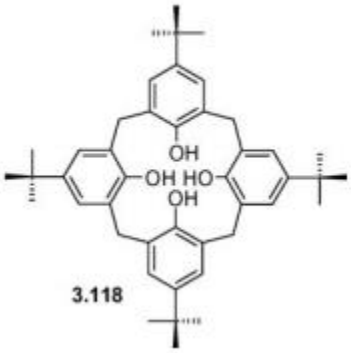
Calixarenes

The calixarenes are a popular and versatile class of macrocycle formed from the condensation of a *p*-substituted phenol (*e.g. p-tert*-butylphenol) with formaldehyde. Since they contain bridged aromatic rings, they are formally members of the cyclophane family. The descriptive name 'calixarene' was coined by David Gutsche because of the resemblance of the bowl-shaped conformation of the smaller calixarenes to a Greek vase called a *calix crater*. The number of phenolic residues is denoted by a number in square brackets. Thus the most common cyclic tetramer with *p-t*-butyl substituents is termed *p-t*-butyl-calix[4]arene.

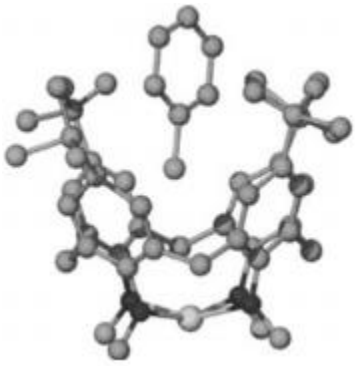


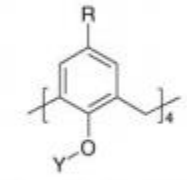
3.118

Cation Complexation by Calixarenes

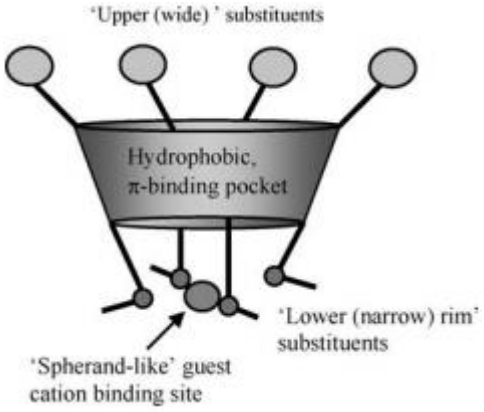
The calixarenes are extremely versatile host frameworks and, depending on their degree of functionalisation, may act as hosts for cations, anions and neutral molecules. As hosts for cations, the phenolic oxygen atoms at the calixarene lower rim have the potential to act in a similar way to the anisole residues of the spherands, either in the original hydroxyl form or as alkyl ether derivatives. This kind of behaviour has been observed for the methyl ether of the parent *p-t*-butylcalix[4]arene upon reaction with a mixture of sodium benzoate, one quivalence of water and trimethyl aluminium. The resulting complex contains an Na cation coordinated by all four oxygen atoms of the calixarene tetraether. The exposed face of the nesting Na cationis

bound to a methyloxyaluminate anion arising from the other components in the reaction mixture. Interestingly, the calixarene hydrophobic cavity also contains a guest molecule of toluene. The host thus serves as a simultaneous receptor for cations and neutral molecules.





R = H, Y = Me, **3.120**
R = *t*-Bu, Y = Me, **3.121**
R = H, Y = *n*-Pr, **3.122**



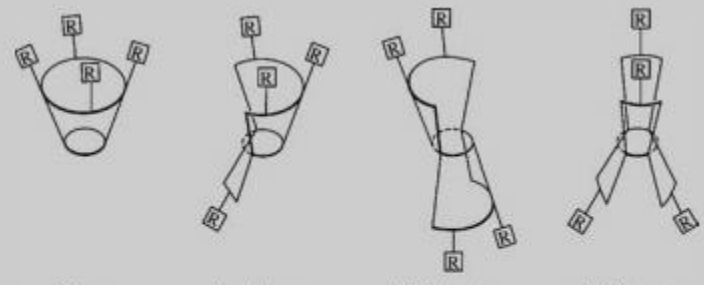


Figure 3.79 Conformers of *p-tert*-butylcalix[4]arene. Cornforth originally suggested that restricted rotation about the aryl–methene bonds should result in these materials being noninterconvertable. In fact, interconversion is slow on the NMR time scale at room temperature (about 150 s^{-1}) but readily observed at 60°C. (Reproduced by permission of The Royal Society of Chemistry.)

