1

Introduction

1.1 What is supramolecular chemistry?

As a distinct area, supramolecular chemistry dates back to the late 1960s, although early examples of supramolecular systems can be found at the beginning of modern-day chemistry, for example, the discovery of chlorine clathrate hydrate, the inclusion of chlorine within a solid water lattice, by Sir Humphrey Davy in 1810 (see Chapter 4, Section 4.4). So, *what is supramolecular chemistry*? It has been described as 'chemistry beyond the molecule', whereby a 'supermolecule' is a species that is held together by non-covalent interactions between two or more covalent molecules or ions. It can also be described as 'lego™ chemistry' in which each lego™ brick represents a molecular building block and these blocks are held together by intermolecular interactions (bonds), of a reversible nature, to form a supramolecular aggregate. These intermolecular bonds include electrostatic interactions, hydrogen bonding, π–π interactions, dispersion interactions and hydrophobic or solvophobic effects (Section 1.3).[†]

Supramolecular Chemistry: The study of systems involving aggregates of molecules or ions held together by non-covalent interactions, such as electrostatic interactions, hydrogen bonding, dispersion interactions and solvophobic effects.

Supramolecular chemistry is a multidisciplinary field which impinges on various other disciplines, such as the traditional areas of organic and inorganic chemistry, needed to synthesise the precursors for a supermolecule, physical chemistry, to understand the properties of supramolecular systems and computational modelling to understand complex supramolecular behaviour. A great

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[†] Note that interactions with units of energy should not be confused with forces which have units of Newtons.

Core Concepts in Supramolecular Chemistry and Nanochemistry Jonathan W. Steed, David R. Turner and Karl J. Wallace
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deal of biological chemistry involves supramolecular concepts and in addition a degree of technical knowledge is required in order to apply supramolecular systems to the real world, such as the development of *nanotechnological* devices (Chapter 5).

Supramolecular chemistry can be split into two broad categories; *host–guest chemistry* (Chapter 2) and *self-assembly* (Chapter 3). The difference between these two areas is a question of size and shape. If one molecule is significantly larger than another and can wrap around it then it is termed the 'host' and the smaller molecule is its 'guest', which becomes enveloped by the host (Figure 1.1(a)). One definition of hosts and guests was given by Donald Cram, who said *The host component is defined as an organic molecule or ion whose binding sites converge in the complex. . . The guest component is any molecule or ion whose binding sites diverge in the complex.*[1] A *binding site* is a region of the host or guest that is of the correct size, geometry and chemical nature to interact with the other

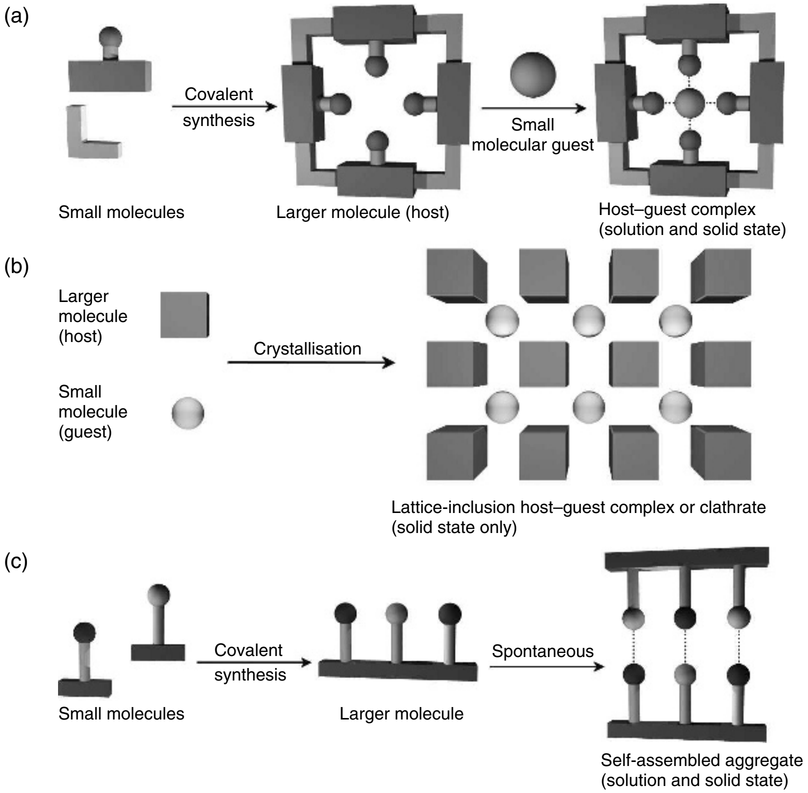


Figure 1.1 The development of a supramolecular system from molecular building blocks (binding sites represented by circles): (a) host–guest complexation; (b) lattice inclusion; (c) self-assembly between complementary molecules.

species. Thus, in Figure 1.1(a) the covalently synthesised host has four binding sites that converge on a central guest binding pocket. Host–guest complexes include biological systems, such as enzymes and their substrates, with enzymes being the host and the substrates the guest. In terms of coordination chemistry, metal–ligand complexes can be thought of as host–guest species, where large (often macrocyclic) ligands act as hosts for metal cations. If the host possesses a permanent molecular cavity containing specific guest binding sites, then it will generally act as a host both in solution and in the solid state and there is a reasonable likelihood that the solution and solid state structures will be similar to one another. On the other hand, the class of solid state *inclusion compounds* only exhibit host–guest behaviour as crystalline solids since the guest is bound within a cavity that is formed as a result of a hole in the packing of the host lattice. Such compounds are generally termed *clathrates* from the Greek *klethra*, meaning 'bars' (Figure 1.1(b)). Where there is no significant difference in size and no species is acting as a host for another, the non-covalent joining of two or more species is termed *self-assembly*. Strictly, self-assembly is an equilibrium between two or more molecular components to produce an aggregate with a structure that is dependent only on the *information* contained within the chemical building blocks (Figure 1.1(c)). This process is usually spontaneous but may be influenced by solvation or templation effects (Chapter 3) or in the case of solids by the nucleation and crystallisation processes (see Chapter 4, Section 4.5).

Nature itself is full of supramolecular systems, for example, deoxyribonucleic acid (DNA) is made up from two strands which self-assemble *via* hydrogen bonds and aromatic stacking interactions to form the famous double helical structure (see Chapter 3, Section 3.2.4). The inspiration for many supramolecular species designed and developed by chemists has come from biological systems.

Host–Guest Chemistry: The study of large 'host' molecules that are capable of enclosing smaller 'guest' molecules *via* non-covalent interactions.

Self-Assembly: The spontaneous and reversible association of two or more components to form a larger, non-covalently bound aggregate.

Binding Site: A region of a molecule that has the necessary size, geometry and functionalities to accept and bind a second molecule *via* non-covalent interactions.

Clathrate: A supramolecular host–guest complex formed by the inclusion of molecules of one kind in cavities of the crystal lattice of another.

1.2 Selectivity

For a host–guest interaction to occur the host molecule must posses the appropriate binding sites for the guest molecule to bind to. For example, if the host has many hydrogen bond donor functionalities (such as primary and secondary amines) then the guest must ideally contain an equal number of hydrogen bond acceptor sites (such as carboxylates), which are positioned in such a way that it is feasible for multiple interactions between host and guest to occur (Section 1.3.2). Alternatively, if the host has Lewis acid centres then the guest must possess Lewis base functionalities. A host that displays a preference for a particular guest, or family of guests, is said to show a degree of *selectivity* towards these species. This selectivity can arise from a number of different factors, such as *complementarity* of the host and guest binding sites (Section 1.2.2), *preorganisation* of the host conformation (Section 1.2.3) or *co-operativity* of the binding groups (Section 1.2.3).

Selectivity: The binding of one guest, or family of guests, significantly more strongly than others, by a host molecule. Selectivity is measured in terms of the ratio between equilibrium constants (see Section 1.2.5).

