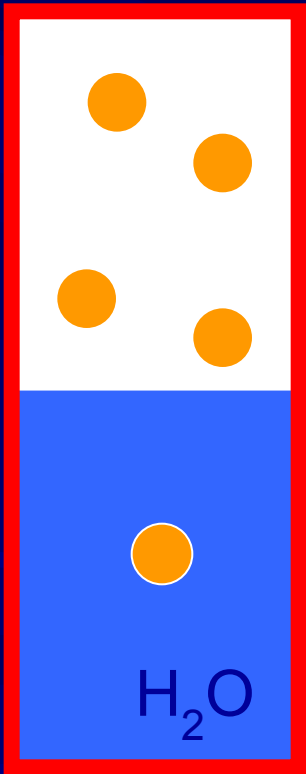


PROTEIN PHYSICS

LECTURES 5-6


**Elementary interactions:
hydrophobic
&
electrostatic;
SS and coordinate bonds**

Hydrophobic effect



Henry's constant

$$(k_{H,cc})^{-1} = \frac{[\text{in gas}]}{[\text{in liquid}]}$$

for  : = 50/1

for ethanol: = 1/47000

Concentration of C₆H₁₄ 
in H₂O:
50 times less
than in gas!

WHY?

ENTROPY:

$$S_E = k_B \cdot \ln[M_E]; \quad M_E = \text{number_of_states}(E)$$

Why k_B ? What is k_B ?

Because **entropy** S_E comes to the **free energy**

$$F_E = E - TS_E \quad (\text{measured in energy units}) \text{ as } TS_E,$$

and T is measured in degrees, while

$\ln[\text{number of states}]$ is dimensionless;

Thus, k_B is energy_unit/degree

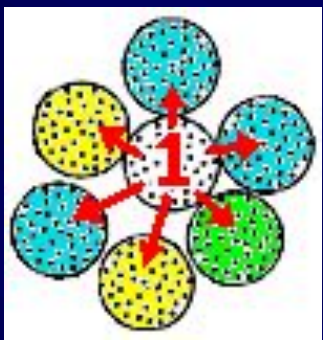
FREE ENERGY:

$$\text{Probability}(E) \sim M_E \cdot \exp(-E/k_B T) = \exp(-F_E/k_B T)$$

Boltzmann

$$F = E - TS \text{ at } V = \text{const};$$

$$G = H - TS = (E + PV) - TS \text{ at } P = \text{const} \text{ (better for experiment)}$$



G^{int} : “Free energy of interactions”
 (“mean force potential”)

Chemical potential:

$$\mu \equiv G^{(1)} = G^{\text{int}} - T \cdot k_B \ln(V^{(1)}) \equiv G^{\text{int}} + T \cdot k_B \ln[C]$$

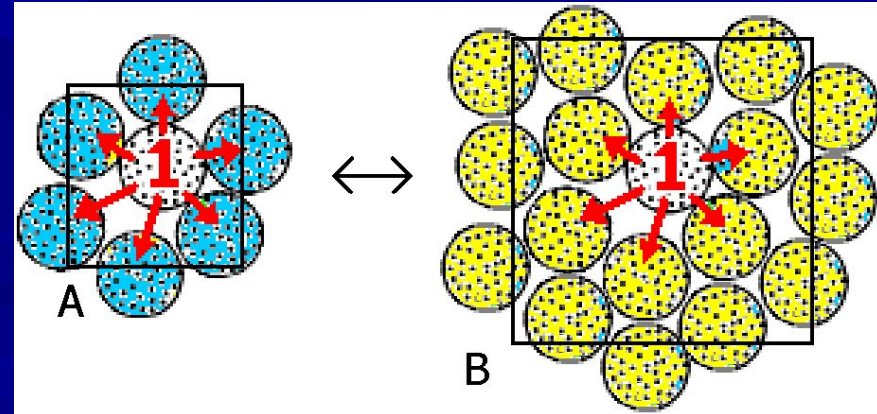
EQUILIBRIUM for transition

of molecule **1** from **A** to **B**: $G_A^{(1)} = G_B^{(1)}$

chemical potentials in **A** and **B** are equal

$$\Delta G_{A \rightarrow B}^{\text{int}} \equiv G_B^{\text{int}} - G_A^{\text{int}}$$


$$\Delta G_{A \rightarrow B}^{\text{int}} = k_B T \cdot \ln([C_{\text{inA}}]/[C_{\text{inB}}])$$

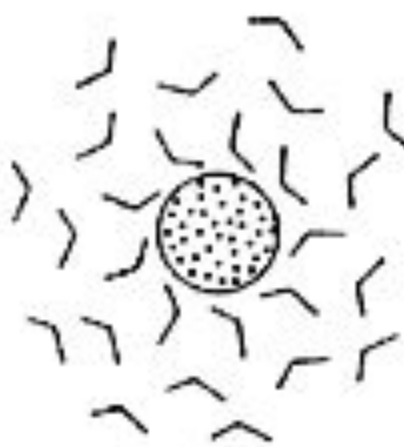
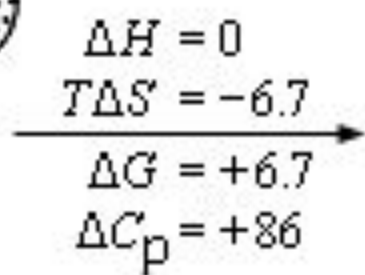
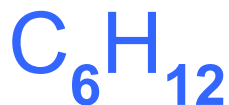
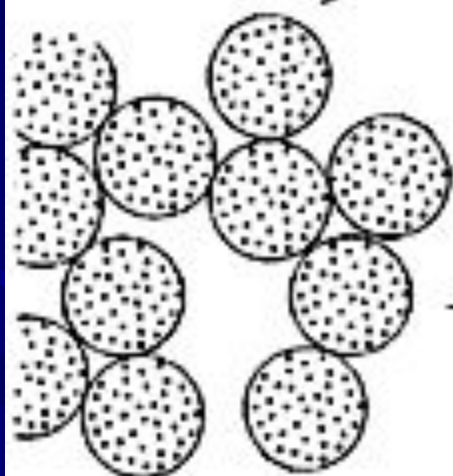


Experiment: $\Delta G_{A \rightarrow B}^{\text{int}} = k_B T \cdot \ln([C_{1 \text{ in } A}]/[C_{1 \text{ in } B}])$

$\Delta S_{A \rightarrow B}^{\text{int}} = -d(\Delta G_{A \rightarrow B}^{\text{int}})/dT$

$\Delta U_{A \rightarrow B}^{\text{int}} = \Delta Q_{A \rightarrow B}^{\text{int}} + T \Delta C_{A \rightarrow B}^{\text{int}}$

$\Delta H = -7.3$		$\Delta H = -7.3$
$T\Delta S = -2.9$		$T\Delta S = -9.6$
$\Delta G = -4.4$		$\Delta G = +2.3$
$\Delta C_p = +8$	Gas	$\Delta C_p = +94$

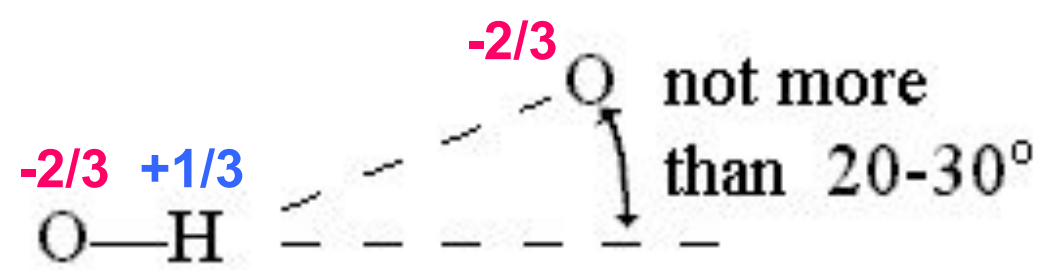


Liquid

$T = 298^{\circ}\text{K} = 25^{\circ}\text{C}$

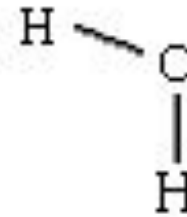
Aqueous solution

[C] of C_6H_{12}
in H_2O :
50 times less
than in gas;
100000 times
less than in
liquid C_6H_{12}



