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Supramolecules

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Abstract

Supramolecules, structures that are literally "beyond molecules," have developed over the past few decades from chemical curiosities to complex systems with well-understood properties and a wide range of applications. Components of these supramolecules range from simple polyethers to macrocycles with functionalized aromatic subunits, from cyclic sugars to DNA. Applications range from highly specific chemosensors to drug delivery agents. They can form molecule-trapping matrices for gas storage or crystallographic elucidation of otherwise flexible species. Harnessing the reversible interactions that drive the formation of supramolecules allows self-healing polymers and gels to be prepared with uses as diverse as materials science and the stabilization of historic artefacts. This chapter covers the background of supramolecules, from their origins in nineteenth century Germany through to Nobel Prize winning work in the twentieth and twenty-first centuries across the globe. Their diverse molecular building blocks and the applications of supramolecular systems are discussed with examples from the literature.

1.1 Introduction

Supramolecules, structures that are literally "beyond molecules," have their origins in descriptive biology where proteins and plant fibers were examined for "the presence of supra-molecular discrete and discontinuous units" (Baas-Becking and Galliher 1931). Observations of structures in the cytoplasm noted that they had "been considered until recently to be devoid of structure at the supramolecular level of organization" (Palade 1955) and, in later work, enzymes had been described as having "supramolecular organization" (Mitchell 1961). The term "supramolecular" itself had been defined over a century ago as referring to systems "composed of an aggregation

of molecules; of greater complexity than the molecule" (Century Dictionary 1909). Later, it was defined as: "The transition between molecular structure and morphology is approached by what we may call 'supra-molecular biology'" (Luria 1970).

The concept entered the chemical lexicon in the 1930s when Wolf and co-authors investigated the physical properties of liquids and reported that certain molecules formed strong associations with others of the same type (Wolf et al. 1937). The simplest of these was acetic acid, which was believed to form dimers held together through strong hydrogen bonds, a concept popularized by Pauling, and called by Wolf an "*übermolecül*." This idea was greatly expanded upon by Lehn who, in his 1987 Nobel Prize lecture, defined supramolecular as: "the chemistry beyond the molecule bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces" (Lehn 1988).

Elsewhere, Lehn has likened molecules to words with their atoms, or letters, linked irreversibly, and supramolecules to sentences in which the words, though not their spelling, may adopt different orders to give different meanings or functions. As Lewis Carroll's Hatter points out, "I see what I eat" is not the same thing as "I eat what I see" (Carroll 1866), and the same can be said to be true for the effect of molecular ordering in supramolecular systems.

Supramolecules form through complementary, and usually reversible, interactions between their component species. These range from individually weak hydrogen bonds and hydrophobic interactions to metal–ligand coordinate bonds and disulfide bonds. Molecules with numerous opportunities to form such interactions result in properties such as gelation, whereas reversibility

ensures allows them to reform broken bonds to give self-healing polymers. Where supramolecules are built upon a surface, carefully designed complementary functionality allows the order of these self-assembling layers to be controlled.

One further aspect of supramolecule formation also has profoundly useful effects; the formation of host–guest complexes (Fieser and Fieser 1959). Previous examples may result in complex polymer-like behavior; however, discrete binding between a host, with converging bonding sites, and a guest, with diverging binding sites, can also occur. Where this is coupled to a chromophore, fluorophore or redox-active group, the host can act as a sensor and disclose the presence of the guest through a change in color, fluorescence, or electrochemical potential.

1.2 Supramolecular Building Blocks

1.2.1 Non-Cyclic Molecules

1.2.1.1 Polyethers

A series of ten non-cyclic polyethers with different aromatic termini, including the podand in Figure 1.1 were synthesized, and their complexation thermodynamics was studied by Vögtle (Tümmler et al. 1979). They acted as neutral ionophores and formed stable 1:1 complexes with alkali metals, with stability constants ranging between 1 and 10^4 M^{-1}. The stability of the complexes depended on factors such as the number of coordinating atoms, cation size, donor strength, and the rigidity of the aromatic end groups. Thermodynamic studies showed complex formation was driven enthalpically, with an unfavorable decrease in entropy caused by forming a pseudo-circular conformation with much lower flexibility than the free ligand. While these

derivatives are excellent at binding alkali metals, they lack the ability to discriminate between cations due to their flexibility when compared with crown ethers, which have a defined cavity size which will be complementary to certain metal ions. An advantage of these acyclic compounds over macrocycles is that the cyclization reaction, which often leads to a low yield, is omitted. In addition, they can be easily tailored to many applications by changing the end groups and they are readily soluble in most organic solvents.

1.2.1.2 Dendrimers

Dendrimers are molecules that branch from a central core. Named after the Greek *dendron*, meaning tree, they have been of continued academic and industrial interest since the pioneering work of Tomalia, Newcome and Fréchet (Tomalia et al. 1985; Newkome et al. 1985; Hawker and Fréchet 1990). Each addition of a branch generates a higher "generation" of dendrimer leading to well-ordered three-dimensional molecules with relative molecular masses usually between 5 and 500 kDa; Figure 1.1 shows an example of a first-generation poly(amidoamine), or PAMAM, dendrimer. Functional terminal groups at the outer surface of the dendrimer can be selected for an intended application. Possibilities for using these "molecular sponges" to absorb and release therapeutic compounds were clear from the outset, and they are now used in the controlled release of non-steroidal anti-inflammatory compounds, anticancer drugs such as doxorubicin, paclitaxel and methotrexate, anti-HIV retrovirals, and glaucoma treatments (Madaan et al. 2014).