1.2.1 The Lock and key principle and induced-fit model

Behr, J.-P. (Ed.), *The Lock-and-Key Principle: The State of the Art 100 Years On*, John Wiley & Sons, Ltd, Chichester, UK, 1995.

Emil Fisher developed the concept of the *lock and key principle* in 1894, from his work on the binding of substrates by enzymes, in which he described the enzyme as the lock and the substrate as the key; thus, the substrate (guest) has a complementary size and shape to the enzyme (host) binding site. Figure 1.2 shows a schematic diagram of the lock and key principle; the key is exactly the correct size and shape for the lock. However, the lock and key analogy is an overly simplistic representation of a biological system because enzymes are highly flexible and conformationally dynamic in solution, unlike the concept of a 'rigid lock'. This mobility gives rise to many of the properties of enzymes, particularly in substrate binding and

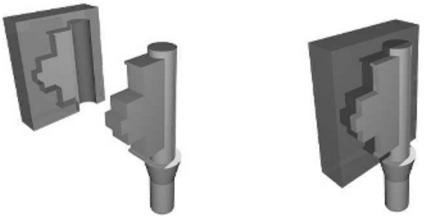


Figure 1.2 The lock and key principle, where the lock represents the receptor in which the grooves are complimentary to the key, which represents the substrate.

catalysis. To address this limitation, Daniel Koshland postulated that the mechanism for the binding of the substrate by an enzyme is more of an interactive process, whereby the active site of the enzyme changes shape and is modified during binding to accommodate the substrate (Figure 1.3). An *induced fit* has occurred and as a consequence the protein backbone or the substrate binding site itself changes shape such that the enzyme and the substrate fit more precisely, *i.e.* are more mutually complementary. Moreover, substrate binding changes the properties of the enzyme. This binding-induced modification is at the heart of many biological 'trigger' processes, such as muscle contraction or synaptic response (see Chapter 5, Section 5.3.4).

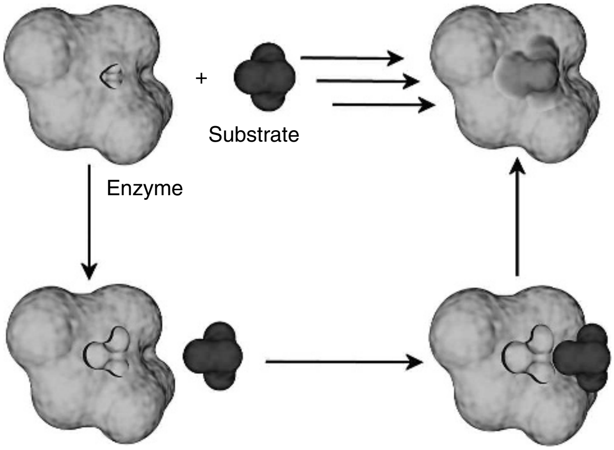


Figure 1.3 The induced-fit model of substrate binding. As the enzyme and substrate approach each other, the binding site of the enzyme changes shape, resulting in a more precise fit between host and guest.

1.2.2 Complementarity

Complementarity plays an important role in biological and supramolecular systems, for example, in the function of enzymes. An enzyme is generally a lot larger than its substrate and only a small percentage of the overall structure is involved in the binding; this region is known as the *active site* of the enzyme. The three-dimensional structure of an enzyme folds itself into a conformation whereby the active site is arranged into a pocket or cleft, which is somewhat complementary in size and shape, and is functionally compatible with the substrate. The enzyme and substrate recognise each other due to this match in size and shape and bind *via* complementary binding sites within this pocket or cleft.

In general, in order to achieve strong, selective binding, the binding site of the host must not only be complementary to the guest in terms of size and shape (*cf.* the lock and key and induced-fit models) but the binding sites on both partners must also be chemically complementary. For example, in coordination chemistry Lewis acids and bases are used to form complexes by the donation of electrons by the Lewis base to the Lewis acid. In the Lewis theory of acids and bases, the species can either be *hard* or *soft*, defined in terms of the polarisability of their electron density. Hard acids/bases are non-polarisable and soft acid/bases are polarisable. As a general rule, hard-to-hard and soft-to-soft complexes are the most stable, displaying complementarity between like species. For example, the hard alkali-metal cations are bound more strongly by the harder oxygen atoms of the crown ethers than the softer nitrogen atoms of azamacrocycles (see Chapter 2, Section 2.3.3).

Complementarity: Both the host and guest must have mutual spatially and electronically complementary binding sites to form a supermolecule.

1.2.3 Co-operativity and the chelate effect

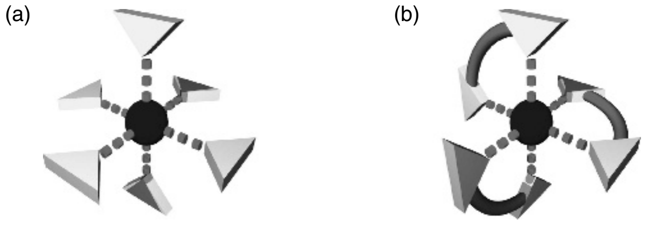
Hancock, R. D., 'Chelate ring size and metal ion selection', *J. Chem. Edu.*, 1992, **69**, 615–621.

A frequently heard saying is that 'the whole is greater than the sum of its parts'. In other words, a team pulling together has greater effect than the sum of many individual efforts. This concept can be easily applied to supramolecular chemistry. A host species with multiple binding sites that are covalently connected (*i.e.* acting as a 'team') forms a more stable host–guest complex than a similar system with sites that are not joined (therefore acting separately from each other). This *co-operativity* between sites is a generalisation of the *chelate effect* in coordination chemistry, derived from the Greek word *chely*, meaning a lobster's claw.

Co-operativity: Two or more binding sites acting in a concerted fashion to produce a combined interaction that is stronger than when the binding sites act independently of each other. The sites are *co-operating* with each other. In the case of binding two guests, co-operativity also represents the effect on the affinity of the host for one guest as a result of the binding of the other.

Chelate Effect: The observation that multidentate ligands (by extension, hosts with more than one binding site) result in more stable complexes than comparable systems containing multiple unidentate ligands, a result of *co-operativity* between interacting sites.

In terms of classical coordination chemistry, Figure 1.4 shows schematically the difference between a metal ion coordinated to six unidentate ligands, such as ammonia, and one coordinated to three bidentate ligands, such as ethylenediamine (*en*, $NH_2CH_2CH_2NH_2$). The nature of the ligand–metal dative bond is almost identical in both cases (*via* nitrogen atom lone pairs), yet the ethylenediamine complex is 10^8 times more stable than the corresponding hexamine complex, as seen from the equilibrium constant (Figure 1.4). Indeed, in practice ethylenediamine readily displaces ammonia from a nickel ion.



$$[Ni(NH_3)_6]^{2+} + 3NH_2CH_2CH_2NH_2 \xrightleftharpoons{\log K = 8.76} [Ni(NH_2CH_2CH_2NH_2)_3]^{2+} + 6NH_3$$

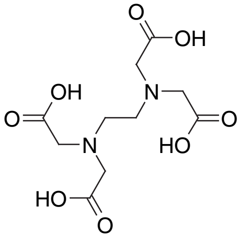
Figure 1.4 A metal ion surrounded by (a) six unidentate ammonia ligands and (b) three bidentate ethylenediamine ligands. The system with bidentate ligands is more stable, an example of the chelate effect. Triangles represent the ligand interaction sites and the sphere represents a metal ion, such as Ni^{2+}.

The enhanced stability of chelating ligands comes from a combination of entropic ($\Delta S°$) and enthalpic ($\Delta H°$) factors that lower the total complexation free energy ($\Delta G°$), as follows (where T is the temperature in Kelvin):

$$\Delta G° = \Delta H° - T\Delta S° \qquad (1.1)$$

In the example shown in Figure 1.4, six unidentate ligands are replaced by three bidentate ligands. During this displacement, a greater number of molecules become free in solution (four species before and seven after). This increase in the number of free molecules gives more degrees of freedom in the system and therefore gives an increase in entropy. The $[Ni(en)_3]^{2+}$ complex is also kinetically stabilised since the bidentate ligands are harder to remove as they have two points of contact with the metal that must be simultaneously broken in order to remove the ligand. The ΔG° values for the reactions of ammonia and ethylenediamine with Ni^{2+} are -49.2 and $-104.4\,kJ\,mol^{-1}$, respectively.