Phase Transport Equilibria

The parent *p-t*-butylcalix[n]arenes (n 4, 6, 8) are almost completely insoluble in water. However,

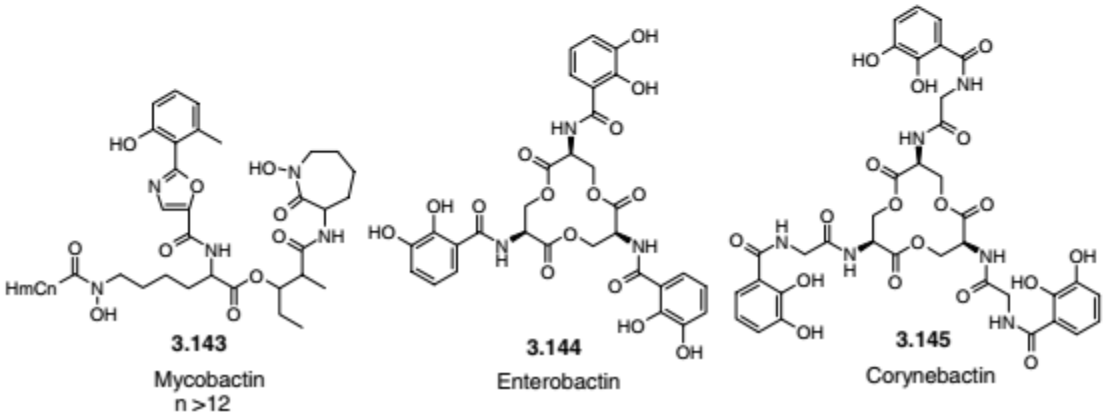
their resemblance to crown ethers and spherands makes them interesting from the point of view of

applications as phase transfer catalysts. In aqueous base the calixarenes are sufficiently soluble to act as phase transfer catalysts as a consequence of deprotonation of one of their phenolic hydroxyl groups. This solubility contrasts to [18]crown-6, which is much more effective in neutral solution. All of the calixarenes are especially good at transporting Cs, but show very little affinity or variation amongst the other metal cations, including the more highly charged metal ions. Although the caesium cation is too large to bind within the square of the four oxygen atoms of the calix[4]arene, it fits beautifully within the calixarene cavity, stabilised by extensive cation–π interactions as evident from the X-ray crystal structure of the nonbutylated Cs calix[4]arene mono-anion complex.

The Siderophores

Naturally Occurring Siderophores

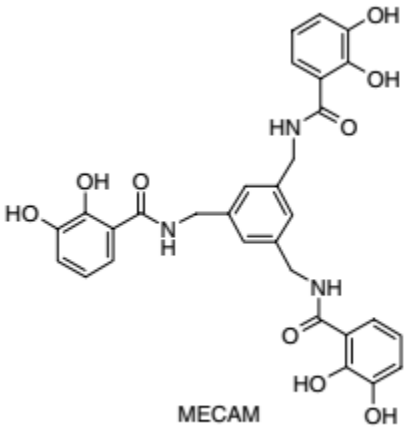
Iron has a crucial biochemical role in an enormous range of cell redox processes in plants, bacteria and higher organisms. In terms of bioavailability, however, iron leaves much to be desired since in its most common naturally occurring oxidation state, Fe(III) (rust), is highly insoluble in aqueous solution. At a physiological pH of 7.4, the solubility of $[Fe(H_2O)_6]^{3+}$ is about 10^{-18} mol dm^{-3}. Vast regions of the Pacific ocean are essentially sterile because of a lack of bioavailable iron and one of the more creative and controversial plans to tackle global warming has been to seed the ocean with iron to promote microorganism growth on a vast scale thereby sequestering atmospheric CO_2. Trials involving addition of iron compounds to the water do indeed result in a rapid flourishing of marine phytoplankton but this is short-lived since the iron does not remain in solution for long enough. Optimum microorganism growth requires an intracellular concentration in the region of 10^{-7} mol dm^{-3}, a factor of about a hundred billion times more concentrated than the solubility-limited concentration of Fe(III). As a result, plants and bacteria require highly effective iron-complexing ligands in order to mobilise Fe^{3+} and deliver it to the cell. These naturally occurring ligands are termed *siderophores* (from the Greek meaning 'iron bearer'), and may be regarded as essential microorganism growth promoters. The sideophores were discovered as early as 1911, but it was not until 1951 that the first natural sideophore, mycobactin (**3.143**) was isolated, as its aluminium complex.



Siderophores such as mycobactin (**3.143**) and enterobactin (**3.144**) are essentially three-armed podands, binding through deprotonated hydroxyl groups. The ligands have an overall 6– charge, making them complementary to highly charged cations; the hard character of the phenolate or catecholate moieties bind strongly to the hard Fe3+. It has been demonstrated by the isolation of a number of siderophores from bacteria and the roots of plants, especially those growing in alkaline soils, that the *o*-dihydroxybenzene (catechol) moiety is a common feature to effective

iron chelators. Enterobactin, with its three catecholate arms, is able to envelop Fe^{3+} in a trigonal prismatic, six-coordinate geometry.

