

Lezione 3

- Cooperativity and the chelate effect
- Selectivity (thermodynamic, kinetic)
- The supramolecular interactions
- H-bonds and supramolecular polymers

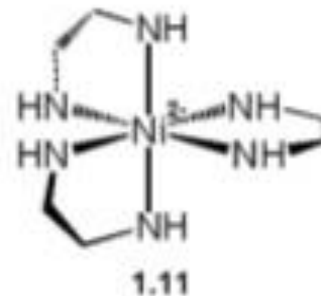
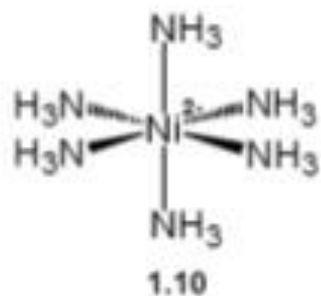
Cooperativity

- Much of the emphasis in the construction of supramolecular host molecules concerns bringing about summative or even multiplicative interactions.
- This means that we can construct a stable host–guest complex using (often weak) non-covalent interactions if we ensure that there are as many as possible of these interactions stabilising the complex.
- The small amount of stabilisation energy gained by any one such interaction when added to all the other small stabilisations from the other interactions (summative) results in a significant binding energy and hence complex stability. In some cases, the interaction of the whole system is synergically greater than the sum of the parts (multiplicative).

Cooperativity and the chelate effect

- The chelate effect is the enhanced affinity of chelating ligands for a metal ion compared to the affinity of a collection of similar nonchelating (monodentate) ligands for the same metal.

The Chelate and Macrocyclic Effects



$$\ln K = -\frac{\Delta G}{R \cdot T}$$

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

$$\rightarrow \ln K = -\frac{\Delta H}{R \cdot T} + \frac{\Delta S}{R}$$

K = complexation constant

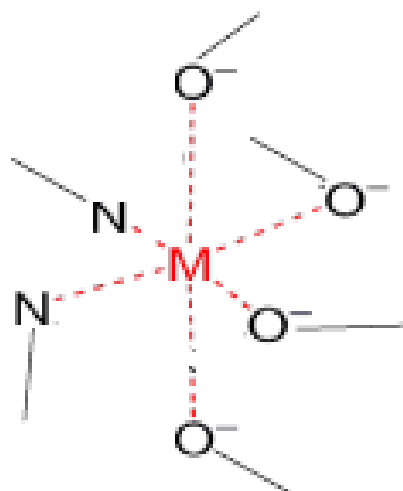
- Thermodynamic; favorable ΔS (4 molecules reactants, 7 products) and ΔH
- Kinetic: once tethered with the first N the attachment of the second N of the bidentate is favored
- If concentrations are converted in mole fraction the chelate effect almost disappears
- Measurements in gas phase indicate little stability difference between chelate and nonchelate complexes

The chelate effect

Why do macrocyclic molecules (e.g. crown ethers) have such high affinities for cations?

Single interaction pairs must be very strong to prevent rapid dissociation

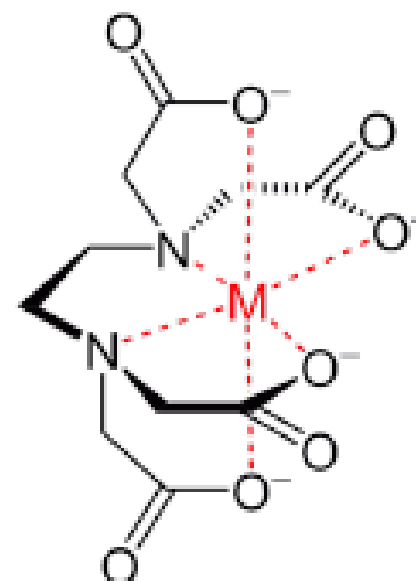
In a chelator (or a macrocyclic molecule) multiple interaction sites are provided by the same molecules



Connect the interacting moieties and the affinity increase by orders of magnitude

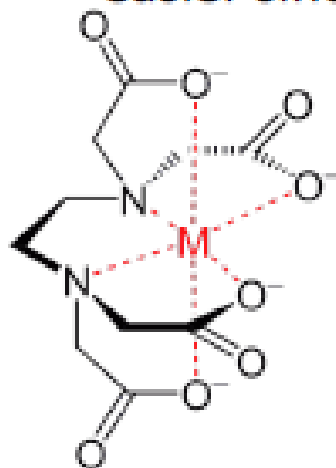


The chelate effect!



The chelate effect

- In order for a chelator to dissociate multiple interaction must be broken simultaneously
- When the first interaction has formed the next interactions form easier since the binding sites are already in close proximity



- The loss in entropy is smaller when only two species associate as compared to a multi-ligand complex
- Topological effects and preorganization can further improve the binding

EDTA: un host ideale

Table 3.1 Stability constants (Log K) in aqueous solution for metal complexes of EDTA⁴⁻.

Mg ²⁺	8.7	Zn ²⁺	16.7	La ³⁺	15.7
Ca ²⁺	10.7	Cd ²⁺	16.6	Lu ³⁺	20.0
Sr ²⁺	8.6	Hg ²⁺	21.9	Sc ³⁺	23.1
Ba ²⁺	7.8	Pb ²⁺	18.0	Ga ³⁺	20.5
Mn ²⁺	13.8	Al ³⁺	16.3	In ³⁺	24.9
Fe ²⁺	14.3	Fe ³⁺	25.1	Th ⁴⁺	23.2
Co ²⁺	16.3	Y ³⁺	18.2	Ag ⁺	7.3
Ni ²⁺	18.6	Cr ³⁺	24.0	Li ⁺	2.8
Cu ²⁺	18.8	Ce ³⁺	15.9	Na ⁺	1.7

Preorganization

A host is **preorganized** if no or very limited structural alterations is needed to effectively bind the guest. The host is optimally preorganized if:

- The geometry allows all interaction sites to be engaged without structural reorganization
- Binding do not result in a build up of strain in either host or guest, i.e. the free energy of the complex is the same as for the lowest energy conformation of the host and guest prior binding

Results in high selective since fewer guest can bind optimally to the host!

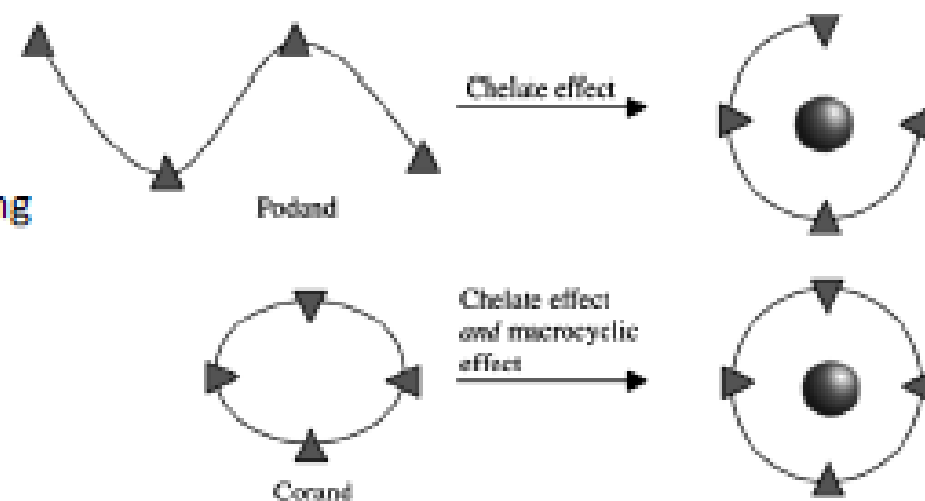


Fig 1. 11 Steed&Atwood

The Chelate and Macrocyclic Effects

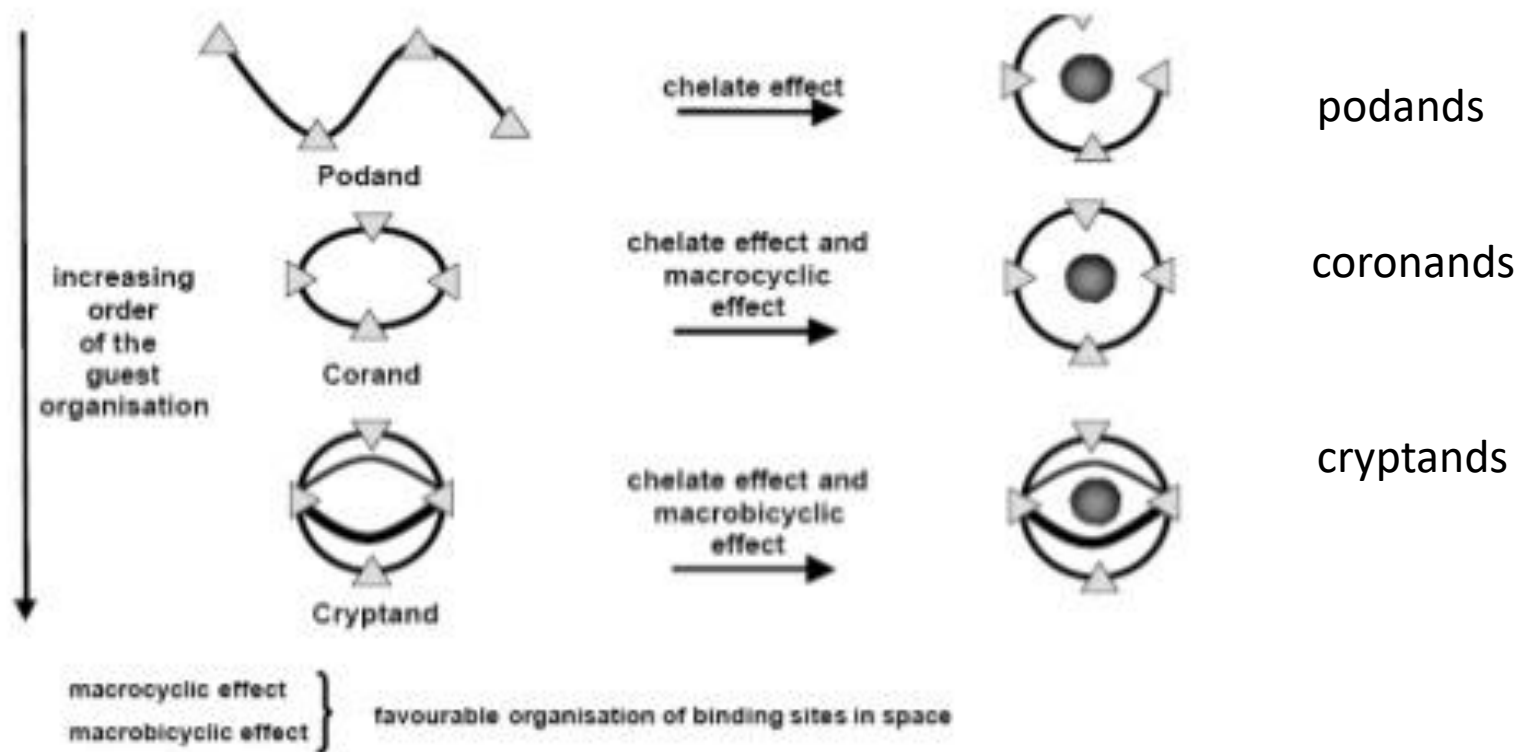
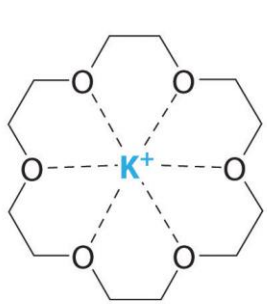


