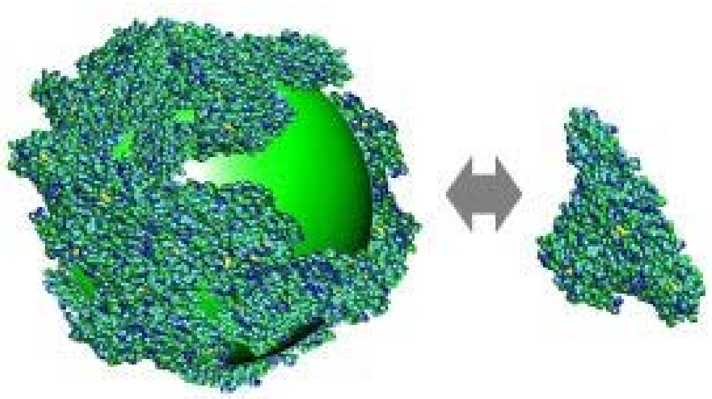
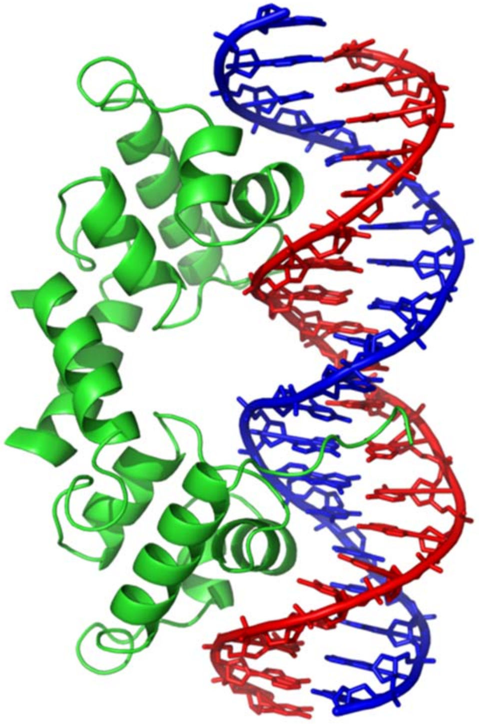
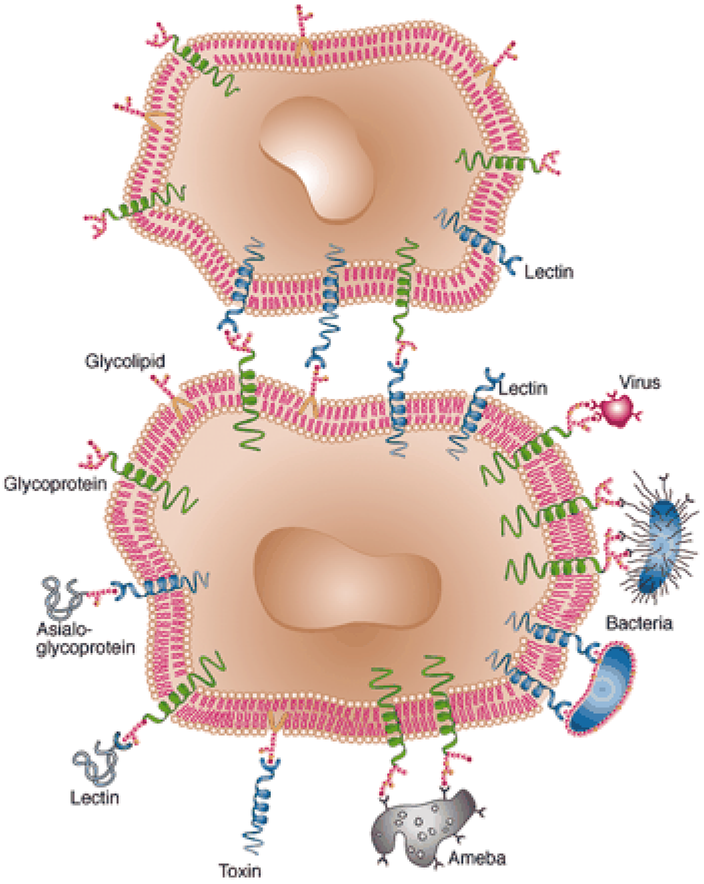
INTERAZIONI INTERMOLECOLARI



Protein corona: strato di proteine plasmatiche adsorbite sulla superficie di una nanoparticelle penetrata in un'organismo

INTERAZIONI INTERMOLECOLARI





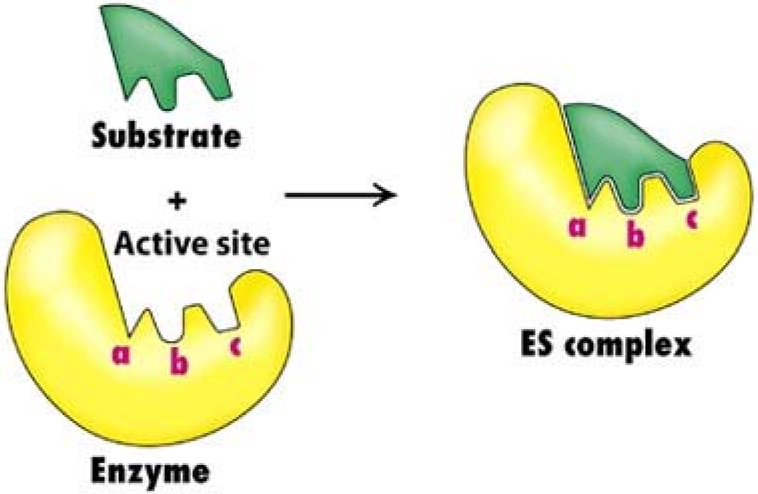
- ➢ Alta affinità
- ➢ Selettività

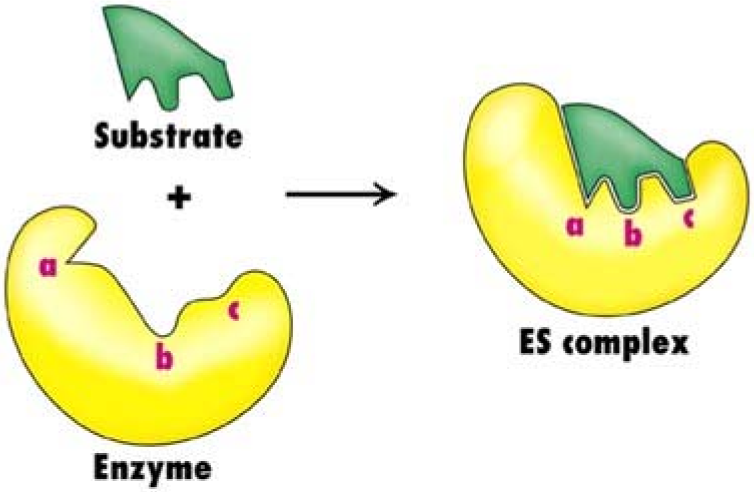
→ Quali ne sono le origini?

SELETTIVITA' IN NATURA

"Lock and key": agli inizi del secolo Emil Fischer introdusse il concetto di chiave e serratura per spiegare l'enorme selettività delle interazioni che avvengono tra le proteine e i loro substrati.

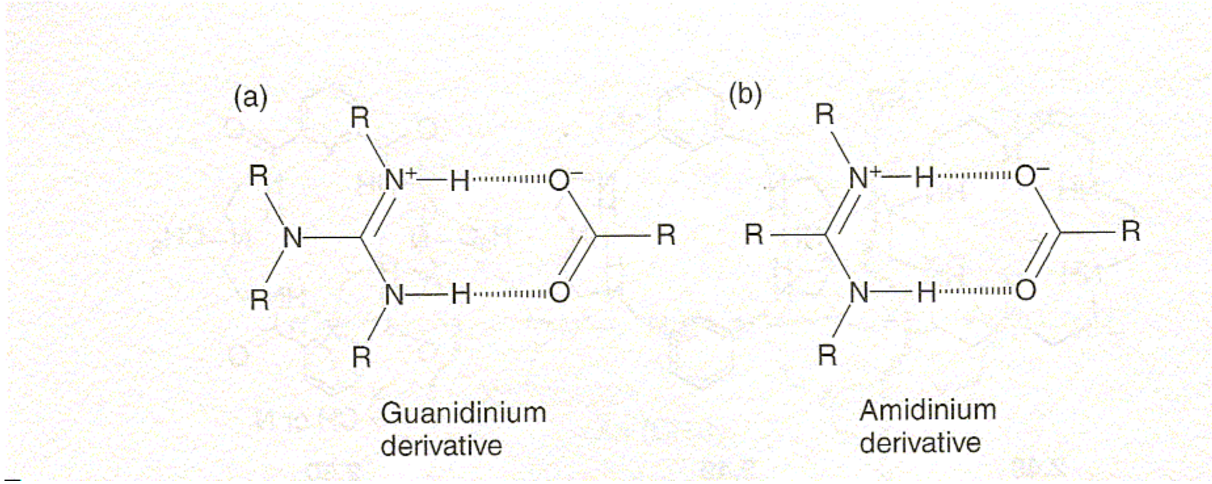
L'idea era che la proteina (**recettore**) potesse contenere una tasca di forma complementare a quella del substrato

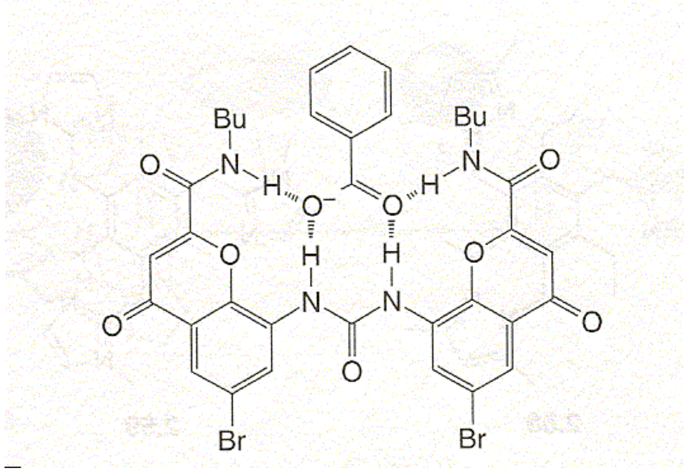


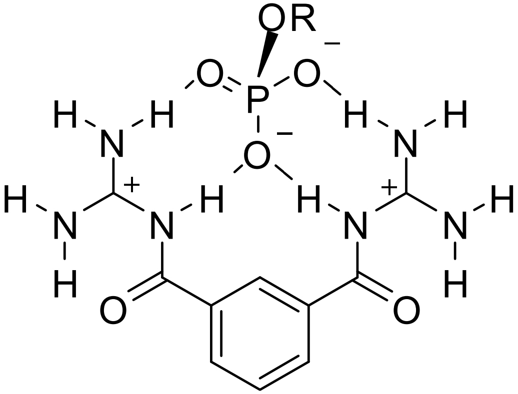


L'idea era geniale, ma non del tutto esatta: la proteina assume una forma complementare al substrato solo quando interagisce con esso (**induced fit**)

Complementarietà di forma/interazione







Energie dei legami covalenti

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**

Le interazioni covalenti sono caratterizzate da:

- Energie molto elevate
- Distanze piccole
- Forte dipendenza dall'orientazione

Interazioni non covalenti

● **idrofobiche**	**<10 kcal/mol**
● **elettrostatiche**	**~5 kcal/mol**
● **legame ad idrogeno**	**2-10 kcal/mol**
● **π-π aromatiche**	**0-10 kcal/mol**
● **van der Waals**	**0.1-1 kcal/mol**

Le interazioni non covalenti sono caratterizzate da:

- Energie piccole
- Poca dipendenza dall'orientazione (eccezione: legame a H)

La forze intermolecolare che agisce tra due molecole è la **somma** di tutte le forze che esercitano l'una con l'altra.