The enormous iron complexing ability of enterobactin has led to the synthesis of a number of synthetic podand and cryptand analogues. In particular, the tricatecholate mesitylene derivative **3.146** bears a close structural resemblance to **3.144** and, moreover, does not feature its hydrolysis-prone ester linkages, making it an easier ligand to handle.



MECAM

3.146

Anion Binding

The applications of cation-binding ligands are legion; from mimics of biological ion transport to mining and the extraction of metals and as selective catalysts. Simple inorganic anions are ubiquitous in the natural world; chloride is a major component of the oceans and it is the dominant anion in biological extra-cellular fluid. Nitrate (from N_2 oxidation) and sulfate from burning organo sulfur compound containing fossil fuels) are key components in acid rain and roadside particulate matter. Hydrogen carbonate and carboxylates are also key biological anions, while carbonates, phosphates and silicates are the major anions in biomineralised materials such as the exoskeletons of radiolarian, and in bone. Phosphates and nitrates in fertilisers are beneficial to agriculture but also major pollution hazards since such bioavailable sources of phosphorus and nitrogen are often *biolimiting*, *i.e.* rate of microorganism growth is limited by the amount of these elements that are present. Excess fertilisers, for example in fresh water lakes from agricultural runoff, causes a process termed *eutrophication*; the uncontrolled growth of large floating masses of algae that deplete local dissolved oxygen levels, killing fish and damaging the aquatic ecosystem. Other anthropogenic anions are also major pollutants, *e.g.* the highly soluble and mobile $^{99}TcO_4$ and ClO_4.

Naturally occurring polluting anions such as arsenate are also a problem, contaminating wells in developing countries. Anions are crucial in biological systems – perhaps this is why imbalances in their concentration have such serious effects. Between 70 and 75 per cent of enzyme substrates and cofactors are anions, very often phosphate residues (as in ATP and ADP) or as inorganic phosphate (H_2PO_4). Chloride anion is the major extracellular anion, and it is responsible for the maintenance of ionic strength.

Challenges in Anion Receptor Chemistry

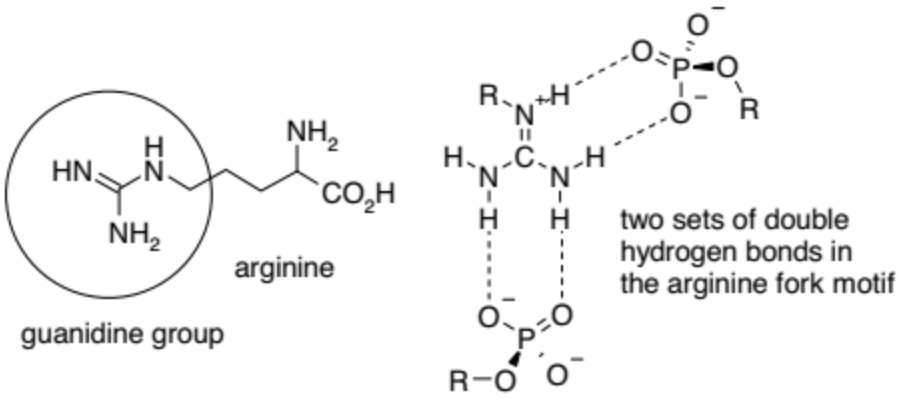
Despite the early discovery of the katapinands, non-covalent anion coordination chemistry was relatively slow to develop in comparison with the development of hosts for cations and even neutral molecules. While it is generally true that anion hosts obey the same rules that govern the magnitude of binding constants and host selectivity in cation hosts (primarily based on preorganisation, complementarity, solvation and size and shape effects), their application is made much more difficult because of some of the intrinsic properties of anions, listed below.

- Anions are relatively large and therefore require receptors of considerably greater size than cations. For example, one of the smallest anions, F^-, is comparable in ionic radius to K^+ (1.33Å versus 1.38Å). Other selected anion radii are shown in Table 4.1.
- Even simple inorganic anions occur in a range of shapes and geometries, *e.g.* spherical (halides), linear (SCN^-, N_3^-), planar (NO_3^-, $PtCl_4^{2-}$), tetrahedral (PO_4^{3-}, SO_4^{2-}), octahedral (PF_6^-, $Fe(CN)_6^{3-}$) as well as more complicated examples as in the case of biologically important oligophosphate anions.
- In comparison to cations of similar size, anions have high free energies of solvation and hence anion hosts must compete more effectively with the surrounding medium, *e.g.* $\Delta G_{\text{hydration}}(F^-) = -465$ kJ mol^{-1}, $\Delta G_{\text{hydration}}(K^+) = -295$ kJ mol^{-1}. Other solvation free energies are given in Table 4.1.
- Many anions exist only in a relatively narrow pH window, which can cause problems especially in the case of receptors based upon polyammonium salts where the host may not be fully protonated in the pH region in which the anion is present in the desired form.
- Anions are usually coordinatively saturated and therefore bind only *via* weak forces such as hydrogen bonding and van der Waals interactions, although they can form dative bonds.

