1 Concepts

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

Max Beerbohm (b. 1872), *Hosts and Guests*

1.1 Definition and Development of Supramolecular Chemistry

Lehn, J.-M., 'Supramolecular chemistry and self-assembly special feature: Toward complex matter: Supramolecular chemistry and self-organization', *Proc. Nat. Acad. Sci. USA*, 2002, **99**, 4763–4768.

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 the 'chemistry of molecular assemblies and of the intermolecular bond'. More colloquially this may be expressed as 'chemistry beyond the molecule'. Other definitions include phrases such as 'the chemistry of the non-covalent bond' and 'non-molecular chemistry'. Originally supramolecular chemistry was defined in terms of the non-covalent interaction between a 'host' and a 'guest' molecule as highlighted in Figure 1.1, which illustrates the relationship between molecular and supramolecular chemistry in terms of both structures and function.

These descriptions, while helpful, are by their nature noncomprehensive and there are many exceptions if such definitions are taken too literally. The problem may be linked to the definition of organometallic chemistry as 'the chemistry of compounds with metal-to-carbon bonds'. This immediately rules out Wilkinson's compound, $RhCl(PPh_3)_3$, for example, which is one of the most important industrial catalysts for organometallic transformations known in the field. Indeed, it is often the objectives and thought processes of the chemist undertaking the work, as much as the work itself, which determine its field. Work in modern supramolecular chemistry encompasses not just host-guest systems but also molecular devices and machines, molecular recognition, so called 'self-processes'

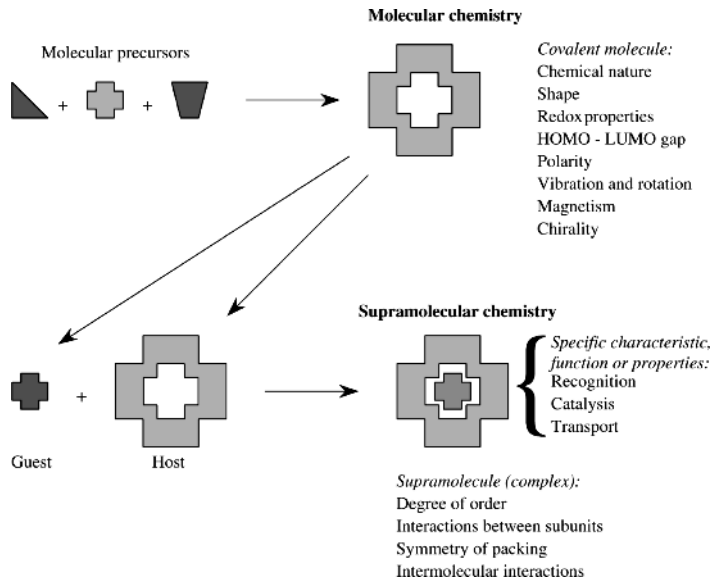


Figure 1.1 Comparison between the scope of molecular and supramolecular chemistry according to Lehn.[1]

Supramolecular Chemistry, 2nd edition J. W. Steed and J. L. Atwood

such as self-assembly and self-organisation and has interfaces with the emergence of complex matter and nanochemistry (Section 1.10). The rapid expansion in supramolecular chemistry over the past 25 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. In particular, workers in the field of supramolecular photochemistry have chosen to adopt a rather different definition of a supramolecular compound as a group of molecular components that contribute properties that each component possesses individually to the whole assembly (covalent or non-covalent). 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 11). Similarly, much recent work has focused on the development of self-assembling synthetic pathways towards large molecules or molecular arrays. These systems often self-assemble using 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.

1.1.2 Host–Guest Chemistry

Kyba, E. P., Helgeson, R. C., Madan, K., Gokel, G. W., Tarnowski, T. L., Moore, S. S. and Cram, D. J., 'Host-guest complexation .1. Concept and illustration', *J. Am. Chem. Soc.*, 1977, **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 cyclic compound possessing a sizeable, central hole or cavity. The guest may be a monatomic cation, a simple inorganic anion, an ion pair or a more sophisticated molecule such as a 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 or hydrogen bond acceptor halide anion). 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 Supramolecular Chemistry Nobel Laureate)[2] as follows:

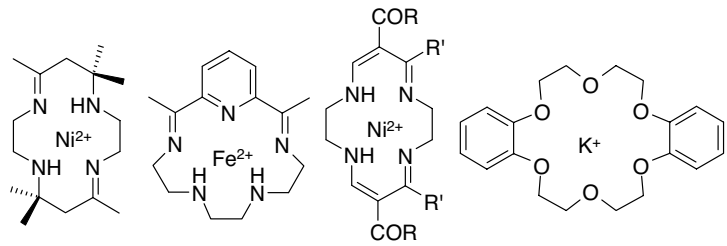
> *Complexes are composed of two or more molecules or ions held together in unique structural relationships by electrostatic forces other than those of full covalent bonds … molecular complexes are usually held together by hydrogen bonding, by ion pairing, by π-acid to π-base interactions, by metal-to-ligand 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 more recent work has revealed a wealth of inorganic hosts, such as zeolites (Section 9.2) and polyoxometallates (Section 9.5.2), 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 falls down at the electronic level, however, since there is no real attractive force between hand and ball. Host and guest *molecules and ions* usually experience an attractive force between them and hence a stabilising binding free energy. The analogy does serve to introduce the term 'inclusion chemistry', however (the ball is included in the hand), hence the inclusion of one molecular 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 clathrate, 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. 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 both in the solid state and in solution. We should also note that there exist purely liquid-phase phenomena, such as liquid crystals and liquid clathrates, that have no direct solid-state analogies (Chapter 13).

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 simple (and not-so-simple) supramolecular chemical 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, three of which used the Schiff base condensation reaction of an aldehyde with an amine to give an imine (Section 3.10.6). Conceptually, these systems may be seen as a development of naturally occurring macrocycles (ionophores, hemes, 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 of the recent developments in the field.



Curtis 1961 **1.1** Busch 1964 **1.2** Jäger 1964 **1.3** Pedersen 1967 **1.4**

Table 1.1 Timeline of supramolecular chemistry.

1810 – Sir Humphry Davy: discovery of chlorine 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

1893 – Alfred Werner: coordination chemistry

1894 – Emil Fischer: *lock and key* concept

1906 – Paul Ehrlich: introduction of the concept of a *receptor*

1937 – K. L. Wolf: the term *Übermoleküle* 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 groundbreaking book *The Nature of the Chemical Bond*

1940 – M. F. Bengen: urea channel inclusion compounds

1945 – H. M. Powell: X-ray crystal structures of β-quinol inclusion compounds; the term 'clathrate' 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}

1959 – Donald Cram: attempted synthesis of cyclophane charge transfer complexes with $(NC)_2C{=}C(CN)_2$

1961 – N.F. Curtis: first Schiff's base macrocycle from acetone and ethylene diamine

1964 – Busch and Jäger: Schiff's base macrocycles

1967 – Charles Pedersen: crown ethers

1968 – Park and Simmons: *Katapinand* anion hosts

1969 – Jean-Marie Lehn: synthesis of the first cryptands

1969 – Jerry Atwood: liquid clathrates from alkyl aluminium salts

1969 – Ron Breslow: catalysis by cyclodextrins

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

1986 – A. P. de Silva: Fluorescent sensing of alkali metal ions by crown ether derivatives

1987 – Award of the Nobel prize for Chemistry to Donald J. Cram, Jean-Marie Lehn and Charles J. Pedersen for their work in supramolecular chemistry

1996 – Atwood, Davies, MacNicol & Vögtle: publication of *Comprehensive Supramolecular Chemistry* containing contributions from many key groups and summarising the development and state of the art

1996 – Award of the Nobel prize for Chemistry to Kroto, Smalley and Curl for their work on the chemistry of the fullerenes

2003 – Award of the Nobel prize for Chemistry to Peter Agre and Roderick MacKinnon for their discovery of water channels and the characterisation of cation and anion channels, respectively.

2004 – J. Fraser Stoddart: the first discrete Borromean-linked molecule, a landmark in topological synthesis.

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, synthetic organic chemists, biochemists and biologists. Within the past decade Supramolecular chemistry has fed into very exciting new research in nanotechnology and at the interface between the two lies the area of *nanochemistry* (Chapter 15). 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 Supramolecular Host–Guest Compounds

Vogtle, F., *Supramolecular Chemistry*, John Wiley & Sons, Ltd: Chichester, 1991.

One of the first formal definitions of a supramolecular cage-like host–guest structure was proposed by H. M. Powell at the University of Oxford in 1948. He coined the term 'clathrate', which he defined 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'. In beginning to describe modern host–guest chemistry it is useful to divide host compounds into two major classes according to the relative topological relationship between guest and host. *Cavitands* may be described as 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 or solid state. The host–guest aggregate formed by a cavitand is termed a *cavitate*, while clathrands form *clathrates*. 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. The distinction between the two host classes and self-assembly is illustrated schematically in Figure 1.2.

A further fundamental subdivision may be made on the basis of the forces between 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 effects, are referred to by the terms *cavitate* and *clathrate*. Some examples of the use of this nomenclature are shown in Table 1.2. The distinctions between these classes are blurred and often the word 'complex' is used to cover all of these phenomena. Within these broad classifications a number of 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. The nomenclature should act as a conceptual framework helping the chemist to describe and visualise the systems being handled, rather than a restrictive and rigid series of 'phyla'.

1.3 Receptors, Coordination and the Lock and Key Analogy

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

Host–guest (or receptor–substrate) chemistry is based upon three historical concepts:

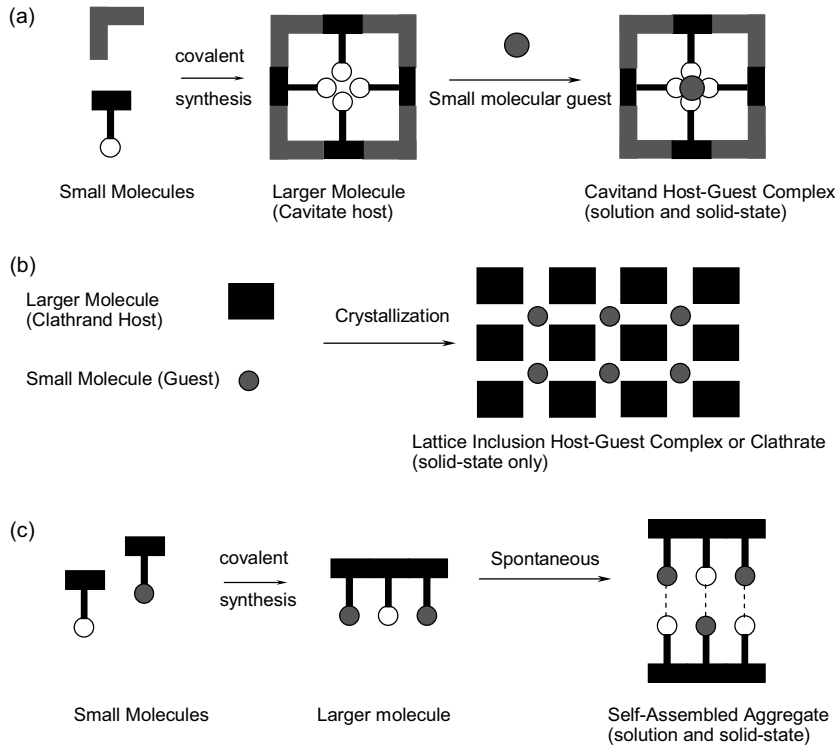


Figure 1.2 Schematic illustrating the difference between a cavitate and a clathrate: (a) synthesis and conversion of a cavitand into a cavitate by inclusion of a guest into the cavity of the host molecule; (b) inclusion of guest molecules in cavities formed between the host molecules in the lattice resulting in conversion of a clathrand into a clathrate; (c) synthesis and self-assembly of a supramolecular aggregate that does not correspond to the classical host-guest description.

