Supramolecular Chemistry

Jonathan W. Steed
Jerry L. Atwood

WILEY

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Second Edition

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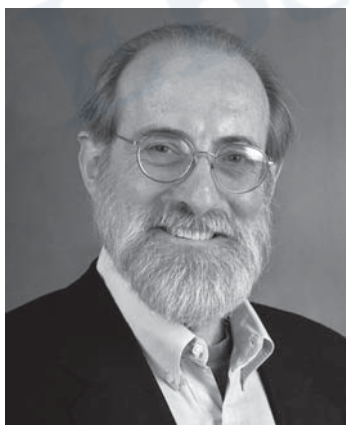
In loving memory of Joan Edwina Steed, 1922–2008

Contents

About the Authors

Jonathan W. Steed was born in London, UK in 1969. He obtained his B.Sc. and Ph.D. degrees at University College London, working with Derek Tocher on coordination and organometallic chemistry directed towards inorganic drugs and new metal-mediated synthesis methodologies. He graduated in 1993, winning the Ramsay Medal for his Ph.D. work. Between 1993 and 1995 he was a NATO postdoctoral fellow at the University of Alabama and University of Missouri, working with Jerry Atwood. In 1995 he was appointed as a Lecturer at Kings College London and in 1998 he was awarded the Royal Society of Chemistry Meldola Medal. In 2004 he joined Durham University where he is currently Professor of Inorganic Chemistry. As well as *Supramolecular Chemistry* (2000) Professor Steed is co-author of the textbook *Core Concepts in Supramolecular Chemistry and Nanochemistry* (2007) and more than 200 research papers. He has published a large number of reviews, book chapters and popular articles as well as two major edited works, the *Encyclopaedia of Supramolecular Chemistry* (2004) and *Organic Nanostructures* (2008). He has been an Associate Editor of *New Journal of Chemistry* since 2001 and is the recipient of the Vice Chancellor's Award for Excellence in Postgraduate Teaching (2006). His interests are in supramolecular sensing and molecular materials chemistry.



Jerry L. Atwood was born in Springfield MO, USA in 1942. He attended Southwest Missouri State University, where he obtained his B.S. degree in 1964. He carried out graduate research with Galen Stuckey at the University of Illinois, where he obtained his Ph.D. in 1968. He was immediately appointed as an Assistant Professor at the University of Alabama, where he rose through Associate Professor (1972) to full Professor in 1978. In 1994 he was appointed Professor and Chair at the University of Missouri – Columbia. Professor Atwood is the author of more than 600 scientific publications. His research interests revolve around a number of themes in supramolecular chemistry including gas storage and separation and the control of confined space. He has also worked on the self-assembly of non-covalent capsules, liquid clathrate chemistry, anion binding and fundamental solid state interactions, and is a world-renown crystallographer. He co-founded the journals *Supramolecular Chemistry* (1992) and *Journal of Inclusion Phenomena* (1983). He has edited an enormous range of seminal works in supramolecular chemistry including the five-volume series *Inclusion Compounds* (1984 and 1991) and the 11-volume *Comprehensive Supramolecular Chemistry* (1996). In 2000 he was awarded the Izatt-Christensen Prize in Supramolecular Chemistry

Preface to the First Edition

Supramolecular chemistry is one of the most popular and fastest growing areas of experimental chemistry and it seems set to remain that way for the foreseeable future. Everybody's doing it! Part of the reason for this is that supramolecular science is aesthetically appealing, readily visualised and lends itself to the translation of everyday concepts to the molecular level. It might also be fair to say that supramolecular chemistry is a very greedy topic. It is highly interdisciplinary in nature and, as a result, attracts not just chemists but biochemists, biologists, environmental scientists, engineers, physicists, theoreticians, mathematicians and a whole host of other researchers. These supramolecular scientists are people who might be described as goal-orientated in that they cross the traditional boundaries of their discipline in order to address specific objectives. It is this breadth that gives supramolecular chemistry its wide allure, and sometimes leads to grumbling that 'everything seems to be supramolecular these days'. This situation is aided and abetted by one of the appealing but casual definitions of supramolecular chemistry as 'chemistry beyond the molecule', which means that the chemist is at liberty to study pretty much any kind of interaction he or she pleases – except some covalent ones. The situation is rather reminiscent of the hubris of some inorganic chemists in jokingly defining that field as 'the chemistry of all of the elements except for some of that of carbon'.