1.2.1.3 DNA

Although usually associated with replication, the base-specific interactions between strands of DNA facilitate their use in molecular design. Extensive work by Seeman has demonstrated how

mismatched terminal sequences can be used as "sticky ends" to recognize other strands (Seeman 1982). Careful consideration of matched and mismatched regions allows DNA to be used to build frameworks much like nanosized wicker baskets or boxes, which could be used to store guest molecules (Chen and Seeman 1991).

1.2.2 Macrocycles

1.2.2.1 Crown Ethers

Crown ethers are cyclic polyethers made up of oxygen atoms bridged by ethylene groups. The name "crown" is reflective of the shape made when a crown ether forms an inclusion complex with a metal ion through ion–dipole interactions between the negatively charged oxygen atoms in the ring and the cation. The structural nomenclature N-crown-M is derived from the number of atoms in the ring N, and the number of those which are oxygen atoms M, for example, 18-crown-6. The structure in Figure 1.1 is therefore 15-crown-5.

Early work by Nobel laureate Pedersen demonstrated the formation of stable 1:1 complexes of crown ethers with alkali and alkali earth metals (Pedersen 1967). The stabilities of these complexes were influenced by factors such as cavity size, the number and basicity of oxygens in the ring, the oxygens' coplanarity and symmetry, steric hindrance, and electrical charge on the cation. He also found that the most easily formed rings were composed of five or six oxygen atoms each separated by two carbon atoms.

It was soon realized that some or all of the oxygen could be replaced by other main group elements such as sulfur and, in particular, nitrogen. The latter gave rise to the azacrown ethers. Following from Pedersen's original nomenclature, the non-carbon atom is included to give, for

example, thia-15-crown-5 or, where two or more heteroatoms are present, their relative positions in the macrocyclic ring are given as in 1,10-diaza-18-crown-6 (Figure 1.1). Replacing oxygen with the softer Lewis base sulfur gives the thiacrowns an affinity for a number of transition metals, whereas incorporating nitrogen enables side chains to be introduced to give the lariat ethers (Schultz et al. 1985). Linking a fluorophore, electroactive substituent or chromophore, as shown in Figure 1.1, to the crown allows guest binding to be detected through a change in the spectroscopic absorption maximum or redox potential, thus turning the crowns into sensors.
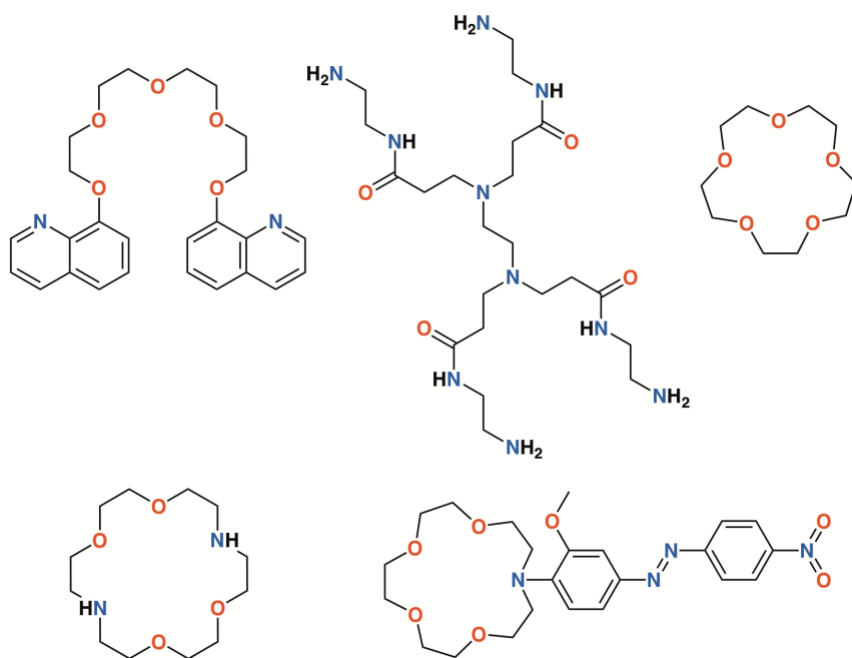

Figure 1.1 Flexible supramolecule components: (left to right, top) podand, dendrimer, crown ether, (bottom) 1,10-diazacrown ether, and lariat ether.

1.2.2.2 Calixarenes and Related Macrocycles

Calixarenes are cyclic oligomers formed through the condensation reaction of p-tert-butylphenol and formaldehyde, which were first synthesized by Baeyer in 1872 (Baeyer 1872a). The name was coined by Gutsche and originates from two Greek root words: *calix* which means chalice,

reflecting the wide upper rim and narrow lower rim of the macrocycle, and *arene* indicating the

presence of aromatic rings (Gutsche and Muthukrishnan 1978). The bracketed number in

calix[n]arene nomenclature reflects the number of aromatic units. Thus, Figure 1.2 shows 4-tert-

butylcalix[4]arene as an example. Calixarenes of varying compositions can be obtained by

varying reaction conditions such as reactant ratios and the use of different bases or solvents. The

basic structure comprises hydrophobic tertiary butyl groups on the upper rim, a hydrophobic

cavity for small organic molecules, and hydroxyl groups on the lower rim for adding functional

components through hydroxyalkylation reactions.