Quindi: molte interazioni che operano in maniera concertata possono portare ad energie simili a quelle di un legame covalente

A. Ion–Ion Interaction

$$\text{Energy} = (k \cdot z_1 \cdot z_2 \cdot e^2) / (\varepsilon \cdot r_{12})$$

Can be a very strong bond - even stronger than covalent bonds in some cases.

Can be an attractive or a repulsive force.

Non-directional force

Long range (1/r)

Highly dependant on the dielectric constant of the medium

B. Ion-Dipole Interaction

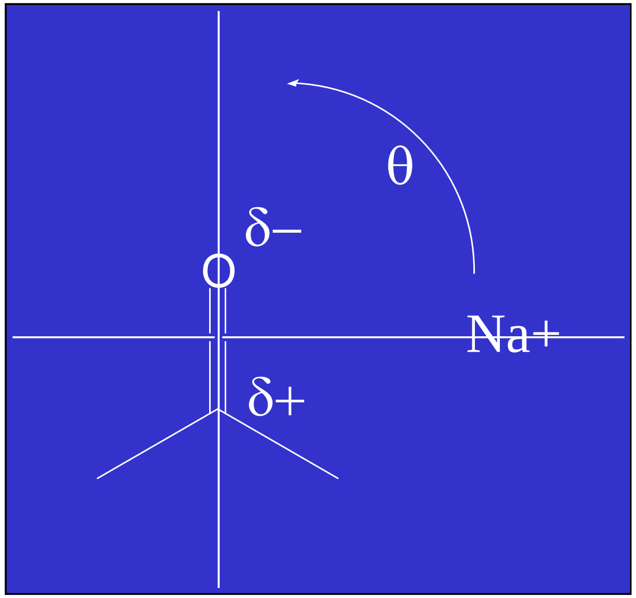
Little-directional forces

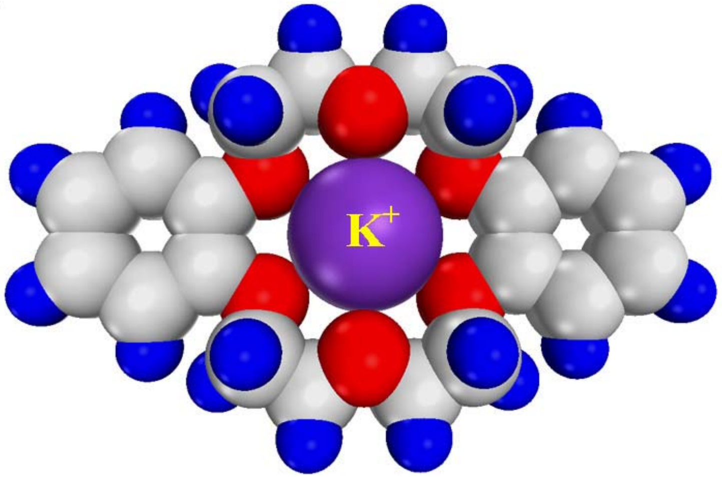
Can be attractive or repulsive

Medium range interactions ($1/r^2$)

Significantly weaker than ion-ion interactions

$$\text{Energy} = (k \cdot z_1 \cdot z_2 \cdot e^2) / (\varepsilon \cdot r_{12})$$

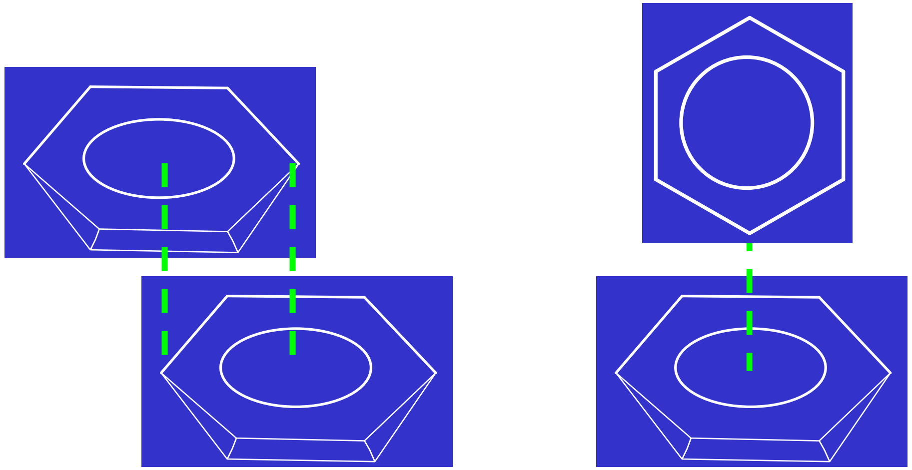


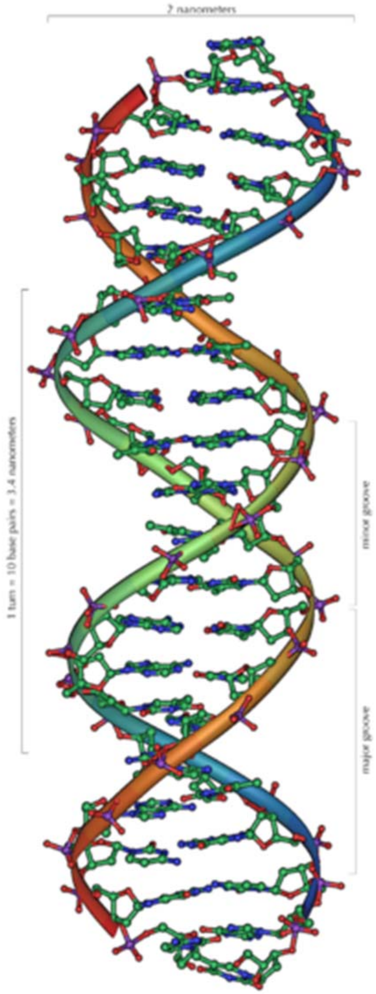


Example: crown ether complex with alkali metal ions

C. π-π interactions

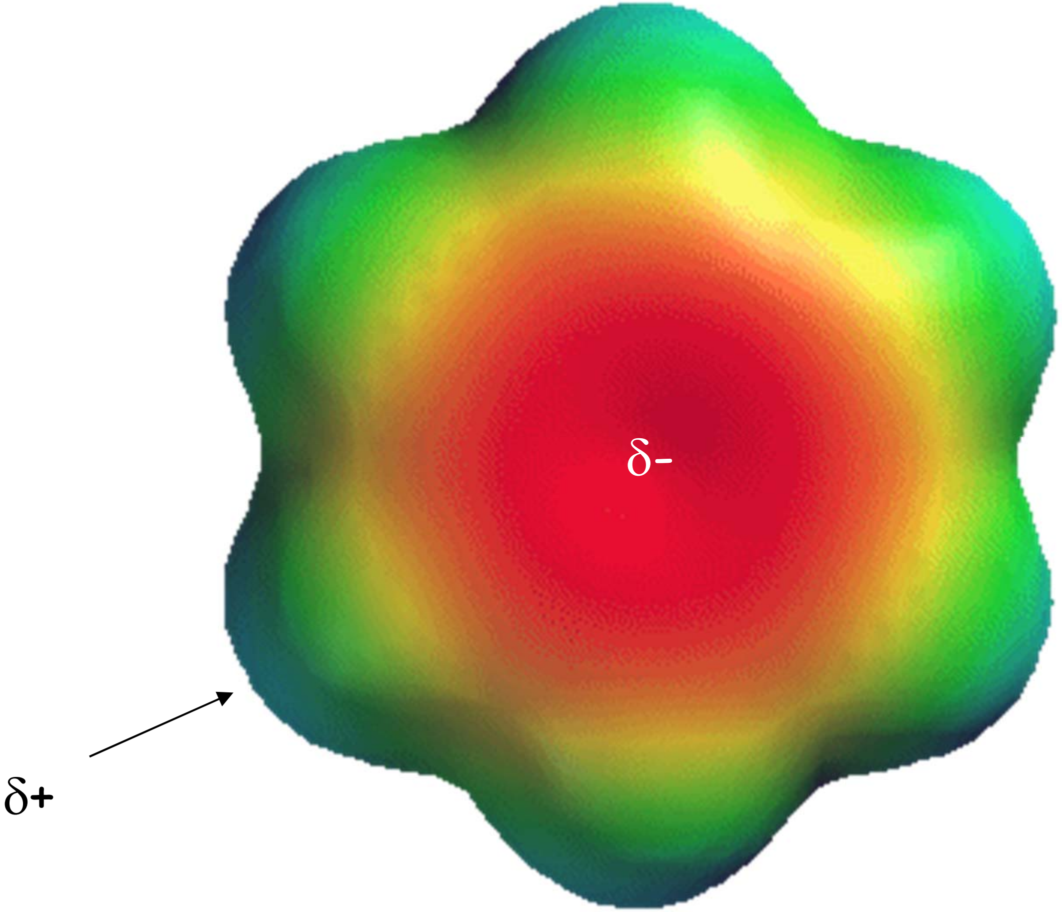
π – π stacking (0 – 10 kcal/mol). Weak electrostatic interaction between aromatic rings. There are two general types: face-to-face and edge-to-face:





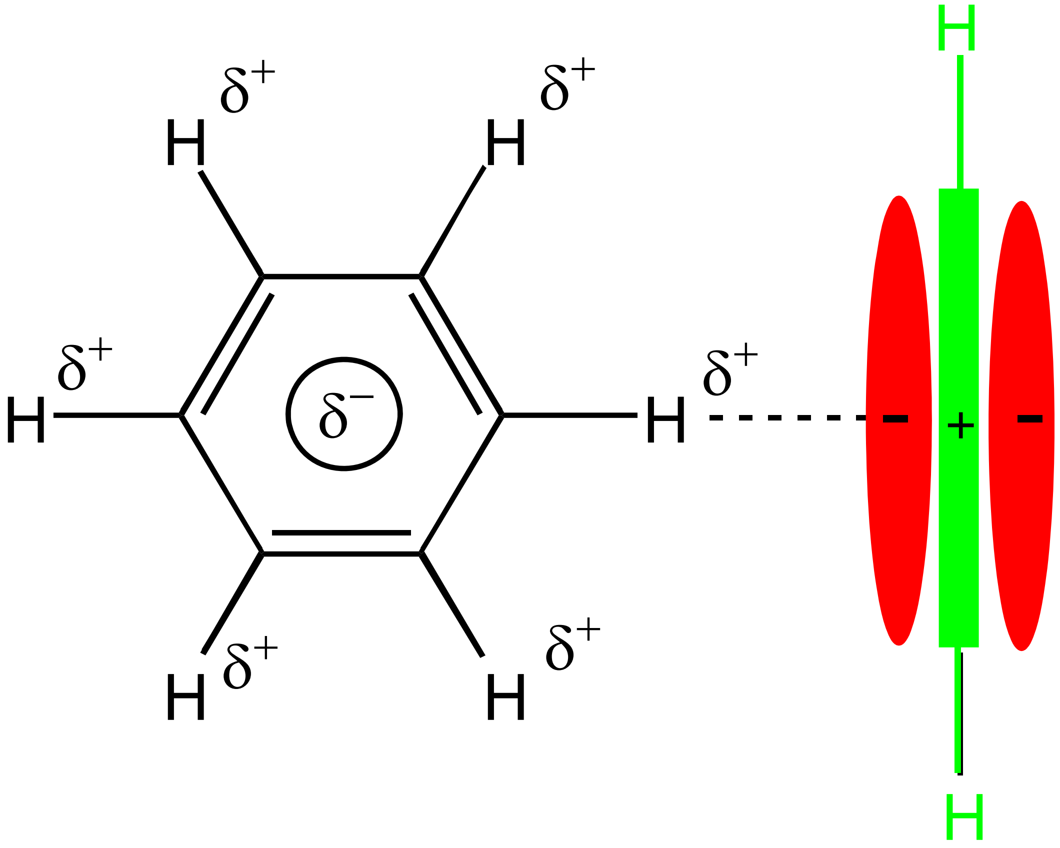
Face-to-face π-stacking interactions are responsible for the slippery feel of graphite. Similar π-stacking interactions help stabilize DNA double helix.