One common chelating ligand is ethylenediaminetetraacetic acid (H_4EDTA) (**1**). This ligand is able to coordinate to a vast range of metals in a hexadentate manner utilising the four deprotonated acid groups and two nitrogen lone pairs. The six interaction sites of $EDTA^{4-}$ arrange themselves in such a way as to form an octahedral array around the central metal atom. As just one $EDTA^{4-}$ fully saturates the metal coordination sites, the resulting complex is extremely stable (*e.g.* the Al^{3+} complex has a log *K* value of 16.3). Figure 1.5 shows an X-ray crystal structure of the complex of $EDTA^{4-}$ ligating an aluminium cation. The hexadentate nature of the ligand can clearly be seen as it wraps around the central guest atom. The EDTA ligand is used extensively in metal analysis applications, such as measuring the Ca^{2+} and Mg^{2+} content of urine.



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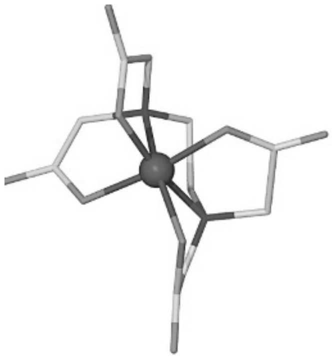


Figure 1.5 A host–guest complex of $EDTA^{4-}$ binding an aluminium cation, where the ligand forms an octahedral geometry around the metal ion.

The stability of metal chelate complexes is also significantly affected by the size of the *chelate ring*. A chelate ring is a ring consisting of the guest metal, two donor atoms and the covalent backbone connecting these donors. Figure 1.6 shows a chelating *podand* (a term applied to any flexible acyclic host capable of wrapping around a guest) with a six-membered chelate ring highlighted. The two nitrogen donor atoms and the metal centre account for three of the ring members; the remaining three are from the C_3 chain bridging the nitrogen atoms.

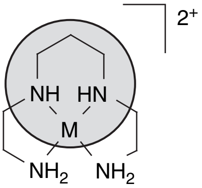


Figure 1.6 A chelating podand, with a six-membered chelate ring highlighted.

The number of members within a chelate ring has an effect on the binding of the guest. If the ring is too small, then the ring will be strained, thus making binding unlikely on enthalpic grounds. The optimum ring geometry for large metal cations is a five-membered chelate ring (Figure 1.7(a)) such as those formed in ethylenediamine complexes. Five-membered rings are particularly stable with large metal cations, such as K^+, as the donor atoms present a larger space for binding. Six-membered rings, on the other hand, are more stable with smaller guests such as Li^+, as the donor atoms result in more limited space to bind the metal (Figure 1.7(b)). As the chelate ring size becomes increasingly large, the chelate effect diminishes, as there is increasing loss of entropy associated with the greater conformational flexibility of the ring. A larger ring requires a larger backbone separating the donor atoms, which becomes less rigid with increasing length. A precise match between optimum chelate ring sizes and metal ionic radii also depends on the orbital hybridisation of the donor atoms.

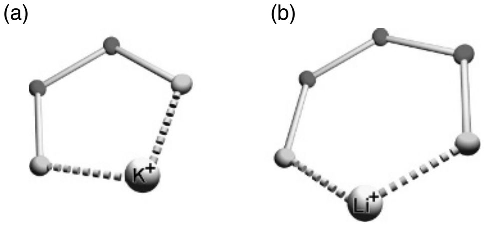


Figure 1.7 Schematic representations of (a) five-membered and (b) six-membered chelate rings (metal–ligand interactions are shown as dashed bonds).

In energy terms, the co-operativity arising from the chelate effect (or more generally from the interaction of a guest with two binding sites, A–B) with a bidentate host can be expressed in terms of the overall binding free energy, ΔG_{AB}° which is equal to the sum of the intrinsic binding free energies of each component A and B ($\Delta G_A{}^i$ and $\Delta G_B{}^i$), plus a factor arising from the summation or connection of A and B (ΔG^s), as follows:[2,3]

$$\Delta G_{AB}{}^{\circ} = \Delta G_A{}^{i} + \Delta G_B{}^{i} + \Delta G^S \tag{1.2}$$

The intrinsic binding energy represents the energies that these groups impart to the rest of the molecule assuming that there are no unfavourable strain or entropy components introduced into the binding by the linking of the group with the rest of the molecule *i.e.* Eq. (1.3) (and similarly for component B):

$$\Delta G_{\mathrm{A}}{}^{\mathrm{i}} = \Delta G_{\mathrm{AB}}{}^{\circ} - \Delta G_{\mathrm{B}}{}^{\circ} \tag{1.3}$$

We can thus write Eq. (1.4) which shows that the connection energy is equal to the sum of the separate affinities of the isolated ligands A or B minus the binding free energy of the connected molecule:

$$\Delta G^{\mathrm{S}} = \Delta G_{\mathrm{A}}{}^{\circ} + \Delta G_{\mathrm{B}}{}^{\circ} - \Delta G_{\mathrm{AB}}{}^{\circ} \tag{1.4}$$

The above equation can be used to give an empirical measure of the co-operativity, since the equilibrium constants for the binding of A, B and A–B by a host can be measured and related to the Gibbs free energy *via* Eq. (1.1). If ΔG^{S} is negative, then the binding sites A and B exhibit unfavourable negative co-operativity. A positive value for ΔG^{S} implies a favourable positive co-operativity.

The chelate effect represents co-operativity between individual binding sites or ligating groups. Co-operativity is also possible when a host binds two guest species. Again, there are two types of co-operativity, either positive or negative. *Positive co-operativity* is when the presence of the first species *increases* the receptor's affinity for the second species. Often this process involves a structural change, *i.e.* an *induced fit* (Section 1.2.1), and occurs in many biological systems and is part of the *allosteric effect* observed in enzymes. An allosteric effect occurs when the binding of a guest at one site is influenced by the binding of another guest at a different site on the same molecule. When the two guests are the same, this is termed a *homotropic effect* and when they are different it is called a *heterotropic effect*. For example, the binding of one molecule of O_2 to one of the four myoglobin units in haemoglobin increases the O_2 affinity of the remaining three myoglobin sub-units, aiding both O_2 absorption in the lungs and O_2 decomplexation in tissues such as muscle. *Negative co-operativity* is the reverse of positive co-operativity and it is believed that there are very few examples of negative co-operativity occurring in nature. The presence of binding co-operativity (either positive or negative) in any system is indicated by a sigmoidal shape to the binding curve and may be subjected to strict, well-defined tests.[4] (The binding curve is a plot of the variation in some observable property such as spectroscopic absorbance as a function of added guest concentration.) Formally, a multiequilibrium system exhibits positive co-operativity if the ratio of the equilibrium constants, $K_{m+1} : K_m$, is higher than the value calculated from Eq. (1.5). A non-co-operative (statistical) system has a value equal to that calculated by this equation, while a lower value means negative co-operativity:

$$\frac{K_{m+1}}{K_m} = \frac{m(t-m)}{(m+1)(t-m+1)} \tag{1.5}$$

where *m* is the number of occupied binding sites in species G_mH_t and *t* is the total number of sites (G, guest; H, host). The *K*-values are the equilibrium constants for the formation of the relevant species.

1.2.4 Preorganisation

Cram, D. J., 'Preorganization – from solvents to spherands', *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1039–1134.