Resorcinarenes are close cousins of calixarenes with an analogous nomenclature and similar

chalice-like structures as illustrated in Figure 1.2. They are formed through the condensation of

resorcinol and aldehydes in acid solution. The first resorcinarene was synthesized in 1872 by

Baeyer who obtained a red product from the condensation reaction of benzaldehyde and

resorcinol in concentrated sulfuric acid; however, he did not have the analytical tools available at

the time to fully characterize them (Baeyer 1872b). Later, Högberg later investigated similar

products and discovered the two stereoisomeric resorcinarene products resulting from a

resorcinol-acetaldehyde condensation (Högberg 1980).

The reaction of veratrole and formaldehyde produces the cyclotrimer, cyclotriveratrylene (CTV).

Originally reported in 1915 (Robinson 1915), and believed to be a dimer, it was not until 1965

that X-ray crystallography revealed it to be the trimer shown in Figure 1.2 (Lindsey 1965).

Despite the lack of accessible central cavity, CTV can be functionalized and used to synthesize

dimeric capsules known as cavitands, which are capable of encapsulating guest solvents (Canceill et al. 1984).

In 2008, Ogoshi reported a new class of macrocycle, the pillar[n]arenes (Ogoshi et al. 2008). Pillar[n]arenes, or pillarenes, are almost structural analogs of calixarenes and are formed by the condensation of 1,4-dimethoxybenzene and paraformaldehyde in the presence of an appropriate Lewis acid. They are also named analogously to the calix[n]arenes, with the bracketed number indicating the number of units that make up the macrocycle. The example in Figure 1.2 is dimethoxypillar[5]arene. While methylene groups link calixarene units in the meta-position, pillarene units are linked at the para-positions, forming a more symmetric topology made up of pillar-like units. An advantage to this increased symmetry is the ability of the macrocycle to form some inclusion complexes without modification, although the pillarenes may be easily functionalized by cleaving the methyl ether bonds and reacting at the resulting hydroxyl groups. Alternatively, other dialkoxybenzene derivatives can be cyclized to introduce functionality as in Ogoshi's phenylethynylpillar[5]arene (Ogoshi et al. 2009).

1.2.2.3 Porphyrins

Porphyrins are macrocycles formed of four modified pyrrole units linked by a methine bridge at the α-carbons as shown in Figure 1.2. Due to the large conjugated system formed of 18 out of 26 π-electrons in a planar, continuous electron cycle, porphyrins absorb light strongly in the visible region. An example of a naturally occurring porphyrin is heme, the pigment in red blood cells, essential in the actions of hemoglobin.

1.2.2.4 Cyclodextrins

Cyclodextrins (CDs) are macrocycles formed of glucose units joined through α-1,4-glycosidic bonds. They are products of enzymatic reactions with starch, α-amylase, and a glycosyltransferase enzyme, with different compositions resulting in varying ratios of differently sized cyclic products, which can be made on a large scale at a low cost. These α-, β-, and γ-CDs, comprising six, seven, or eight units, respectively, are separated based on their relative solubilities. The least water-soluble, β-CD (Figure 1.2), crystallizes from an aqueous solution, whereas the smaller α-CD and larger γ-CD require selective complexation and membrane filtration to be isolated. The secondary hydroxyl groups at the upper rim and primary hydroxyl groups at the lower rim provide aqueous solubility and the hydrophobic central cavity provides a chiral environment for guest encapsulation.
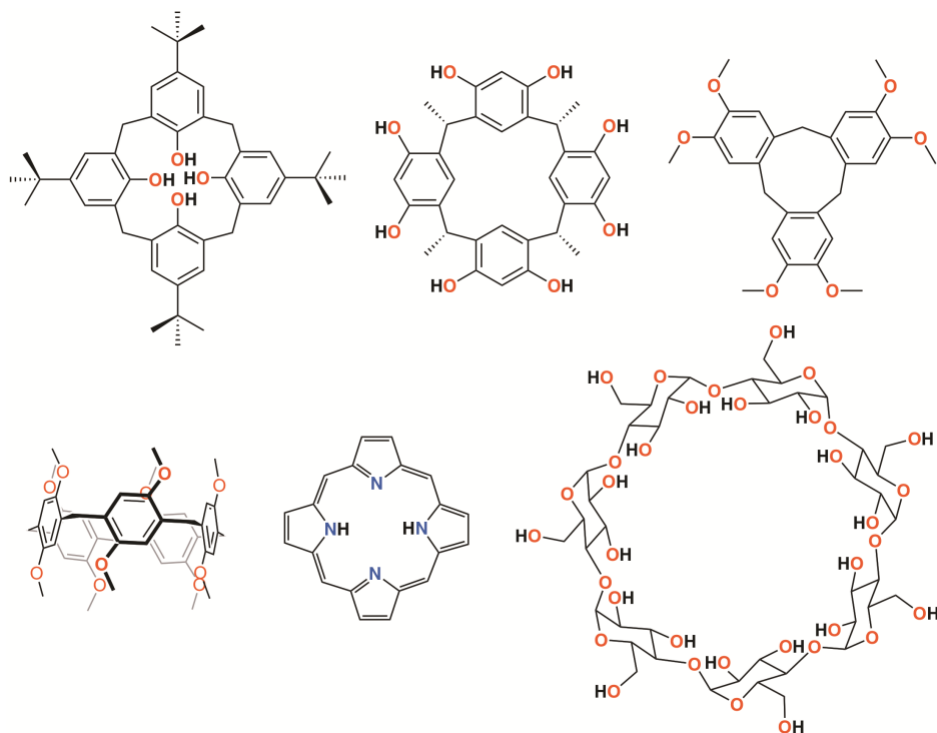

Figure 1.2 Rigid supramolecule components: (left to right, top) calixarene, resorcinarene, cyclotriveratrylene, (bottom) pillarene, porphyrin, and cyclodextrin.