The funny thing about supramolecular chemistry is that despite all of this interest in doing it, there aren't that many people who will actually teach it to you. Most of today's practitioners in the field, including the present authors, come from backgrounds in other disciplines and are often self-taught. Indeed, some people seem as if they're making it up as they go along! As university academics, we have both set up undergraduate and postgraduate courses in supramolecular chemistry in our respective institutions and have found that there are a lot of people wanting to learn about the area. Unfortunately there is rather little material from which to teach them, except for the highly extensive research literature with all its jargon and fashions. The original idea for this book came from a conversation between us in Missouri in the summer of 1995. Very few courses in 'supramol,' existed at the time, but it was clear that they would soon be increasingly common. It was equally clear that, with the exception of Fritz Vögtle's 1991 research-level book, there was nothing by way of a teaching textbook of the subject out there. We drew up a contents list, but there the idea sat until 1997. Everybody we talked to said there was a real need for such a book; some had even been asked to write one. It finally took the persuasive powers of Andy Slade from Wiley to bring the book to fruition over the summers of 1998 and 1999. We hope that now we have written a general introductory text for supramolecular chemistry, many more courses at both undergraduate and postgraduate level will develop in the area and it will become a full member of the pantheon of chemical education. It is also delightful to note that Paul Beer, Phil Gale and David Smith have recently written a short primer on supramolecular chemistry, which we hope will be complementary to this work.

In writing this book we have been very mindful of the working title of this book, which contained the words 'an introduction'. We have tried to mention all of the key systems and to explain in detail all of the jargon, nomenclature and concepts pertaining to the field. We have not tried to offer any kind of comprehensive literature review (for which purpose JLA has co-edited the 11 volumes of *Comprehensive Supramolecular Chemistry*). What errors there are will be, in the main, ones of over-simplification in an attempt to make accessible many very complicated, and often still rapidly evolving, topics. To the many fine workers whose insights we may have trivialised we offer humble apology. We hope that the overwhelming advantages will be the excitement of the reader who can learn about any or all aspects of this hydra-like field of chemistry either by a tobogganing plunge from cover to cover, or in convenient, bite-sized chunks.

Preface to the Second Edition

Since the publication of the first edition of *Supramolecular Chemistry* in 2000 the field has continued to grow at a tremendous pace both in depth of understanding and in the breadth of topics addressed by supramolecular chemists. These developments have been made possible by the creativity and technical skill of the international community and by continuing advances in instrumentation and in the range of techniques available. This tremendous activity has been accompanied by a number of very good books particularly at more advanced levels on various aspects of the field, including a two-volume encyclopaedia that we edited.

In this book we have tried to sample the entire field, bringing together topical research and clear explanations of fundamentals and techniques in a way that is accessible to final year undergraduates in the chemical sciences, all the way to experienced researchers. We have been very gratified by the reception afforded the first edition and it is particularly pleasing to see that the book is now available in Russian and Chinese language editions. For a short while we attempted to keep the book current by updating our system of key references on a web site; however it has become abundantly clear that a major overhaul of the book in the form of a refreshed and extended second edition is necessary. We see the strengths of the book as its broad coverage, the care we have tried to take to explain terms and concepts as they are encountered, and perhaps a little of our own personal interpretation and enthusiasm for the field that we see evolving through our own research and extensive contact with colleagues around the world. These strengths we have tried to build upon in this new edition while at the same time ameliorating some of the uneven coverage and oversimplifications of which we may have been guilty.

The original intent of this book was to serve as a concise introduction to the field of supramolecular chemistry. One of us (JWS) has since co-authored a short companion book *Core Concepts in Supramolecular Chemistry and Nanochemistry* that fulfils that role. We have therefore taken the opportunity to increase the depth and breadth of the coverage of this longer book to make it suitable for, and hopefully useful to, those involved at all stages in the field. Undergraduates encountering Supramolecular Chemistry for the first time will find that we have included careful explanations of core concepts building on the basics of synthetic, coordination and physical organic chemistry. At the same time we hope that senior colleagues will find the frontiers of the discipline well represented with plenty of recent literature. We have retained the system of key references based on the secondary literature that feedback indicates many people found useful, but we have also extended the scope of primary literature references for those wishing to undertake more in-depth reading around the subjects covered. In particular we have tried to take the long view both in temporal and length scales, showing how 'chemistry beyond the molecule' continues to evolve naturally and seamlessly into nanochemistry and molecular materials chemistry.

We have added a great deal to the book in this new edition including new chapters and subjects (*e.g.* supramolecular polymers, microfabrication, nanoparticles, chemical emergence, metal-organic frameworks, ion pairs, gels, ionic liquids, supramolecular catalysis, molecular electronics, polymorphism, gas sorption reactions, anion-π interactions… the list of exciting new science is formidable). We have also extensively updated stories and topics that are a part of ongoing research with new results published since 2000. The book retains some of the 'classics' which no less striking and informative for being a little long in the tooth these days. As before we apologise to the many fine colleagues whose work we did not include. The objective of the book is to cover the scope of the field with interesting and

representative examples of key systems but we cannot be comprehensive. We feel this second edition is more complete and balanced than the first edition and we have really enjoyed putting it together. We hope you enjoy it too.