Arginine as an Anion Binding Site

Of particular importance in anion binding proteins and enzymes is the arginine residue, which contains a guanidine group. Guanidinium, the protonated form of guanidine, is an excellent anion binding site because it remains protonated over an extremely wide pH range ($pK_a = 13.5$ for the parent CN_3H_6) and can participate in double hydrogen bonds with carboxylates, phosphate, sulfate *etc.*, as well as a unique interaction with two anions termed the *arginine fork* motif (Figure 4.3).

Important arginine-containing biological systems include superoxide dismutase (a Cu, Zn enzyme that catalyses the transformation of superoxide (O_2^-) into hydrogen peroxide and dioxygen), and citrate synthase. It has been proposed that argentine-based proteins are able to use the argentine fork motif to recognise particular loops and bulges in RNA and indeed RNA-binding regions in proteins such as the human immuno-deficiency (HIV) virus tat protein exhibit argentine-rich regions.



Another enzyme that uses an arginine residue to bind its anionic substrate is carboxypeptidase A (CPA). The role of this zinc-containing enzyme is the hydrolytic cleavage of the terminal peptide or ester bond at the carboxylate end of polypeptide or ester substrates bearing *β*-aromatic side chains on the last residue. The binding of the carboxylate anion portion of a substrate is carried out by a positively charged arginine residue (Arg145) forming a 'salt bridge' of two identical, charge assisted hydrogen bonds.

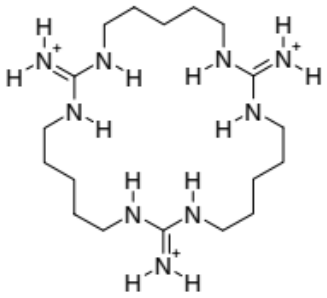
Homework (to be prepared by the students)

Various concepts in Anion Host Design

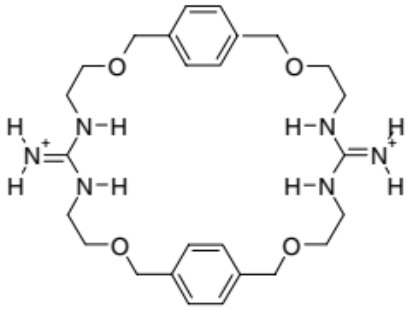
- **Preorganisation**
- **Entropic Considerations**
- **Considerations Particular to Anions**

Guanidinium-Based Receptors

The guanidinium ion has proved to be a very popular motif in the design of anion complexation hosts. Interest in it was sparked by its common occurrence as part of arginine residues in naturally occurring anion binding hosts (Section 4.2.2). The native guanidinium ion has a pK_a of 13.5, meaning that it is protonated and therefore positively charged and an effective hydrogen bond donor, over a wide pH range. In the solid-state, methylguanidinium forms a 1:1 complex with dihydrogen phosphate, indicating clearly its bidentate hydrogen bonding coordination mode (Figure 4.17). In an attempt to take advantage of this behaviour in a macrocyclic host, Lehn's group prepared the macromonocycles **4.25** and **4.26**.[27] The 3+ charge and three-fold symmetry of **4.25** in particular suggests that this host should bind strongly to PO_4^{3-}. Because of the low Brønstead acidity of the protonated guanidinium moieties, the host should remain protonated under the highly basic conditions required for the existence of PO_4^{3-}. Surprisingly, the observed log *K* values are only 2.4 and 1.7 for **4.25** and **4.26**, respectively. It was suggested initially that this may arise from the low charge density of the guanidinium moiety, implying weak electrostatic interactions, although this would be surprising given its biological ubiquity. It is also possible that the macrocycles are both too small to accommodate the large phosphate anion and too inflexible to direct their guanidinium moieties towards an anion in a perching geometry. The high degree of solvation of the guanidinium ion in polar solvents is probably also detrimental to strong binding, although this is less of a factor in other work involving this moiety.