We have already seen that complexes containing a chelating ligand, with multiple interaction sites that are covalently connected, have increased stability compared to similar non-chelating systems due to co-operativity between the sites. Introducing an element of *preorganisation* to a host can further enhance this stability. A preorganised host is one that has a series of binding sites in a well-defined and complementary geometry within its structure and does not require a significant conformational change in order to bind to a guest in the most stable way possible. This can be achieved by making a host that is rigid, with a preformed cavity that is already of the correct size to accept the potential guest species and with the appropriate interaction sites already in place. This arrangement is most frequently accomplished by using a host that contains one or more large rings, *macrocycles*, within its structure. Such rings are either rigid or have relatively restricted conformational freedom. The increased stability of ring-based host complexes compared to acyclic analogues has been traditionally referred to as the *macrocyclic effect* and is really just an example of the preorganisation principle.

Preorganisation: A host is said to be preorganised when it requires no significant conformational change to bind a guest species.

Macrocyclic Effect: Host systems that are preorganised into a large cyclic shape form more stable complexes as there is no energetically unfavourable change in conformation in order to bind a guest.

Figure 1.8(a) shows a podand binding to a metal cation. For binding to occur, the host must undergo a conformational change to adapt its shape and binding site disposition to that of the potential guest. Figure 1.8(b) shows the binding of the same guest by a macrocyclic host. This ring is already of the correct geometry to bind the guest and therefore does not have to change shape in order for the binding to take place.

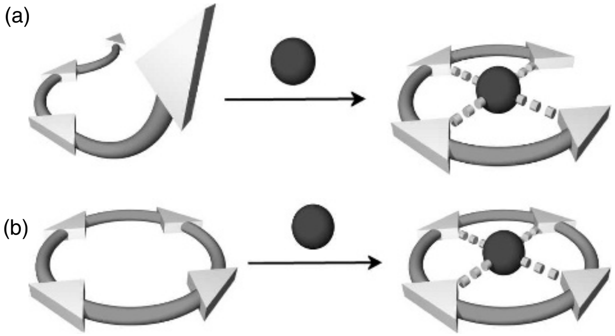


Figure 1.8 (a) A podand is not preorganised and must undergo a change in conformation in order to bind a guest destabilising the complex. (b) A macrocycle that is preorganised for a specific guest does not need to change conformation significantly for binding to occur.

Macrocyclic hosts show enhanced guest binding because of both entropic and enthalpic factors (Eq. (1.1)). Entropically, the binding of a podand results in the loss of many degrees of freedom from the system as the 'floppy' molecule must rigidify as it wraps around the host. This decreases the entropy of the system, meaning that the ΔS of binding is negative and the ΔG of the binding process becomes more positive and unfavourable. A free macrocyclic host does not have such conformational freedom and so the change in entropy between the free and binding host is much less and hence more favourable than that of an analogous podand host. Unfavourable enthalpic contributions from the binding of a podand come from bringing mutually repulsive donor groups into close proximity as the conformation changes. The free podand in solution will minimise its energy by tending to adopt the conformation with the maximum possible distance between repulsive groups, but when binding a guest such groups are brought closer together and the repulsions are overcome by the favourable interaction enthalpy between the binding sites. The macrocyclic host has the donor groups placed into the correct conformation during the synthesis, meaning that energy does not need to be expended during binding, therefore lowering the ΔG of the binding process. Figure 1.9 shows a polyamine podand and a related macrocycle, both of which are capable of binding metal cations such as Zn^{2+} and Cu^{2+}. The macrocyclic host is capable of binding guests 10 000 times more strongly than the podand as a

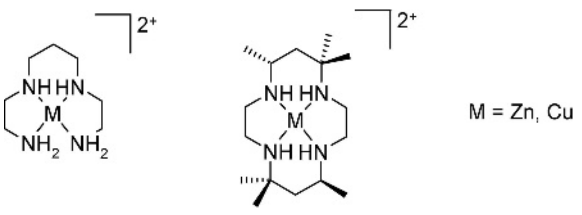


Figure 1.9 Polyamide acyclic and macrocyclic host complexes. The macrocycle displays enhanced binding compared to the podand due to the macrocyclic effect.

consequence of the macrocyclic effect. A further enthalpic effect comes from the negation of repulsions within the macrocycle when a guest binds. The binding sites within a macrocycle, usually electron lone pairs for metal guests, are all pointing towards each other, producing an unfavourable interaction. When a guest is bound to these sites, the unfavourable interactions are reduced in favour of the favourable binding interactions.

Additional enthalpic consequences of binding by macrocyclic ligands concern the desolvation of the host prior to guest binding. The donor sites of a macrocycle are less accessible to solvent molecules than those of a podand as they are generally orientated towards the interior of a cavity. This conformation prevents some solvent molecules from reaching them (Figure 1.10(b)). Podands can be fully solvated as they are flexible, with the donor sites well-separated (Figure 1.10(a)). When a podand binds to a guest, more host–solvent interactions must be broken before the guest is able to bind and therefore a greater amount of energy is required for the binding to occur.

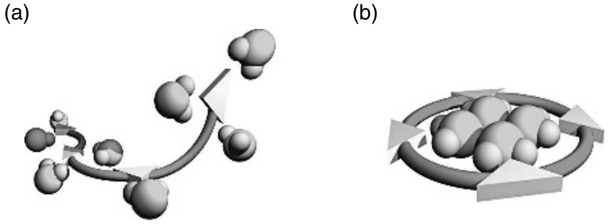


Figure 1.10 A podand (a) is fully solvated in solution as it is flexible and the donor sites are easily accessible and (b) macrocycles are often not fully solvated as the solvent molecules would have to be packed in close proximity in the centre of the host.

The macrocyclic effect can be taken one step further by synthesising *macrobicycles* (Figure 1.11). Such species can provide a three-dimensional array of interactions so that a guest is 'more surrounded' by the host. A simple macrocycle leaves the top and bottom of the guest accessible to the bulk environment, whereas a bicyclic host isolates the guest.

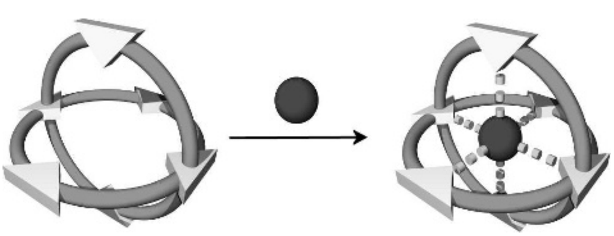


Figure 1.11 A macrobicycle is more rigid and preorganised than a macrocycle (Figure 1.8), hence resulting in stronger guest binding.

1.2.5 Binding constants

Connors, K. A., *Binding Constants: The Measurement of Molecular Complex Stability*, John Wiley & Sons, Ltd, Chichester, UK, 1987.

The binding of a guest by a host species, or the interaction of two or more species by non-covalent bonds, is an equilibrium process. The equilibrium constant for a binding process is called the *binding constant* or *association constant*. The equilibrium that exists for a simple 1:1 host–guest system is shown in Scheme 1.1. The binding constant is calculated by Eq. (1.6), using the concentrations of the species present at equilibrium: host (H), guest (G) and the resulting complex ($H \cdot G$). The final value, K, has units of mol dm^{-3} or M^{-1}.[‡] These values can range from near zero to very large and so for convenience a log scale is utilised and values are commonly seen quoted as log K. Binding constants are calculated from experimental data (from titrations monitored by NMR, UV–Vis or fluorescence spectroscopy, for example), which supply information about the position of the equilibrium.

$$\text{Host + Guest} \rightleftharpoons \text{Host} \cdot \text{Guest}$$

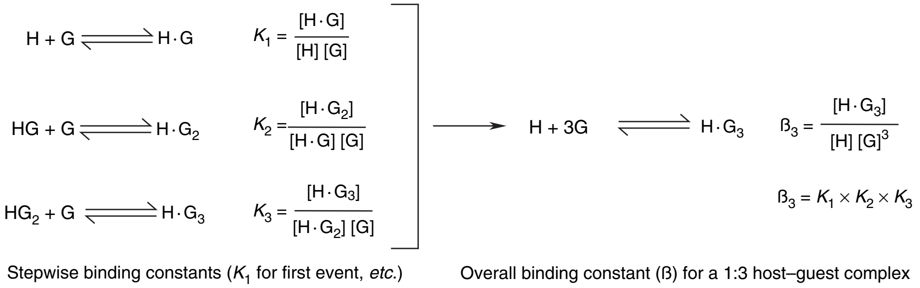
Scheme 1.1 The equilibrium between a host–guest complex and the free species.

$$K = \frac{[H \cdot G]}{[H][G]} \tag{1.6}$$

Binding Constant, *K*: The equilibrium constant for the interaction of a host with one or more guests. The *binding constant* provides a quantitative representation of the degree of association and is also called the association constant.

