

Vorlesung Supramolekulare Chemie

„Beyond molecular chemistry based on the covalent bond there lies the field of supramolecular chemistry, whose goal it is to gain control over the intermolecular bond.“

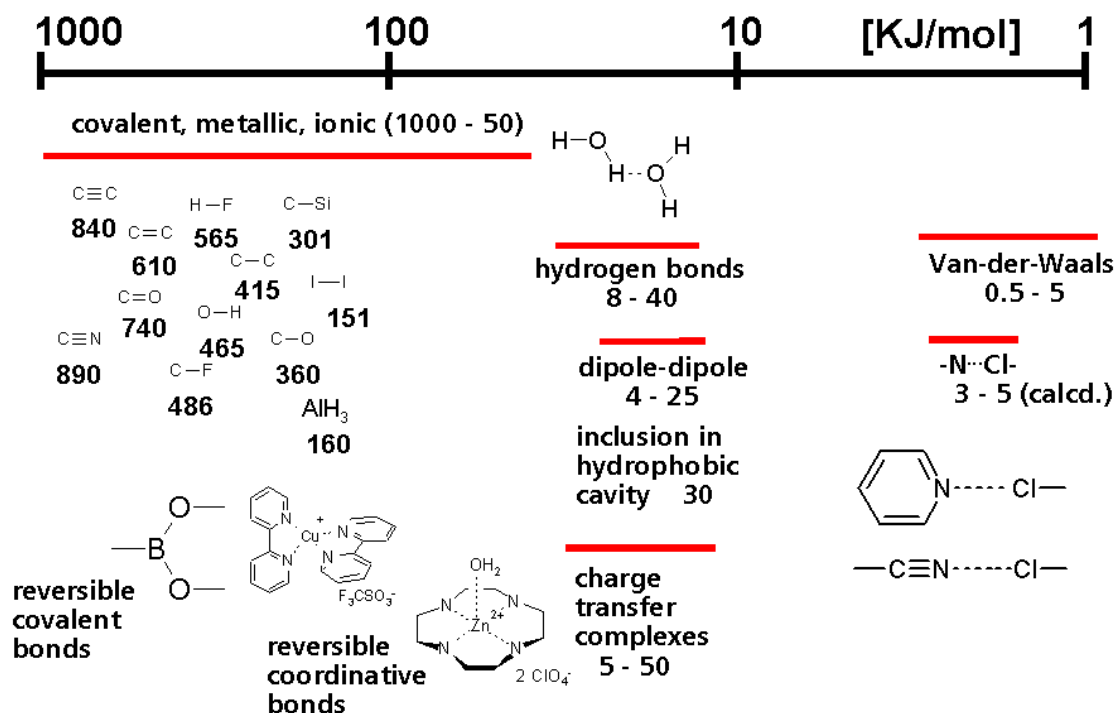
Jean-Marie Lehn, noble laureate 1987



Supramolecular chemistry is not a discipline of its own. The field contains elements of organic and inorganic synthesis, physical chemistry, coordination chemistry and biochemistry. Supramolecular chemistry is the *interdisciplinary* approach to understand and control intermolecular, typically weak interactions in chemistry, molecular biology and physics.

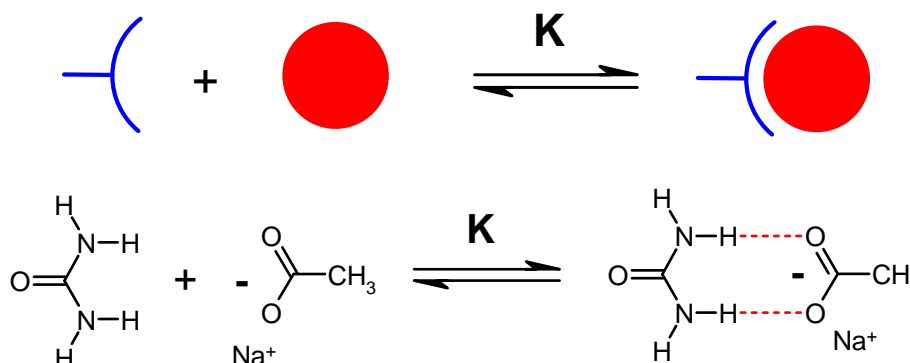
Molecules are made by the covalent connection of atoms. Salts are held together by ionic interactions and metals by the metallic bond. All of these bonds are very strong (1000 – 50 KJ/mol) and typically not reversible at normal laboratory conditions.

Chemical Bonds - from strong to very weak



However, molecules interact with each other. The weakest interactions are van-der-Waals type interactions based on spontaneous and induced dipoles. Such intermolecular interactions are the basis for the formation of cell walls, micelles, vesicles or membranes.

Billions of amphiphilic molecules interact weakly in these systems to form macroscopic structures. The individual interactions are weak (0.5 – 5 KJ/mol) and depend on the contact area (nm²). Hydrogen bonds, dipole-dipole and charge transfer interactions have bond energies in the range of 5-50 KJ/mol that are higher, but are still significantly lower than covalent bonds. Special cases are reversible covalent or reversible coordinative bonds that have high bond strengths, but are kinetically labile. To understand intermolecular interactions, we need to take a closer look at the thermodynamics of equilibria.



The equilibrium is defined by the equilibrium constant (Gleichgewichtskonstante) K . Please note that the symbol for an equilibrium constant is always a capital K , while a rate constant (Geschwindigkeitskonstante) is abbreviated by a lower case k . From our classes in physical chemistry and thermodynamics we know that

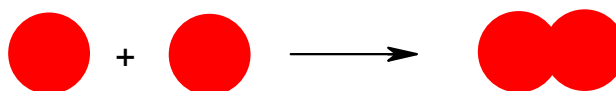
$$\Delta G = \Delta H - T\Delta S$$

, whereby G is the free enthalpy, H is the enthalpy, T is the temperature and S is the entropy. The relation to K is defined by

$$\Delta G = -RT \ln K$$

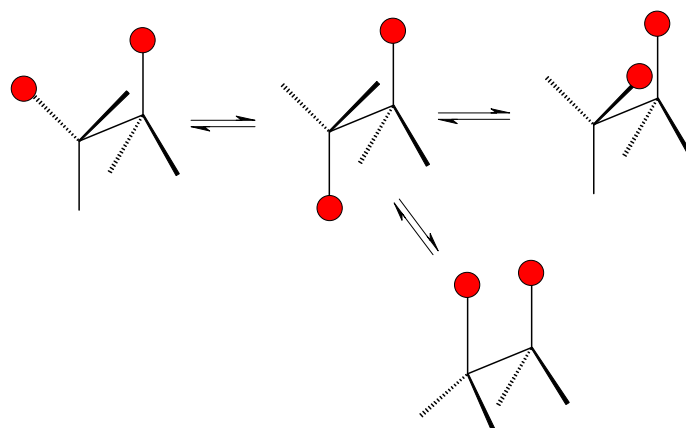
Changes in enthalpy and changes in entropy both contribute to the overall change in free enthalpy which determines the equilibrium constant K . Let's estimate some values for changes in entropy occurring in intermolecular contacts of molecules.

1. Loss of translational entropy. Molecules or ions move randomly in solution. If two of such particles form an aggregate (a dimer) in millimolar solution they loose about $-T\Delta S \sim +23$ KJ/mol.



$$T \Delta S_{\text{trans}} \sim RT \ln [c]_{\text{solution}}/[c]_{\text{pure}} \sim RT \ln [10^{-3}]/[10] \sim 23 \text{ kJ/mol}$$

2. Loss of entropy from conformational restrictions. We assume that a molecule rotates around a single carbon-carbon bond freely. Each carbon atom bears a binding site; if both binding sites interact intermolecularly with a second molecule the rotation is hindered. For each single bond that we "freeze" in intermolecular interactions or aggregate formation we will lose $-T\Delta S \sim + 3 \text{ KJ/mol}$.



We consider only the staggered conformation, which should be more or less equal in energy. The eclipsed conformation is certainly higher in energy.

$$T\Delta S_{\text{conformation}} \sim RT \ln 1/3 \sim 3 \text{ KJ/mol}$$

The individual contributions to entropy loss in an aggregation or binding event are small, but they add up. If we now look at the enthalpies of covalent bonds, it is obvious that entropy does not play a significant role in the formation of bonds.

Example: Reaction of two molecules forming one new C-C bond: $\Delta G = - 415 \text{ KJ/mol} + 23 \text{ KJ/mol}$. The entropic effect accounts for less than 5% of the overall reaction enthalpy. The situation changes dramatically with weak interactions, such as hydrogen bonds. The binding enthalpy gained by a hydrogen bond is in the order of 8 to 40 KJ/mol.

Example: Two molecules form an aggregate by two hydrogen bonds, which are each worth 20 KJ/mol: $\Delta G = - 40 \text{ KJ/mol} + 23 \text{ KJ/mol}$. Now the entropic term accounts for nearly 50% of the energetic balance of the binding event and most of the binding enthalpy must be used to compensate the entropic energy loss.

Receptor molecule or guest binding site for intermolecular molecular recognition must be preorganized. The conformation and orientation of functional groups in the non-bound state should already be close to the one in the host-guest complex to minimize entropic loss.

Simple non-covalent aggregates using hydrogen bonds or dipole-dipole interactions for assembly in a solvent that does not interfere with the binding process can be understood and even predicted with these considerations. However, the thermodynamics of binding and self-organization in biological systems is very difficult to understand, because

- water is a very complex solvent
- the hydrophobic effect and its thermodynamic consequences are poorly understood

- changes in solvation spheres and mobility of solvent molecules can significantly contribute to the entropy change of a binding process
- many biomolecules are macromolecules and interact via large contact areas (typically 1-5 nm²). Many individual contacts of functional groups are involved and an individual analysis is complicated. The contact area of a single functional group is 0.05 – 0.5 nm².

Supramolecular chemistry uses special terms and names

Molecular recognition is the more or less selective reversible intermolecular interaction of two functional groups, molecules, ions or biomacromolecules.

Chemical example: Crown ether + metal cation; biological example: antibody and antigen.

A *synthetic receptor, binding site or host molecule* is one of the binding partners, typically the larger one. If ions are bound the host molecule is called *ionophore*.

The *guest molecule* is the complementary binding partner. It is called a *ligand* in the binding to biological receptors in pharmacy, the *analyte* in analytical applications of molecular recognition.

Self-assembly or self-organisation is a sequence of molecular recognition typically involving many molecules or ions and leading to a certain aggregate. The aggregate structure is always the thermodynamic minimum structure for the specific experimental conditions. Chemical example: Oligonuclear coordination compounds or hydrogen bond networks. Biological example: Tobacco mosaic virus.

The *binding constant* K describes the equilibrium between host and guest. Its unit depends on the stoichiometry of the equilibrium and is L/mol for a 1:1 guest to host binding.

Association constant or affinity constant are used as terms as well. The binding constant describes the thermodynamics of the equilibrium.

The *on- and off-rate* k of a binding event are rate constants and describe the velocity of the binding process and its dynamics. Most molecular recognition events and self-assembly processes have fast assembly rates in the millisecond range or faster.

Thermodynamic selectivity = $K_{\text{guest1}}/K_{\text{guest2}}$

Kinetic selectivity is related to the rate constants of aggregate formation, which means one guest molecule is simply bound faster (not necessary with higher binding affinity). Such kinetic selectivity is of importance for self-assembly processes and observed in enzyme catalysis.

A little history

The term Supramolecular chemistry is rather new and was coined in the 1970's. However, the origin of Supramolecular chemistry dates back:

- 1891 Villiers and Hebd observe cyclodextrin inclusion compounds
- 1893 Alfred Werner: Coordination chemistry
- 1894 Emil Fischer: Lock and key principle
- 1906: Paul Ehrlich introduces the concept of a receptor
- 1937: K. L. Wolf uses the term "Übermolekül" to describe the dimer formation of acetic acid by hydrogen bonding
- 1939: Linus Pauling: nature of the chemical bond – including hydrogen bonds
- 1953: Watson and Crick: Structure of DNA
- 1967: Charles Petersen prepares crown ethers
- 1969: Jean-Marie Lehn prepares the first cryptands
- 1973: Donald Cram describes spherand hosts
- 1978: Jean-Marie Lehn introduces the definition of Supramolecular chemistry
- 1987: Nobel Prize for Chemistry recognizes the contributions of D. Cram, C. Petersen and J.-M. Lehn to the field

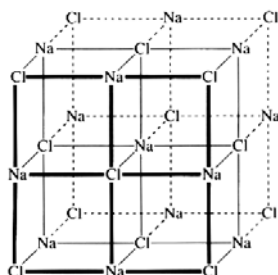
In the last 15 years several areas with specific applications have been developed, e.g.:

- Molecular sensors for use in medicinal diagnostic or analytical chemistry
- Specific ionophores used in analytical applications
- Bioorganic tools for applications in molecular biology, e.g. inhibitors of protein-protein interactions
- Self-assembly processes for applications in material sciences.
- Biomineralization and control of crystal growth
- Molecular machines (no applications so far)
- Self-replicating systems that help to understand to origin of life

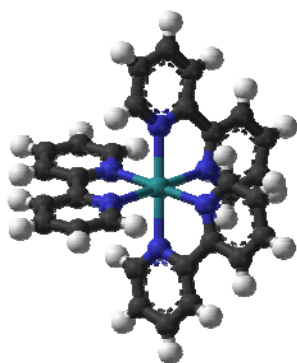
Nature of Supramolecular Interactions

The term "noncovalent" bonding interactions encompasses an enormous range of attractive and repulsive forces. We review the most important ones.

Ion-ion interactions: Ionic bonding is comparable in strength to covalent bonds with bond energies of 100 – 350 KJ/mol. A typical ionic solid is NaCl. An active field of research are ionic liquids, which are salts that are fluid at room temperature.

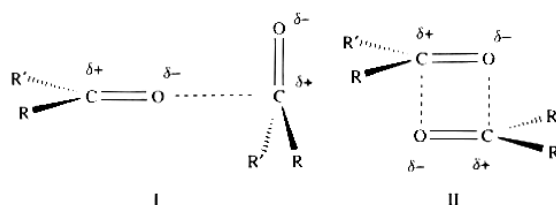


Ion-dipole interactions: The interaction of an ion, such as Na⁺, with a polar molecule, such as water, is an example of an ion-dipole interaction. The bond strength is in the range of 50 – 200 KJ/mol. These interactions include coordinative (dative) bonds that may have high bond strength and a significant covalent component, such as in Ru(bipy)₃Cl₂.



Molecular structure of Ru(bipy)₃Cl₂; anions not shown

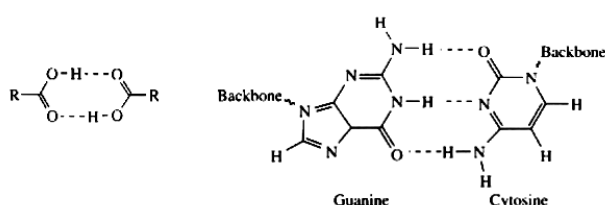
Dipole – dipole Interactions (5 - 50 KJ/mol): Alignment of one dipole with another can result in significant attractive forces. The interaction can be between a single pair of poles on adjacent molecules (type I) or the opposing alignment of one dipole with another (type II). A typical example for type II interactions are carbonyl compounds; the energy of such an interaction is about 20 KJ/mol and corresponds to a strong hydrogen bond.



Hydrogen bonding (4-120 KJ/mol): A hydrogen bond may be regarded as a special kind of dipole-dipole interaction: The hydrogen atom is attached to an electronegative atom (leading to a dipole) and interacts with another electronegative atom. Hydrogen bonds are directional and therefore of special importance in molecular recognition. The lengths, strengths and orientation of hydrogen bonds vary over a large range. In the solid state a single hydrogen bond can be sufficient to determine the structure; in solution or gas phase it may influence the aggregate structure. In the case of hydrogen bonds between neutral molecules, a direct correlation between the hydrogen bond strengths and the crystallographic determined distance between hydrogen bond donor and acceptor is found. In the case of charged binding partners this correlation is not always observed.

Typical hydrogen bond donors: -OH, -NH, -(CO)NH, but also C-H is possible in special cases.

Typical hydrogen bond acceptors: -OH, -O-, =N-, C=O.

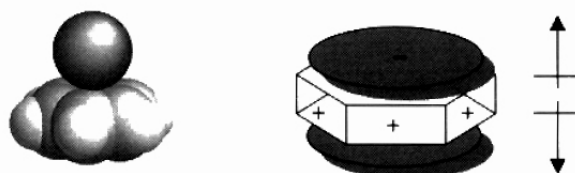


Properties of hydrogen bonded interactions

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

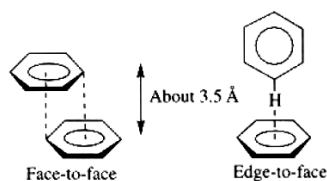
Cation – π Interactions (5-80 KJ/mol): Many transition metal cations, such as Fe²⁺, Pt²⁺ or Ag⁺ form complexes with π-systems. These interactions are strong and are not considered non-covalent, because of the bonding situation involving the π-orbital of the unsaturated ligand and the d-orbitals of the metal ion. However, alkali- and earth alkali metal cations show much weaker interactions to π-systems and these are clearly non-covalent. An example is the interaction of benzene with K⁺ in the gas phase, which has a bond energy of 80 KJ/mol. For comparison, the interaction of K⁺ with a single water molecule is worth about 75 KJ/mol. The better solubility of K⁺ in water than in benzene has its reason in the

possible interaction of the potassium ion with many water molecules, while the sterically more demanding benzene restricts multiple interactions.



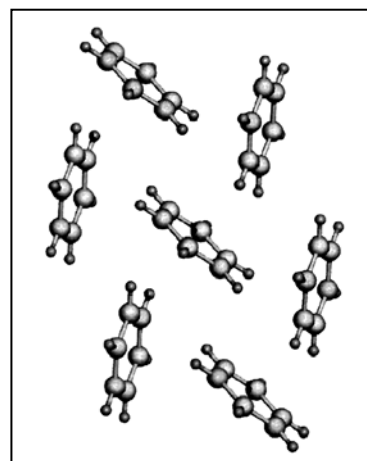
Schematic illustration of a cation- π interaction (left) and benzene dipoles (right)

$\pi - \pi$ Stacking (0-50 KJ/mol): It is a weak electrostatic interaction, typically between aromatic rings with one binding partner more electron rich, the other more electron poor. There are two possible orientations observed in this interaction: A *face to face* orientation and an *edge to face* orientation. In crystal structures of aromatic compounds a so called herringbone motif is sometimes observed resulting from edge to face orientations. The edge to face interaction can be interpreted as a special hydrogen bond between the slightly electron deficient aromatic hydrogen atoms and the electron rich π -system. In DNA the π -stacking of nucleobases contributes significantly to the stability of the helix structure. More recently, p-stacking has been used to construct *foldamers*. These are molecules that fold in solution in a stable conformation. The physical origin of the p-stacking interaction is still under debate: There are suggested models of competing electrostatic and van der Waals interactions, but also London dispersion may play an important role.



Limiting types of π - π stacking. Note the offset to the face to face mode; direct overlap is repulsive!

Right: X-ray crystal structure of benzene showing the herringbone motif arising from edge to face interactions



Charge-transfer complexes (CT complexes) are a special case of π -stacking or ion-ion interaction. Here an electron rich π -system interacts with an electron poor π -system and transfers an electron (sometimes with the help of light). This leads to either a temporary or permanent to a π -cation and a π -anion with strong attractive electrostatic forces.

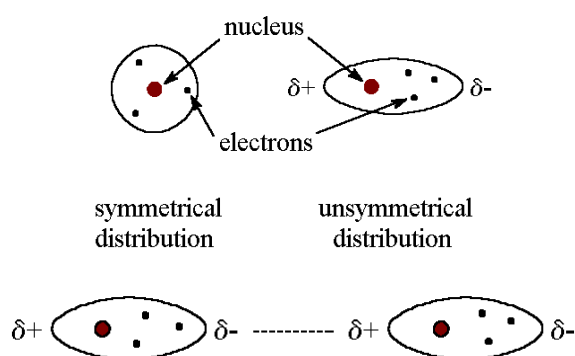
Van der Waals forces (< 5 KJ/mol): These interactions are very weak and arise from the polarisation of the electron cloud by the proximity of an adjacent nucleus, resulting in a weak electrostatic interaction. They are non directional and lead to macroscopic effects only if combined in large numbers. Typical examples are membranes, vesicles or micelles in

which many alkane chains interact. Another example is Gecko feet: many tiny hairs interact with a surface leading to an attractive force that is large enough to keep the Gecko on the ceiling.

Van der Waals interactions may be divided into *dispersion* (London) and exchange-repulsion terms. The dispersion interaction is an attractive force resulting from the interaction of fluctuating multipoles in adjacent molecules. The attraction decreases with $\sim r^6$.

Exchange-repulsion: Electrons can be exchanged between molecules, which again results in an attractive force. If they occupy the same space at the same time, repulsion occurs.

London dispersion:



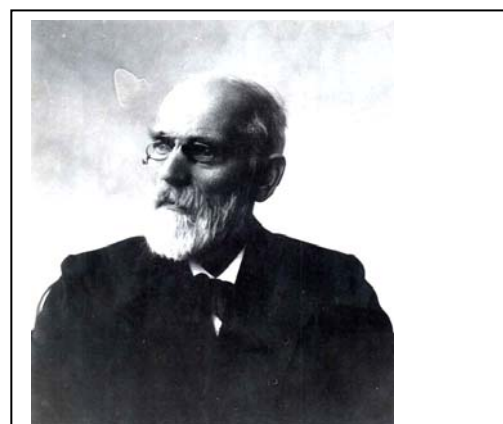
Cl_2 and Br_2 have approximately the same shape and neither is polar.

1) Upon cooling, both Cl_2 and Br_2 form solids. Why?

2) At 25°C , chlorine (Cl_2) is a gas whereas bromine (Br_2) is a liquid. Why?

1) London dispersion forces are responsible for the formation of the solids. As the elements are cooled, the kinetic energy of the Cl_2 and Br_2 molecules decreases and the London forces are strong enough to overcome the kinetic energy and hold the molecules in a solid.

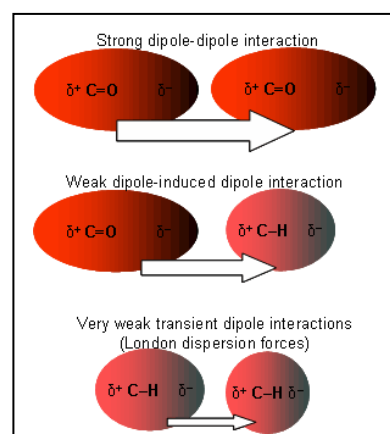
2) London dispersion forces between the larger Br_2 molecules are sufficient to cause them to form a liquid at 25°C , whereas London dispersion forces between the smaller Cl_2 molecules are not.



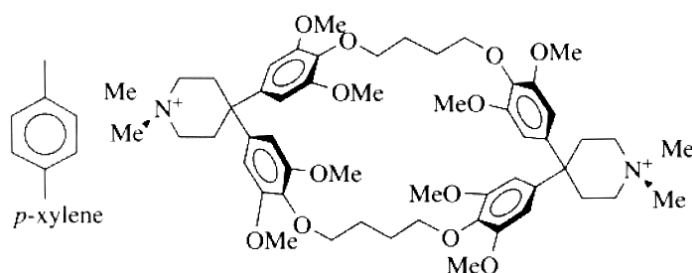
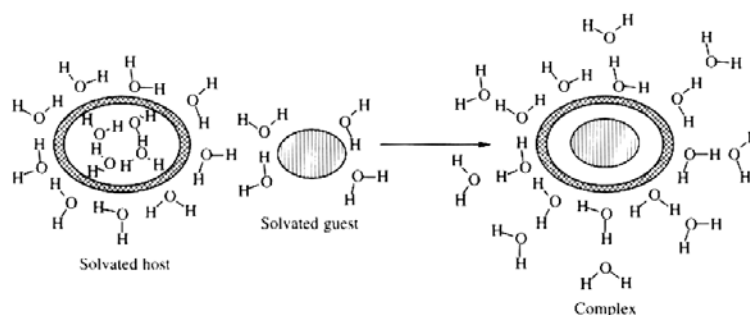
Van der Waals, 1837-1923

Nach seiner Schulausbildung war er als Lehrer in seiner Heimatstadt Leiden tätig. Ohne das Abitur als Zugangsberechtigung zu einem Hochschulstudium zu besitzen, besuchte van der Waals in der Zeit von 1862 bis 1865 an der Universität Leiden Vorlesungen und Seminare. Hierdurch erlangte er in den Fächern Mathematik und Physik eine Erweiterung seiner Lehrzertifikate. 1866 übernahm van der Waals eine Stelle an einer weiterführenden Schule in Den Haag, an der er später auch Schuldirektor wurde. Eine Gesetzesänderung ermöglichte es, dass er auch ohne Abitur ein Studium der Naturwissenschaften durchführen konnte. Van der Waals schloss 1873 sein Studium mit einer Dissertation in Physik ab. Als Professor für Physik war er von 1877 bis 1908 an der Universität Amsterdam tätig.

Intermolecular forces that arise from the interaction of permanent or induced dipoles become weaker if transient or induced dipoles are involved.



Hydrophobic effects: Binding events driven by hydrophobic effects relate to the exclusion of non-polar surfaces from polar solvents. The hydrophobic effect is not a bonding force! The effect is very obvious in immiscible mixtures of oil and water. It is typically observed in Supramolecular chemistry with water soluble host molecules having a hydrophobic interior. Non-polar guests "escape" from the polar solvent water into the cavity of the host molecule. The contribution of the hydrophobic effect to the overall binding energy is entropic (releasing ordered water molecules) and enthalpic (allowing new interactions between host and guest or within the solvent, which becomes less disrupted in its structure after aggregate formation).



Host and guest molecules – molecular recognition

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

Max Beerholm, 1872

We discuss the different types of natural and artificial host compounds in the order of the guest they can bind.

I) Host molecules for the recognition of cations

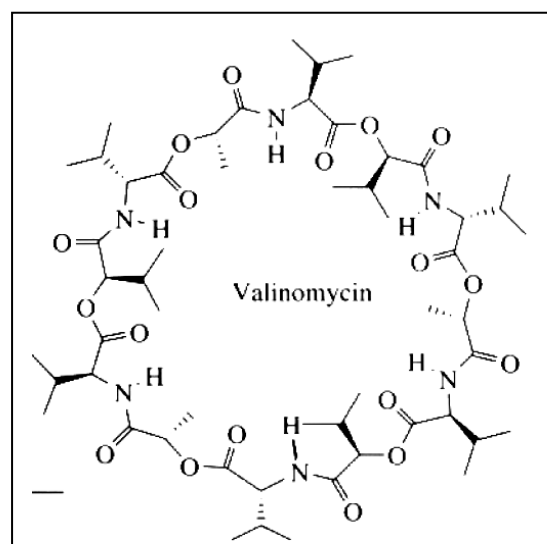
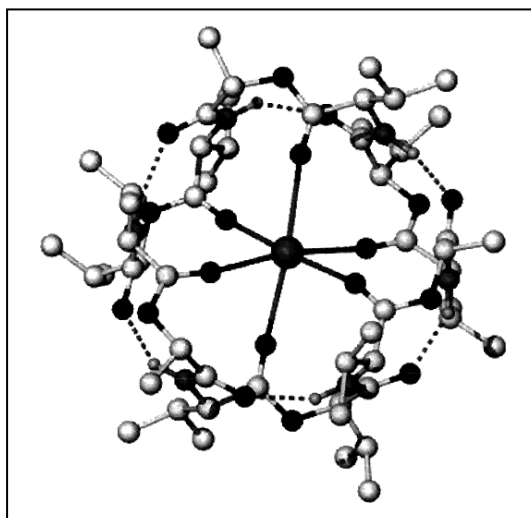
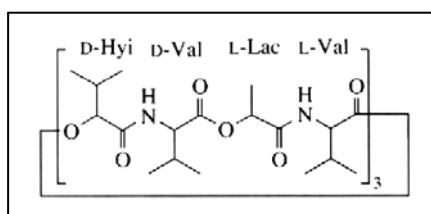
The binding of cations is, compared to other guest species, simple: Cations are spherical and bear a positive charge. Lewis-basic groups will interact with cations, bonds are not directional and selectivity can be introduced by the cavity size of a host.

Natural Ionophores

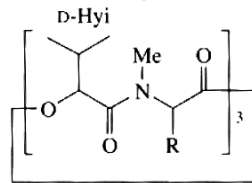
Several natural products are known that show high binding affinity and selectivity for cations.

Valinomycin group: Depsi-peptide (alternating ester, amide linkage); chirality pattern: LLDDLLDDLLDD

Isolated from *Streptomyces fulvissimus*, 1955; total synthesis: 1963. Valinomycin catalyzes the exchange of potassium and protons over a membrane without affecting the sodium ion concentration.

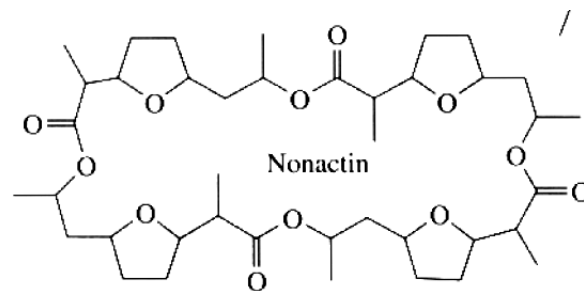


Closely related: Enniatins; smaller, made up of half the number of amino acids; transport alkali metal and alkaline earth metal cations; less selective than Valinomycin.