4.25



4.26

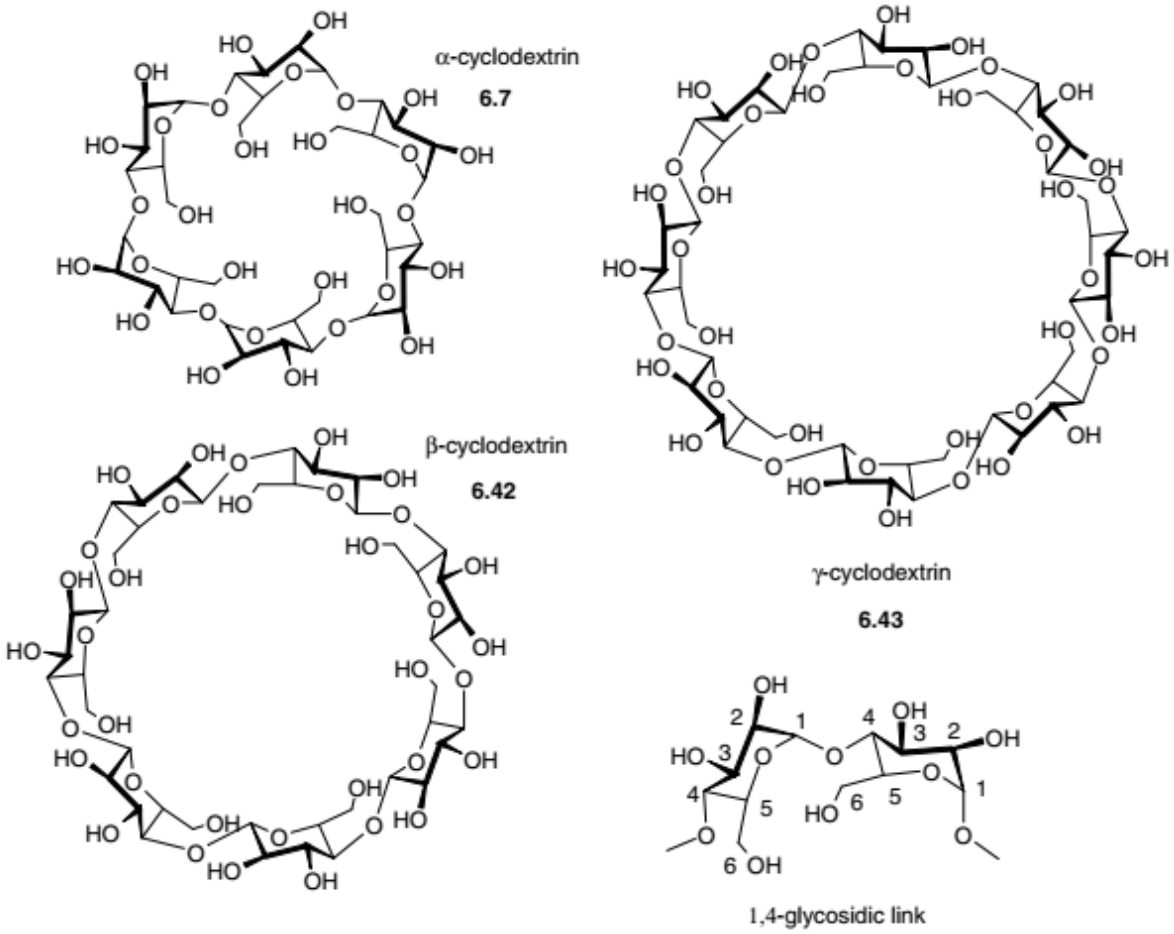
Neutral Receptors

Despite the strong binding by charged hosts, there are two potential disadvantages to the use of cations as anion complexing agents. Firstly, the non-directional nature of electrostatic forces means that *all* anions are bound with some degree of strength, which can reduce anion selectivity. What selectivity there is must be a result of additional interactions, such as hydrogen bonds, size fit *etc.*, which often represent proportionately small contributions to the overall binding and can be swamped by the electrostatic forces. As well as being non-selective, each cationic host must have a counter anion, incorporated at the time of synthesis, in order to fulfil the requirement of overall electroneutrality. These counter anions generally interfere with binding of the target anion, and observed binding constants are ratios of the affinity for one anion over the other, rather than representing absolute host guest affinity. As a result of both the non-

directional electrostatic binding and inter-anion competition, it is more difficult to incorporate selectivity into charged hosts. The neutral hosts should exhibit much better membrane transport properties because of their more lipophilic nature, as in biological systems. The corollary, of course, is that a neutral host does not interact solely with an anion, but in fact must bind both the anion and its counter-cation and so is formally a host for an ion pair.

