

CHAPTER 1

Concepts

Mankind is divisible into two great classes: hosts and guests.

Max Beerbohm (1872–1956), *Hosts and Guests*, 1918

1.1 DEFINITION AND DEVELOPMENT OF SUPRAMOLECULAR CHEMISTRY

Key Lehn, J.M. (2017). Supramolecular chemistry: where from? Where to? *Chem. Soc. Rev.* 46: 2378–2379.

1.1.1 What is Supramolecular Chemistry?

Supramolecular chemistry has been defined by one of its leading proponents, Jean-Marie Lehn, who won the Nobel Prize for his work in the area in 1987, as ‘chemistry beyond the molecule’. According to Lehn, supramolecular chemistry ‘aims at designing and implementing functional chemical systems based on molecular components held together by non-covalent intermolecular forces’. Taken literally, this means that the field is concerned with any interaction between atoms or molecules that is distinct from covalent bonding. Key examples of such interactions include ionic bonding, hydrogen bonding, and other dipolar interactions, metal coordination interactions, halogen bonding, and aromatic stacking. More recently, the award of the 2016 Nobel Prize in Chemistry in the area of molecular machines has also cemented the position of the *mechanical bond* as a further important supramolecular interaction (Chapter 11). Other less common interactions also fit the broad non-covalent umbrella, as we will see in Section 1.8. In practice, the limitation of ‘functional chemical systems’ means that work in supramolecular chemistry is dominated by interactions that are relatively strong, directional, and are subject to synthetic manipulation or to facile incorporation into molecular building blocks.

Originally, supramolecular chemistry was defined in terms of the non-covalent interaction between a *host* and a *guest* molecule, and was applied to hosts such as crown ethers, cryptands, and spherands for alkali metal cation guests. The term Supramolecular Chemistry was coined by Lehn in 1978¹ but the host–guest chemistry of metal ions and macrocyclic hosts in both artificial and biochemical systems far predates this description. As originally conceived, a host is prepared using conventional chemical synthesis from molecular precursors and then undergoes a thermodynamically controlled binding equilibrium with the target guest. Host and guest have a measurable mutual binding energy and the resulting host guest complex or ‘supermolecule’ is held together by non-covalent interactions in which the guest resides within the host’s intrinsic binding cavity, a feature that is installed when the host is synthesised. The supermolecule potentially exhibits functional characteristics arising from its multicomponent nature, Figure 1.1.

Work in modern supramolecular chemistry has gone far beyond host–guest systems, however, and now encompasses molecular devices and machines, molecular recognition, self-assembly, self-organisation, crystal engineering, supramolecular materials, and dynamic covalent chemistry. Moreover, it has significant interfaces with biology, the

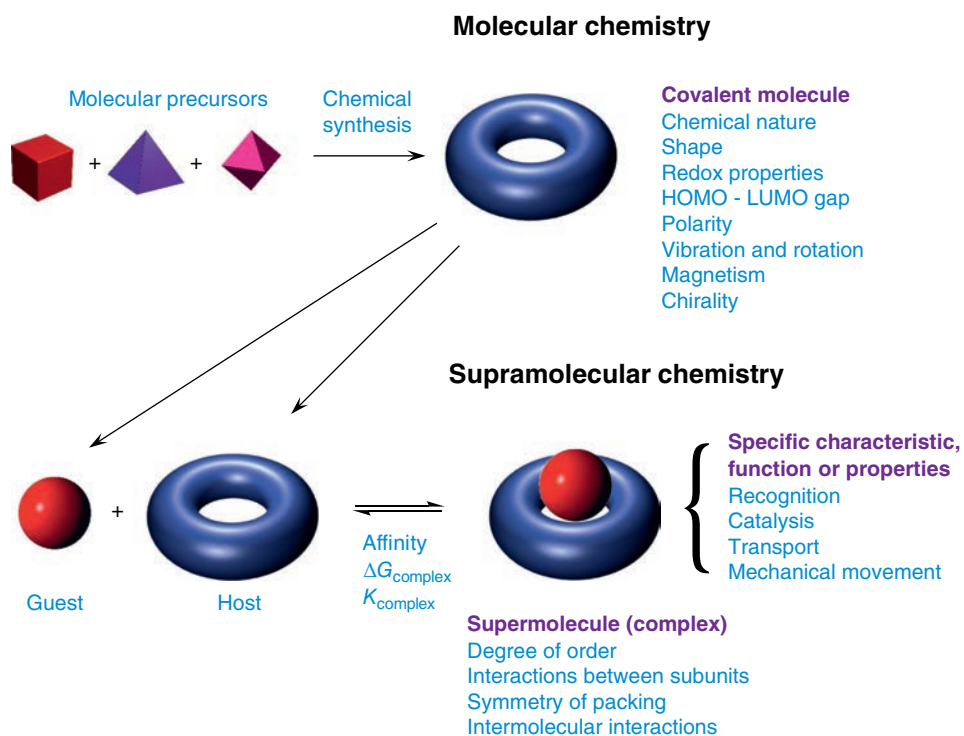


FIGURE 1.1 Comparison between the scope of molecular and supramolecular chemistry.²

emergence of complex matter and nanochemistry (Section 1.10). The rapid expansion in supramolecular chemistry over the past 35 years has resulted in an enormous diversity of chemical systems, both designed and accidentally stumbled upon, which may lay some claim, either in concept, origin, or nature, to being supramolecular. Supramolecular concepts are now sufficiently well understood that they are used along with molecular and materials chemistry as part of the toolbox of modern technology.

There are also a number of partially or fully covalent molecules that are of interest to the supramolecular community, particularly when their functionality is linked to the interactions between discrete components of the molecule. Examples include supramolecular photonic devices, molecular motors, and self-assembled coordination arrays. In supramolecular photochemistry, a supermolecule can be a group of molecular components that contribute properties that each component possesses individually to the whole assembly (be it a covalent or non-covalent assembly). Thus, an entirely covalent molecule comprising, for example, a *chromophore* (light-absorbing moiety), *spacer*, and *redox centre* might be thought of as supramolecular because the chromophore and redox centre are able to absorb light, or change oxidation state, whether they form part of the supermolecule or not (see Chapter 12). Similarly, the self-assembly of large systems or molecular arrays can utilise a variety of interactions, some of which are clearly non-covalent (e.g. hydrogen bonds) and some of which possess a significant covalent component (e.g. metal–ligand interactions, see Chapter 10). Ultimately, these self-assembly reactions and the resulting self-organisation of the system rely solely on the intrinsic information contained in the structure of the molecular components and hence there is an increasing trend towards the study and manipulation of intrinsic *molecular information*. This shift in emphasis is nothing more than a healthy growth of the field from its roots in host–guest chemistry to encompass and inform a much broader range of concepts and activities. Reflecting on the field that he did so much to create, Lehn commented in 2017 in the key reference to this section:

Arguably the major conceptual contribution of supramolecular chemistry to chemistry has been to extol and implement the notion of chemical information, as it operates in molecular recognition processes, being stored at the molecular level in the framework of molecules and implemented at the supramolecular level in the build-up (synthesis!) of discrete or extended assemblies of chemical objects. It forms the basis of the universal principle of self-organisation, the feature that on the wide scene is the driving force of the development of complex matter in our universe.

1.1.2 Host–Guest Chemistry

Key Kyba, E.P., Helgeson, R.C., Madan, K. *et al.* (1977). Host-guest complexation. 1. Concept and illustration. *J. Am. Chem. Soc.* 99: 2564–2571.

If we regard supramolecular chemistry in its simplest sense as involving some kind of (non-covalent) binding or complexation event, we must immediately define what is doing the binding. In this context, we generally consider a molecule (a host) binding another molecule (a guest) to produce a *host–guest complex* or *supermolecule*. Commonly, the host is a large molecule or aggregate such as an enzyme or synthetic macrocycle possessing a sizeable hole or cavity. The guest may be a monatomic cation, a simple inorganic anion, an ion pair, or a more complex molecule such as a dye, analyte, hormone, pheromone, or neurotransmitter. More formally, the host is defined as the molecular entity possessing *convergent* binding sites (e.g. Lewis basic donor atoms, hydrogen bond donors, *etc.*). The guest possesses *divergent* binding sites (e.g. a spherical, Lewis acidic metal cation, a hydrogen bond acceptor anion, or a molecular guest such as the ammonium cation, NH_4^+ , with its four tetrahedrally arranged NH hydrogen bond donor functionalities). In turn, a *binding site* is defined as a region of the host or guest capable of taking part in a non-covalent interaction. The host–guest relationship has been defined by Donald Cram (another 1987 Supramolecular Chemistry Nobel Laureate)³ as follows:

Complexes are composed of two or more molecules or ions held together in unique structural relationships by electrostatic forces other than those of full covalent bonds . . . molecular complexes are usually held together by hydrogen bonding, by ion pairing, by π -acid to π -base interactions, by metal-to-ligand binding, by van der Waals attractive forces, by solvent reorganising, and by partially made and broken covalent bonds (transition states). . . High structural organisation is usually produced only through multiple binding sites. . . A highly structured molecular complex is composed of at least one host and one guest component. . . A host–guest relationship involves a complementary stereoelectronic arrangement of binding sites in host and guest. . . The host component is defined as an organic molecule or ion whose binding sites converge in the complex. . . The guest component as any molecule or ion whose binding sites diverge in the complex. . .

This description might well be generalised to remove the word ‘organic’, since extensive work since Cram’s 1977 definition has revealed a wealth of inorganic hosts, such as zeolites (Section 9.2) and polyoxometallates, or mixed metal–organic coordination compounds (e.g. Section 5.2), which perform similar functions and may be thought of under the same umbrella. The host–guest binding event may be likened to catching a ball in the hand. The hand, acting as the host, envelops the ball providing a physical (steric) barrier to dropping it (disassociation). This analogy fails at the electronic level, however, since there is no real attractive force between the hand and ball. In contrast, host and guest *molecules and ions* experience an attractive interaction between one another and hence a stabilising binding free energy. Molecular species are really very ‘sticky’ entities experiencing both specific bonding such as ionic and coordination and hydrogen bonding interactions, and more general dispersion interactions arising from mutual induced dipoles. This general mutual attraction of all matter was articulated by Aristotle in the adage *horror vacui* (Nature abhors a vacuum). The hand-in-ball analogy does serve to introduce the term *inclusion chemistry*, however (the ball is included in the hand), hence the inclusion of one molecule in another.

One key division within supramolecular host–guest chemistry in its general sense relates to the stability of a host–guest complex in solution. The field of solid-state *clathrate* chemistry, or more generally, inclusion chemistry, relates to hosts that are often only stable in the solid (crystalline) state and disassociate on dissolution in a solvent. Gas hydrates, urea clathrates, and a wide variety of crystalline solvates (Chapter 7) fall into this category. The host cavity in such systems arises as a result of the mutual packing of a number of host molecules around a solid-state void or channel. On the other hand, molecular hosts for ions such as the crown ethers, cryptands, and spherands (Chapter 3), or hosts for neutral molecules such as the carcerands and cryptophanes (Chapter 6), display significant binding in all phases of matter because the host molecules possess an *intrinsic molecular cavity*. The solid-state inclusion field dramatically predates molecular host–guest chemistry and has its origins at least as far back as Sir Humphrey Davy’s observation of chlorine clathrate hydrate in 1810. There are also purely liquid-phase phenomena, such as liquid crystals and liquid clathrates that have no direct solid-state analogies (Chapter 14).

1.1.3 Development

Supramolecular chemistry, as it is now defined, is a young discipline dating back to the late 1960s and early 1970s. However, its concepts and roots, and indeed many supramolecular systems, may be traced back almost to the beginnings of modern chemistry itself. An illustrative (although necessarily subjective and non-comprehensive) chronology is given in Table 1.1. Much of supramolecular chemistry has sprung from developments in macrocyclic chemistry in the mid-to-late 1960s, particularly the development of macrocyclic ligands for metal cations. Four systems of fundamental importance may be identified, prepared by the groups of Curtis, Busch, Jäger, and Pedersen (Figure 1.2), three of which used the Schiff base condensation reaction of an aldehyde or ketone with an amine to give an imine (Section 3.10.5). Conceptually, these systems may be seen as a development based on naturally occurring macrocycles (ionophores, porphyrins, *etc.*). To these may be added the work of Donald Cram on macrocyclic cyclophanes (which dates back to the early 1950s) and, subsequently, on spherands and carcerands, and the tremendous contribution by Jean-Marie Lehn who prepared the cryptands in the late 1960s and has since gone on to shape many developments in the field. Cram, Lehn, and Pedersen were recognised for their development of macrocyclic hosts for alkali metal cation binding by the award of the 1987 Nobel Prize in Chemistry.

As it is practised today, supramolecular chemistry is one of the most vigorous and fast-growing fields of chemical endeavour. Its interdisciplinary nature has brought about wide-ranging collaborations between physicists, theorists, and computational modellers, crystallographers, inorganic and solid-state chemists, pharmacists, synthetic organic chemists, biochemists, and biologists. Within the past two decades, supramolecular chemistry has fed into very exciting new research in nanotechnology and at the interface between the two lies the area of *nanochemistry* (Chapter 17). The field has been dramatically stimulated by remarkable developments in the production of topologically complex interlocked and knotted systems; rotaxanes, catenanes, and molecular knots starting with the high-yield template synthesis work of Jean-Pierre Sauvage and J. Fraser Stoddart in the 1980s on metal auxiliary linkage and aromatic donor–acceptor templates, respectively. Sauvage and Stoddart, along with Ben Feringa were awarded the 2016 Nobel Prize in Chemistry for their development of mechanically linked molecular machines. Stoddart in particular has done much to popularise mechanically linked molecular systems, proposing the field of *mechanostereochemistry* (Section 1.8.12 and Chapter 11) which sits in between supramolecular chemistry and chemical topology.⁴ The aesthetically pleasing nature of supramolecular compounds and the direct links established between the visualisation, molecular modelling, and practical experimental behaviour of hosts and their complexes has fuelled increasing enthusiasm in the area to the extent that it is now a full member of the pantheon of scientific disciplines.

1.2 CLASSIFICATION OF SUPERMOLECULE FORMATION

 Weber, E. (2004). Classification and nomenclature of supramolecular compounds. In: *Encyclopedia of Supramolecular Chemistry* (ed. J.L. Atwood and J.W. Steed), vol. 1, 261–273. New York: Dekker.

There are several different types of process that may be thought of as being supramolecular complex formation and it is worth explicitly making the distinction between them, particularly from the point of view of the energetic driving forces involved. In terms of the host–guest paradigm, there is a clear distinction between guest binding by a cavity-containing host which occurs typically in solution but is applicable in any phase of matter, and solid-state inclusion, or clathrate, chemistry. *Cavitands* are hosts possessing permanent intramolecular cavities. This means that the cavity available for guest binding is an intrinsic molecular property of the host and exists both in solution and in the solid state. Conversely, *clathrands* are hosts with extramolecular cavities (the cavity essentially represents a gap between two or more host molecules) and is of relevance only in the crystalline solid state. The host–guest aggregate formed by a cavitand is termed a *cavitate*, while clathrands form *clathrates*. Crucially, cavitate formation is a thermodynamically driven equilibrium binding process in which the cavitate product is more stable than the unbound species (Figure 1.3a). In contrast, clathrate formation involves a crystallisation process typically starting from a dissolved solution of host and guest (Figure 1.3b). Because crystallisation involves a phase change from solution to solid, there are considerable kinetic considerations as well as thermodynamic factors and *polymorphism* (the existence of the same molecule in more than one crystal packing arrangement) is possible. The detailed mechanism of the crystallisation process is

TABLE 1.1 Timeline of supramolecular chemistry.

1706 – Johann Jacob Diesbach: synthesis of Prussian Blue, $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3 \cdot x\text{H}_2\text{O}$ in Berlin, the first coordination polymer with a carbon-containing ligand
1756 – Swedish mineralogist Axel Fredrik Cronstedt observes that heating naturally occurring stilbite produces steam and terms the material a <i>zeolite</i> meaning ‘boiling stone’
1810 – Sir Humphry Davy: discovery of chlorine clathrate hydrate
1823 – Michael Faraday: formula of chlorine hydrate
1841 – C. Schafhäutl: study of graphite intercalates
1849 – F. Wöhler: β -quinol H_2S clathrate
1891 – Villiers and Hebd: cyclodextrin inclusion compounds
1891 – Agnes Pockles: the first surface balance, leading to the development of the Langmuir trough and the Langmuir–Blodgett technique
1893 – Alfred Werner: coordination chemistry
1894 – Emil Fischer: <i>lock and key</i> concept
1906 – Paul Ehrlich: introduction of the concept of a <i>receptor</i>
1937 – K. L. Wolf: the term <i>Übermoleküle</i> is coined to describe organised entities arising from the association of coordinatively saturated species (e.g. the acetic acid dimer)
1939 – Linus Pauling: hydrogen bonds are included in the ground-breaking book <i>The Nature of the Chemical Bond</i>
1940 – M. F. Bengen: urea channel inclusion compounds
1945 – H. M. Powell: X-ray crystal structures of β -quinol inclusion compounds; the term <i>clathrate</i> is introduced to describe compounds where one component is enclosed within the framework of another
1949 – Brown and Farthing: synthesis of [2.2]paracyclophane
1953 – Watson and Crick: structure of DNA
1956 – Dorothy Crowfoot Hodgkin: X-ray crystal structure of vitamin B_{12}
1958 – Daniel Koshland: induced fit model
1959 – Donald Cram: attempted synthesis of cyclophane charge transfer complexes with $(\text{NC})_2\text{C}=\text{C}(\text{CN})_2$
1960 – Ed Wasserman: first artificial catenane produced in just 1% yield by a statistical approach
1961 – Neil Curtis: first Schiff’s base macrocycle from acetone and ethylene diamine
1964 – Busch and Jäger: Schiff’s base macrocycles
1965 – Olga Kennard and J. D. Bernal: The Cambridge Structural Database
1967 – Charles Pedersen: crown ethers
1968 – Park and Simmons: <i>Katapinand</i> anion hosts
1969 – Jean-Marie Lehn: synthesis of the first cryptands
1969 – Jerry Atwood: liquid clathrates from alkyl aluminium salts
1969 – Ronald Breslow: catalysis by cyclodextrins
1971 – G. M. J. Schmidt: topochemistry
1973 – Donald Cram: spherand hosts produced to test the importance of preorganisation
1978 – Jean-Marie Lehn: introduction of the term ‘supramolecular chemistry’, defined as the ‘chemistry of molecular assemblies and of the intermolecular bond’
1979 – Gokel and Okahara: development of the lariat ethers as a subclass of host
1981 – Vögtle and Weber: podand hosts and development of nomenclature

(Continued)

TABLE 1.1 (Continued)

1984 – Dietrich-Buchecker, Sauvage, and Kern: auxiliary linkage template synthesis of a catenate – the first high-yield synthesis of topologically interlocked molecules
1986 – A. P. de Silva: fluorescent sensing of alkali metal ions by crown ether derivatives
1987 – Award of the Nobel Prize in Chemistry to Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen for their work in supramolecular chemistry
1987 – Ripmeester, Tse, Ratcliffe, & Powell: structure H clathrate hydrate
1989 – Hoskins & Robson: designed coordination polymers
1989 – J. Fraser Stoddart: the first electron donor–acceptor template [2]catenane synthesis; the ‘blue box’
1989 – Dietrich-Buchecker and Sauvage: the first molecular knot (a trefoil)
1989 – G. M. Whitesides: self-assembled thiol monolayers on gold
1994 – M. Brust: thiol-stabilised gold nanoparticles
1995 – Makoto Fujita: first self-assembled hollow container compound (using the semi-labile palladium(II) ethylene diamine fragment)
1995 – Gautam Desiraju: supramolecular synthon approach to crystal engineering
1996 – J. K. M. Sanders: first dynamic combinatorial chemistry system
1998 – A. Rowan and R. Nolte: helical supramolecular polymers from self-assembly
1999 – Ben L. Feringa: light-driven monodirectional molecular rotor
1999 – Omar Yaghi: synthesis of MOF-5, the first robust, porous metal–organic framework
2004 – J. Fraser Stoddart: the first discrete Borromean-linked molecule
2012 – David Leigh: metal-directed synthesis of a pentafoil knot, the first chemical knot synthesis more complicated than the simplest knot, the trefoil
2016 – Award of the Nobel Prize in Chemistry to J. Fraser Stoddart, Jean-Pierre Sauvage, and Ben Feringa for their design and production of molecular machines

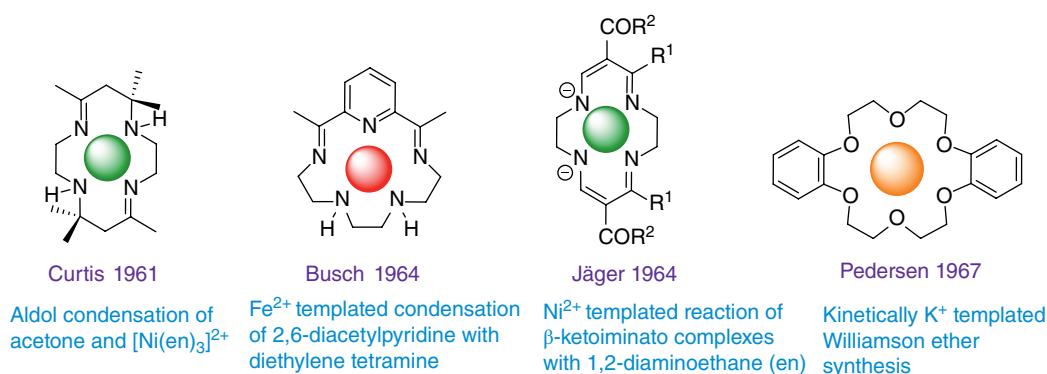


FIGURE 1.2 Important early macrocyclic complexes.

discussed in Chapter 8 but the key point is that a solid-state clathrate is not necessarily the most thermodynamically stable arrangement of the host and guest. In addition, clathrates can also differ from cavitates in that not every cavity in a clathrate is always occupied, and hence clathrates can be non-stoichiometric.

A further fundamental subdivision in host–guest compounds may be made on the basis of the bonding between the host and guest. If the host–guest aggregate is held together by primarily electrostatic interactions (including ion–dipole, dipole–dipole, hydrogen bonding, *etc.*), the term *complex* is used. On the other hand, species held together by less specific (often weaker), non-directional interactions, such as hydrophobic, van der Waals. or crystal close-packing

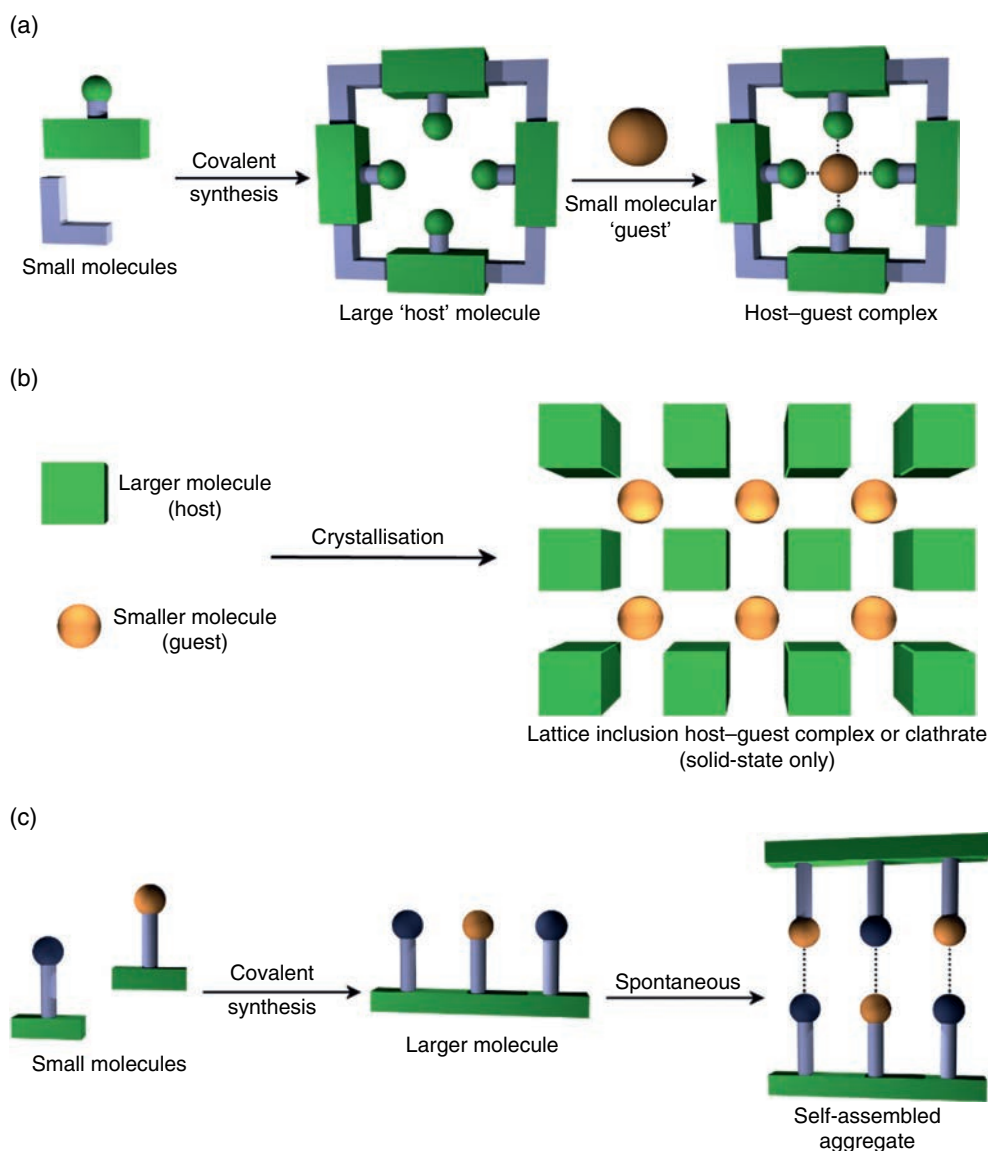


FIGURE 1.3 Types of supramolecular assembly process. (a) Synthesis and guest binding by a molecular host with an intrinsic central void to give a complex or cavitate by inclusion of a guest into the host cavity; complexes are typically bound by ion-dipole interactions while cavitates exhibit weaker van der Waals-type inclusion. (b) Inclusion of guest molecules in cavities formed by the crystal packing of host molecules (clathrands) in the solid state to give a solid-state clathrate or lattice inclusion complex. (c) Synthesis of a molecule containing a number of binding sites that undergoes spontaneous self-assembly into a supramolecular aggregate in which there is no classical host-guest relationship (spheres represent binding sites).

effects, are referred to by the terms *cavitate* and *clathrate*. The distinctions between these classes are blurred and often the word 'complex' is used to cover all these phenomena. Within these broad classifications, intermediate types exist; indeed, it is often very much a matter of opinion as to exactly what the classification of a given material might be.

In addition to the host-guest complexes, cavitates, and clathrates depicted in Figure 1.3a, b, we can also distinguish a third situation in which two molecules associate using non-covalent forces but do not fit the descriptions of 'host' and 'guest'. Under these circumstances, we talk about the self-assembly of a mutually complementary pair (or series) of molecules. *Strict self-assembly* is thermodynamically driven and the resulting aggregate is a thermodynamic product (Figure 1.3c). However, self-assembled materials such as gels, liquid crystals, and supramolecular polymers may also be regarded as undergoing a phase change as part of the assembly process and kinetic factors also play a significant role under these circumstances. Unlike host-guest chemistry in which there are always at

least two chemically distinct entities (the host and the guest), self-assembly can involve just one type of molecule. The crystallisation process is sometimes talked of as being a self-assembly process but because of the kinetic and thermodynamic complexities of crystal nucleation and growth, crystallisation is not strict self-assembly by any means.

To complicate matters yet further, even the apparently straightforward complexation of a guest by a cavitand host in solution can deviate from thermodynamic control in cases such as the *carcerands* and *hemicarcerands* where the guest is sterically or mechanically trapped within the host and thermodynamic equilibrium is never established on any meaningful time scale. Such trapped systems involve what is termed *constrictive binding* (Section 6.7). Guest inclusion is either fixed at the time of synthesis (carcerands) or, by heating the host in the presence of the guest. Upon cooling, the guest becomes sterically trapped within the host (hemicarcerands). This kind of constrictive binding is linked to the concept of *mechanical bonding* in rotaxanes, catenanes, and knots (Chapter 11) in which one molecule is threaded through another at the time of synthesis and the individual molecules cannot be separated without breaking a covalent bond.

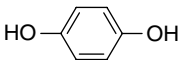
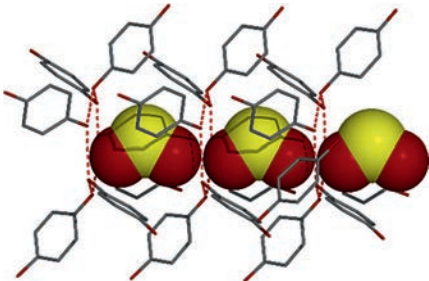
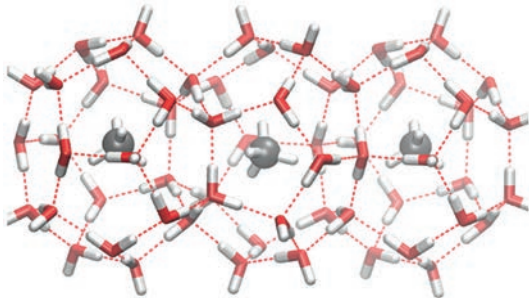
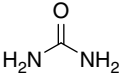
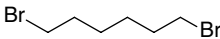
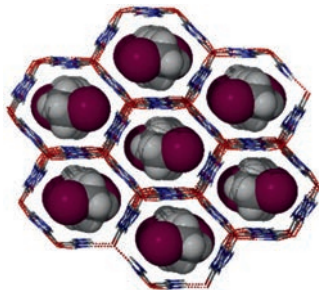
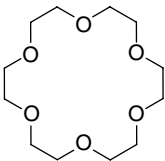
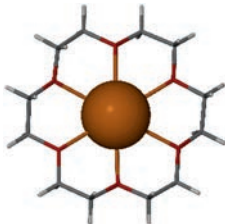
Some fundamental examples of each type of supramolecular construct are shown in Table 1.2. Table 1.2a shows a clathrate of the host hydroquinone forming a hydrogen-bonded solid encasing a cavity that can hold small molecule guests such as methanol, SO_2 , and H_2S . The term *clathrate* to describe a supramolecular cage-like host-guest structure was proposed by H. M. Powell at the University of Oxford in 1948.⁵ Powell defined a clathrate as a kind of inclusion compound ‘in which two or more components are associated without ordinary chemical union, but through complete enclosure of one set of molecules in a suitable structure formed by another’. The term comes from the Latin *clathratus* meaning ‘to fit with bars’ and the imprisoned nature of the SO_2 guest within the hydroquinone cage is evident from Table 1.2a. The 3 : 1 ideal stoichiometry of the sulfur dioxide hydroquinone clathrate $[\text{C}_6\text{H}_4(\text{OH})_2]_3 \cdot \text{SO}_2$ is apparent from the observation that each cage contains a single SO_2 molecule and is made up of a total of six hydroquinone walls with each hydroquinone being shared between two such cages. Real samples can deviate significantly from this ideal 3 : 1 ratio, however, because not every cage is always occupied. The formation of the hydroquinone sulfur dioxide clathrate is immediately visually apparent because of its yellow colour which arises from charge transfer interactions between the electron-rich hydroquinone and electron-deficient sulfur dioxide guest.¹⁵

Similarly, clathrate hydrates (Section 7.3) arise from the trapping of a small molecule guest such as a hydrocarbon, CO_2 , or H_2S within a cage of water molecules, Table 1.2b.^{6, 16} The cage-like arrangement in hydroquinone and hydrate clathrates contrasts to more open channel-type geometries such as those formed by urea. Mutual hydrogen bonding of urea molecules gives rise to a hexagonal network of channels through which guests can often move quite freely.⁸ While the urea structure is not stable in the absence of guest, guests can be exchanged with retention of the urea host crystalline structure. While these species are also clathrates as opposed to cavitands or strongly bound complexes, they are often referred to as *inclusion compounds*.

The stronger ion-dipole interactions in alkali metal complexes of the crown ethers (Section 3.3) means that they are examples of supramolecular complexes,⁹ Table 1.2d. In contrast, the weaker van der Waals interactions between cyclodextrins (Section 6.3) and neutral molecular guests mean that they are of the cavitare type. A great deal of cyclodextrin chemistry involves solid-state crystalline compounds, however, so it is not uncommon to see cyclodextrin supermolecules referred to as clathrates, despite the fact that the host possesses an intrinsic cavity and is capable of solution guest complexation. Table 1.2e shows the β -cyclodextrin cavitare of benzamide. While the small aromatic guest is included in the cavity only *via* weak dispersion-type interactions, the amide group protrudes from the primary hydroxyl side of the host and forms a hydrogen bond with an adjacent β -cyclodextrin molecule.¹⁰ The solid-state structure also has a claim to be regarded as a clathrate since it exists as a hexahydrate.

Both coordination complexes of the type shown in Table 1.2f and the important biomolecule DNA (Table 1.2g) are examples of thermodynamically driven self-assembly. In the case of the square planar Pd^{II} tetramethylethylenedimine complex and 4,4'-bipyridine, the square assembly is the only one which satisfies the 90° bond angle at the metal and 180° angle at the ligand and does not leave any uncoordinated sites.¹¹ In the case of two complementary DNA oligonucleotide strands, the combination of hydrogen-bonded base pairing and π - π stacking make the double helical structure the most stable under ambient conditions (see Section 2.8).¹² The example in Table 1.2h involves a tetrachloroethane guest trapped within a hemicarcerand host (Section 6.7). There is a clear host-guest relationship in that the guest is

TABLE 1.2 Examples of different types of supramolecular assembly. (a) The hydroquinone sulfur dioxide clathrate. The material only persists in the solid state and involves trapping SO_2 within cages formed by hexagonally hydrogen bonded hydroquinone molecules.⁵ (b) Methane is included within the void space left by hydrogen-bonded water molecules in a clathrate hydrate.⁶ (c) A rare crystallographically ordered channel inclusion compound of urea.⁷ Often in urea inclusion compounds, guests are highly disordered and move freely.⁸ (d) Strong binding of K^+ by [18]crown-6 to give a crown ether complex.⁹ (e) Inclusion of benzamide within the cavity of β -cyclodextrin cavitate.¹⁰ (f) Self-assembled molecular square based on square planar Pd^{II} tetramethylethylenediamine (tmen) corners and 4,4'-bipyridyl edges.¹¹ (g) DNA nucleobase pairing to give a self-assembled double helix.¹² (h) Hemicarceplex in which a large hollow covalent cavity sterically traps a guest molecule.¹³ (i) Mechanically bonded [2]rotaxane formed by adding bulky triphenylphosphonium stoppers to an intermediate host-guest complex.¹⁴

Host and guest	Interactions and type	Structure
a Hydroquinone and SO_2 	Van der Waals and charge transfer Clathrate	
b Water and methane 	Van der Waals Clathrate	
c Urea and 1,6-dibromohexane  	Van der Waals Clathrate (channel inclusion compound)	
d [18]crown-6 and K^+ 	Ion-dipole complex	

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TABLE 1.2 (Continued)

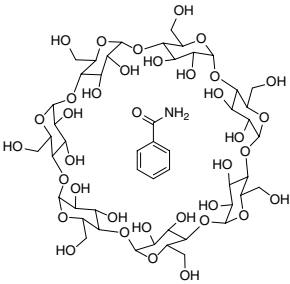
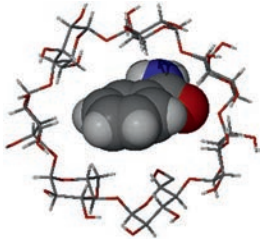
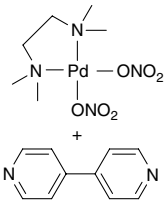
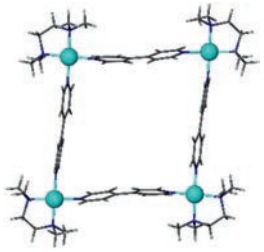
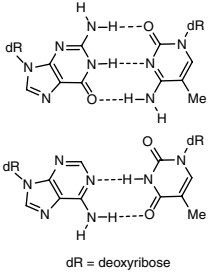
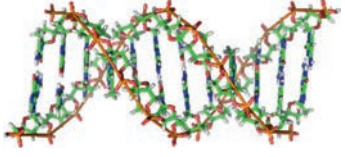
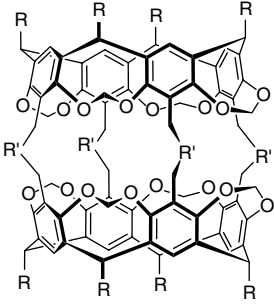
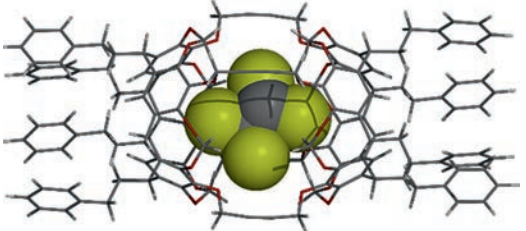
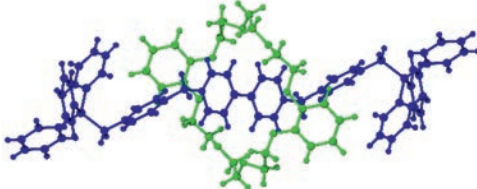
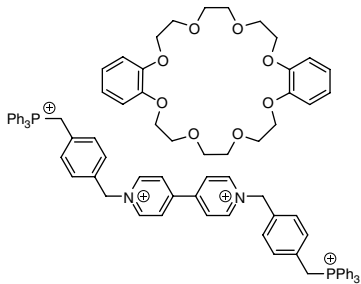
Host and guest	Interactions and type	Structure
e β -Cyclodextrin and benzamide 	Van der Waals Cavitare	
f $[\text{Pd}(\text{tmen})(\text{NO}_3)_2]$ and 4,4'-bipyridine 	Dative bond (ion-dipole with significant covalent contribution) Self-assembly	
g DNA  dR = deoxyribose	Hydrogen bonding and π - π stacking Self-assembly	
h Hemiacarcerand and 1,1,2,2-tetrachloroethane  $R = \text{CH}_2\text{CH}_2\text{Ph}$ $R' = \text{CH}_2\text{CCl}_2\text{CH}_2$ 	Constrictive binding Hemiacerplex	

TABLE 1.2 (Continued)

Host and guest	Interactions and type	Structure
i Dibenzo[24]crown-8 and bistriphenylphosphonium-4, 4'-bipyridinium axel	Mechanical bond Rotaxane	
		

included with the spherical host cavity, but unlike conventional cavitands, the guest cannot escape because of the small size of the apertures.¹³ The guest is retained even when the alkyne linkers between the two hemispheres of the hemicarcerand are chemically reduced to butylene groups and so the compound is a *hemicarceplex*. Finally, the rotaxane shown in Table 1.2i is formed by capping in intermediate host–guest complex (a *pseudorotaxane*) of dibenzo[24]crown-8 with a bromomethyl viologen precursor. The pseudorotaxane is a conventional host–guest complex with a measurable binding constant of around 100 M^{-1} in acetonitrile, with the guest bound by aromatic stacking and $\text{CH}\cdots\text{O}$ hydrogen bonding. Capping with the bulky triphenylphosphonium stopper gives a mechanically bonded rotaxane because the stopper is too large to fit through the crown ether ring.¹⁴

1.3 RECEPTORS, COORDINATION, AND THE LOCK AND KEY ANALOGY

1.3.1 Historic Milestones

 Behr, J.P. (1994). *The Lock and Key Principle. The State of the Art – 100 Years on*. New York: Wiley.

