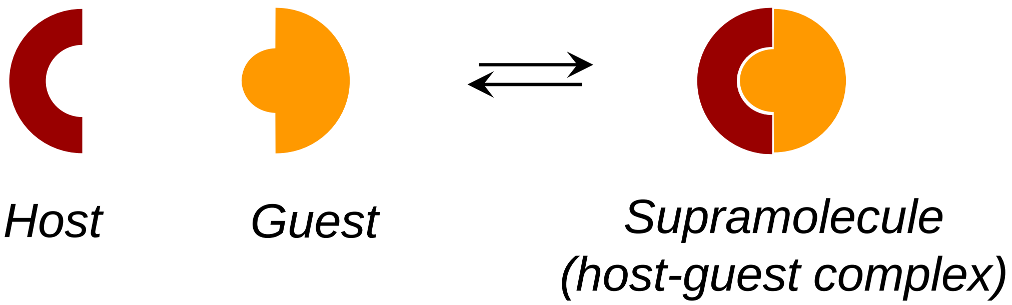
The strength of the interaction



- When is the host capable to recognize the guest?
- How do we define selectivity
- Which element will we use to design the host for the target guest

$$K = \frac{[Supramolecule]}{[Host][Guest]}$$

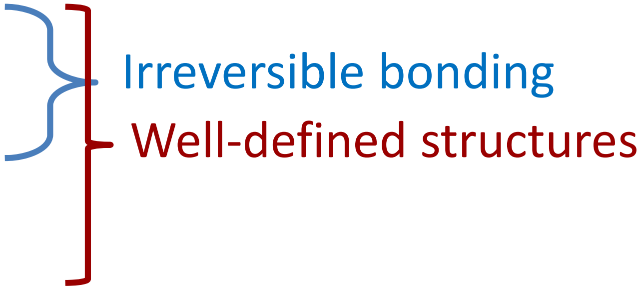
$$\ln K = -\frac{\Delta G^\circ}{RT} = \boxed{-\frac{\Delta H^\circ}{RT}} + \frac{\Delta S^\circ}{R}$$

Covalent bonds strenghts

C-O bond	**81 kcal/mol**	**1.43 Å**
C-C bond	**86 kcal/mol**	**1.54 Å**
C-H bond	**103 kcal/mol**	**1.11 Å**
C=C bond	**143 kcal/mol**	**1.33 Å**
C=O bond	**165 kcal/mol**	**1.21 Å**

Covalent bonds are characterized by:

- High bond energies (strong bonds)
- Short distances
- High directionality



Irreversible bonding

Well-defined structures

Non-covalent interactions

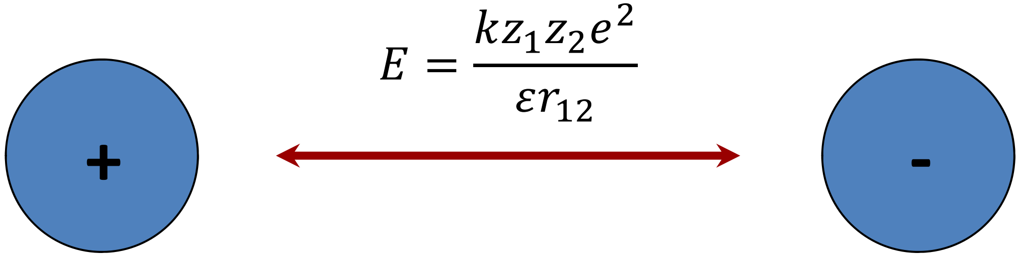
hydrophobic	**<10 kcal/mol**
electrostatic	**1-20 kcal/mol**
Hydrogen bond	**2-30 kcal/mol**
π-π aromatic stacking	**0-10 kcal/mol**
van der Waals	**0.1-1 kcal/mol**

Non-covalent interactions are characterized by:

- Low energies
- Poor directionality (exception: H-bond)

Notwithstanding, accumulation of many weak interactions may lead to strong bonding ⇒ **cooperativity**

A. Ion pairing interaction



$$E = \frac{kz_1z_2e^2}{\varepsilon r_{12}}$$

Ion pair: a cation and anion close enough in space that the energy associated with their electrostatic interaction is higher than the thermal energy (RT)

- It can be an attractive or a repulsive force
- It is a long range (1/r) interaction
- Highly dependent on the dielectric constant of the medium

ΔH for placing two charges at the distance of 3 A in

H_2O

$E = 9 \cdot 10^{9} \cdot 1 \cdot (-1) \cdot (1.6 \cdot 10^{-19})^2 / 78.5 \cdot 3 \cdot 10^{-10}$
$= -2.3 \cdot 10^{-28} / 2.4 \cdot 10^{-8}$
$= -9.8 \cdot 10^{-21}$ J
$\Delta H = -1.4$ kcal/mol

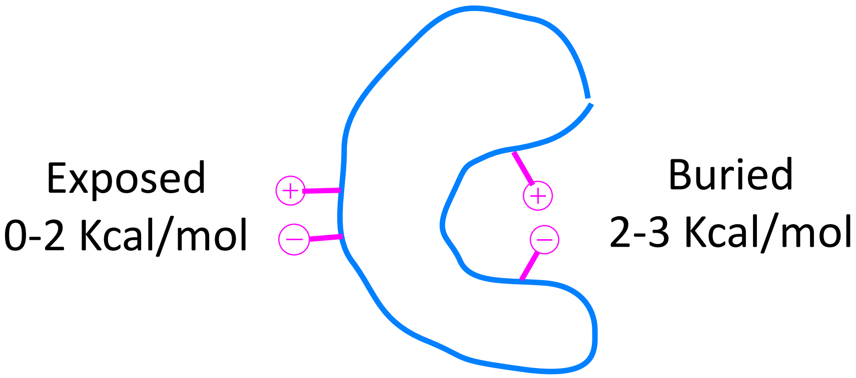
$CDCl_3$

$E = 9 \cdot 10^{9} \cdot 1 \cdot (-1) \cdot (1.6 \cdot 10^{-19})^2 / 4.8 \cdot 3 \cdot 10^{-10}$
$= -2.3 \cdot 10^{-28} / 1.44 \cdot 10^{-9}$
$= -1.6 \cdot 10^{-19}$ J
$\Delta H = -23$ kcal/mol $\Rightarrow$ 27 % of a C-C bond

A. Ion pairing interaction

Other factor to take into account include:

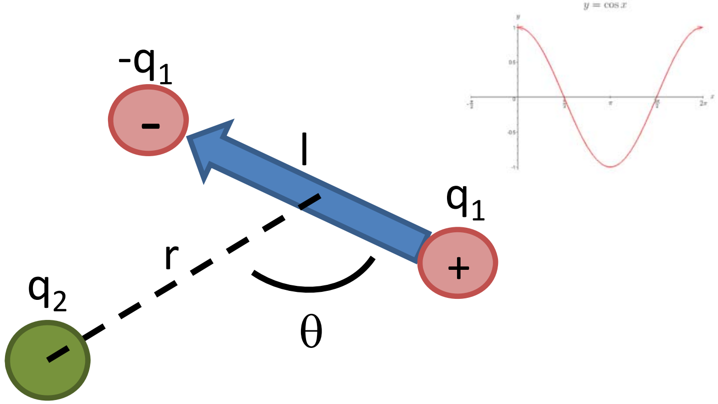
- Size and shape of the ions (charge density)
- Modification of the “pure” electrostatic interaction as a result of ion pair formation
- Specific coordination ability of the solvent
- Solvent reorganization (see hydrophobic effect)
- Local environment (solvent exclusion may affect the effective dieletric) constant



Ionic interaction is substantially stronger for **polyions**: while sodium acetate is completely dissociated in water, polyacrylate [-($CH_2CHCO_2^-$)$_n$-] has a substantial fraction of sodium ions bound to the polymer.

