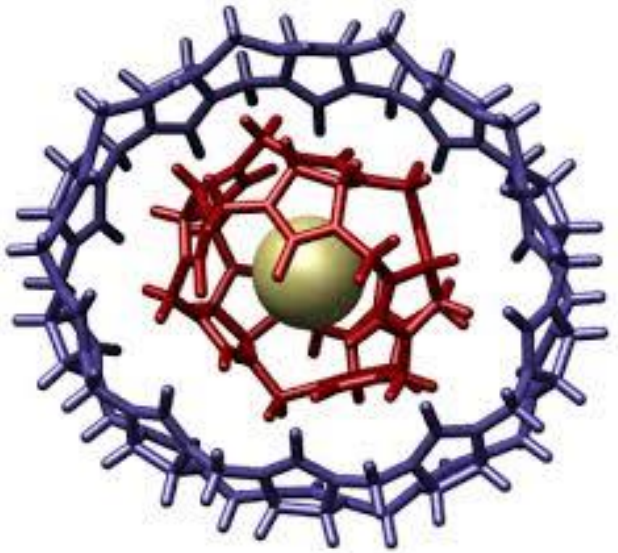
Module VI: Supramolecular Chemistry



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Nobel Prize in Supramolecular Chemistry

“Beyond" molecular chemistry

Nobel Prize in Chemistry 1987

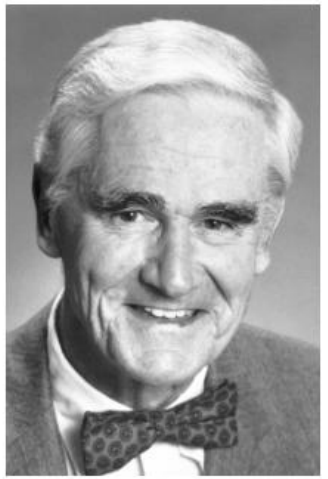


Photo from the Nobel Foundation archive.

Donald J. Cram

Prize share: 1/3

Photo from the Nobel Foundation archive.

Jean-Marie Lehn

Prize share: 1/3

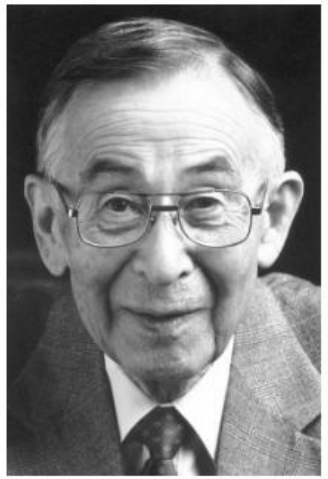


Photo from the Nobel Foundation archive.

Charles J. Pedersen

Prize share: 1/3

The Nobel Prize in Chemistry 1987 was awarded jointly to Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen "for their development and use of molecules with structure-specific interactions of high selectivity."

History of Supramolecular Chemistry

The foundation stone of "Supramolecular Chemistry" was laid down in the late 19th century

The idea of lock-and-key (LK) concept was introduced by Emil Fischer in 1894

Villiers and Hebd discovered cyclodextrins, the first host molecules in 1891

Daniel Koshland formulated the **induced fit concept** for binding events to biomolecules, which undergo conformational changes (1958)

What is Supramolecular Chemistry?

The chemistry of non-covalent interactions

Electrostatic
(Ionic, Hydrogen bonding, Halogen bonding)

Van der Waals forces
(Dipole–dipole
Dipole-induced dipole
London dispersion forces)

π-effects
(π–π interaction,
Cation–π, anion–π,
Polar–π)

Hydrophobic effect

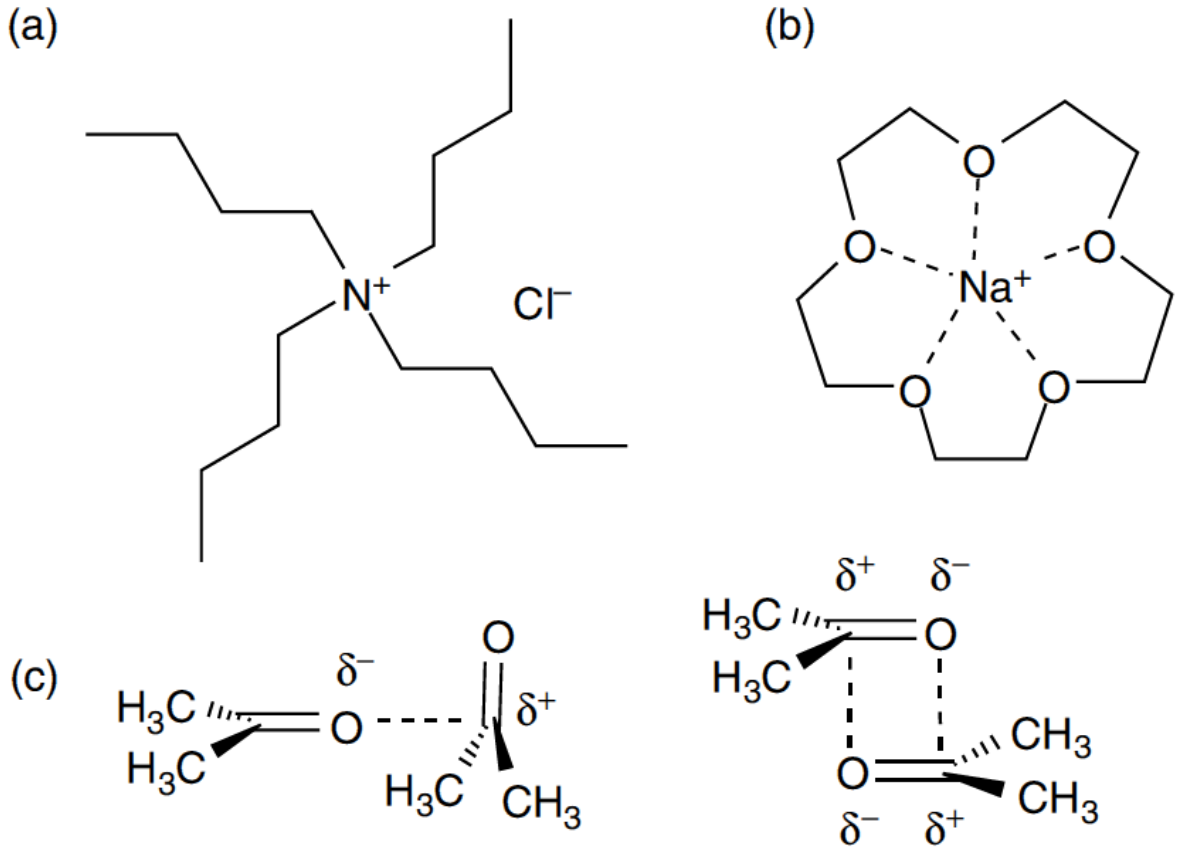
These all are the secondary interactions, such as hydrogen bonding, van der Waals, and π- π stacking interactions.

The distance between the charges and the extent of delocalization

Strength of Supramolecular Interactions

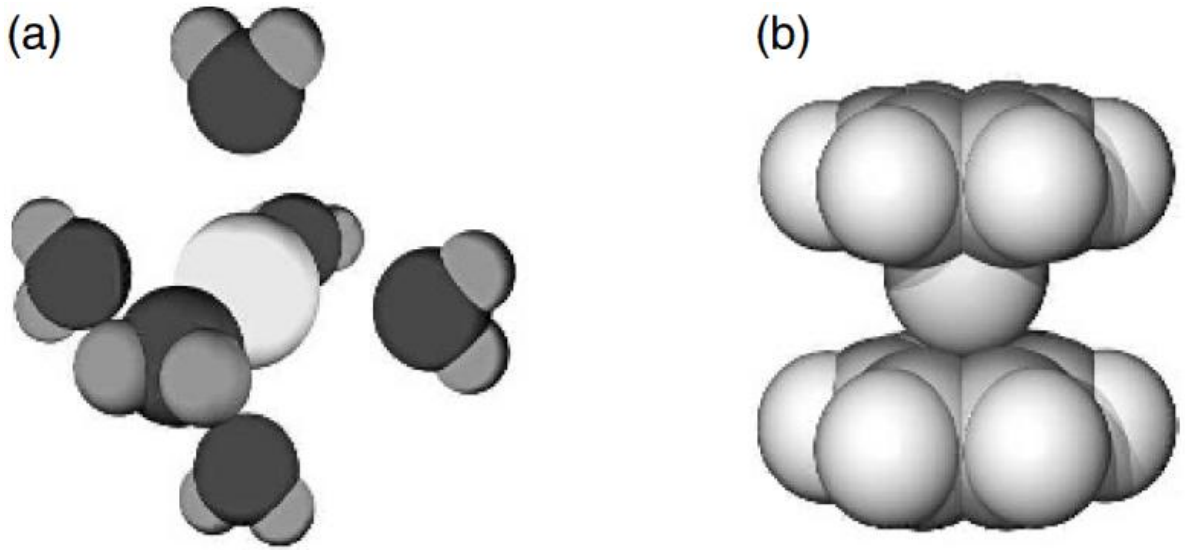
Interaction	Strength (kJ mol^{-1})	Example
Ion–ion	200–300	Tetrabutylammonium chloride
Ion–dipole	50–200	Sodium [15]crown-5
Dipole–dipole	5–50	Acetone
Hydrogen bonding	4–120	(See Table 1.2)
Cation–π	5–80	K^+ in benzene
π–π	0–50	Benzene and graphite
van der Waals	< 5 kJ mol^{-1} but variable depending on surface area	Argon; packing in molecular crystals
Hydrophobic	Related to solvent–solvent interaction energy	Cyclodextrin inclusion compounds

