Mie University
Department of Chemistry for Materials

General Principles and Selected Examples in Supramolecular Chemistry

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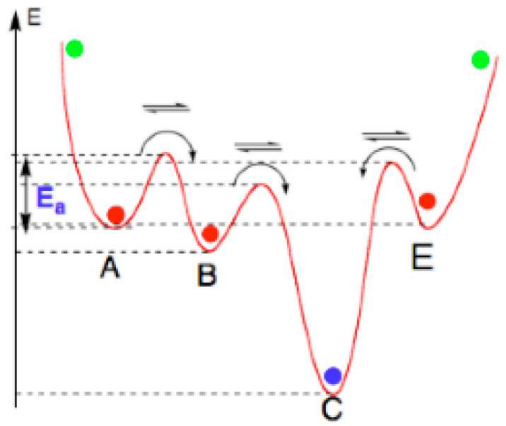
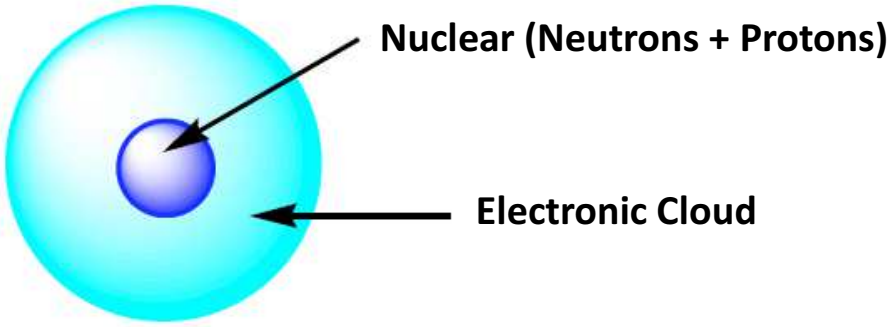
1. Introduction



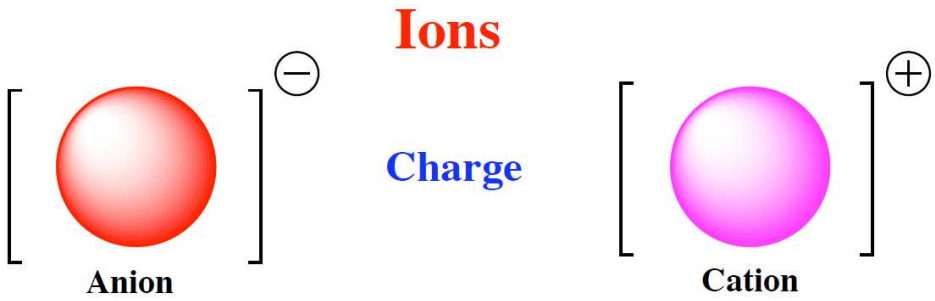
Low activation barriers (E_a):
Self-healing process.
Many different intermediate states but **one** final state.

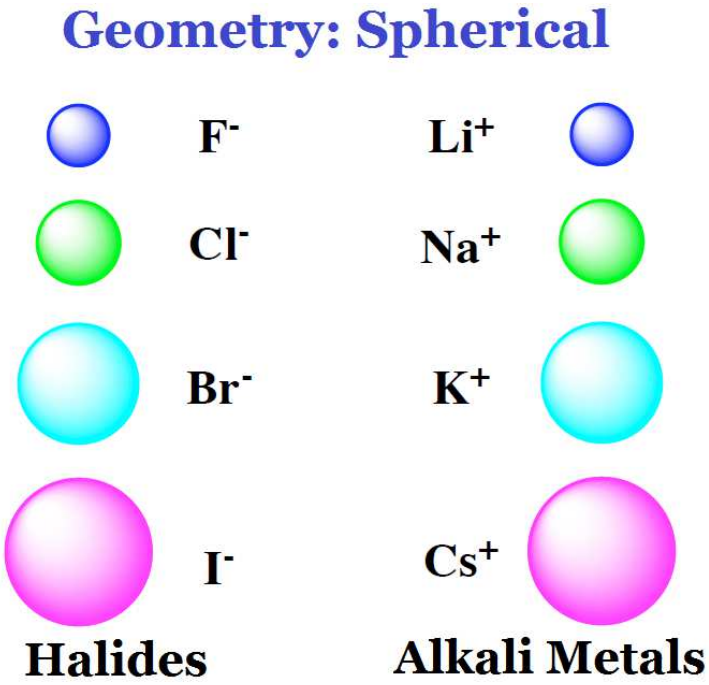
Atoms: a small and vast world



Dimension
- Nuclear : 10^{-14} m
- Atom : 10^{-10} m
- 1 Å = 10^{-10} m

- **Molecule** = **atoms** connected by strong bonds (interactions) or covalent bonds.
- The bond or cement that connects the atoms is an electronic density.
- While the atom is spherical, the molecules may have very simple or complex geometries.
- 103 Chemical elements "usable".
- This leads to an infinity of possible combinations.

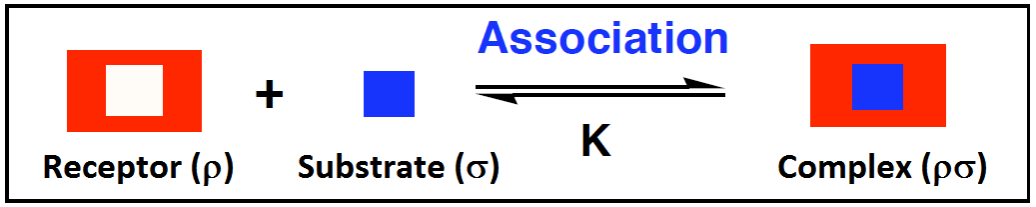




Intermolecular Interactions and Molecular Recognition

- ***Beyond molecular chemistry***, based on the covalent bond, thus extends a domain that can be called **supramolecule**.
- The chemistry of **molecular interactions**, **associations** of two or more chemical species, **complexes**, and **intermolecular bonding**.
- **Jean-Marie Lehn**, "Inaugural Lesson at the Collège de France", 7 March 1980

- **Molecular recognition** involves a complementarity of forms, fillers and sizes between the receptor and the substrate.



$$K = \frac{[\rho\sigma]}{[\rho] \times [\sigma]}$$

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

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

$$K = \frac{k_f}{k_d}$$

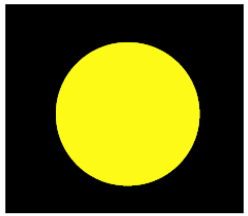
K_f = Formation constant
K_d = Dissociation constant

- **Molecular recognition** results from an association between a host receptor or molecule (ρ) and a guest molecule or substrate (σ) leading to a molecular complex.

- This association is made by reversible processes leading to an equilibrium characterized by a constant ***K***.

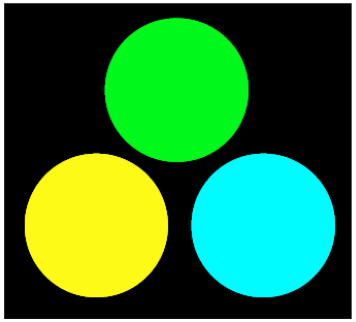
Topology of Receivers

- The topicity of a receiver is defined by the number of poles it possesses.
- The poles may be identical (**homopolytopic receptor**) or different (**heteropolytopic receptor**).



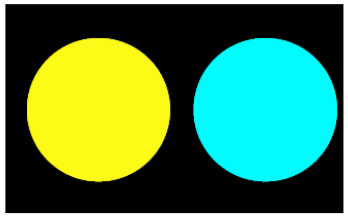
Monotopic

Monotopic receiver
has a single recognition pole.



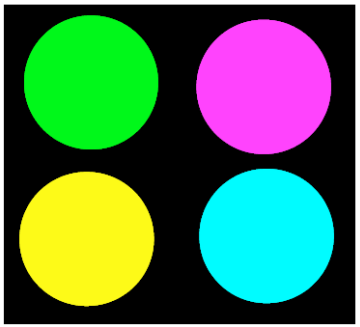
Tritopic

Tritopic receptor
has three recognition poles.



Ditopic

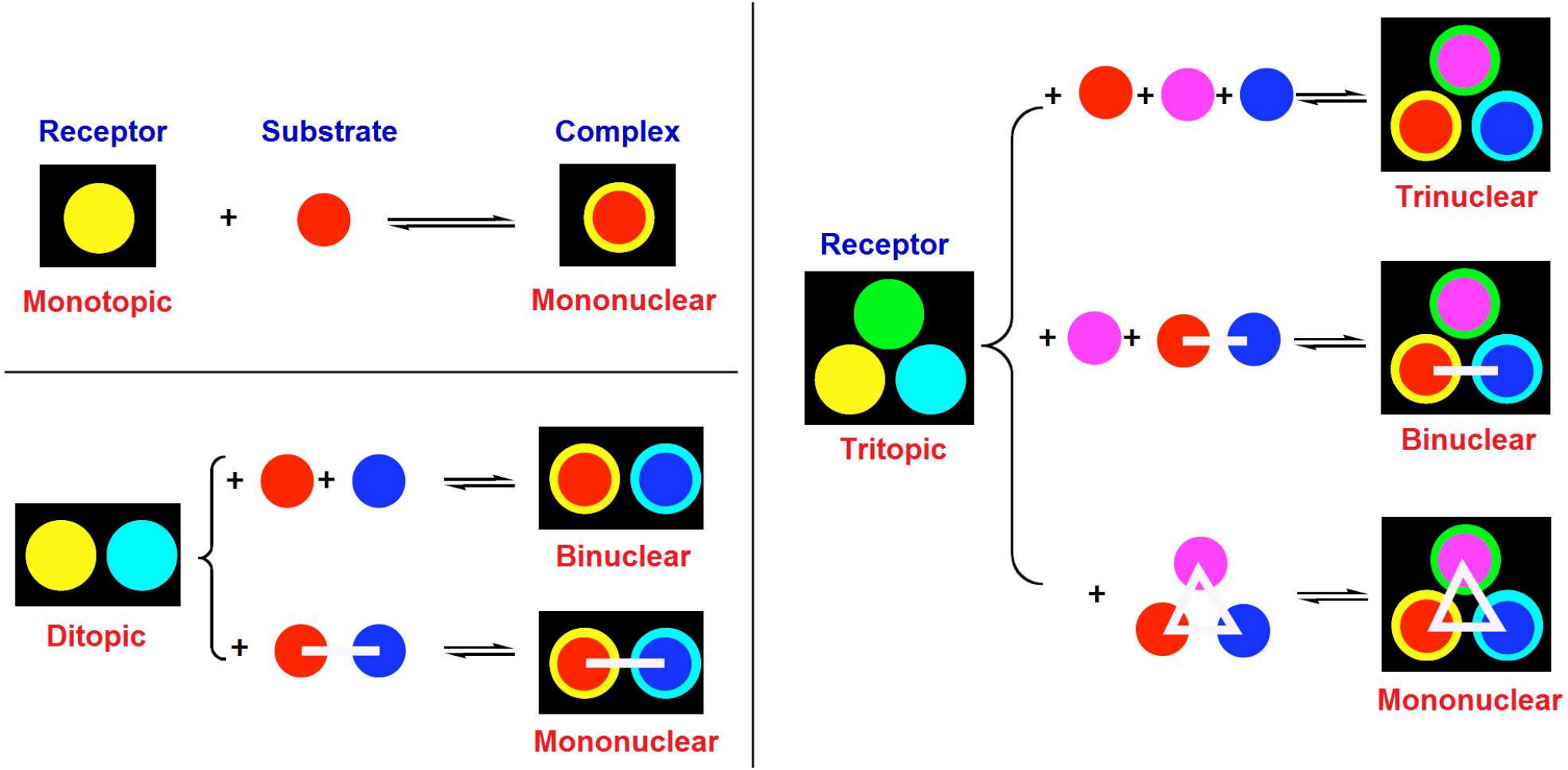
Ditopic receiver
has two recognition poles.



Tetratopic

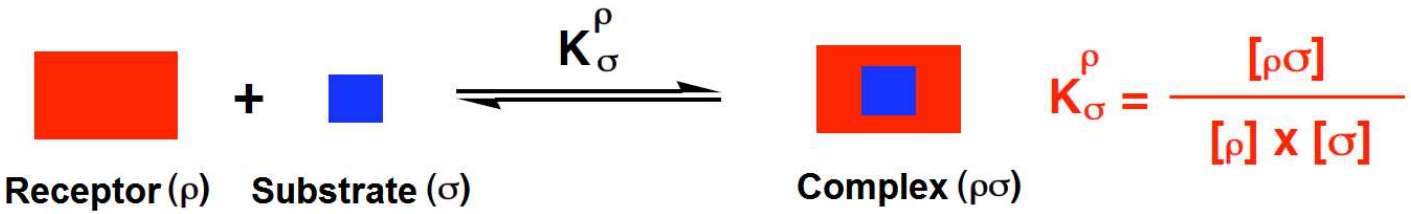
Tetratopic receptor
has four recognition poles.

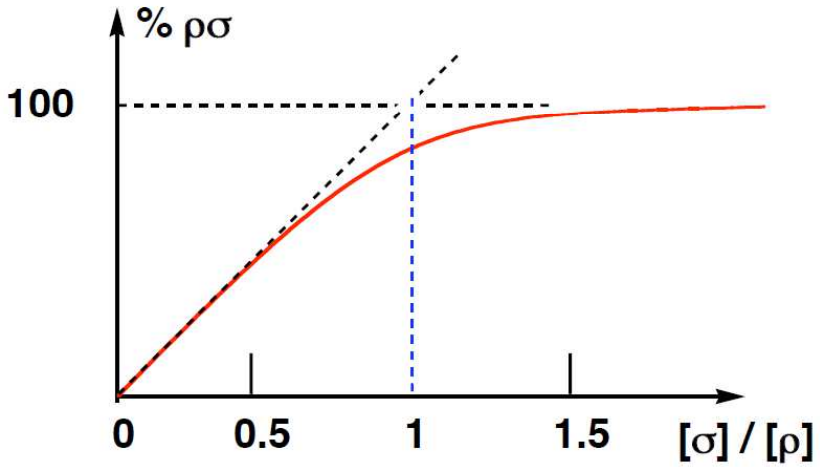
Topology of Receptors and stoichiometry of complexes



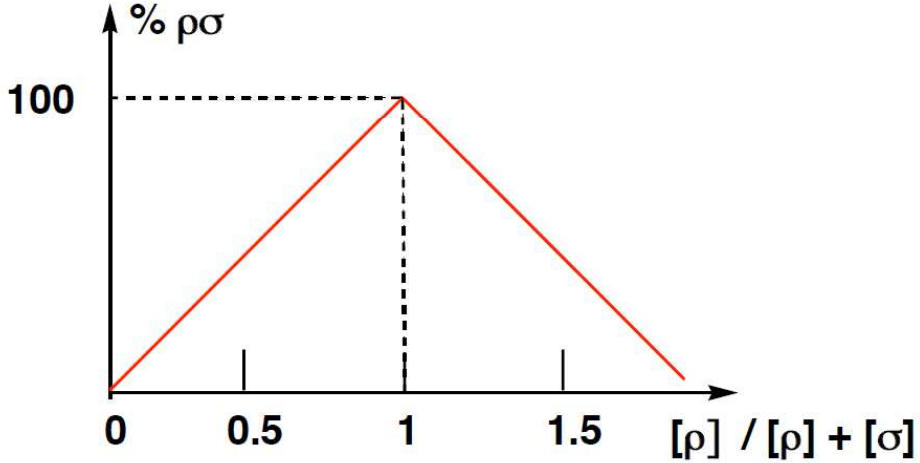
The stoichiometry or nucleation

- **Mononuclear complex:** a receptor associates with a single substrate to form a mononuclear complex.
- Nuclearity is 1: 1.





The higher value of K,
the smaller linearity deviation

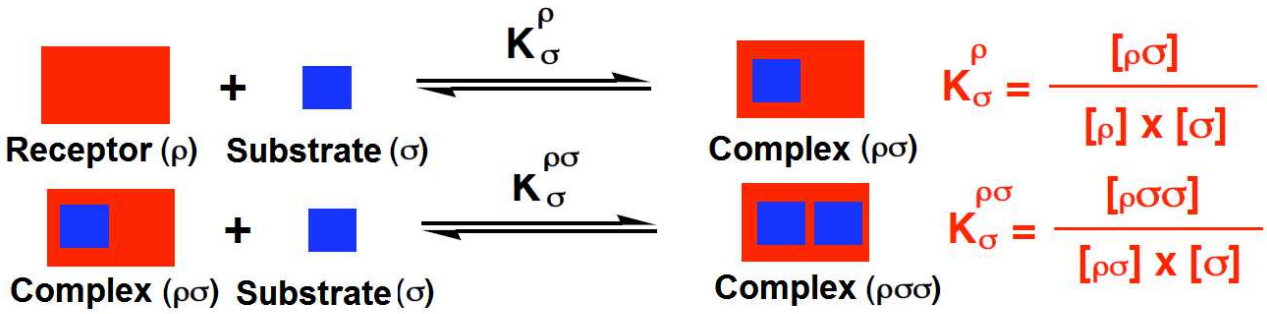


Job Method (Job plot)

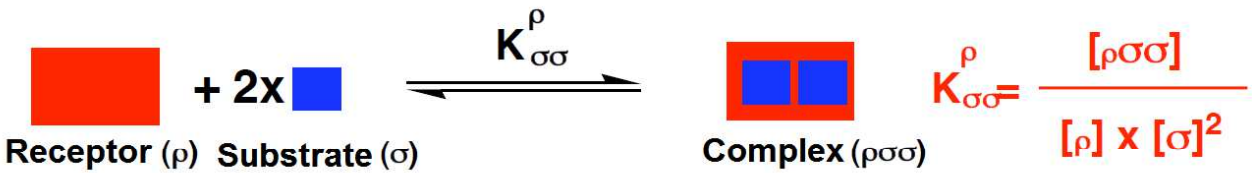
The stoichiometry or nucleation

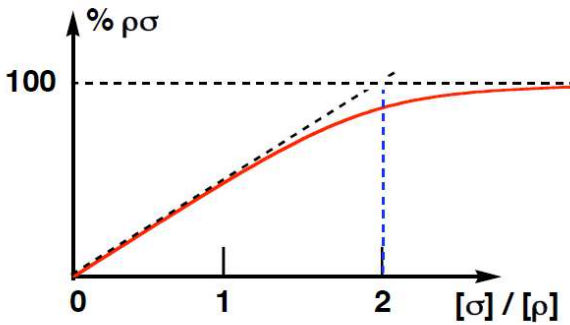
- **Binuclear complex:** a receptor associates with two substrates to form a binuclear complex.
- Nuclearity is 1: 2.

Stepwise formation

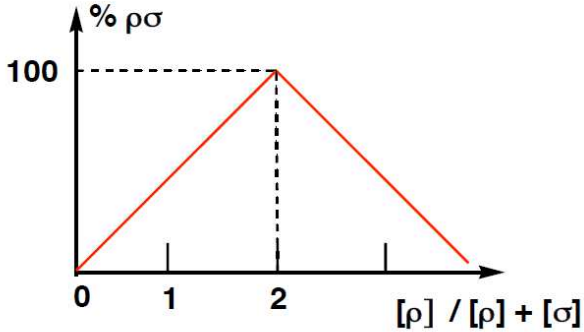


Overall formation



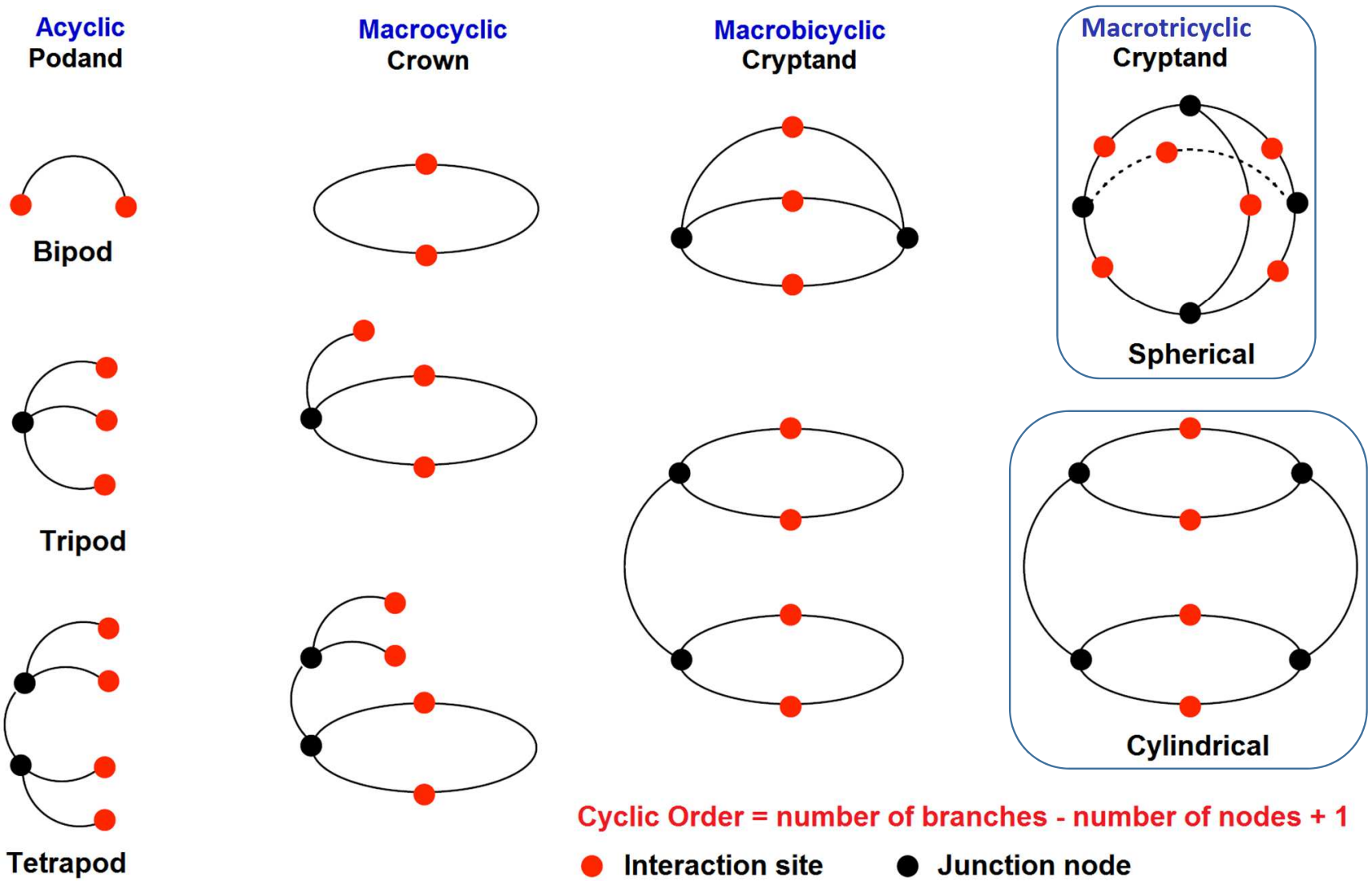


The higher value of K,
the smaller linearity deviation



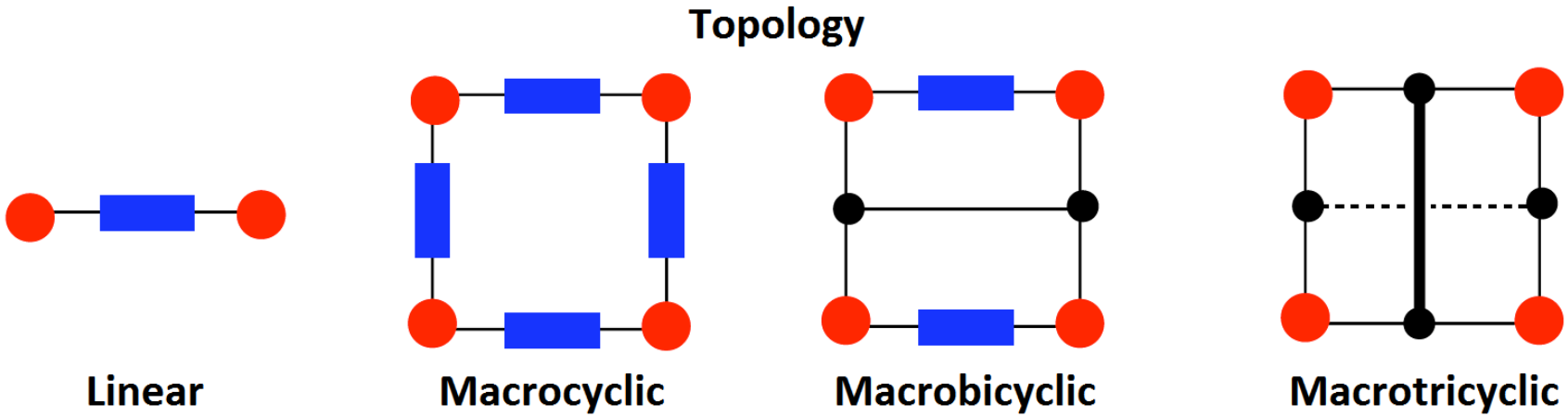
Job Method (Job plot)

