

# Lecture 11

## Physics of Biomolecules:

### Forces of interactions

# Molecular biophysics

- Studies biomolecules such as proteins, DNA, lipids, carbohydrates and ions and their interactions
- To understand intra- and inter-molecular physical interactions which define structural architecture of these molecules and their functional properties
- Building blocks – atoms:
  - Carbohydrates and lipids – H, C, O
  - Proteins / nucleic acids – H, C, O, N, S/P
  - Important metal ions: Ca, K, Na, Mg,
  - and traces of Fe, Cu, Zn, Co, Mo
  - Water molecules

# Molecular Forces

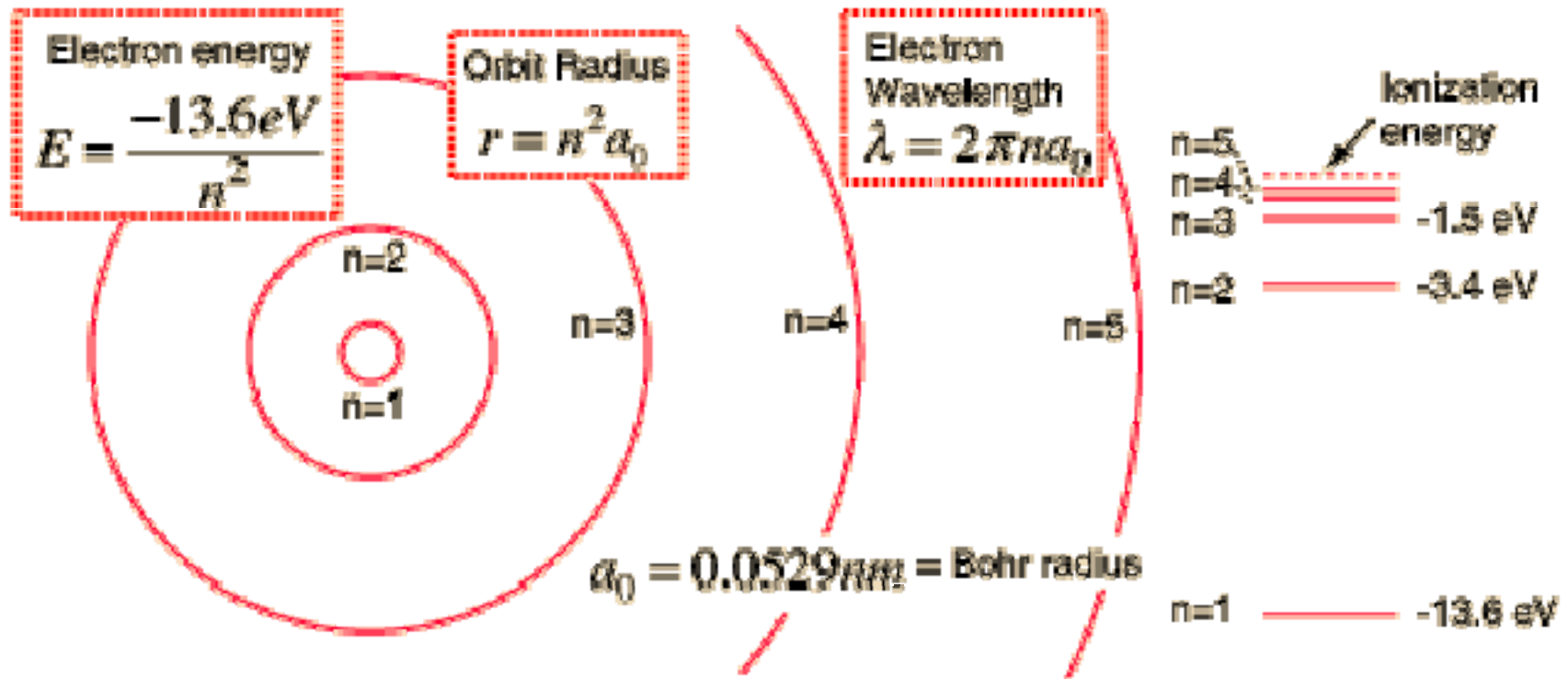
- To understand the structure of biomolecules we need to know the forces which bind atoms together in biomolecules
- Large biomolecules have
  - a) primary structure – strong forces
  - b) secondary, and higher structures – weak forces
- Energetically a molecule is a stable arrangement of two or more atoms
- When the molecule is stable - the energy of a combined system (molecule) is less than the sum energy of separate atoms.
- To break the bonds between the atoms – requires energy
- In opposite, when atoms come together to form a molecule the energy is released.
- The energy in strong bonds is around few electron-volts ( $1\text{eV}=1.6\times 10^{-19}\text{J}$ )
- Weak forces  $\sim 0.1\text{ eV}$

Atom: Bohr's model is based on two postulates:

- Electrons do not lose energy via radiation while they are in a discrete set of orbits around the nucleus (allowed orbits)
- Electron loses or gains energy when it moves to another orbit, the energy lost equals to the energy difference of the initial and final orbits of the transition

$$\Delta E = E_{final} - E_{initial} = h\nu$$

# Hydrogen Energy Levels Bohr's model



$a_0$  Bohr radius is the radius of the smallest orbit,  $n=1$

# Quantum mechanics: Schrodinger Equation

$$\hat{H}\psi = E\psi$$

**Schrödinger equation** is a partial differential equation that describes the quantum state of some physical system. When the Hamiltonian operator ( $H$ ) acts on the wavefunction  $\Psi$ , the result **might** be proportional to the same wavefunction  $\Psi$ . If it **is**, then  $\Psi$  is a stationary state, and the proportionality constant,  $E$ , is the energy of the state  $\Psi$ .

In relation to atoms and molecules  $\Psi$  wavefunction is a stationary state (also called "orbitals", as atomic orbitals or molecular orbitals, which describe the probability to find electron in space near the nucleus.

$$\psi(r, \theta, \varphi) = R(r)P(\theta)F(\varphi)$$

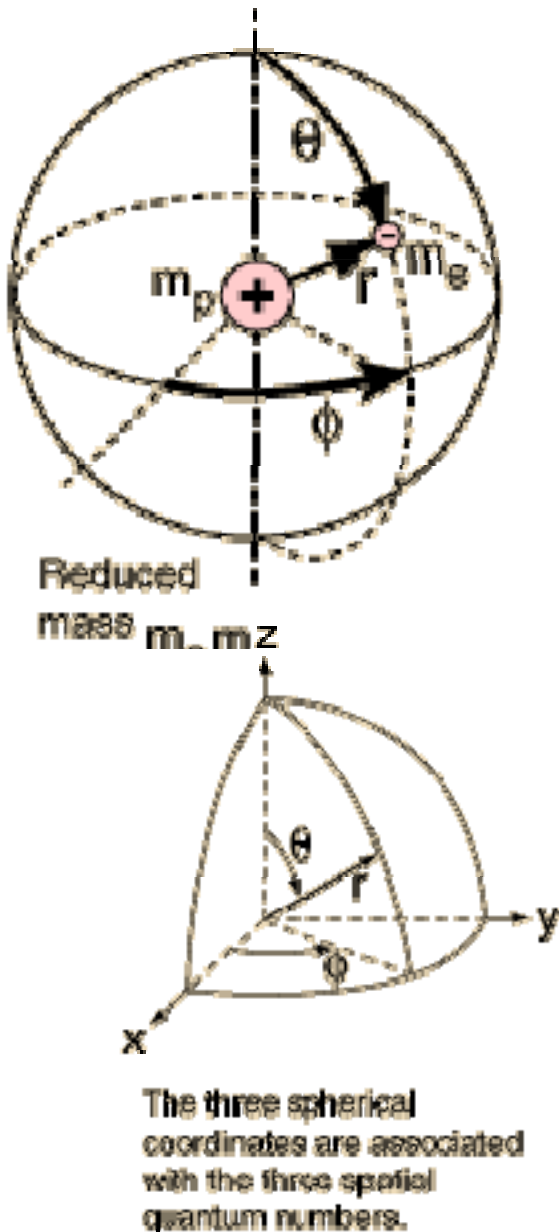
$R(r)$  principal quantum number, size, energy,  $n=1,2,3$

$P(\theta)$  angular momentum number, shape, (s,p,f,d-orbitals)

$$l=0,1,2\dots n-1$$

$F(\varphi)$  magnetic quantum number (second angular dependence, orientation of orbit)  
 $m_l = -l, -l+1, 0, l-1, l, \text{ or } 2l+1$

↑↓ Spin quantum number,  $m_s = 1/2 \text{ or } -1/2$

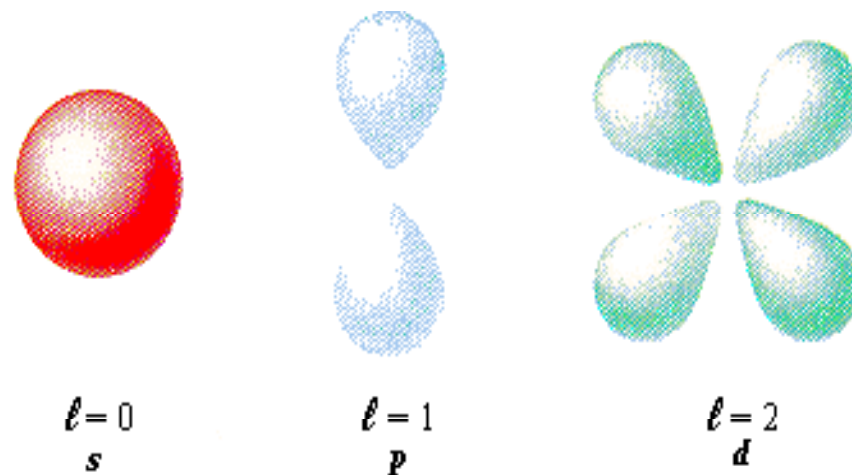


**Pauli exclusion principle:** No two electrons in an atom can have the same quantum numbers

## Quantum Numbers

The Bohr model was a one-dimensional model that used one quantum number to describe the distribution of electrons in the atom. The only information - size of the orbit, described by the  $n$  quantum number. Schrödinger's model - three-dimensional space. Therefore - three coordinates, or three **quantum numbers**:

principal ( $n$ ), angular ( $l$ ), and magnetic ( $m$ ) quantum numbers. These quantum numbers describe the size, shape, and orientation in space of the orbitals on an atom.