Host–guest (or receptor–substrate) chemistry is based upon three key historical concepts first articulated by three key figures of early chemistry (Figure 1.4).

1. The recognition by Paul Ehrlich in 1906 that molecules do not act if they do not bind, ‘*Corpora non agunt nisi fixata*’; in this way Erlich introduced the concept of a biological receptor.
2. The recognition in 1894 by Emil Fischer that binding must be selective, as part of the study of receptor–substrate binding by enzymes. He described this by a *lock and key* image of steric fit in which the guest has a geometric size or shape complementarity to the receptor or host (Figure 1.5a). This concept laid the basis for *molecular recognition*, the discrimination by a host between several different guests.
3. The fact that selective binding must involve *attraction* or mutual affinity between the host and guest. This is, in effect, a generalisation of Alfred Werner’s 1893 theory of coordination chemistry, in which metal ions are coordinated by a regular polyhedron of ligands binding by dative bonds.

These three concepts arose essentially independently of one another and it was to be many years before the various disciplines in which they were born grew together to give birth to the highly interdisciplinary field of supramolecular chemistry. Ehrlich was working on the treatment of a range of infectious diseases. As part of his work he noticed that the dye methylene blue has a surprising affinity for some living cells, staining them an intense blue (his

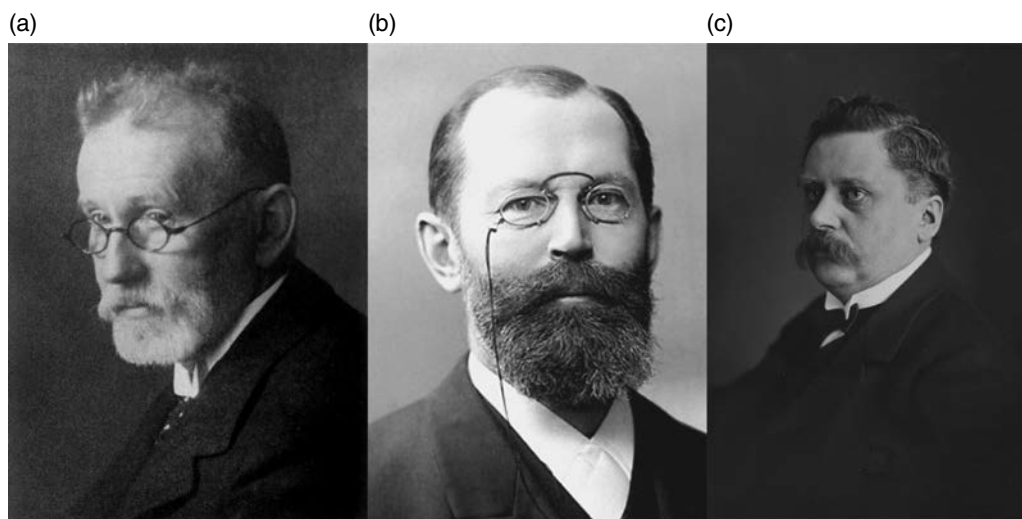


FIGURE 1.4 (a) Paul Erlich (1854–1915) recipient of the 1908 Nobel Prize in Physiology or Medicine, (b) Hermann Emil Louis Fischer (1852–1919) recipient of the 1902 Nobel Prize in Chemistry, (c) Alfred Werner (1866–1919) recipient of the 1913 Nobel Prize in Chemistry. Image courtesy of ETH-Bibliothek Zürich, Bildarchiv.

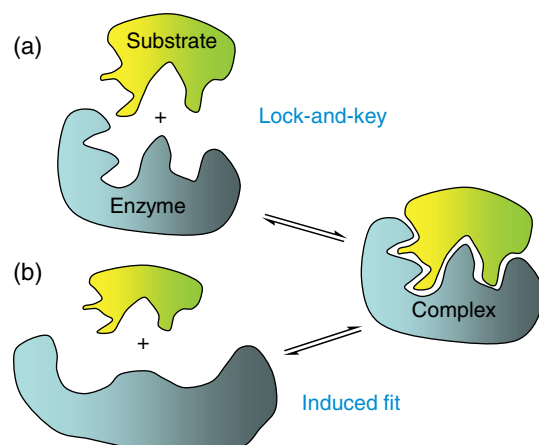


FIGURE 1.5 (a) Rigid lock and key and (b) induced fit models of enzyme–substrate binding.

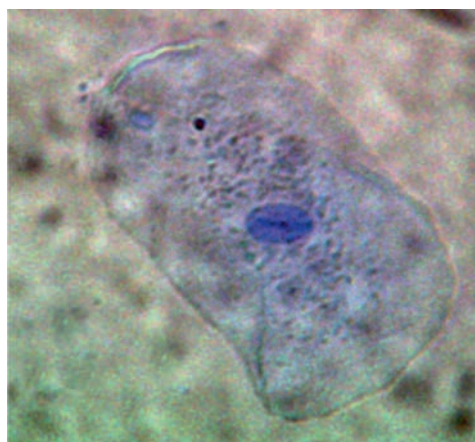
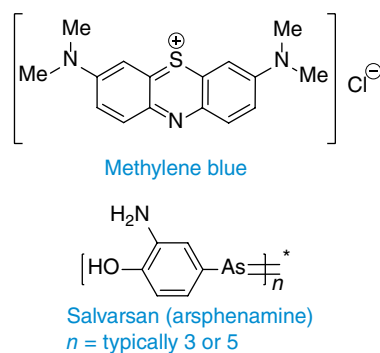


FIGURE 1.6 Structures of methylene blue and salvarsan along with a cell from the mucous membrane of a human mouth stain *in vivo* with methylene blue.

tutor Robert Koch had used methylene blue to discover the tubercle bacillus, and Ehrlich had a ready supply of this synthetic dye from Farbwerke Hoechst, who had been manufacturing it since 1885), Figure 1.6. ‘If only certain cells are coloured’, reasoned Ehrlich, ‘then may there not be dyestuffs which colour only the carriers of illnesses and at the same time destroy them without attacking the body’s own cells?’ Ehrlich eventually went on to develop the arsenic-based anti-syphilis drug Salvarsan (arsphenamine) in 1910,¹⁷ one of the most effective drugs known for that disease. In the process, he became the founder of modern chemotherapy.

Emil Fischer published the Lock and Key theory in a famous 1894 article in *Chemische Berichte* with the title ‘Einfluß der Konfiguration auf die Wirkung der Enzyme’ (Effect of Configuration on the Activity of Enzymes). Fischer carried out a range of experiments on enzyme specificity which ultimately led him to conclude: ‘To use a metaphor, I would say that enzyme and substrate must fit together like lock and key in order to exert a chemical effect on each other. In any case, this notion becomes more likely and its value for stereochemical research increases when the phenomenon itself is transferred from the biological to the chemical realm’.¹⁸ Fischer’s work was revolutionary because it reduced biology to chemistry at the molecular level and implied that the substances of life itself fit together like a lock and key.

Alfred Werner won the 1913 Nobel Prize in Chemistry for his theory of coordination chemistry, proposing specifically that the metal complex $\text{CoCl}_3 \cdot 6\text{NH}_3$ involved a central Co^{III} ion octahedrally coordinated to six ammonia ligands with the chloride ions in the second coordination sphere. This results in a 3 : 1 electrolyte, which Werner confirmed by conductivity measurements. Prior to Werner’s time, the *chain theory* of coordination compounds proposed by Swedish chemist Christian Wilhelm Blomstrand was popular. The chain and Werner formulations of ‘ $\text{Co}(\text{NH}_3)_4\text{Cl}_3$ ’ and ‘ $\text{Co}(\text{NH}_3)_3\text{Cl}_3$ ’ are shown in Figure 1.7. While both theories predict that ‘ $\text{Co}(\text{NH}_3)_4\text{Cl}_3$ ’ will exhibit one labile (kinetically reactive) chloride ion per molecule, the chain theory also predicts that ‘ $\text{Co}(\text{NH}_3)_3\text{Cl}_3$ ’ will have one labile chloride, while Werner’s theory correctly predicts that the chloride is not labile in this case because it is directly coordinated to the inert Co^{III} centre. Werner’s model also explained the existence of the green *trans* and purple *cis* isomers of $[\text{Co}(\text{NH}_3)_4\text{Cl}_2]\text{Cl}$.¹⁹

The marrying of the fields of coordination chemistry, chemotherapy, and enzymology was finally spurred on by the advent of modern instrumental and synthetic techniques, and not least by the dramatic developments in organic synthesis, which was itself born as a discipline in 1828 with Friedrich Wöhler’s synthesis of urea from silver cyanate and ammonium chloride.* In the course of the development of supramolecular chemistry, enormous progress has been made on quantifying the factors that govern the affinity of a receptor for a particular guest. The lock and key

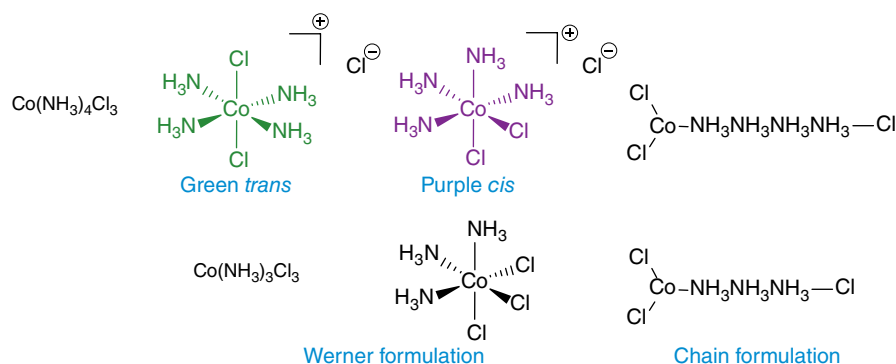


FIGURE 1.7 Werner and historical chain formulations of ‘ $\text{Co}(\text{NH}_3)_4\text{Cl}_3$ ’ and ‘ $\text{Co}(\text{NH}_3)_3\text{Cl}_3$ ’. Werner’s theory correctly predicts that $[\text{Co}(\text{NH}_3)_3\text{Cl}_3]$ will not possess any labile chloride ions in contrast to $[\text{Co}(\text{NH}_3)_4\text{Cl}_2]\text{Cl}$ in which one chloride ion is not coordinated to the metal centre. It also explains the isomerism of this complex. The chain theory does not distinguish between the chloride ions in the two isomers.

*The synthesis of urea, a biomolecule, from inorganic precursors was a fundamental shock to the prevailing theory of *vitalism* which held that ‘living organisms are fundamentally different from non-living entities because they contain some non-physical element or are governed by different principles than are inanimate things’. This led Wöhler to write to Berzelius ‘I cannot, so to say, hold my chemical water and must tell you that I can make urea without thereby needing to have kidneys, or anyhow, an animal, be it human or dog’ (Wöhler, F. (1828). ‘Ueber künstliche Bildung des Harnstoffs’ (On the artificial formation of urea), *Annalen der Physik und Chemie* 88: 253–256.).

image especially has suffered successive waves of modification by the concepts of cooperativity, preorganisation and complementarity, solvation, and the very definition of ‘molecular shape’ as we will see in the following sections. In particular, in enzyme catalysis, the lock-and-key image has been replaced by the *induced fit* model of Daniel Koshland²⁰ in which both enzyme and substrate (host and guest) undergo significant conformational changes upon binding to one another (Figure 1.4b). It is these conformational changes that allow the enzymatic catalytic rate acceleration since the substrate is more like the reaction transition state in its bound form than in its unbound form, a concept termed the *entatic state*. The occurrence of a conformational change upon guest binding is in fact a very common phenomenon both in biological chemistry, where it lies at the heart of ‘trigger’ processes such as muscle contraction and synaptic response, and in supramolecular chemistry.

1.3.2 Macrocycles

Key Liu, Z.C., Nalluri, S.K.M., and Stoddart, J.F. (2017). Surveying macrocyclic chemistry: from flexible crown ethers to rigid cyclophanes. *Chem. Soc. Rev.* 46: 2459–2478.

A great deal of supramolecular chemistry has involved the use of macrocyclic receptors to bind selectively to particular guests. A macrocycle is a large ring molecule comprising typically more than about 12 atoms. The preorganisation and reduced binding site solvation of macrocycles lead to significantly stronger and selective guest binding in comparison to acyclic analogues. As a result, there are certain key macrocyclic components that crop up time and time again in both natural and artificial supramolecular systems. In Table 1.3, we give a brief introduction to some of the more common cyclic scaffolds. We will return to many of these classic receptors in more detail in subsequent chapters but for now it is worth bearing these very well-known systems and their basic properties in mind.

1.4 BINDING CONSTANTS

1.4.1 Definition and Use

Key Connors, K.A. (1987). *Binding Constants*. Chichester: Wiley.

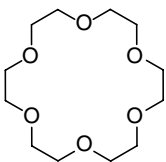
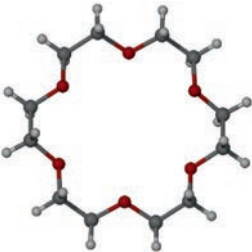
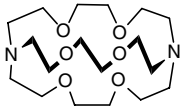
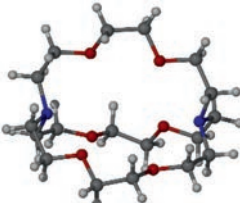
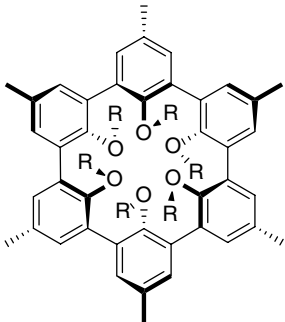
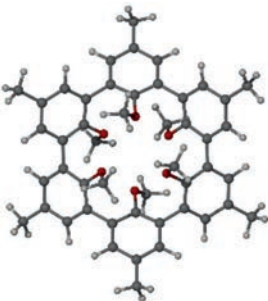
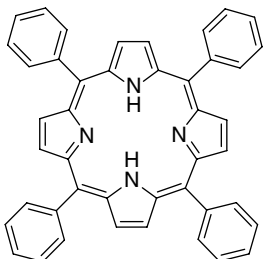
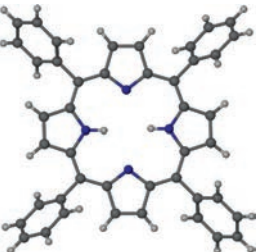
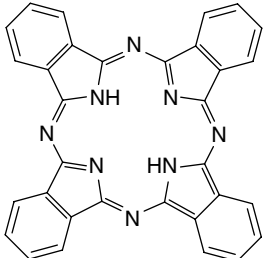
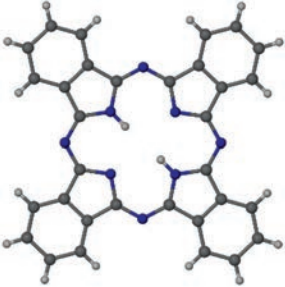
The thermodynamic stability of a host–guest (e.g. metal–macrocycle) complex in a given solvent (often water or methanol) at a given temperature is gauged by measurement of the thermodynamic binding constant, K . Strictly the binding constant is dimensionless, but it is often calculated approximately using concentrations and thus has units of $\text{dm}^3 \text{mol}^{-1}$, or M^{-1} , for a 1 : 1 complex. The binding constant is also known by the terms formation constant, K_f , association constant, K_a , or stability constant, K_s . In biological systems, the dissociation constant, K_d , is commonly used. This quantity is the reciprocal of the binding constant and has units of concentration. The K_d value is rather more intuitive because it is a direct measure of the concentration below which a complex such as a drug–receptor complex will dissociate. The binding constant is the main method by which host–guest affinity in solution is assessed and so is of fundamental importance in supramolecular chemistry. Ignoring activity effects, the binding constant (Equation 1.2) is merely the equilibrium constant for the reaction shown in Equation 1.1 (e.g. between a metal, M, and host ligand, L, in water):



$$K = \frac{[\text{ML}^{m+}]}{[\text{M}(\text{H}_2\text{O})_n^{m+}][\text{L}]} \quad (1.2)$$

Thus, a large binding constant corresponds to a high equilibrium concentration of bound metal or guest, and hence a more stable metal–macrocycle complex. Typical binding constants for crown ethers and alkali metal cations

TABLE 1.3 Discovery and properties of key macrocyclic receptors.

Name and example	Structure	Comments
Crown ether  [18]Crown-6		Discovered by Charles Pedersen in 1968. ²¹ Complexation of hard metal ions such as the alkaline and alkaline earths. Number in parentheses indicates the ring size, second number gives the number of oxygen donor atoms.
Cryptand  [2.2.2]Cryptand		Discovered by Jean-Marie Lehn in 1969. ²² Strongly preorganised binding of alkali metal ions. The numbers in parentheses indicate the number of oxygen donor atoms in each strand.
Spherand  Spherand-6		Discovered by Donald Cram in 1981. ²³ Near-perfect preorganisation for Li ⁺ complexation.
Porphyrin  Tetraphenylporphyrin		First prepared by Johann Ludwig Wilhelm Thudichum in 1867 (hematoporphyrin). ²⁴ Key biomolecule component found in systems such as haemoglobin and chlorophyll. Aromatic with 18 π -electrons in a continuous planar cycle (out of 26). Significant redox activity. Binds strongly to metal cations typically in the double deprotonated state.
Phthalocyanine 		First reported as an unknown blue material by Braun and Tcherniac in 1907 from the reaction of phthalamide with acetic anhydride. ²⁵ Important pigment. Metal complexes are important in catalysis, organic solar cells, and photodynamic therapy.

(Continued)

TABLE 1.3 (Continued)

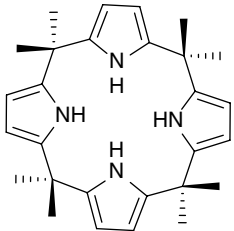
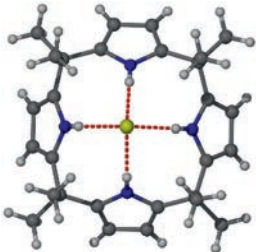
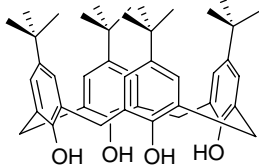
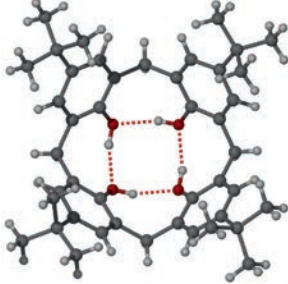
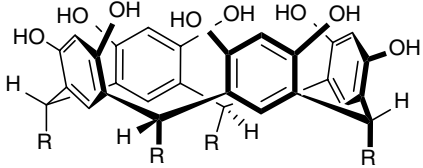
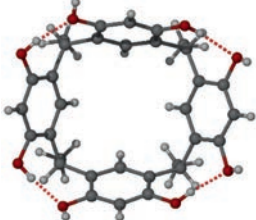
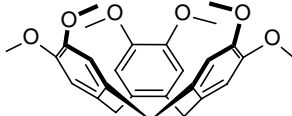
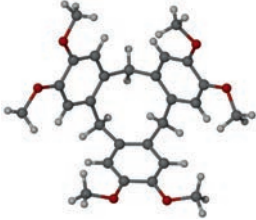
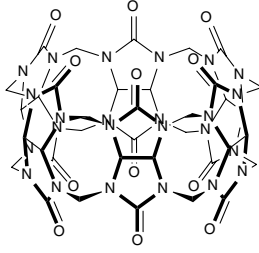
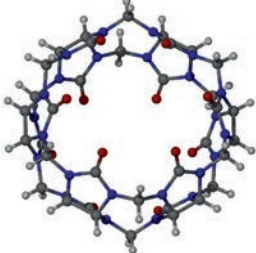
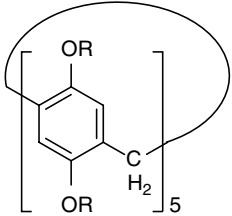
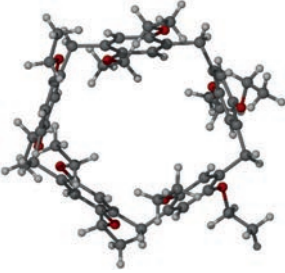
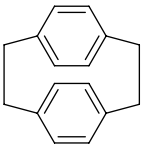
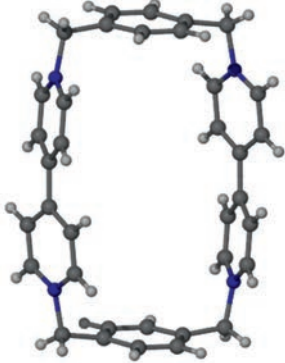
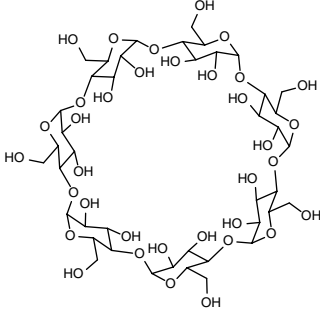
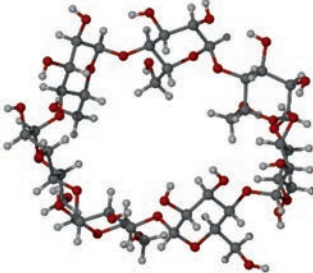
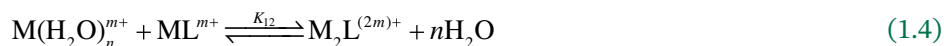
Name and example	Structure	Comments
Calixpyrrole (porphyrinogen)  Calix[4]pyrrole·Cl ⁻		First discovered by Adolph von Bayer in 1886 from the acid-catalysed condensation of pyrrole with acetone. Key anion binding receptor popularised from 1996 onwards by Gale, Sessler, and co-workers. ²⁶
Calixarene  <i>p-t</i> -Butylcalix[4]arene		Discovered by Alois Zinke in 1941 from the base-catalysed condensation of substituted phenol and formaldehyde. Popularised by C. David Gutsche in the 1970s initially as scaffolds for enzyme mimics. ²⁷
Resorcarene  [4]Resorcarene		Initially discovered by Adolph von Bayer in 1872 from the reaction of aldehydes with resorcinol. Properly identified by Neiderl and Vogel in 1940. Core component of hemicarcerands.
Cyclotrimeratrylene 		First synthesised by Gertrude Robinson in 1915 but misassigned as a dimer. The correct structure was identified by Lindsey in 1965. ²⁸ Shallow cavity and the key component of cryptophanes.
Cucurbituril  Cucurbit[6]uril		First synthesised in 1905 by Robert Behrend, by condensing glycoluril with formaldehyde and fully characterised in 1981. ²⁹ Versatile building block forming rotaxane-type structures by threading guests through the ring.

TABLE 1.3 (Continued)

Name and example	Structure	Comments
Pillararene  Pillar[5]arene		Discovered in 2008 by Tomoki Ogoshi. ³⁰ The number in parentheses refers to the number of aromatic units. Used in the complexation of hydrophobic guests. Pillararenes are planar chiral and higher homologues with up to 10 aromatic residues are known. Highly topical receptors for molecular guests.
Cyclophane  [2.2]Paracyclophane	 	General term for a bridged aromatic ring. The numbers in parentheses refer to the number of atoms in each bridge. [2.2]Paracyclophane was first reported in 1949 ³¹ and the cyclophane name in 1951. ³² The most famous cyclophane is the 'blue box', first reported by J. Fraser Stoddart in 1988. ³³ It is a host for electron-rich guest binding by charge transfer and aromatic stacking interactions and is a key component of many mechanically bonded systems. The blue colour is Stoddart's code for electron-deficient components.
Cyclodextrin  β-Cyclodextrin		Derived from enzymatic degradation of starch. Discovered by Antoine Villiers in 1891. ³⁴ Encapsulation of a variety of molecular guests. Applications as food additives, in analytical chemistry and as enzyme mimics.

in water are in the range 10^1 – 10^2 . In methanol, this increases up to 10^6 for $[K([18]\text{crown-6})]^+$.[†] The binding constant in methanol for K^+ and [2.2.2]cryptand is about 10^{10} . Because the binding constant value depends strongly upon conditions, particularly solvent, it is vitally important to state the conditions of the measurement when quoting binding constant values and to ensure that any comparison between binding constants involves measurements under the same circumstances (solvent, temperature, concentration range, *etc.*)

If a sequential process involving the binding of more than one metal ion is involved, then two K values may be measured for the 1 : 1 and 1 : 2 complexes, respectively: K_{11} and K_{12} (e.g. binding of two Na^+ ions by dibenzo[30]crown-10).



$$K_{12} = \frac{[\text{M}_2\text{L}^{(2m)+}]}{[\text{M}(\text{H}_2\text{O})_n^{m+}][\text{ML}^{m+}]} \quad (1.5)$$

In these circumstances, an overall binding constant, β_{12} may be defined for the overall process, the individual K values are then known as the stepwise binding constants:

$$\beta_{12} = K_{11} \times K_{12} \quad (1.6)$$

Or, more generally,

$$\beta_{xn} = \frac{[\text{M}_x\text{L}_n]}{[\text{M}]^x[\text{L}]^n} \quad (1.7)$$

Magnitudes of binding constants can vary widely, so they are often reported as $\log K$, hence:

$$\log \beta_{12} = \log(K_{11} \times K_{12}) = \log K_{11} + \log K_{12} \quad (1.8)$$

The subscript numbers in stepwise binding constant notation refer to the ratio of one complexing partner to another, thus in a multistep process the association of the host with the first guest might be denoted K_{11} , while the association of the resulting 1 : 1 complex with a further guest to produce a 1 : 2 complex has an equilibrium constant K_{12} , *etc.* Strictly speaking, it is only possible to take a logarithm of a dimensionless quantity (*i.e.* logs can only come from a number, not something with units) but we must remember that the strict definition of a binding constant is based on the activities of the chemical species, not their concentrations. The activity (a) of a chemical species, i , is its effective concentration for the purposes of mass action, $a_i = \gamma_i C_i / C_\ominus$ where C_i is the concentration of i , $C_\ominus$ is equal to 1 mol dm^{-3} if C_i is given in mol dm^{-3} , and γ_i is the *activity coefficient*, a factor that accounts for deviations from ideal behaviour. In approximate assessment of binding constants in supramolecular chemistry, we make the approximation that $\gamma_i = 1$ and, activity (dimensionless) $\approx$ concentration.

Because binding constants are thermodynamic parameters, they are related to the free energy of the association process according to the Gibbs equation: $\Delta G^\ominus = -RT \ln K$ (R = gas constant, $8.314 \text{ J K}^{-1} \text{ mol}^{-1}$, T = temperature in

[†] Take care with square brackets. In equations, square brackets are used to denote ‘concentration of’, however, coordination chemists also use square brackets to denote a coordination complex ion, thus in a mathematical equation ‘ $[\text{ML}^{m+}]$ ’ means the ‘concentration of the chemical species ML^{m+} ’. If ML^{m+} is a coordination complex ion, then the charge should be written outside an equation ‘ $[\text{ML}]^{m+}$ ’, *i.e.* a chemical entity comprising a metal of charge $m+$ and a ligand, L . The square brackets are useful because they always denote the ligands directly bound to the metal so, for example, $[\text{Co}(\text{1,2-diaminoethane})_2\text{Cl}_2]\text{Br}$ contains two Cl^- ligands bound to Co^{III} with a bromide counter anion balancing the overall charge, whereas $[\text{Co}(\text{1,2-diaminoethane})_2\text{ClBr}]\text{Cl}$ contains both Co-Cl and Co-Br bonds and an unbound chloride counter anion.

TABLE 1.4 Binding constants for a range of complexation processes.

Guest	Host	Solvent	K_{11} (M^{-1})	ΔG° ($kJ\ mol^{-1}$)
Na^+	ClO_4^-	H_2O	3.2	-3
Iodine	Hexamethylbenzene	CCl_4	1.35	-0.8
Tetracyanoethylene	Hexamethylbenzene	CH_2Cl_2	17	-7.1
7,7,8,8-Tetracyanoquinodimethane	Pyrene	CH_2Cl_2	0.94	~0.0
Salicylic acid	Caffeine	H_2O	44	-9.7
Hydrocortisone	Benzoate ion	H_2O	2.9	-2.5
Methyl <i>trans</i> -cinnamate	Imidazole	H_2O	1.0	~0.0
<i>p</i> -Hydroxybenzoic acid	α -Cyclodextrin	H_2O	1130	-17.6
Caffeine	Caffeine	H_2O	19	-7.1
Phenol	Dimethylformamide	C_6H_6	442	-15.0
K^+	[18]Crown-6	H_2O	100	-11.4
K^+	[18]Crown-6	Methanol	10^6	-34.2
K^+	[2.2.2]Cryptand	Methanol	10^{10}	-57.0
Fe^{3+}	Enterobactin	H_2O	10^{52}	-296

Kelvin). Thus, the general affinity of a host for a guest under specific conditions (solvent, temperature, *etc.*) may be given either in terms of K or $-\Delta G^\circ$ values. In energy terms, complexation free energies may range from magnitudes of 20 to 100 $kJ\ mol^{-1}$ (5–25 $kcal\ mol^{-1}$; 1 $kJ = 4.184\ kcal$) for alkali metal cation complexes. A large K value of about 10^{10} corresponds to a $-\Delta G^\circ$ of about 57 $kJ\ mol^{-1}$ (13 $kcal\ mol^{-1}$). Some very general examples of the magnitudes of binding constants and their corresponding complexation free energies are given in Table 1.4.

Binding constants may also be defined in terms of the rate constants (k) of the complexation and decomplexation reactions:



$$K = \frac{k_1}{k_{-1}} \quad (1.10)$$

In systems exhibiting 1 : 2 binding stoichiometry in the absence of any positive or negative cooperativity (Section 1.5.3), this dependence on rate results in the statistical relationship $K_{11} = 4K_{12}$. This is because, given the existence of two possible binding sites in the host, there are two ways for the first guest to bind and hence the rate of 1 : 1 complexation appears twice as fast as in a host with a single binding site. Similarly, in the fully bound 1 : 2 complex there are two ways that the second guest can decomplex making the reverse rate constant also appear twice as fast.

1.4.2 Measurement of Binding Constants

Key Thordarson, P. (2011). Determining association constants from titration experiments in supramolecular chemistry. *Chem. Soc. Rev.* 40: 1305–1323.

In principle, binding constants may be assessed by any experimental technique that can yield information about the concentration of a host–guest complex, $[H \cdot G]$, as a function of changing concentration of the host or guest. While in biochemistry it is sometimes possible to directly measure $[H \cdot G]$, this is rarely true in supramolecular chemistry with the exception of species in slow exchange by NMR spectroscopy (see below). However, analysis of titration data can yield

accurate measurements of K_a . During the titration, a change in a measured quantity such as UV-Visible absorbance or NMR spectroscopic chemical shift change, ΔY , is plotted as a function of guest added to give a titration curve termed a *binding isotherm*. The data is then fitted to a mathematical model to obtain the association constant by solving (in the case of 1 : 1 binding) a quadratic equation containing only the total host and guest concentrations, $[H]_0$ and $[G]_0$, along with K_a . The physical change under study (Y) is proportional to $[H \cdot G]$ and is an aggregate of the individual components as a function of concentration in techniques such as UV-Vis spectroscopy (Equation 1.11) or as a function of mole fraction f_x ($f_x = [X]/[X]_0$) in the case of NMR spectroscopy (Equation 1.12).

$$Y = Y_H[H] + Y_G[G] + Y_{HG}[HG] \quad (1.11)$$

$$Y = Y_H f_H + Y_G f_G + Y_{HG} f_{HG} \quad (1.12)$$

The concentration of host-guest complex in a 1 : 1 equilibrium is then given by quadratic equation 1.13 (for the derivation of this equation, see the key reference to this section). There exists a related cubic equation for 2 : 1 equilibria and higher-order expressions for yet more complex binding models.

$$[HG] = \frac{1}{2} \left([G]_0 + [H]_0 + \frac{1}{K_a} \right) - \sqrt{\left([G]_0 + [H]_0 + \frac{1}{K_a} \right)^2 - 4[H]_0[G]_0} \quad (1.13)$$

In the older literature, expressions such as Equation 1.13 were simplified or linearised and plotted by hand to obtain K_a . These methods include the Benesi–Hildebrand plot (also known as the Lineweaver–Burk plot in enzyme kinetics), the Scott or Hanse–Woelf transformations and the Scatchard plot. With the advent of modern computers and powerful software for the analysis of titration data, these methods are now considered obsolete and can be inaccurate. Moreover, these methods distort experimental error and rely on assumptions that may not be true, such as the guest being in vast excess or the host being fully complexed at the end of the titration. Powerful open-source software for the analysis of titration data is now available *via* the supramolecular.org web resource created by Pall Thordarson of the University of New South Wales, who has given a comprehensive overview of modern titration methods and the pitfalls of older treatments.³⁵

A range of electronic structure and empirical force-field-based methods have also been used to theoretically calculate or predict binding constants. The area is a challenging one and regular blind tests are carried out in the SAMPL series. The latest SAMPL results, SAMPL6 in 2018, saw 10 research groups attempt to calculate the affinity of three supramolecular hosts: ‘octa-acid’, the closely related ‘tetra-endo-methyl-octa-acid’ (both [4]resorcarene-based deep cavity cavitand cage molecules), and cucurbit[8]uril (Section 6.2.4), for 21 small organic guest molecules. The accuracy of the different methods proved to be highly dependent on the system. In comparison to previous SAMPL rounds, there was an overall improvement in the correlation obtained by the affinity predictions for the cavitands but no improvement was found for the root mean square error over the past several challenge rounds. The challenge concluded that further refinement of force field parameters, as well as improved treatment of chemical effects such as buffer salt conditions and protonation states, may be required to further enhance predictive accuracy.³⁶

The Binding Model

A key aspect of fitting titration data is the determination of an appropriate binding model. The model is imposed by the user as part of the calculation and incorporates considerations such as stoichiometry (*i.e.* the ratio of host to guest) and cooperativity. There is a strong bias in the supramolecular chemistry literature towards the fitting of data to 1 : 1 stoichiometries, and it is a common mistake to neglect higher aggregates. Incorrectly fitting a 1 : 2 complex to a 1 : 1 model, however, results in physically meaningless apparent association constant values. To take one example, for a titration at a host concentration of 0.01 M with real $K_{11} = 1000$ and $K_{12} = 250$ fitted to a 1 : 1 model, the apparent K_a is 104 M^{-1} ; an order of magnitude out!³⁷ Traditionally, stoichiometry has been determined using the method of continuous variation known as the *Job plot*. The Job plot experiment involves making up a series of solutions with varying host:guest ratios such that the total concentration of host and guest is a constant. Monitoring a parameter proportional to the changing concentration of the host–guest complex in these samples allows a plot of that parameter (*e.g.* absorbance) against mole fraction to be constructed. For a 1 : 1 complex, this kind of representation should give a peak at

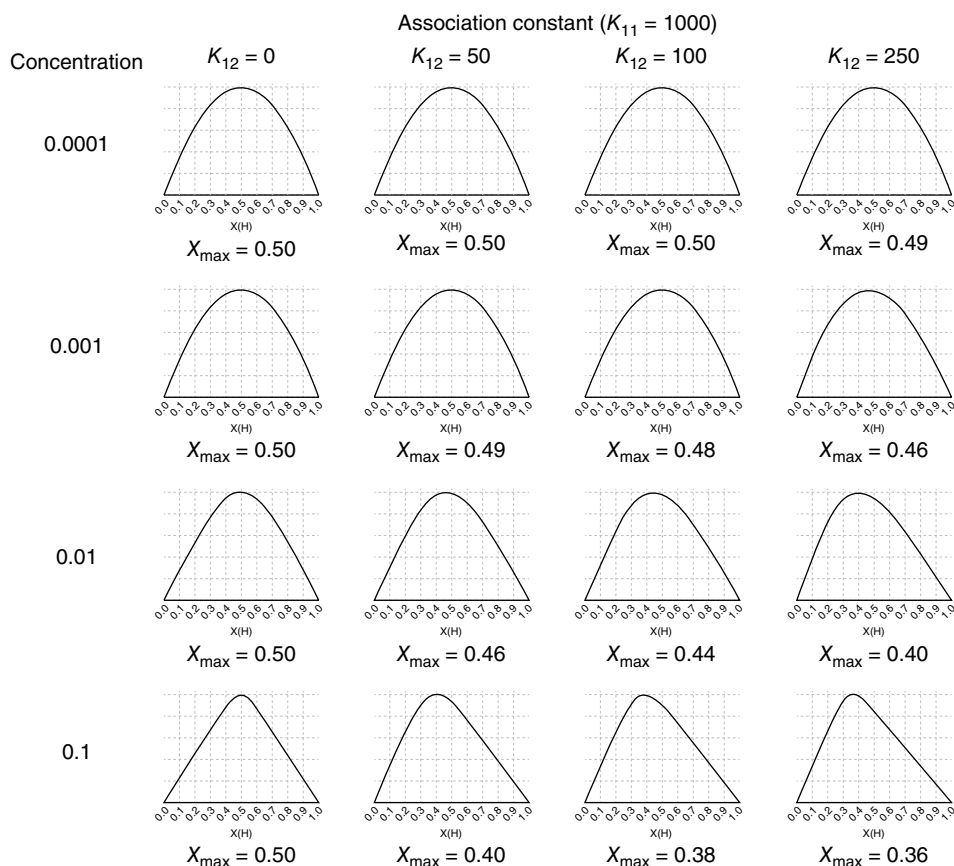


FIGURE 1.8 Simulated Job plots for 1 : 1 (column 2, $K_{12} = 0$) and various cases of 1 : 2 stoichiometry. In each case $K_{11} = 1000 \text{ M}^{-1}$ and $Y_{\text{HG}} = 1$ and $Y_{\text{HG}2} = 2$ (an additive model). The host concentration is shown in column 1 and the simulated maxima in the Job plot are shown as $x_{\max}$.³⁷ © 2016, Reproduced with permission from American Chemical Society.