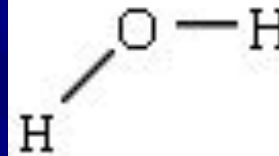
H-bond: directed

Loss: S



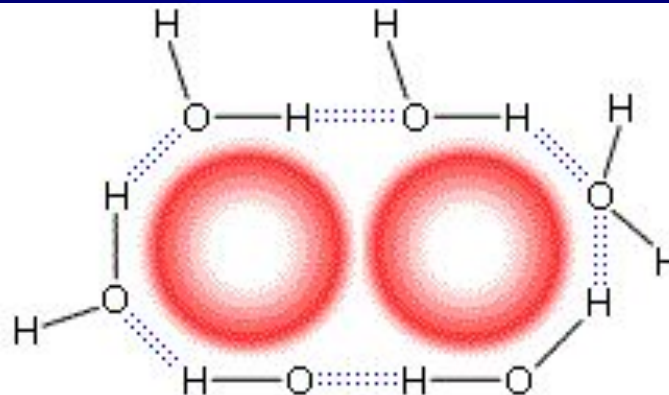
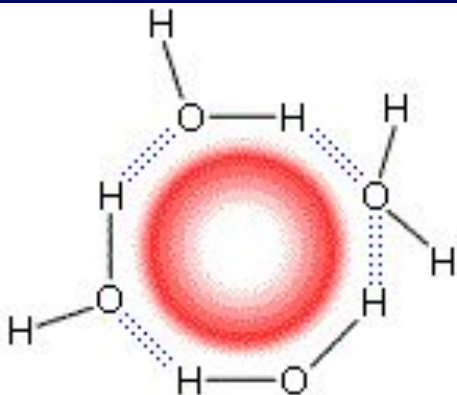
usual case

Loss: LARGE E

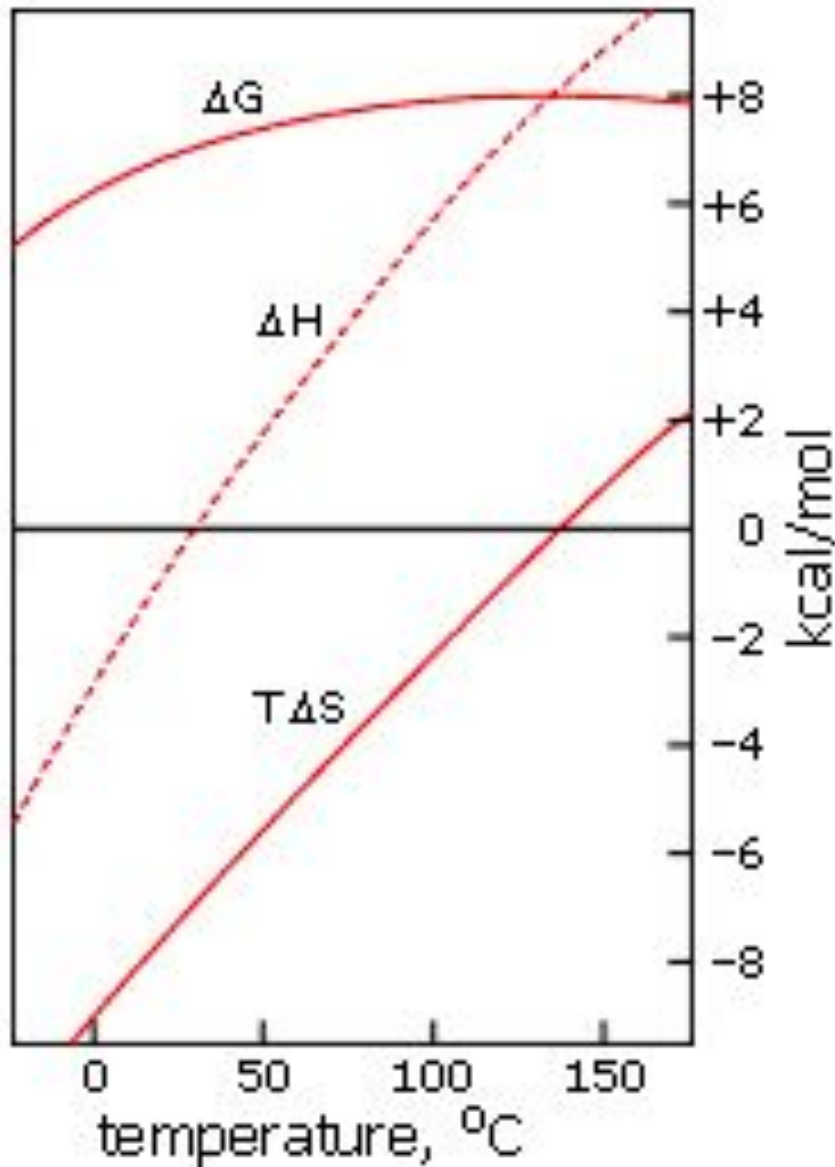


rare case

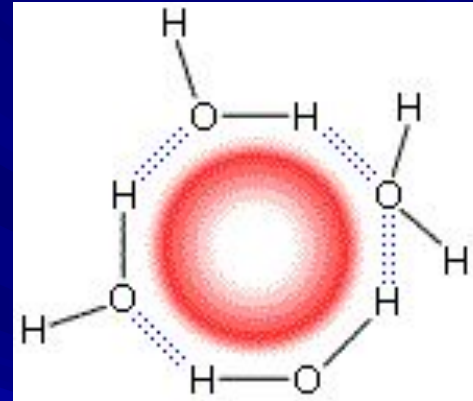
Non-polar body

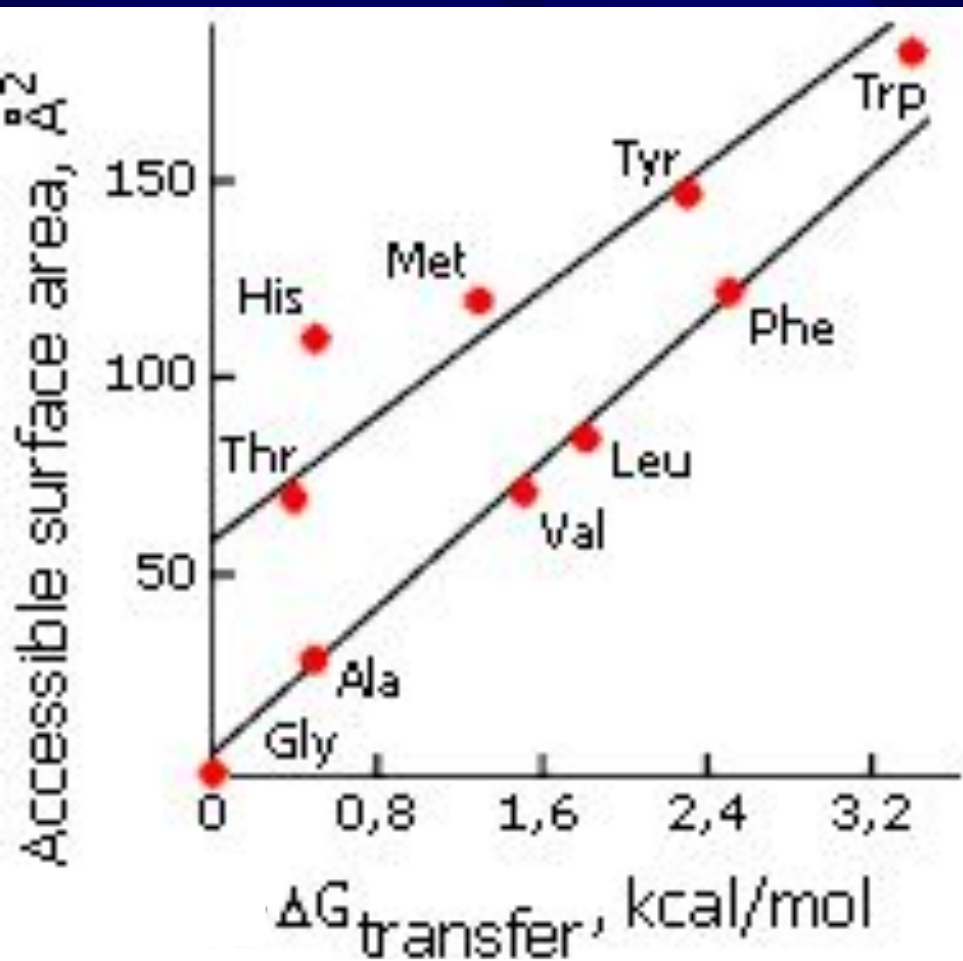


“hydrophobic bond”

