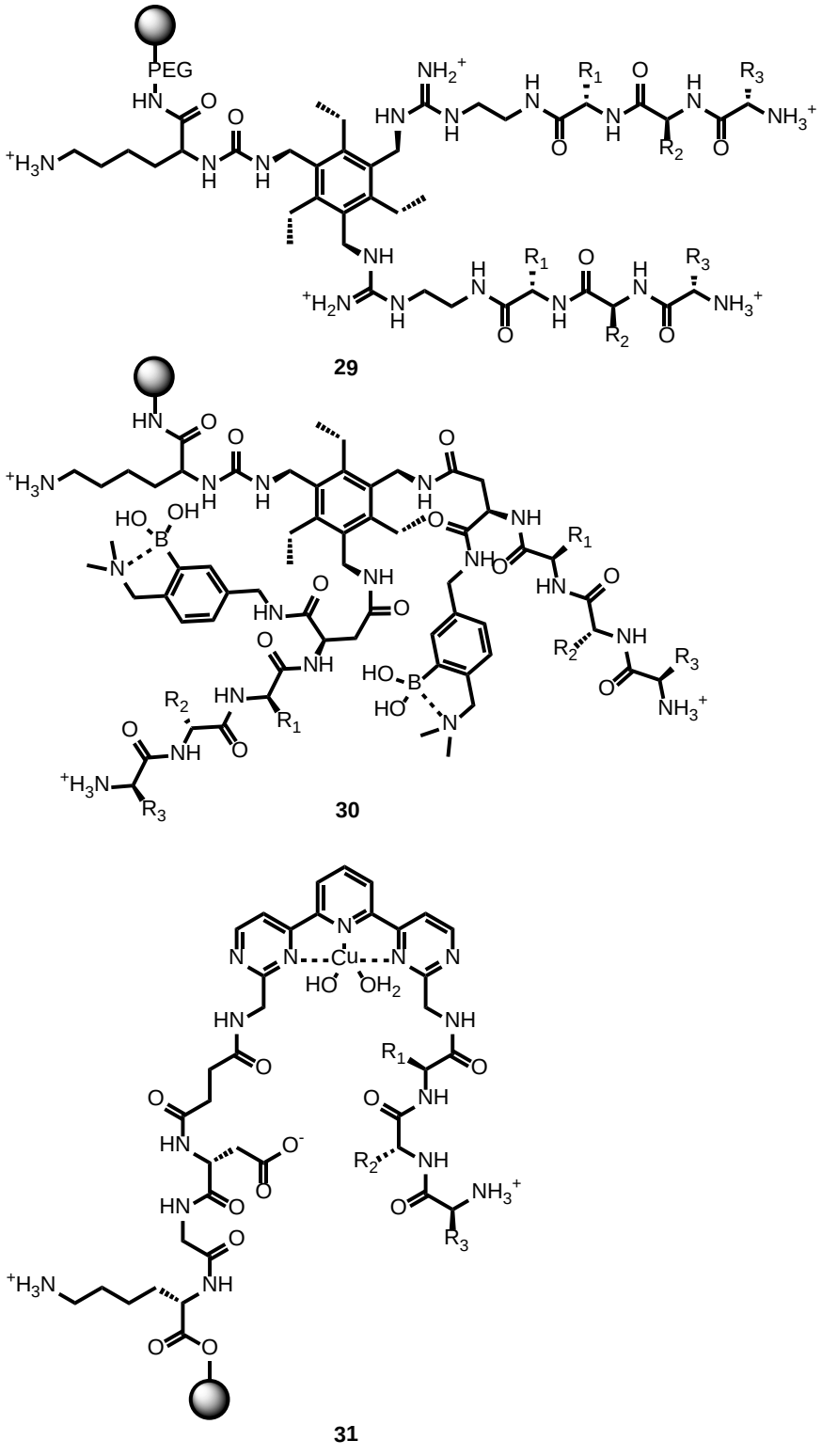

Figure 1.21. The libraries of compounds used in differential arrays to sense nucleotide phosphates (**29**), proteins (**30**) and tripeptides (**31**).[102-104]