C. π-π interactions



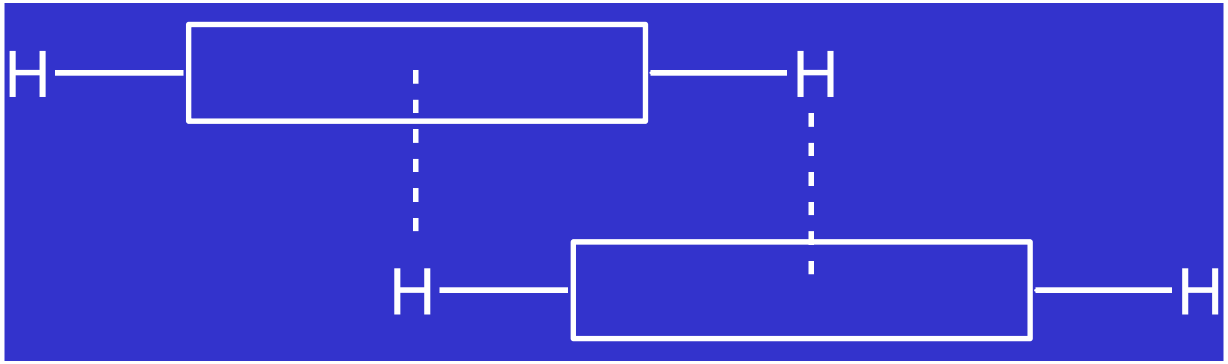
Distribution of electron density in benzene molecule

C. π-π interactions

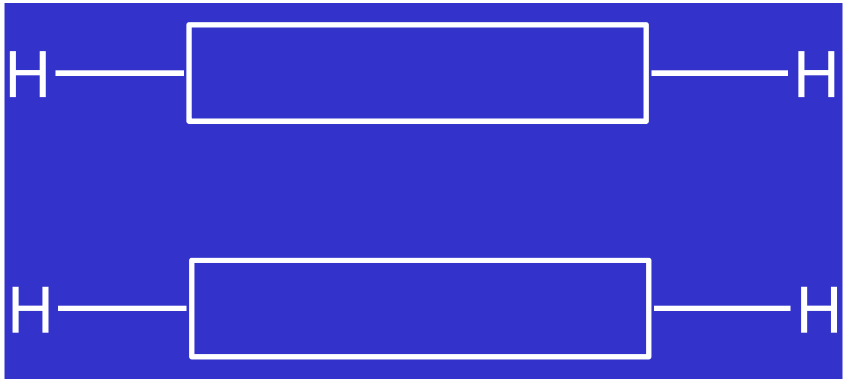


Edge-to-face

C. π-π interactions



Offset, face-to-face



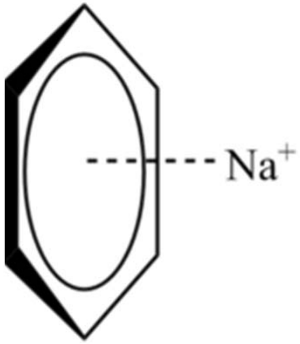
Face-to-face, not favorable

C. **Cation-π interactions**

It is an electrostatic interactions between the negative electronic surface of the aromatic ring and the positive cation.

It is different from the coordination of transition metal ions to aromatic rings, which is mainly convalent.

Not only metal ions but also ammonium cations.



D. **Dipole-Dipole Interactions**

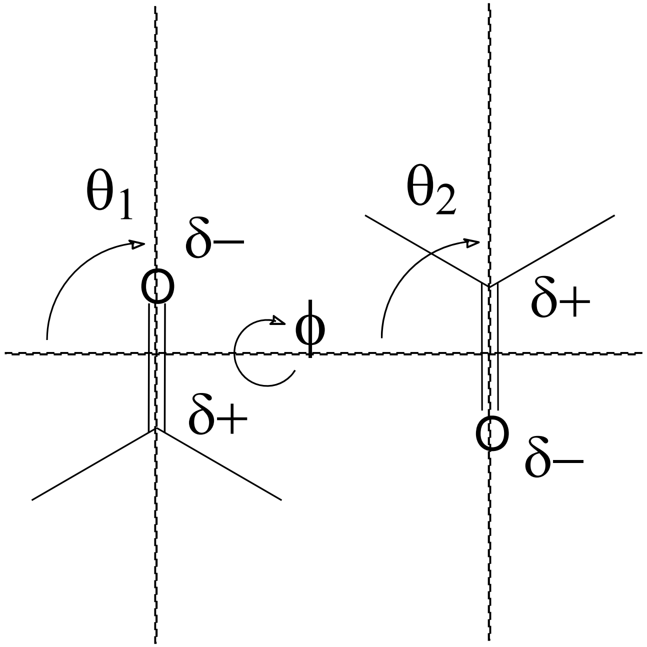
Can be attractive or repulsive

Short range ($1/r^3$)

Significantly weaker then ion-dipole interactions

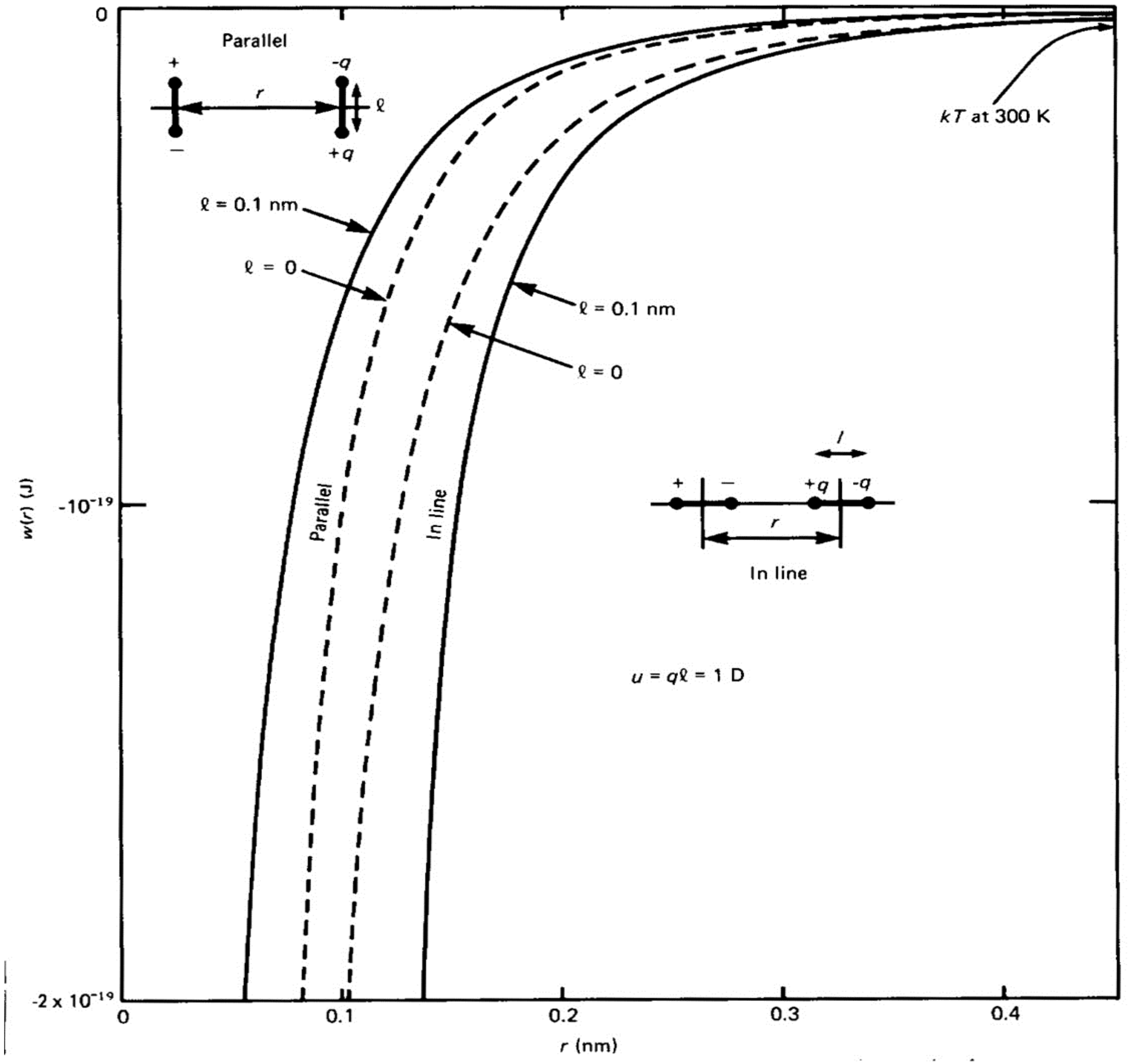
Occur between molecules that have permanent net dipoles (polar molecules).