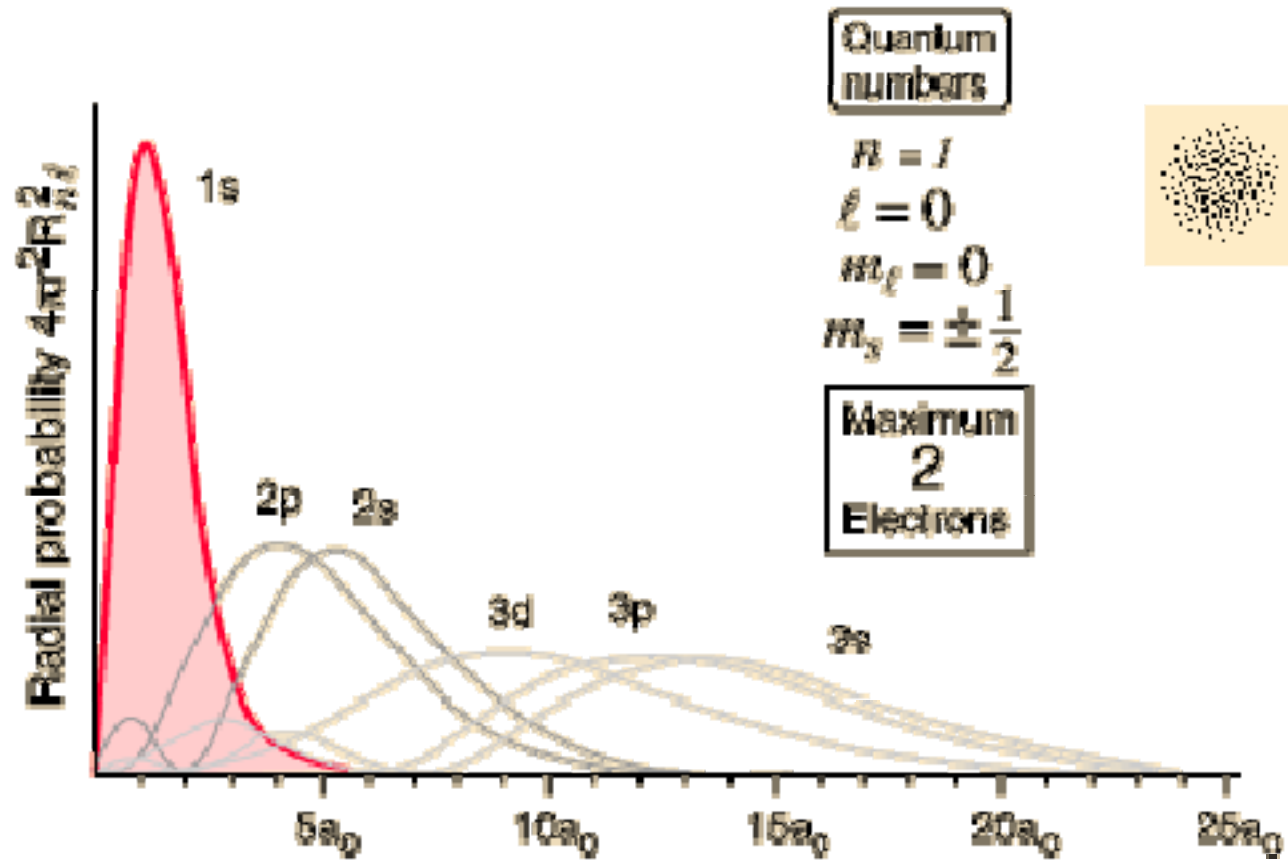
The **principal quantum number** ( $n$ ) describes the size of the orbital. Orbitals for which  $n = 2$  are larger than those for which  $n = 1$ , for example. Because they have opposite electrical charges, electrons are attracted to the nucleus of the atom. Energy must therefore be absorbed to excite an electron from an orbital in which the electron is close to the nucleus ( $n = 1$ ) into an orbital in which it is further from the nucleus ( $n = 2$ ). The principal quantum number therefore indirectly describes the energy of an orbital.

The **angular quantum number** ( $l$ ) describes the shape of the orbital. Orbitals have shapes that are best described as spherical ( $l = 0$ ), polar ( $l = 1$ ), or cloverleaf ( $l = 2$ ). They can even take on more complex shapes as the value of the angular quantum number becomes larger.

There is only one way in which a sphere ( $l = 0$ ) can be oriented in space. Orbitals that have polar ( $l = 1$ ) or cloverleaf ( $l = 2$ ) shapes, however, can point in different directions.

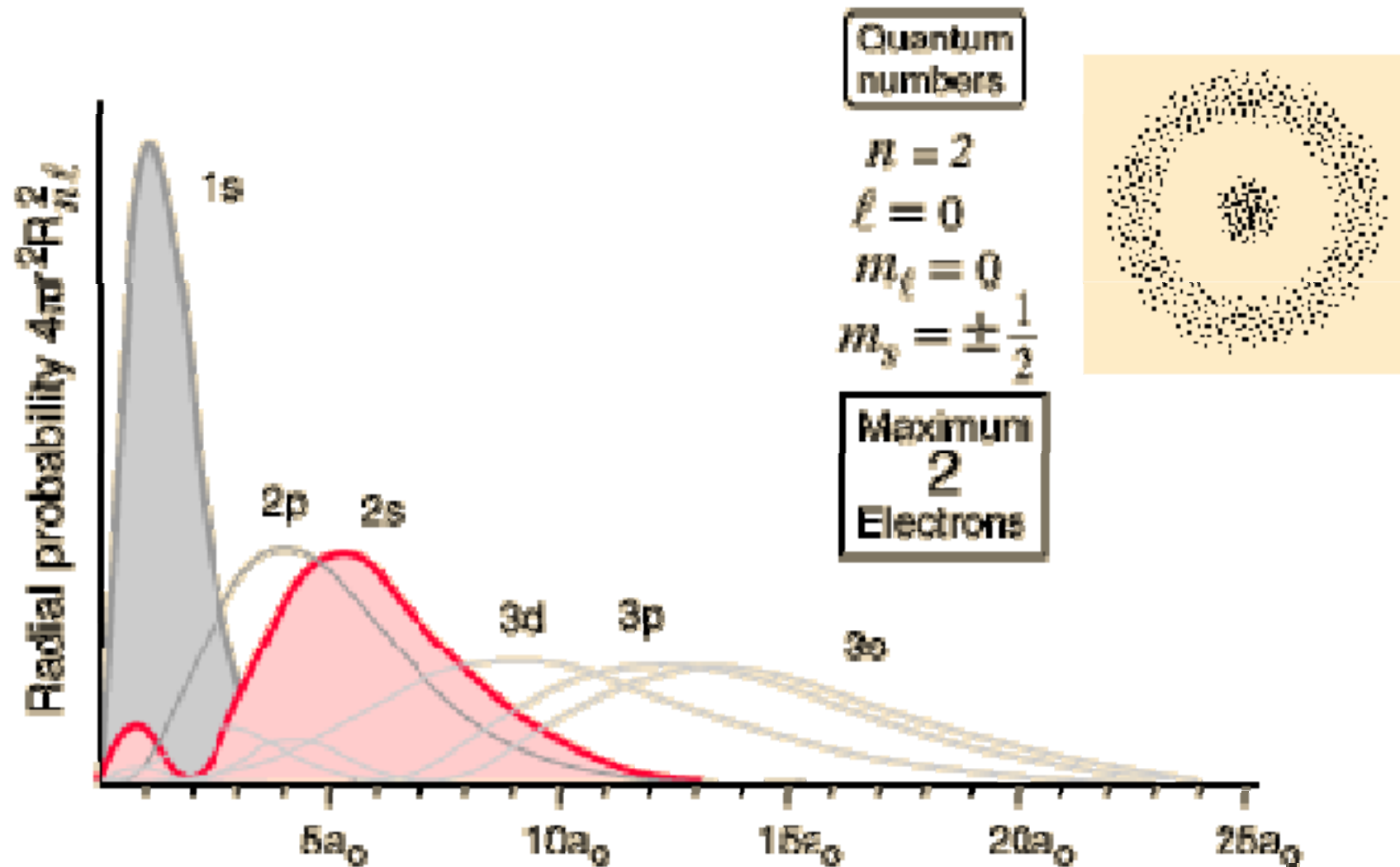
The third quantum number, known as the **magnetic quantum number** ( $m$ ), is used to describe the orientation in space of a particular orbital. (It is called the *magnetic* quantum number because the effect of different orientations of orbitals was first observed in the presence of a magnetic field.)

