Noncovalent design principles and the new synthesis

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1 Introduction

Like most disciplines, organic chemistry has evolved through several phases. From a predominantly physical-chemical basis in the earlier part of the twentieth century emerged, when the technology made it possible, a stage of hard-fought, target-oriented synthetic chemistry, which has continued into the present with a strong emphasis on methodology and stereoselectivity. A new genre of experimentalist co-evolved in the late 1960's with a keen interest in what has today become known as *supramolecular chemistry.* This branch of science, although nominally organic with respect to the chemical species involved, defined aims which set it apart from mainstream chemistry. This review will examine these aims and look at how synthesis has undergone a conceptual revolution, no longer only addressing the making of covalent bonds to create molecules, but also noncovalent bonds to create 'supermolecules'. To appreciate why molecular assemblies have emerged as 'synthetic' targets, the collective behaviour of species at the molecular level will briefly be considered, followed then by a survey of the principles applied to the generation of such assemblies.

1.1 Supermolecules and information

Supramolecular chemistry is the chemistry of the noncovalent bond.[1] Conceptually, it can be loosely divided into two categories, which may be termed host-guest chemistry and self-assembly. In host-guest systems, species combine in a small integer ratio (most often one to one) where one component, the 'host', is perceived to spatially accommodate (or include) the 'guest', while self-assembly describes the building up of noncovalent arrays of defined geometry by specifically 'engineered' molecular components. There is, unsurprisingly, a degree of overlap between these two areas and certain cases will defy categorization. A classic example of host-guest chemistry is the complex between 18-crown-6 and ammonium ion (**Figure 1**). Self-assembly can be illustrated by the spontaneous organization of mixtures of barbituric acid and triaminopyrimidine derivatives into a supramolecular 'rosette' (**Figure 2**).

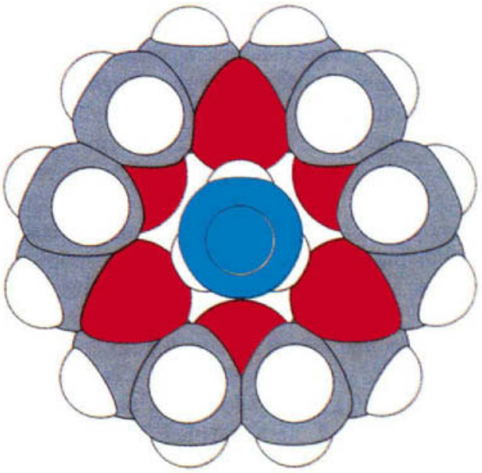

Figure 1 Crystal structure of the 18-crown-6/ammonium ion inclusion complex.[2]

The role of supramolecular science in the life process cannot be overstated. Nucleic acid transcription and translation, enzymatic function, antibody specificity, virus assembly and action, lipid biomembranes, and the mechanical strength of structural protein/mineral composites serve as an inspiration: if nature uses the noncovalent organization of molecules to drive the very life process itself, can we not apply the same principle to our own (less ambitious) aims?

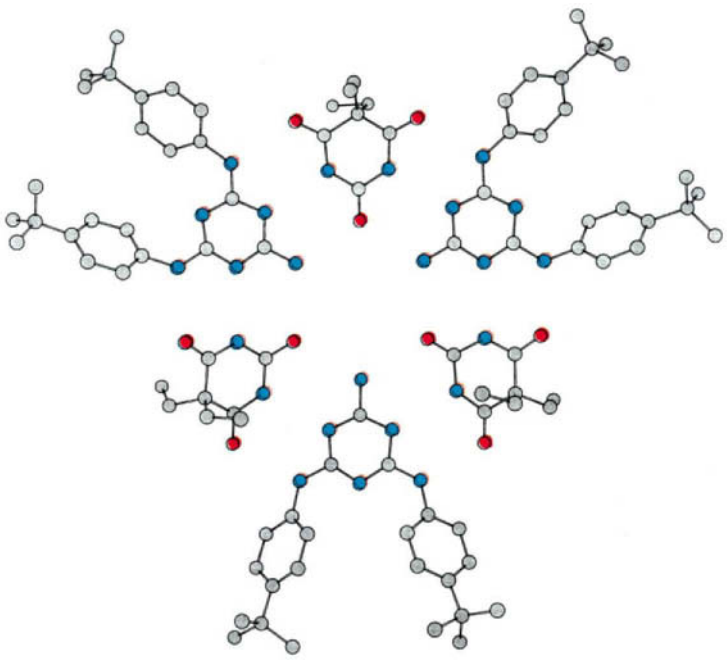

Figure 2 Crystal structure of the assembly generated from 5,5-diethylbarbituric acid and 2-amino-4,6-di(4-t-butylphenyl)aminopyrimidine.[3]

Collective behaviour in molecular systems involves the coherence of vast numbers of degrees of freedom. The spontaneous organization seen in systems under (certain) conditions of equilibrium, where intermolecular forces dominate kinetic energy, can be superimposed on nonequilibrium conditions in the bulk material to generate order on a grand scale. The intermolecular forces (see below), which operate over a range of a few angstroms, are the *design principles* of supramolecular chemistry since they can be catalogued as a repertory for the design of self-assembling systems. They are quite simply the energetic currency for payment of entropy. The far-from-equilibrium physics of matter, on the other hand, which describes a subtle balance between extensive (macroscopic) order and chaos, is the next frontier of the supramolecular scientist.[4]

Intermolecular forces are much weaker than covalent bonds (*e.g.* 20 kJ mol^{-1} for a typical hydrogen bond *versus* 350 kJ mol^{-1} for a C–C single bond) and are easily disrupted. Thus the mean lifetime of a hydrogen bond in solution is in the order of 10^{-10} of a second, whereas covalent bonds are, in the absence of external influence, long lived if not permanent. And yet it is the relative weakness of the noncovalent bond which makes it ideally suited to the chemistry of living organisms, where the processes involved in motion and perception require events on the molecular level much faster than the making and breaking of covalent bonds. In terms of economy of energy, the encoding of genetic information by means of reversible noncovalent assembly is far more efficient than if, for example, the unwinding of DNA and the readout of messenger RNA were of a covalent nature. Despite the fleeting lifetime of the isolated noncovalent bond, many higher order structures are capable of discrete existence on the same time scale as covalent species due to the large number and (often) cooperative nature of the interactions involved. Recognition-directed organization in simpler systems is also observable by freezing out the interactions in the solid state.

Finally, recognition, or the capacity to distinguish one spatial relationship from another, requires the presence of *information*. There are two fundamental types of complementarity by which information is expressed at the molecular level: *steric* and *functional*. The shape of a subunit and thus its steric requirements in the context of an assembly derives from its primary covalent structure, over which the synthetic chemist exercises a degree of control. Although not a noncovalent force in itself, steric complementarity is important in achieving an optimal geometry and interface for weak interactions, leading to a maximum gain in enthalpy on association and, in the case of multiple interactions, cooperativity. Functional complementarity refers to the reciprocal functionality with which subunits enter into noncovalent bonding relationships with partner subunits. Thus, one begins with an idea, the desire to express a certain geometrical motif on the molecular scale. To do this, one will require a species which possesses the functional and steric information to unambiguously describe such a structure. Hence *programming* is the first step of a process which further consists of *realization* (synthesis), *recognition*, and finally *organization* to the desired supermolecule (*i.e.* supramolecular synthesis).

2 The design principles

2.1 Simple coulombic interactions

Although they will be discussed under several headings, all intermolecular forces are fundamentally electrostatic in character. Those, however, which are not associated with specific functionalities are referred to as van der Waals forces, and include the mutual attraction between any combination of point charges, permanent dipoles, and induced dipoles.

The bonding between species with formal charges, often called ion pairs or salt bridges, is the most significant of these interactions. Opposite charges in a vacuum attract each other with a potential energy which varies inversely with the distance that separates them. Thus the bond energy between sodium and chloride ions in an ionic lattice can be calculated at 494 kJ mol^{-1}. In solution, however, the relative permittivity of the medium diminishes this interaction. For example, in water the attraction is about two orders of magnitude weaker or *ca.* 5 kJ mol^{-1}.[5] Because the relationship is non-directional, at least three points of contact would be necessary to fix components in 3-d space. Alternatively, control can be achieved in combination with other constraints. Carboxypeptidase A for example binds substrates (such as glycyltyrosine in **Figure 3**) by both ion pairing *and* coordination to Zn^{2+} at the active site. Hydrogen bonding is often found coupled with ionic interactions wherever these involve NH or OH functions, and this is discussed further in section 2.2.