For example, dipole-dipole interactions occur between SCl_2, PCl_3, and $(CH_3)_2CO$ molecules.



$$\text{Energy} = -(k \cdot u_1 \cdot u_2 / e \cdot r^3) \cdot ((2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2) \cdot \cos\phi)$$

D. **Dipole-Dipole Interactions**



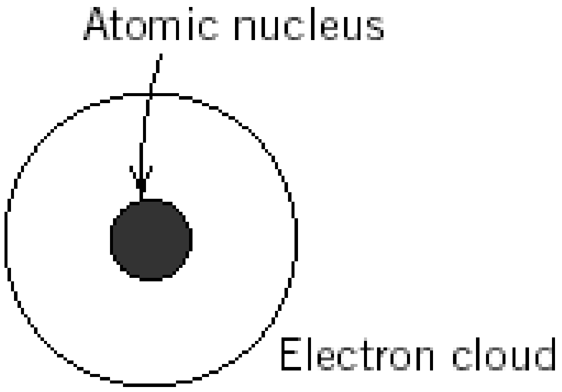
D. van der Waals Forces

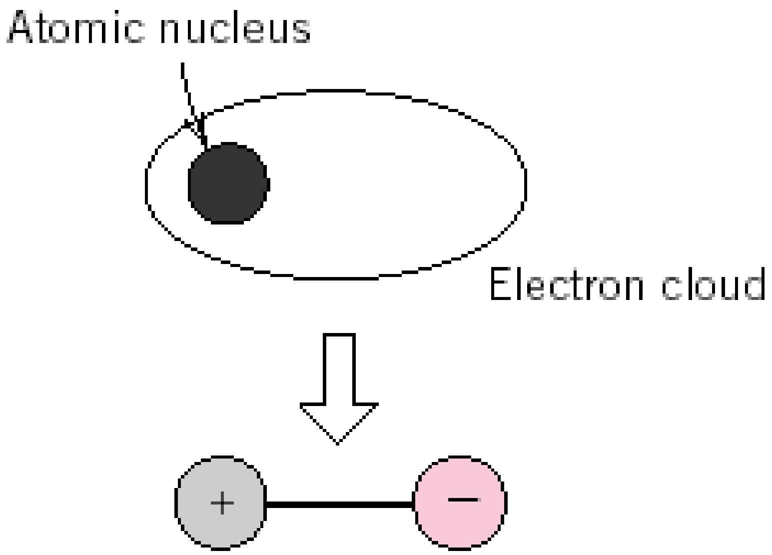
Often described as dispersion forces, i.e. instantaneous dipole interactions. More general definition includes ion-induced dipole, and dipole-induced dipole interactions.

Bond energy is very weak (0.01-0.5 kcal/mol)

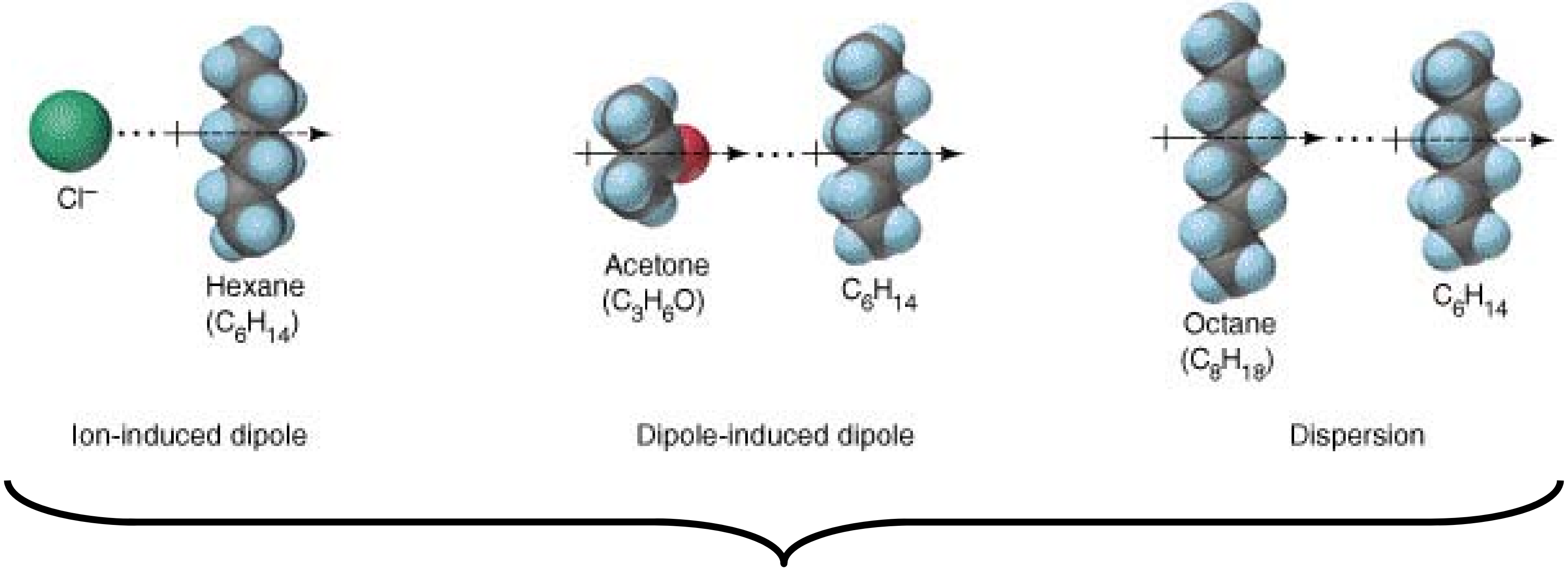
Exists between almost all atoms and molecules

Dispersion forces arise from fluctuating induced dipoles (due to instantaneous and short-lived vibrational distortions)



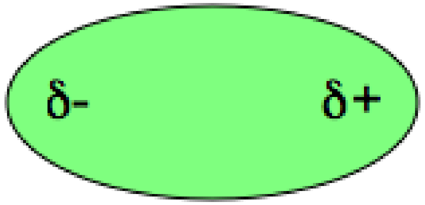


D. van der Waals Forces

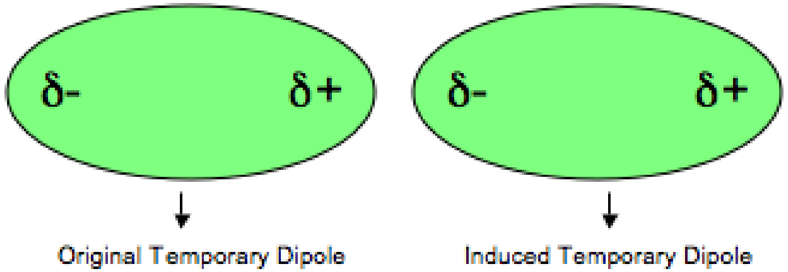


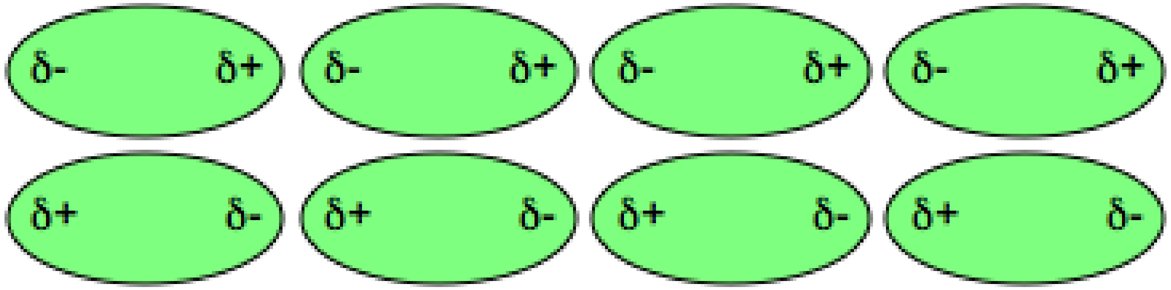
Three main types of VDW interactions

D1. **Dispersion Forces**



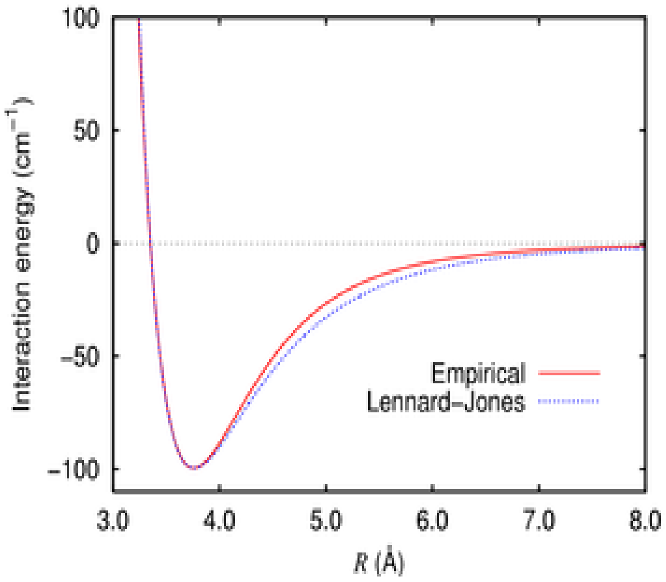
Arise from instantaneous polarization in molecules that induced polarization in the surrounding molecule causing an attractive interaction.





Array of molecules, which have a temporary dipole

D1. **Dispersion Forces**



Lennard-Jones equation

The London equation 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.

D1. **Dispersion Forces**

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

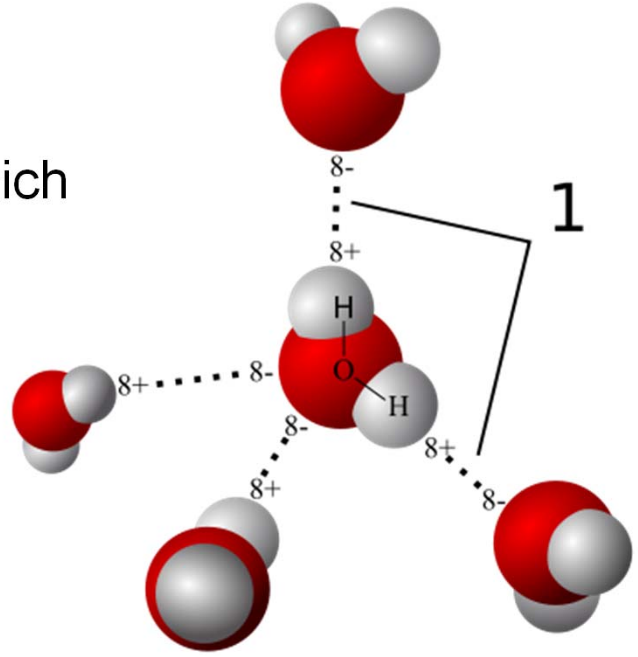
It is a special case of dipole-dipole interactions, which have a certain amount of covalent character and directionality

It can be significantly stronger than typical dipole-dipole interaction

Highly directional

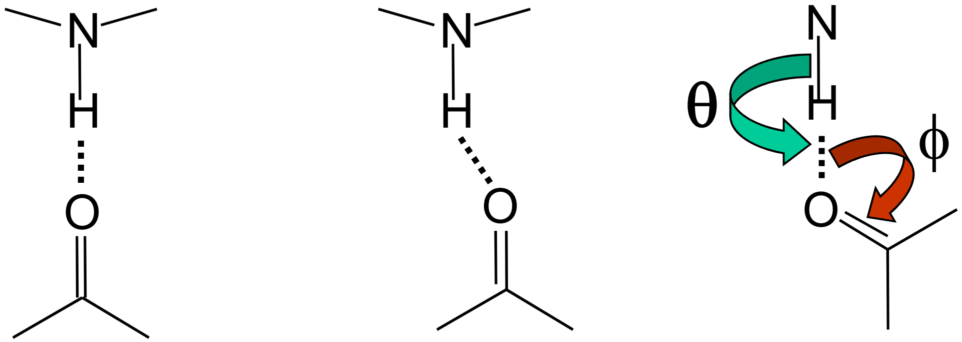
Short range (2.5-3.5 Å)

Forms when a hydrogen atom is positioned between two electronegative atoms, mainly O and N (but <u>QUESTIONED</u> C!) : **D-H---A**



E. Hydrogen bonding: geometry

Most stable



θ= D-H-A angle

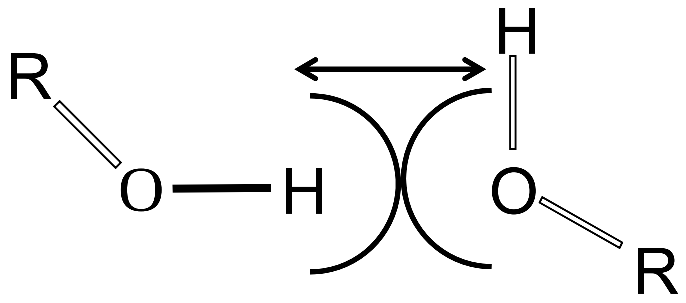
ϕ = H-A-X angle

$\theta=180^{o}$

$\phi=120^{o}$

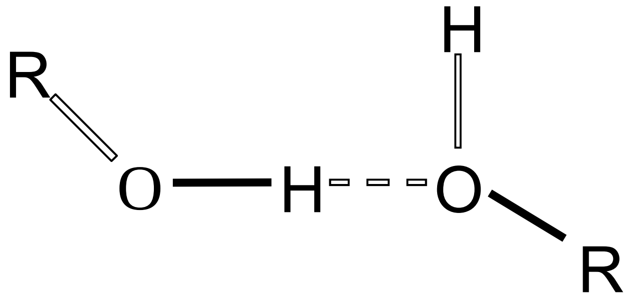
Ideal angles

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**

O-H---O bond

oriented toward the free electron lone pair on the acceptor oxygen

Water (2A/2D), alcohols (2A/D), ketones (2A), ethers (2A), carboxylic acids (4A/D), etc.