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

Table 1.2 Classification of common host–guest compounds of neutral hosts.

Host	Guest	Interaction	Class	Example
Crown ether	Metal cation	Ion–dipole	Complex (cavitand)	$[K^+([18]crown–6)]$
Spherand	Alkyl ammonium cation	Hydrogen bonding	Complex (cavitand)	Spherand$\cdot(CH_3NH_3^+)$
Cyclodextrin	Organic molecule	Hydrophobic/ van der Waals	Cavitate	(α–cyclodextrin)$\cdot$ (p–hydroxybenzoic acid)
Water	Organic molecule, halogen *etc.*	Van der Waals/ crystal packing	Clathrate	$(H_2O)_6\cdot(CH_4)$
Calixarene	Organic molecule	Van der Waals/ crystal packing	Cavitate	(p–t–butylcalix[4]arene)$\cdot$ (toluene)
Cyclotriveratrylene (CTV)	Organic molecule	Van der Waals/ crystal packing	Clathrate	(CTV)$\cdot$0.5(acetone)

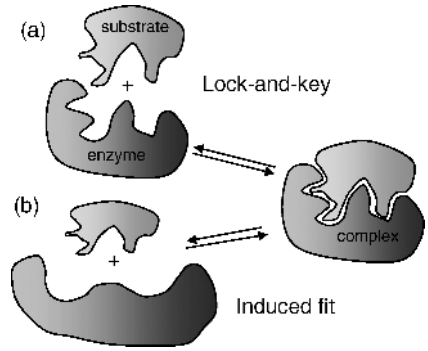
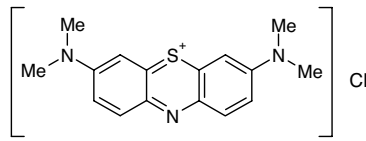


Figure 1.3 (a) Rigid lock and key and (b) induced fit models of enzyme–substrate binding.

guest has a geometric size or shape complementarity to the receptor or host (Figure 1.3a). This concept laid the basis for *molecular recognition*, the discrimination by a host between a number of different guests.

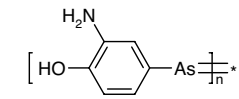
3. The fact that selective binding must involve *attraction* or mutual affinity between host and guest. This is, in effect, a generalisation of Alfred Werner's 1893 theory of coordination chemistry, in which metal ions are coordinated by a regular polyhedron of ligands binding by dative bonds.

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, for example, 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 tutor Robert Koch had used methylene blue (**1.5**) 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). '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, **1.6**) in 1910,[3] one of the most effective drugs known for that disease. In the process he became the founder of modern chemotherapy.



methylene blue

1.5



Salvarsan (arsphenamine)
n = typically 3 or 5

1.6

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 born as a discipline in itself in 1828 with Friedrich Wöhler's synthesis of urea from ammonium cyanate. In the course of the development of supramolecular chemistry, enormous progress has been made on quantifying the details of receptors with an affinity for guests which fit inside them. The lock and key 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' theory of Daniel Koshland[4] in which both enzyme and substrate (host and guest) undergo significant conformational changes upon binding to one another (Figure 1.3b). It is these conformational changes that allow the enzymatic catalytic rate acceleration since the substrate is commonly more like the reaction transition state in its bound form than in its unbound form. 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.

1.4 Binding Constants

1.4.1 Definition and Use

Connors, K. A., *Binding Constants*, John Wiley & Sons, Ltd: Chichester, 1987.

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 binding constant, K. Strictly the binding constant is dimensionless, but it is often calculated approximately using concentrations and thus has units of $dm^3\ mol^{-1}$, 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 sometimes useful 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 it is of fundamental importance in supramolecular chemistry and so it is worth spending some time looking into its proper definition and usage. Ignoring activity effects, the binding constant 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):

$$M(H_2O)_n^{m+} + L \rightleftharpoons ML^{m+} + nH_2O \tag{1.1}$$

$$K = \frac{[ML^{m+}]}{[M(H_2O)_n^{m+}][L]} \tag{1.2}$$

Thus a large binding constant corresponds to a high equilibrium concentration of bound metal, and hence a more stable metal–macrocycle complex. Typical binding constants for crown ethers and alkali metal cations in water are in the range 10^1–10^2. In methanol, this increases up to 10^6 for $[K([18]crown-6)]^+$.* The binding constant for K^+ and [2.2.2]cryptand is about 10^{10}. Some other examples are given in Table 1.3.

* 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 '$[ML^{m+}]$' means the 'concentration of the chemical species ML^{m+}'. If ML^{m+} is a coordination complex ion, then it should be written outside an equation '$[ML]^{m+}$', *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, $[Co(1,2\text{-diaminoethane})_2Cl_2]Br$ contains two Cl^- ligands bound to Co(III) with a bromide counter anion balancing the overall charge, whereas $[Co(1,2\text{-diaminoethane})_2ClBr]Cl$ contains both Co–Cl and Co–Br bonds and a chloride counter anion.

Table 1.3 Binding constants for a range of complexation processes.

Guest	Host	Solvent	K_{11}/M^{-1}	$\Delta G°/kJ\ mol^{-1}$
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 *trans*-cinnamate	Imidazole	H_2O	1.0	0.0
p-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

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).

$$M(H_2O)_n^{m+} + L \overset{K_{11}}{\rightleftharpoons} ML^{m+} + nH_2O \tag{1.3}$$

$$M(H_2O)_n^{m+} + ML^{m+} \overset{K_{12}}{\rightleftharpoons} M_2L^{(2m)+} + nH_2O \tag{1.4}$$

$$K_{12} = \frac{[M_2L^{(2m)+}]}{[M(H_2O)_n^{m+}][ML^{m+}]} \tag{1.5}$$

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:

$$\beta_{12} = K_{11} \times K_{12} \tag{1.6}$$

$$\text{Or, more generally, } \beta_{xn} = \frac{[M_xL_n]}{[M]^x[L]^n} \tag{1.7}$$

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

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

The subscript numbers in stepwise binding constant notation refer to the ratio of one complexing partner to another, thus in a multi-step 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 have to 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, $a_i = \gamma_i C_i / C_\Theta$ where C_i is the concentration of i, C_Θ 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) ≈ concentration.

Because binding constants are thermodynamic parameters, they are related to the free energy of the association process according to the Gibbs equation: $\Delta G^o = -RT \ln K$. (R = gas constant, 8.314 J K^{-1} mol^{-1}, T = temperature in 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 $-\Delta G^o$ values. In energy terms, complexation free energies may range from magnitudes of 20 to 100 kJ mol^{-1} (5 to 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 $-\Delta G^o$ 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 1.3.

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

$$M(H_2O)_n^{m+} + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ML^{m+} + nH_2O \tag{1.9}$$

$$K = \frac{k_1}{k_{-1}} \tag{1.10}$$

1.4.2 Measurement of Binding Constants

J. Polster and H. Lachmann, *Spectrometric Titrations*, VCH: Weinheim, 1989.

In principle, binding constants may be assessed by any experimental technique that can yield information about the concentration of a complex, [Host·Guest], as a function of changing concentration of the host or guest. In practice the following methods are 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. 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.

Potentiometric Titration

In the case of macrocycles that are susceptible to protonation (*e.g.* the cryptands with their basic tertiary amine nitrogen bridgeheads), 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$^+$).[5] 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.

$$K_a = \frac{[H^+][L]}{[HL^+]} \qquad HL^+ \underset{+\,H^+}{\overset{K_a\ -\,H^+}{\rightleftharpoons}} L \underset{-\,M^+}{\overset{K_{11}\ +\,M^+}{\rightleftharpoons}} ML^+ \underset{-\,M^+}{\overset{K_{12}\ +\,M^+}{\rightleftharpoons}} M_2L^+ \textit{ etc.}$$

Scheme 1.1 Competing equilibria in a potentiometric titration.

Analysis of the various equilibria by a curve-fitting computer program (such as *Hyperquad*) 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

Nuclear Magnetic Resonance 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. 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 and bound species. 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.* ^{1}H in ^{1}H 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 1.4) gives quantitative information about the binding constant. NMR spectroscopic methods are useful for binding constants in the range 10–10^4 M^{-1}. Such titration curves are often analysed by computer least-squares curve fitting (*e.g.* by a program such as EQNMR[6]) using Equation 1.14 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 1.4a fits a stoichiometry model involving both 1:1 and 1:2 host:guest complexes with log β_{11} = 2.3 and log β_{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.

$$\delta_{calc} = \sum_{m=1}^{m=i} \sum_{n=0}^{n=j} \frac{\delta_{mn}\beta_{mn}m[G]^m[H]^n}{[G]_{total}} \tag{1.11}$$

Method of Continuous Variation (Job Plots)

A key aspect of such calculations is the use of the correct stoichiometry model (*i.e.* the ratio of host to guest, which must be assumed or determined). 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. Binding stoichiometry may be confirmed in most kinds of titration experiments that allow the concentration of complex to be determined by making up a series of solutions with varying host:guest ratios such that the total concentration of host and guest is a constant. Monitoring the