Examples of Supramolecular Interactions

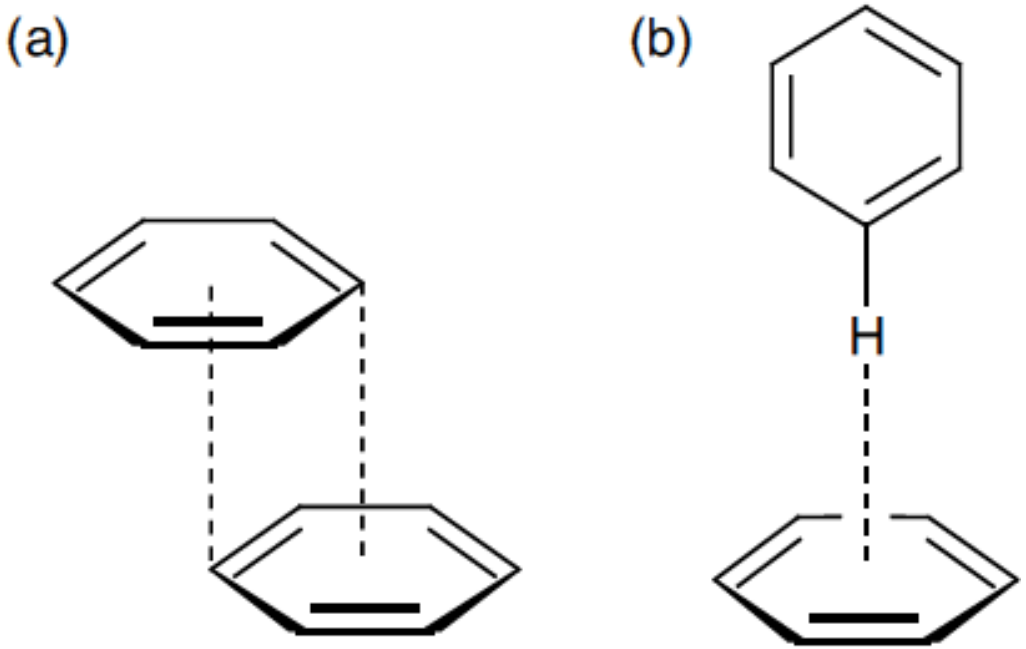


(a) ion–ion interaction in tetrabutylammonium chloride; (b) ion–dipole interaction in the sodium complex of [15]crown-5; (c) dipole–dipole interactions in acetone

Examples of Supramolecular Interactions



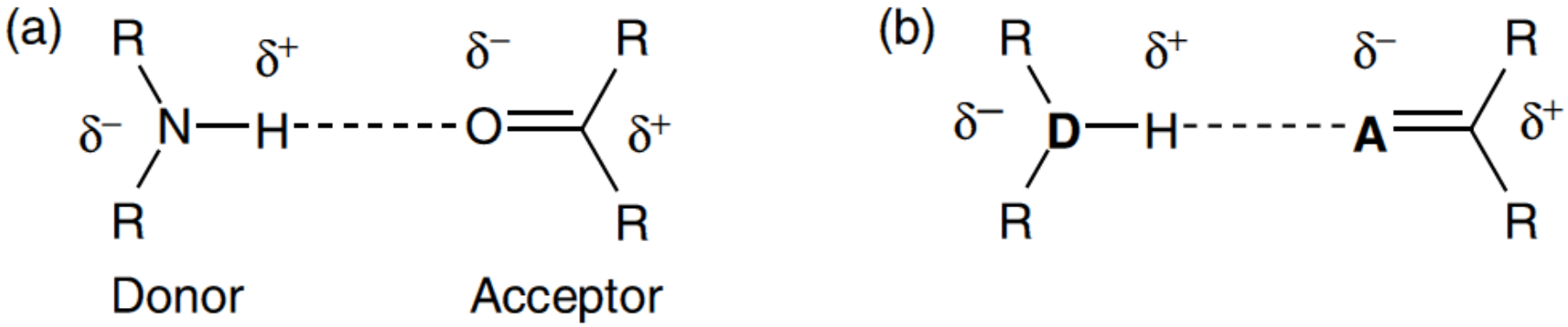
(a) Six or more water molecules can fit around K^+, whereas (b) there is space for only two benzene molecules



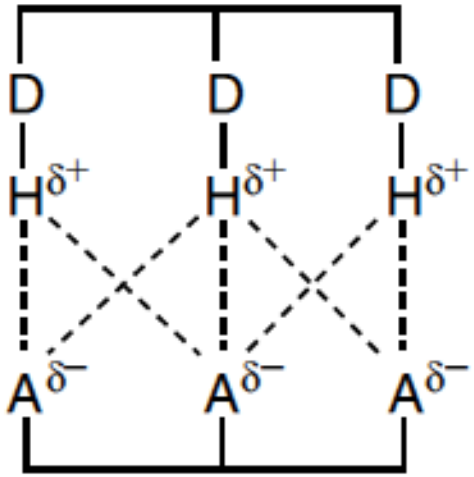
(a) face-to-face; (b) edge-to-face

Various Types of H-bonds in Supramolecular Chemistry

The hydrogen bond is one of the most important non-covalent interactions in the design of supramolecular assemblies, due to its variable strength and high degree of directionality