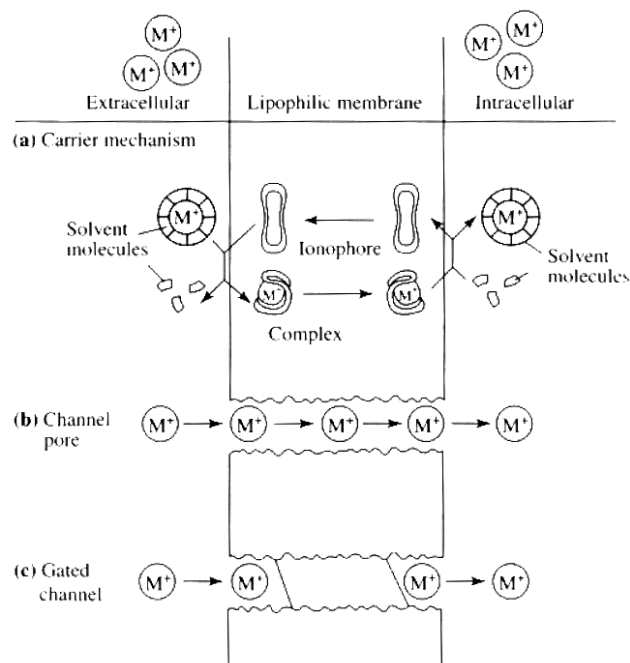
Enniatin A: R = *N*-methyl-L-isoleucine
 Enniatin B: R = *N*-methyl-L-valine
 Enniatin C: R = *N*-methyl-L-leucine
 Baeuvericin: R = *N*-methyl-L-phenylalanine

Nactin-group: Methyl-substituents in Nonactin; Ethyl- and methyl substituents in Monactin;
 Selectivity of binding: $K^+ > Rb^+ > Cs^+ \sim Na^+ > Li^+$; NH_4^+ forms most stable complexes



Other natural ionophores: cyclic peptides, Monesin poly-ether antibiotics,

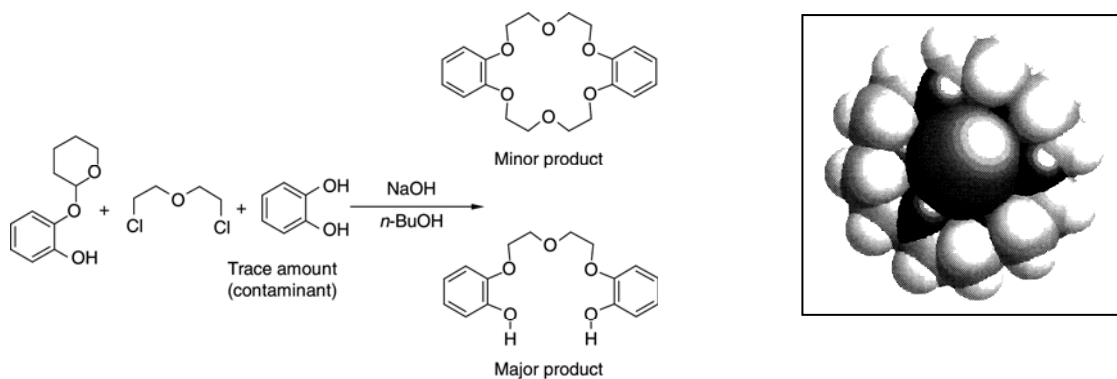
Ion-transport mechanisms through membranes



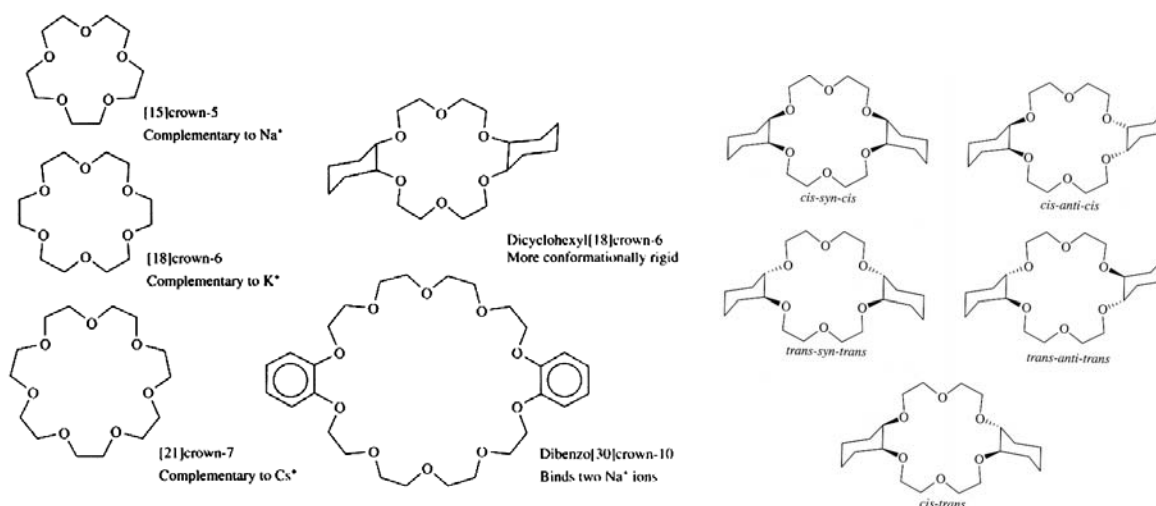
Synthetic ionophores

Crown ethers

Accidental discovery of crown ethers by Charles Pedersen in 1967:



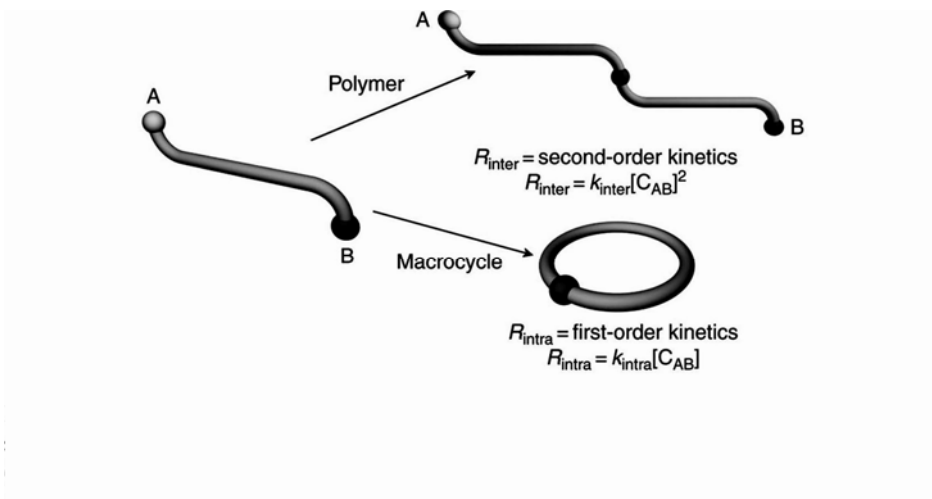
Examples of crown ether structures (left) and chiral crown ethers (right):



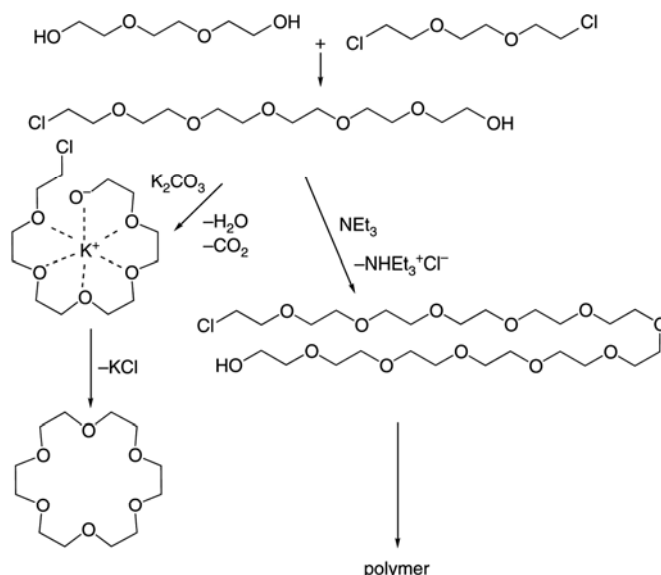
The synthesis of macrocyclic compounds requires the use of **high dilution technique**. The ring closure is performed at very low concentration, which favours the intramolecular reaction (yielding the cycle) over the intermolecular reaction (giving oligo- and polymers).

If a catalytic ring closing reaction is used, a pseudo-dilution effect can be used: The substrate is slowly added to a highly diluted solution of the catalyst.

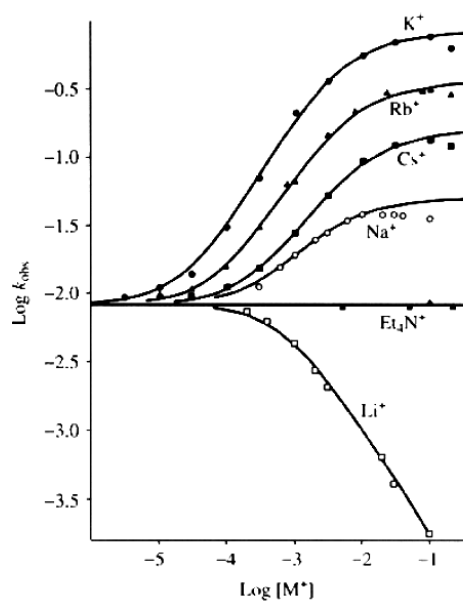
Cyclizations under high pressure allow macrocycle synthesis at higher concentrations. At high pressure the viscosity of the solvent increases, the diffusion is reduced and intramolecular reactions are favoured over intermolecular reactions.



In addition, **template effects** are used to preorganize the reacting groups.

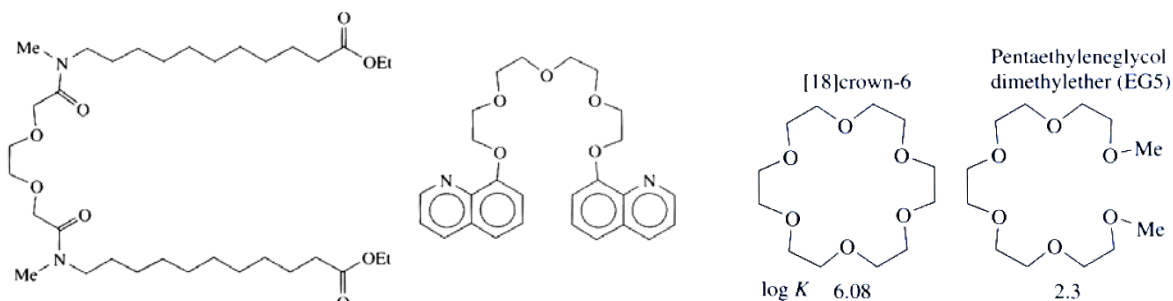


The figure shows a kinetic study of the effect of various cations on the template synthesis of benzo[18]crown-6. Clearly, potassium cations give the largest rate acceleration.



Podants

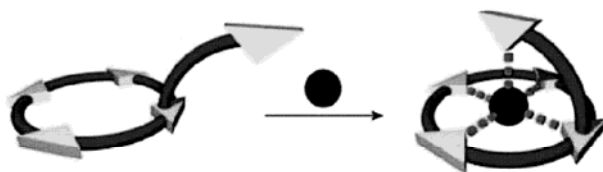
Acyclic hosts with pendant binding sites are called podants. They exhibit less cation affinity and lower binding selectivity, but they are much easier prepared. Beside 2-D podants (with two arms) there are podants known with three or even six arms.



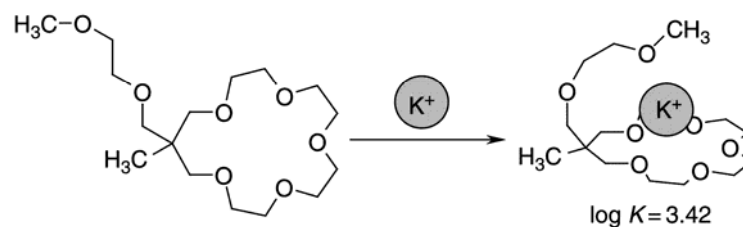
Lariat ethers

The term "lariat ether" refers to crown ether with one or more additional appendages to enhance the metal cation binding. The name comes from the Spanish word "la reata" = the rope.

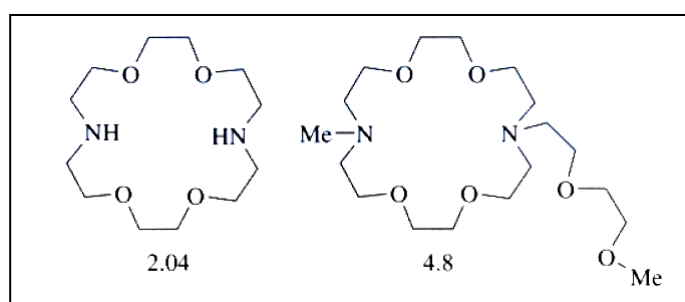
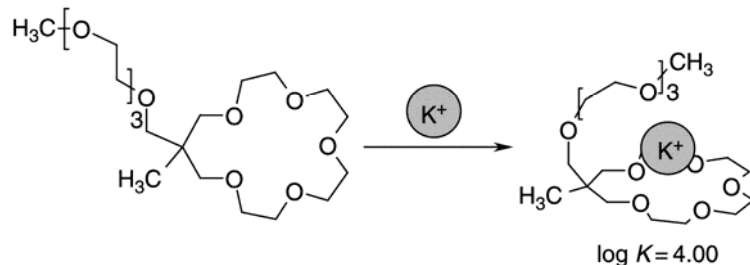
(a)



(b)



(c)



Cryptands

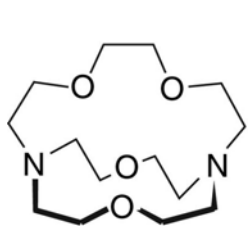
Cryptands are three dimensional analogues of crown ethers. The compounds were first introduced by J.-M. Lehn. The [2.2.2]cryptand is sold commercially under the name kryptofix®. The ionophore binds, like [18]crown-6, potassium ion, but the affinity is by 10^4 higher in methanol. Synthesis of cryptands requires more steps.

Binding constants for [2.2.2]:

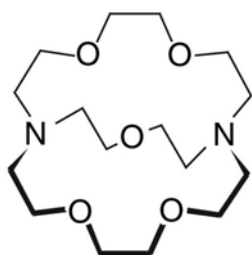
In water: $\lg K_{Na^+} = 3.9$; $\lg K_{K^+} = 5.4$

In MeOH:H₂O, 95:5: $\lg K_{Na^+} = 7.2$; $\lg K_{K^+} = 9.7$

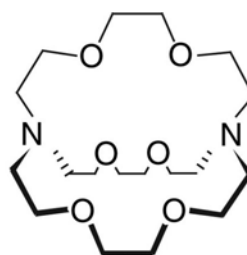
Selectivity $K^+/Na^+ \sim 30$



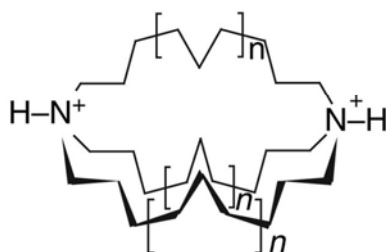
[2.1.1] Cryptand



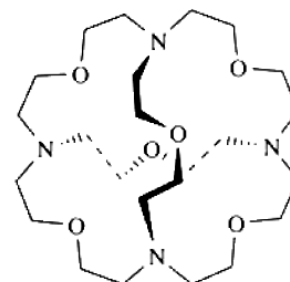
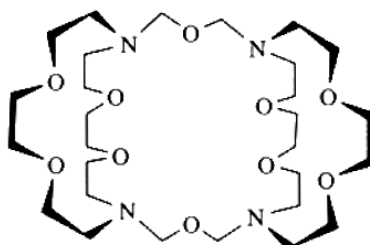
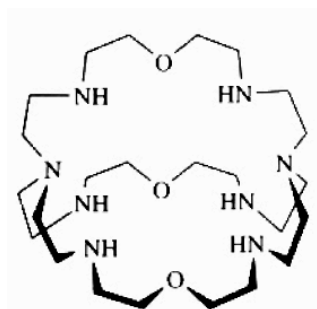
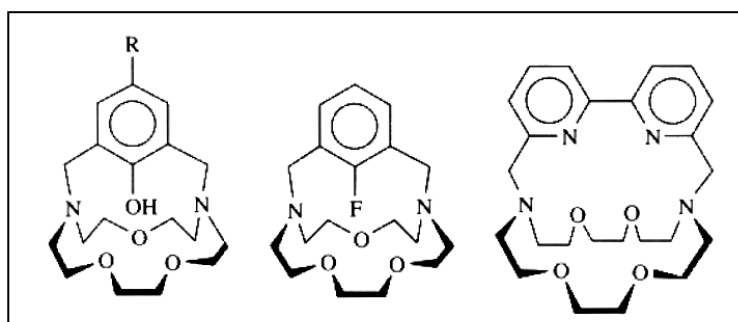
[2.2.1] Cryptand



[2.2.2] Cryptand

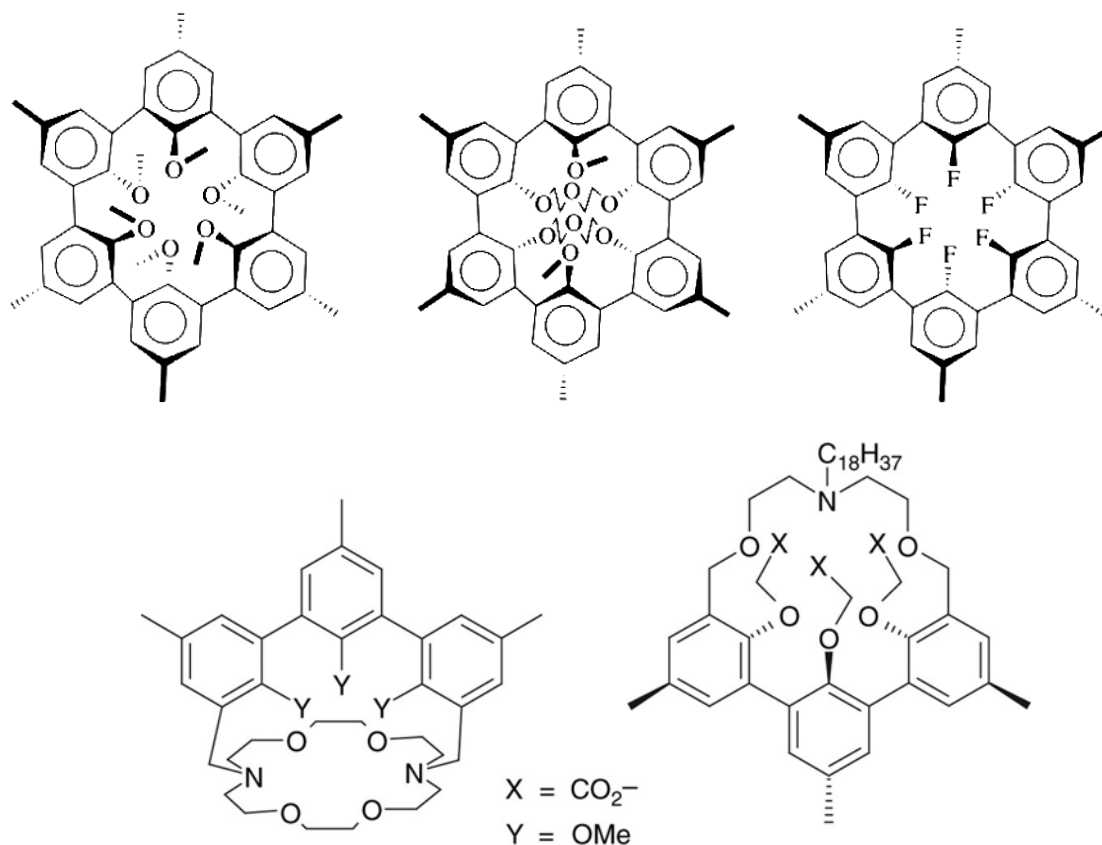


Katapinands

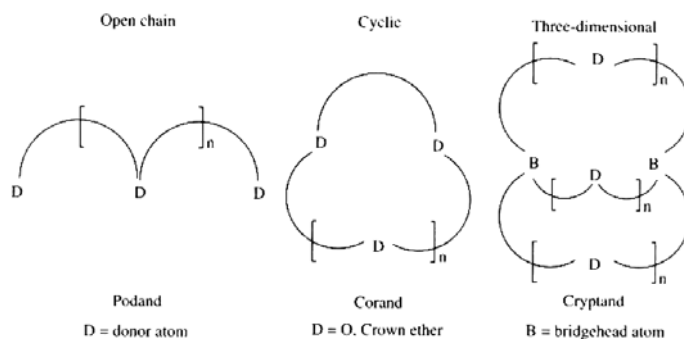


Spherands

Spherands are another class of host compounds. Compared to crown ether and cryptands, which have a rather flexible structure in solution, spherands are rigid. The left compound shows a high binding affinity to lithium ions. All other cations are too big to fit in the cavity. The fluoro derivative does not display any metal ion binding properties. Hybrid compounds consisting of a half-spherand and a crown ether part have been prepared.

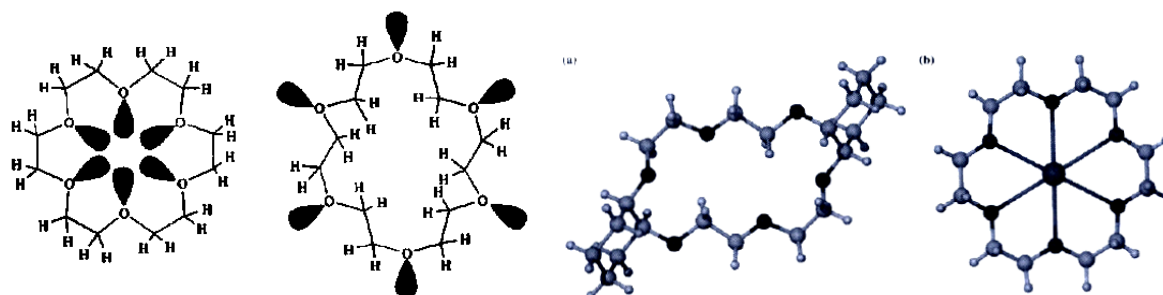


In general, all crown ether related host compounds can be categorized in three classes.



Comparison of solution binding properties of crown compounds

Crown ether, such as [18]crown-6, are soluble in a wide range of solvents in the absence of guests. Their conformation depends on the polarity of the solvent: In non-polar organic solvents, such as dichloromethane, the crown ether behaves like a “droplet of water in oil”, while in water the structure resembles a “droplet of oil in water”.

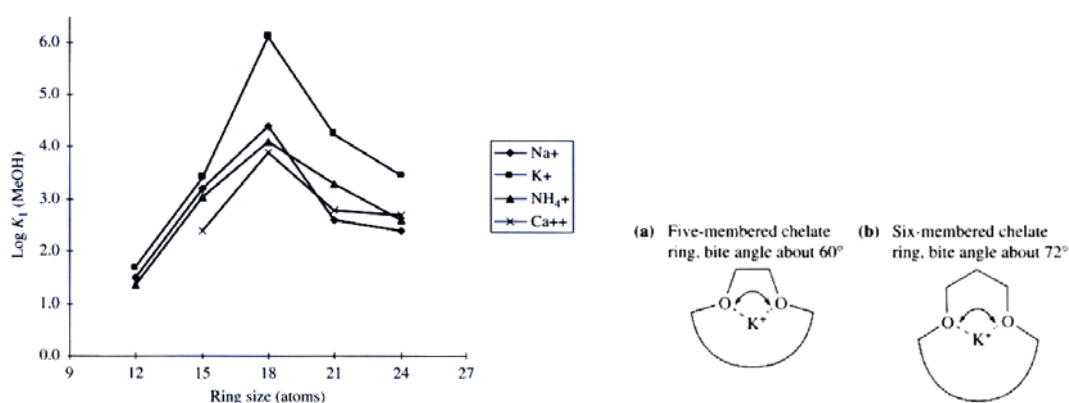


Left: Conformation of a crown ether in a) a non-polar organic solvent, b) water. Right: Structure of crown ethers in the solid state in the a) absence or b) presence of a cationic guest.

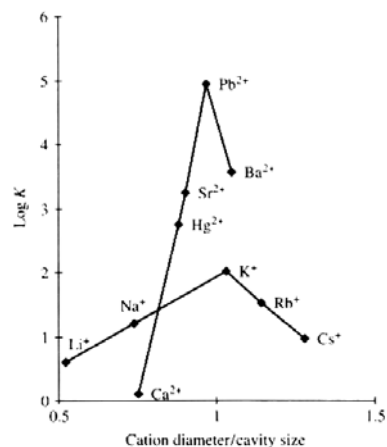
The amphoteric character of crown ethers can be used to transport cations into organic solvents. In particular, trinitrophenol salts (picrates) have been used to visualize the process. The crown ether cation binding has been used for phase transfer catalysis and to generate “naked” anions for synthesis, which are more reactive than ion pairs.

The prediction of binding selectivities is always difficult. However, in the case of crown ethers a rational for cation binding selectivities can be derived. The binding affinity of a crown ether to a cation depends on the

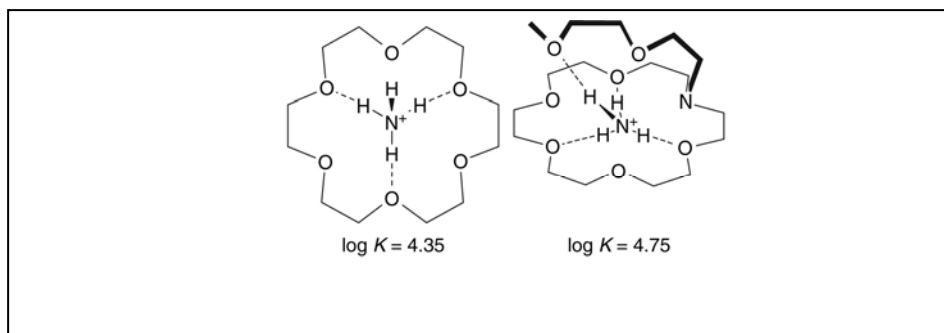
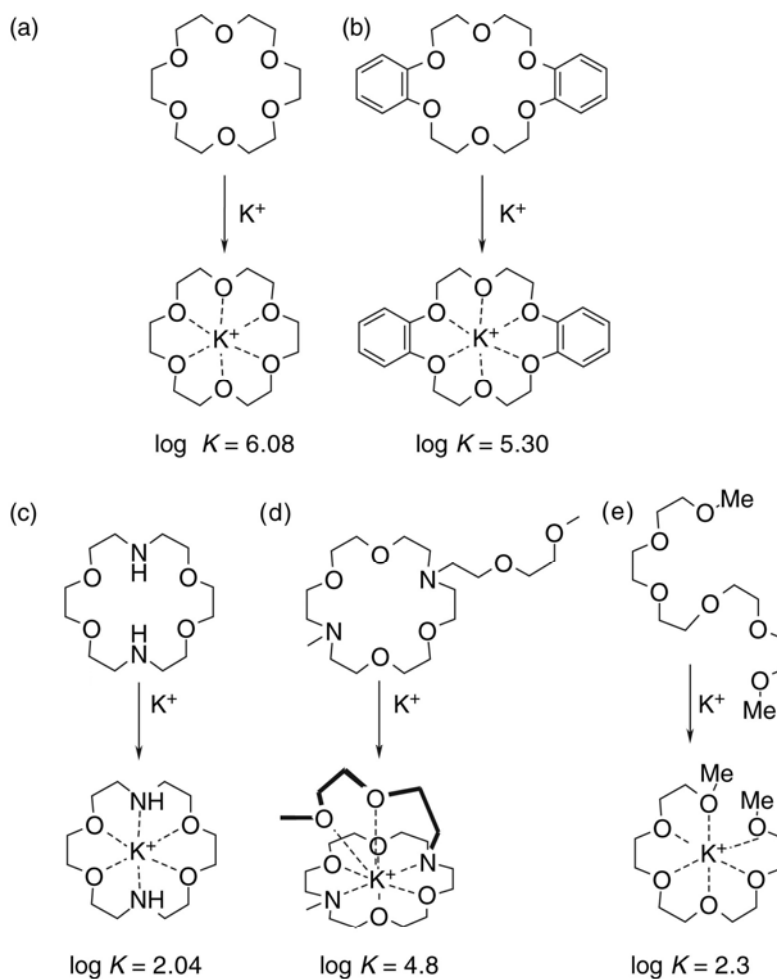
- size match between the host cavity and the guest cation
- the number of donor atoms (the more interactions, the better; gives rise to the plateau selectivity observed for most cations with larger crown ethers)
- solvation of cation and anion (a larger cation or a cation with lower charge has a lower free solvation energy: $K^+ < Na^+ < Ca^{2+}$)
- Chelate ring size (ligand bite angle): Smaller cations (e.g. Li^+) cannot bridge the chelate.



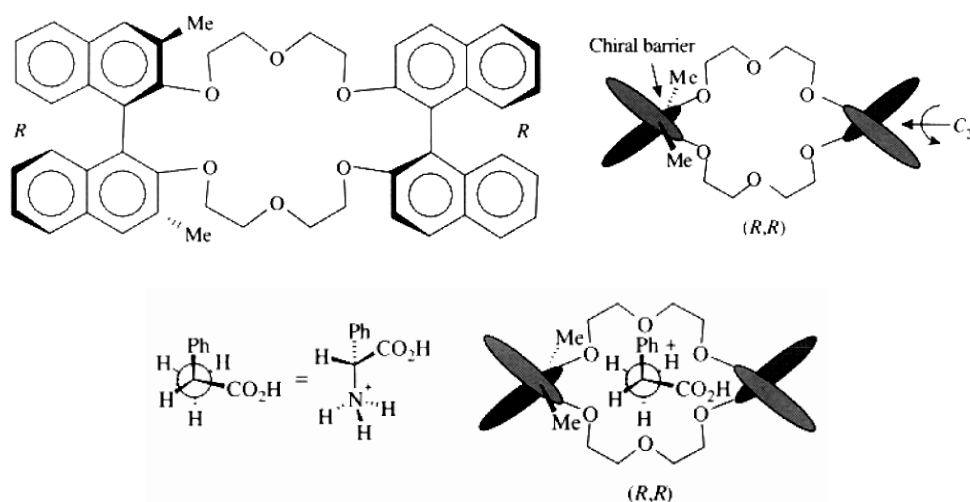
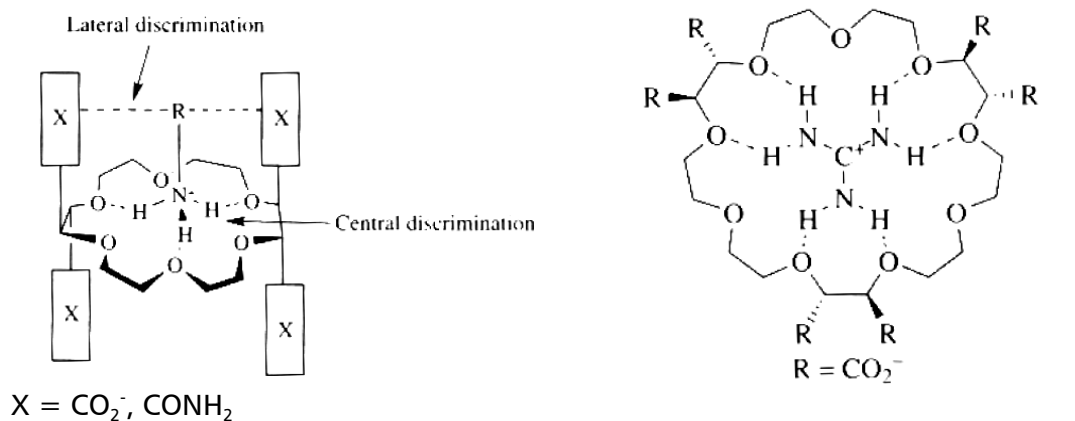
For well-matched cations and cavities (cation diameter/cavity size = 1) and in the absence of large hydration energies, the formal positive charge of a cation is a dominant factor of the binding.



Potassium ion binding affinities of different crown ether types (MeOH, 25°C).

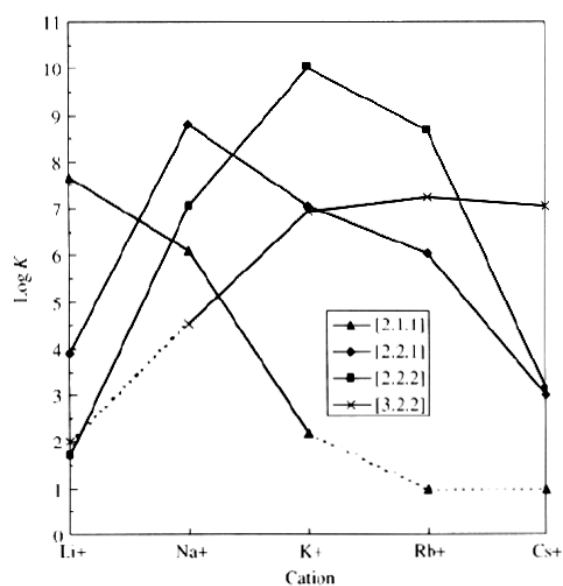


The size of ammonium and potassium cations is similar. Both cations are bound by the same crown ethers. Ammonium ions are found in many compounds of biological origin, e.g. amino acids. Therefore attempts have been made to distinguish chiral ammonium ions by chiral crown ethers.



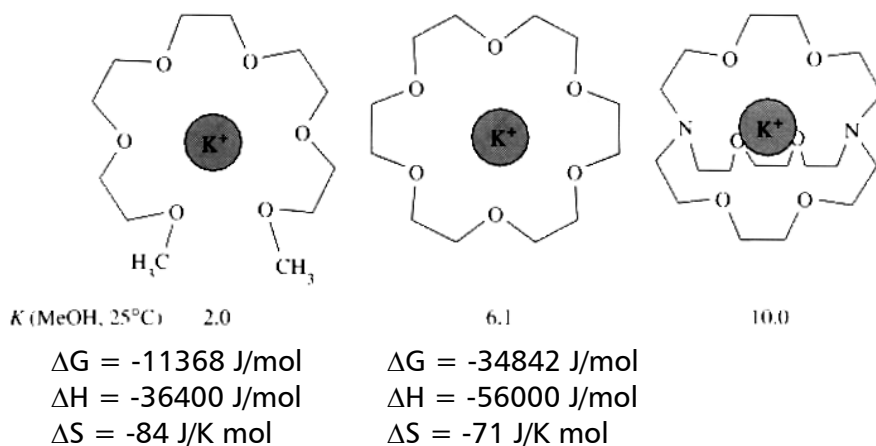
In contrast to crown ether, the three dimensional cryptands display peak selectivity in cation binding. The cavities are more rigid and unable to adapt to bind cations that are too small or too large for the cavity.