A second method of creating differential sensor arrays relies on utilising combinatorial chemistry. Anslyn *et al* have exploited arrays of receptors for sensing nucleotide phosphates[102], proteins[103] and glycoproteins[104]. The receptors are generated with a core that possesses appropriate binding functionalities and is pre-organised for binding particular analyte structures. Different peptide arms are then incorporated onto the periphery of the receptor using split-and-pool combinatorial chemistry and a randomly chosen selection of receptors are used in the arrays. The libraries used for the sensing arrays are presented in Figure 1.21. For the recognition of nucleotide phosphates ATP, AMP and GTP, an indicator displacement assay (IDA) was utilised.[105] The indicator (fluorescein) was initially passed through the array to "colour" the beads, then a 20 mM nucleotide phosphate solution was injected through the array. The rate of indicator displacement could be calculated using the changes in absorbance of the beads over the displacement period. The cumulative displacement profiles for each receptor in the array gave a distinctive fingerprint for each nucleotide phosphate. The data was best visualised using principal component analysis[106] (PCA) and this method allowed successful discrimination between the three nucleotide phosphates.

Suslick and co-workers have taken an "electronic nose" approach to analyte sensing using metalloporphyrins.[107] The array is formed by spots of different tetraphenyl metalloporphyrins which are spotted onto reverse phase silica TLC plates. The image of the array was taken using a scanner both before and after exposure to various volatile organic compounds (VOCs), including alcohols, amines, thiols and phosphines (Figure 1.22). The interaction of the analyte gases with the metalloporphyrin core resulted in a colour change, which could be quantified by subtracting the RGB values of the 'before' and 'after' images. Resolutions down to 2 ppm were obtained and in some cases concentrations as low as 100 ppb were detected.