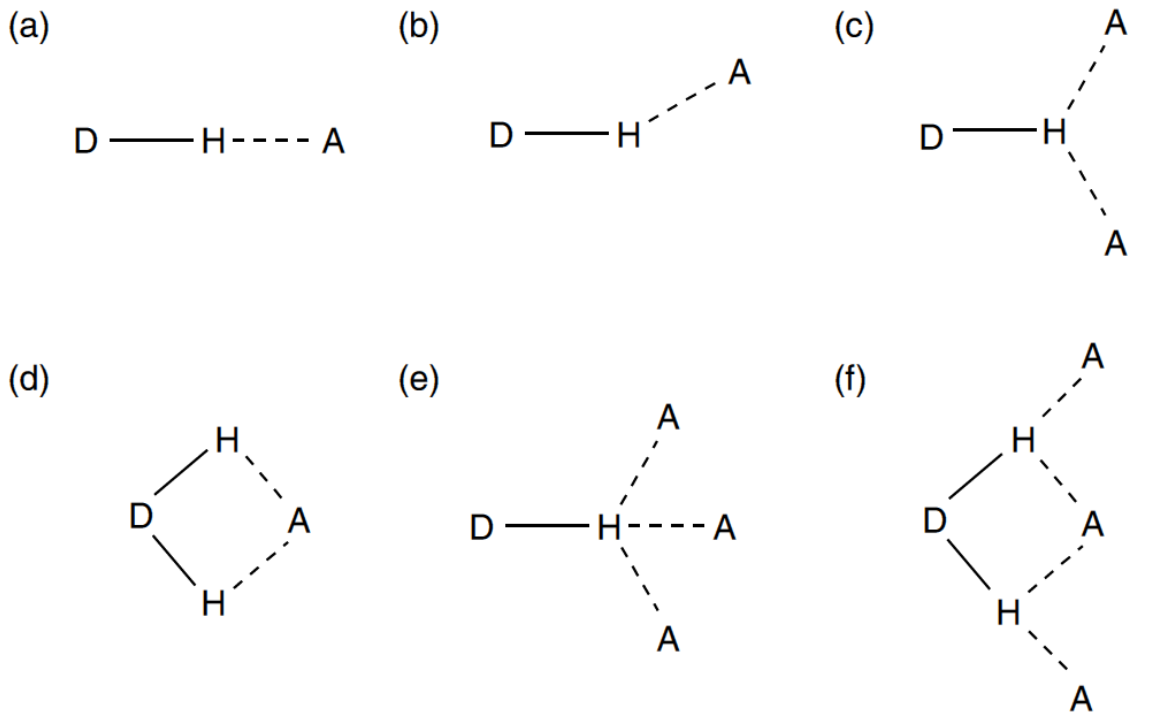


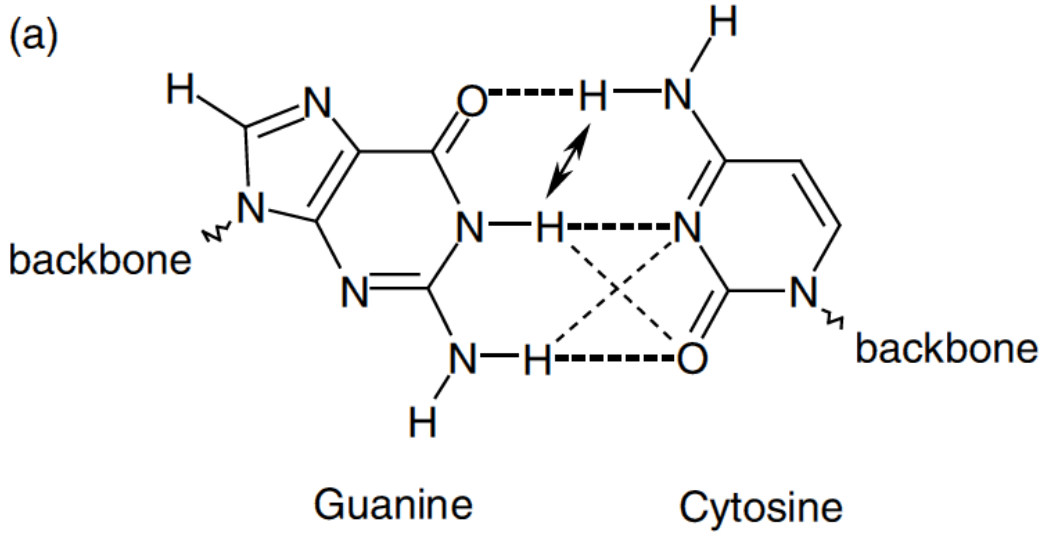
A carbonyl accepting a hydrogen bond from a secondary amine donor (a) and (b) the standard way of expressing donor and acceptor atoms (D, donor atom; A, acceptor atom).



A real-life example of hydrogen bonding is the double helix of DNA.
There are many hydrogen bond donors and acceptors holding base pairs together

Various Types of Hydrogen Bonding Geometries





(a) linear; (b) bent; (c) donating bifurcated; (d) accepting bifurcated;
(e) trifurcated; (f) three-centre bifurcated

Strength of H-bonds

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 geometry of a hydrogen bond and the type of donor and acceptor groups determine the strength, length and nature of the interaction

Hydrogen Bonding that Affects the FT-IR Spectra

Hydrogen bonding alters the force constant of both groups

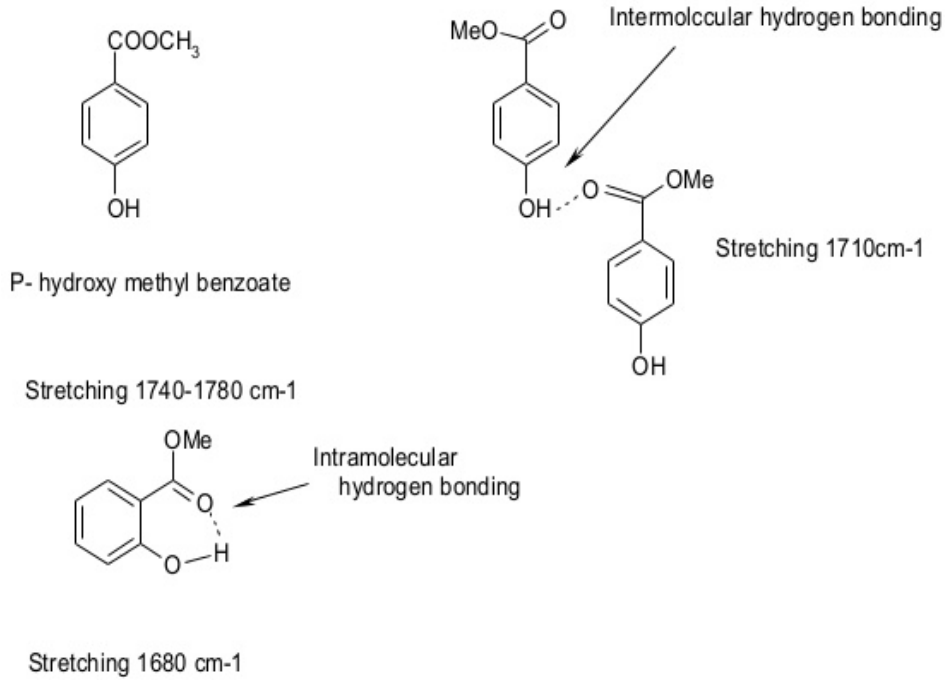
- **H-bonding occurs between a proton donor and a proton acceptor**
- **S-orbital of the H atom interacts with p or π orbitals of the acceptor**
- **The stronger the H-bonding, the longer the bond length, thus the stretching frequency of the acceptor functional group decreases**
- **The amine ($-NH_2$) stretching frequency is also affected by the H-bonding. But the effect is less than that of the alcohol group (-OH). It's because of less electronegativity of N over O.**
- **Other weak electronegative groups are also affected by the H-bonding, which reflects the lower shifting IR spectra**

Consequence of Hydrogen Bonding in FTIR Spectra

Can we distinguish intra- & intermolecular H-bonding using infrared spectroscopy?
YES

If so, then how? By varying the concentration. Intermolecular H-bonding is concentration-dependent, thus frequency decreases upon dilution. On the other hand, intramolecular H-bonding is concentration independent.

If the H-atom and the electronegative atom like fluorine, chlorine, oxygen and nitrogen are close enough they form **Intramolecular H bond** and if they are far away, form **Inter molecular H bond**



Hydrogen bonding plays key roles in biological process in ds DNA and protein folding, etc

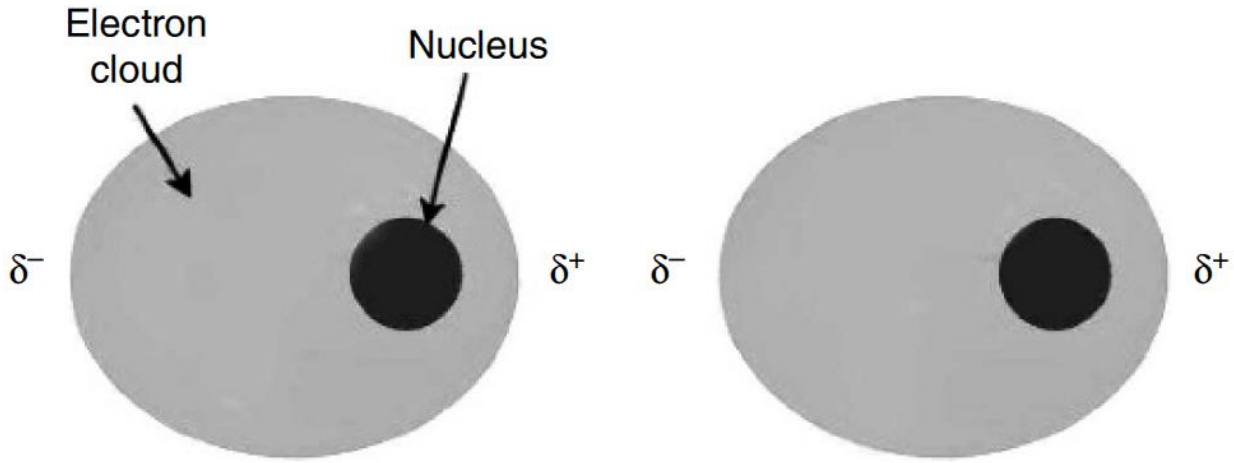
van der Waals Interactions

Van der Waals interactions occur due to the fluctuations of the electron cloud, creating induced dipole interacting between neighboring species (atoms/molecules/surfaces)

Named after Dutch physicist Johannes Diderik van der Waals

The VdW is highly distance-dependent interaction between atoms/molecules

A dipole is defined as molecules or atoms with equal and opposite electrical charges separated by a distance between them