Cation binding of several cryptands:

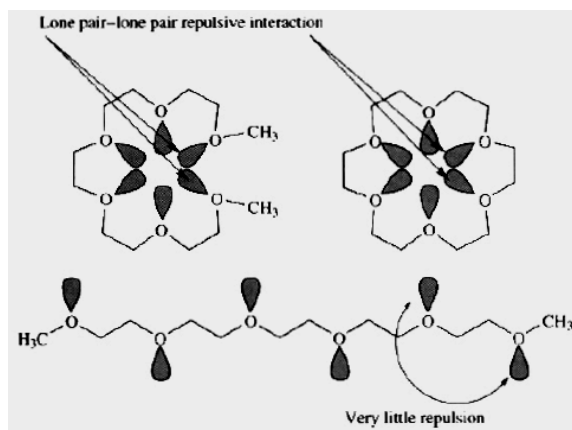


The macrocyclic and the macrobicyclic effect

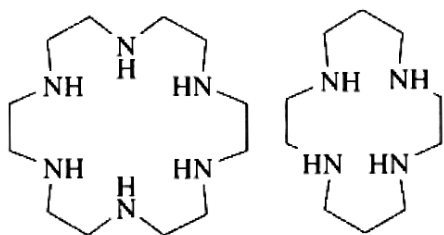
Macrocyclic and macrobicyclic host compounds bind cations stronger. Both, enthalpic and entropic effects contribute to this effect. The macrocycle is more preorganized for guest binding; the entropic "price" has been already paid during synthesis. The binding sites are oriented towards the guest molecule.



Type of complex	K (MeOH)	Effect
Podate	$10^2 - 10^4$	Chelate
Corate	$10^4 - 10^6$	Macrocyclic
Cryptate	$10^6 - 10^{10}$	Macrobicyclic

**Heterocrown compounds**

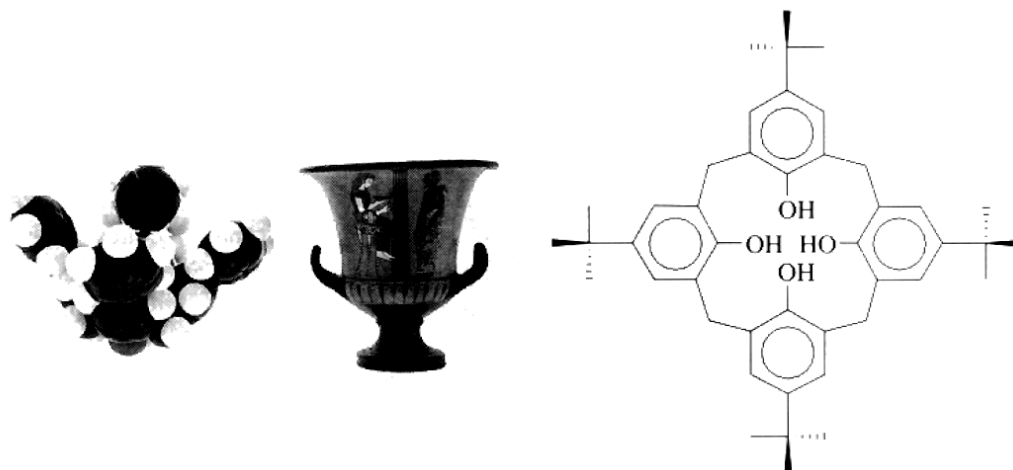
The complete or partial exchange of the oxygen atoms of a crown ether or cryptand changes the binding properties of the host compound dramatically. According to Pearson's principle of hard and soft acids and bases the binding selectivity of such compounds favours the coordination of soft transition metal cations, such as silver(I), copper(II) etc. The compounds find use to remove traces of heavy metal cations from solutions or in metal refining.



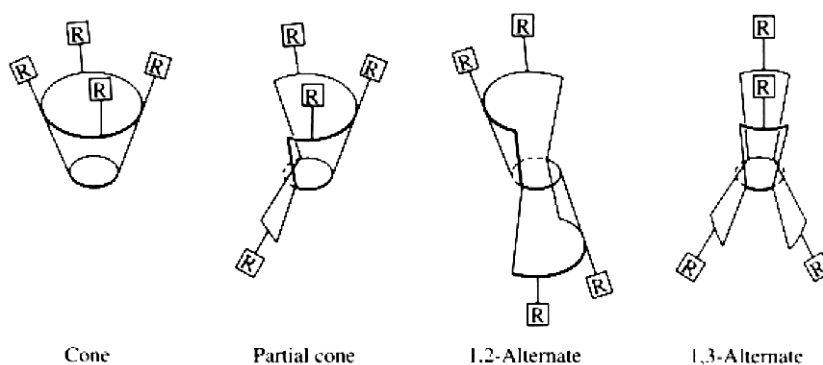
Examples of aza-crown compounds.

Calixarenes

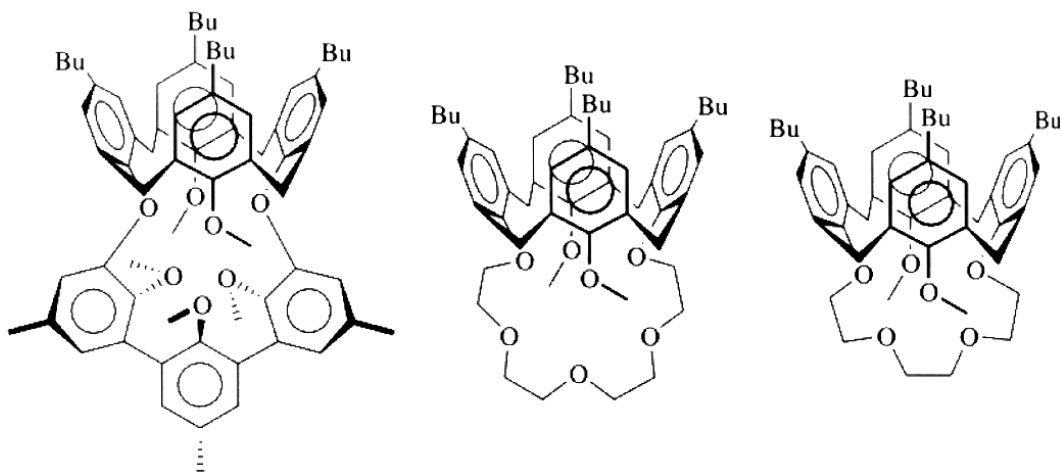
Calixarenes are formed from the controlled condensation of substituted phenols with formaldehyde. The compound's shape resembles a calyx crater vase. The parent systems can be functionalized by classic reactions of aromatic chemistry and many derivatives have been prepared. With suitable functional groups they are able to selectively bind cations, e.g. potassium or sodium. Some derivatives have been made for specific binding of radioactive cations from nuclear waste.



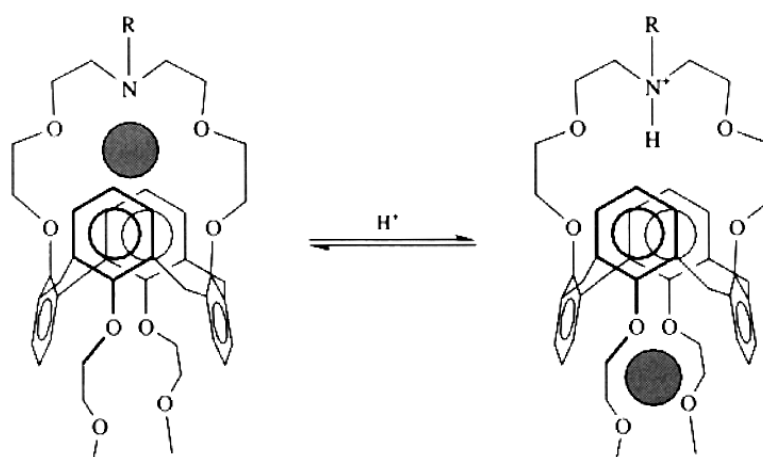
Calixarenes have specific conformations depending on the orientation of the arene rings. If substituents (R) are large enough, the conformers are stable and can be separated. The properties of the conformers in molecular recognition are different and this is used to create specific host compounds.



Calixarene – crown hybrid compounds can have high cation binding selectivities. The large cavity can be used to bind radioactive metal cations and extract them from contaminated waste water.

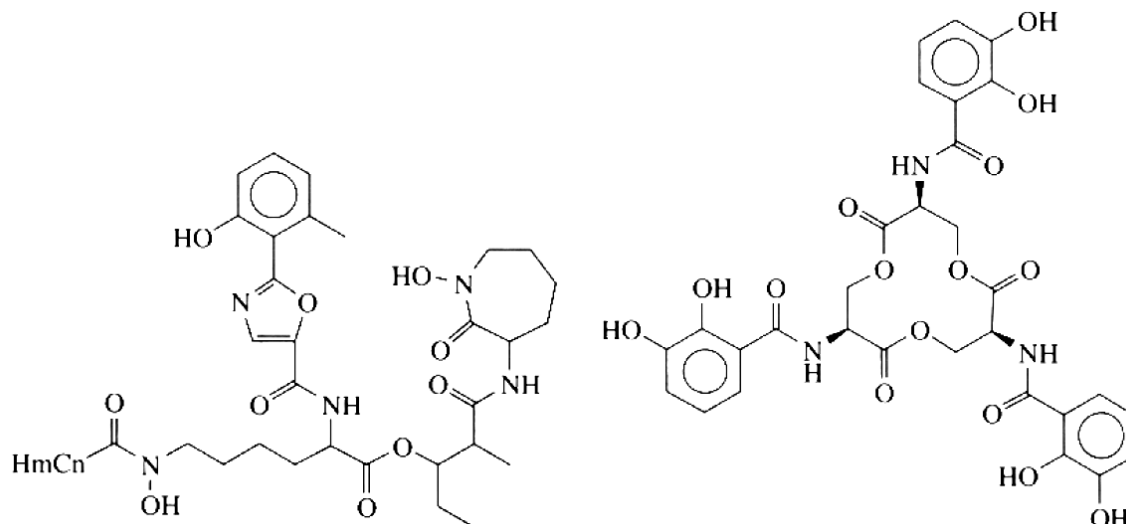


Calixarenes have been used to build molecular machines. Here is an example of a molecular syringe that pumps metal cations with the help of a proton from the lower binding site to the upper binding site.



Siderophores

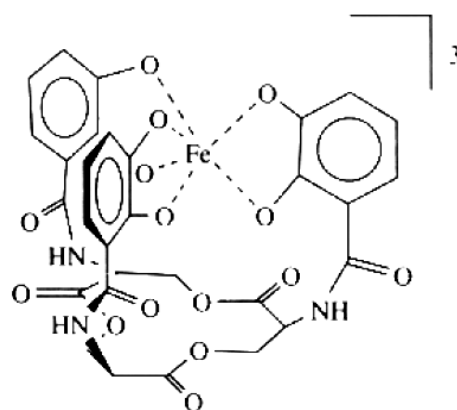
Iron is a crucial element for bacteria and all higher organisms. Although iron is an abundant element, its bioavailability is very poor. Most iron is found as iron oxides (rust) and not water soluble. The solubility of Fe(III)hydrate at pH 7.4 is about 10^{-18} mol/dm³. To collect and store iron, nature invented siderophores, which are specific ionophores for iron binding. The compounds are tri-armed podants with specific binding sites for iron. Enterobactin is the most typical example of a siderophore. Several synthetic systems have been prepared.



Myobactin, N > 12

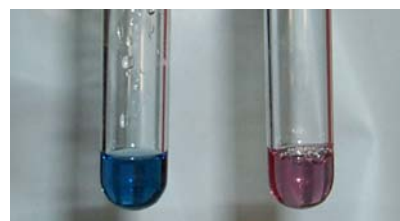
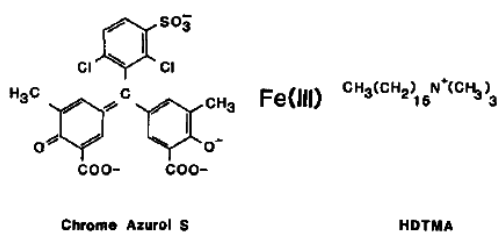
Enterobactin

Structure of Fe(III) bound in enterobactin.



Siderophore bacteria

The change in color of the blue dye- chrome azurol sulphonate (CAS) assay solution to orange indicates the presence of siderophore (Iron chelating compounds) production by a marine bacterium. The indicator used, a complex of unknown structure, comprised of chrome azurol S, iron(III), and HDTMA, has an extinction coefficient of approximately $100.000 \text{ M}^{-1} \text{ cm}^{-1}$ at 630 nm and pH 5.6.

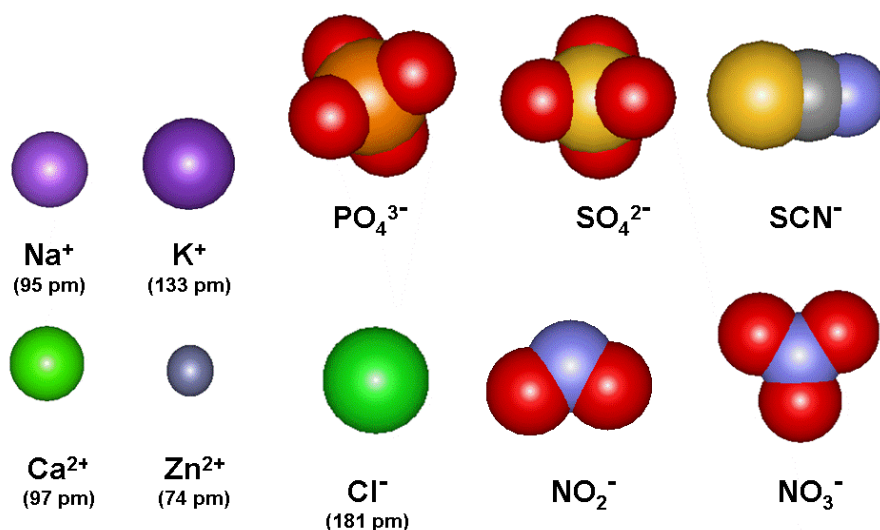


Handout continues with SupraChem-2, binding of anions.

Binding of Anions

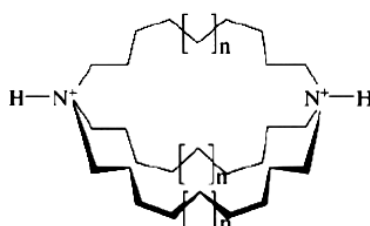
The selective binding of anions by synthetic receptors is more difficult, because

- anions are larger than cations; a larger cavity is required for binding and the charge is distributed over a larger area leading to weaker forces
- the receptor binding sites must have a positive charge; the number of functional groups having a positive charge is far smaller than functional groups with negative charge
- anions like phosphate, sulphate or nitrate are not spherical. They have a certain geometry and a receptor must have the complementary shape for selective binding
- many anions are basic; dependent on the pH of the solution the anion is more or less protonated, which changes the hydrogen bond binding pattern
- in comparison to cations of similar size, anions have high free energies of solvation; host compounds for anions must compete more effectively with the surrounding medium.



Hofmeister Serie: $\text{ClO}_4^- > \text{SCN}^- > \text{I}^- > \text{NO}_3^- > \text{Br}^- > \text{Cl}^- > \text{HCO}_3^- \sim \text{CH}_3\text{CO}_2^- \sim \text{SO}_4^{2-} \sim \text{HPO}_4^{2-}$

The first example (1968) of an anion receptor was 1,11-diazabicyclo[9.9.9]nonacosane ($n=1$). Such compounds are called katapinands; larger and smaller derivatives with $n = 0$ and $n = 2$ are known. The name comes from the Greek word katapino, meaning swallow up or engulf.

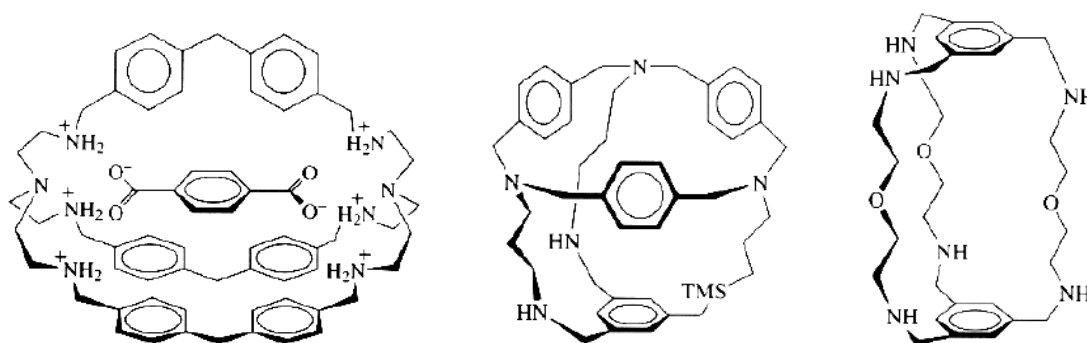


The binding of anions can occur in several ways:

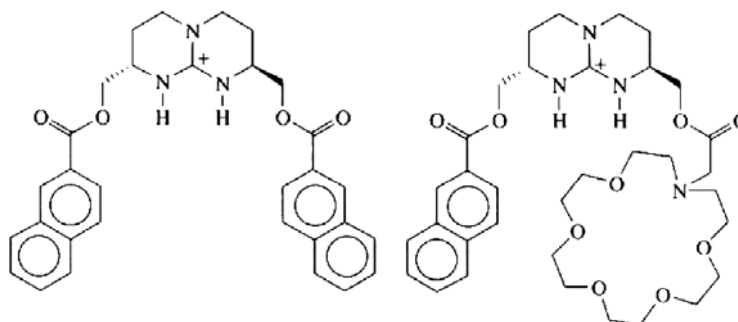
- 1) Electrostatic interaction, e.g. of a tetraalkyl ammonium ion with a chloride anion
- 2) Electrostatic + hydrogen bond.
Example: urea + carboxylate anion
Salt bridge: guanidinium cation + carboxylate anion
- 3) Reversible coordinative bond, e.g. metal complex with vacant coordination site + basic, anionic ligand filling this gap.

Many enzymes and biological receptors bind anions. Typical binding situations involve the arginine side chain (binding situation 2) or coordination to a zinc ion (binding situation 3).

Many two and three dimensional anion receptors have been prepared and tested. The following examples are cyclophanes (compounds containing a bridged aromatic ring) with protonated nitrogen atoms as binding sites. Anionic guest accommodated by these receptors are the terphthalate dianion (left); the cyclophanes shown on the right bind pH dependent to a variety of mono- and dianions with $\lg K$ values of 2.5 – 6.

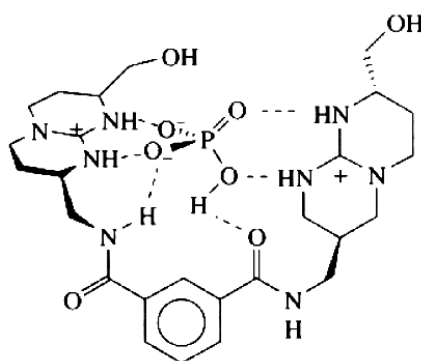


The guanidinium ion has proved to be a very popular motif in the design of anion complexation hosts. If combined with aromatic groups and azacrowns, the simultaneous recognition of the ammonium cation, the carboxylate anion and the side chain functional group of amino acids becomes possible. The shown host compounds are selective for the binding of amino acids with aromatic side chains (tryptophan, phenylalanine) and allow stereodifferentiation between amino acid stereo isomers (enantioselective recognition).

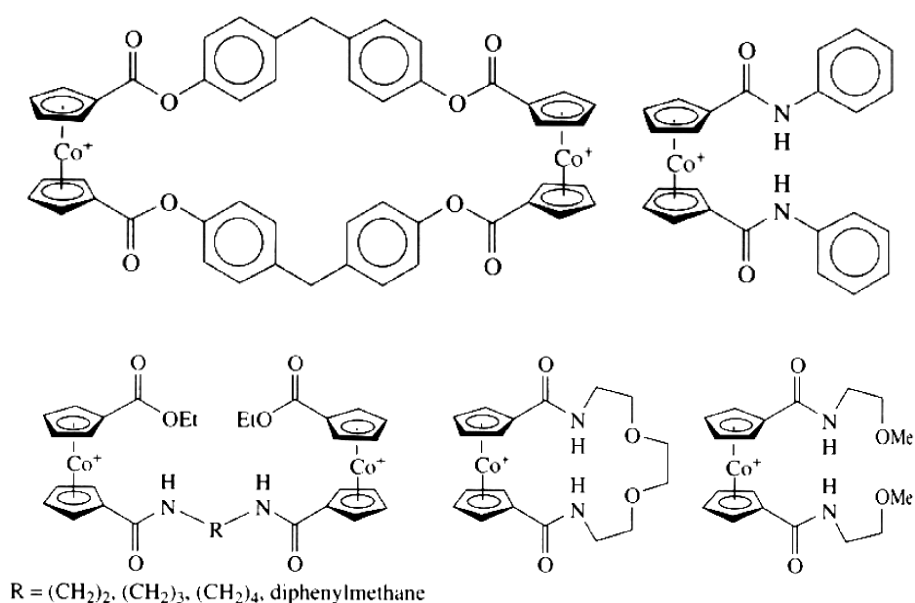




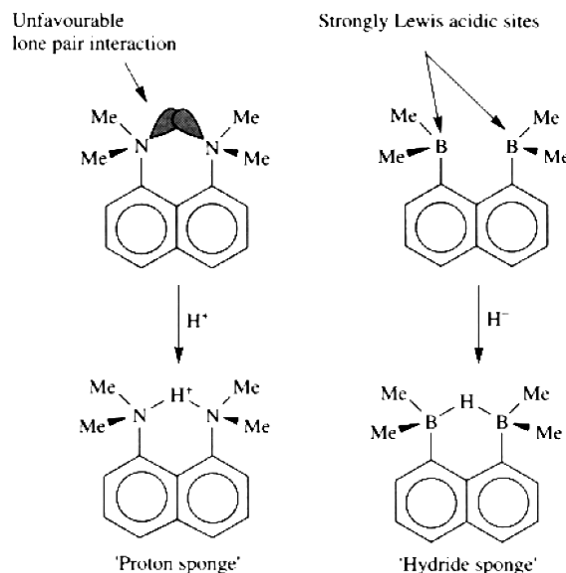
Bis-guanidinium receptors allow the selective recognition of tetrahedral oxoanions, like phosphate. The host type has been used to bind even complex pyrophosphates in water.



Another interesting class of anion receptors are organometallic receptors. A stable organometallic group, like bis(cobaltocenium), is introduced into a macrocycle or a cyclophane. The organometallic group provides the positive charge necessary for anion binding, while the macrocycle or additional functional groups control the selectivity. The presence or absence of a guest anion is easily monitored by cyclic voltammetry of the redox active metal centers. The redox potential changes in the presence of the bound anion, which leads to a shift of the cyclic voltammetric waves.

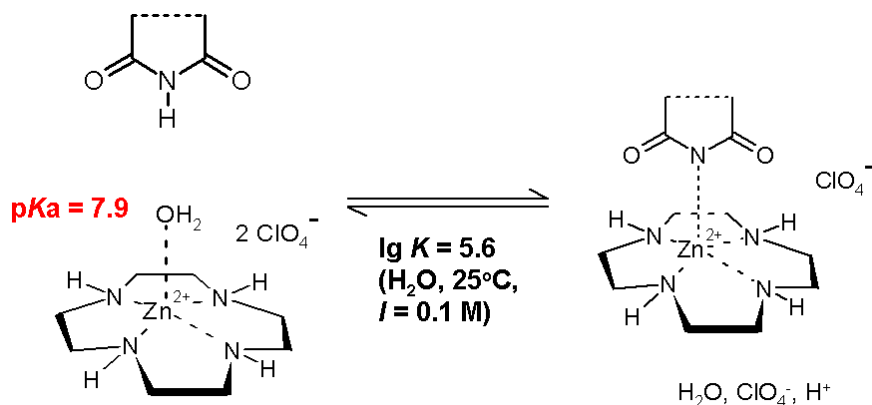


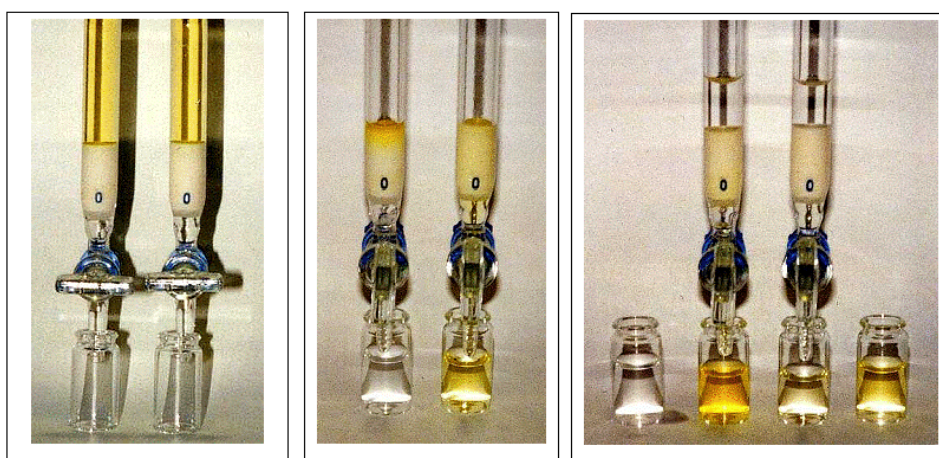
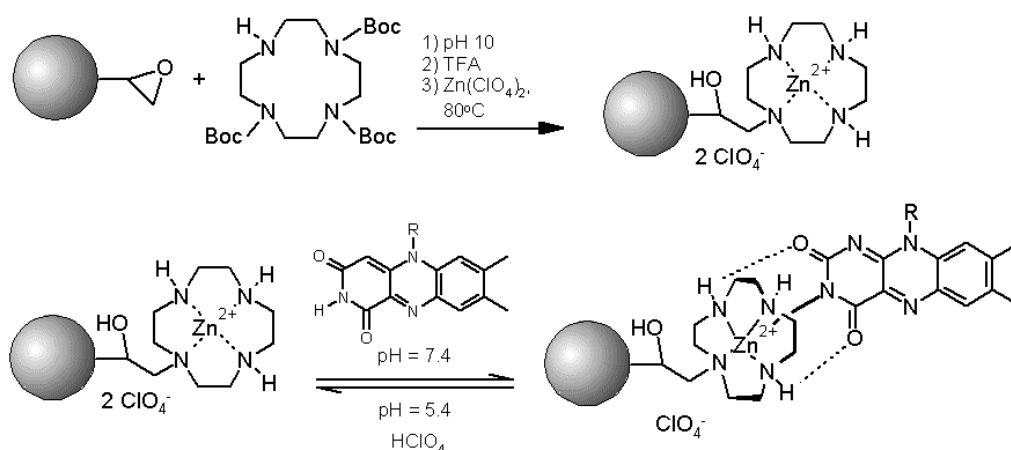
The smallest anion for binding is the hydride anion. To provide a receptor for this guest the well known concept of a proton sponge for proton binding was converted by Howard Katz into a hydride sponge. Two strongly Lewis acidic boron binding sites hold the hydride in an asymmetric three-centre, two electron bond.



An example for the use of reversible coordinative bonds for anion binding uses zinc(II) complexes of azamacrocycles. The zinc ion does not fit into the cavity of the macrocycle, it is a little too large. Therefore the coordinating nitrogen atom orbital cannot overlap ideally with the zinc d-orbitals. This leads to a non-compensated charge on the zinc ion, leading to a strong Lewis acid in the complex (pK_a of zinc ions in water ~ 10 ; zinc complexes in the azamacrocycle ~ 8). The complexation of the zinc ion in the azamacrocycle is high with complexation constants of about $\lg K = 18$. The fifth coordination site on zinc remains open and is occupied by water or by an anionic guest, such as an imide or phosphate anion. Note: The equilibrium is pH dependent. The given equilibrium constant is the anion affinity constant and corresponds to the case of a completely deprotonated imide.

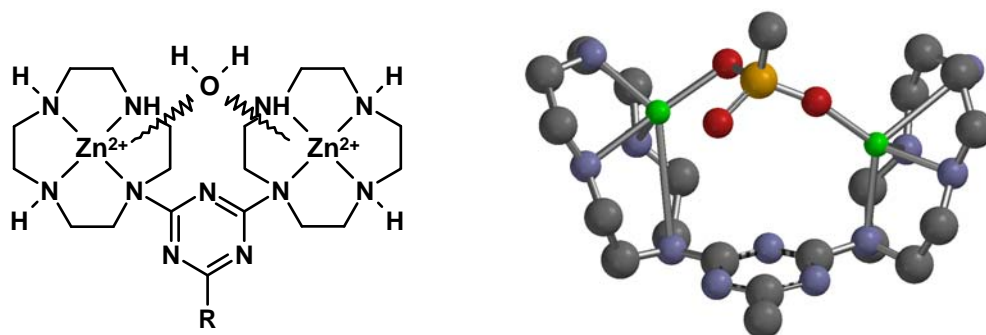
The metal complex can be immobilized on a polymer. The metal complex binding sites on the material reversibly coordinates vitamin B₂, which has an imide functional group. The vitamin is bound to the polymer at neutral pH and released at pH 5.

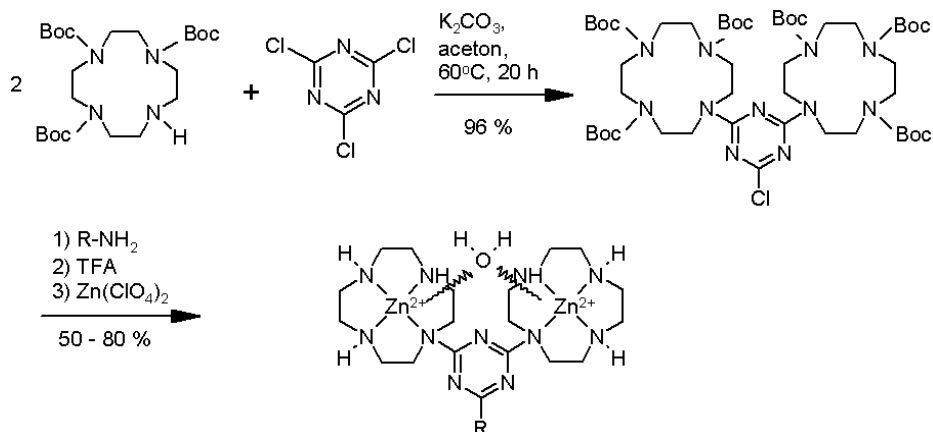




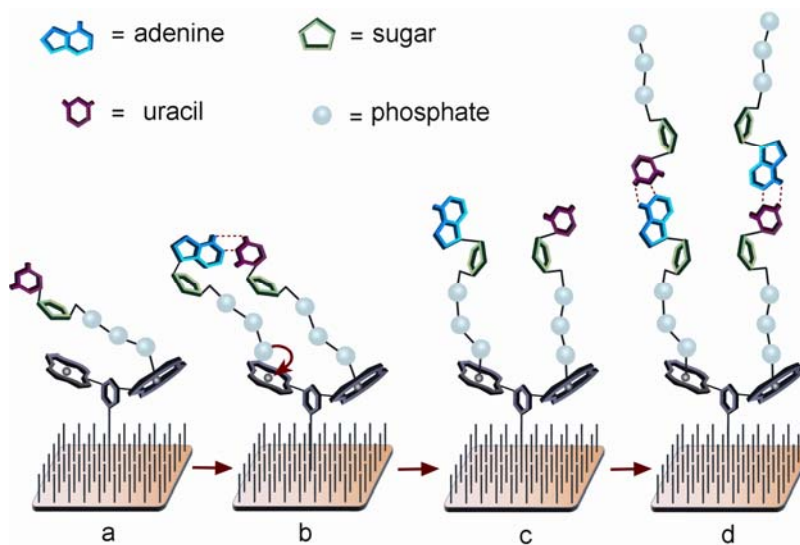
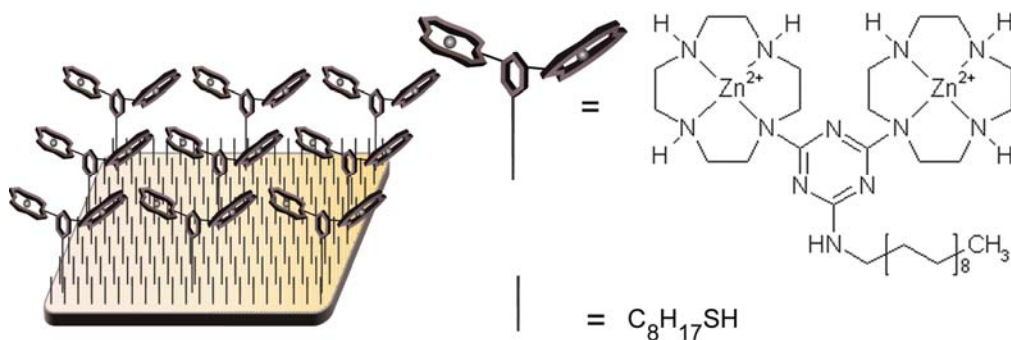
The left column contains the polymer with zinc-cyclen binding sites, and the right column contains a polymer without binding sites. The yellow solution is a 10^{-5} mol/L aqueous solution of riboflavin (vitamin B2). The left column absorbs all riboflavin (picture in the middle); if rinsed with an acidic buffer the riboflavin is eluted from the column.