B. Ion-Dipole interaction

$$E = \frac{\mu q_2 cos\theta}{4\pi\varepsilon\varepsilon_0 r^2} \qquad \mu = q_1 l \qquad r \gg l$$



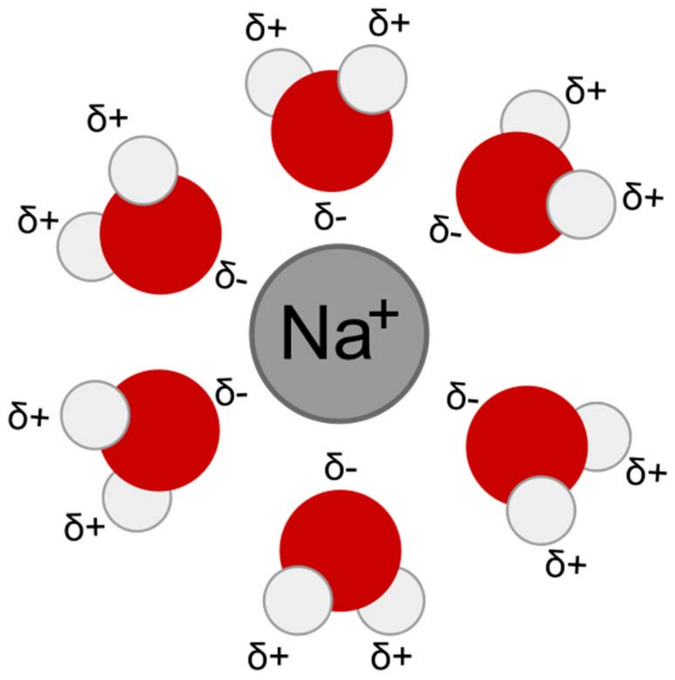
- Significantly weaker than ion-ion interactions
- Longer range interaction ($1/r^2$) than ion pairing
- **Some directionality**
- Can be attractive or repulsive

$E = -9 \cdot 10^9 \cdot 1.6 \cdot 10^{-19} \cdot 2.9 \cdot 3.336 \cdot 10^{-30} / e \cdot r^2$
$= -1.39 \cdot 10^{-38} / 4.8 \cdot (3 \cdot 10^{-9})^2$
$= -2.9 \cdot 10^{-20}$ J
$= -4.7$ kcal/mol

ΔH for placing Na^+ at the 3 A distance from acetone ($\theta = 0°$)

B. Ion-Dipole interaction

Hydration energies



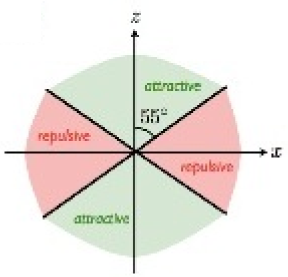
Hydration heats of ions

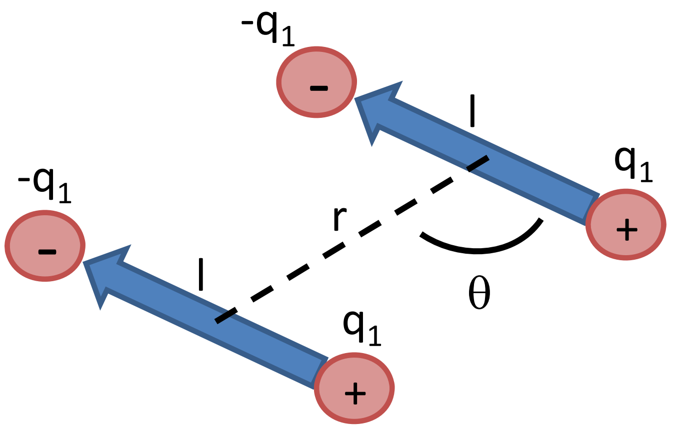
M^+	ΔH° (kcal/mol)	Ionic radius (A)
Li^+	-122	0.60
Na^+	-98	0.95
K^+	-81	1.33
Rb^+	-76	1.48
F^-	-114	1.36
Cl^-	-82	1.81
Br^-	-79	1.81
I^-	-65	2.16

Solvation heats closely correlates with ionic radii, this suggest a stong electrostatic (ion-dipole interaction) component in solvation energies.

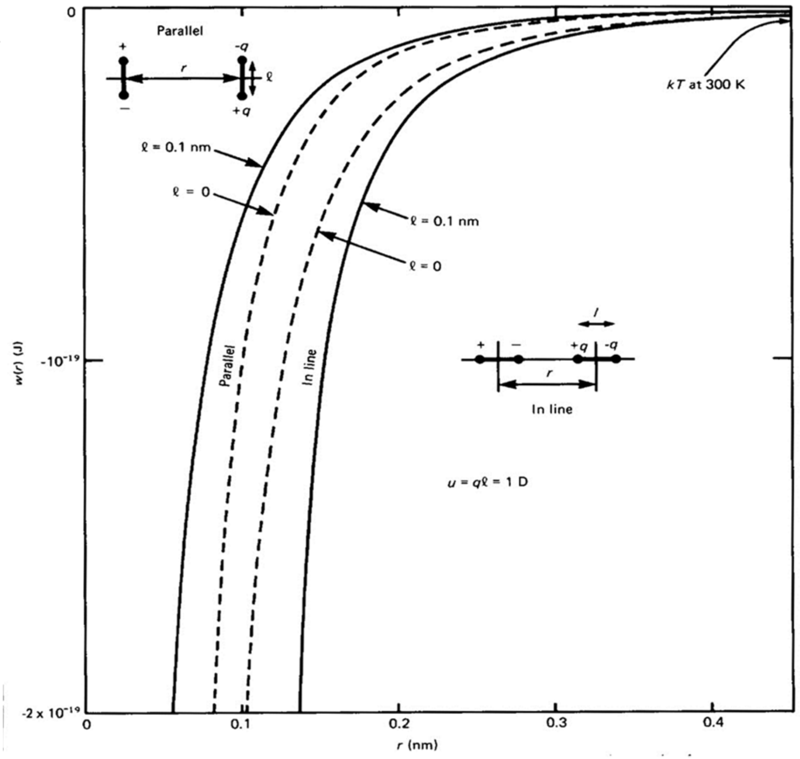
C. Dipole-Dipole interaction

$$E = \frac{-\mu_1\mu_2(3cos^2\theta - 1)}{4\pi\varepsilon\varepsilon_0 r^3}$$



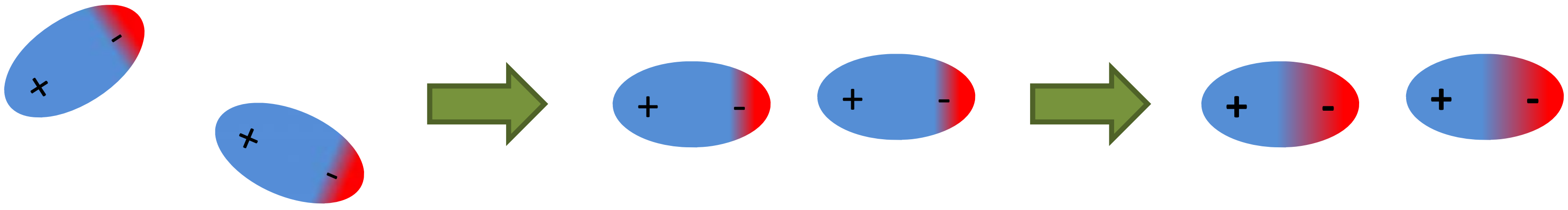


- Significantly weaker than previous interactions
- Longer range interaction ($1/r^3$) than ion dipole
- **Some directionality**
- **In line alignment preferred**



D. Van deer Waals interactions

Polarization: when a charged molecule (or a polar molecule) get close to another, mutual changes of the electronic wavefunctions strengthen the interaction.