Topology of Ligands



Molecular Receptors

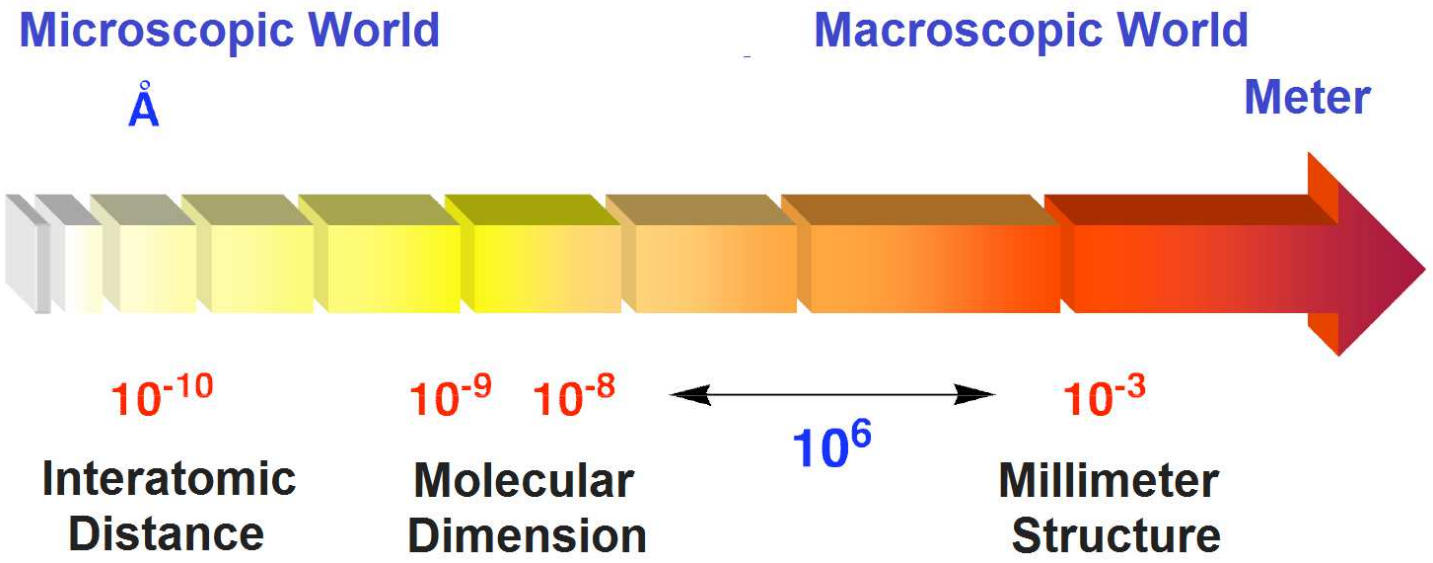
- A **receiver** is composed of two parts:
  - **Skeleton** (part allowing to organize sites of interaction in the space)
  - **Interaction sites** capable of interacting with the substrate



Interaction site, charged or neutral, rich or poor in electron density.

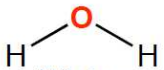
Spacer (flexible or rigid) controlling the spacing (distance) between interaction sites.

Scale of Dimensions

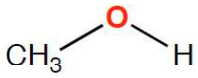


The Solvents

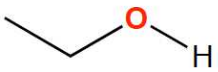
Protic Solvent



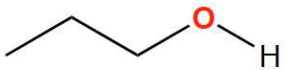
Water



Methanol

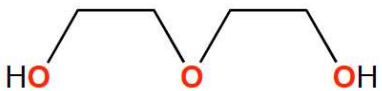


Ethanol



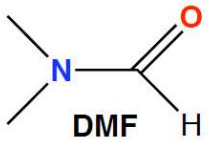
Propanol

Glycol

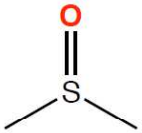


Diethylenglycol

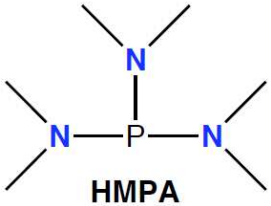
Aprotic Solvent



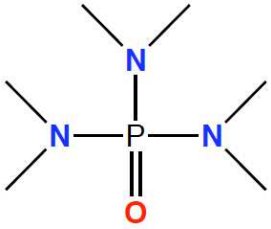
DMF



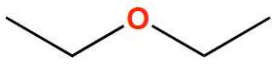
DMSO



HMPA



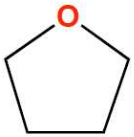
HMPT



Ether

CH_2Cl_2

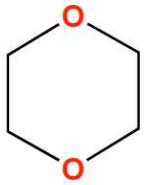
Dichloromethane



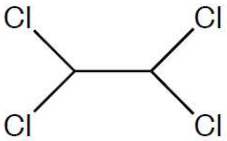
THF

$CHCl_3$

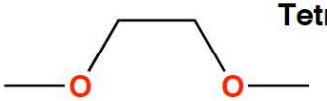
Chloroforme



Dioxane



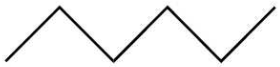
Tetrachloroethane

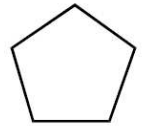


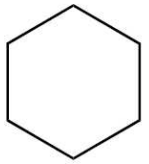
1,2-dimethoxyethane
(Glyme)

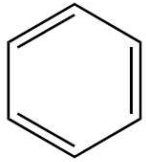
Bis(2-methoxyethyl) ether
(Diglyme)

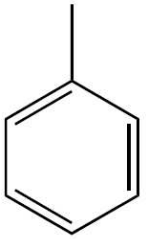

Pentane

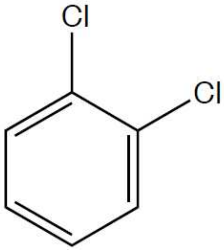

Hexane


Cyclopentane


Cyclohexane

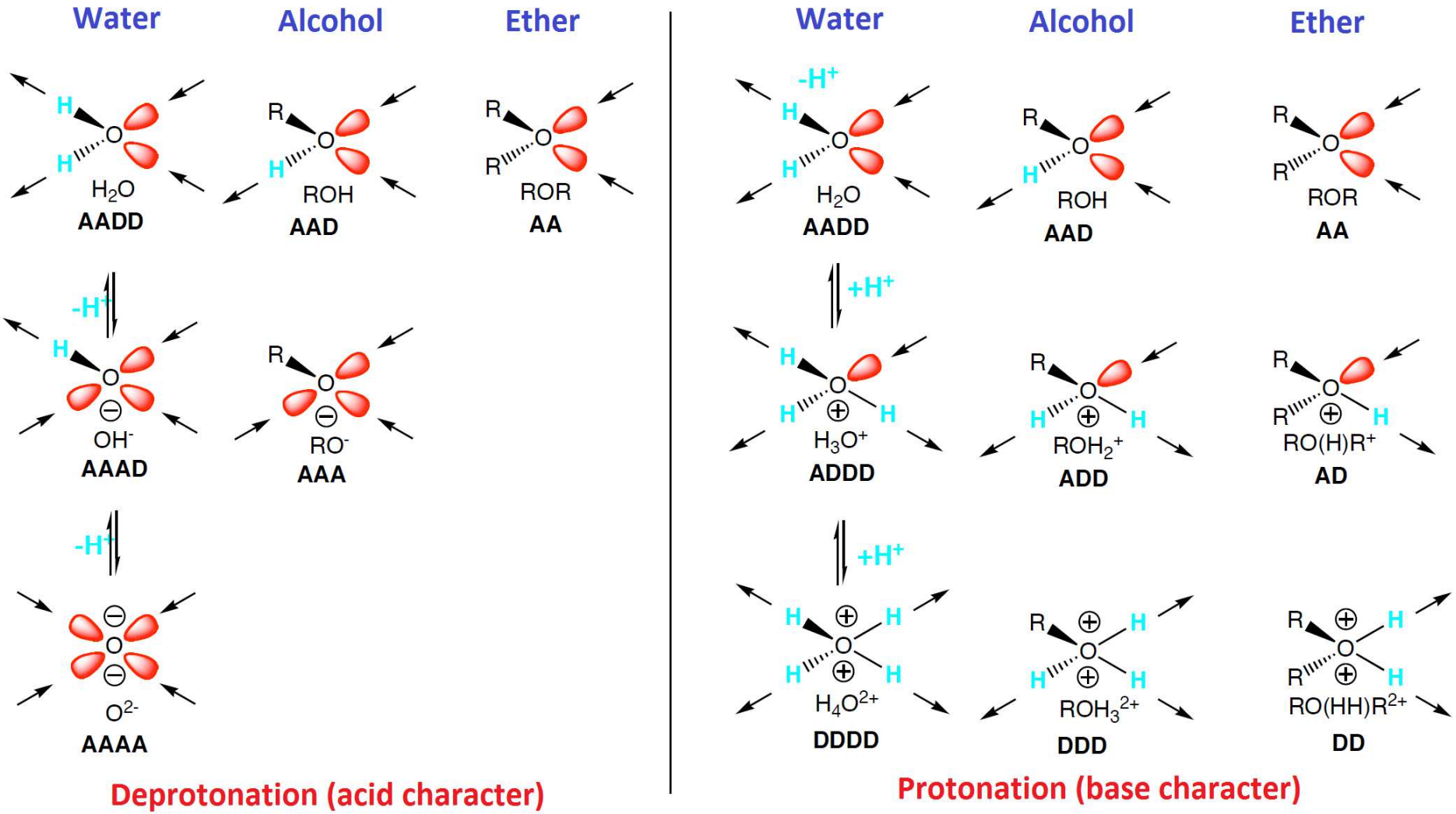

Benzene


Toluene



1,2-Dichlorobenzene

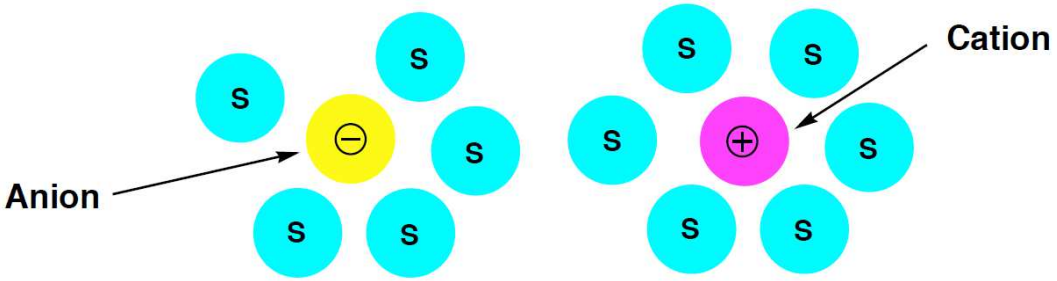
Acid and Base Character of Water, Alcohol and Ether



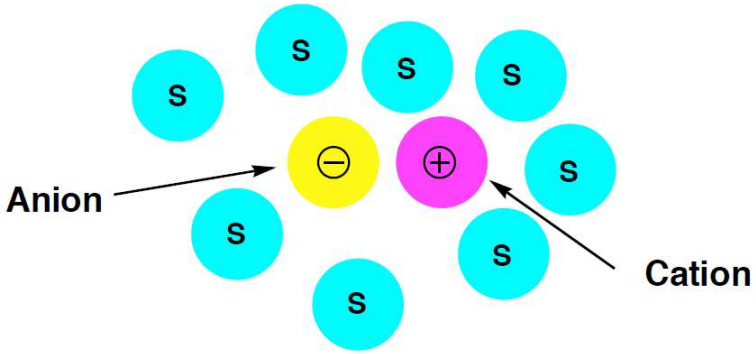
The Solvation

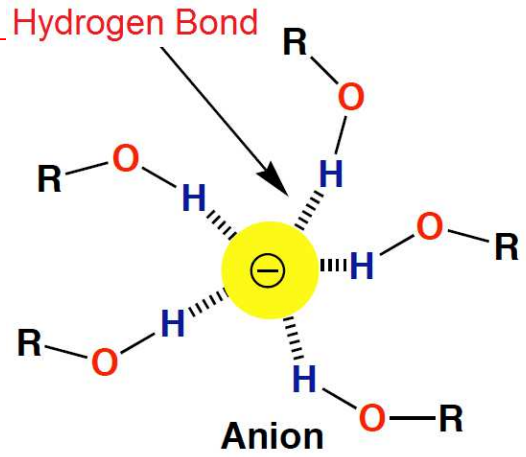
- **The more polar compound**:
  - ▶ less soluble in nonpolar solvents (low ε: alkane, benzene toluene, etc.)
  - ▶ more soluble in polar solvents

- The polar solvent dissociate the charged species:
  It leads to a separation of the charges (pair of separated ions).

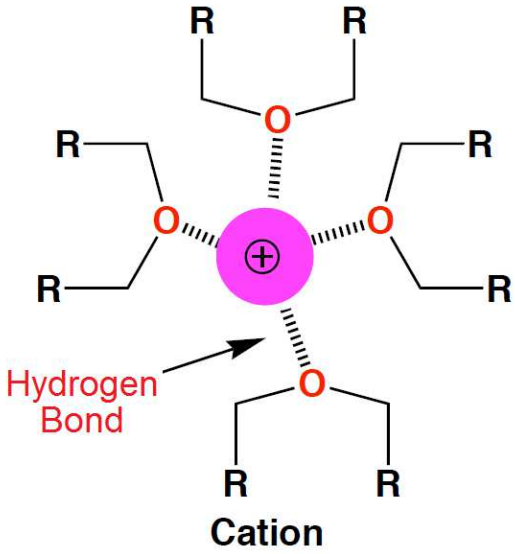


- The less-polar solvent has less dissociating power
  (no separation of the charges).
- The charged species form a pair of intimate ions (associated).



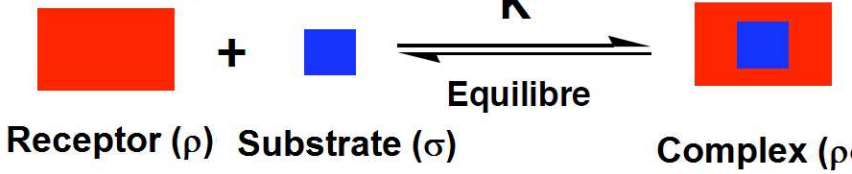


Ion/Dipole Interaction



Molecular Recognition

Thermodynamic

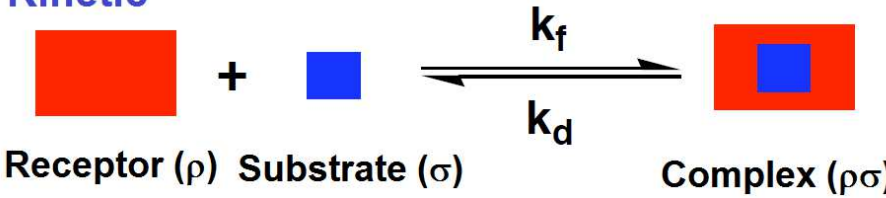


$$K = \frac{[\rho\sigma]}{[\rho] \times [\sigma]}$$

$$\Delta G = -RT\ln K$$
$$\Delta G = -2.3RT\log K$$
$$\Delta G = \Delta H - T\Delta S$$

- A high equilibrium constant corresponds to a high association energy (high absolute value of ΔG).
- An association can be favored (negative ΔG) by the enthalpic factor (ΔH) and/or entropic factor (ΔS).

Kinetic



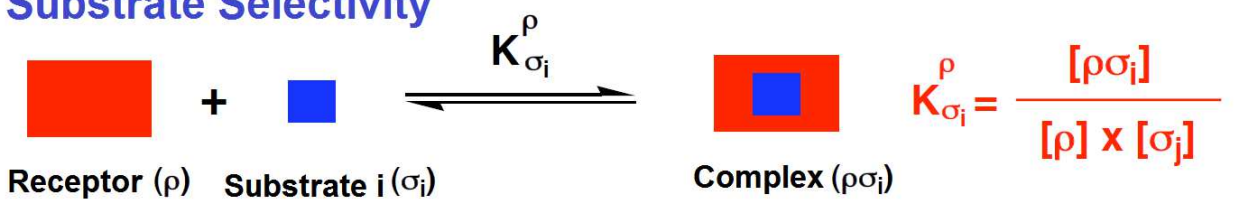
$$K = \frac{k_f}{k_d}$$

K_f = Formation constant
K_d = Dissociation constant

- The equilibrium constant K (thermodynamic parameter) corresponds to the ratio of kinetic (k_f) and dissociation (k_d) constants.
- A strong association constant K corresponds to a high formation constant k_f and a low dissociation constant k_f.

Recognition selectivity - Substrate selectivity

Substrate Selectivity



$$K^{\rho}_{\sigma_i} = \frac{[\rho\sigma_i]}{[\rho] \times [\sigma_j]}$$

$$K^{\rho}_{\sigma_j} = \frac{[\rho\sigma_j]}{[\rho] \times [\sigma_j]}$$

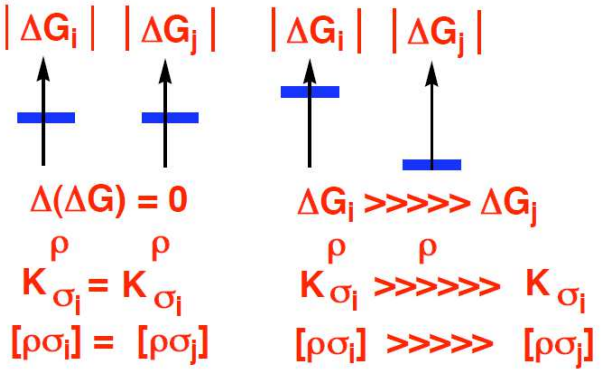
Competition

- When the receptor ρ is placed in the the substrates ρ^i and ρ^j, the two complexes $\rho\sigma^i$ and $\rho\sigma^j$ are formed.

$$S^{\rho}_{\sigma_i\sigma_j} = \frac{K^{\rho}_{\sigma_i}}{K^{\rho}_{\sigma_i}}$$

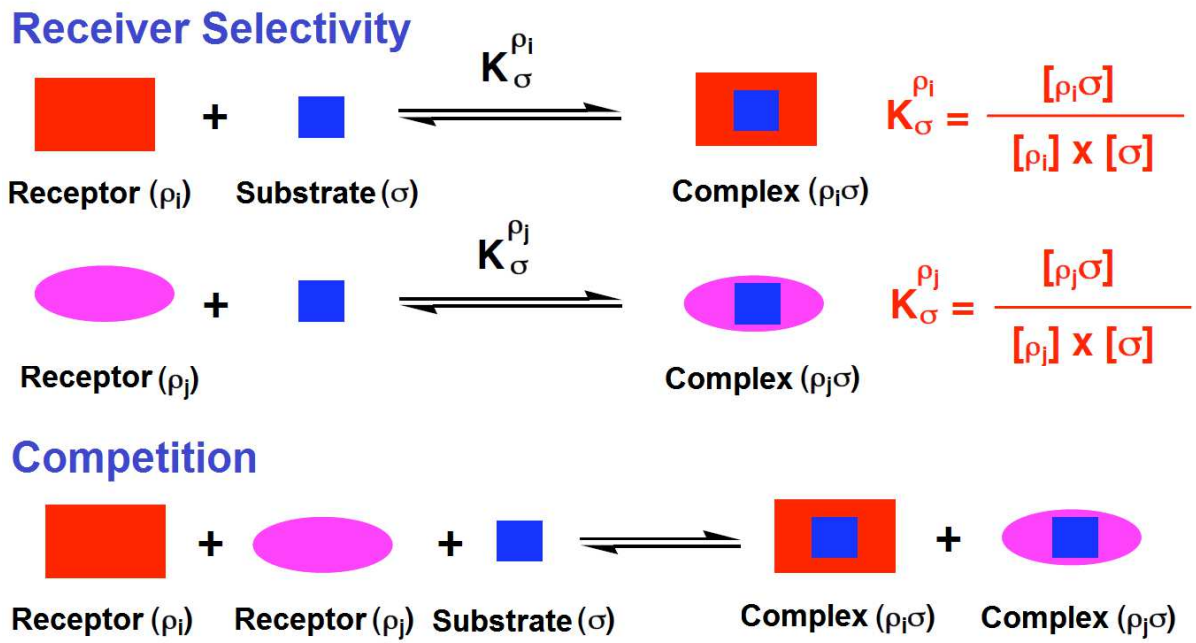
Selectivity of complexation or recognition of the receptor ρ between the substrates σ_i and σ_j.

$$\Delta G_i = -RT\ln K_i$$



- The quality of a molecular recognition process results in the preference for one of the substrates, in other words by the difference of the association constants.

Recognition selectivity – Receiver selectivity

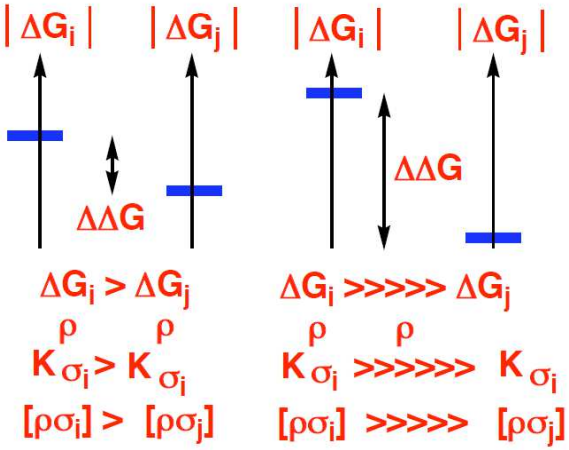


- When the substrate is placed in the receptors ρ_i and ρ_j, the two complexes $\rho_i\sigma$ and $\rho_j\sigma$ are formed.
- It is a competition between the two receptors ρ_i and ρ_j for the substrate.
- The higher affinity of one of the two receptors for the substrate, the higher concentration of the corresponding complex.

$$S^{\rho}_{\rho_i\rho_j} = \frac{K_\sigma^{\rho_i}}{K_\sigma^{\rho_j}}$$

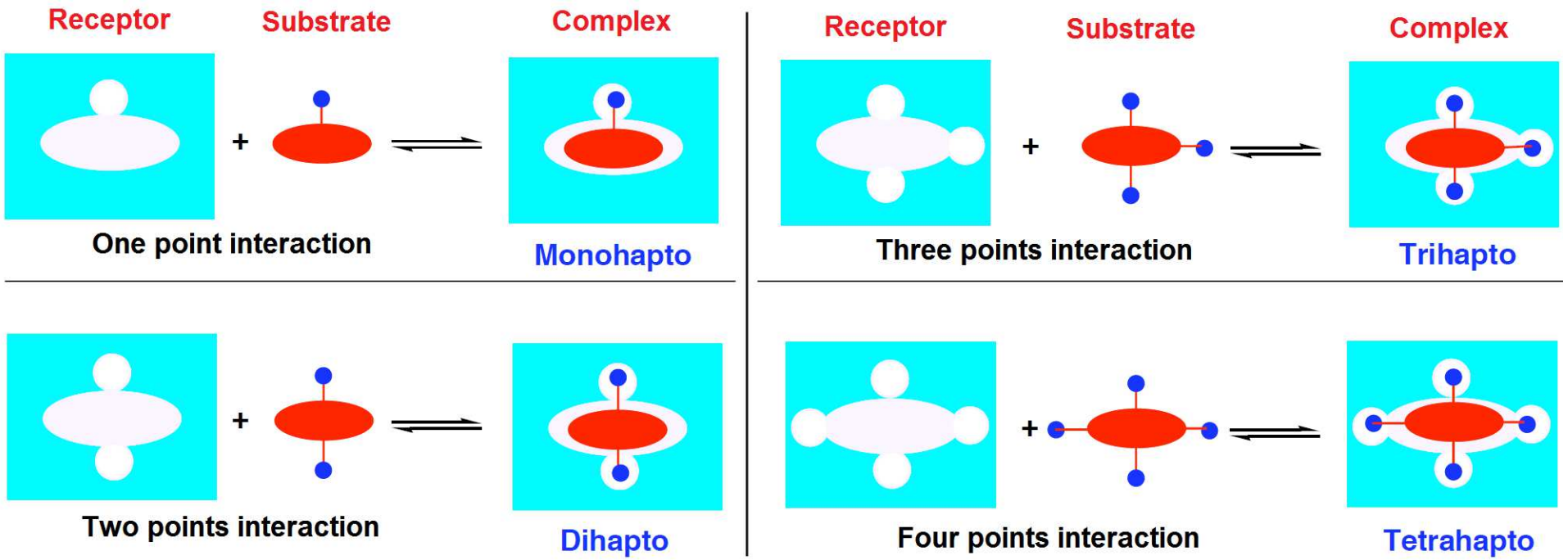
Selectivity of complexation or recognition of the substrate σ between the receptors ρ_i and ρ_j.

$$\Delta G_i = -RT\ln K_i$$



- The greater free energy difference of association ($\Delta\Delta G$) between the two complexes, the greater the competition in favor of the complex with the highest ΔG.