Consequently, CDs have found extensive use as delivery agents for poorly soluble drugs and as extractants in air fresheners where volatile odoriferous molecules are extracted from the air. Their inherent chirality, coupled with hydrogen bonding potential, has been exploited in technologies such as the separation of chiral compounds using CD-coated columns for HPLC. The CDs can be easily functionalized, either through all accessible hydroxyl groups or through just one, such that solubility or guest binding properties can be modified.

1.3 Supramolecular Assemblies

1.3.1 Supramolecular Polymers

Conventional polymers are formed when monomers react to form covalent bonds, but if, instead of covalent bonds, reversible interactions hold the structure together, then a supramolecular polymer result (Brunsveld et al. 2001). Complementary hydrogen bonding involving alternating donors, such as amines, and acceptors, such as pyridines or carbonyls, allows very strong and specific polymeric assembly to occur (Kotera et al. 1994), whereas the alternating amide interactions in cyclic peptides result in stacking and nanotube formation (Ghadiri et al. 1993). Other interactions, such as enforced π-stacking of naphthyl and quaternarized bipyridyl groups inside cucurbit[8]uril macrocycles (Figure 1.3), can be used to prepare di-block co-polymers (Rauwald and Scherman 2008) which can stabilize waterlogged archaeological artefacts (Walsh et al. 2014).
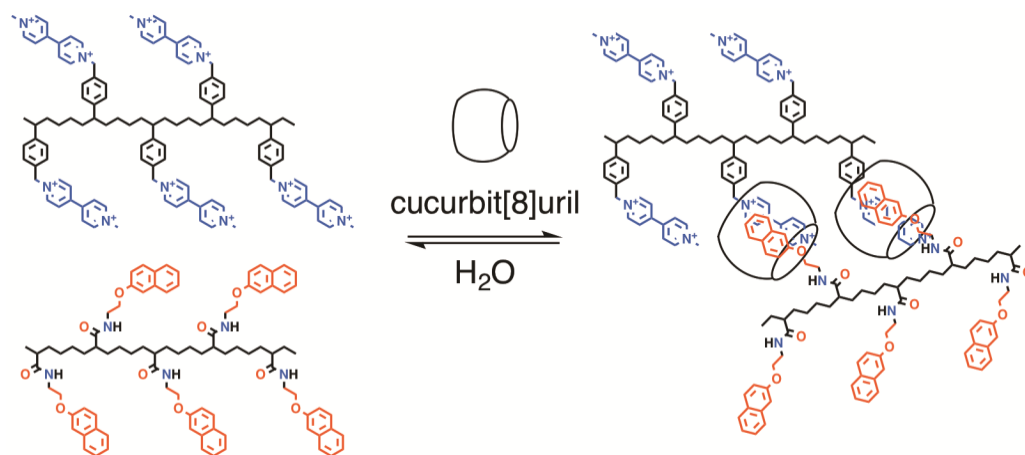
Figure 1.3 Supramolecular polymerization.

1.3.2 Supramolecular Gels

Gelation occurs when molecules crosslink, usually in the presence of a large excess of solvent, and expand in volume (Sangeetha and Maitra 2005). In supramolecular gels, the intermolecular interactions are those associated with supramolecule formation. While hydrogen bonding is the most obvious driving force, other interactions, such as the addition of metal cations to change molecular conformation and induce gelation, exist. What distinguishes these gels from supramolecular polymers is their ability to form expanded structures when they trap solvent or gas. Hydrogels are those that form in water, while xerogels are those with a gaseous second phase. For gels, and specifically hydrogels, to form, other functional groups capable of binding solvent molecules, such as urea moieties (Figure 1.4), amides or alcohols, are also present. The small amount of gelator present is able to trap the solvent and provide an extended porous surface for solvent binding.
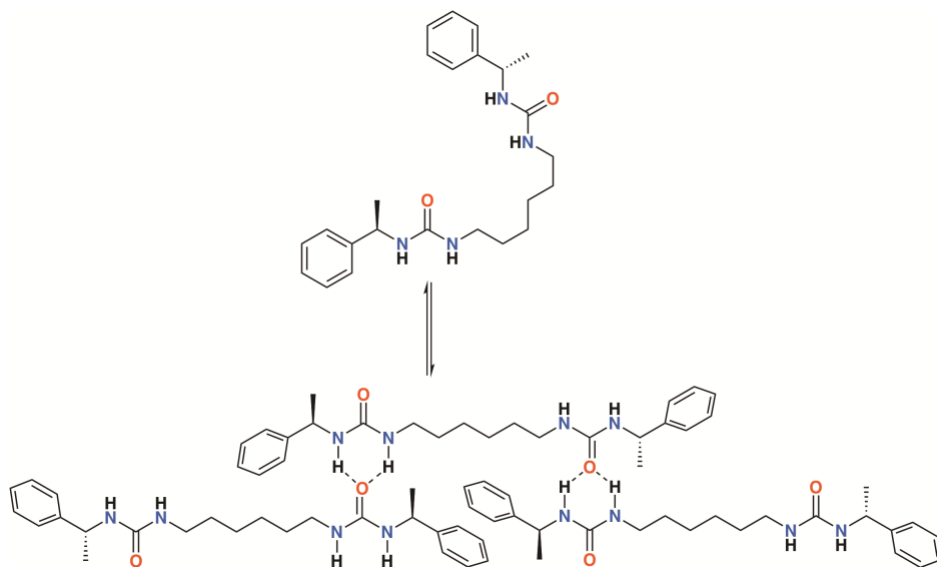
Figure 1.4 A supramolecular gel.