Frequently, host–guest complexes do not form exclusively in a straightforward 1:1 ratio. In such cases, there is more than one binding constant as subsequent guests bind to the host. Multiple equilibria of this type are described by stepwise binding constants for each guest as it binds, and an overall binding constant for the final complex which is termed beta (β). The definition of the overall binding constant is shown in Scheme 1.2.

[‡] Formally binding constants are defined as ratios of activities, which are dimensionless. After all, it is not possible to take a logarithm of a unit! Chemists thus make the approximation that concentrations are very similar to the activities.



Scheme 1.2 Derivation of stepwise and overall binding constants for a 1:3 host–guest complex.

1.2.6 Kinetic and thermodynamic selectivity

One of the most important factors in the design of host–guest systems is to ensure that a host has a preference for the target guest species above all other possible guests. The host must be able to discriminate between species and hence show a good degree of *selectivity* for the desired guest. There are two kinds of selectivity that may come about; thermodynamic and kinetic.

Thermodynamic selectivity is the ratio of the binding constants for a host binding two different guests (Eq. (1.7)). The relationship between the binding constant of any given supramolecular complex is directly related to the change in free energy during the association process by Eq. (1.8), where R is the gas constant (8.314 J mol^{-1} K^{-1}), T is the temperature (K) and ln K is the natural logarithm of the binding constant. The energy of association can be controlled to a certain extent when the host system is designed, by applying design principles such as the chelate and macrocyclic effects (Sections 1.2.2 and 1.2.3). The correct selection of supramolecular interactions between the two species is also of great importance (Section 1.3). This means that thermodynamic selectivity can be enhanced through rational changes to the design of the host.

$$\text{Selectivity} = \frac{K_{\text{GUEST 1}}}{K_{\text{GUEST 2}}} \tag{1.7}$$

$$\Delta G = -RT \ln K \tag{1.8}$$

Kinetic selectivity is based on a very different principle to thermodynamic selectivity. The word 'kinetic' implies that there is a time-element involved. Kinetic selectivity is usually found in the context of catalytic or enzyme-based processes, whereby a guest (substrate) is transformed upon binding. The rate at which competing substrates are transformed is the determining factor for kinetic selectivity, with the enzyme or catalyst being selective for the fastest-reacting substrate. To cater for a reacting guest, enzyme binding sites are not rigidly preorganised as they have to change to be complementary to the substrate at any given time along the reaction profile. Strong binding would slow down the exchange rate at the enzyme active site and therefore reduce the activity of the enzyme. Enzymes are usually selective for the transition state of a given substrate transformation, adopting a strained geometry, referred to as the *entatic state*. It is this strained geometry that lowers the activation energy for the substrate reaction and gives the enzyme its catalytic properties.

1.2.7 Solvent effects

Smithrud, D. B., Sanford, E. M., Chao, I., Ferguson, S. B., Carcanague, D. R., Evanseck, J. D., Houk, K. N. and Diederich, F., 'Solvent effects in molecular recognition', *Pure Appl. Chem.*, 1990, **62**, 2227–2236.

So far, we have looked at the interactions between a host and its guest(s) as if they were isolated from any other influences. This is not the case in real systems as there are competing interactions from other potential guests and surrounding solvent molecules. Solvent molecules greatly outnumber the amounts of the host and guest present and therefore can have a very pronounced effect upon the dynamics and energetics of association.

When in solution, host and guest species are surrounded by solvent molecules which interact with them. In order for binding to occur, many of these interactions must be broken, which has both enthalpic and entropic consequences. This desolvation process is shown in a simplified way in Figure 1.12. Enthalpically, energy must be expended to break the solvent–host and solvent–guest bonds. The removal of solvent molecules from the host and the guest leads to the solvent molecules having more freedom in the solution, which increases the entropy and also leads to the formation of solvent–solvent bonds. The choice of solvent can have significant consequences on the binding of a guest.

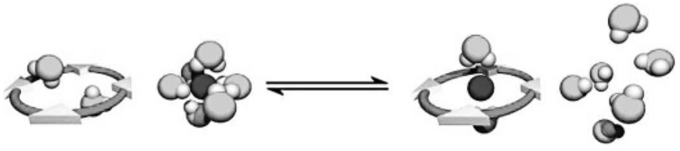


Figure 1.12 Host–guest binding equilibrium showing the desolvation of both species required prior to the binding occurring. The final complex is still solvated but overall there are more free solvent molecules present, hence increasing the entropy of the system.

Solvent effects can be understood by the way in which the individual molecules can interact with the host and the guest. Polar solvents are able to interact with host molecules *via* electrostatic interactions (Section 1.3.1). Such solvents are particularly able to inhibit binding of charged species, as the solvent dipole can interact strongly with a charged centre, thus making the solvent–host or solvent–guest interactions harder to break. Other solvents are able to disrupt the binding by means of electron-pair or hydrogen bond donation and acceptance. Many solvents display both of these properties, for example, dimethyl sulfoxide (DMSO, $OSMe_2$) acts as both an electron-pair donor and hydrogen bond acceptor by virtue of oxygen and sulfur lone pairs. The vast majority of supramolecular interactions are electrostatic in nature (Section 1.3), meaning that polar solvents often act to reduce the observed binding. For this reason it is usual for any studies to be carried out in the least polar solvent possible to reduce the competition for the host. The conditions used can help to moderate the binding process, for example, if the binding is too strong to be conveniently measured, more polar solvents can be employed to reduce the binding constant.

1.3 Supramolecular interactions

Non-covalent interactions represent the energies that hold supramolecular species together. Non-covalent interactions are considerably weaker than covalent interactions, which can range between ca. 150 kJ mol^{-1} to 450 kJ mol^{-1} for single bonds. Non-covalent bonds range from 2 kJ mol^{-1} for dispersion interactions to 300 kJ mol^{-1} for 'ion-ion' interactions. However, when these interactions are used in a co-operative manner a stable supramolecular complex can exist. The term 'non-covalent' includes a wide range of attractions and repulsions which are summarised in Table 1.1 and will be described in more detail in the following sub-sections.

Table 1.1 Summary of supramolecular interactions

Interaction	Strength (kJ mol^{-1})	Example
Ion–ion	200–300	Tetrabutylammonium chloride
Ion–dipole	50–200	Sodium [15]crown-5
Dipole–dipole	5–50	Acetone
Hydrogen bonding	4–120	(See Table 1.2)
Cation–π	5–80	K^+ in benzene
π–π	0–50	Benzene and graphite
van der Waals	< 5 kJ mol^{-1} but variable depending on surface area	Argon; packing in molecular crystals
Hydrophobic	Related to solvent–solvent interaction energy	Cyclodextrin inclusion compounds

1.3.1 Ionic and dipolar interactions

Anslyn, E. V. and Dougherty, D. A., *Modern Physical Organic Chemistry*, University Science Books, Sausalito, CA, USA, 2006, pp. 162–168.

Ionic and dipolar interactions can be split into three categories: (i) *ion–ion interactions*, (ii) *ion–dipole interactions*, and (iii) *dipole–dipole interactions*, which are based on the Coulombic attraction between opposite charges. The strongest of these interactions is the ion–ion (Figure 1.13(a)), which is comparable with covalent interactions. Ion–ion interactions are non-directional in nature, meaning that the interaction can occur in any orientation. Ion–dipole (Figure 1.13(b)) and dipole–dipole interactions (Figure 1.13(c)), however, have orientation-dependant aspects requiring two entities to be aligned such that the interactions are in the optimal direction. Due to the relative rigidity of directional interactions, only mutually complementary species are able to form aggregates, whereas non-directional interactions can stabilise a wide range of molecular pairings. The strength of these directional interactions depends upon the species involved. Ion–dipole interactions are stronger than dipole–dipole interactions (50–200 and 5–50 kJ mol^{-1}, respectively) as ions have a higher charge density than dipoles. Despite being the weakest directional interaction, dipole–dipole interactions are useful for bringing species into alignment, as the interaction requires a specific orientation of both entities.