The second example of coordinative anion binding uses a related dinuclear binding site. Two zinc-cyclen complexes are covalently connected via a triazine heteroaromatic linker. A water molecule or a phosphate anion can be bound in the cavity formed by the two metal complexes. The synthesis of the binding site starts from threefold Boc-protected cyclen. Nucleophilic aromatic substitution provides the ligand system that is deprotected and reacts with zinc salts.



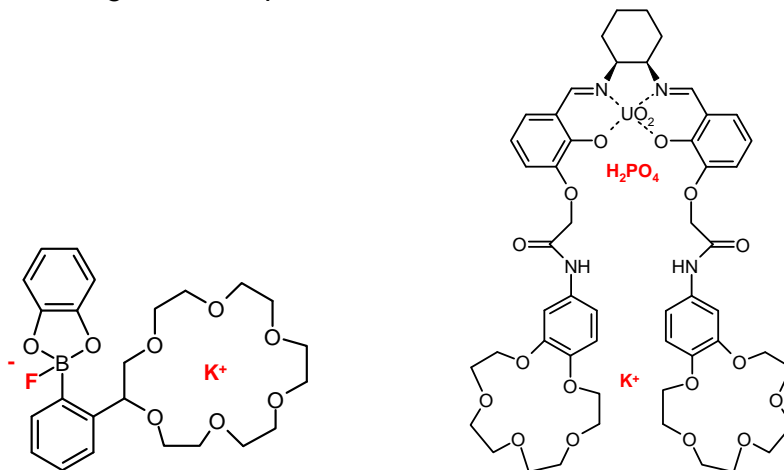


The binding site can be immobilized on a hydrophobic surface if R is a long alkyl chain. The surface now covered with metal complex binding sites shows high affinity for phosphate ions. Particularly interesting is the assembly of nucleotide triphosphates on this surface: If solutions of the complementary base pairs are alternatingly added to the surface, a double layer of DNA base pairs is formed.



Simultaneous binding of anions and cations

Combined hosts for simultaneous anion and cation binding have been designed (selective salt binding). Such compounds can select a given pair of ions from a mixture of salts. This is particularly interesting if the receptor is used as a membrane carrier.



Examples of salt receptors

Membrane transport

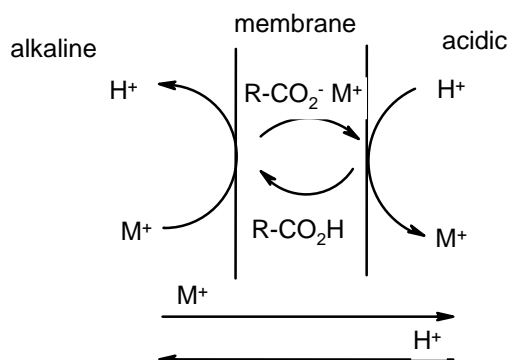
The transport of ions across membranes is of importance in biology (e.g. nervous system) and chemistry (desalting of sea water). The ion transported can be carrier mediated or through ion channels.

Carrier mediated transport is molecular catalysis; the carrier molecule catalyzes the transport. The ion transport is described as the ion flux: $J = \text{mol}/\text{cm}^2 \cdot \text{s}$ and influenced by the following parameters: concentration gradient, binding and decomplexation of the ions by the carrier, diffusion coefficient in the membrane, viscosity of the membrane, and phase transfer of particles. *Criteria for carrier design*: High binding selectivity, moderate affinity, fast rates of complexation and decomplexation, hydrophobic (to stay in the membrane).

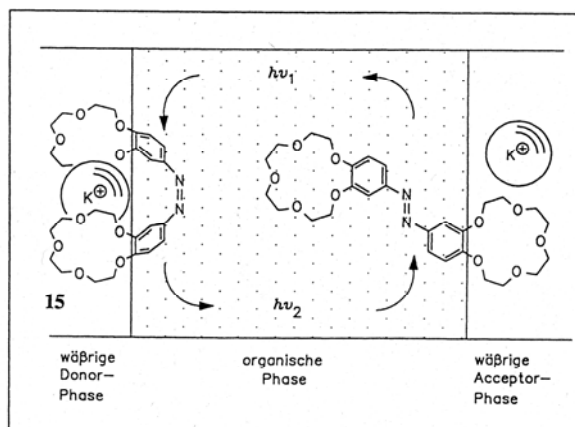
Membrane materials: Organic solvent, supported liquid membrane, polymer membranes.

While cation, anion and salt transport need a concentration gradient, coupled transport mechanisms (proton, light, redox) can be used to pump ions against a gradient.

Proton-coupled transport:



Light-coupled transport:



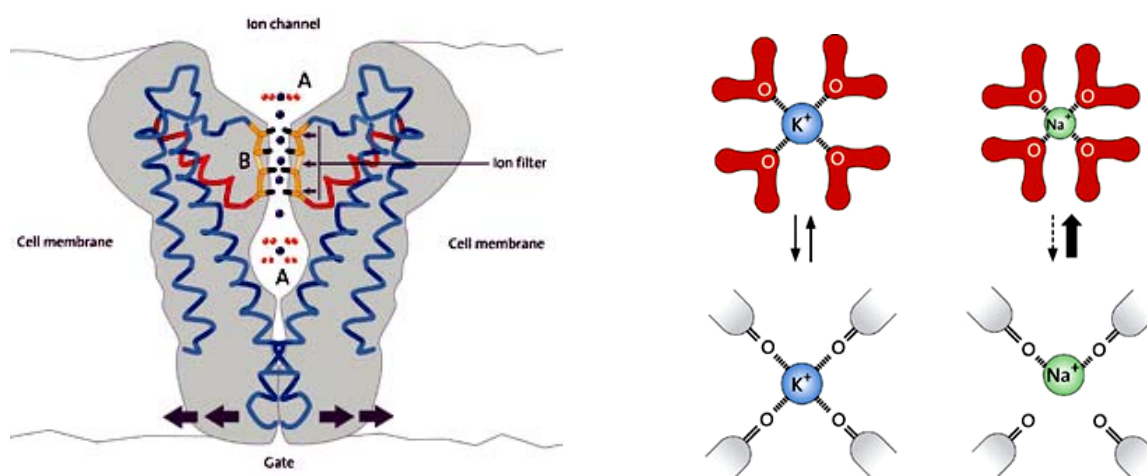
Natural and artificial ion channels

The presence of ion channels in biology has been known for a long time. Ion channels are able to admit one ion type selectively, but not another. It is possible for the channels to open and shut and sometimes to conduct ions in one direction only. How this molecular machinery really works remained a mystery until recently.

During the 1970s it was shown that the ion channels were able to admit only certain ions, because they are equipped with some kind of "ion filter". Of particular interest was the finding of channels that admit potassium ions, but not sodium ions – even though the sodium ion is smaller than the potassium ion. It was suspected that oxygen atoms in the transport protein play an important role as "substitutes" for the water molecules with which the potassium ion surrounds itself in a solution of water and from which it must free itself during entry to the channel. Only the ion can pass, not its hydrated counterpart.

In 1998 MacKinnon determined the first high-resolution X-ray structure of an ion channel, called KcsA, from the bacterium *Streptomyces lividans*. MacKinnon revealed for the first time how an ion channel functions at the atomic level: The ion channel permits passage of potassium ions but not sodium ions. The oxygen atoms of the ion filter form an environment very similar to the water environment outside the filter. Both hydrates cations, potassium and sodium, are too large to pass through the ion channel.

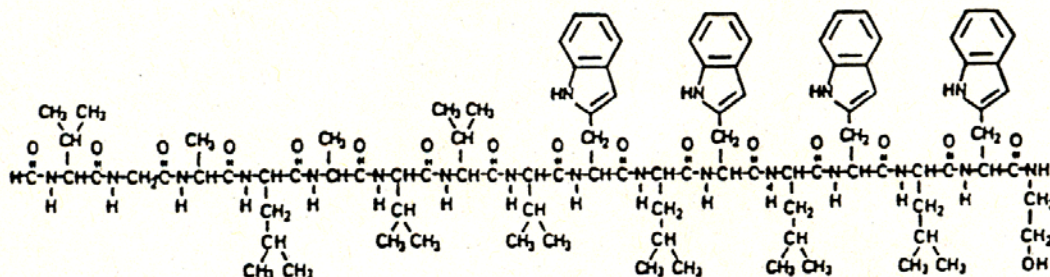
The distance between the potassium ion and the oxygen atoms of the amino acids of in the filter region is the same as that between the potassium ion and the oxygen atoms in the water molecules surrounding the potassium ion when it is hydrated in aqueous solution outside the filter. Thus it can slide through the filter unopposed. However, the sodium ion, which is smaller than the potassium ion, can *not* pass through the channel. This is because it does not fit between the oxygen atoms in the filter and therefore remains in the water solution. The ability of the channel to strip the potassium ion of its water and allow it to pass at no cost in energy is a kind of selective catalyzed ion transport.



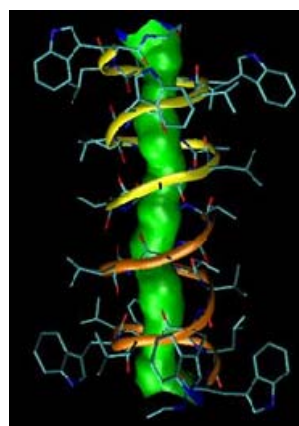
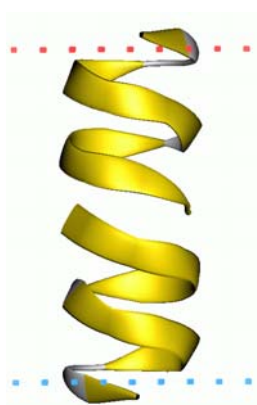
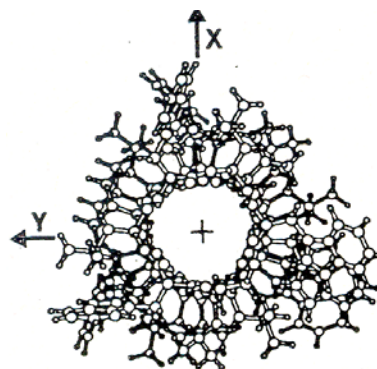
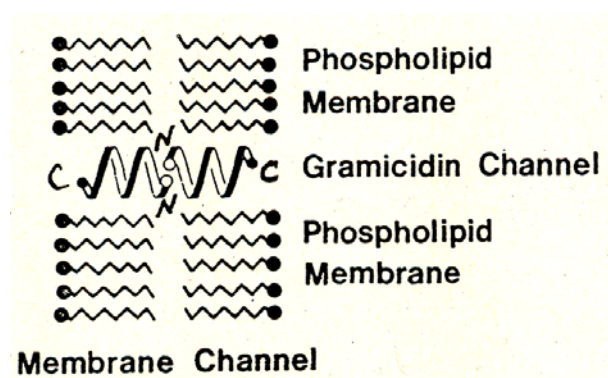
Left: Schematic structure of the ion channel; right top: Coordination of potassium and sodium outside the ion filter; right bottom: Coordination of potassium and sodium inside the ion filter

Gramicidin A was the first antibiotic clinically used. It is too toxic for human use, but still applied in veterinary medicine. The molecule is a peptide with the following structure:

HCO-NH-L-Val-Gly-L-Ala-D-Leu-L-Ala-D-Val-L-Val-D-Val-L-Trp-D-Leu-L-Trp-D-Leu-L-Trp-D-Leu-L-Trp-Co-NHCH₂-CH₂OH



The structure of the channel formed by two of the peptides in the membrane is a head to head dimer. The channel is 32 Å long and has a diameter of 6.8 Å. Cations like H⁺, K⁺ and Na⁺ are transported through the channel with a turnover of about 10⁷ ions per second. This transport speed is much higher as observed with carrier mediated transports.

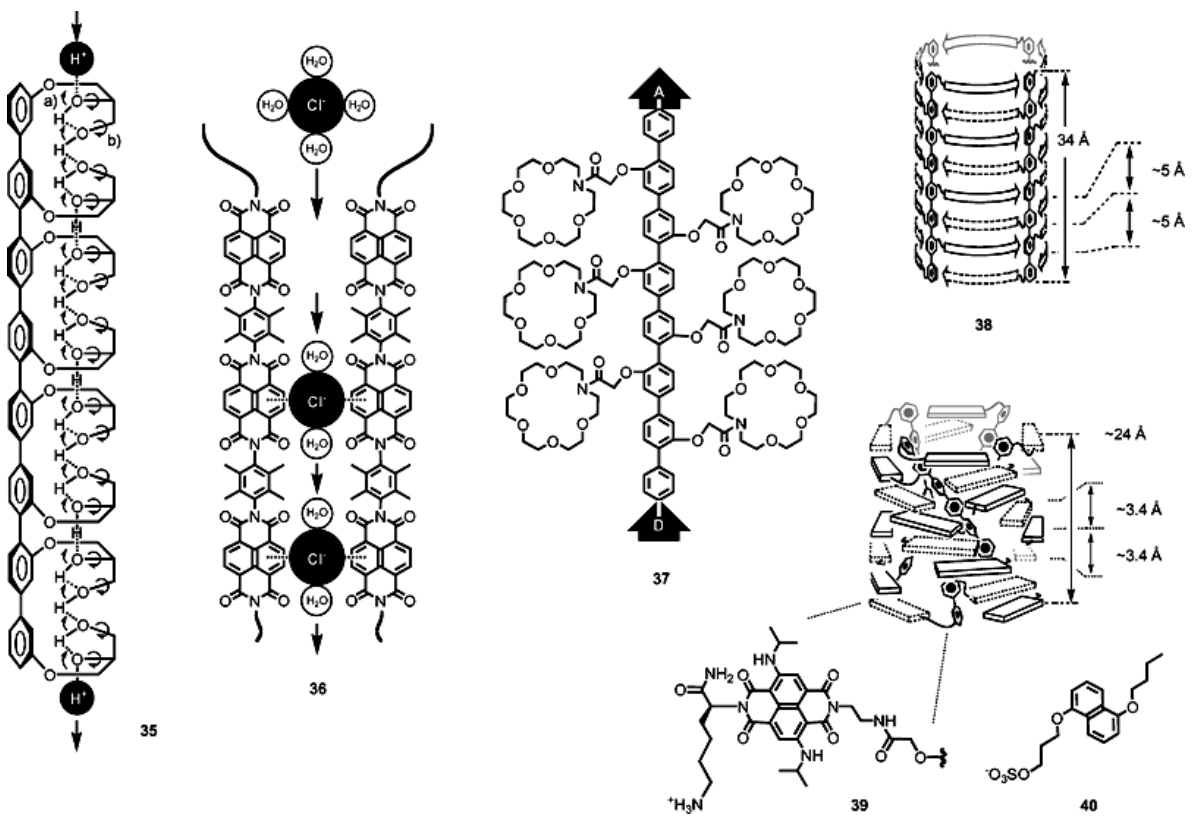
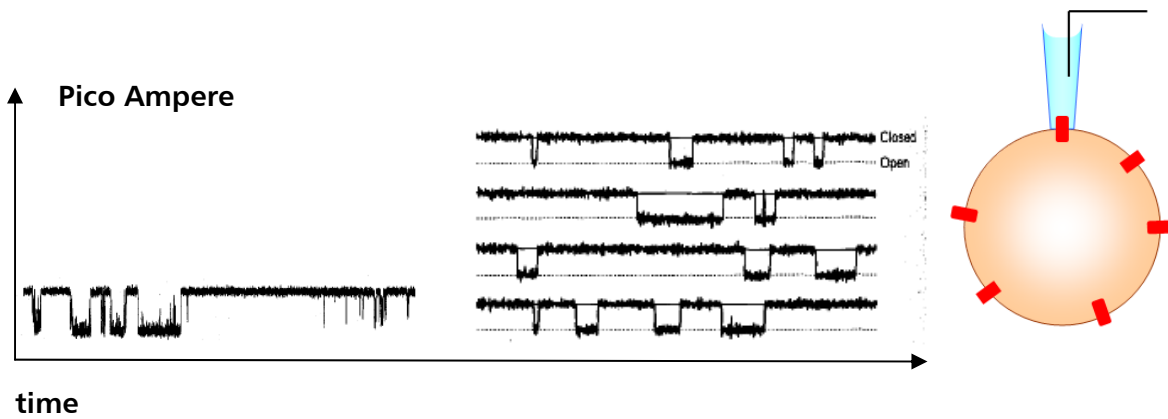


Schematic representations of the Gramicidin A dimer channel in a membrane and view inside the channel (top right)

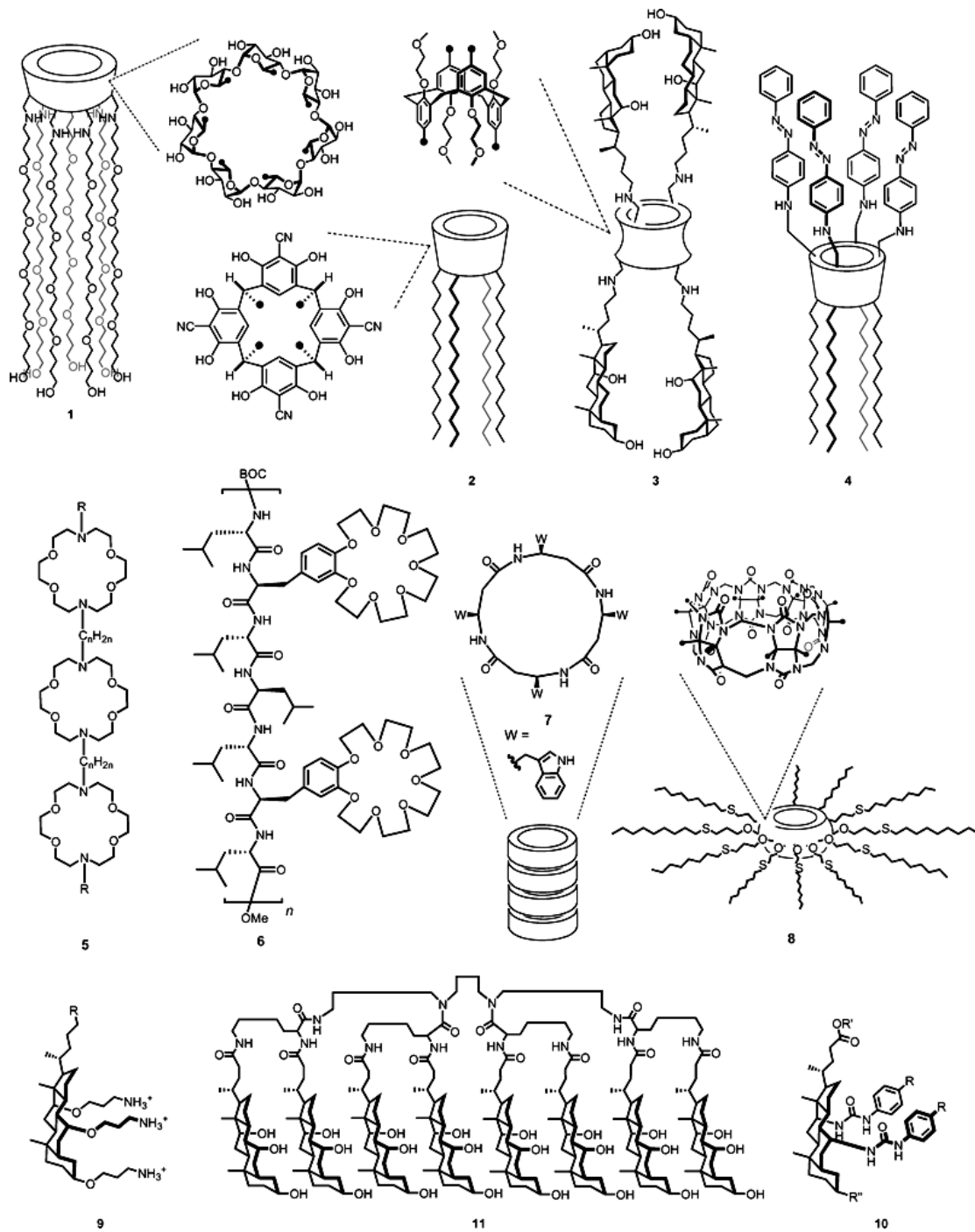
A variety of synthetic molecules have been prepared to mimic the function of a membrane ion channel. The intention behind synthetic ion channels is to investigate the mechanism of ion transport and the search for new antibiotics. A compound that forms a synthetic ion

channel in bacterial membranes harms the bacteria and acts like an antibiotic. It is difficult for bacteria to develop defence mechanisms against such antibiotic and they are therefore less prone to resistance formation by the bacteria.

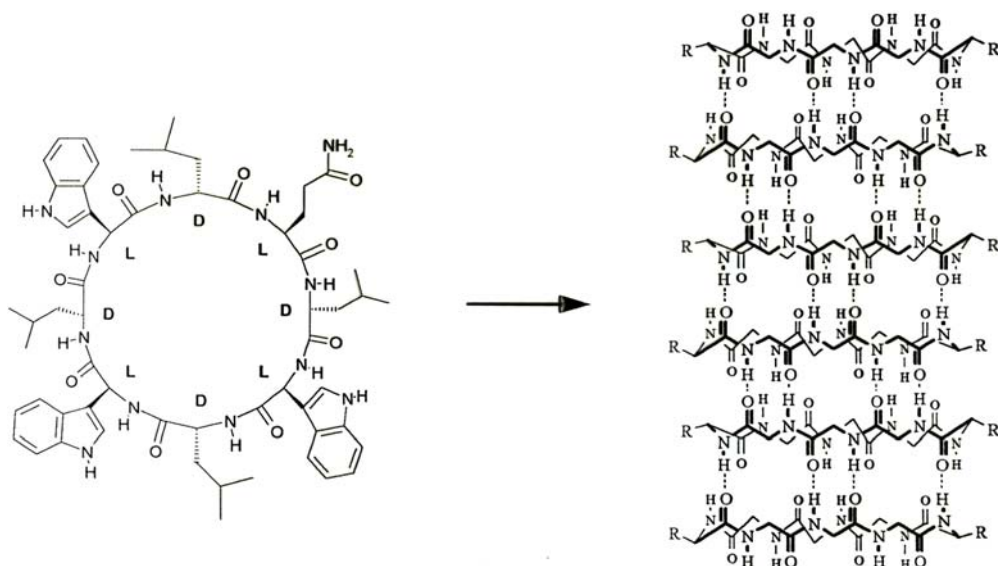
The ion transport through a natural or synthetic ion channel is measured by the patch clamp technique. A micrometer pipette is placed with suction on the cell surface and the electrical conductance through the ion channel is measured by a set of electrodes and amplifiers. The time and frequency of channel opening and closing is monitored.



Synthetic ion channel forming molecules



Synthetic ion channel forming molecules (cont.)



Ion channel from self-assembly of cyclopetides

Handout continues with SupraChem-3, binding of neutral molecules

Binding of neutral molecules

The interactions involved in the binding of neutral molecules are

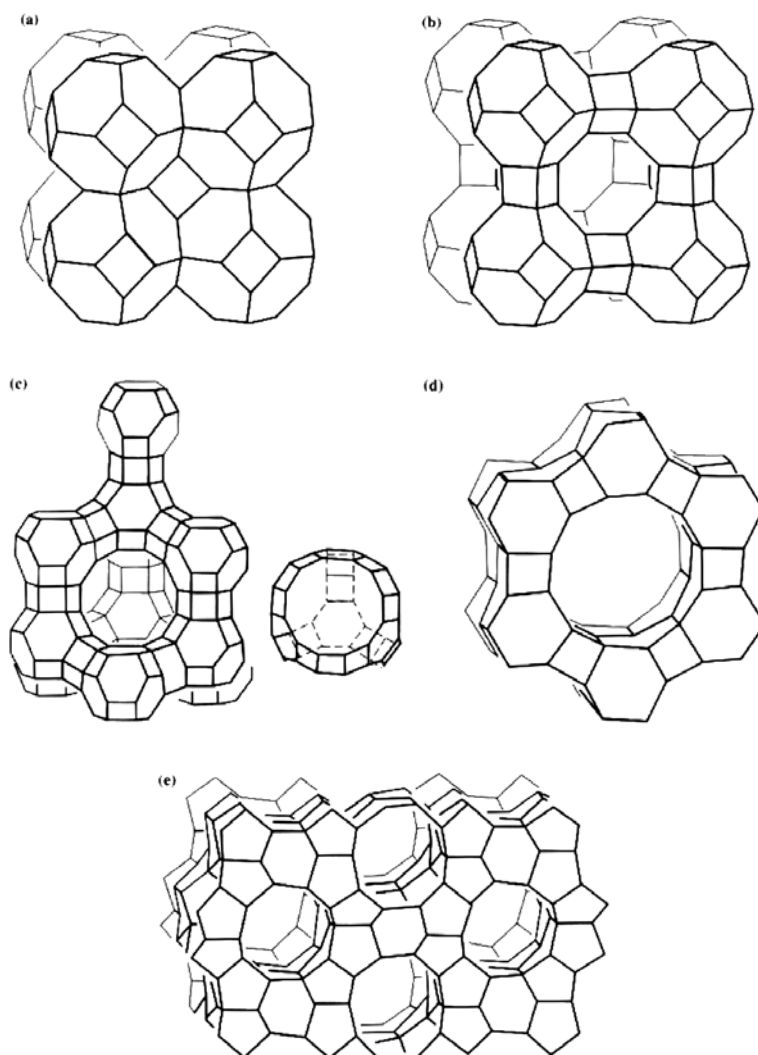
- hydrogen bonds
- van der Waals interactions and hydrophobic effects.

Co-crystals. Inclusion complexes of neutral molecules can be obtained by co-crystallization. A typical matrix compound is urea. The structure of the resulting co-crystals is difficult to predict. Applications: Reactions in chiral co-crystals.

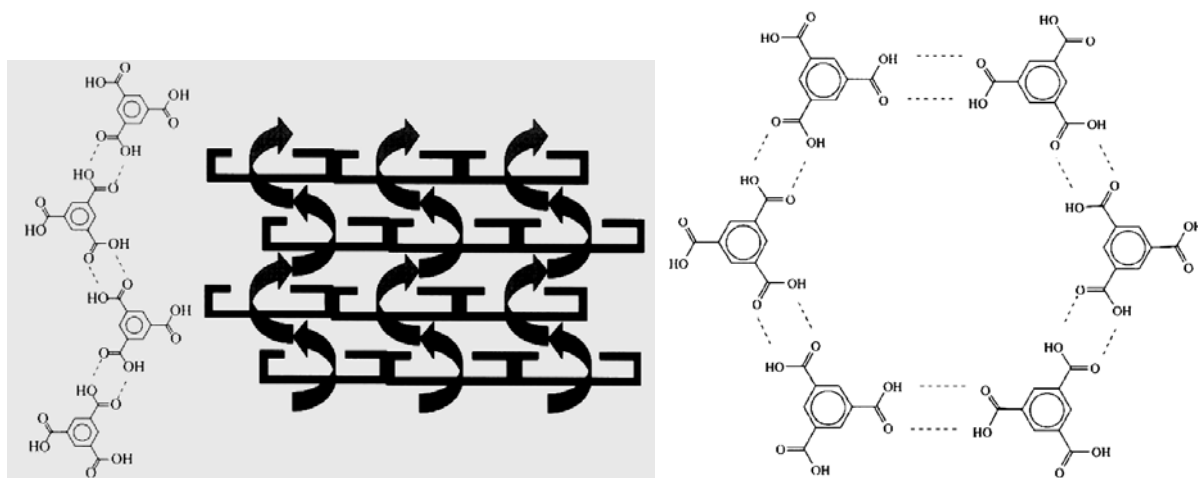
Inclusion complexes.

Several types of materials or molecules have cavities in which guest molecules can be incorporated. Typical examples are **Zeolites**. Zeolites are porous aluminosilicates. Their industrial importance is high; they find applications as catalysts or in separation processes, particular in the petrochemical industry. About 60 naturally occurring zeolites are known and many synthetic.

Some typical structures (a: Sodalite; b: Linde type A; c: Faujasite; d: $\text{AlPO}_4\text{-5}$; e: ZSM-5)



Hydrogen-bonded networks can form defined solid state structures with cavities. One example are the structures of trimesic acid (1,3,5-benzene-tri-carboxylate). Depending on the guest molecules present different arrangements are observed.

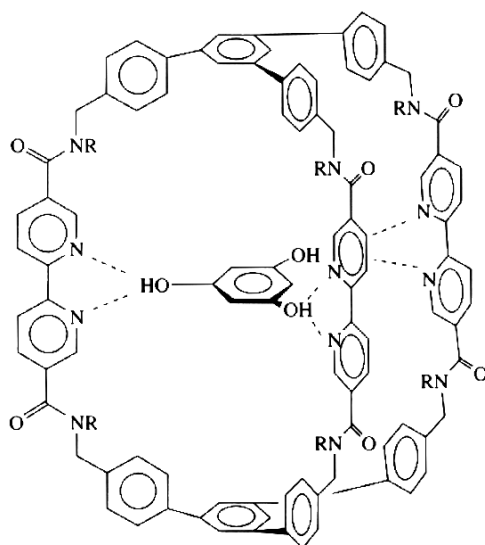


Left: offset layer packing; right: hexagonal arrangement.

Cyclophanes are a large class of molecules with a cavity. The term 'cyclophane' literally means any organic host molecule containing a bridged aromatic ring. Therefore compounds like calixarenes or cyclic bipyridinium salts are all cyclophanes. They are discussed separately, because of their differences in properties.

The classic cyclophanes can be distinguished by

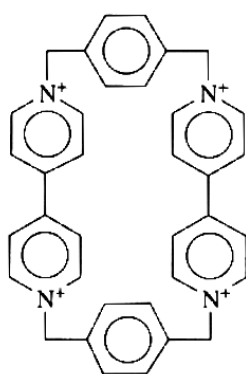
- *endo basic* compounds, having basic groups pointing inwards, e.g. bipyridine nitrogen atoms
- *endo acidic* compounds, having acidic groups pointing inwards, e.g. hydroxyl groups
- *endo lipophilic* compounds, which are typically polar on the outside (water solubility!) and non polar in the interior.



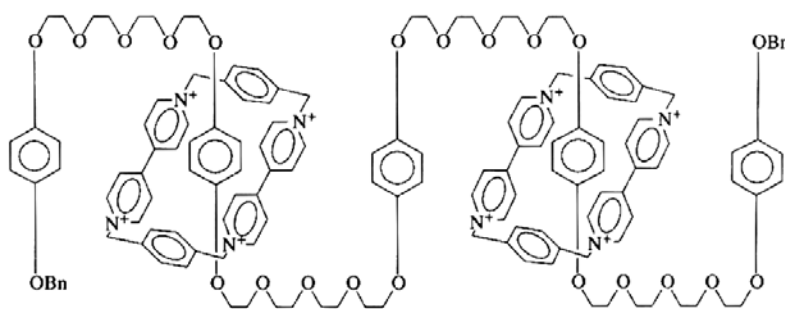
Example of an endo-basic cyclophane binding trihydroxybenzene

Cyclic bipyridinium salts

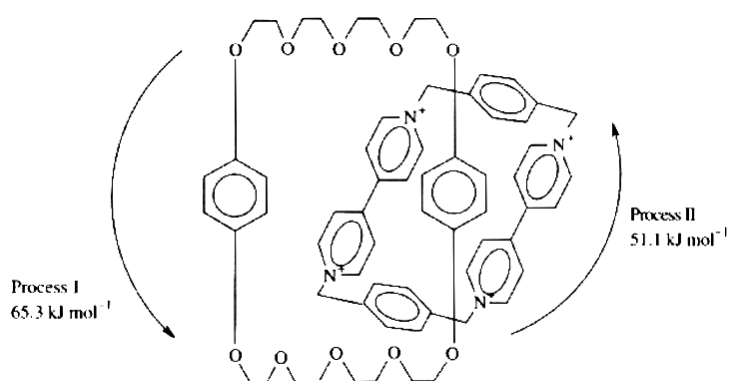
Cyclic bipyridinium salts combine two interesting features: positive charge and electron deficient aromatic groups. Electron-rich arenes slip into the cavity of the host compound stabilized by π -stacking and charge-transfer interactions between the aryl rings. Solvation of the positively charged nitrogen atoms by ethylene glycol oxygens and C-H \cdots O hydrogen bonds from the relatively acidic aryl C-H protons to the ethylene glycol oxygen atoms provide further stabilization of the aggregate. The interaction of cyclic bipyridinium salts with electron-rich arenes has been used for the preparation of *pseudorotaxanes*. The pseudorotaxane becomes a *rotaxane* if bulky substituents are attached to the ends that block the de-slipping of the macrocycles from the rotaxane axis. *Catenanes* are another class of mechanically interlocked molecules. Here, the assembly of the bipyridinium salt with electron-rich arenes is used during synthesis to preorganize the system.