1.3.3 Coordination Polymers and Metal Organic Frameworks

The term "coordination-polymère" was coined by Shibata in 1916 to describe cobalt complexes

linked through ambidentate ligands (Shibata 1916). Subsequent usage covers any solid where

bridging ligands impart a polymeric repeat pattern, generally in two or three dimensions.

Consequently, metal–organic frameworks (MOFs), where the key "framing" ligands are organic,

are a subset of coordination polymers. MOFs are materials made up of two main structural

components; metal ions (or metal ion clusters) and organic linker molecules which can form a

diverse range of one-, two- or three-dimensional network structures through molecular self-

assembly (Perry et al. 2009). Figure 1.5 shows how a linear ditopic ligand can combine with a

metal exhibiting a square planar geometric preference to generate a two-dimensional grid. In the

context of supramolecular design, these ligand and metal components may also be referred to as

supramolecular building blocks. Having metallic nodes separated by organic linkers results in

unique material properties such as high surface area and high porosity, making them ideal for the inclusion of small molecules.

Pore size can be easily adapted by changing the length of the linker molecules and the topology, structure and functionality can also be controlled through careful selection of each structural component while the overall geometry of the network is largely determined by the coordination modes and geometry of the nodes. The pore size of MOFs can be used to make them function as selective sponges for gases and small organic molecules with the rate of release controlled by heat or pressure changes (Li et al. 2009).
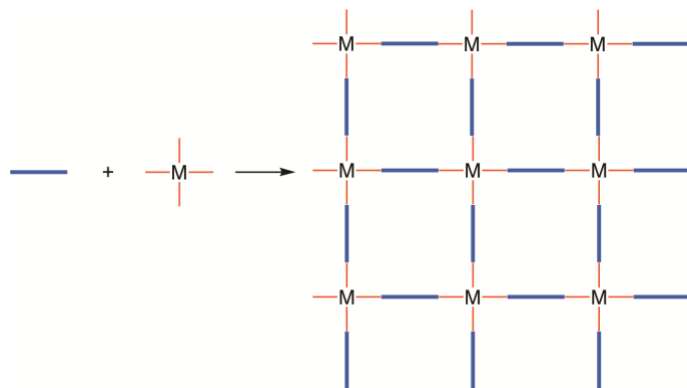

Figure 1.5 Constructing a metal–organic framework.

Perhaps the most ingenious application is to trap flexible organic molecules inside the crystalline matrix (Figure 1.6). Fujita demonstrated that it was possible to take single crystals of MOFs, determine their solid-state structure, then soak them in solutions of the desired guest and re-determine the X-ray structure (Hoshino et al. 2016). Subtraction of the electron density due to the framework reveals the density due to the guest and allows its structure to be calculated. There are drawbacks with this approach as the guests will not be uniformly distributed within the

crystalline network, which can render the crystallographic solution ambiguous, but, in general, it is an excellent method by which the structures of rare natural products or complex drug molecules can be elucidated.
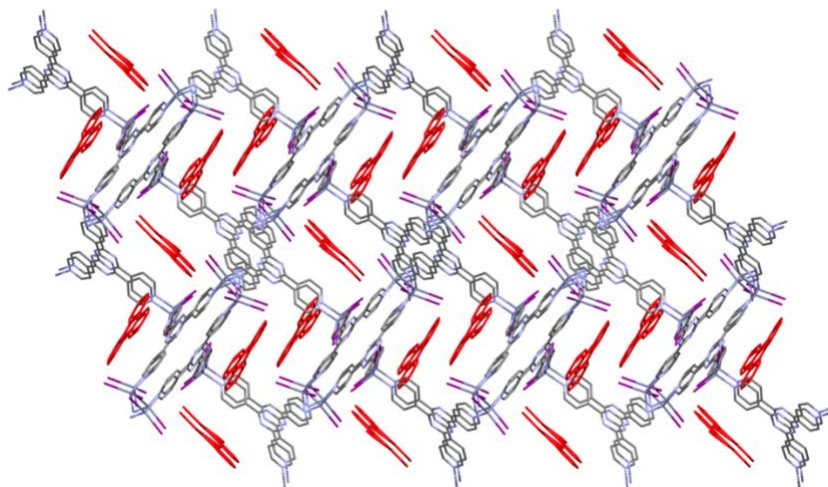

Figure 1.6 Guest (shown in red) inclusion inside a metal–organic framework (Cambridge Crystallographic Data Centre, CCDC 241417).