Jonathan W. Steed, Durham, UK
Jerry L. Atwood, Columbia, Missouri, USA

Acknowledgements

Our thanks go to the many fine students, researchers and colleagues who have passed through our groups over the years, whose discussions have helped to both metaphorically and literally crystallize our thinking on this rapidly evolving field. Many colleagues in both Europe and the USA have been enormously helpful in offering suggestions and providing information. In particular we are grateful to Jim Tucker, Mike Hannon, Jim Thomas and the late Fred Armitage for their help in getting the ball rolling and constructive comments on the first edition. The second edition has benefited tremendously from input by Kirsty Anderson and Len Barbour, and we are also very grateful to Len for the brilliant X-Seed which has made the crystallographic diagrams much easier to render. David Turner also provided some excellent diagrams. We thank Graeme Day for useful information on crystal structure calculation and a number of colleagues for providing artwork or additional data, particularly Sir Fraser Stoddart, John Ripmeester, Peter Tasker, Travis Holman and Bart Kahr. Beth Dufour, Rebecca Ralf and Hollie Budge, Andy Slade, Paul Deards, Richard Davies and Gemma Valler at Wiley have worked tirelessly to bring the book to the standard and accessibility it needs to have. JWS is very grateful to Durham University for providing a term of research leave which made this book so much easier to write, and we are both as ever indebted to the many fine co-workers who have passed through our labs over the years who make chemistry such an enjoyable subject to work in.

About the Front Cover

The front cover shows two views of the Lycurgus cup – a 4th century Roman chalice made of dichroic glass impregnated with nanoparticles made of gold-silver alloy. When viewed under normal lighting conditions the cup appears green but if light is shone through the glass the nanoparticles impart a gorgeous crimson colour. The chemistry of metallic nanoparticles remains a highly topical field in supramolecular chemistry. (Images courtesy of the British Museum, London, UK).

Website

Powerpoint slides of all figures from this book, along with the answers to the problems, can be found at http://www.wiley.com/go/steed

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'

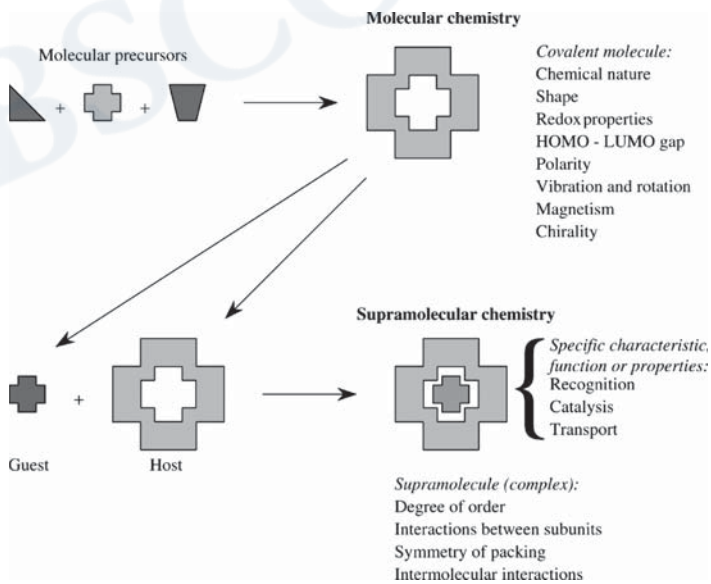


Figure 1.1 Comparison between the scope of molecular and supramolecular chemistry according to Lehn.[1]

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:

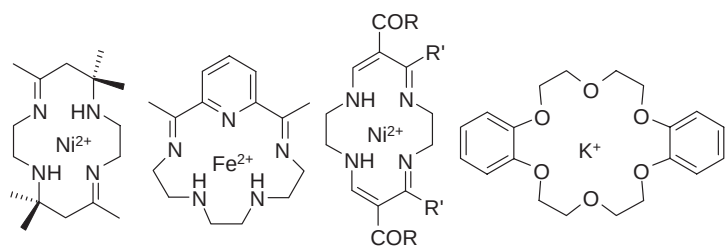
> *Complexes are composed of two or more molecules or ions held together in unique structural relationships by electrostatic forces other than those of full covalent bonds … molecular complexes are usually held together by hydrogen bonding, by ion pairing, by π-acid to π-base interactions, by metal-to-ligand 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 Busch 1964 Jäger 1964 Pedersen 1967

1.1 **1.2** **1.3** **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:

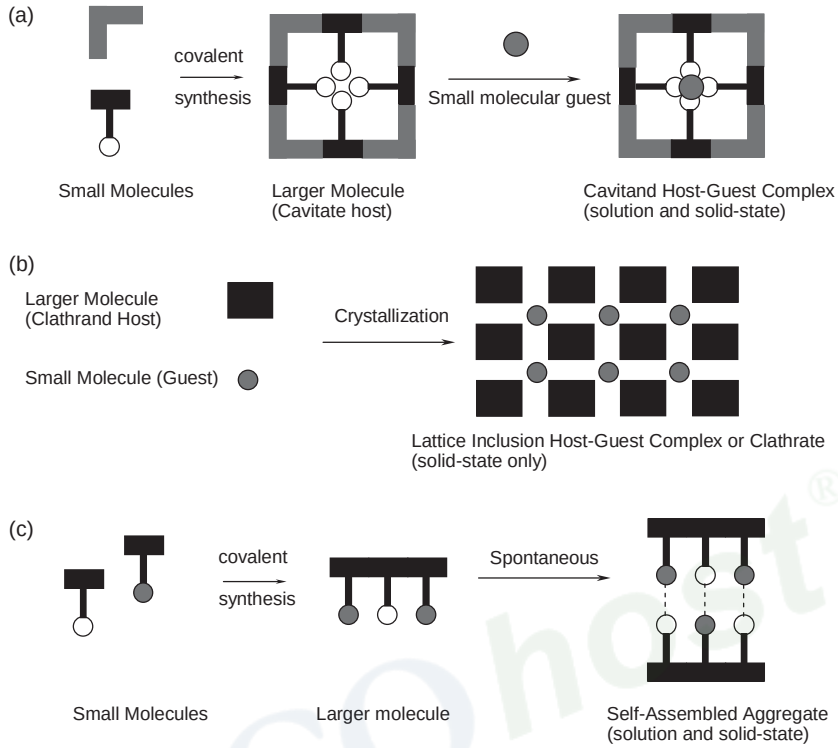


Figure 1.2 Schematic illustrating the difference between a cavitate and a clathrate: (a) synthesis and conversion of a cavitand into a cavitate by inclusion of a guest into the cavity of the host molecule; (b) inclusion of guest molecules in cavities formed between the host molecules in the lattice resulting 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)

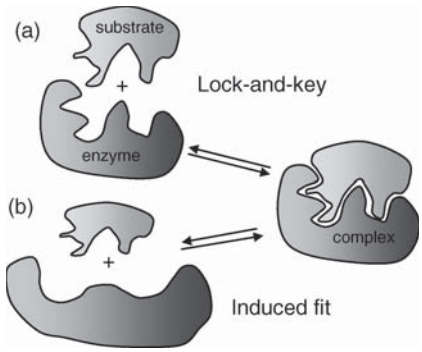
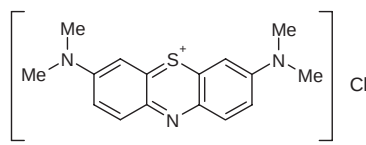


Figure 1.3 (a) Rigid lock and key and (b) induced fit models of enzyme–substrate binding.

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.

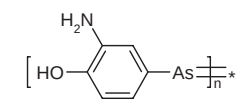
3. The fact that selective binding must involve *attraction* or mutual affinity between host and guest. This is, in effect, a generalisation of Alfred Werner's 1893 theory of coordination chemistry, in which metal ions are coordinated by a regular polyhedron of ligands binding by dative bonds.

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.