Responsible for the unusual properties of water (high melting & boiling point, high surface tension, etc.)

Typical distances and angles

Energy 2-10 kcal/mol

NH---O 1.80 to 2.00 Å

OH---O 1.60 to 1.80 Å

θ (D-H-A) 150 – 160°

ϕ (H-A-X) 120 – 130°

E. Hydrogen bonding: distance

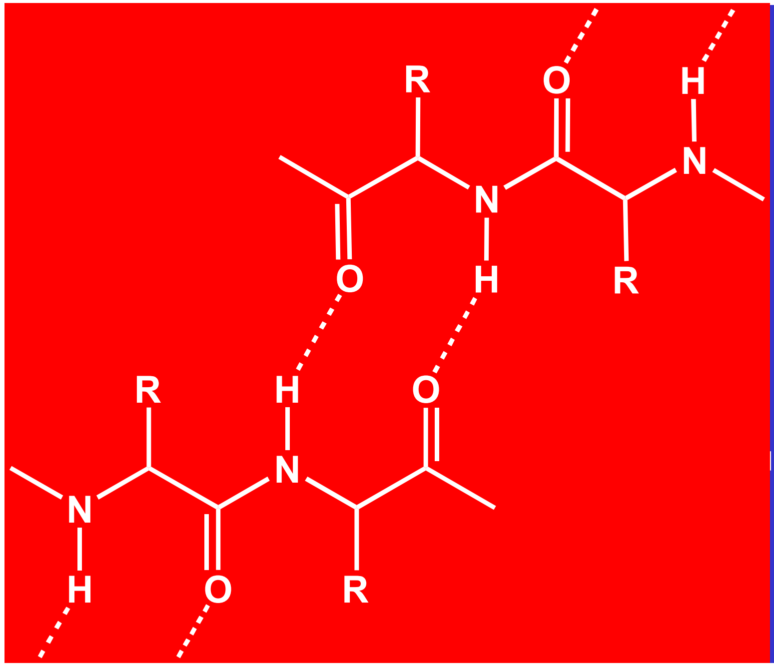
N-H---O bond
N-H---N bond

N-H---O distance is roughly 2.7Å

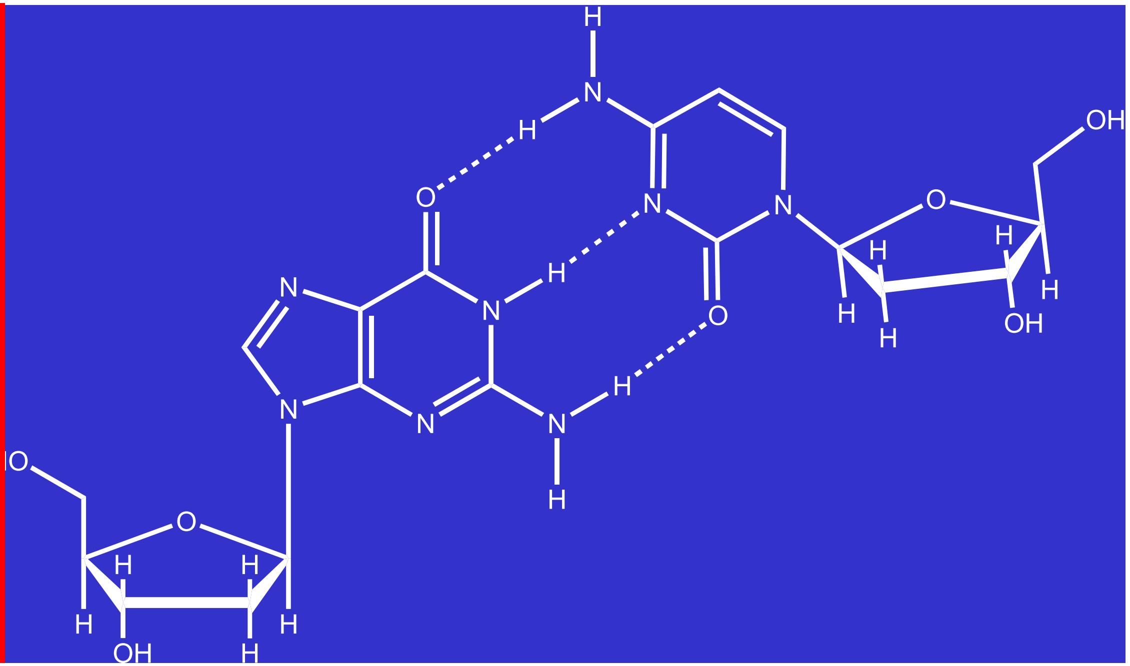
↔

Amines, amides, heterocycles, etc.

hydrogen bonding in proteins



hydrogen bonding in DNA



E. Hydrogen bonding: strenght

How much is a hydrogen bond worth?

experimental value is extremely variable: values in the literature from 0.1 to 10 kcal/mol

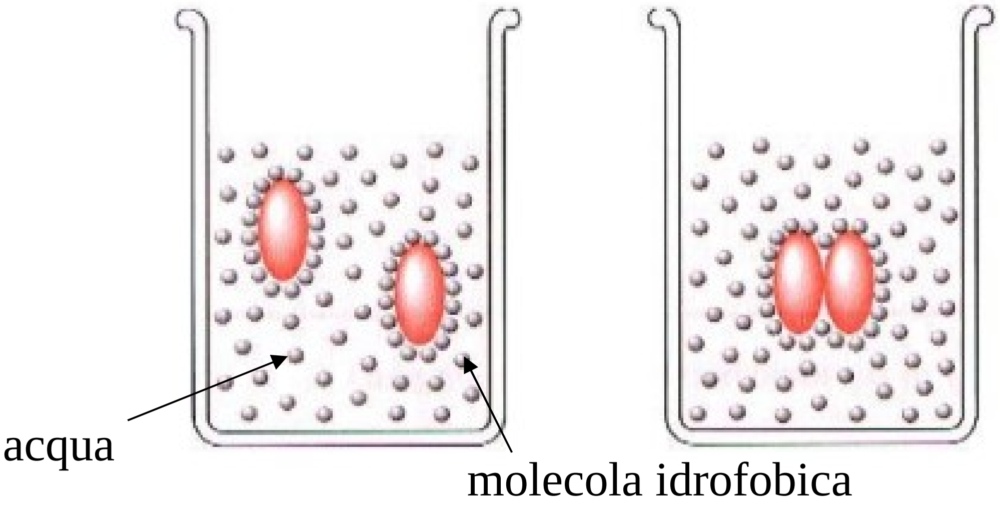
Strength of an H-bond is related to the **D-H---A** distance and the DHA angle. The shorter the distance between D & A the stronger the interaction. Ideally, DHA angle should be 180.

E. Hydrogen bonding: strenght

Proprietà dei legami d'idrogeno

	forte	moderato	debole
Interazione A-H…B	Principalmente covalente	principalmente elettrostatico	elettrostatico
Energia di legame (kJ mol^{-1})	60-120	16-60	<12
Lunghezza di legame (Å) H…B A…B	 1.2-1.5 2.2-2.5	 1.5-2.2 2.5-3.2	 2.2-3.2 3.2-4.0
Angoli di legame (°)	175-180	130-180	90-150
Shift vibraz. IR (cm^{-1})	25%	10-25%	<10%
Aumento del chemical shift, ^{1}H NMR (ppm)	14-22	<14	?
Esempi	Dimeri in fase gas con forti acidi/basi. Spugne protoniche. Complessi HF.	Acidi , alcoli, molecole biologiche.	Legami idrogeno con C-H e legami O-H…π

Interazione? Effetto idrofobico

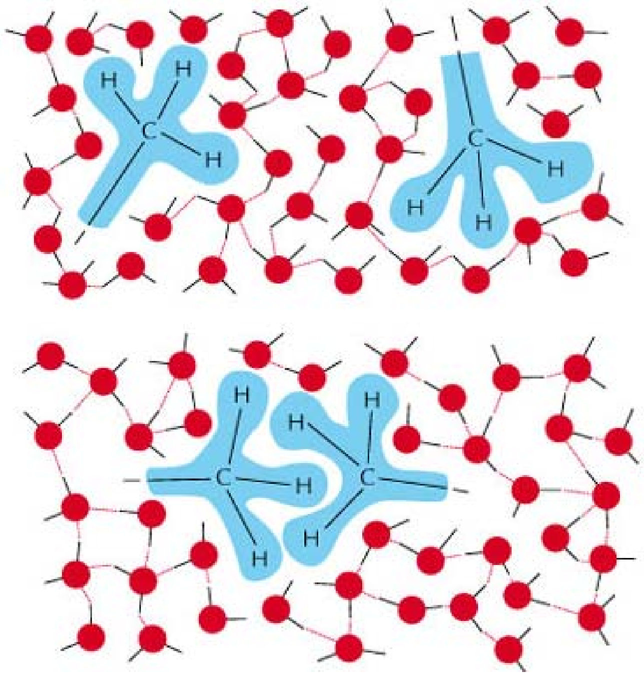


Molecole non polari, se disperse in acqua, tendono a formare dimeri ed aggregati non covalenti. L'interazione che tiene insieme tali entità si chiama **effetto idrofobico.**

La natura dell'effetto idrofobico è essenzialmente **entropica**. Infatti l'interazione tra due molecole poco polari (es. idrocarburi) è basata solo sulle deboli interazioni di Van der Waals. Al contrario, l'interazione tra acqua e una molecola poco polare è basata su interazioni dipolo-dipolo indotto, generalmente più forti.