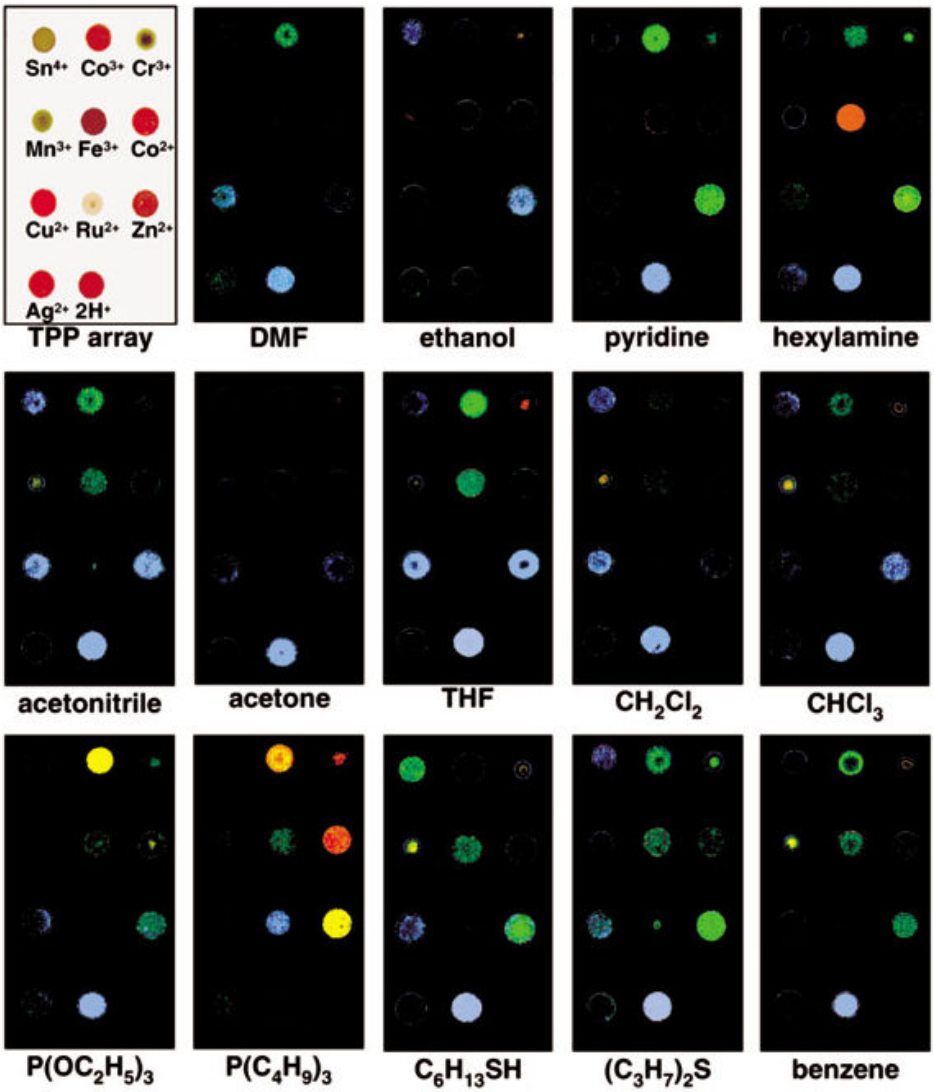

Figure 1.22. A metalloporphyrin sensor array used to detect volatile organic compounds including alcohols, amines, thiols and phosphines.[107] A series of metallated porphyrins are deposited on a reverse phase silica thin layer chromatography plate (top left). The plates are visualised using a flat-bed scanner before and after exposure to the analyte gases and the colour change profile generated gives a unique fingerprint for each analyte. Reprinted by permission from Macmillan Publishers Ltd: [Nature], N. A. Rakow and K. S. Suslick, *Nature*, 2000, **406**, 710-713, copyright 2000.

Work continued on this technique by developing a range of bis-pocketed zinc porphyrins, based on the *ortho*-substitution of the tetraphenyl groups by large, hindered silyl groups.[108] This forced the meso phenyl groups perpendicular to the plane of the porphyrin core and allowed various substituted amines to be differentiated on the basis of their shape and size. These studies were all carried out in solution and the shape selectivities determined by measuring the binding constant between the metalloporphyrin core and the amines. In this way, shape selectivities of $>10^7$ were obtained compared to the unhindered metalloporphyrins.

More recently, the group have been using three different chemo-responsive dyes mixed with the bis-pocketed Zn porphyrins in order to enhance the colorimetric response of the arrays.[109] Chemo-responsive dyes change colour upon changes in their chemical environment. The three dyes classes that were used in this study were: (1) Lewis acid/base dyes (metal ion containing dyes), (2) Brønsted acidic or basic dyes (pH indicators) and (3) dyes with large permanent dipoles (zwitterionic solvatochromic dyes). The presence of these dyes coupled with the excellent selectivity of the zinc porphyrins allowed accurate detection of amines, arenes, alcohols, aldehydes, carboxylic acids, esters, halocarbons, ketones, phosphines, sulphides and thiols. Additionally, the hydrophobicity of both the dyes and the silica support meant that the response was not affected by the humidity of the surroundings.

1.5 Conclusions

The field of supramolecular chemistry has developed rapidly over the past forty years and we are now at a stage where it is possible to design and synthesise a huge range of sophisticated and diverse supramolecular systems. Many researchers would argue that the future of supramolecular chemistry lies in the development of systems that can perform valuable functions, for example acting as nanoscale machines and sensors. An increasing understanding of the way weak intermolecular forces shape the natural world provide a wealth of inspiration for the supramolecular chemist.

1.6 Aims

The aims of this project are to synthesise systems that will allow us to further probe the nature of intermolecular interactions as well as providing a useful function. Firstly, in Chapter 2, we will investigate the strength of hydrogen bonding interactions between biologically relevant ions and neutral host molecules by ^{1}H and ^{31}P NMR titrations in order to quantify their hydrogen bond donor and acceptor abilities on the same scale as for non-electrolytes. The scale employed will be that developed by Hunter[110] which is based on electrostatic interactions and is independent of solvent. Indeed, the transferability of the method employed will be demonstrated by carrying out titrations in different solvents and comparing the results obtained. Additionally, the reliability of the hydrogen bonding parameters obtained using our method will be verified by comparing our experimental data to other systems found in the literature.

In Chapter 3, the synthesis of novel zinc calixarene-porphyrin conjugates will be investigated. Metal-ligand interactions between the zinc centre of the porphyrins and a bidentate ligand, DABCO, mean that these molecules can form intramolecular and intermolecular sandwich complexes. The stoichiometry of binding with DABCO will be investigated by carrying out UV/visible and ^{1}H NMR titrations and comparing the association constants obtained in the two concentration regimes. Additionally, the effect of flexibility of the linker chain between the calixarene and porphyrin moieties will be quantified using effective molarity (EM).

Finally, Chapter 4 will describe the synthesis of another calixarene-porphyrin conjugate that will be used in thin solid films as an amine gas detector. Previous work in the field has concentrated on using monomeric porphyrins mixed with calix[8]arene in order to reduce film aggregation and improve sensor response. Covalently attaching four porphyrins to one calixarene scaffold should further improve the film reliability and the magnitude of the sensor response.

1.7 References

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