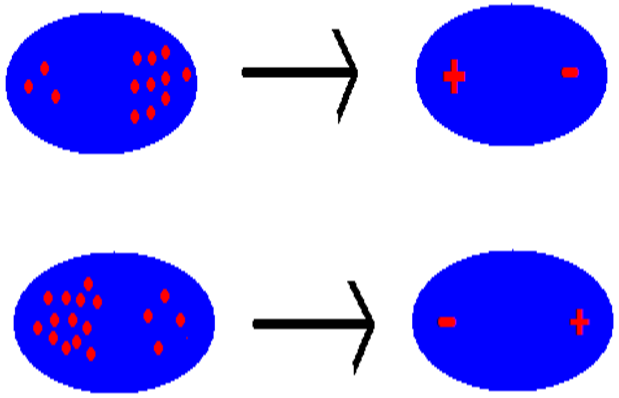


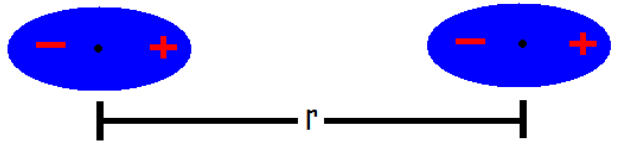
VdW der Waals interaction is the weakest one among all intermolecular attractions between molecules

However, with many VdW forces interacting between two objects, the interaction can be increased

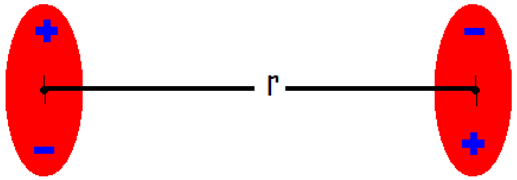
van der Waals Interactions

Van der Waals **0.4-4.0 kJ/mol** **0.3-0.6 nm**





$V = -\mu_A\mu_B/4\pi\epsilon_o r^3$

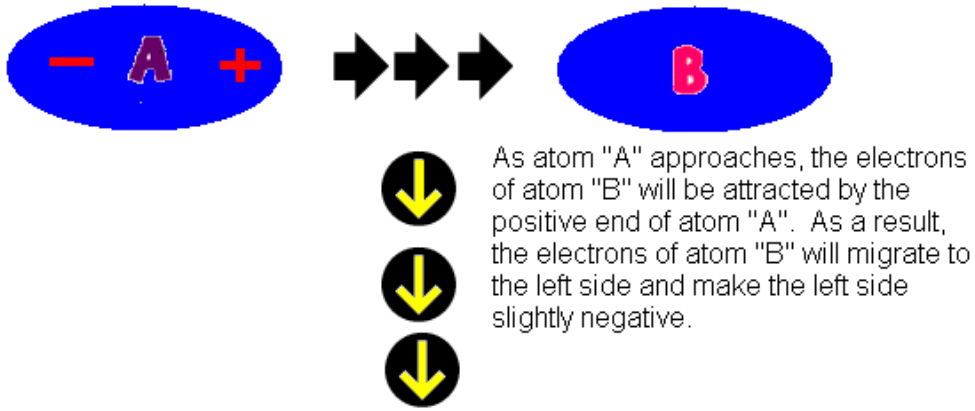


The energy of the electron can never be zero; therefore, it is constantly moving around its orbital

However, with many VdW forces interacting between two objects, the interaction can be increased

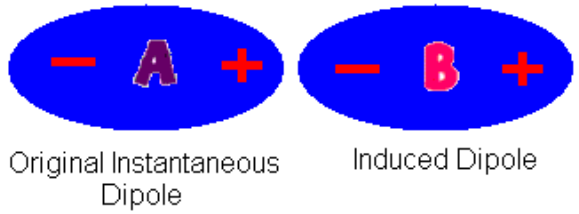
The potential energy in the latter case is double than the former one, guess why?

van der Waals Interactions



Induced-dipoles highly depends on the polarizability of the non-polar molecules/atoms

Polarizability describes how easily electron density of an atom or a molecule can be distorted upon applying an external electric field

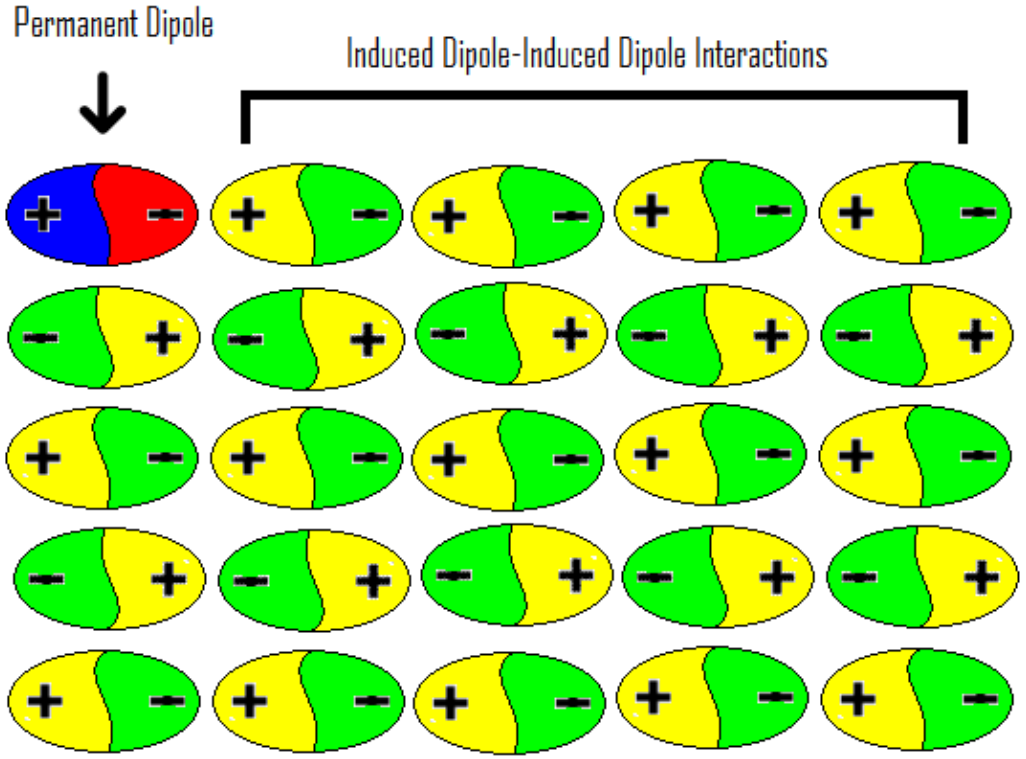


An induced dipole moment in a nonpolar atom (i.e. Helium) occurs spontaneously if it comes close contact in a polar environment. This results in separation of charges due to electron density fluctuations.

When an instantaneous dipole atom approaches a neighboring atom, it can cause that atom to also produce dipoles. The neighboring atom is then considered to have an induced dipole moment

van der Waals Interactions

Spontaneous dipole-induced dipole interactions are also known as dispersion or London forces
This was named after the German physicist Fritz London
The potential energy of the London interaction decreases rapidly as the distance between the interacting species increases (V is inversely proportional to r^6)



They are the large networks of such intermolecular forces between nonpolar and non-charged molecules and atoms (i.e. alkanes, noble gases)
Molecules that have induced dipoles may also induce neighboring molecules to create dipole moments, so a large network of induced dipole-induced dipole interactions may exist
These interactions are non-directional and do not feature highly in supramolecular design

Hydrophobic Interactions

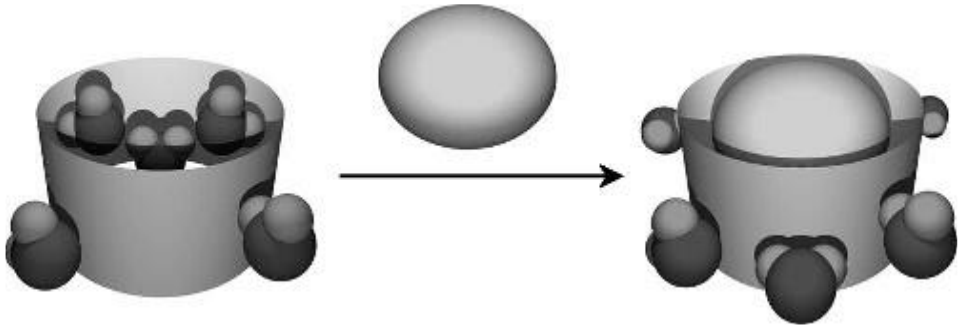
Hydrophobic interactions relate the interaction between water and non-polar hydrophobes (long chain alkanes)

Hydrophobic interactions play an important role in supramolecular architectures

The binding of organic molecules by cyclophanes and cyclodextrins in water

Hydrophobic effects can be explained by two energetic components, namely an enthalpic hydrophobic effect and an entropic hydrophobic effect

Enthalpic hydrophobic interactions occur when a guest replaces the water within a cavity



This occurs quite easily as water in such systems does not interact strongly with the hydrophobic cavity of the host molecule and the energy in the system is high

Once, water leaves the cavity, previously ordered within the cavity becomes disordered, thus increasing in entropy of the process

"A view of the hydrophobic effect", J. Phys. Chem., 2002, 106, 521–533

Why do we need to study non-covalent interactions (NCIs)?