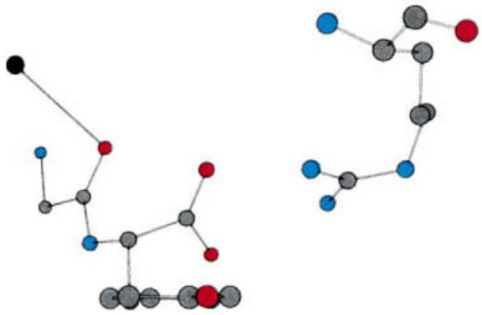

Figure 3 The guanidinium function of an arginine residue of carboxypeptidase A (right) interacts with the carboxyl terminus of the dipeptide Gly-Try (left) in the crystal structure of the complex. The ions are separated by about 2.9 Å.[6]

The description of mixed ion, dipole and induced dipole interactions is more complex than for purely ionic forces, and potential energy abruptly drops off as the interaction becomes less defined, as is demonstrated by the greater inverse power dependence on increasing separation (**Table 1**). As a result the interaction potential may be only slightly above the average thermal energy of the molecules, and so these forces are only of utility as design principles when they operate *en masse* and/or in combination with other types of bonding. Dipole–dipole interactions would be expected to influence spatial relationships in molecular crystals, especially in the absence of more pronounced interactions. Crystals themselves can be considered supramolecular assemblies of a sort, and much work has been devoted to crystal engineering, whose ultimate objective is to favour 'topochemical' reactions leading to ordered materials.[7] The outcome of a crystallization is, however, non-trivial to predict and as much a matter of efficient lattice packing as optimizing electrostatic interactions. For example, recent work demonstrated no correlation between the magnitude of the dipole and the relative molecular orientations in noncentrosymmetric crystals, or indeed even the population of centrosymmetric *versus* non-centrosymmetric space groups.[8]

The attainment of the liquid crystalline state is a manifestation of a non-isotropic distribution of van der Waals forces. Rod or disk shaped molecules (**Figure 4**) adhere more weakly to each other along their short contact axes (x and z rods, y for disks) than their long contact axes (y for rods, x and z for disks), allowing transition to non-isotropic states ('mesophases') of varying degrees of order as thermal energy overcomes intermolecular forces. Thus, moderating the magnitude of weak interactions with respect to direction by synthetic design literally makes possible the creation of ordered states of matter. The generation of *macroscopic* order will again be taken up in Section 2.6.

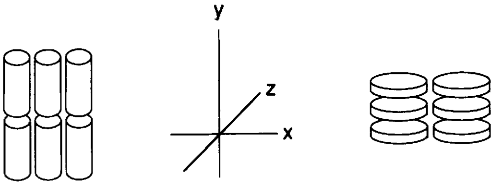

Figure 4 Cylindrical and discotic molecular shapes which undergo transitions to liquid crystalline phases.

The final entry in **Table 1**, repulsion, is related to the second type of complementarity by which molecular information is communicated, *i.e.* steric. The extremely disfavourable energetics involved in co-occupying the same space make this an important

Table 1 Dependence of separation (r) on the potential energy (V) of van der Waals forces

Interaction	n in $V \propto r^{-n}$	Remarks
Ion–ion	1	Idealized point charges
Ion–dipole	2	Dependence on dipole moment μ
Dipole–dipole (parallel)	3	Dependence on orientation θ
Dipole–dipole (free rotation)	6	'Keesom' force
Dipole–induced dipole	6	'Debye' force
Induced dipole–induced dipole	6	'London' force
Repulsion	9–15	$n = 12$ standard value

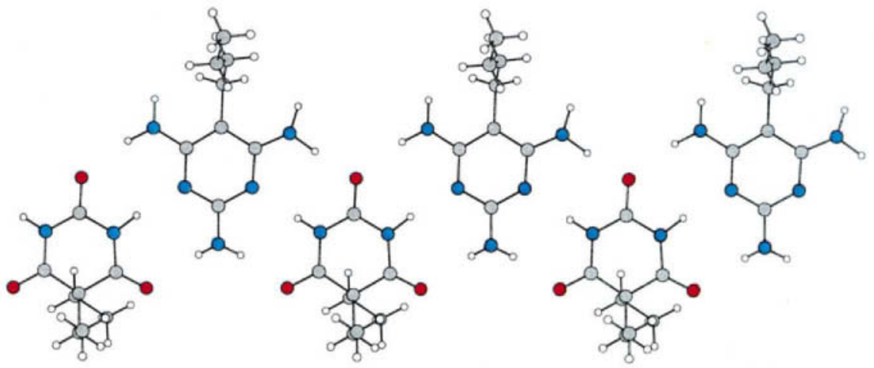

Figure 5 Crystal structure of the assembly generated from 5,5-diethylbarbituric acid and 5-butyl-2,4,6-triaminopyrimid

consideration in component design. Indeed, Whitesides used this principle to drive the formation of the cyclic hexamer in **Figure 2**.[3] Because of the functional symmetry of the barbituric acid and triaminopyrimidine components, their association may lead to the formation of either a cyclic or zig-zag chain motif. Under normal circumstances the chain is observed (**Figure 5**),[9] but in the example in **Figure 2** the steric bulk of the substituents on the nitrogen atoms disfavours the chain and leads to the observation of the 'rosette', where the *p*-t-butylphenyl substituents point out towards the corners of a hexagon instead of being lined up in rows.

2.2 Hydrogen bonding

The hydrogen bond is not only one of the strongest intermolecular forces (bond energies up to 30 kJ mol^{-1}, depending on the medium) but has the added advantage of being directional and therefore has immediate appeal as a design principle. Hydrogen bonding is the attraction between a hydrogen attached to an electronegative atom (A) and a second species (B) bearing a lone pair, as shown below.

where A = O,N,F,S,C
B = O,N,F,S,X$^-$

It is chiefly electrostatic in nature but rigorous descriptions include a number of higher order energy terms. Although halogens, sulfur, and even acidic protons on carbon may participate in hydrogen bonding, for practical purposes A and B are either oxygen or nitrogen. To maximize the interaction, the geometrical requirement is that the A–H–B angle be near 180° and that the hydrogen approximately align itself with an unshared pair of the donor atom B.[10] This is observed by sp^2- more than sp^3-hybridized B, where the proton resides in the lone-pair plane but not necessarily on the lone-pair axis. A simple example which illustrates this is the H-bonding between water molecules in ice, the crystal structure of which (**Figure 6**) clearly shows the hydrogens directed towards the neighbouring oxygen atoms. The O–O distance is 2.7 Å, which is less than the sum of the van der Waals radii of the oxygen atoms themselves. Such geometric constraints constitute a high degree of information, which has been applied in numerous instances to the design of supramolecular species.

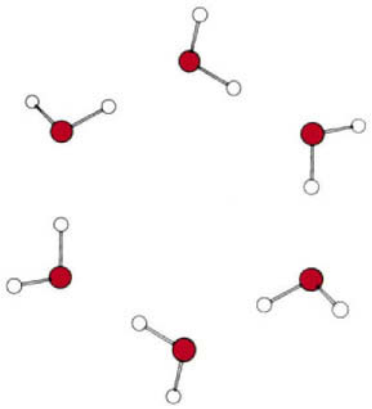

Figure 6 Cyclic hexamer extracted from the unit cell of ice II.[11]

The quality of hydrogen bonds can vary, and the aptitude of A as a hydrogen bonding donor and of B as a hydrogen bonding acceptor has been estimated using a number of techniques. **Table 2** gives values of H-bond donor acidity (α_2^H) and acceptor basicity (β_2^H) for several species after Abraham.[12] There is some correlation between these properties and the Brønsted acidity and basicity of HA and B, but the relationship has its limitations. For example, sulfoxides and phosphine oxides, though nonbasic, are among the best acceptors. As the donor and acceptor ability increase, the distance between A and B decreases and the proton is more evenly shared. Cases where the proton is approximately equidistant between A and B are known, and this interaction is called 'very strong hydrogen bonding', with bond energies calculated in excess of 50 kJ mol^{-1}.[13] As is shown in **Figure 7**, this typically involves a negatively charged acceptor B. Likewise, exceptionally weak hydrogen bonds have also been characterized. In particular, examples of well defined C–H···O and C–H···N relationships where the proton is consistently found in the plane of the heteroatom lone pair have been described, and these are also known to influence solid state structure.[14] Such interactions apparently operate even beyond the accepted van der Waals limit for C–H···O contact (*ca.* 3.4 Å).