Cyclic bipyridinium salt



Pseudorotaxane

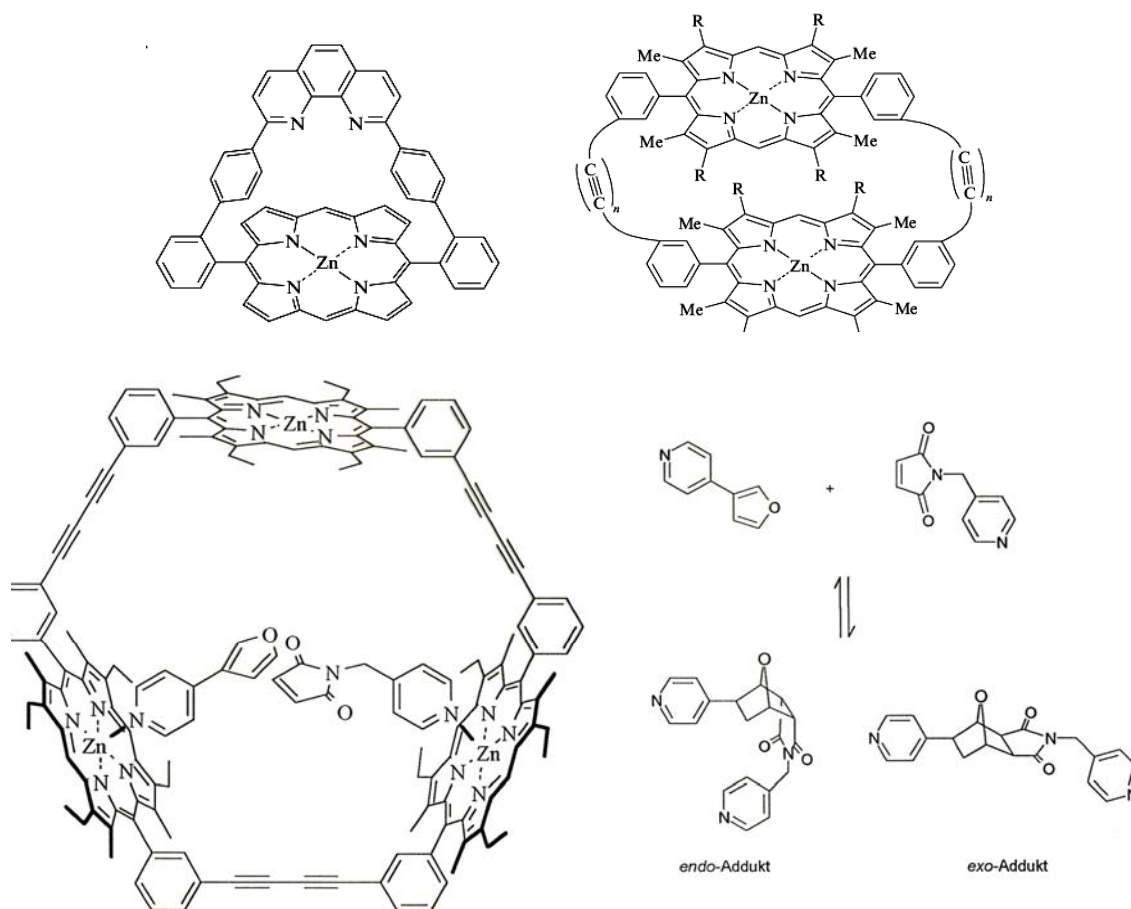


Catenane

Porphyrin macrocycles

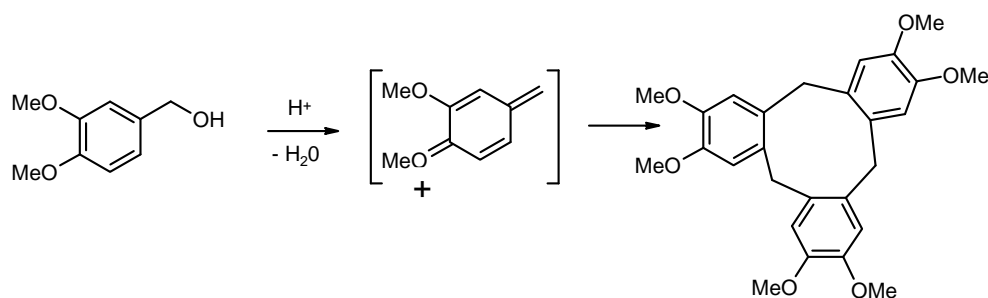
Porphyrins have been used in host compounds to provide a large flat hydrophobic surface. Metalloporphyrines can, in addition, coordinate Lewis basic groups, such as pyridine nitrogen atoms, reversibly. Porphyrins are coloured; the presence of a guest molecule is

indicated by a change in colour or fluorescence. Macrocyclic porphyrins have been used as "enzyme-like" catalysts for Diels-Alder reactions.

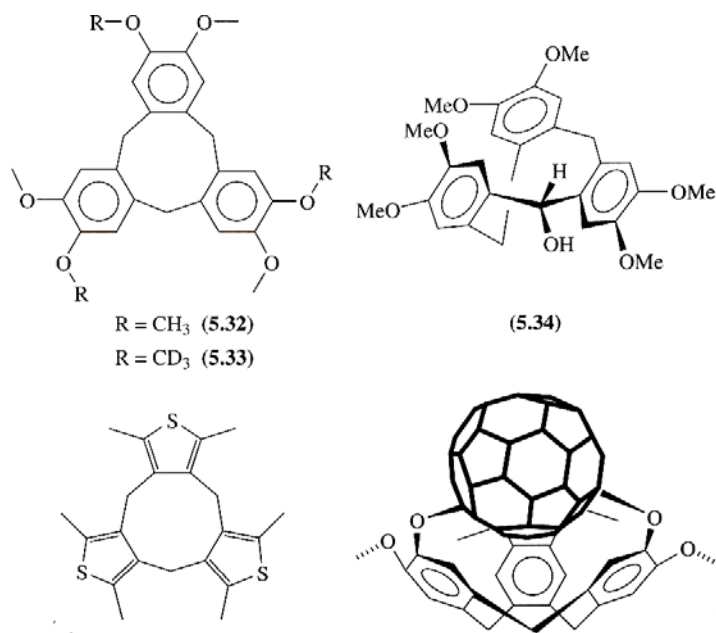


Cycloveratrylene

Cycloveratrylene is a versatile bowl-shaped host compound. Variable NMT temperature studies show conformational mobility of the macrocycle. However, the crown like bowl shape conformation is preferred. In the solid state the compound includes non polar aromatic compounds, like benzene, as guests. In solution an interaction with C₆₀ was observed. The curvature of the cycloveratrylene inner part and C₆₀ are complementary. The interaction can be monitored by UV spectroscopy. Cycloveratrylene is prepared by a cyclocondensation reaction.



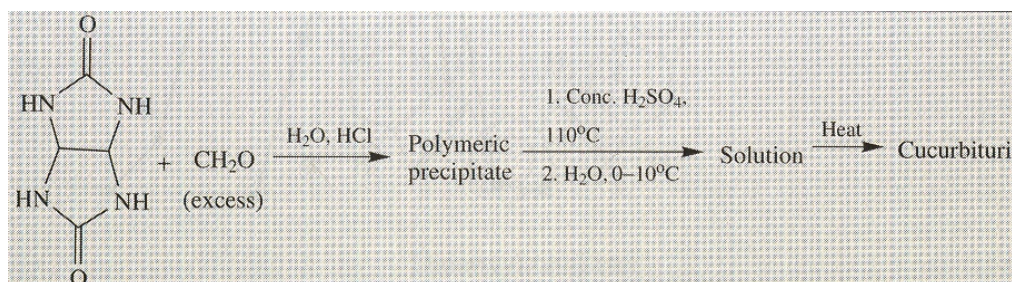
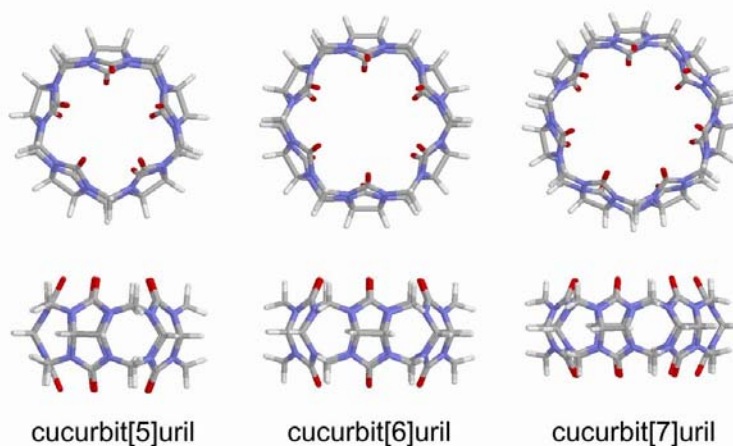
Synthesis of cycloveratrylene

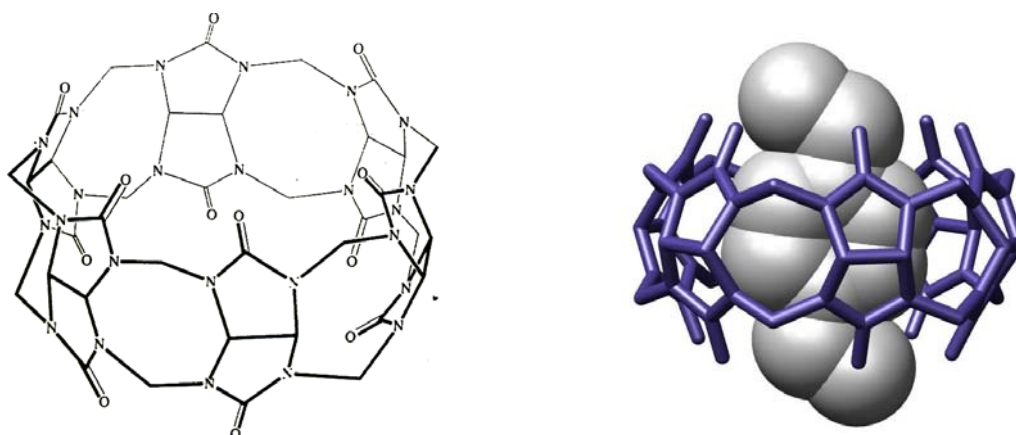


Cyclohexaerythrene derivatives and $\text{C}_{60}@\text{C}_{60}\text{H}_{12}$ cyclophane

Cucurbituril

Cucurbituril (pronounced 'kyu ker bit yur eel') is named because of the resemblance of the barrel-shaped molecule to a pumpkin of the *Cucurbitaceae* family. The compound is readily prepared by the condensation of glycoluril with formaldehyde. Alkane-diammonium ions $\text{H}_3\text{N}^+(\text{CH}_2)_n\text{NH}_3^+$ are bound by the compound with a preference for alkyl chain length of $n = 5$ or 6 .



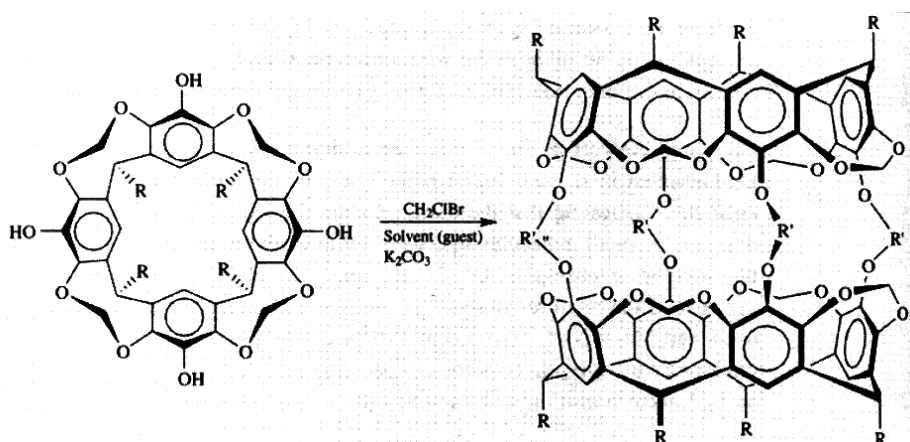


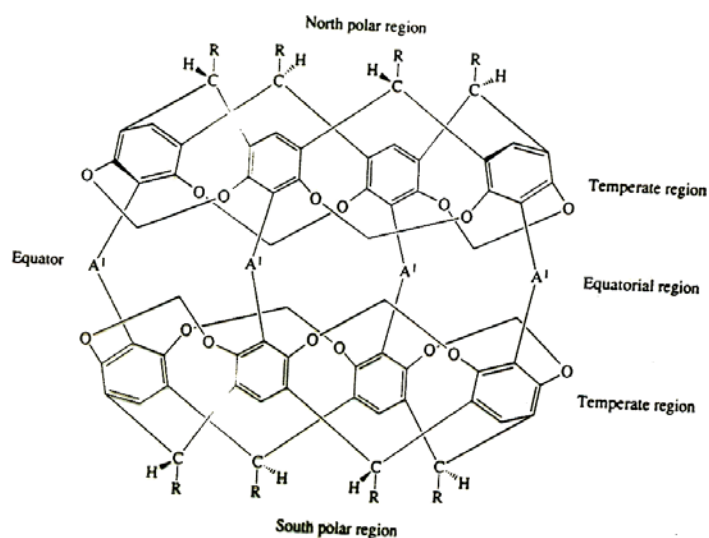
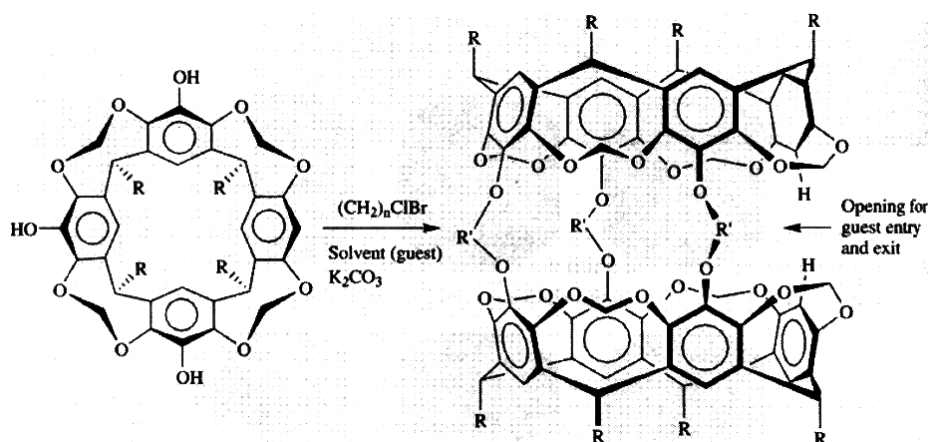
Molecular structure of cucurbit-6-uril (left) and 1,4-dibenzylamine@cucurbit-6-uril (right)

Carcerands and Hemicarcerands

The cyclocondensation of resorcin (1,3-dihydroxy benzene) and aldehydes yields resorcin-calixarenes. Covalent connection of the aromatic hydroxyl groups gives spherands. Functionalisation of the 2-position of the arene units and covalent connection of two of the bowl-shaped precursors yields carcerands and hemicarcerands. Both compounds can include guest molecules, which are permanently trapped in a carcerand and can leave and enter in a hemicarcerand. The complex of guest and carcerand is called carceplex.

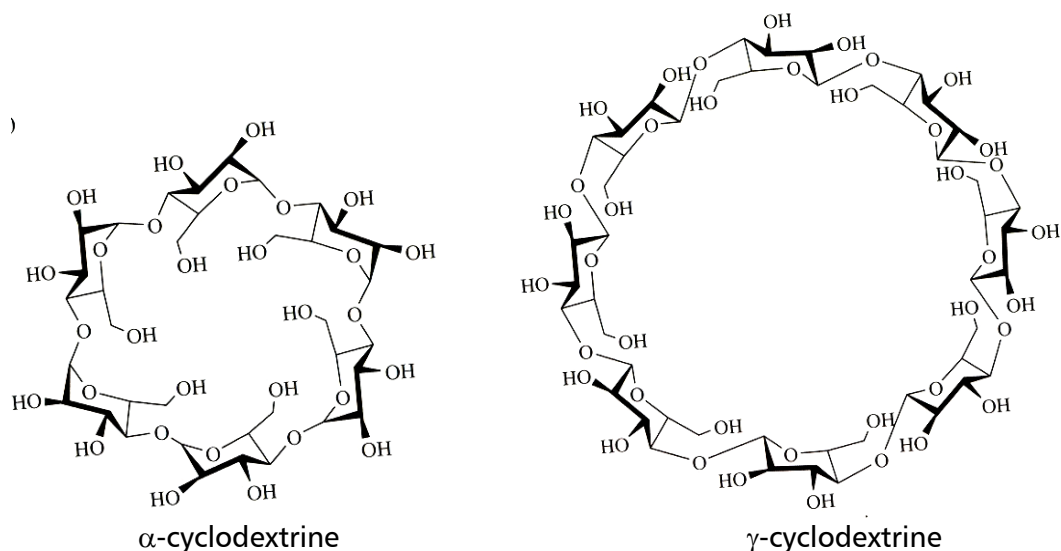
Carcerands and hemicarcerands can be used to trap reactive intermediates from reactions in their inside. Examples are benzyne, carbenes or highly strained hydrocarbons. Typically a reaction precursor is trapped during the carcerand synthesis in the inside and its reaction is initiated by light or heat. The method allows the spectroscopic (NMR) investigation of otherwise unstable reaction intermediates in solution.





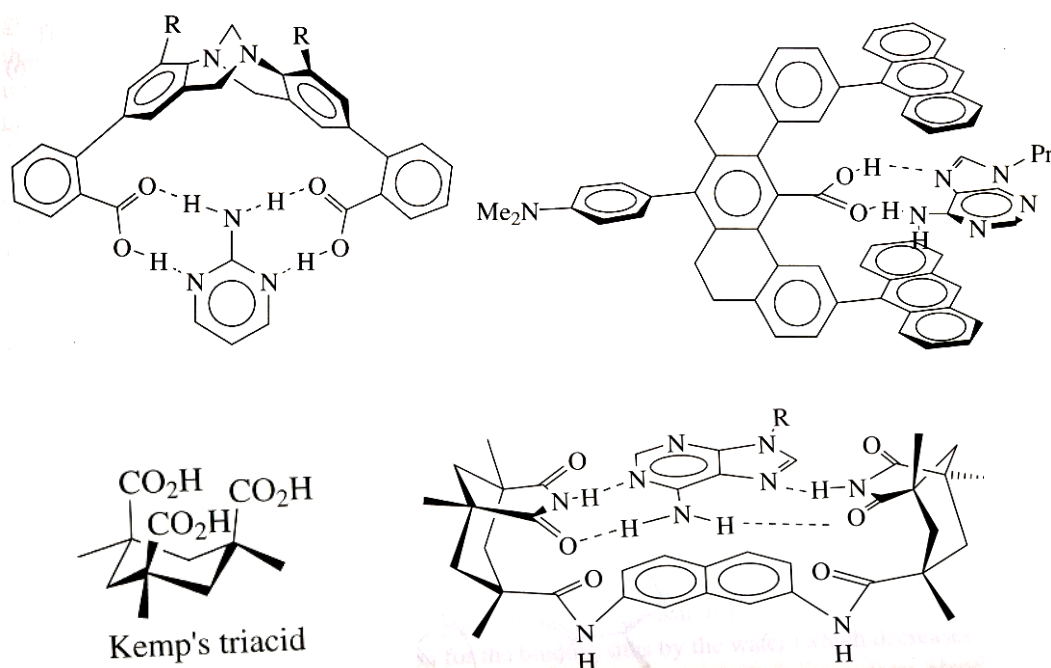
Cyclodextrines

Cyclodextrines 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 large class of compounds are α -cyclodextrines (six units), β -cyclodextrines (seven units), and γ -cyclodextrines (eight units). Cyclodextrines are prepared biotechnologically by enzymatic degradation of polysaccharides on industrial scale, e.g. at Wacker in Burghausen. The compounds bind in aqueous solution to non-polar compounds in their interior. Applications: Solubilisation of drugs, binding of fragrances.

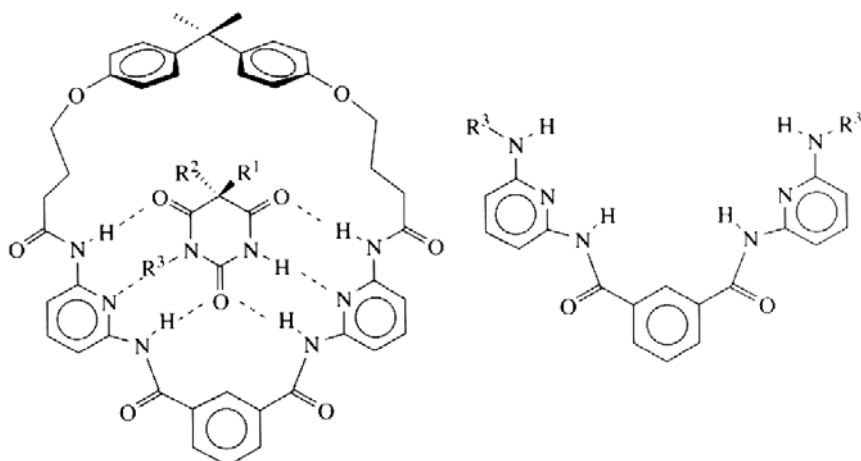


Host compounds forming hydrogen-bonded aggregates

Cleft and tweezer-type host compounds have been prepared that combine π - π -stacking or hydrophobic interactions with hydrogen bonding. This increases selectivity and binding strength. The Träger base and Kemp's triacid are typical molecular building blocks in the preparation of molecular clefts and tweezers.



A nice example of complementary hydrogen bonding is the use of 1,6-diaminopyridine to bind the imide structures of barbituric acid in a macrocyclic systems. The compound with $R^1, R^2 = \text{Et}$, $R^3 = \text{H}$ is a sedative.



$$R^1 = R^2 = R^3 = H$$

$$R^1 = R^2 = Et, R^3 = H$$

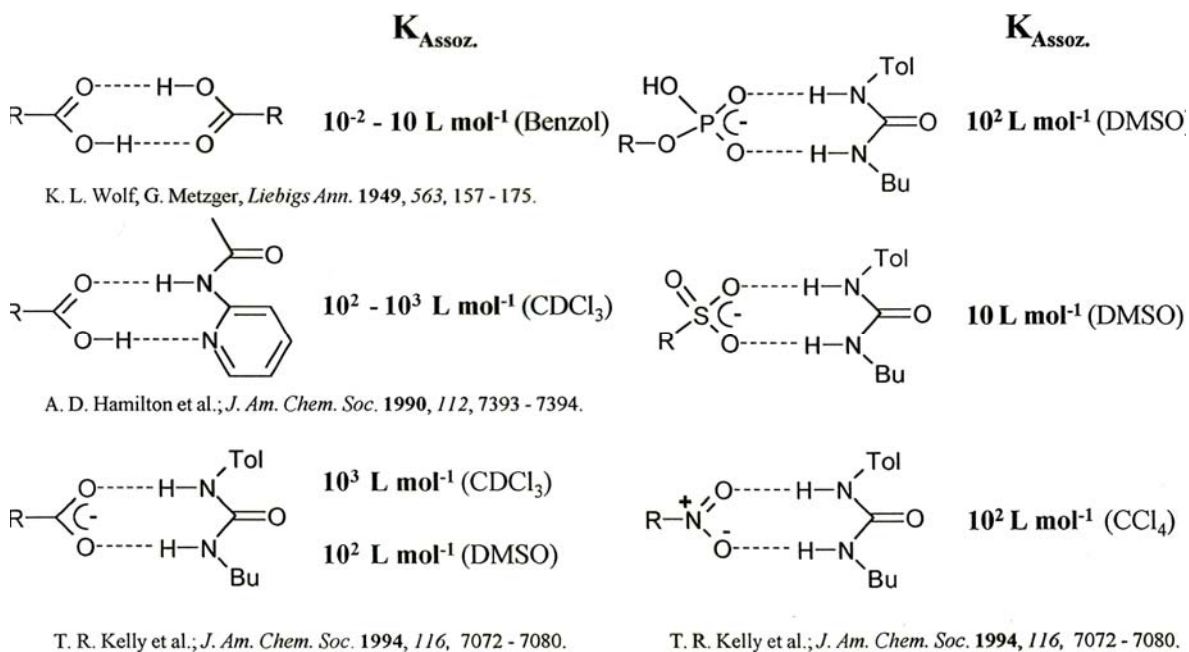
$$R^1 = Et, R^2 = Ph, R^3 = H$$

$$R^1 = Et, R^2 = Ph, R^3 = Me$$

$$R^3 = CO(CH_2)_2Me$$

Hydrogen bonds

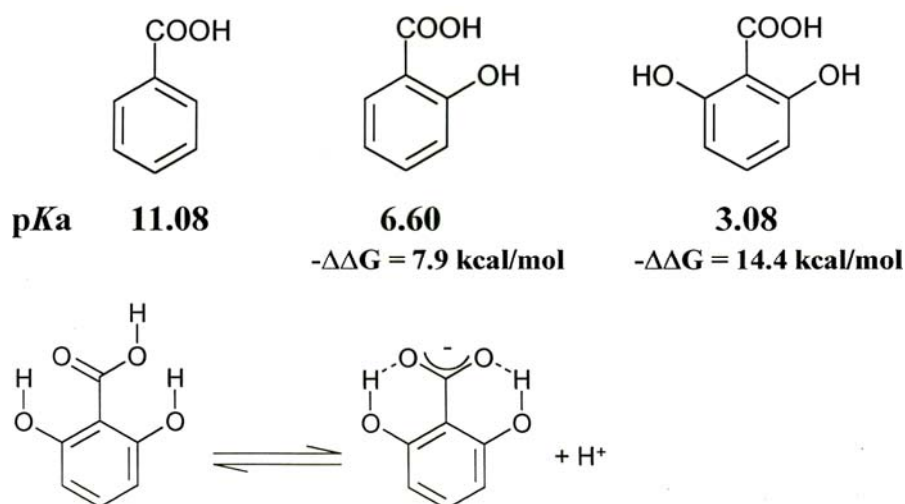
Hydrogen bonds can be very different in strength, even if their geometry is similar. Important parameters are the basic character of the hydrogen bond acceptor site and the acidity of the hydrogen bond donor site.



**.. Optimized Interaction Energies for Hydrogen Bonds in the Gas Phase
with the OPLS Potentials^a**

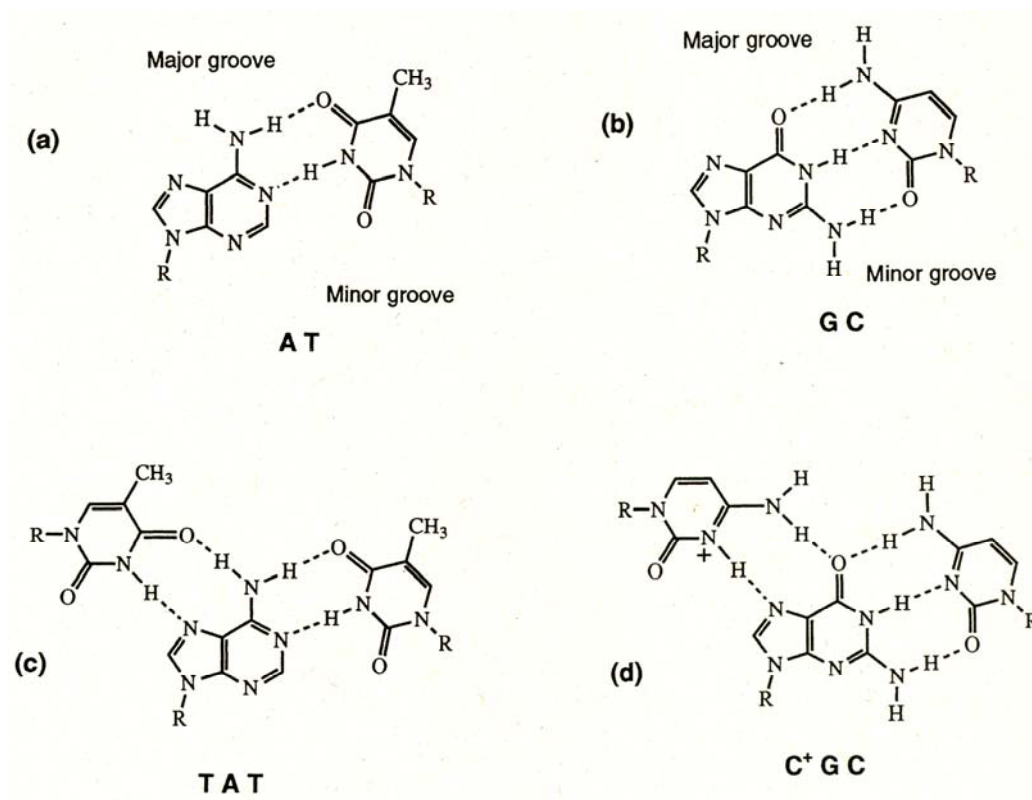
Complex	$-\Delta E(\text{kcal/mol})$	Complex	$-\Delta E(\text{kcal/mol})$
B ... HOH		A-H ... OH ₂	
(NH ₂) ₂ CO ... HOH	9.1	CH ₃ COOH ... OH ₂	8.8
CH ₃ CONHCH ₃ ... HOH	7.4	OC(NH ₂) ₂ ... OH ₂	7.5
CH ₃ NH ₂ ... HOH	6.8	pyrrole ... OH ₂	6.9
CH ₃ OH ... HOH	6.8	HCONH ₂ ... OH ₂	6.8
CH ₃ COOH ... HOH	6.7	CH ₃ CONHCH ₃ ... OH ₂	6.7
H ₂ O ... HOH	6.2	HOH ... OH ₂	6.2
(CH ₃) ₂ O ... HOH	5.8	CH ₃ OH ... OH ₂	6.0
CH ₃ COOCH ₃ ... HOH	5.6	CH ₃ SH ... OH ₂	6.0
imidazole ... HOH	5.5	CH ₃ NH ₂ ... OH ₂	3.5
(CH ₃) ₂ CO ... HOH	5.5	A-H ... B	
CH ₃ CN ... HOH	4.9	OC(NH ₂) ₂ ... O(CH ₂) ₄	7.9
pyridine ... HOH	4.7	OC(NH ₂) ₂ ... O(CH ₃) ₂	7.4
(CH ₃) ₂ S ... HOH	4.6	CH ₃ COOH ... pyridine	7.3
pyrimidine ... HOH	4.2	OC(NH ₂) ₂ ... pyridine	7.0
pyrazine ... HOH	4.1	CH ₃ COOH ... pyrazine	6.9
benzene ... HOH	3.8	OC(NH ₂) ₂ ... CH ₃ COOCH ₃	6.6
CH ₃ COOH ... HOH	3.7	A-H ... A-H	
CH ₃ SH ... HOH	3.7	CH ₃ CONHCH ₃ ...	9.0
CH ₃ COOCH ₃ ... HOH	2.9	CH ₃ CONHCH ₃	
		CH ₃ CH ₂ OH ... OHCH ₂ CH ₃	7.0
		CH ₃ OH ... OHCH ₃	6.8
		CH ₃ SH ... SHCH ₃	3.8

The presence of hydrogen bonds may change the properties of functional groups significantly. Here are some simple examples of acidity change of benzoic acids. Note: The hydrogen bond stabilization of the carboxylate anion leads to an increase in acidity of eight orders of magnitude.