0.5, while a peak at 0.33 corresponds to a 1 : 2 stoichiometry and *so on*. However, while Job plots remain useful in inorganic chemistry where binding constants are generally very large, at the kinds of concentrations and binding constant values commonly encountered in supramolecular chemistry, Job plots can be misleading. Simulations by Jurczak and co-workers for a 1 : 2 binding system showed that the Job plot gives a value close to the correct value of 0.33 in just one set of circumstances in which the concentration of species is high and the value of K_{12} is reasonably large, Figure 1.8.³⁷ In the opinion of some workers in the field, the failure of the method under the kinds of conditions often encountered in supramolecular systems signals the ‘death of the Job plot’.³⁵

So, how do we decide on an appropriate binding model? The answer is that the data should be fit to all probable models based on a good theoretical understanding of the system, and the fitting results subsequently compared with one another. This does not necessarily mean that the best fit to the experimental data is always the right model – it is generally possible to improve the fit by adding more parameters. The right model should be independent of concentration and hence repeating the titration at multiple concentrations is a good practice. The correct model is assessed using a number of indicators. The calculated parameters should be physically realistic (*e.g.* a calculated ^1H NMR chemical shift for the host–guest complex of 100 ppm is a sure sign of a bad model) and the residuals (the point-by-point differences between calculated and observed titration data) should be random rather than varying in a regular sinusoidal fashion. There are also more rigorous statistical criteria that can be used to give confidence in a binding model. A good illustration of the issues is given by the binding of two Mg^{2+} cations by the ditopic receptor shown in Figure 1.9.

The host shown in Figure 1.9 is capable of binding up to two Mg^{2+} ions (as well as chloride anions as we will see in Section 1.5.3) and the process has been studied by ^1H NMR spectroscopic titration. As a result, there are four possible 1 : 2 binding models to choose from depending on whether the binding of the second Mg^{2+} ion is cooperative (*i.e.* influenced by the binding of the first ion) and whether the NMR spectroscopic chemical shift values are additive or not (*i.e.* whether the chemical shift change upon adding the second equivalent of Mg^{2+} is the same as it is when

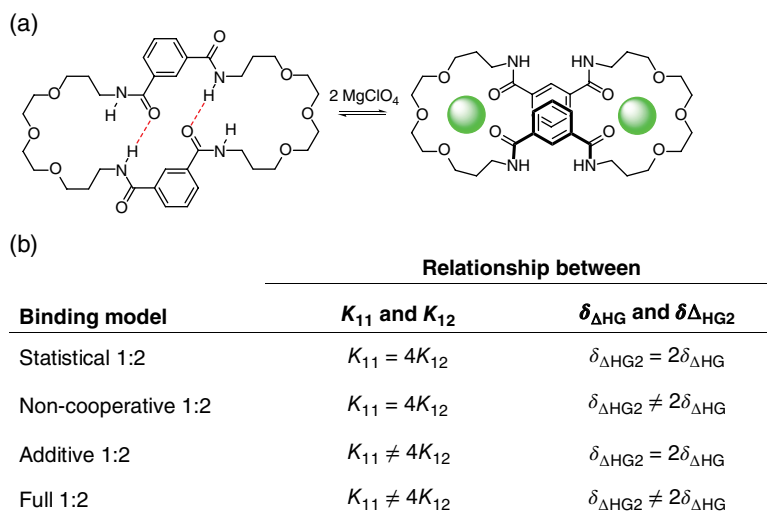


FIGURE 1.9 (a) Binding of two Mg^{2+} cations by a ditopic receptor. (b) Possible binding models used to describe the ^1H NMR titration data for this system in $\text{CD}_3\text{CN}/\text{CDCl}_3$ 1 : 1 v/v.³⁸

TABLE 1.5 Comparison of four different 1 : 2 binding models in the analysis of NMR titration data monitoring Mg^{2+} binding by the system shown in Figure 1.9a.

Binding model	K_{11} (M^{-1})	K_{12} (M^{-1})	cov_{fit} ratio ^a
Full	4139	1059	5.6
Non-cooperative	4252	1063 ($=\frac{1}{4} K_{11}$)	5.6
Additive	3×10^6	1784	0.5
Statistical	15 986	3997 ($=\frac{1}{4} K_{11}$)	1

^aRatio between the cov_{fit} value of the model and that for the simple statistical model.

adding the first equivalent; that is to say whether $\delta_{\Delta\text{HG}2} = 2\delta_{\Delta\text{HG}}$). The results of fitting the NMR titration isotherm to the four different models are shown in Table 1.5.

Clearly, the choice of model exerts a very strong influence on the results with the additive and statistical models differing very significantly from the full and non-cooperative models. An indicator that the additive model in particular is likely to be incorrect is the very large value of K_{11} which is physically improbable compared to other known systems in the literature. Compared to the simple statistical model, the non-cooperative and particularly the full model require extra parameters. We can judge whether these extra parameters are justified in fitting the data by looking at the variance[‡] of fit parameter, cov_{fit} . This measure is the ratio of the variances of the fitted and raw data, Equation 1.14. The more complex models should give a cov_{fit} that is at least 3–5 times better (lower) if they are to represent a significant improvement on the simpler description. In this case, the cov_{fit} for the full and non-cooperative models are 5.6 times better than the statistical model (Table 1.5) and hence both represent a good description of the system. A rigorous statistical analysis shows that the non-cooperative binding model is the most appropriate.³⁸

$$\text{cov}_{\text{fit}} = \frac{\text{variance}(y_{\text{calc}})}{\text{variance}(y_{\text{data}})} \quad (1.14)$$

[‡]The variance of a data set measures how far a set of numbers are spread out from their average value. Variance is the square of the standard deviation, σ^2 .

Titration Methods

Below, we give a brief description of practical titration methods in common use. In every case a concentration range must be chosen such that there is an equilibrium between significant amounts of bound and free host and guest, limiting the range of binding constants that can be measured by a particular technique. Ideally, the technique is primarily determined by the concentration range of the complex being studied and the concentration range should be chosen so that the measurements span a probability of binding (p) in the range 0.2–0.8 where $p = [\text{HG}]/[\text{G}]_0$.³⁹ Generally, in supramolecular systems, ¹H NMR spectroscopy is the best choice as long as the association constant is less than about 10^5 M^{-1} . For larger association constants, hosts become saturated at the kinds of concentration needed to obtain an NMR signal and hence UV-Vis titration is a viable alternative. For UV-Vis methods, the molecule needs to contain a chromophore and the technique is limited to concentration regions in which the Beer Lambert Law applies (*i.e.* in which absorbance is proportional to concentration). Fluorescence titration is more sensitive and can deal with concentrations approaching the nanomolar range depending on the strength of the emitter. However, the low concentrations of UV-Vis and fluorescence titration methods can mask the formation of higher stoichiometries because in a 1 : 2 complexation process, for example, the low concentration of HG_2 may not be detectable. If binding by the target host is too strong, then a competing host is sometimes added in order to reduce the apparent (measured) binding constant according to the difference in guest affinity between the two hosts. The true affinity can then be extrapolated from a knowledge of the binding constant of the guest for the host with the lower affinity.

Thordarson in the key reference outlines a number of do's and don'ts of supramolecular titration experiments:

1. Do try to obtain as much information as possible before carrying out the experiment based on related systems, and a reasonable conception of likely binding constant and stoichiometry.
2. Do not apply a 'black box' bonding model without understanding the underlying assumptions.
3. Do carry out the titration with as much care and precision as possible. Check purity, clean glassware, use precise pipettes, and avoid dilution of the host by dissolving the guest in host solution rather than blank solvent. Record the temperature!
4. Do choose a technique that is appropriate to the anticipated chemistry.
5. Do aim to get a reasonable number of titration points to fully define the shape of the binding isotherm. However, the effects of cumulative errors and solvent evaporation can mean that *too many* points can also reduce the accuracy of the result. Around 15 points is typical for an NMR titration experiment, with most measurements focused around the anticipated region of maximum gradient change in the curve.
6. Do not use shortcut data analysis methods such as linearisation.
7. Do consider all sensible possible stoichiometries and use multiple means to decide on the correct model. If using a Job plot, ensure that the concentration range and binding constants are appropriate.
8. Do consider global analysis methods in which more than one data set is fit to a single bonding model to ensure robustness.
9. Do not forget to critically evaluate indicators such as calculated chemical shift values and the stability of the result to changes in starting values, as well as the likely physical meaning of the results.
10. Do repeat the titration; repetitions are invaluable in estimating uncertainties and eliminating user error.
11. Do not blindly accept the output; think about the shape and information content of the binding isotherm and residual plot.
12. Do estimate the uncertainty in the final results including uncertainties from all possible source rather than just classical statistical methods.
13. Do not focus only on the association constants but think also in terms of energy. Doubling the association constant increases the magnitude of ΔG by -1.7 kJ mol^{-1} . Going from K_a of $50\text{--}100 \text{ M}^{-1}$ results in an 18% increase in binding energy whereas for a K_a of $500\,000 \text{ M}^{-1}$, the increase in ΔG is just 5% upon doubling K_a .

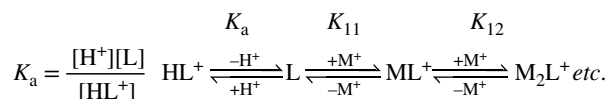
Potentiometric Titration

In the case of macrocycles that are susceptible to protonation (e.g. the cryptands with their basic tertiary amine nitrogen bridgehead atoms), the protonation constants (and hence pK_a values) may be determined readily using pH (glass) electrodes to monitor a simple acid–base titration. Initially, this will give the acid dissociation constant (pK_a) of the ligand's conjugate acid, HL^+ .⁴⁰ Addition of a metal cation will perturb the macrocycle's basicity (ability to bind one or more protons) by competition between the metal ion and H^+ for the ligand lone pair(s) and hence will affect the shape of the titration curves.

Analysis of the various equilibria by a curve-fitting computer program (such as *Hyperquad*⁴¹) along with knowledge of the ligand's pK_a allows the determination of the amount of uncomplexed ligand and hence the concentration of the complex and the stability constants for the metal complexation reaction, Scheme 1.1. The technique allows detailed characterisation of the complex species present in the system which can be displayed as a distribution diagram such as the one shown in Figure 1.10 for the terpyridinophane ligand showing binding copper(II) and zinc(II). In this case, the experiment shows that mixed metal complexes predominate under basic conditions.⁴²

Nuclear Magnetic Resonance Spectroscopic Titration

If the exchange of complexed and uncomplexed guest is slow on the nuclear magnetic resonance (NMR) time scale, then the binding constant may be approximately evaluated under the prevailing conditions of concentration, temperature solvent, *etc.*, by simple integration of the NMR signals for bound and unbound host or guest. The difference in chemical shift between bound and free species is termed the *complexation-induced shift* and arises from the differences in local magnetic environment caused by the presence of the host (see Box 3.1). Most host–guest equilibria are fast on the (relatively slow) NMR spectroscopic time scale,[§] however, and the chemical shift observed for a particular resonance (that is sensitive to the complexation reaction) is a weighted average between the chemical shift of the free



SCHEME 1.1 Competing equilibria in a potentiometric titration.

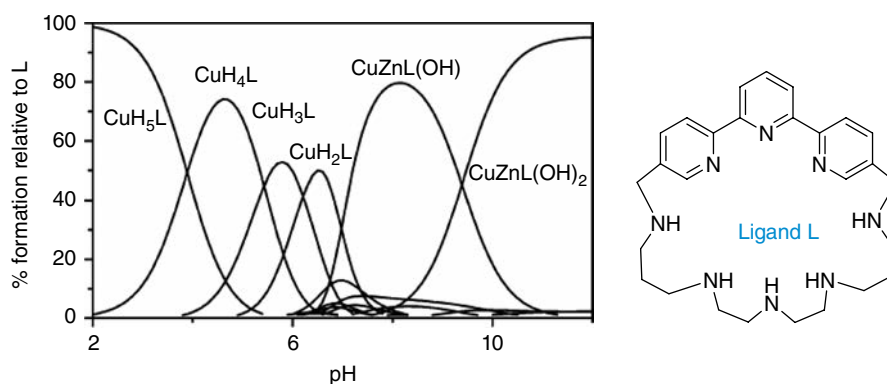


FIGURE 1.10 Distribution diagram for the Cu^{2+} – Zn^{2+} –ligand L system determined by potentiometric titration. In this experiment, the ligand as a 1 mM solution of the hydrobromide salt is titrated with 1 mM solutions of the metal perchlorates over a pH range 2.5–11.0 using a glass pH electrode and an Ag/AgCl reference electrode in 0.15 M $NaClO_4$ electrolyte solution.⁴² © 2007, Reproduced with permission from Royal Society of Chemistry.

[§]The exchange rate required to cause two NMR resonances to coalesce is related to the chemical shift difference between them in Hz. Typically, in 1H NMR at a field strength of 300 MHz, this is in the range 0.2 s to 75 μ s. For a detailed explanation, see Bryant, R.G. (1983). The NMR time scale. *J. Chem. Ed.* 60: 933.

and bound species (Figure 1.4b). In a typical NMR titration experiment, small aliquots of guest are added to a solution of host of known concentration in a deuterated solvent and the NMR spectrum of the sample monitored as a function of guest concentration, or host:guest ratio. Commonly, changes in chemical shift ($\Delta\delta$) are noted for various atomic nuclei present (e.g. ^1H in ^1H NMR) as a function of the influence the guest binding has on their magnetic environment. As a result, two kinds of information are gained. Firstly, the location of the nuclei most affected may give qualitative information about the regioselectivity of guest binding (is the guest inside the host cavity?). More importantly, however, the shape of the titration curve (a plot of $\Delta\delta$ against added guest concentration, e.g. Figure 1.10a) gives quantitative information about the binding constant. NMR spectroscopic methods are useful for binding constants in the range $10\text{--}10^5\text{ M}^{-1}$. Such titration curves are often analysed by computer least-squares curve fitting (popular programs include *WinEQNMR2*⁴³ or *HypNMR*⁴⁴ or the online tools on the web site supramolecular.org). *WinEQNMR2* uses Equation 1.15 to determine optimum values of δ_{mn} (chemical shift of each species present where mn is the ratio of host, H, and guest, G) and β_{mn} (stepwise binding constant). The isotherm shown in Figure 1.11a fits a stoichiometry model involving both 1 : 1 and 1 : 2 host:guest complexes with $\log K_{11} = 2.3$ and $\log K_{12} = 4.5$. The plot also shows the relative percentage amounts of each species present in the solution for a given host and guest concentration.

$$\delta_{\text{calc}} = \sum_{m=1}^{\infty} \sum_{n=0}^{\infty} \frac{\delta_{mn} \beta_{mn} m [\text{G}]^m [\text{H}]^n}{[\text{G}]_{\text{total}}} \quad (1.15)$$

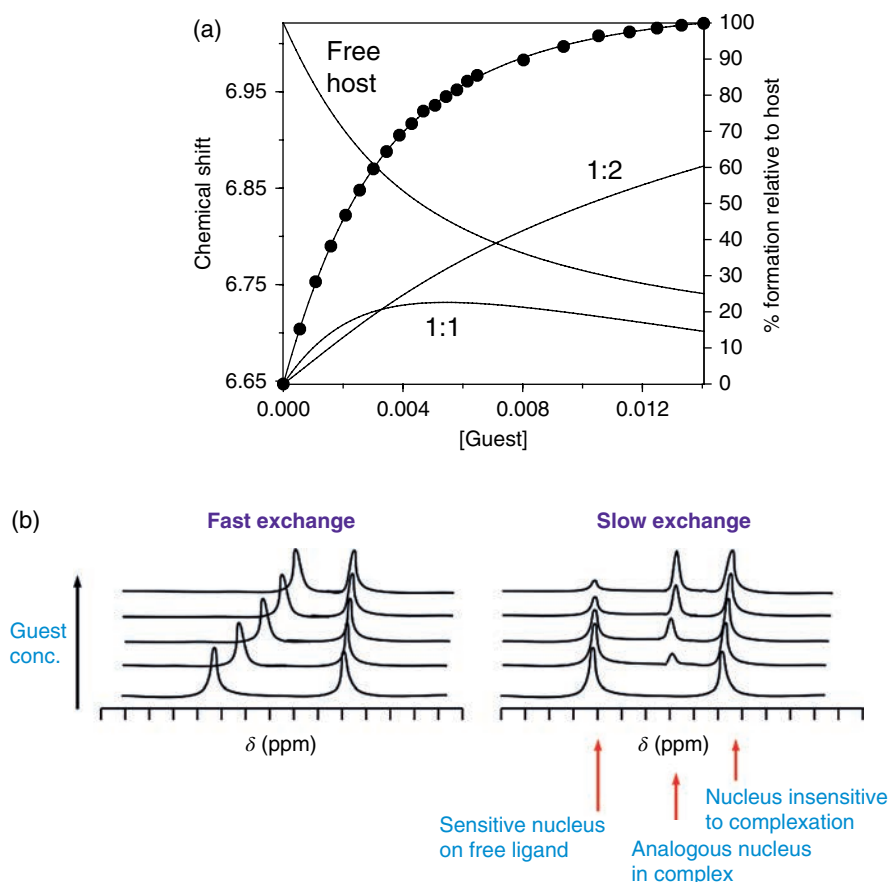


FIGURE 1.11 (a) NMR titration plot (isotherm) and corresponding speciation plots for a system undergoing fast equilibration on the NMR time scale, with $\log K_{11} = 2.3$ and $\log K_{12} = 4.5$. (b) Schematic NMR spectra of slowly equilibrating mixtures of free host, guest, and host–guest complex.

Fluorescence Titration

Fluorescence titration measurements are based on the proportion of fluorescence intensity to fluorophore concentration (concentration of fluorescent species in solution; this is often a fluorescent guest, G). For a 1 : 1 complex with host, H, with stability constant $K_{11} = [\text{HG}]/[\text{H}][\text{G}]$ the fluorescence intensity F is given by:

$$F = k_{\text{G}}[\text{G}] + k_{11}[\text{HG}] \quad (1.16)$$

where k_{G} and k_{11} represent proportionality constants for the guest and the 1 : 1 host–guest complex, respectively. In the absence of host, the fluorescence intensity, F_0 , is given by:

$$F_0 = k_{\text{G}}^0 G_{\text{total}} \quad (1.17)$$

where $G_{\text{total}} = [\text{G}] + [\text{HG}]$.

Combining these two relationships gives Equation 1.18, which provides the basis for most fluorimetric methods for stability constant (K_{11}) determination:

$$\frac{F}{F_0} = \frac{k_{\text{G}}/k_{\text{G}}^0 + (k_{11}/k_{\text{G}}^0)K_{11}[\text{H}]}{1 + K_{11}[\text{H}]} \quad (1.18)$$

This equation is greatly simplified for cases where either the guest or host–guest complex are non-fluorescent (*i.e.* the fluorescence is ‘turned on’ by complexation, or in the case of quenching by the host), in which case either k_{G} or k_{11} becomes zero. For example, for $k_{\text{G}} = k_{\text{G}}^0$ and $k_{11} = 0$, we obtain:

$$\frac{F_0}{F} = 1 + K_{11}[\text{H}] \quad (1.19)$$

A simple plot of F_0/F against $[\text{H}]$ from titration of the quenching host into a guest solution should yield a straight line of slope K_{11} . Common fluorescent guests such as 8-anilino-1-naphthalenesulfonate (ANS) may be used to probe complexation ability of various hosts in this way.

UV-Vis Spectrophotometric Titration

UV-Vis spectroscopic titration (or spectrophotometric titration) involves monitoring the intensity of an electronic absorption band at a particular wavelength that is characteristic of either the complex or free host or guest and is closely analogous to fluorescence titration methods. A plot is generated of absorbance intensity vs. concentration of added guest to a solution of constant host concentration. Software such as the program *Specfit*[®] or the online tools at supramolecular.org can then be used, in conjunction with an appropriate stoichiometry model, to extract the binding constant(s). Both fluorescent and UV-Vis spectroscopic methods have the advantage over NMR methods that they are more sensitive and hence lower concentrations of host and guest can be used. Unlike fluorescence methods, the observation of one or more clear *isosbestic points* is common in absorption spectroscopic titrations. An isosbestic point is where the observed absorption intensity is constant throughout the titration. The observation of an isosbestic point is good evidence for the conversion of free host into complex without the involvement of significant intermediate species. Figure 1.12 shows the observed UV-Vis spectra during a titration of diisobutyl-acridono-18-crown-6 with Pb^{2+} . The isosbestic point occurs at 256 nm.⁴⁵

Calorimetric Titration

Calorimetric titration, also known as isothermal titration calorimetry (ITC), involves careful measurement of the heat (enthalpy) evolved from a carefully insulated sample as a function of added guest or host concentration. The gradient of the ITC curve can be fitted to determine the binding constant and hence $\Delta G_{\text{complex}}$. Integration of the total area under

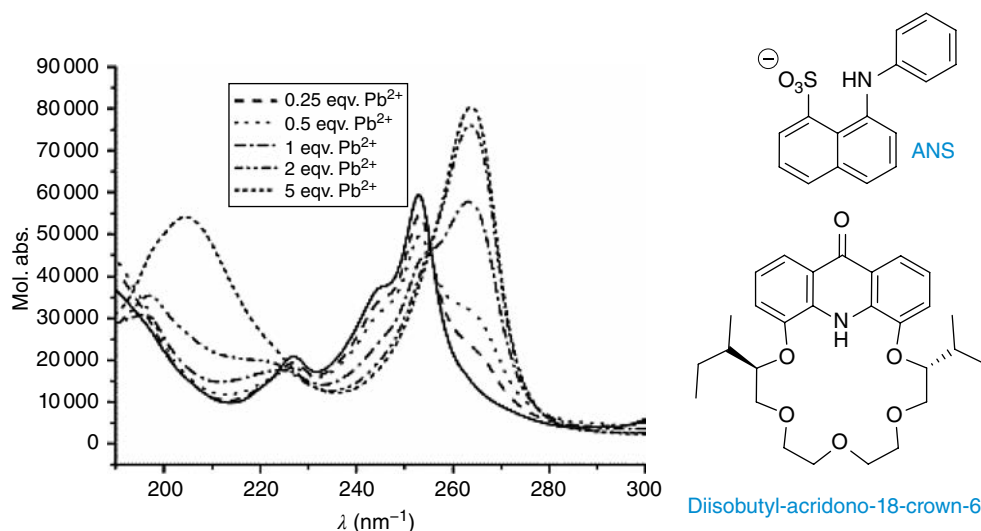


FIGURE 1.12 UV-monitored titration of diisobutyl-acridono-18-crown-6 with Pb^{2+} showing an isosbestic point at 271 nm (solid line represents free ligand spectrum).⁴⁵ © 2004, Reproduced with permission from Elsevier.

the ITC plot gives the complexation enthalpy ($\Delta H_{\text{complex}}$) and hence the technique can give a measurement of all thermodynamic parameters of the system since $\Delta G_{\text{complex}} = \Delta H_{\text{complex}} - T\Delta S_{\text{complex}}$. ITC is useful for determination of binding constants that range from c. 10^2 to 10^7 M^{-1} . ITC has been used in an interesting case study to probe solvent and counter-cation effects on the binding of anions such as chloride to calix[4]pyrrole (Section 4.5.5).⁴⁶ Figure 1.13 shows the ITC data and resulting fit for the binding of $\text{NBu}_4^+\text{Cl}^-$ by calix[4]pyrrole in nitromethane, giving $K_{11} = 19\,200 \text{ M}^{-1}$, $\Delta G = 11.3 \text{ kJ mol}^{-1}$, $\Delta H = 8.55 \text{ kJ mol}^{-1}$, and $\Delta S = -9.1 \text{ J K}^{-1} \text{ mol}^{-1}$.

Extraction Experiments

The distribution (or partition) coefficient, K_d , of a metal cation between an aqueous (aq) and organic (org) phase may also be used to assess the selectivity of a given host for a range of metal cations under standard conditions, using the equilibrium constants (K) for the following processes (Equations 1.20–1.23) (for metal picrate (Pic) salt, water, and water-saturated chloroform phases, 25°C).

$$[\text{M}^+ \cdot \text{Pic}^-]_{\text{org}} + [\text{Host}]_{\text{org}} = [\text{M}^+ \cdot \text{Host} \cdot \text{Pic}^-]_{\text{org}} \quad K_{11} \text{ (binding constant)} \quad (1.20)$$

$$[\text{M}^+]_{\text{aq}} + [\text{Pic}^-]_{\text{aq}} + [\text{Host}]_{\text{org}} = [\text{M}^+ \cdot \text{Host} \cdot \text{Pic}^-]_{\text{org}} \quad K_e \text{ (extraction constant)} \quad (1.21)$$

$$[\text{M}^+]_{\text{aq}} + [\text{Pic}^-]_{\text{aq}} = [\text{M}^+ \cdot \text{Pic}^-]_{\text{org}} \quad K_d \text{ (distribution coefficient)} \quad (1.22)$$

$$K_{11} = K_e / K_d \quad (1.23)$$

The concentration of picrate anion (and hence, necessarily, M^+ by charge balance) is determined by measurement of the electronic absorbance (380 nm) of each layer. Picrate is chosen as a convenient yellow-coloured lipophilic counter anion to allow the distribution of the salt to be observed by eye, Figure 1.14a. The host is assumed to be essentially insoluble in the aqueous layer. The technique is of relatively low precision but is quick and lends itself readily to the screening of a wide range of compounds. It is suitable for measurement of binding free energies in the range $25\text{--}70 \text{ kJ mol}^{-1}$ (i.e. binding constants of ca. $10^4\text{--}10^{12}$). Binding energies in excess of 70 kJ mol^{-1} are assessed by competition with hosts of known binding energy. While the picrate is assumed to be relatively innocent, it is capable of significant $\pi\text{--}\pi$ stacking effects with hosts bearing aromatic rings. This gives rise to a ‘picrate effect’ in which extraction selectivities of aromatic group-containing hosts for metal picrates may vary significantly from those for alkali metal salts with inorganic anions, Figure 1.14b.⁴⁸

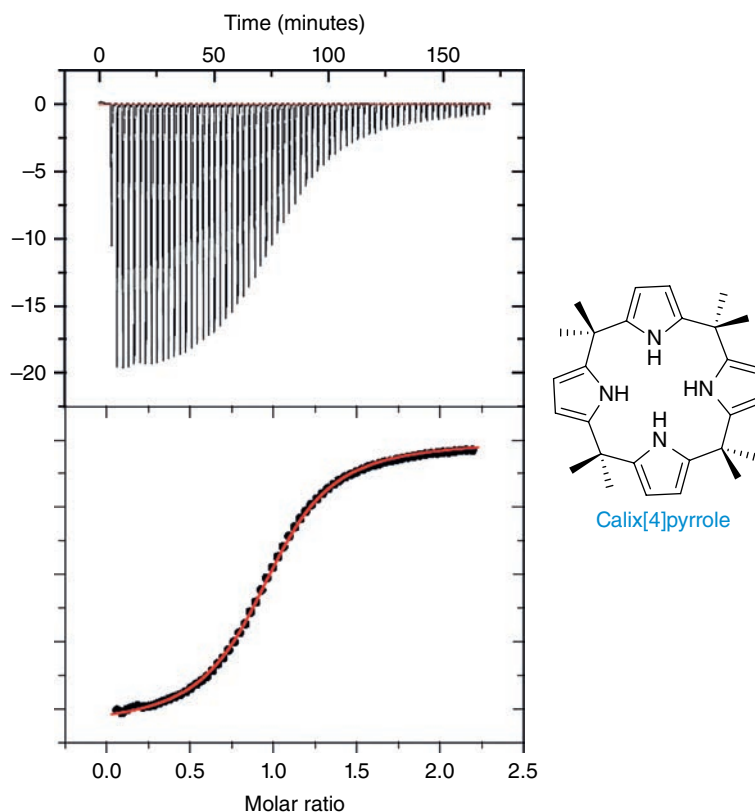


FIGURE 1.13 ITC data at 25 °C for the binding of $\text{NBu}_4^+\text{Cl}^-$ by calix[4]pyrrole in nitromethane – the top plot represents the raw data with the calorimetric response in $\mu\text{cal s}^{-1}$ for each addition of $\text{NBu}_4^+\text{Cl}^-$ while the lower plot is the titration isotherm fitted to a 1 : 1 model, scale kcal mol^{-1} vs. mole ratio of $\text{NBu}_4^+\text{Cl}^-$ to calix[4]pyrrole.⁴⁶

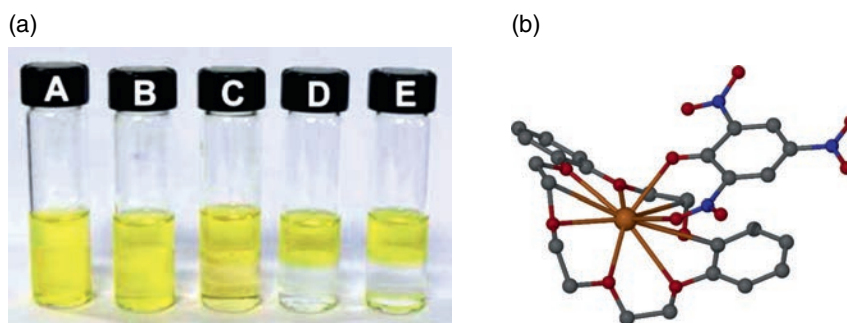


FIGURE 1.14 (a) Aqueous solutions of caesium picrate (top layer) showing how the yellow colour of the picrate is efficiently extracted into the organic layer (dichloromethane, bottom layer) by Cs^+ binding benzocrown[6]calix[4]arene and calix[4]pyrrole derivatives (A–C) while control samples with either polymethyl methacrylate or no extractant at all result in the picrate salt remaining in the aqueous layer (D and E).⁴⁷ © 2010, Reproduced with permission of Royal Society of Chemistry. (b) Aromatic π – π stacking in the potassium picrate complex of dibenzo[18]crown-6.⁴⁸

1.4.3 Relationship to Enthalpy and Entropy

Key Atkins, P. and De Paula, J. (2006). *Physical Chemistry*, 8 e. W. H. Freeman and Company, 212.

Measurement of binding constants over a range of temperatures allows a van't Hoff analysis which gives the underlying enthalpic and entropic parameters of the system. This in turn gives insight into the nature of the interactions and driving force for complexation, which in turn can provide insight into the nature of the binding itself. Compensation

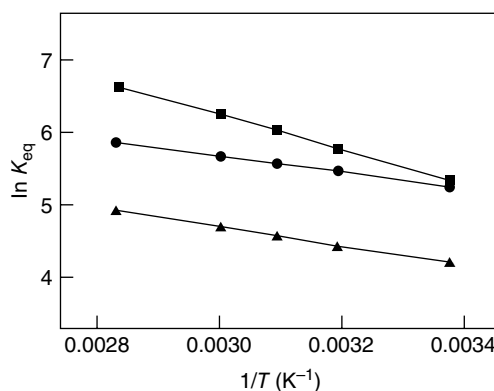


FIGURE 1.15 van't Hoff plot for the encapsulation of aqueous alkylammonium cations into a $[\text{Ga}_4\text{L}_6]^{12-}$ tetrahedral receptor cavity.⁴⁹ © 1998, Reproduced with permission from American Chemical Society.

between competing enthalpic and entropic contributions is a common feature as we will see in Section 1.9.2. The van't Hoff analysis involves a plot of $\ln K_a$ vs. T^{-1} according to Equation 1.24 and gives the complexation enthalpy (ΔH) from the slope of the regression line and the entropy (ΔS) from the y-intercept. Implicit in this analysis is the assumption that both quantities do not change significantly over the temperature range of the experiments, which is usually valid.

$$\ln K_a = \frac{-\Delta H}{RT} + \frac{\Delta S}{R} \quad (1.24)$$

where K_a = equilibrium/association constant, T = temperature (K) and $R = 8.31 \text{ J K}^{-1} \text{ mol}^{-1}$.

This kind of analysis has been applied in a temperature range 295–353 K to tetrahedral molecular containers based on the aqueous binding of alkylammonium cations by bifunctional catechol-based ligand (L)-linked gallium anionic cages, $[\text{Ga}_4\text{L}_6]^{12-}$.⁴⁹ The van't Hoff plots are shown in Figure 1.15 and reveal a significantly unfavourable enthalpic contribution to the binding with ΔH in the range 9.2–19.7 kJ mol⁻¹. This endothermic contribution was ascribed to the unfavourable desolvation of the cationic guests upon entering the container cavity. The complexation is therefore entropy driven with $\Delta S = 71.1$ –108.7 J K⁻¹ mol⁻¹. This favourable entropy arises from the release of bound water from the solvation shell of the guest, and from the host cavity upon complexation.

1.5 COOPERATIVITY, MULTIVALENCY, AND THE CHELATE EFFECT

1.5.1 Binding Site Cooperativity and Multivalency

Key Anslyn, E.V. and Dougherty, D.A. (2006). *Modern Physical Organic Chemistry*, 213–215. Sausalito, CA: University Science Books.

Much of the emphasis in the construction of supramolecular host molecules concerns bringing about summative or even multiplicative interactions. This means that we can construct a stable host–guest complex using (often weak) non-covalent interactions if we ensure that there are as many as possible of these interactions stabilising the complex. The small amount of stabilisation energy gained by any one such interaction when added to all the other small stabilisations from the other interactions (*summative*) results in a significant binding energy and hence complex stability. In some cases, the interaction of the whole system is synergically greater than the sum of the parts (*multiplicative*). When two or more binding sites (A and B) on a host cooperate in this fashion to bind to a guest, the phenomenon is termed *binding site cooperativity*. If the overall stability of the complex is greater than the sum of the energies of the interaction of the guest with binding groups A and B individually, then the result is *positive cooperativity*. On the other hand, if unfavourable steric or electronic effects arising from the linking of A and B together into one host cause the overall binding free energy for the complex to be less than the sum of its parts, then the phenomenon is termed *negative cooperativity*. Binding site

cooperativity in a supramolecular host–guest interaction is simply a generalisation of the *chelate effect* found in classical coordination chemistry.

In energy terms the cooperativity arising from the chelate effect, or more generally from the interaction of a two-binding-site guest (A–B), with a bidentate host can be expressed in terms of the overall binding free energy ΔG_{AB}^o which is equal to the sum of the intrinsic binding free energies of each component A and B (ΔG_A^i and ΔG_B^i) plus a factor arising from the summation or connection of A and B (ΔG^s), Equation 1.25.⁵⁰

$$\Delta G_{AB}^o = \Delta G_A^i + \Delta G_B^i + \Delta G^s \quad (1.25)$$

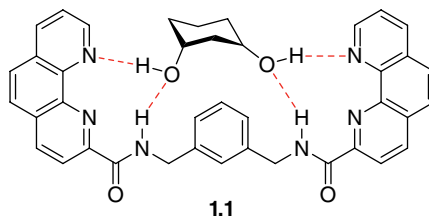
The intrinsic binding energy represents the energy group A or B imparts to the rest of the molecule assuming there are no unfavourable strain or entropy components introduced into the binding by the linking of the group with the rest of the molecule, *i.e.* Equation 1.26 (and similarly for component B)

$$\Delta G_A^i = \Delta G_{AB}^o - \Delta G_B^o \quad (1.26)$$

we can thus write Equation 1.27 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.

$$\Delta G^s = \Delta G_A^o + \Delta G_B^o - \Delta G_{AB}^o \quad (1.27)$$

Equation 1.27 can be used to give an empirical measure of the cooperativity, since equilibrium constants (K) for the binding of A, B, and A–B by a host can be measured and related to the Gibbs free energy according to $\Delta G^o = -RT \ln K$. If ΔG^s is negative, then the binding sites A and B exhibit unfavourable negative cooperativity. A positive value for ΔG^s implies a favourable positive cooperativity. A good example of positive binding site cooperativity is given by the dialcohol binding system **1.1**. The binding constant is 1150 M^{-1} compared to just 13 M^{-1} in the analogous single binding site system binding the monoalcohol cyclohexanol.⁵¹



The idea of multiple interaction site cooperating to give rise to enhanced binding is also reflected in the concept of *multivalency*. In multivalent systems, multiple receptors are tethered together, for example, on a surface such as a biological cell in order to bind multiple tethered guests (or ‘ligands’ in biology). Tethering the guests together can result in significant enhancement of the affinity of the tethered ligands for the tethered receptors.⁵² The process is ubiquitous in Nature and can be seen in cellular adhesion, migration, immune response, antibody recognition, bacterial adhesion, and signal transduction. The fact that multivalent ligands engage in multiple copies of a recognition element, means that they have significant advantages over monovalent analogues. These include (i) high affinity and slow dissociation kinetics, (ii) blockage of pathogen adhesion by steric stabilisation, (iii) improved properties of existing drugs, (iv) specific targeting of biological surfaces, (v) receptor clustering and modulation of signal transduction pathways, (vi) formation of matrices for process modulation, (vii) targeting of more than one receptor simultaneously.⁵³ Effects of multivalency in cell surface interactions are illustrated schematically in Figure 1.16.