As mentioned above, hydrogen bonding may be reinforced by ionic interactions. Benzamidinium

Table 2 Some values of the solute hydrogen bond acidity and basicity parameters α_2^H and β_2^H.[12]

Solute (CCl_4)	α_2^H	Solute (CCl_4)	β_2^H
Alkanes	0.00	Alkanes	0.00
Alkenes	0.00	Alkenes	0.07
RNH_2	0.00	PhCl	0.09
RSH	0.00	C_6H_6	0.14
PhSH	0.12	RCl, RBr, RI	0.15–0.18
CH_3NO_2	0.12	$Me_3C_6H_3$	0.20
CH_2Cl_2	0.13	Alkynes	0.20
$RC{\equiv}CH$	0.13	PhOH	0.22
$CHCl_3$	0.20	RNO_2	0.25
$PhNH_2$	0.26	R_2S	0.29
ROH	0.32–0.33	$PhNH_2$	0.38
H_2O	0.35	H_2O	0.38
$CH_3CONHCH_3$	0.38	RCHO	0.40
FCH_2CH_2OH	0.40	RCN	0.44
4-nitro-$PhNH_2$	0.42	R_2O	0.45
RCO_2H	0.54	RCO_2R	0.45
F_3CCH_2OH	0.57	ROH	0.45–0.49
$PhCO_2H$	0.59	RCOR	0.48
PhOH	0.60	Pyrimidine	0.53
4-fluoro-PhOH	0.63	R_3N	0.61
3-fluoro-PhOH	0.68	Pyridine	0.62
4-nitro-$PhCO_2H$	0.68	$HCONR_2$	0.66
FCH_2CO_2H	0.77	$(RO)_3PO$	0.77
4-nitro-PhOH	0.82	Me_2SO	0.78
t-C_4F_9OH	0.86	R_3PO	0.98
F_3CCO_2H	0.95	HMPA	1.00

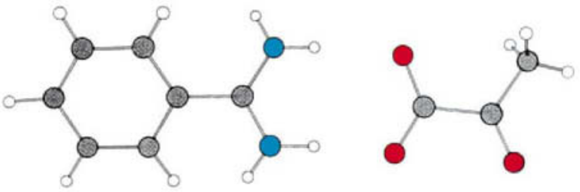

Figure 8 *X*-ray crystal structure of benzamidinium pyruvate.[18]

pyruvate (**Figure 8**) is an example of a hydrogen bonded ion pair. Whereas simple hydrogen bonds are easily disrupted in the presence of competing donors or acceptors, H-bonding 'salts' associate strongly even in dimethylsulfoxide and water.[17] Since the medium of assembly is a primary concern, the effectiveness of the interaction under the required conditions must be taken into account. The expression, but not the quality of information is circumstance-dependent, either in a fundamental sense, such as in solvophobic forces (Section 2.6) or due to competition.

In the case of multiple hydrogen bonding, there are yet additional design considerations. If the acidic proton is designated '+', interaction with the lone pair donor ('−') as above defines the hydrogen bond. However, secondary electrostatic relationships between donors and acceptors in such close proximity have a considerable influence on the overall energetics of association. This is demonstrated by comparing K_{assoc} for the triply hydrogen bonded complexes **1** + **2**, **3** + **4**, and **5** + **6** below (**Figure 9**).[19] These experimental values are consistent with Jorgensen's theoretical analysis of such systems, in which secondary interactions between diagonally situated partial charges were found to be energetically worth about one-third of the primary H-bond.[20]

Interestingly, symmetry operations allow reading the information in partners **1** + **2** and **5** + **6** from either direction, as discussed above for the barbituric acid/triaminopyrimidine systems. Partners **3** and **4**, on the other hand, only recognize each other as shown, and thus may be considered to possess a higher degree of information than the other pairs.

Finally, yet another advantage of hydrogen bonding as a design principle is that its presence can be demonstrated spectroscopically. Indeed, the case for simple H-bonding host-guest interactions is often advanced on the basis of shifts in the proton NMR and infrared spectra. In the NMR, deshielding of A–H is experienced proportional to the extent of association, which can be evaluated by titrating one component into the other and plotting concentration *versus* $\Delta\delta$.[21] In the infrared, the A–H stretching band moves to lower wavenumbers with an accompanying increase in breadth and intensity. Likewise, the degree of H-bonding can be estimated by the magnitude of these effects. A correlation of A–B distance with the A–H stretching frequency gives good curves where the $\Delta\nu/\Delta r$ slope is about 1850 cm^{-1}/Å for the N–H···N hydrogen bond and between 1500 and 12000 cm^{-1}/Å for O–H···O.[22] The O–H stretch may drop from its normal range of 3500–3600 down to less than 1000 cm^{-1} in some cases. An AH···B stretch also appears in the far infrared between 250–100 cm^{-1}.

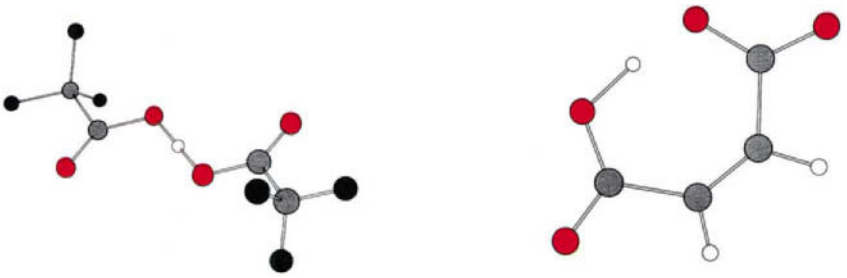

Figure 7 Left: trifluoroacetic acid-trifluoroacetate cocrystal; the hydrogen is precisely equidistant between the oxygens (O–O distance only 2.42 Å).[15] Right: hydrogen maleate anion; O–O distance 2.44 Å, with the proton 1.16 Å from the carboxyl oxygen and 1.29 Å from the carboxylate oxygen.[16]

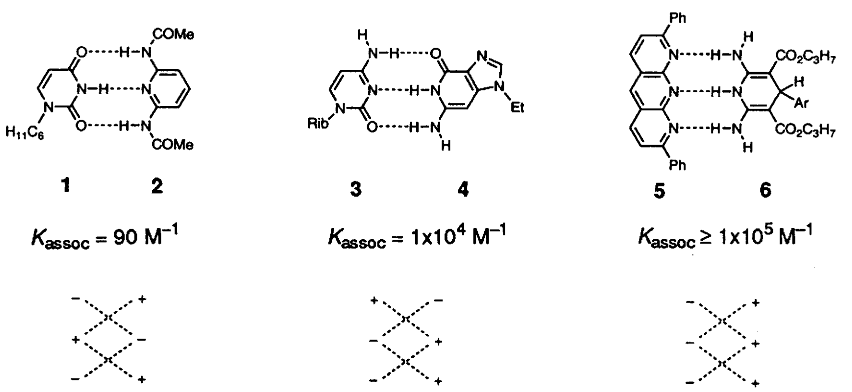

Figure 9 Association constants and partial charge distribution for complexes **1** + **2**, **3** + **4**, and **5** + **6**.[19,20]

2.3 Noncovalent interactions involving π-systems only

Two major types of molecular association, face-to-face and edge-to-face aromatic interactions, will now be considered together under the same heading. This is not because the nature of the interactions are necessarily comparable but rather that it is convenient in terms of design principles.