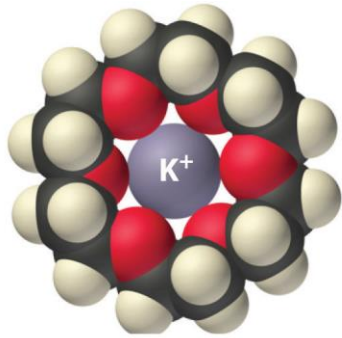
Fig. 1.7 The chelate, macrocyclic and macrobicyclic effect.

Chelate effect, preorganization of the host

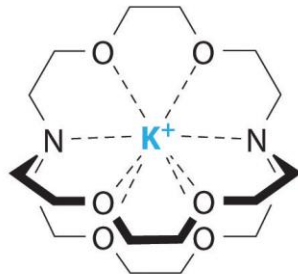
preorganization



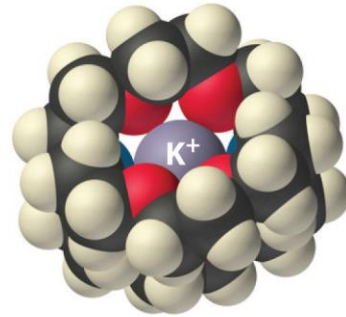
(a) Crown ether



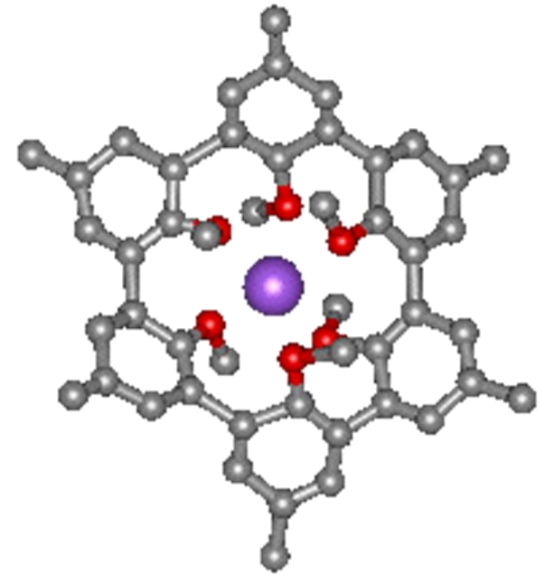
[18]CROWN-6



(b) Cryptand



CRYPTAND



SPHERAND-6

The macrocyclic effect

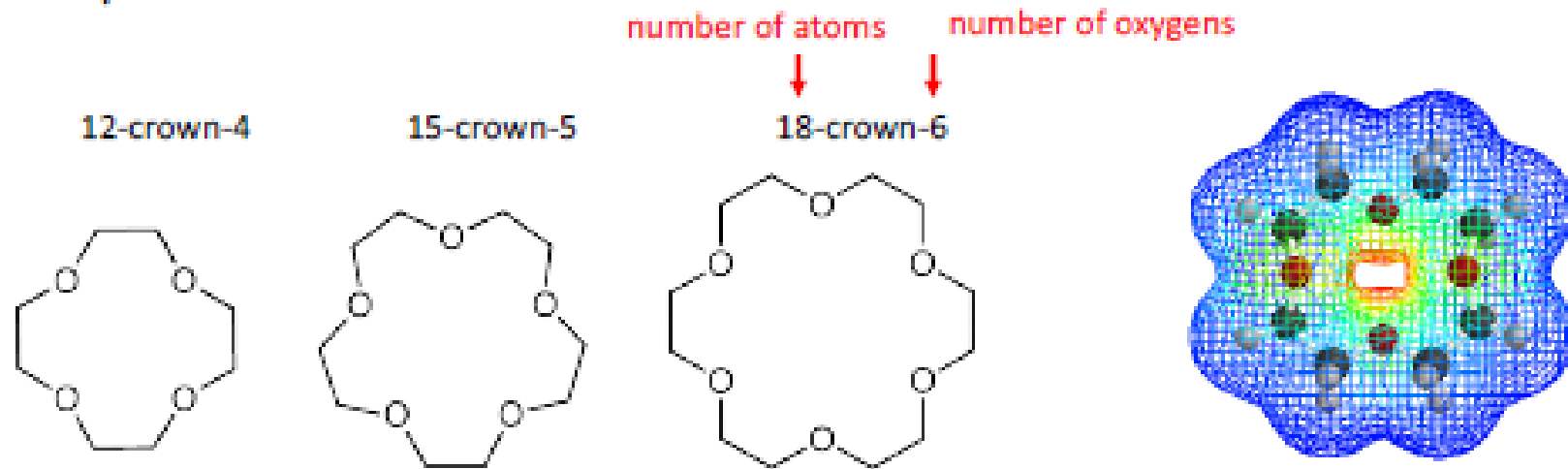
- A cyclic host (e.g. a crown ether) is more preorganized than a linear host (e.g. a normal linear ether) which result in both higher affinity and selectivity for binding of the guest:
 - More rigid (fewer degrees of freedom) leads to less conformational entropic loss upon binding of the guest
 - Can provide multiple optimally preorganized interaction sites without structural reorganization

$$\text{Macrocyclic effect} = \Delta \log \beta = \log \beta_{\text{macrocycle}} - \log \beta_{\text{linear}}$$

Affinity and Selectivity

High complementarity often result in high affinity!

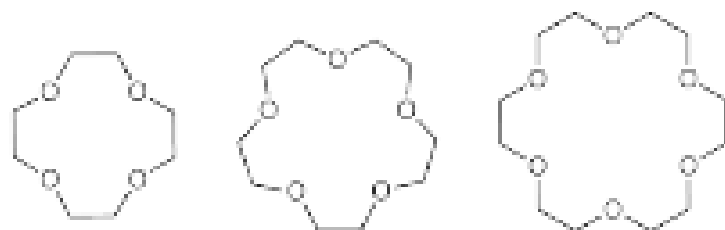
Example: Crown ethers



Charles Pedersen was awarded with the Noble prize in chemistry in 1987 for the discovery of the crown ethers

The lone electron pair of the oxygen atoms give the cavity a net negative charge

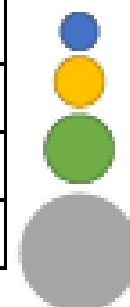
Crown ethers



Guest

	12-crown-4	15-crown-5	18-crown-6
Diameter (Å)	1.2-1.5	1.5-2.2	2.6-3.2
Li ⁺ (1.36 Å)	-0.57	1.21	-
Na ⁺ (1.94 Å)	1.67	3.32	4.28
K ⁺ (2.66 Å)	1.6	3.5	5.67
Cs ⁺ (3.34 Å)	1.63	2.74	4.5

(Log K_a in methanol)



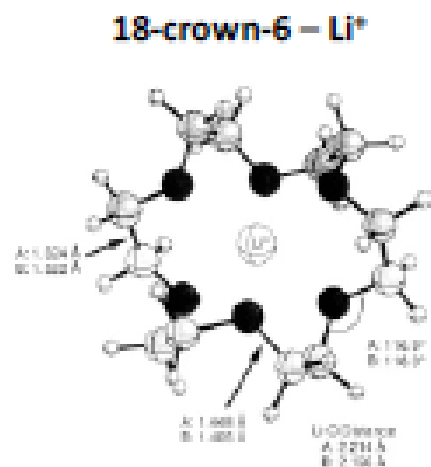
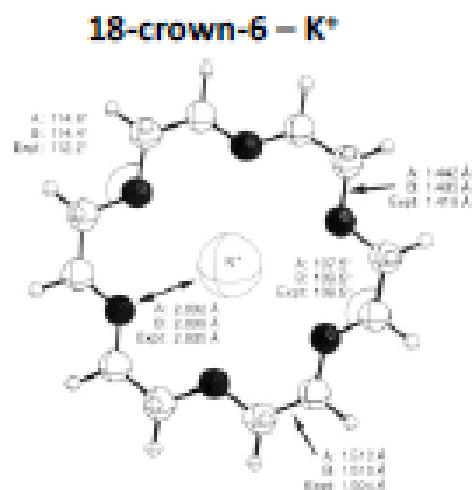
Balance between steric complementarity and number of possible interactions!

Note that solvation energy increases as:
 $\text{Cs}^+ < \text{K}^+ < \text{Na}^+ < \text{Li}^+$

Crown ethers are not completely rigid

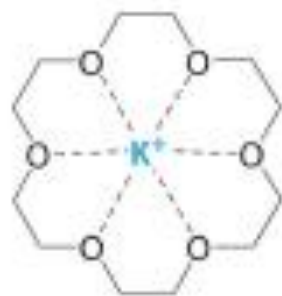
Crown ethers

Structural flexibility enables the crown ethers to bind cat ions with different sizes but at cost of build up of strain.

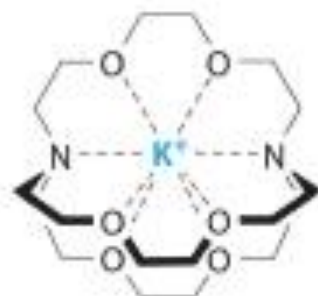


Cryptands – the more rigid version

What happens when we make the host more rigid?