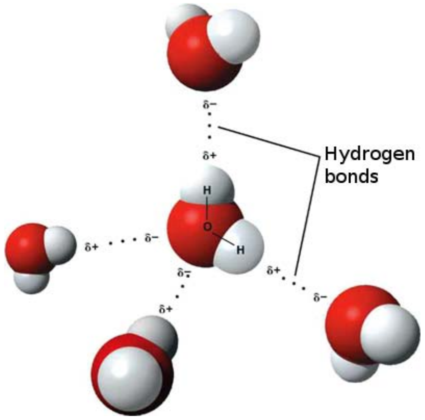
Dal punto di vista energetico, l'interazione tra le molecole d'acqua ed un soluto non polare dovrebbe quindi essere positiva.

Effetto idrofobico



n-butano in H_2O

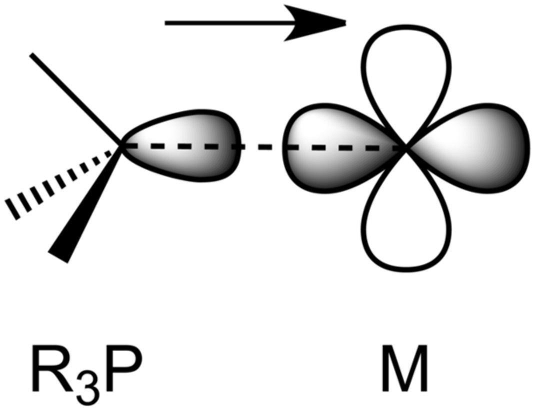
$$\begin{cases} \Delta H = -4.3 \text{ kJ/mol} \\ -T\Delta S = +28.7 \text{ kJ/mol} \end{cases}$$

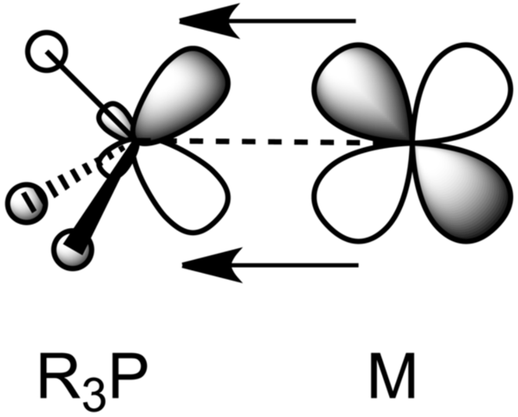


L’inserimento di una molecola non polare nell’acqua provoca però un’**interruzione** del network di legami a idrogeno. Le molecole d’acqua sono costrette a disporsi come una **gabbia** introno al soluto, e perdono libertà di movimento.

L’associarsi di due molecole idrofobiche porta ad una diminuzione del numero di molecole d’acqua intrappolate negli strati esterni: l’entropia totale aumenta anche se l’entalpia diminuisce.

Coordination bond





Between a metal (or metal ion) with empty orbitals and a atom (or molecule) with low energy orbitals.

It involves multiple orbitals overlapping, as retrodonation.

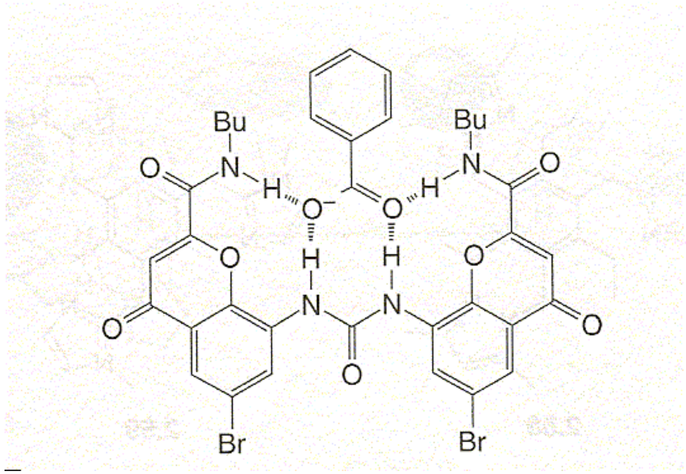
It has also a ionic charachter

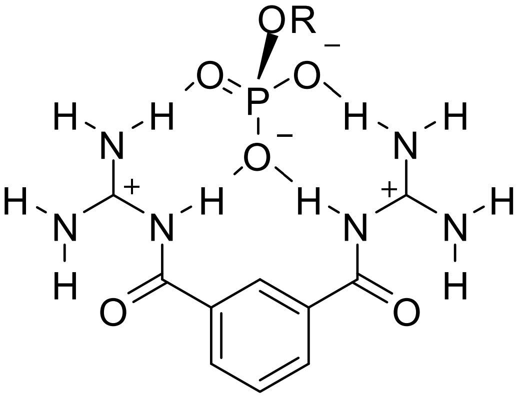
Energies in the 5-150 kcal/mol range

They can be either kinetically labile or inert

Interazioni non covalenti

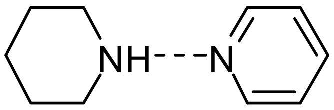
idrofobiche	**<10 kcal/mol**
elettrostatiche	**~5 kcal/mol**
legame ad idrogeno	**2-10 kcal/mol**
π-π aromatiche	**0-10 kcal/mol**
van der Waals	**0.1-1 kcal/mol**





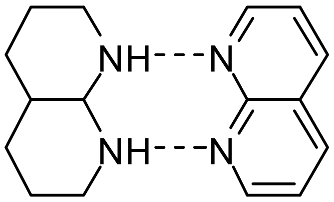
Additivity (?)

In order to obtain a strong recognition between the host and the guest using weak non-covalent interaction, multiple interactions must be used.



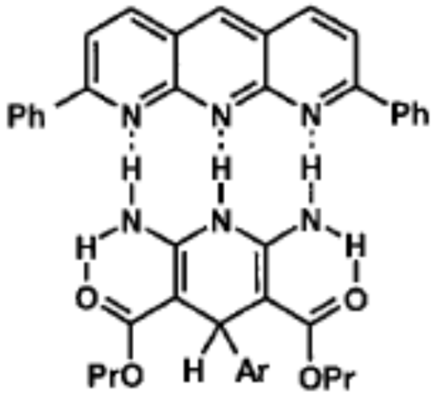
$K_{ass} = 25\ M^{-1}$

$\Delta G = -7.9\ kJ\ mol^{-1}$



$K_{ass} = 6.4 \times 10^{3}\ M^{-1}$

$\Delta G = -21.6\ kJ\ mol^{-1}$

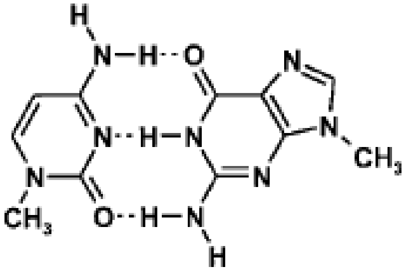


$K_{ass} = 1.5 \times 10^{6}\ M^{-1}$

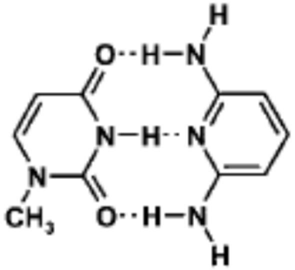
$\Delta G = -35.3\ kJ\ mol^{-1}$

Additivity (?)

In some cases however, binding constant are much lower: H-bond acceptors and donors are also charge centers!



$K_{ass} = 10^4\ M^{-1}$



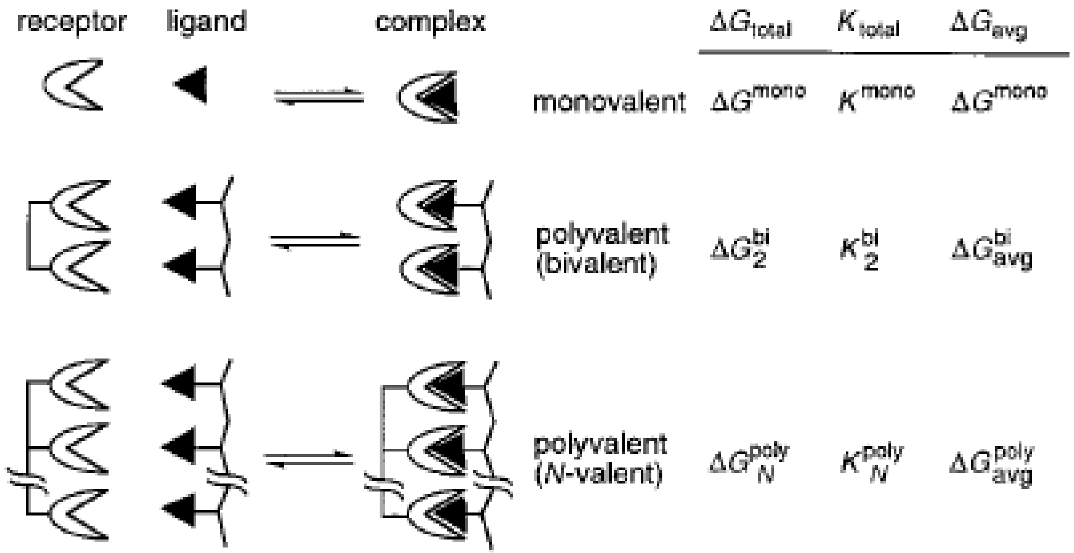
$K_{ass} = 10^2\ M^{-1}$

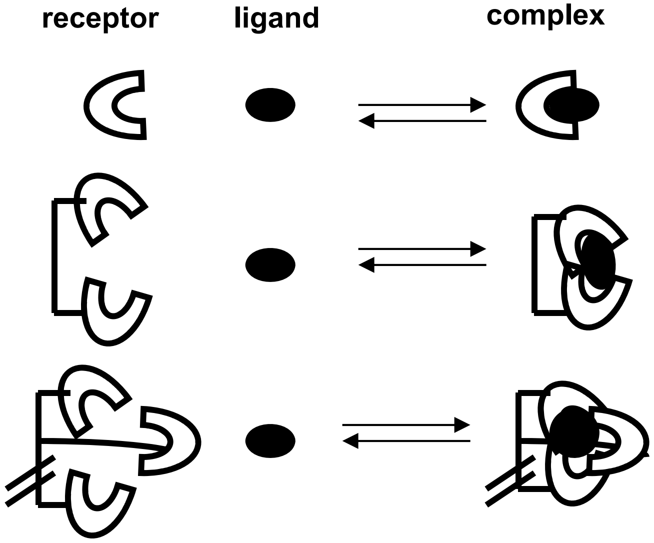
100 times less than expected

10000 times less than expected

Multiple interactions in binding: definitions

(reference: *Angew. Chem. Int. Ed.* **1998**, *37*, 2754 – 2794 **)**

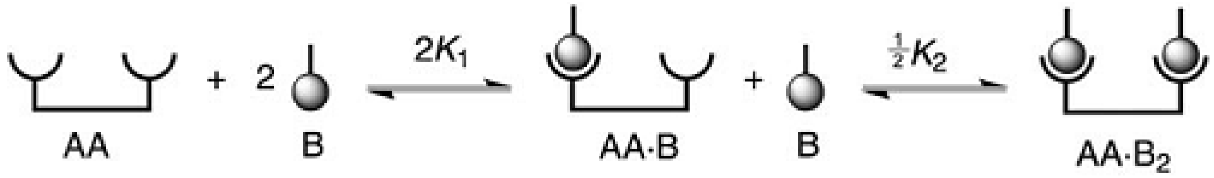




multiple binding sites: receptor interacts with a multivalent ligand

multiple binding sites: receptor interacts with a monovalent ligand

Multiple interactions in binding: statistical corrections



Statistical correction:

B can choose different binding sites,

apparent increase of binding constant

Measuring cooperativity: a value

$$\Delta G_N^{poly} = \alpha \sum_1^n \Delta G^{mono} = \alpha N \Delta G^{mono}$$

$$\Delta G^{avg} = \Delta G_N^{poly} / N = \alpha \Delta G^{mono}$$

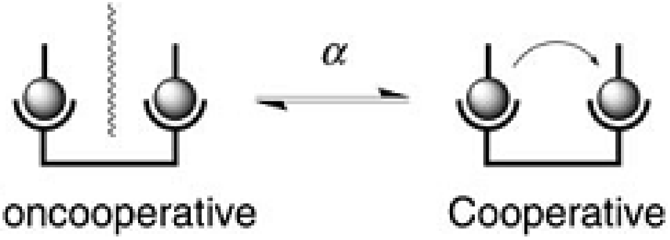
$$\alpha = \Delta G^{avg} / \Delta G^{mono}$$

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

$$K_N^{poly} = (K^{avg})^N = (K^{mono})^{\alpha N}$$

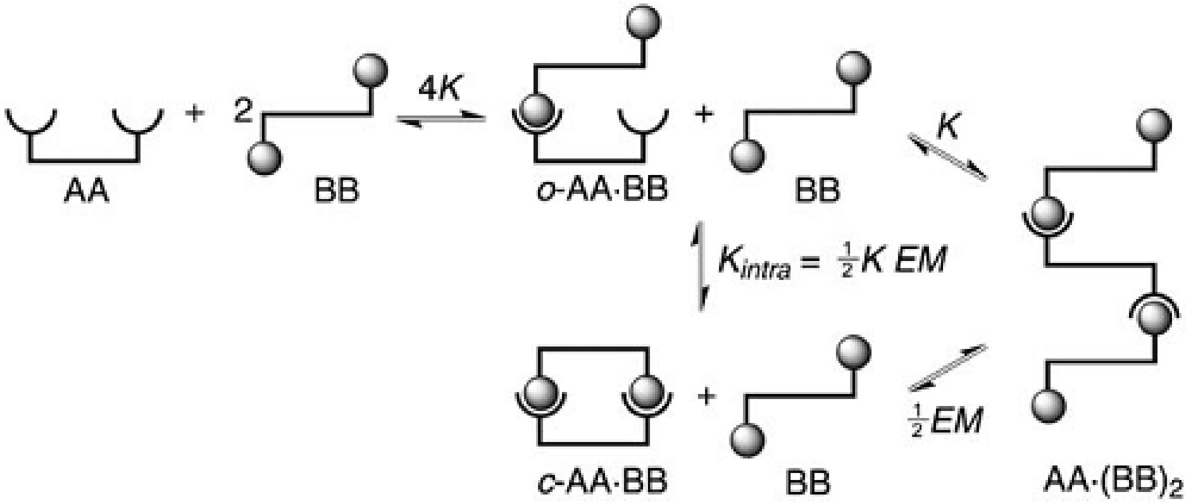
$$\alpha = \frac{\lg(K_N^{poly})}{\lg(K^{mono})^N}$$

α ?



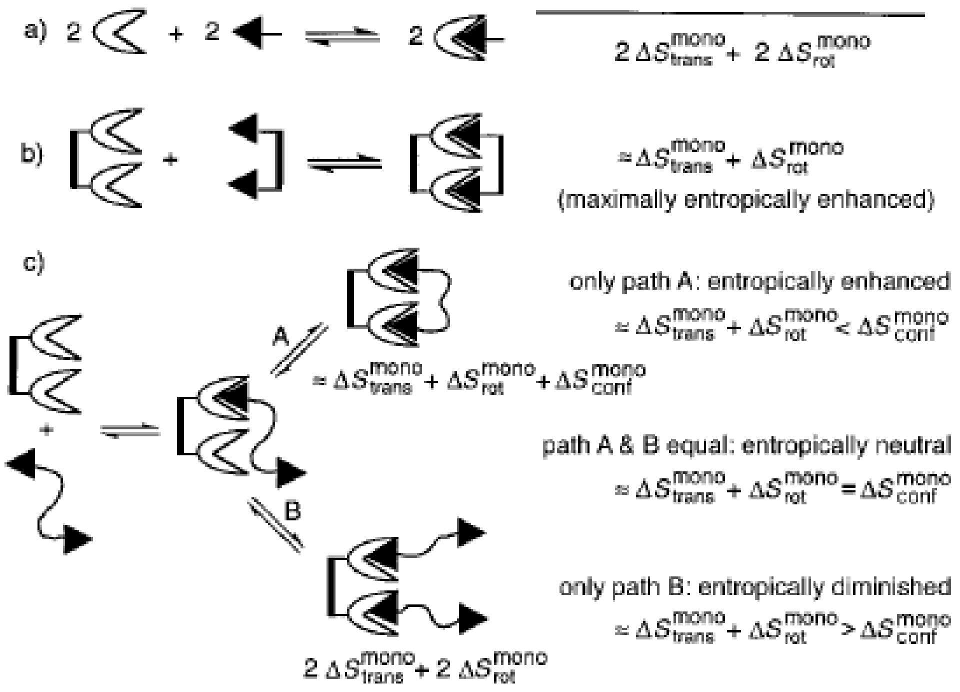
George M. Whitesides et al. Angew. Chem. Int. Ed. 1998, 37, 2754.

Multivalency: the chelate effect

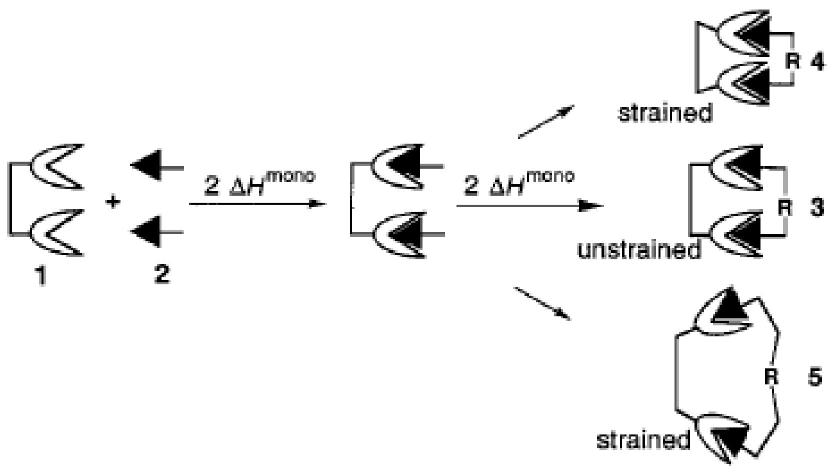


EM = effective molarity, accounts for the ease of an intramolecular process

ErcolaniG. et al. Angew. Chem. Int. Ed.2011, 50,1762.



Entropy



Enthalpy

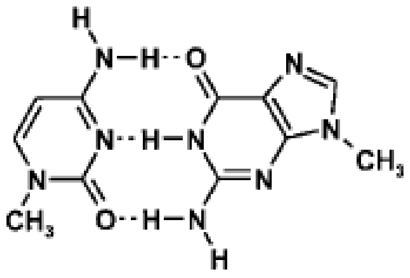
Positive cooperativity is due to entropic and enthalpic contributions to binding.

Entropy: loss of motion of the molecule, including internal rotation and vibrations (contribution already paid for in connecting together the recognition elements)

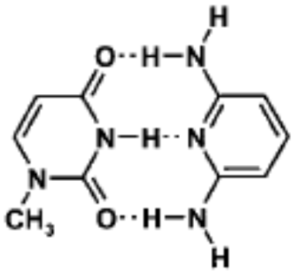
Enthalpy: secondary functional groups interactions, conformational changes, polarization of the interacting groups

Additivity (?)

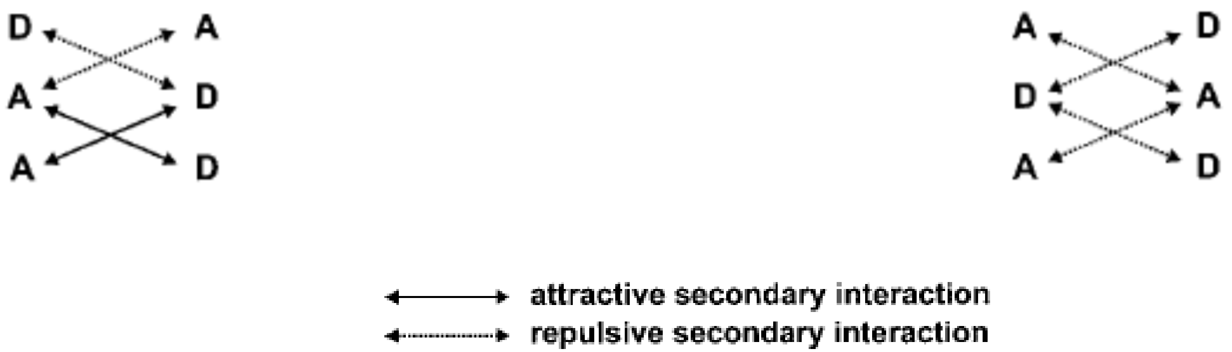
In some cases however, binding constant are much lower: H-bond acceptors and donors are also charge centers!



$K_{ass} = 10^4\ M^{-1}$

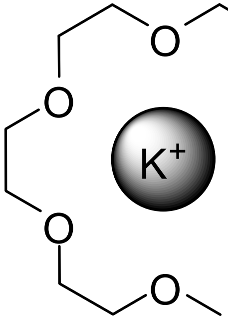


$K_{ass} = 10^2\ M^{-1}$



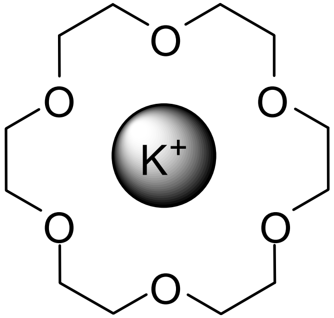
Each H-bond contributes with 7.8 kJ mol^{-1}, each secondary interaction with ± 2.9 kJ mol^{-1}

Crown eters: preorganization



Log K (MeOH, 25 °C) = 2.0

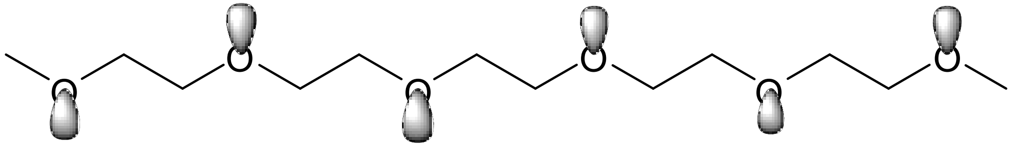
ΔH = -36.4 KJ/mol
ΔS = -84 J/mol

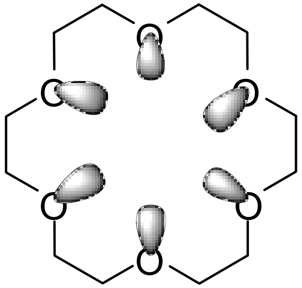


Log K (MeOH, 25 °C) = 6.1

ΔH = -56.0 KJ/mol
ΔS = -71 J/mol

Its is much more an enthalpic than entropic effect!