1.3.4 Nanocontainers

Encapsulation of molecules has long held a fascination in the field of supramolecular chemistry whether the interior space is only large enough for a solvent molecule or is capable of facilitating an "impossible" reaction. At the smallest end of the scale are the cryptates developed by Lehn (Dietrich et al. 1969) to bind alkali metals and which, subsequently, allowed Dye to isolate alkali metal anions (Tehan et al. 1974). These molecules were prepared by linking the two nitrogen atoms in a diazacrown to give a relatively flexible "three-dimensional" crown ether (Figure 1.7). Similar examples include Sargeson's ethylenediamine cobalt complexes which, when reacted with formaldehyde and ammonia or nitromethane, form sepulchrates and sarcophagenes (Figure

1.7), respectively (Creaser et al. 1977). More rigid examples include Schiff bases formed from

tris(2-aminoethyl)amine and aromatic dialdehydes (Arthurs et al. 2001).
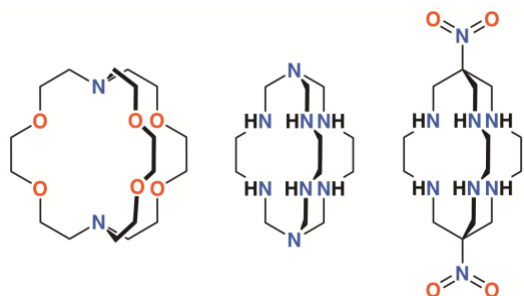

Figure 1.7 Cryptate, sepulchrate and sarcophagene.

Continuing with the early trend in nomenclature to describe encapsulating macrocycles in

descriptive terms, Cram linked two resorcinarene derivatives to form a carcerand in which to

imprison guest molecules (Cram et al. 1985). It was noted that the restrictive interior of the

carcerands could protect guests from the effects of external gases or solvents. This was

demonstrated by the cyclization of butadiene inside a carcerand, resulting in the stabilization of a

molecule that is quite simply too reactive to prepare under any other conditions (Cram et al.

1991).

One question that arose concerned the small volumes that these compounds can enclose and

asked how much of that space could be occupied by guest molecules. This was answered by

Rebek who prepared self-assembling capsules, such as those in Figure 1.8, to trap a number of

guest molecules (Mecozzi and Rebek 1998). Several dimeric capsules were investigated

computationally to determine an internal volume and then assembled in solution with a number

of guest molecules. Evidence from relative integration of host and guest molecules indicated that

the most efficient packing occurred when the guest occupied 55% of the available space within the capsule.
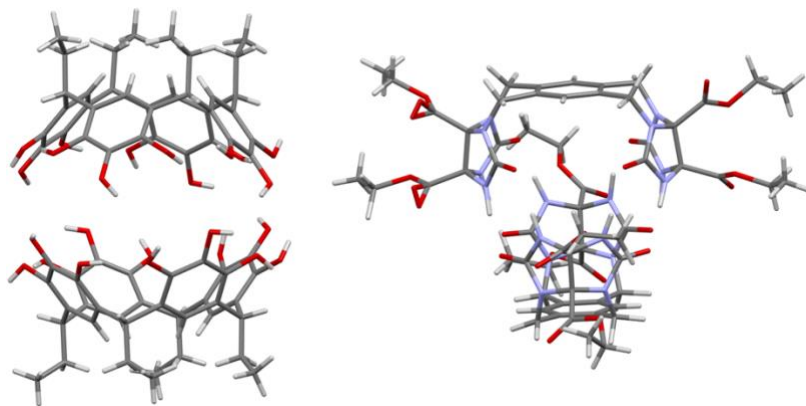

Figure 1.8 Hydrogen bonded molecular capsules (CCDC 131412 and 220346).

Coordination chemistry can also be used to create capsules through careful choice of rigid ligand and metal center. Using principles now much more widely understood through their application to the construction of MOFs, Raymond showed that four tin(IV) or titanium(IV) atoms could bind to four tripodal ligands and adopt a tetrahedral geometry although the central cavity appeared too small to contain a guest (Brückner et al. 1998).

A similar approach taken by Nitschke, in which six rigid, twisted bidentate ligands assemble around four iron centers to form a tetrahedron with enough room to bind a tetrahedral P_4 molecule as shown by its X-ray crystal structure in Figure 1.9 (Mal et al. 2009). The encapsulated air-sensitive white phosphorus molecule becomes air-stable and, as the complex, water-soluble. The spontaneously combustible guest can then be hydrolyzed under controlled conditions to the far safer phosphoric acid.

Careful consideration of a rigid ligand's geometry and the preferred coordination mode of transition metals has allowed Fujita to create a number of capsules including one with a $M_{24}L_{48}$ formula and an inner diameter of 3.6 nm (Sun et al. 2010). Evidence of the capsule's formation came initially from mass spectrometry but was proved by X-ray crystallography (Figure 1.9).
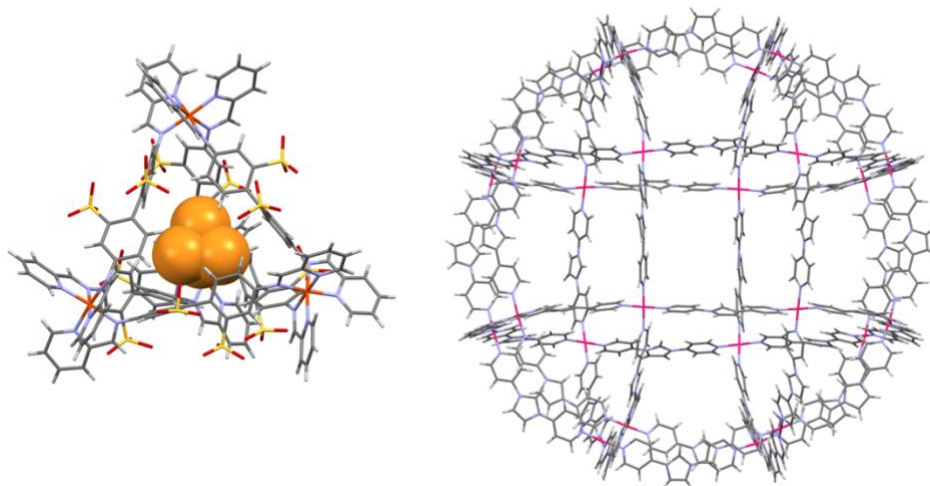

Figure 1.9 Tetrahedral and spherical capsules (CCDC 727817 and 860617).