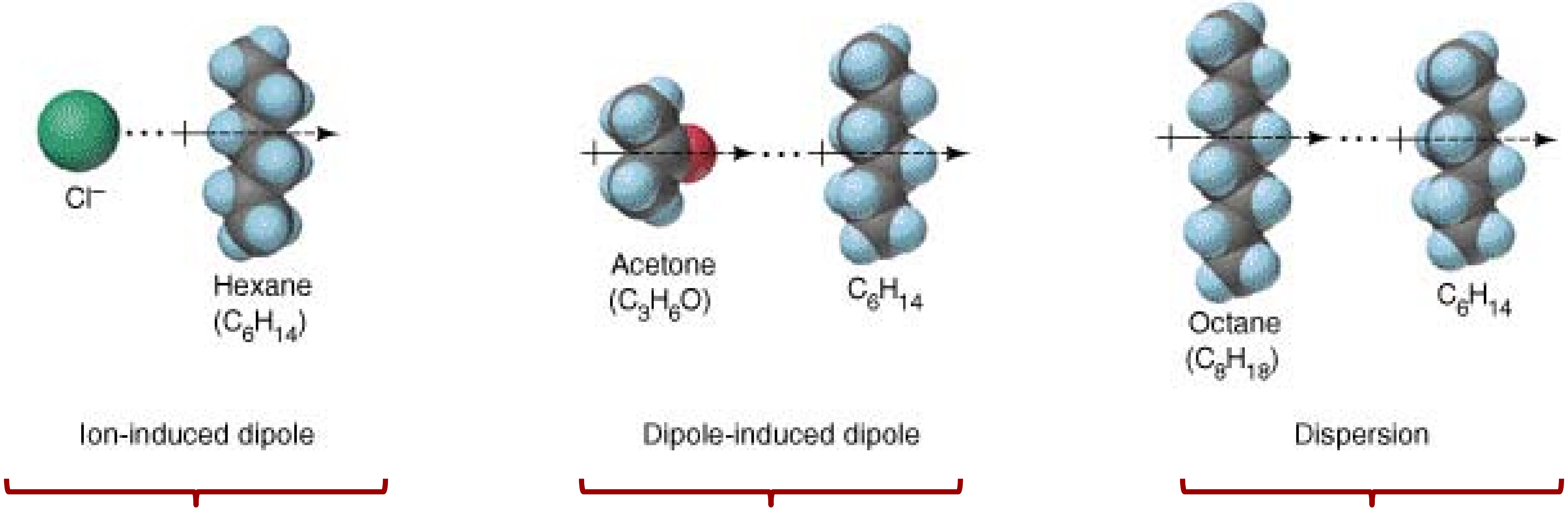
In the case of non-polar molecules, polarization introduce new interaction modalities. Polarizable molecules produce a dipole when exposed to an electric field:

$$\mu=\alpha E_{field}$$

Often described as Van der Waals forces, induced-dipole based interactions include dispersion forces, i.e. instantaneous dipoles interactions, ion-induced dipole, and dipole-induced dipole interactions.

- Bond energy is very weak (0.01-0.5 kcal/mol)
- Very short range forces ($1/r^4$ -$1/r^6$)
- Exist between **all** atoms and molecules

D. Van deer Waals interactions



$$E = \frac{-q^2\alpha}{(4\pi\varepsilon\varepsilon_0)^2\, r^4}$$

$$E = \frac{-2\mu_1{}^2\alpha_2}{(4\pi\varepsilon\varepsilon_0)^2\, r^6}$$

$$E = B/r^{12} - A/r^6$$

D. Polarization and London forces

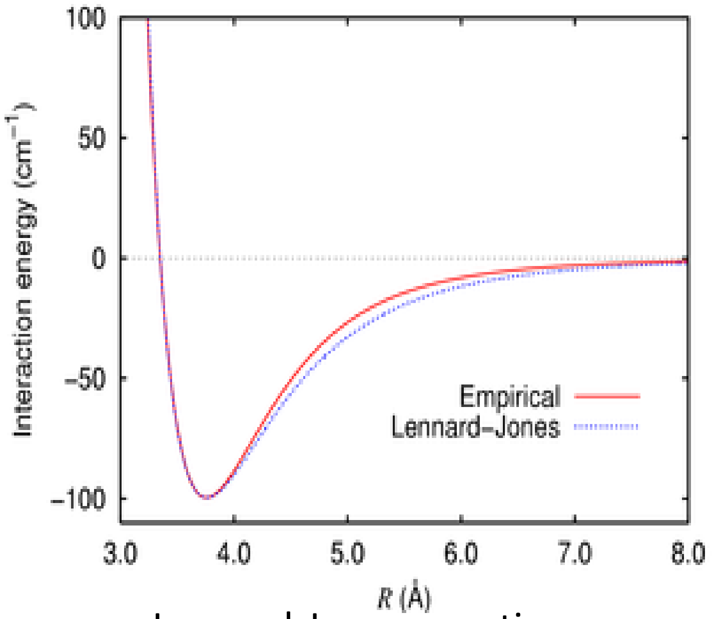
The London equation emipirically describes the ubiquitous weak attraction between all atoms.

$E = -A/r^6$

Lennard-Jones potential combines London interaction with the “hard sphere” repulsion ($+B/r^{12}$) between atoms at very close distance.

$E = B/r^{12} - A/r^6$

This equation allows us to find the “van der Waals radii” of atoms. This is the size of an atom or the preferred distance atoms will pack to if there are no other significant interactions.



Lennard-Jones equation

D. Van deer Waals interactions

The strength of the interaction is essentially a function of the surface area of contact and the polarizability of electron shells. The **larger** the surface area the **stronger** the interaction will be.

Regardless of other interactions found within a complex there will always be a contribution from vdw.

Molecules	%London	Molecules	%London
Ne-Ne	100	CH_4-CH_4	100
HI-HI	99	HBr-HBr	96
HCl-HI	96	H_2O-CH_4	87
HCl-HCl	86	CH_3Cl-CH_3Cl	68
NH_3-NH_3	57	H_2O-H_2O	24

This is what drives molecules to eliminate spaces or vacuums and makes it difficult to engineer porous or hollow structures and gives rise to the phrase “Nature abhors a vacuum”.

E. Hydrogen bonding

Probably the **most important** of all intermolecular interactions

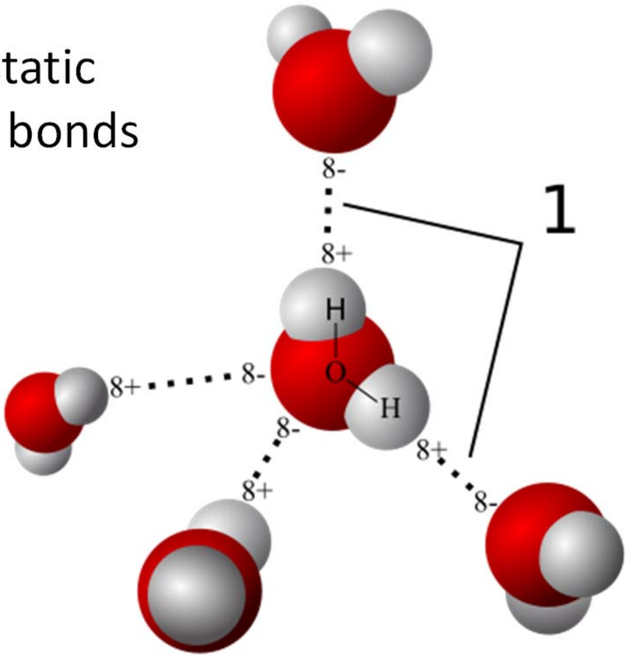
It forms when a hydrogen atom is positioned between two electronegative atoms, mainly O and N: **D-H**---**A**

It is a special case of dipole-dipole interactions, electrostatic description holds for weak and moderate bonds, strong bonds which have a certain amount of covalent character

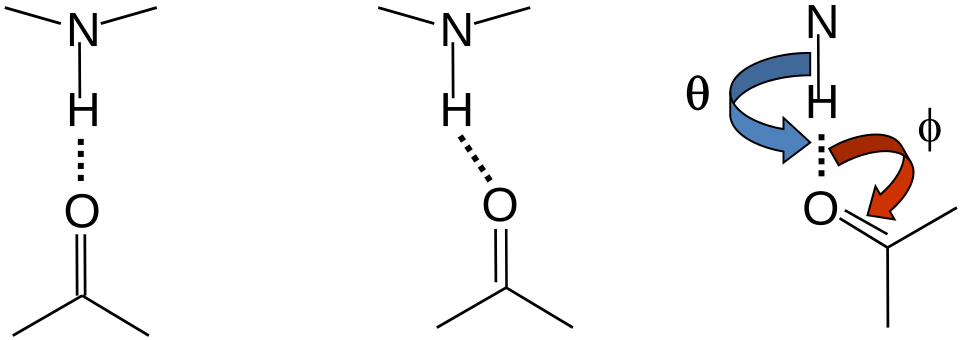
It can be significantly stronger than typical dipole-dipole interaction

Short range (2.5-3.5 Å)