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

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

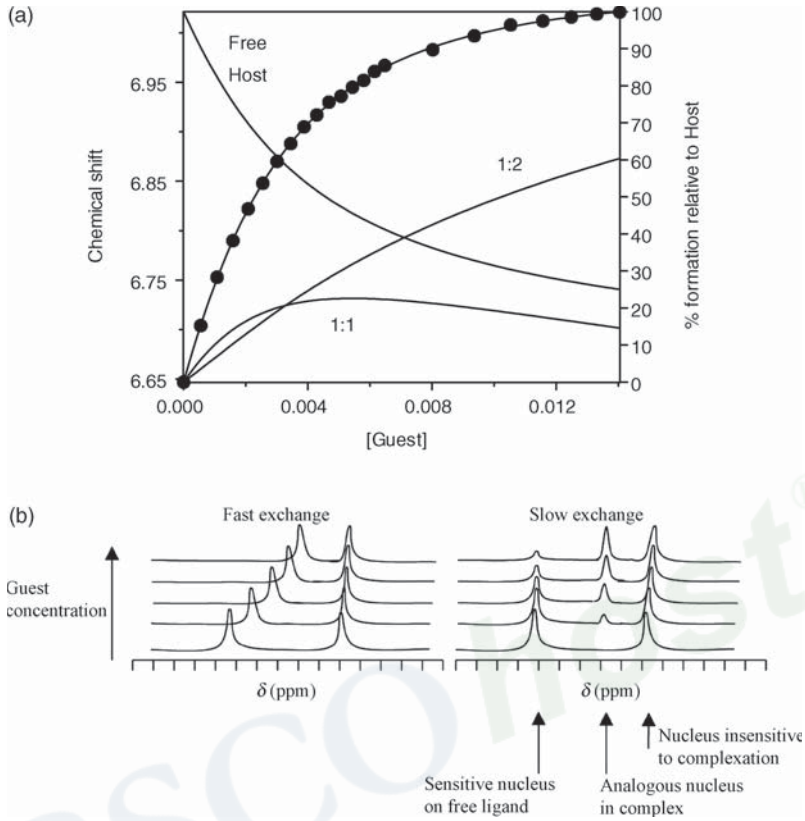


Figure 1.4 (a) NMR titration plot (isotherm) and corresponding speciation plots for a system undergoing fast equilibration on the NMR time scale, with log $\beta_{11} = 2.3$ and log $\beta_{12} = 4.5$. (b) Schematic NMR spectra of slowly equilibrating mixtures of free host, guest and host–guest complex.

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:

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

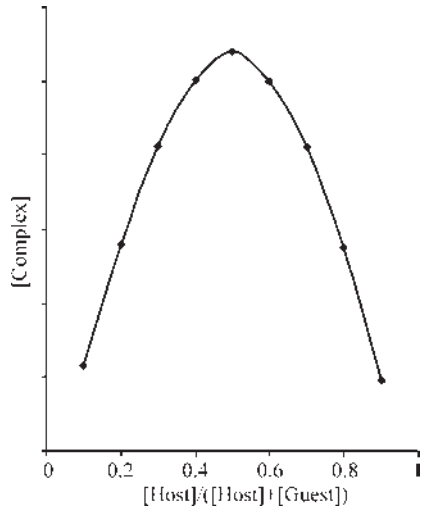


Figure 1.5 Job plot for a 1:1 host–guest complex.

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

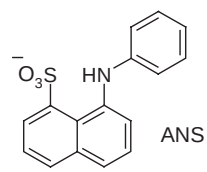
Combining these two relationships gives Equation (1.15), which provides the basis for most fluorimetric methods for stability constant (K_{11}) determination:

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

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.



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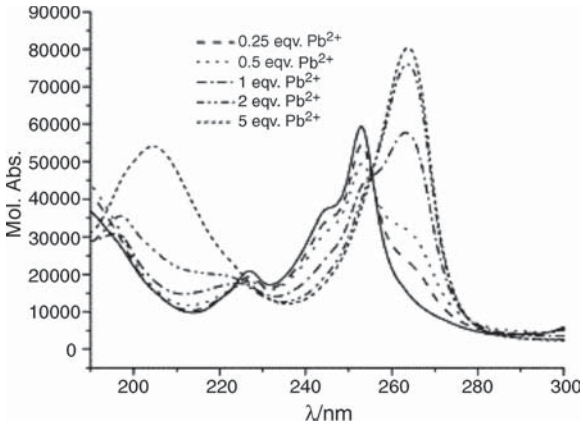
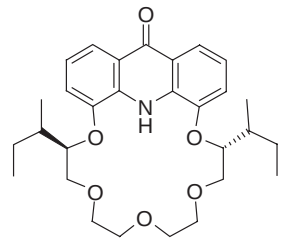




1.8

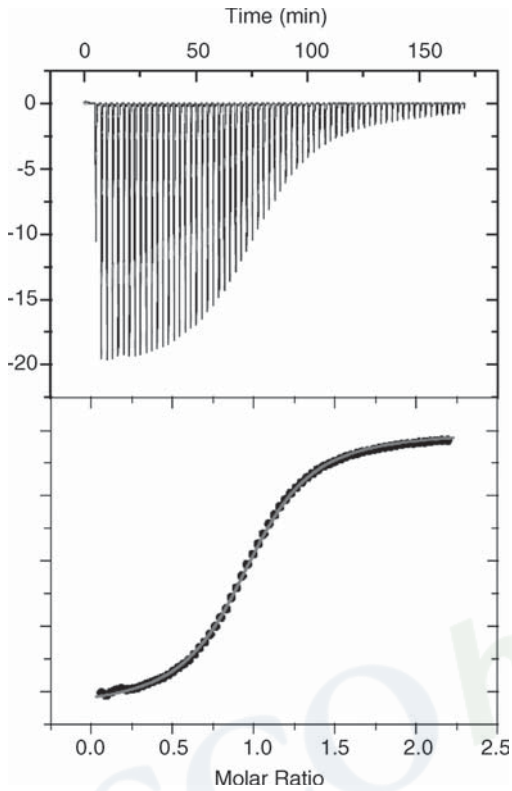
Figure 1.6 UV-monitored titration of a diisobutyl-substituted acridono-18-crown-6 ligand **1.8** with Pb^{2+} showing an isosbestic point at 271 nm (solid line represents free ligand spectrum, reproduced from [7] with permission from Elsevier).