1.3.5 Supramolecular Machines

Supramolecular chemists have exploited reversible interactions in many ways, from selective detection of small molecules to the creation of nanospheres, but the greatest challenge is surely to create analogues of simple machines on the molecular scale. When interlocked molecules, whether the interpenetrating catenands or shuttle-like rotaxanes (Figure 1.10), incorporate recognition motifs then the movement of one molecule between them becomes possible with the appropriate external stimulus. In doing so, mechanical movement becomes an on-off switch or a binary 0 and 1. Stoddart has used this phenomenon to create "nanoelevators"; rotaxanes linked through an aromatic moiety that rise and fall in concert (Badjic et al. 2004). The same system could be used as a piston, to pump drugs as the rotaxane reaches one of its termini, but perhaps

the most interesting application is in molecular computing where electronic components, cross-linked by an array of rotaxanes, can move between "on" and "off" states (Collier et al. 1999). Molecules become detached over time so using an array, such as 10×10, allows for some redundancy so that, as long as a majority of the shuttles are in one of the two positions, the correct 0 or 1 will be recorded.
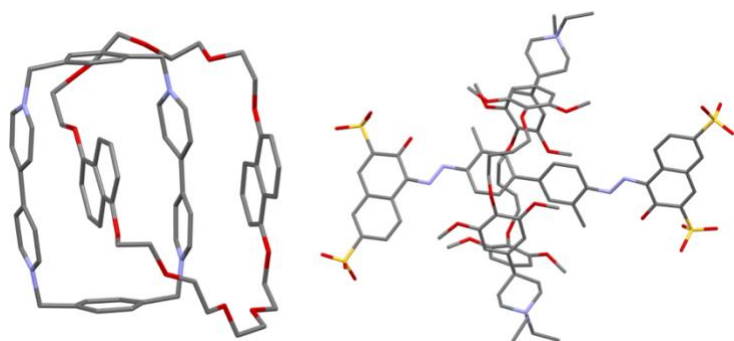

Figure 1.10 Catenane (left) and rotaxane (right) (CCDC 1197478 and 104321).

Simple molecular ratchets, where part of a molecule can be made to rotate while the remainder acts as the stator in a motor (Figure 1.11), were first demonstrated by Kelly (Kelly et al. 1999) and Feringa (Feringa et al. 1999). The rotor may be attached by a double bond, such as an imine (Greb and Lehn 2014), that can be partially broken for rotation to occur or may interact through remote hydrogen or disulfide bonding while rotating around a single bond. The former method has been used by Tour to power "nanocars" by illuminating a paddle-like rotor which responds to incoming photons (Morin et al. 2006). The latter has been used by Leigh to create a "nanoassembler" (Figure 1.11) which can be programmed to prepare one specific enantiomer resulting from a multi-step synthesis with four possible products (Kassem et al. 2017).
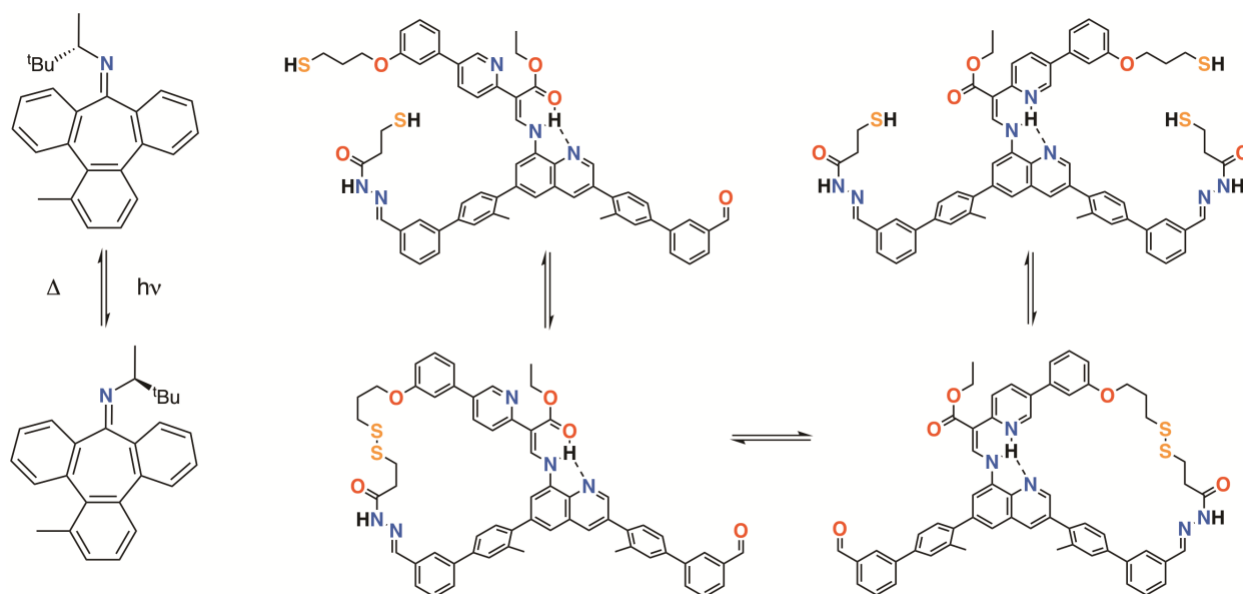
Figure 1.11 Molecular machines: a rotor (left) and nanoassembler (right).