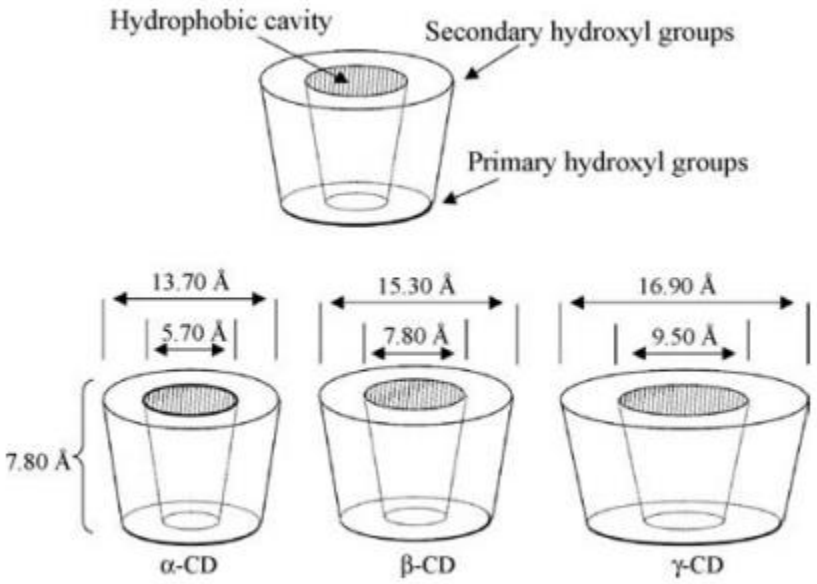
Cyclodextrins

The chemistry of the calixarenes and cavitands demonstrates clearly that as a molecular cavity becomes more rigid (and therefore preorganised) and deeper, its ability to complex organic guest species in solution is enhanced. The cyclodextrins, are fully saturated and rely upon a combination of intramolecular hydrogen bonding and a sharp radius of curvature in order to introduce rigidity. Cyclodextrins as a class are enormously important host compounds, with a wide variety of industrial uses in the food, cosmetics and pharmaceuticals sectors, generally as slow-release and compound-delivery agents. They have the particular advantage of being entirely nontoxic over a wide dosage range.



Cyclodextrins are cyclic oligosaccharides comprising (usually) six to eight D-glucopyranoside units, linked by a 1,4-glycosidic bond. The three most important members of the cyclodextrin family are *α*-cyclodextrin (*α*-CD), *β*-cyclodextrin (*β*-CD, and *γ*-cyclodextrin (*γ*-CD), which possess, respectively, six, seven and eight glucopyranoside units. Several other (minor) cyclodextrins are known, including *δ*-cyclodextrin and ∑-cyclodextrin (nine and ten units, respectively), and the five-membered pre-*α*-cyclodextrin. The *α*, *β*, *γ* nomenclature serves to distinguish the different ring sizes of the homologous series and is essentially historical in nature. The shape of a cyclodextrin is often represented as a tapering torus or truncated funnel and, like the upper and lower rims of calixarenes, there are two different faces to the cyclodextrins, referred to as the primary and secondary faces. The primary face is the narrow end of the torus, and comprises the primary hydroxyl groups. The wider secondary face contains the —CH_2OH groups. The six-membered D-glucopyranoside rings are linked edge to edge, with their faces all pointing inwards towards a central hydrophobic cavity of varying dimensions. It is this cavity, coupled with the water solubility derived

from the hydrophilic alcohol functionalities, that gives the cyclodextrins their unique complexation ability in aqueous solution.



Anatomy of the cyclodextrins.

Cyclodextrin's water solubility

Which is significantly less for the odd-numbered *β*-CD than for *α*- and *γ*-CD. The solubility of the odd-numbered *δ*-CD is also less than for *α*- and *γ*-CD, although the deviation is less marked. This relative insolubility of *β*-CD has important consequences on its applications as a solution host. A number of explanations have been put forward for this anomalous behaviour. Examination of the enthalpy and entropy of hydration show that both are less favourable for *β*-CD than for the smaller and larger analogues. This has been attributed to the interruption of the hydrogen-bonded structure of water by aggregated *β*-CD. The reasoning is that the six- and eight-fold symmetries of the other cyclodextrins are more compatible with the solvent cage, which has an even number of hydrogen-bond donors and acceptors. It has also been suggested that the intramolecular hydrogen bonds on the secondary face of *β*-CD are responsible for its low solubility, limiting the interactions with solvent water. The

analogous hydrogen-bonded network is incomplete in α-CD because of strain, whereas γ-CD is more flexible. Indeed, methylation of the secondary hydroxyl groups increases β-CD solubility. All of the cyclodextrins crystallise from water as hydrates containing varying amounts of water, depending on crystallisation conditions. In each case, the semi-polar cyclodextrin cavity is filled with water molecules, which are of relatively high energy as a consequence of their limited interactions with the walls of the cyclodextrin cage.