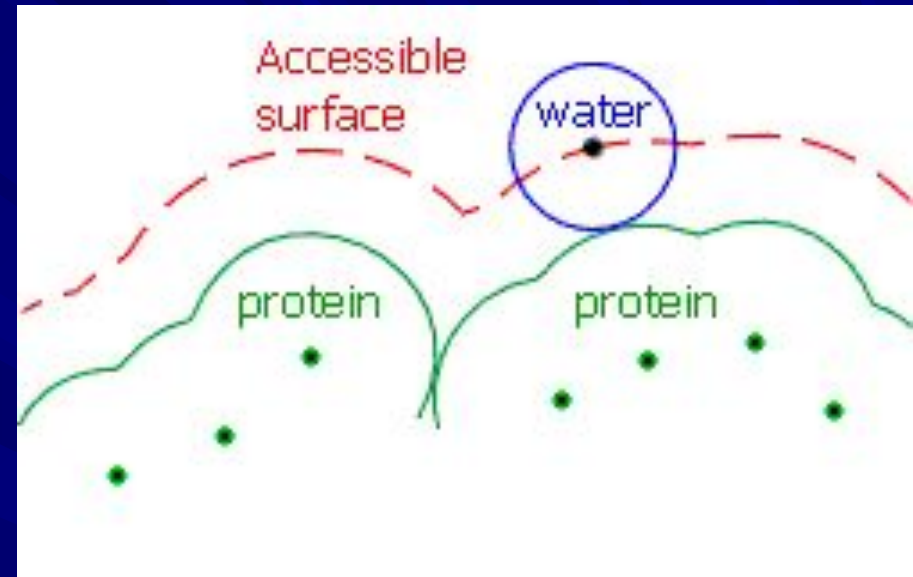


**High
heat capacity
 $d(\Delta H)/dT$:
Melting of
“iceberg”**

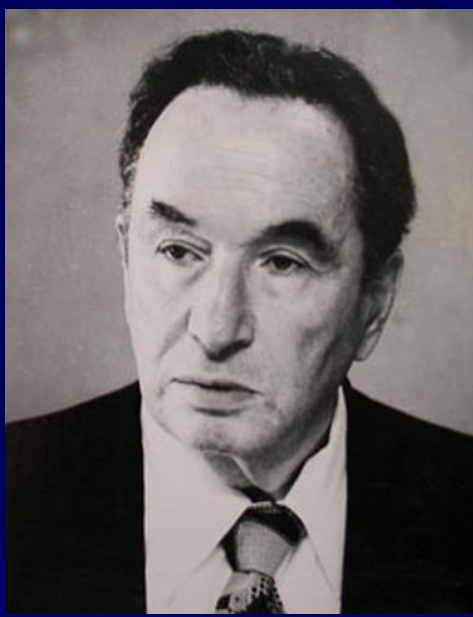




Octanol \rightarrow Water



20-25 cal/mol per \AA^2 of molecular accessible non-polar surface



Семён Ефимович **Бреслер**

(1911 – 1983)

Hypothesis on a role of hydrophobic effect in protein folding



Давид Львович **Талмуд**

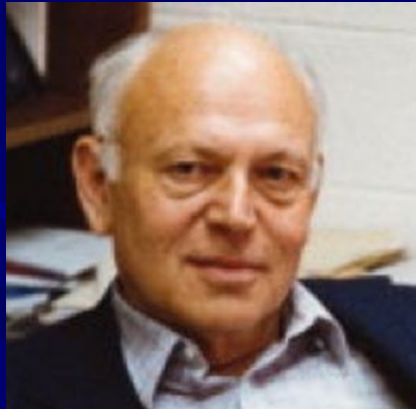
(1900 - 1973)

Hydrophobic
effect
&
denaturation
of proteins



WALTER
KAUZMANN

1916-2009



Charles **Tanford**

(1921 - 2009)

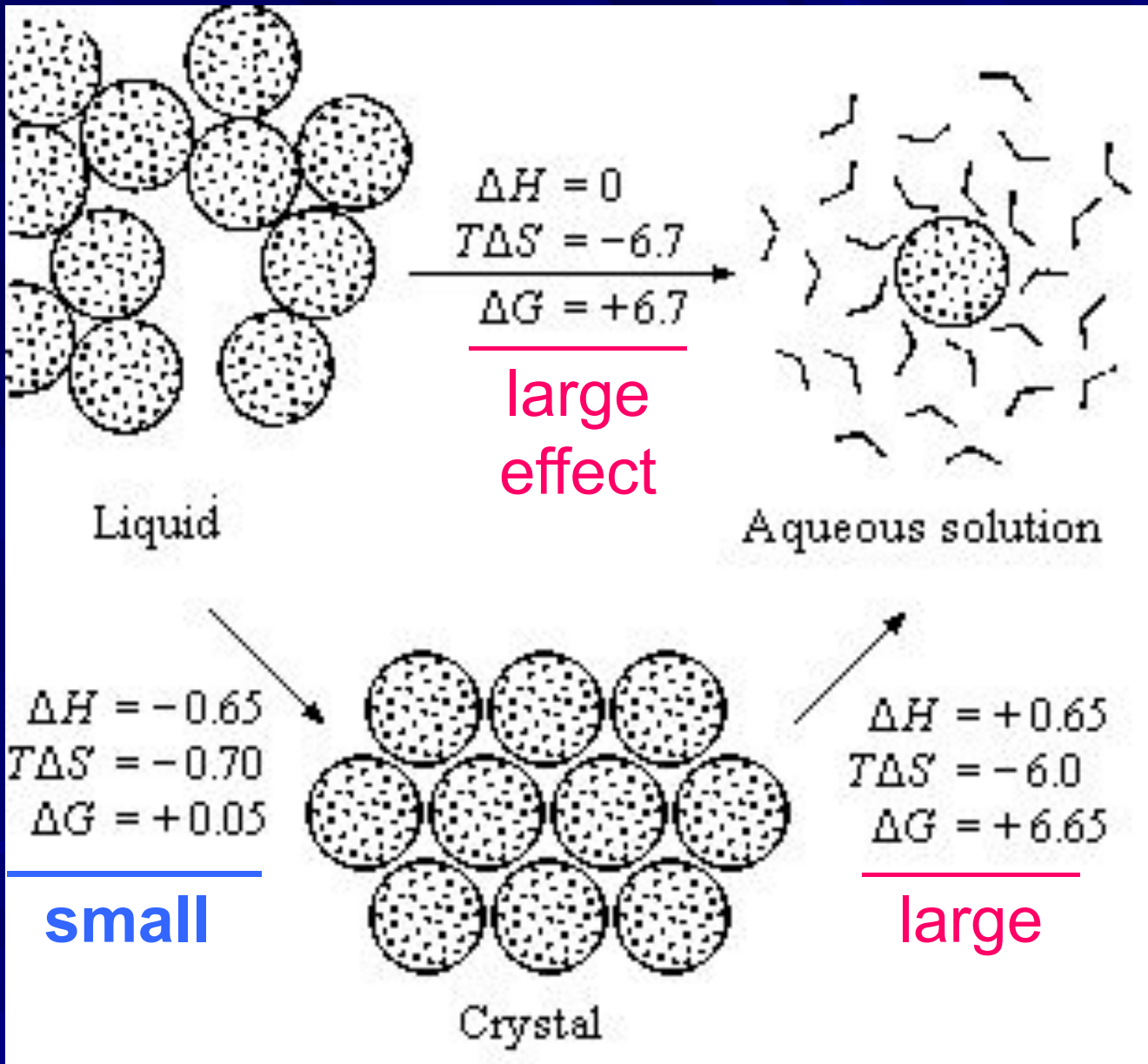
General physical
features of
Hydrophobic
effect



Cyrus Homi **Chothia**,

1942

Hydrophobic
effect
&
amino acid
water-accessible
surface



Electrostatics in uniform media:

potential $\phi_1 = q_1/\epsilon r$

Interaction of two charges:

$$U = \phi_1 q_2 = \phi_2 q_1 = q_1 q_2 / \epsilon r$$

$\epsilon = 1$ vacuum

$\epsilon \approx 3$ protein

$\epsilon \approx 80$ water

Protein/water interface

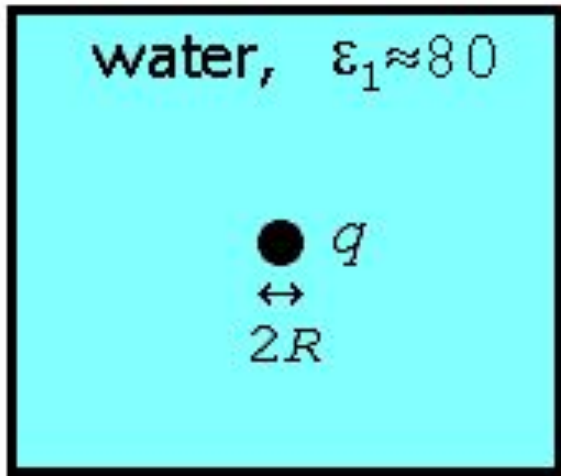
In non-uniform media: $\epsilon_{\text{eff}} = ?$