Modes of complexation



- Molecular recognition occurs when one or more interaction sites at the receptor and the substrate come into contact and thereby define a recognition pattern.
- When the number of interaction points between the receptor and the substrate increases, the **interaction energy increases** (equilibrium constant increasing).
- An adequate arrangement of the interaction sites at the receptor and the substrate leads to an efficient recognition process.

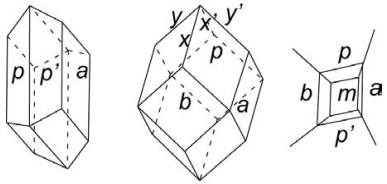
Historical Notes on Supramolecular Chemistry?

1810 Humphrey Davy

- ▶The first clathrate: Chlorine hydrates ("chlorine ice")
  Characterised by Michael Farady (1823)
- ▶ **Clathrate**: Solid state host–guest compounds in which the guest is trapped within a void in the solid state lattice
- ▶ *Clathrus* (Lt. word): 'surrounded on all sides'
- ▶ Clathrate hydrate that are formed from water molecules resulting in cages
- ▶Supramolecular systems
  can be found at the beginning of modern-day chemistry

Humphry Davy
(1778-1829)

Clathrate

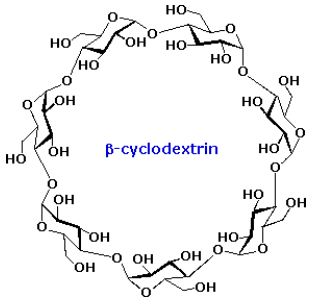


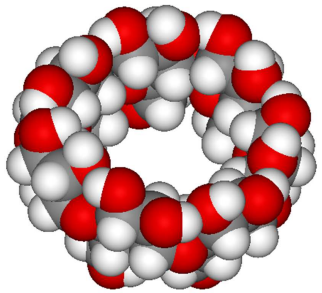
Chlorine hydrate crystals
A.K. Nordenskjöld (1874)

Host-Guest

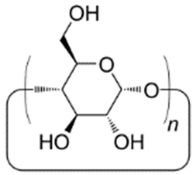
1891 Antoine Villiers (1854–1932)
First cyclodextrin synthesis from potato starch
(*Compt. Rend. Fr. Acad. Sci.* **1891**: 435–438)

1905~1911 Franz Schardinger (1853-1920) identified
the three naturally occurring cyclodextrins -α, -β, and -γ.
▶These compounds were therefore referred to as "**Schardinger sugars**".



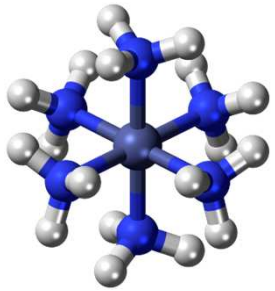


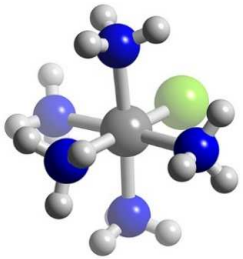
- ▶**α (alpha)-cyclodextrin**: 6-membered sugar ring molecule
- ▶**β (beta)-cyclodextrin**: 7-membered sugar ring molecule
- ▶**γ (gamma)-cyclodextrin**: 8-membered sugar ring molecule

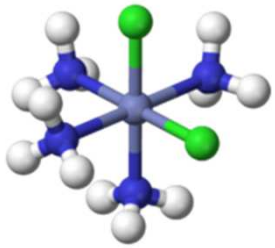


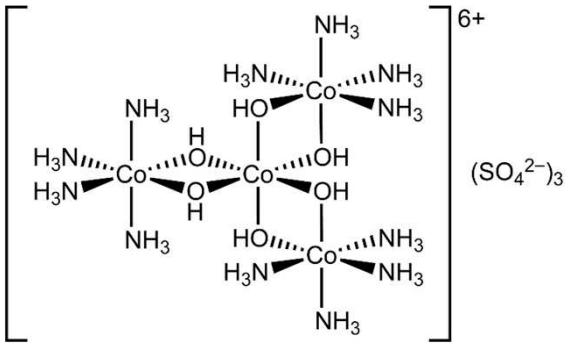
1893 Alfred Werner (Uni ZH, Nobel Prize in Chemistry 1913)

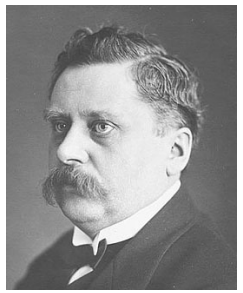
Coordination Chemistry: Electronically saturated molecules can still bind if they have a 'mutual affinity' to form 'complexes'











Affinity
Attraction
Complexation

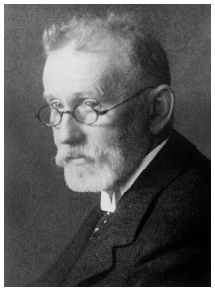
1894 Emil Fisher (Berlin, Nobel Prize in Chemistry 1902)

Enzyme-Substrate Interactions: 'lock-and key' principle';
'binding must be selective', which requires size and shape complementarity

Selectivity
Recognition

1906 Paul Ehrilich (Berlin, Nobel Prize in Physiology or Medicine 1908)

Immunology: '*corpora non agun nisi fixate*',
i.e., molecules do not react if they do not bind.



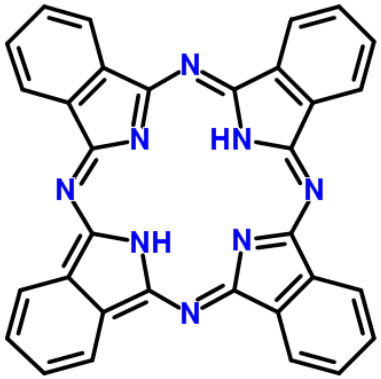
Recptors
Fixation
Reaction

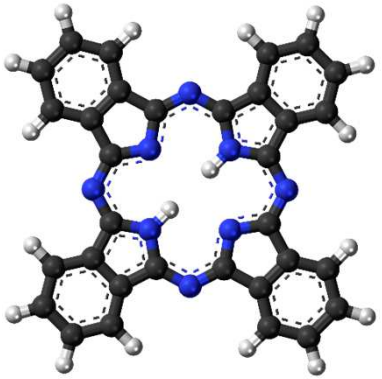
1907 A. Braun & J. Tcherniac

Metal-free phthalocyanine (H_2Pc)

1927 Henri De Diesbach & Edmond von Der Weid

Copper phthalocyanine



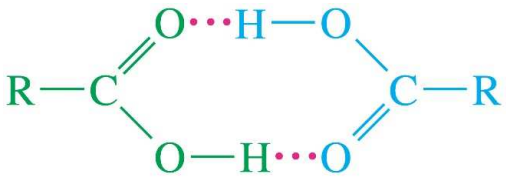


Macrocycle

1937 Karl Lothar Wolf

Supramolecules

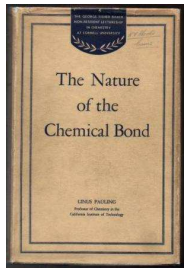
► He introduced the term **supermolecule** (or **supramolecule**) (*Übermoleküle* = About molecules) in 1937 to describe hydrogen-bonded acetic acid dimers.



hydrogen-bonded acid dimer

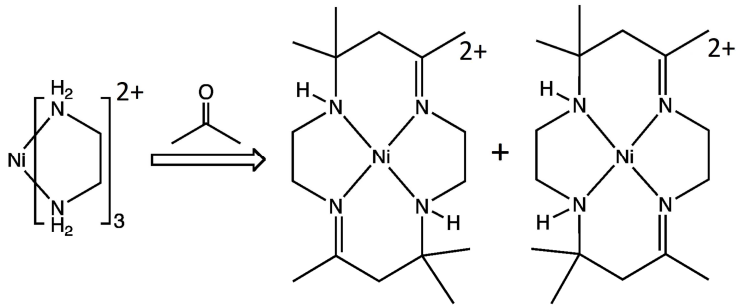
1939 Linus Pauling (Caltech, Nobel Proze in Chemistry 1954)

Bond Theory: 'hydrogen bonding' mentioned in 'The nature of the Chemical Bond"



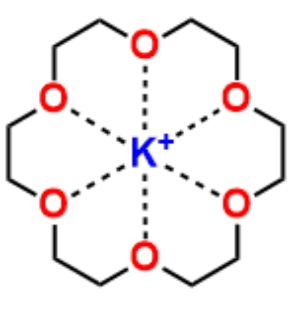
Hydrogen Bond

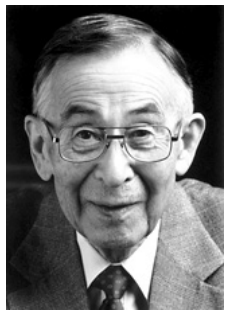
1961 Neil F. Curtis & D. A. House

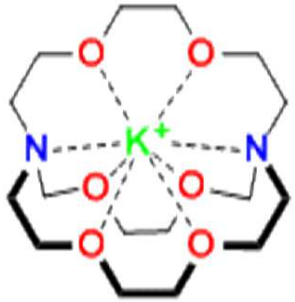


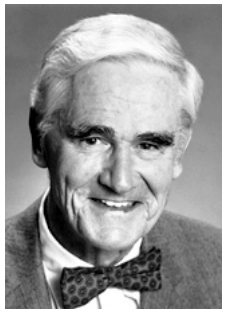
Macrocycle

1967 Worked by **Charles J. Pedersen**, **Jean-Marie Lehn** and **Donald J. Cram** on ***crown ether***, ***cryptands*** and ***spherands***



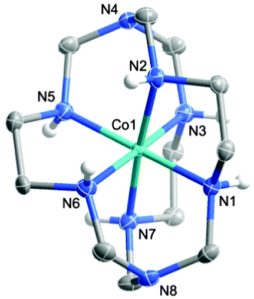


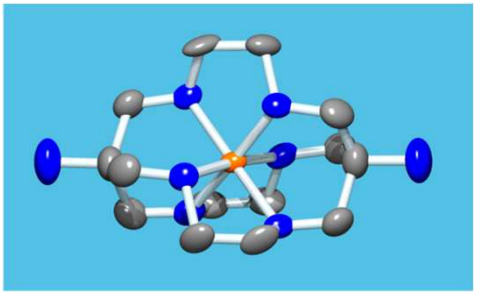




Preorganization
Recognition
Templating

1977 Alan M. Sargeson & Jack M. Harrowfield





Cages

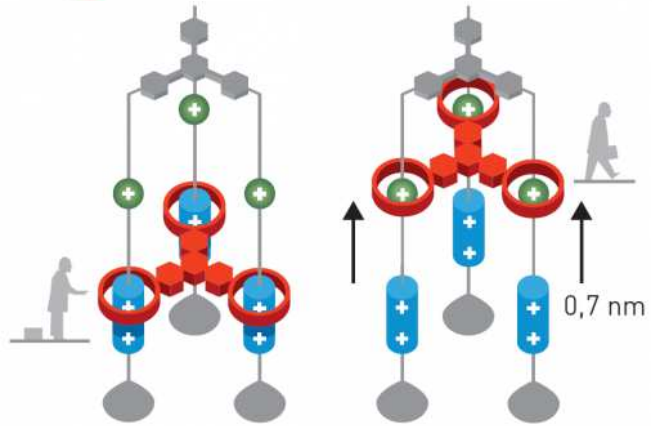
1987 Nobel Prize for **Lehn, Cram, Pederson**

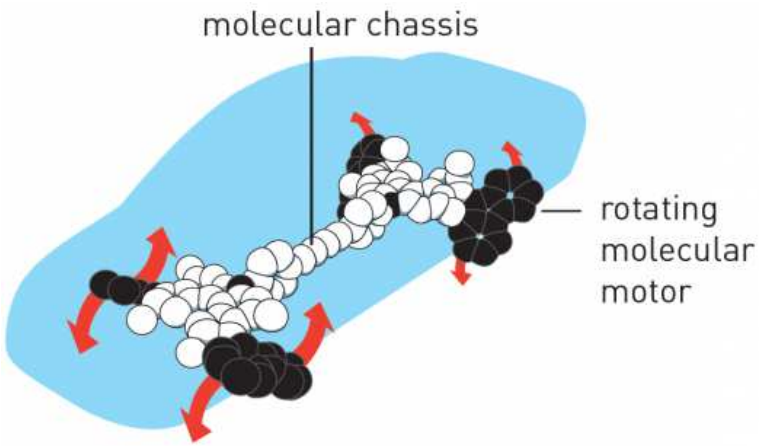
"Supramolecular chemistry is chemistry 'beyond the molecule',
the science of non-covalent, intermolecular interactions"

2016 Nobel Prize for **Jean-Pierre Sauvage, Sir J. Fraser Stoddart, Bernard L. Feringa**

Supramolecular Chemistry

Molecular machines





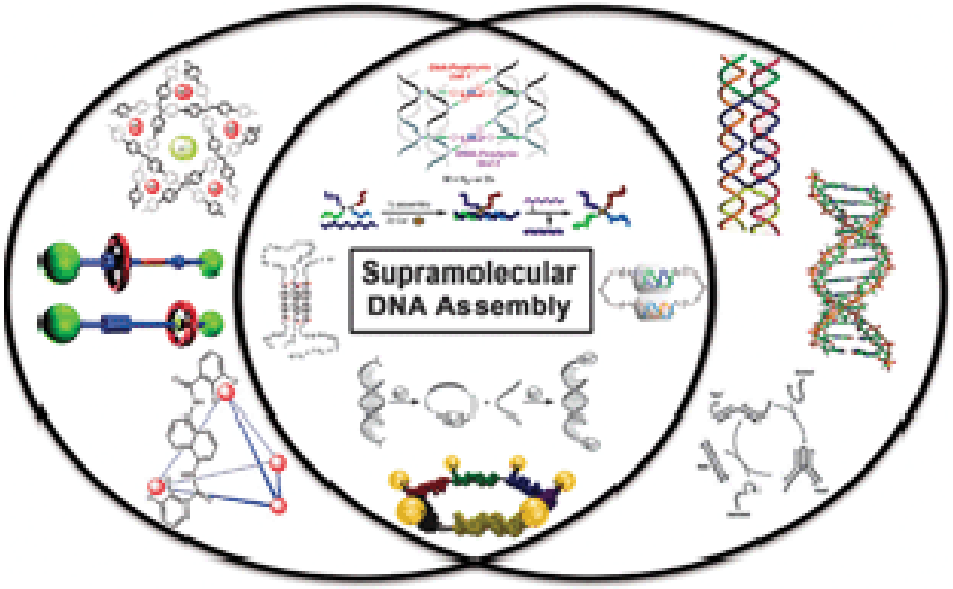
1.1 What is supramolecular chemistry?

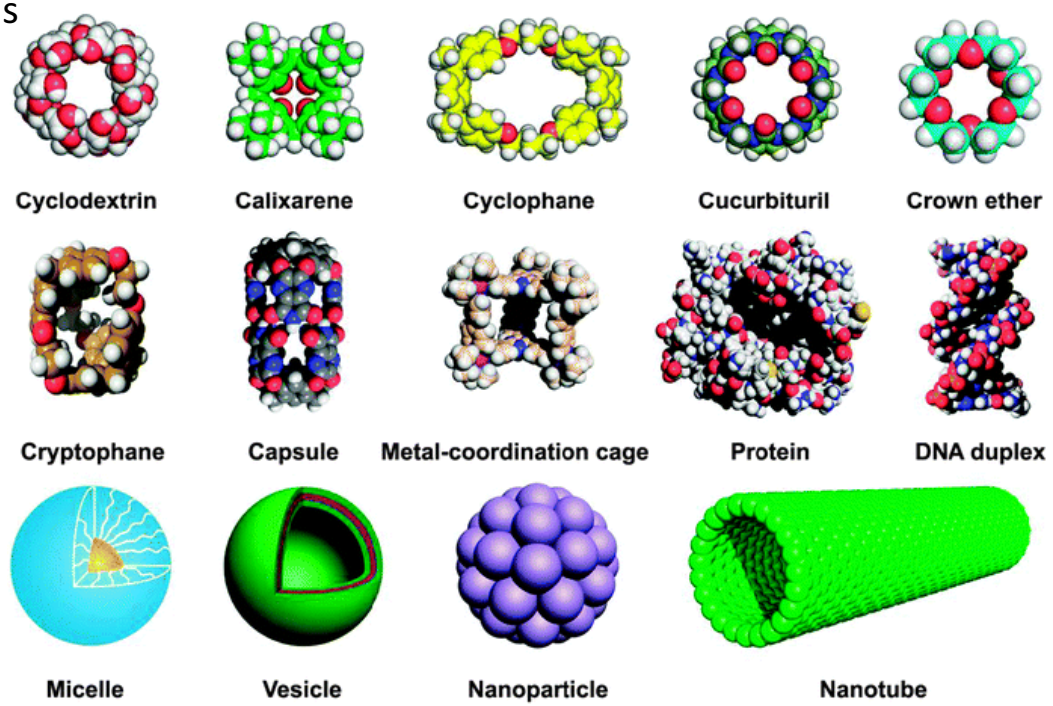
- *What is **supramolecular chemistry***? → **'Chemistry beyond the molecule'**
  - The study of systems involving aggregates of molecules or ions held together by **non-covalent interactions** (such as electrostatic interactions, hydrogen bonding, ion-ion, ion-dipole and dipole-dipole interactions, π–π stacking and cation-π interactions, van de Waals forces, dispersion interactions and solvophobic effects)

- **'Supramolecule' : molecular assemblies using noncovalent bonds**

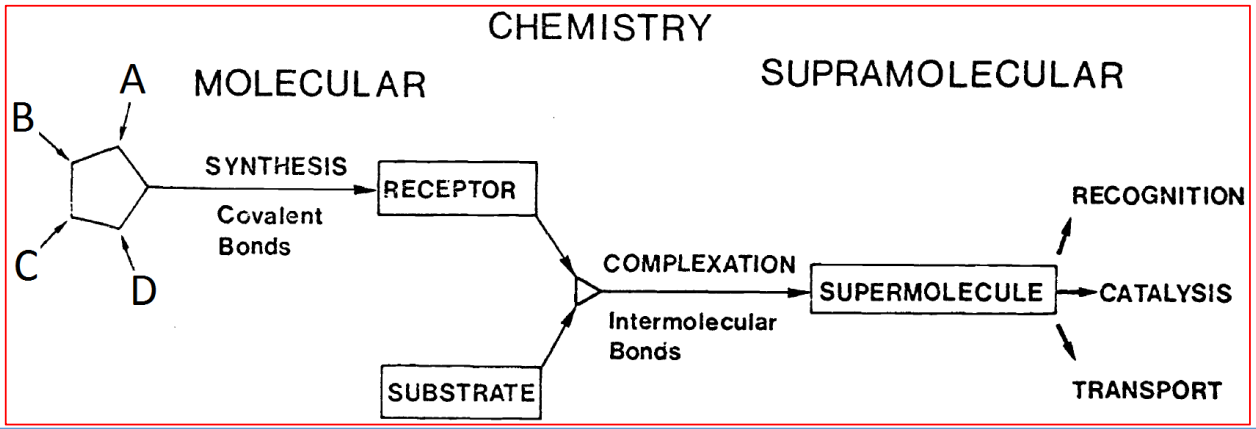
J.-M. Lehn, *Science* 2002, *295*, 2400

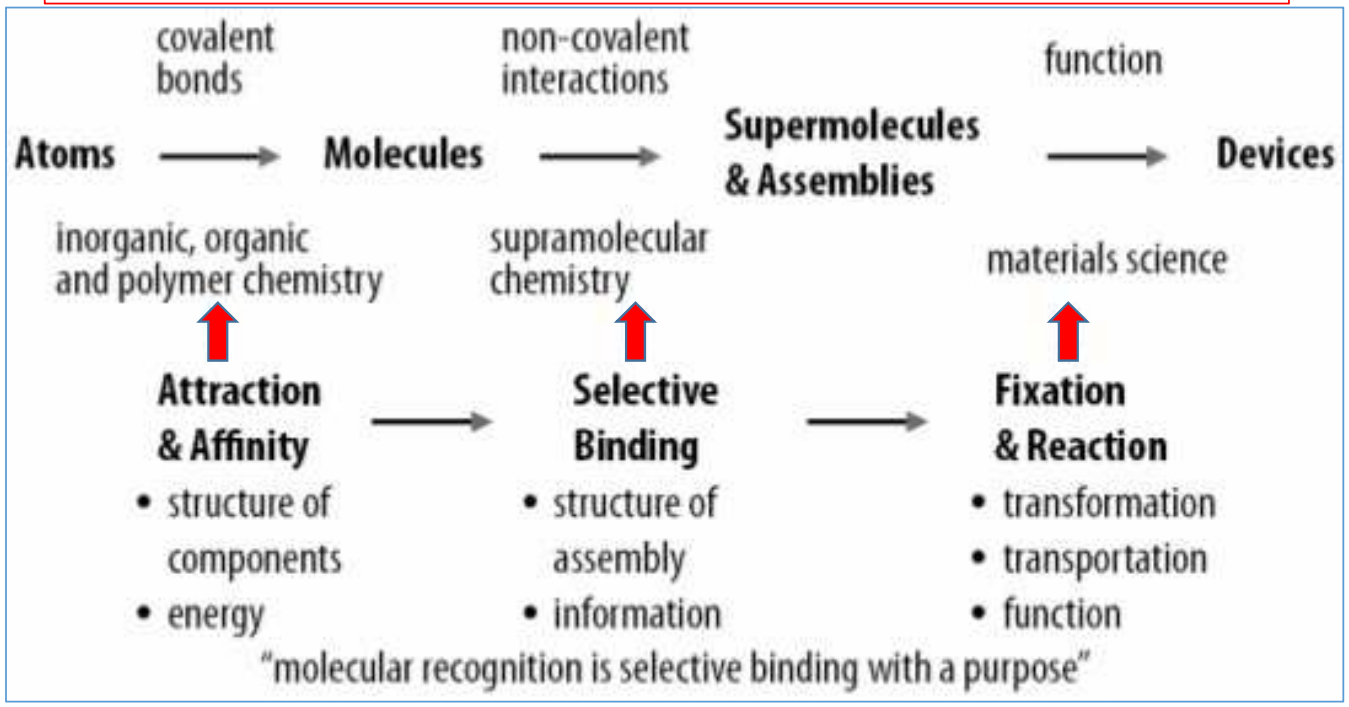
  - A species that is held together by non-covalent interactions between two or more covalent molecules or ions.