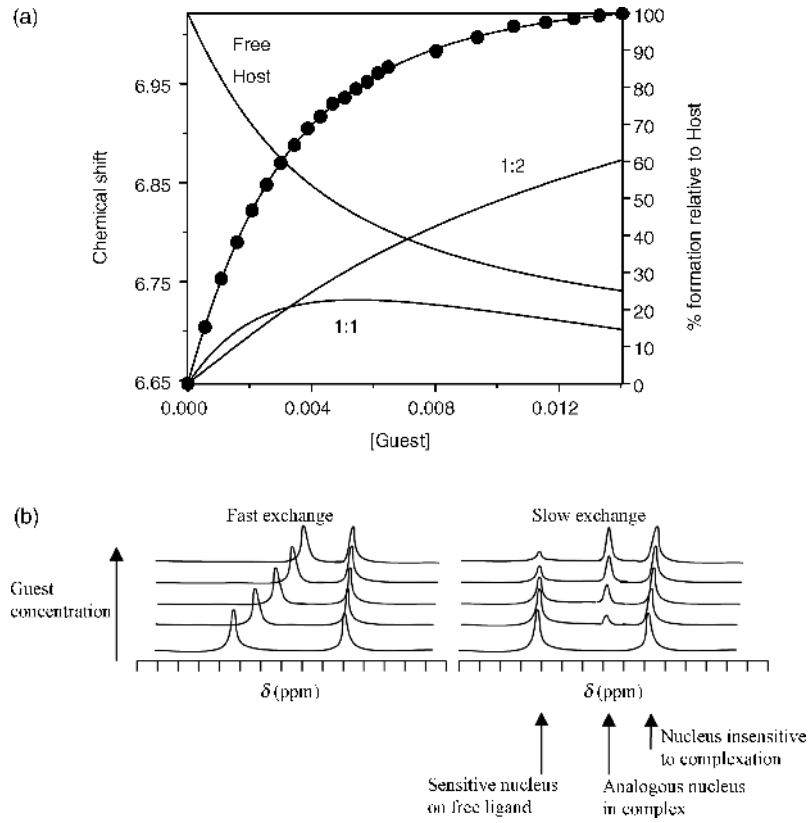


Figure 1.4 (a) NMR titration plot (isotherm) and corresponding speciation plots for a system undergoing fast equilibration on the NMR time scale, with log $\beta_{11} = 2.3$ and log $\beta_{12} = 4.5$. (b) Schematic NMR spectra of slowly equilibrating mixtures of free host, guest and host–guest complex.

changing concentration of the host–guest complex in these samples allows a plot of [Complex] against ([Host]/([Host] + [Guest])) to be constructed. For a 1:1 complex, this kind of representation (referred to as a Job plot) should give a peak at 0.5 (Figure 1.5), a peak at 0.66 would correspond to a 2:1 stoichiometry and so on. The concentration of the complex is generally taken to be related to an observable quantity such as $\Delta\delta$ according to Equation 1.12. In a spectrophotometric experiment absorbance at a properly chosen wavelength is usually directly proportional to complex concentration.

$$[\text{Complex}] \propto \Delta\delta \times \text{mole fraction of host} \tag{1.12}$$

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:

$$F = k_{\text{G}}[\text{G}] + k_{11}[\text{HG}] \tag{1.13}$$

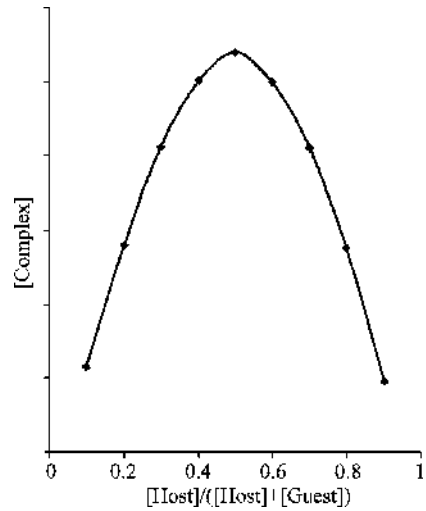


Figure 1.5 Job plot for a 1:1 host–guest complex.

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_o, is given by:

$$F_o = k_G^o G_{total} \tag{1.14}$$

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

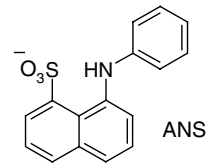
Combining these two relationships gives Equation (1.15), which provides the basis for most fluorimetric methods for stability constant (K_{11}) determination:

$$\frac{F}{F_o} = \frac{k_G/k_G^o + (k_{11}/k_G^o)K_{11}[H]}{1 + K_{11}[H]} \tag{1.15}$$

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} become zero. For example, for $k_G = k_G^0$ and $k_{11} = 0$, we obtain:

$$\frac{F_o}{F} = 1 + K_{11}[H] \tag{1.16}$$

A simple plot of F_o/F against [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, **1.7**) may be used to probe complexation ability of various hosts in this way.



ANS

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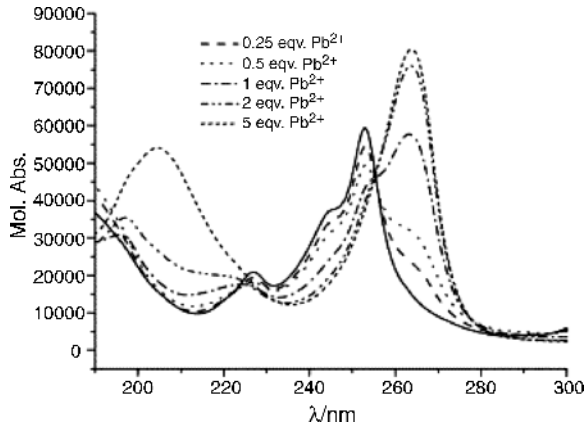
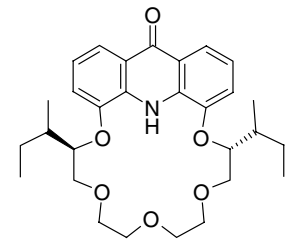




1.8

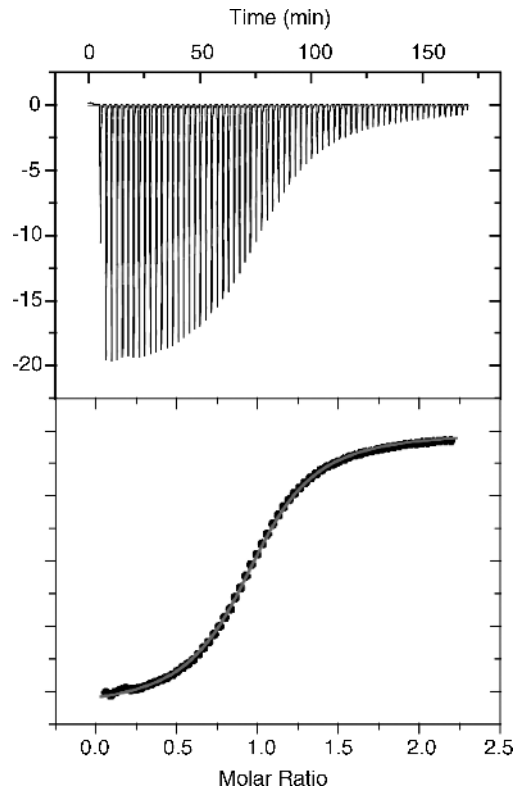
Figure 1.6 UV-monitored titration of a diisobutyl-substituted acridono-18-crown-6 ligand **1.8** with Pb^{2+} showing an isosbestic point at 271 nm (solid line represents free ligand spectrum, reproduced from [7] with permission from Elsevier).

UV-Vis Spectrophotometric Titration

UV-Vis spectroscopic titration (or spectrophotometric titration) involves monitoring the intensity of a 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*® 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 1.6 shows the observed UV-Vis spectra during a titration of a diisobutyl-substituted acridono-18-crown-6 ligand **1.8** with Pb^{2+}. The isosbestic point occurs at at 271 nm.[7]

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 $\Delta G_{complex}$. Integration of the total area under the ITC plot gives the complexation enthalpy ($\Delta H_{complex}$) and hence the technique can give a measurement of all thermodynamic parameters of the system since $\Delta G_{complex} = \Delta H_{complex} - T\Delta S_{complex}$. ITC is useful for determination of binding constants that range from *ca.*$10^2 - 10^7$ 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, **1.9** (Section 4.6.4).[8] Figure 1.7 shows the ITC data and resulting fit for the binding of $NBu_4^+Cl^-$ by **1.9** in nitromethane, giving K_{11} = 19,200 M^{-1}, ΔG = 11.3 kJ mol^{-1}, ΔH = 8.55 kJ mol^{-1} and ΔS = −9.1 J K^{-1} mol^{-1}.



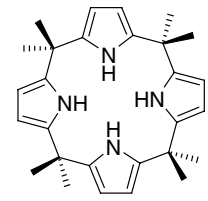


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Figure 1.7 ITC data at 25 °C for the binding of $NBu_4^+Cl^-$ by **1.9** in nitromethane – the top plot represents the raw data with the calorimetric response in μcal s^{-1} for each addition of $NBu_4^+Cl^-$ while the lower plot is the titration isotherm fitted to a 1:1 model with kcal per mol $NBu_4^+Cl^-$ added *vs.* mole ratio of $NBu_4^+Cl^-$ to **1.9**. (Reproduced with permission from [8] © 2006, American Chemical Society).

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 1.17–1.20) (for metal picrate (Pic) salt, water (aq) and water-saturated chloroform (org) phases, 25 ºC).

$$[M^+ \cdot Pic^-]_{org} + [Host]_{org} = [M^+ \cdot Host \cdot Pic^-]_{org} \quad K_{11} \text{ (binding constant)} \tag{1.17}$$

$$[M^+]_{aq} + [Pic^-]_{aq} + [Host]_{org} = [M^+ \cdot Host \cdot Pic^-]_{org} \quad K_e \text{ (extraction constant)} \tag{1.18}$$

$$[M^+]_{aq} + [Pic^-]_{aq} = [M^+ \cdot Pic^-]_{org} \quad K_d \text{ (distribution coefficient)} \tag{1.19}$$

$$K_{11} = K_e / K_d \tag{1.20}$$

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. 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 25–70 kJ mol^{-1} (*i.e.* binding constants of *ca.* 10^4–10^{12}). Binding energies in excess of 70 kJ mol^{-1} are assessed by competition with hosts of known binding energy.

1.5 Cooperativity and the Chelate Effect

Hancock, R. D., 'Chelate ring size and metal ion selection', *J. Chem. Ed.*, 1992, **69**, 615–621; Ercolani, G., 'Assessment of cooperativity in self-assembly', *J. Am. Chem. Soc.*, 2003, **125**, 16097–16103.

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 *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 $\Delta G_{AB}{}^{o}$ which is equal to the sum of the intrinsic binding free energies of each component A and B ($\Delta G_A{}^{i}$ and $\Delta G_B{}^{i}$) plus a factor arising from the summation or connection of A and B (ΔG^{s}), Equation 1.21.[9]

$$\Delta G_{AB}{}^{o} = \Delta G_A{}^{i} + \Delta G_B{}^{i} + \Delta G^{s} \tag{1.21}$$

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 1.22 (and similarly for component B)

$$\Delta G_A{}^{i} = \Delta G_{AB}{}^{o} - \Delta G_B{}^{o} \tag{1.22}$$

we can thus write Equation 1.23 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.

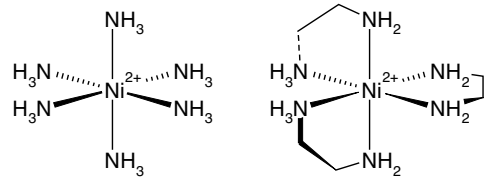
$$\Delta G^{s} = \Delta G_A{}^{o} + \Delta G_B{}^{o} - \Delta G_{AB}{}^{o} \tag{1.23}$$

Equation 1.23 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.