At atomic distances: $\epsilon_{\text{eff}} = ?$

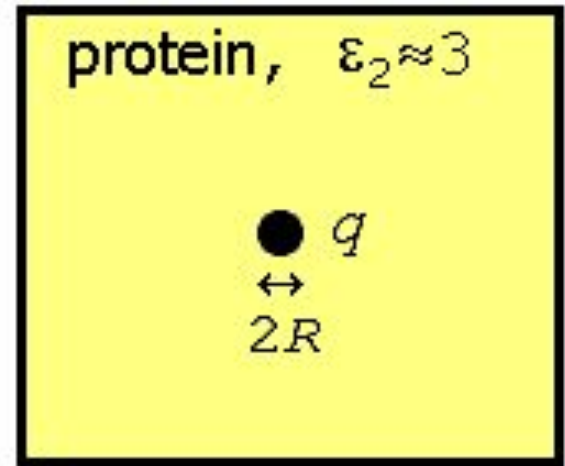
Charles-Augustin de Coulomb



(1736-1806)



CHARGE inside PROTEIN



$$\Delta U_{1 \Rightarrow 2} = q^2/2\epsilon_2 R - q^2/2\epsilon_1 R$$

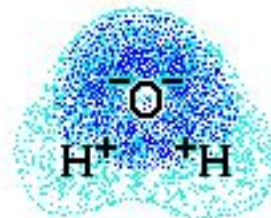
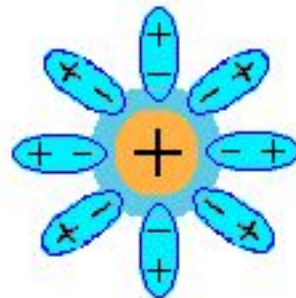
Water => vacuum:
 $\Delta U \approx +100$

kcal/mol

— $R=(1.5-2 \text{ \AA}) +0.1\text{\AA}$

+ $R=(1-1.5 \text{ \AA}) +0.7\text{\AA}$

++ $R=(0.5-1 \text{ \AA}) +0.7\text{\AA}$



Water => PROTEIN
($\epsilon \approx 3$)

$R \approx 1.5 - 2 \text{ \AA}$

$\Delta U \approx +30 - 40 \text{ kcal/mol}$

CHARGE inside
PROTEIN:
VERY BAD

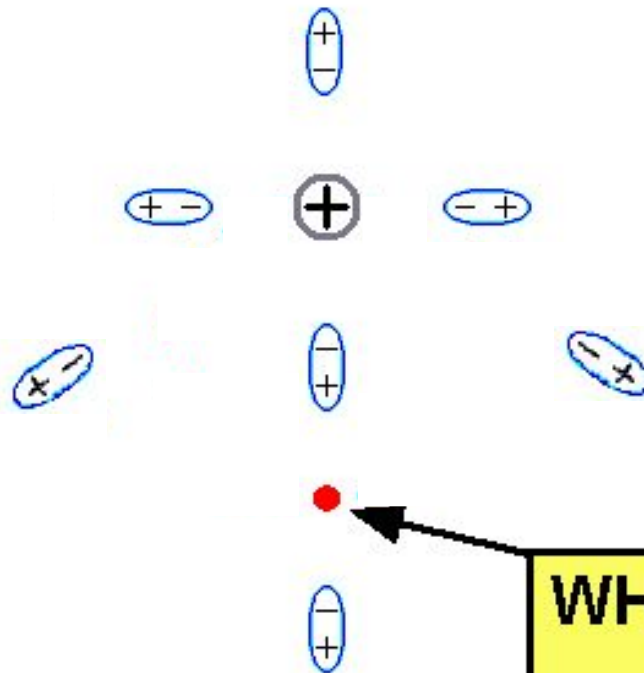
Non-uniform media:

$$\epsilon_{\text{eff}} = ?$$

KNOWN:

molecules (dipoles) decrease potential:

$$U \sim 1/\epsilon r$$



WHICH dipoles
decrease
potential here?

Non-uniform media:

$$\epsilon_{\text{eff}} = ?$$

KNOWN:

molecules (dipoles) decrease potential:

$$U \sim 1/\epsilon r$$



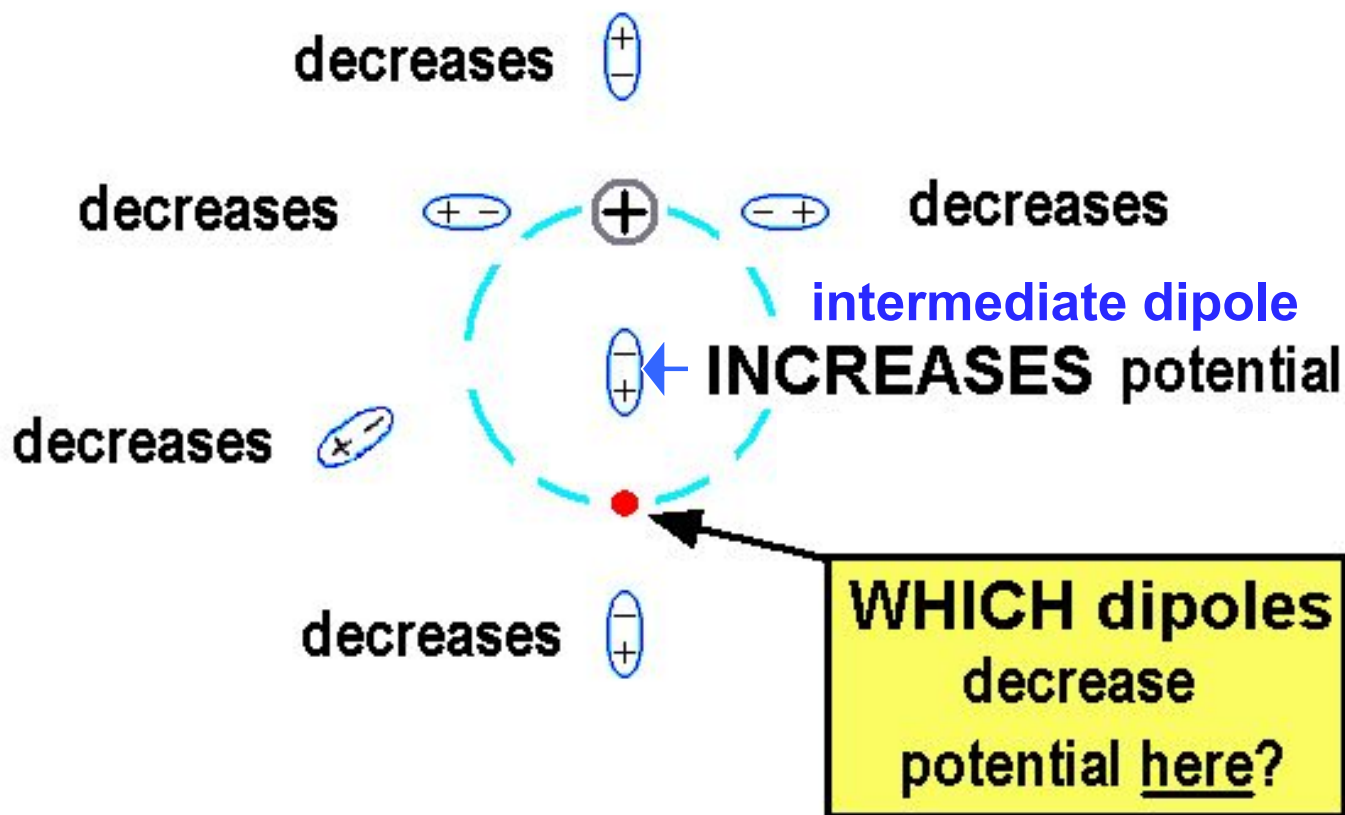
Non-uniform media:

$$\epsilon_{\text{eff}} = ?$$

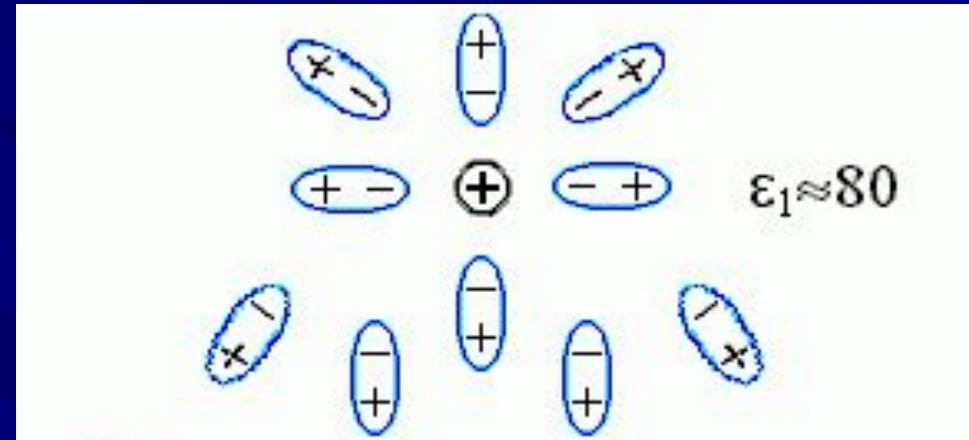
KNOWN:

molecules (dipoles) decrease potential:

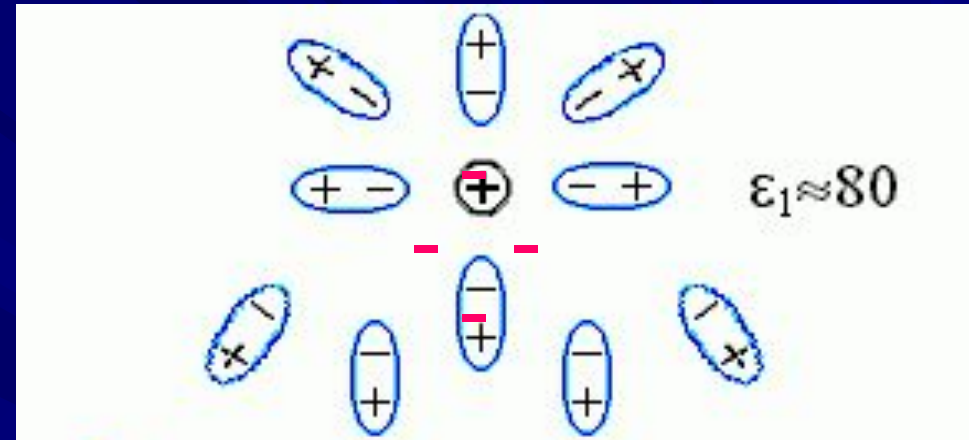
$$U \sim 1/\epsilon r$$



$$\phi = q/\epsilon_1 r$$

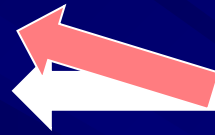


$$\phi = (q/\epsilon_1)/r$$



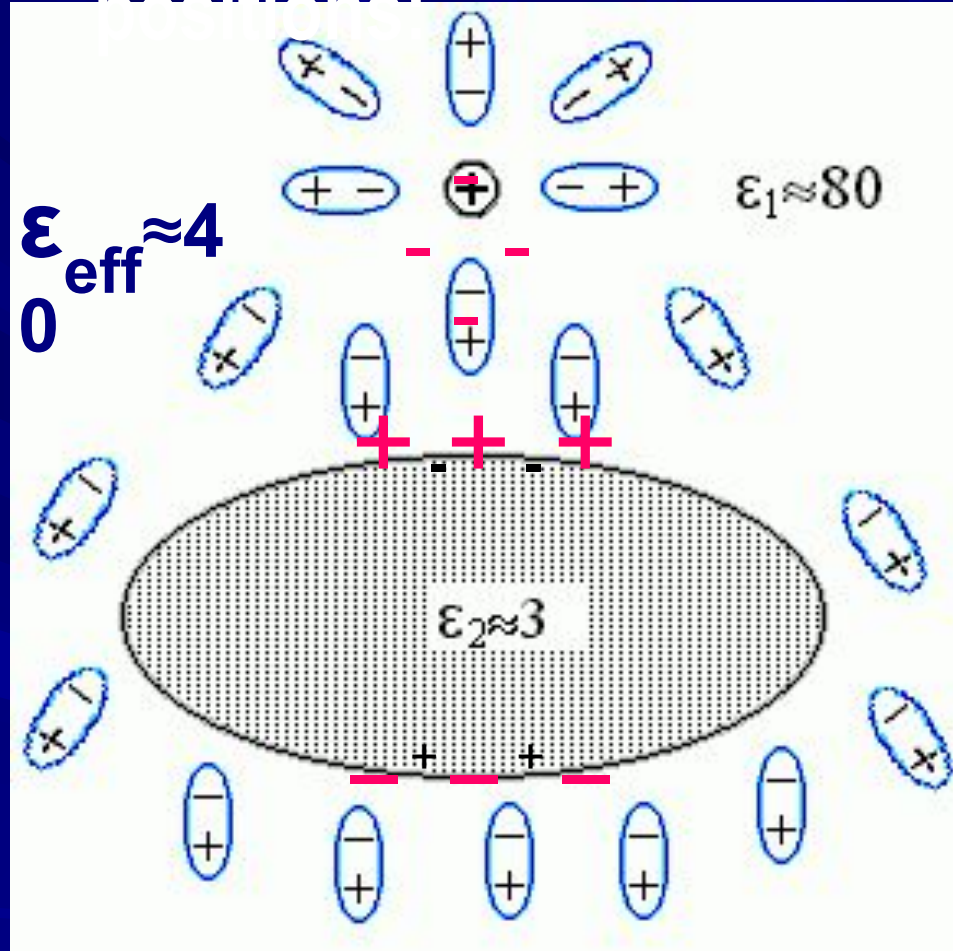
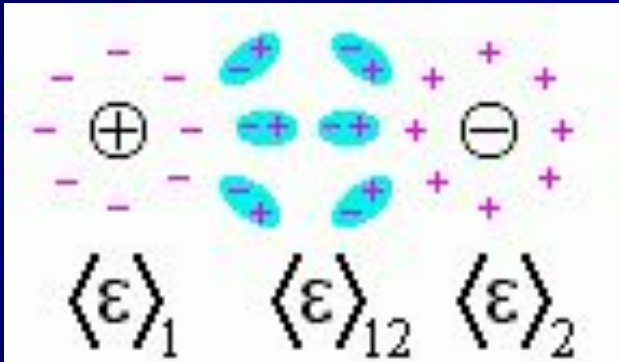
$$\phi = q/r\epsilon_{\text{eff}} \text{ in}$$

$$\vec{E} = -d\phi/d\vec{r}$$



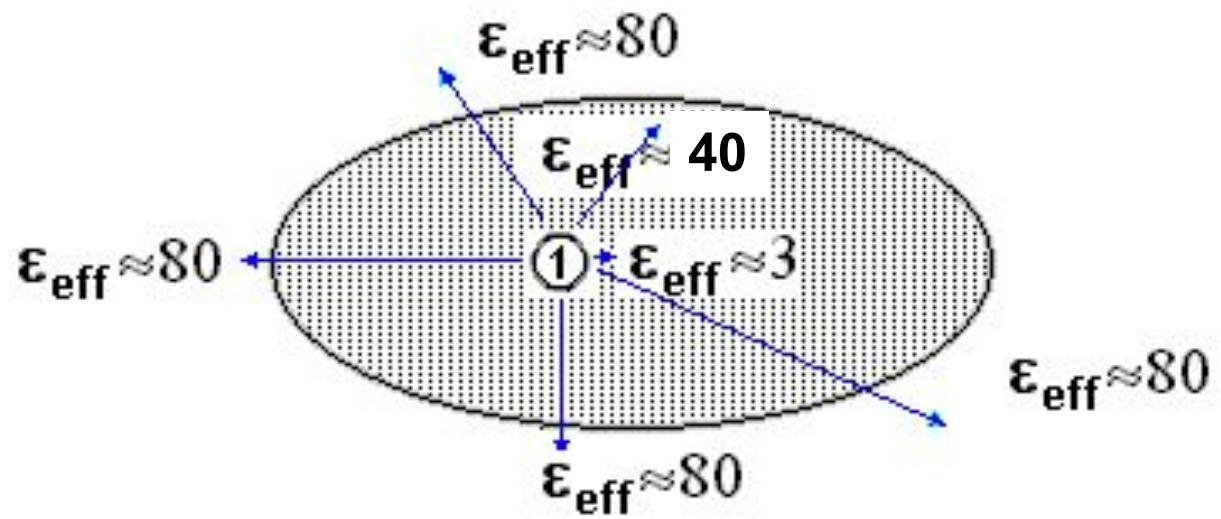
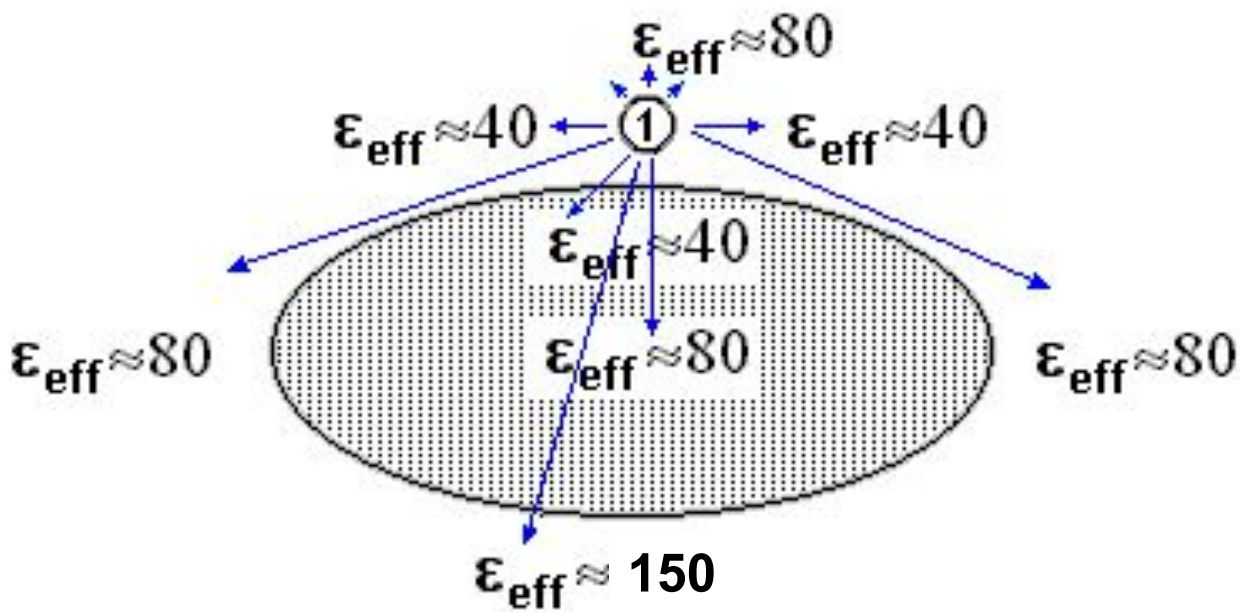
$$U = q_1 q_2 / \epsilon_{\text{eff}} r =$$