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}, $\Delta G = 11.3$ kJ mol^{-1}, $\Delta H = 8.55$ kJ mol^{-1} and $\Delta S = -9.1$ J K^{-1} mol^{-1}.



1.9

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 °C).

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

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

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

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

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.

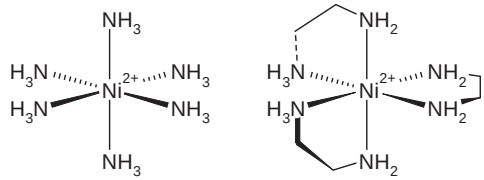
$$\Delta G^{s} = \Delta G_A{}^{o} + \Delta G_B{}^{o} - \Delta G_{AB}{}^{o} \tag{1.23}$$

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

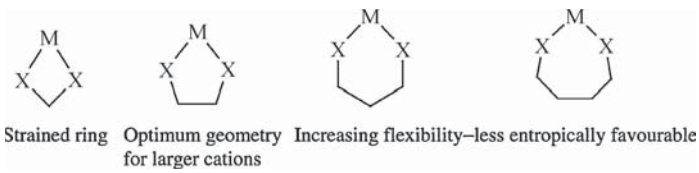
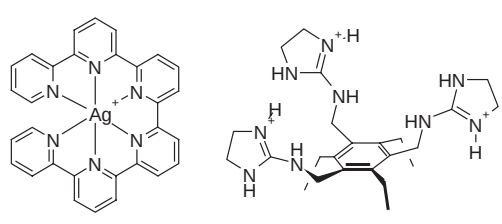


Figure 1.8 Ring size dependence of the stabilisation offered by the chelate effect.

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.

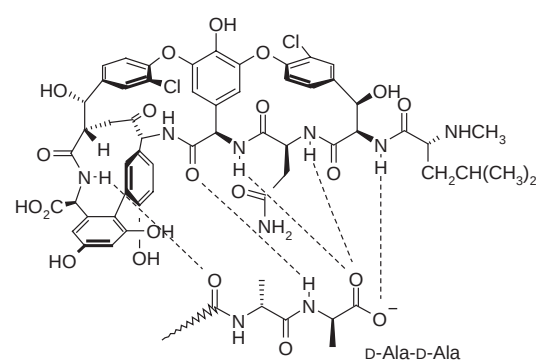
In supramolecular chemistry, the thermodynamic stability of a host–guest complex may be enhanced by the operation of a chelate effect giving rise to positive cooperativity. The ligand donor atoms are generalised to host binding sites (of whatever nature) and the metal is generalised to the guest (which 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



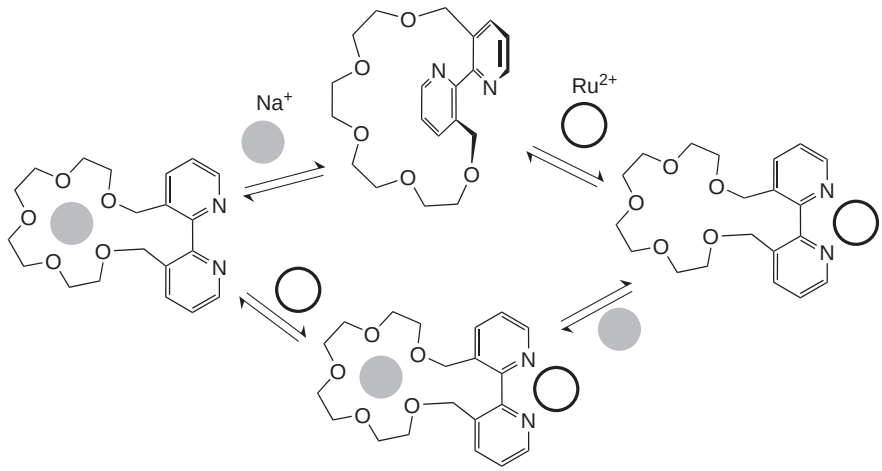
1.12

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 $n_H > 1$ indicates positive cooperativity, while systems exhibiting negative cooperativity have $n_H < 1$. Hill and Scatchard plots for the binding of ammonia to Ni^{2+} are shown in Figure 1.10. 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