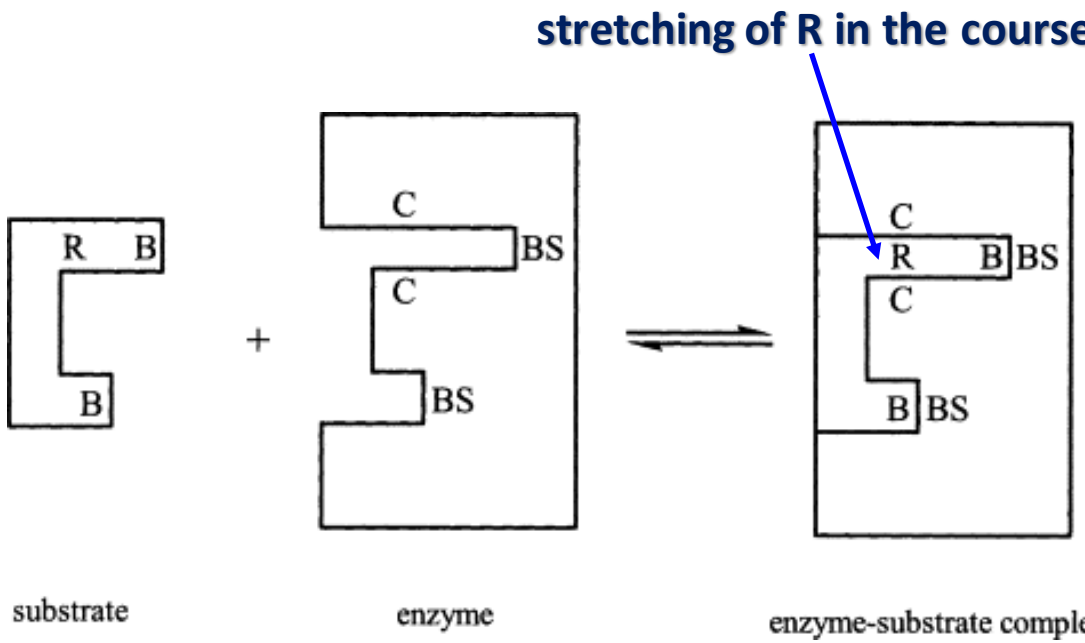
NCIs lead to form nanostructures via "bottom up" approach.
This approach is highly beneficial over the "top down" approach such as micro/nano-lithography technique producing micro/nano-structures devices.
The "top down" approach requires huge efforts (A clean room facility required) to fabricate the devices

"Lego"

Molecular Recognition: Lock & Key Model

The lock-and-key model is the earliest, simplest model to describe molecular recognition

If the active site of an enzyme is rigid, then the substrate must be distorted slightly in order to interact the enzyme efficiently. This distortion might result in the stretching, (called 'strain' effect) and thus weakening, of a bond that can be cleaved



enzyme-substrate complex → transition-state → products

Salient Features of L&K Model

The enzyme (lock) recognizes the substrate (key) through the shape complementarity between the enzyme's active site and the substrate

This model is insightful, but too simple to reflect the reality

The protein often undergoes certain conformational changes during enzyme-substrate, can't be explained by L&K model

So, a dynamic model is crucial

Structures of a protein in complexes is called "holo" structures

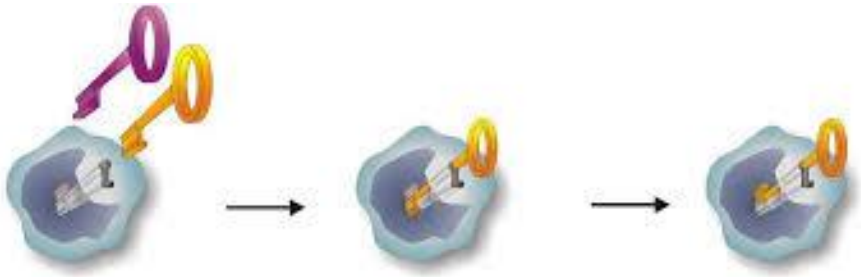
While unbound protein structures is called "apo" structures

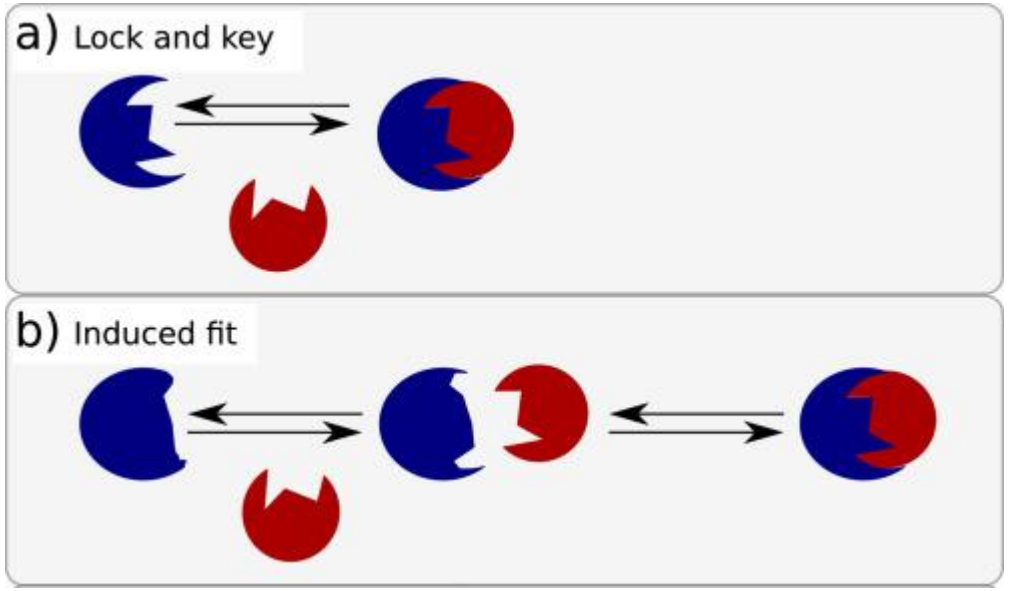
L&K vs Induced Fit Model

Both the enzyme (i.e., a protein) and the substrate (e.g., a small compound or a protein) are dynamic entities

The induced fit model provides a more dynamic view of the binding event, compared with the rather static key-lock principle
Thus more easily able to explain phenomena such as cooperativity

Both the lock-and-key and induced fit models can help understanding enzyme specificity, but doesn't explain details mechanism by which a catalyzed reaction driving forward





Dynamic Induced Fit Model

The induced-fit model was first proposed by Koshland in 1958 to explain the protein conformational changes in the binding process

Optimizes the interface through physical interactions to form the final complex structure

The induced-fit model is supported by the fact that many ligands are buried in the protein binding sites in the protein–ligand complex structures

However, conformational changes such as backbone collective motions, domain rearrangements, and disorder-to-order transition for highly flexible proteins cannot be fully explained by this model

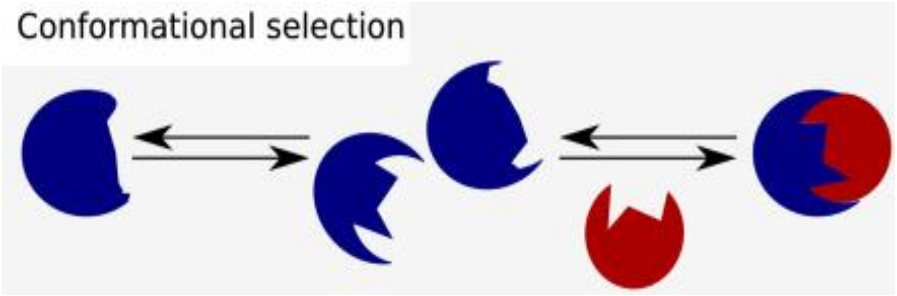
Conformational-Selection (population shift) Model

This model was proposed by many researchers in 1990s

This model suggests that unbound protein receptor fluctuates in multiple conformational states, with their occupancy probabilities being determined by their relative free energies according to the Boltzmann distribution

Only a subset of these states allows the binding of its partner. The encounter with its binding partner shifts the distribution toward these states to form the final complex structure

The main difference between the induced-fit model and the conformational-selection model is whether the holo structure pre-exists before forming the complex



Conformational-Selection (population shift) Model

Recent studies suggest that induced-fit and conformational-selection may co-exist in many cases

Efforts were devoted to reconciling these two models into a unified model by coupling the induced-fit and the conformational-selection in a “serial” or “parallel” way

In the serial coupling, multiple protein conformations pre-exist in the unbound state, and the ligand recognizes a subset of these conformations to first reach a loose complex state, which is followed by the induced optimization to form the final complex structure

The parallel coupling provides a different scenario, for which the induced-fit pathway and the conformational-selection pathway co-exist and compete

Molecular Recognitions

Host-Guest (H-G) interaction between single acceptor and donor site is a weaker non-covalent interaction

Then, how to achieve stronger binding interactions?