Interdisciplinary Nature of Supramolecular Chemistry





J.-M. Lehn.
Pure. Appl. Chem. *50*, 871(1978)

Supramolecule vs. Supramolecular Assemblies

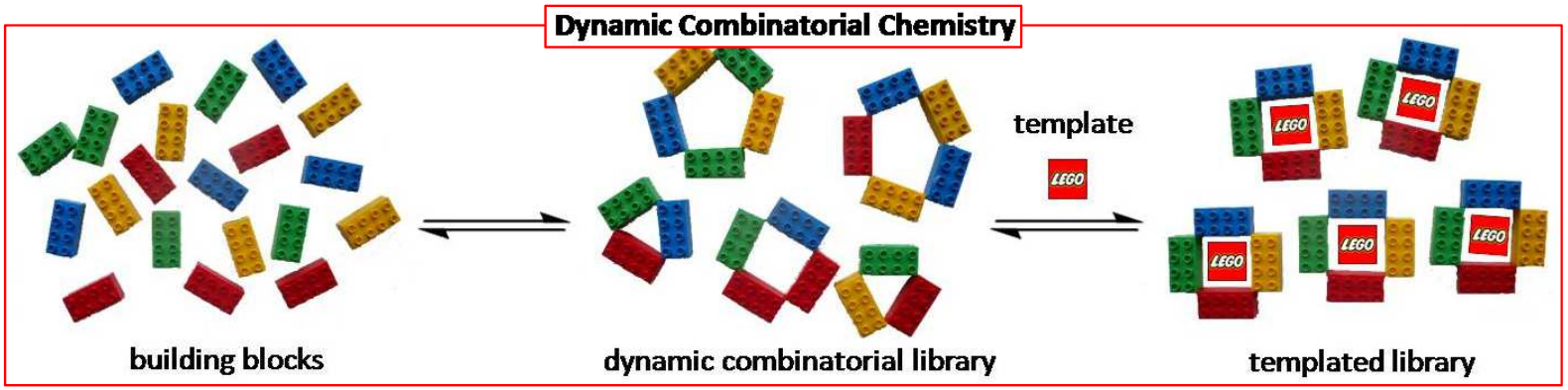
Supramolecule	Supramolecular Assemblies
❑ Well-defined, discrete species formed from a defined, finite number of molecules ❑ The equivalent of low molecular weight organic molecules ❑ Host-guest chemistry	❑ Poly-molecular entities from spontaneous, but defined association of many molecules ❑ The equivalent of high molecular weight polymers and macromolecules ❑ Supramolecular assembly

Individual non-covalent interactions may be weak,
but many of them will still yield “stable” structures while allowing for :self-healing”

J.-M. Lehn

1.1 What is supramolecular chemistry?

- **Supramolecule** can also be described as '**lego™ chemistry**' in which each lego™ brick represents a molecular building block and these blocks are held together by intermolecular interactions (bonds), of a reversible nature, to form a supramolecular aggregate.
- These intermolecular bonds include **electrostatic interactions**, **hydrogen bonding**, **π–π interactions**, **dispersion interactions** and **hydrophobic or solvophobic effects.**



- **Metallosupramolecular Chemistry**
  - ▶The metals act as a type of "glue" to hold together assemblies of organic molecules – a term introduced by Constable (1994)
  - ▶By employing donor groups in organic molecules (ligands) that bridge more than one metal center, it is possible to construct **one- two- or three dimensional architectures**, based on M-L interactions.

- **Nature itself** is full of supramolecular systems
  ex. **DNA** is made up from two strands
  which **self-assemble *via* hydrogen bonds** and **aromatic stacking interactions**
  to form the double helical structure.
- The inspiration for many supramolecular species designed and developed by chemists has come from biological systems.

Strength of Several Noncovalent Forces

type of interaction or bonding	strength (kJ mol^{-1})
covalent bond	100−400
Coulomb	250
hydrogen bond	10−65
ion−dipole	50−200
dipole−dipole	5−50
cation−π	5−80
$\pi-\pi$	0−50
van der Waals forces	<5
hydrophobic effects	difficult to assess
metal−ligand	0−400

Freek J. M. Hoeben, E. W. Meijer, *Chemical Reviews* 2005, *105*, 1491

Non-covalent interactions

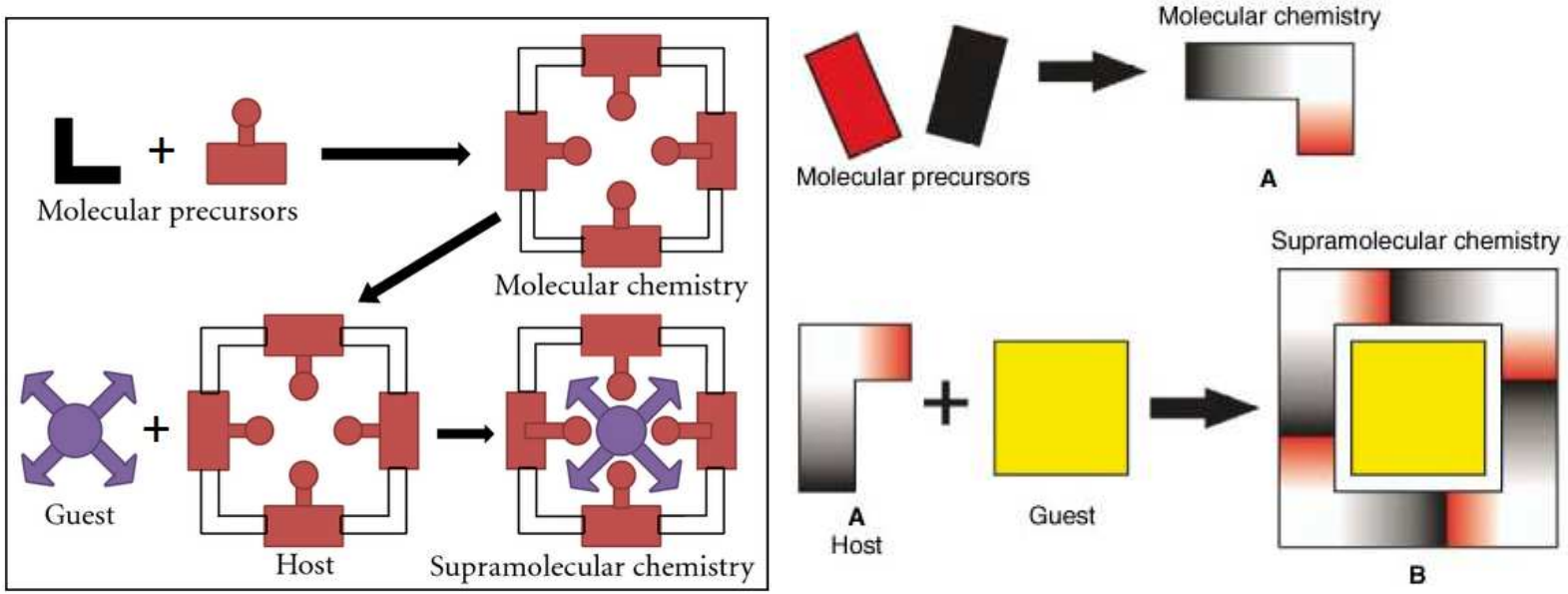
- Intermolecular forces are relatively weak comparing to covalent bonds
- Supramolecular species are
  i) thermodynamically less stable
  ii) kinetically more labile
  iii) dynamically more flexible than covalent molecules.
- Due to there relatively weak interactions,
  non-covalent bonds are often called soft bonds and their chemistry **'soft chemistry'.**

- **Supramolecular chemistry can be split into two broad categories depends on size and shape**
  (1) Host–Guest Chemistry (crown ethers, cryptands, spherands)
  (2) Self-Assembly

- Recent trends include the use of transition metal centres to control the assembly of novel supramolecular architectures, this is called "**metallosupramolecular chemistry**".

Host-Guest Chemistry

❑ If one molecule is significantly larger than another and can wrap around it then it is termed the '**host**' and the smaller molecule is its '**guest**', which becomes enveloped by the host.



► *The **host component** is defined as an organic molecule or ion whose binding sites converge in the complex.*

► *The **guest component** is any molecule or ion whose binding sites diverge in the complex*.

(Donald J. Cram, *Angew. Chem. Inr. Ed. Engl.* 25, 1039(1986))

❑ Host–guest complexes include

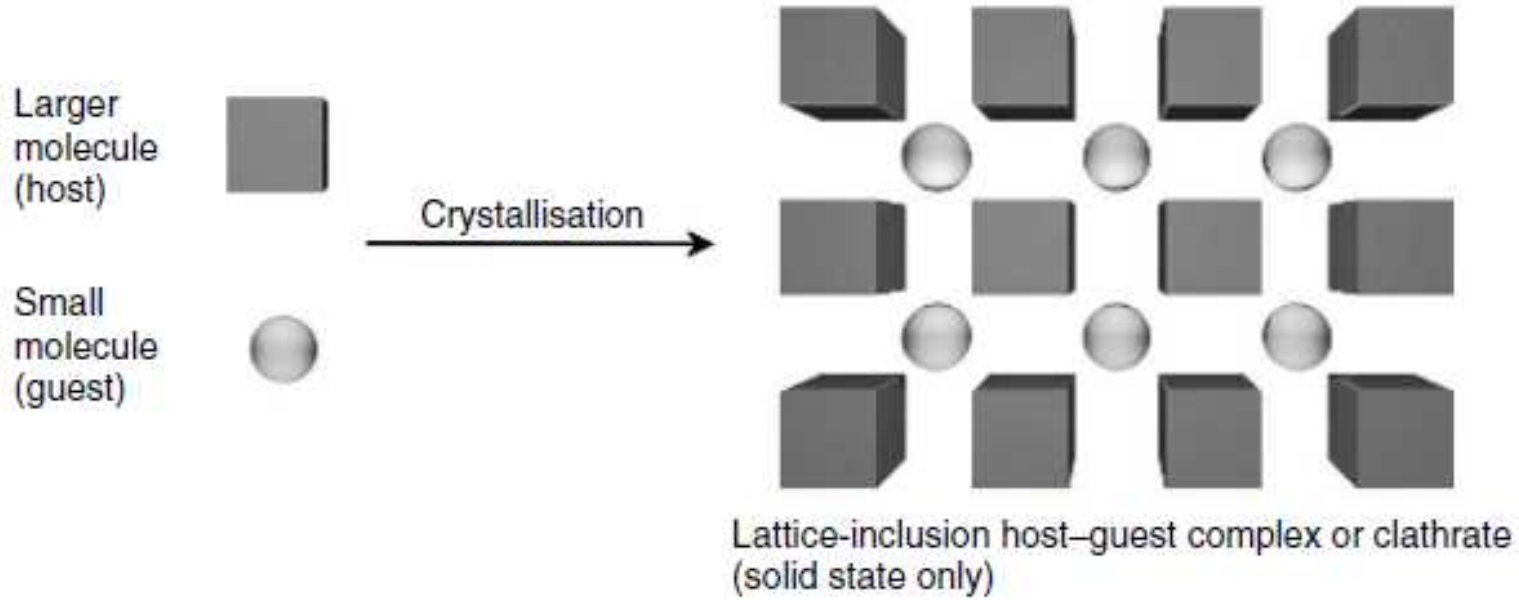
Biological systems (enzymes and their substrates): enzymes being the host and the substrates the guest.

Coordination chemistry: metal–ligand (macrocyclic) complexes.

- Solid state ***inclusion compounds*** exhibit host–guest behaviour as crystalline solids

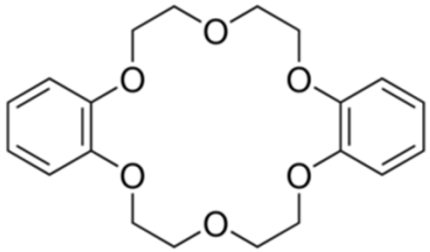
  since the guest is bound within a cavity that is formed as a result of a hole in the packing of the host lattice.
- Such compounds are generally termed *clathrates* from the Greek *klethra*, meaning 'bars'

  (in prison or a steel-barred window).



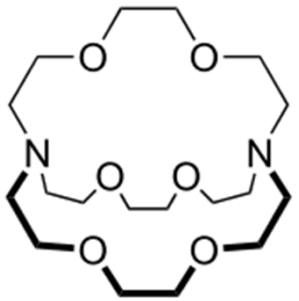
a) Crown Ethers (C.J. Pedersen. 1967)

The first crown ether:
dibenzo[18]crown-6 was discovered
by accident as a by-product for the synthesis of the linear diol.



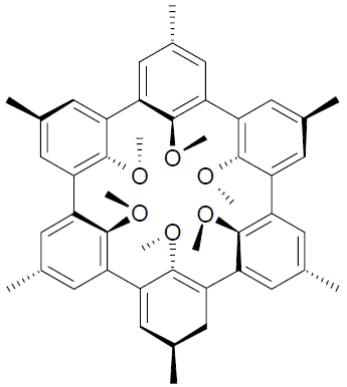
b) Cryptands (J.-M. Lehn. 1969)

Three-dimensional analogue to the crown ether
Crypt from the Greek "*kruptos*" meaning "hidden".



c) Spherands (D. J. Cram. 1973)

Inflexible and rigid structure



Degree of preorganization of the host: spherands > cryptands > corands > podands > solvents

Self-Assembly

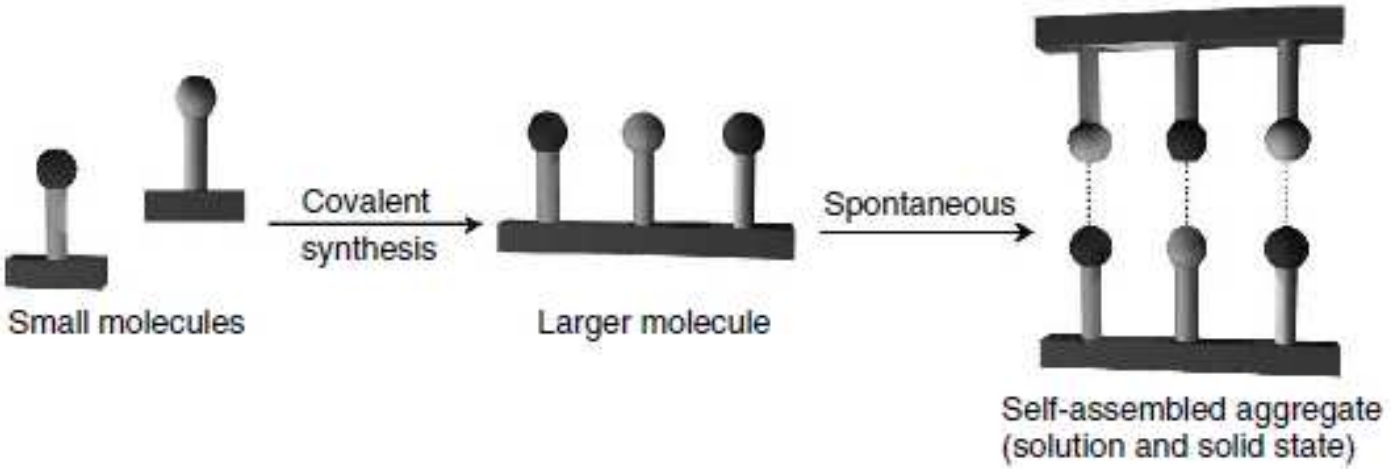
❑ **Self-Assembly**:

Autonomous organization of components into patterns or **structures without human intervention.**

Spontaneous ordering of "**building blocks**" structure through non-covalent interactions.

(e.g.: Formation of molecular crystals, folding of globular proteins

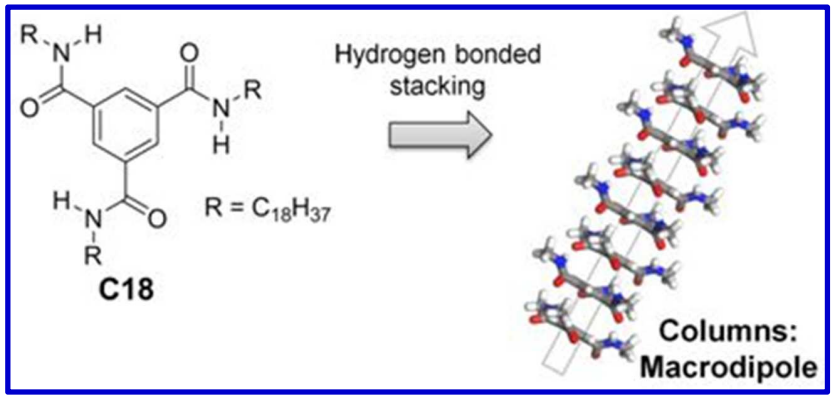
- ✓ The spontaneous and reversible association of two or more components to form a larger, non-covalently bound aggregate.
- ✓ Strictly, an equilibrium between two or more molecular components to produce an aggregate with the chemical building blocks.
- ✓ This process is usually spontaneous but may be influenced by solvation or templation effects

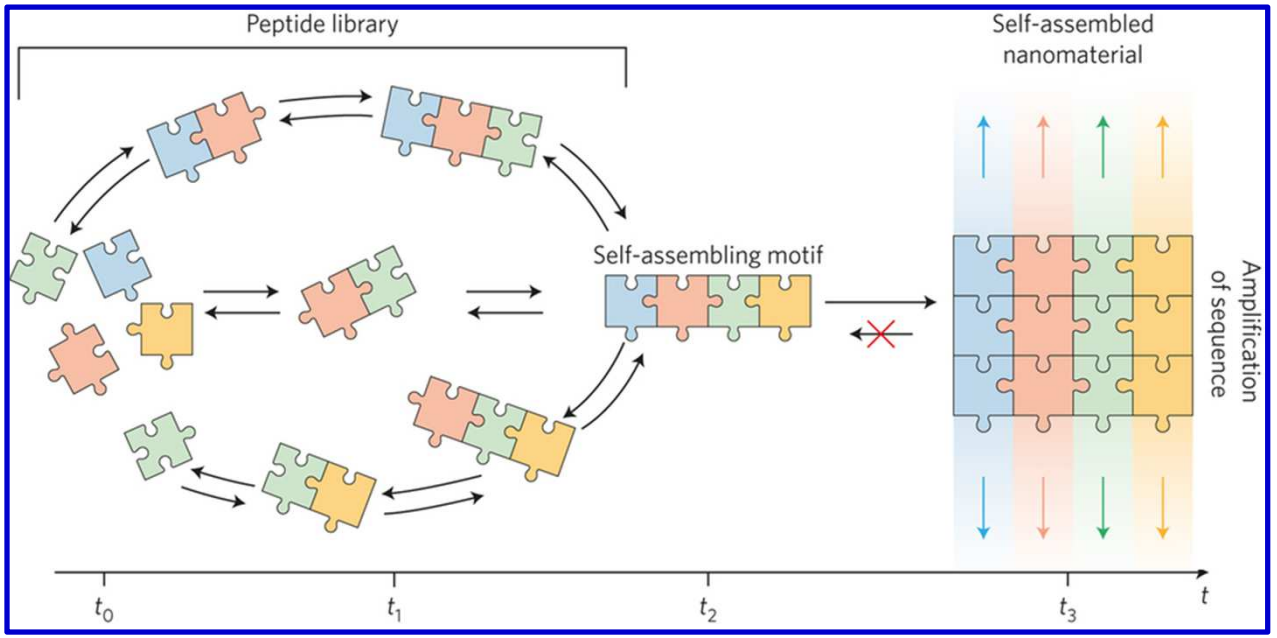


- Mixing of the components spontaneously affords only one well-defined product.
- **Strict self-assembly**: directly proceeds toward the formation of a well-defined aggregate
- **Directed (templated) self-assembly**: controlled/influenced by some additional species, e.g., templates (Lindsey, 1991)

  This means, in an idealized case self-assembly follows a "**cooperative**" or "**allosteric**" process.

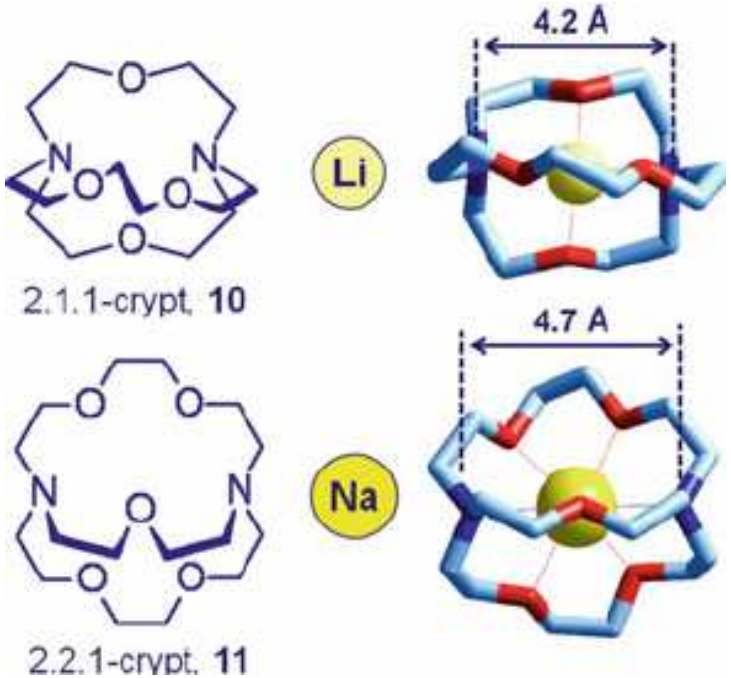
- **Thermodynamically most stable species are formed!**

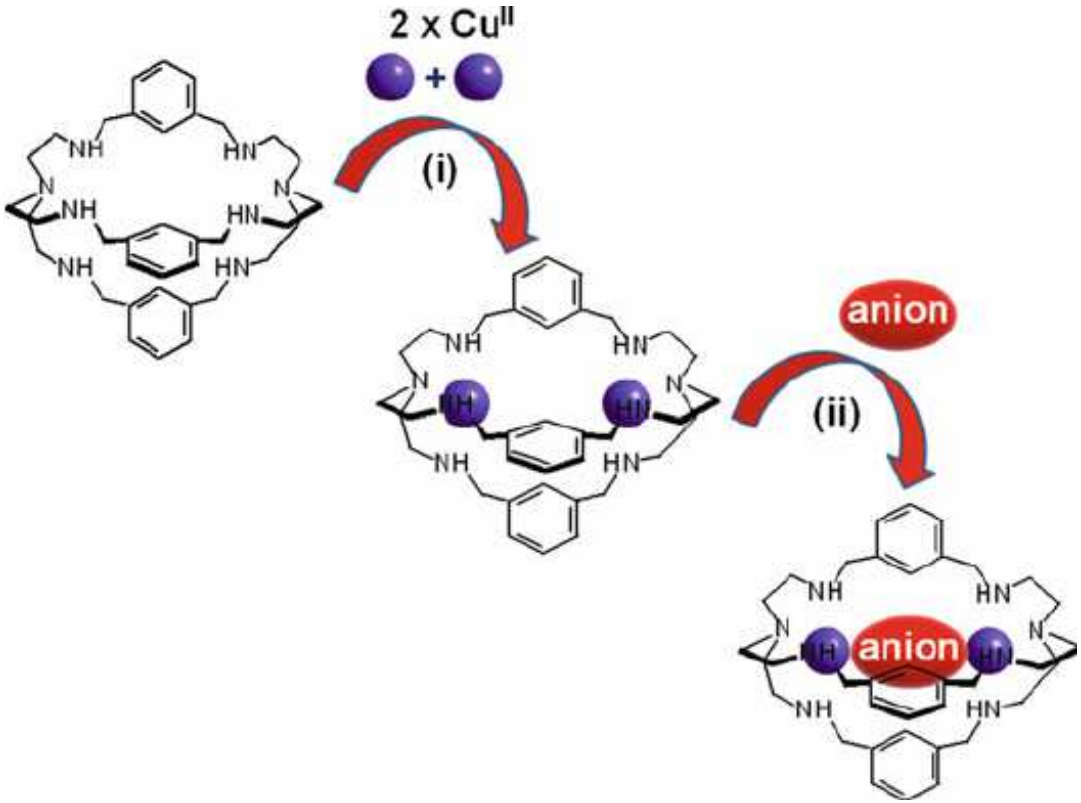




1.2 Selectivity

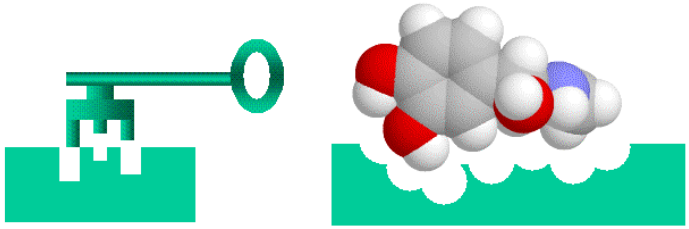
- The binding of one guest, or family of guests, significantly more strongly than others, by a host molecule.
- Selectivity is measured in terms of the ratio between equilibrium constants (*see later*).