Certain amount of directionality



E. Hydrogen bonding: geometry



θ= D-H-A angle
ϕ = H-A-X angle

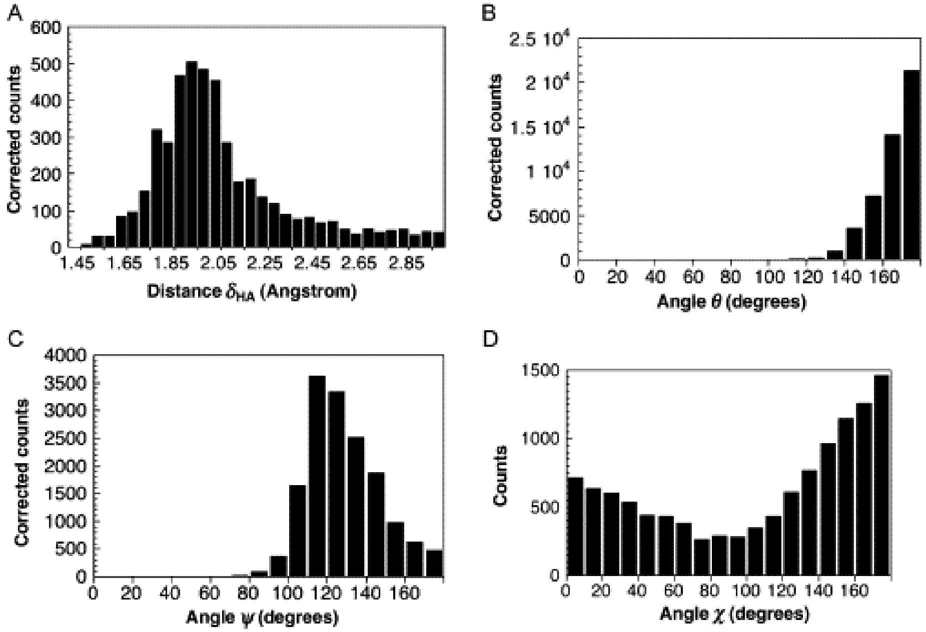
Most stable

$\theta=180^o$

$\phi=120^o$

Ideal angles

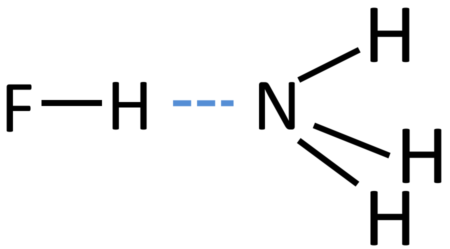
- Dipole interaction diretionality
- Coincidence with imagined axis of acceptor lone pairs



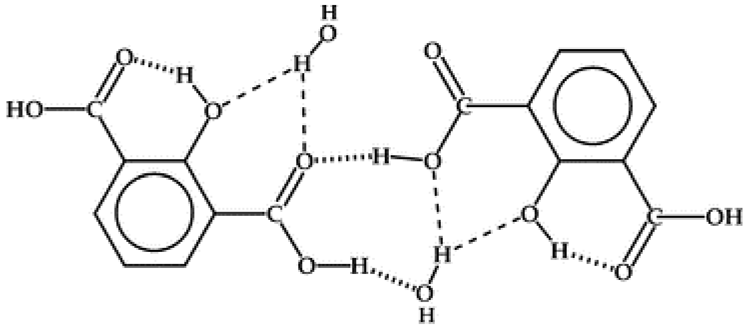
E. Hydrogen bonding: geometry

$F{-}H \cdots N{\equiv}C{-}R$

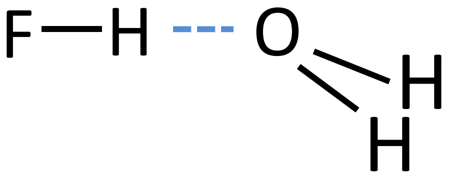
180°



55°

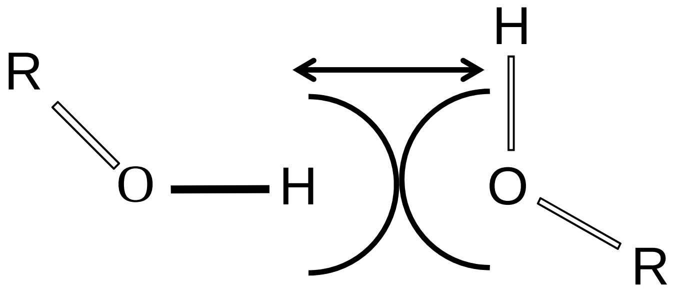


2-hydroxyisphtalic acid

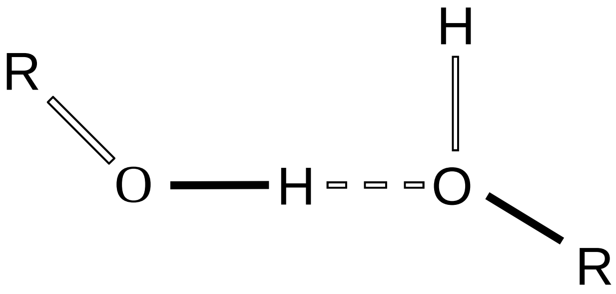


55°

E. Hydrogen bonding: distance



Van der Waals radii; H: 1.1Å, O: 1.5 Å. Therefore closest approach should be 2.6 Å.



Actual separation is about 1Å less! Distance of 1.76 Å.

It is intermediate between vdw distance and the typical O-H covalent bond lenght of 0.96Å.

E. Hydrogen bonding: strenght

- 40-15 Kcal/mol: strong
- 14-4 Kcal/mol: moderate
- 4-0 Kcal/mol: weak → **Most common**

Several factors affect H-bonds strength:

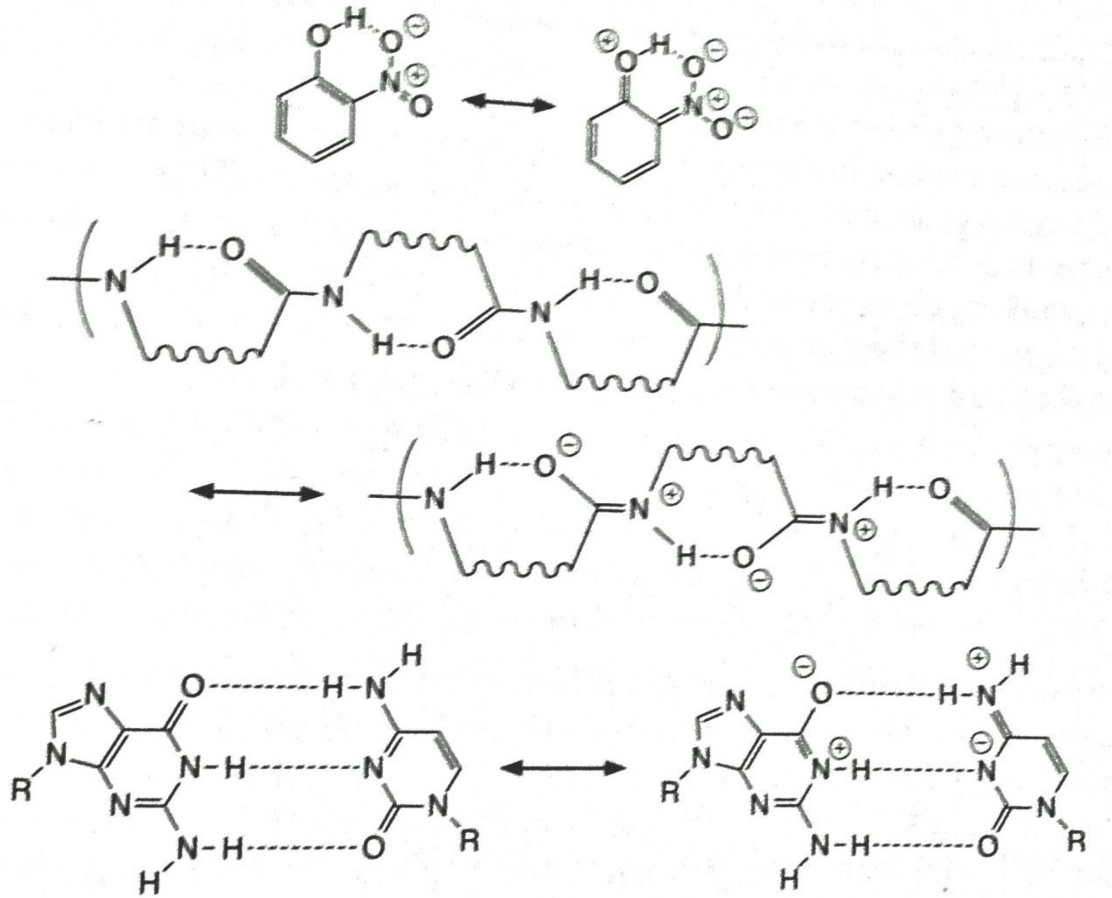
- **Solvatation** (dielectric constant, H-bond donating/accepting ability)
- **Electronegativity**