$$(q_1 / \langle \epsilon \rangle_1) \cdot (\langle \epsilon \rangle_{12} / r) \cdot (q_2 / \langle \epsilon \rangle_2)$$



$$\epsilon_{\text{eff}} \approx 150 !!$$

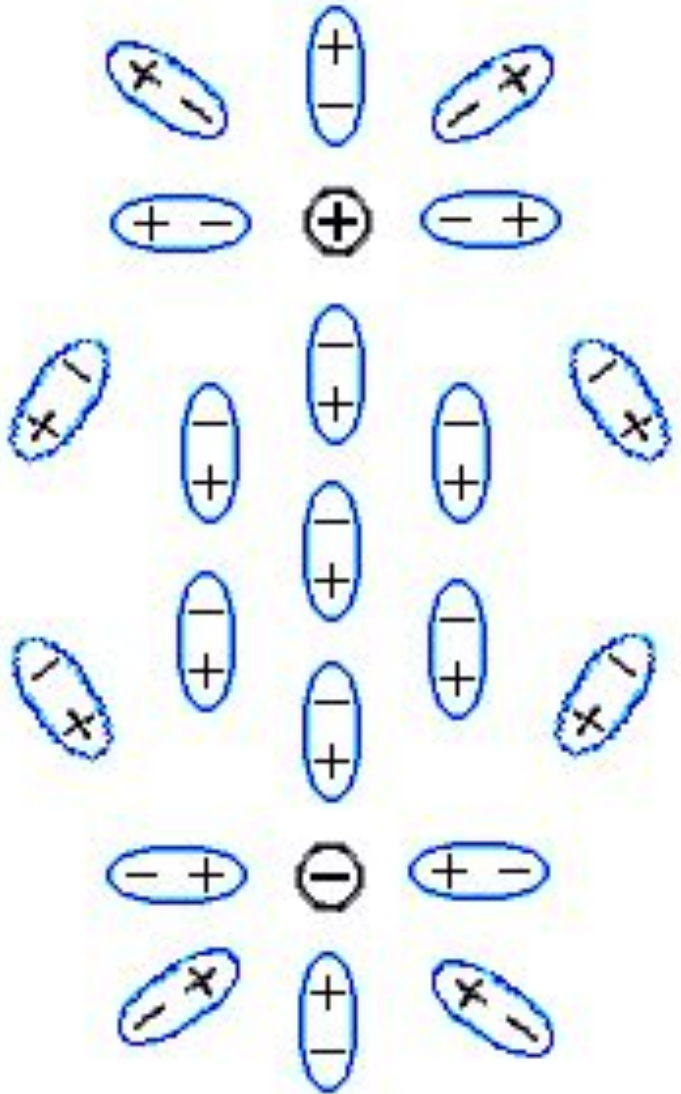
Good estimate for non-uniform media



$\epsilon_{\text{effective}}$
in non-uniform media

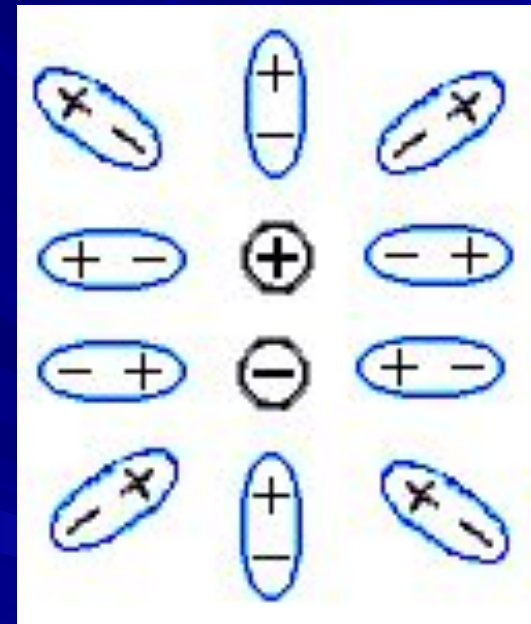
Large distance:

$$\epsilon_{\text{eff}} = \epsilon = 80$$



Atomic distance:

$$\epsilon_{\text{eff}} = ?$$

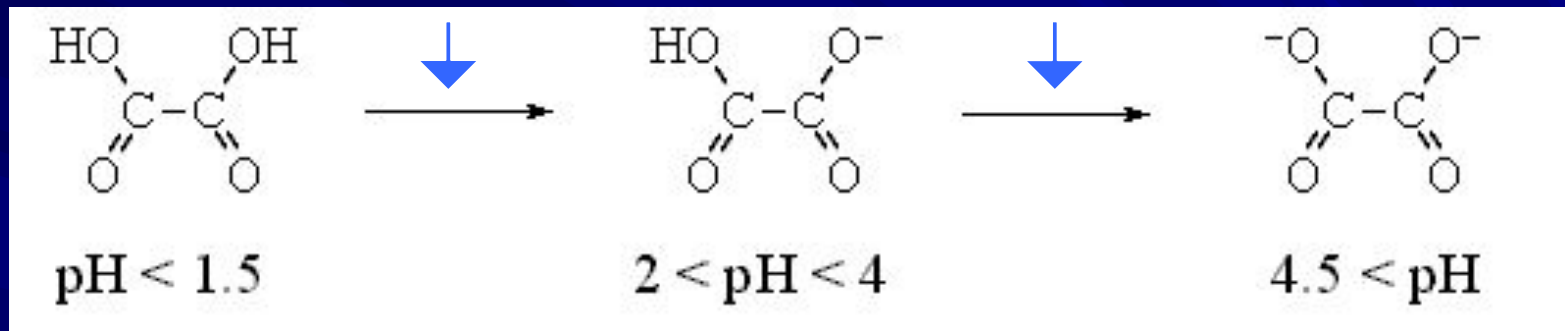


intermediate
“vacuum”, $\epsilon \sim 1$?
but the absence
of intermediate
dipoles can
only increase
interaction...

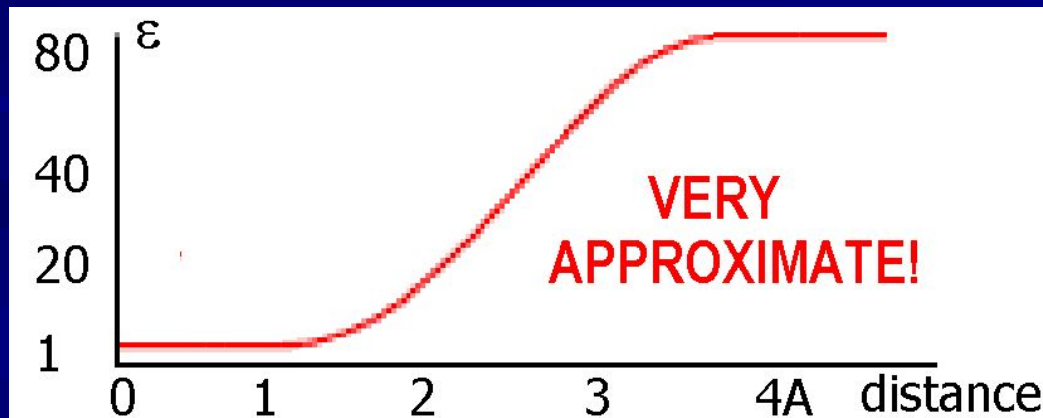
At atomic distances in water:

1) $\epsilon=80$ is not a bad approximation (much better than $\epsilon = 1$ or 3 !!)
(salt does not dissolve, if $\epsilon < 50$ at 3\AA !)