Face-to-face aromatic π interactions were observed even before the concept of aromaticity was understood.[23] It was known that when π-deficient aromatics such as picric acid or trinitrobenzene encountered π-excessive or π-neutral species a stable, highly coloured 1:1 complex formed which could be recrystallized or even chromatographed. These were known as 'charge transfer complexes' and were convenient derivatives for characterizing aromatic hydrocarbons in the days before modern spectroscopy. *X*-Ray crystallography reveals that the components of such complexes normally lie in parallel, alternating planes with a spatial interval of 3.2 to 3.5 Å. The relative orientation within the plane of the complementary π systems is, however, difficult to predict and varies widely between perfect superimposition and minimal overlap. A recent study proposed a model for these interactions and established a set of rules for the geometrical and electronic requirements, in which offset face-to-face and centred edge-to-face geometries were favoured.[24] The crystal structure of the complex between 1,3,5-trinitrobenzene and 1,3,5-triaminobenzene is shown in **Figure 10** from a perspective normal to the plane. In this example, alternate rings are spaced between 3.24 and 3.29 Å apart, which is less than the sum of the van der Waals radii (3.4 Å), and the overlap is 29%. The magnitude of electron donor–acceptor ('EDA') interactions loosely correlates with the ionization potential of the donor and the electron affinity of the acceptor. For example, the enthalpies of complexation of chloranil (tetrachlorobenzoquinone) with benzene and hexamethylbenzene are about 7 and 22 kJ mol^{-1} respectively.[25] Even where no apparent electronic complementarity exists, aromatic 'stacking' may still be observed, especially among polycyclic and expanded aromatic systems (**Figure 11**). Under these circumstances an attraction of the π cloud of one system to the σ framework of another is implicated, rather than a π–π* interaction.[24] An example of the application of aromatic EDA relationships to directed self-assembly can be seen in Section 2.7.

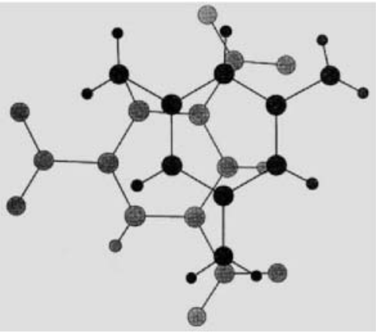

Figure 10 The 1,3,5-trinitrobenzene/ 1,3,5-triaminobenzene EDA complex.[26]

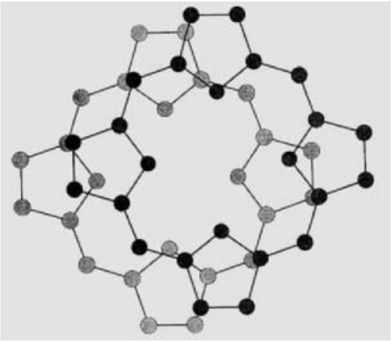

Figure 11 Stacking interactions in porphine. The aromatic planes are 3.4 Å apart.[27]

Complexes of this type are also known where association is only brought about by excitation of one of the two partners.[28] These are referred to as eximers and their geometry is presumed to be analogous to ground state complexes. A classic example is that of pyrene, whose fluorescence spectrum undergoes marked changes with increasing concentration due to the presence of a pyrene-pyrene* EDA complex.

Simple olefins with an electronic bias interact with complementary species in a similar way. **Figure 12** shows how tetracyanoethylene stacks with hexamethylbenzene. As above, the interplane separation (3.35 Å) is less than the van der Waals distance, indicating the operation of cohesive forces. Complexes are observed likewise between aromatic rings and acid anhydrides, simple carbonyl compounds, sulfur dioxide, sulfur trioxide, and sulfur haloxides. Weak but measurable interactions even exist between noble gas atoms and aromatic donors.[29]

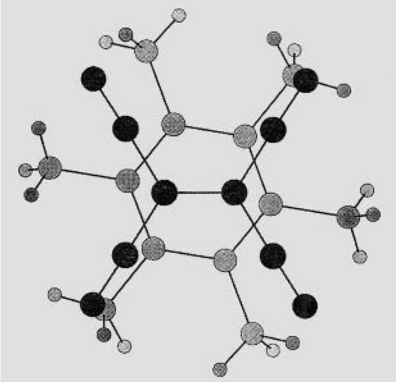

Figure 12 The tetracyanoethylene–hexamethylbenzene EDA complex.[30]

In extreme cases a redox reaction occurs to give a radical cation–anion salt, the components of which formally reside in 'fractional' oxidation states. The classic example of this is the tetracyanoquinodimethane–tetrathiafulvalene co-crystal (**Figure 13**), which was the first example of a now extensive family of 'organic metals'.[31] Unlike the previous examples, in these materials the components are organized into segregated stacks of donors and acceptors, and indeed this is a prerequisite for conductivity. Despite the presence of like charges, the interplane spacing is approximately that of the van der Waals radii.

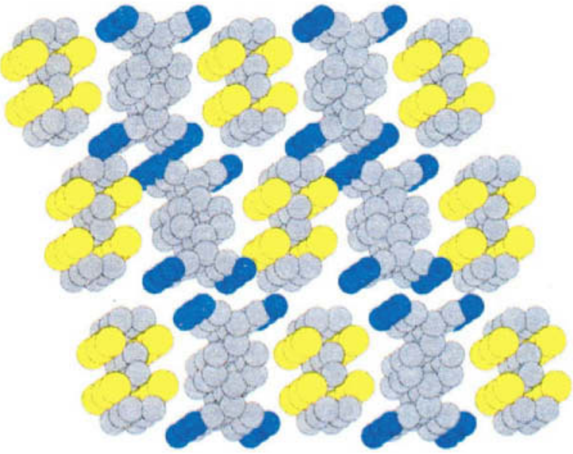

Figure 13 Stacking arrangement in the tetracyanoquinodimethane–tetrathiafulvalene co-crystal.[32]

Edge-to-face aromatic complexes involve the attraction of a proton of one aromatic molecule to the electron rich centre of a second. It emerges as the dominant motif in crystals of simple aromatics, and benzene itself crystallizes with just such 'herringbone' packing.[33] This type of noncovalent relationship is also routinely observed in proteins and has a significant influence on tertiary structure.[34] As above, the geometry of the association is well defined, which makes it worth consideration as a design principle. Interacting aromatic residues on peptide chains are shown by *X*-ray crystallography to have centre to centre distances at an average of 5.5 Å and a dihedral angle between the aromatic planes which tends to the perpendicular. The energies involved are in the order of 5 kJ mol^{-1}, which is somewhat less than that of most hydrogen bonding and EDA complexes. **Figure 14** shows the relationship between two phenyl rings in carp parvalbumin, where Phe 66 and Phe 85 are fixed in planes inclined 88° to each other and have a centre to centre distance of 5.44 Å. This type of interaction is also relevant to the organization of acetylene molecules in the solid state, where the hydrogens are directed towards the centres of triple bonds of neighbouring molecules.[35]

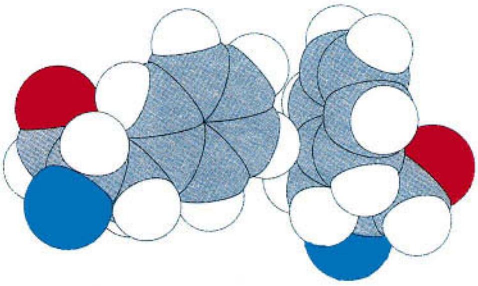

Figure 14 Detail from the crystal structure of carp parvalbumin.[36]

2.4 Noncovalent interactions involving heteroatoms

In this section Lewis acid-base chemistry will be considered from the perspective of the noncovalent assembly. As with the above design principles, self-organization based on intermolecular heteroatom–heteroatom links has been described, and thus it is worth examining the nature of the association from a fundamental standpoint.

This familiar interaction is brought about by the affinity of vacant orbitals for nonbonded electron pairs. The essential character of the bond is seen in the classic borane–ammonia complex (**Figure 15a**). Geometrically, it is as if the two species were covalently linked, but the boron–nitrogen distance is greater than that of the analogous covalent bond (1.60 *versus* 1.45 Å) and the dissociation energy is 123 kJ mol^{-1},[37] less than half that of the C–C bond of ethane, with which $H_3N–BH_3$ is formally isoelectronic. Combinations of lesser donors and acceptors naturally form weaker complexes. Although boranes and alanes with their outer shell sextets are the classic nonmetal Lewis acids, elements capable of expanding their valences show similar behaviour. Typical of these are the group V nonmetals (*e.g.* in **Figure 15b**), sulfur, and the halogens.