The effect of multivalency on overall affinity has been quantified in the so-called multivalent enhancement factor, or the *KiEM factor*.⁵⁴ Overall thermodynamic affinity (K_{ov}) can be related to the intrinsic binding affinity of any one receptor and substrate pair (K_i) within a multivalent system by Equation 1.28.

$$K_{ov} = K_i (K_i \cdot EM)^{n-1} \quad (1.28)$$

Here, EM is the effective molarity and n is the valency (*i.e.* the number of interactions holding the system together). EM is related to the length and flexibility of the linker between the two (or more) different binding sites and depends on the probability that the two reactive groups find each other in the restricted volume imposed by this molecular

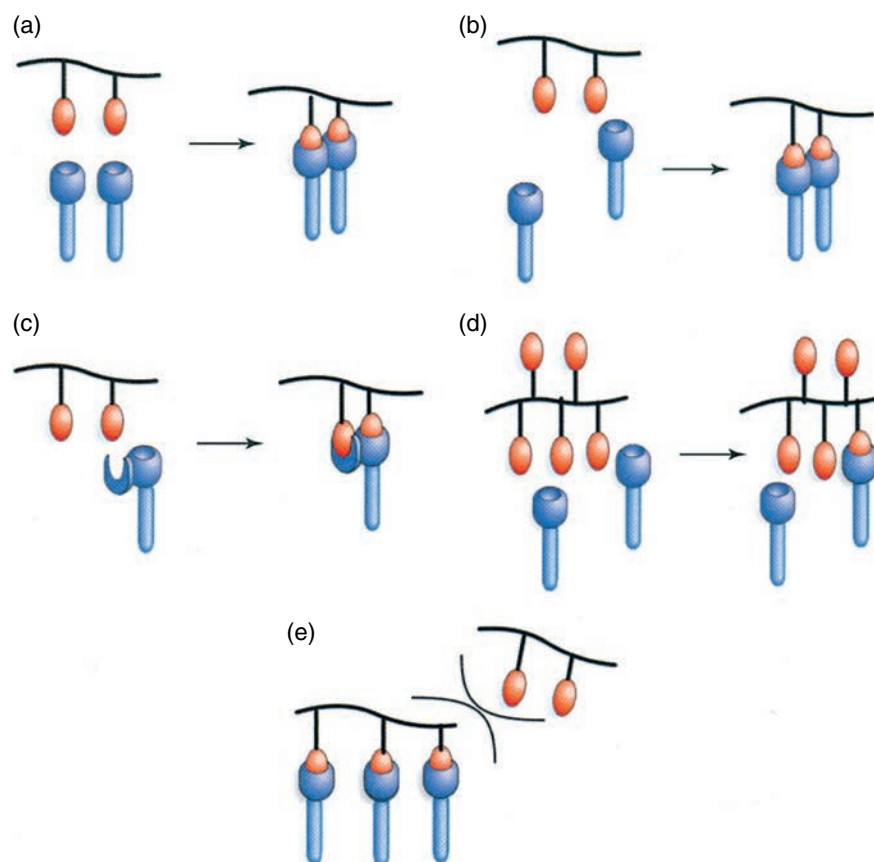


FIGURE 1.16 Mechanism by which multivalent ligands can interact with cell-surface receptors. (a) Multivalent ligands can bind oligomeric receptors by occupying multiple binding sites (chelate effect). (b) Multivalent ligands can cause receptors to cluster on the cell surface leading to the activation of signalling pathways. (c) Multivalent ligands can occupy primary and secondary binding sites on a receptor. (d) Multivalent ligands display higher local concentration of binding sites, which can result in higher apparent affinities. (e) The steric bulk of the multivalent ligand precludes further ligand interactions.⁵³ © 2012, Reproduced with permission from John Wiley & Sons.

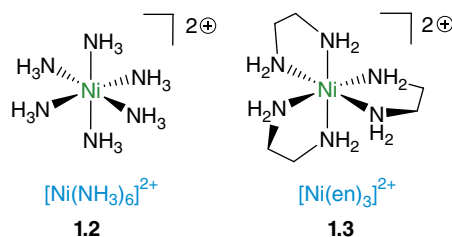
connection between them. For weakly multivalent systems, $KiEM$ is in the range 1–10. Above 10, the multivalent effect becomes quite significant and can reach values of many thousand. The $KiEM$ enhancement factor affects not only the overall thermodynamic stability of a system but also its kinetics in terms of the time taken for dissociation which becomes exponentially longer with increasing $KiEM$.

1.5.2 The Chelate Effect

Key Hancock, R.D. (1992). Chelate ring size and metal ion selection. *J. Chem. Ed.* 69: 615–621.

The chelate effect is well known in coordination chemistry and relates to the observation that metal complexes of bidentate ligands (such as 1,2-diaminoethane, en) are significantly more stable than closely related materials that contain unidentate ligands (such as ammonia). For example, in the reaction shown in Equation 1.29, the value of the equilibrium constant for the replacement of ammonia in **1.2** with 1,2-diaminoethane indicates that the 1,2-diaminoethane chelate complex **1.3** is more than 10^8 times more stable.





The special stability of chelate complexes in solution may be traced to both thermodynamic and kinetic effects. Thermodynamically, reaction of a metal with a chelating ligand results in an increase of the number of free particles (four on the left-hand side of Equation 1.29, seven on the right) and hence a favourable entropy contribution (ΔS°) to the overall free energy of the reaction (ΔG°), given by $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$. In addition, clever design of the macrocycle to maximise conformational and electrostatic aspects of ligand–metal interactions can result in a favourable enthalpy of reaction as well. The entropic contribution is reinforced further by a statistical aspect, since for the chelate complex to dissociate, both of the metal–donor atom bonds must be broken simultaneously. Finally, kinetic effects are involved in the formation of the chelate complex. It is likely that the reaction of the metal with a ligand, L, proceeds at a similar rate to the binding of the first donor atom of a chelating ligand, L–L. The binding of the second donor atom of L–L proceeds much more rapidly, however, because in its ‘tethered’ state it has a much higher effective concentration than a second molecule of unidentate L. This rate increase feeds into a higher binding constant because of Equation 1.10.

While an experimental fact in solution coordination chemistry, the nature of the chelate effect has been the topic of much debate. The first problem concerns the definition of the stability constants; the second stepwise stability constant K_{12} for the binding of two unidentate ligands (when calculated using concentrations instead of activities) does not have the same dimensions as the first stability constant for the bidentate ligand with which it is being compared. As a result, the influence of the solvent concentration is neglected. When this difference is taken into account by converting concentrations as mole fractions (*i.e.* concentration in mol dm^{-3} /concentration of solvent), the chelate effect almost disappears. Furthermore, measurements of gas-phase stability also indicate little difference between comparable chelate and non-chelate complexes. Nevertheless, it is an experimental fact that, in the solution phase at least, chelate ligands will almost invariably displace their monodentate analogues.

The stabilisation afforded by the chelate effect is highly dependent on the size of the chelate ring (Figure 1.17).⁵⁵ Five-membered rings, as in metal complexes of 1,2-diaminoethane, are often the most stable by far because they contain the least amount of ring strain, particularly for larger cations. Four-membered rings (*e.g.* chelating acetate) are highly strained, while as the chelate ring’s size increases the statistical likelihood of two donor atoms pointing directly at the metal becomes increasingly less probable, resulting in an unfavourable entropy. The strain energy in the chelate ring is dependent on the size of the metal cation, however. For very small cations such as Li^+ and Be^{2+} , six-membered chelate rings are common because the small cation results in cation–donor bond lengths similar to those found in unstrained six-membered ring molecules such as cyclohexane.

In supramolecular chemistry, the thermodynamic stability of a host–guest complex may be enhanced by the operation of a chelate effect giving rise to positive binding site cooperativity. The ligand donor atoms are generalised to host binding sites (of whatever nature) and the metal is generalised to the guest (which indeed often is a metal cation, although guests may also be anions or neutral species). The operation of the chelate effect is observed in the binding of metal cations by *podands* – chain-like hosts with a number of donor atoms situated at intervals along their length as in **1.4** (see Section 3.2)⁵⁶ and, more generally, positive binding site cooperativity is similarly observed in hydrogen bonded complexes such as receptor **1.5** which selectively binds citrate anion through multiple hydrogen bonding interactions.⁵⁷ Another good example of cooperativity is seen in the drug–receptor complex **1.6** formed between the antibiotic vanco-

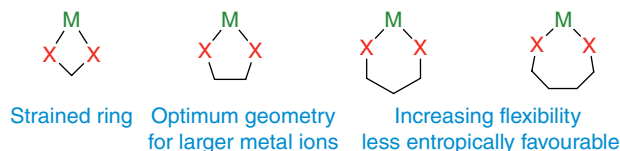


FIGURE 1.17 Ring size dependence of the stabilisation offered by the chelate effect.

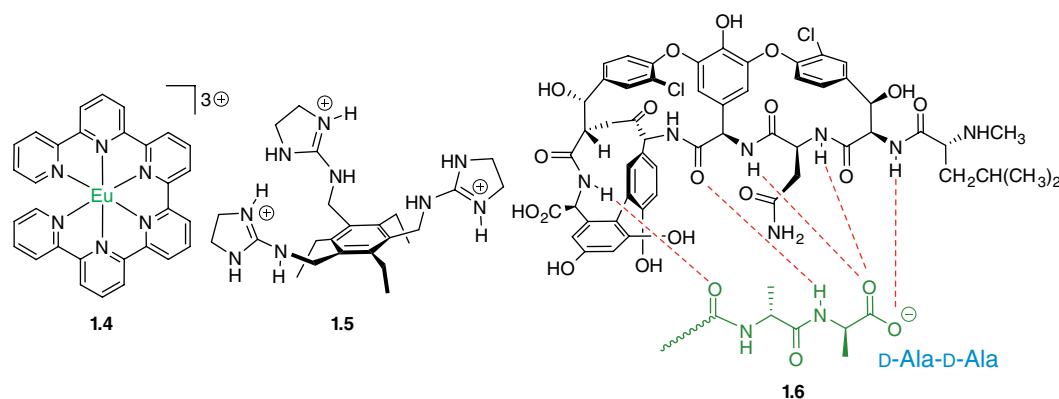


FIGURE 1.18 Supramolecular host-guest complexation stabilised by positive cooperativity between binding sites: Eu^{3+} binding by (1.4), a host for citrate anion (1.5) and a drug-receptor complex formed by vancomycin (1.6).

mycin and proteins that are used in the synthesis of bacterial cell walls.⁵⁰ The proteins end in the sequence D-alanine-D-alanine which form numerous hydrogen bonded and hydrophobic contacts to the drug (Figure 1.18).

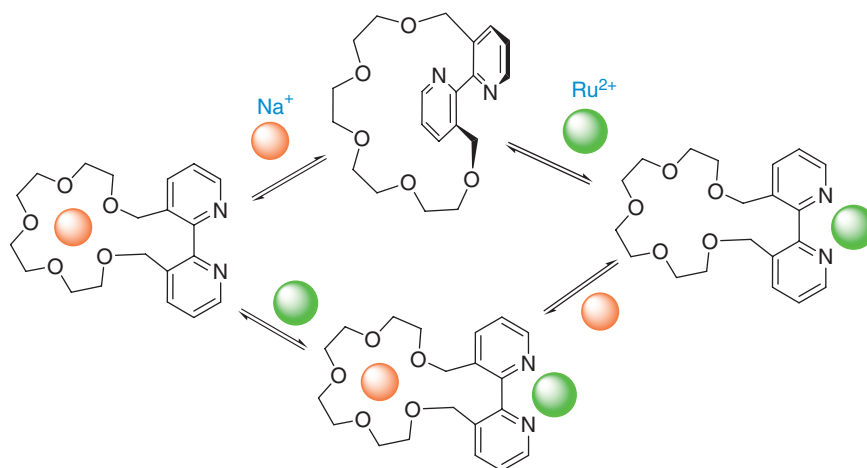
1.5.3 Cooperative Binding of More than One Guest

Key von Krabek, L.K.S., Schalley, C.A., and Thordarson, P. (2017). Assessing cooperativity in supramolecular systems. *Chem. Soc. Rev.* 46: 2622–2637.

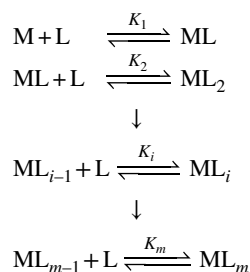
In addition to cooperativity between two or more host binding sites in binding a single guest, we can also recognise both positive and negative cooperativity in the binding of multiple guests by a single host, as in the binding of multiple ligands by a single metal, or in multicomponent self-assembly processes. Multicomponent self-assemblies are complicated by the occurrence of both intra- and inter-molecular associations, however, and simple binding models are not appropriate. This issue is of considerable relevance in self-assembled, multicomponent metal complexes and we will look at models for these processes further in Section 10.4. Cooperativity in cases where the binding of a first guest influences (particularly enhances) the affinity of a host for a second guest at a remote site is termed an *allosteric effect*. A good example is shown in Scheme 1.2.⁵⁸ Here, binding of Ru^{II} to the bipyridyl portion of the host changes its conformation by rotation about the pyridyl-pyridyl bond to create a cavity suitable for chelating an alkali metal cation such as Na^+ . Similarly, binding of Na^+ to the polyether site predisposes (*preorganises* – see Section 1.6) the bipyridyl portion for Ru^{II} binding. The strength of the sequential binding of the two metal cations can be quantified by the binding constants K_{11} and K_{12} . The allosteric effect means that K_{12} , the affinity for the second cation, is always greater than the K_{11} binding constant for that same cation alone, in the absence of the other metal. Allosteric effects are very important in biological systems, particularly in the case of the binding of O_2 by haemoglobin (see Section 2.5). For example, cryo-electron microscopy has revealed that drug-induced inhibition of human ATP-citrate lyase (a central metabolic enzyme responsible for the ATP-dependent conversion of coenzyme A into acetyl-CoA using citrate and hence core to cholesterol synthesis and fatty acid metabolism) relies on allosteric binding of the drug into a hydrophobic cavity next to the hydrophilic citrate binding site.⁵⁹

Cooperativity may be recognised by the deviation from well-defined statistical relationships. Consider again the interaction of two binding sites –A and –B capable only of interaction with one another to give a species –A·B– in a reaction, with the microscopic interaction equilibrium constant K_{inter} (i.e. the equilibrium constant for the individual reaction step). We can examine the equilibria shown in Scheme 1.3 for a metal, M, with m identical binding sites of type –B (for example, m could be the metal's coordination number) involved in a series of equilibria binding a number of ligands, L, each with a unique binding site –A.

On statistical grounds, it can be shown that Equation 1.30 holds true. Equation 1.30 implies that the binding constant for each added ligand is less than the previous one. In fact, successive equilibrium constants decrease by a factor of at least a half as more ligands are added because of the increasing likelihood of displacing a ligand if there



SCHEME 1.2 Allosteric (cooperative) enhancement of Na^+ binding by preorganisation of the polyether binding site by Ru^{II} , and *vice versa*.⁵⁸



SCHEME 1.3 Equilibrium constants (K) for multiple ligands (L) binding to a single metal (M) via a binding site on the ligand termed 'A' interacting with a binding site on the metal termed 'B'.

are more of them. This effect is evident, for example, in the stability constants for the successive reaction of $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ with six molecules of NH_3 : $\log K_{1-6} = 2.80, 2.24, 1.73, 1.19, 0.75, 0.03$.

$$K_i = K_{\text{inter}} (m - i + 1)/i \quad (1.30)$$

$$\frac{K_{i+1}}{K_i} = \frac{i(m-i)}{(i+1)(m-i+1)} \quad (1.31)$$

From Equation 1.30, we can derive Equation 1.31. The quantity K_{i+1}/K_i may be used as a measure of cooperativity. If the statistical relationship shown in Equation 1.31 holds true, the system is non-cooperative. For a simple system involving two-guests bound by one host, then this becomes $K_1 = 4K_2$ as we saw in Section 1.4.1. If K_{i+1}/K_i is higher than would be expected from Equation 1.31, the system exhibits positive cooperativity, whereas if it is lower, the system exhibits negative cooperativity and the binding of one ligand inhibits the binding of the next. For the simple two-guest case, we can define an *interaction parameter* $\alpha = 4K_2/K_1$. If $\alpha > 1$, the system displays positive cooperativity while if $\alpha < 1$, the system displays negative cooperativity. A value of exactly 1 implies that the system is non-cooperative.⁶⁰

Experimentally, cooperativity is often assessed by graphical methods based on a parameter r (Equation 1.32), known as the *occupancy*, i.e. the average number of occupied binding sites, in this case on the metal, M .

$$r = \frac{\sum_{i=1}^m i \beta_i [\text{L}]^i}{1 + \sum_{i=1}^m \beta_i [\text{L}]^i} \quad (1.32)$$

where β_i represents the stepwise stability constants and $[L]$ is the concentration of *free* ligand. If the system is non-cooperative (*i.e.* Equation 1.31 holds true), then Equation 1.32 becomes Equation 1.33:

$$r = \frac{mK_{\text{inter}}[L]}{1 + K_{\text{inter}}[L]} \quad (1.33)$$

Equation 1.33 can be put into two alternate linear forms known as the Scatchard (1.34) and Hill (1.35) equations. While linearisation can be problematic in binding constant determination, it can still provide evidence for cooperativity if used appropriately, and these methods remain popular in biology.

$$\frac{r}{[L]} = -K_{\text{inter}}r + mK_{\text{inter}} \quad (1.34)$$

$$\log\left(\frac{r}{m-r}\right) = \log[L] + \log K_{\text{inter}} \quad (1.35)$$

A Scatchard plot is thus a plot of $r/[L]$ as a function of r and appears as a straight line for non-cooperative systems, a convex curve for negative cooperativity, and a concave curve for positive cooperativity. A Hill plot is a plot of $\log[r/(m-r)]$ vs. $\log[L]$. Cooperativity results in two straight lines connected by a S-shaped curve. The value of the slope in the central region of the curve is called the Hill coefficient (n_H). A value of $n_H > 1$ indicates positive cooperativity, while systems exhibiting negative cooperativity have $n_H < 1$. Hill and Scatchard plots for the binding of ammonia to Ni^{2+} are shown in Figure 1.19. The value of the Hill coefficient of 0.59 and the convex shape of the curve indicates that the process exhibits negative cooperativity, as exemplified in the binding constants which are lower even than would be expected from statistical effects. A word of warning, however, cooperativity can *only* be assessed in this way for *inter-molecular* processes involving the binding of multiple guests to a single host (*e.g.* multiple metal ions to a protein, multiple ligands to a metal). Multimolecular self-assembly that mixes intra- and inter-molecular processes requires a different treatment (Section 10.4) and this distinction has resulted in many erroneous claims of positive cooperativity in the literature.⁶¹

A nice example of the interplay of complex negative and positive cooperative has been reported for the receptor shown in Scheme 1.4. In addition to binding Mg^{2+} as we saw in Section 1.4.2, the receptor can also hydrogen bond to chloride anion guests *via* the amide NH groups. However, this interaction is strongly negatively cooperative because of unfavourable conformational effects, with α values of 0.01–0.05 depending on solvent system (*i.e.* significantly less than 1). Similarly, binding to metal ions such as Ca^{2+} and Mg^{2+} is also either non-cooperative or negatively cooperative.

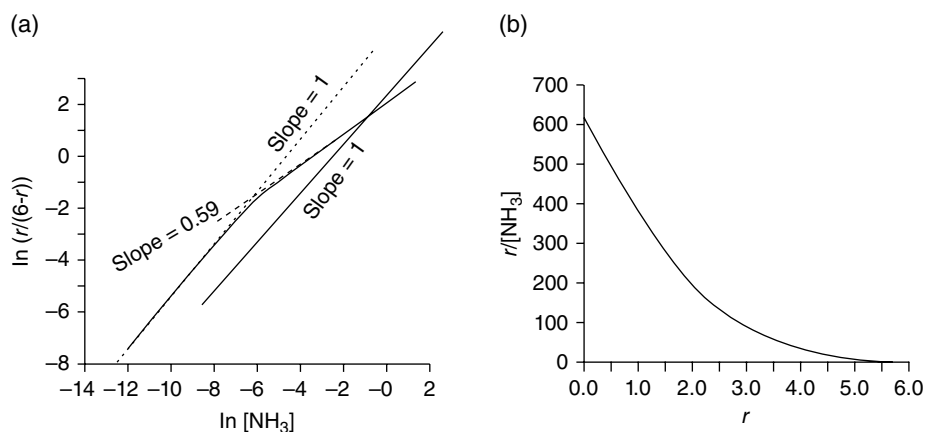
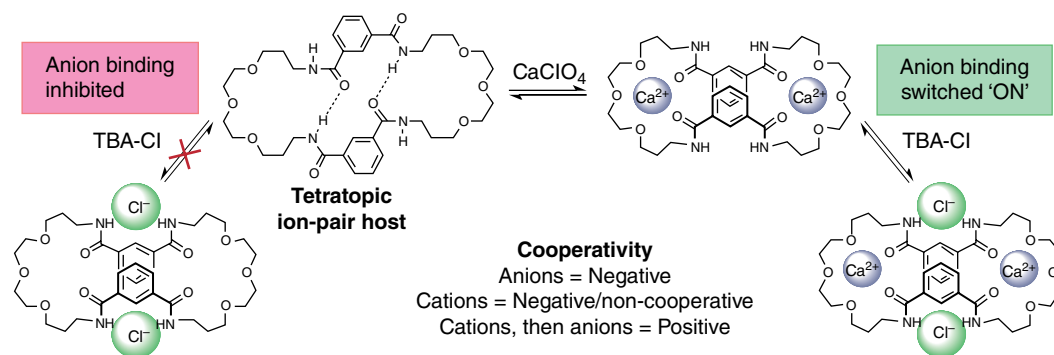


FIGURE 1.19 (a) Hill plot and (b) Scatchard plot for the successive intermolecular connections of ammonia to bivalent nickel to give $[\text{Ni}(\text{NH}_3)_i]^{2+}$, the concentration of the free ligand $[L]$ is computed by using the known stability constants. $[\text{Ni}]_{\text{total}} = 1 \times 10^{-3} \text{ M}$; $[\text{NH}_3]_{\text{total}}$ varies between 10^{-5} and 1 M .⁶¹ © 2006, Reproduced with permission from Royal Society of Chemistry.



SCHEME 1.4 An anion/cation tetratopic receptor exhibits strongly negative cooperative anion binding, and non-cooperative Ca^{2+} binding. However, Ca^{2+} binding allosterically switches on chloride binding exhibiting positive cooperativity.⁶⁰ Reproduced with permission © 2011 American Chemical Society.

However, binding to Ca^{2+} allosterically switches on chloride binding because the metal ion reorientates the anion binding pocket into a conformation suitable for chloride complexation, Scheme 1.4.⁶⁰

1.6 PREORGANISATION AND COMPLEMENTARITY

Key Cram, D.J. (1986). Preorganisation – from solvents to spherands. *Angew. Chem. Int. Ed. Engl.* 25: 1039–1134.

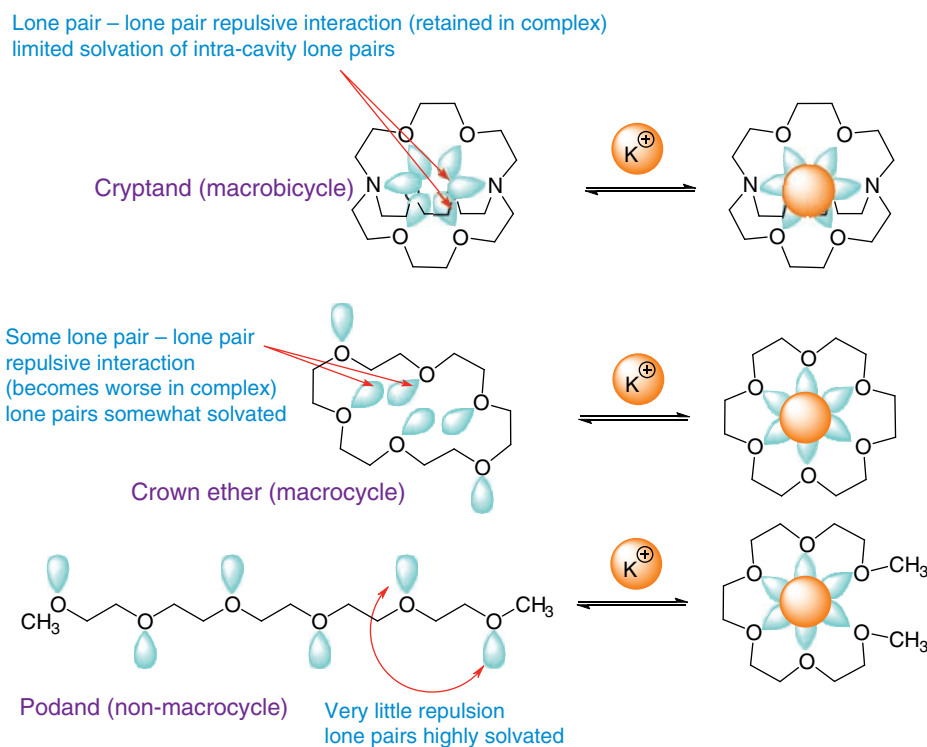
1.6.1 Macrocycles and Preorganisation

Many supramolecular host–guest complexes are based on macrocyclic (*i.e.* large-ring) hosts in which there is significant binding site cooperativity resulting in complexes that are considerably more stable than would be expected from the chelation of the guest by a number of binding sites alone and indeed as we saw in Section 1.3.2, macrocycles have been a mainstay of supramolecular chemistry from the very outset. Macrocyclic complexes are stabilised by what is traditionally termed the *macrocyclic effect*. This effect relates not only to the chelation of the guest by multiple binding sites, but also to the *organisation* of those binding sites in space prior to guest binding (*i.e.* *preorganisation*) such that free energy is not expended in the guest having to ‘wrap’ the host about itself in order to benefit from the most chelation. Furthermore, the enthalpic penalty associated with bringing potentially mutually repulsive binding sites (*e.g.* donor atom lone pairs) into close proximity to one another (with consequent unfavourable repulsion and desolvation effects) has been ‘paid in advance’ during the synthesis of the macrocycle. This makes macrocycles more difficult to prepare than their linear analogues, but the payoff is that they are stronger complexing agents than analogous non-macrocyclic hosts (*podands*). Some of the ‘tricks’ in macrocycle synthesis are discussed in Section 3.9. The macrocyclic effect makes complexes with cyclic hosts such as *corands* (*e.g.* crown ethers) up to a factor of 10^4 times more stable than closely related acyclic *podands* with the same type of binding sites. It was first elucidated by Cabbiness and Margerum in 1969 who studied the Cu^{II} complexes **1.7** and **1.8**.⁶² Both ions benefit from the stability associated with four chelating donor atoms. However, the macrocyclic complex **1.7** is about 10^4 times more stable than the acyclic analogue **1.8** because of the additional preorganisation imparted by the macrocyclic structure.

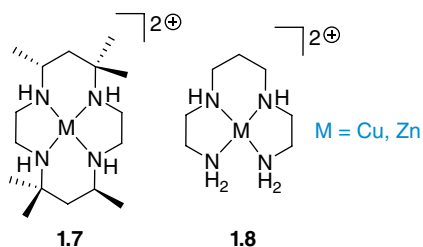
Thermodynamic measurements on the analogous (unmethylated) Zn^{2+} complexes reveal that the stabilisation by macrocyclic preorganisation has both enthalpic and entropic contributions (Table 1.6). The enthalpic term arises from the fact that macrocyclic hosts are frequently less strongly solvated than their acyclic analogues. This is because they simply present less solvent-accessible surface area. As a result, there are fewer solvent–ligand bonds to break than in the extended, acyclic case. Entropically, macrocycles are less conformationally flexible and so lose fewer degrees of freedom upon complexation. In general, the relative importance of the entropic and enthalpic terms varies according to the system studied although the enthalpy is frequently dominant as a result of additional factors such as lone pair

TABLE 1.6 Thermodynamic parameters for Zn^{2+} complexes of **1.7** and **1.8** (298 K).

	1.7	1.8
Log K	15.34	11.25
ΔH° (kJ mol ⁻¹)	-61.9	-44.4
$-T\Delta S^\circ$ (kJ mol ⁻¹)	-25.6	-19.8

**SCHEME 1.5** Comparison of preorganisation effects in K^+ binding by a macrobicycle, macrocycle, and non-preorganised podand pentaethyleneglycol dimethyl ether.

repulsions.** Bicyclic hosts such as *cryptands* (Section 3.4) are found to be even more stable than monocyclic *corands* for much the same reasons. Historically, this further additional stability is referred to as the *macrobicyclic effect* and simply represents the more rigid, preorganised nature of the macrobicycle. The macrocyclic and macrobicyclic effects make an important contribution to hosts for alkali metal binding (Scheme 1.5 and Section 3.7).



**The issue of lone pair–lone pair repulsion is complicated by the fact that in oligoethylene glycol derivatives, the operation of a *gauche effect* arising from hyperconjugation of the $\text{CH } \sigma$ electron density with the $\text{CH } \sigma^*$ orbital adjacent to the electronegative oxygen atom means that the *gauche* rather than *anti* conformation is actually more stable in free oligo ethylene chains (Connor, T.M. and McLauchlan, K.A. (1965). High resolution nuclear resonance studies of the chain conformation of polyethylene oxide. *J. Phys. Chem.* 69: 1888), however, the basic principle of an increase in unfavourable interactions and poorer solvation of binding groups in preorganised cyclic structures is a general one.

The macrocyclic and macrobicyclic effects are simply manifestations of increasing *preorganisation*. We can say that if a host molecule does not undergo a significant conformational change upon guest binding, it is *preorganised*. Host preorganisation is a key concept because it represents a major (in some cases decisive) enhancement to the overall free energy of guest complexation. Neglecting the effects of solvation, the host guest binding process may be divided very loosely into two stages. First, there is an activation stage in which the host undergoes conformational readjustment in order to arrange its binding sites in the fashion most complementary to the guest and at the same time minimising unfavourable interactions between one binding site and another on the host. This is energetically unfavourable, and because the host must remain in this binding conformation throughout the lifetime of the host–guest complex, this energy is never paid back. Following rearrangement, binding occurs which is energetically favourable because of the enthalpically stabilising attraction between mutually complementary binding sites of host and guest. The overall free energy of complexation represents the difference between the unfavourable reorganisation energy and the favourable binding energy. If the reorganisation energy is large, then the overall free energy is reduced, destabilising the complex. If the host is preorganised, this rearrangement energy is small.

The corollary of preorganisation is in the guest binding kinetics. Rigidly preorganised hosts may have significant difficulty in passing through a complexation transition state and so tend to exhibit slow guest binding kinetics. Conformationally, mobile hosts can adjust rapidly to changing conditions, and both complexation and decomplexation are fast. Solvation enhances the effects of preorganisation since the solvation stabilisation of the unbound host is often greater than the case when it is wrapped around the guest, effectively presenting less surface area to the surrounding medium.

1.6.2 Complementarity

In addition to the degree of host preorganisation, the other principal factor in determining the affinity of a host for a guest is *complementarity*. In order to bind its guest, a host must have binding sites that are of the correct electronic character (polarity, hydrogen bond donor/acceptor ability, hardness or softness, *etc.*) and spatial disposition to complement those of the guest. Hydrogen bond donors must match acceptors, Lewis acids must match Lewis bases, and *so on*. Furthermore, those binding sites must be spaced out on the host in such a way as to make it possible for them to interact with the guest in the binding conformation of the host molecule. If a host fulfils these criteria, it is said to be *complementary*. The principle of complementarity has been summed up by Donald Cram:

*To complex, hosts must have binding sites which cooperatively contact and attract binding sites of guests without generating strong nonbonded repulsions.*⁶³

The combined effects of preorganisation and complementarity are startlingly illustrated by a comparison of the binding constants under standard conditions for the alkali metal complexes shown in Figure 1.20. All of the hosts bind through six ether oxygen atoms. The fairly hard (non-polarisable) oxygen donors are complementary to fairly hard alkali metal cations such as K^+ . However, the stability constants range over nearly 14 orders of magnitude, reflecting the increasing preorganisation of the oxygen atom donor array. The amine nitrogen atoms in some hosts do not significantly enhance the binding because the softer amine is not complementary for alkali metal cations. Thus, replacing two oxygen atoms in [18]crown-6 with two secondary amine nitrogen atoms in diaza[18]crown-6 lowers the binding constant to below the value found for the podand EG5.

1.7 THERMODYNAMIC AND KINETIC SELECTIVITY, AND DISCRIMINATION

 Schneider, H.-J. and Yatsimirsky, A.K. (2008). Selectivity in supramolecular host-guest complexes. *Chem. Soc. Rev.* 37: 263–277.

The goal of supramolecular host design, both in Nature (enzymes, transport proteins, *etc.*) and in artificial systems, is the achievement of selectivity; some kind of differentiation between different guests. In the blood, the iron haem transport protein haemoglobin is fine-tuned to selectively take up O_2 in the presence of N_2 , water, and CO_2 , and even substances such

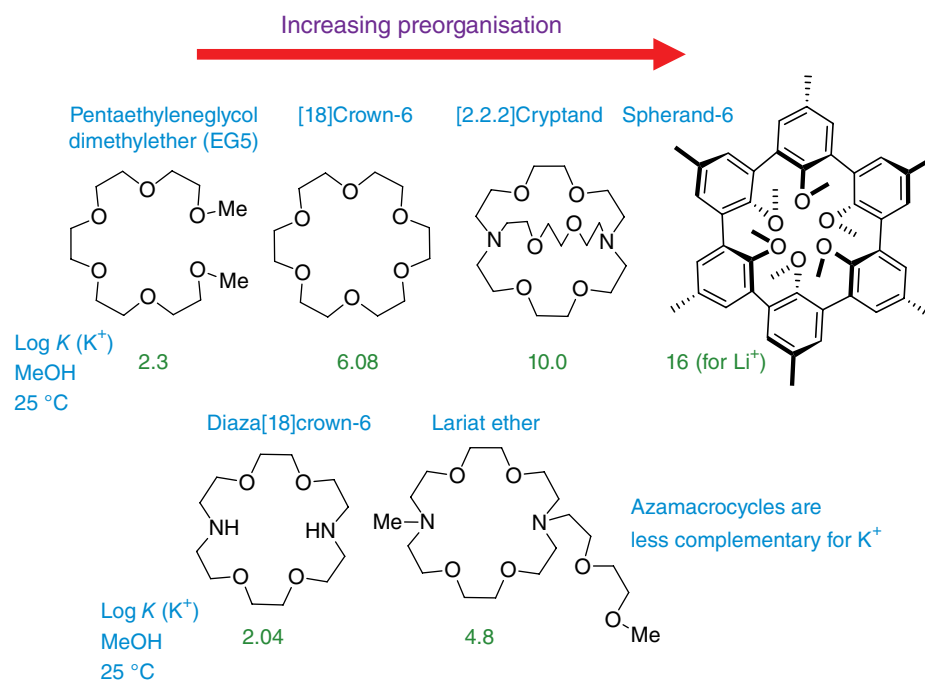


FIGURE 1.20 Comparison of the effects of preorganisation and complementarity on the magnitudes of the binding constant of polyether hosts for alkali metal cations. The figure for Li^+ is given for the highly preorganised spherand-6 since it is too small to accommodate K^+ .

as CO, which normally bind very strongly to iron. We can readily assess the affinity of a host for a particular receptor by its binding constant (Section 1.4). In thermodynamic terms, selectivity is simply the ratio of the binding constant for one guest over another as in Equation 1.36.

$$\text{Selectivity} = \frac{K_{\text{Guest1}}}{K_{\text{Guest2}}} \quad (1.36)$$

This kind of selectivity tends to be the easiest to achieve because it is highly susceptible to manipulation by intelligent application of concepts such as the lock and key analogy, preorganisation, and complementarity, coupled with a detailed knowledge of the host–guest interactions. So, we can say that [18]crown-6, with a binding constant for K^+ of 10^6 M^{-1} , is 100-fold selective for K^+ over Na^+ , which it binds with a binding constant of only about 10^4 M^{-1} under the same conditions. There is another kind of selectivity, however, which relates to the rate of transformation of competing substrates along a reaction path. This is *kinetic selectivity* and is the basis for directing the flow of directional processes such as supramolecular (enzymatic) catalysis and some aspects of guest sensing and signalling. In this sense, it is the guest that is transformed *fastest*, rather than the one that is bound the strongest, that the system is said to be selective for. Indeed, in such time-resolved processes, large binding constants are inhibitory to the system since kinetics are slowed down. Many enzymes are kinetically selective, and examination of their structures reveals that they are typically complementary for the transition state of a biochemical reaction rather than for the substrate itself. Moreover, they are not generally preorganised in a rigid way since this would preclude rapid catalysis (*cf.* the induced fit model, Section 1.3). In artificial systems, the engineering of such time-resolved selectivity (as in the design of enzyme mimics, Chapter 13) is a much more difficult process since it requires the adaptation of the host to the changing needs of the guest as the system proceeds along its reactive pathway.