  Donor: HF > HCl > HBr > HI

  Acceptor: $H_2O > H_3N > H_2S > H_3P$ (but F is very poor!)
- **Charge** (hydrogen bond may be strengthened or weakened by concurrent electrostatic interactions

E. Hydrogen bonding:

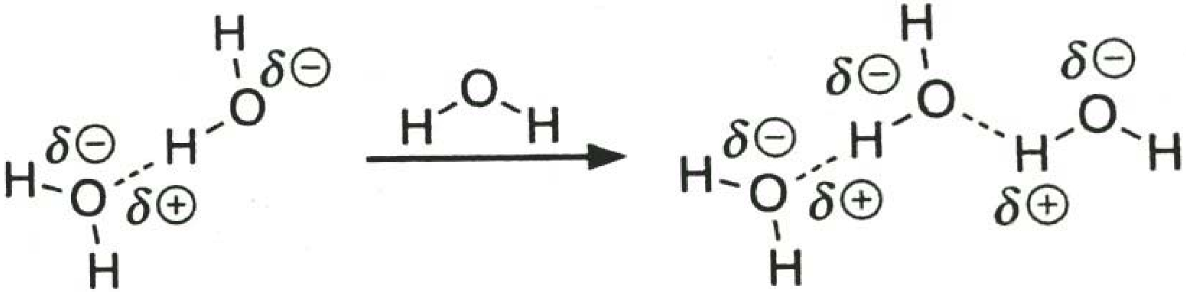
Resonance Assisted H-Bonds (RAHB)



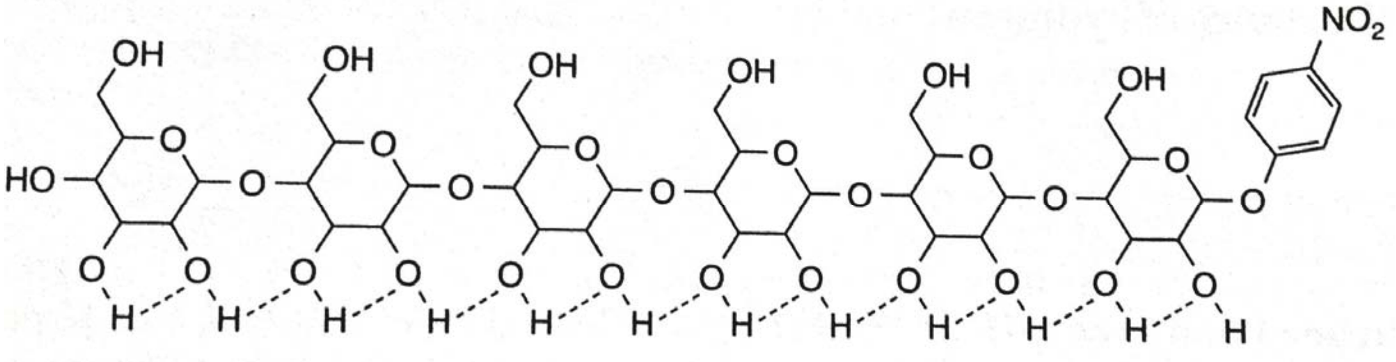
Hydrogen bonds that benefit from a particular resonance structure of the donor of acceptor. From a different point of view, RAHB may be considered as a form of H-bond assisted resonance structures.

E. Hydrogen bonding:

Polarization enhanced H-Bonds



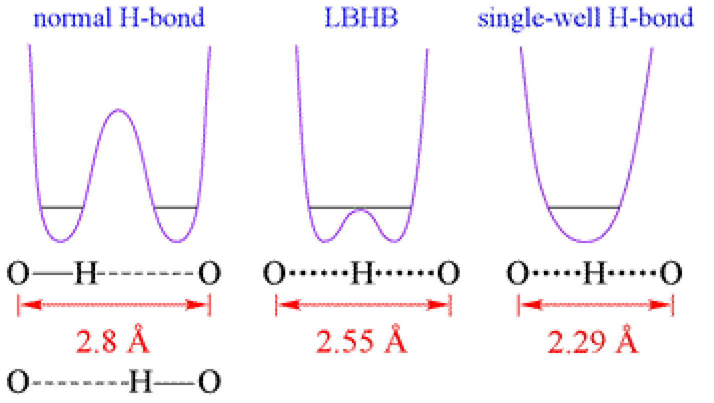
The formation of an H-bond may polarize a donor and enhance its ability to form H-bonds

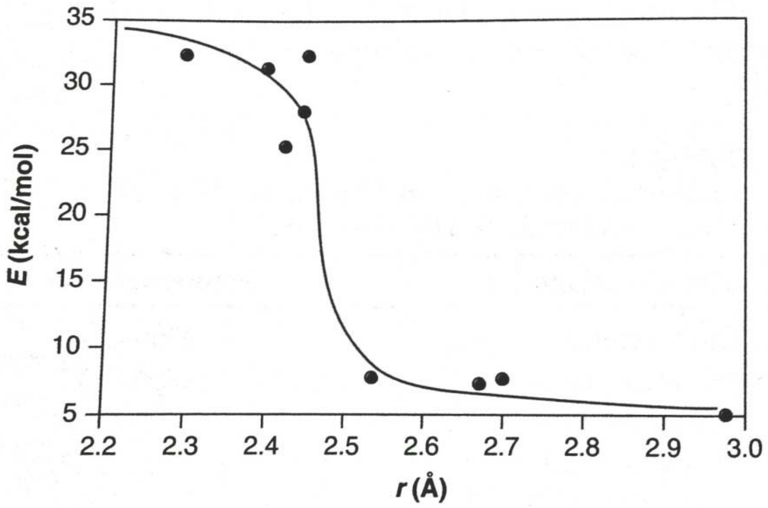


Intramolecular hydrogen bonding in oligosaccharides

E. Hydrogen bonding:

Short-strong H-bonds





The formation of the hydrogen bond can be described by a two-well potential energy plot.

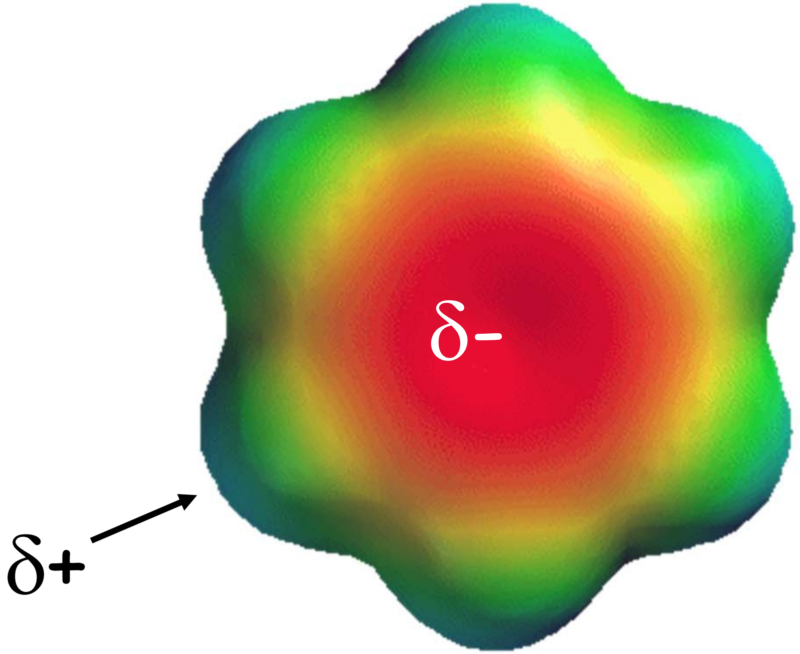
In normal cases, the second minimum has a **higher** energy and there is a **high barrier** between the two minima (which corresponds to the possibility of the transfer of the hydrogen from the donor to the acceptor).

If the pK_a of the acceptor becomes **similar** to that of the donor, and the distance **decreases**, the energy of the two minima becomes similar and the energy barrier decreases.