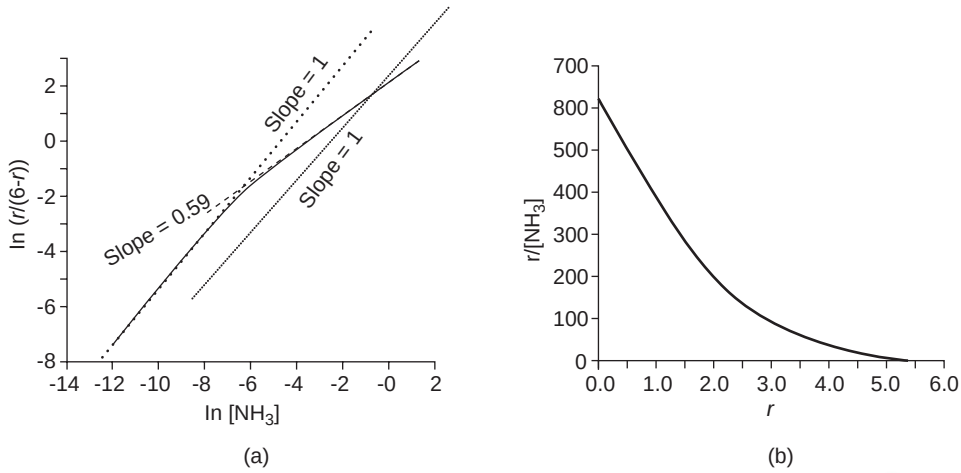


Figure 1.10 (a) Hill plot and (b) Scatchard plot for the successive intermolecular connections of ammonia to bivalent nickel to give $[Ni(NH_3)_i]^{2+}$, the concentration of the free ligand [L] is computed by using the known stability constants. $[Ni]_{total} = 1 \times 10^{-3}$ M; $[NH_3]_{total}$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

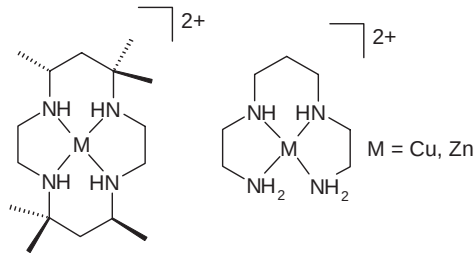
intra- and intermolecular processes requires a different treatment (Section 10.4) and this distinction has resulted in many erroneous claims of positive cooperativity in the literature.[12]

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

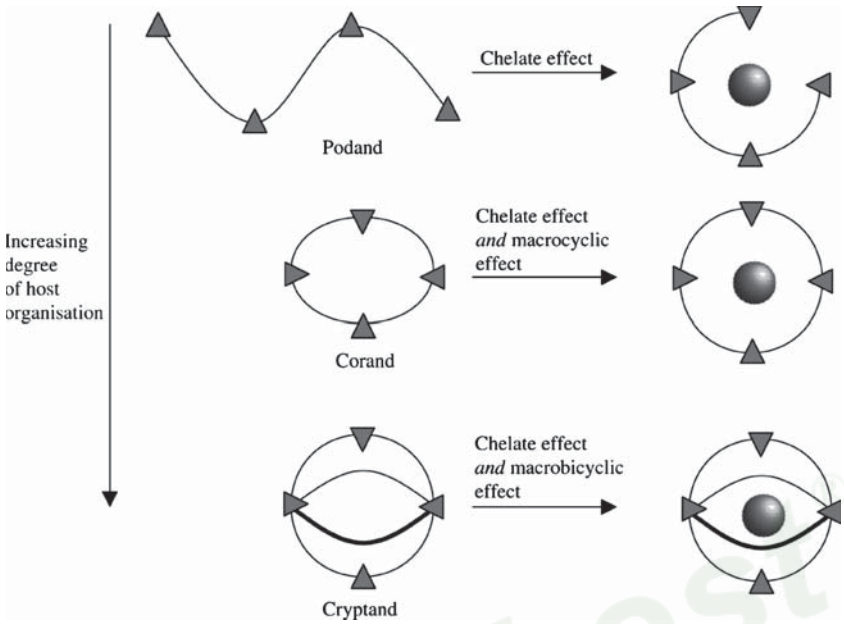
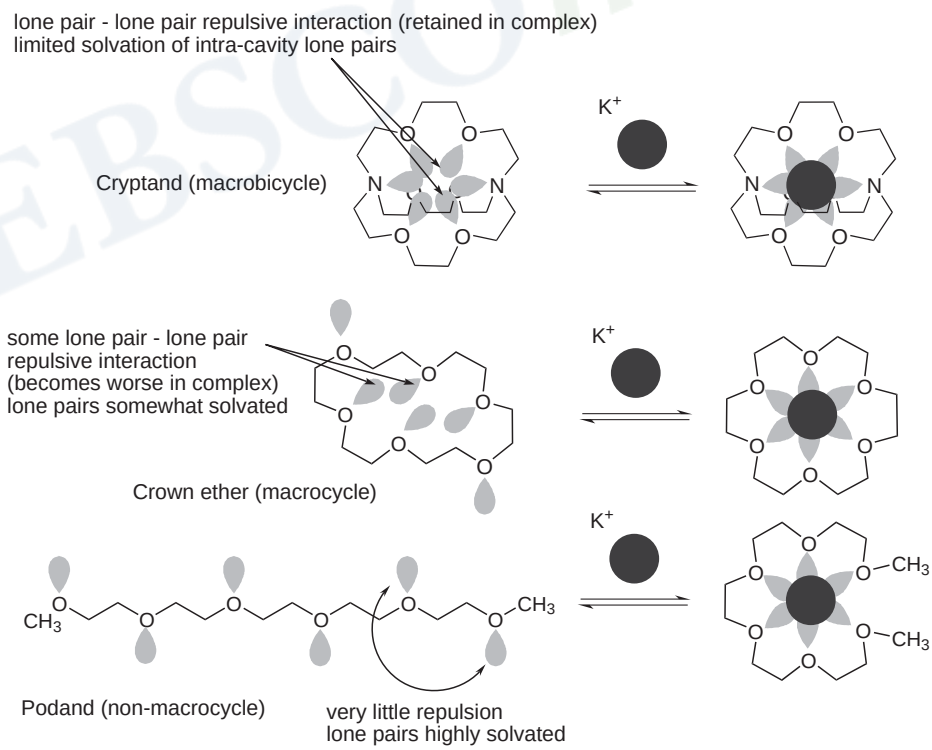