## Hydrogen 3d Radial Probability

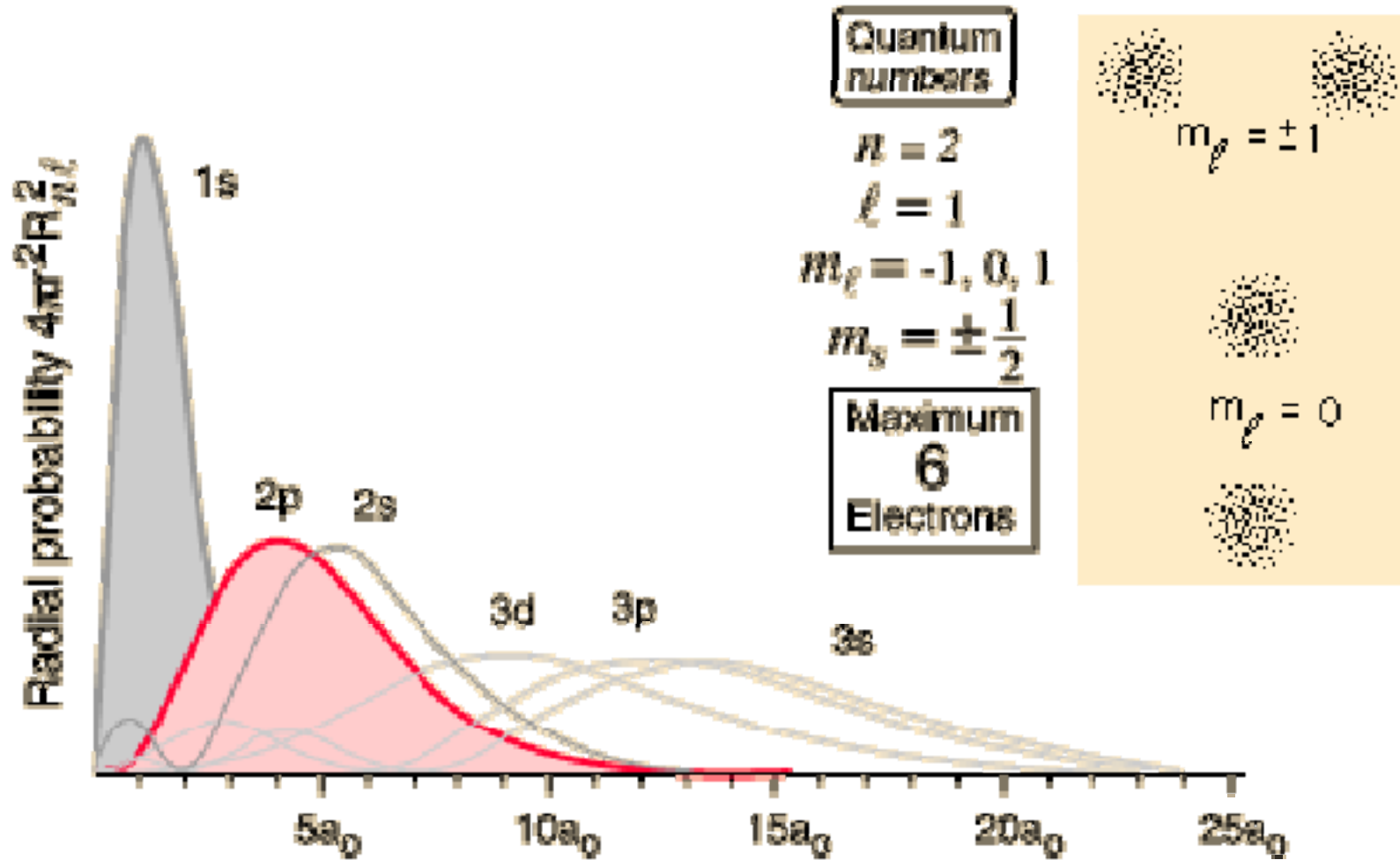




## Hydrogen 2s Radial Probability



# Hydrogen 2p Radial Probability

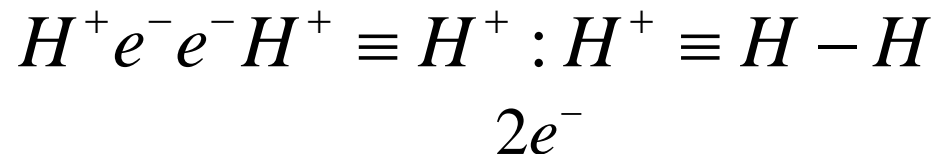


# Chemical Bonding

- Chemical compounds are formed by the joining of two or more atoms. A stable compound occurs when the total energy of the combination has lower energy than the separated atoms. The bound state - a net attractive force between the atoms - a chemical bond - atomic orbitals mix to form a molecular orbital
- The two extreme cases of chemical bonds are:
- **Covalent bond** : bond in which one or more pairs of electrons are shared by two atoms.
- **Ionic bond**: bond in which one or more electrons from one atom are removed and attached to another atom, resulting in positive and negative ions which attract each other electrostatically.

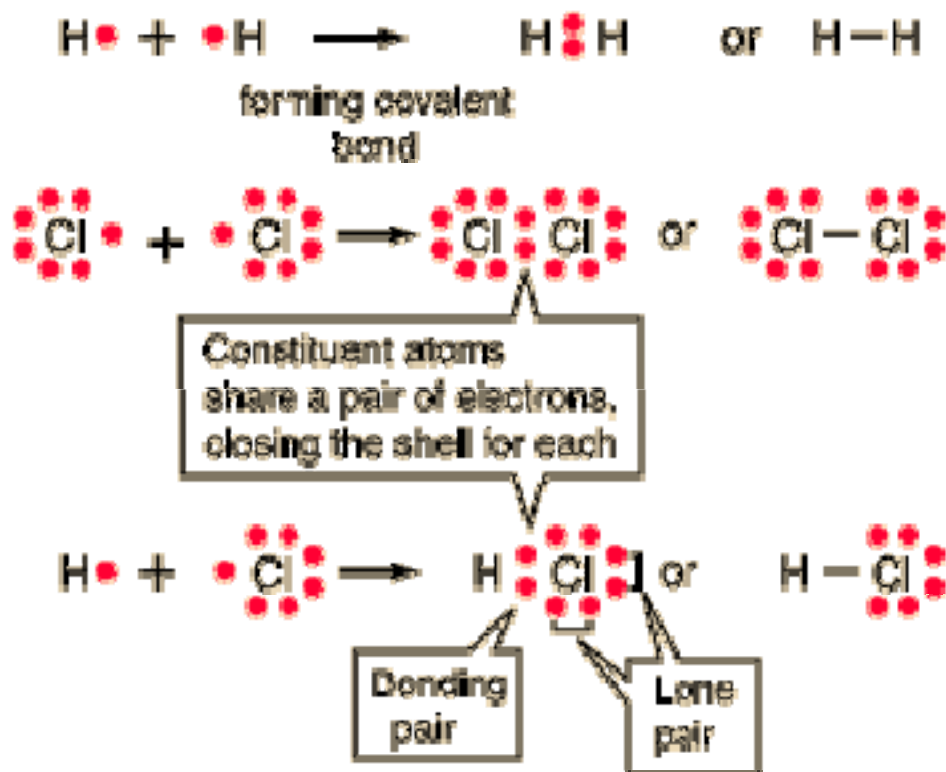
# Strong Force

- **Covalent bond and ionic bonds are strong bonds**
- According to Pauli exclusion principle no two electrons in an atom can have identical quantum numbers. Two electrons can be shared only when they have opposite spins.
- The exchange interaction (quantum mechanical effect, which depends on the spin orientation) overcomes the electrostatic repulsion between electrons and leads to a strong bond for the hydrogen molecule with dissociation energy 4.52 eV at a separation of 0.074 nm.
- Electrons are between protons and balance electrostatic repulsion between them



- There is no more unpaired e and therefore third H atom cannot bind to H<sub>2</sub> molecule

The formation of many common compounds can be visualized with the use of **Lewis diagram**. In a Lewis symbol, the inner closed shells are not considered, and the outer shell or valence electrons are represented by dots.



Another schematic representation of bonds:

H-H, Cl-Cl,

H-Cl

Carbon chains:

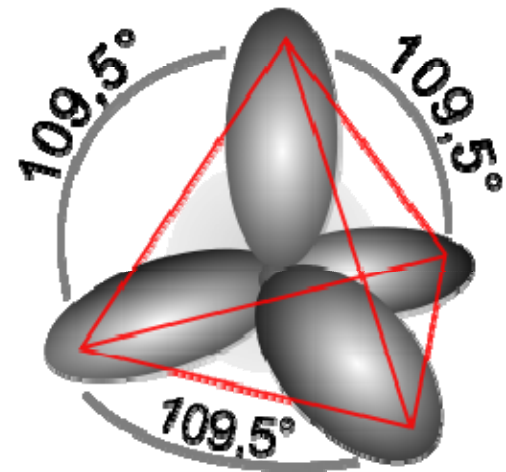
CH<sub>3</sub>-CH<sub>2</sub>-

CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>



- All atoms have electrons in outer shell – valence electrons – form bonds
- Inner shell electrons generally do not participate in bonding, but
- sometimes two atoms come together and Coulomb interaction between them causes hybridization – inner shell electrons can participate in bond formation:

- Carbon has 6 electron with configuration:
- $1s^2 2s^2 2p^2$  in isolated atom it has 2 unpaired e,
- in most compounds C has  $sp^3$  hybridization,
- and forms 4 bonds
- Final energy of  $CH_4$  is less than  $C + 4H$
- Each C-H bond is 4 eV



$sp^3$  hybridization common  
for Carbon

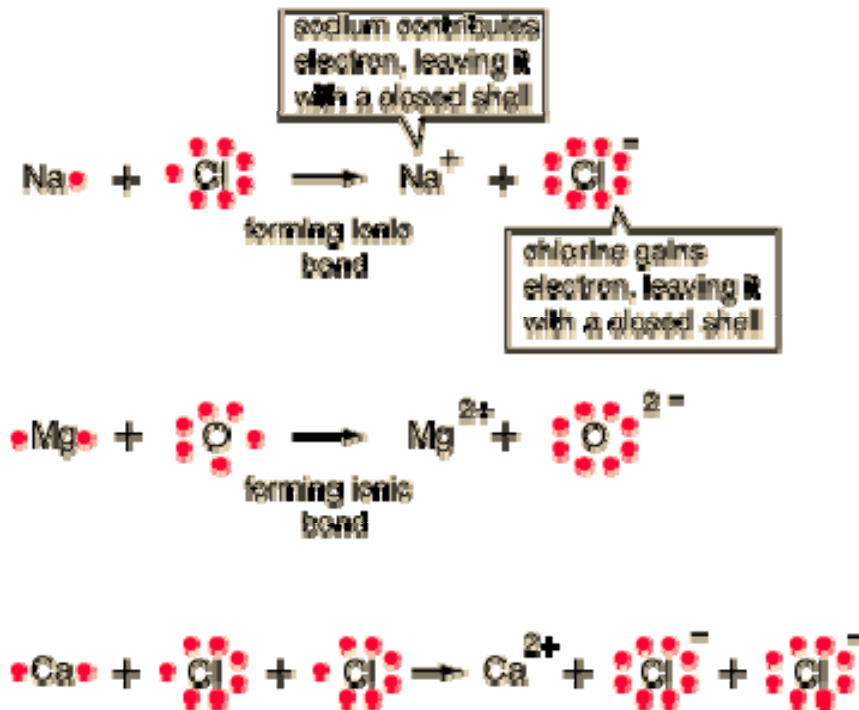
## Binding energies of some covalent bonds