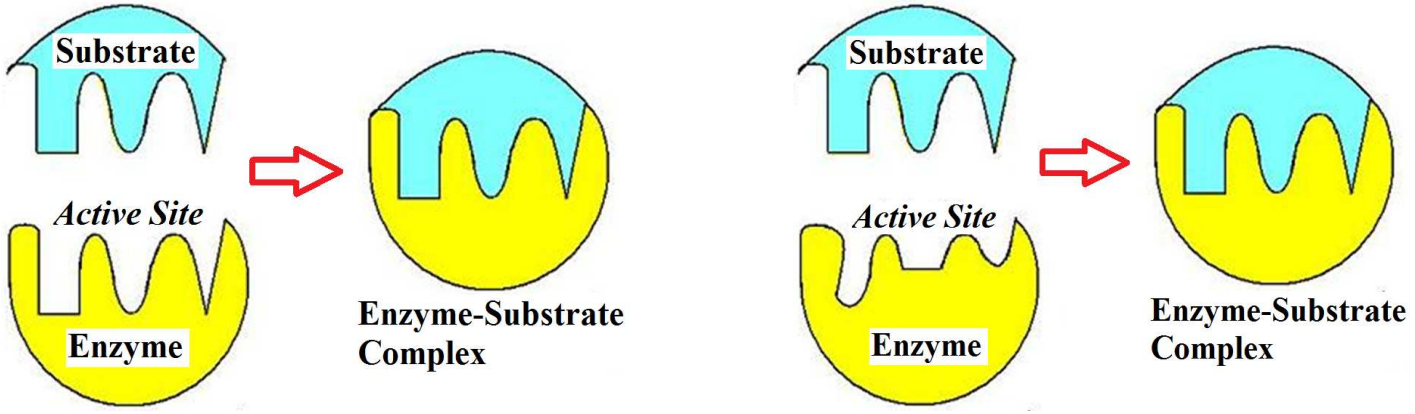


1.2.1 The Lock and key principle and induced-fit model

❑ The concept of the **lock and key principle**: Emil Fisher (1894)

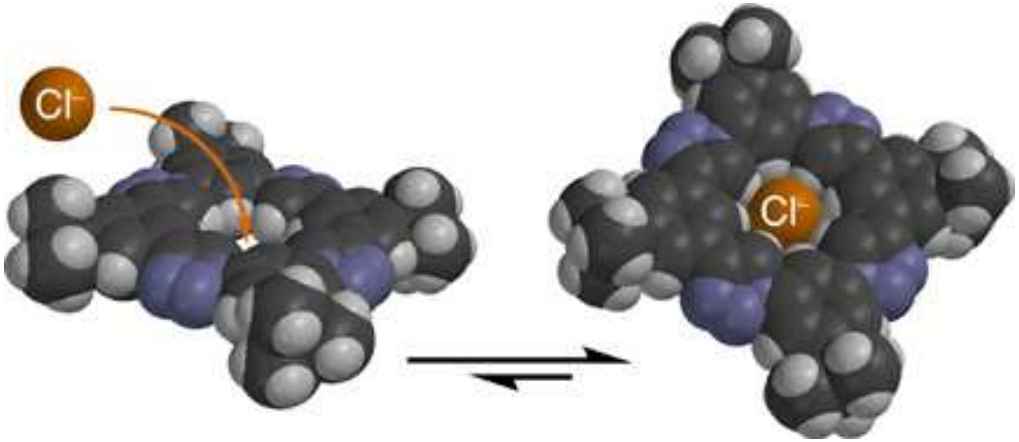


- ✓ from the binding of substrates by enzymes
- ✓ the enzyme = the lock; the substrate = the key
- ✓ the substrate (guest) has a complementary size and shape to the enzyme (host) binding site.



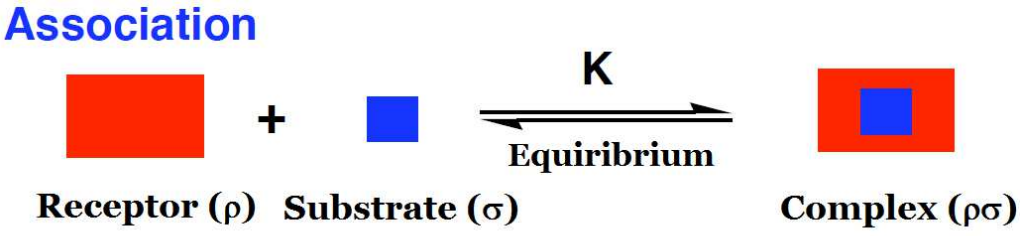
Molecular Recognition

- ►Molecular recognition is the specific interaction between two molecules, Which are complementary in their geometric and electronic features (like two fitting pieces of a jigsaw puzzle)
- ►The classical lock and key principle describes the interaction of components due to their shape and rigidity (**preorganization**).



Molecular Recognition

- Molecular recognition results from
  an association between a receptor (ρ: or host molecule) and a substrate (σ : guest molecule).
- This association is achieved by reversible processes
  which lead to a chemical equilibrium between the receptor and the free substrate and the complex.
- This equilibrium corresponds to an **equilibrium constant K (thermodynamic parameter).**
- Sometimes we use K_s (stability constant) or K_{ass} (association constant).



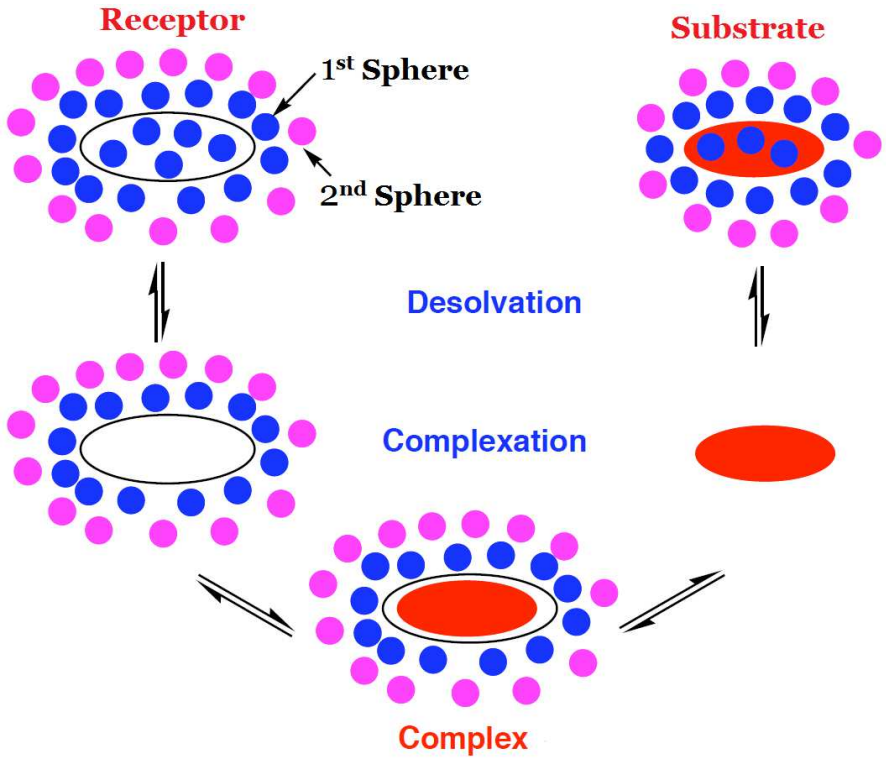
$$K = \frac{[\rho\sigma]}{[\rho] \times [\sigma]}$$

K = Equilibrium Constant

- A strong association corresponds to a high equilibrium constant.
- For given receptor and substrate concentrations, the higher the K value,
  the higher the concentration of the complex and
  therefore the free receptor and substrate concentrations are low.

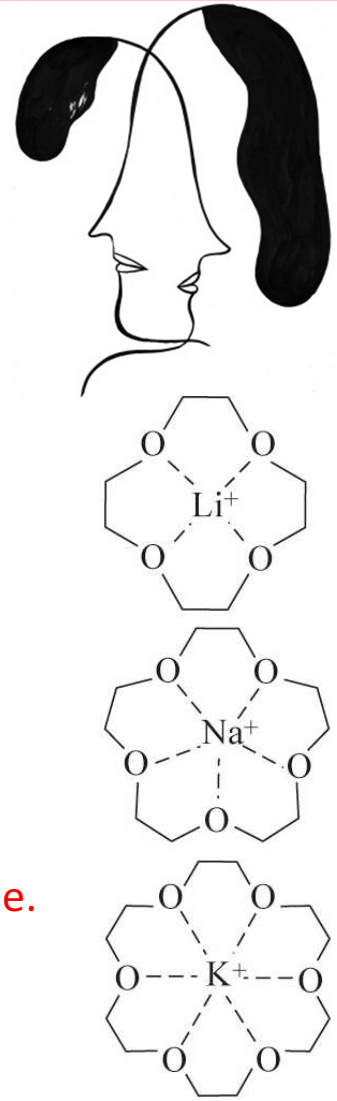
Molecular Association

- The recognition process often takes place in the liquid phase.
- Both the receptor and the substrate in solution are solvated.
- In order to the substrate and the receptor form a complex, both must be at least partly desolvated and the complex solvated.
- Consequently, the complexation of the substrate by the receptor is in competition with the at least partial desolvation of the two entities.
- This desolvation requires a certain energy (the solvation energy).



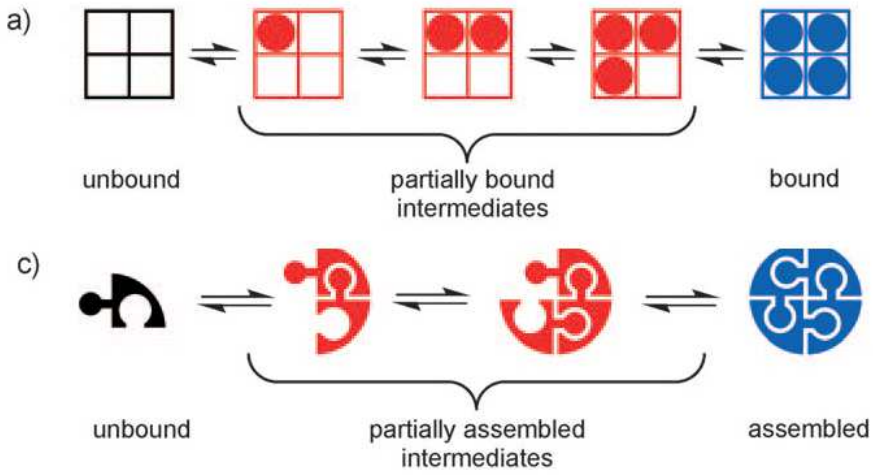
1.2.2 Complementarity

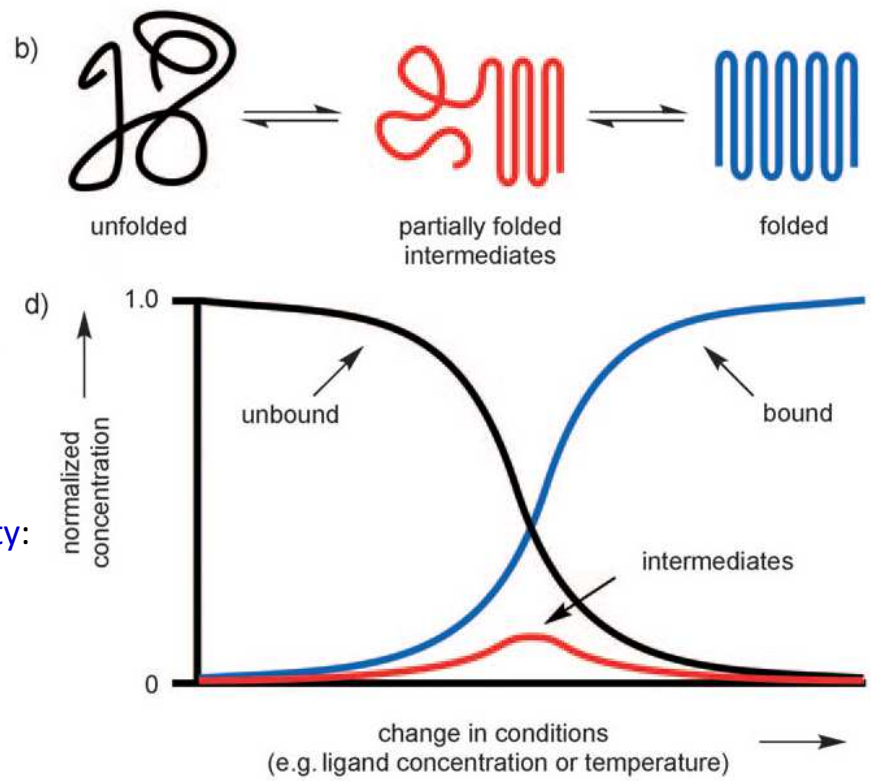
- ***Complementarity*** plays an important role in biological and supramolecular systems
  - ▶(ex) in the function of enzymes.
- An enzyme is generally a lot larger than its substrate
  - ▶Only a small percentage of the overall structure is involved in the binding: *active site*
- In order to achieve strong and selective binding
  1. The binding site of the host must be complementary to the guest in terms of **size and shape**
     (*cf.* the lock and key and induced-fit models)
  2. The binding sites on both partners must be chemically complementary.
     (ex) Lewis theory of **HSAB in coordination chemistry** (the polarisability of the electron density)
     Hard acids/bases are non-polarizable; soft acid/bases are polarisable.
- Hard-to-hard and soft-to-soft complexes are the most stable,
  displaying complementarity between like species.
- Both the host and guest must have
  mutual spatially and electronically complementary binding sites to form a supermolecule.



1.2.3 Co-operativity and the chelate effect

- **Co-operativity:** two types of cooperativity — allosteric and chelate cooperativity — in multivalent systems.
  - Central concept for understanding molecular recognition and supramolecular self-assembly.
  - Key feature of systems chemistry that leads to collective properties.
  - Does not present in the individual molecular components.





- Representation of processes that display positive cooperativity:
  a) hemoglobin binding oxygen,
  b) protein folding
  c) Supramolecular self-assembly
  d) Speciation profiles.
- Positive cooperativity leads to a low peak concentration of intermediates and a sharp transition from unbound to bound.

Angew. Chem. Int. Ed. 48, 7488(2009)

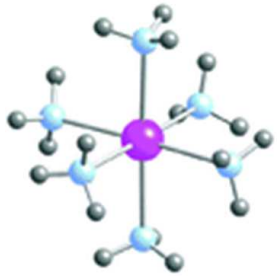
Chelate effect

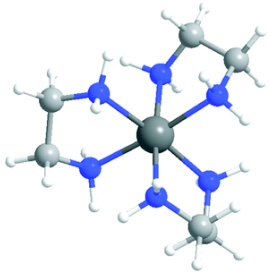
❑ Chelate Effect:

Multidentate ligands (by extension, hosts with more than one binding site) result in more stable complexes than comparable systems containing multiple unidentate ligands

→ This *co-operativity* between sites is the ***chelate effect***.

❑ $[Ni(en)_3]^{2+}$ complex is 10^8 times more stable than the corresponding hexamine complex (the equilibrium constant)



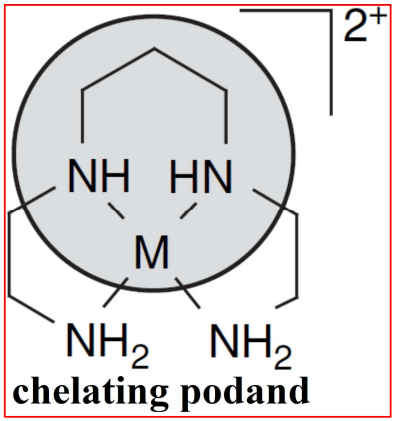


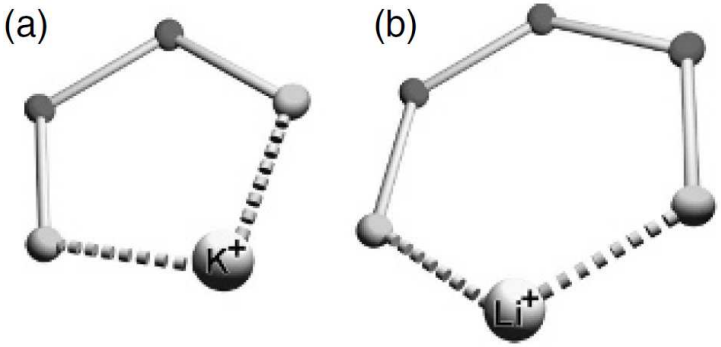
$$[Ni(NH_3)_6]^{2+} + 3NH_2CH_2CH_2NH_2 \underset{}{\overset{\log K = 8.76}{\rightleftharpoons}} [Ni(NH_2CH_2CH_2NH_2)_3]^{2+} + 6NH_3$$

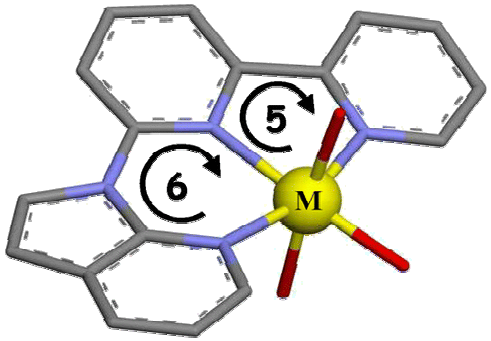
Total complexation free energy $\Delta G^o = \Delta H^o - T\Delta S^o$		
$Ni^{2+} + 6\ NH_3 \rightleftharpoons Ni(NH_3)_6^{2+}$	ΔG^o = -49.2	log β = 8.61
$Ni^{2+} + 3\ en \rightleftharpoons Ni(en)_3^{2+}$	ΔG^o = -104.4	log β = **18.28**

Chelate effect

- **Podand**: a term applied to any **flexible acyclic host** capable of wrapping around a guest
- The stability of metal chelate complexes is significantly affected by **the size of the *chelate ring***.
- The **optimum ring geometry** for large metal cations (K^+): **5-membered chelate ring**
- **Six-membered rings** are more stable with smaller guests such (Li^+)
- A precise match between optimum chelate ring sizes and metal ionic radii depends on the orbital hybridisation of the donor atoms.



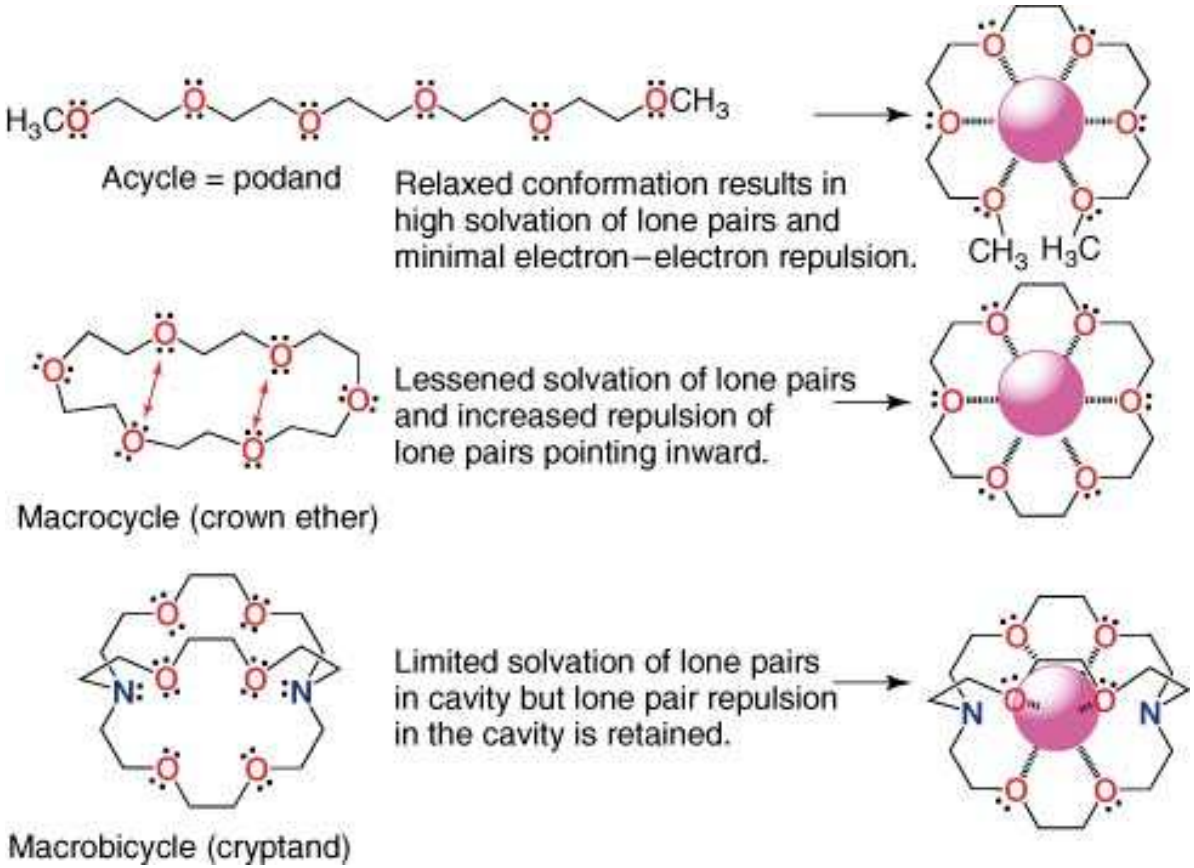


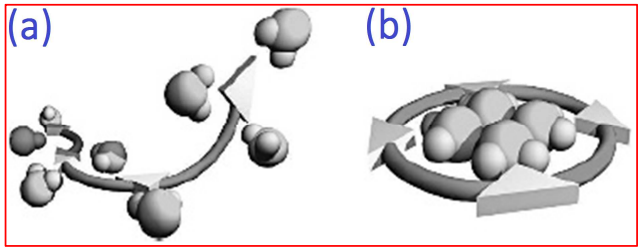


- As the chelate ring size becomes increasingly large, the chelate effect diminishes, as there is increasing loss of entropy associated with the greater conformational flexibility of the ring.

1.2.4 Preorganisation

- **Preorganised host:** A host that is already of the correct size to accept the potential guest species and with the appropriate interaction sites already in place.
- **Preorganisation:** A host without significant conformational change to bind a guest species.

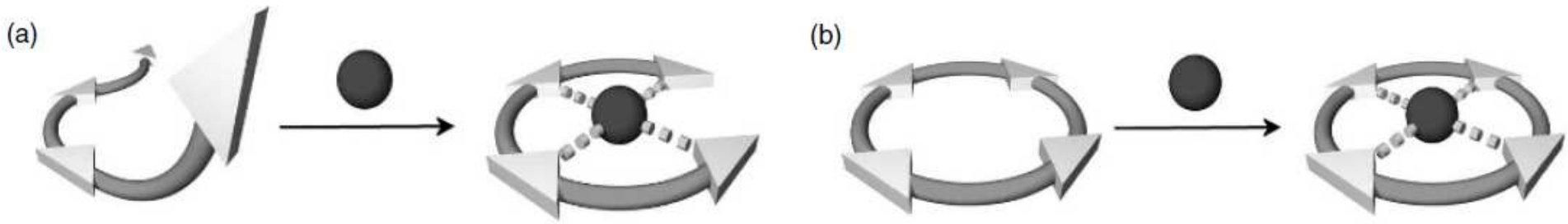




Podand (a) is fully solvated in solution as it is flexible and the donor sites are easily accessible.