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 1.24, the value of the equilibrium constant for the replacement of ammonia with 1,2-diaminoethane indicates that the 1,2-diaminoethane chelate complex is more than 10^8 times more stable.

$$[Ni(NH_3)_6]^{2+} + 3NH_2CH_2CH_2NH_2 \xrightarrow{\log K = 8.76} [Ni(NH_2CH_2CH_2NH_2)_3]^{2+} + 6NH_3 \quad (1.24)$$



$[Ni(NH_3)_6]^{2+}$ $[Ni(en)_3]^{2+}$

1.10 **1.11**

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 1.24, seven on the right) and hence a favourable entropy contribution (ΔS^o) to the overall free energy of the reaction (ΔG^o), given by $\Delta G^o = \Delta H^o - T\Delta S^o$. 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 in order 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.

While an experimental fact in solution coordination chemistry, the nature of the chelate effect has been the topic of much debate in the literature. The first problem concerns the definition of the stability constants; the second stepwise stability constant β_{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 a 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 1.8). Five-membered rings, as in metal complexes of 1,2-diaminoethane, are often the most

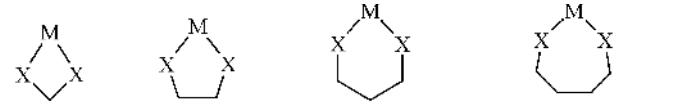
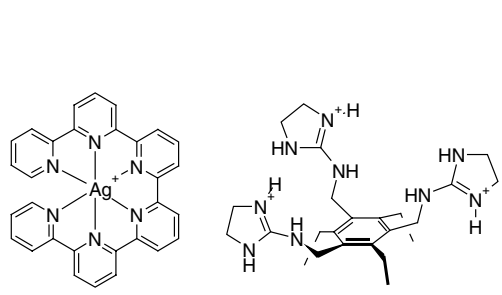


Figure 1.8 Ring size dependence of the stabilisation offered by the chelate effect.

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 rings 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 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 **1.12** (see Section 3.3.1) and, more generally, positive binding site cooperativity is similarly observed in hydrogen bonded complexes such as receptor **1.13** which selectively binds citrate anion through multiple hydrogen bonding interactions.[10] Another good example of cooperativity is seen in the drug-receptor complex **1.14** formed between the new generation antibiotic vancomycin and proteins that are used in the synthesis of bacterial cell walls.[9] The proteins end in the sequence D-alanine-D-alanine which form numerous hydrogen bonded and hydrophobic contacts to the drug (Figure 1.9).

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, multiple ligands by a single metal or in multi-component self-assembly processes. Multi-component 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 highly topical self-assembled, multi-component 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.[11] Here a 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



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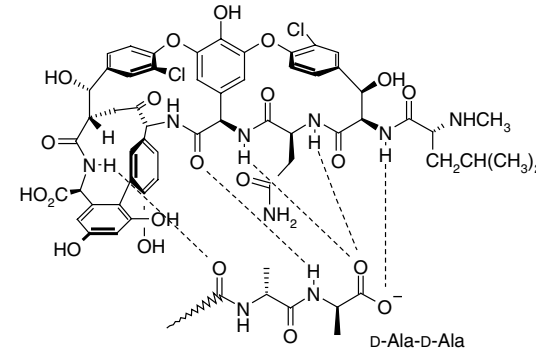
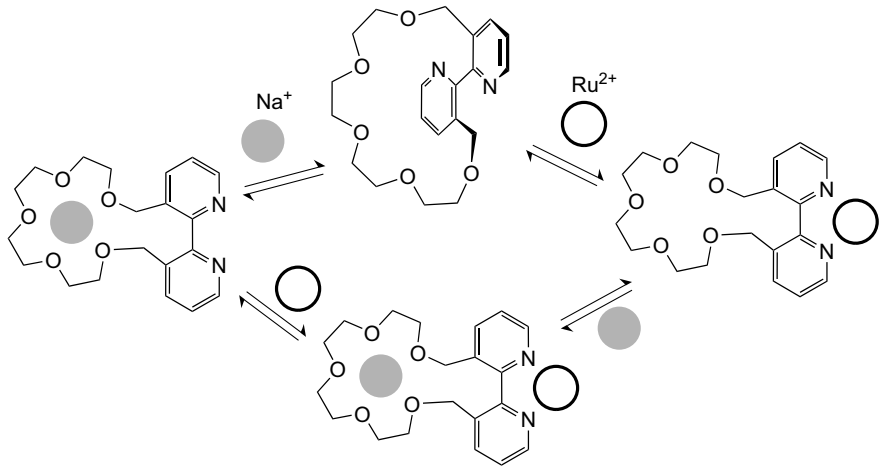
1.13



1.14

Figure 1.9 Supramolecular host–guest complexation stabilised by positive cooperativity between binding sites: Ag^+ binding by **1.12**, a host for citrate anion (**1.13**) and a drug-receptor complex formed by vancomycin (**1.14**).



Scheme 1.2 Allosteric (cooperative) enhancement of Na^+ binding by preorganisation of the polyether binding site by Ru(II), and *vice versa*.[11]

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 bonding of O_2 by haemoglobin (see Section 2.5).

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* would 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 1.25 holds true. Equation 1.25 implies that the binding constant for each added ligand is less than the previous one. In fact successive equilibrium

$$M + L \overset{K_1}{\rightleftharpoons} ML$$

$$ML + L \overset{K_2}{\rightleftharpoons} ML_2$$

$$\downarrow$$

$$ML_{i-1} + L \overset{K_i}{\rightleftharpoons} ML_i$$

$$\downarrow$$

$$ML_{m-1} + L \overset{K_m}{\rightleftharpoons} ML_m$$

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'.

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 are more of them. This effect is evident for example, in the stability constants for the successive reaction of $[Ni(H_2O)_6]^{2+}$ with six molecules of NH_3: log K_{1-6} = 2.80, 2.24, 1.73, 1.19, 0.75, 0.03.

$$K_i = K_{\text{inter}}(m - i + 1)/i \tag{1.25}$$

$$\frac{K_{i+1}}{K_i} = \frac{i(m-i)}{(i+1)(m-i+1)} \tag{1.26}$$

From Equation 1.25 we can derive Equation 1.26. The quantity K_{i+1}/K_i may be used as a measure of cooperativity. If the statistical relationship shown in Equation 1.26 holds true the system is non-cooperative. If K_{i+1} / K_i is higher than would be expected from Equation 1.26 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. Experimentally, cooperativity is often assessed by graphical methods based on a parameter r (Equation 1.27), known as the *occupancy*, *i.e.* the average number of occupied binding sites, in this case on the metal, M.

$$r = \frac{\sum_{i=1}^{m} i\beta_i[\text{L}]^i}{1 + \sum_{i=1}^{m} \beta_i[\text{L}]^i} \tag{1.27}$$

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 1.26 holds true) then Equation 1.27 becomes Equation 1.28:

$$r = \frac{mK_{\text{inter}}[\text{L}]}{1 + K_{\text{inter}}[\text{L}]} \tag{1.28}$$

Equation 1.28 can be put into two alternate linear forms known as the Scatchard (1.29) and Hill (1.30) equations.

$$\frac{r}{[\text{L}]} = -K_{\text{inter}}r + mK_{\text{inter}} \tag{1.29}$$

$$\log\left(\frac{r}{m-r}\right) = \log[\text{L}] + \log K_{\text{inter}} \tag{1.30}$$

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 $n_{\text{H}} > 1$ indicates positive cooperativity, while systems exhibiting negative cooperativity have $n_{\text{H}} < 1$. Hill and Scatchard plots for the binding of ammonia to Ni^{2+} are shown in Figure 1.10. 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 a statistical effects. A word of warning, however, Cooperativity can *only* be assessed in this way for *intermolecular* 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

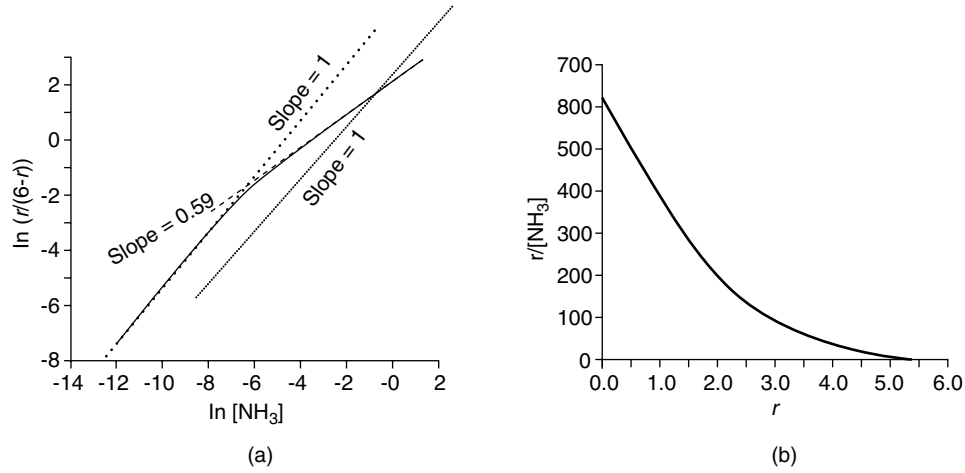


Figure 1.10 (a) Hill plot and (b) Scatchard plot for the successive intermolecular connections of ammonia to bivalent nickel to give $[Ni(NH_3)_i]^{2+}$, the concentration of the free ligand [L] is computed by using the known stability constants. $[Ni]_{total} = 1 \times 10^{-3}$ M; $[NH_3]_{total}$ varies between 10^{-5} and 1 M. (Reproduced from [12] by permission of the Royal Society of Chemistry).

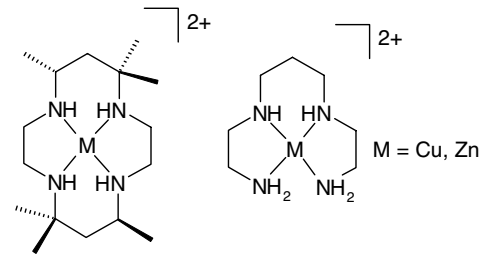
intra- and intermolecular processes requires a different treatment (Section 10.4) and this distinction has resulted in many erroneous claims of positive cooperativity in the literature.[12]

1.6 Preorganisation and Complementarity

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

Many supramolecular host–guest complexes are even more stable than would be expected from cooperative / chelate effects alone. The hosts in these species are usually macrocyclic (large ring) ligands that chelate their guests, again *via* a number of binding sites. Such compounds are stabilised additionally 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 binding 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 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 difficult to make but 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 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. The macrocyclic effect was first elucidated by Cabbiness and Margerum in 1969 who studied the Cu(II) complexes **1.15** and **1.16**.[13] Both ions benefit from the stability associated with four chelating donor atoms. However, the macrocyclic complex **1.15** is about 10^4 times more stable than the acyclic analogue **1.16** as a consequence of the additional preorganisation of the macrocycle.

Thermodynamic measurements on the analogous (unmethylated) Zn^{2+} complexes reveal that the stabilisation by macrocyclic preorganisation has both enthalpic and entropic contributions (Table 1.4).



1.15 **1.16**

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 enthaplic terms varies according to the system studied although the enthalpy is frequently dominant as a result of additional factors such as lone pair 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* (Figure 1.11) 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 1.4 and Section 3.7).