Inclusion Chemistry of Cyclodextrin

Generally, interaction of a cyclodextrin with an apolar guest molecule in water results in the formation of 1:1 molecular inclusion compounds, in which the guest in included within the cyclodextrin cavity. Higher equilibria involving the formation of 1:2 complexes, or multiple aggregates involving more than one cyclodextrin, are common, and often exist simultaneously. The driving force for guest inclusion involves a number of contributions, the importance of which is still a matter of some debate. The subject has been discussed in depth in the key reference for this section. Chiefly the factors of importance are:

steric fit;

release of high-energy water;

hydrophobic effects;

van der Waals interactions;

dispersive forces;

dipole–dipole interactions;

charge-transfer interactions;

electrostatic interactions; and

hydrogen bonding

In general, the size of guest that may be accommodated increases as the size of the cyclodextrin becomes larger, although there is some flexibility in the host structures and size fit is not a rigid criterion. Release of high-energy water and the hydrophobic effect (Section 1.9), comprise two energetic components: enthalpic gain as high-energy solvent molecules rejoin the bulk and, entropic

gain as two holes in the solvent (host and guest) are reduced to one (complex). The classical hydrophobic effect involves a clearly negative ΔS_o, but this is not always the case for cyclodextrin complexes because the cavity is not really non-polar. It has a variety of functionalities and is better described as 'semipolar'. Nonetheless, non-classical hydrophobic effects may well be highly important. In addition to size fit and solvation effects, solid and solution complexes are often stabilised by additional enthalpically favourable interactions, such as hydrogen bonds between the guest and the primary or secondary cyclodextrin hydroxyl groups and dipolar interactions.

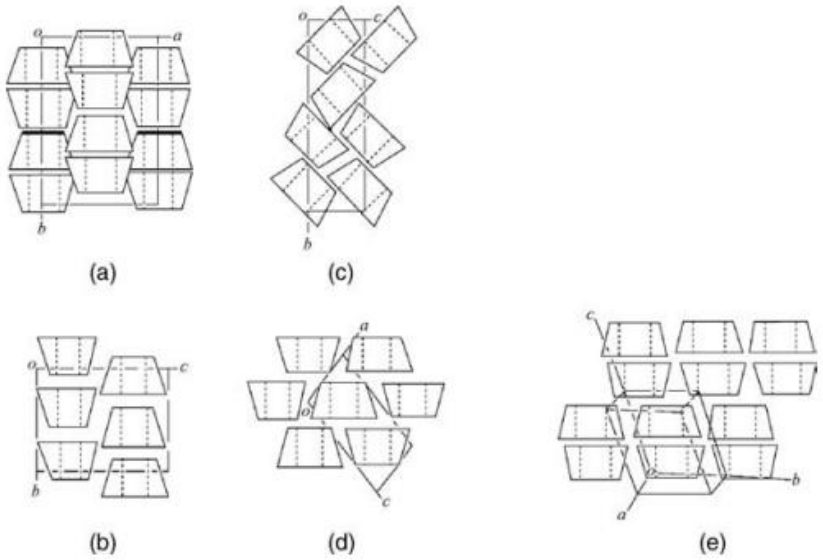


Figure 6.23 Schematic representation of the packing of cyclodextrin structures. (a) Head-to-head channel type; (b) head-to-tail channel type; (c) cage type; (d) layer type; and (e) layer type composed of β-CD dimers. (Reproduced from [24] with permission of Elsevier).

Industrial Applications of cyclodextrins

Cyclodextrins have a large range of industrial applications as aconsequence of their unique inclusion properties and decomplexation kinetics in conjunction with their stability, non-toxicity and relative cheapness. Cyclodextrins are the main active ingredient in Procter and Gamble's deodorising product *Febreze*, for example, where their complexation ability binds molecules responsible for household odours. The food industry, where cyclodextrins are favoured because of their high-temperature stability during

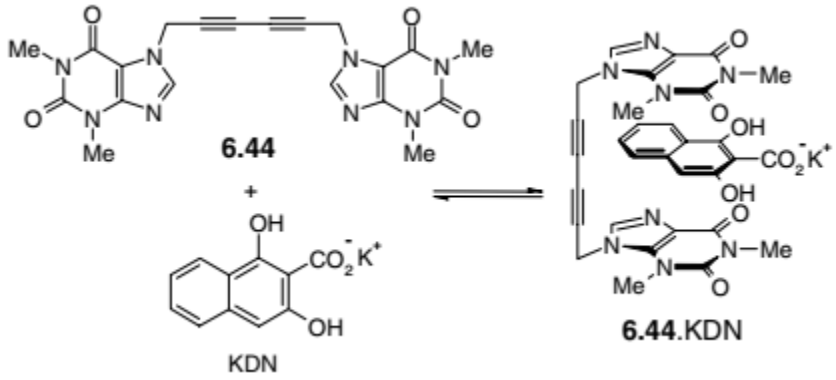
food processing. One of the most prevalent use of cyclodextrins is as a process aid in the removal of cholesterol from animal products such as eggs and dairy products. The cholesterol is bound as a guest in the cyclodextrin cavity which is typically successful in removing *ca.* 80 per cent of this unwanted component. Complexation of expensive flavour oils and spices, such as apple, citrus fruits, cinnamon, garlic, ginger, menthol, spearmint and thyme, by cyclodextrins dramatically reduces the amounts that need to be added to foods in order to achieve the required flavour strength. Complexation by the cyclodextrin makes the flavourings much more resistant to oxidation, photochemical degradation, thermal decomposition or loss by sublimation. Similar stabilisation is achieved for food colourings and pigments, which are apt to decompose photolytically or upon pH changes. To make cyclodextrins even more attractive to food manufacturers, cyclodextrins also impart benefits such as ease of handling and weighing (dry powder as opposed to volatile oil), reduced packaging and storage costs, and reduction of microbial contamination.