Several binding sites concerted way is the way to achieve strong and specific complexation (recognition) of a guest molecule.

For e.g., multi-site complexation is present in biological systems such as enzyme-substrates, antigen-antibody interactions.

Stronger interaction is observed in coordination chemistry, due to chelate effect

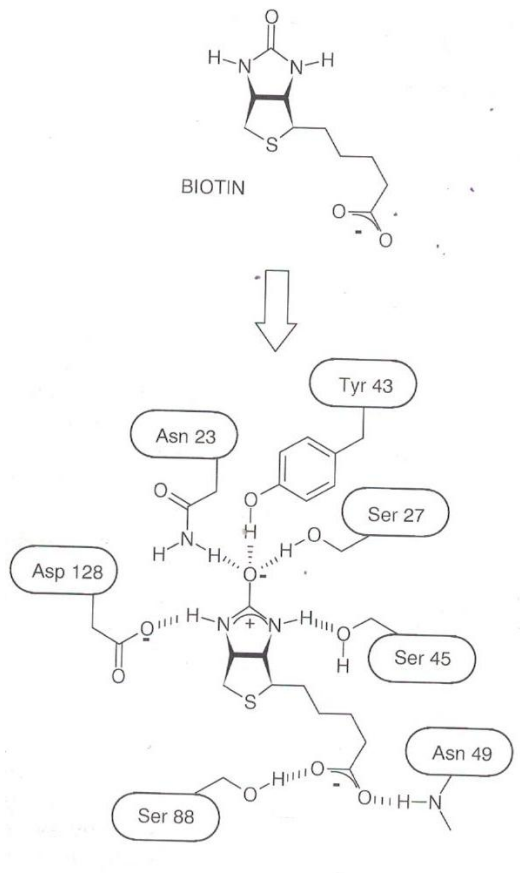
Multi-site binding constant in biotin (a small guest)-streptavidin (a protein host) is reported as high as $K = 2.5 \times 10^{13}\ M^{-1}$

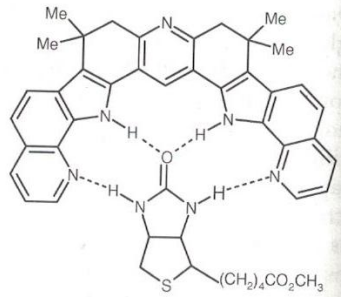
A large binding free energy of ~ -76 KJ/mol, arises from multiple non-covalent interactions (van der Waals, electrostatic, H-bonding)

Molecular Recognitions

However, a synthetic receptor for biotin will have less K = 9.3 x 10^3 M^{-1}, as there are only 4 H-bonds in H-G interaction

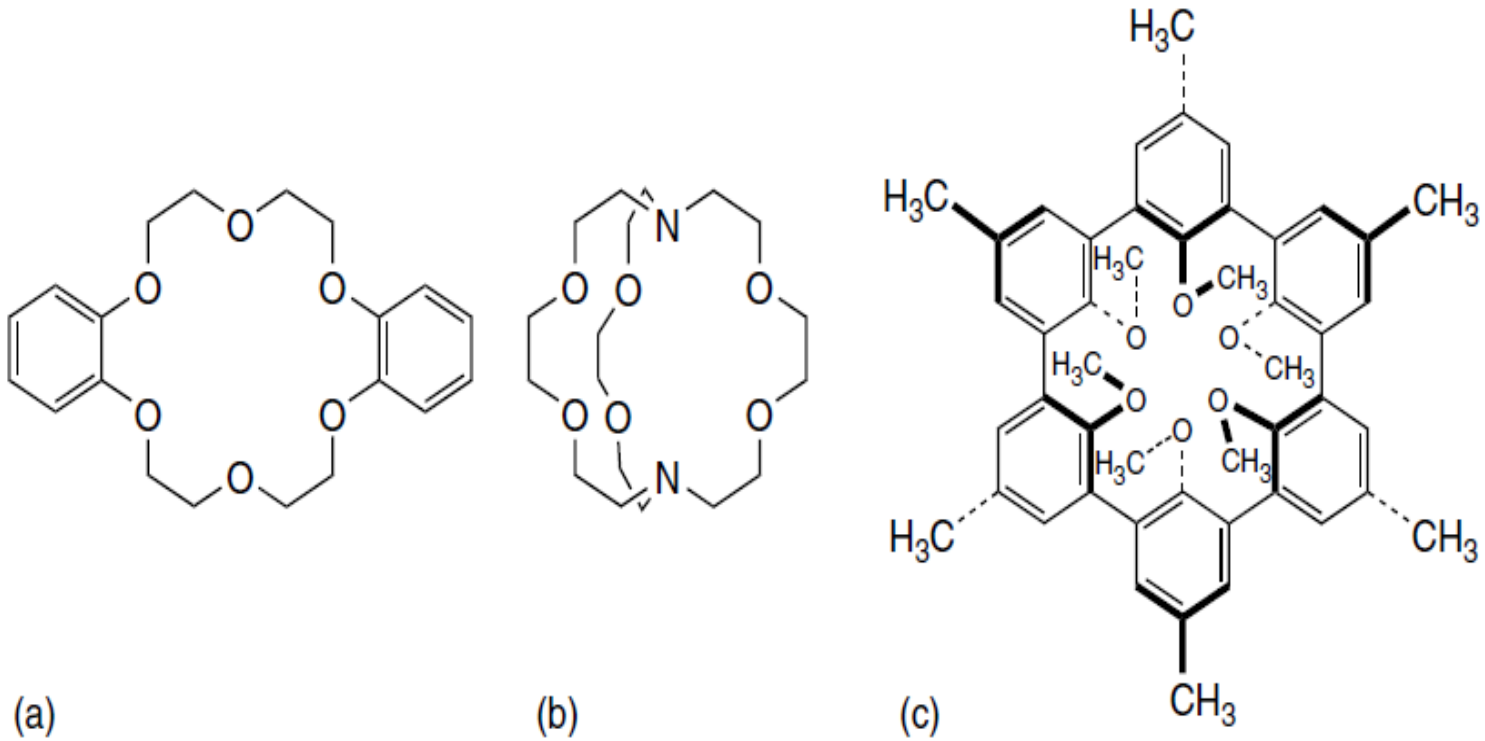
Crown ethers, cryptands can bind alkali cations with similar or even higher binding constant but with selectivity





Early developments in supramolecular chemistry

(a) crown ether by Pedersen
(b) cryptand by Lehn
(c) spherands by Cram



"For their development and use of molecules with structure-specific interactions of high selectivity"

Thermodynamics in Host-Guest Chemistry

Thermodynamics, a spontaneous process in which it releases free energy, and it moves to a lower, more thermodynamically stable energy state

Thermodynamics can forecast whether a process can occur spontaneously

The sign convention for free energy change follows the general convention for thermodynamic measurements, in which a release of free energy from the system corresponds to a negative change in the free energy of the system and a positive change in the free energy of the surroundings

The normal boiling point of water is 373.15 K because, at 373.15 K at 1 atm, $\Delta G = \Delta H - T\Delta S = 0$, and $\Delta H = T\Delta S$. Above the normal boiling point, the $T\Delta S$ term is greater than ΔH, making $\Delta G < 0$; hence, liquid water evaporates spontaneously.