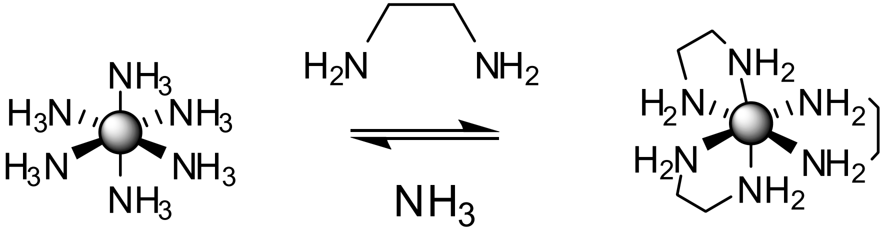




- Repulsione tra i siti di legame (diminuita dalla complessazione)
- Desolvatazione (resa meno “costosa” dalla struttura ciclica)

Chelate effect

Host with multiple binding sites results in more stable complexes than multiple unidentate ligand (cooperativity)



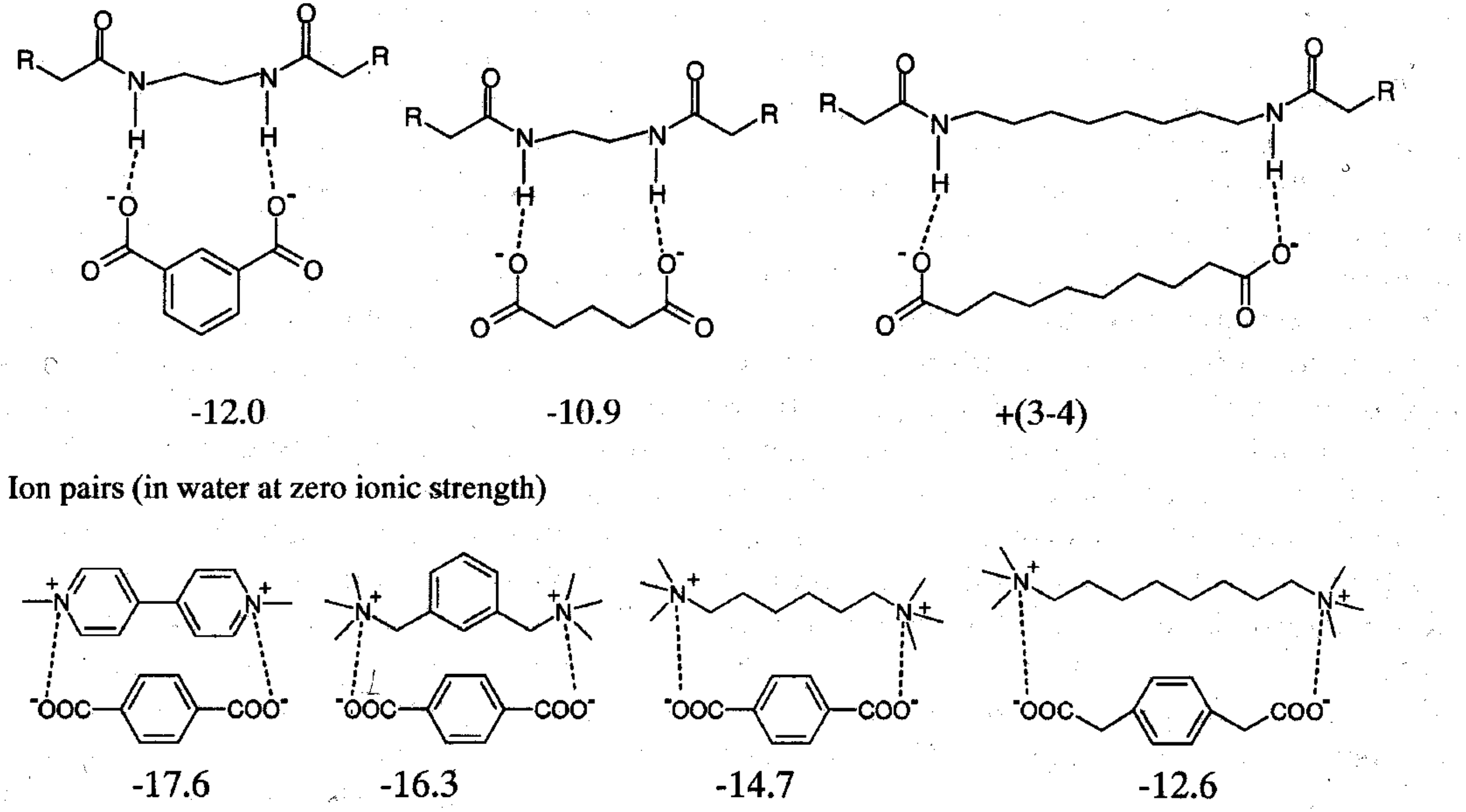
M = Ni^{2+}
log K = 8.76

ΔH° = -29 kJ mol^{-1}
-TΔS° = -25 kJ mol^{-1}

1. Greater basicity of primary amines
2. Weaker solvatation of primary amines
3. Decresed repulsive interaction between binding sites
4. Steric interactions and strain in the complex

1. Conformational changes
2. Greater number of free species

Chelate effect



Energie di associazione (ΔG in kJ mol^{-1}) tra molecole in seguito alla formazione di legami ad idrogeno o coppie ioniche in funzione del numero di legami singoli che separano i siti di interazione.

(vedi: Angew. Chem. Int. Ed Eng. 1998, 37, 826; Chem. Eur. J. 1999, 5, 1284)

Degree of cooperativity

$\alpha>1$: **positive cooperativity (synergistic)**

$\alpha=1$: **noncooperative (additive)**

$\alpha<1$: **negative cooperativity (interfering)**

$\Big\}$ **in all cases overall binding constants increase!**

when talking about cooperativity (in binding) we often consider $\alpha>1$ as the typical situation.

Don't be fooled by the overall strength of binding which is easily larger:

On the contrary this is a rare situation!

most of the available examples are characterized by $\alpha<1$

$$\Delta G_N^{poly} = \Delta G^{mono} - RT\ \ln(\beta)$$

$$\beta = K_N^{poly} / K^{mono}$$

A real case

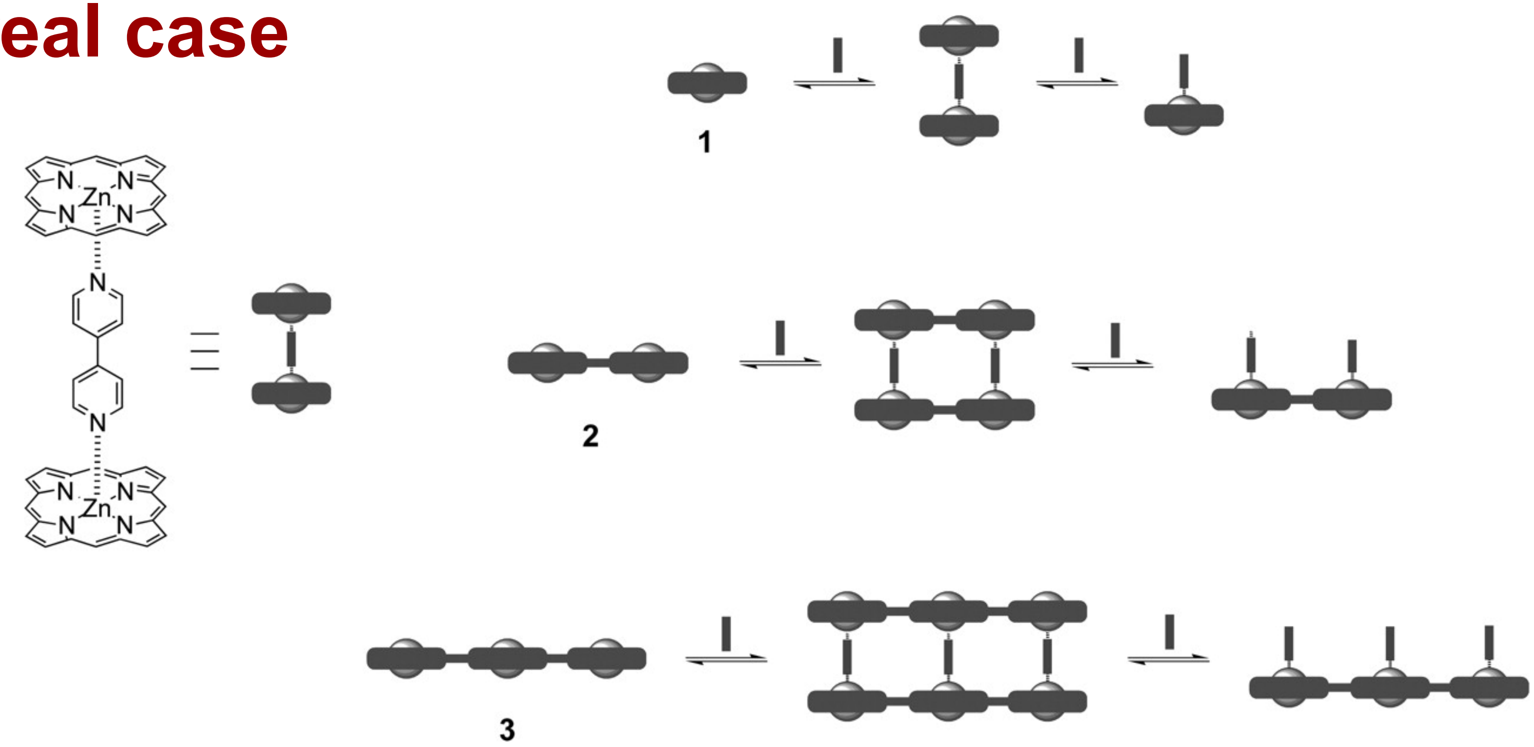


Table 1. Stability constants of the porphyrin ladder and enthalpy per interaction

Porphyrin	K_m,* M^{-1}	$\log K_{Open}$†	$\log K_{ladder}$†	ΔG_{ladder},† $kJ \cdot mol^{-1}$	ΔH/interaction,‡ $kJ \cdot mol^{-1}$
1a	1,660	3.6 ± 0.1	6.3 ± 0.1	−35.2 ± 0.6	−33.4 ± 3.3
1b	3,750	4.1 ± 0.1	7.1 ± 0.3	−39.8 ± 1.7	−36.2 ± 1.2
2	2,120	7.5 ± 0.1	12.3 ± 0.1	−68.8 ± 0.8	−34.0 ± 3.1
3	2,620	12.1 ± 0.4	19.9 ± 0.6	−111.2 ± 3.4	−35.9 ± 3.1

$\alpha = 0.87$

$\alpha = 0.92$

Errors are quoted at 95% of confidence.

*Determined by UV/V is titration.

†Determined by NMR titration. K_{open} and K_{ladder} are the overall stability constants for formation of the ladder and the open complex from free porphyrin and bipyridine.

‡Determined by ITC.

C.A. Hunter, S. Thomas, PNAS 2006, 103, 3034-3038