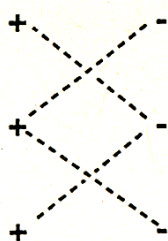
DNA base pairs

DNA base pairing is the classical example of complementary hydrogen bonding. Different hydrogen bonding patterns lead to Watson-Crick or Hougsteen pairing situations.

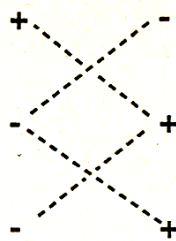


Secondary hydrogen bonds

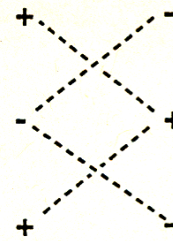
The comparison of the binding strengths of related hydrogen bonded systems shows that the relative orientation of the hydrogen bond donor and acceptor sites matters. Only the alternating orientation leads to maximum affinity due to favourable secondary hydrogen bond interactions. The concept allows an estimation of the relative binding strengths of hydrogen bonds.



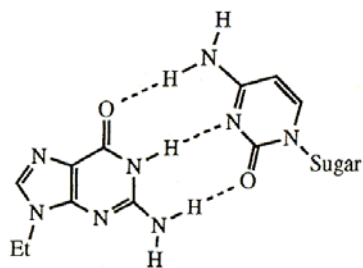
System A:
4 favorable
secondary
interactions



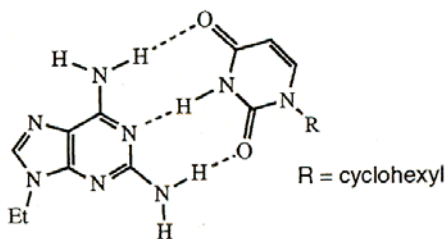
System B:
2 favorable and
2 unfavorable secondary
interactions cancel out



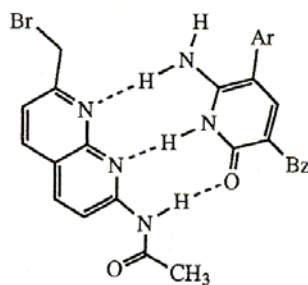
System C:
4 unfavorable
secondary
interactions



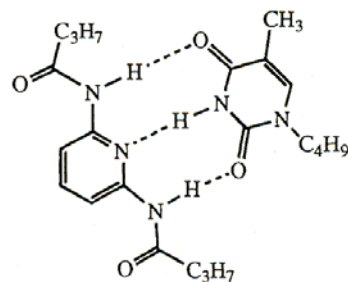
$$K_a \approx 10^4 - 10^5 \text{ L mol}^{-1}$$



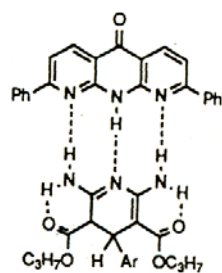
$$K_a \approx 170 \text{ L mol}^{-1}$$



$$K_a = 1.7 \times 10^4 \text{ L mol}^{-1}$$

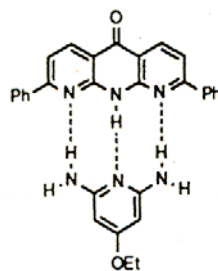


$$K_a \approx 90 \text{ L mol}^{-1}$$

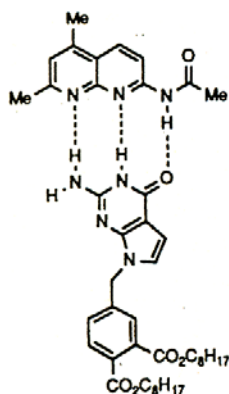


Ar = 2-nitrophenyl

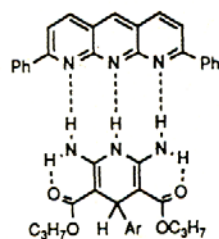
5 (DAD-ADA)
 $K_a 78 \text{ M}^{-1}$



6 (DAD-ADA)
 $K_a 70 \text{ M}^{-1}$ (CDCl₃, 298 K)



7 (DDA-AAD)
 $K_a 9.3 \times 10^3 \text{ M}^{-1}$



Ar = 3-nitrophenyl
 8 (DDD-AAA)
 $K_a > 10^5 \text{ M}^{-1}$

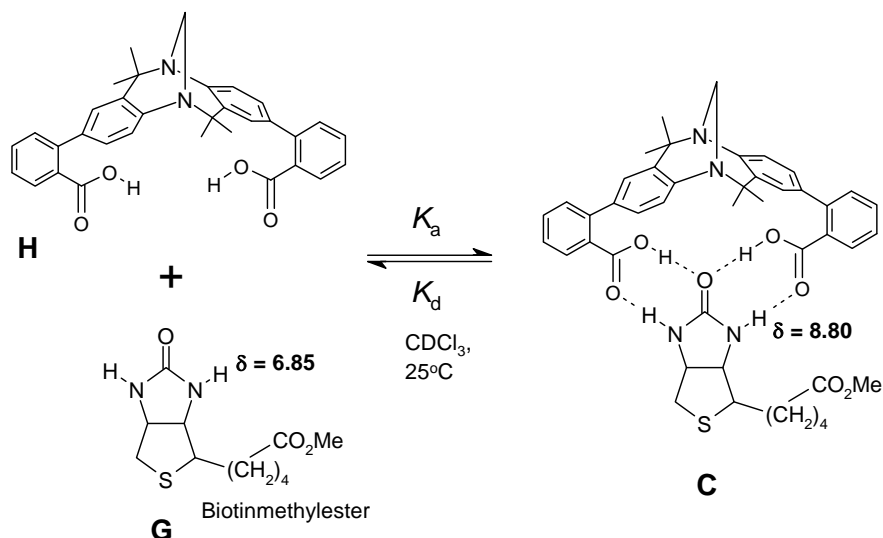
Examples of hydrogen-bonded systems and the effect of secondary hydrogen bond interactions on their association

Handout continues with SupraChem-4, determination of binding constants

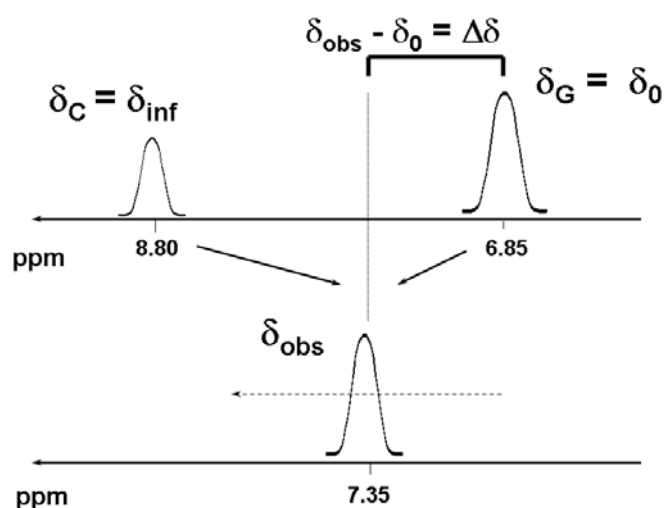
Determination of binding constants

Depending on the association strengths, a suitable method to determine the binding constant must be selected. The sensitivity of the technique must allow for the detection of free and bound species (guest, host and host-guest complex) in solution.

NMR titration. NMR spectroscopy operates on a rather slow time scale. Most non-covalent equilibria are faster and therefore average signals of chemical shifts are observed. NMR titration is suitable to determine binding constants in the range of $K = 10 - 10^4$.



Example of a hydrogen-bonded aggregate in solution



The average chemical shift of the free and the bound hydrogen atoms is observed in the NMR spectrum. During the titration the resonance signal moves along the chemical shift axis. The change in chemical shift caused by hydrogen bonding is called "induced chemical shift change". This situation is true for equilibria that are faster than the NMR time scale.

For slower equilibria we observe a separate resonance for the free and the bound hydrogen atoms and can determine their relative abundance by integration.

$$K_a = \frac{[C]}{[H][G]} = \frac{[C]}{([H]^0 - [C])([G]^0 - [C])}$$

Change in chemical shift (fast exchange on NMR time scale):

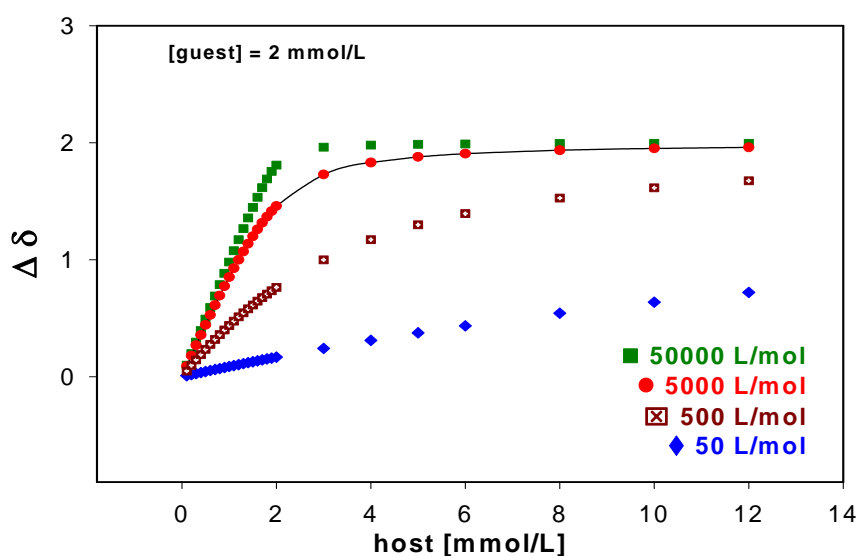
$$\delta_{obs} = \frac{[G]^0 - [C]}{[G]^0} \delta_0 + \frac{[C]}{[G]^0} \delta_{inf}$$

$$\text{with } x = \frac{[C]}{[G]^0} : \quad \delta_{obs} = x (\delta_{inf} - \delta_0) + \delta_0$$

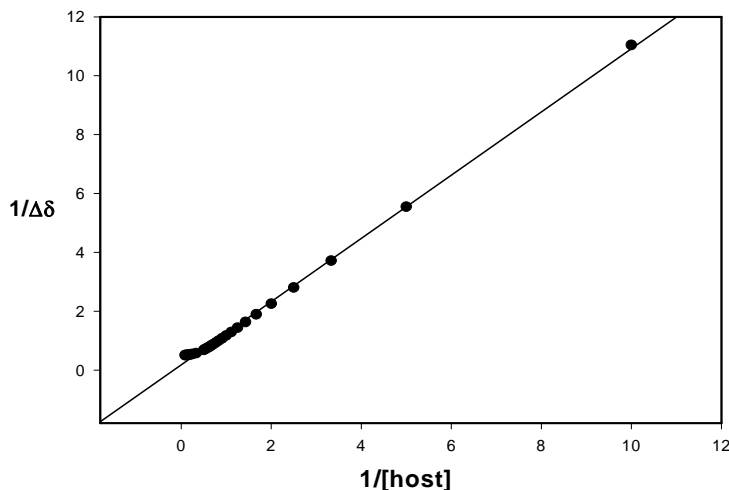
Concentration of the aggregate:

$$[C] = \frac{1}{2} ([G]^0 + [H]^0 + 1/K_a) - \sqrt{\frac{1}{4} ([G]^0 + [H]^0 + 1/K_a)^2 - [G]^0 [H]^0}$$

Using the mass balance the observed change in chemical shift is related to the ratio of free and bound species in the system. The equation is then used to fit the experimental data with the help of a computer program giving the binding constant. Note: This equation is only valid for an equilibrium with a stoichiometry of 1:1. Depending on the binding constant the change in chemical shift during titration is different (see next scheme). However, the value of the overall induced chemical shift is not related to the binding constant.

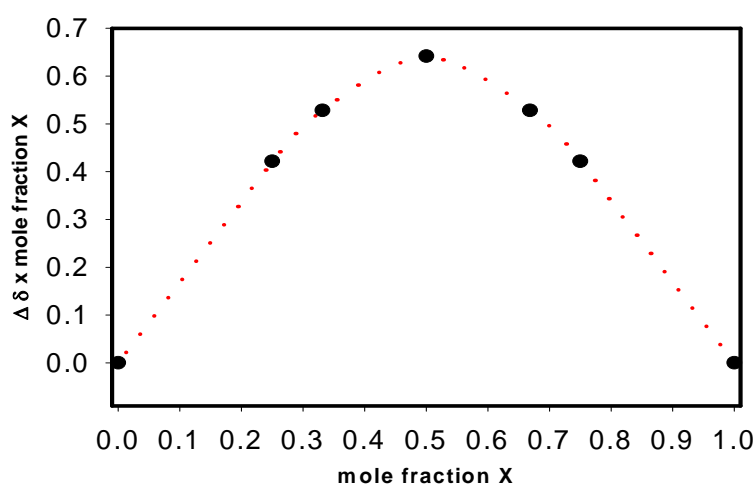


Theoretical titration NMR curves for different values of the binding constant



Benesi Hildebrand plot

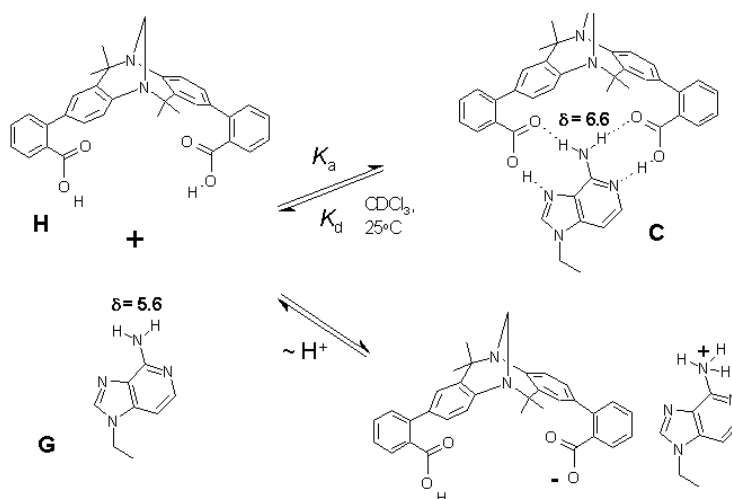
A graphical method to determine the binding constant is the Benesi-Hildebrand plot. The slope of the double reciprocal representation gives the binding constant and it is a quick test if the 1:1 binding model is valid. WARNING: This treatment requires $[G]_0 \gg [H]_0$ or $[H]_0 \gg [G]_0$ so that $[G]_0 \cong [G]$ or $[H]_0 \cong [H]$.



Job's plot analysis

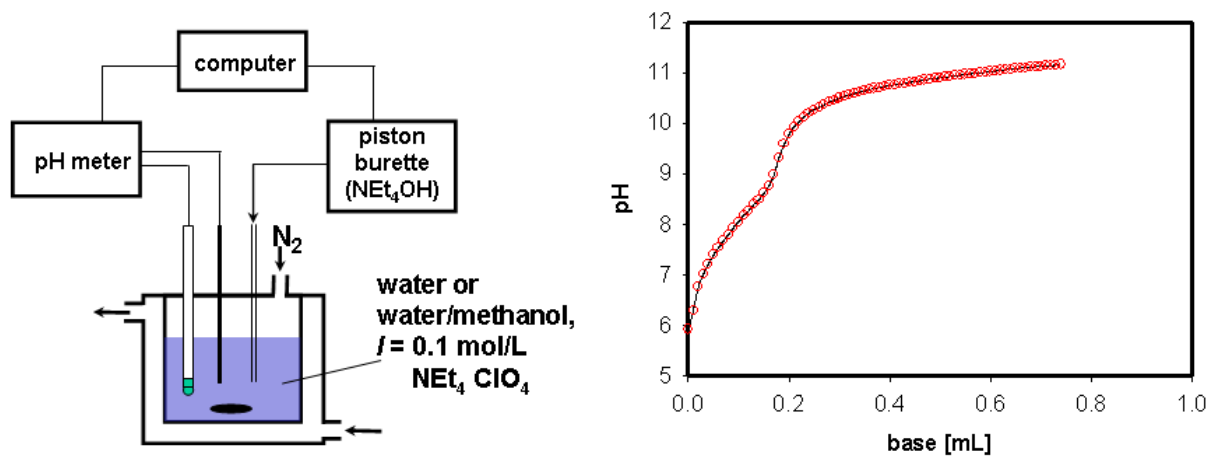
The determination of a binding constant requires that we know the stoichiometry of the equilibrium. The Job's plot analysis or method of continuous variation allows for the determination of the stoichiometry of simple equilibria. A series of mixtures having the same overall concentration but different mol fractions of the binding partners are measured. The maximum in the Job's plot gives the stoichiometry. Note: the method fails for multiple equilibria.

In the case of very basic hydrogen bond acceptor sites and acidic hydrogen bond donor sites the question arises if we have a hydrogen bond or a salt formation by transfer of a proton. A simple dilution experiment of a 1:1 mixture gives the answer: while $[C]$ and therefore $\Delta\delta$ changes with concentration of $[G]_0$ and $[H]_0$, the proton transfer is independent of the concentration (no change in $\Delta\delta$).

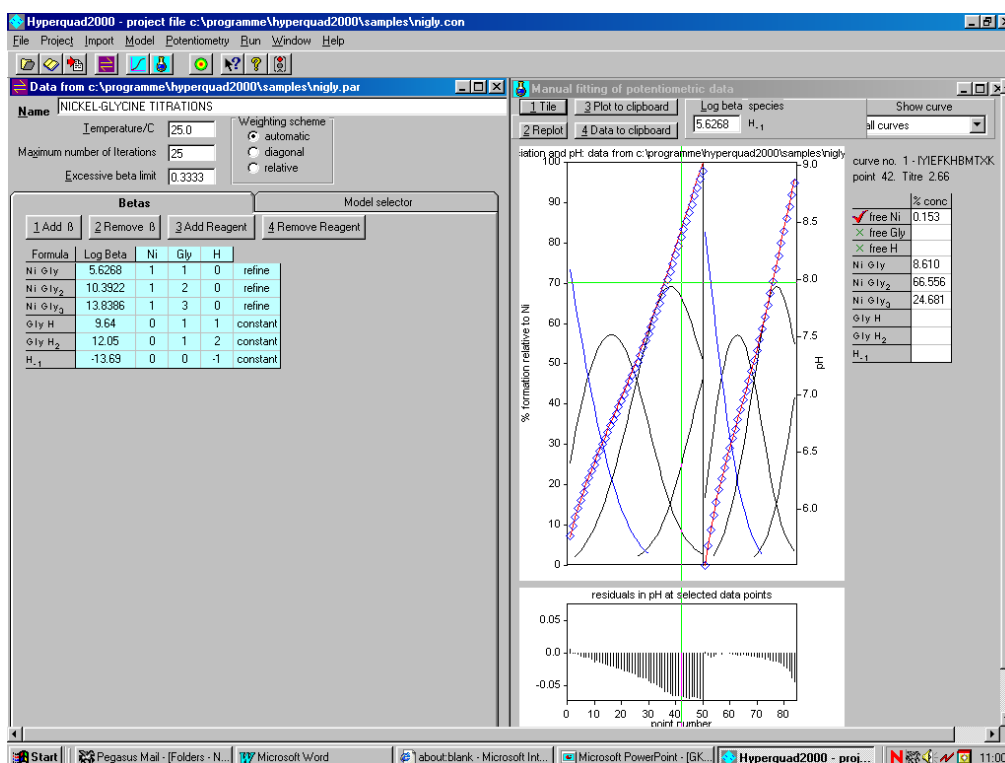


Potentiometric titration.

This technique is particularly suitable to determine pK_a values of molecules and stability constants of ligand to metal ion complexes. It is a pH titration. We start at acidic pH and by the addition of base slowly reach very basic pH. The change in pH is monitored by a pH electrode; titrations are typically automatic. During the titration the ligand is deprotonated and forms the complex with the metal ion present. This changes the pH profile from a "normal" acid – base titration curve. A computer program calculates the pH value at each point of the titration varying the constants to be determined.



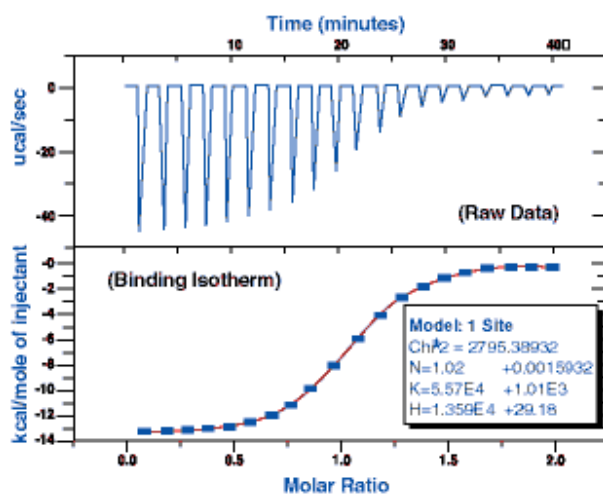
Left: Experimental set up for a potentiometric titration; right: experimental and fitted pH profile



Screenshot of a computer assisted fit of potentiometric data

Isothermal titration calorimetry

Isothermal Titration Calorimetry (ITC) is a technique which allows the investigator to study the heat of interaction between two molecules. In ITC a syringe containing a "guest" is titrated into a cell containing a solution of the binding partner (which can be a molecule, a metal complex, or a protein). As the two species interact, heat is released or absorbed in direct proportion to the amount of binding that occurs. When the macromolecule in the cell becomes saturated with added guest, the heat signal diminishes until only the background heat of dilution is observed. ITC allows for the determination of binding constants in the range of $K = 10^3 - 10^9$.



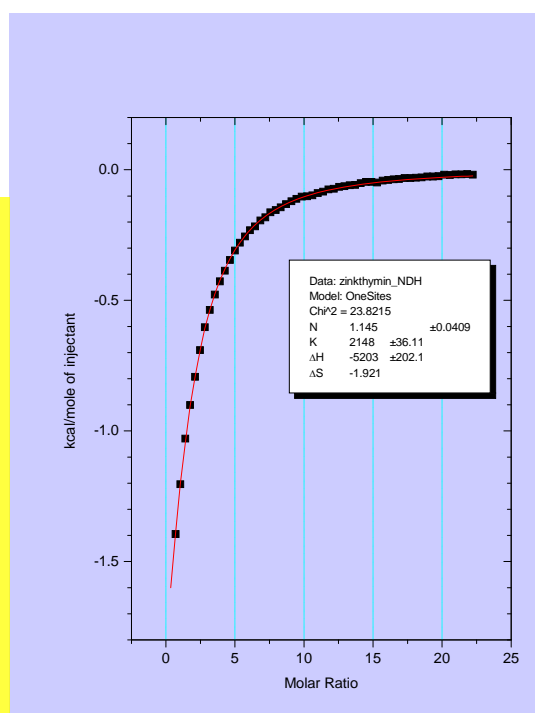
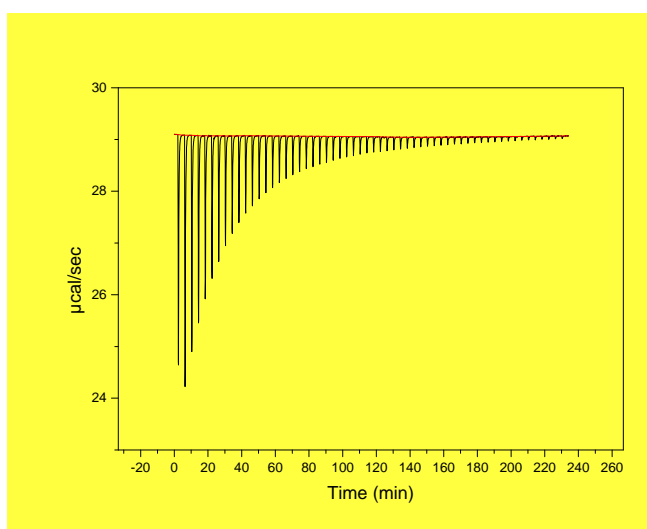
The area underneath each injection peak is equal to the total heat released for that injection. When this is plotted against the molar ratio of guest added to host molecule in the cell, a complete binding isotherm for the interaction is obtained.

Advantages of the method:

- No labeling necessary
- Association constants and thermodynamic data are obtained
- Solution method; works in all solvents
- Easy experiment to perform

Disadvantages:

- Sensitivity is limited
- Solubility or availability of material may limit application of ITC
- Expensive equipment necessary
- No structural information

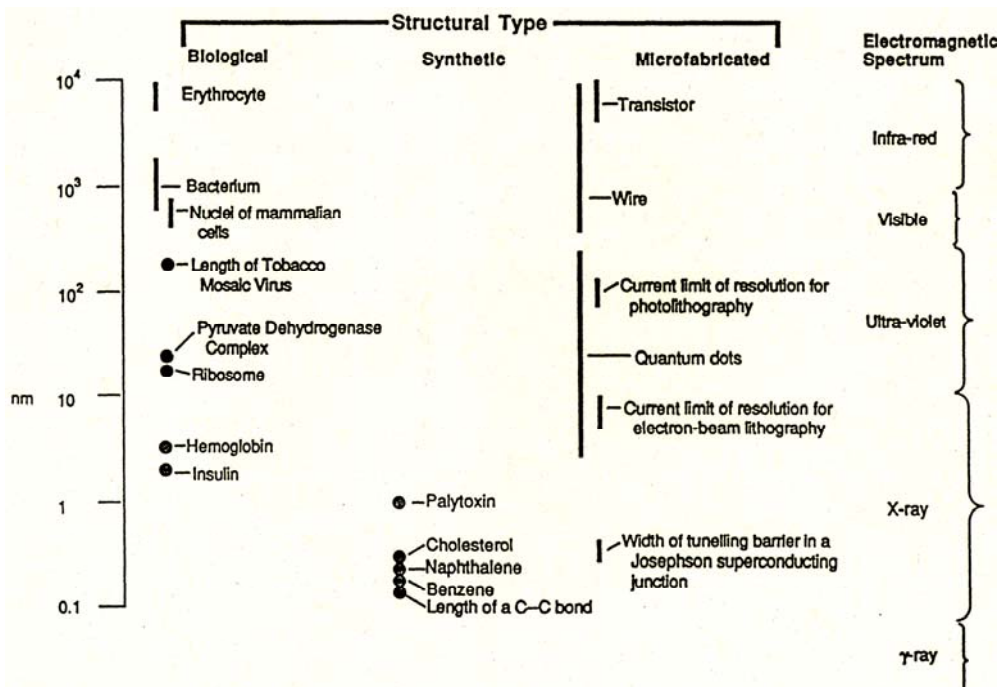


Example of an ITC experiment

In principle, many other techniques can be used to determine binding constants. *Fluorescence* and *absorption spectroscopy* are widely used and very sensitive (range $K = 10^4 - 10^9$). The most sensitive are methods involving *radioactive labelled compounds*. *Electrochemical methods* and *analytical ultracentrifugation* are other options.

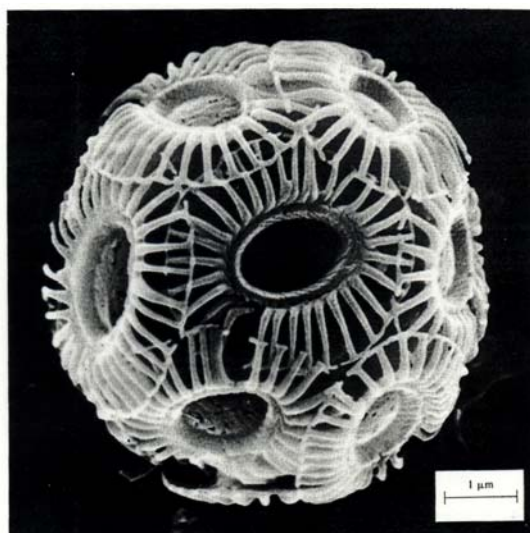
Self-assembly

Intermolecular interactions that involve more than two molecules and lead to large ordered structures are called self-assembly processes. Self-assembly is an interesting strategy for the synthesis of structures that are too large for conventional chemical synthesis, but too small for microfabrication techniques. The assembly structure represents the thermodynamic minimum of the system for the given concentrations. Due to their dynamic structure, self-assembled aggregates can react to a stimulus (change of conditions) and self-repair if damaged.



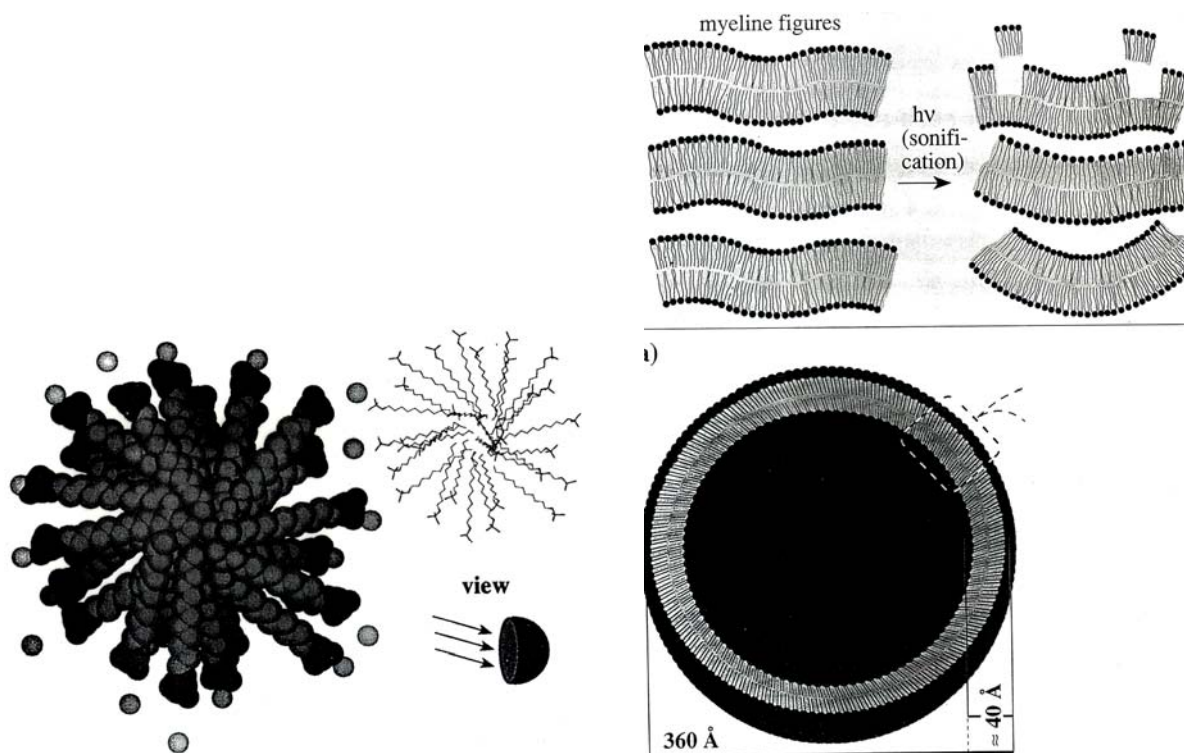
Biomineralization

The control of crystallization leads to impressive structures in nature. Proteins control the crystallization in biomineralization, but the details of such processes are still unknown. Attempts to use biomineralization for the controlled preparations of materials have been made, but so far, are rather limited.



Micelles, membranes and vesicles

The self-assembly of amphiphilic molecules, like fatty acids, leads to defined supra-molecular structures in solution. Left: micelle structure; right: formation of a vesicle.



Biochemical self-assembly

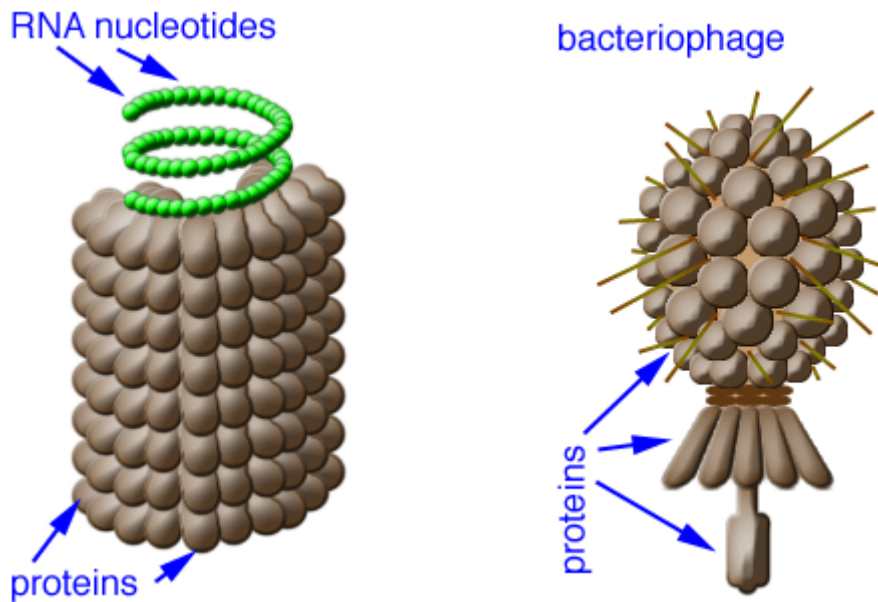
Self-assembly is the main construction strategy of biology. Numerous examples show the power of self-assembly for the formation of defined large structures.