Below the normal boiling point, ΔH term is greater than $T\Delta S$, making $\Delta G > 0$, thus liquid water does not evaporate spontaneously

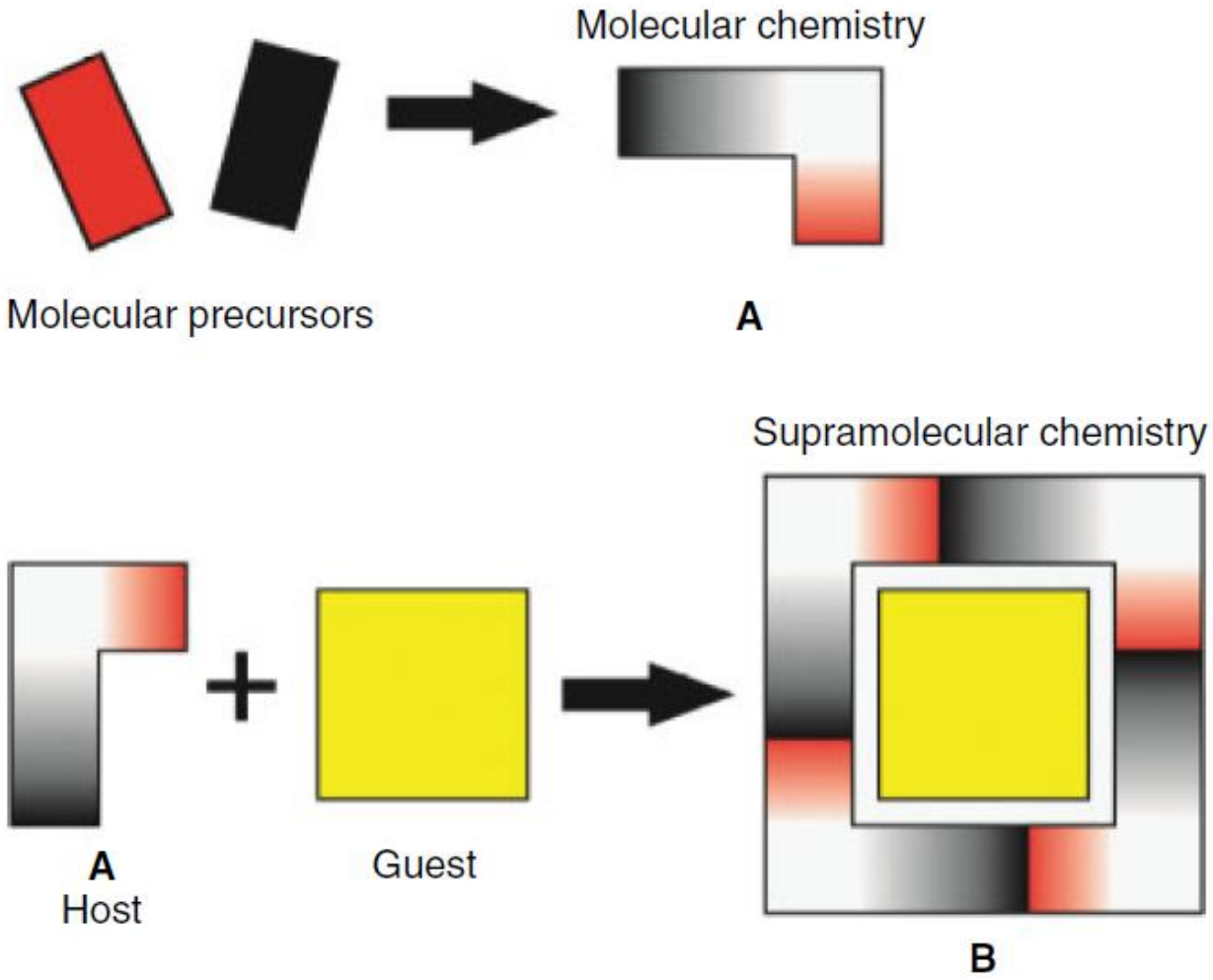
Thermodynamics Aspects of Spontaneous vs Non-spontaneous Process

The Gibbs free energy is considered when the process occurs at constant temp. and pressure and follow the below equation;

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

i. If ΔG = – ve, the process is spontaneous
ii. If ΔG = + ve, the process is non-spontaneous
iii. If $\Delta G = 0$, no net change in the system and it will be in eqbm
iv. If $\Delta S > 0$, $\Delta H < 0$ the process is spontaneous
v. If $\Delta S < 0$, $\Delta H > 0$ the process is non-spontaneous and moves to the backward direction
vi. If $\Delta S > 0$, $\Delta H > 0$ the process is spontaneous but at high temp, and non-spontaneous at low temp.
vii. If $\Delta S < 0$, $\Delta H < 0$ the process is spontaneous at low temp, and non-spontaneous at high temp

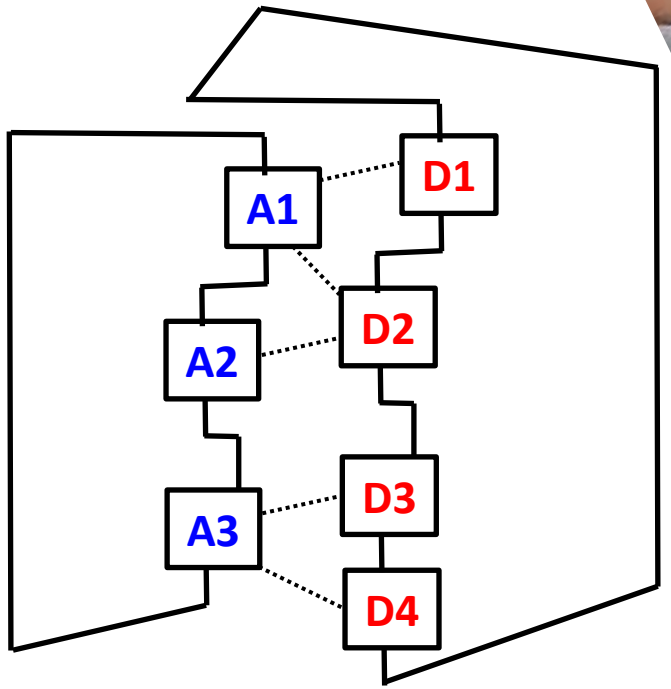
Molecular vs. Supramolecular Chemistry



Concept of multi-site host-guest complexations

Within a single H-G complex, several acceptor-donor interactions possible

How many A-D interactions you see in the below example?



Pairwise multi-site host-guest interactions

Concept of Binding Constant & Dissociation Constant

The binding constant, K is an important parameter to realize when studying supramolecular chemistry

What is a binding constant?

It's a measure of interaction between the species, donor-acceptor (ligand-metal ion/metal, enzyme-substrate, antigen-antibody, so on

Stronger the interaction/association, higher the binding constant

$$L + R \leftrightarrow LR \qquad k_{on}[L][R] = k_{off}[LR]$$

The rate, by which the ligand and receptor molecule becomes a ligand-molecule complex is called the on-rate constant. Similarly, the rate at which the ligand-molecule complex breaks down into free ligands and receptor is called the off-rate constant

$$K_a = \frac{kon}{koff} = \frac{[LR]}{[L][R]}$$

Concept of Binding Constant & Dissociation Constant

Calculate the binding constant of below reaction

A+B ⟷C,

Concentration of [A], [B], [C] 5 mol/L, 4 mol/L, 10 mol/L, respectively

The association reaction involves two reactants, so it is by definition a second order reaction

Explain the situation of A⟷B+ C, what about the binding constant?

In the above example, dissociation happens, thus it must be considered dissociation constant rather than the association/binding constant.

Consider the conc. of A, B, C as given above, calculate Kd.

Find the relation between binding and dissociation constant.

Explain which one has stronger binding constant between two

Kd1 = 10 μM; Kd2 = 10 nM

Relation Between Gibbs Free Energy and Binding Constant

Higher the binding constant lower the Gibbs free energy

Binding constant is also called 'thermodynamic equilibrium constant'

THERMODYNAMIC STABILITY

$$G + H \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HG$$

$$K = \frac{k_1}{k_{-1}} = \frac{[HG]}{[H]\,[G]}$$

$$\Delta G^0 = -RT \ln K = \Delta H^0 - T\Delta S^0$$

ΔG^0 (kJ mol^{-1})	K (M^{-1})
-5.7	10^1
-11.4	10^2
-17.1	10^3
-22.8	10^4
-34.2	10^6
-45.6	10^8
-57.0	10^{10}

Derivation of stepwise and overall binding constants

Calculate the binding constant of below reaction

A+B ⟷C,

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

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

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

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 (ß) for a 1:3 host–guest complex

Co-operativity and the chelate effect

'the whole is greater than the sum of its parts' meaning a team pulling together has greater effect than the sum of many individual efforts

This concept can be implemented to design supramolecular assemblies

This co-operativity between sites is a overview of the chelate effect in the host-guest chemistry

Co-operativity: **Multi-binding sites act in a concerted fashion to produce a combined effective interaction that is stronger than the individual one**

Chelate Effect: **Multidentate ligands binds the guest simultaneously, resulting in more stable complexes formation than that of multiple unidentate ligands. This is the result of co-operativity between interacting sites**

