# Core Concepts in Supramolecular Chemistry and Nanochemistry

**Jonathan W. Steed,**
*Durham University, UK*

**David R. Turner,**
*Monash University, Australia*

**Karl J. Wallace,**
*University of Southern Mississippi, USA*


John Wiley & Sons, Ltd

# Core Concepts in Supramolecular Chemistry and Nanochemistry

# Core Concepts in Supramolecular Chemistry and Nanochemistry

**Jonathan W. Steed,**
*Durham University, UK*

**David R. Turner,**
*Monash University, Australia*

**Karl J. Wallace,**
*University of Southern Mississippi, USA*


John Wiley & Sons, Ltd

John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester,
West Sussex, PO19 8SQ, England

Telephone (+44) 1243 779777

Email (for orders and customer service enquiries): cs-books@wiley.co.uk
Visit our Home Page on www.wiley.com



***Other Wiley Editorial Offices***

John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons, Australia Ltd, 33 Park Road, Milton, Queensland 4064, Australia

John Wiley & Sons, (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons, Canada Ltd, 6045 Freemont Blvd, Mississauga, Ontario, L5R 4J3

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Anniversary Logo Design: Richard J. Pacifico

***Library of Congress Cataloging in Publication Data***

Steed, Jonathan W., 1969–
Core concepts in supramolecular chemistry and nanochemistry / Jonathan W. Steed, David R. Turner, Karl J. Wallace.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-470-85866-0 (cloth : alk. paper) — ISBN 978-0-470-85867-7 (pbk. : alk. paper)
1. Supramolecular chemistry. 2. Nanochemistry. I. Turner, David R.
II. Wallace, Karl J. III. Title.
QD878.S73 2007
547′.7—dc22 2007001274

***British Library Cataloguing in Publication Data***

A catalogue record for this book is available from the British Library

ISBN-13: 978-0-470-85866-0 (HB)
ISBN-13: 978-0-470-85867-7 (PB)

The front cover depicts the Minoan Phaestos disc, ca. 1600 BC. This disc bears hieroglyphic characters, separately impressed by means of punches and arranged in a spiral. Like many aspects of the molecular world, the characters have yet to be deciphered. Photo courtesy of Iain Forbes, Department of Archaeology, Cambridge University, UK.

Typeset in 10/12pt Palatino by Integra Software Services Pvt. Ltd, Pondicherry, India
Printed and bound in Great Britain by Antony Rowe Ltd., Chippenham, Wiltshire
This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

*To Ben and Joshua*

# Contents

# Preface

Supramolecular Chemistry is now a mature and highly vigorous field. In 2005 alone, some 2532 scientific papers used the word 'supramolecular' in their titles, keywords or abstracts! The term 'supramolecular' has origins at least to Webster's Dictionary in 1903, but was first applied in the modern sense by Jean-Marie Lehn in 1978 as the '. . . chemistry of molecular assemblies and of the intermolecular bond'. Lehn shared the 1987 Nobel Prize in Chemistry with Charles Pedersen and Donald Cram for their pioneering work in the field in the late 1960s and subsequent decades. Since that time, chemists have attained an astonishing degree of control over the 'non-covalent bond' and have used these techniques to synthesise a plethora of beautiful and intricate functional structures with dimensions on the nanometre scale. More recently, this ability to 'synthesise-up' nanoscale architectures and components has given rise to the field of 'nanochemistry' – the preparation and manipulation of molecular structures on length-scales of ca. 1–500 nm. The boundaries of nanochemistry and supramolecular chemistry are highly subjective although they are somewhat distinct areas. The modern explosion in nanochemistry is very much based, however, upon the fundamental understanding of intermolecular interactions engendered by supramolecular chemists. It thus makes sense for this book to provide a 'one-stop' brief introduction which traces the fascinating modern practice of the chemistry of the non-covalent bond from its fundamental origins through to its expression in the emergence of nanochemistry.