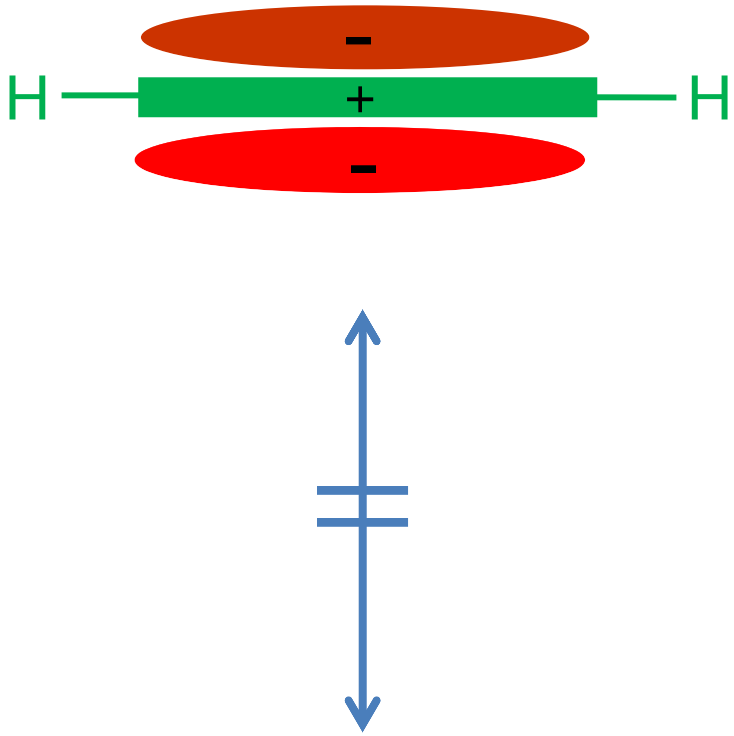
These bonds are called **Low Barrier H-Bonds** (LBHB) and **No-Barrier** (or single well) H-bonds, and are quite strong (20-40 Kcal/mol). They can be described as three senter-four electron bonds with a strong **covalent** character.

F. π-Interactions:

Conjugate systems as negative charge centers



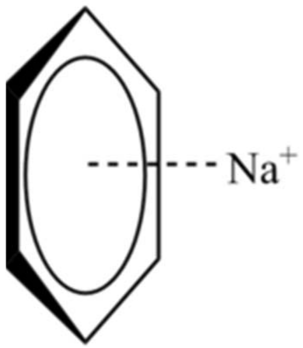
Distribution of electron density in benzene molecule



Charge distribution in benzene produces a large quadrupole moment, in the form of two dipoles aligned end-to-end.
Quadrupoles are not necessarily weaker than dipoles.

F. Cation-π Interactions:

Much stronger than expected



Gas phase binding energies of cations to benzene

M^+	ΔG° (kcal/mol)
Li^+	-38
Na^+	-27
K^+	-19
Rb^+	-16

Binding energies correlate with the ionic radii of the cations, this indicates that the interaction is mainly electrostatic. (Different form coordination with transition metals)

Gas phase ΔG° for water binding to K^+ is -18 kacl/mol: cation-π interaction can be as strong as ion-dipole interactions!

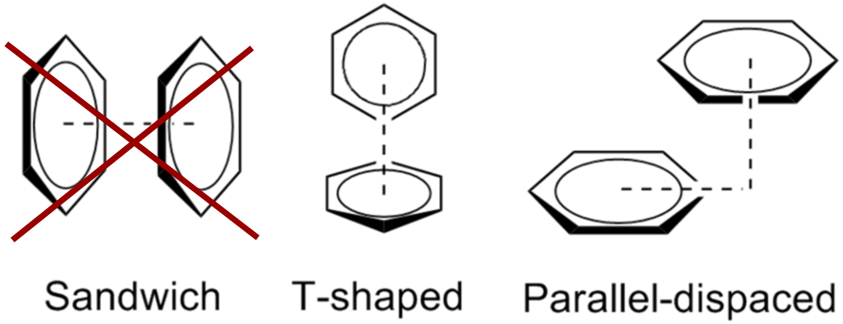
Cation-π interaction are less sensitive to environment polarity: methylammonium-benzene interaction in water (5 kcal/mol) is stronger than methylammonium-acetate (<2 Kcal/mol)!

Inductive effects by aromatic substituents are more effective than conjugation in modulating the interaction

F. polar-π Interactions:

Also permanent dipoles interact with aromatic rings. The geometry of interaction between water and benzene appears reminiscent of H bonds (1.9 kcal/mol in the gas phase) but is just an electrostatic interaction

F. π-π Interactions (π Stacking):

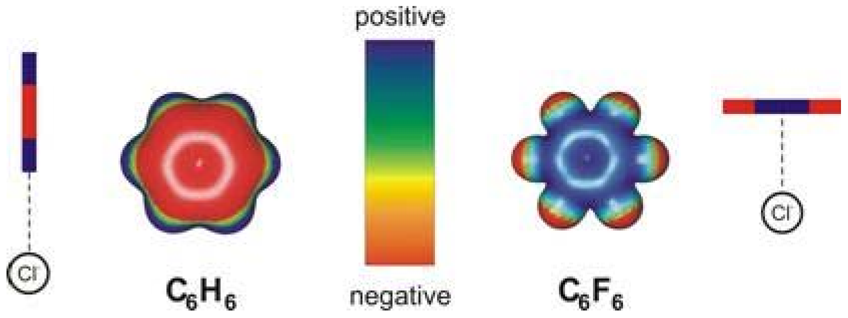


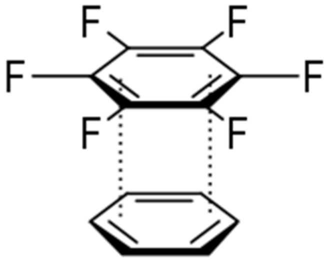
Aromatic stacking is a largely misused concept.

Face-to face interaction (sandwich) is largely unfavorable because the negative surfaces of the two molecules are in contact.

T-shaped interaction is the most favorable (2 kcal/mol in gas phase).

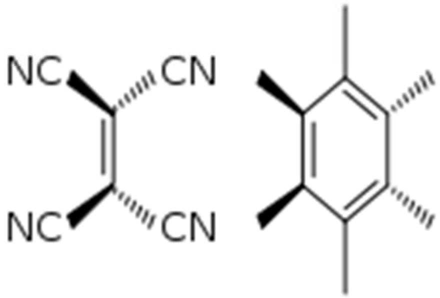
Parallel-displaced is preferred in water and for large aromatic molecules as it enhances also hydrophobic interaction

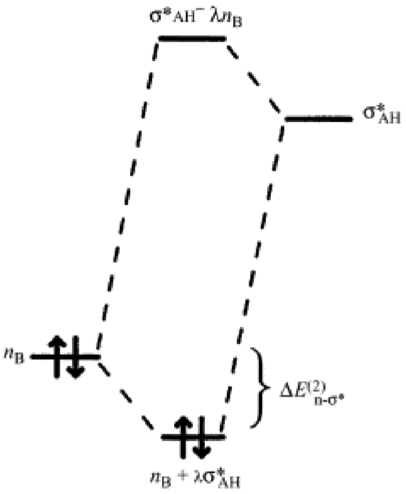




Fluorine elctronegativity inverts electrostatic potential surfaces: arene-perfluoroarene sandwich interaction is favorable. A mixture of benzene and hexafluorobenzene melts at higher temperature than the pure compounds

F. Donor-Acceptor Interaction:





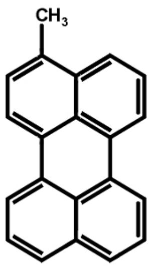
A **donor-acceptor** interaction occurs between two molecules with respectively a low energy empty orbital (**acceptor**) and an high energy filled orbital (**donor**).

When the two orbitals are properly aligned, **mixing** occur associated with an **charge transfer**.

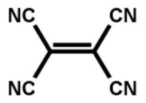
The interaction has both an **electrostatic and covalent nature**.

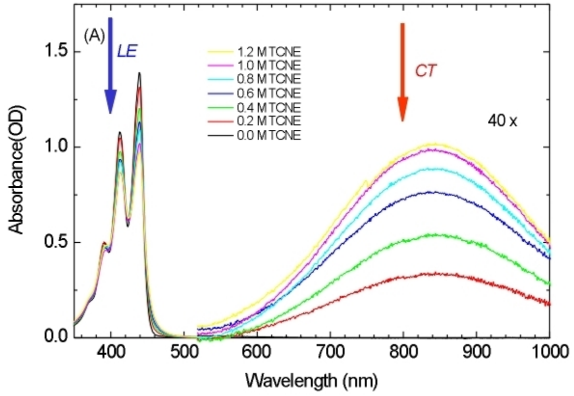
Generally, a strong charge transfer is associated with the arising of a new, red-shifted and broad **absorption band**.