Among the best characterized molecular complexes between heteroatoms are those involving halogen acceptors.[40] These are sometimes referred to as 'face-

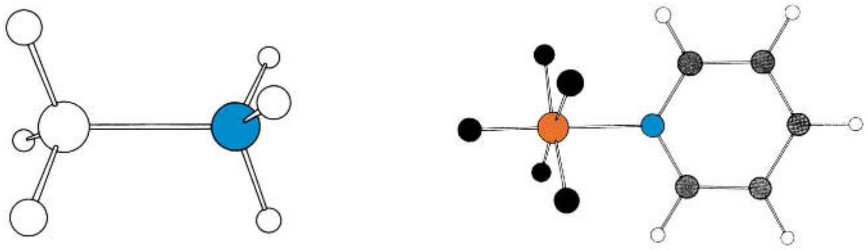

Figure 15 (a) (left); crystal structure of the H_3N-BH_3 complex;[38] (b) (right); crystal structure of PF_5-pyridine.[39] The P–N distance is 1.89 Å (typical covalent bond length 1.70 Å).

Figure 16 *X*-ray structure of the bromine–dioxane molecular complex.[41]

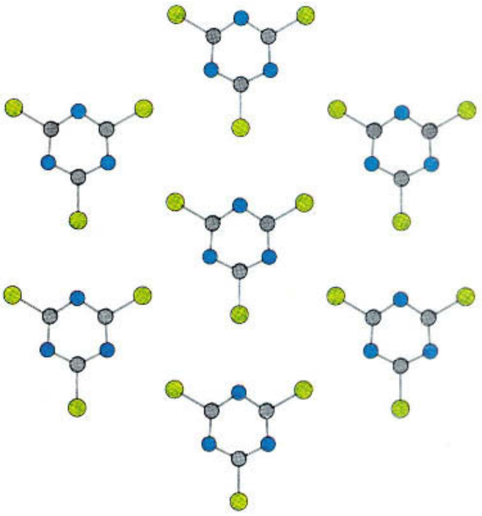

Figure 17 The self-complementary cyanuric chloride molecule in the crystal, featuring six linear N···Cl contacts (2 × 3.100 and 4 × 3.113 Å, vdW = 3.30 Å). The interplane spacing is 3.26 Å.[42]

centred' donor–acceptor complexes and were first examined in detail by Hassel, who was awarded the 1969 Nobel Prize for this work. The interaction bears remarkable similarity to the hydrogen bond (*cf.* Section 2.2):

where X = Cl,Br,I
B = N,O,Se,S,X⁻

In hydrogen bonding the magnitude of the interaction is related to the Brønsted acidity of A–H. Face-centred bonding has an analogous correlation with the Lewis acidity of X, and thus likewise on the nature of A as a potential 'leaving group'. As with the hydrogen bond, most of what is known about this intermolecular relationship comes from looking at *X*-ray crystal structures. Those of the bromine–dioxane, cyanuric chloride, and diselenane–diiodoacetylene complexes (**Figures 16–18**) are given below as representative examples. As is seen, the A–X–B angle does not stray far from 180°, and the intermolecular contacts are substantially closer than the sum of the van der Waals radii. Compare, for example, the Br–O distance of 2.71 Å in **Figure 16** with the 3.35 Å van der Waals contact. A slight elongation of the Br–Br axis (2.31 *versus* 2.28 Å in the gas phase) is also observed. With nitrogen–halogen and selenium–halogen adducts, van der Waals violations of greater than one ångstrom are common, making the link not much longer than the sum of the covalent radii and thus comparable to classic Lewis acid–base complexes. In examining the literature the following generalizations about relative donor and acceptor strengths can be made:

donors:

sp^3N, sp^2N > sp^3O > sp^2O ~ spN

Se > S

acceptors:

$I_2 > Br_2 > Cl_2 >$ X-spC > X-sp^2C > X-sp^3C

Despite the similarity to hydrogen bonding, both in geometry and association energy (estimates as high as 50 kJ mol^{-1})[44] this particular type of interaction has rarely been exploited as a supramolecular design principle. One potential problem is the chemical reactivity of the species involved, particularly the molecular halogens. Indeed, preliminary charge transfer complexation is thought to mediate several types of reactions.[45] Consider for instance the complex in **Figure 19**, which resembles a frozen transition state of an *N*-halogenation reaction.

Related to the above is the weak molecular association observed between halogens and aromatic donors. In this case, the halogen occupies the sixfold symmetry axis of the aromatic ring and thus interacts equally with each ring atom. **Figures 20 and 21** show *X*-ray crystal structures of the bromine–benzene and carbon tetrabromide–xylene complexes, respectively. Likewise, multiple bonds may serve as donors. The crystal structure of diiodoacetylene is remarkably like that of acetylene itself, with the participation of a perpendicular triple-bond···I interaction in place of the triple-bond···H hydrogen bond.[47]

Under certain circumstances other types of bonding involving heteroatoms are observed, most of which

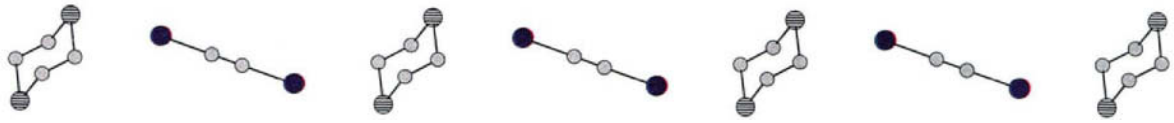

Figure 18 *X*-ray structure of the diiodoacetylene–diselenane molecular complex, with Se···I distance 3.34 Å (vdW= 4.10 Å).[43]

Figure 19 Crystal structure of the trimethylamine–I_2 complex.[46] The distances are N···I 2.27 Å (vdW 3.65, covalent 2.15), I–I 2.83 Å (2.70 in I_2).

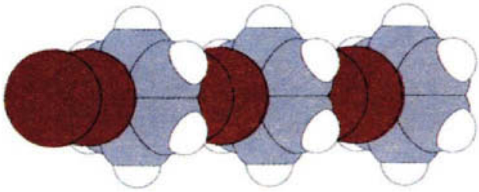

Figure 20 The benzene–bromine molecular complex.[48] The distance from each bromine atom to the adjacent benzene plane is 3.36 Å (vdW 3.65 Å). An analogous crystalline complex is formed with chlorine.[49]

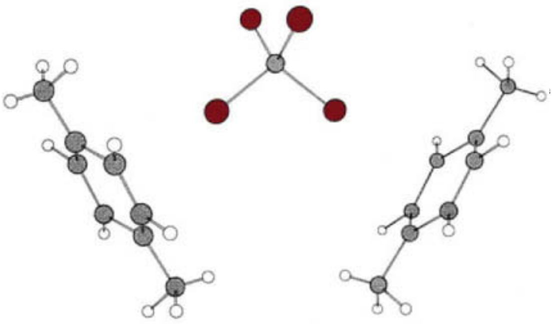

Figure 21 Crystal structure of carbon tetrabromide/ xylene.[50] The Br···Ar distance is 3.53 Å.

would have escaped notice but for *X*-ray crystallography. Carbonyl compounds for example sometimes show a perpendicular oxygen–carbon contact as illustrated in **Figure 22** for alloxan. Remarkably, this interaction dominates hydrogen bonding, which is absent despite four carbonyl and two N–H functions present in each molecule. Weak intermolecular halogen–halogen and chalcogen–chalcogen bonding has also been recognized in a number of both organic and inorganic crystals through close interatomic contacts. Such interactions are, however, much more pronounced when they occur intramolecularly. Thus, in 2-nitrobenzenesulfenyl chloride the sulfur–oxygen distance is 2.38 Å (van der Waals 3.20 Å) and in tetrasulfurtetranitride the sulfur–sulfur distance is 2.58 Å; not as short as the covalent bond length of 2.05 Å, but considerably less than the closest nonbonded sulfur–sulfur contact in S_8 (3.32 Å) (**Figure 23**). Although these of the weaker noncovalent associations generally serve to bring molecules into each other's vicinity, it is obvious that their nature is much less specific than, for example, the hydrogen bond. Despite this, they have been discussed in the literature in terms of 'topochemical control' and directed reactivity in crystals, and as such can be considered design principles for the solid state.