Both supramolecular chemistry and nanochemistry are now featuring ever more strongly in undergraduate and postgraduate degree courses throughout the world. The amount of each discipline which is taught is highly variable but is often a relatively small component of the undergraduate curriculum. The need for a concise introductory book that could serve as a basis for supramolecular chemistry courses of varying lengths was recognised by Jerry Atwood and one of us (JWS) in 1995. Andy Slade at Wiley (UK) has been a great believer in the concept and in 2000 Steed and Atwood published the very successful *Supramolecular Chemistry*, a book that has since even made it into a Russian-language edition. To Andy's dismay, however, this 'concise introduction' weighed in at over 700 pages. It turned out that there was a lot to cover! Five years later in 2005, Geff Ozin and Andre Arsenault did the same thing for nanochemistry, producing an extremely comprehensive overview of research in the field. Andy never gave up the idea of the concise textbook, however, and the idea rumbled around a South Kensington pub one evening while the three present authors were all working together in London. Since then, we have all moved institutions and it has taken

three years and a great deal of e-mails between three continents to bring the book to fruition but we hope that it will have been worth the wait. In this book, we have tried to provide a topical overview and introduction to current thinking in supramolecular chemistry and to show how supramolecular concepts evolve into nanochemical systems. By definition, this book is not comprehensive and we apologise in advance to the many fine researchers whose work we could not include. The examples we have chosen are those that best illustrate the fundamental concepts and breadth of the field. In order to highlight important (and readable!) entries into the supramolecular chemistry literature, we have chosen to adopt a system of 'key references' which are marked by a 'key symbol' at the start of most major sections. Key references are chosen predominantly from the secondary or review literature to give the interested student an up-to-date and, above-all, focused entry into the research literature for any subsection of the material which catches their interest (or is assigned as homework!). It is hoped in this way to guide the reader to the most useful or influential work as quickly as possible without the often bewildering effect that a mass of more or less obscure citations to the primary literature may have. Additional citations are given to provide useful further reading.

Finally, no book is written without the help and support of very many people. We would particularly like to thank Andy Slade at Wiley (UK) for championing the concept for this book and for many pleasant lunches! We are very grateful to Drs Stuart Batten, Mark Gray, Gregory Kirkovits, Ian van der Linde, Craig Forsyth, Anand Bhatt, Leigh Jones and Kirsty Anderson for their constructive criticism and helpful comments and suggestions. Thanks to Dr Kellar Autumn for his useful comments on Chapter 5. DRT wishes to thank his family for their unwavering support, his friends in both England and Australia and especially Jodie for always being there when needed. KJW would like to thank his partner Terri Tarbett for her endless love, support and patience throughout the last couple of years.

**Jonathan W. Steed**, *Durham, UK*
**David R. Turner**, *Melbourne, Australia*
**Karl J. Wallace**, *Mississippi, USA*

# About the authors

**Jonathan W. Steed** was born in Wimbledon, 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 Professor Jerry L. Atwood, where he developed a class of organometallic supramolecular hosts for anions. In 1995, he was appointed as a Lecturer at King's College, London where he built up a reputation for supramolecular chemistry, including anion binding and sensing, and crystal engineering studies using strong and weak hydrogen bonds. In 1998, he was awarded the Royal Society of Chemistry Meldola Medal and was promoted to Reader in 1999. In 2004, he was appointed as Reader in Inorganic Chemistry at the University of Durham and was elected FRSC in 2005. Dr Steed is co-author of the textbook *Supramolecular Chemistry* (2000) and more than 200 research papers. He has published a large number of reviews, book chapters and popular articles, as well as a major edited work, the *Encyclopedia of Supramolecular Chemistry* (2004). He has been an Associate Editor of the *New Journal of Chemistry* since 2001.