(a) Crown ether

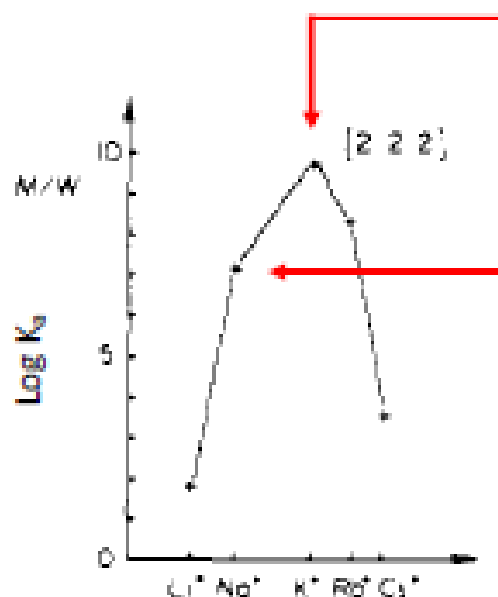
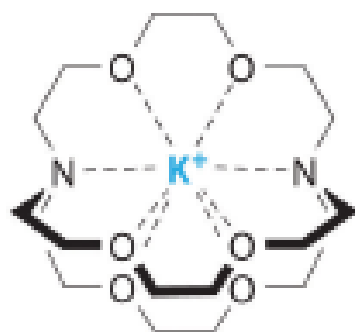


(b) Cryptand



Cryptands

[2.2.2]cryptand



More than 10^5 times higher K_a than the corresponding crown ether (10^{10} vs $10^{1.6}$)!

Much more selective, i.e. large difference in affinity for different ions!



High complementarity result in high affinity!
Constrained flexibility results in high selectivity!



Selectivity is the basis for molecular recognition!

Thermodynamic and kinetic selectivity and discrimination

- The goal of supramolecular host design in nature (enzymes, receptors) and in artificial systems is the achievement of selectivity.
- That means discrimination of different guests
- In the blood, hemoglobin is finely tuned to selectively take up the O₂ and not N₂ or CO₂ and even substances as CO that normally binds strongly to iron.
- In **thermodynamic terms, the selectivity is simply the ratio of the binding constant of a guest over another:**

$$\text{SELECTIVITY} = K_{\text{guest1}}/K_{\text{guest2}}$$

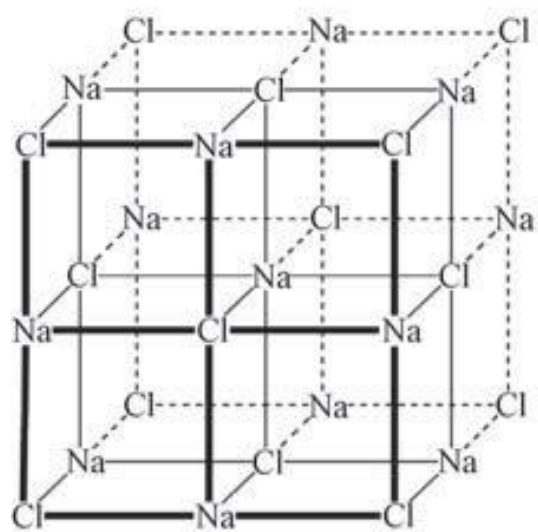
- This kind of selectivity is the most easy to achieve because is susceptible to manipulation by intelligent applications of concepts such as lock and key analogy, proorganization and complementarity.
- So we can say that [18]crown-6 is 100 folds selective on K^+ ($K_a = 10^6$) over Na^+ ($K_a = 10^4$).
- There is another selectivity which relates to rate of transformation of competing substrates along a reaction path.
- This is a **kinetic selectivity** and is the basis for directing the flow of directional processes such as supramolecular (enzymatic) catalysis and guest sensing and signalling.
- The guest that is transformed fastest, rather than the one that is bound stronger, the system is said to be selective for.
- This selectivity is much more difficult to achieve because it requires the **adaptation of the host to the changing needs of the guest.**

Nature of supramolecular interactions

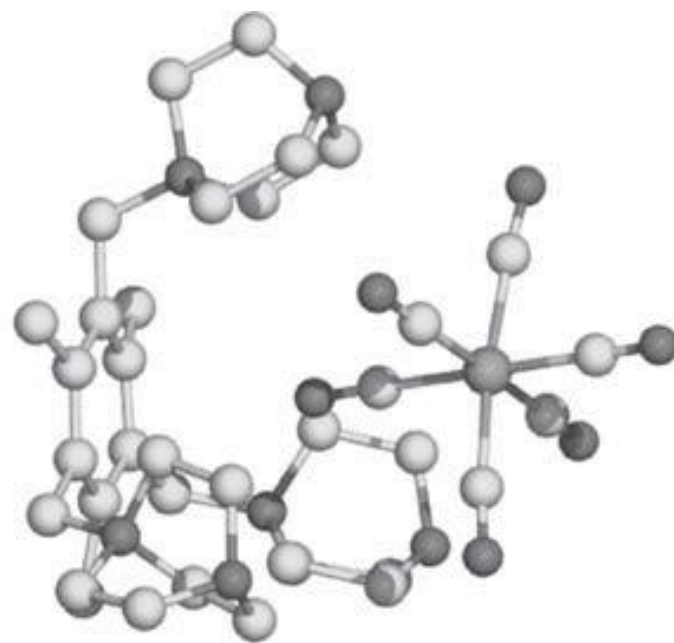
- When considering a supramolecular system it is important to consider the interplay of all interactions: host (convergent), guest (divergent), solvation, ion pairing, crystal lattice, gas phase, etc...).
- The main forces playing a role are the following interactions:
 - Ion-ion
 - Ion-dipole
 - Dipole-dipole
 - Hydrogen bonding
 - Cation- π
 - Anion- π
 - π - π
 - Van der Waals forces
 - Closed shell interactions
 - Hydrophobic effect
 - solvation

Ion-ion interactions

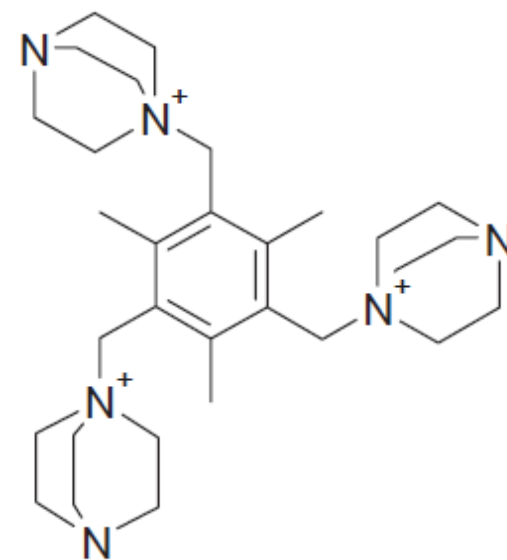
- Comparable strength to covalent bond (100-350 kJ/mol)
- Na Cl supramolecular compound (ionic lattice): Na^+ organizes 6 complementary donor atoms (anions) around himself in order to maximize non-covalent ion-ion interactions
- The lattice structure breaks down in the solvent because solvation effects giving the labile, octahedral $\text{Na}(\text{H}_2\text{O})_6$
- More supramolecular example: tris(diazbicyclooctane) host with $[\text{Fe}(\text{CN})_6]^{3-}$



(a)



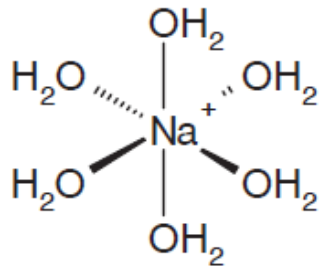
(b)



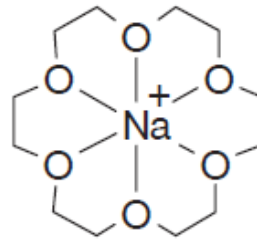
1.17

Ion-dipole interactions

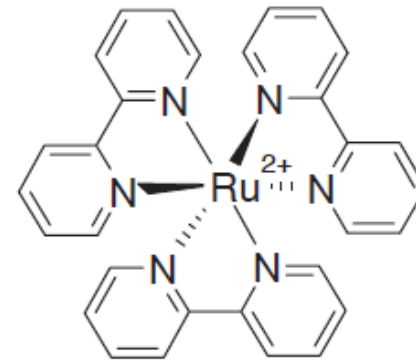
- The binding of an ion Na^+ with a polar molecule such as water, ion-dipole interaction with an energy of about 50-200 kJ/mol.
- Interaction between cations and macrocyclic ethers (crown ethers), in which the oxygen are convergent donors, same role than water molecules but with chelate effect and preorganization
- Coordinative dative bonds with a significative covalent character in $[\text{Ru}(\text{bpy})_3]^{2+}$



1.18

Na⁺ crown ether complex

1.19

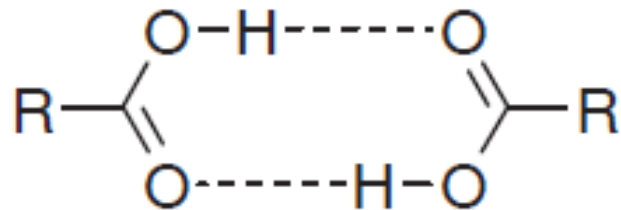


bpy = 2,2'-bipyridyl

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

Hydrogen bonding

- D.....H-A where A is an electronegative etheroatom (O, N)
- H attached to carbon can give H bonds too
- Highly directional nature: H bonds have been defined as «masterkey interaction in supramol chem»
- Energy: from 5 to 30 kJ/mol
- Excellent example are carboxylic acids dimers
- Hydrogen bonds are ubiquitous in supramolecular chemistry. In particular, hydrogen bonds are responsible for the overall shape of many proteins, recognition of substrates by numerous enzymes, and (along with π - π stacking interactions) for the double helix structure of DNA .



O-H, N-H but also C-H are H bond donors

- While C—H donor hydrogen bonds are at the weaker end of the energy scale of hydrogen bonds, the presence of electronegative atoms near the carbon can enhance significantly the acidity of the C—H proton, resulting in a significant dipole.
- An elegant example of C—H ... N and C—H ... O hydrogen bonds is the interaction of the methyl group of nitromethane with the pyridyl crown ether.