We should also distinguish between guest selectivity and inter-guest *discrimination*. While thermodynamic selectivity relates to the magnitude of observed binding constants, discrimination is applied to the magnitude of other observable outcomes from specific host–guest interactions. Good examples are fluorescent or colorimetric molecular sensing. The guest that is bound most strongly is not necessarily the guest that gives the largest change in colour or in

fluorescent emission intensity. This is because the changes in light absorption or emission may result from a particular, guest-specific host–guest interaction, rather than being directly proportional to binding affinity. Thus, a host or sensing ensemble may effectively *discriminate* between two potential guests even if their binding constants are similar. The concept of guest discrimination is particularly interesting in the context of binding patterns by arrays of different hosts (for a fuller discussion, see Section 12.3.3).⁶⁴

1.8 NATURE OF SUPRAMOLECULAR INTERACTIONS

Key Biedermann, F. and Schneider, H.J. (2016). Experimental binding energies in supramolecular complexes. *Chem. Rev.* 116: 5216–5300.

In general, supramolecular chemistry concerns non-covalent bonding interactions. The term ‘non-covalent’ encompasses an enormous range of attractive and repulsive effects. The most important, along with an indication of their approximate energies, are explained below. While some interactions such as hydrogen bonding are immediately recognisable from undergraduate chemistry courses, other phenomena such as anion– π interactions have only recently been explicitly recognised. When considering a supramolecular system, it is vital to consider the interplay of all of these interactions and effects relating both to the host and guest as well as their surroundings (e.g. solvation, ion pairing, crystal lattice, gas phase, *etc.*). Indeed, while it is convenient to partition intermolecular interactions into a variety of classes that appear distinct from one another, this differentiation is artificial and a holistic treatment of intermolecular interactions, including their relative energies and the trade-offs between them within the context of solvation and entropic effects can lead to a much better understanding of the system. The issue has been discussed in some detail by Hunter.⁶⁵

1.8.1 Ion–Ion Interactions

Ionic bonding is comparable in strength to covalent bonding (bond energy = 100–350 kJ mol^{−1}). The energy of the interaction between two charged species follows Coulomb’s law (Equation 1.37, where q_1 and q_2 are the charges on the particles, ϵ is the *permittivity* of the solvent or medium, and ϵ_0 is the permittivity of a vacuum):

$$E = \frac{q_1 q_2}{4\pi\epsilon\epsilon_0 r} \quad (1.37)$$

Electrostatic interactions are long-range attractive (or repulsive) interactions since they depend on the reciprocal of the distance between the particles (r^{-1}) and solvent (especially water) that is particularly important in screening ion–ion interactions. A typical ionic solid is sodium chloride, which has a cubic lattice in which each Na⁺ cation is surrounded by six Cl[−] anions (Figure 1.21a). It would require a large stretch of the imagination to regard NaCl as a supramolecular compound, but this simple ionic lattice does illustrate the way in which a sodium cation is able to organise six complementary donor atoms about itself in order to maximise non-covalent ion–ion interactions. Note that this kind of lattice structure breaks down in solution because of solvation effects to give species such as the labile, octahedral Na(H₂O)₆⁺. A much more supramolecular example of ion–ion interactions is the interaction of a tris(diazabicyclooctane) host (**1.9**), which carries a 3⁺ charge, with anions such as [Fe(CN)₆]^{3−} (Figure 1.21b).⁶⁶

1.8.2 Ion–Dipole Interactions

The bonding of an ion, such as Na⁺, with a polar molecule, such as water, is an example of an ion–dipole interaction, which range in strength from *ca.* 50–200 kJ mol^{−1} (**1.10**). The total hydration energies decrease for the alkali metal ions in the order Li⁺ > Na⁺ > K⁺ > Cs⁺; 510 > 410 > 338 > 297 kJ mol^{−1}. These energies are significant and arise from both primary and second hydration spheres. The small, highly polarising Li⁺ ion is particularly effective at ordering a second hydration sphere giving it a particularly low ionic mobility.⁶⁷ Ion dipole bonding is seen both in the solid state and in solution and is governed by Equation 1.38 (where θ is the angle between the dipole and the point charge and μ is the dipole moment ($\mu = q_1 l$); this holds where $r \gg l$, where l is the distance between the charges making up the dipole). A supramolecular

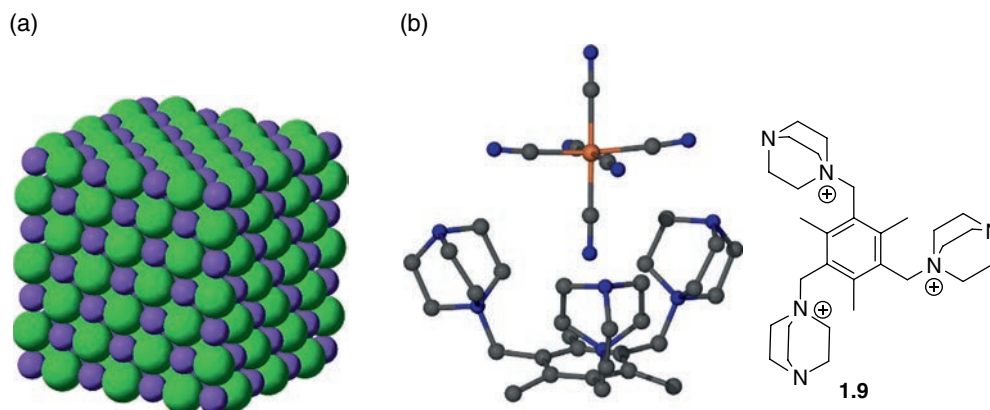
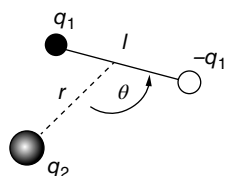
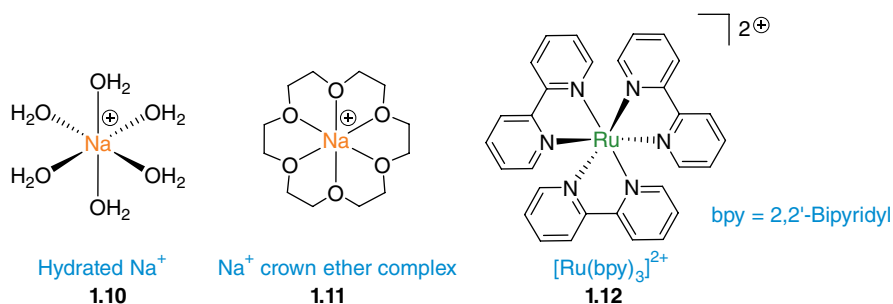


FIGURE 1.21 (a) The NaCl ionic lattice. (b) Supramolecular ion–ion interactions exemplified by the interaction of the organic cation **1.9** with [Fe(CN)₆]³⁻.⁶⁶

analogue is readily apparent in the structures of the complexes of alkali metal cations with the macrocyclic crown ethers (**1.11** and Chapter 3) in which the ether oxygen atoms play the same role as the polar water molecules, although the complex is stabilised by the chelate effect and the effects of macrocyclic preorganisation. This is very much a supramolecular host–guest system since the crown ether host has convergent binding sites while the metal ion guest is divergent. The oxygen lone pairs are attracted to the cation positive charge.



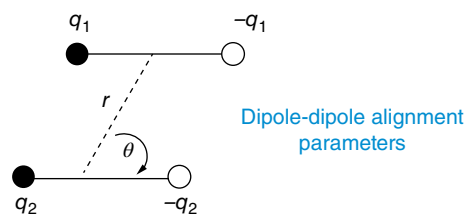
$$E = \frac{\mu q_2 \cos \theta}{4\pi\epsilon\epsilon_0 r^2} \quad (1.38)$$



Ion–dipole interactions also include coordinative bonds, which are mostly electrostatic in nature in the case of the interactions of non-polarisable metal cations and hard bases. Coordinate (dative) bonds with a significant covalent component, as in [Ru(bpy)₃]²⁺ (**1.12**), are also often used in supramolecular assembly and, as we will see in Chapter 12, the distinction between supramolecular and molecular species can become rather blurred. Hydration energies of anions arising from ion–dipole interactions are also very large, so that any receptor for an anion must compensate for this significant desolvation penalty. Anion receptors that operate in water therefore are much more likely to bind strongly if the receptor is positively charged such as ammonium or guanidinium compounds, or cationic metal complexes (Chapter 4).

1.8.3 Dipole–Dipole and $n \rightarrow \pi^*$ Interactions

Dipolar interaction energies are very dependent on orientation but are commonly weak and fall in the range 4–25 kJ mol⁻¹. The interaction energy for dipoles in the same plane is given by Equation 1.39. Hydrogen bonding is a specific example of a dipole–dipole interaction and can be much stronger in highly acidic systems (where there is also a covalent component). Because of its unique place in supramolecular chemistry, we will deal with hydrogen bonding separately in Section 1.8.4.



$$E = \frac{-\mu_1 \mu_2 (3 \cos^2 \theta - 1)}{4\pi\epsilon\epsilon_0 r^3} \quad (1.39)$$

Alignment of one dipole with another can result in significant attractive interactions from matching of either a single pair of poles on adjacent molecules (type I) or opposing alignment of one dipole with the other (type II, Figure 1.22a). Organic carbonyl compounds show this behaviour well in the solid state and calculations have suggested that type II interactions have an energy of about 20 kJ mol⁻¹, comparable to a moderately strong hydrogen bond. Type I interactions have been shown to be quite weak using a molecular torsion balance approach (3–10 kJ mol⁻¹).⁶⁸ The boiling point of ketones such as acetone (56 °C) demonstrates that dipole–dipole interactions are relatively weak in solution but are non-negligible. For example, the polar interhalogen ICl has approximately the same molecular weight as Br₂. However, ICl is a solid around room temperature because of dipolar interactions (it has two polymorphs melting at 27 and 15 °C, respectively), while non-polar bromine is a liquid above -7.2 °C. Dipolar interactions involving amide carbonyl groups are of significant importance in protein structure, although it has been recently recognised that there may also be a significant component involving delocalisation of a lone pair of electrons (n) from a carbonyl oxygen atom to the antibonding orbital (π^*) of a subsequent carbonyl group giving rise to an $n \rightarrow \pi^*$ interaction.⁶⁹ A survey of X-ray crystal structures in the Cambridge Structural Database suggests that where there is a short C–X...C=O contact, there is no preferred C–X...C=O dihedral angle and hence an $n \rightarrow \pi^*$ description is more appropriate, Figure 1.22b.⁷⁰

1.8.4 Hydrogen Bonding

Key Arunan, E., Desiraju, G.R., Klein, R.A. *et al.* (2011). Definition of the hydrogen bond (IUPAC Recommendations 2011). *Pure Appl. Chem.* 83: 1637–1641.

Hydrogen bonding has tremendous effects on molecular and supramolecular properties. It is the strong hydrogen bonding in water that makes its boiling point of 100 °C some 160 °C higher than the heavier H₂S, simply because of the more polar nature of the O–H bonds. Similarly, at room temperature (25 °C), butanone gas (C₄H₈O) which has a

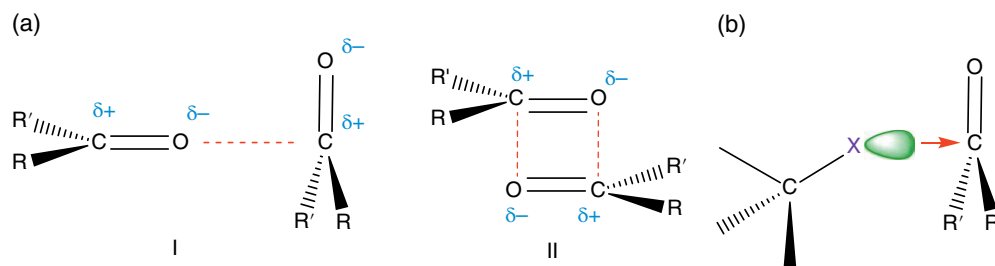


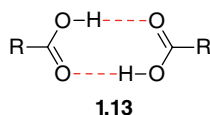
FIGURE 1.22 (a) Dipole–dipole interactions in carbonyls. (b) The $n \rightarrow \pi^*$ interaction.

hydrogen bonding carbonyl (C=O) functionality is a factor of 1.7×10^4 more soluble in water than the non-polar gaseous butane (C₄H₁₀). Conversely, the inhibition of firefly luciferase activity (the reaction that causes the firefly's glow) by butane is a factor of 74 times more efficient than butanone in water. The increased solvation of the butanone prevents it from blocking the enzyme hydrophobic binding site.

A hydrogen bond may be regarded as a particular kind of dipole–dipole interaction in which a hydrogen atom attached to an electronegative atom (or electron-withdrawing group) is attracted to a neighbouring dipole on an adjacent molecule or functional group. The hydrogen bond has been well recognised since at least 1939 where it appeared in Pauling's *Nature of the Chemical Bond* (Table 1.1). Pauling attributes the concept of the hydrogen bond to M. L. Huggins (1919, Graduate Thesis) and independently to W. M. Latimer and W. H. Rodebush (1920).⁷¹ The current IUPAC definition given in the section key reference dates from 2011 and states that:

The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.

Hydrogen bonds are commonly written D–H...A and usually involve a hydrogen atom attached to an electronegative atom such as O or N as the donor (D) and a similarly electronegative atom, often bearing a lone pair, as the acceptor (A). There are also significant hydrogen bonding interactions involving hydrogen atoms attached to carbon, rather than more electronegative atoms such as N and O (electronegativities: C: 2.55, H: 2.20, N: 3.04, O: 3.44). Because of its relatively strong and highly directional nature, hydrogen bonding has been described as the ‘master-key interaction in supramolecular chemistry’.² Normal hydrogen bonds typically range in strength from *ca.* 4–60 kJ mol^{−1}, although certain highly acidic compounds such as HF₂[−] have hydrogen bond energies up to 161.5 kJ mol^{−1}.⁷² An excellent example of hydrogen bonding in supramolecular chemistry is the formation of carboxylic acid dimers (Wolf's *Übermoleküle* in Table 1.1; **1.13**), which results in the shift of the $\nu(\text{OH})$ infrared stretching frequency from about 3400 to 2500 cm^{−1}, accompanied by a significant broadening and intensifying of the absorption. Typically, hydrogen bonded O...O distances are 2.50–2.80 Å in length, though interactions in excess of 3.0 Å may still be significant. Hydrogen bonds to larger atoms such as chloride are generally longer and may be weaker as a consequence of the reduced electronegativity of the larger halide acceptor, although the precise strength of the hydrogen bond is greatly dependent on its environment. Hydrogen bonds are ubiquitous in supramolecular chemistry. Hydrogen bonds are responsible for the overall shape of many proteins, recognition of substrates by numerous enzymes, and (along with π – π stacking interactions) for the double helix structure of DNA (Sections 2.8 and 10.3).



The 2011 definition includes the key stipulation that there should be evidence of bond formation and IUPAC recommends six criteria for the existence of a hydrogen bond:

1. The forces involved in the formation of a hydrogen bond include those of an electrostatic origin, those arising from charge transfer between the donor and acceptor leading to partial covalent bond formation between H and A, and those originating from dispersion.
2. The atoms D and H are covalently bonded to one another and the D–H bond is polarised, the H...A bond strength increasing with the increase in electronegativity of A.
3. The D–H...A angle is usually linear (180°) and the closer the angle is to 180°, the stronger is the hydrogen bond and the shorter is the H...A distance.
4. The length of the D–H bond usually increases on hydrogen bond formation leading to a red shift in the infrared D–H stretching frequency and an increase in the infrared absorption cross-section for the D–H stretching vibration. The greater the lengthening of the D–H bond in D–H...A, the stronger is the H...A bond. Simultaneously, new vibrational modes associated with the formation of the H...A bond are generated.

5. The D–H...A hydrogen bond leads to characteristic NMR signatures that typically include pronounced proton deshielding for H in D–H, through-hydrogen-bond spin–spin couplings between D and A, and nuclear Overhauser enhancements.
6. The Gibbs energy of formation for the hydrogen bond should be greater than the thermal energy of the system for the hydrogen bond to be detected experimentally.

Hydrogen bonds come in a wide range of lengths, strengths, and geometries and can be divided into three broad categories, the properties of which are listed in Table 1.7. 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 a strong acid and a good hydrogen bond acceptor, for example, in the H_5O_2^+ ion or in complexes of ‘proton sponge’, which are practically linear with the hydrogen atom almost equally positioned between the two electronegative atoms. In biochemical systems, strong hydrogen bonds are implicated in enzyme catalysis and in proton-transfer reactions in photoreceptors and ion channels.⁷³ 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, or amide interactions in proteins. Moderate hydrogen bond interactions do not usually 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 (Section 8.4). 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 result in a larger cone, and therefore there are more possible positions for the bond to occur in. In the case of hydrogen bonds between neutral species, it is generally accepted that there is a direct correlation between hydrogen bond strength (in terms of formation energy) and the crystallographically determined distance between hydrogen bond donor and acceptor. Distances tend to be shorter in ‘charge-assisted’ hydrogen bonds involving ions. The strength of similar hydrogen bonds can be very different between various systems and is not necessarily correlated with the Brønsted acidity of the proton (hydrogen) donor, although the $\text{p}K_{\text{a}}$ of D–H and $\text{p}K_{\text{b}}$ of the acceptor in a given solvent do correlate strongly with the energy of the hydrogen bond formed between them unless there are significant steric effects. It depends on the type of electronegative atom to which the hydrogen atom is attached and the geometry that the hydrogen bond adopts. Scales of empirically determined hydrogen bond acidity and basicity exist that quantify these effects.⁷⁴ A single, strong hydrogen bond per molecule may be sufficient to determine solid-state structure and exert a marked influence on the solution and gas phases, although hydrogen bonding is much more significant in non-polar

TABLE 1.7 Properties of hydrogen bonded interactions.

	Strong	Moderate	Weak
D—H...A interaction	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol^{-1})	60–161	16–60	<12
Bond lengths ($\text{\AA}$)			
H...A	1.2–1.5	1.5–2.2	2.2–3.2
D...A	2.2–2.5	2.5–3.2	3.2–4.0
Bond angles ($^\circ$)	175–180	130–180	90–150
Relative IR vibration shift (stretching symmetrical mode, cm^{-1})	25%	10–25%	<10%
^1H NMR chemical shift downfield (ppm)	14–22 (variable)	<14	?
Examples	Gas-phase dimers with strong acids/bases Proton sponge HF complexes	Acids Alcohols Biological molecules	Minor components of bifurcated bonds C–H hydrogen bonds O–H... π hydrogen bonds

A, hydrogen bond acceptor; D–H, hydrogen bond donor.

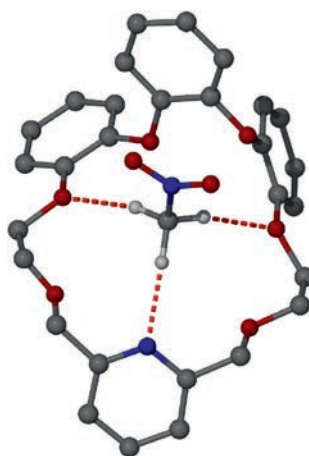


FIGURE 1.23 X-ray crystal structure showing C–H $\cdots$ N (2.21 Å) and C–H $\cdots$ O (2.41 Å, average) hydrogen bonding in a complex of a pyridyl crown ether with nitromethane.⁷⁵

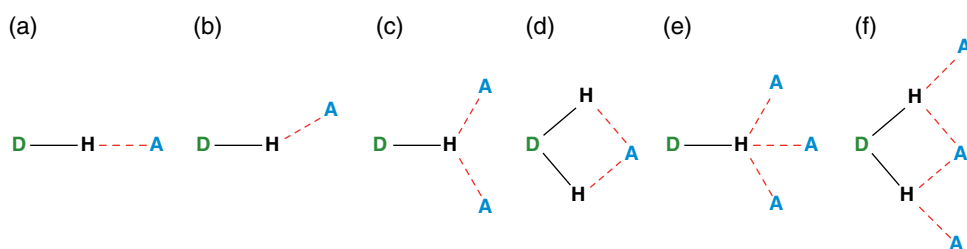


FIGURE 1.24 Various types of donor (D) acceptor (A) hydrogen bonding geometries; (a) linear, (b) bent, (c) donating bifurcated, (d) accepting bifurcated, (e) trifurcated, (f) three-centre bifurcated.

solvents than in water, where hydrogen bond donors and acceptors are highly solvated and hydrophobic interactions tend to dominate. Weaker hydrogen bonds play a role in structure stabilisation and can be significant when large numbers act in concert. They tend to be highly non-linear and involve unconventional donors and acceptors such as C–H groups, the π -systems of aromatic rings or alkynes or even transition metals and transition metal hydrides.

While C–H donor hydrogen bonds are at the weaker end of the energy scale of hydrogen bonds, the presence of electronegative atoms near the carbon can enhance significantly the acidity of the C–H proton, resulting in a significant dipole. An elegant example of C–H $\cdots$ N and C–H $\cdots$ O hydrogen bonds is the interaction of the methyl group of nitromethane with a pyridyl crown ether shown in Figure 1.23.⁷⁵

The types of geometries that can be adopted in a hydrogen bonding complex are summarised in Figure 1.24. These geometries 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 opposite charges or decrease the affinity due to repulsion between like charges. Figure 1.25 shows two situations in which arrays of hydrogen bond donors and acceptors are in proximity. An array of three donors (DDD) facing three acceptors (AAA) (Figure 1.25a) has only attractive interactions between adjacent groups and therefore the binding is enhanced. Mixed donor/acceptor arrays (ADA, DAD) suffer from repulsions by partial charges of the same sign being brought into proximity by the primary interactions (Figure 1.25b).

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 1.26. The CG base pair has three primary interactions (*i.e.* traditional hydrogen bonds) and has both attractive and repulsive secondary interactions. The adenine–thymine base pair is less stable with only two primary hydrogen bonds. The importance of secondary interactions in the construction of supramolecular polymers is discussed in Chapter 15.

In 2013, a controversial report appeared purporting to show direct AFM imaging of hydrogen bonding. The compelling image is shown in Figure 1.27.⁷⁶ However, as we have seen hydrogen bonds have a primarily electrostatic origin

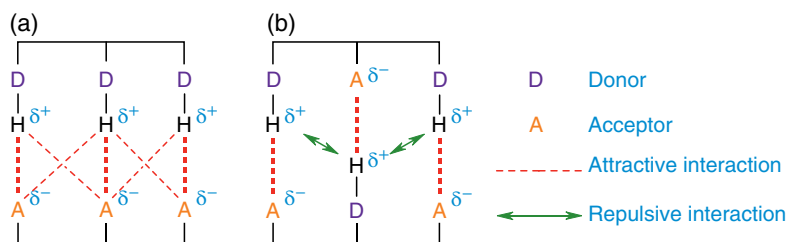


FIGURE 1.25 (a) Secondary interactions providing attractions between neighbouring groups between DDD and AAA arrays (primary interactions in bold) and (b) repulsions from mixed donor/acceptor arrays (ADA and DAD).

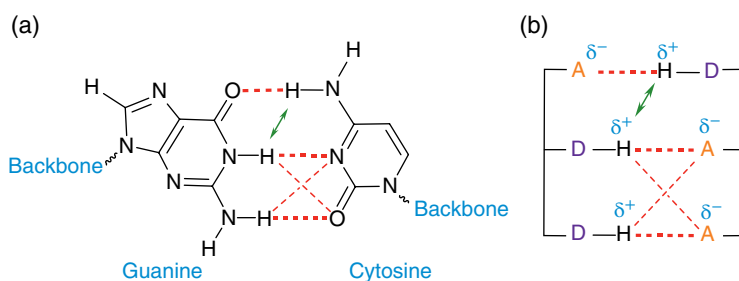


FIGURE 1.26 (a) Primary and secondary hydrogen bond interactions between guanine and cytosine base pairs in DNA and (b) a schematic representation.

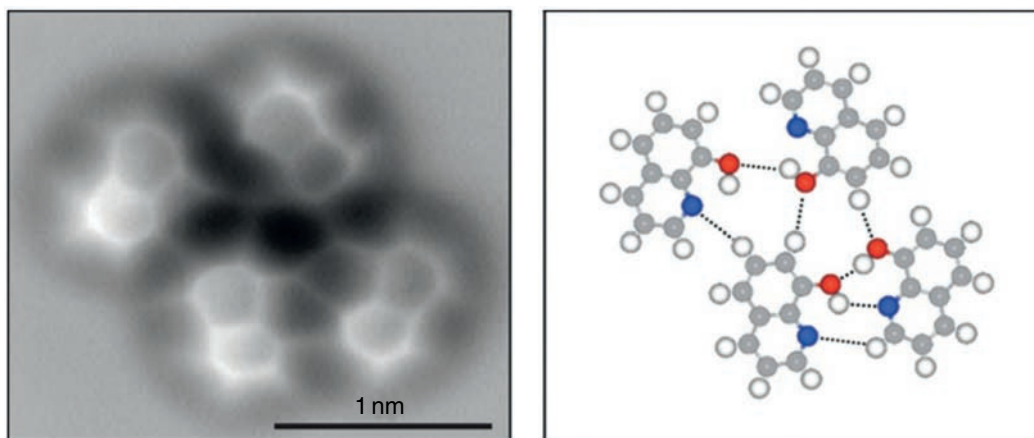


FIGURE 1.27 AFM image purporting to show direct hydrogen bonding along with the molecular network. In fact, such hydrogen bond-like features can be observed even in regions without a hydrogen bond and cannot be directly interpreted as intermolecular interactions.⁷⁶ © 2014, Reproduced with permission from American Physical Society.

with perhaps some covalent character in the strong limit, and so it is not clear why they should yield significant repulsive contrast in AFM. A later study showed that such hydrogen bond-like features can be observed even in regions without a hydrogen bond and appear to arise from AFM tip flexibility and hence such intermolecular contrast cannot be directly interpreted as intermolecular hydrogen bonds.⁷⁷ The individual bonding in a cobalt porphyrin on a gold surface has also been imaged using STM with a molecule of CO appended to the probe tip. This study directly imaged the bonding using inelastic tunnelling spectroscopy. The images revealed covalent C–C bonds, metal–nitrogen bonds,

and both intra- and inter-molecular hydrogen bonds, which appeared to be bifurcated. Again, however, the claims of direct hydrogen bonding imaging are controversial.⁷⁸

1.8.5 Cation- π Interactions

Key Mahadevi, A.S. and Sastry, G.N. (2013). Cation- π interaction: its role and relevance in chemistry, biology, and material science. *Chem. Rev.* 113: 2100–2138.

Transition metal cations such as Fe^{2+} , Pt^{2+} , etc., are well known to form complexes with olefinic and aromatic hydrocarbons, as in ferrocene [$\text{Fe}(\text{C}_5\text{H}_5)_2$] and Zeise's salt [$\text{PtCl}_3(\text{C}_2\text{H}_4)^-$], for example. The bonding in such complexes is strong and could by no means be considered non-covalent, since it is intimately linked with the partially occupied d -orbitals of the metals. Even species such as $\text{Ag}^+ \cdots \text{C}_6\text{H}_6$ have a significant covalent component. The interaction of alkaline and alkaline earth metal cations with $\text{C}=\text{C}$ double bonds is, however, a much more non-covalent interaction that may be regarded as the interaction of the polarising cation with the quadrupole on the aromatic ring, arising from the six $\text{C}^{\delta-}-\text{H}^{\delta+}$ bond dipoles, strongly attenuated by solvent polarity, Figure 1.28. For example, the interaction energy of K^+ and benzene in the gas phase is 79 kJ mol^{-1} (the figures for Na^+ and Li^+ are 113 and 160 kJ mol^{-1} , respectively).⁷⁹ By comparison, the association of K^+ with a single water molecule is similar at 75 kJ mol^{-1} . The reason K^+ is more soluble in water than in benzene is related to the fact that many water molecules can interact with the potassium ion, whereas only a few bulkier benzene molecules can fit around it. The more electron rich the aromatic ring, the stronger the cation- π interaction and so electron withdrawing groups such as cyano weaken the interaction, while electron-donating substituents such as the amino group strengthen it (the interaction energy of Na^+ with benzonitrile [PhCN], for example, is 66 kJ mol^{-1} , rising to 133 kJ mol^{-1} for aniline, PhNH_2). The interaction of non-metallic cations such as RNH_3^+ with double bonds may be thought of as a form of $\text{X}-\text{H} \cdots \pi$ hydrogen bond and is of significant biological importance since in the nicotinic acetylcholine receptor, acetylcholine forms a cation- π interaction between the NMe_3^+ group and a tryptophan residue.⁸⁰ This has considerable implications for the selective brain uptake of nicotine and hence nicotine addiction.⁸¹ It is increasingly recognised that cation- π interactions also play an important role in chemical reactions in which they can enhance the reaction rate and control regio-, chemo-, and stereoselectivities in solution and the solid state as well as in supramolecular systems and biocatalysts.⁸²

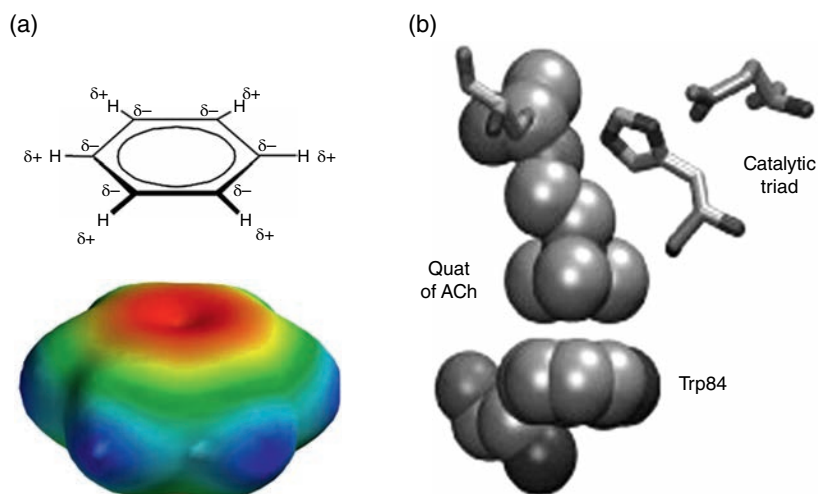


FIGURE 1.28 (a) The electrostatic origin of the cation- π interaction. Top: the six individual bond dipoles that create the overall electrostatic potential. Bottom: electrostatic potential: red for negative; blue for positive. (b) Binding of acetylcholine to the active site of acetylcholine esterase, showing the catalytic triad: Ser/His/Glu.⁷⁹ © 2007, Reproduced with permission from Oxford University Press.

1.8.6 Anion- π Interactions

Key Frontera, A. and Pallester, P. (2017). Anion- π interactions: theoretical studies, supramolecular chemistry and catalysis. In: *Aromatic Interactions* (ed. D.W. Johnson and F. Hof), 39–97. Cambridge: Royal Society of Chemistry.

Cation- π interactions (see Section 1.8.5) have been known since the early 1980s and were christened as such by Dennis Dougherty in 1990. Analogous anion- π interactions were observed as short anion-aromatic contacts in 1995 for organometallic calixarene derivatives⁸³ and were described in 1996 as arising as a direct consequence of the withdrawal of π -electron density from the aromatic ring by the transition metal centres (Figure 1.29a and Section 4.5.9).⁸⁵ The term ‘anion- π interaction’ was first used by Frontera and co-workers in 2002 who used a combination of theoretical and crystallographic evidence to establish that the interaction of anions with fluoroarenes is a favourable interaction arising from electrostatic and polarisation components.⁸⁶ The first explicit experimental reports to use the term ‘anion- π interaction’ occurred in 2004 in the form of copper chloride complexes of a pyridylaminotriazinylcyclam derivative⁸⁷ and, independently, in a copper(II) chloride complex of a *hexakis*(pyridin-2-yl)-[1,3,5]-triazine-2,4,6-triamine.⁸⁴ In both cases, the position of the chloride anion above the electron-deficient triazine ring matches theoretical predictions, Figure 1.29b. These examples typify anion- π interactions which usually involve an electron-deficient aromatic ring. Since that time there has been considerable interest in anion- π interactions. Intuitively, the interaction of an anion with π -electron density seems like it should be repulsive, however, there is a charge difference between an overall neutral aromatic ring and an anion and therefore in principle the possibility exists for an electrostatic attraction. Work by Kochi⁸⁸ has shown that anions form stable charge transfer complexes with a variety of electron-deficient aromatic compounds such as 1,2,4,5-tetracyanobenzene. The formation constants for the anion-aromatic complexes are in the range $1\text{--}10\text{ M}^{-1}$ and there is a linear correlation between the energy of the charge transfer band in the electronic spectrum and the formal reduction potential of the aromatic compound. This is referred to as a Mülliken correlation and provides strong evidence for the charge transfer nature of the interaction. The charge transfer also results in strong red or yellow colourations for the complexes and a number have been characterised by X-ray crystallography. The crystal structures reveal that the anion sits in an offset fashion at the edge of the aromatic rings rather than above the centroid with anion-carbon distances as short as $2.93\text{ \AA}$ for tetrachloro *o*-quinone and Br^- , shorter than the sum of the van der Waals radii ($3.55\text{ \AA}$). Similar anion- π interactions have also been implicated as controlling elements in

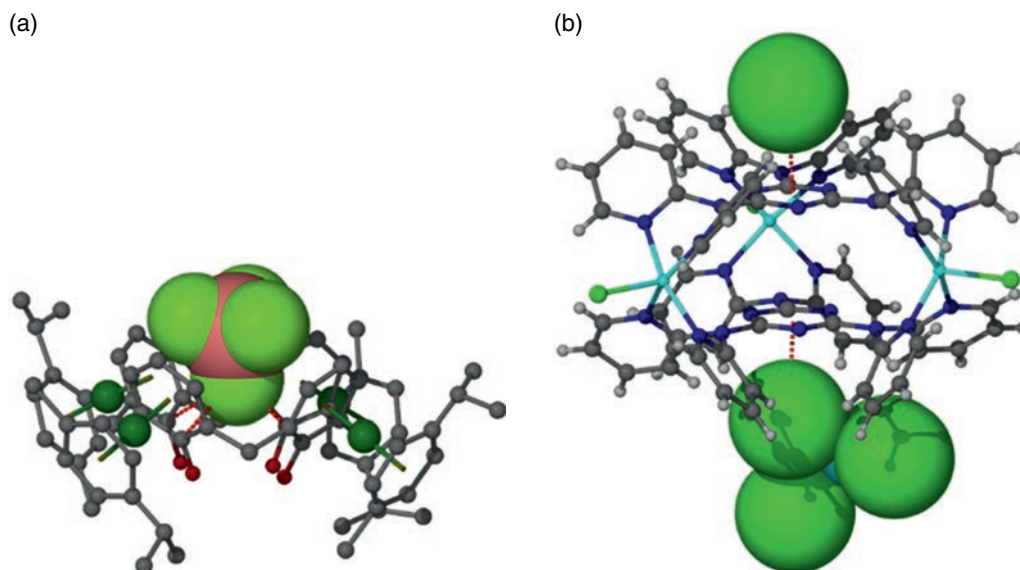


FIGURE 1.29 Anion- π interactions involving electron-deficient aromatic rings: (a) a BF_4^- complex of an organometallic calix[4]arene with $\text{F}\cdots\text{C}_{\text{aryl}}\ 2.85\text{ \AA}$ ⁸³ and (b) a $\text{Cl}^-\cdots$ triazine anion- π complex with $\text{Cl}^-\cdots$ triazine centroid $3.17\text{ \AA}$. (BF_4^- , Cl^- , and CuCl_4^{2-} anions shown in spacefilling mode).⁸⁴

self-assembly reactions of Ag^{I} complexes with π -acidic aromatic rings.⁸⁹ Since 2013, there has been interesting work on the use of anion– π interactions in organocatalysis. The anion– π catalysis functions by stabilising anionic transition states on π -acidic aromatic surfaces.⁹⁰

1.8.7 π – π Interactions

Key Riley, K.E. and Hobza, P. (2013). On the importance and origin of aromatic interactions in chemistry and biodisciplines. *Acc. Chem. Res.* 46: 927–936.