Figure 1.11 The chelate, macrocyclic and macrobicyclic effects.



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

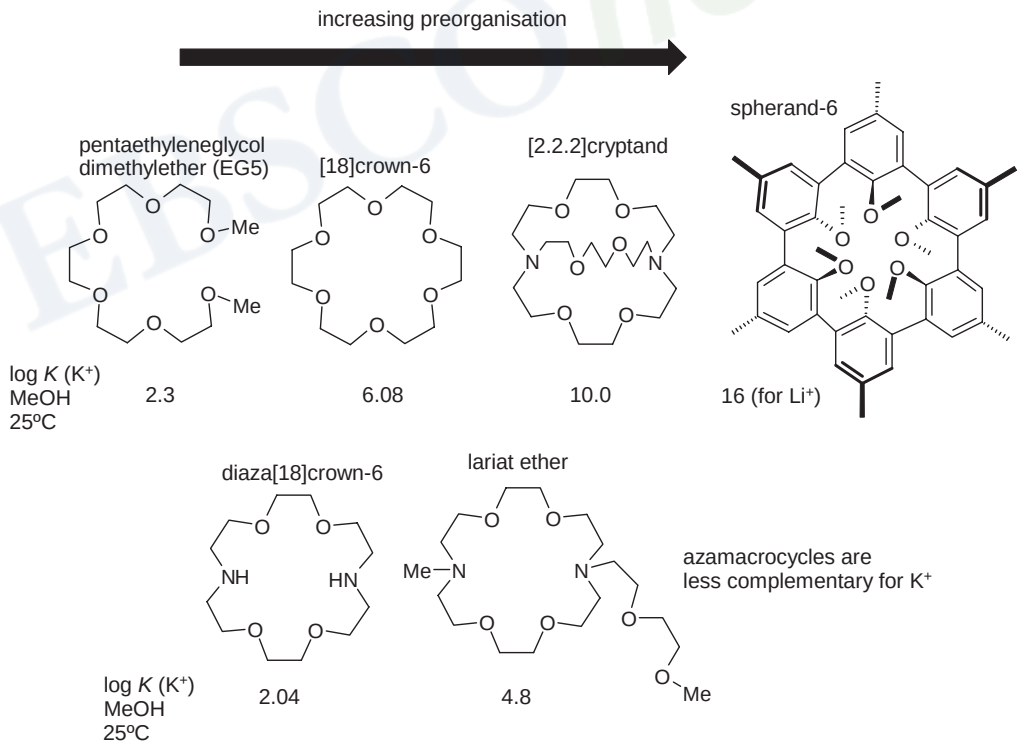


Figure 1.12 Comparison of the effects of preorganisation and complementarity on the magnitudes of the binding constant of polyether hosts for alkali metal cations. The figure for Li^+ is given for the highly preorganised spherand-6 since it is too small to accommodate K^+.