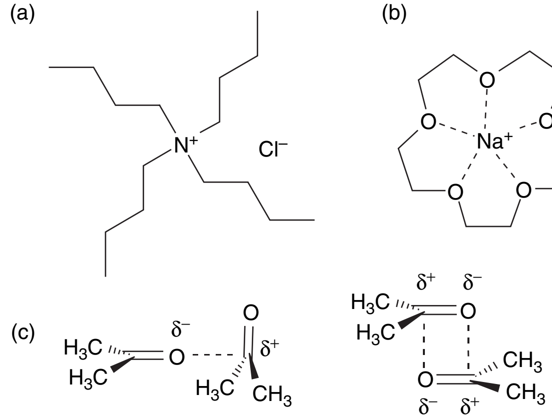


Figure 1.13 Examples of electrostatic interactions: (a) ion–ion interaction in tetrabutylammonium chloride; (b) ion–dipole interaction in the sodium complex of [15]crown-5; (c) dipole–dipole interactions in acetone.

Electrostatic interactions play an important role in understanding the factors that influence high binding affinities, particularly in biological systems in which there is a large number of recognition processes that involve charge–charge interactions; indeed these are often the first interactions between a substrate and an enzyme.

1.3.2 Hydrogen bonding

Jeffery, G. A., *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford, UK, 1997.

The *hydrogen bond* is arguably the most important non-covalent interaction in the design of supramolecular architectures, because of its strength and high degree of directionality. It represents a special kind of dipole–dipole interaction between a proton donor (D) and a proton acceptor (A). There are a number of naturally occurring 'building blocks' that are a rich source of hydrogen bond donors and acceptors (*e.g.* amino acids, carbohydrates and nucleobases). Hydrogen bond donors are groups with a hydrogen atom attached to an electronegative atom (such as nitrogen or oxygen), therefore forming a dipole with the hydrogen atom carrying a small positive charge. Hydrogen bond acceptors are dipoles with electron-withdrawing atoms by which the positively charge hydrogen atom can interact, for example, carbonyl moieties (Figure 1.14).

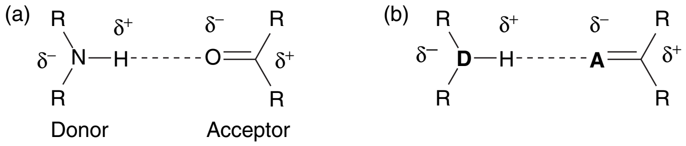


Figure 1.14 A carbonyl accepting a hydrogen bond from a secondary amine donor (a) and (b) the standard way of expressing donor and acceptor atoms (D, donor atom; A, acceptor atom).

The strength of hydrogen bonds can be very different between various systems and is not necessarily correlated with the Brønstead acidity of the proton donor. It depends on the type of electronegative atom to which the hydrogen atom is attached and the geometry that the hydrogen bond adopts in the structure. Typically, the strengths range from 4 to 120 kJ mol^{-1}, with the vast majority being under 60 kJ mol^{-1} and scales of hydrogen bond acidity and basicity have been developed.[5] The types of geometries that can be adopted in a hydrogen bonding complex are summarised in Figure 1.15.

The geometries displayed in Figure 1.15 are termed *primary hydrogen bond interactions* – this means that there is a direct interaction between the donor group and the acceptor group. There are also *secondary interactions* between neighbouring groups that must be considered. The partial charges on adjacent atoms can either increase the binding strength by virtue of attraction between

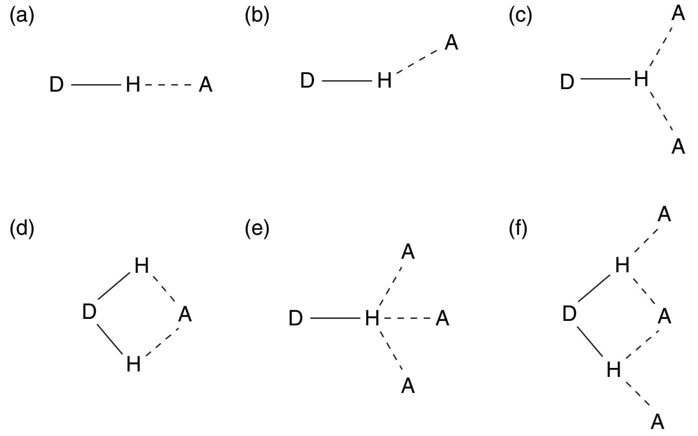


Figure 1.15 Various types of hydrogen bonding geometries: (a) linear; (b) bent; (c) donating bifurcated; (d) accepting bifurcated; (e) trifurcated; (f) three-centre bifurcated.

opposite charges or decrease the affinity due to repulsion between like charges. Figure 1.16 shows two situations in which arrays of hydrogen bond donors and acceptors are in close proximity. An array of three donors (DDD) facing three acceptors (AAA) (Figure 1.16(a)) has only attractive interactions between adjacent groups and therefore the binding is enhanced in such a situation. Mixed donor/acceptor arrays (ADA, DAD) suffer from repulsions by partial charges of the same sign being brought into close proximity by the primary interactions (Figure 1.16(b)).

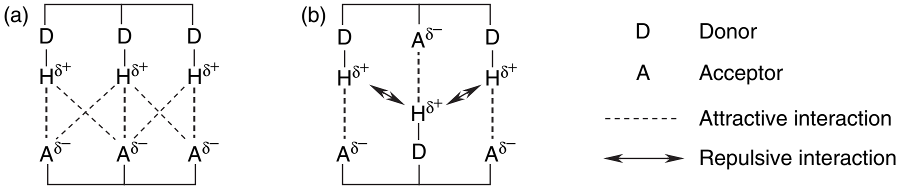


Figure 1.16 (a) Secondary interactions providing attractions between neighbouring groups in DDD and AAA arrays and (b) repulsions from mixed donor/acceptor arrays (ADA and DAD), with primary interactions shown in 'bold'.

A real-life example of hydrogen bonding is the double helix of DNA. There are many hydrogen bond donors and acceptors holding base pairs together, as illustrated between the nucleobases cytosine (C) and guanine (G) in Figure 1.17. The CG base pair has three primary interactions (*i.e.* traditional hydrogen bonds) and also has both attractive and repulsive secondary interactions.

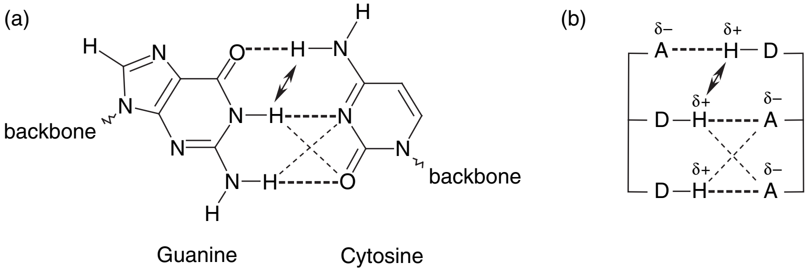


Figure 1.17 (a) Primary and secondary hydrogen bond interactions between guanine and cytosine base-pairs in DNA and (b) a schematic representation.