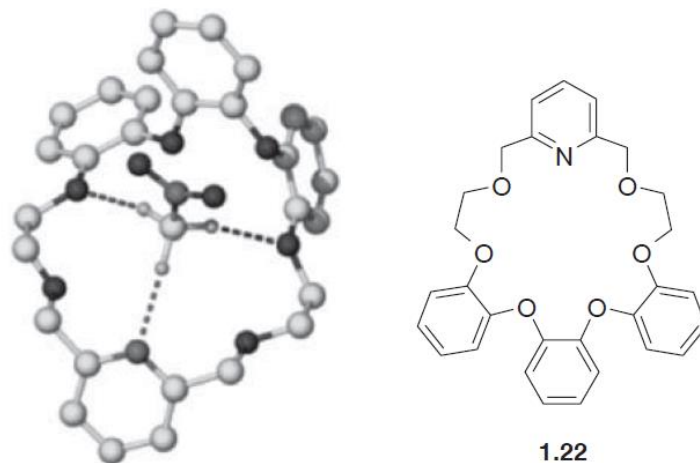
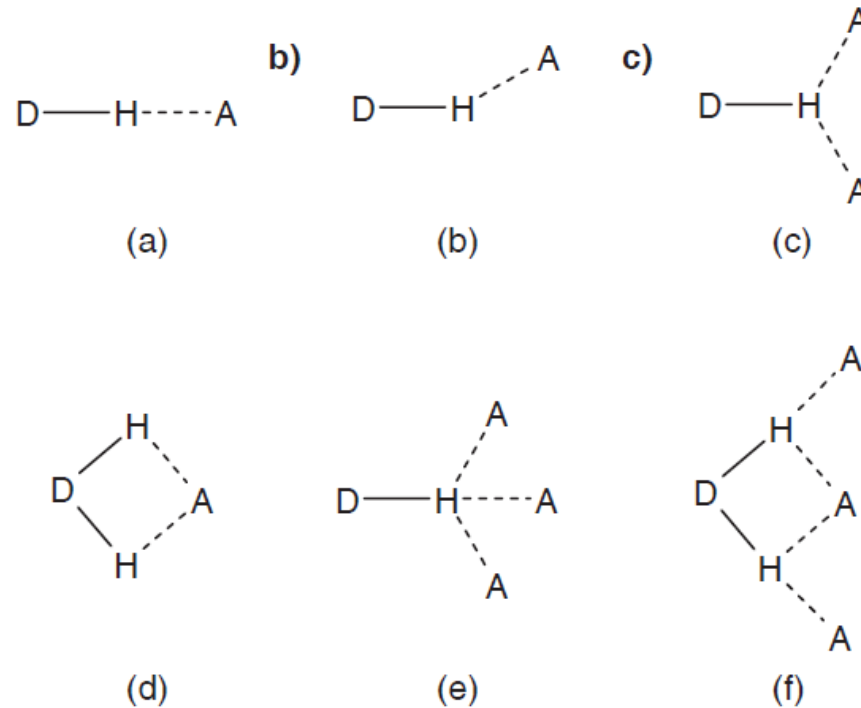


Figure 1.15 X-ray crystal structure showing C—H...N (2.21Å) and C—H...O (2.41Å, average) hydrogen bonding in a complex of crown ether **1.22** with nitromethane.¹⁷

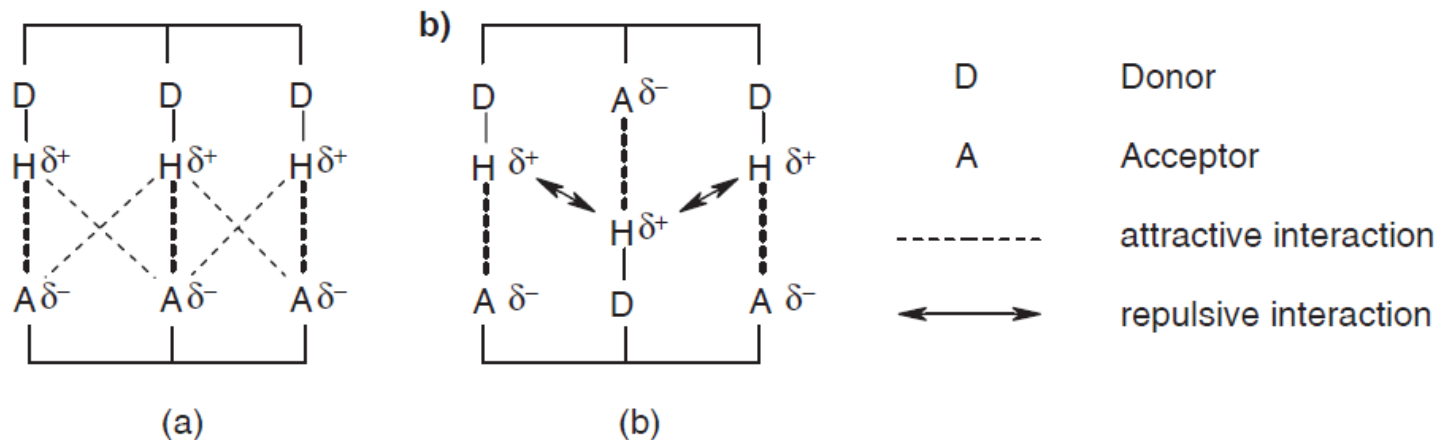
Different geometries: two- and three-center are weaker than two-center



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

Sequences of H bonds

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



Nel DNA, la coppia G-C è meglio di A-T perché ha 3 H bond primari e due interazioni secondarie attrattive e due repulsive contro 3 primari e 4 repulsive, masi può fare di meglio

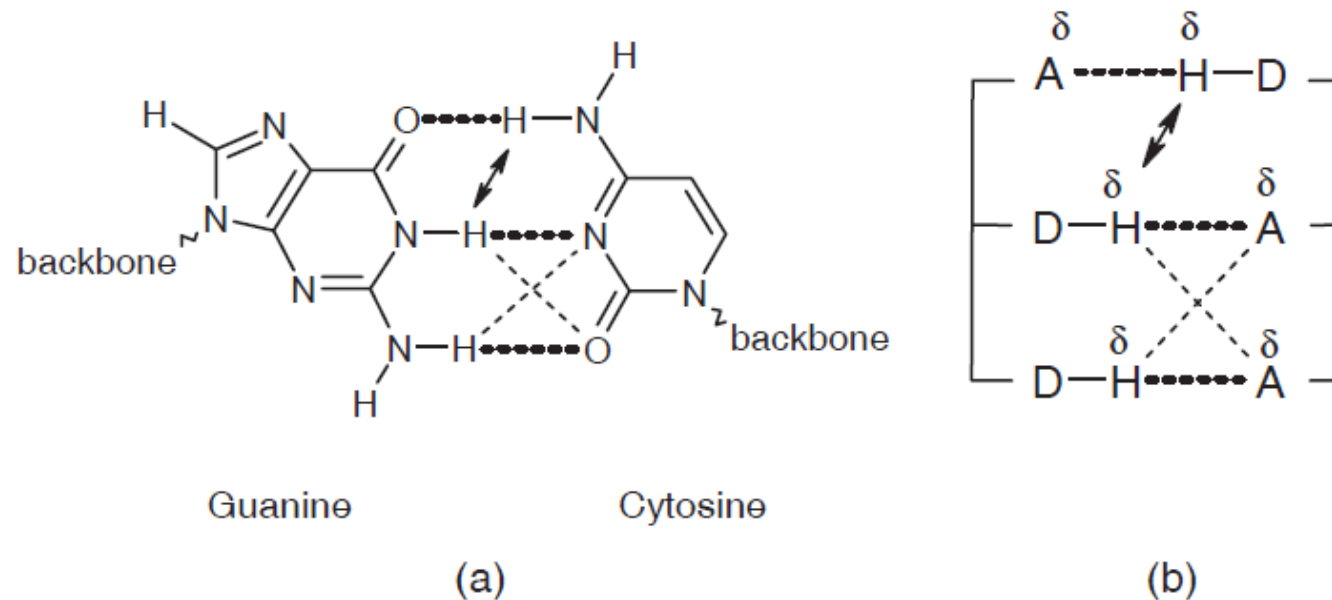
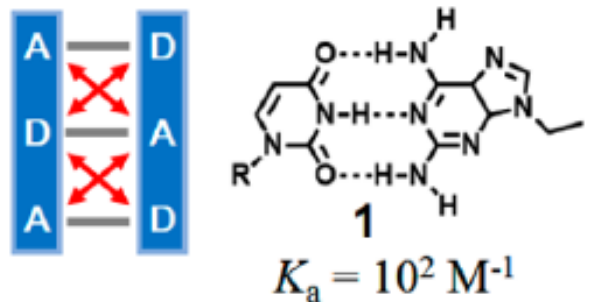
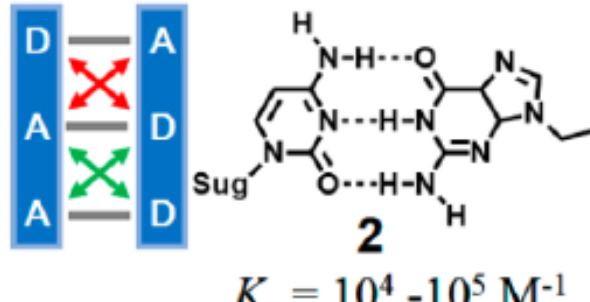
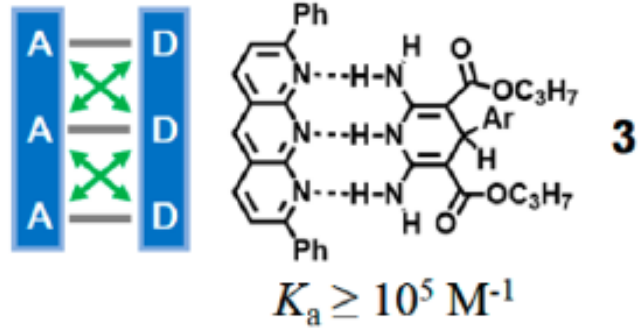


Figure 1.18 (a) Primary and secondary hydrogen bond interactions between guanine and cytosine base pairs in DNA and (b) a schematic representation.