Donor D

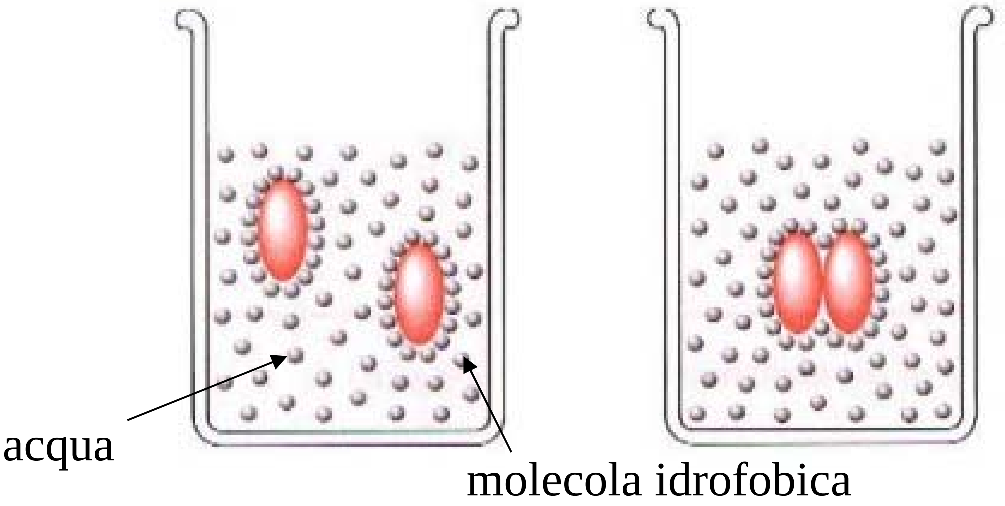


Acceptor A





G. Hydrophobic effect

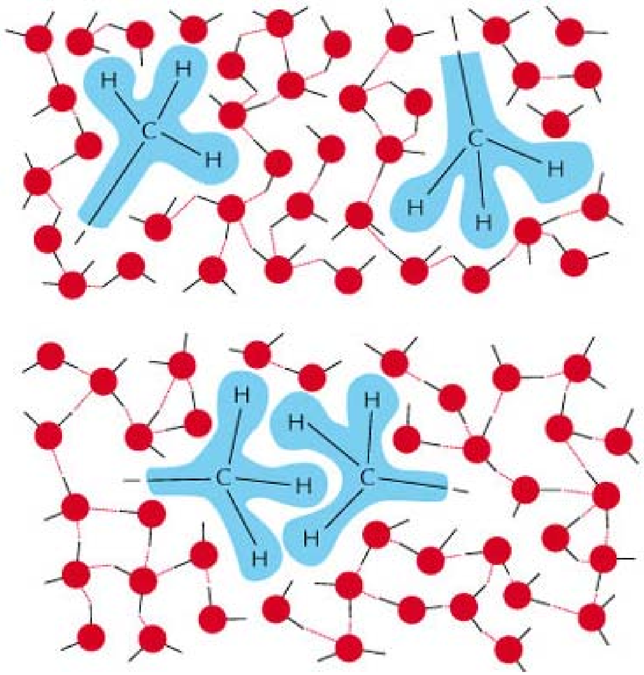


Hydrocarbons, once dispersed in water, form **dimers** and **larger aggregates**. The interaction that keep together such entities is called hydrophobic effect.

The **enthalpy** change associated with such interactions is usually **negative**. In fact, the direct interaction between the two non-polar molecules is generally based on dispersion forces, which arise from instantaneous dipoles, while interaction between a non-polar molecule and water arise from stronger permanent dipole-instant dipole interactions.

Hence, hydrophobic effect is not due to intermolecular force but is controlled by **enthalpy**.

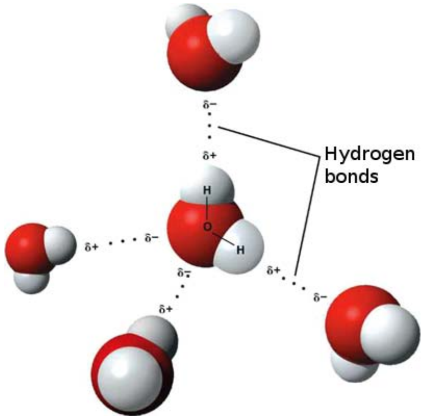
G. Hydrophobic effect



n-butano in H_2O

$\Delta H = -4.3$ kJ/mol

$-T\Delta S = +28.7$ kJ/mol

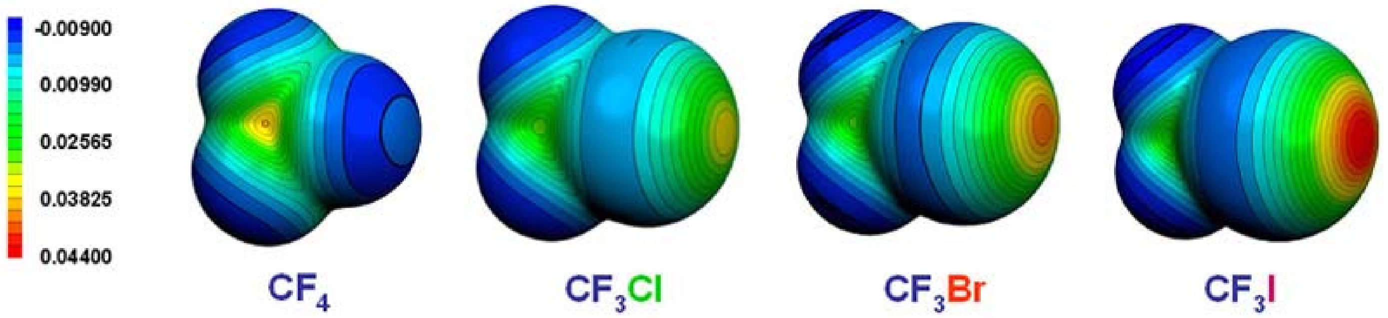


Insertion of a non-polar molecule in water causes an **interruption** of the loose H-bond network. Water molecules are forced to form H-bond only with outer molecules creating a **cage** around the solute. The new bonds are stronger, and this causes and **entropy loss**.

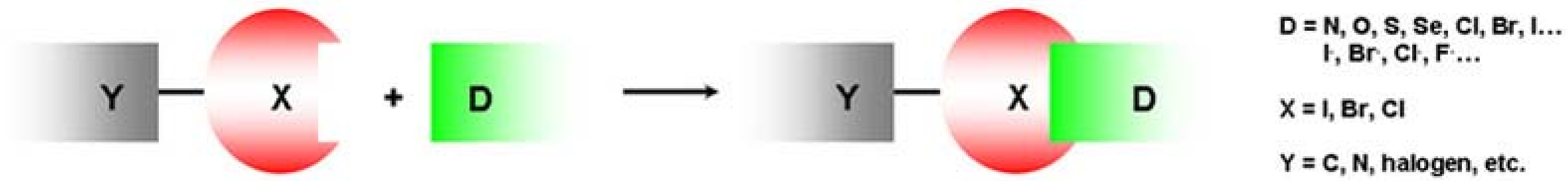
Association between two hydrophobic molecules leads to a decrease of the number of water molecule trapped in the cages formation. Total entropy increases and compensate the enthalpy loss.

F. Halogen bond

Halogen bonding (XB) is an electron density donation-based interactions of halogen atoms and neutral or anionic Lewis bases, such as N, O, S, P or halogen functionalities and π electron donors.



Electron density around the covalently bound halogens is highly anisotropic, and in the larger member of the group positively charged regions are found at the poles. In that regions, halogens can act as **Lewis acids**.