**David R. Turner** was born in London, UK in 1979. He obtained his M.Sci. in Chemistry at King's College, London where he became interested in crystal nucleation and organometallic anion sensors. He stayed on to do a Ph.D. with Jonathan Steed at King's College and at Durham University, on urea-functionalised anion receptors, including tripodal organic host species and molecular tweezers. His work also involved aspects of crystal engineering and solid state phenomena involving transition metal/ureido systems. He graduated in 2004. In January 2005, he changed

countries and disciplines to begin a post-doctoral position at Monash University, Melbourne, Australia with Professor Peter Junk and Professor Glen Deacon, working on the synthesis and structural characterisation of novel lanthanoid – pyrazolate complexes. In January 2006, he was awarded an Australian Research Council post-doctoral fellowship in collaboration with Dr Stuart Batten at Monash University. His current research is focused on the synthesis and control of lanthanoid-containing coordination networks targeting systems with novel magnetic properties, in addition to pursuing his interest in hydrogen bonding networks. Dr Turner is the co-author of 20 scientific papers and is co-lecturer of the metallo-supramolecular course at his current university.

**Karl J. Wallace** was born in Essex (a true Essex boy!), UK in 1978. He obtained his B.Sc. at the University of the West of England, Bristol in 1999, where he developed an interest in inorganic chemistry and coordination polymers. He then completed a Ph.D. at King's College, London (2003), working with Jonathan W. Steed on the synthesis and binding studies of hosts for small molecule recognition. In 2003, he moved to the laboratories of Eric V. Anslyn at the University of Texas at Austin, USA as a post-doctorial fellow, synthesizing molecular 'scaffolds' for applications as practical sensor devices. In 2006, he was appointed as an Assistant Professor in Inorganic and Supramolecular chemistry at the University of Southern Mississippi, USA, where his research interests are in supramolecular chemistry, particularly molecular recognition and the synthesis of molecular sensors and devices.

# 1
# Introduction

## 1.1 What is supramolecular chemistry?

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

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

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

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

*Core Concepts in Supramolecular Chemistry and Nanochemistry* Jonathan W. Steed, David R. Turner and Karl J. Wallace
 ISBN: 978-0-470-85866-0 (Hardback); 978-0-470-85867-7 (Paperback)

deal of biological chemistry involves supramolecular concepts and in addition a degree of technical knowledge is required in order to apply supramolecular systems to the real world, such as the development of *nanotechnological* devices (Chapter 5).