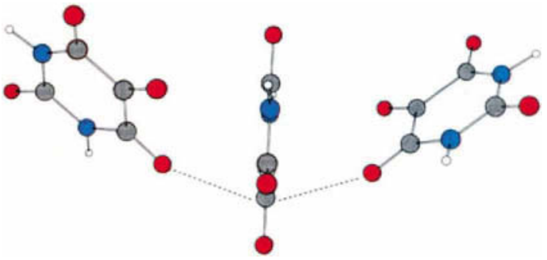

Figure 22 Oxygen–carbon interaction (2.73 Å) in crystalline alloxan.[51]

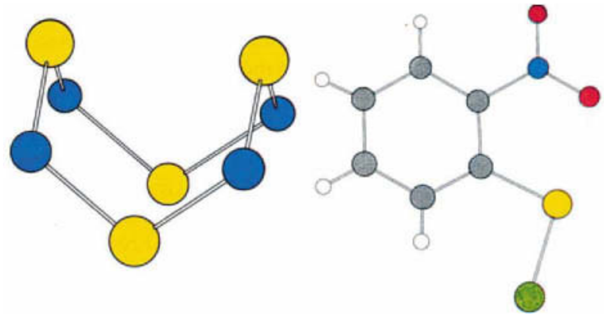

Figure 23 Close S–S contacts in tetrasulfurtetranitride[52] (left) and S–O contact in 2-nitrobenzenesulfenyl chloride.[53]

2.5 Noncovalent interactions involving transition metals

Based on our present definition of self-assembly we must, strictly speaking, include metal–ligand complexes under the heading of supramolecular species since the coordinate bond is not covalent. Yet for obvious reasons we need to restrict the context to cases where particular feats of organization are achieved or specific purposes are served, examples of which will now be considered.

The way in which we approach this subject depends on the role of the metal. Is it part of the fabric of the self-assembled species, or does it simply serve to bridge organic subunits of interest? In the former context we imagine the metal participating as the guest in a host–guest system or in the backbone of a metallopolymer; in the latter as a template to a covalent reaction, where the metal is ultimately to be dispensed with, or purely in its capacity as a design principle akin to hydrogen bonding. If the metal is regarded as such, its presence or indeed absence in the final product may be inconsequential, but all the same, the assembly does not stick together of its own accord and the presence of a third party fundamentally differentiates this from other design principles. Consider, for example, bis(acetylacetonato)platinum (II)[54] and compare it with the benzoic acid dimer (**Figure 24**).[55]

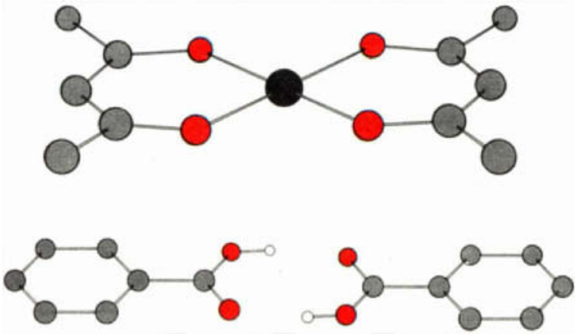

Figure 24 Noncovalent docking of two organic molecules by coordination to a metal (top) and hydrogen bonding (bottom).

Although our requirements vary from case to case, the ideal design principle would make possible the spontaneous assembly from subunits of any given molecular construct, with links which are permanent when we want them to be permanent and yet reversible if dissociation is desired. The metal–ligand bond actually approaches this ideal in many respects: generally speaking, it is the strongest of the noncovalent interactions, with bond energies commonly on the same order as those of covalent bonds. The thermodynamic stability of metal complexes thus allows for directed assembly under a wider range of conditions than, for example, hydrogen bonds, and yet such complexes are kinetically labile to certain influences (*e.g.* acid, light, ligand exchange). Further, not only is the geometry of the interaction predictable, but with transition metals the presence of *d*-electrons provides a choice of symmetries about the metal centre as dictated by ligand field theory. The common octahedral and tetrahedral stereochemistries are exemplified by tris(1,3-diaminopropane)cobalt (III) chloride[56] and tetrakis(pyridine)copper (I) perchlorate,[57] respectively (**Figure 25**), while square planar was represented by bis(acetylacetonato)platinum (II) in **Figure 24**. Five-coordinate trigonal bipyramidal and square pyramidal complexes are also known but the energy difference between these configurations is small and the two may even undergo rapid interconversion, thus limiting their use as design principles. Coordination states higher than six are also possible, but limitations involving configurational flux also apply. An example of an eight-coordinate complex is the dodecahedral [tetrakis(catecholato)gadolinium (III)]$^{5-}$ anion (**Figure 26**).

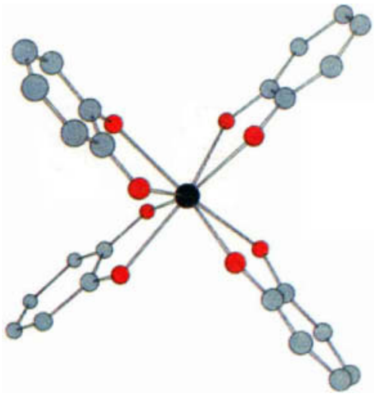

Figure 26 Crystal structure of the dodecahedral [terakis(catecholato)gadolinium(III)]$^{5-}$ anion.[58]

Olefins and aromatic π-systems also interact with metals to give defined assemblies, such as the silver ion/1,5-hexadiene complex in **Figure 27** and the methylcyclooctatetraene dianion/uranium sandwich compound in **Figure 28**.

Figure 27 Crystal structure of 2Ag·3C_6H_{10}.[59]

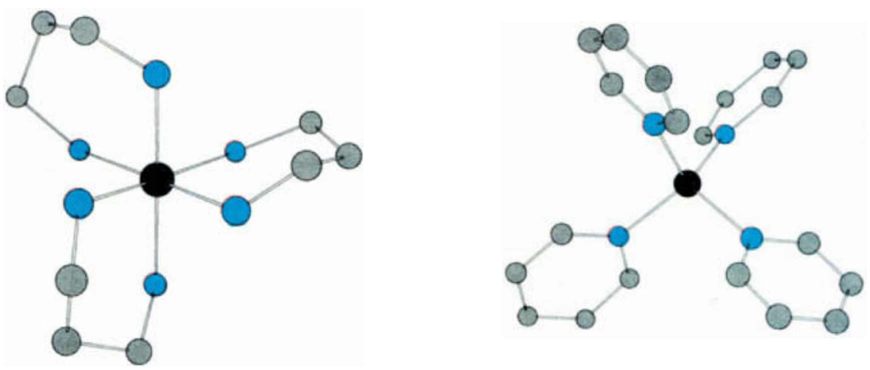

Figure 25 Octahedral and tetrahedral ligand organization about the transition metals cobalt(III) and copper(I), respectively.

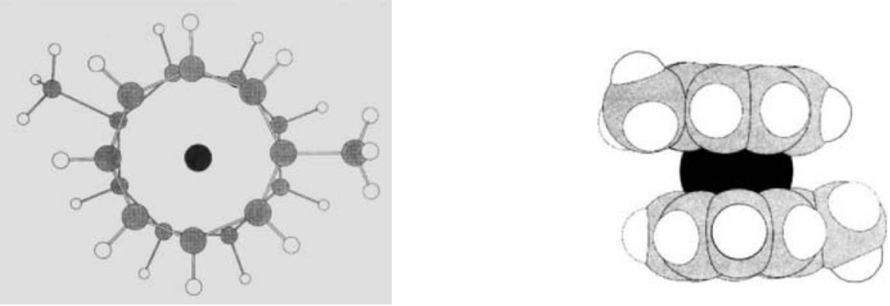

Figure 28 Views of $U^{III}(MeC_8H_8^{2-})_2$ from the top (left) and edge on (right).[60]

Since we are only concerned with introducing metal–ligand chemistry conceptually as a design principle, theoretical discussions and classification of the common stereochemistries of transition metal complexes are deferred to other sources.[61]

Finally, the adsorption of alkane thiols and sulfides onto the surfaces of elemental gold, silver, and copper has recently been applied to the generation of molecular arrays with long-range order.[62] Highly stable, structurally coherent, close-packed monolayers analogous to the intensively investigated Langmuir–Blodgett films result when solutions of the substrate are exposed to the clean metal surfaces. Including end groups on the alkyl chain makes possible the spontaneous organization of (comparatively) vast self-assembled functional surfaces, which are relevant to studies in electrochemistry, catalysis, corrosion, lubrication, adhesion, and sensor technology. Clearly, the noncovalent relationship between the components and the metal is not convergent in the same sense as for the above-described complexes, where a single metal ion gathers the ligands to itself. Rather, subunit–subunit intercohesion results from the mutual attraction to a continuous lattice of occupation sites in addition to multiple van der Waals interactions in the nearly crystalline 'organic phase'. For this reason, structurally well-defined monolayer formation is really only successful for $H_3C(CH_2)_nSH$ where $n \geq 10$. This organizational phenomenon also manifests itself in solvophobic interactions (Section 2.6).