Bond type	Energy eV	Bond type	Energy eV
Single bond:		Double bond	
O-H	4.77	C=O	7.37
H-H	4.51	C=N	6.37
C-H	4.29	C=C	5.27
N-H	4.30		
C-C	3.60	Triple bond	
C-N	3.03	C≡C	8.45
O-N	2.30		

# Ionic bonds

- In chemical bonds, when atoms are different, the electron density shifts to one atom, producing a dipole, and in extreme case one or more atoms lose electrons and other atoms gain them, such a bond is called an ionic bond:

Ionic bond = Positive ion + Negative ion



Dipole moment is used to distinguish

Pure covalent bond :

dipole moment  $< 0.1 \text{ D}$

Ionic bond:

dipole moment  $> 1 \text{ D}$

Summary: Covalent and ionic bonds - strong attractive forces  
few eV



# Intermolecular weak forces

- Long range weak forces between molecules (inter-molecular forces) or distant segments of the same molecule (intra-molecular forces)
- These forces define secondary and higher structures in proteins and DNA and therefore their functions
- These forces are:
  - Electrostatic forces,
  - Van der Waals forces
  - Hydrogen bonds
  - Hydrophobic – hydrophilic forces

## Electrostatic forces:

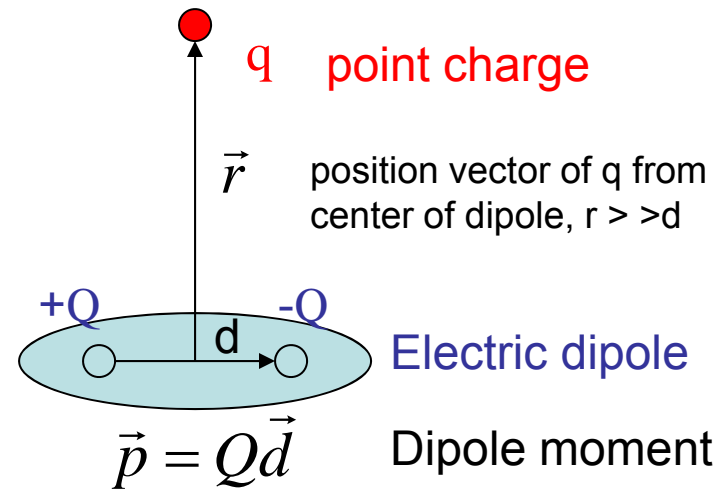
- 1. **Coulomb force** – interaction between two point charges  $q_1$  and  $q_2$  separated by the distance  $r$  in a medium of dielectric constant  $\epsilon$

$$F_{cc} = \frac{q_1 q_2}{(4\pi\epsilon_o\epsilon)r^2}$$

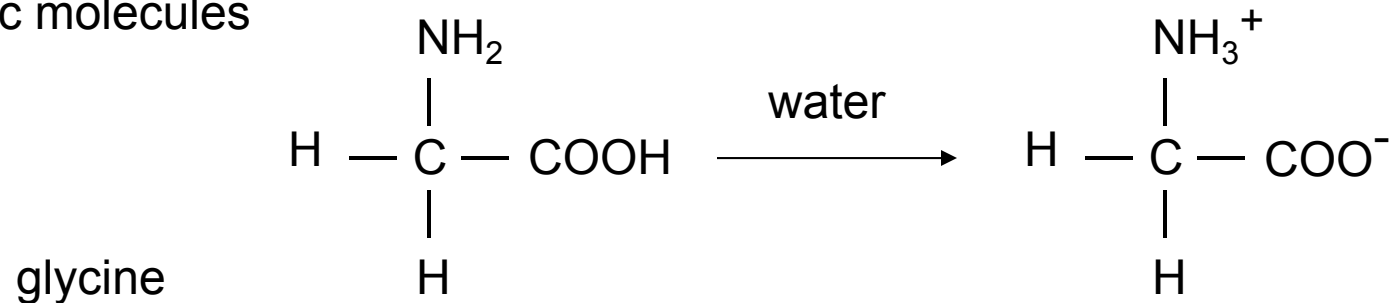
- Can be applied to describe ionic bonds, each ion = point charge
- There are groups in proteins and DNA which can be ionized by body fluids. This ionic groups interact with counter-ions.

- 2. **Charge-dipole force:**
- Electrostatic potential energy of the system:

$$U_{c-dip} = \frac{q\vec{p} \cdot \vec{r}}{(4\pi\epsilon_o\epsilon)r^3}$$



- Charge-dipole interactions - ions interact with polar molecules,
- Example – charged groups in proteins interact with other polar molecules such as:
- water,  $p=1.48D$ ,
- zwitterionic molecules



- Charge-dipole interaction is much stronger than kT, at intermolecular separation 0.2-0.4 nm
- Responsible for ionic solvation
- Charge-dipole interaction is reduced in water by 80 (dielectric constant of water)
- and also due to thermal movement of a dipole
- The average (Boltzmann) energy of system:

$$\langle U \rangle_{c-dip} = - \frac{q^2 p^2}{6(4\pi\epsilon_0\epsilon)^2 kT r^4}$$

for  $d \ll r$ ,  
for small dipole  
 $d < 0.1\text{nm}$

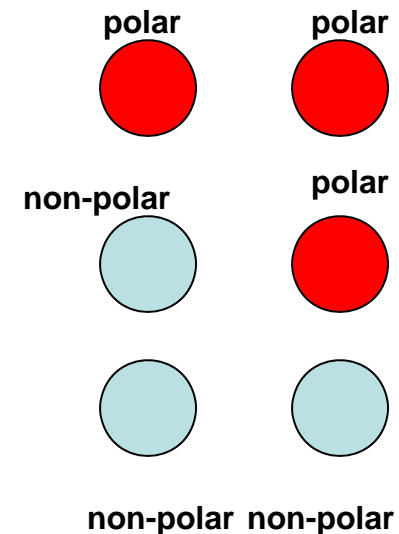
- Large dipoles – zwitterions – need to calculate individual Coulomb interactions

# Van der Waals Forces

- Weak attractive forces ( $\sim 1/r^7$ ), (non-covalent, non-ionic)
- van der Waal's forces include momentary attractions between molecules, and individual atoms. They are not stable, but are caused by momentary polarization of particles.
- These forces are responsible for condensation of gases into liquids and freezing of liquids to solids, determine bulk properties, such as surface tension, viscosity

- Van der Waals forces include:

- 1. **Dipole-Dipole force.** (Keesom Force)
- 2. **Inductive force.** (Debye or polarization force)
- 3. **Dispersion force** (London force)



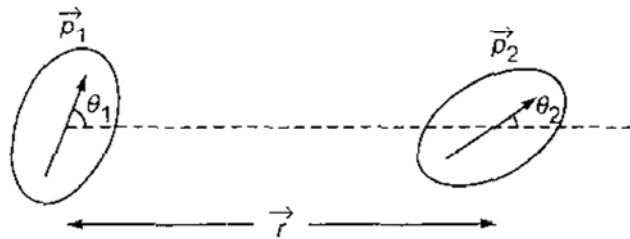
- 1. **Dipole-Dipole (Keesom) force.**

- The electrostatic interactions between charges (molecular ions), permanent dipoles, or multipoles. (Keesom interaction)

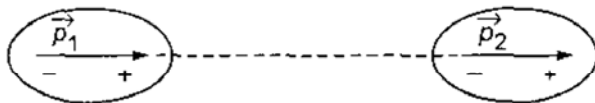
- $\sim kT$

$$\langle U \rangle_{dip-dip} = -\frac{2p_1^2 p_2^2}{3(4\pi\epsilon_o\epsilon)^2 kTr^6}$$

Keesom  
energy



$$U_{dip-dip} = \frac{1}{(4\pi\epsilon_o\epsilon)r^3} [\vec{p}_1 \cdot \vec{p}_2 - 3(\vec{p}_1 \cdot \vec{r})(\vec{p}_2 \cdot \vec{r})/r^2]$$



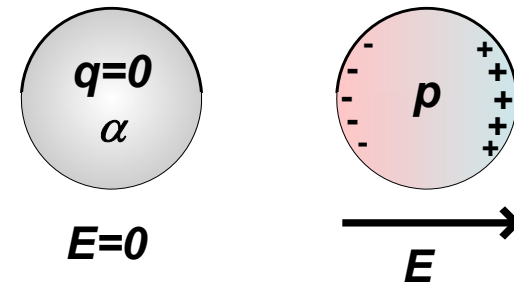
$$U_{dip-dip} = -\frac{2p_1 p_2}{(4\pi\epsilon_o\epsilon)r^3}$$

Dipoles oriented - Minimum Energy

- **Inductive force. (Debye or polarization force)**

- interaction between a permanent dipole on one molecule with an induced dipole on another.
- Electric field  $E$  produced by the dipole of polar molecule induces dipole in non-polar molecule

- Induced dipole moment:  $\vec{P}_{ind} = \alpha \vec{E}$
- $\alpha$  - **polarizability** - the ease with which the electron distribution around an atom or molecule can be distorted in electric field