Triple H-bond interaction: A-T and C-G interactions in DNA: chemist could create a stronger interaction!!

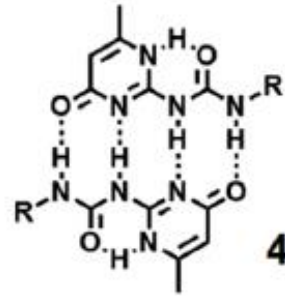
Type	Example
Triple	 <p data-bbox="1019 806 1274 863">$K_a = 10^2 \text{ M}^{-1}$</p>
	 <p data-bbox="1630 821 1987 878">$K_a = 10^4 - 10^5 \text{ M}^{-1}$</p>
	 <p data-bbox="1312 1192 1567 1249">$K_a \geq 10^5 \text{ M}^{-1}$</p>

It was found that although the DAA–AAD and ADA–DAD arrays have an equal number of hydrogen bonds, the binding constant of DAA–AAD arrays 2 is significantly higher than that of ADA–DAD arrays 1 ($K_a \approx 10^4$ vs 10^2 M^{-1}), on account of the additional attractive secondary electrostatic interactions in DAA–AAD arrays.

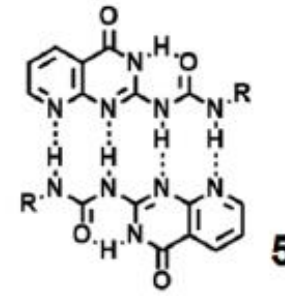
Later on, Zimmerman et al. confirmed that the AAA–DDD arrays 3 indeed have a significantly higher binding constant ($K_a > 10^5 \text{ M}^{-1}$ in CDCl_3), due to the solely attractive secondary interactions

Quadruple and sextuple interaction

Quadruple



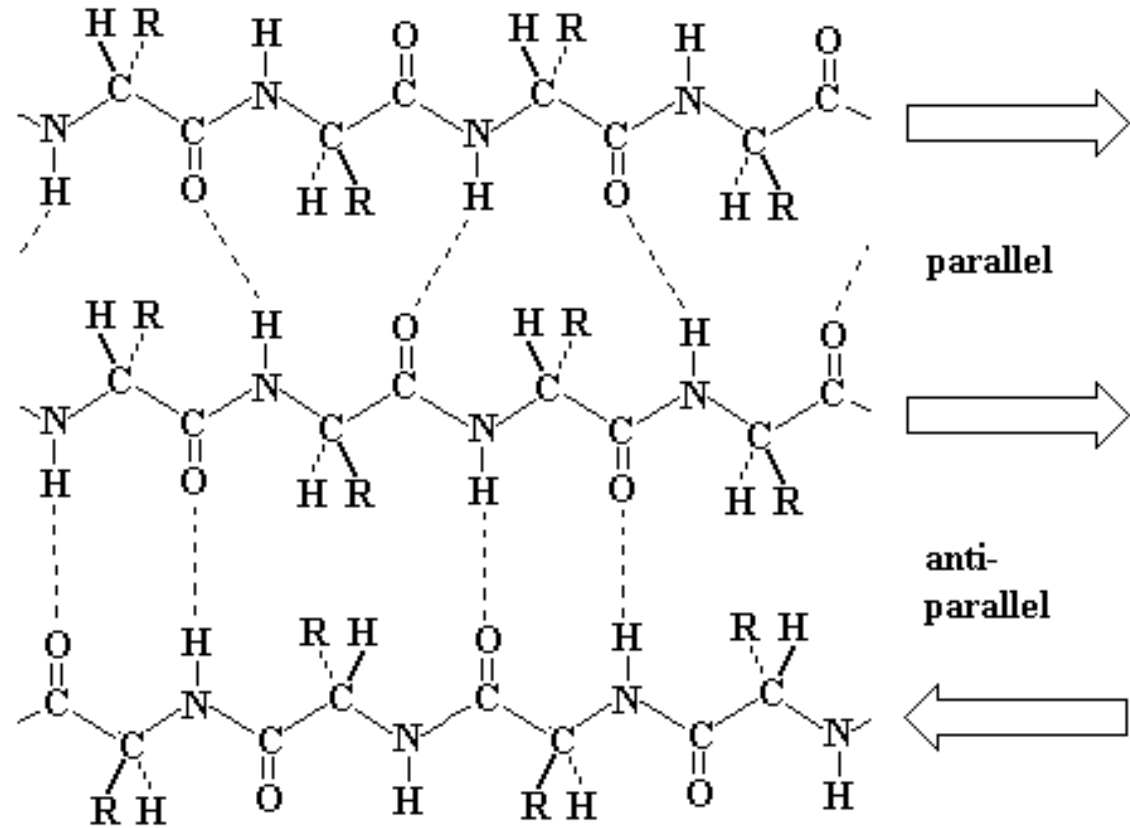
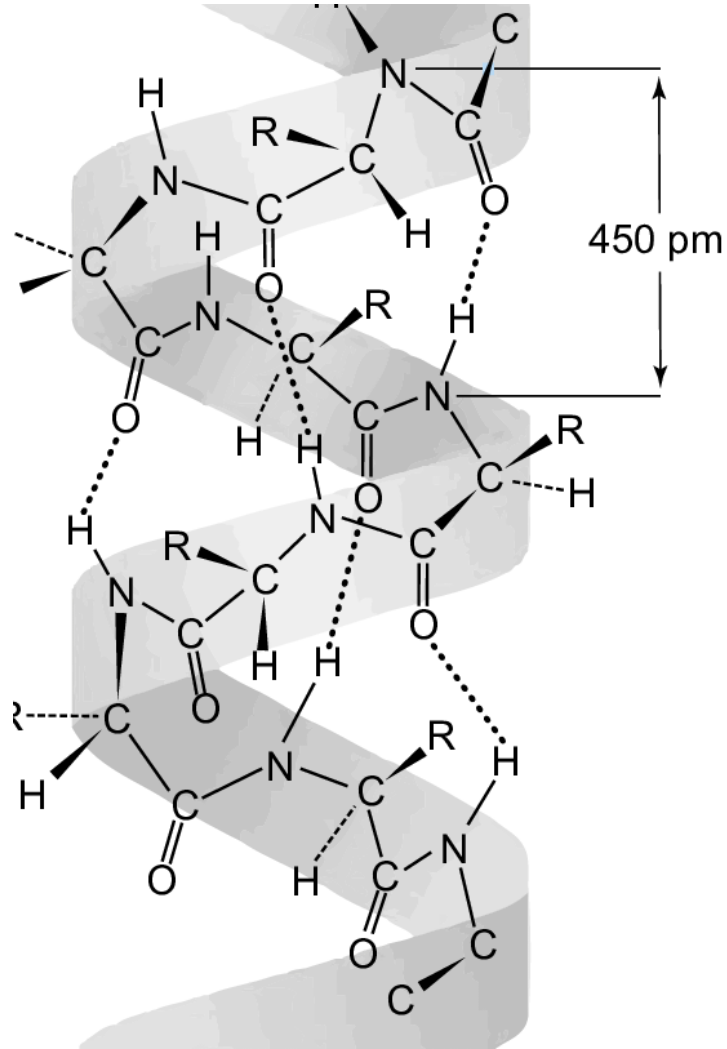
$K_a = 10^7 \text{ M}^{-1}$
Upy-Upy in CHCl_3



$K_a = 10^7 \text{ M}^{-1}$
DeAP-DeAP in CDCl_3

According to this secondary interaction rule, multiple-hydrogen-bonding arrays were designed, with binding constants even higher than those of triple-hydrogen-bonding arrays. In 1997, Meijer et al. reported a self-complementary quadruple-hydrogen-bonding unit, ureidopyrimidinone (UPy) 4, with a dimerization constant K_{dim} of up to $6 \times 10^7 \text{ M}^{-1}$ in CHCl_3 (Table 1).^{16,17} The high dimerization constant of UPy derives from its AADD array of donor and acceptor groups. Analogous

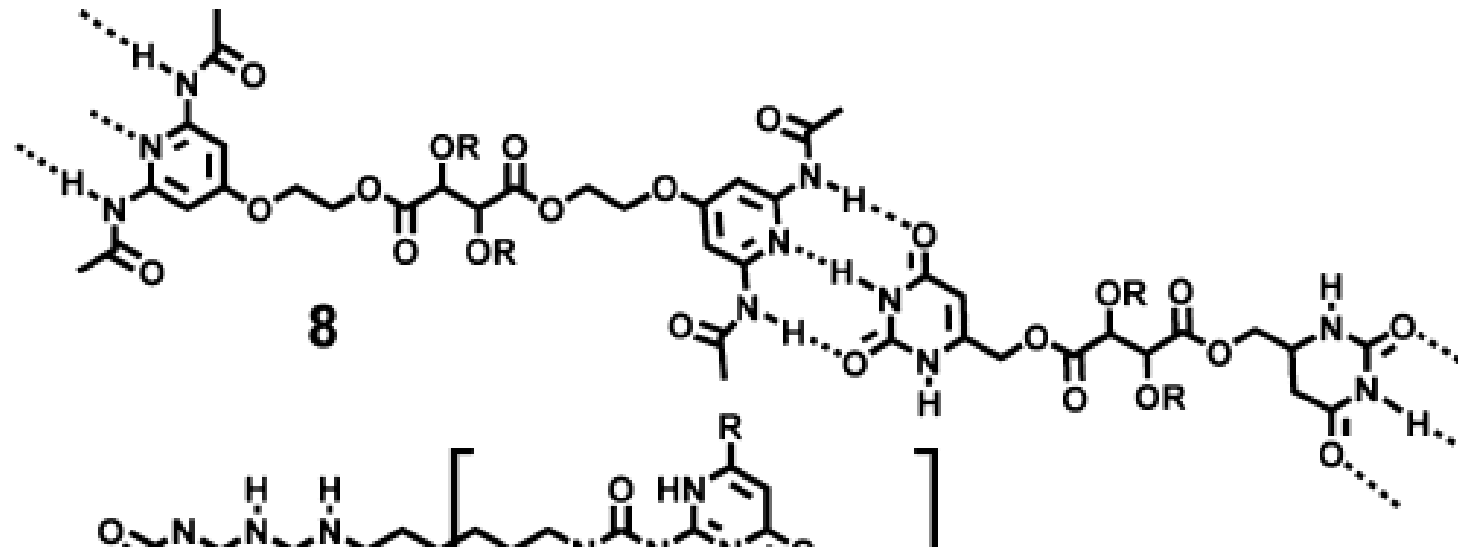
Protein's secondary structures: α -helices and β -sheets