Aromatic π – π interactions (sometimes called π – π stacking interactions) occur between aromatic rings, often in situations where one is relatively electron rich and one is electron poor. There are two general types of π -interactions: face-to-face and edge-to-face, although a wide variety of intermediate geometries are known (Figure 1.30a). Face-to-face π -stacking interactions are responsible for the slippery feel of graphite and its useful lubricant properties. Similar π -stacking interactions between the aryl rings of nucleobase pairs also help to stabilise the DNA double helix. Edge-to-face interactions may be regarded as weak forms of $\text{CH}\cdots\pi$ hydrogen bonds between the slightly electron-deficient hydrogen atoms of one aromatic ring and the electron rich π -cloud of another.⁹² However, unlike hydrogen bonds, interactions in aromatic systems, particularly of the face-to-face type are predominantly dispersion interactions (*i.e.* induced dipole – Section 1.8.8). Strictly, edge-to-face interactions should not be referred to as ‘ π -stacking’ since there is no stacking of the π -electron surfaces. Edge-to-face interactions are responsible for the characteristic herringbone packing in the crystal structures of a range of small aromatic hydrocarbons including benzene (Figure 1.30b)⁹¹ while larger polycyclic aromatic hydrocarbons exhibit face-to-face interactions (Section 8.9.2).⁹³ The stabilisation energy in the benzene dimer in the gas phase is rather small (10 kJ mol^{-1}) but in substituted arenes, it can become much stronger particularly in mixed donor–acceptor systems. Aromatic stacking in nucleobases such as DNA is of considerable importance with an energy per nucleobase pair in the most stable stacked pair, guanine and cytosine of around 70 kJ mol^{-1} . Importantly, unlike hydrogen bonding, π – π interactions are not significantly weakened when passing from the gas phase into an aqueous environment. As a result, they are the principal stabilisation energy contribution in biomacromolecules and in some large-scale artificial aromatic systems such as the self-assembled cage shown in Figure 1.31 which is stabilised by the stacking of the naphthalene-derived spacer groups.⁹⁴

Sanders and Hunter have proposed a simple model based on competing electrostatic and van der Waals influences, in order to explain the variety of geometries observed for π – π stacking interactions and to predict quantitatively the interaction energies.⁹⁵ Their model is based on an overall attractive van der Waals interaction (Section 1.8.8), which is proportional to the contact surface area of the two π -systems. This attractive interaction dominates the overall energy of the π – π interaction and may be regarded as an attraction between the negatively charged π -electron cloud of one molecule and the positively charged σ -framework of an adjacent molecule. The relative orientation of the two

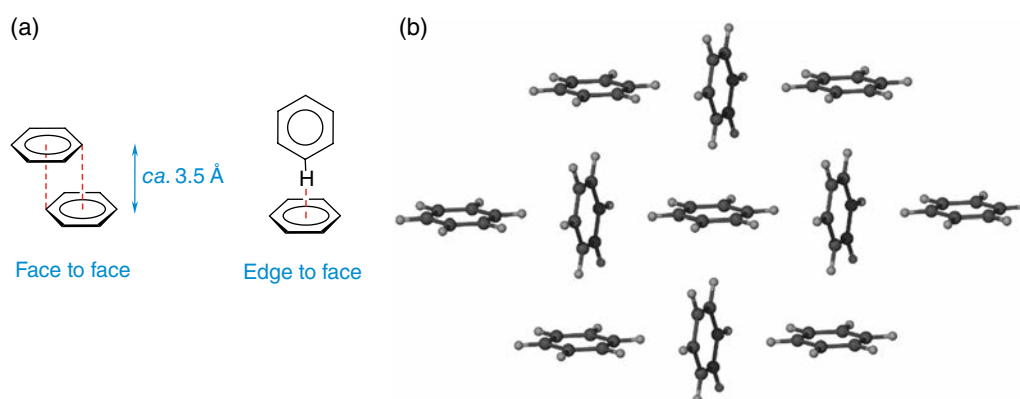


FIGURE 1.30 (a) Limiting types of π – π interaction. Note the offset to the face-to-face mode (direct overlap is repulsive). (b) X-ray crystal structure of benzene showing herringbone motif arising from edge-to-face interactions.⁹¹

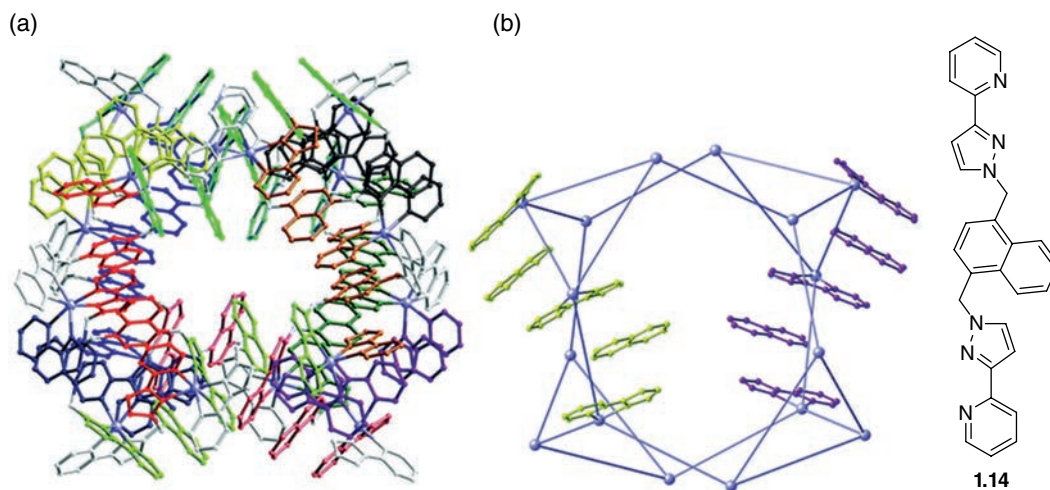


FIGURE 1.31 X-ray crystal structure of the discrete coordination cage $[\text{Cd}_{16}(\mathbf{1.14})_{24}]^{32+}$: (a) full structure, (b) π -stacking of the naphthalene-derived rings.⁹⁴ © 2013, Reproduced with permission from Royal Society of Chemistry.

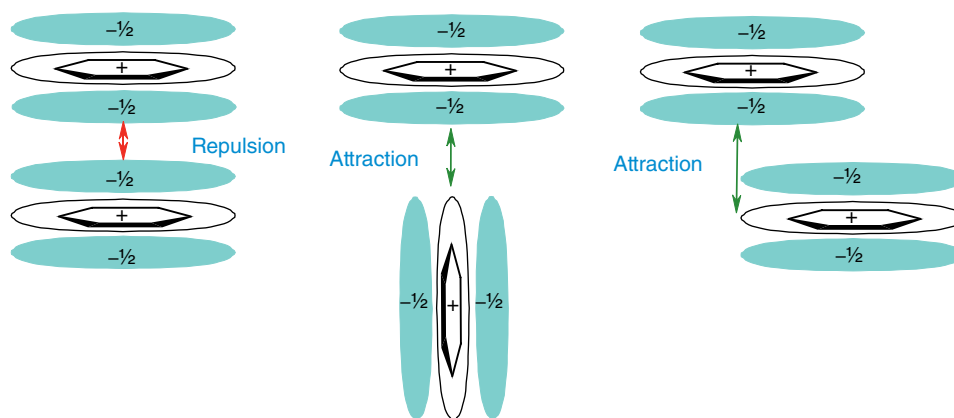


FIGURE 1.32 Interacting π -quadrupoles.

interacting molecules is determined by the electrostatic repulsions between the two negatively charged π -systems (Figure 1.32).

Sanders and Hunter stress the importance of the interactions between individual pairs of atoms rather than molecules as a whole and, while their approach has been relatively successful, there is ongoing debate over the nature of π - π interactions. Work involving substituent effects suggests that London dispersion forces might play a more important role than electrostatic interactions.⁹⁷ π -stacking interactions are of considerable interest and importance in the crystal structures of both organic and coordination compounds and have a marked influence on solution binding *via* the hydrophobic effect (Section 1.9.1). Edge-to-face π -interactions give rise to common motifs such as the sixfold phenyl embrace often found in compounds containing three or more aromatic rings, such as metal complexes of PPh_3 or ClGePh_3 (Figure 1.33).⁹⁶ A survey of π -interactions in crystalline coordination compounds found that a slipped (parallel displaced) interaction is the most common with the vector between the ring centroids forming an angle of about 20° and aromatic ring centroid – centroid distances of up to $3.8 \text{ \AA}$. This parallel-displaced structure is thought to have a contribution from π - σ attractive interactions that increases with increasing offset.⁹⁸

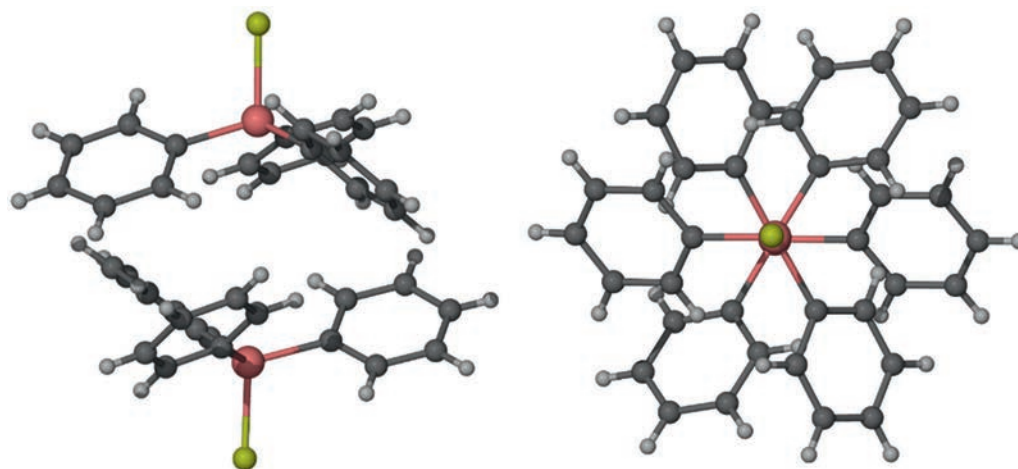


FIGURE 1.33 Sixfold edge-to-face phenyl embrace in ClGePh_3 .⁹⁶

1.8.8 Induced Dipolar Interactions and Polarisability

Key Schneider, H.-J. (2015). Dispersive interactions in solution complexes. *Acc. Chem. Res.* 48: 1815–1822.

When a molecule or ion approaches another species, polarisation occurs according to the polarisability (*i.e.* the tendency of molecules to form charge separation, α) of their respective electron clouds. The perturbation of a non-polar molecule or ion by a polar one leads to electrostatic interactions that otherwise might not have existed. These terms can be considered to contribute in addition to the primary electrostatic contributions to binding free energy. In the case of an ion interacting with a neutral molecule, there is an *ion-induced dipole interaction* governed by Equation 1.40 (note the r^{-4} dependence). Cation- π and anion- π interactions have a significant ion-induced dipole component to them.

$$E = \frac{-q^2\alpha}{4\pi\epsilon\epsilon_0 r^4} \quad (1.40)$$

Interactions between a molecule with a permanent dipole and a non-polar but polarisable molecule are termed *dipole-induced-dipole interactions*. The electric field associated with the dipole induces a dipole in the polarisable molecule, determined by the polarisability of that molecule. The induced dipole is aligned with the permanent dipole of the approaching molecule and so there is no $(3\cos^2\theta - 1)$ term and hence the interaction energy is governed by Equation 1.41 and has an r^{-6} dependence.

$$E = \frac{-2\mu_1^2\alpha_2}{(4\pi\epsilon\epsilon_0)^2 r^6} \quad (1.41)$$

1.8.9 Van der Waals Forces and Crystal Close Packing

Key Kitaigorodskii, A.I. (1961). *Organic Chemical Crystallography* (Originally published in Russian by Press of the Academy of Sciences of the USSR, Moscow, 1955). New York: Consultants Bureau.

Van der Waals interactions (induced dipole–induced dipole) arise from the polarisation of an electron cloud by the proximity of an adjacent nucleus, resulting in a weak electrostatic attraction. They are non-directional and hence possess only limited scope in the design of specific hosts for selective complexation of particular guests. In general, van der Waals interactions provide a general attractive interaction for most ‘soft’ (polarisable) species with an interaction energy proportional to the surface area of contact. In supramolecular chemistry, they are most important in the

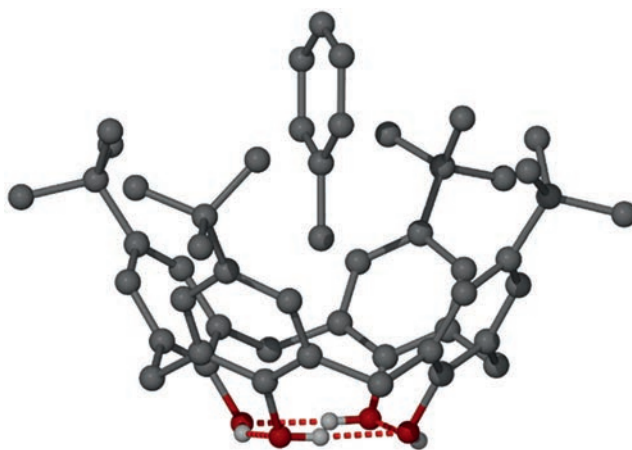


FIGURE 1.34 X-ray crystal structure of a typical van der Waals inclusion complex *p*-*t*-butylcalix[4] arene-toluene.⁹⁹

formation of inclusion compounds in which small, typically organic molecules are loosely incorporated within crystalline lattices or molecular cavities, *e.g.* the inclusion of toluene within the molecular cavity of the *p*-*t*-butylphenol-based macrocycle, *p*-*t*-butylcalix[4]arene (Section 6.2.2 and Figure 1.34).⁹⁹ van der Waals interactions may be divided into dispersion (London) and exchange–repulsion terms. The dispersion interaction is the attractive component that results from the interactions between fluctuating multipoles (quadrupole, octupole, *etc.*) in adjacent molecules. The attraction decreases very rapidly with distance (r^{-6} dependence) and is additive with every bond in the molecule contributing to the overall interaction energy. The exchange–repulsion defines molecular shape and balances dispersion at short range, decreasing with the twelfth power of interatomic separation. While van der Waals interactions are relatively weak, they become highly significant if there is a large contact surface area over which two or more molecules interact. As a result, van der Waals interactions give rise to the strongly favourable interactions that occur between long chain hydrocarbons that occur in processes such as micelle formation and the formation of lipid bilayers in cell membranes.

In examination of solid-state (*i.e.* crystal) structures, the need to achieve a close packed arrangement is also a significant driving force. This has been summed up in the truism ‘Nature abhors a vacuum’, but, according to the close packing theory of Kitaigorodsky, it is simply a manifestation of the maximisation of favourable isotropic van der Waals interactions. Kitaigorodsky’s theory tells us that molecules undergo a shape simplification as they progress towards dimers, trimers, higher oligomers, and ultimately crystals. This means that one molecule dovetails into the hollows of its neighbours so that a maximum number of intermolecular contacts are achieved, rather like the popular computer game *Tetris*. Very few solid-state structures are known to exhibit significant amounts of ‘empty’ space (a typical organic solid has a packing efficiency of around 70%¹⁰⁰). Those which do (*e.g.* zeolites, Section 9.2) possess a very rigid framework that can resist implosion under what amounts effectively to an enormous pressure differential between atmospheric pressure and the empty crystal pore or channel. Such materials often exhibit very interesting and useful properties in catalysis and separation science.

1.8.10 Halogen Bonding

Key Gilday, L.C., Robinson, S.W., Barendt, T.A. *et al.* (2015). Halogen bonding in supramolecular chemistry. *Chem. Rev.* 115: 7118–7195.

Halogen bonds involve an electron-deficient halogen bond donor R–X and an electron-rich halogen bond acceptor, typically a Lewis base, B. The R–X⋯B unit has a well-defined, linear geometry (160–180°) with X⋯B distances considerably less than the sum of the van der Waals radii. The 2013 IUPAC definition states that a halogen bond (XB) occurs when ‘there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity’. The most obvious example is the I[−]⋯I₂ interaction found in the I₃[−] ion which has an energy of *ca.* 200 kJ mol^{−1}, and indeed

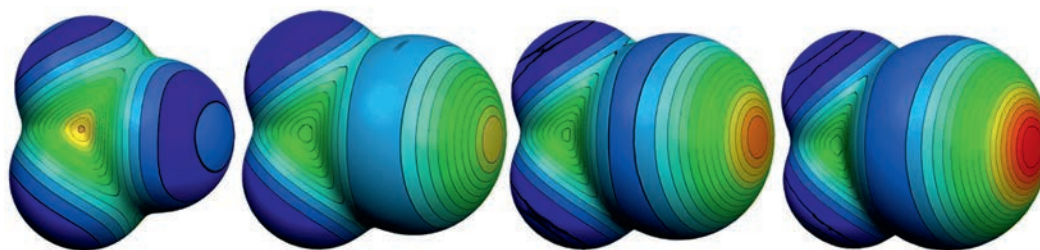


FIGURE 1.35 Molecular electrostatic potential isodensity surface of CF_3X (from left to right, $\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$) – red cationic σ -hole region, blue negatively charged region.¹⁰¹ © 2007, Reproduced with permission from Springer Nature.

halogen bonds have been known since the discovery of $\text{Me}_3\text{N}\cdots\text{Br}_2$ in 1896. In the past two decades, halogen bonding has become an extremely important topic in supramolecular chemistry. Halogen bonding arises because of the presence of a region of positive charge on the halogen atom surface opposite the substituent group, a so-called σ -hole, Figure 1.35. The size of the σ -hole increases $\text{Cl} < \text{Br} < \text{I}$ but it is absent for organofluorine compounds because of the high electronegativity and significant sp -hybridisation of the fluorine atom. Following this sequence logically, the heaviest halogen astatine should exhibit the highest halogen-bond donating ability, although with such a heavy element the halogen bonding ability could be mitigated by relativistic effects, as illustrated by the metallic character of astatine. Experimental and theoretical evidence based on the bonding of astatine monoiodide with a series of organic ligands in cyclohexane solution has established that astatine compounds do indeed exhibit halogen bonds that are stronger than the analogous iodo species.¹⁰² Electron-withdrawing substituents also enhance the σ -hole and hence compounds such as iodopentafluorobenzene, perfluoroalkyl iodides, and iodoalkynes are among the most potent halogen bond donors. Halogen bonds in general tend to be weaker in strength than hydrogen bonds, however, they are less attenuated by solvation and combinations of hydrogen and halogen bonding which are self-sorting can be used in fine-tune assembly. X-ray Absorption Spectroscopy in halogen-bonded complexes shows intense pre-edge features that imply charge transfer from the halide to its bonding partner. This measurement, in conjunction with DFT calculations, allows the degree of covalency of the halogen bond to be assessed, which proves to be similar to the covalency of transition metal coordinate covalent bonds.¹⁰³ *N*-alkyl iodoimidazolium receptors such as in the tripodal bromide complex shown in Figure 1.36a has been shown to bind and transport anions by halogen bonding in solution¹⁰⁴ and a combination of pyridyl $\cdots$ diiodotetrafluorobenzene halogen bonding and urea hydrogen bonding interactions has been used to make organogels (Figure 1.36b and Section 15.7).¹⁰⁵ Halogen bonding is now finding applications in topological synthesis, medicinal chemistry, liquid crystals, drug delivery, nanoparticles, and optical and magnetic materials.^{106,107} The advantages of halogen bonding in these contexts include the following characteristics.

- Directionality – halogen bonds tend to be more linear than hydrogen bonds.
- Tunability – halogen bond strength increases $\text{F} \ll \text{Cl} < \text{Br} < \text{I} (< \text{At})$.
- Donor atom size and effect on photophysics – the heavy iodine atom can promote inter-system crossing and hence access triplet states.
- Hydrophobicity – halogen bonds are hydrophobic equivalents of hydrogen bonds.

An interaction closely related to halogen bonding is *chalcogen bonding*.¹⁰⁸ Chalcogen bonding involves an interaction between a positively polarised chalcogen atom ($\text{Ch} = \text{O}, \text{S}, \text{Se}, \text{and Te}$) and a Lewis-base. While it has been recognised since the mid-1970s, it is relatively under-researched. The interaction involves electrostatics, charge-transfer, and dispersion. As in halogen bonds, the electrostatic contribution comes from the anisotropic electron distribution around the chalcogen giving rise to a σ -hole that is attracted to the lone pair electron density. The charge transfer component comes from donation of the Lewis Base lone pair into the $\text{R}-\text{Ch} \sigma^*$ orbital. The strength of a chalcogen bond depends on the Lewis basicity of the interacting partner, the nature of the chalcogen atom ($\text{Te} > \text{Se} > \text{O} > \text{S}$), the polarisation of the chalcogen atom (which may be increased by using cationic heteroarene or polyfluorinated arene backbones), and the $\text{R}-\text{Ch}\cdots\text{Lewis Base}$ interaction angle. The strength is at a maximum when the angle is close to 180° .

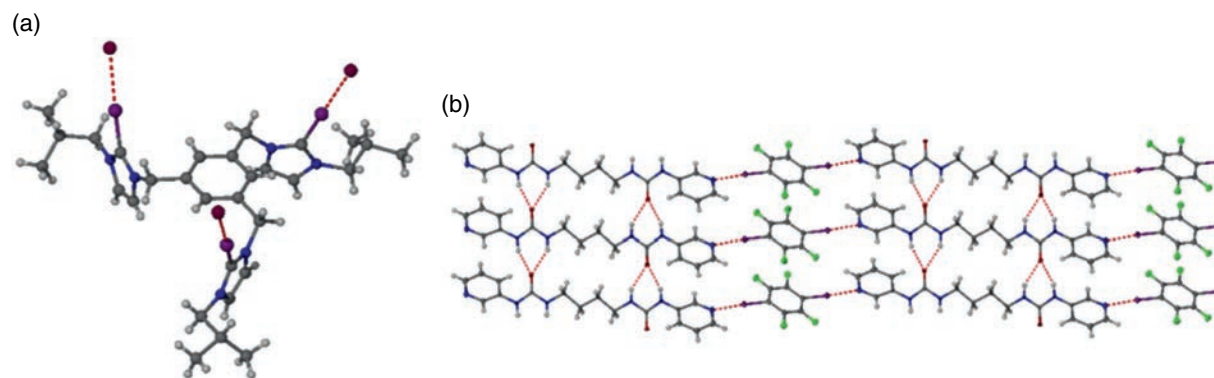


FIGURE 1.36 (a) Bromide binding by a tripodal halogen bonding receptor.¹⁰⁴ (b) Organogel formation by a combination of urea...urea hydrogen bonding and pyridyl...diiidotetrafluorobenzene hydrogen bonding.¹⁰⁵ © 2013, Reproduced with permission from Springer Nature.

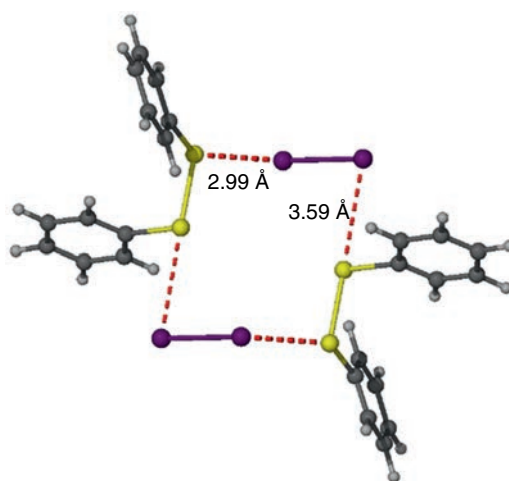


FIGURE 1.37 Halogen and chalcogen bonding in $\text{Ph}_2\text{Se}_2 \cdot \text{I}_2$.¹⁰⁹

A good example is the complex between iodine and diphenyldiselenide (Figure 1.37). This forms a rectangular adduct involving two strong halogen bonds with $\text{I} \cdots \text{Se}$ distances 2.99 Å and two chalcogen bonds ($\text{I} \cdots \text{Se}$ 3.59 Å) shorter than the 3.88 Å sum of van der Waals radii of iodine and selenium.¹⁰⁹ Chalcogen bonds have been used in crystal engineering, anion binding and transport, and organocatalysis.¹⁰⁸

1.8.11 Metalphilic Interactions and Secondary Bonding

Key Pyykkö, P. (1997). Strong closed-shell interactions in inorganic chemistry. *Chem. Rev.* 97: 597–636.

Atoms with unfilled electron shells form strong, covalent bonds. Ions generally have closed valence electron shells but experience strong attractions between oppositely charged pairs. We would not intuitively expect closed shell atoms of neutral or like charges to form significant interactions, however, in some cases they do. These interactions are termed closed shell interactions and include secondary bonding interactions,¹¹⁰ metalphilic interactions,¹¹¹ and halogen and chalcogen bonding (Section 1.8.10). Closed shell interactions are broadly comparable in strength with moderate-strength hydrogen bonds and are thought to arise from electron correlation effects, significantly strengthened by relativistic effects in heavy elements, particularly gold and to a lesser extent silver (where they are termed *aurophilic* and

argentophilic interactions¹¹²). Thus, closed shell interactions are most pronounced for heavy metals with examples reported for electron configurations from d^8 to $d^{10}s^2$, and the heavier halogens.

Aurophilic interactions experience significant relativistic shortening and the Au...Au distances which are in the range 2.8–3.0 Å are typically shorter than silver(I) analogues. The relativistic factor comes from the fact that electrons moving near highly charged nuclei have a velocity close to that of the speed of light and therefore experience a relativistic mass that is larger than their resting mass. The increased mass causes a decrease in the orbital radius and hence a decrease in atomic radius that is particularly pronounced for gold. Aurophilic interactions are ubiquitous in linear, 2-coordinate Au^I complexes with many examples having the ‘A-frame’ geometry as in $[\text{Au}_2(\mu\text{-Cl})(\text{PPh}_3)_2](\text{ClO}_4)$, Au...Au 3.06 Å, Figure 1.38.¹¹³ Interestingly, in the compound $[\text{Au}_2(\text{dmpm})_3](\text{ClO}_4)_2$ which exhibits an Au...Au distance of 3.05 Å, it proved possible to measure a Raman vibrational stretching band for the Au...Au bond at 79 cm⁻¹. The energy of this band *increases* to 165 cm⁻¹ on UV irradiation suggesting that aurophilic interaction is strengthened in the excited state.¹¹⁴ Systems based on a central square-planar Pt^{II} motif often exhibit unique optical properties, which can be attributed to closed shell Pt...Pt metallophilic interactions. The classic example is Magnus’ green salt, $[\text{Pt}(\text{NH}_3)_4][\text{PtCl}_4]$ comprising an alternating chain of platinum(II) hexamine cations and tetrachloroplatinate anions first reported in 1826. The green colour is attributed to nearest-neighbour Pt...Pt interactions between adjacent layers. Interestingly, it took until 2014 for the structure of the elusive isomer Magnus’ pink salt to be determined. The pink salt has a non-columnar arrangement of square-planar Pt units which precludes any possibility of metallophilic Pt...Pt interactions and the inter-platinum distances is over 5 Å.¹¹⁵

Secondary bonding (a term coined by Nat Alcock in 1972¹¹⁰) is a closed shell interaction of type X–A...X' where X is commonly a heavier halogen or chalcogenide element (Cl, Br, S, *etc.*). Secondary bonds closely resemble hydrogen bonds except that A is often a multivalent heavy atom such as Hg, Tl, Sn, Pb, Sb, Bi, Se, or Te instead of hydrogen. The X–A bond is a normal covalent bond and while the A...X' is a closed shell interaction involving donation of a non-bonding lone pair on X' into an antibonding σ^* orbital of the X–A bond, Figure 1.39. Secondary bonding is a very significant interaction in determining the solid-state structures of heavy element compounds.

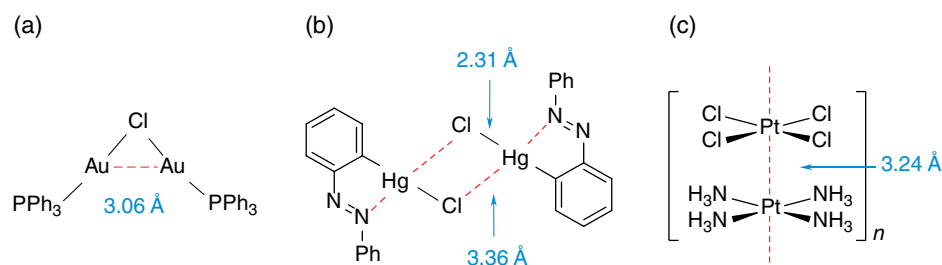


FIGURE 1.38 Examples of closed shell interactions: (a) aurophilic interactions in $[\text{Au}_2(\mu\text{-Cl})(\text{PPh}_3)_2](\text{ClO}_4)$, (b) secondary bonding in $[\{\text{HgCl}(\text{C}_6\text{H}_4\text{N}_2\text{Ph})\}_2]$, (c) metallophilic interactions in Magnus’ green salt.

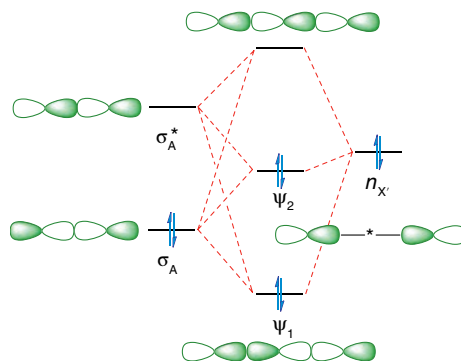


FIGURE 1.39 Molecular orbital description of secondary bonding and related interactions showing the $n \rightarrow \sigma^*$ interaction.

1.8.12 The Mechanical Bond

Key Bruns, C.J. and Stoddart, J.F. (2017). *The Nature of the Mechanical Bond*. Chichester: Wiley.

A *mechanical bond* is an entanglement in space between two or more component parts, such that they cannot be separated without breaking or distorting (usually covalent) chemical bonds between atoms. Unlike the other supramolecular interactions we have seen, a mechanical bond does not necessarily involve any enthalpically stabilising attraction between the component parts and so its strength depends only on the strength of the weakest covalent bond holding the *mechanically interlocked molecule* (MIM) together. The first mechanical bond originated with the work of Ed Wasserman in 1960 who produced the first MIM – a *catenane* (Section 11.2) *via* a very low-yielding statistical approach.¹¹⁶ It was not until the supramolecular template approaches pioneered by the groups of Jean-Pierre Sauvage¹¹⁷ and J. Fraser Stoddart¹¹⁸ in the 1980s, however, that meaningful quantities of mechanically interlocked molecules became available. These achievements led to the award of the 2016 Nobel Prize in Chemistry to Sauvage and Stoddart, along with Ben Feringa for their work in the design and synthesis of molecular machines (Chapters 11 and 12). Mechanical bonding gives rise to the field of *chemical topology* and hence *topological isomerism* whereby supermolecules may differ in their spatial entanglement because, while they contain the same molecules, they cannot be interconverted without breaking and making chemical bonds. Key examples of MIMs are rotaxanes (in which one molecule is threaded through another) and catenanes (involving two or more mutually interlocked rings). Molecular knots are single molecules that also exhibit topological isomerism. A knotted molecule is a topological isomer of the analogous *unknot* – for example, a macrocycle tangled into the simplest knot, a trefoil knot, is a topological isomer of an unknotted macrocycle. The rich landscape of mechanically bonded and knotted systems is described in Chapter 11. Mechanical bonding is also relevant to the steric imprisonment of guests termed *constrictive binding* within the closed cavity *carcerand* and *hemicarcerand* hosts (Section 6.7). Stoddart has characterised mechanical bonding as being central to the field of *mechanostereochemistry* sitting in between the fields of supramolecular chemistry (which involves non-covalent interactions between at least two molecules) and *chemical topology* involving entanglements of a single molecule, Figure 1.40.

1.8.13 Dynamic Covalent Interactions

Key Jin, Y., Yu, C., Denman, R.J., and Zhang, W. (2013). Recent advances in dynamic covalent chemistry. *Chem. Soc. Rev.* 42: 6634–6654.

While supramolecular chemistry is fundamentally concerned with non-covalent interactions, there is some ‘wiggle room’ in the definition and supramolecular concepts can inform systems and materials linked by relatively strong

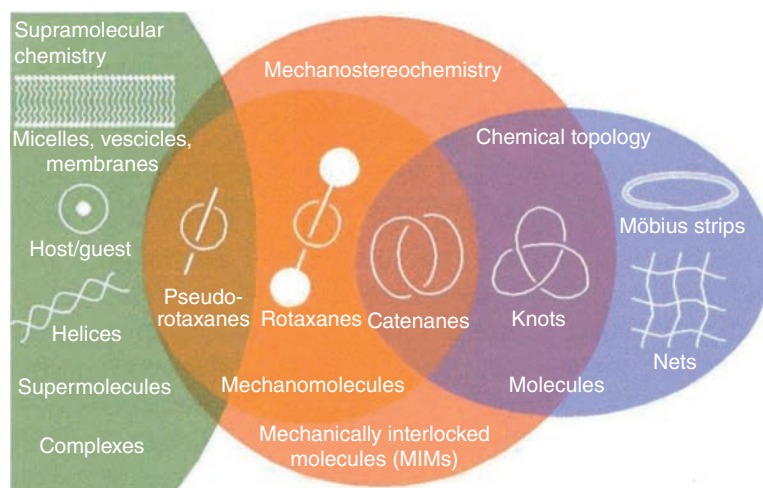


FIGURE 1.40 A Venn diagram illustrating Stoddart's classification of different types of molecular species into the intersecting fields of supramolecular chemistry, mechanostereochemistry, and chemical topology. Reproduced with permission © 2017 John Wiley & Sons.

covalent bonds that can be broken and re-formed on a time scale short enough to allow the establishment of a thermodynamic equilibrium and the consequent error-checking that comes with it. Systems based on these kinds of breakable covalent bonds are topical and are thought of as having *dynamic covalent interactions*. An equilibrating mixture of components linked by dynamic covalent bonds can be thought of as a *dynamic combinatorial library* of compounds and can be subject to selective templation and even autocatalysis in which a template stabilises particular components from the equilibrating mixture and hence favours their formation. Examples of dynamic covalent bonding include C–C bond formation (e.g. the Diels–Alder reaction), C=N bonding (e.g. amine–aldehyde condensation to give an imine), C–O bonding (e.g. acetal formation), B–O bond formation (e.g. boric acid condensation), and S–S bond exchange in disulfides. Compared with typical supramolecular interactions, dynamic covalent bonds usually exhibit slower kinetics and require the use of catalysts to achieve equilibrium on a useful time scale. Particularly, prominent recent work has involved artificial self-replicating systems based on macrocyclic disulfides¹¹⁹ and adaptive orthoester cryptands¹²⁰ (Chapter 16). The discovery of covalent organic frameworks (COFs) based on boronic acid condensation is also conceptually based on the dynamic nature of the interaction (Chapter 9).¹²¹

1.9 SOLVATION EFFECTS

1.9.1 The Hydrophobic and Hofmeister Effects

Key Cremer, P.S., Flood, A.H., Gibb, B.C., and Mobley, D.L. (2018). Collaborative routes to clarifying the Murky waters of aqueous supramolecular chemistry. *Nature Chem.* 10: 8–16.

Supramolecular chemistry in water is dominated by two principal factors: the hydrophobic effect and the Hofmeister effect. The hydrophobic effect governs the solvation (or lack thereof) of organic residues in water while the Hofmeister effect concerns the way in which salts modulate the properties of aqueous solutions particularly how they influence the hydrophobic effect. Neither effect is fully understood at the molecular level although it is clear that the hydrophobic effect depends on the size and shape of a solute. The Hofmeister effect seems to relate to the way in which salts can directly interact with a solute and hence modify its aqueous solubility behaviour.¹²²

The Hydrophobic Effect

Although occasionally mistaken for a force, the hydrophobic effect generally relates to the exclusion from polar solvents, particularly water, of large particles or those that are weakly solvated (e.g. *via* hydrogen bonds or dipolar interactions). The effect is obvious in the immiscibility of oil and water. Essentially, the water molecules are attracted strongly to one another resulting in a natural agglomeration of other species (such as non-polar organic molecules) as they are squeezed out of the way of the strong inter-solvent interactions. This can produce effects resembling attraction between one organic molecule and another, although there are in addition van der Waals and π – π stacking attractions between the organic molecules themselves. The hydrophobic effect is very important in biological systems in the creation and maintenance of protein and polynucleotide structure and in the maintenance of phospholipid bilayer cell walls. Hydrophobic effects are of crucial importance in the binding of organic guests by cyclodextrins, cucurbituril, pillararene, cavitand, and cyclophane hosts in water (Chapter 6)¹²² and may be divided into two energetic components: enthalpic and entropic. The enthalpic hydrophobic effect involves the stabilisation of water molecules that are driven from a host cavity upon guest binding. Because host cavities are often hydrophobic, intracavity water does not interact strongly with the host walls and is therefore of high energy. Upon release into the bulk solvent, it is stabilised by interactions with other water molecules, Figure 1.41a. The entropic hydrophobic effect arises from the fact that the presence of two (often organic) molecules in solution (host and guest) creates two ‘holes’ in the structure of bulk water. Combining host and guest to form a complex results in less disruption to the solvent structure and hence an entropic gain (resulting in a lowering of overall free energy). The process is represented schematically in Figure 1.41b.

As an example, consider the binding of the guest *p*-xylene by the cyclophane host **1.15** (part of a class described in more detail in Section 6.5). The binding constant in water is $9.3 \times 10^3 \text{ M}^{-1}$. At 293 K, the complexation free energy, ΔG° , is -22 kJ mol^{-1} which divides into a favourable enthalpic stabilisation, $\Delta H^\circ = -31 \text{ kJ mol}^{-1}$, and an unfavourable entropic component, $T\Delta S^\circ = -9 \text{ kJ mol}^{-1}$. In this case, it is the enthalpic contribution to the hydrophobic binding that

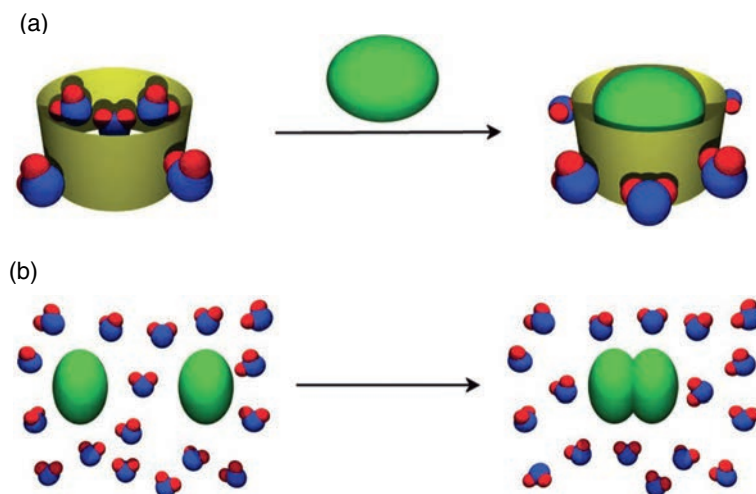
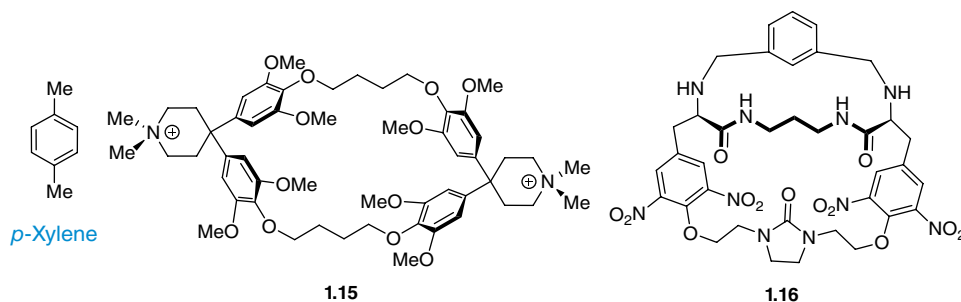


FIGURE 1.41 Hydrophobic binding of organic guests in aqueous solution. (a) The displacement of water molecules from a hydrophobic cavity is responsible for the enthalpic hydrophobic effect. (b) Two organic molecules creating a hole within an aqueous phase, giving rise to the entropic hydrophobic effect – one hole is more stable than two.

dominates. The enthalpic contribution is too great to result from attractive forces between the host and guest (which experience only weak π -stacking and van der Waals interactions) and thus must arise from specific solvent–solvent forces. In methanol solvent, the enthalpic component is reduced greatly as a result of weaker solvent–solvent interactions.¹²³



The Hofmeister Effect

Key Okur, H.I., Hladílková, J., Rembert, K.B. *et al.* (2017). Beyond the Hofmeister series: ion-specific effects on proteins and their biological functions. *J. Phys. Chem. B* 121: 1997–2014.