"chely" meaning a lobster's claw

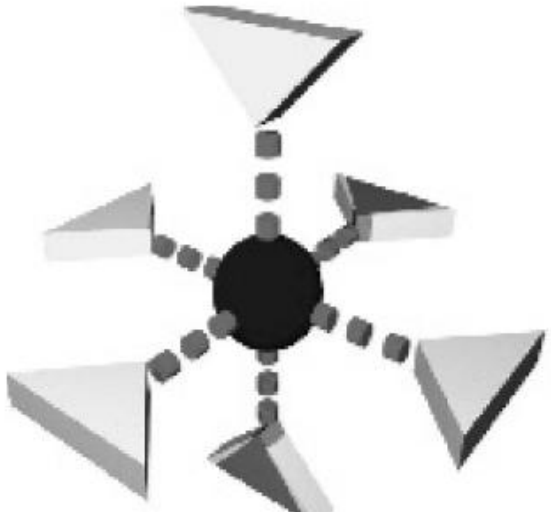
Example of Chelate Effect

Complexes with six unidentate ligands vs three bidentate ligands

The nature of the ligand–metal dative bond is almost identical in both cases (via nitrogen atom lone pairs), yet the ethylenediamine complex is 10^8 times more stable than the corresponding hexamine complex

Thus ethylenediamine (en) readily displaces ammonia in the nickel complex

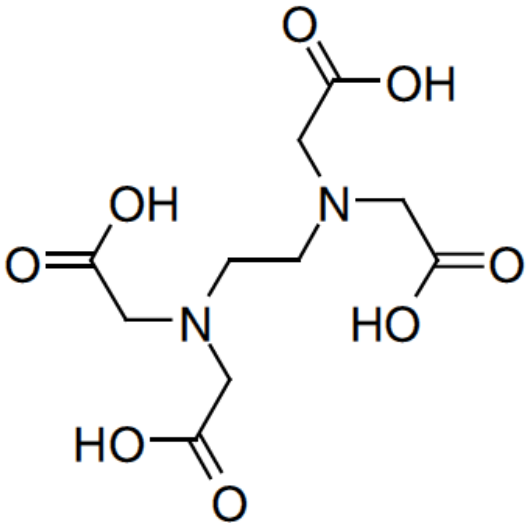
(a)



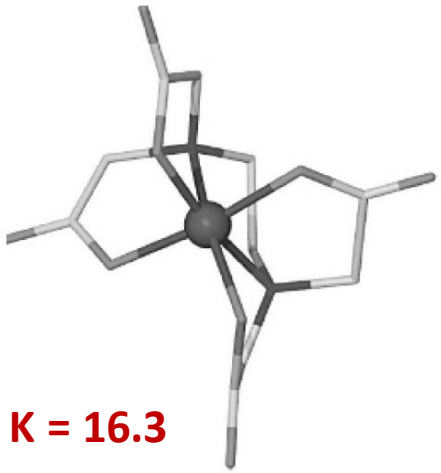
(b)

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

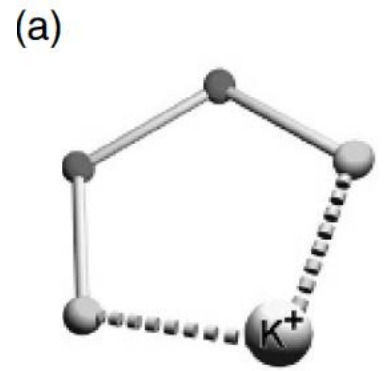
Examples of Chelate Effect

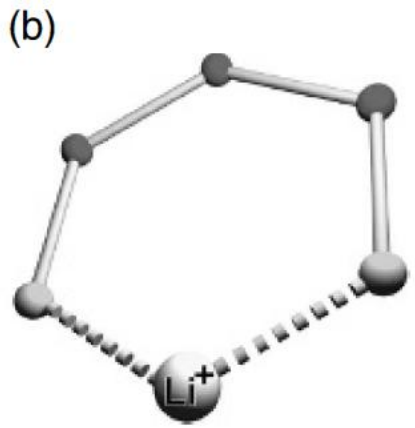


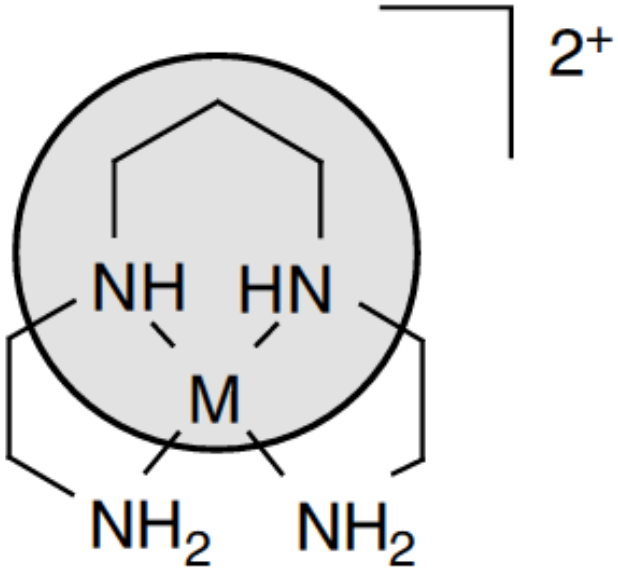
ethylenediaminetetraacetic acid (H_4EDTA)



log K = 16.3







A chelating podand

Where Does the Extra Stability Come From in Chelating Complexes?

The improved stability of chelating complexes comes from both the entropic and enthalpic factors that actually lower the total complexation free energy $\Delta G = \Delta H - T\Delta S$

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

six unidentate ligands are replaced by three bidentate ligands

During this displacement, a greater number of molecules become free in solution (four species before and seven after)

This increase in the number of free molecules gives more degrees of freedom in the system and therefore gives an increase in entropy

The **ΔG** for the reactions of ammonia and ethylenediamine with Ni^{2+} are −49.2 and −104.4 kJ/mol, respectively

The $Ni(en)_3^{2+}$ complex is also kinetically stabile, as the bidentate ligands are harder to remove, since they have two points of contact

Where Does the Extra Stability Come From in Chelating Complexes?

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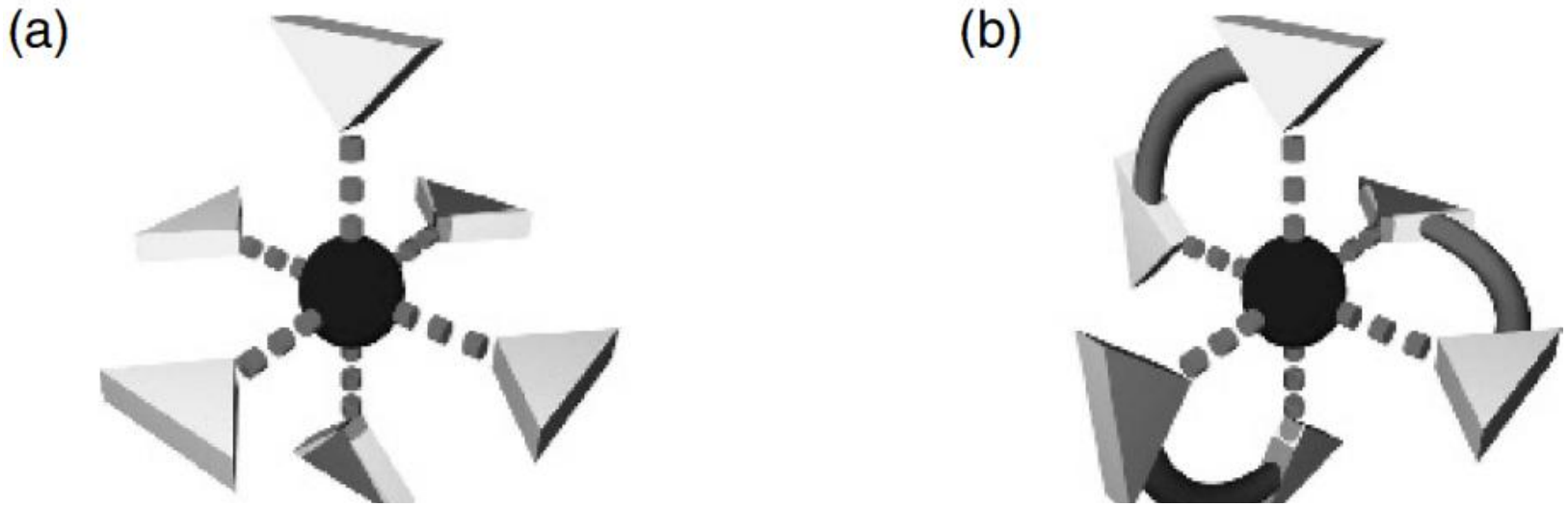

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