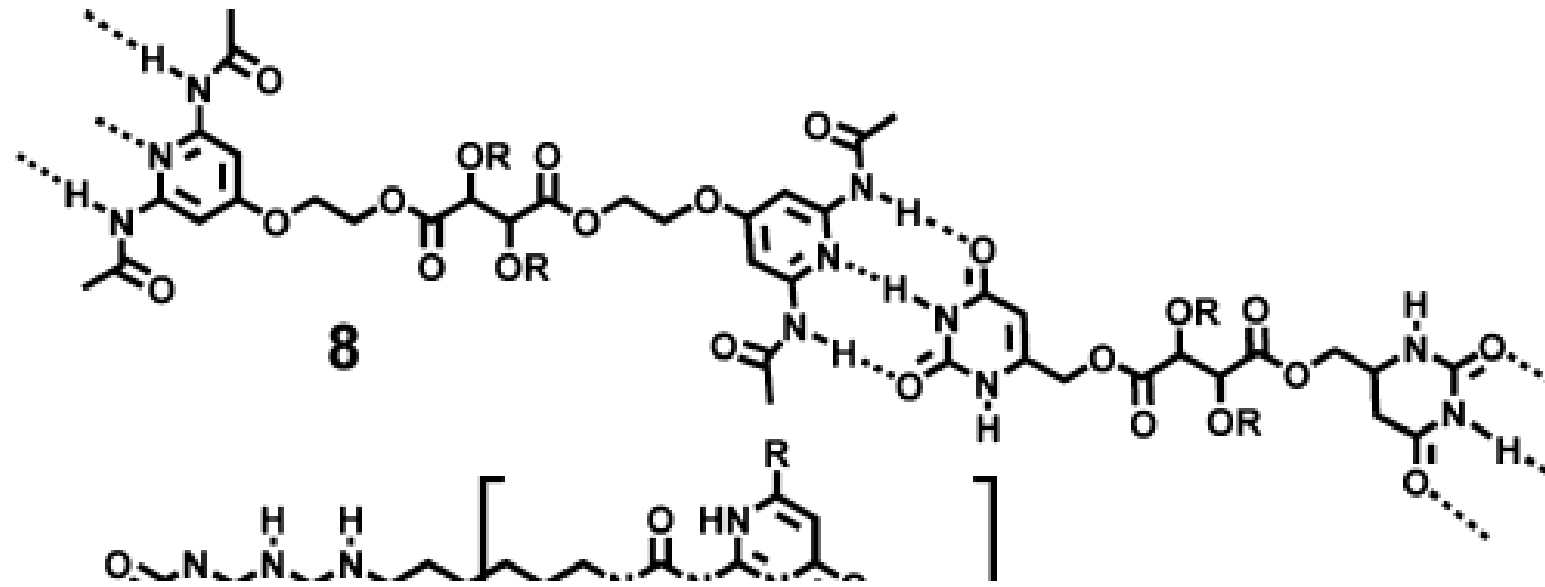
Arrays of hydrogen bonds and supramolecular chemistry

A single hydrogen bond is not strong enough to fabricate supramolecular polymers. However, both the strength and the directionality can be increased when multiple hydrogen bonds are arrayed to create hydrogen bonding arrays. Typical examples of multiple-hydrogen bonding arrays are summarized in Table 1. The binding strength between arrays is also dependent on the order of the donor and acceptor in the arrays

Hydrogen-Bonded Supramolecular Polymers

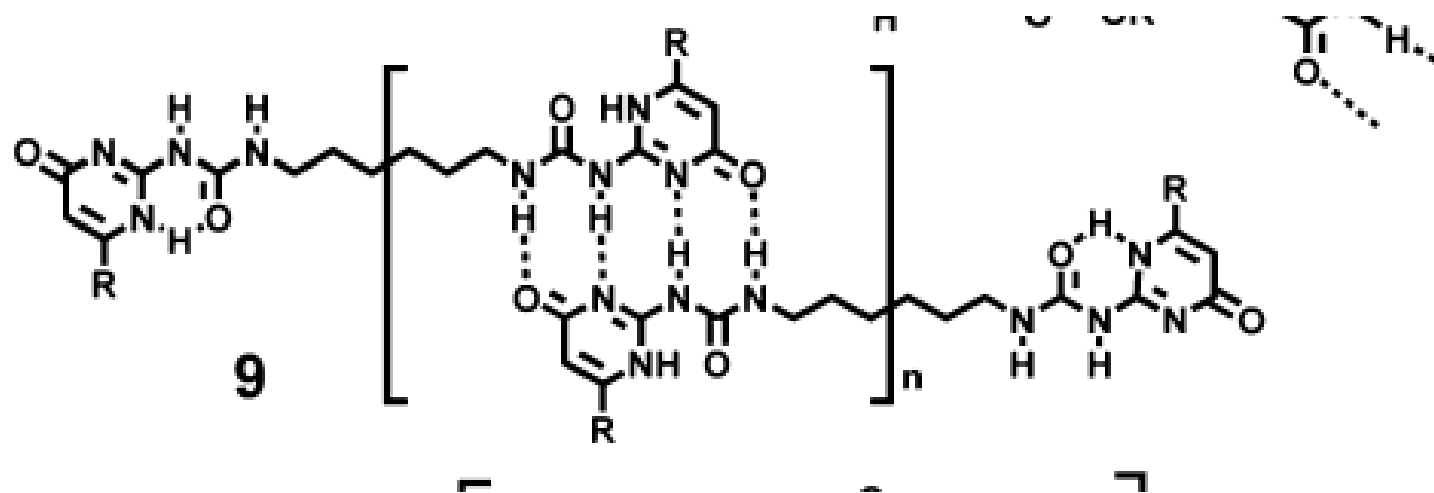


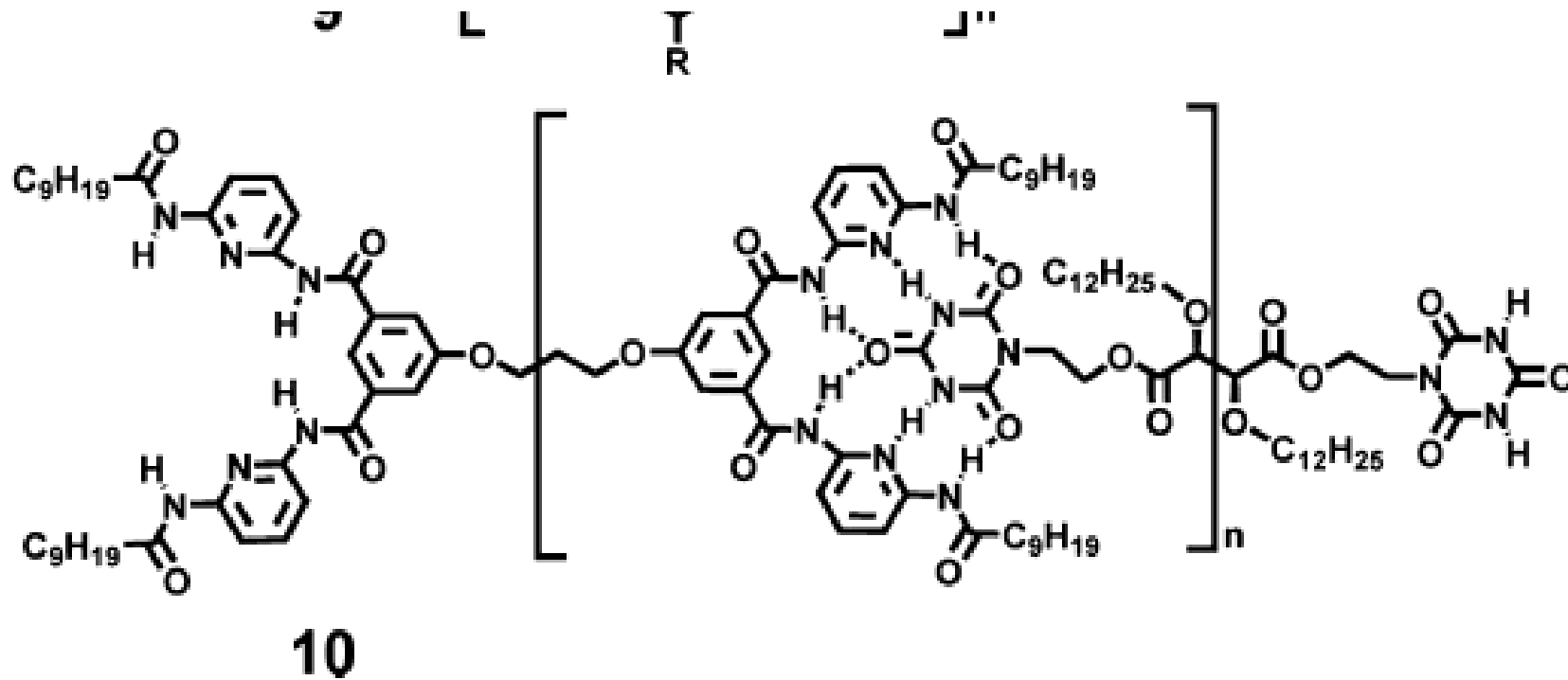
Multiple hydrogen bonds were the first kind of noncovalent bond that was adopted to fabricate supramolecular polymers. In 1990, Lehn et al. first reported this type of supramolecular polymer. Bifunctional diamidopyridines and uracil derivatives were mixed to form linear polymeric chains **8** via triple hydrogen-bonding interactions.



In contrast to the behavior of each monomer, the supramolecular polymers displayed liquid crystallinity in the solid phase.

displayed liquid crystallinity in the solid phase. To achieve supramolecular polymers with a high degree of polymerization (DP), multiple-hydrogen-bonding arrays with a higher binding constant, such as quadruple-hydrogen-bonding arrays, were employed. In 1997, Meijer et al. reported that bifunctional AA-type monomers containing two UPy end groups were able to form linear supramolecular polymers **9** (Figure 1).¹⁶ The





Lehn et al. also reported a series of supramolecular polymers based on barbiturate/cyanurate–isophthaloyldiamidopyridine sextuple arrays 10. Rigid fibers were observed in toluene, while small-angle neutron scattering in decane demonstrated the formation of gel-like assemblies.