1.4 Host–Guest Complexes

Many supramolecules are complexes between a host, often a macrocycle with convergent

binding sites, and a guest, a smaller molecule with divergent binding sites. At its simplest, this

could be an alkali metal cation and a macrocycle as in Bell's torand complex shown in Figure

1.12 (Bell et al. 1992). Complexation occurs through mutually beneficial, or complementary,

interactions such as hydrogen bond donors aligned with acceptors, stacking of hydrophobic

aromatic rings or simple electrostatic attraction. With careful design, made easier by powerful

computational chemistry programs to model the systems, it is possible to design hosts with high

specificity for their chosen guests. An excellent example of this can be seen in the work of

Hamilton (Chang and Hamilton 1988) who used complementary arrays of hydrogen bond donors

and acceptors to bind barbituric acid derivatives (Figure 1.12). The incorporation of sterically

hindering moieties resulted in high specificity for barbital over phenobarbital. To demonstrate

how this could be used to detect illegal substances, Kondo incorporated a phenylethynyl group

that signals barbiturate binding by switching on fluorescence (Kondo et al. 2017). The molecule was fashioned as a molecular cleft that allows any barbiturate to bind (Figure 1.12) which, while it gives reduced selectivity for barbital, allows a broad group of chemically related barbituric acid derivatives to be detected by a single sensor. Host–guest complexes are discussed in Chapter 2.
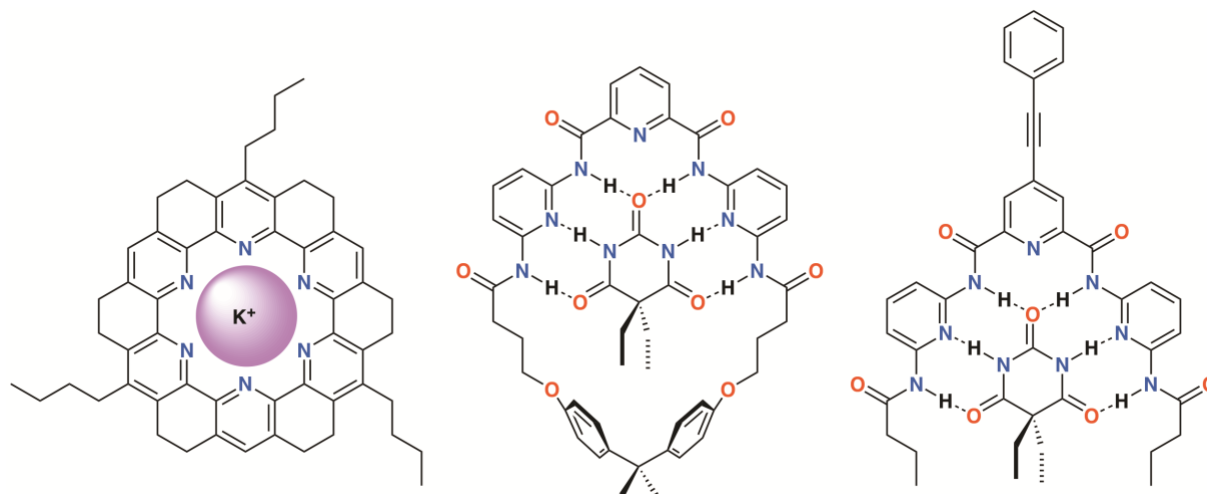

Figure 1.12 Host–guest complexes: Bell's [K·torand]$^+$ complex (left), Hamilton's barbiturate receptor (center) and Kondo's fluorescent barbiturate sensor (right).

1.5 Conclusions and Perspectives

Supramolecules, structures that are literally "beyond molecules," have developed over the past few decades from chemical curiosities to complex systems with well-understood properties and a wide range of applications. Supramolecules range from macrocyclic complexes of guest molecules, which reveal the nature of these guests, to complex MOFs that restrict guest molecule motion to facilitate the determination of their structures. Dendrimers are capable of releasing life-saving drugs in response to external stimuli and nanoassemblers also fall into the same category. In every case, the properties and behaviors of the supramolecules relate to weak,

reversible interactions between the molecular components which can be harnessed by the supramolecular chemist. Once the fundamental chemistry behind supramolecule formation had been understood – through the work of Nobel laureates Pedersen, Lehn, Cram, Feringa, Sauvage, Stoddart, and many other chemists – it can be used in the design of functional supramolecules. Since there is a wide range of data presently available and advances in computational chemistry, complex supramolecular systems can now be designed, modeled, and created for a range of applications.

Supramolecular chemistry has come a long way from the early days of Baeyer's isolation of cyclic products from experiments on phenol-formaldehyde resins and Pedersen's serendipitous discovery of alkali metal-binding crown ethers. Research is directed outward from the field to impact drug delivery, the detection of illicit substances, preserving ancient artifacts, self-healing materials, and inhibition of corrosion processes.

Acknowledgment

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