XB donor XB acceptor

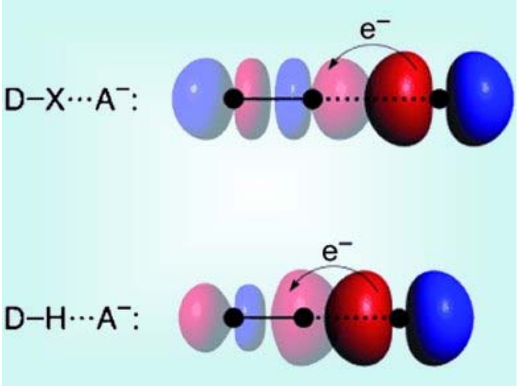
H. Halogen bond

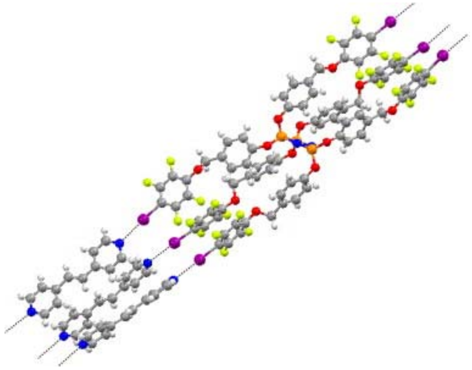
Halogen bonds share several feature with H-bonds:

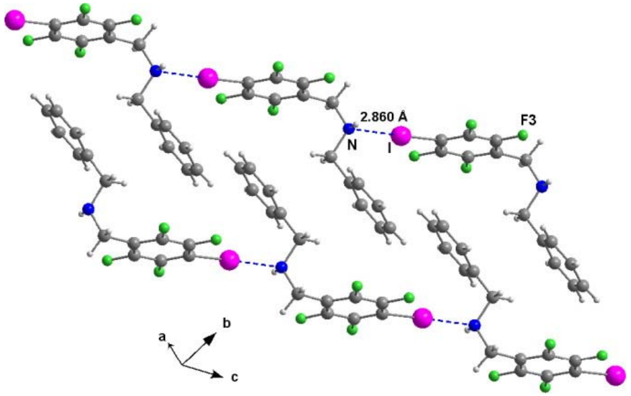
- Interaction strengths in the 1-10 kcal/mol range, up to 45 kcal/mol
- Directionality (Y-X-D angle of 180°)
- The distance between the donor and the acceptor is below the sum of the WdW radii (20%)

Possible interpretations:

- Electrostatic interaction (explain most)
- Donor-acceptor interaction with charge transfer (explains correlation with polarizability and low dependence form solvent polarity)







I. Coordination bond

A coordination entity constitutes a central metal atom or ion bonded to a fixed number of ions or molecules

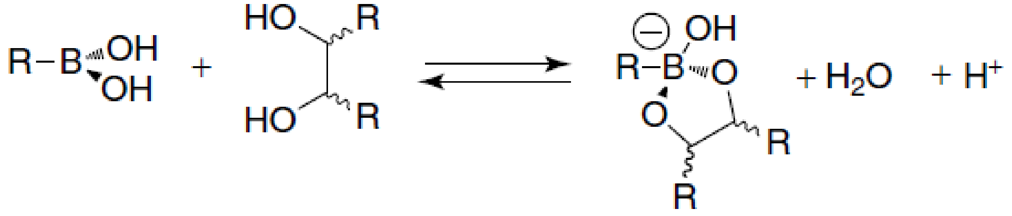
From electrostatic…

… to covalent

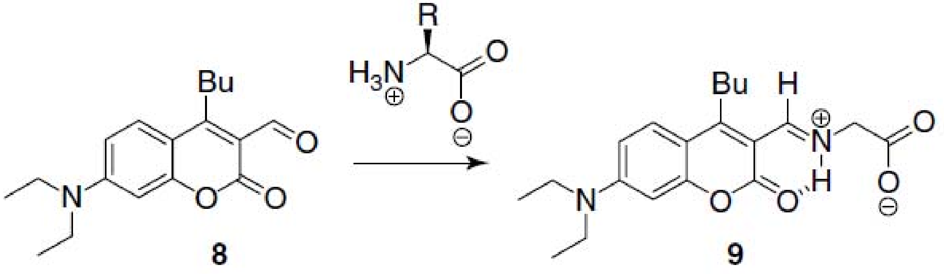
- It may be reversible (supramolecular)
- It has directionality (coordination geometry)
- Strong also in polar solvent and water (Energies in the 5-150 kcal/mol range)

L. Reversible covalent bond

Also covalent bond that forms in equilibrium reactions (K ~ 1) may be used as source of reversible interactions



boronic acid-diols



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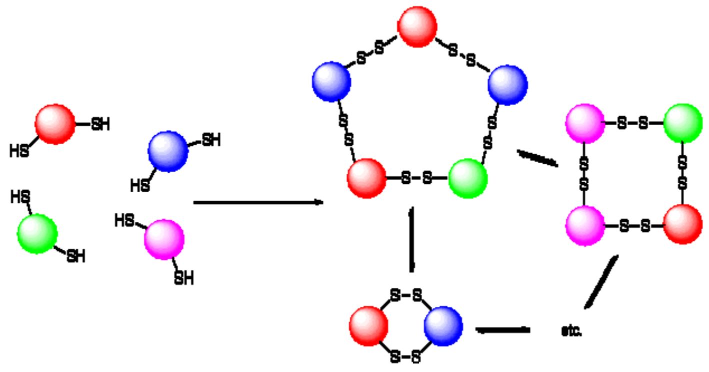
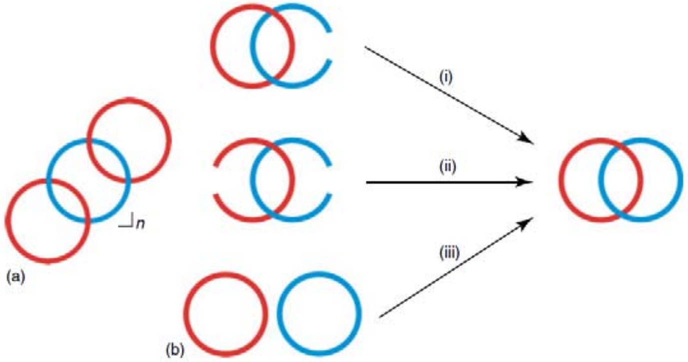


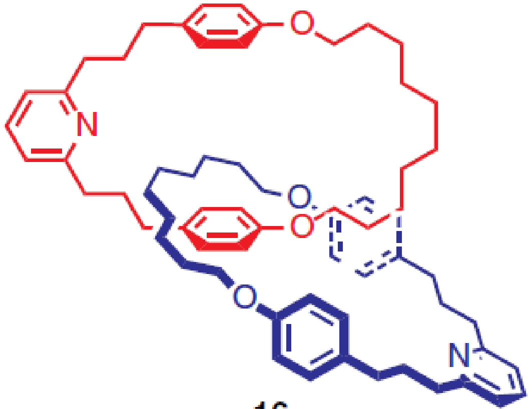
disulfides

M. Mechanical bond

Mechanically-interlocked molecules are made by two or more individual molecules that cannot dissociate becouse of steric or mechanical constraints. Such interaction is define mechanical bond.



Catenani



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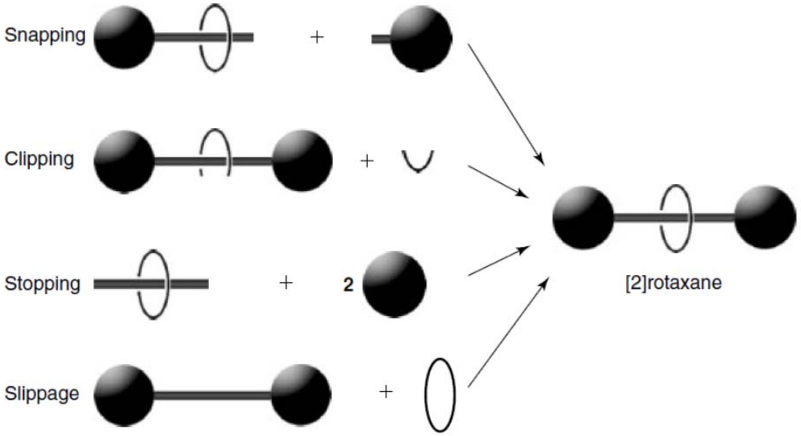

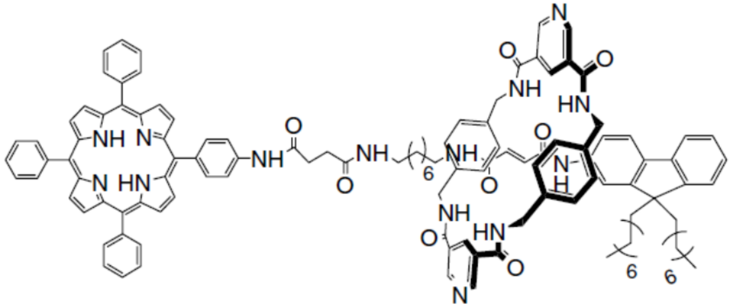

***E*-R3**

Rotaxani