2.6 Solvophobic interactions

The remaining noncovalent relationship to be considered is the behaviour of *domains* of philicity. The concept of solvophobicity, where a chemical species finds itself in an environment where no mechanism exists for enthalpic gain, is in itself within the realm of supramolecular science. The species concerned may migrate into less hostile surroundings, for example the bulk phase which it departed, or, given the possibility, take refuge in the cavity of a receptor thus becoming the guest in an inclusion complex. **Figure 29** gives an example of inclusion based principally on solvophobic circumstances. Thermodynamically, a balance between entropy and enthalpy of interaction leads to an expression of chemical potential where a cost of approximately 3 kJ mol^{-1} per CH_2 group of an alkyl chain is required to send a hydrocarbon molecule into water.[63] This accounts for their remarkably low miscibility, for example 9.5 ± 1.3 g n-hexane per 10^6 g H_2O.[64] The situation, however, becomes interesting when larger molecules associate with a relatively small number of partners to form stable, definable superstructures. Such species exhibit *domain oriented behaviour.* Amphiphilic surfactant molecules are the classic example. They possess large hydrophobic surfaces capped by highly hydrophilic head groups ('domains'), and to minimize the water–lipid interface, while maximizing the lipid–lipid (Section 2.1) and headgroup-water (Section 2.2) interfaces, they self-organize in aqueous media into what can only be described as spectacular examples of macromolecular architecture.

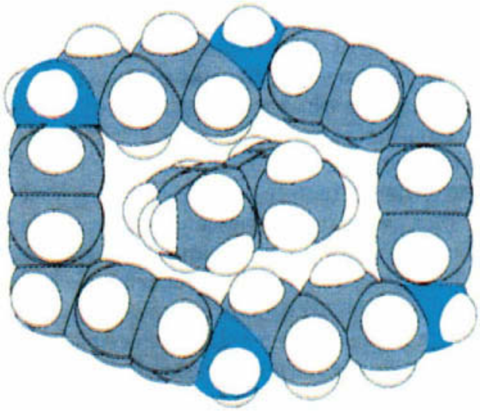

Figure 29 Inclusion of durene in 1,6,20,25-tetraaza(6.1.6.1)paracyclophane·4HCl.[65]

In the simplest case, the introduction of a fatty acid to the surface of water results in monolayer formation (*cf.* Section 2.5). The vast body of literature on monolayers stretching from the days of Langmuir to the present is witness to the interest in molecular order and its applications. Langmuir–Blodgett monolayers[66] are prepared as shown in **Figure 30** by compressing surfactant films until closest packing is achieved. The monolayer is then usually transferred from the water to a glass surface, thereby depositing what is essentially a crystal one molecule thick. By redipping the slide, multilayers of precise composition can be prepared.

Figure 30 Schematic of the preparation of a condensed Langmuir–Blodgett monolayer using a film balance.

When agitated in an aqueous medium, amphiphiles will take up and organize against water to form a supramolecular aggregate known as a micelle. The basic concept of the micelle is presented in **Figure 31**, although it should be borne in mind that they are highly fluid and have been shown to possess a rather unexpected degree of disorder.[67] The optimal shape for a simple micelle is elliptical, but in ranges of higher viscoelasticity, rod-like assemblies are observed.[68]

In cases where the surfactant tail is of about the same volume as the head group, the aggregates no longer tend to the convex, and *bilayer* formation occurs. The components of a bilayer are commonly referred to as lipids, and lipid membranes close upon themselves under certain conditions to give spherical *liposomes*, true giants of supramolecular construction (**Figure 32**). Synthetic liposomes range in diameter between 200 and 1 000 000 Å depending on the method of preparation, and may be either simple or compound (*i.e.* interleaved).[69] The enclosed aqueous compartment, which houses the machinery of cells in living organisms, is ideal for studies of membrane permeability and can also be used as a vehicle for drug delivery.[70] Along these lines, Ringsdorf has employed modified lipids with unsaturations in the tail, headgroup, or even counter-ion in the preparation of liposomes which can be stabilized by polymerization, giving what are essentially little plastic capsules.[71] This is an excellent example of using supramolecular preorganization to template the synthesis of a macromolecule which would be inaccessible by non-directed processes.

The hydrophobic effect is also a major contributor to the tertiary structure of proteins, which analogously take on a globular form with charged groups at the surface and hydrophobic residues mainly on the inside. A great deal of work has been done on the prediction of higher order structure in polypeptides from the primary amino acid sequence based on an understanding of the attractive interactions and hydrophobicity.[72]

Although clearly a powerful organizing influence, hydrophobic forces are non-specific and tend to operate collectively, as do van der Waals interactions. In terms of design principle repertory, solvophobicity is the key to the complexation of neutral guests in water soluble hosts such as cyclophanes and cyclodextrins. The organization of amphiphiles into expansive molecular assemblies has been extended to the preparation of functional (*e.g.* electroactive) films and model membranes, the templated synthesis of macromolecules, the understanding of crystallization processes, and the controlled nucleation of mineral growth in approaches to the fabrication of bioceramics.[73]

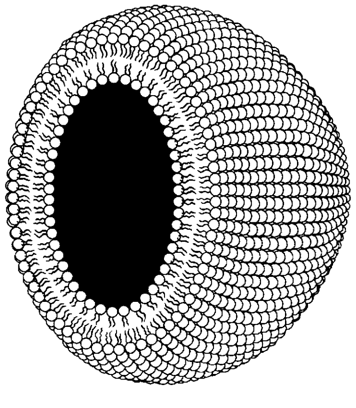

Figure 32 Representation of a liposome.

2.7 Topological bonding and incarceration

Like the concept of steric complementarity, topological bonding and incarceration are design principles without being noncovalent interactions. In the former, two or more species, which do not necessarily show mutual affinity, are confined to each other's company by being physically intertwined. In the latter and as the name suggests, a guest species is retained not by attractive forces but rather total envelopment. Escape may only be possible under fierce conditions or even by destruction of the host.

Catenanes are topological isomers of cyclic compounds. As illustrated schematically in **Figure 33**, two interpenetrating rings give a simple [2]-catenane, whilst four distinct isomeric [3]-catenanes are possible. The most elementary catenane, in theory, is the C_{18}–C_{18} hydrocarbon, which is just feasible with the rings at maximum aperture. However, no alkyl chain has yet been threaded through a ring smaller than

Figure 31 Representations of elliptical (right) and cylindrical rod-like (left) micelles.

C_{24}.[74] Schill, who recorded most of the early developments in catenane chemistry, has reported the only example of the isolation and characterization of an all hydrocarbon catenane, C_{28}–C_{46}.[75] Catenanes also occur naturally in the form of interlocked deoxyribonucleic acid rings, dramatic examples of which have been observed *in vivo*.[76]

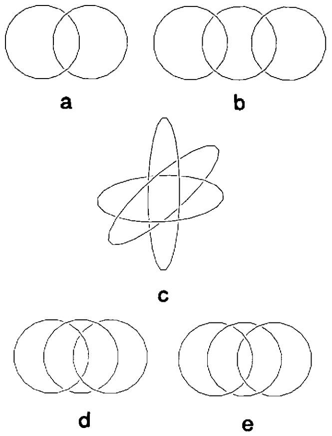

Figure 33 (a) [2]-Catenane; (b)–(e) the isomeric [3]-catenanes. Structures (d) and (e) are chiral.

Rotaxanes are a related species, the concept of which is presented graphically in **Figure 34**. Cases where the chain cannot withdraw from the ring without the breaking of a covalent bond are analogous to catenanes and true topological isomers of their components. Imaginative combinations of rings (hydrocarbons, crown ethers, cyclodextrins, cyclophanes), chains (arene, ether, amine, polymer) and stoppers (triphenylmethyl, porphines, trialkylsilyl, transition metal complexes) have been employed.

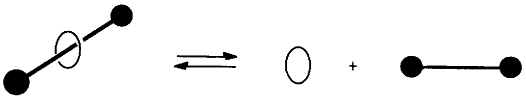

Figure 34 Schematic representation of a rotaxane.