2) $[\text{H}]_{1/2} = 10^{-1.75}$ $[\text{H}]_{1/2} = 10^{-4.25} = 10^{-1.75} \times e^{-\Delta G_{el}/RT}$

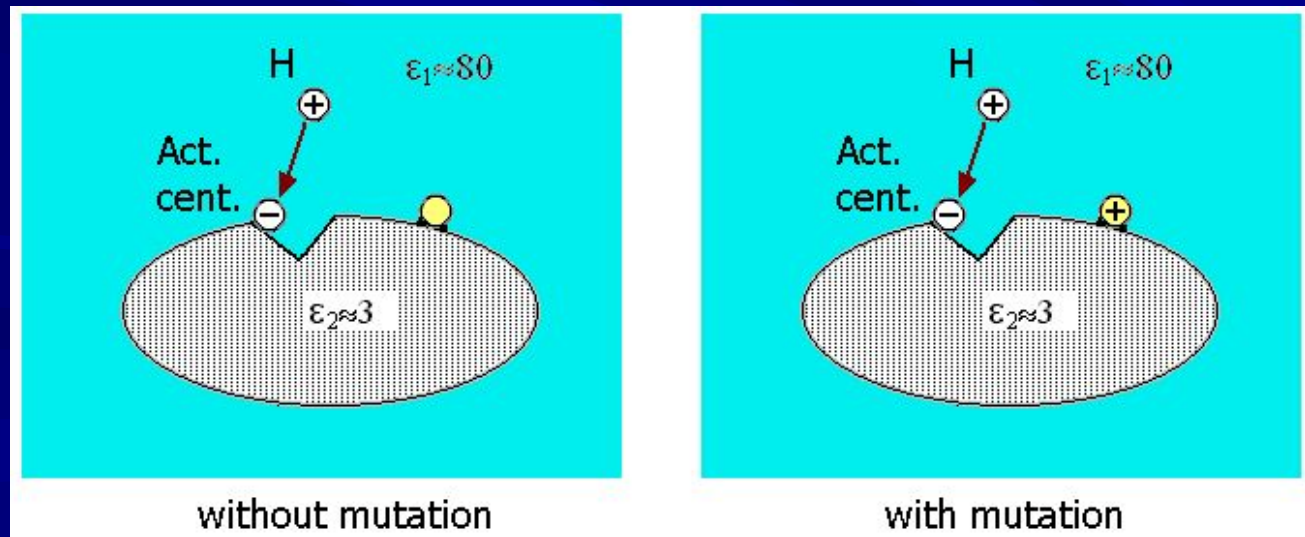
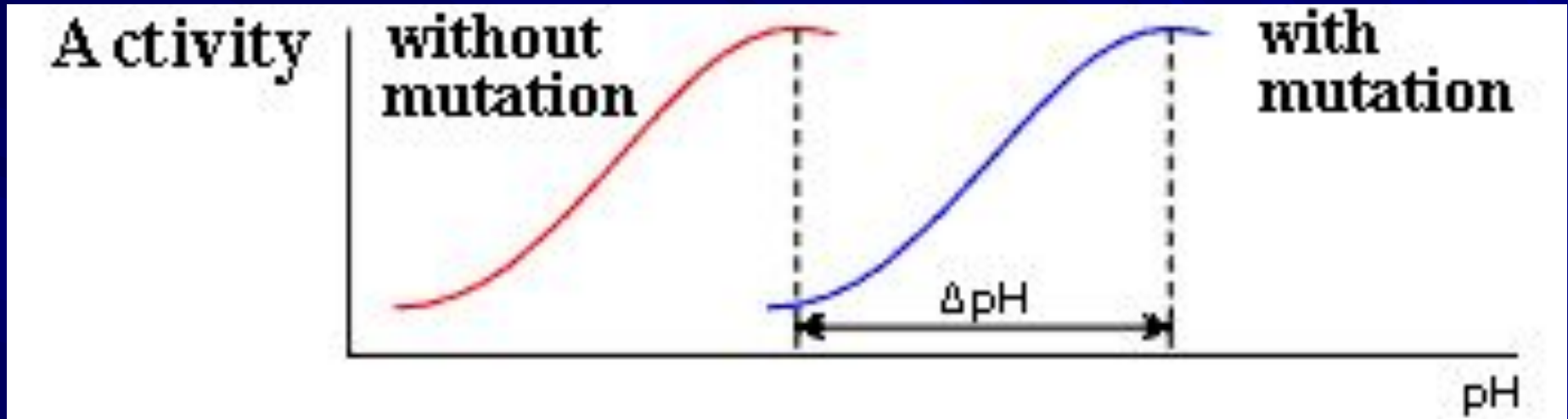


$\Delta G_{el} = 2.5 \times \ln(10) \times RT \approx 6RT \approx 3.5 \text{ kcal/mol}$ at $\approx 2.5\text{\AA}$
 $\epsilon \approx 30-40$ at $\approx 2.5\text{\AA}$!



Protein engineering experiments:

$$\phi(r) = \Delta\text{pH} \times 2.3RT \Rightarrow \Rightarrow \epsilon_{\text{eff}}(r)$$

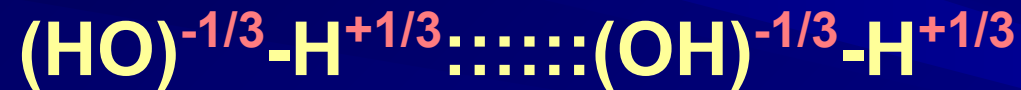
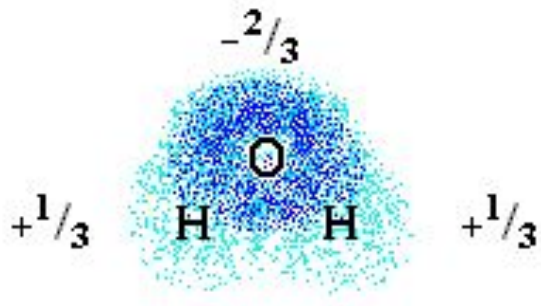
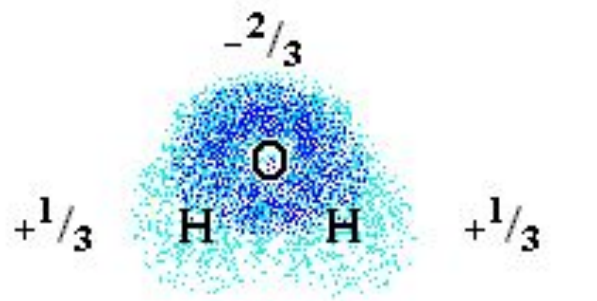




Sir Alan Roy Fersht, 1943

Protein engineering

Dipole interactions (e.g., H-bonds):



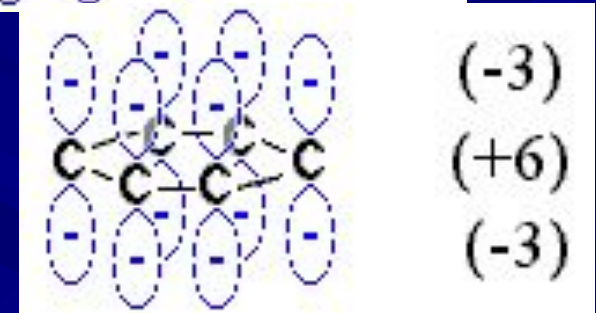
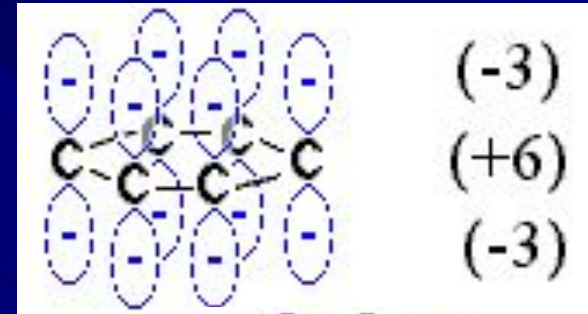
Also: charge-dipole, dipole-quadrupole, etc.