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 are able to adjust rapidly to changing conditions,

Table 1.4 Thermodynamic parameters for Zn^{2+} complexes of **1.15** and **1.16** (298 K).

	1.15	**1.16**
Log K	15.34	11.25
ΔH^{o} (kJ mol^{-1})	–61.9	–44.4
$-T\Delta S^{o}$ (kJ mol^{-1})	–25.6	–19.8

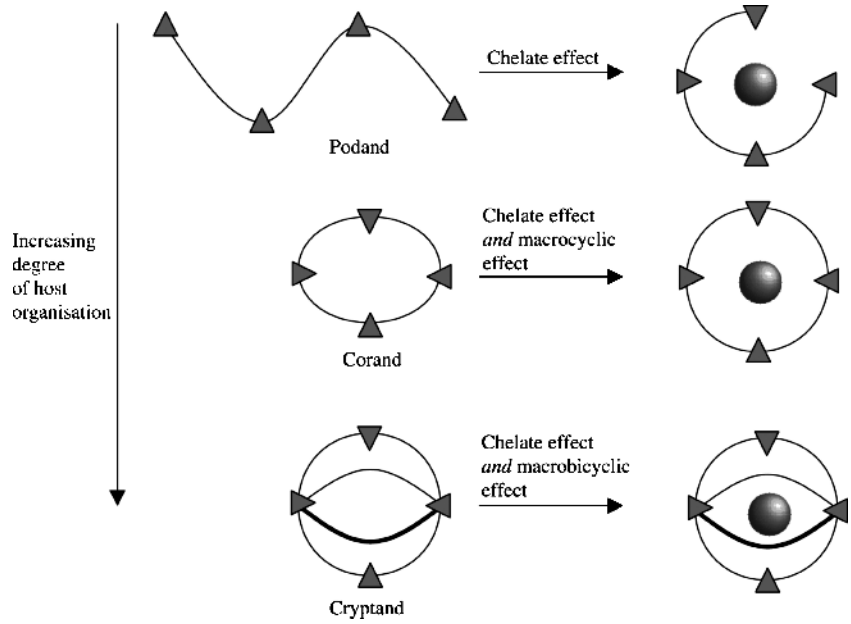
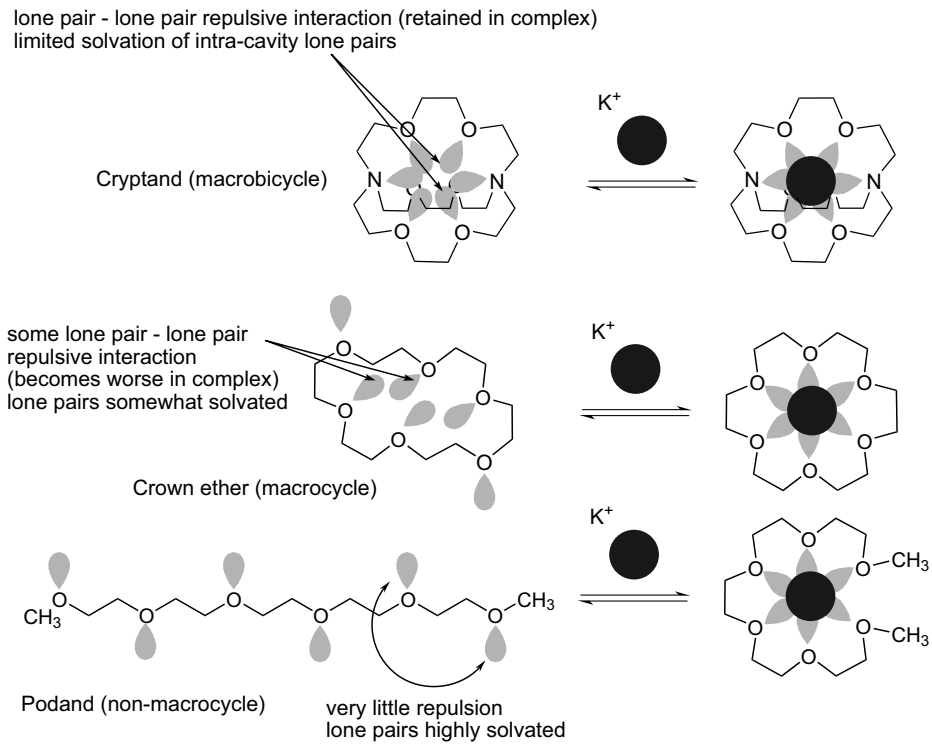


Figure 1.11 The chelate, macrocyclic and macrobicyclic effects.



Scheme 1.4 Comparison of preorganisation effects in K^+ binding by a macrobicycle, macrocycle and non-preorganised podand pentaethyleneglycol dimethyl ether.

and both complexation and decomplexation are rapid. 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.

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, a host must have binding sites that are of the correct electronic character (polarity, hydrogen bond donor/acceptor ability, hardness or softness *etc.*) 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.'

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 1.12. 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

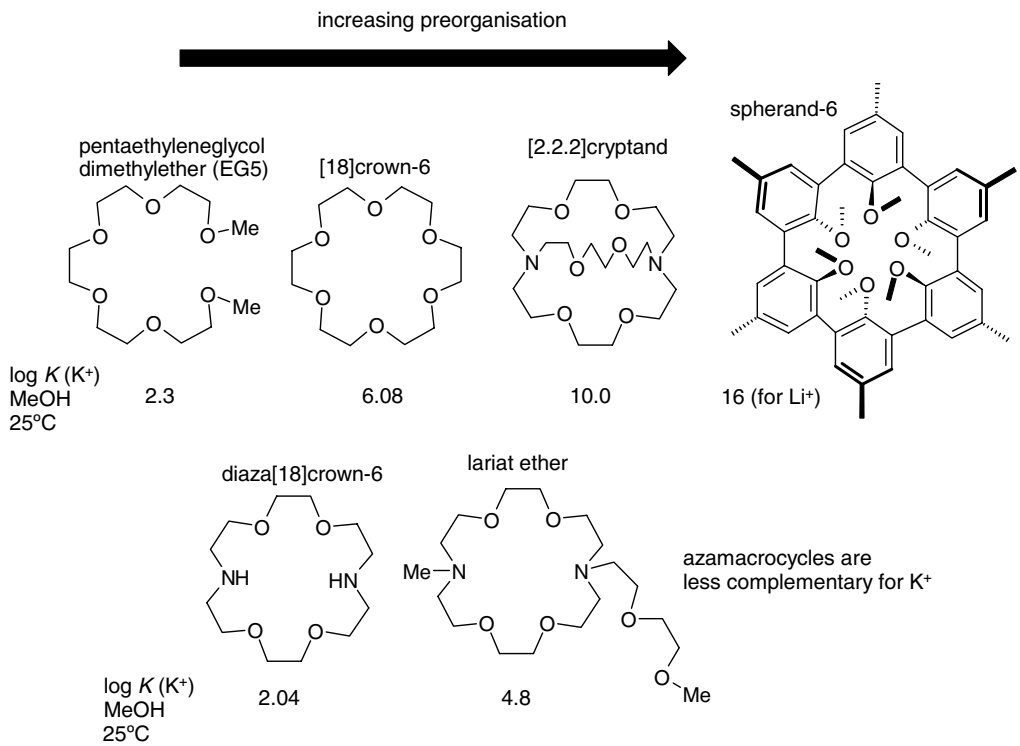


Figure 1.12 Comparison of the effects of preorganisation and complementarity on the magnitudes of the binding constant of polyether hosts for alkali metal cations. The figure for Li^+ is given for the highly preorganised spherand-6 since it is too small to accommodate K^+.

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., 'Selectivity in supramolecular host-guest complexes', *Chem. Soc. Rev.*, 2008, **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 of 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 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:

$$\text{Selectivity} = \frac{K_{\text{Guest1}}}{K_{\text{Guest2}}} \tag{1.31}$$

This kind of selectivity tends to be the most easy 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 *ca.* 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 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 biochemical enzymes are kinetically selective and examination of their structures reveals that while they are perfectly complementary for the desired (sometimes transitory) state of the guest at any given instant, they are not generally preorganised in a rigid way since this would preclude rapid catalysis. In artificial systems, the engineering of time-resolved selectivity (as in the design of enzyme mimics, Chapter 12) 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 results of often highly specific host-guest interactions. Good examples are fluorescent or colorimetri 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 11.3.3).[14]

1.8 Nature of Supramolecular Interactions

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

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. 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.*).

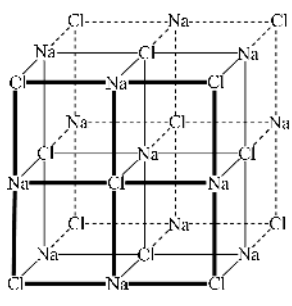
1.8.1 Ion–ion Interactions

Ionic bonding is comparable in strength to covalent bonding (bond energy = 100–350 kJ mol^{-1}). A typical ionic solid is sodium chloride, which has a cubic lattice in which each Na^+ cation is surrounded by six Cl^- anions (Figure 1.13a). 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 an Na^+ 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 $Na(H_2O)_6^+$.

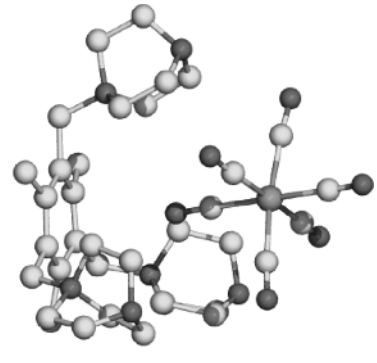
A much more supramolecular example of ion–ion interactions is the interaction of the *tris*(diazabicyclooctane) host (**1.17**), which carries a 3+ charge, with anions such as $[Fe(CN)_6]^{3-}$ (Figure 1.13b).[15]

1.8.2 Ion–Dipole Interactions

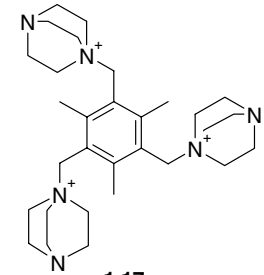
The bonding of an ion, such as Na^+, with a polar molecule, such as water, is an example of an ion–dipole interaction, which range in strength from *ca.* 50 – 200 kJ mol^{-1}. This kind of bonding is seen both in the solid state and in solution. A supramolecular analogue is readily apparent in the structures of the complexes of alkali metal cations with macrocyclic (large ring) ethers termed crown ethers



(a)



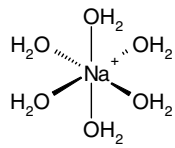
(b)



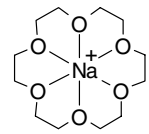
1.17

Figure 1.13 (a) The NaCl ionic lattice. (b) Supramolecular ion–ion interactions exemplified by the interaction of the organic cation **1.17** with $[Fe(CN)_6]^{3-}$.

(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. The oxygen lone pairs are attracted to the cation positive charge.