Heterodimerizing motifs are attractive for constructing supramolecular block copolymers. Meijer et al. prepared AA/BB-type supramolecular block copolymers using Napy and Upy motifs, in view of the strong and selective complexation of these two units.

They designed a poly(tetrahydrofuran) macromonomer, 11, with UPy units as the chain ends and a ditopic Napy monomer, 12

The composition of the supramolecular polymers could be tuned from a pure homopolymer to an alternating heteropolymer by controlling the stoichiometry of UPy and Napy groups.

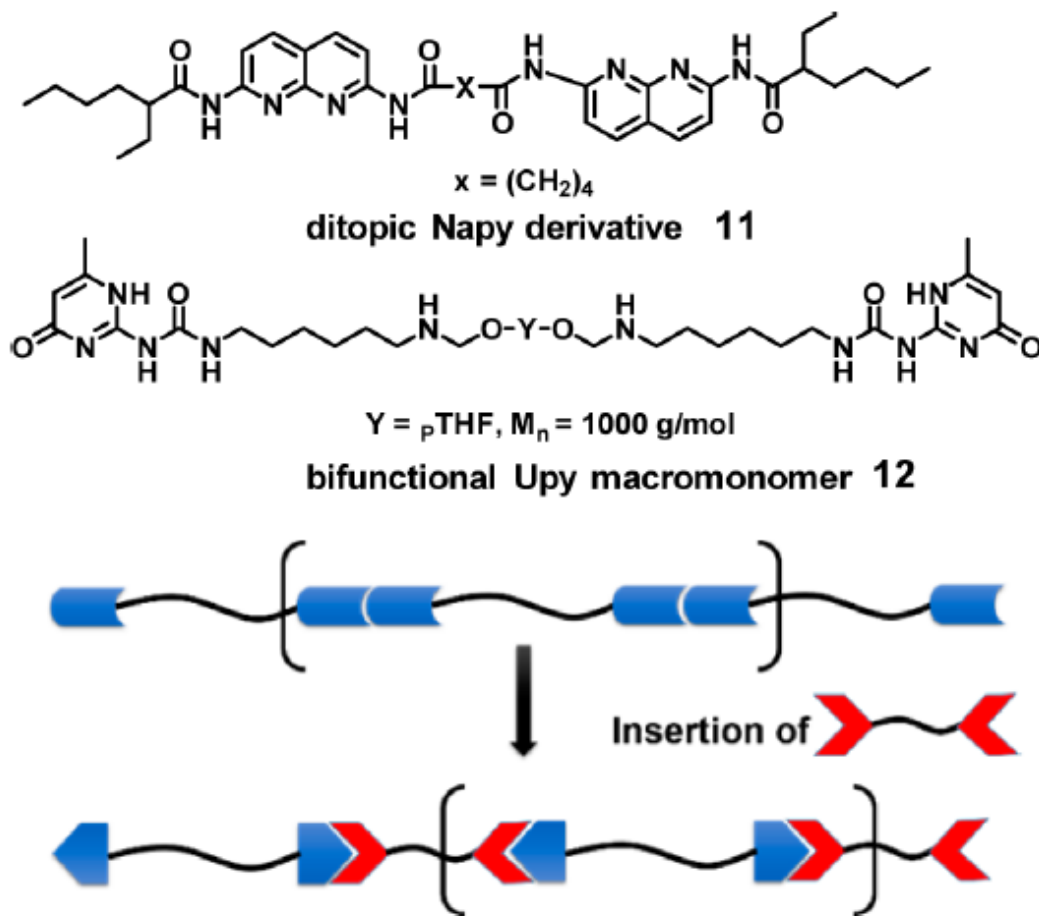


Figure 2. Transition from a supramolecular homopolymer to an alternating polymer by tuning the stoichiometry of two monomers. Reprinted from ref 32. Copyright 2004 American Chemical Society.

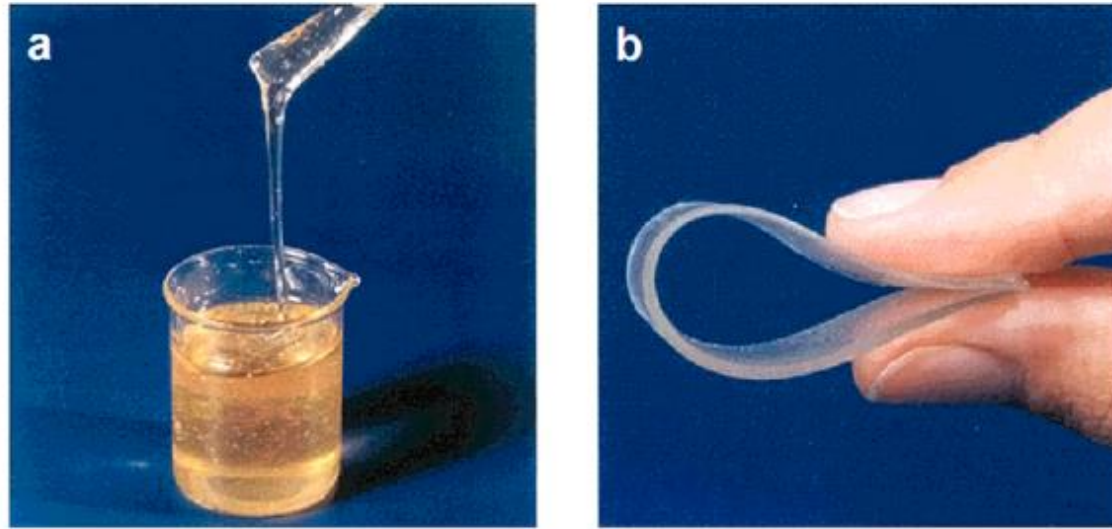


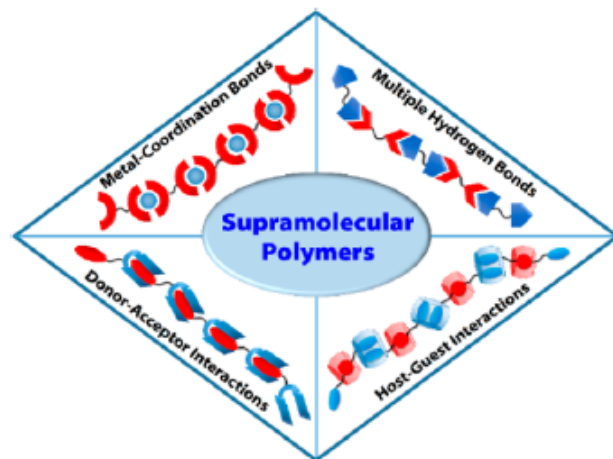
Figure 4. Poly(ethylene/butylene) with OH end groups (a) and poly(ethylene/butylene) functionalized with multiple-hydrogen-bonded units (b). Reprinted with permission from ref 42. Copyright 2000 John Wiley & Sons, Inc.

Introduction of Upy end groups results in significant changes of the properties of polymers, and the obtained materials combine the mechanical properties of conventional polymers with the low melt viscosity of organic compounds (Figure 4).

Supramolecular Polymers: Historical Development, Preparation, Characterization, and Functions

Liulin Yang, Xinxin Tan, Zhiqiang Wang, and Xi Zhang*

Key Laboratory of Organic Optoelectronics & Molecular Engineering, Department of Chemistry, Tsinghua University, Beijing 100084, China



5.2. Viscometry	7222
5.3. NMR Spectroscopy	7222
5.4. AFM-Based Single-Molecule Force Spectroscopy	7222
5.5. Light Scattering	7223
5.6. Small-Angle Neutron Scattering	7223
5.7. Asymmetric Flow Field-Flow Fractionation	7224
5.8. Other Methods	7225
6. Application of Supramolecular Polymers	7225
6.1. Optoelectronic Materials	7225

Cation- π interactions

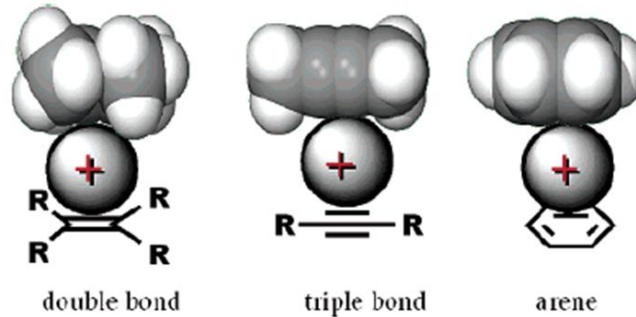
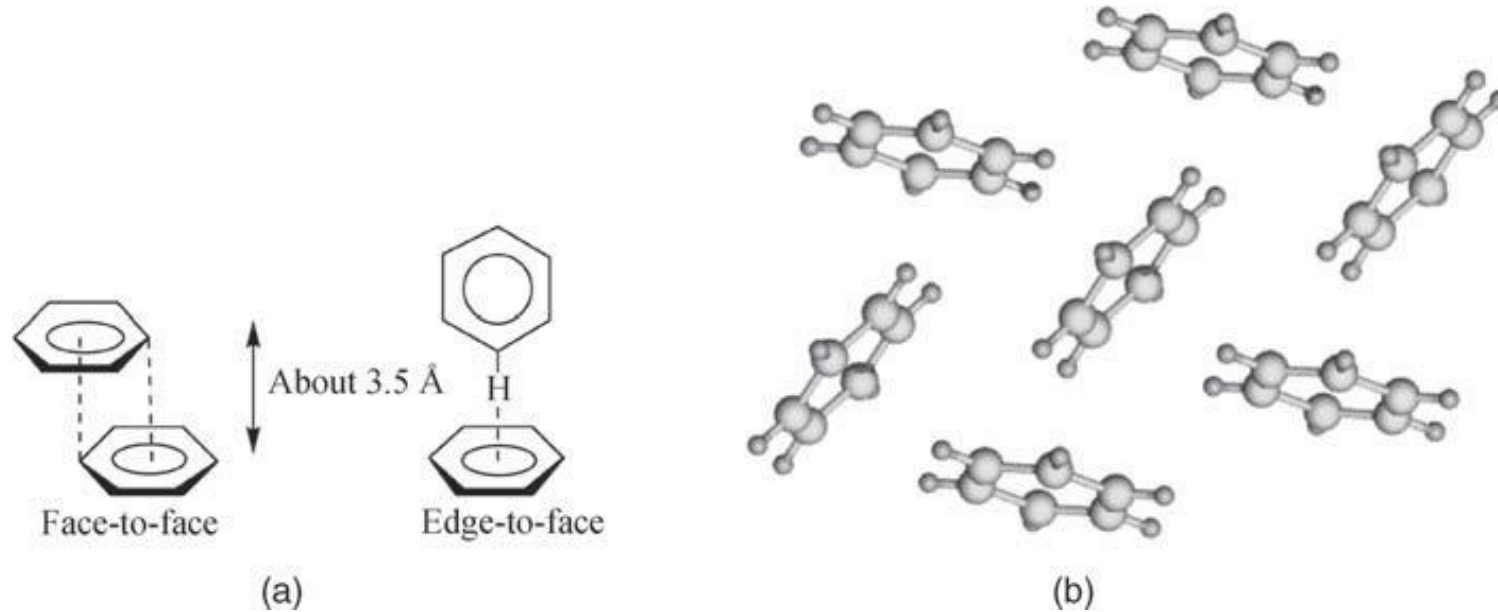


FIGURE 1. Space-filling molecular models of tetramethylethylene, 2-butyne, and benzene coordinating to an alkali metal cation.