- assuming that induced dipole is aligned along  $E$
- The system in which induced polarization is linearly proportional to external electric field  $E$  is called electrically linear and isotropic
- Potential energy of interaction between  $E$  field and induced dipole in a linear and isotropic system is:

$$U_{ind} = -\frac{1}{2} \alpha E^2$$

- If electric field  $E$  is produced by an ion – use Coulomb Law
- the potential energy of interaction between charge and induced dipole:

$$E = \frac{q}{(4\pi\epsilon_o\epsilon)r^2}$$

$$U_{ind} = -\frac{1}{2} \frac{\alpha q^2}{(4\pi\epsilon_o\epsilon)^2 r^4}$$

- If electric field  $E$  is produced by a polar molecule with dipole moment  $p$ , the field at angle  $\theta$  to the axis of dipole is  $U_{ind}$  :

$$E = \frac{p(1+3\cos\theta)^{1/2}}{(4\pi\epsilon_o\epsilon)r^3}$$

$$U_{ind} = -\frac{1}{2} \frac{\alpha p^2 (1+3\cos\theta)^{1/2}}{(4\pi\epsilon_o\epsilon)^2 r^6}$$

Induced polarization (**Debye force**)– long range attractive force, energy  $\sim 1/r^6$  , does not depend on T

Strength of inductive force is less than D-D force

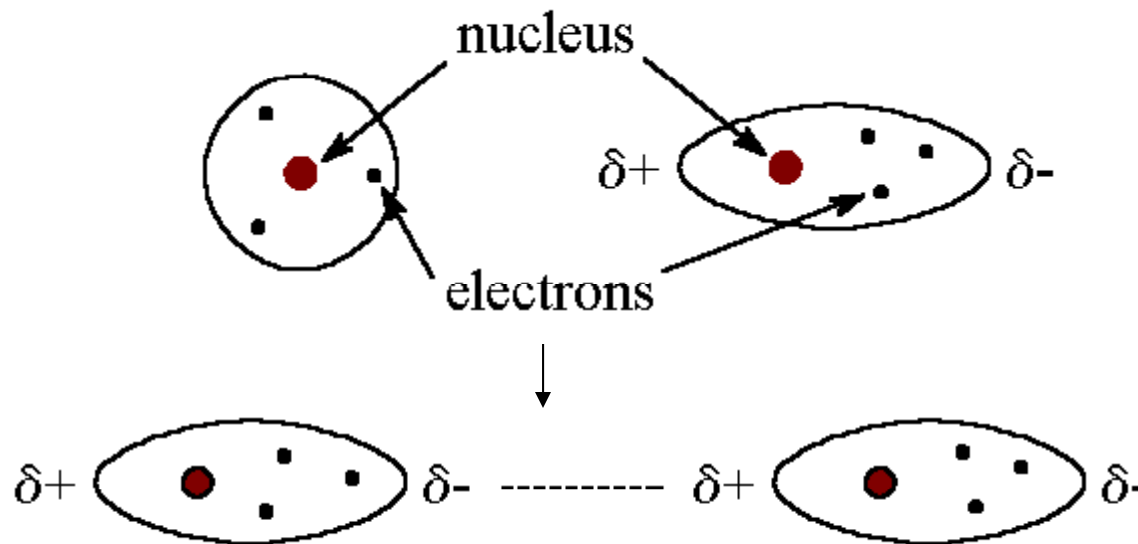
Not all molecules oriented – Boltzmann distribution

$$U_{ind} = -\frac{\alpha p^2}{(4\pi\epsilon_o\epsilon)^2 r^6}$$

**average Debye energy**



- **London Dispersion Force:** inter-molecular force between two non-polar molecules. Induced dipole-induced dipole attraction.
- 
- The London dispersion force is the weakest intermolecular force. The London dispersion force is a temporary attractive force that results when the electrons in two adjacent atoms occupy positions that make the atoms form temporary dipoles.
- London forces are the attractive forces that cause nonpolar substances to condense to liquids and to freeze into solids when the temperature is lowered sufficiently.
- Because of the constant motion of the electrons, an atom or molecule can develop a temporary (instantaneous) dipole when its electrons are distributed un-symmetrically about the nucleus.



Dispersion forces are present between **all** molecules - polar and nonpolar.

Long range – 0.2 – 10 nm

- **London Dispersion Force depends on**

- **Molecular Size**

- Larger and heavier atoms and molecules - stronger dispersion forces.
- In a larger atom or molecule, the valence electrons are, on average, farther from the nuclei than in a smaller atom or molecule. They are less tightly held and can more easily form temporary dipoles – larger polarizability.
- London dispersion forces tend to be:
  - stronger between molecules that are easily polarized.
  - weaker between molecules that are not easily polarized.

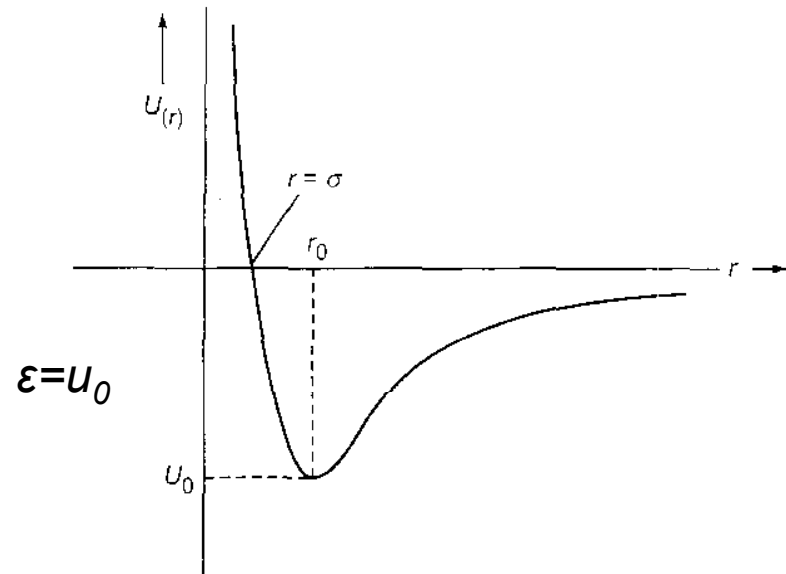
- **Molecular Shape**

- More symmetrical shape – less London dispersion forces
- At room temperature, neopentane (C<sub>5</sub>H<sub>12</sub>) is a gas whereas *n*-pentane (C<sub>5</sub>H<sub>12</sub>) is a liquid.
- London dispersion forces between *n*-pentane molecules are stronger than those between neopentane molecules even though both molecules are nonpolar and have the same molecular weight.
- cylindrical shape of *n*-pentane molecules allows them to come in contact with each other more effectively than spherical neopentane molecules.

- **Lennard-Jones Potential** - dependence of weak intermolecular forces on distance

$$U(r) = 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right]$$

- Long –range attractive
- Short range – repulsive



- $r > \sigma$  - **Van-der-Waals attractive**

$$U(r) = -4\varepsilon \left( \frac{\sigma}{r} \right)^6$$

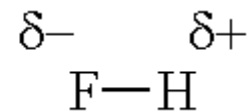
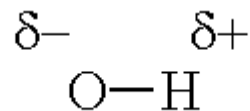
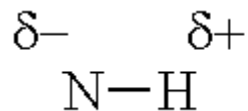
- $r < \sigma$  - **Pauli repulsion**

$$U(r) = 4\varepsilon \left( \frac{\sigma}{r} \right)^{12}$$

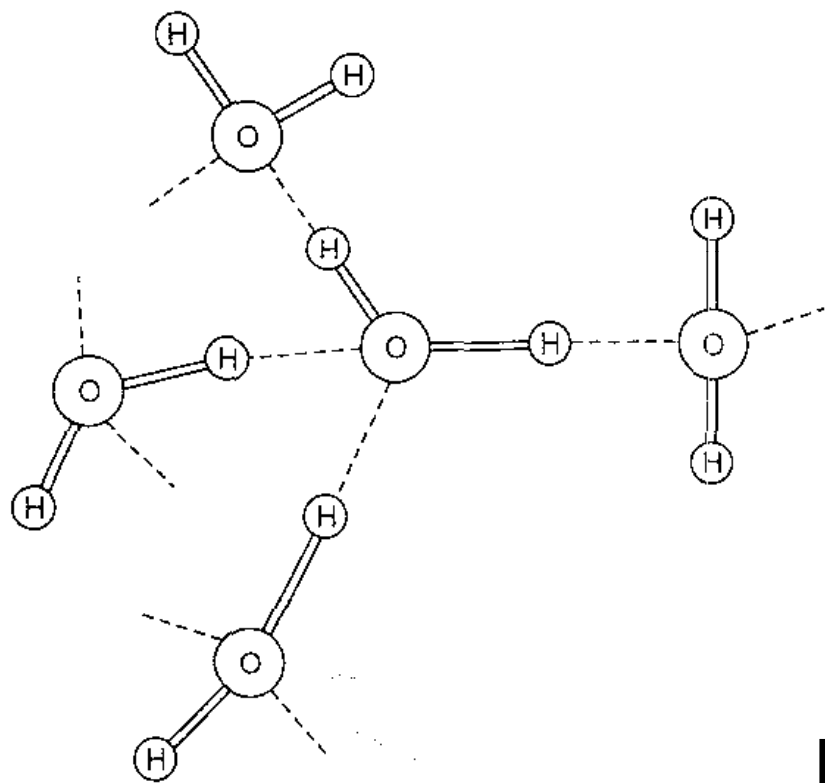
where  $\varepsilon$  is the depth of the potential well ( $u_0$ ),  $\sigma$  is the finite distance at which the inter-particle potential is zero,  $r$  is the distance between the particles, and  $r_0$  is the distance at which the potential reaches its minimum. At  $r_0$ , the potential function has the value  $-\varepsilon$  ( $u_0$ ). The distances are related as  $r_0 = 2^{1/6}\sigma$ . These parameters can be fitted to reproduce experimental data or accurate quantum chemistry calculations. Due to its computational simplicity, the Lennard-Jones potential is used extensively in computer simulations even though more accurate potentials exist.