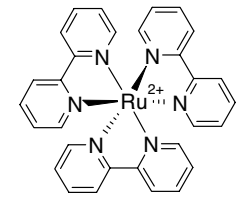


1.18



Na^+ crown ether complex

1.19



bpy = 2,2'-bipyridyl

$[Ru(bpy)_3]^{2+}$ **1.20**

Ion–dipole interactions also include coordinative bonds, which are mostly electrostatic in nature in the case of the interactions of nonpolarisable metal cations and hard bases. Coordinate (dative) bonds with a significant covalent component, as in $[Ru(bpy)_3]^{2+}$, are also often used in supramolecular assembly and, as we will see in Chapters 10 and 11, the distinction between supramolecular and molecular species can become rather blurred.

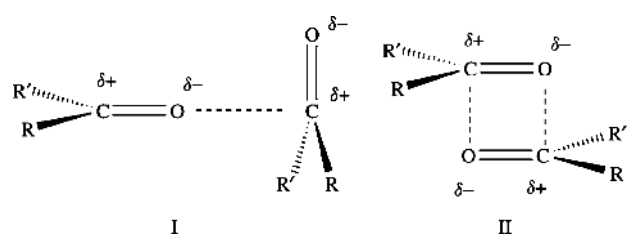
1.8.3 Dipole–Dipole Interactions

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 1.14) with energies in the range 5–50 kJ mol^{-1}. 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. The boiling point of ketones such as acetone (56 °C), however, demonstrates that dipole–dipole interactions of this type are relatively weak in solution.

1.8.4 Hydrogen Bonding

Jeffrey, G. A., *An Introduction to Hydrogen Bonding*, Oxford University Press: Oxford, 1997.

Hydrogen bonding has tremendous effects on molecular properties. It is the strong hydrogen bonding in water that makes its boiling point of 100 °C some 160 °C higher than the heavier H_2S, simply

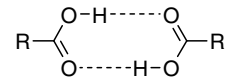


I II

Figure 1.14 Dipole–dipole interactions in carbonyls.

because of the more polar nature of the O–H bonds. Similarly at room temperature (298 K) butanone gas (C_4H_8O) which has a hydrogen bonding carbonyl (C=O) functionality is a factor of 1.7×10^4 more soluble in water than the non-polar gaseous butane (C_4H_{10}). 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. 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 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 'masterkey interaction in supramolecular chemistry'.[1] Normal hydrogen bonds typically range in strength from *ca*. 4–60 kJ mol^{-1}, although certain highly acidic compounds such as HF_2^- have hydrogen bond energies up to 120 kJ mol^{-1}. An excellent example of hydrogen bonding in supramolecular chemistry is the formation of carboxylic acid dimers (**1.21**), which results in the shift of the ν(OH) infrared stretching frequency from about 3400 cm^{-1} to about 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 also 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 bonds is greatly dependent on its environment. Hydrogen bonds are ubiquitous in supramolecular chemistry. In particular, 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 2.9 and 10.3).



1.21

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 1.5. 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' (Section 4.7.3), which are practically linear with the hydrogen atom between the two electronegative atoms. 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 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

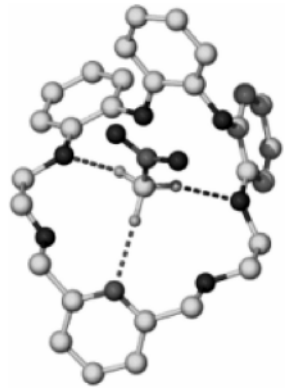
Table 1.5 Properties of hydrogen bonded interactions (A–H = hydrogen bond acid, B = hydrogen bond base).

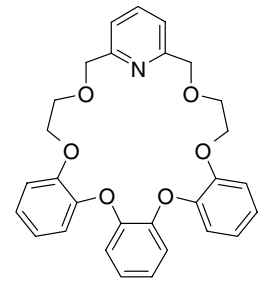
	Strong	Moderate	Weak
A—H···B interaction	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol^{-1})	60–120	16–60	<12
Bond lengths (Å)			
H···B	1.2–1.5	1.5–2.2	2.2–3.2
A···B	2.2–2.5	2.5–3.2	3.2–4.0
Bond angles (°)	175–180	130–180	90–150
Relative IR vibration shift (stretching symmetrical mode, cm^{-1})	25%	10–25%	<10%
^{1}H NMR chemical shift downfield (ppm)	14–22	<14	?
Examples	Gas phase dimers with strong acids/bases	Acids	Minor components of bifurcated bonds
	Proton sponge	Alcohols	C—H hydrogen bonds
	HF complexes	Biological molecules	O—H···π hydrogen bonds

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. 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 hydrogen bond acidity and basicity exist that partially quantify these effects.[16] 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 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 (Section 8.9).

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···N and C—H···O hydrogen bonds is the interaction of the methyl group of nitromethane with the pyridyl crown ether shown in Figure 1.15.[17]

The types of geometries that can be adopted in a hydrogen bonding complex are summarised in Figure 1.16. 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 1.17 shows two situations in which arrays of hydrogen bond donors and acceptors are in close proximity. An array of three donors (DDD) facing





1.22

Figure 1.15 X-ray crystal structure showing C—H···N (2.21Å) and C—H···O (2.41Å, average) hydrogen bonding in a complex of crown ether **1.22** with nitromethane.[17]

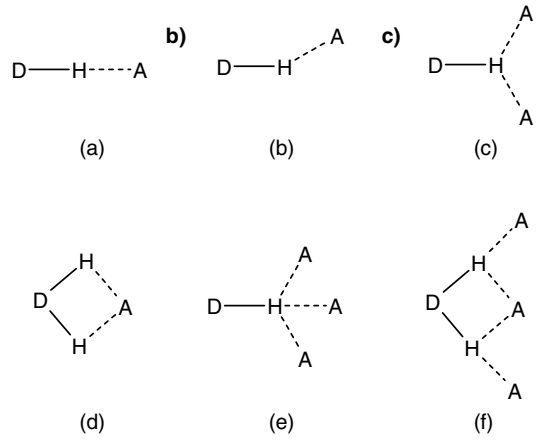


Figure 1.16 Various types of hydrogen bonding geometries; (a) linear (b) bent (c) donating bifurcated (d) accepting bifurcated (e) trifurcated (f) three centre bifurcated.

three acceptors (AAA) (Figure 1.17a) has only attractive interactions between adjacent groups and therefore the binding is enhanced in such a situation. Mixed donor/acceptor arrays (ADA, DAD) suffer from repulsions by partial charges of the same sign being brought into close proximity by the primary interactions (Figure 1.17b).

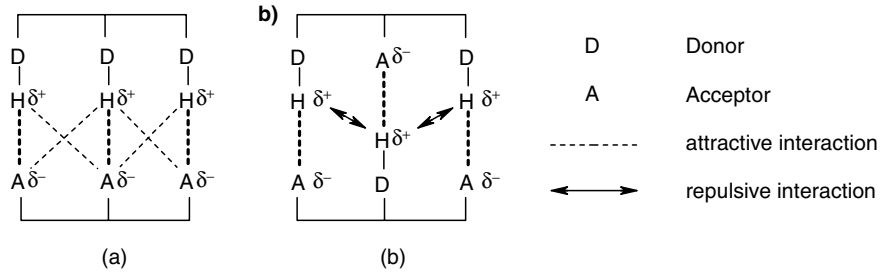


Figure 1.17 (a) Secondary interactions providing attractions between neighbouring groups between DDD and AAA arrays (primary interactions in bold) and (b) repulsions from mixed donor/acceptor arrays (ADA and DAD).

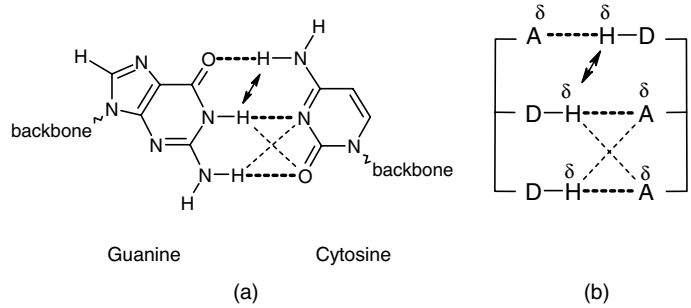


Figure 1.18 (a) Primary and secondary hydrogen bond interactions between guanine and cytosine base pairs in DNA and (b) a schematic representation.

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 1.18. The CG base pair has three primary interactions (*i.e.* traditional hydrogen bonds) and also has both attractive and repulsive secondary interactions.

1.8.5 Cation–π Interactions

Ma, J. C., and Dougherty, D., 'The cation-π interaction', *Chem. Rev.*, 1997, **97**, 1303–1324.

Transition metal cations such as Fe^{2+}, Pt^{2+} *etc.* are well known to form complexes with olefinic and aromatic hydrocarbons such as ferrocene $[Fe(C_5H_5)_2]$ and Zeise's salt $[PtCl_3(C_2H_4)]^-$. 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 $Ag^+ \cdots C_6H_6$ have a significant covalent component. The interaction of alkaline and alkaline earth metal cations with C=C double bonds is, however, a much more non-covalent 'weak' interaction, and is suggested to play an important role in biological systems. For example, the interaction energy of K^+ and benzene in the gas phase is about 80 kJ mol^{-1} (Figure 1.19). 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 interaction of nonmetallic cations such as RNH_3^+ with double bonds may be thought of as a form of X—H $\cdots$ π hydrogen bond.

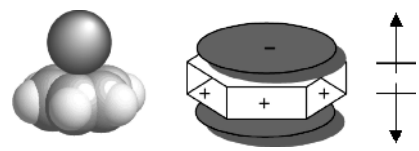
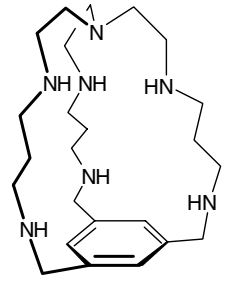


Figure 1.19 Schematic drawing of the cation–π interaction showing the contact between the two. The quadrupole moment of benzene, along with its representation as two opposing dipoles, is also shown.

1.8.6 Anion-π Interactions

Berryman, O. B., Bryantsev, V. S., Stay, D. P., Johnson, D. W. and Hay, B. P., 'Structural criteria for the design of anion receptors: The interaction of halides with electron-deficient arenes', *J. Am. Chem. Soc.*, 2007, **129**, 48–58.