The geometry of a hydrogen bond and the type of donor and acceptor groups determine the strength, length and nature of the interaction. Hydrogen bond interactions can be divided into three broad categories, the properties of which are listed in Table 1.2. A strong interaction is somewhat similar in character to a covalent bond, whereby the hydrogen atom is close to the centre-point of the donor and acceptor atoms. Strong hydrogen bonds are formed between two strong bases, for example in the HF_2^- ion, which is practically linear with the hydrogen atom between the two fluorine atoms $[F \cdots H \cdots F]^-$. Moderate-strength hydrogen bonds are formed between neutral donor and neutral acceptor groups *via* electron lone pairs, for example, the self-association of carboxylic acids. Moderate hydrogen bond interactions do not have a linear geometry but are slightly bent. Hydrogen bonds commonly deviate from linearity and their angular distribution is influenced by statistical factors. A 'conical correction' for statistical effects often appears in the analysis of hydrogen bond-angle distributions, particularly from searches of the Cambridge Structural Database (see Chapter 4, Section 4.5.2). A linear hydrogen bond requires a fixed position of the hydrogen atom in relation to the acceptor, whereas non-linear hydrogen bonds have many possible positions that form a conical shape around the linear position. Larger bond angles

Table 1.2 Hydrogen bond interactions and their properties (A, acceptor; D, donor)

Interaction/property	Strong	Moderate	Weak
$D{-}H \cdots A$	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol^{-1})	60–120	16–60	< 12
Bond length (Å)			
$H \cdots A$	1.2–1.5	1.5–2.2	2.2–3.2
$D \cdots A$	2.2–2.5	2.5–3.2	3.2–4.0
Bond angle (degrees)	175–180	130–180	90–150
Example	HF complexes	Acids	$C{-}H \cdots A$
	$H_5O_2^+$	Alcohols	$D{-}H \cdots \pi$
	—	DNA/RNA	—

result in a larger cone, and therefore there are more possible positions for the bond to occur in. Weak hydrogen bonds are even less linear and in some cases can form perpendicular interactions, for example the $C-H\cdots\pi$ interaction between benzene rings when the $C-H$ bonds point directly towards the conjugated system (Section 1.3.3).

The highly directional nature of hydrogen bonding interactions, together with the specific alignment of hydrogen bond donors and acceptors, has proved to be a fruitful asset for the design of supramolecular systems.

1.3.3 π-Interactions

Ma, J. C. and Dougherty, D. A., 'The cation-π interaction', *Chem. Rev.*, 1997, **97**, 1303–1324.
Hunter, C. A., Lawson, K. R., Perkins, J. and Urch, C. J., 'Aromatic interactions', *J. Chem. Soc., Perkin Trans. 2*, 2001, 651–669.

There are two main π-interactions that can be found in supramolecular systems, namely (i) cation–π interactions and (ii) π–π interactions. Cation–π interactions are well known in the field of organometallic chemistry, whereby olefinic groups are bound to transition metal centres, for example, ferrocene and Zeise's salt ($[PtCl_3(\eta^2\text{-}C_2H_4)]^-$), but these are not regarded as non-covalent interactions.[6] However, alkaline- and alkaline-earth metals also form interactions with double-bond systems, typically between 5 and 80 kJ mol^{-1}. For example, the interaction of potassium ions with benzene has a similar energy to the K^+–OH_2 interaction. The potassium cation is more soluble in water than in benzene, however, as it is not sterically possible to fit as many benzene molecules around the metal ion as water molecules (Figure 1.18).

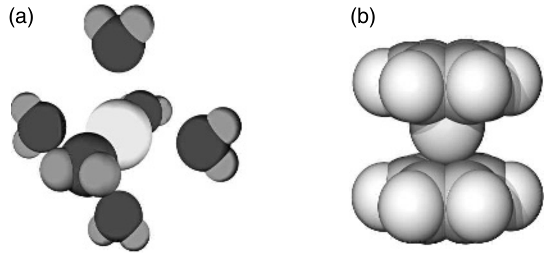


Figure 1.18 (a) Six or more water molecules can fit around K^+ whereas (b) there is space for only two benzene molecules.

The two types of π–π interactions are *face-to-face*, whereby parallel ring-systems, separated by ca. 3.5 Å, are offset and the interaction is between the centre of one ring and the corner of another (Figure 1.19(a)), and *edge-to-face*, whereby a hydrogen atom from one ring interacts in a perpendicular orientation with respect to the centre of another ring (Figure 1.19(b)). These π–π interactions arise from the attraction between the negatively charge π-electron cloud of one conjugated system and the positively charged σ-framework of a neighbouring molecule.[7]

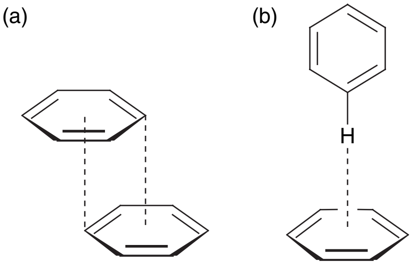


Figure 1.19 The two types of π–π interactions: (a) face-to-face; (b) edge-to-face.

The layered structure of graphite is held together by weak, face-to-face π-interactions and therefore feels 'slippery' (Figure 1.20). It is because of the slippage between layers that graphite can be used as a lubricant (albeit in the presence of oxygen). Interactions involving π-systems can be found in nature, for example, the weak face-to-face interactions between base-pairs along the length of the double helix are responsible for the shape of DNA (see Chapter 3, Section 3.2.4).

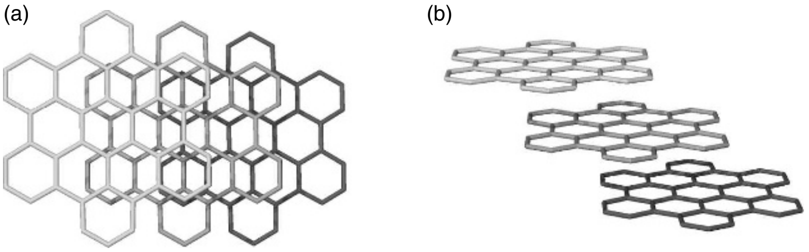


Figure 1.20 (a) Top and (b) side views of the layered structure of graphite, held together by face-to-face π-interactions.

1.3.4 van der Waals interactions

Schneider, H.-J., 'Van der Waals forces', in *Encyclopedia of Supramolecular Chemistry*, Vol. 2, Steed, J. W. and Atwood, J. L. (Eds), Marcel Dekker, New York, NY, USA, 2004, pp. 1550–1556.

Van der Waals interactions are dispersion effects that comprise two components, namely the *London interaction* and the *exchange and repulsion* interaction.

Van der Waals interactions arise from fluctuations of the electron distribution between species that are in close proximity to one another. As the electron cloud moves about a molecule's momentary location, an instantaneous dipole is formed within the molecule. This 'flickering' of electron distribution (or dipole) between two adjacent species will align the molecules such that a partial positive charge from one species will be attracted to a partial negative charge from another molecule (Figure 1.21); therefore, the two instantaneous dipoles attract one another and produce a London interaction. The strength of these interactions is dependant on the polarisability of the molecule; the more polarisable the species, then the greater the strength of the interaction. The potential energy of the London interaction decreases rapidly as the distance between the molecules increases (this depends on the reciprocal of the sixth power of the distance r – an r^{-6} dependence). These interactions are non-directional and do not feature highly in supramolecular design. However, van der Waals interactions are important in the formation of inclusion compounds (see Chapter 4, Section 4.3), in which small organic molecules are incorporated into a crystalline lattice, or where small organic molecules have been encapsulated into permanent molecular cavities.

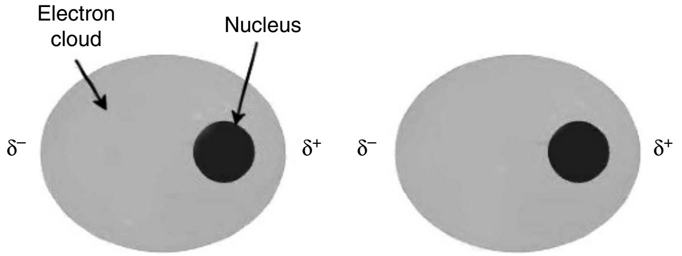


Figure 1.21 A London interaction between two argon atoms. The shift of the electron cloud around the nucleus produces instantaneous dipoles that attract each other.