In addition to their uses in the food industry, the cyclodextrins are also of application in the pharmaceuticals industry as drug-delivery systems. As in the food industry, the cyclodextrins may act as protecting agents, preventing premature drug metabolism thus allowing, for example, oral rather than intravenous delivery. They may also modify the drug's solubility and biological transport properties, increasing specificity for the target site. Cyclodextrins may also enhance the solubility of poorly soluble drugs without the need to chemically modify the drug itself to include hydrophilic residues, which may interfere with membrane transport of the drug. Finally, cyclodextrin complexation is known to relieve local irritation or drug-induced damage, and to mask unpleasant or bitter tastes.

Molecular Clefts and Tweezers

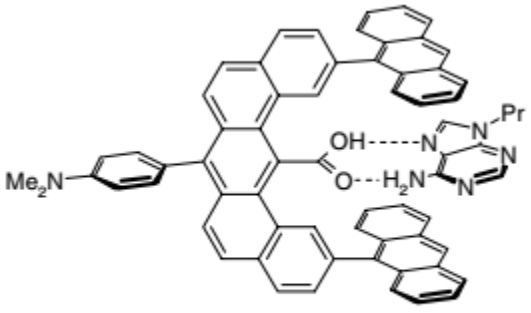
Molecular clips and tweezers are two closely related types of compound. Molecular tweezers represent a simple kind of receptor in which two guest-binding domains usually comprising flat, aromatic groups, are positioned by a relatively rigid tether (in a more or less preorganised fashion) on either side of the proposed binding site. The guest is then held between the two 'pincers' of the host. In general, aromatic rings or alkynes are used as rigid spaces in order to hold the host pincers

at the required distance apart, typically about 7 Å in the case of aromatic guests that π-stack with aromatic binding sites. The spacer and nature of the binding sites should also prevent selfassociation.



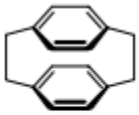
exemplified in molecular tweezers **6.44**, which rely upon a combination of *π–π* stacking and ion–dipole interactions for guest binding. The distance between the two theophylline pincers in **6.44** is held fairly rigidly by a six-carbon diyne spacer, which allows some pivoting at the *sp*3 methylene linkers.

The molecular tweezers concept has been extended by Zimmerman to the double recognition of guests *via π–π* stacking pincers with a hydrogen bonding core. The compounds incorporate a rigid backbone that enforces a *syn* conformation hence increasing preorganisation and 'turning off' the kind of conformational mobility shown in Scheme 6.5. Host **6.45** binds 9-alkyl adenines such as 9-propyladenine (9PA) in chloroform.



Molecular ‘Iron Maidens’

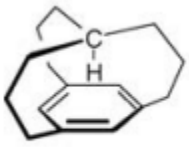
Molecular ‘iron maidens’ are highly sterically strained cyclophanes that exhibit bonding way outside the normal realm of chemistry.



[2.2]paracyclophane

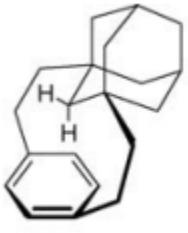
6.54

[2.2]Paracyclophane exhibits a significant degree of boat-shaped out of plane deformation of the aryl rings as a consequence of steic strain with interesting consequences on its electronic structure.

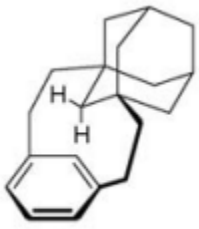


3.93

In Cyclophane **3.93** the *endo* CH bond becoming highly compressed because of a repulsive interaction with the aromatic ring. The CH bond is sterically crushed up against the arene and its IR frequency rises from a typical value of *ca.* 2900 cm^{-1} for aliphatic CH stretches to 3325 cm^{-1}. This means the bond is getting in effect stronger since IR frequency is related to the square root of the bond force constant. It is this ‘crushing’ that gives these kinds of compound their ‘iron maiden’ nickname after the medieval torture device as ‘an iron frame in human form hinged to admit a victim, who, as the frame closed, was impaled on the spikes which stud the interior’), The world record holders for steric compression are the adamantine-derived cyclophanes **6.60** and **6.61**.



6.60



6.61