Cation-π interactions (see Section 1.8.5) have been known for many years, however it is only relatively recently that there has been interest in anion-π interactions. Intuitively, the interaction of an anion with π-electron density seems like it should be repulsive and indeed the affinity of the aromatic ring containing cryptand **1.23** for halides rapidly falls off in the order $F^- >> Cl^- > Br^- \sim I^-$ because of anion-π repulsions in the case of the larger halides, with all except F^- showing a constant anion-ring centroid distance of *ca.* 3.7 Å.[18] 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 Kochi[19] has shown that anions form stable charge transfer complexes with a variety of electron deficient aromatic compounds such as **1.24**. The formation constants for the anion-aromatic complexes are in the range 1–10 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 a offset fashion at the edge of the aromatic rings rather than above the centroid with anion–carbon distances as short as 2.93 Å for tetrachloro *o*-quinone and Br^-, shorter than the sum of the a van der Waals radii (3.55 Å). Similar short anion-carbon contacts have been noted for organometallic calixarene derivatives such as **4.34** (see Chapter 4) where the aromatic ring bears a significant positive charge. Anion-π interactions have also been implicated as controlling elements in self-assembly reactions of Ag(I) complexes with π-acidic aromatic rings.[20]



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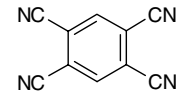

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1.8.7 π–π Interactions

Hunter, C. A., Lawson, K. R., Perkins, J. and Urch, C. J., 'Aromatic interactions', *J. Chem. Soc., Perkin Trans. 2* 2001, 651–669.

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

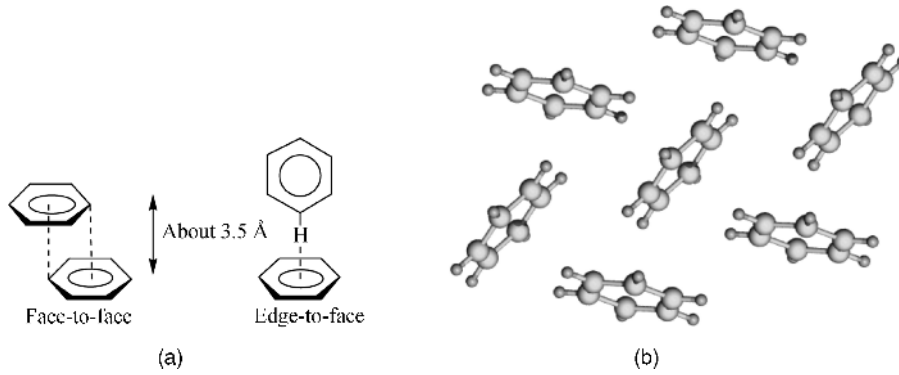


Figure 1.20 (a) Limiting types of π–π interaction. Note the offset to the face-to-face mode (direct overlap is repulsive). (b) X-ray crystal structure of benzene showing herringbone motif arising from edge-to-face interactions.

known (Figure 1.20a). 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 hydrogen bonds between the slightly electron deficient hydrogen atoms of one aromatic ring and the electron rich π-cloud of another. Strictly they 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 1.20b).

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. 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 interacting molecules is determined by the electrostatic repulsions between the two negatively charged π-systems (Figure 1.21).

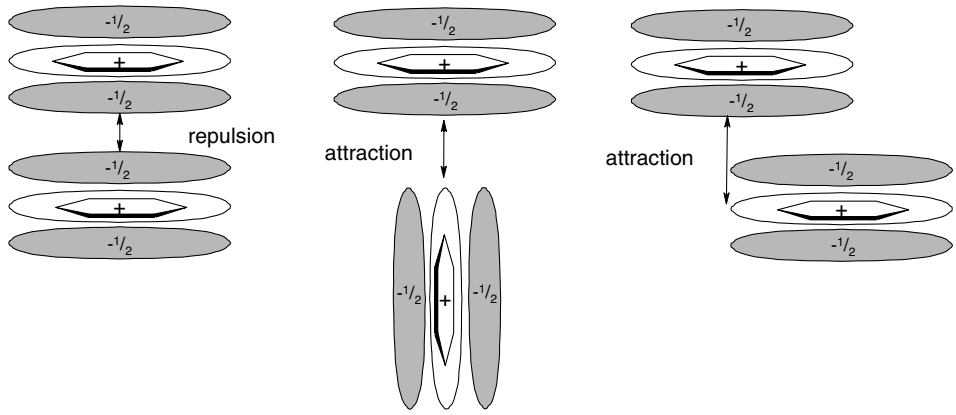


Figure 1.21 Interacting π-quadrupoles.

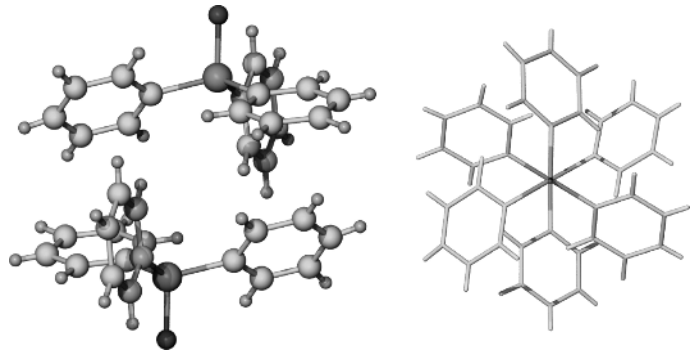


Figure 1.22 Sixfold edge-to-face phenyl embrace in $ClGePh_3$.[23]

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 still a great deal of current debate over the nature of π–π stacking interactions. In particular, work involving substituent effects suggests that London dispersion forces might play a more important role than electrostatic interactions.[21] 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 (Figure 1.22). 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 Å. This parallel-displaced structure is thought to have a contribution from π-σ attractive interactions that increases with increasing offset.[22]

1.8.8 Van der Waals Forces and Crystal Close Packing

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

Van der Waals interactions arise from the polarisation of an electron cloud by the proximity of an adjacent nucleus, resulting in a weak electrostatic attraction. They are nondirectional 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 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-tert*-butylphenol-based macrocycle, *p-tert*-butylcalix[4]arene (Section 6.2.2 and Figure 1.23).[24] Strictly, 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.

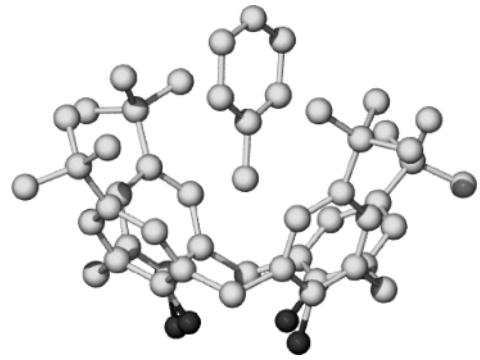


Figure 1.23 X-ray crystal structure of a typical van der Waals inclusion complex *p-tert*-butylcalix[4]arene·toluene.[24]

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. Those which do (*e.g.* zeolites, Section 9.2) possess a very rigid framework that is able to 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.

1.8.9 Closed Shell Interactions

Pyykkö, P., 'Strong closed-shell interactions in inorganic chemistry', *Chem. Rev.*, 1997, **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,[25] metalophilic interactions[26] and halogen bonding.[27] 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 (where they are termed *aurophilic interactions*). 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 with halogen bonding strength decreasing in the order I > Br > Cl >> F. Structural studies have shown that halogen bonds of type D···X–C (where D is an electron-pair donor and X is a halogen electron pair acceptor) have a well-defined, linear geometry (160–180°) with D···X distances considerably less than the sum of the van der Waals radii of D and X. The most obvious example is the $I^-\cdots I_2$ interaction found in the I_3^- ion which has an energy of *ca.* 200 kJ mol^{-1}, and indeed halogen bonds have been known since the discovery of $Me_3N\cdots Br_2$ in 1896. The geometries adopted by halogen bonding are influenced by 'polar flattening', the anisotropic distribution of electron density about halogen and some other polarisable atoms, however they represent a genuine attractive interaction (see further discussion in Section 8.4)

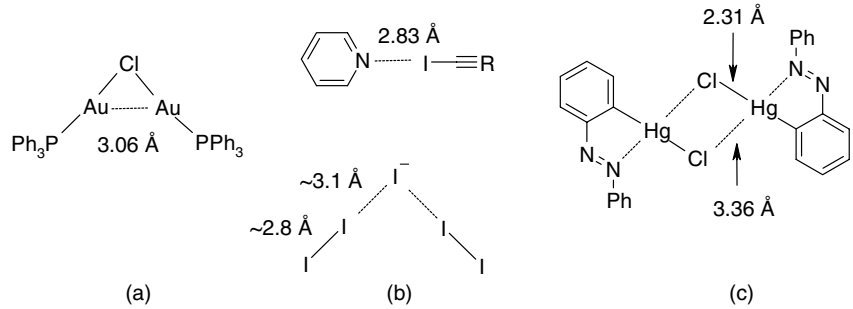


Figure 1.24 Examples of closed shell interactions (a) Aurophilic interactions in $[Au_2(\mu\text{-}Cl)(PPh_3)_2](ClO_4)$, (b) halogen bonding in pyridine···I–CCR and I_5^- and (c) secondary bonding in $[\{HgCl(C_6H_4N_2Ph)\}_2]$.

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 $[Au_2(\mu\text{-}Cl)(PPh_3)_2](ClO_4)$, Au···Au = 3.06 Å, Figure 1.24.[28] Interestingly in the compound $[Au_2(dmpm)_3](ClO_4)_2$ 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.[29]

Secondary bonding (a term coined by Alcock in 1972) 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 multi-valent 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 1.25. Secondary bonding is a very significant interaction in determining the solid state structures of heavy element compounds.

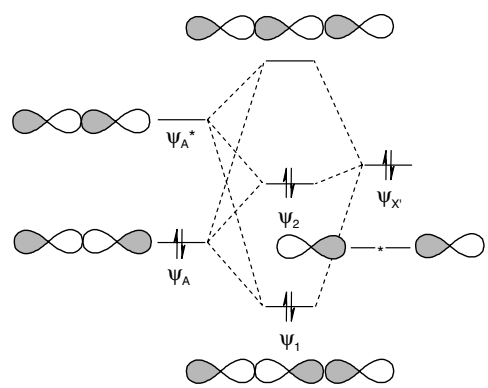


Figure 1.25 Molecular orbital description of secondary bonding and related interactions showing the $n \rightarrow \sigma^*$ interaction.

1.9 Solvation and Hydrophobic Effects

1.9.1 Hydrophobic Effects

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

Although occasionally mistaken for a force, hydrophobic effects generally relate 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 mineral 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 and cyclophane hosts in water (Chapter 6) 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. 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 1.26.