Potentials:

$$\phi_{\text{dipole}} \sim 1/\epsilon r^2$$

$$\phi_{\text{quadrupole}} \sim 1/\epsilon r^3$$

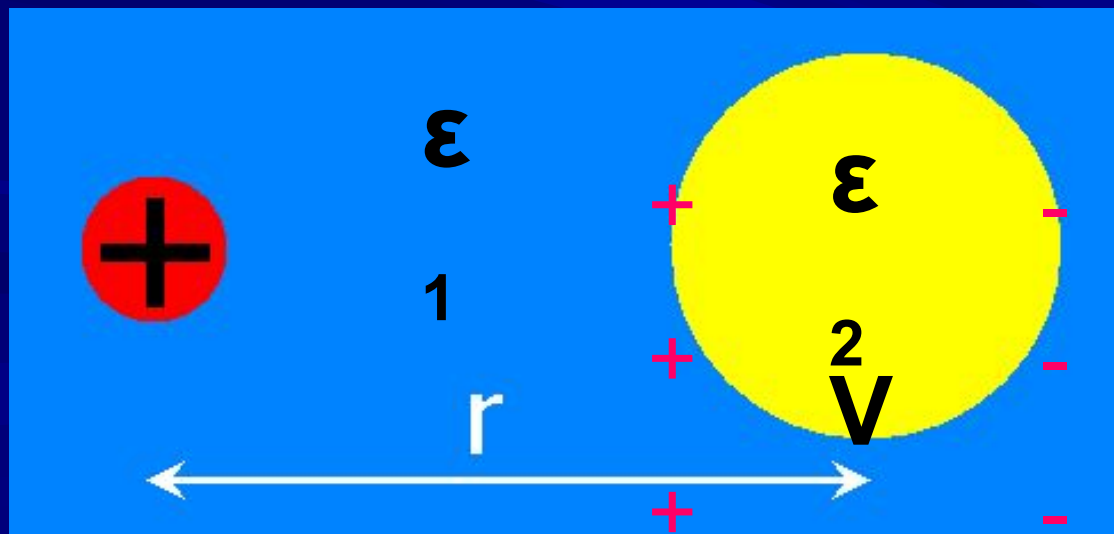
Quadruple interactions



Electrostatic interactions also occur between charge (q) and non-charged **body**, if its ϵ_2 differs from the media's ϵ_1 :

$$U \sim q \cdot [1/\epsilon_2 - 1/\epsilon_1] \cdot [\epsilon_2 / (\epsilon_1 + \epsilon_2 / 2)] \cdot V \cdot (1/r^4) \quad \text{at large } r$$

In water: repulsion of charges from non-polar molecules (since here $\epsilon_1 \gg \epsilon_2$);
 in vacuum (where $\epsilon_1 < \epsilon_2$): just the opposite!



Debye-Hückel screening of electrostatic by ions:

$$U = [q_1 q_2 / \epsilon r] \cdot \exp(-r/D) ;$$

$$\text{in water: } D = 3\text{\AA} \cdot I^{-1/2} ;$$

$$\text{Ionic strength } I = \frac{1}{2} \sum_i C_i (Z_i^{\text{ion}})^2 .$$

$$\text{Usually: } I \approx 0.1 \text{ [mol/liter]}; \quad D \approx 8\text{\AA}.$$

Electrostatics is an example of a multi-body
(charge1, charge2, media, ions) interaction

Electrostatics is T-dependent;

$$U = (1/\varepsilon) \cdot (q_1 q_2 / r)$$

is free energy ($U = H - TS$);

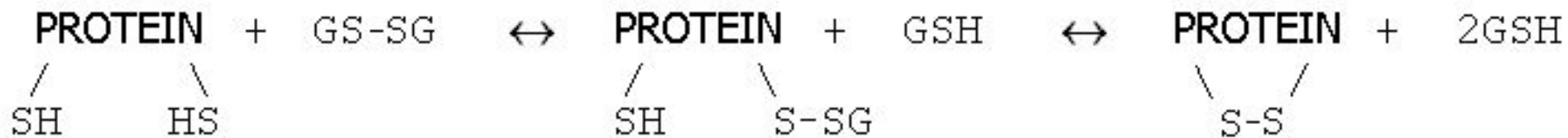
$$\begin{aligned} TS &= T \cdot (-dU/dT) = -T \cdot [d(1/\varepsilon)/dT] \cdot (q_1 q_2 / r) = \\ &= [d \ln(\varepsilon) / d \ln T] \cdot U \end{aligned}$$

in water: when T grows from 273° to 293°K (by 7%),
ε decreases from 88 to 80 (by 10%):

$$-TS \approx 1.3 U; \quad H \approx -0.3 U$$

In water the entropic term ($-TS$) is the main
for electrostatics!

S-S bonds (Cys-Cys)

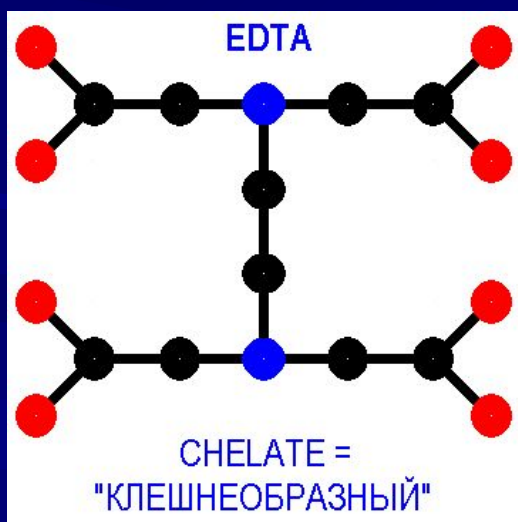
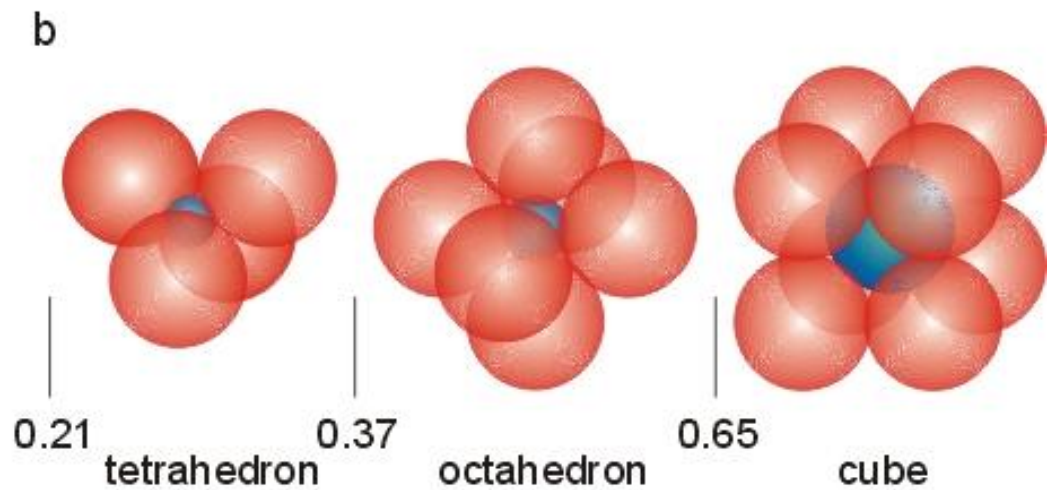
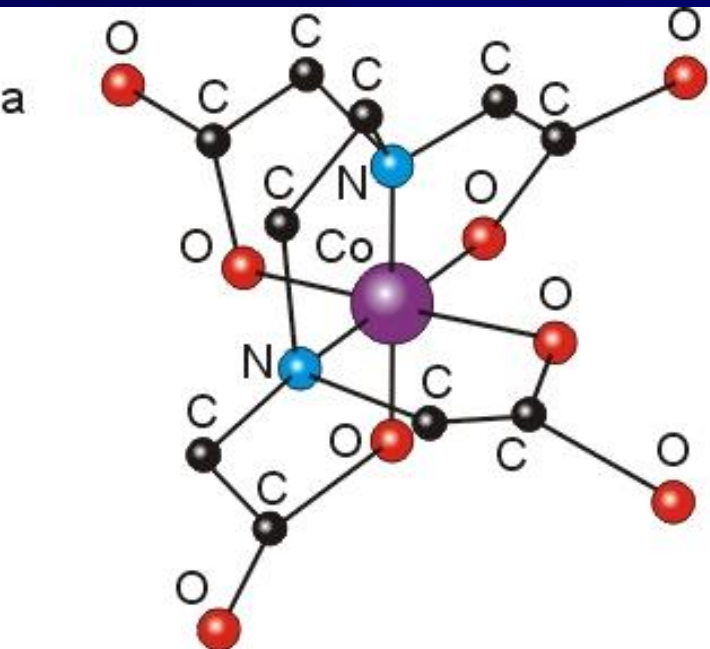


exchange:

entropic force

S-S bond is not stable
within a cell

Coordinate bonds (with Zn^{++} , Fe^{+++} , ...)



exchange:

entropic

force