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

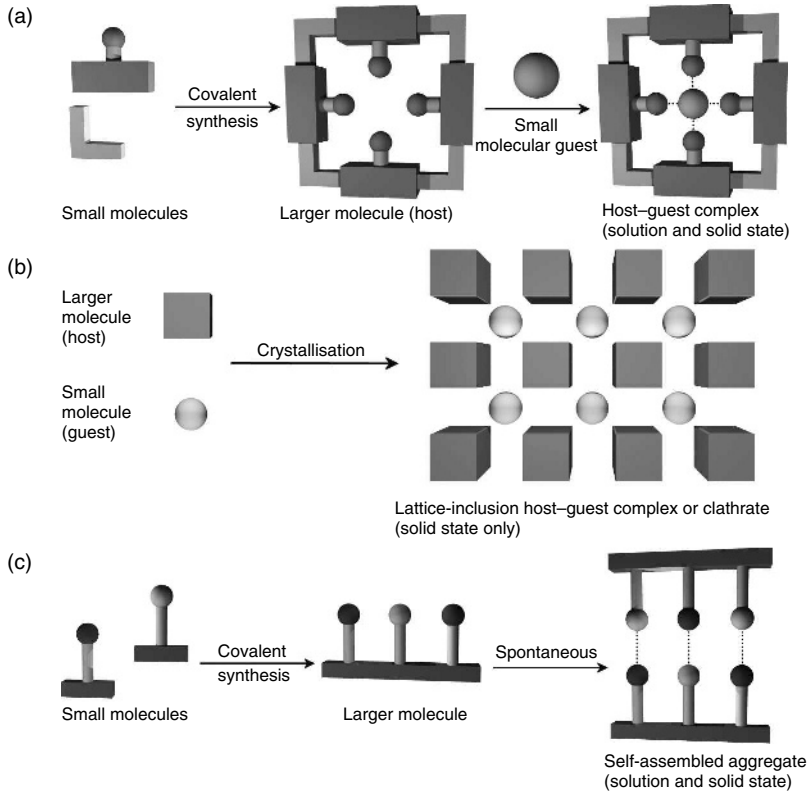



**Figure 1.1** The development of a supramolecular system from molecular building blocks (binding sites represented by circles): (a) host–guest complexation; (b) lattice inclusion; (c) self-assembly between complementary molecules.

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

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

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

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

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

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

## 1.2 Selectivity

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

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

### 1.2.1 The Lock and key principle and induced-fit model

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

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

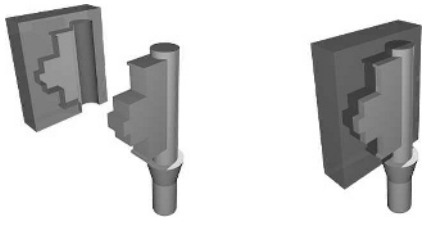


**Figure 1.2** The lock and key principle, where the lock represents the receptor in which the grooves are complimentary to the key, which represents the substrate.

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

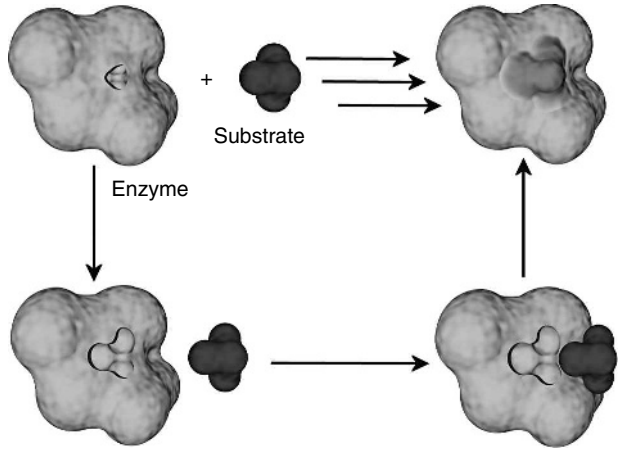



**Figure 1.3** The induced-fit model of substrate binding. As the enzyme and substrate approach each other, the binding site of the enzyme changes shape, resulting in a more precise fit between host and guest.

## 1.2.2 Complementarity

*Complementarity* plays an important role in biological and supramolecular systems, for example, in the function of enzymes. An enzyme is generally a

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

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

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

## 1.2.3 Co-operativity and the chelate effect

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

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

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

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

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

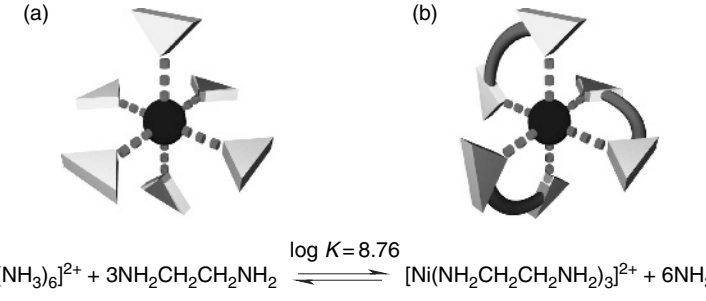


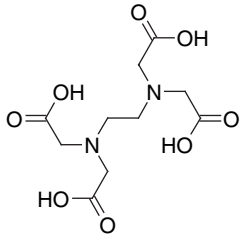

**Figure 1.4** A metal ion surrounded by (a) six unidentate ammonia ligands and (b) three bidentate ethylenediamine ligands. The system with bidentate ligands is more stable, an example of the chelate effect. Triangles represent the ligand interaction sites and the sphere represents a metal ion, such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