As an example, consider the binding of the guest *p*-xylene by the cyclophane host **1.25** (part of a class described in more detail in Section 6.5). The binding constant in water is $9.3 \times 10^3\,M^{-1}$. At 293K, the complexation free energy, ΔG^o, is –22 kJ mol^{-1} which divides into a favourable enthalpic stabilisation, $\Delta H^o = -31$ kJ mol^{-1}, and an unfavourable entropic component, $T\Delta S^o = -9$ kJ mol^{-1}. In this case it is the enthalpic contribution to the hydrophobic binding that dominates. The enthalpic contribution is too great to result from attractive forces between host and guest (which experience only weak π-stacking

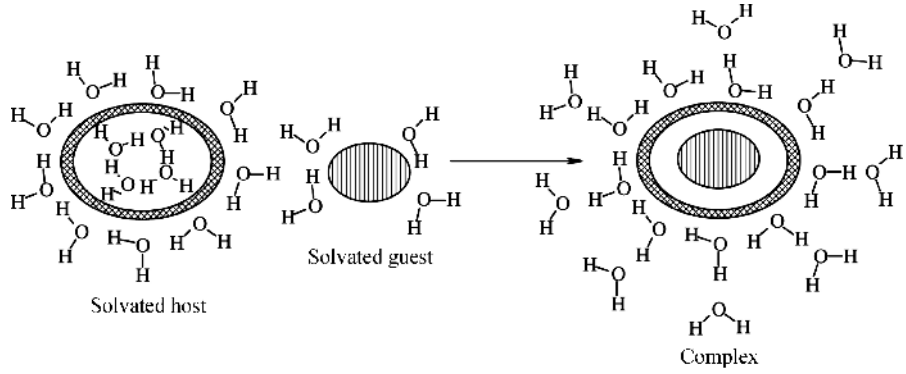
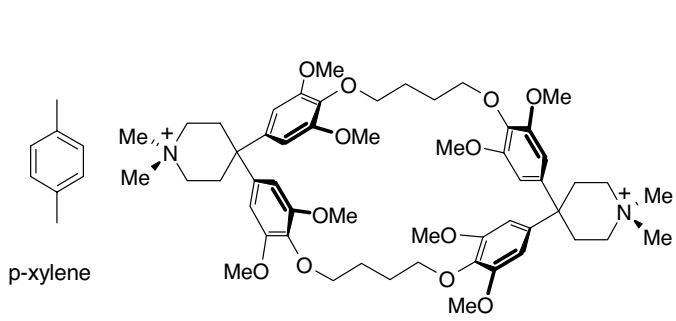


Figure 1.26 Hydrophobic binding of organic guests in aqueous solution.

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.



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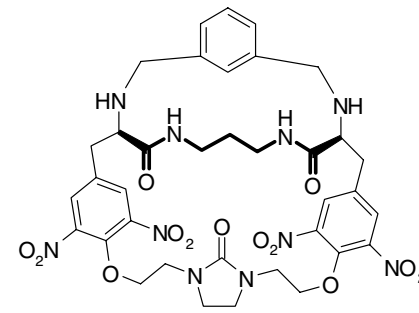


1.26

1.9.2 Solvation

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

The importance of solvent in supramolecular chemistry can hardly be overstated. In the solid state solvent 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 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 of binding constant is shown in Table 1.6. 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.

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 resolvation of the resulting complex, often with release of free solvent and consequent formation of solvent-solvent interactions, Figure 1.27.

Unfortunately specific solvation effects are very difficult to understand, although molecular mechanics simulations have recently gone some way towards modelling complexation phenomena

Table 1.6 Influence of solvent on the binding constant of host **1.26** 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	8161
$CHCl_2CHCl_2$	Non-polar	
	Larger size	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	1067
tetrahydropyran	Non-polar, coordinating	104
1,4-dioxane	Non-polar, coordinating	87
tert-butyl methyl ether	Non-polar, coordinating	566
iso-propanol	Polar, protic	13
tert-butyl alcohol	Polar, protic	66
acetonitrile	Polar, aprotic, coordinating	No association

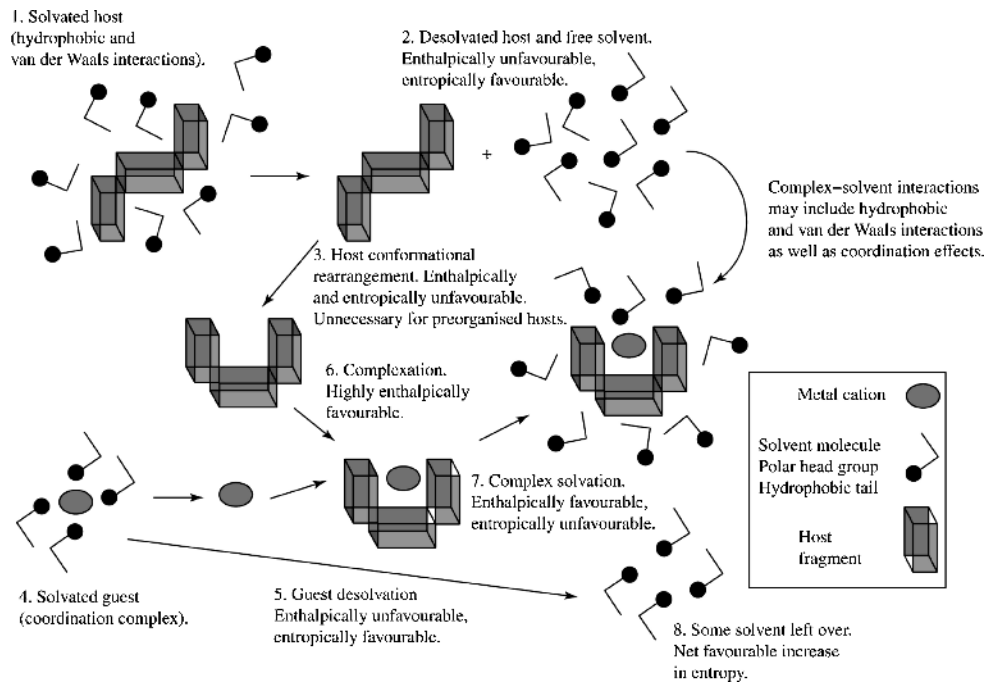
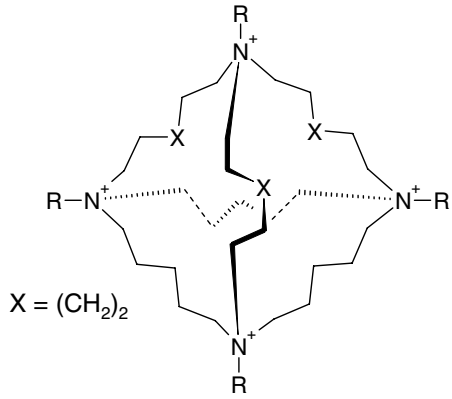


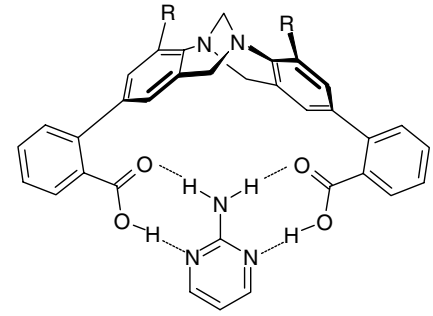
Figure 1.27 Solvation considerations during the host-guest complexation of a metal cation.

in solution. For example a molecular dynamics study of halide anion inclusion complexes of a macrotricyclic tetrahedral host **1.27** compared halide binding in 'dry' and 'wet' forms of an ionic liquid solvent. In the 'dry' ionic liquid the uncomplexed halides are surrounded by 4–5 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 are all displaced by water molecules, while other halides exhibit a mixture. 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 **1.27** is selective for Cl^-. In the 'wet' ionic liquid, there is no F^- / Cl^- selectivity, highlighting the importance of even small amounts of water on the complexation selectivity.[30]

An experimental comparison of the effect of 'wet' and 'dry' solvent has been carried out for host **1.28** which is capable of binding 2-aminopyrimidine (APy) to give a 1:1 complex **1.28**·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 organisation of the complex (*cf.* the hydrophobic effect in neat water). A fortuitous case of cancellation of enthalpic and entropic effects.[31]



1.27



1.28.AMP

1.10 Supramolecular Concepts and Design

1.10.1 Host Design

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

In order to design a host that will selectively bind a particular guest, 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 nonspherical 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 ligand 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 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.

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 12).

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 Informed and Emergent Complex Matter

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

We saw in Figure 1.2c 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 multi-component 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 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 topic[32] that is part of the field of complexity science and cuts across a very broad range of disciplines. 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 1.28). 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 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 (= non biochemical) systems.

Figure 1.28 A termite mound in Australia's Northern Territory. Termite mounds are classic examples of Natural emergent structures.

1.10.3 Nanochemistry

Ozin, G. and Arsenault, A. *Nanochemistry*, Royal Society of Chemistry: Cambridge, 2005.

We can refer to the synthesis and study of chemical systems with features and functionality on the multi-nanometre length scale as *nanochemistry* and materials with features of size of the order of 1–100 nm as *nanomaterials*. Very broadly there are two approaches to the nanoscale dimension – 'synthesising-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 synthesising-up approach (*nanochemistry*) 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. Indeed the very first reports of functional molecular computing using supramolecular species have already begun to appear.[33] Geff 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. They are typically more or less spherical in shape (Figure 1.29) 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 very 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. Crucially the wavelength of this absorption (and hence the observed colour) depend on the size of the nanoparticle.

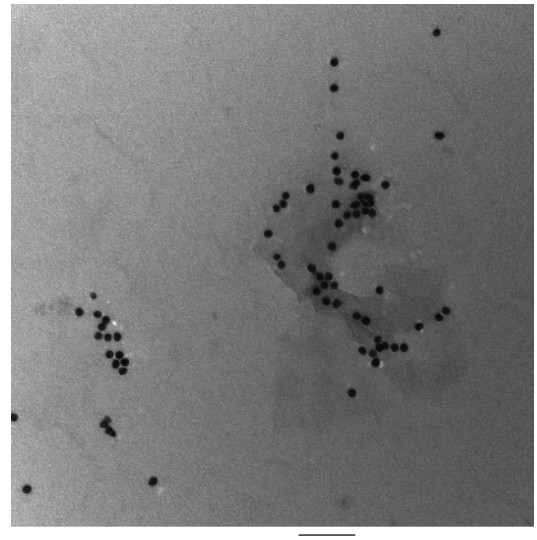


Figure 1.29 TEM micrograph showing gold nanoparticles. Note the regular shape and uniform size distribution. Scale bar = 100 nm.

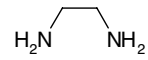
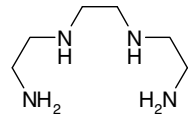
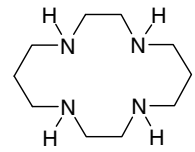
We can also include in the definition of nanochemistry molecular systems exhibiting designed or emergent nanometer-scale features, functionality or properties. For example, interlocked molecules termed *catenanes* can exhibit complex nanoscale molecular motions somewhat analogous to the mechanical interlocking of gears (Section 11.5). As we will see in Chapter 15 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 nanometer 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.[34] 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.

Summary

- Supramolecular Chemistry involves the chemistry of the non-covalent bond.
- Non-covalent bonds include ionic and dipolar interactions, hydrogen bonds, aromatic interactions ($\pi-\pi$, cation-π and anion-π), closed shell interactions and van der Waals interactions.
- 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 and preorganisation and complementarity, which encapsulate more traditional concepts such as the macrocyclic effect.
- Solvation and desolvation 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.

Study Problems

1.1 Thermodynamic parameters for the reaction of $Cu^{2+}_{(aq)}$ with various ligands are given below (aqueous solution, 25 ºC). 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^{o} (kJ mol^{-1})	$T\Delta S^{o}$ (kJ mol^{-1})
	−105	7.1
	−90.4	24.3
	−76.6	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?

Suggested Further Reading

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