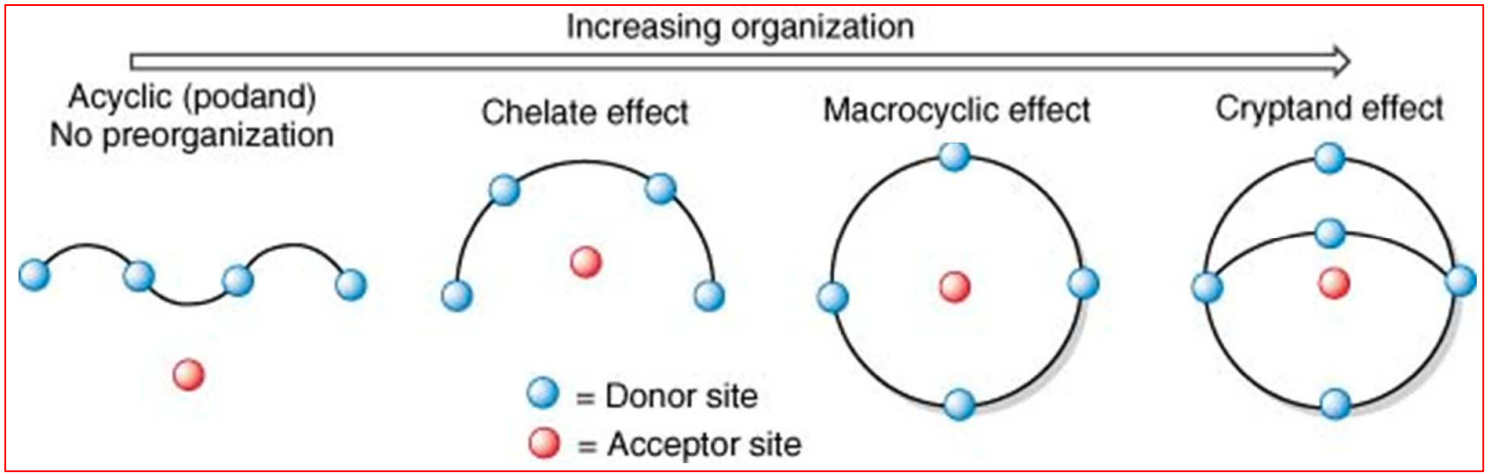
Macrocycle (b) is **not** fully solvated as the solvent molecules would have to be packed in close proximity in the centre of the host.

Macrocyclic Effect



(a) A podand is **not** preorganised and must undergo a change in conformation in order to bind a guest destabilising the complex.

(b) A macrocycle that is preorganised for a specific guest does not need to change conformation significantly for binding to occur.

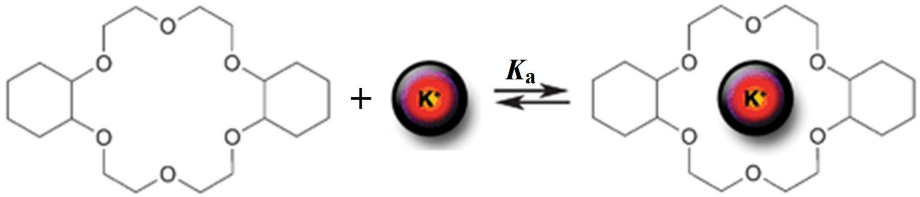


1.2.5 Binding constants

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

$$\text{Host} + \text{Guest} \rightleftharpoons \text{Host} \cdot \text{Guest}$$

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



- Binding constants are calculated from experimental data (from titrations monitored by NMR, UV–Vis or fluorescence spectroscopy), which supply information about the position of the equilibrium.

$$H + G \rightleftharpoons H \cdot G \qquad K_1 = \frac{[H \cdot G]}{[H]\,[G]}$$

$$HG + G \rightleftharpoons H \cdot G_2 \qquad K_2 = \frac{[H \cdot G_2]}{[H \cdot G]\,[G]}$$

$$HG_2 + G \rightleftharpoons H \cdot G_3 \qquad K_3 = \frac{[H \cdot G_3]}{[H \cdot G_2]\,[G]}$$

Stepwise binding constants (K_1 for first event, *etc.*)

$$H + 3G \rightleftharpoons H \cdot G_3 \qquad \beta_3 = \frac{[H \cdot G_3]}{[H]\,[G]^3}$$

$$\beta_3 = K_1 \times K_2 \times K_3$$

Overall binding constant (β) for a 1:3 host–guest complex

1.2.6 Kinetic and thermodynamic selectivity

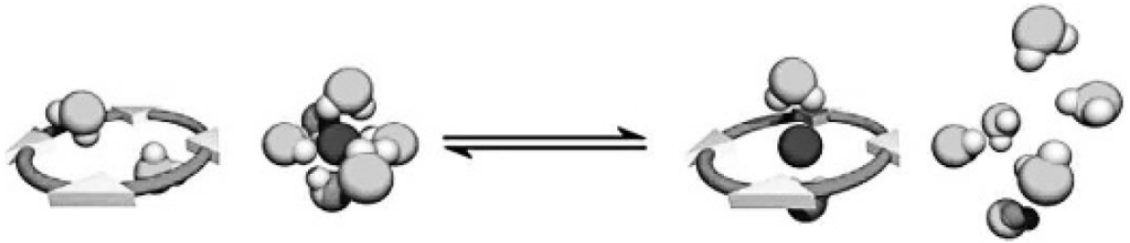
- The most important factors in the design of host–guest systems
  - **Preference** for the target guest species above all other possible guests.
  - Good degree of ***selectivity*** for the desired guest.
- ***Thermodynamic selectivity*****:** the ratio of the binding constants for a host binding two different guests

$$\text{Selectivity} = \frac{K_{Guest\ 1}}{K_{Guest\ 2}} \qquad \Delta G = -RT \ln K$$

- ***Kinetic selectivity*****:** time-element is involved
  - Usually found in the context of catalytic or enzyme-based processes

1.2.7 Solvent effects

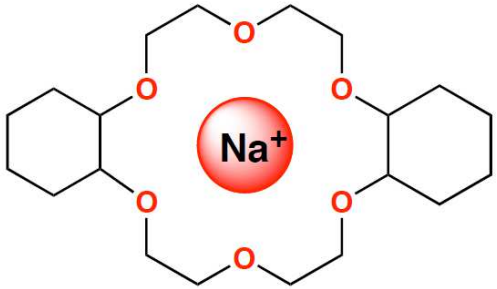
- In solution: In order to host and guest species interact and bond
  the interactions by solvent molecules **must be broken**,
  which has both enthalpic and entropic consequences.



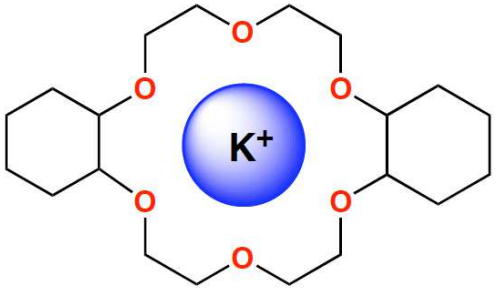
- Enthalpically, energy must be consumed to break the solvent–host and solvent–guest bonds.
- Entropically, more freedom by the removal of solvent molecules from the host and the guest increase entropy
  and also leads to the formation of solvent–solvent bonds.
- The choice of solvent can have significant consequences on the binding of a guest.

- **Polar solvents** are particularly able to inhibit binding of charged species,
  as the solvent dipole can interact strongly with a charged centre,
  thus making the solvent–host or solvent–guest interactions harder to break.

Complexation is in competition with solvation



DiCh[18]O_6



DiCh[18]O_6

logK_f (25° C)

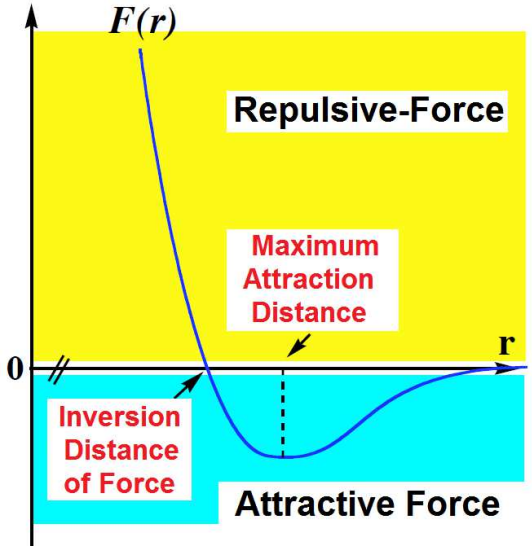
	Na^+	K^+
H_2O	1.21	2.02
MeOH	4.08	6.01

H_2O: Very polar solvent Protic (ε = 78)
MeOH: Protic polar solvent (ε = 33)

- The complexation of charge species is markedly more favored in methanol.
- The water, very polar, solvates very well both the cation (charge / dipole interactions) and crown ether (interactions by the formation of hydrogen bonds with the oxygen of the crown).

Energy and Interaction Force

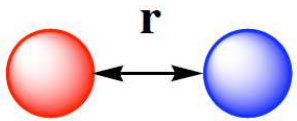
Force



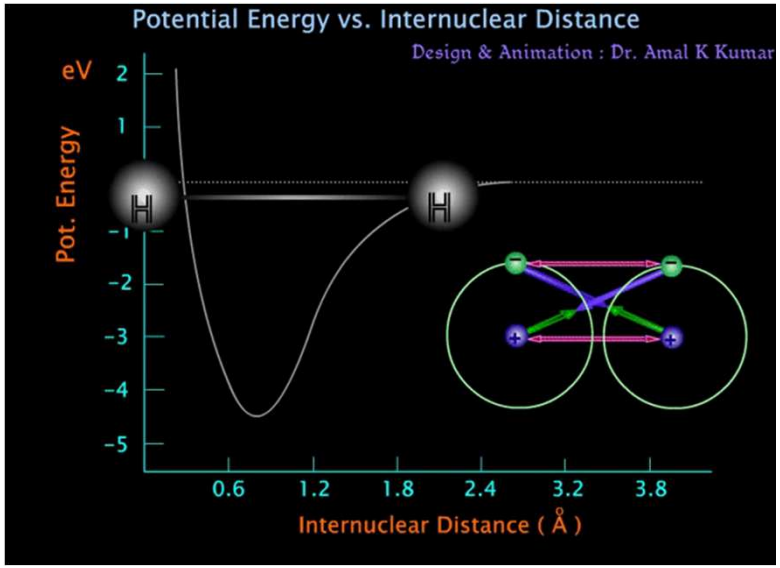
$$F(r) = -\frac{dU(r)}{dr}$$

At infinity, there is no interaction

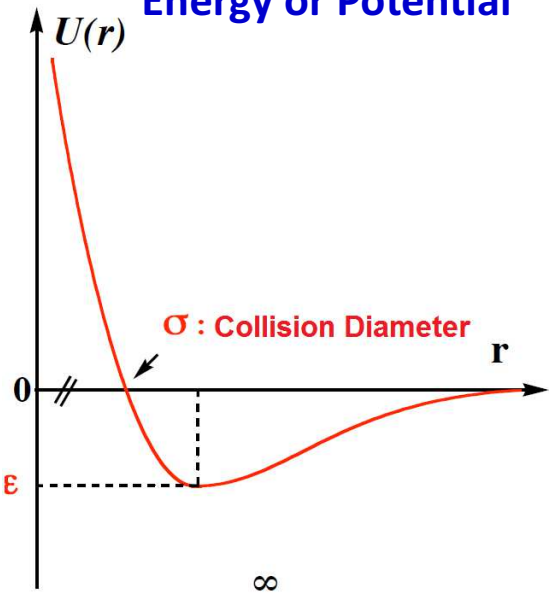
Simplification:



Two Spherical Molecules (Isotropy)
No dependency Angular



Energy or Potential

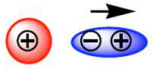
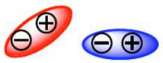


$$U(r) = \int_{r}^{\infty} F(r)dr$$

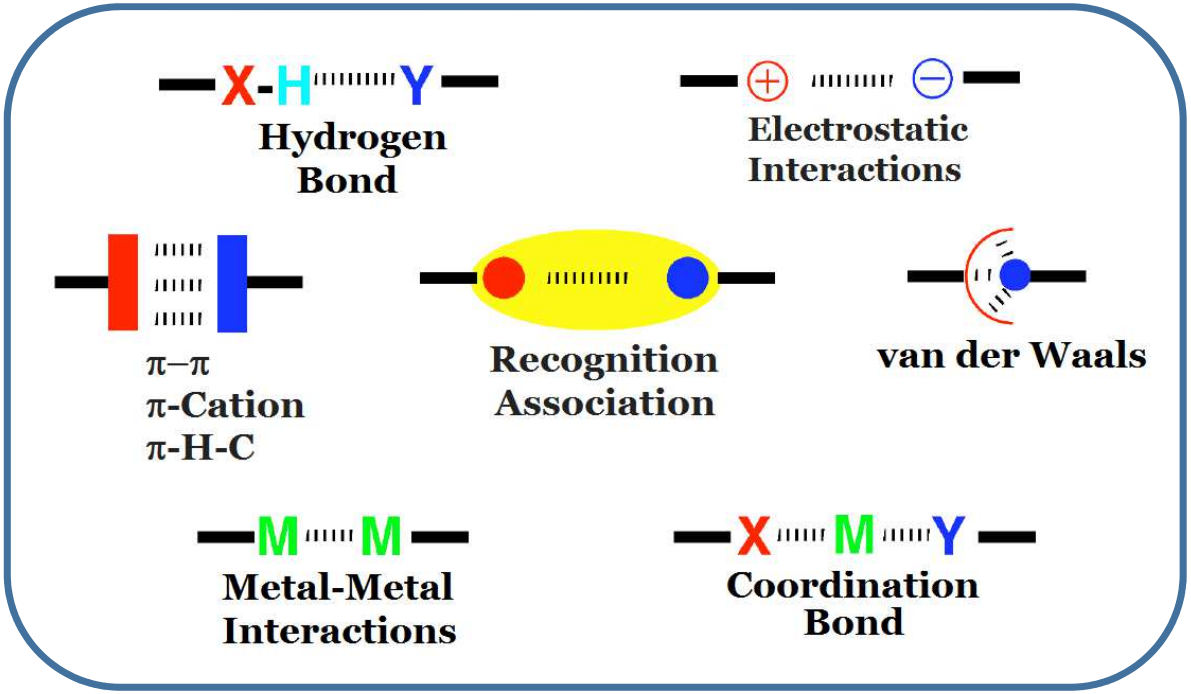
Work done to bring
the two molecules to the distance r

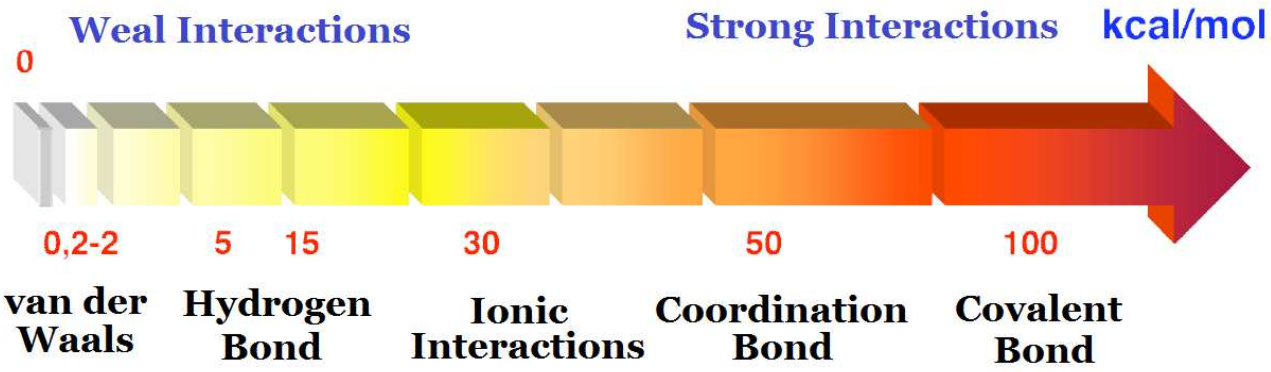
1.3 Supramolecular interactions

Chemical Forces and Interaction

Origin	*Intensity*	Relationship of energy-distance
Coulomb  Ion-Ion	Very strong	$\frac{1}{r}$
 Ion-Dipole	Strong	$\frac{1}{r^2}$
Dipole  Dipole-Dipole	Properly strong	$\frac{1}{r^3}$
Polarization  Ion-Molecule	Weak	$\frac{1}{r^4}$
Dispersion  Molecule-Molecule	Very weak	$\frac{1}{r^6}$

The Toolkit for Supramolecular Chemistry





Summary of supramolecular interactions		
Interaction	Strength kJ mol^{-1}	Example
Ion–ion	200–300	Tetrabutylammonium chloride
Ion–dipole	50–200	Sodium [15]crown-5
Dipole–dipole	5–50	Acetone
Hydrogen bonding	4–120	H_2O and alcohols
Cation–π	5–80	K^+ in benzene
π–π	0–50	Benzene and graphite
van der Waals	< 5 kJ mol^{-1} but variable depending on surface area	Argon; packing in molecular crystals
Hydrophobic	Related to solvent–solvent interaction energy	Cyclodextrin inclusion compounds

1.3.1 Ionic and dipolar interactions

❑ **Ionic** and **dipolar interactions**

(i) *ion–ion interactions* > (ii) *ion–dipole interactions* > (iii) *dipole–dipole interactions*

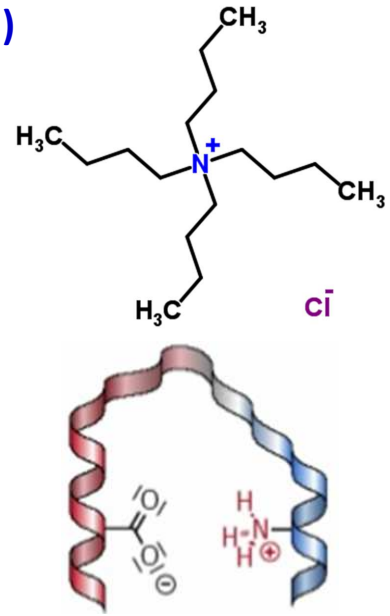
(i) Ion–ion interactions are *non-directional* in nature and can occur in any orientation.

(ii) Ion–dipole and dipole–dipole interactions have *orientation-dependent* aspects

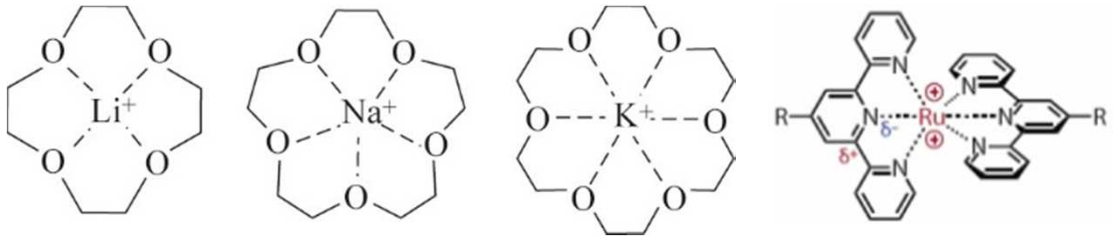
(iii) Dipole–dipole interactions are useful for bringing species into alignment,

as the interaction requires a specific orientation of both entities.

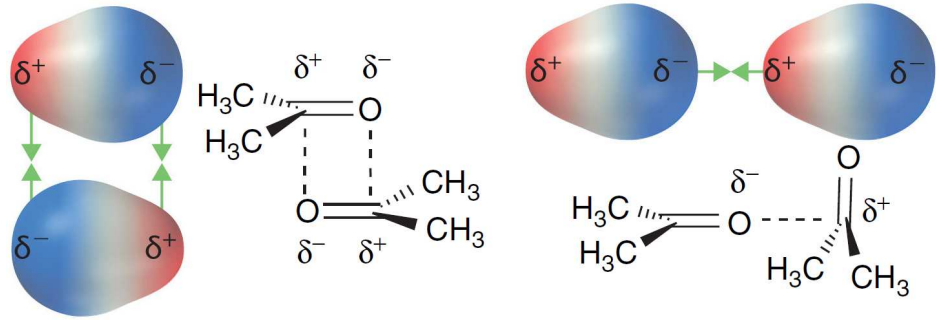
(i)

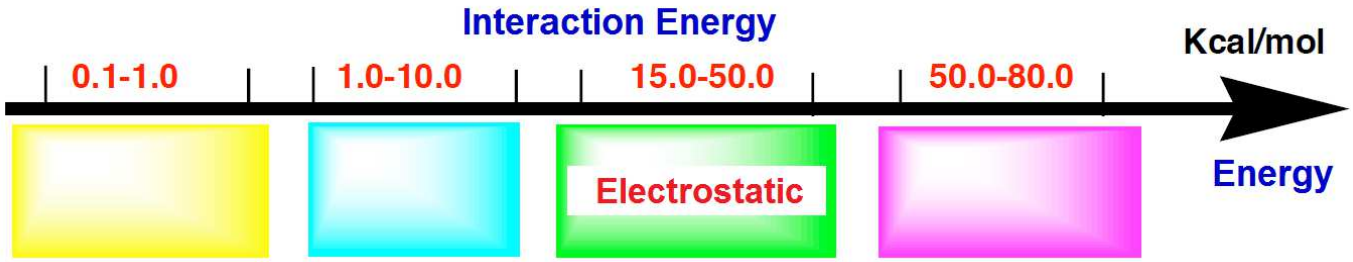


(ii)

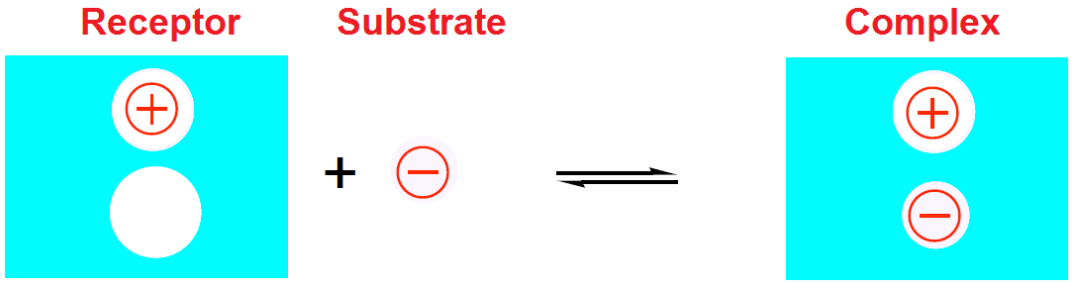


(iii)

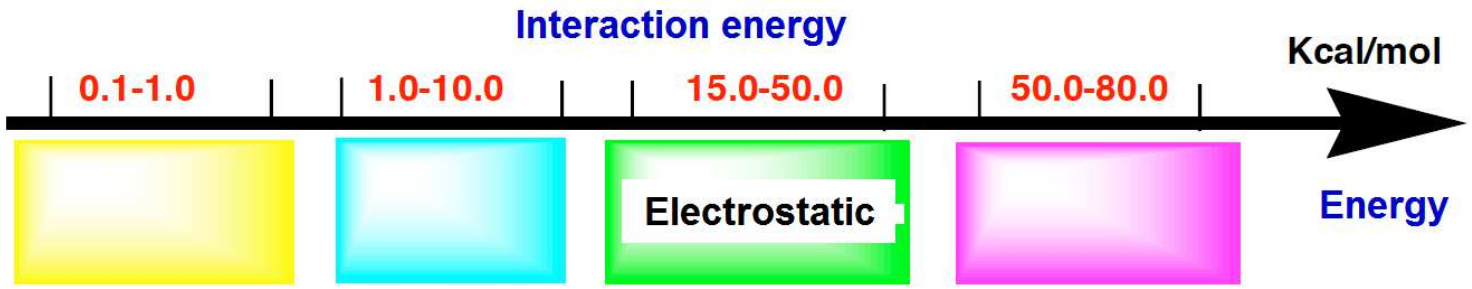




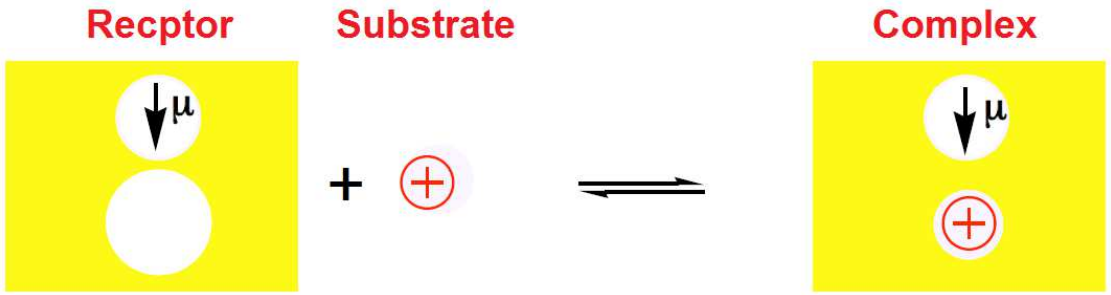
- **Electrostatic charge / charge interactions:**
  The charge / charge electrostatic interaction is established
  when two entities carrying opposite charges are present and at an interaction distance.
- This interaction is not directional.
- Its strength depends on the distance between the cationic site (C^+) and the anionic site (A^-).