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

$$\Delta G° = \Delta H° - T\Delta S° \tag{1.1}$$

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

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




**1**

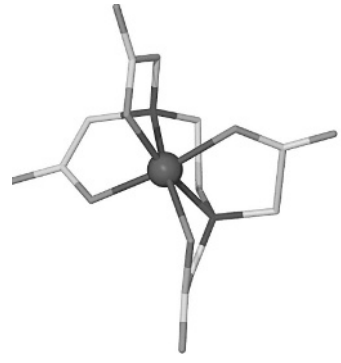


**Figure 1.5** A host–guest complex of $EDTA^{4-}$ binding an aluminium cation, where the ligand forms an octahedral geometry around the metal ion.

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

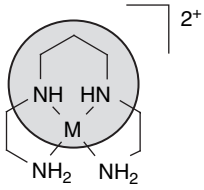



**Figure 1.6** A chelating podand, with a six-membered chelate ring highlighted.

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

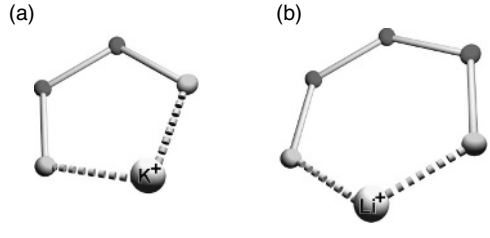



**Figure 1.7** Schematic representations of (a) five-membered and (b) six-membered chelate rings (metal–ligand interactions are shown as dashed bonds).

In energy terms, the co-operativity arising from the chelate effect (or more generally from the interaction of a guest with two binding sites, A–B) with a bidentate host can be expressed in terms of the overall binding free energy, $\Delta G_{AB}^{\circ}$ 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 ($\Delta G^s$), as follows:[2,3]

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

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

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

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

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

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

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

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

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

## 1.2.4 Preorganisation

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

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

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

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

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

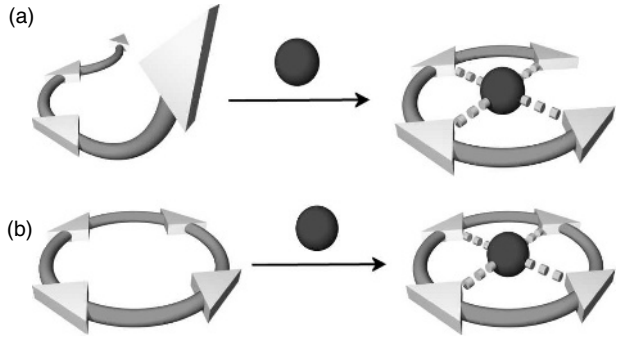



**Figure 1.8** (a) A podand is not preorganised and must undergo a change in conformation in order to bind a guest destabilising the complex. (b) A macrocycle that is preorganised for a specific guest does not need to change conformation significantly for binding to occur.

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

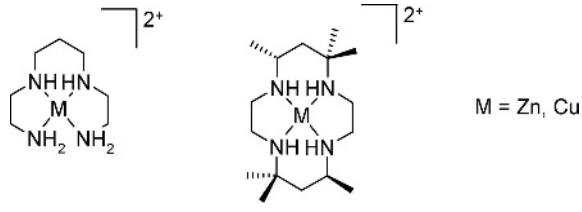



**Figure 1.9** Polyamide acyclic and macrocyclic host complexes. The macrocycle displays enhanced binding compared to the podand due to the macrocyclic effect.