- Transition metal cations such as Fe^{2+} , Pt^{2+} *etc.* are well known to form complexes with olefinic and aromatic hydrocarbons such as ferrocene [$\text{Fe}(\text{C}_5\text{H}_5)_2$] and Zeise's salt [$\text{PtCl}_3(\text{C}_2\text{H}_4)$]. The bonding in such complexes is strong and could by no means be considered non-covalent, since it is intimately linked with the partially occupied *d*-orbitals of the metals.
- Even species such as $\text{Ag} \dots \text{C}_6\text{H}_6$ have a significant covalent component. The interaction of alkaline and alkaline earth metal cations with CC double bonds is, however, a much more non-covalent 'weak' interaction, and is suggested to play an important role in biological systems. For example, the interaction energy of K and benzene in the gas phase is about 80 kJ mol^{-1}

π - π interactions



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

Attrazione tra il sistema π di un anello e quello σ dell'altro

- Sanders and Hunter have proposed a simple model based on competing electrostatic and van der Waals influences, in order to explain the variety of geometries observed for π - π stacking interactions and to predict quantitatively the interaction energies.
- Their model is based on an overall attractive van der Waals interaction, which is proportional to the contact surface area of the two π -systems. This attractive interaction dominates the overall energy of the π - π interaction and may be regarded as an attraction between the negatively charged π -electron cloud of one molecule and the positively charged σ -framework of an adjacent molecule. The relative orientation of the two interacting molecules is determined by the electrostatic repulsions between the two negatively charged π -systems

Attrazione tra il sistema π di un anello e quello σ dell'altro

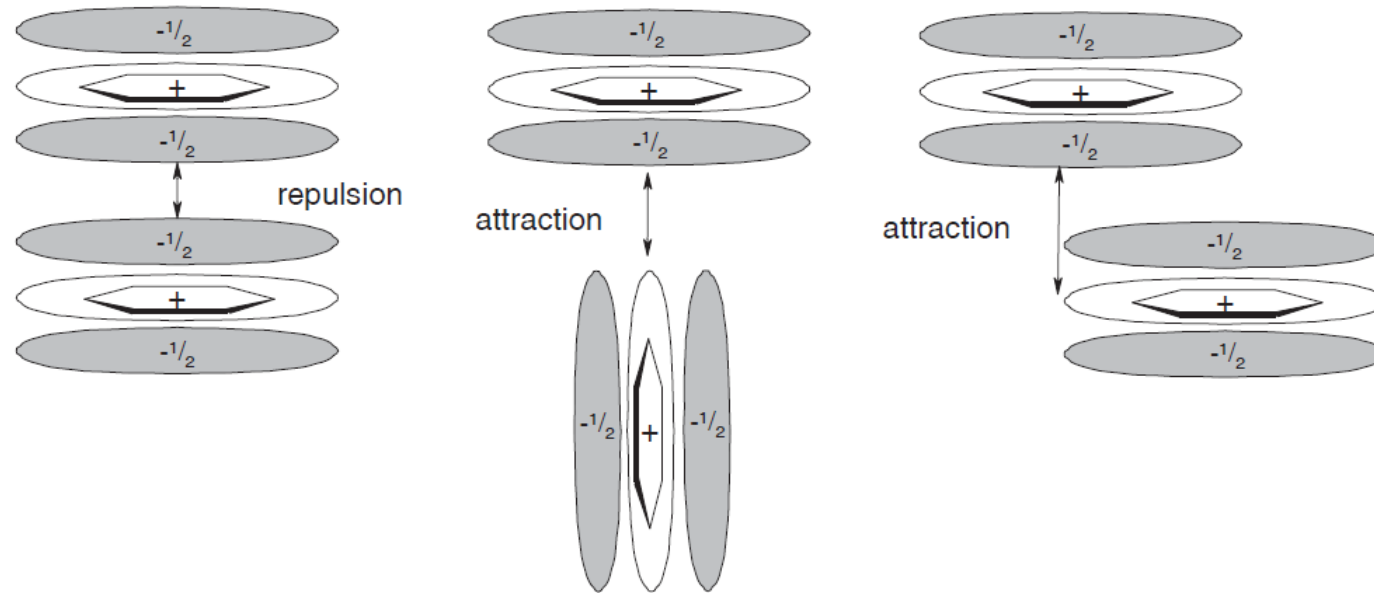


Figure 1.21 Interacting π -quadrupoles.

Hydrophobic Effects

The hydrophobic effect is very important in biological systems in the creation and maintenance of protein and polynucleotide structure and in the maintenance of phospholipid bilayer cell walls.

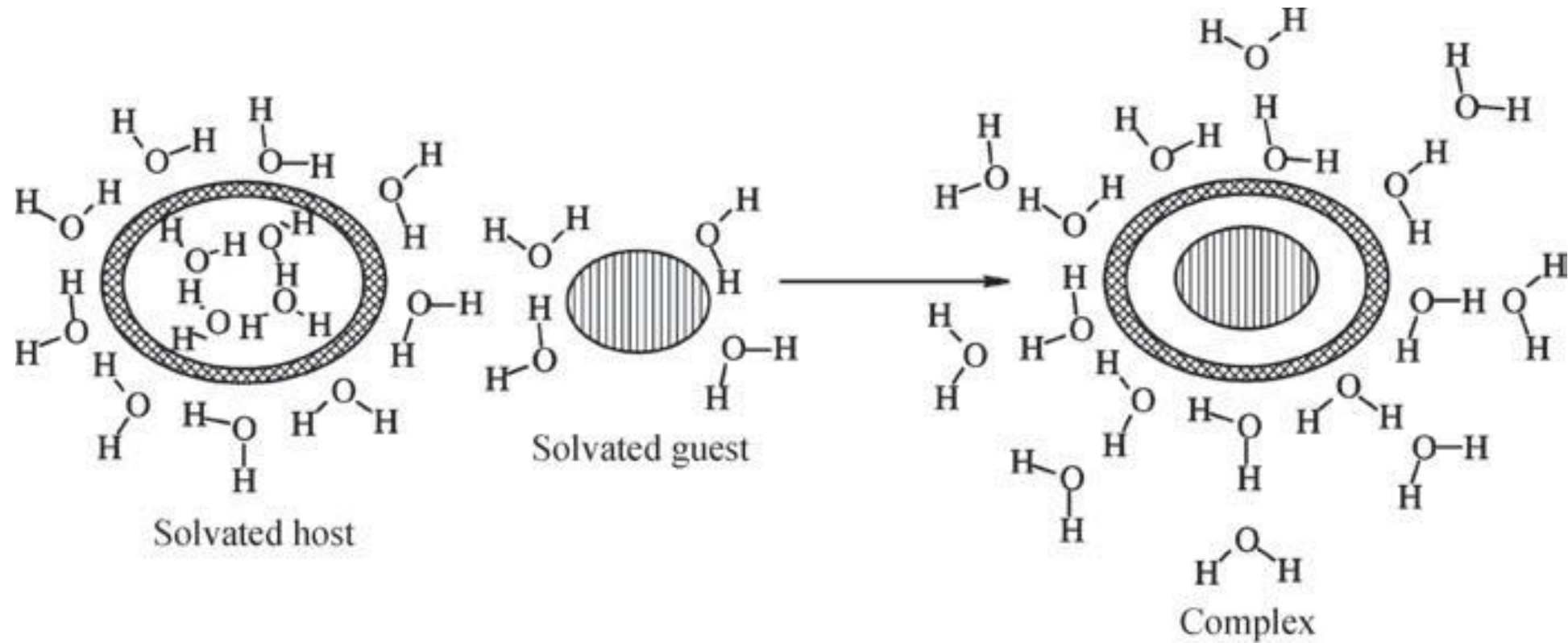
Hydrophobic effects are of crucial importance in the binding of organic guests by cyclodextrins and cyclophane hosts in water and may be divided into two energetic components: enthalpic and entropic.

The enthalpic hydrophobic effect involves the stabilisation of water molecules that are driven from a host cavity upon guest binding. Because host cavities are often hydrophobic, intracavity water does not interact strongly with the host walls and is therefore of high energy.

Upon release into the bulk solvent, it is stabilised by interactions with other water molecules. The entropic hydrophobic effect arises from the fact that the presence of two (often organic) molecules in solution (host and guest) creates two 'holes' in the structure of bulk water.

Combining host and guest to form a complex results in less disruption to the solvent structure and hence an entropic gain (resulting in a lowering of overall free energy). The process is represented schematically in Figure

The hydrophobic effect or the high-energy inclusion water



High-energy water molecules in CB cavity

Typically, aqueous environments cause a drop in host– guest affinity, compared to organic solvents, as water can compete strongly for hydrogen bonds and efficiently solvate charged species.

CB[n]s overcome this issue via the presence of **high-energy water**, which is present in the CB[n] cavity and supplies a driving force for guest complexation.