- In order for the electrostatic bond to be established,
  the receiver and the substrate must carry complementary charges.
- The cationic and anionic sites may be carried by the receptor or the substrate.



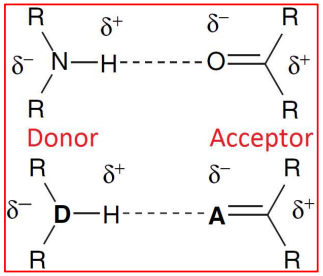
- **Electrostatic charge / dipole interactions:**
  The charge/dipole electrostatic interaction is established when a load is in the vicinity of an appropriately oriented dipole.



- In order for the charge/dipole interaction to be established, either the receiver carries the charge and the substrate the dipole is the reverse.
- Interactions of the dipole/dipole or dipole/quadrupole or quadrupole/quadrupole type can also be used.

1.3.2 Hydrogen bonding

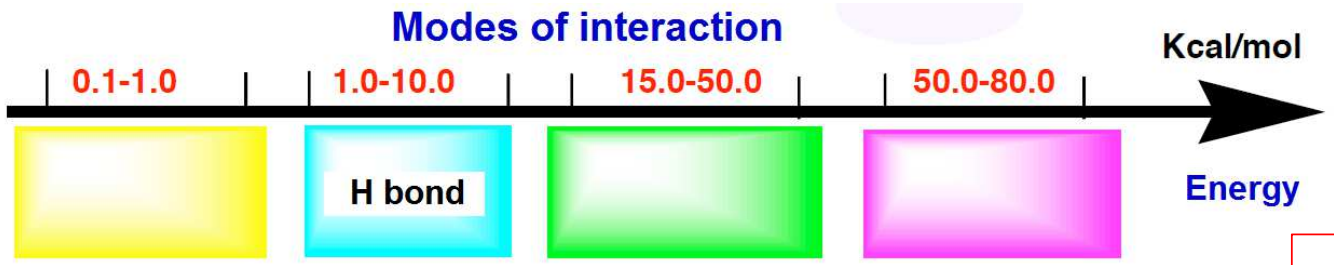
- ***Hydrogen bond***: the most important non-covalent interaction in the design of supramolecular architectures, because of its strength and high degree of directionality.
- Naturally occurring 'building blocks' of hydrogen bond: amino acids, carbohydrates and nucleobases

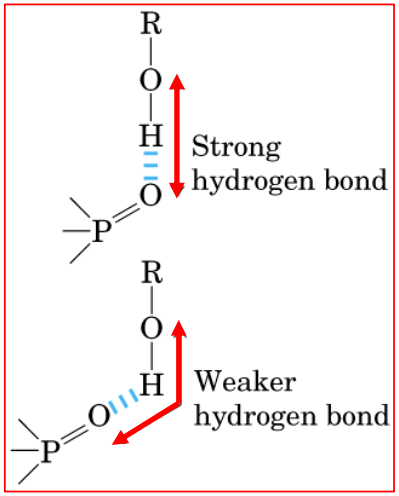


Carbonyl accepting a hydrogen bond from a secondary amine donor

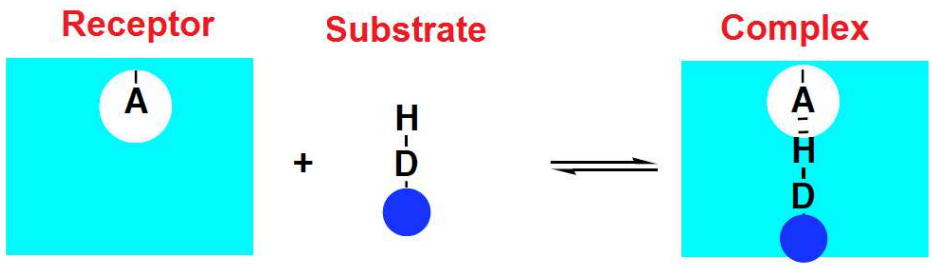
Hydrogen bond interactions and their properties (A, acceptor; D, donor)

Interaction/property	Strong	Moderate	Weak
D–H···A	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol^{-1})	60–120	16–60	< 12
Bond length (Å)			
H···A	1.2–1.5	1.5–2.2	2.2–3.2
D···A	2.2–2.5	2.5–3.2	3.2–4.0
Bond angle (degrees)	175–180	130–180	90–150
Example	HF complexes	Acids	C–H···A
	$H_5O_2^+$	Alcohols	D–H···π
	—	DNA/RNA	—

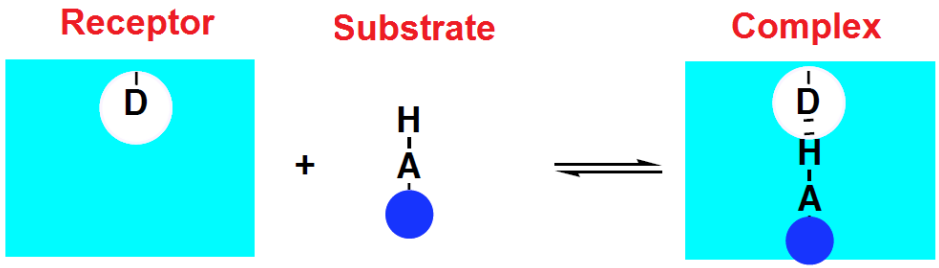


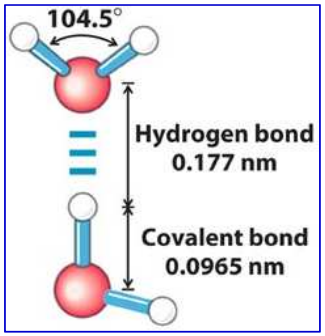


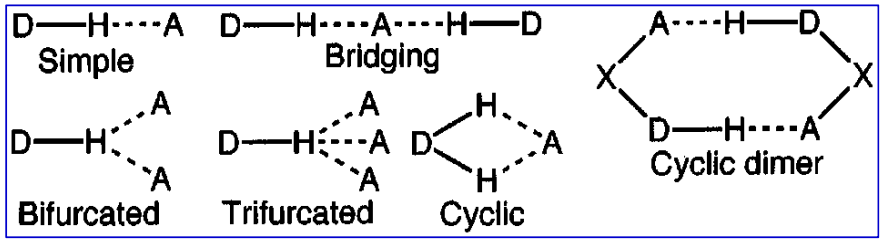
- The **hydrogen bond** is directional (angular dependence).
- Its strength depends on the distance between the donor site (D) and the binding acceptor site (A) H and the DHA angle.

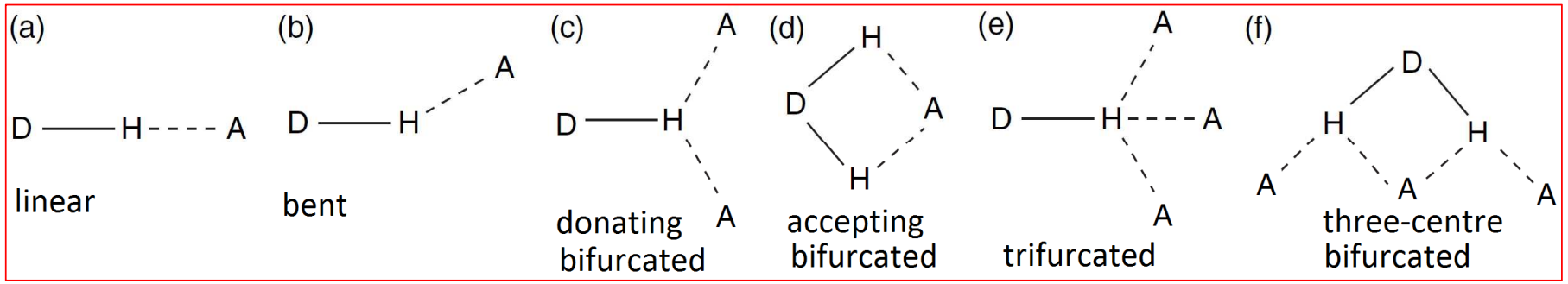


- In order for the H bond to be established, the receiver and the substrate must be complementary.
- The donor and acceptor sites may be carried by the receptor or the substrate.

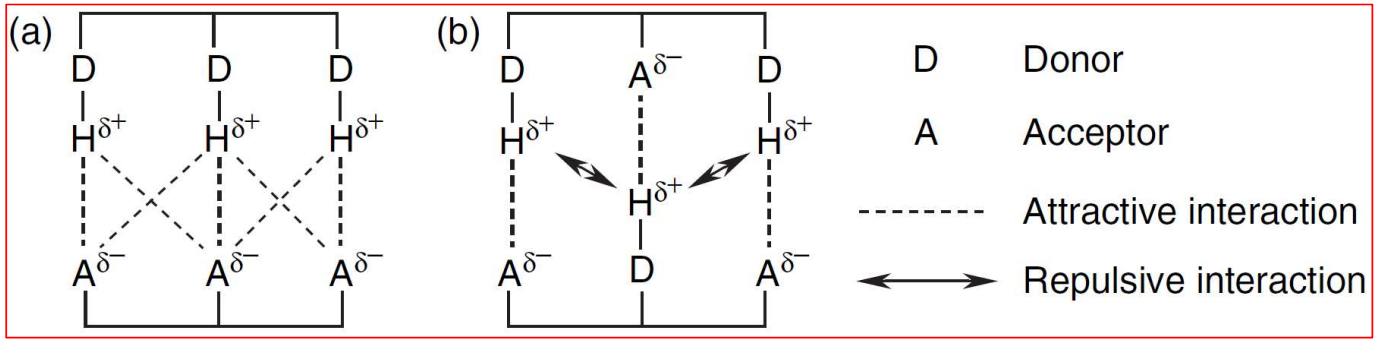








Various types of hydrogen bonding geometries

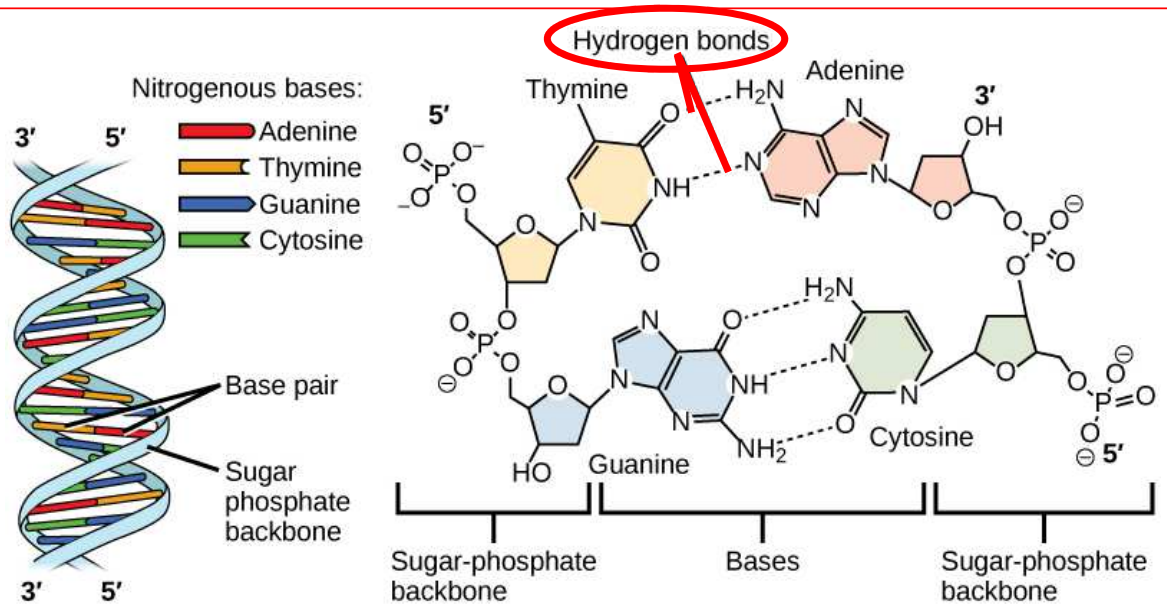


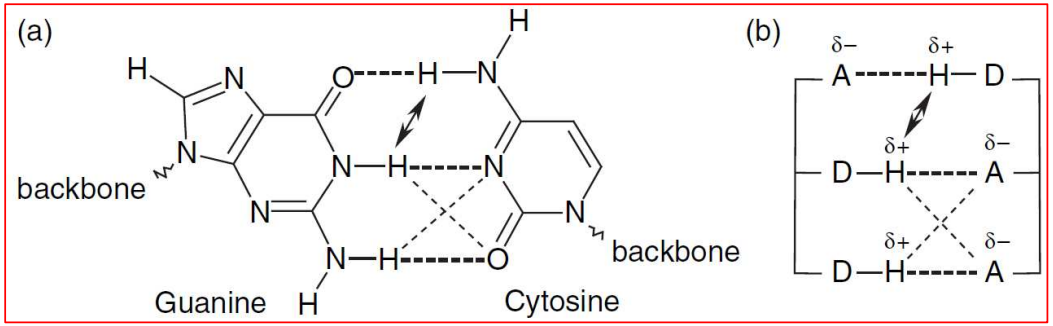
Primary interactions shown in 'bold'

(a) Secondary interactions providing attractions between neighboring groups in DDD and AAA arrays

(b) Repulsions from mixed donor/acceptor arrays (ADA and DAD)

A real-life example of hydrogen bonding (double helix of DNA)

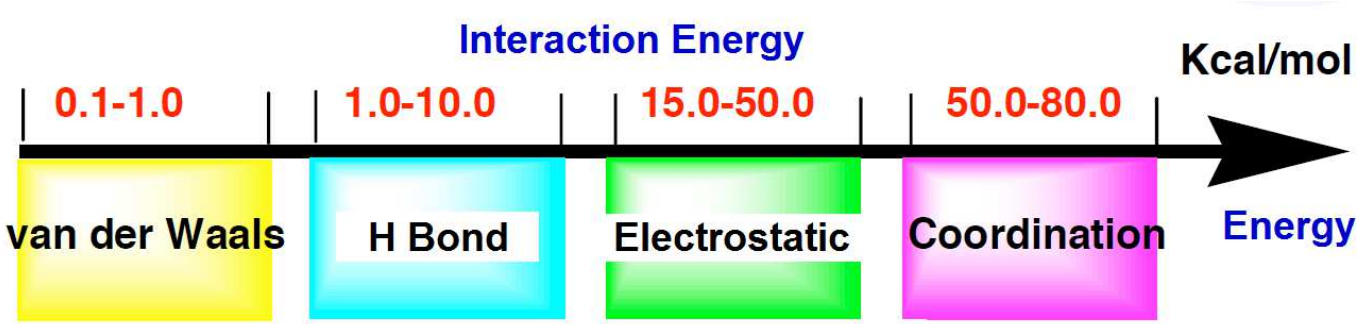




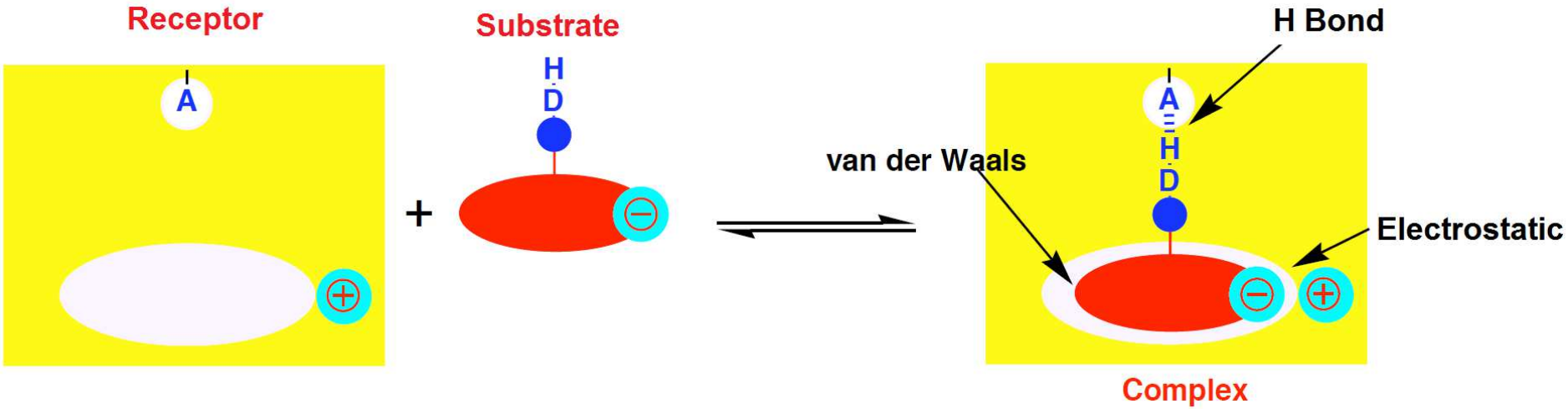
(a) Primary and secondary hydrogen bond interactions between guanine and cytosine base-pairs in DNA

(b) Schematic representation.

Modes of complexation



- **Combination of interactions:** the recognition phenomenon often combines several interactions.
- In particular, van der Walls interactions with the H bond and electrostatic interactions.



1.3.3 π-Interactions

- Two main -interactions in supramolecular systems: **(i) cation–π interactions**, **(ii) π–π interactions**.

  (i) Cation–π interactions in the field of organometallic chemistry (ferrocene and Zeise's salt $[PtCl_3(\eta^2\text{-}C_2H_4)]^-$)

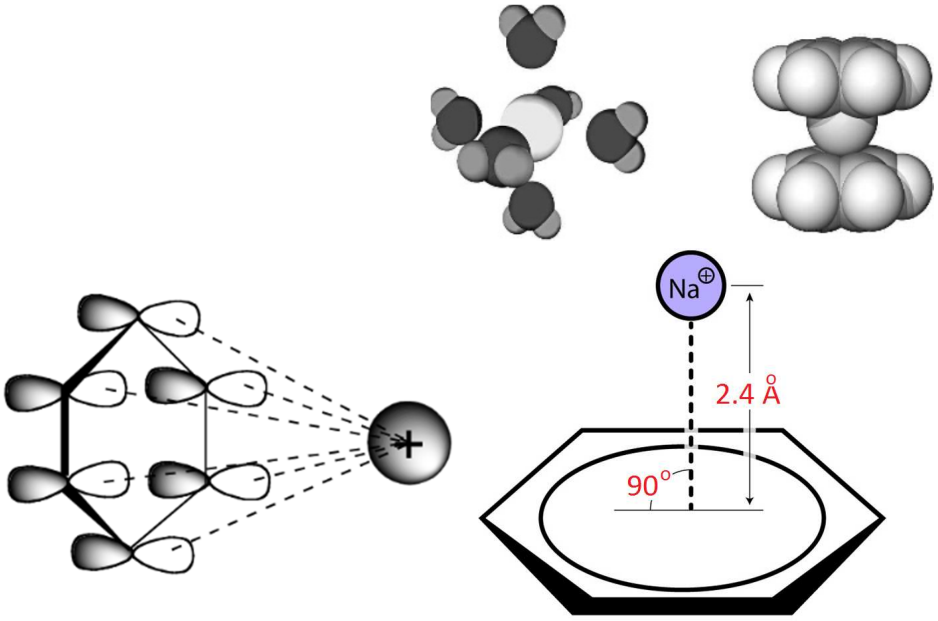
  but these are not regarded as non-covalent interactions

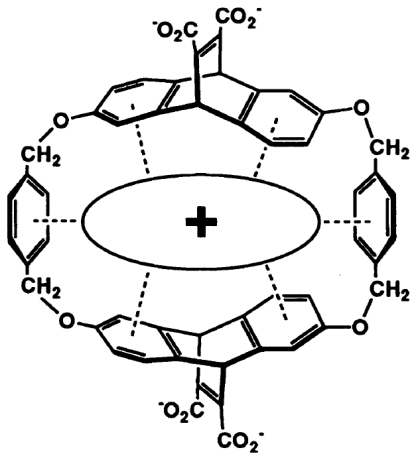
  ▶ However, alkaline- and alkaline-earth metals also form interactions with double-bond systems (5~80 kJ mol^{-1})

  (e.g.) the interaction of K^+ with benzene has a similar energy to the K^+–OH_2 interaction

  K^+ is more soluble in water than in benzene, however,

  as it is not sterically possible to fit as many benzene molecules around the metal ion as water molecules.



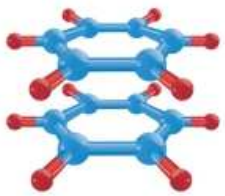


Water-soluble cyclophane

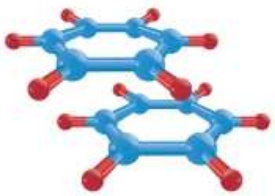
Science **1996**, *271*, 163

(ii) π–π interactions :

arise from the attraction between the negatively charge -electron cloud of one conjugated system and the positively charged σ-framework of a neighbouring molecule.