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

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

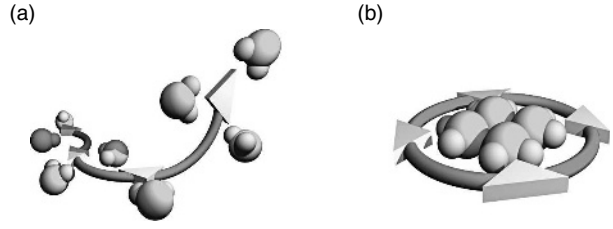



**Figure 1.10** A podand (a) is fully solvated in solution as it is flexible and the donor sites are easily accessible and (b) macrocycles are often not fully solvated as the solvent molecules would have to be packed in close proximity in the centre of the host.

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

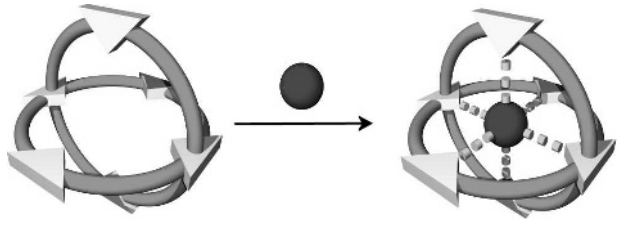


**Figure 1.11** A macrobicycle is more rigid and preorganised than a macrocycle (Figure 1.8), hence resulting in stronger guest binding.

## 1.2.5 Binding constants

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

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

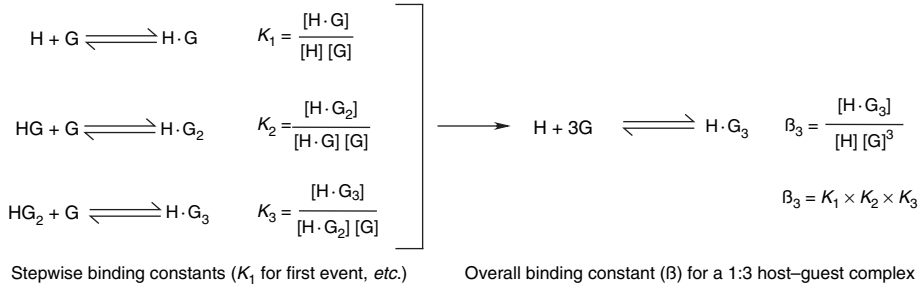

**Scheme 1.1** The equilibrium between a host–guest complex and the free species.

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

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

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

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




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

## 1.2.6 Kinetic and thermodynamic selectivity

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

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

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

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

*Kinetic selectivity* is based on a very different principle to thermodynamic selectivity. The word 'kinetic' implies that there is a time-element involved. Kinetic selectivity is usually found in the context of catalytic or enzyme-based processes, whereby a guest (substrate) is transformed upon binding. The rate at which competing substrates are transformed is the determining factor for kinetic selectivity, with the enzyme or catalyst being selective for the fastest-reacting substrate. To cater for a reacting guest, enzyme binding sites are not rigidly preorganised as

they have to change to be complementary to the substrate at any given time along the reaction profile. Strong binding would slow down the exchange rate at the enzyme active site and therefore reduce the activity of the enzyme. Enzymes are usually selective for the transition state of a given substrate transformation, adopting a strained geometry, referred to as the *entatic state*. It is this strained geometry that lowers the activation energy for the substrate reaction and gives the enzyme its catalytic properties.

## 1.2.7 Solvent effects

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

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

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

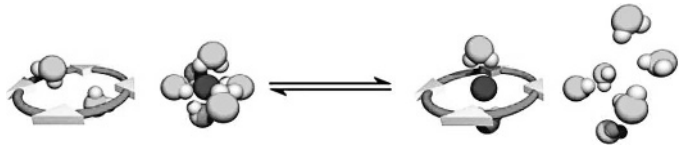


**Figure 1.12** Host–guest binding equilibrium showing the desolvation of both species required prior to the binding occurring. The final complex is still solvated but overall there are more free solvent molecules present, hence increasing the entropy of the system.

Solvent effects can be understood by the way in which the individual molecules can interact with the host and the guest. Polar solvents are able to interact with