# Hydrogen Bond

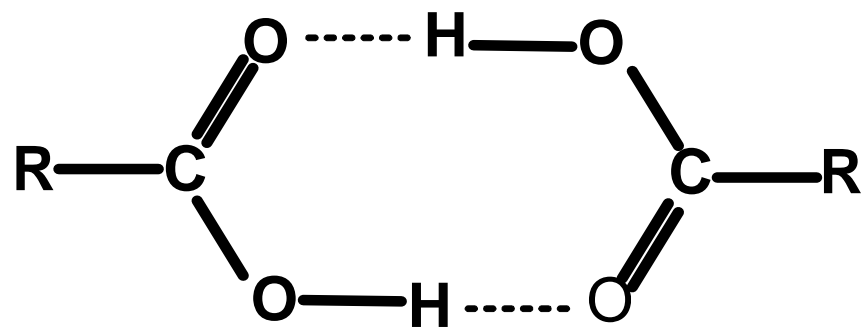
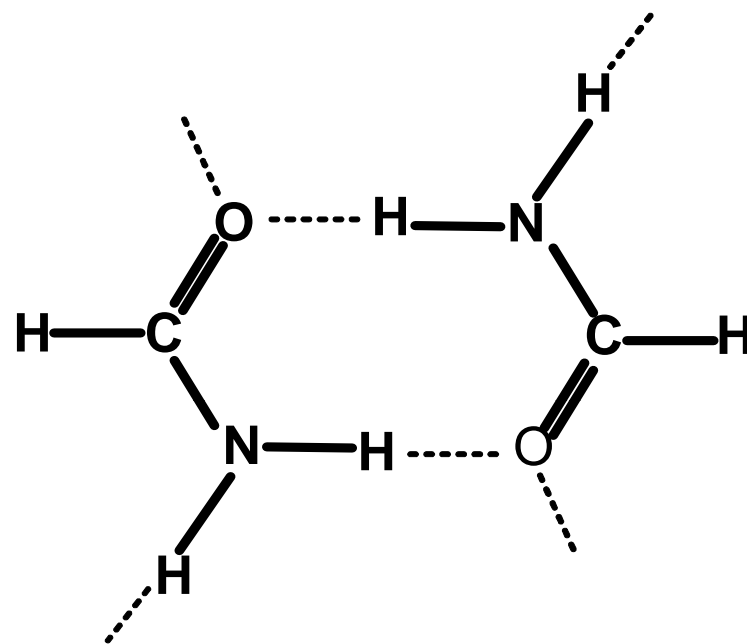
- Long range interaction force between a hydrogen atom covalently bonded to a very electronegative atom such as a N, O, or F atom and another very electronegative atom
- Weaker than covalent bond, stronger than usual van der Waals bond –
- H – bond - medium strength bond, 10 – 40 kJ/mol ( $\sim 4\text{-}15\text{ }kT$  @ 300 K)
- Because of the difference in electronegativity, the covalent bond is polar, the H (donor) atom bears a large partial positive charge and the N, O or F atom bears a large partial negative charge (acceptor)



H-bond in water:



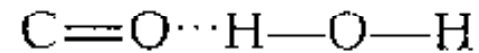
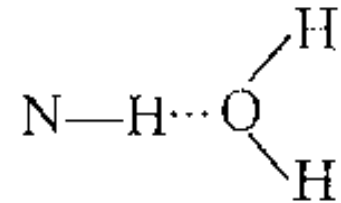
Other examples:



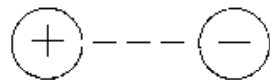
- Due to H bonding water is highly interactive with other polar molecules,
- N-H and C=O form H-bond  
without water:



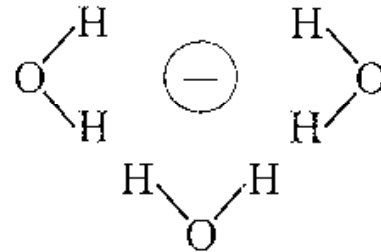
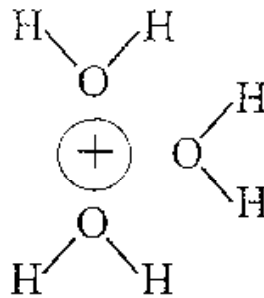
with water:



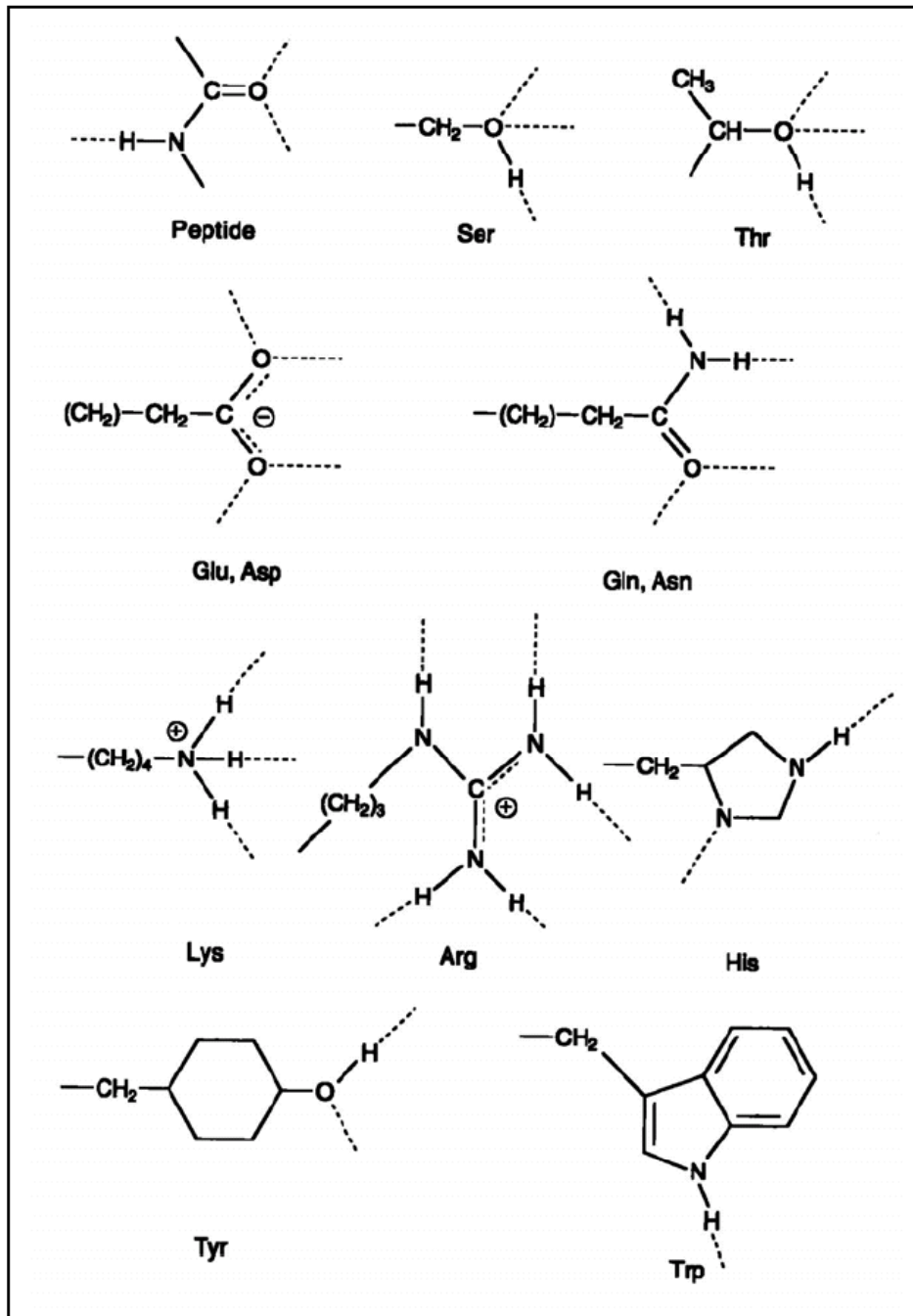
- Water dissolves ionic compounds:



In non-polar  
environment



In water environment



## Hydrogen bonds in proteins

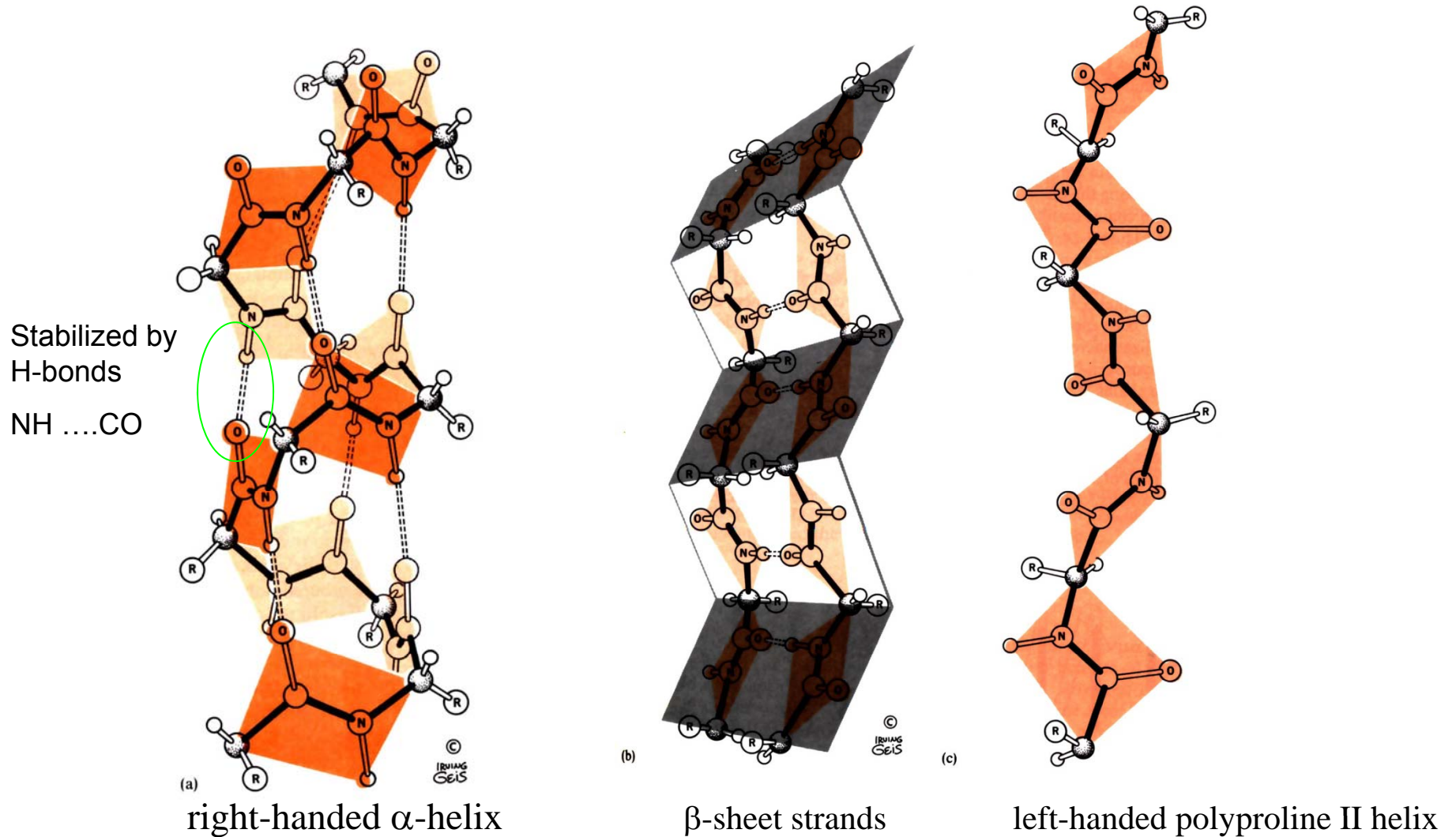
Groups that form hydrogen bonds in proteins

In proteins nearly all (~90%) peptide N-H and C=O groups form H-bonds.

Side chains H-bonding:

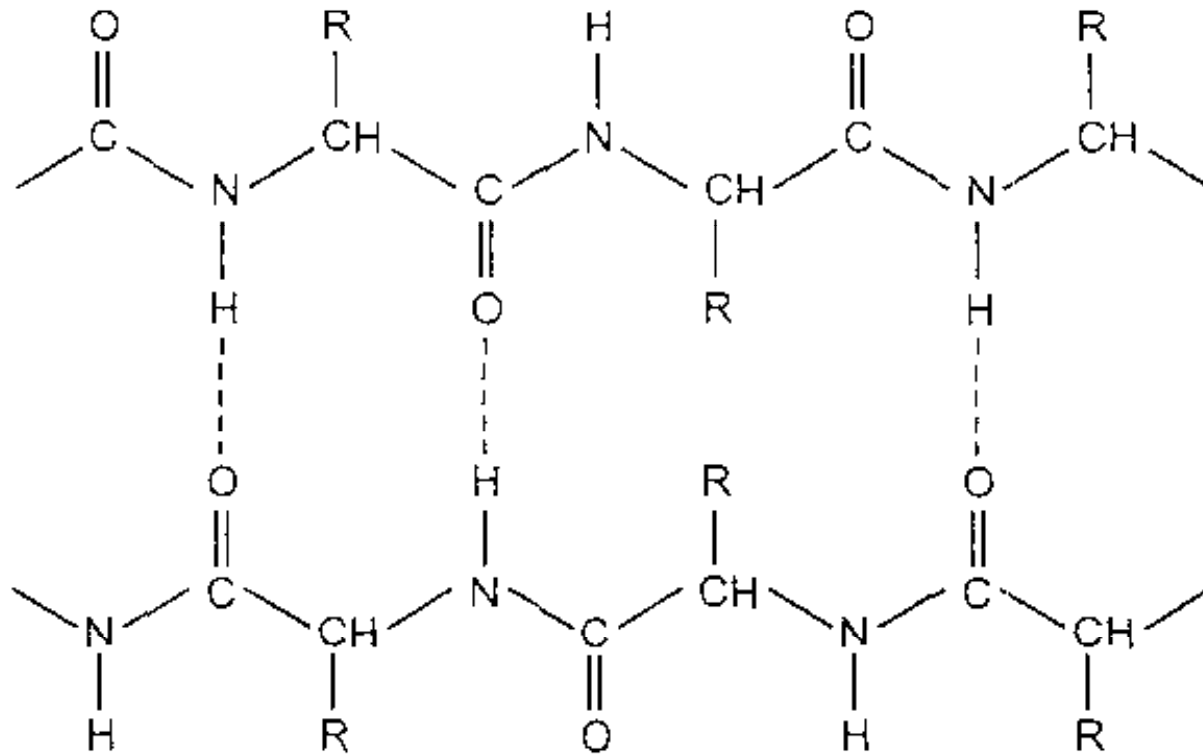
His	100%
Asp, Trp	85%
Glu	77%
Tyr	68%
Ser, Thr, Lys, Gln, Asn, Arg	50%

# H-bonding in proteins define secondary and tertiary structure



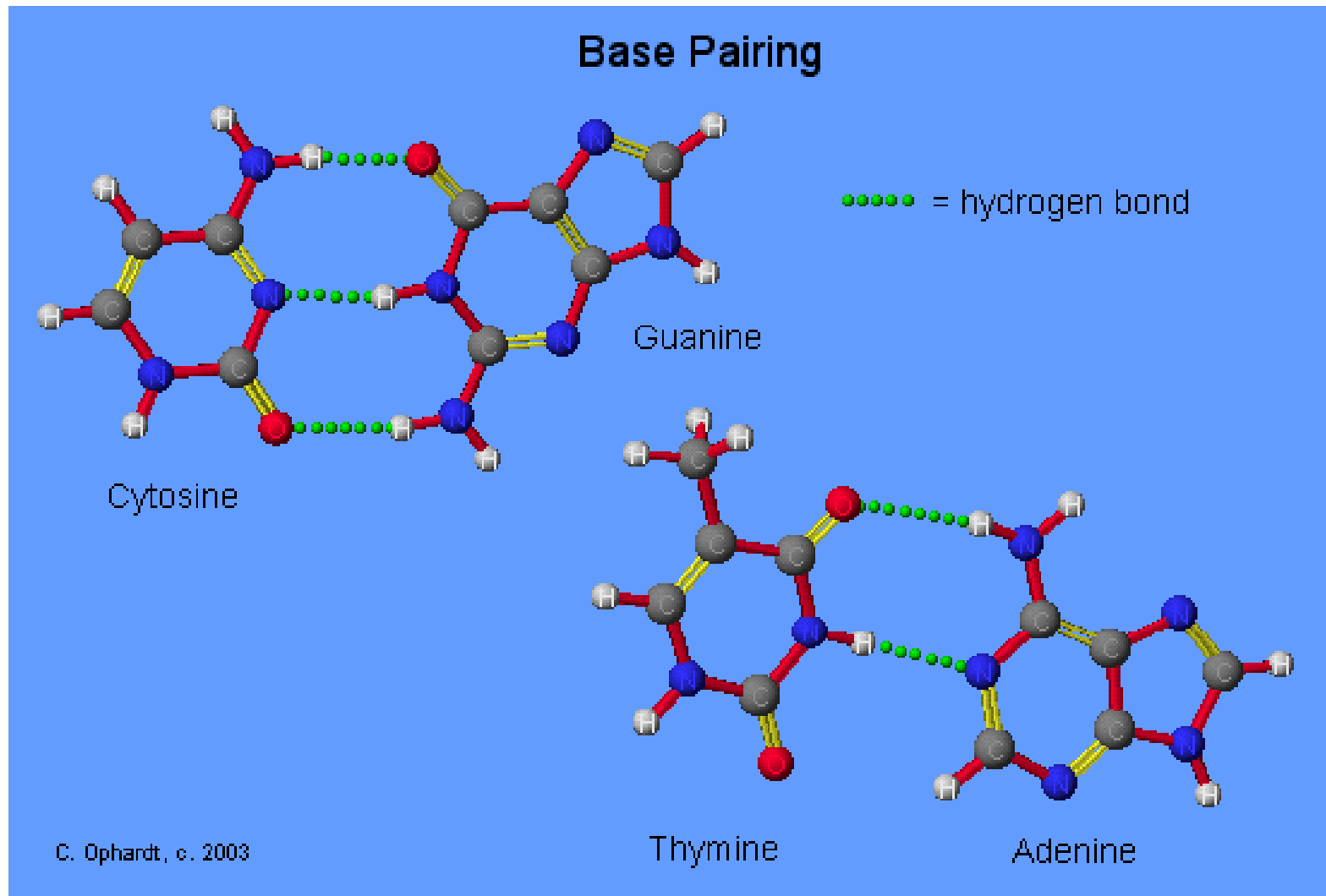


## Hydrogen bonds in protein Beta sheets



Beta - sheets structure is characterized by linking two or more linear polypeptide chains

- H-bonds bind DNA strands together



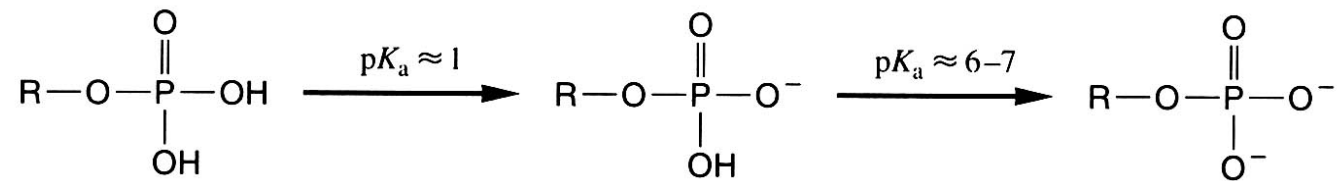
## Hydration of nucleic acids - electrostatic interactions

~20 water molecules per nucleotide (~10 in the first solvation shell)

Bases hide from water

In water solution phosphate groups are ionized and have negative charge:

Charges are shielded by counter-ions.