In the solid state, species tend to align so there is a maximum number of interactions between each molecule, which minimises the lattice energy of the solid state structure. This close packing arrangement has been rationalised by Kitaigorodskii in a classic treatise.[8] As molecules 'grow' into a crystal, they arrange themselves so that all of the void space is occupied, to achieve the maximum interaction with their neighbours and hence the most stable lattice energy for the crystal. This close-packed arrangement is achieved by most solid state structures but there are a few examples were there is a void space, *i.e.* zeolites and channel coordination polymers (see Chapter 4, Sections 4.2 and 4.6, respectively) where the rigid framework is strong enough to withstand external forces.

1.3.5 Hydrophobic effects

Southall, N. T., Dill, K. A. and Haymet, A. D. J., 'A view of the hydrophobic effect', *J. Phys. Chem.*, 2002, **106**, 521–533.

Hydrophobic effects arise from the exclusion of non-polar groups or molecules from aqueous solution. This situation is more energetically favourable because water molecules interact with themselves or with other polar groups or molecules preferentially. This phenomenon can be observed between dichloromethane and water which are immiscible. The organic solvent is forced away as the inter-solvent interactions between the water molecules themselves are more favourable than the 'hole' created by the dichloromethane. Hydrophobic interactions play an important role in some supramolecular chemistry, for example, the binding of organic molecules by cyclophanes and cyclodextrins in water (see Chapter 2, Sections 2.7.1 and 2.7.5, respectively). Hydrophobic effects can be split into two energetic components, namely an enthalpic hydrophobic effect and an entropic hydrophobic effect.

Enthalpic hydrophobic interactions occur when a guest replaces the water within a cavity. This occurs quite readily as water in such systems does not interact strongly with the hydrophobic cavity of the host molecule and the energy in the system is high. Once the water has been replaced by a guest, the energy is lowered by the interaction of the former water guest with the bulk solvent outside the cavity (Figure 1.22). There is also an entropic factor to this process, in that the water that was previously ordered within the cavity becomes disordered when it leaves. An increase in entropy increases the favourability of the process.

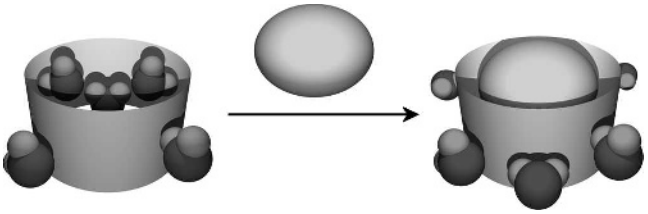


Figure 1.22 The displacement of water molecules from a hydrophobic cavity is responsible for the enthalpic hydrophobic effect.

Entropic hydrophobic interactions come about when there are two or more organic molecules in aqueous solution, the combination of which creates a hole in the water to form a supramolecular complex (Figure 1.23). There is less disruption (one hole in the aqueous phase instead of multiple holes) and hence an entropic gain, as the overall free energy of the system is lowered.

The hydrophobic effect is also very important in biological systems in the creation and maintenance of the macromolecular structure and supramolecular

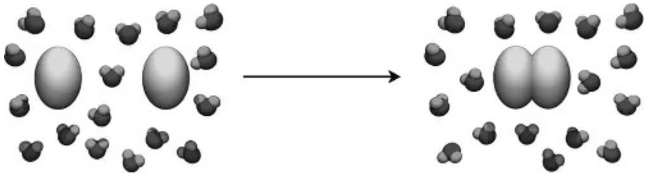


Figure 1.23 Two organic molecules creating a hole within an aqueous phase, giving rise to the entropic hydrophobic effect – one hole is more stable than two.

assemblies of the living cell or the formation of amphiphilic structures such as micelles, where hydrophilic 'heads' assemble in a roughly spherical geometry and lipid bilayers where the heads meet end-to-end (see Chapter 5, Section 5.4.1).

1.4 Supramolecular design

The principles and phenomena outlined within this introductory chapter are the basic concepts upon which supramolecular chemistry is based. A union of these phenomena can lead to intricate and complex designs that form the heart of the many facets of supramolecular chemistry.

In terms of 'designer' host–guest chemistry, it is necessary to understand the nature of the target guest molecule. The host must be designed to be complementary to the guest in terms of size, shape and chemical properties (charge, hardness, acidity, *etc*.). Other factors must also be considered in the design process, such as the medium in which the binding must occur and any competing molecules which must be excluded from binding, therefore requiring a more selective host. Once all of the guest properties have been taken into consideration, the host may be designed in a specific manner, incorporating the basic phenomena outlined in this chapter, followed by a process of 'trial and improvement' based on laboratory results. Moving away from the host–guest aspect of supramolecular chemistry, the underlying principles remain the same although the systems formed are often much more complex. For example, protein tertiary structure (folding of a protein to give a three-dimensional entity by non-covalent interactions) results in a very complicated system when viewed as a whole, but the individual interactions are quite easily understood. Biological systems have provided an inspiration to chemists who design and synthesise complex supramolecular architectures capable of practical applications.

Supramolecular systems have a wide variety of uses, such as trapping molecules within solid state lattices (Chapter 4), sensing and remediation of species from solution (Chapter 2), understanding biological self-assembly (Chapter 3) and nanotechnological devices (Chapter 5). Together, these topics form the core concepts upon which supramolecular chemistry is based.

References

1. Cram, D. J., 'Preorganization – from solvents to spherands', *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1039–1134.
2. Jencks, W. P., 'On the attribution and additivity of binding-energies', *Proc. Nat. Acad. Sci. USA*, 1981, **78**, 4046–4050.
3. Williams, D. H. and Westwell, M. S., 'Aspects of weak interactions', *Chem. Soc. Rev.*, 1998, **27**, 57–63.
4. Perlmutter-Hayman, B., 'Co-operative binding to macromolecules. A formal approach', *Acc. Chem. Res.*, 1986, **19**, 90–96.
5. Laurence, C. and Berthelot, M., 'Observations on the strength of hydrogen bonding', *Persp. Drug Disc. Des.*, 2000, **18**, 39–60.
6. Elschenbroich, C., *Organometallics: A Concise Introduction*, 3rd Edn, VCH, Weinheim, Germany, 2006.
7. Hunter, C. A. and Sanders, J. K. M., 'The nature of π–π interactions', *J. Am. Chem. Soc.*, 1990, **112**, 5525–5534.
8. Kitaigorodskii, A. I., *Organic Chemical Crystallography*, Consultants Bureau, New York, NY, USA, 1961 (originally published in Russian by Press of the Academy of Sciences of the USSR, Moscow, USSR, 1955).

Suggested further reading

Buckingham, A. D., Legon, A. C. and Roberts, S. M. (Eds), *Principles of Molecular Recognition*, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1993.

Cragg, P. J., *Practical Supramolecular Chemistry*, John Wiley & Sons, Ltd, Chichester, UK, 2006.

Desiraju, G. R. (Ed.), *The Crystal as a Supramolecular Entity*, John Wiley & Sons, Ltd, Chichester, UK, 1996.

Lehn, J.-M., *Supramolecular Chemistry*, VCH, Weinheim, Germany, 1995.

Lehn, J.-M., Atwood, J. L., Davies, J. E. D., MacNicol, D. D. and Vögtle, F. (Eds), *Comprehensive Supramolecular Chemistry*, Pergamon, Oxford, UK, 1996.

Ozin, G. A. and Arsenault, A. C., *Nanochemistry*, The Royal Society of Chemistry, Cambridge, UK, 2005.

Schneider, H.-J. and Yatsimirski, A. K., *Principles and Methods in Supramolecular Chemistry*, Wiley-VCH, Weinheim, Germany, 2000.

Steed, J. W. and Atwood, J. L., *Supramolecular Chemistry*, John Wiley & Sons, Ltd, Chichester, UK, 2000.

Steed, J. W. and Atwood, J. L. (Eds), *Encyclopedia of Supramolecular Chemistry*, Marcel Dekker, New York, NY, USA, 2004.