Both statistical and directed synthetic approaches to topologically linked compounds have been registered, and the field has seen a recent flurry in the efforts of Sauvage and Stoddart, who have applied directed self-assembly to the problem. Sauvage[77] templated his catenane/rotaxane synthesis by metal–ligand bonding, while Stoddart[78] made use of aromatic EDA interactions (**Figure 35**). Hydrogen bonding has also been used.[79]

A general scarcity of organic compounds which form entirely closed cavities means that examples of molecular *incarceration* are uncommon. The advent of the fullerenes has perhaps generated an awareness of the possibility of *absolute* incarceration of any species from the size of a proton up to the 7 Å cavity of C_{60}. However, it is the work of Cram which makes addressing this subject something more than an afterthought. Carcerands (**Figure 36**) is the name given by Cram to a family of compounds conceptualized

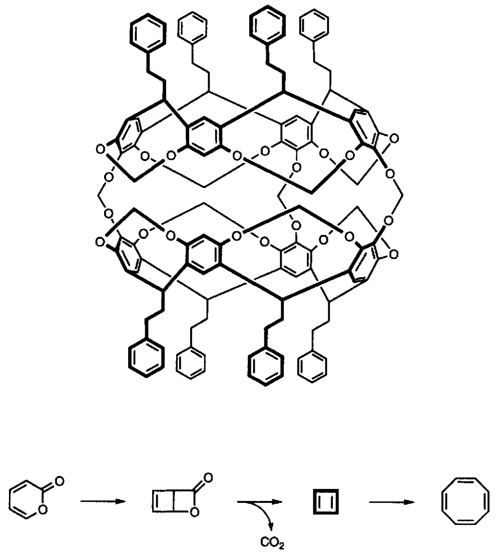

Figure 36 The hemicarcerand within which the reaction sequence leading up to cyclobutadiene took place. Expulsion of the product led to dimerization and rearrangement to cyclooctatetraene.

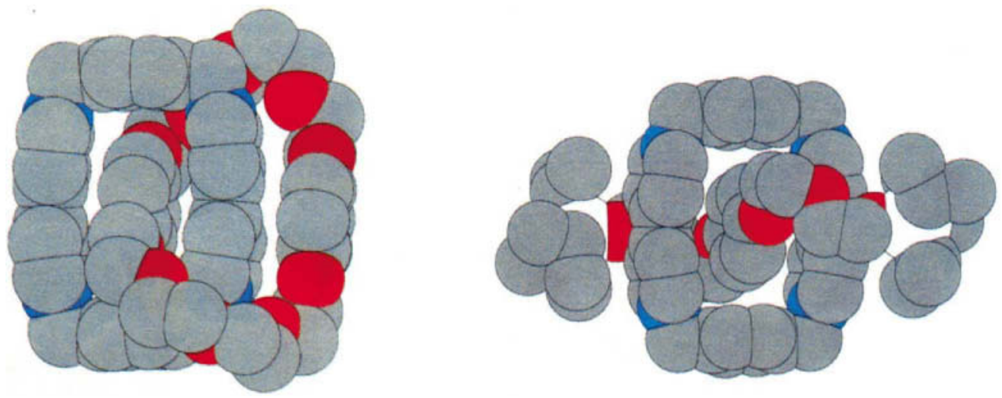

Figure 35 Crystal structures of Stoddart's catenane (left) and rotaxane (right), the syntheses of which were templated by aromatic EDA interactions between complementary hydroquinone and bipyridinium dication recognition units in the components.[78]

wholly to the purpose of incarceration.[80] These molecules with rugby ball-shaped interiors trap guests by capture during synthesis or by the thermally assisted ingression of small species through the 'portals' of carcerands lacking one link between the two shells (hemicarcerands). The crowning accomplishment of this work has been the inclusion of α-pyrone and its conversion into cyclobutadiene,[81] which is stable at room temperature in the interior of the hemicarcerand, which Cram has likened to a new phase of matter.

The *supramolecular* containment of a non-associating guest is a rather more common phenomenon, but is observable only as long as the host system remains associated. A case already mentioned is compartmentalization within liposomes (Section 2.6). Another example is molecules which can accomodate guests in their crystal lattices, such as hydroquinone, urea, and water. The inclusion networks generated by such species are referred to as *clathrates*,[82] over 1000 of which have been characterized by X-ray crystallography. These have been compared structurally to zeolites with their regular array of channels. Examples of hydrate and thiourea clathrates are given in **Figure 37**.

3 Conclusion

The purpose of this review has been to catalog, in simple terms, the means at the disposal of the chemist for the design and synthesis of molecular assemblies. The analogy to the design of 'atomic assemblies' by synthesis in the traditional sense suggests itself. A number of practical applications of supramolecular chemistry have already emerged,[85] and ever more ingenious work is continuously being published. Be that as it may, the accomplishments of three thousand million years of evolution will not be duplicated too soon, and the development of supramolecular devices to rival nature's will only become possible in principle through an in-depth understanding of the information–structure–function relationship.

To exemplify this let us briefly consider the tobacco mosaic virus. The viral particle assembles itself from its subunits without assistance or instruction from any external agent. This is solely the consequence of the information intrinsic to these subunits by virtue of their morphology and functionality. Thus information gave rise to recognition and hence self-assembly. But if we now assume that this virus never existed, we can assert that we could have created it *if we had had the necessary information, i.e.* that the combination of a particular 6 kilobase strand of RNA with 2130 protein subunits 158 specific residues in length would result in a device which not only has a function, but belongs to a family of species which occupies the borderline between the animate and inanimate. The same case might be made for any functional biomolecule. It may, however, be pointed out that even if the information required for the synthesis of such supramolecular devices were to become available to us, the state of the art of synthesis would be yet another hurdle to making the components of assemblies of high complexity. For example, although the protein subunit of tobacco mosaic virus is currently within the capabilities of the synthetic chemist, the RNA core may not be, the longest synthetic gene to date containing some 1000 bases.[86] However, as synthetic methodology advances, the emphasis in the development of chemistry will be increasingly on information and its application to the design of task-specific devices, as inspired by nature. It is no longer only *discovery* and *effect* but also *function* which the synthetic chemist may exercise with his art. In the drive towards the ultimate goal of function, an interesting turn of events has taken place. It has recently been remarked[87] that chemists, who for years have been using (for the most part) unnatural means to access *natural* products, now turn to means reminiscent of natural processes to access completely *unnatural* products.

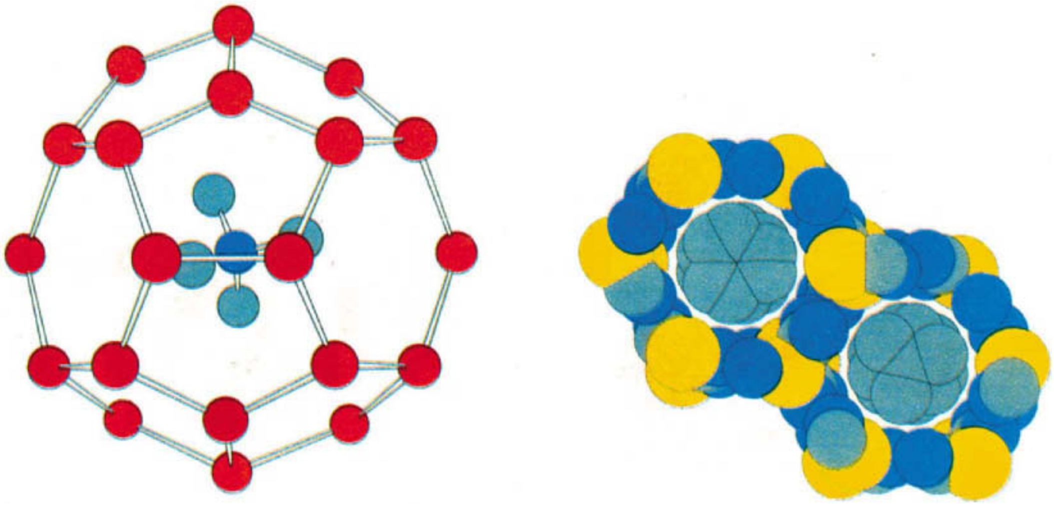

Figure 37 Left, trimethylammonium ion in (part) of its ice cage,[83] the 'bonds' between the oxygens representing H-bonding axes; right, cross-section of two cells of the thiourea–adamantane clathrate.[84]

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