The most prominent example is the *tobacco mosaic virus*. The tobacco mosaic virus, as its name suggests, infects tobacco plants causing considerable distress to the invaded plant cells and to the productivity of the whole plant. A virus particle, when viewed under the electron microscope, appears as a cylinder that is 16 nm wide and about 300 nm long. It has a mass of 40×10^6 daltons and contains a single strand of RNA. This is its genetic material, in which 6500 nucleotides hold the codes necessary for producing more virus particles.

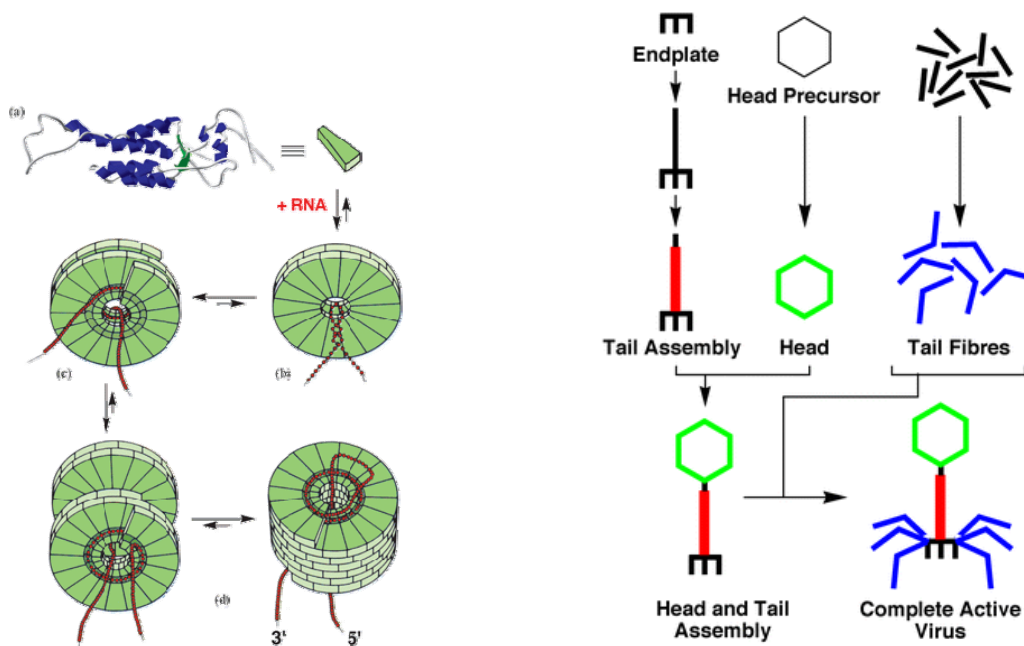
In an intact particle, the viral RNA is wound into a helix that has a radius of 4 nm, and stretches all the way from one end of the cylinder to the other. Associated with this polynucleotide helix are 2130 identical polypeptides, folded into 2130 identical globular protein shapes. These protein molecules bind and complex with three adjacent nucleotides along the RNA molecule, and with other proteins on either side of them.

Bacteriophages are more complex virus particles that invade, take over and destroy bacteria during their active reproductive cycle. One such bacteriophage attacks the

bacterium *Bacillus subtilis* by injecting a double stranded DNA molecule (about 5.7 μm long) through the bacterial cell wall and into the cytoplasm of the host. Once inside the host cell, the DNA takes over and directs the synthesis of more bacteriophage proteins (and DNA), which then assemble into new intact virus particles for release and further infection. These bacteriophage particles consist of 145 identical protein molecules which assemble into the "head" or DNA containing capsid, and six other proteins that have roles to play in the "tail" of the phage particle and help in the DNA injection process.



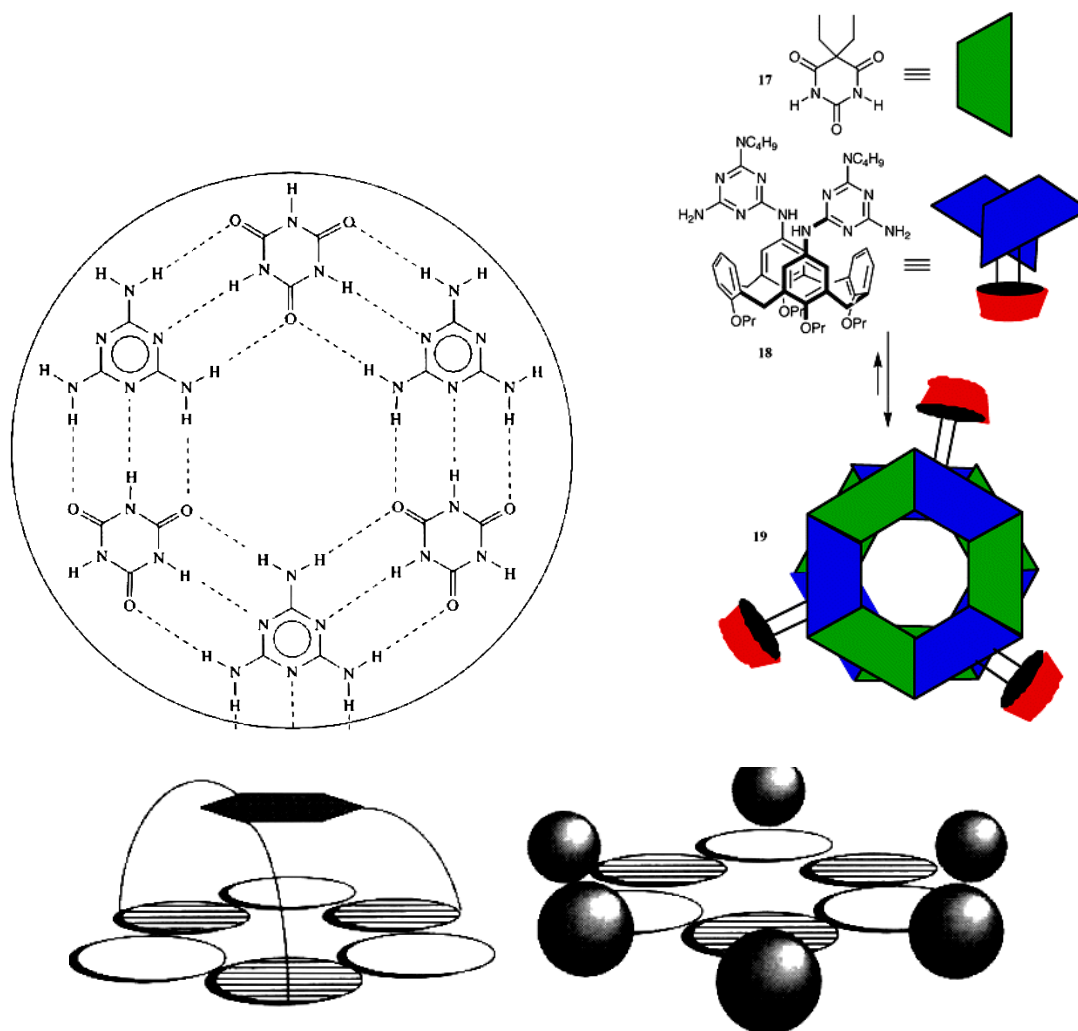
Left: tobacco mosaic virus; right: bacteriophage



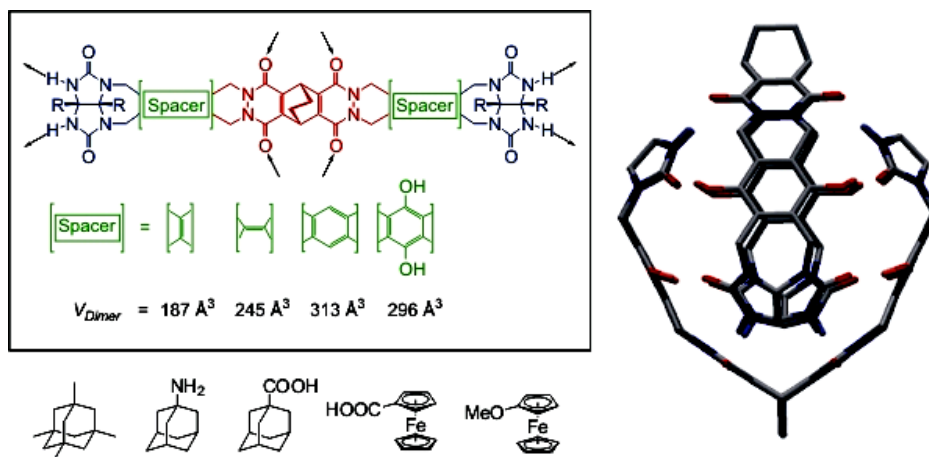
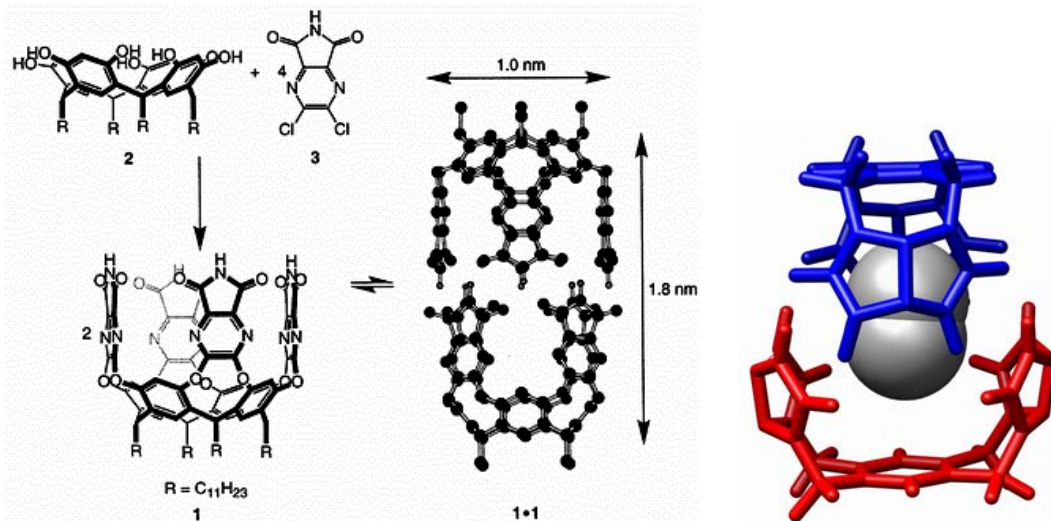
Self assembly pathways for TMV (left) and T4 bacteriophage (right)

Hydrogen-bonded self assembly

Hydrogen bonds have been used to construct rosettes and capsules from smaller building blocks. The complementary hydrogen bonding pattern of triamino-triazine (melamine) and cyanuric acid allows for the controlled assembly of planar structures (left) and, if combined with rigid structures, such as calixarenes, of three dimensional aggregates (right).

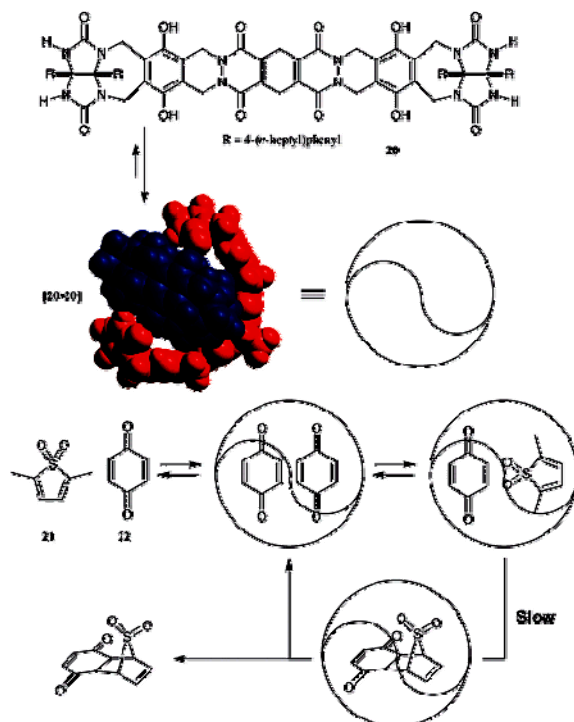


The reversible formation of molecular capsules uses similar principles: Typically two complementary halves of the capsule interact by hydrogen bonds and enclose the inner space. Suitable guest molecules can be trapped inside the cavity. Such systems may find applications in drug delivery. If two reactive molecules are entrapped inside the cavity they can react. The kinetic, regio- and stereochemistry of the reaction is controlled by the capsule.



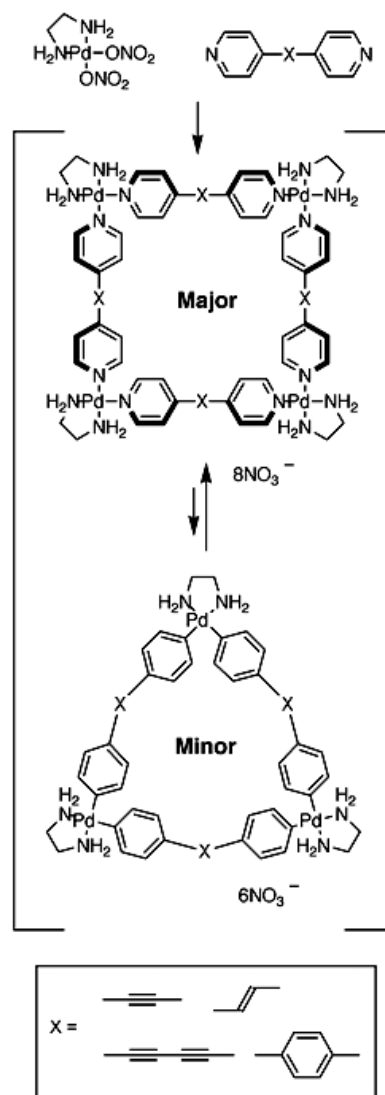
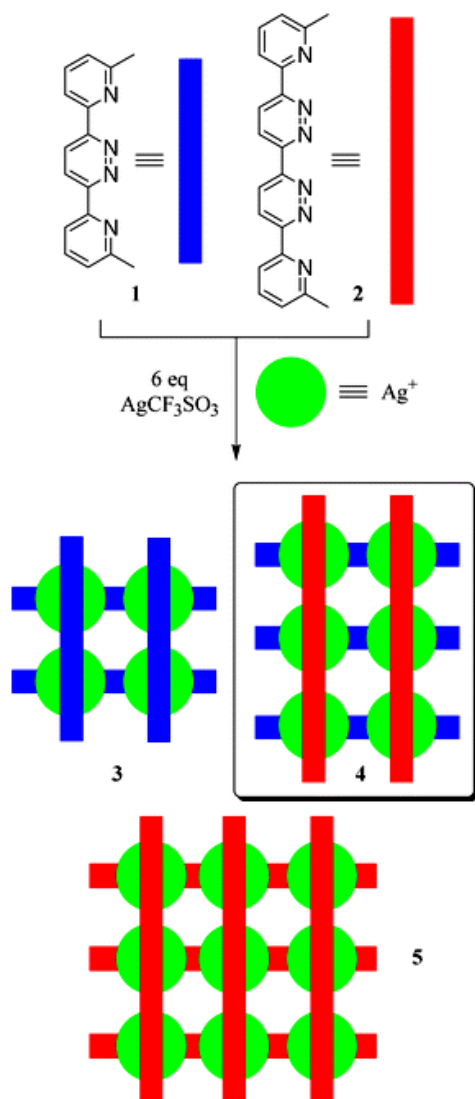
Examples of hydrogen-bonded capsules

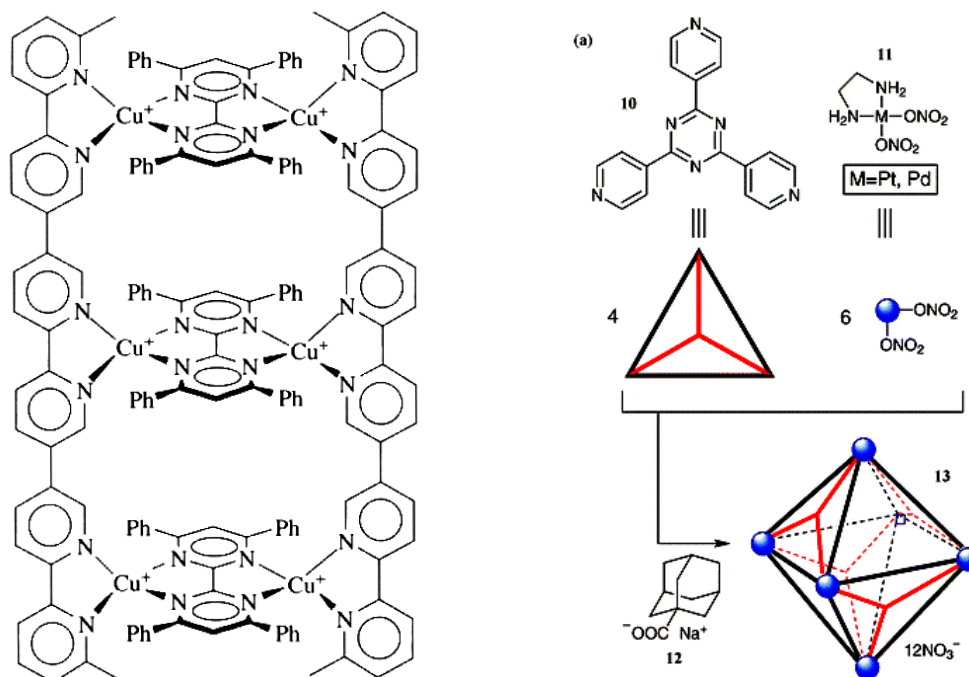
Reaction inside a capsule: The Diels-Alder reaction is significantly accelerated by the entrapment of the reactants in the capsule.



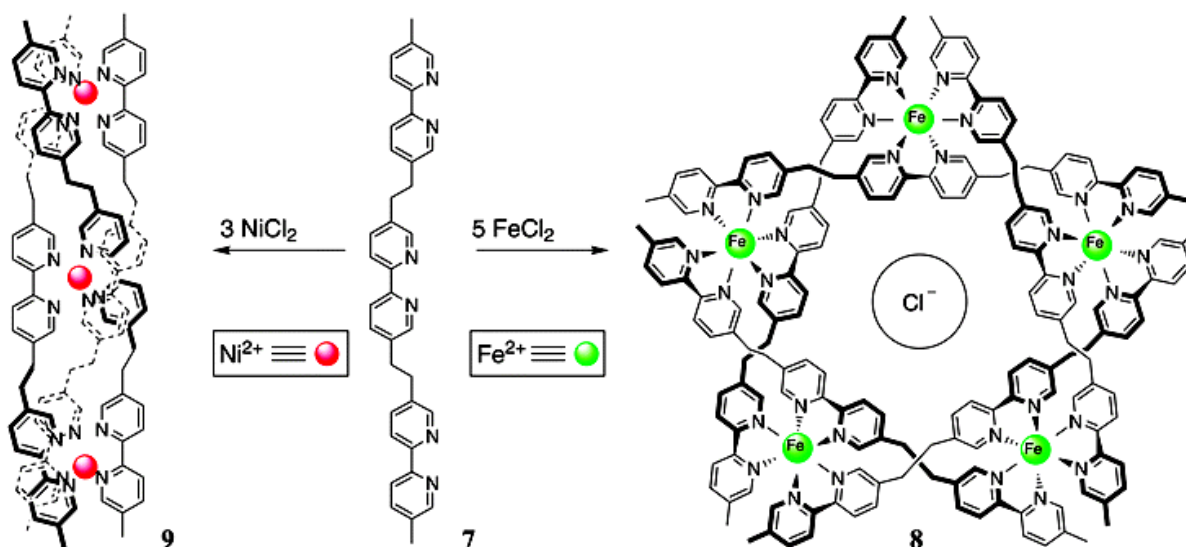
Self-assembly by metal coordination

Multiple metal complex formations give to highly order structures with the right combinations of ligands and metal ions. Linear ligands and metal ions with tetrahedral coordination geometry lead to molecular grids (left), while palladium complexes and rigid pyridine ligands yield squares and boxes (right).

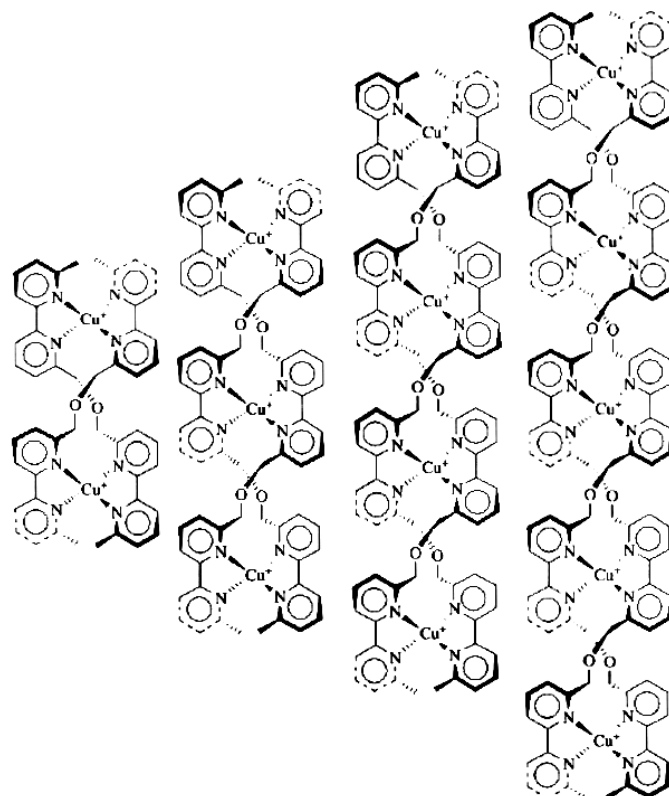




Double or triple helices are obtained from oligomeric bipyridine ligands and copper, iron or nickel ions, respectively. Although iron and nickel have similar octahedral coordination geometries, different molecular structures are observed. The chloride ion is important for the formation of the circular assembly.



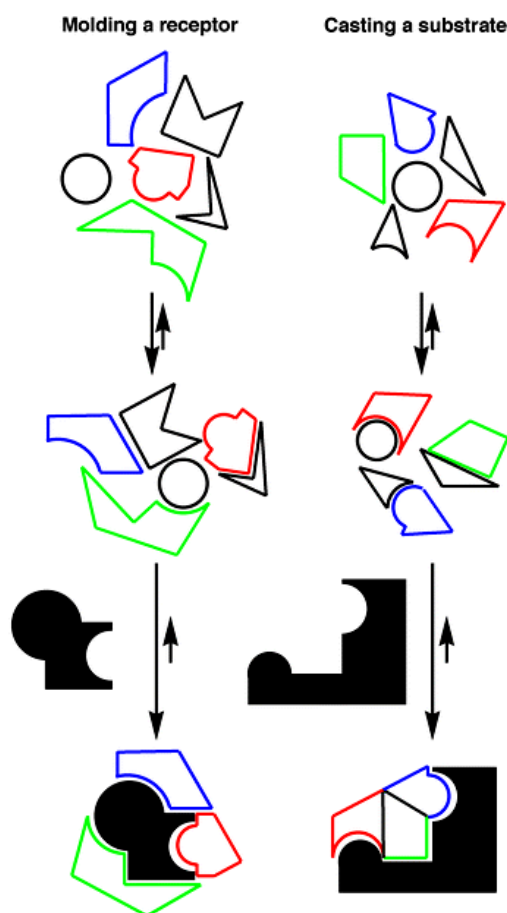
Self-assembly processes can sort molecules. If a mixture of bipyridine ligands of different lengths is treated with copper ions, only helices of ligands with the same lengths are found. The assembly with the most ligand sites complexed is the thermodynamically most favourable one. In helices consisting of longer and shorter bipyridine chains some coordinations sites would remain without copper complexation. As the assembly process is reversible, the thermodynamic most stable structure is formed.

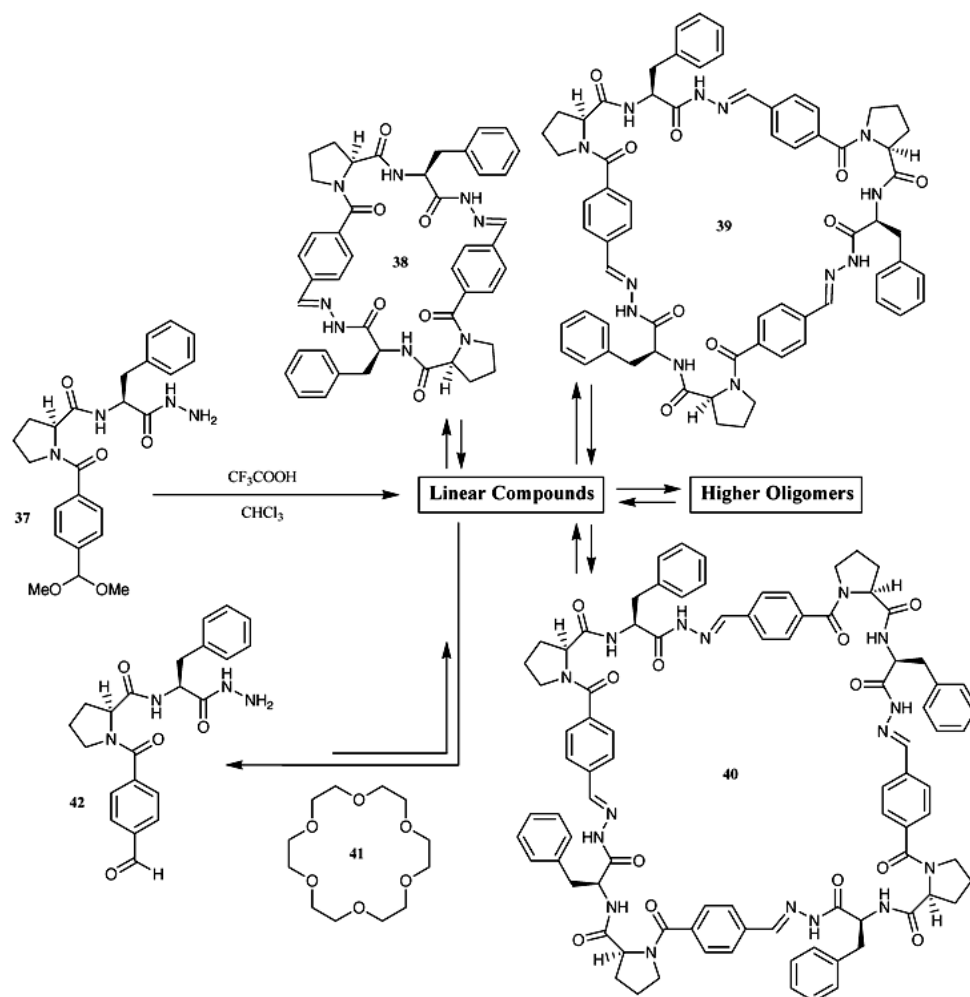


Dynamic combinatorial libraries

A new concept in supramolecular chemistry uses self-assembly to create receptor sites for a given guest molecule or guest molecules (ligands) for a given receptor (host). A library of small building blocks, which dynamically and reversibly forms aggregates, is used. From all possible combinations of assembly of the library members, the one that fits best to the target structures are selected. It is essential that the aggregate formation of the library building blocks is reversible. Typical reactions for the aggregate formation are Schiff base or hydrazone condensations.

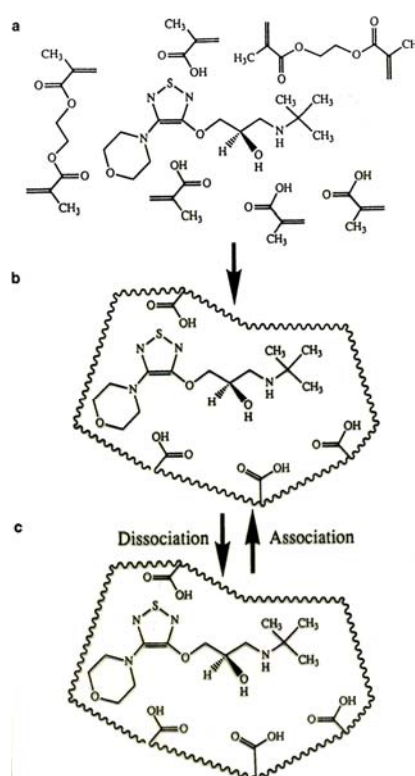
The oligomerization of a dipeptide is given as an example. In the presence of acid the acetal becomes labile and the resulting aldehyde reacts with the hydrazone. Linear and cyclic compounds are obtained. The presence of "template" molecules or additives (crown ether) shifts the equilibrium.





Molecular imprinting

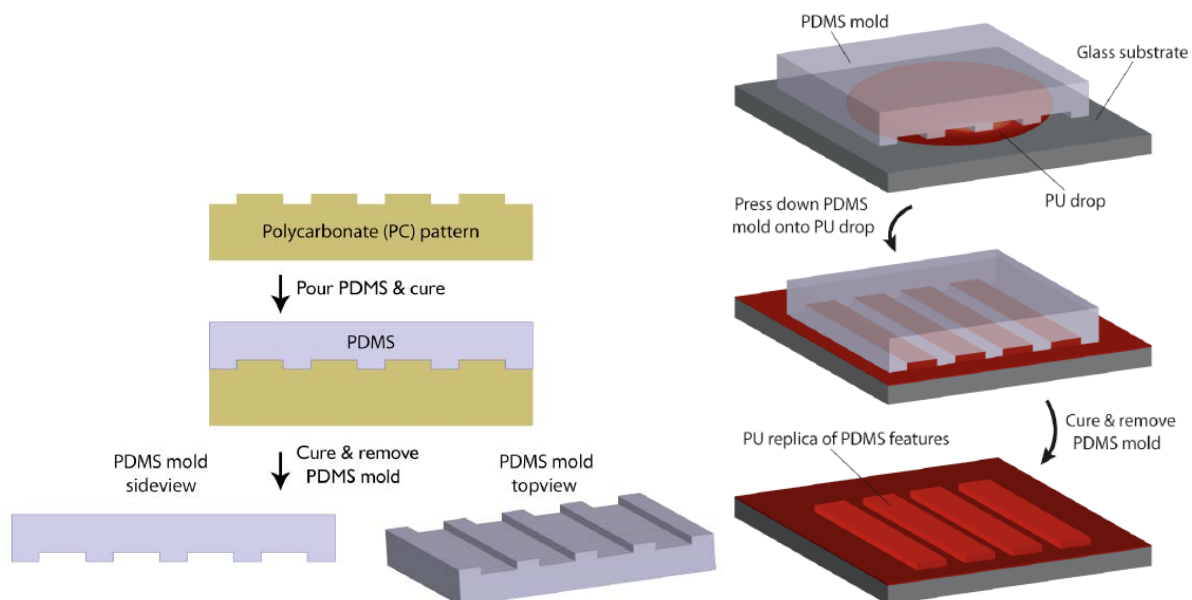
Creating a molecular imprint in a polymeric material is another approach to selective binding sites. A template molecule is dissolved in a polymerizable monomer. Intermolecular forces arrange the monomer molecules around the template. Radical polymerization then covalently locks the arrangement. The obtained polymeric material is ground into small pieces, and the template molecule is extracted. Such materials have been used for chromatographic separations or catalysis. However, the observed selectivities are in many cases only moderate due to the fact that all binding sites are randomly created and different in affinity. This corresponds to the situation in polyclonal antibodies in biology.



Microcontact printing (Softlithographie)

The generation of microstructures is of importance in information technology (micro chip production) and nano science in general (e.g. the fabrication of structured surfaces that show super hydrophobic or super hydrophilic or Lotus effects). The established method to prepare such structures is photolithography: The surface is covered with a photosensitive protection, which is irradiated through a mask. Where light reaches the protection film, it can be dissolved and the uncovered part of the surface is etched.