The *Hofmeister series* or lyotropic series was first outlined by Czech protein scientist Franz Hofmeister in the 1870s from experiments based on the ability of various ions to ‘salt out’ proteins from water. The Hofmeister series is shown in Table 1.8, where the left-hand side represents ions that dissolve and denature proteins in concentrated salt solutions, and the right-hand side represents precipitation of proteins. Anions are generally more important than cations and the series is correlated with anion hydration energy. While early assumptions attributed the origin of the series to the ordering of the water solvent by the various species, the effect is likely to arise from a complex mixture of specific ion–solute interactions occurring typically at concentrations over 100 mM that cannot be explained by classical theories.

The strongly hydrophilic (*kosmotropic*) members of the series are traditionally said to cause strong ordering of water around themselves. They increase surface tension and as a result cause non-polar molecules to precipitate (*salt out*). They can be thought of as in effect strengthening the hydrophobic effect. In contrast, the more hydrophobic ions (*chaotropes*) increase the solubility of nonpolar molecules (*salt in*) without being as highly hydrated. In effect, they

TABLE 1.8 The Hofmeister series.

Weakly hydrated (hydrophobic)	Strongly hydrated (hydrophilic)
Anions:	
$\text{ClO}_4^- > \text{I}^- > \text{SCN}^- > \text{NO}_3^- > \text{ClO}_3^- > \text{Br}^- > \text{Cl}^- \gg \text{F}^-, \text{IO}_3^- > \text{CH}_3\text{CO}_2^-, \text{CO}_3^{2-} > \text{HPO}_4^{2-}, \text{SO}_4^{2-} > \text{citrate}^{3-}$	
Cations:	
$\text{N}(\text{CH}_3)_4^+ > \text{NH}_4^+ > \text{Cs}^+ > \text{Rb}^+ > \text{K}^+ > \text{Na}^+ > \text{H}^+ > \text{Ca}^{2+} > \text{Mg}^{2+}, \text{Al}^{3+}$	
↓ Surface tension	↑ Surface tension
↑ Protein solubility	↓ Protein solubility
↓ Salting out (aggregate)	↑ Salting out (aggregate)
↑ Protein denaturation	↓ Protein denaturation
↓ Protein stability	↑ Protein stability

weaken the hydrophobic effect. Chaotropic ions are likely to directly interact with hydrophobic solutes such as proteins. Ions such as I^- and SCN^- have a significant denaturing (protein unfolding) effect because they interact strongly with the unfolded form of the protein, disrupting intramolecular dipolar and hydrogen bonding interactions. They have been described as ‘pulling’ the unfolding process and their polarisability may result in specific interactions with aromatic residues, for example. The Hofmeister series is increasingly controversial since it can serve to mask true molecular-level understanding which involves primarily specific interactions of salt ions with the backbone and charged side chain groups located near a protein surface in water. Furthermore, because of ion pairing, it can be misleading to separate Hofmeister effects into independent cationic and anionic contributions. A modern interpretation is beginning to emerge based on understanding specific roles of ions in particular biological functionalities and it is sometimes the case that generic Hofmeister-type interactions can be complemented or even overruled by particular steric arrangements in protein ion binding sites. Studies on anion binding by hydrophobic cavitands have shown that chaotropic anions bind within concave, hydrophobic pockets and competition between a convex hydrophobic group and the anion for a binding site leads to the observed weakening of the hydrophobic effect by chaotropes. As a result, it has been suggested that chaotropes induce protein solubilisation by direct binding to concave pockets in the molten globule state of proteins.¹²⁴

1.9.2 Solvation

 Smithrud, D.B., Sanford, E.M., Chao, I., *et al.* (1990). Solvent effects in molecular recognition. *Pure Appl. Chem.* 62: 2227–2236.

The importance of solvent in supramolecular chemistry can hardly be overstated. In the solid-state, it is often included as a guest in the crystal lattice and usually mediates the nucleation and deposition of a crystalline (or otherwise) compound from solution. In solution, all complexation phenomena are in competition with solvation interactions and the solvent is almost invariably in a huge molar excess. Polar solvents, particularly water, compete very effectively for binding sites, particularly hydrogen bonding functionality, making hydrophobic (or solvophobic) effects of paramount importance. In non-polar solvents and in the gas phase, specific host–guest dipolar and hydrogen bonding interactions are much more significant. It is thus essentially meaningless to discuss the magnitude of binding constants without mention of solvent and impossible to compare binding constants or even relative affinity across different solvent media. Indeed, a common ‘trick’ to differentiate the affinity of a particularly effective host for various guests is to lower the apparent binding constants by moving to a more competitive (generally more polar) solvent. Thus, binding constants that are too high to measure in one solvent become lower and hence experimentally accessible in a more competitive one. An example of the influence of solvent on binding constant for the polar organic guest imidazole by the bicyclic host **1.16** is shown in Table 1.9. Binding is clearly enhanced in non-polar solvents with a dramatic maximum value for 1,1,2,2-tetrachloroethane coming from the fact that this solvent is too large to enter the macrobicyclic cavity and hence it does not compete for the guest binding site.

TABLE 1.9 Influence of solvent on the binding constant of host **1.16** for the neutral organic molecule imidazole (298 K).

Solvent	Solvent type	K_{11} (M^{-1})
CH_2Cl_2	Non-polar	240
$CHCl_3$	Non-polar, H-bond acidic	490
CH_3CCl_3	Non-polar	8 161
$CHCl_2CHCl_2$	Non-polar, too large for cavity	128 000
Tetrahydrofuran (THF)	Non-polar, coordinating	29.0
2-Me-THF	Non-polar, coordinating	77.0
2,5-Me ₂ -THF	Non-polar, coordinating	185
2,2-Me ₂ -THF	Non-polar, coordinating	156
2,2,5,5-Me ₄ -THF	Non-polar, coordinating, sterically hindered	1 067
Tetrahydropyran	Non-polar, coordinating	104
1,4-Dioxane	Non-polar, coordinating	87
<i>t</i> -Butyl methyl ether	Non-polar, coordinating	566
<i>iso</i> -Propanol	Polar, protic	13
<i>t</i> -Butyl alcohol	Polar, protic	66
Acetonitrile	Polar, aprotic, coordinating	No association

So far, we have regarded the host–guest binding process as being the interaction of a more-or-less preorganised host with a naked guest. In reality, both host and guest are highly solvated in solution and the solvation stabilisation of the free host may well be significantly different from its interactions to solvent in the complexed state, particularly if there is a significant conformational change (induced fit) on binding. A fuller picture of both the energetics and kinetics of the complexation process must take into account the desolvation of both host and guest upon binding and the re-solvation of the resulting complex, often with release of free solvent and consequent formation of solvent–solvent interactions, Figure 1.42.

Unfortunately, specific solvation effects are very difficult to understand, although molecular mechanics simulations have gone some way towards modelling complexation phenomena in solution. For example, a molecular dynamics study of halide anion inclusion complexes of a macrotricyclic tetrahedral host **1.17** compared halide binding in ‘dry’ and ‘wet’ forms of an ionic liquid solvent. In the ‘dry’ ionic liquid, the uncomplexed halides are surrounded by four or five 1-butyl-3-methylimidazolium cations whose binding mode changes from hydrogen bonding to facial coordination going from F^- to I^- . In the wet solvent, the first shell organic ionic liquid cations on the fluoride ion are all displaced by water molecules, while other halides exhibit a mixture of water and imidazolium interactions. The solvation of the host and its halide complexes mainly involves PF_6^- anions in the ‘dry’ medium, and additional water molecules in the ‘wet’ ionic liquid. The calculations predict that the anion binding selectivity is different in the two different media. In the ‘dry’ ionic liquid, F^- is preferred over the other halides but in aqueous solution, **1.17** is selective for Cl^- . In the ‘wet’ ionic liquid, there is no F^-/Cl^- differentiation, highlighting the importance of even small amounts of water on the complexation selectivity.¹²⁵

An experimental comparison of the effect of ‘wet’ and ‘dry’ solvent has been carried out for host **1.18** which is capable of binding 2-aminopyrimidine (APy) to give a 1 : 1 complex **1.18**·APy. The binding constant in dry chloroform is up to $2.4 \times 10^4 M^{-1}$, although this decreases significantly with temperature. Saturation of the chloroform with water does not result in a significant diminution of the host–guest affinity, as measured by the overall complexation free energy. This is because the competition for the binding sites by the water (which decreases the enthalpic contribution to the binding) is compensated by a more favourable entropy term associated with the release of water upon

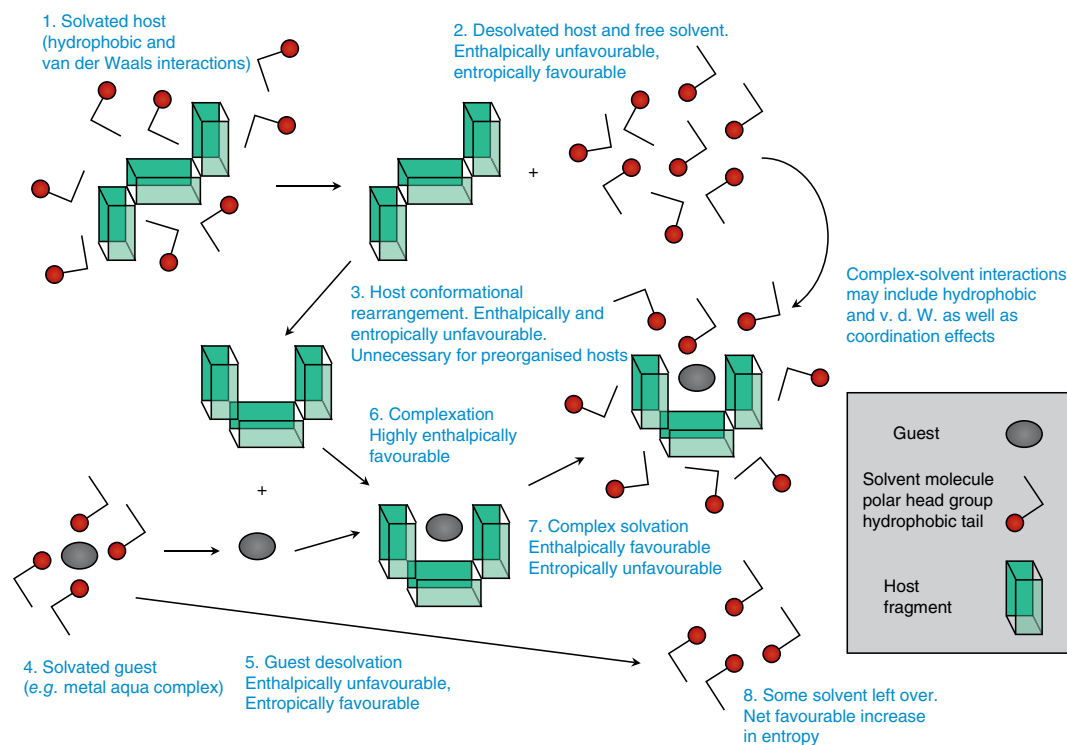
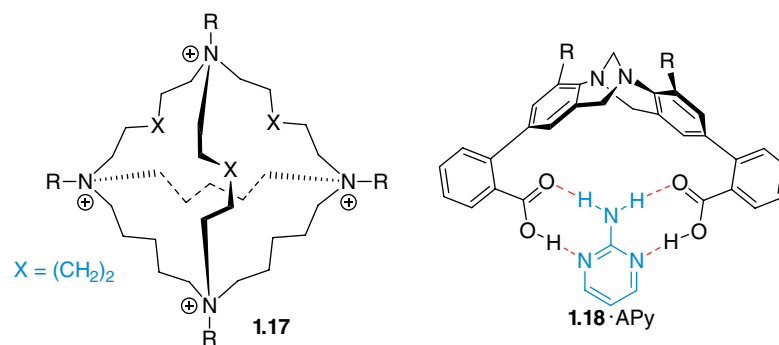


FIGURE 1.42 Solvation considerations during host-guest complexation.

organisation of the complex (*cf.* the hydrophobic effect in neat water). This example represents a fortuitous case of cancellation of enthalpic and entropic effects.¹²⁶



1.10 SUPRAMOLECULAR CONCEPTS AND DESIGN

1.10.1 Host Design

Key Lehn, J.-M. (1994). Perspectives in supramolecular chemistry—from molecular recognition towards self-organisation. *Pure Appl. Chem.* 66: 1961–1966.

In order to design a host that will selectively bind a particular guest within a given medium, we make use of the chelate and macrocyclic effects as well as the concept of complementarity (matching of host and guest steric and electronic requirements) and, crucially, host preorganisation. The first step in host design is a clear definition and

careful consideration of the target. This leads immediately to conclusions about the properties of the new host system. If a metal cation is to be the guest (Chapter 3), then its size (ionic radius), charge density, and ‘hardness’ (Section 3.1.2) are important (*e.g.* soft donor atoms such as sulfur are suited to the binding of soft guests such as Hg^{2+} , Ag^+ , and Pb^{2+}). For anion complexation (Chapter 4), these factors also affect spherical anions such as chloride, bromide, *etc.*, but for non-spherical anionic guests, other factors such as shape, charge, and hydrogen bond donor characteristics come into play. Organic cations and anions may require hosts with both hydrophilic and hydrophobic regions, while neutral molecule guests may lack specific ‘handles’ such as polar groups that can strongly interact with the host.

Having defined parameters such as the required host size, charge, character of the donor atoms, *etc.*, the intellectual process of host tailoring can begin. The key concept in this process is organisation. Host–guest interactions occur through binding sites. The type and number of binding sites must be selected in a fashion that is most complementary to the characteristics of the binding sites of the guest (recall the definition of a guest as the partner with divergent binding sites), and these binding sites must be arranged on a (usually) organic scaffold or framework of suitable size and shape to accommodate the guest. Binding sites should be spaced somewhat apart from one another to minimise repulsions between them but arranged so that they can all interact simultaneously with the guest. The more favourable interactions there are, the better. The most stable complexes are generally obtained with hosts that are preorganised for guest binding, thus where there is no entropically and enthalpically unfavourable rearrangement on binding that reduces the overall free energy of complexation. Such hosts are ideally ‘sinks’ for their guests in which binding is entirely irreversible. This kind of complexation is ideal, for example, for the removal of toxic metal ions from polluted water. Hosts that bind guests less strongly (*i.e.* there is some equilibrium between bound and unbound species) find applications as sensors and carriers in which event sequences such as ‘bind–detect–release’ or ‘bind–transport–release’ are needed. Interestingly, there is a balance between rigid preorganisation in order to maximise enthalpically stabilising host–guest interactions and restriction of the guest’s conformational and vibrational freedom. Binding a guest too rigidly can result in entropically unfavourable factors arising from restricted guest motion within the binding pocket and this penalty can be avoided by a binding site in which the guest retains some freedom of motion.¹²⁷ Moreover, the binding is highly dependent on the solvent and solvent rearrangement on going from free to complexed state as well as buffers, background electrolytes, or other components introduced as part of the analysis process.

The nature of the organic framework of the host itself, whether lipophilic or hydrophilic, plays a fundamental role in host behaviour. This determines the solubility characteristics of the host and its complexes. The thickness of the ligand and the ease of access to the binding pocket, cavity, or cleft affect both thermodynamic stability and binding kinetics. Addition of side arms may enhance lipophilicity (*e.g.* long alkyl chains) or encourage interaction with some external entity such as a polymer support or biomolecule. Such hosts are used to transport radioactive isotopes to targeted regions of the human body for medical radioimaging purposes or to develop artificial *enzyme mimics* (Chapter 13). The architecture of the host may also need to take into account guest reactivity (as in *organocatalysis*) or the transduction of a fluorescent or electrochemical signal in an analyte sensing context, including energy transfer between the host and guest.

Overall, the thorough application of these very broad principles has been generalised into what has been referred to as *complete coordination chemistry*, encompassing both supramolecular and classical (Werner) inorganic coordination chemistry.

1.10.2 Molecular and Supramolecular Chirality

 Crego-Calama, M. and Reinhoudt, D.N. (eds.) (2010). Supramolecular chirality. *Top. Curr. Chem.* 265. Berlin: Springer.

Optical isomerism occurs when a molecule or supermolecule contains either a centre of symmetry (inversion centre, *i*) or a mirror plane (*m*) or other reflection operation such as improper rotation (S_n). The system is thus chiral and if there is an unequal amount of the two mirror image forms (termed *enantiomers*) in a sample, it will rotate the plane of polarised light. There are many ways to generate chirality including some that are sometimes intrinsic properties of large molecules of interest in supramolecular chemistry and some that arise only as a consequence of a

supramolecular association between more than one molecule. In this section, we briefly review the origins and consequences of chirality in a supramolecular context.

Distinguishing Enantiomers

Enantiomers may be distinguished by their influence on the rotation of plane-polarised light. This is measured by a type of electronic spectroscopy called *circular dichroism*. The ability of the complex to rotate plane-polarised light is given in terms of an optical rotation given in degrees at a particular wavelength (see Box 1.1). X-ray crystallography may also distinguish enantiomers as long as there are ‘heavy’ atoms present (usually heavier than Na, although careful experiments can distinguish enantiomers of organic compounds as well). This is a special type of crystallographic experiment termed *absolute structure determination* and makes use of a property of crystals termed *anomalous dispersion*.¹²⁸

Box 1.1 Circular Dichroism Spectroscopy

Circular dichroism spectroscopy (CD) is a type of electronic spectroscopy (*i.e.* it probes electronic transitions in the UV-visible region of the electromagnetic spectrum) that measures the difference in absorbance and hence difference in molar extinction coefficient ($\Delta\epsilon$) between enantiomers of chiral compounds. Unlike conventional electronic spectroscopy which uses linearly polarised light (all of the wave vectors propagate in the same plane), CD uses circularly polarised light in which the electric field vector has a constant length, but rotates about its propagation direction and so it forms a helix in space while propagating. This helix can be a left- or right-handed helix and so we refer to left or right circularly polarised light. When light interacts with a molecule, then the electric field component causes the electron charge to be linearly displaced. The magnetic field component causes charge circulation. As a result, there is a helical displacement of charge when light interacts with a molecule. If the light is circularly polarised, then it is itself chiral and hence will interact differently with the left or right enantiomers of a chiral molecule with the two types of circularly polarised light being absorbed to different extents. In the CD experiment, a resolved chiral molecule is subjected to equal amounts of left- and right-hand circularly polarised light usually in solution. One ‘handedness’ of light is absorbed more than another at a given wavelength and it is this wavelength-dependent difference that gives the CD spectrum. Thus, examination of Figure 1.43 reveals that the CD spectrum is a plot of the difference in molar extinction coefficient, $\Delta\epsilon$ (obtained from the difference in measured absorbance *via* the Beer–Lambert law) over a range of wavelengths.

If, in two separate experiments, the CD spectra of two resolved, pure enantiomers are measured, then they should be equal and opposite in the sign of $\Delta\epsilon$ and this represents a good test as to whether the resolution has been successful. Of course, if we measure the CD spectrum of a racemic mixture, then there is no net absorbance; the rotation of the two enantiomers present in the solution cancels one another out. Choosing a wavelength where $\Delta\epsilon$ is large allows measurement of the *specific rotation* of the compound. Single wavelength measurements can be made using a polarimeter.

The specific rotation of a compound ($[\alpha]/\text{deg cm}^2 \text{ g}^{-1}$) is defined as the observed angle of optical rotation when plane-polarised light is passed through a sample of path length 1 decimeter (10 cm) and a sample concentration 1 g decilitre⁻¹ (100 mL). The value is accompanied by the temperature in °C as a superscript and the wavelength of the light used to make the measurement as a subscript. A subscript ‘D’ means the wavelength of the sodium-D line (589 nm). In solution, specific rotation is given by Equation 1.42, where l is the path length in decimetres and c is the concentration of the compound in g/100 mL. The sign of the rotation ($\pm$) is always given, as is the solvent used to make the measurement. The observed rotation α is obtained directly from the absorbance difference (or $\Delta\epsilon$).

$$[\alpha]_{\lambda}^T = \frac{100\alpha}{l \times c} \quad (1.42)$$

(continued)

(continued)

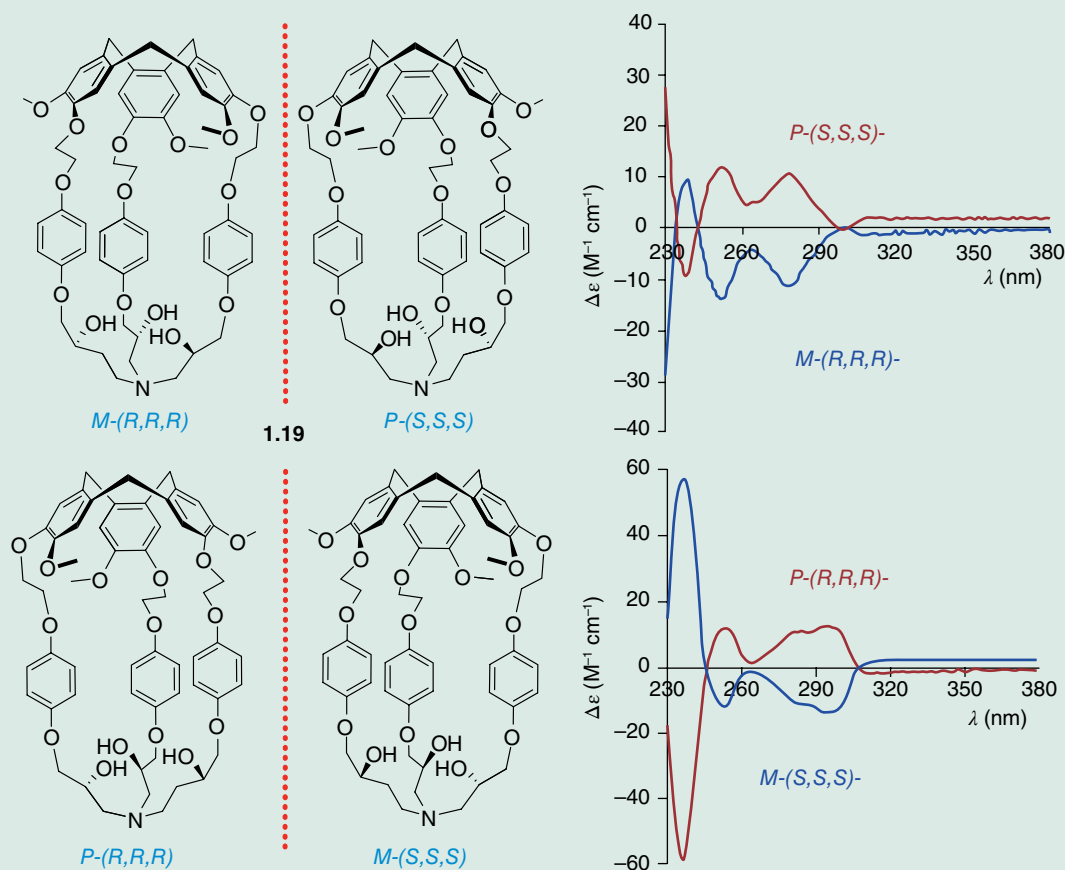


FIGURE 1.43 The four isolated isomers of hemicryptophane **1.19** showing the two pairs of enantiomers along with their respective circular dichroism spectra.¹²⁹ © 2005, Reproduced with permission from American Chemical Society.

Point Chirality

In organic compounds, we can usually discover whether a molecule is chiral by looking for an atom (usually carbon) with four different substituents and we can assign its absolute handedness (*R* or *S* according to the Cahn–Ingold–Prelog rules). It takes a combination of structural and optical rotation measurements to tie together the ($\pm$) optical rotation properties with the absolute configuration. In older literature, chiral molecules are labelled with a relative configuration *d* or *l* (from the Latin *dextro*- and *laevo*- meaning right and left relative to the configuration of glyceraldehyde). Note there is no relationship between the *d* or *l* relative configuration and the direction of rotation of plane-polarised light.

Axial Chirality

Axial chirality is observed in compounds that do not have a chiral centre but have an axis about which a set of substituents is held in a spatial arrangement that is not superimposable on its mirror image. Axially chiral system can be designated *R* or *S* by the precedence of the groups attached to the axial section of the molecule when viewed along that

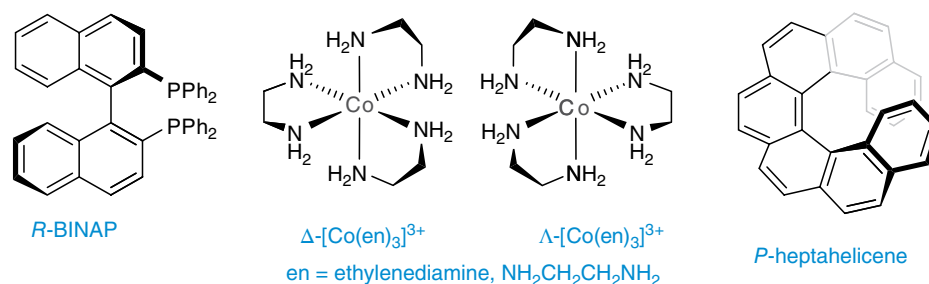


FIGURE 1.44 Axially and helically chiral systems showing both helical enantiomers of [Co(en)₃]³⁺.

axis. For example, axial chirality is also observed for *atropisomeric*^{***}-substituted biaryl compounds wherein the rotation about the aryl–aryl bond is restricted as in 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP – a ligand widely used in asymmetric synthesis), Figure 1.44.

Helical Chirality

Helical chirality is closely related to axial chirality and relates to the chirality of a helical, propeller, or screw-shaped entity. The systems are described using helical notation Δ (*dextro*) and Λ (*laevo*) when there is a chiral metal centre, or *P* and *M* (plus and minus) in the Cahn–Ingold–Prelog system. In coordination chemistry, helical chirality is usually observed when chelate rings are present and hence is common in supermolecules. For example, octahedral [M(L–L)₃] and *cis*-[M(L–L)₂X₂] complexes (where L–L = didentate chelate ligand) are chiral, although *trans*-[M(L–L)₂X₂] is not (neglecting ligand backbone conformational effects), e.g. [Co(en)₃]³⁺, Figure 1.44. Other helically chiral compounds include the single helical heptahelicene and double helical metal helicates (Section 10.5).

Planar Chirality

Plane chirality is exhibited by a molecule or supermolecule without an asymmetric centre in which there are two non-coplanar rings that are each unsymmetrical and which do not rotate about the chemical bond connecting them on a meaningful time scale. Common examples are substituted organometallic ‘piano stool’ and sandwich compounds. An interesting example is **1.20** which has both point and planar chirality and forms a fourfold hydrogen-bonded supramolecular helix as the *pR,R* enantiomer as a result of its highly dissymmetric shape. The planar chiral element is designated with a ‘*p*’ prefix.¹³⁰ The naturally occurring cyclophane cavitandin¹³¹ also exhibits plane chirality, Figure 1.45. Plane chiral enantiomers are denoted *R* or *S* according to atom priority.

Inherent Chirality

The term *inherent chirality* was first used by Böhmer in 1994 in the context of chiral calix[4]arenes with substituents on the hydroxyl groups of type either XXYZ or WXYZ and has most recently been defined by Szumna: ‘inherent chirality arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation’.¹³² It applies generally to a range of fullerenes, cavitands, and capsular assemblies. Inherently, chiral systems are designated with the *M* and *P* nomenclature as in *M*-**1.21**.

Supramolecular Chirality

The construction of multicomponent supermolecules gives rise to further unique ways in which the system as a whole can become asymmetric and hence exhibit supramolecular chirality; the non-symmetric arrangement of molecular

^{***} Atropisomers are stereoisomers arising because of hindered rotation about a single bond where the interconversion energy barrier is sufficiently large to allow the isolation of the individual forms under ambient conditions.

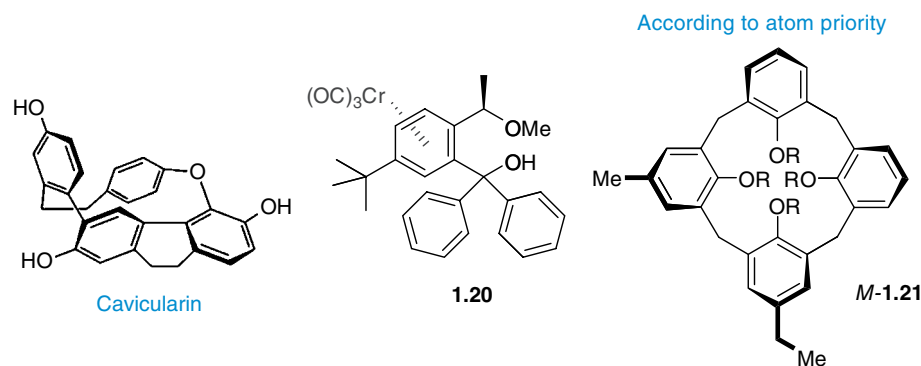


FIGURE 1.45 Planar chiral cavicularin, organometallic **1.20** which forms a fourfold hydrogen-bonded helix as the *pR,R* enantiomer and inherently chiral **1.21**.

components in a non-covalent assembly. Supramolecular analogues of each kind of molecular chirality exist. Without being comprehensive there are three principal types of chirality exhibited by multicomponent systems, namely the generation of chiral assemblies (e.g. self-assembled chiral capsules and chiral arrangements of guest molecules within them), mechanical chirality, and surface chirality.

Chiral capsules have been prepared by self-assembly of achiral hydrogen-bonded building blocks using curved glycoluril derivatives and calixarenes, for example.¹³³ Interconversion between enantiomers involves complete dissociation and reassembly of the entire cage. Such assemblies can include chiral guest species to give supramolecular diastereoisomers and guest exchange is generally faster than enantiomer interconversion. However, capsules with chiral shells rarely exhibit significant guest binding enantioselectivity. In addition, tightly bound guests can exhibit *carcerisomerism* involving slow exchange between different guest orientations at least on the NMR time scale.¹³⁴ For an unsymmetrical guest, this could potentially result in enantiomeric carceplexes even for an achiral capsule.

Mechanically chiral systems arise from the presence of a mechanical bond between two or more components and may be planar, axial, or helical. A good example of mechanically planar chiral systems are directional [2]rotaxanes designated S_{mp} and R_{mp} which have unsymmetrical rings and non-equivalent ends of the axel. The first such system was reported in 1997 by Vögtle and co-workers. The two enantiomers were successfully separated by chiral HPLC and shown to give rise to significant circular dichroism.¹³⁵ In 2019, a high-yielding enantioselective chiral catenane synthesis was reported based on the use of a classical chiral auxiliary, Figure 1.46. The method is based on an active-template copper catalyst-mediated azide-alkyne cycloaddition ('click') methodology for the synthesis of sterically crowded catenanes. The sterically crowded small macrocycles is the most influenced by the chiral auxiliary giving an 89% yield of [2]catenane, which can be separated easily into two diastereomers. The fact that the two possible products form in unequal amounts shows that there is an influence from the chiral auxiliary.¹³⁶

The assembly of individually achiral units into supramolecular polymers or fibres, of their aggregation onto a well-defined surface has also been shown to give rise to very marked chiral structures. Scanning probe microscopy has been particularly effective in recent years in elucidating chiral 2D self-assembled patterns and chiral helical soft materials including chiral arrays of nanoparticles are as fascinating as they are beautiful. Such systems can give rise to interesting behaviour such as chiral recognition, transfer of chirality from single molecules into supramolecular structures, and cooperatively driven chiral amplification phenomena.¹³⁷ Figure 1.47a shows a magnetic field-induced self-assembly of iron oxide nanocubes into a supramolecular helical aggregate,¹³⁸ while Figure 1.47b shows chiral braided self-assembled helices based on a pentakis(urea) gelator and a Brunnian aggregate. Filtration through cotton wool (itself a chiral natural product) causes all the helices to become homochiral by strong chiral templation.¹³⁹

Multiple Chiral Centres and Optical Resolution

The presence of more than one chiral centre or element significantly increases the stereochemical possibilities of the system. In the simplest case, a symmetrical molecule with two identical stereocentres exists as two diastereoisomers, the optically pure *meso* form (for example, *RS* or $\Delta\Delta$) and the racemic or *rac* form which itself occurs as two pairs of

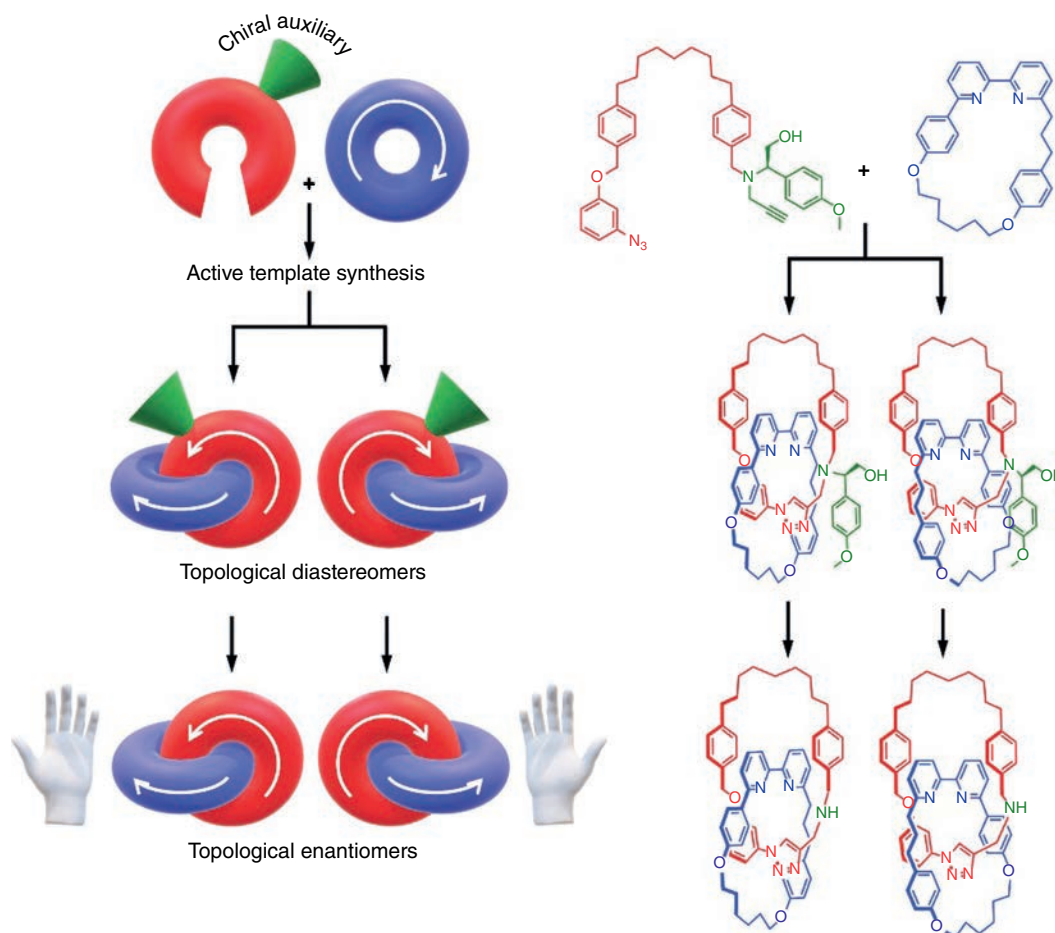


FIGURE 1.46 High-yield, chiral auxiliary approach to topologically chiral catenanes.¹³⁶ © 2019, Reproduced with permission from Cell Press.

enantiomers (*RR/SS* or $\Delta\Delta$ and $\Lambda\Lambda$). If the two chiral centres are different to one another, then there are four unique compounds since *RS* is no longer equivalent to *SR*, for example. Diastereoisomers differ in their physical properties, for example, they have different NMR spectra and can be separated by achiral chromatography. In contrast, enantiomers have identical physical and chemical properties to one another except the direction in which they rotate plane-polarised light. Interaction of a racemic mixture of enantiomers with a second chiral species offers a route to chiral separations. This may take the form of a chiral chromatography in which each enantiomer has a different affinity for a chiral stationary phase or it may be in the form of diastereoisomer formation, commonly as a salt. Scheme 1.6 shows the experimental resolution of $[\text{Co}(\text{en})_3]^{3+}$ using the different solubilities of the two possible diastereoisomeric salts formed with optically pure (+)tartrate (*en* = ethylene diamine).

If diastereoisomer formation is not feasible, the alternative is chiral chromatography which relies on different affinities of each enantiomer for a chiral stationary phase (*i.e.* chromatography column). While chiral chromatography is an accepted and relatively ‘certain’ method to resolve enantiomers, chiral columns are expensive and often a number of variants must be tried before an effective separation protocol is achieved. Moreover, chromatographic techniques are very difficult and expensive to scale up. As a result, industrial processes favour either asymmetric synthesis or crystallisation-based methods as in Scheme 1.6. In the past 20 years, there has been a remarkable progress in enantioselective crystallisation with techniques such as Dutch resolution¹⁴⁰ and, since 2004, Viedma ripening¹⁴¹ becoming of intense interest. The Viedma method involves mechanical abrasion by means of a magnetic stirrer for example and can convert a racemic mixture of crystals of an interconverting substrate into a 100% yield of enantiopure solid by means of nonlinear autocatalysis and recycling.