Phosphate backbone charges are important in DNA condensation

# Hydrophobic –hydrophilic force

- Polar molecules attract water and easily dissolve in water – **hydrophilic** – (loving water)
- Hydrophilic force is a sum of intermolecular (electrostatic) forces between charged or polar molecules and leads to hydration
- Non-polar molecule are **hydrophobic** – (afraid of water) they repel water
- Hydrophobic force is a sum of all forces which reduce solubility of molecules (usually large molecules)
- Example: water and oil do not mix
- Hydrophobic molecules do not form hydrogen bonds with water,

## Hydration of hydrophobic molecules

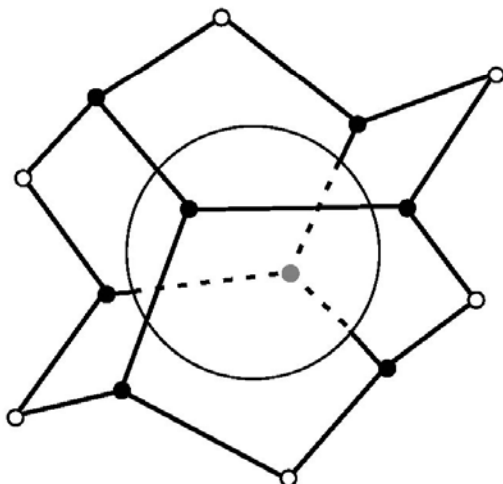
$$\Delta G_{hydr} = \Delta H_{hydr} - T \cdot \Delta S_{hydr}$$

is unfavorable ( $>0$ )

$\Delta H_{hydr}$  is usually small and negative,  $\Delta S_{hydr}$  is large and negative for hydrocarbons:

$\Delta H_{hydr}$  is in the range from  $-12$  to  $3$  kJ/mol (favorable interaction),  
 $-\Delta S_{hydr}$  ranges from  $75$  to  $100$  J/(mol\*K)

Decrease in entropy of water is due to “caging” effect:

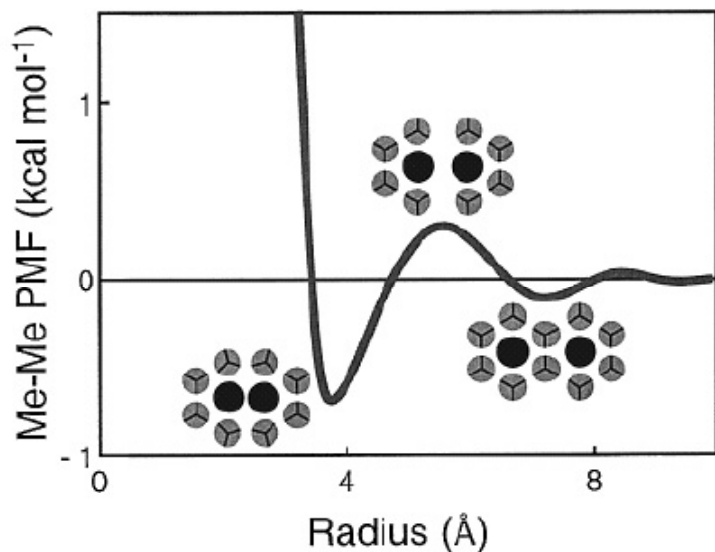


Imagined H-bonding pattern near a hydrophobic solute. (Pratt et al *Chemical Physics* **2000**, 258, 349-370)

in order to maintain H-bonding network water molecules rearrange and maintain more ordered structure.  
Structure of water around hydrophobic molecules is different from the ice structure.

## Hydrophobic interactions

- The energy to transfer a hydrophobic molecule into water is approximately proportional to the surface area of the molecule. This leads to hydrophobic interaction: attraction between two hydrophobic molecules.



Example: Dimerization of cyclohexane ( $\sigma = 0.57$  nm)  $\Delta G \sim -11$  kJ/mol,

here  $\sigma$  – diameter of one molecule in nm

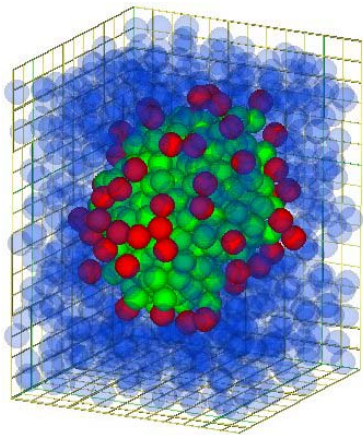
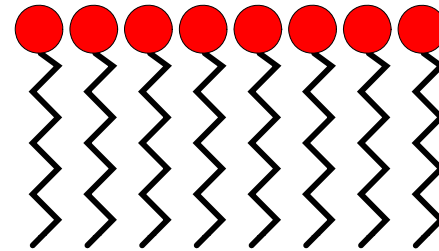
$$\Delta G_{\text{dim}} \approx -20 \cdot \sigma (\text{kJ} / \text{mol})$$

CH<sub>4</sub> - CH<sub>4</sub> potential according to MB model

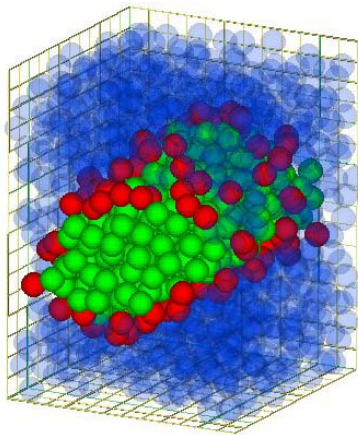
*J. Phys. Chem. B* **2002**, 106, 521

## Amphiphilic molecules – hydrophobic forces drive self assembly

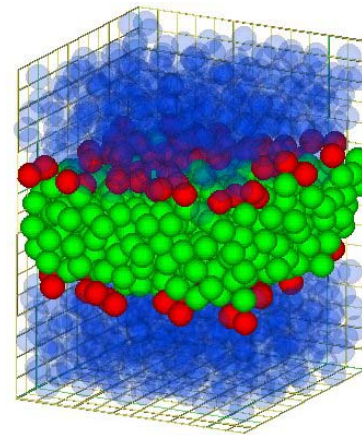
- Amphiphilic molecules (phospholipids) have both polar and non-polar groups – they are oriented at the water interface
- solubilize oil in water - surfactants
- At high enough concentration  
amphiphilic molecules self-assemble:
- Different structures can be formed depending on concentration of amphiphiles and properties of solution (ionic strength, temperature).



micelle



rod-like micelle



bilayer

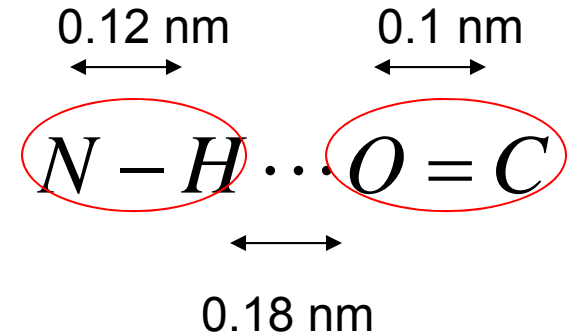
## example

dipole moment  $P_{CO}=8 \times 10^{-30}$  C.m,  $P_{NH}=3 \times 10^{-30}$  C.m,

distance (bond length) 0.12 and 0.1 nm ,

distance between CO and NH is 0.18nm

Estimate electrostatic interaction between two dipoles.



Distance between dipoles is not too much larger than dipole lengths  
therefore we need to calculate Total potential = sum of Coulomb potentials  
of each pair

$$U = U_{CH} + U_{CN} + U_{OH} + U_{ON} \qquad F_{cc} = \frac{q_1 q_2}{(4\pi\epsilon_o\epsilon)r^2}$$

$$U = \frac{1}{4\pi\epsilon_o} \left[ \frac{Q_C Q_H}{r_{CH}} + \frac{Q_C Q_N}{r_{CN}} + \frac{Q_O Q_H}{r_{OH}} + \frac{Q_O Q_N}{r_{ON}} \right]$$



## Solution continue

$$Q_C = -Q_O = \frac{P_{CO}}{r_{CO}} = \frac{8 \times 10^{-30}}{0.12 \times 10^{-9}} = 6.6 \times 10^{-20} C \quad \text{-charge on each atom – from } P=Qr$$

$$Q_H = -Q_N = 3 \times 10^{-20} C$$

$$U = 9 \times 10^9 \times (6.6 \times 3 \times 10^{-40}) \times \frac{1}{10^{-9}} \left( \frac{1}{0.3} - \frac{1}{0.4} - \frac{1}{0.18} + \frac{1}{0.28} \right) =$$
$$-21 \times 10^{-20} J = -0.13 eV$$

Negative potential means force is attractive, the value is typical for H-bond

# Additional information

## Lewis Dot Diagrams of Selected Elements

I	II											III	IV	V	VI	VII	0	
H •																		He •
Li •	• Be •											• B •	• C •	• N •	• O •	• F •	• Ne •	
Na •	• Mg •											• Al •	• Si •	• P •	• S •	• Cl •	• Ar •	
K •	• Ca •											• Ga •	• Ge •	• As •	• Se •	• Br •	• Kr •	
Rb •	• Sr •											• In •	• Sn •	• Sb •	• Te •	• I •	• Xe •	
Cs •	• Ba •											• Tl •	• Pb •	• Bi •	• Po •	• At •	• Rn •	

Metal

Metalloid

Nonmetal

<http://hyperphysics.phy-astr.gsu.edu/hbase/hframe.html>