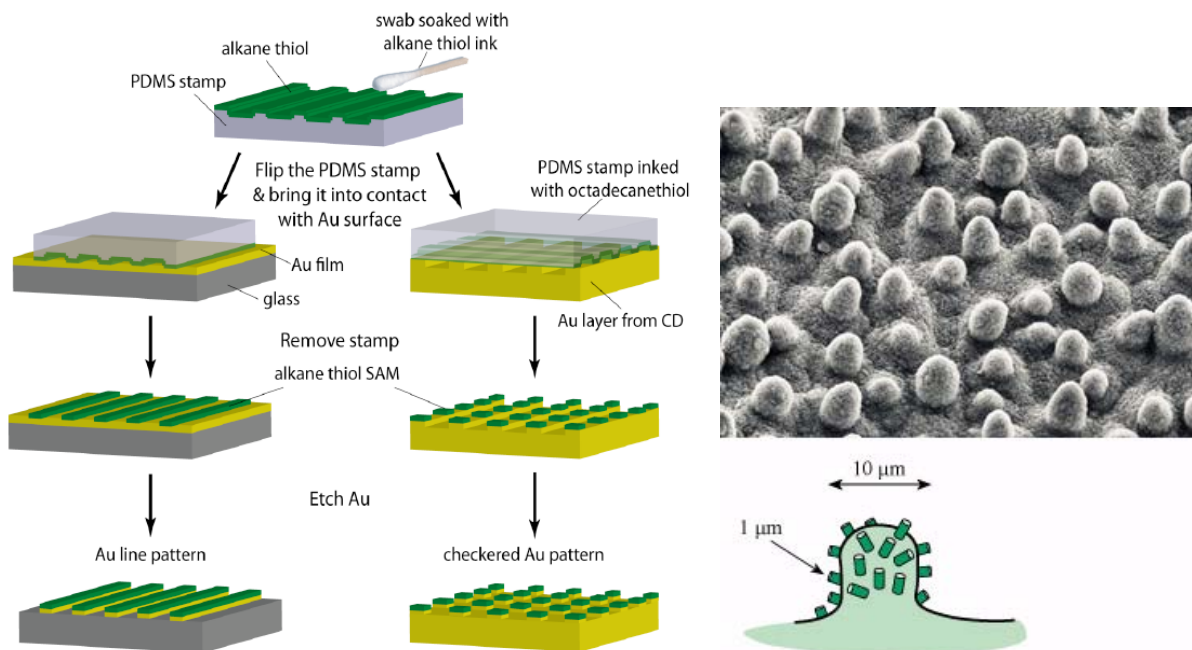
Microcontact printing is an alternative way to prepare structures with dimensions of 30 nm bis 500 μm very efficiently. The procedure is rather simple: We start with a master that can be made from many materials. Poly(dimethylsiloxan) (PDMS), a silicon-based organic polymer, is used to create a mold (Abdruck). The pre-polymer, which is not completely cross-linked, is cured at 70°C for an hour. The PDMS mold is then used as a stamp to create structures on surfaces, e.g. glass or polymers. Using the stamp in different orientations and combining the technique with etching allows to prepare quickly complex structures.



Left: Preparation of PDMS mold; right: printing of replicas of the original master

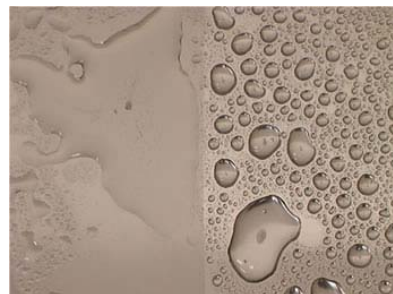
Patterning of a surface leads to interesting effects. The most well known one is the Lotus effect. Microscope observations reveal that the waxy surface of the lotus leaf is made of micron-sized bumps that, in turn, are covered with nanoscale hair-like tubes. This two-fold structure traps air under any rain drops that fall on the leaf, creating a surface that efficiently repels water. Drops merge and roll off taking the dirt of the surface with them.





Left: Microcontact printing and etching of a gold surface; right: Lotus-effect surface

Surfaces that are super hydrophobic can be created, e.g. on silicon. The effect originates from the nanostructure of the surface and leads to a complete repulsion of a water drop (left picture). Super hydrophilic surfaces are the other extreme (left side of the left picture). Coating of a surface with TiO_2 or polar functional groups leads to such effects.



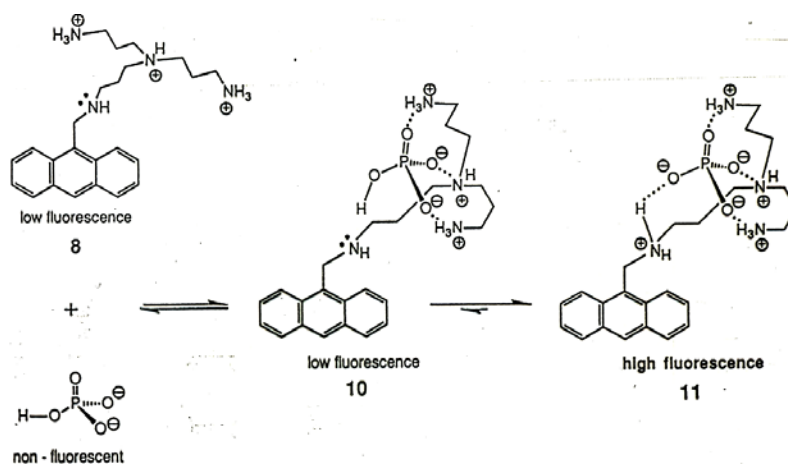
Moving a drop of a liquid on a surface without pumps? This is possible with surfaces that can be switched in their surface properties from hydrophilic to hydrophobic and reverse. Manipulation of liquid drops is of importance for applications in medicinal diagnostics and analytic devices.

Molecular sensors

One important application of supramolecular chemistry is molecular sensors. Molecular sensors are used as molecular probes to determine analytes, e.g. in biological systems (inside a cell, in an organism) that are otherwise difficult to analyse. The table gives some ions of interest in biology; the typical concentration range and the name of the chemosensor used for determination are given.

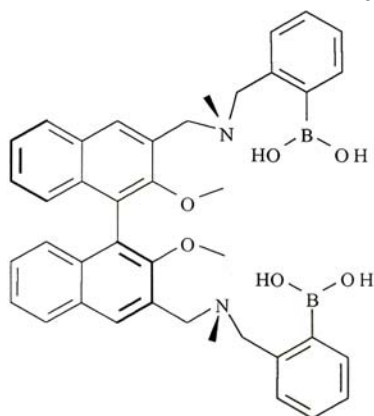
Analyte	Typical Conc. in Resting Cells ^a	Intracellular Physiological Range ^b	Representative Fluorescent Chemosensor(s) ^c	Effective Dissociation Constant ^d	Typical Excitation Wavelengths ^e (nm)	Typical Emission Wavelengths ^e (nm)	Best Detection Mode ^f
H ⁺	100 nM	10-1000 nM	DHPN BCECF SNARF-1	10 nM 107 nM 32 nM	360/420 440/490 517/576	455/512 530 587/640	Em. ratio Exc. ratio Em. ratio
Na ⁺	4-10 mM	0-100 mM	SBFI	18 mM	340/385	530	Exc. ratio
K ⁺	100-140 mM	20-160 mM	PBFI	100 mM	340/350	530	Exc. ratio or Intensity
Cl ⁻	5-100 mM	0-100 mM	SPQ TMAPQ	83 mM 50 mM	350 355	442 450	Intensity Intensity
Mg ²⁺	0.5-2 mM	0.2-5 mM	FURAPTRA= Mag-fura-2	1.5 mM	335/370	510	Exc. ratio
Ca ²⁺	50-200 nM	10 nM-10 μM	quin-2 fura-2 indo-1 fluo-3	115 nM 224 nM 250 nM 400 nM	340 340/380 331/349 500	505 505 405/485 530	Intensity Exc. ratio Em. ratio Intensity
cAMP	<50 nM	0-10 μM	FICHR	100 nM	490	520/590	Em. ratio

To turn an ionophore or a host compound into a sensor, an output must be created to signal the presence of the guest. In most cases fluorescence is used as output, because it can be detected with high sensitivity. A widely employed mechanism to control the emission of a fluorophore by molecular recognition is *photo induced electron transfer* (PET): The nearby presence of a basic site with a free electron pair, e.g. on a nitrogen atom, quenches the emission of a fluorophore by PET. Upon hydrogen bonding to the basic site, the quench mechanism is interrupted and the fluorophore lights up.

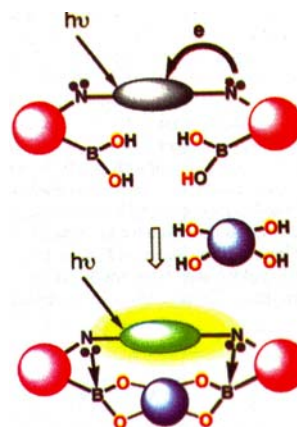


One application is the enantioselective determination of sugars. The chemosensor is based on a chiral binaphthyl core. Boronic acids form boronic esters reversibly with sugar

hydroxyl groups. This process interrupts the PET quenching mechanism and leads to an enhanced emission intensity.

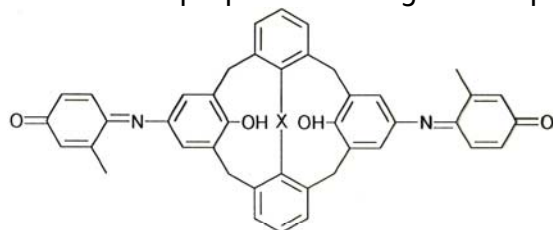


Zucker	Bindungskonstanten	
	D logK	L logK
Fructose	4.0 (3.7)	3.5 (4.0)
Glucose	3.3 (3.4)	3.1 (3.5)
Galactose	3.1	3.3
Mannose	< 2.4	-

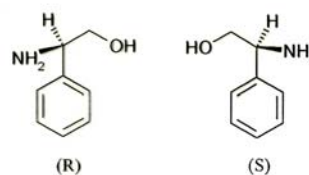
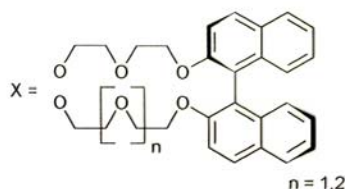


A chiral calixarene-based receptor has been used to distinguish enantiomers of chiral amino alcohols. The binding of the enantiomers to the chiral calixarene has different strengths which leads to different colours of the chemosensor – analyte complex.

The reporting chromophore must not be covalently attached to the synthetic receptor. In an “indicator displacement assay” a weakly bound fluorophore in the receptor site is displaced by the analyte of higher affinity. The bound and free chromophore or indicator has different emission properties and signals the presence or absence of the analyte.



rot

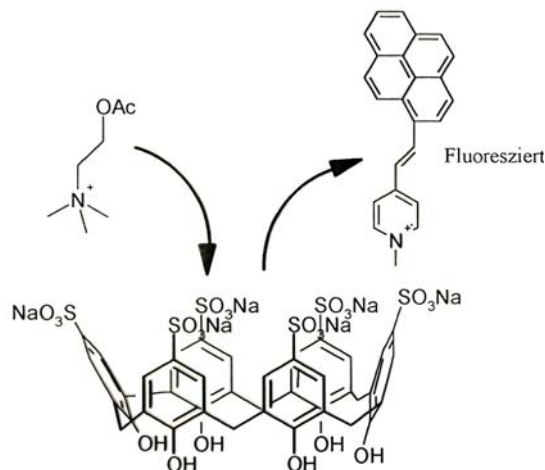


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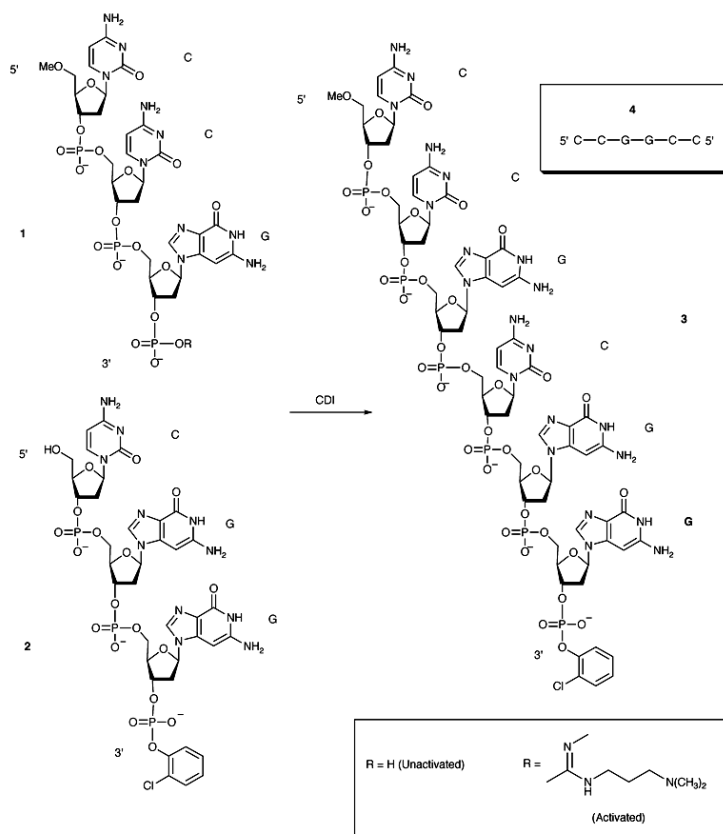
Chemosensor for enantiomers



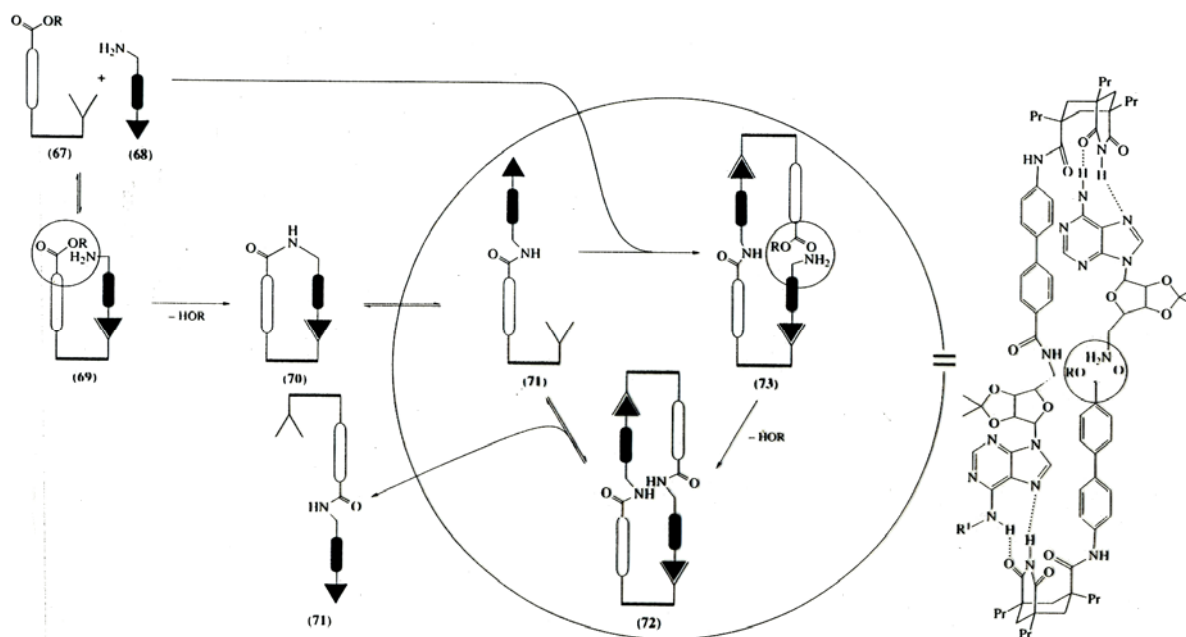
Example of an indicator displacement assay for the neurotransmitter acetyl choline

Replication of molecules

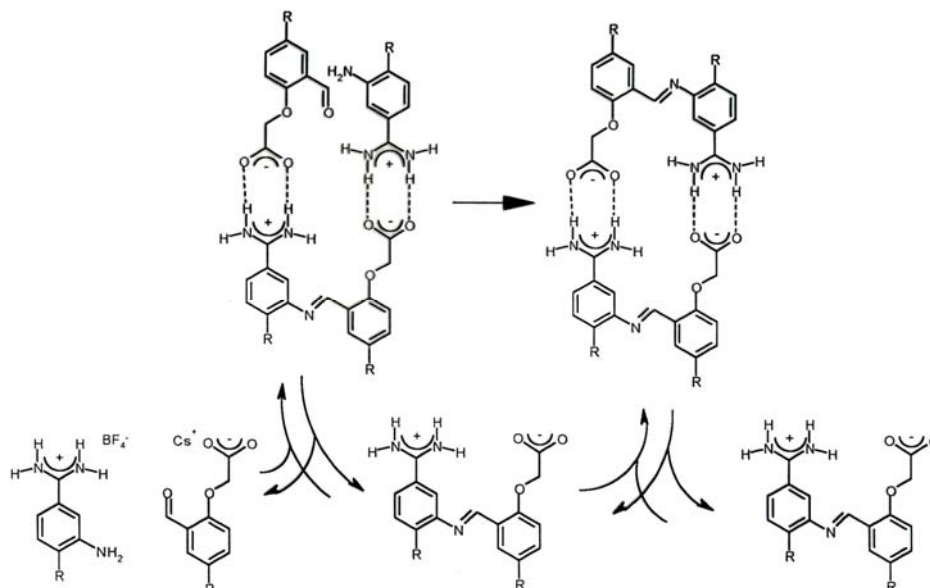
The molecular origin of life is still one of the big unanswered scientific questions. The important characteristic of living systems is their ability to reproduce. To imitate this, chemical systems have been developed that catalyzed their own formation. The first systems were based on DNA. A template DNA strand catalyzes the formation of its complementary copy from two shorter DNA fragments (CDI = carbodiimide).



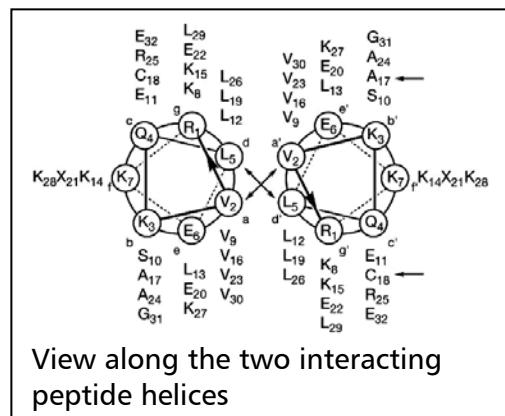
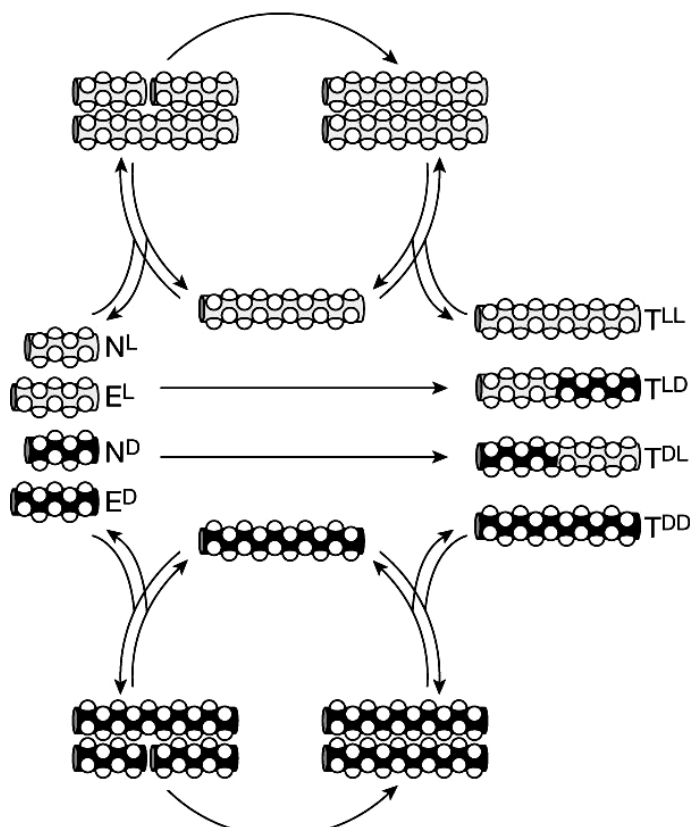
A self-complementary hydrogen bonded system based on Kemp's triacid catalyzes its own formation by the intramolecular formation of an amide bond from an ester and an amine functional group. The preorganisation on the template catalyzes the amide bond formation.



Salt-bridges as intermolecular forces for preorganization have been used in another example, which uses a Schiff base formation to replicate a molecule.

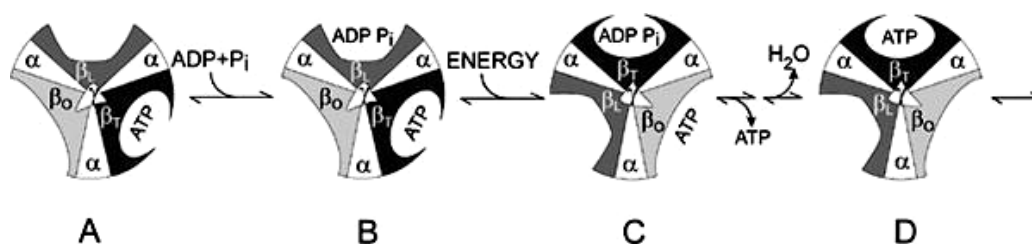
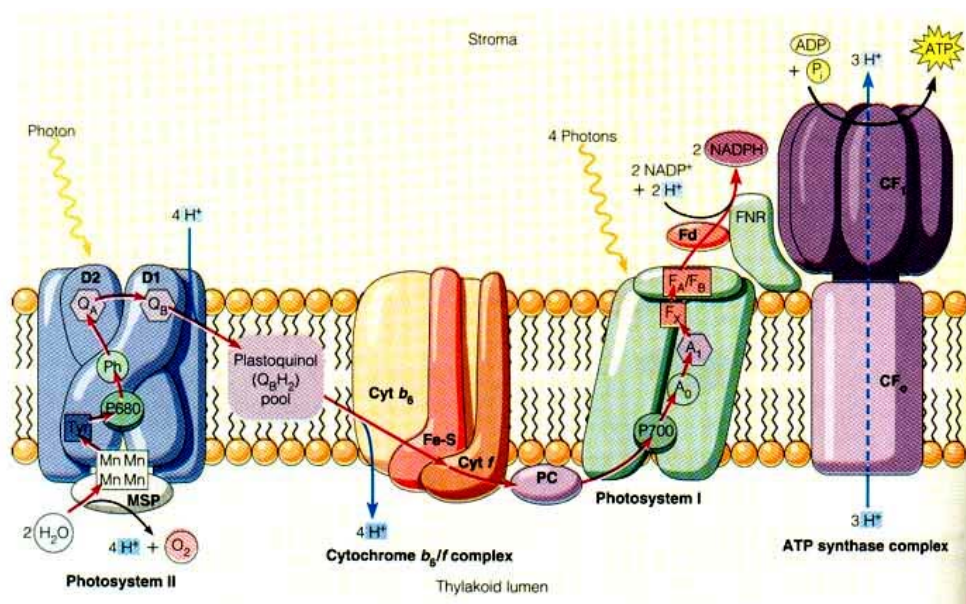


The interaction of hydrophobic functional groups of peptide alpha helices can also serve as an intermolecular interaction in a replication system. Leucine and valine rich parts of a template helix orient two shorter peptide helix parts so that they spontaneously form a covalent connection giving a new template peptide helix. Two of such replicating systems can operate in the same flask without interference. In such minimal replicating systems molecular evolution can be investigated: Which peptide helix replicates faster? Do we see hybrid structures of mixed helices? Is there a survival of the fittest molecule?



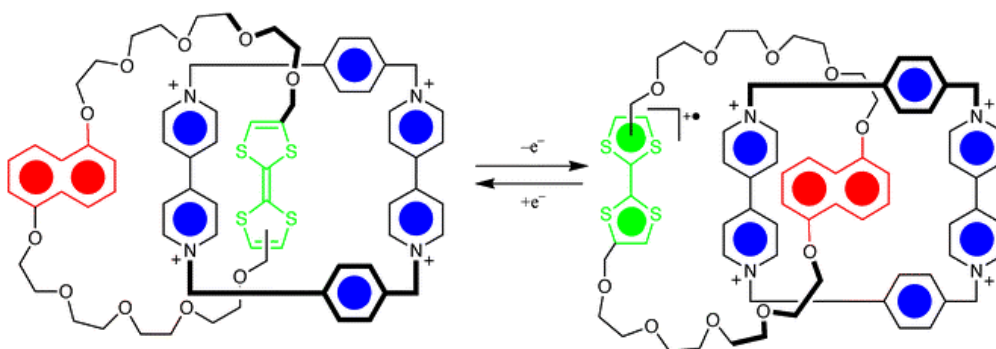
Molecular machines

Is it possible to create machines that operate on a molecular level? Yes, but it is not easy. A perfect example from nature is the enzyme ATP synthase, which converts ADP and inorganic phosphate into ATP using mechanical rotation driven by a proton gradient (Nobel prize in chemistry in 1997, see: <http://nobelprize.org>).

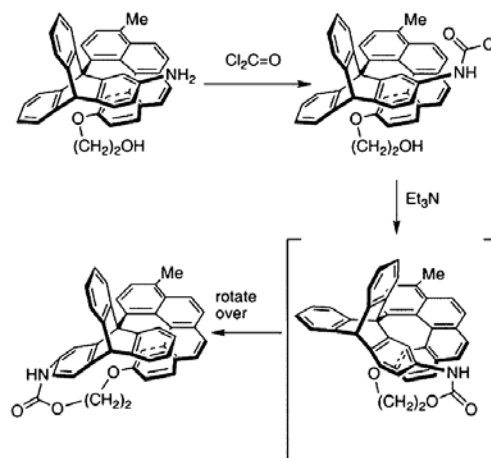


The ATP synthase as part of the cellular machinery (top) and the rotational mechanism of ATP synthesis.

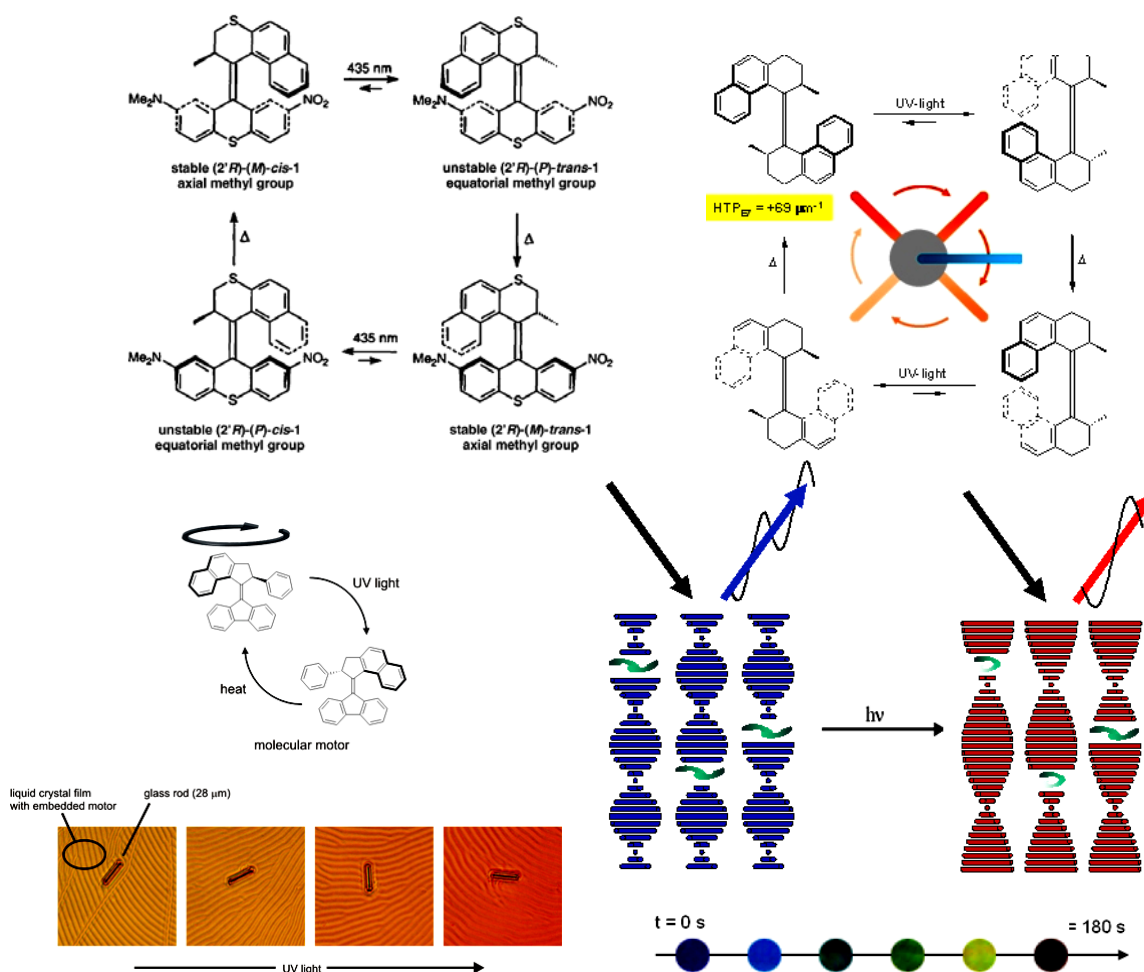
Catenanes made from electron rich and electron poor arenes can undergo a ring-slipping movement on oxidation or reduction. However, the direction of the movement is random.



Unidirectional movement on the molecular level has been achieved with very few systems. A molecular ratchet (right) was one of the earlier molecules, but the movement is not completely controlled in its direction.

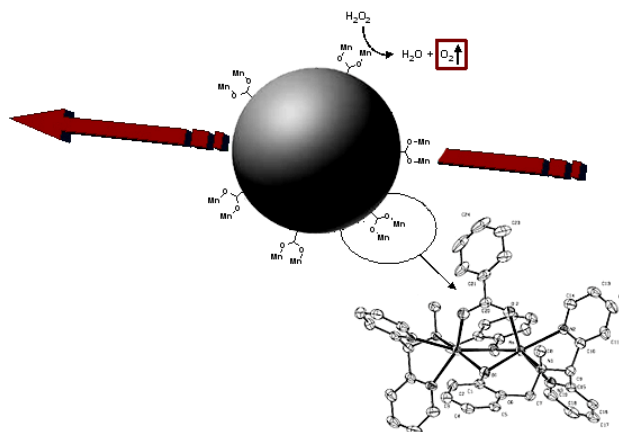


A sequence of photoisomerization and thermal relaxation steps is the most advanced and practical systems known today. The light-induced isomerization of such a molecular motor in a liquid crystalline (LC) matrix leads to a rotational reorganization of the LC film and rotation of microscale particles floating on top. Doping of a nematic liquid crystalline film with 6 wt% molecular motor resulted in a colored cholesteric phase which, upon irradiation, changed color due to the conformational change of the motor.



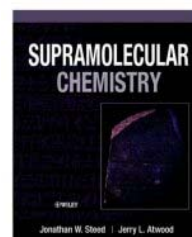
Left: Movement of a small glass rod on a liquid crystalline matix by the embedded molecular motors; right: colour change by moving the chiral motors along the liquid crystalline structure

A synthetic catalase mimic, covalently attached to a SiO₂ microparticle, induces the catalytic disproportionation of hydrogen peroxide to oxygen and water, resulting in both translational and rotational motion of the microparticle.

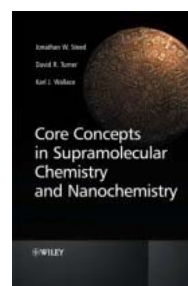


Literature

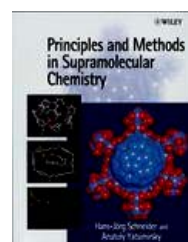
Supramolecular Chemistry
Jonathan W. Steed, Jerry L. Atwood,
Wiley



Core Concepts in Supramolecular Chemistry and Nanochemistry
Jonathan W. Steed, David R. Turner, Karl Wallace,
Wiley



Principles and Methods in Supramolecular Chemistry,
Schneider, Hans-Jörg / Yatsimirsky, Anatoly, Wiley-VCH



End of the handout