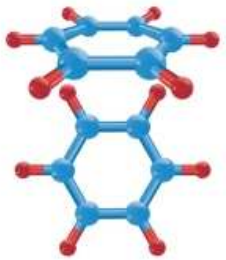


Sandwich geometry (S)

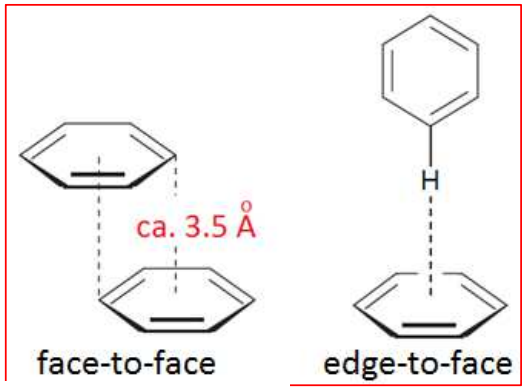


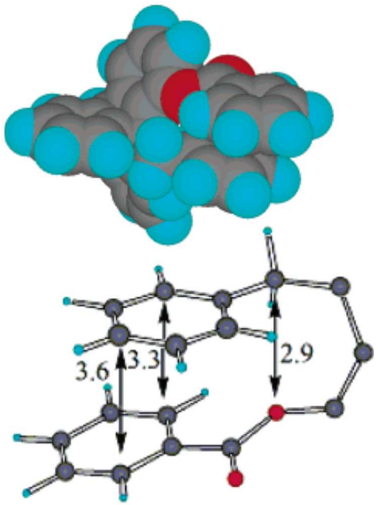
Parallel displaced geometry (PD)

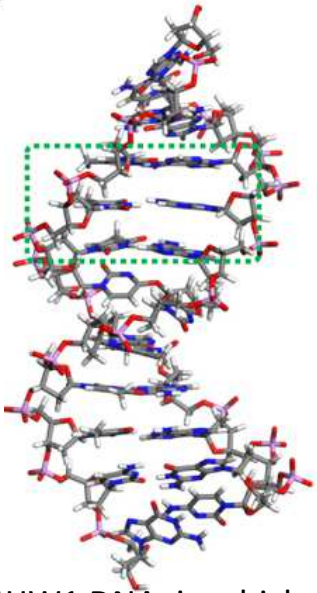
T-shaped geometry (T)

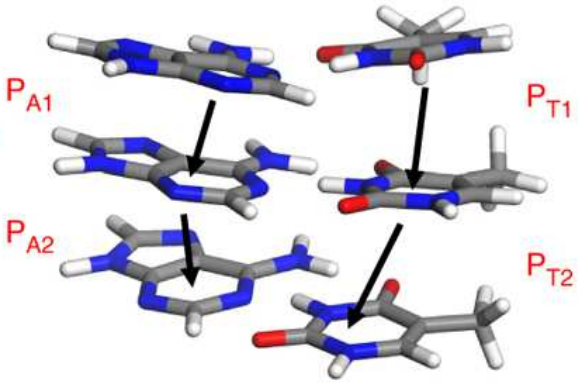


Y-shaped geometry (Y)



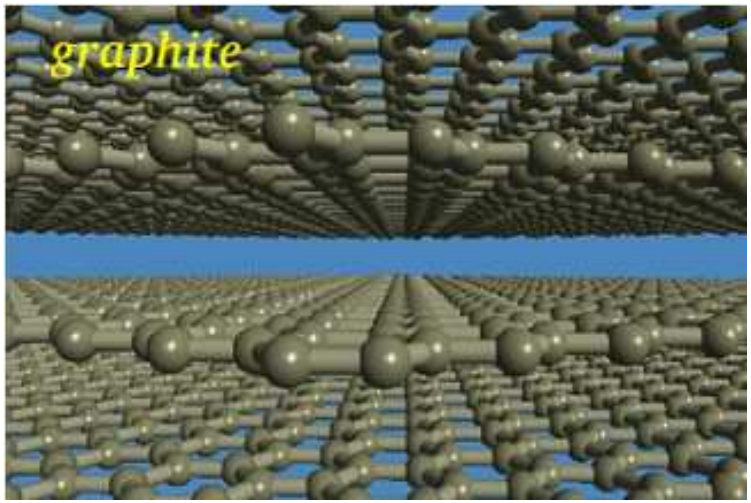


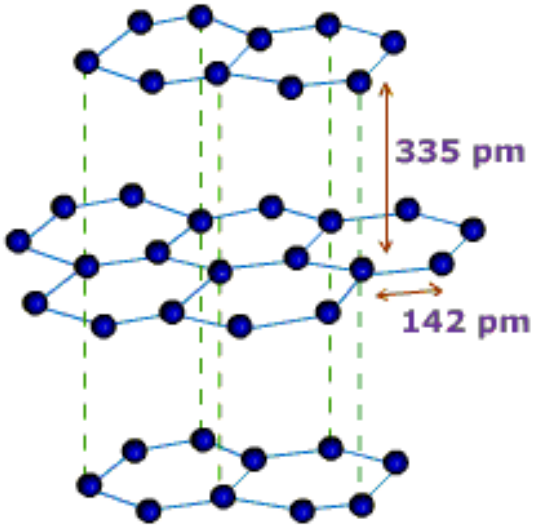


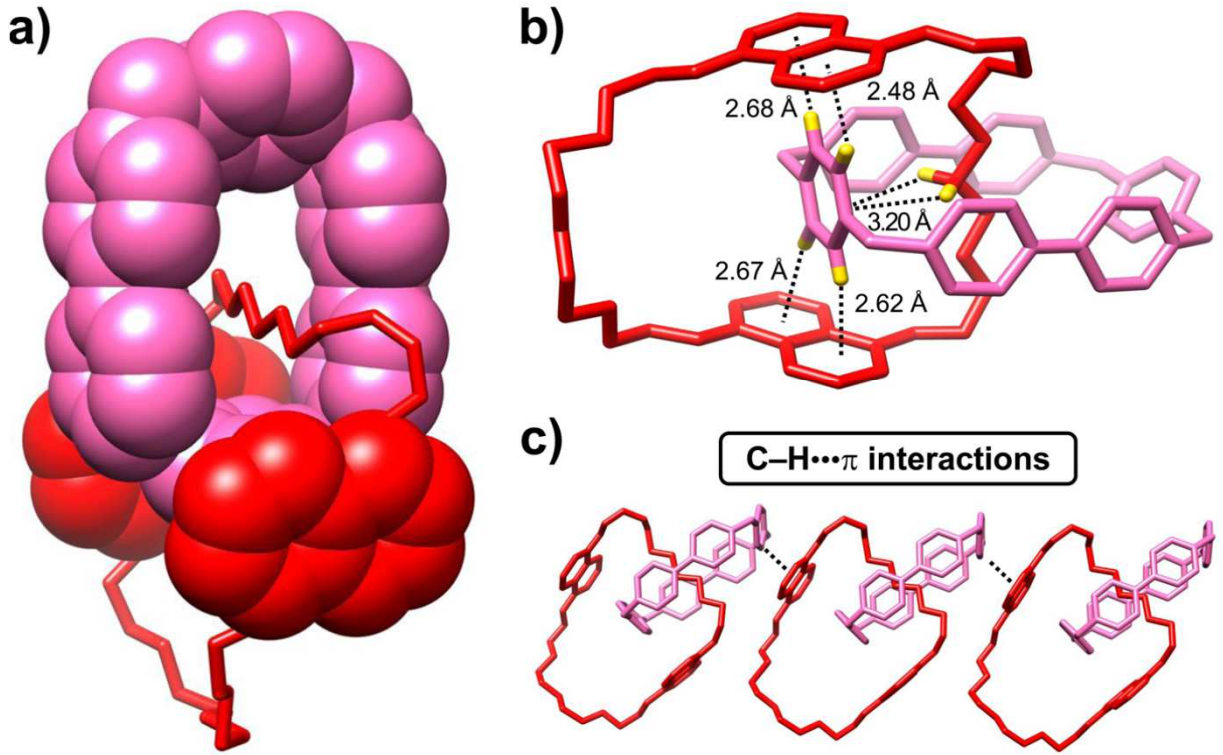


Crystal structure of 4HW1 DNA, in which three continuous A-T base pairs are marked by the green dotted line

- The layered structure of **graphite**:
  weak, **face-to-face π-interactions** and therefore feels 'slippery' (lubricant)





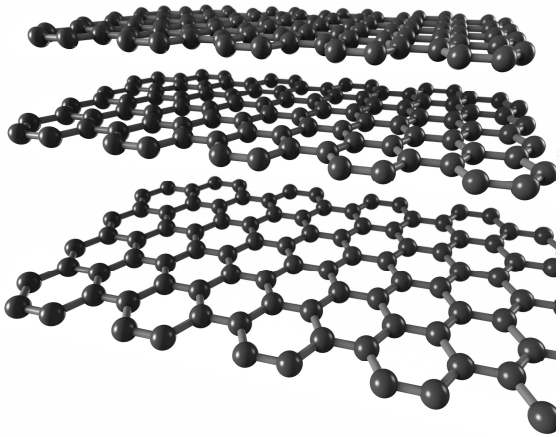


Intermolecular [CH···π] interactions between the hydrogens of the phenylene rings and the 1,5-dinaphtho units in the neighboring catenanes.

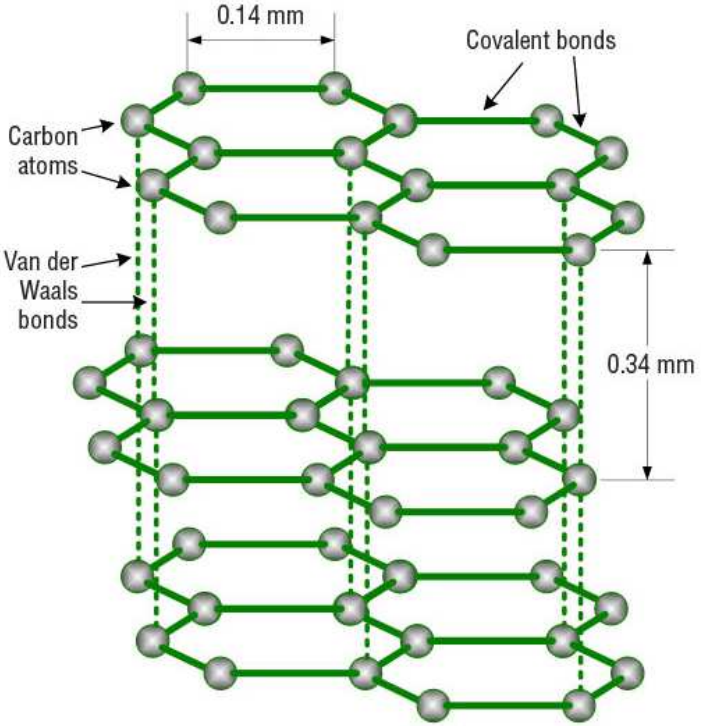
J. Am. Chem. Soc. **2016**, *138*, 10214.

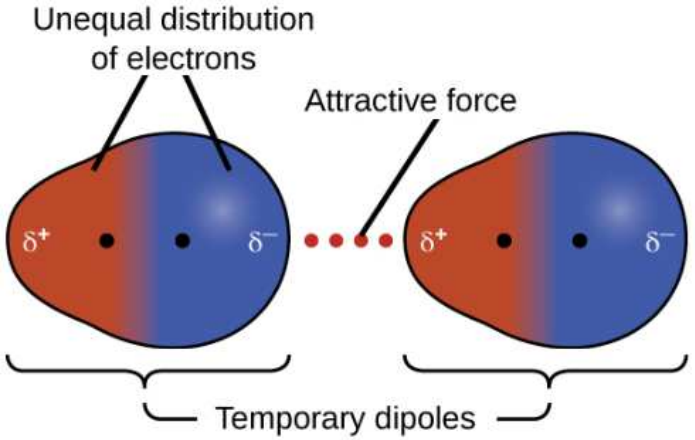
1.3.4 van der Waals interactions

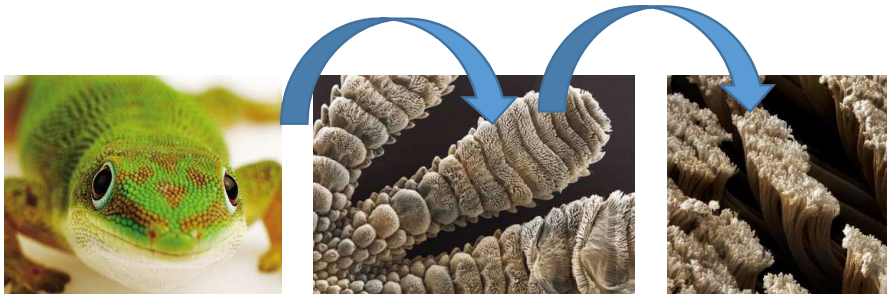
- **van der Waals interactions** (*London force* or *dispersion force*) are dispersion effects that comprise two components.
- The weakest of the intermolecular forces in existence in nature
- Same for the layers of **graphite** which are held together by thousands of van der Waals forces



Graphite structure

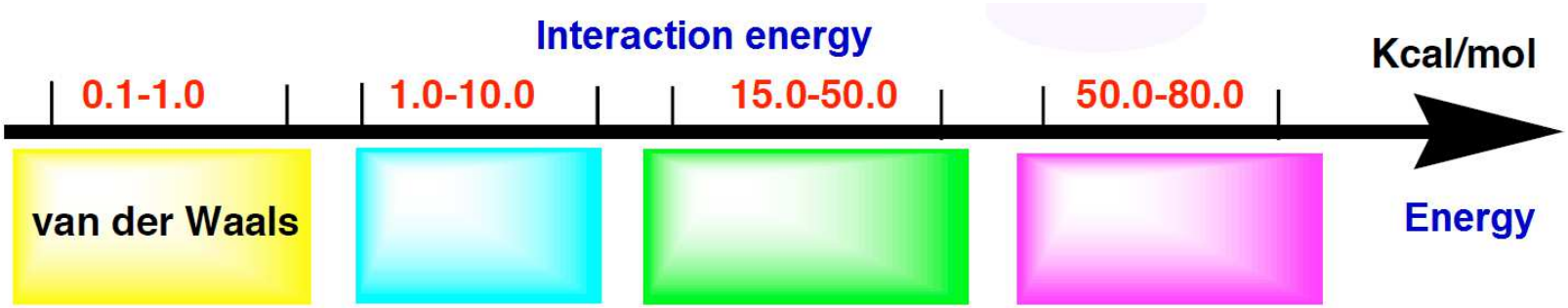




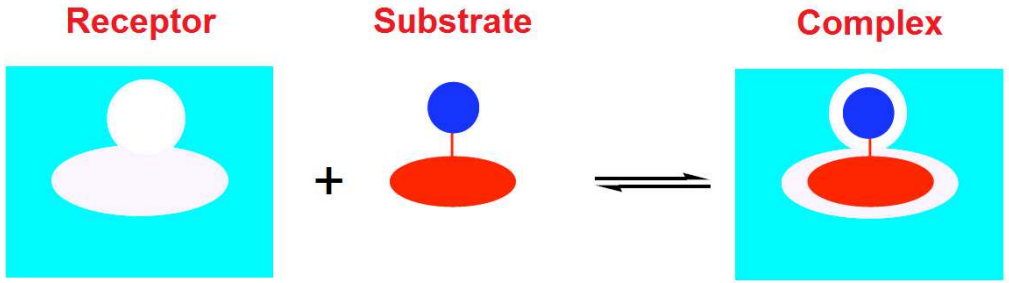


Geckos' toes contain large numbers of tiny hairs. By changing how the spatula contact the surface, Geckos can turn their stickiness "on" and "off".

Modes of van der Waals interaction

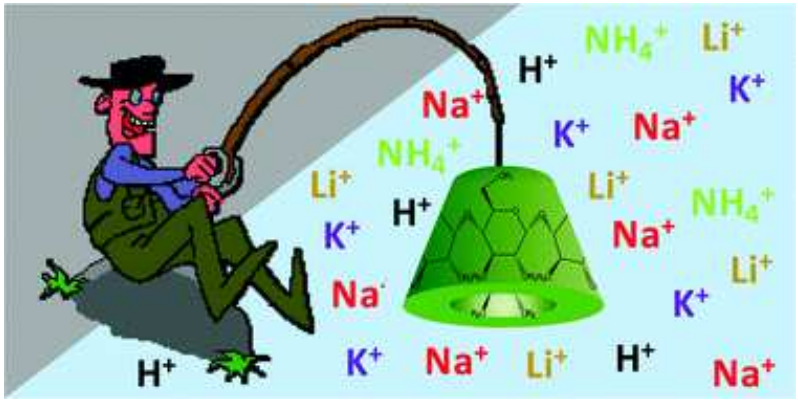


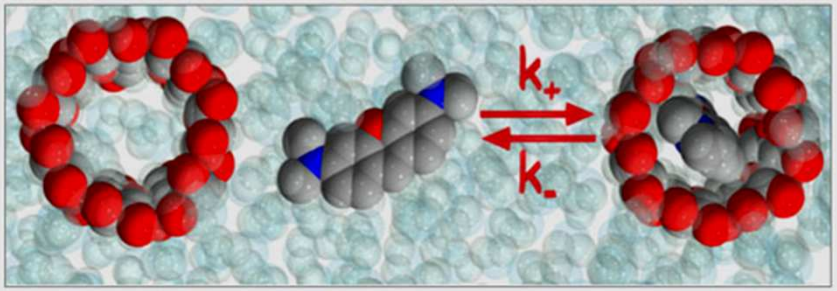
Van der Waals: Van der Waals interactions are non-directional.
They increase with the contact surface.



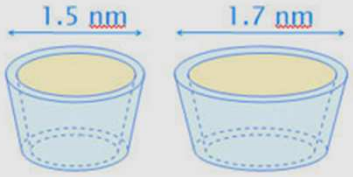
❑ **Non-covalent interactions**:

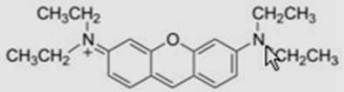
► the energies that hold supramolecular species together
considerably weaker than covalent interactions
for single bonds, ca. 150 kJ mol^{-1} ~ 450 kJ mol^{-1}
2 kJ mol^{-1} (dispersion interactions) ~ 300 kJ mol^{-1} ('ion-ion' interactions)
when these interactions are used in a co-operative manner, a stable supramolecular complex can exist.



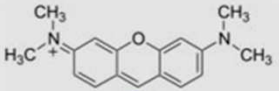


Host: Cyclodextrin Guest: Pyronine Inclusion Complex





PB



PY

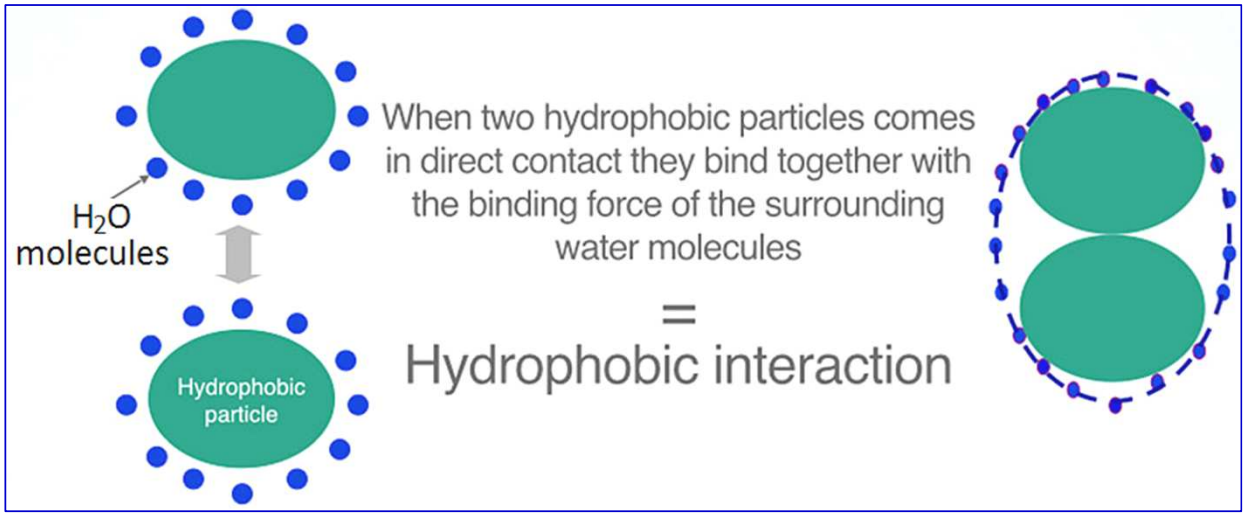
Binding constant

K/M^{-1}	β-CD	γ-CD
PY	400	40
PB	2100	200

1.3.5 Hydrophobic effects

- **Hydrophobic effects** arise from the exclusion of non-polar groups or molecules from aqueous solution.
  → more energetically favorable because H_2O molecules interact with themselves or with other polar groups or molecules preferentially.
- The **hydrophobic effect** is the observed tendency of nonpolar substances to aggregate in aqueous solution and exclude water molecules.

A droplet of water forms a spherical shape, minimizing contact with the hydrophobic leaf.



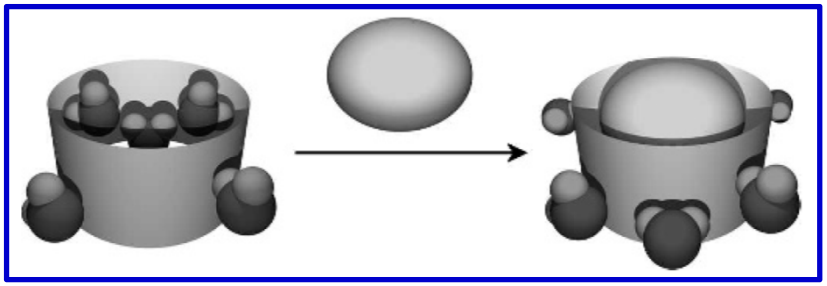
- Hydrophobic interactions play an **important role in some supramolecular chemistry**, (e.g.) the binding of organic molecules by cyclophanes and cyclodextrins in water (see later).

1. Enthalpic hydrophobic interactions:

- This occurs when a guest replaces the water within a cavity.
- This occurs quite readily

  when (1) such systems does not interact strongly with the hydrophobic cavity of the host molecule

  (2) the energy in the system is high
- Once the water has been replaced by a guest, the energy is lowered.

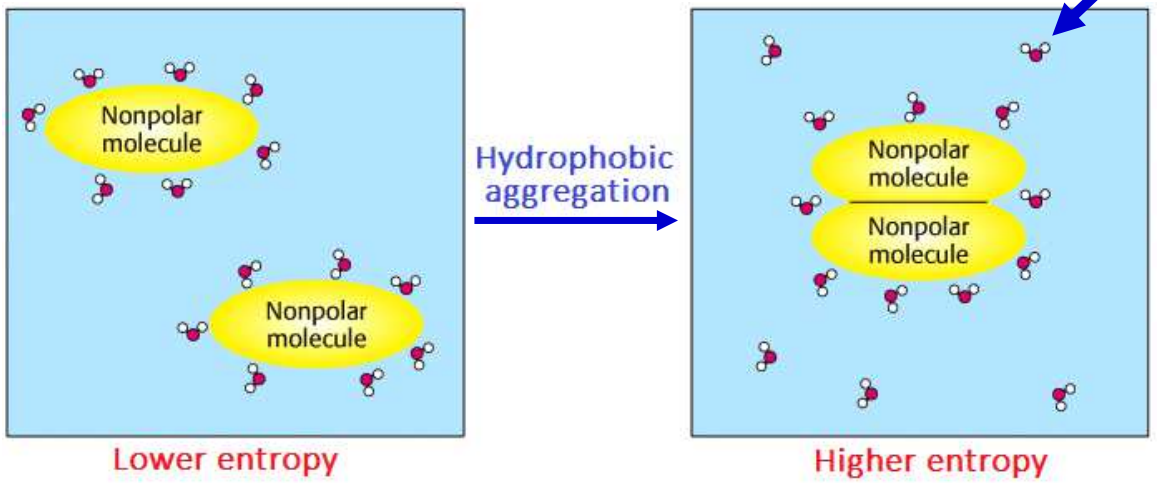


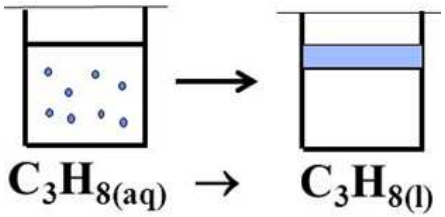
The displacement of water molecules from a hydrophobic cavity is responsible for the enthalpic hydrophobic effect.

2. Entropic hydrophobic interactions:

- the water that was previously ordered within the cavity becomes disordered when it leaves
- an increase in entropy increases the favourability of the process
- the combination of which creates a hole in the water to form a supramolecular complex
- There is less disruption and hence an entropic gain, as the overall free energy of the system is lowered.

Two organic molecules creating a hole within an aqueous phase,
giving rise to the **entropic hydrophobic effect**
– one hole is more stable than two.





$\Delta G^o_{298} = \Delta H^o - T\Delta S^o$

$\Delta H^o_{298} \approx +\ 8$ kJ/mol

$\Delta S^o_{298} \approx +\ 80$ J/mol

$\Delta G^o_{298} = 8 - 298 \times 0.080$

$= 16$ kJ/mol

1.4 Supramolecular design

- Necessary understanding the nature of the target guest molecule
- The host must be designed to be complementary to the guest
  in terms of size, shape and chemical properties (charge, hardness, acidity, *etc*.).
- The design process, requiring a more selective host
- After consideration of the guest properties, the host may be designed in a specific manner
- Supramolecular systems have a wide variety of uses:
  - trapping molecules within solid state lattices
  - sensing and remediation of species from solution
  - understanding biological self-assembly
  - nanotechnological devices

Suggested further reading

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