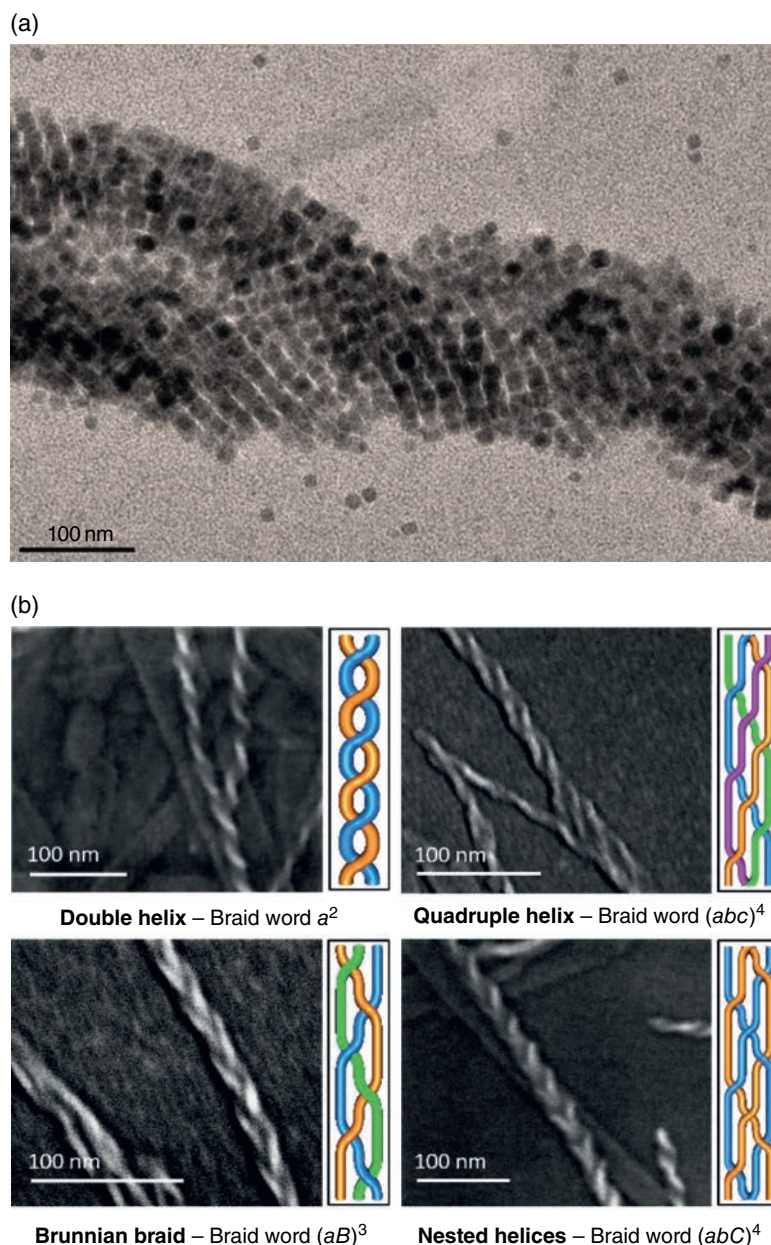
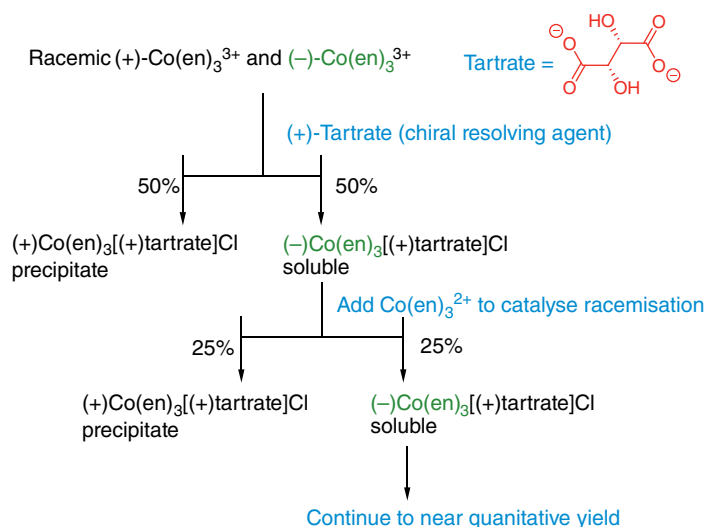


FIGURE 1.47 (a) Magnetic field-induced self-assembly of iron oxide nanocubes into a supramolecular helical aggregate.¹³⁸ © 2015, Reproduced with permission from Royal Society of Chemistry. (b) Chiral braided self-assembled helices and a Brunnian aggregate.¹³⁹ © 2019, Reproduced with permission from Springer Nature.

Differential supramolecular interactions of two enantiomers with a chiral ‘probe molecule’ are also of significant use in NMR spectroscopy. While enantiomers have identical NMR spectra, addition of a resolved *chiral shift reagent* of one handedness often results in sufficient association to split the NMR resonances and give diastereomeric signals and hence differentiate the two enantiomers. Chiral paramagnetic lanthanide acetylacetonato derivatives such as [Eu(fod)₃] [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium or Sievers’ Reagent] are particularly useful because of the large chemical shift changes induced by the paramagnetic Eu^{III} centre. The phosphorus(V) anion TRISPHAT [tris(tetrachlorobenzenediolato) phosphate(V)] is also common.¹⁴²

One of the most elegant uses of optical activity was the experiment by Mills and Quibell¹⁴³ which demonstrated the square planar geometry of platinum(II). They prepared the Pt^{II} complex of isobutylenediamine and *meso*-stilbene-diamine and found that it was chiral. If the geometry at platinum is tetrahedral, the complex has a mirror plane and so is not chiral, Figure 1.48.



SCHEME 1.6 Experimental resolution of [Co(en)₃]³⁺ using optically pure (+)-tartrate.

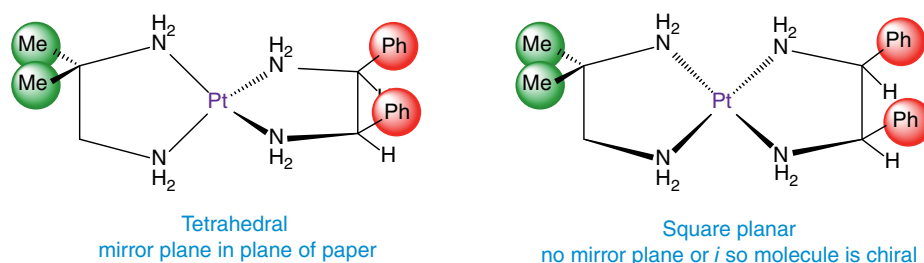


FIGURE 1.48 The 1935 use of chirality by complexation of the achiral *meso*-diastereoisomer of stilbenediamine to establish the square planar geometry of platinum(II).

1.10.3 Informed and Emergent Complex Matter

Self-assembly, Self-organization, and Emergent Properties

Key Lehn, J.-M. (2002). Toward complex matter: supramolecular chemistry and self-organization. *Proc. Nat. Acad. Sci. USA* 99: 4763–4768.

We saw in Figure 1.3c that supramolecular chemistry is not just about solid state or solution host–guest chemistry but increasingly emphasises self-assembly and the construction of multi-nanometre scale devices and ultimately materials based on nanometre-scale components (a nanometre is 10^{−9} of a metre). Strict supramolecular self-assembly (Chapter 10) involves the spontaneous formation of a multicomponent aggregate under thermodynamically controlled conditions based on information encoded within the individual building blocks (referred to as *tectons*) themselves. The aggregate might comprise only one kind of molecule (as in the multiple copies of the same protein that comprise the coat of many viruses such as the tobacco mosaic virus) or more than one type. In the latter case, the different components are usually mutually complementary. Strict self-assembly implicitly carries with it the notion of reversibility of inter-component bond formation in that the final aggregate is the most thermodynamically stable structure under the prevailing conditions. This means that there is an inbuilt error-checking mechanism – malformed aggregates are less stable than the true minimum energy structure and decompose and are reassembled correctly if sufficient time is allowed to pass. Self-assembly processes may be regarded as the result of a series of supramolecular templated steps that build the aggregate. In turn, the interactions and synergy of self-assembled components, leading to the emergence of collective behaviour and properties, may be regarded as *self-organisation*. The hierarchical sequence of *templation* leading to *self-assembly* leading to *self-organisation* represents a supramolecular information

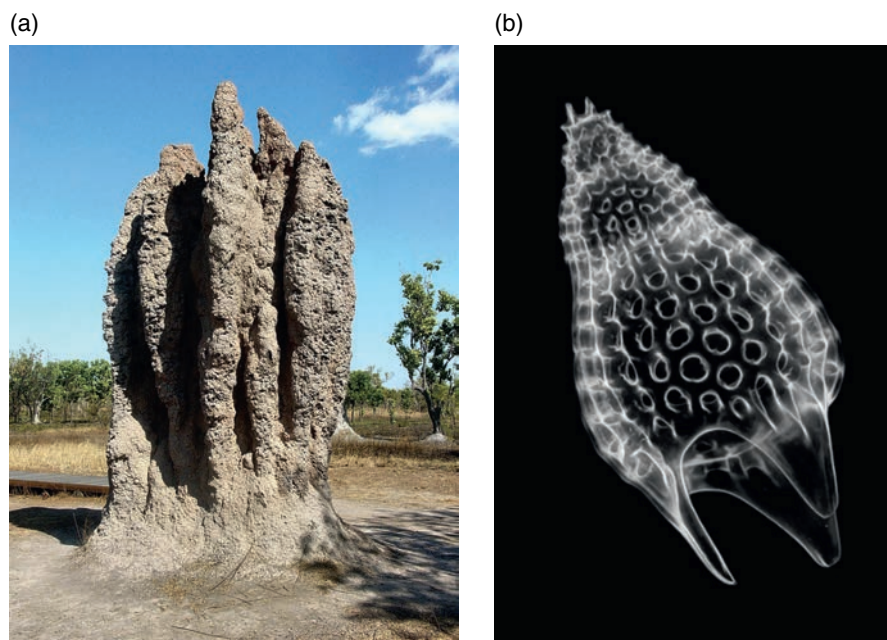


FIGURE 1.49 (a) A termite mound in Australia's Northern Territory. Termite mounds are classic examples of natural emergent structures. Image: Brian Voon Yee Yap. (b) Silica shell of a fossil radiolarian – *Podocyrthis* (*Lampterium*). Image: Andreas Drews.

concept in which all the information needed to produce a complex, functioning device, or material with some measure of sophisticated responsiveness to external stimuli is contained in the molecular components themselves.

When we talk of the *emergence* of a self-organised system, we are talking very specifically about complex properties arising over time as a result of non-linear and perhaps unpredictable interactions between the molecular components. Emergence is a powerful, if controversial and often misunderstood topic that is part of the field of complexity science and cuts across a very broad range of disciplines.¹⁴⁴ Darwinian evolution is perhaps the most famous example. Emergence is in some sense the opposite of *convergence*, another possible outcome of templation and self-assembly, in which a single stable structure results from the interactions of the molecular components. A good example of an emergent structure in the everyday world is the complex network of tunnels and vents that regulate the environment within a termite mound (Figure 1.49a). The mound is not planned by the termites and does not arise from a predictable template. It emerges from the individual, synergic efforts of the individual termites over time. From a chemical point of view, it is possible to exert a high degree of control over the structure and shape and hence information content of small molecules (*i.e.* around 1 nm or less in size) using chemical synthetic techniques. Self-organisation then leads to multi-nanometre scale structures and systems that, because of their complexity and large number of components, cannot be made in a linear one-step-at-a-time fashion. Emergent structures and properties arising from the self-assembly and self-organisation of molecules on a multi-nanometre scale are ubiquitous in Biochemistry (*e.g.* self-replication and enzymic catalysis) and are increasingly being studied by chemists in artificial, abiotic (*i.e.* non-biochemical) systems.

The mechanical bond can be thought of as an emergent type of bond and Stoddart has defined as emergent any new properties that arise as a result of an increase in the complexity of a system.⁴ In the context of self-assembled discrete metallocages, Fujita has identified emergent behaviour in slight changes in ligand bend angle which critically switches the final convergently self-assembled structure between $M_{24}L_{48}$ and $M_{12}L_{24}$ coordination spheres (Chapter 10), describing the ‘amplification of this small initial difference into an incommensurable difference in the resultant structures [as] a key mark of emergent behaviour’.¹⁴⁵ Emergent morphologies are also a striking characteristic of biomineralisation as in the silica exoskeletons of radiolaria, Figure 1.49b, and have been mimicked by surfactant template deposition of inorganic materials (Section 17.3).¹⁴⁶ We will look at emergent and non-equilibrium systems in detail in Chapters 16 and 17.

1.10.4 Nanochemistry

Key Cademartiri, L. and Ozin, G.A. (2009). *Concepts of Nanochemistry*. Weinheim: Wiley-VCH.

We can refer to the synthesis and study of chemical systems with features and functionality on the multi-nanometre length scale as *nanotechnology* and materials with features of size of the order of 1–100 nm as *nanomaterials*. Very broadly there are two approaches to accessing the nanoscale dimension – ‘synthesis-up’ and ‘engineering-down’. The engineering down approach includes the latest in modern techniques for producing electronic components and originates in a bulk sense. Engineering down to the nanoscale (*nanotechnology*) involves doing the same sorts of things that an engineer or artisan does on a macroscopic scale but using specialised techniques in order to miniaturise. In contrast, the synthesis-up approach (*nanotechnology*) is modelled on biology, particularly biological self-assembly, and aims to produce nanoscale functional components (perhaps with molecular device or molecular-scale computing applications in mind) by chemical synthesis. Functional molecular nanoscale computers using supramolecular species were reported by the Stoddart group back in 1999, who fabricated logic gates from an array of configurable switches, each consisting of a monolayer of redox-active rotaxanes sandwiched between metal electrodes.¹⁴⁷ Geoff Ozin of the University of Toronto, one of the leading proponents of nanochemistry and the synthesis of nanomaterials, has defined nanomaterials as materials whose properties change according to their size, or the size of their components. An excellent example is gold *nanoparticles*. Nanoparticles are tiny fragments of a material such as metallic gold, silver, or fluorescent semiconductor materials such as cadmium selenide (also referred to as *quantum dots*). Nanoparticles are often more or less spherical in shape (Figure 1.50a) and may have a regular, faceted crystalline morphology and structure (in which case they are referred to as *nanocrystals*). Nanoparticles are typically 2–30 nm in radius and very interestingly often exhibit intense colours. You may already have seen such colours in red or purple suspensions of gold colloids. The colour arises from a visible absorption termed a *surface plasmon resonance* absorption and it arises from the collective motion of free electrons around across the surface of the nanoparticle (Figure 1.50b). Crucially, the wavelength of this absorption (and hence the observed colour) depend on the size of the nanoparticle. Similarly, the emission wavelength of fluorescent quantum dots is also highly dependent on both the size and shape of the particles (Figure 1.50c), allowing fine tunability in sensing and diagnostic roles, for example.¹⁴⁸ Non-metallic nanoparticles are also of growing interest such as fluorescent carbon quantum dots (nanoparticles of functionalised graphene)¹⁴⁹ and carbon nitride quantum dots¹⁵⁰ are of interest in energy storage and in sensing applications, particularly in biological systems because of their low toxicity and high luminescence quantum yield accompanied by synthetic versatility. Graphitic carbon nitride is of tremendous current interest in artificial photosynthesis and environmental remediation.¹⁵¹ Mesoporous silica nanoparticles can be tailored to exhibit large surface area and pore volume can be functionalised with molecular, supramolecular, or polymer moieties and used as efficient carriers for various therapeutic agents.¹⁵² Hybrid nanosystems involving nanoparticle-polymer and

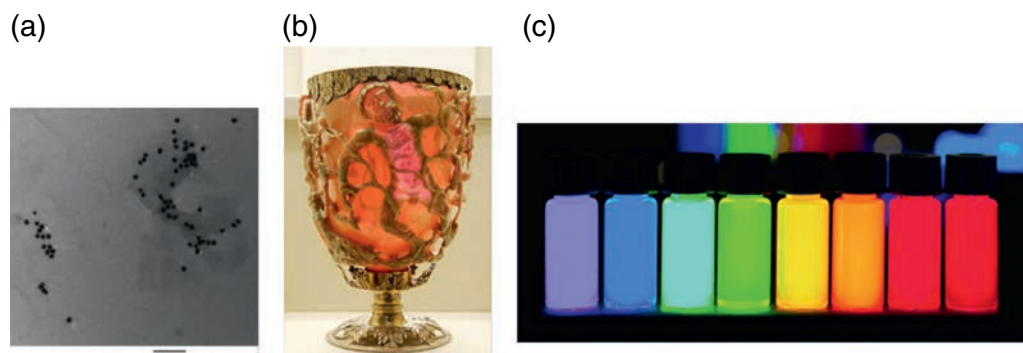


FIGURE 1.50 (a) TEM micrograph showing gold nanoparticles. Note the regular shape and uniform size distribution. Scale bar = 100 nm. (b) The fourth century CE Roman Lycurgus cup made of dichroic glass impregnated with gold/silver alloy nanoparticles – the red colour arises from surface plasmin resonance absorption. Image: Marie-Lan Nguyen. The cup appears red in transmitted light and green in reflected light. (c) Fluorescent ZnCdSe alloyed quantum dot nanoparticles. The emission wavelength 470–630 nm depends on the nanoparticle size. Average nanoparticle diameter *ca.* 6 nm. Image: Antipoff.

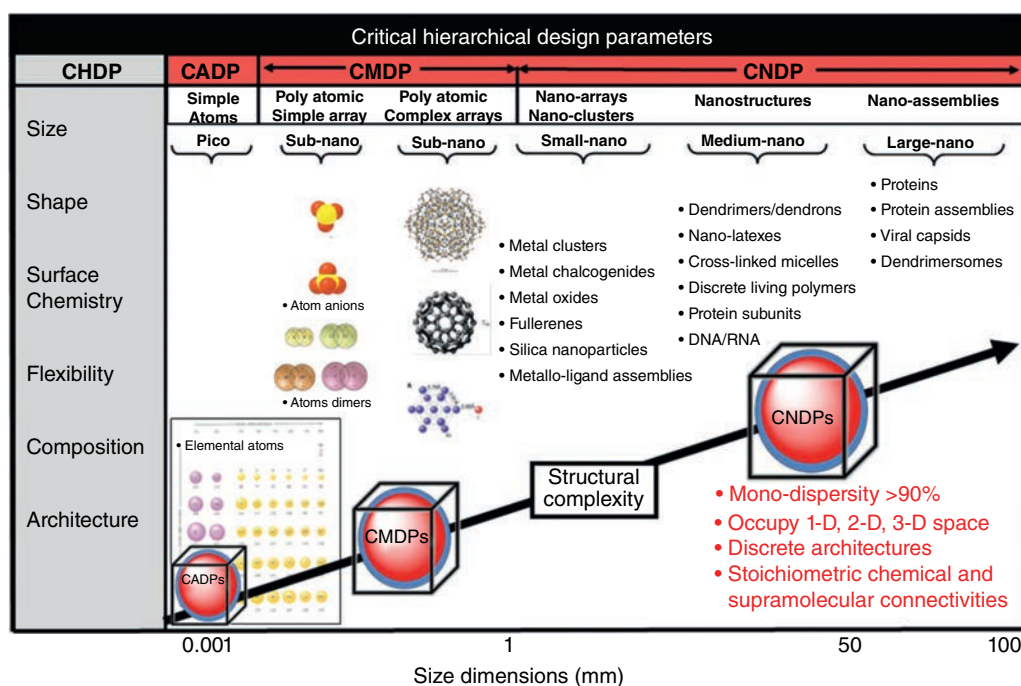


FIGURE 1.51 Chemical building blocks based on critical design parameters (CDPs) spanning length scales from the sub-atomic to the macroscale.¹⁵⁶ © 2016, Reproduced with permission from American Chemical Society.

nanoparticle gels are also of increasing importance in materials and sensing chemistry.¹⁵³ In addition, many recent nanoparticles and nanoscale assemblies have complex shapes and interesting properties such as hollow architectures¹⁵⁴ and chirality, with potential technological applications in biosensing, chiral catalysis, and chiral photonics.¹⁵⁵ Appropriately, given the celebrations in 2019 as the UNESCO International Year of the Periodic Table (the 150th Anniversary of Mendeleev's first articulation of the periodic table), a consensus is now beginning to coalesce around a periodic table of nanoparticles based on discrete, nanoscale objects comprising collections of traditional inorganic/organic atoms. These nanoparticles can be referred to as either hard or soft superatoms and represent categories of nanoelements.¹⁵⁶ The periodic table of nanoparticles fits somewhere in between the periodic table of the elements and larger scale 'meta-atoms' (micron-scale collections of atoms that behave in ways that parallel a traditional atom) and molecules, Figure 1.51.

We can also include in the concept of nanochemistry molecular systems exhibiting designed or emergent nanometre-scale features, functionality, or properties. For example, the interlocked catenanes can exhibit complex nanoscale molecular motions somewhat analogous to the mechanical interlocking of gears (Section 11.2). As we will see in Chapter 17, there are also hybrid systems coupling molecular hosts to nanomaterials such as nanoparticles. It is also possible to carry out nanochemistry using a variety of scanning probe microscopy-based techniques such as Scanning Tunnelling Microscopy (STM) and Atomic Force Microscopy (AFM). Because they operate on the nanometre scale, these techniques give unique insight into molecular behaviour. In addition, scanning probe microscope tips may be used to carry out molecular manipulations and redox chemistry. Tips may even be modified by attaching a probe molecule and using molecular recognition to examine a surface. Chemical reactions may even be carried out by physically pushing individual molecules into close mutual proximity using an STM tip.^{157, 158} Chemical assembly thus represents one facet of the preparation and study of nanoscale materials and there is a continuum of increasing complexity and decreasing predictability and control between molecular and materials properties. Within this continuum, we can make a useful distinction between situations where an observed property is an emergent consequence of the interactions between molecules or ions and where it is a distinctive molecular property. In this book, we aim to show the full series of steps from the grass roots of simple intermolecular interactions through to emergent nanomaterials and nanochemical systems.

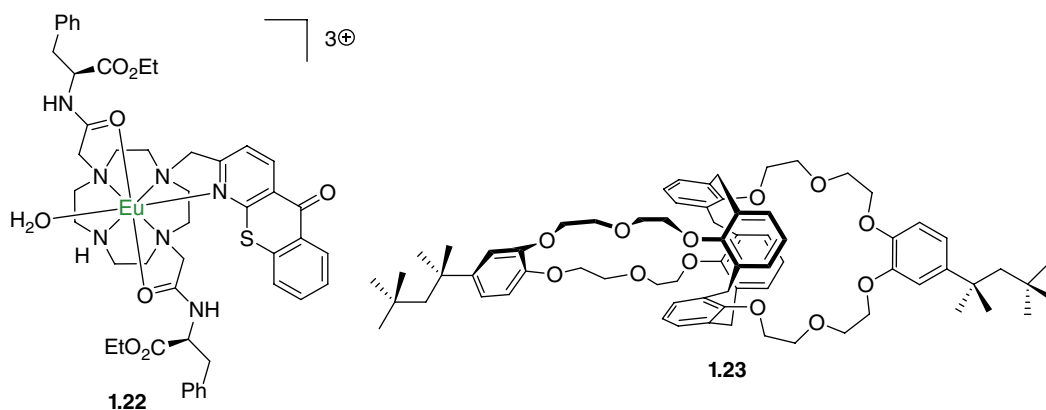
1.11 PRACTICAL APPLICATIONS OF SUPRAMOLECULAR CHEMISTRY

Key Kolesnichenko, I.V. and Anslyn, E.V. (2017). Practical applications of supramolecular chemistry. *Chem. Soc. Rev.* 46: 2385–2390.

As of 2019, we are 50 years on from Charles Pedersen's discovery of the crown ethers and in that time supramolecular chemistry and the intermolecular bonding concepts behind it have grown exponentially. One reason for the field's popularity is that it is fundamentally a creative and visual area. Chemists can literally create in molecules the kinds of architectures they can imagine. Coupled with the huge advances in synthetic methods, techniques for structure determination and in microscopy we now have an unprecedented ability to view and design the nanoworld. Given these huge leaps forward, it is worth asking the question what practical benefits has supramolecular chemistry brought us? Some key areas where supramolecular chemistry is making a real difference include supramolecular sensors, medical imaging, selective extraction of valuable metals from ores, nuclear waste separations, and in targeted drug formulation and delivery. A select few of these applications are highlighted in this section and we will see plenty more of them throughout the coming chapters. Perhaps, more importantly, however, the growing recognition and understanding of the 'chemistry of the non-covalent bond' has given us something much more subtle and much more far-reaching than a list of commercial spin-offs. It has given us a way of thinking that embraces intermolecular bonds from the bottom up. As a discipline with roots in chemistry, it deals with a rigorous understanding of structure and bonding at the molecular level. It also allows us to reach upwards into the nano, and micro and even bulk scale and to recognise that bulk material properties are an emergent result of intermolecular interactions on the scale of individual molecules.

In terms of real illustrations of practical supramolecular systems, David Parker in Durham has produced a commercial test for prostate cancer based on carefully designed luminescent europium complexes such as **1.22**, which is capable of recognising citrate anions in cells.¹⁵⁹ Citrate is a significant cancer biomarker and its concentration in diluted body fluids gives a simple and easy ratiometric test. First, a sample of prostatic fluid is taken from patient in hospital using local anaesthetic. The 1 μ L sample is diluted 200-fold with a buffer solution into pre-coated disposable cuvettes. The citrate binds selectively to the luminescent europium complex and the luminescence intensity is then read out in just a few minutes using a versatile bench top instrument with easy to use software. Comparison with a calibrated scale indicates whether further investigation is required. This technology is currently marketed commercially by the company FScan.

In another medical sensing application, Tony James in Bath has shown that phenylboronic acids bearing with amino methyl group in the *ortho* position bind saccharides at physiological pH. Conjugating this recognition system with a fluorophore results in photoinduced electron transfer (PET) which quenches the emission. When the boronic acid binds an analyte such as glucose, however, the PET mechanism is turned off and the fluorescent emission is turned on. This concept is now applied to the commercial GlySure Continuous Intravascular Glucose Monitoring Sensor (CIGMS), using two *o*-(aminomethyl)phenyl boronic acids with a six-carbon linker between the amines which makes the receptor glucose-specific, Figure 1.52. This chemistry is now used in central venous catheters, which are inserted into the jugular veins of a patient during intensive care allowing precise and continuous monitoring of blood glucose levels.¹⁶⁰



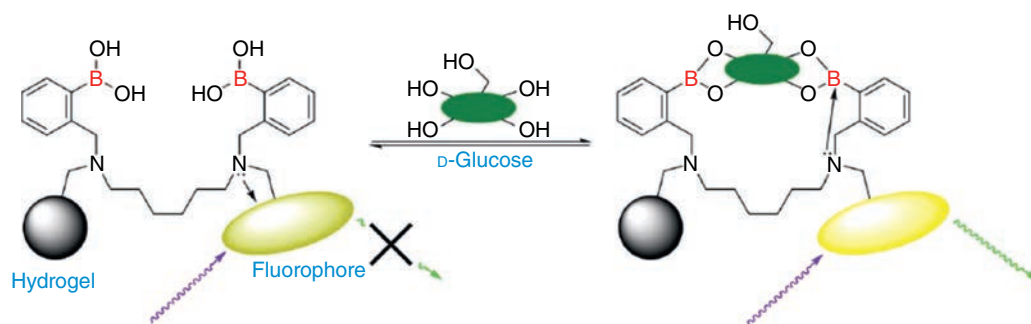


FIGURE 1.52 GlySure CIGMS sensing mechanism. Binding of glucose switches the fluorescence of the receptor ‘on’ upon binding.¹⁶⁰

In terms of metal separations, we will see in Section 3.8.3 how early work by Izatt, Bradshaw, and Christensen at Brigham Young University gave rise to IBC Advanced Technologies (IBC) in 1988 and the annual Izatt-Christensen Award in Supramolecular Chemistry. This commercially successful company carries out metal ion separations based on molecular recognition using crown ethers and a range of other macrocycles supported on silica to give highly selective solid supports useful in separating precious, base, and minor metals as well as rare earth elements, radionuclides, and toxic elements. These separation media are marketed under the trade name SuperLig®.

In Section 5.1.5, we will look at the work of Peter Tasker from the University of Edinburgh on copper-selective hydrometallurgical extraction using phenolic oximes which form a highly copper-selective cavity in between two oxime ligands. As of 2013, these oximes and the extraction methods in which they are used, accounted for about 25% of the world’s copper recovery from crude ores.¹⁶¹

In Section 3.14.3, we will look at the development of the calix-crown ligands such as **1.23** by Bruce Moyer of Oakridge National Lab. These systems extract radioactive ¹³⁷Cs out of high-level nuclear waste. The ligands are the basis of the caustic-side solvent extraction (CSSX) process which has been in operation since 2008 at the US Savannah River Site. The advantage of the calix-crowns is that the lipophilicity of the ligands can be carefully designed and hence their solubility in alkane solvent extraction mixtures adjusted without reducing metal ion affinity and selectivity. The ligands also prevent emulsification of the organic and aqueous phases during the extraction process.¹⁶²

One of the most ubiquitous class of supermolecule in commercial applications is the cyclodextrins. These cheap, readily available macrocycles, particularly β-cyclodextrin, are used extensively as food additives as preservatives, flavour enhancers, and processing additives. They also find applications in analytical chemistry as chiral stationary phases and in drug delivery. α-Cyclodextrin also has commercial potential in the ‘green’ recovery of gold from crude ores. A method based on the self-assembly of KAuBr₄ and α-cyclodextrin in aqueous solution to give a 1 : 2 complex, KAuBr₄·(α-CD)₂ was patented by Stoddart in 2014.¹⁶³ We will look at cyclodextrins in Section 6.3.

Drug delivery in general is a huge area of interest for macrocyclic and ‘container’-type systems. Cyclodextrins are by far the most commercially important, although cucurbiturils, functional polymers, and self-assembled systems such as micelles and liposomes are also relevant.

Substituted β-cyclodextrins are very common in pharmaceutical formulations since they do not suffer from the insolubility of the parent compound and are of the right size to include many ‘druglike’ molecules. Common examples are 2-hydroxypropyl-β-cyclodextrin (HPBCD), sulfobutylether β-CD sodium salt (SBEB CD), and randomly methylated β-cyclodextrin (RAMEB).¹⁶⁴ Cyclodextrins can overcome formulation challenges such as the increasing insolubility of hydrophobic drugs. To take one example, the antipsychotic ziprasidone has a water solubility of only 0.003 mg mL⁻¹ in its free base form. Complexation with SBEB CD increases the solubility to 0.35 mg mL⁻¹. Salt formation as the mesylate further increases the solubility of the SBEB CD complex to 44 mg mL⁻¹ which is a viable commercial formulation for intramuscular injections.⁴¹ Cyclodextrins also have applications as scavengers. A substituted γ-cyclodextrin sold under the trade name ‘Sugammadex’ is used to bind the anaesthetic rocuronium inside the body, reversing its effects after surgery. Overall, the number of marketed drugs containing cyclodextrins was about 35 in 2010.¹⁶⁴

Zeolites have been important commercial compounds for many years in areas as diverse as such as catalytic cracking in the petroleum industry to cat litter trays. Applications are also being realised in the metal-organic framework (MOF) arena in gas storage, separations, and catalysis, and we will discuss this exciting area in Chapter 9. Some

20 years of careful refinement from the original porous MOF-5 has led to precise control and tailoring of sorption and reactivity. A range of MOFs are commercially available from BASF with applications in areas such as methane storage.¹⁶⁵ The company MOF Technologies also carries out industrial-scale manufacture and devises specialist MOF applications such as prevention of fruit spoilage in transit. Perhaps, the most significant emerging MOF application is in harvesting pure water from air using only low-grade, renewable energy sources (Chapter 9).

The soft materials area, particularly supramolecular gels (Section 15.7), has a very large range of applications that have been described in a recent article by David Smith.¹⁶⁶ Industrial applications include the role of gels as lubricants, polymer additives, in dentistry, as drilling fluids in the oilfield sector, in personal care products, adhesives, in the food industry, as inks and dyes, and in art conservation. There is also the less savory role of gels in the incendiary napalm. Smith also identifies a number of future high-tech applications in environmental remediation, drug formulation and delivery, tissue engineering, controlled crystallisation, catalysis, tissue engineering, sensing and photonics.

Perhaps, one of the biggest growth areas in recent years is in supramolecular catalysis, particularly organocatalysis and we will return to this field in Section 13.8.¹⁶⁷ Organocatalysts are used in labs throughout the world in a very wide range of often green organic synthetic applications. Common organocatalysts include biomolecules such as proline and phenylalanine, secondary amines either in the form of enamine catalysis (in which the catalyst forms an active enamine nucleophile), or iminium catalysis (involving catalytic quantities of an activated iminium electrophile). Other organocatalysts include cinchona alkaloids, oligopeptides, and synthetic catalysts derived from biomolecules. Hydrogen bonding catalysts are especially popular and directly derive inspiration from supramolecular chemistry. Examples include TADDOLS (tetraaryl-disubstituted dioxolane dimethanol; readily accessed chiral auxiliaries), derivatives of the chiral 1,1'-bi-2-naphthol (BINOL), and a huge range of organocatalysts based on thioureas.¹⁶⁸ Triazolium salts are also important organocatalysis for the Stetter reaction. A particularly exciting recent development is the emergence of anion- π catalysis.¹⁶⁹

This chapter has covered the fundamental concepts in the field of Supramolecular Chemistry. While there is a great deal of detail to come in the ensuing sections, we can already see that the chemistry of intermolecular interactions has opened up a new creative scientific space in which technology that relies on an understanding of the interactions between molecules can be devised. It was as recently as 2002 that Jean-Marie Lehn spelled out a molecular information paradigm approach to Supramolecular Chemistry in which he articulated for the first time how the concepts of supramolecular chemistry provide a way of thinking that leads to complex matter and self-organised systems.¹⁷⁰ This is a significant extension of the field from the formation of a discrete cryptand-like *supermolecule* that Lehn described in formulating some of the original definition of the area back in 1978.¹⁷¹ It is an illustration of the power of this supramolecular way of thinking that can lead concepts rooted in macrocyclic complexes of alkali metals to be applicable and helpful in sectors as diverse as healthcare, the oilfields, energy, and pharmaceuticals. As a result, supramolecular chemistry has achieved a fully recognised place in the way modern scientists think about chemistry and materials. It is those scientists and the way in which they creatively approach a problem that shapes and improves the world around us in ways that are impossible to predict when an idea germinates for the first time.

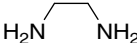
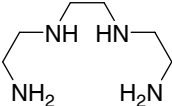
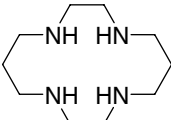
SUMMARY

- Supramolecular Chemistry involves the chemistry of the non-covalent bond.
- Non-covalent bonds include ionic and dipolar interactions, hydrogen bonds, aromatic interactions (π - π , cation- π , and anion- π), halogen bonds and other closed shell interactions, and van der Waals interactions.
- Mechanical and dynamic covalent bonds are also of considerable interest in Supramolecular systems, particularly since the award of the 2016 Nobel Prize in Chemistry.
- Supermolecules generally comprise a host component with convergent binding sites and a guest component with divergent binding sites.
- In solid-state host-guest or clathrate compounds, the guest is included within a gap in the packing of host molecules.
- Self-assembling systems do not involve hosts and guests but rather self-complementary molecules or complementary partners (tectons).

- The affinity of a host for a guest is measured by the binding constant; selective hosts have a high binding constant for one particular guest.
- Supramolecular chemistry makes use of ‘generalised’ coordination chemistry and binding cooperativity.
- The traditional picture of ‘lock-and-key’ binding is generally less appropriate than an induced-fit approach.
- Perhaps, the most important concepts in supramolecular host design are preorganisation and complementarity, which encapsulate more traditional concepts such as the macrocyclic effect.
- Solvation, desolvation, and hydrophobic effects are of tremendous importance in assessing binding equilibria.
- Modern supramolecular chemistry is progressing towards concepts such as molecular information content and intermolecular interaction algorithms, leading to the self-organisation of increasingly complex, informed matter with emergent properties that arise spontaneously in the multi-nanometre length scale.
- Supramolecular chemistry underpins a huge range of commercial applications in sensing, imaging, drug formulation, catalysis, metals extraction, and separations.

STUDY PROBLEMS

- 1.1 Thermodynamic parameters for the reaction of $\text{Cu}_{(\text{aq})}^{2+}$ with various ligands are given below (aqueous solution, 25 °C). Use these data to calculate the binding constants ($\log K$) for the resulting 1 : 1 metal-to-ligand complexes. Explain the differences in stability observed.

Ligand			
ΔH° (kJ mol ⁻¹)	-105	-90.4	-76.6
$T\Delta S^\circ$ (kJ mol ⁻¹)	7.1	24.3	64.0

- 1.2 Give a concise definition of the term ‘supramolecular chemistry’. Explain the distinction between molecular and supramolecular interactions. Illustrate your answer with examples of supramolecular interactions and discuss their relative importance.
- 1.3 Draw up a relative scale of the strengths of non-molecular interactions using the information given in Section 1.8. Correlate this with a second scale of the importance of these interactions in supramolecular design of host for metal cations, taking into account factors such as directionality, ease of incorporation into host frameworks, and propensity of binding enhancement *via* multiple binding sites. Would this ranking change if you were to design hosts for anions or neutral organic molecules? What interactions might be important in designing a host for the following species: methane, benzene, methanol, phenol, ammonia, Cl^- , Na^+ , and Ni^{2+} ?
- 1.4 Using the timeline given in Table 1.1, suggest what may be some of the most important discoveries in supramolecular chemistry. Why do you think it has taken so long for the topic to evolve as a separate discipline?

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