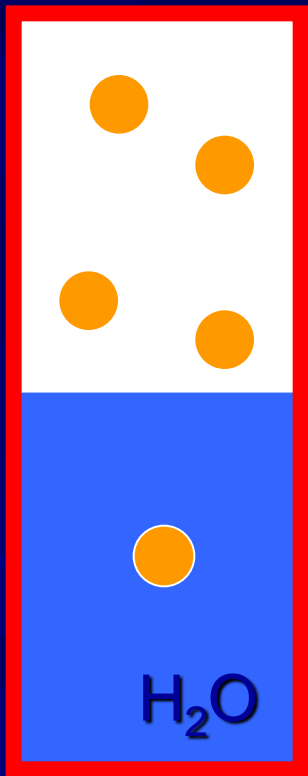


PROTEIN PHYSICS

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 C_6H_{14} 
in H_2O :
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**

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

and T is measured in degrees, while

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

Thus, k_B is energy_unit/degree

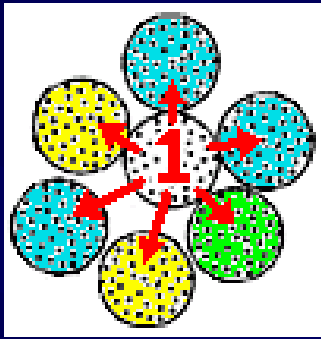
FREE ENERGY:

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

Boltzmann

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

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



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

Chemical potential:

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

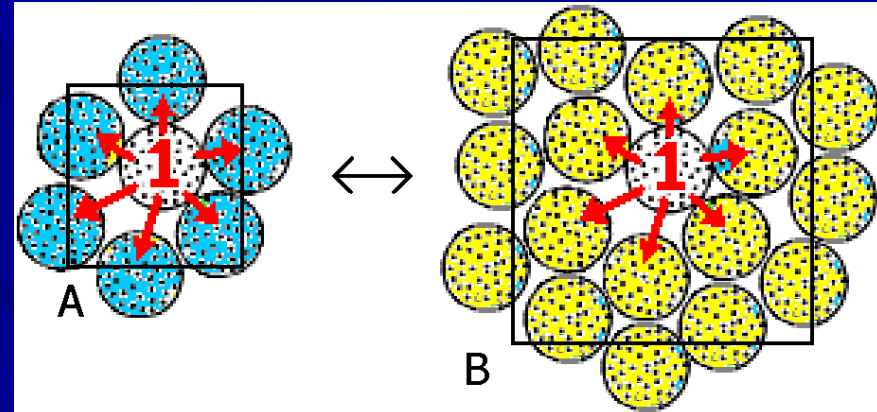
EQUILIBRIUM for transition

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

chemical potentials in A and B are equal

$$\Delta G^{\text{int}}_{A \rightarrow B} \equiv G^{\text{int}}_B - G^{\text{int}}_A$$

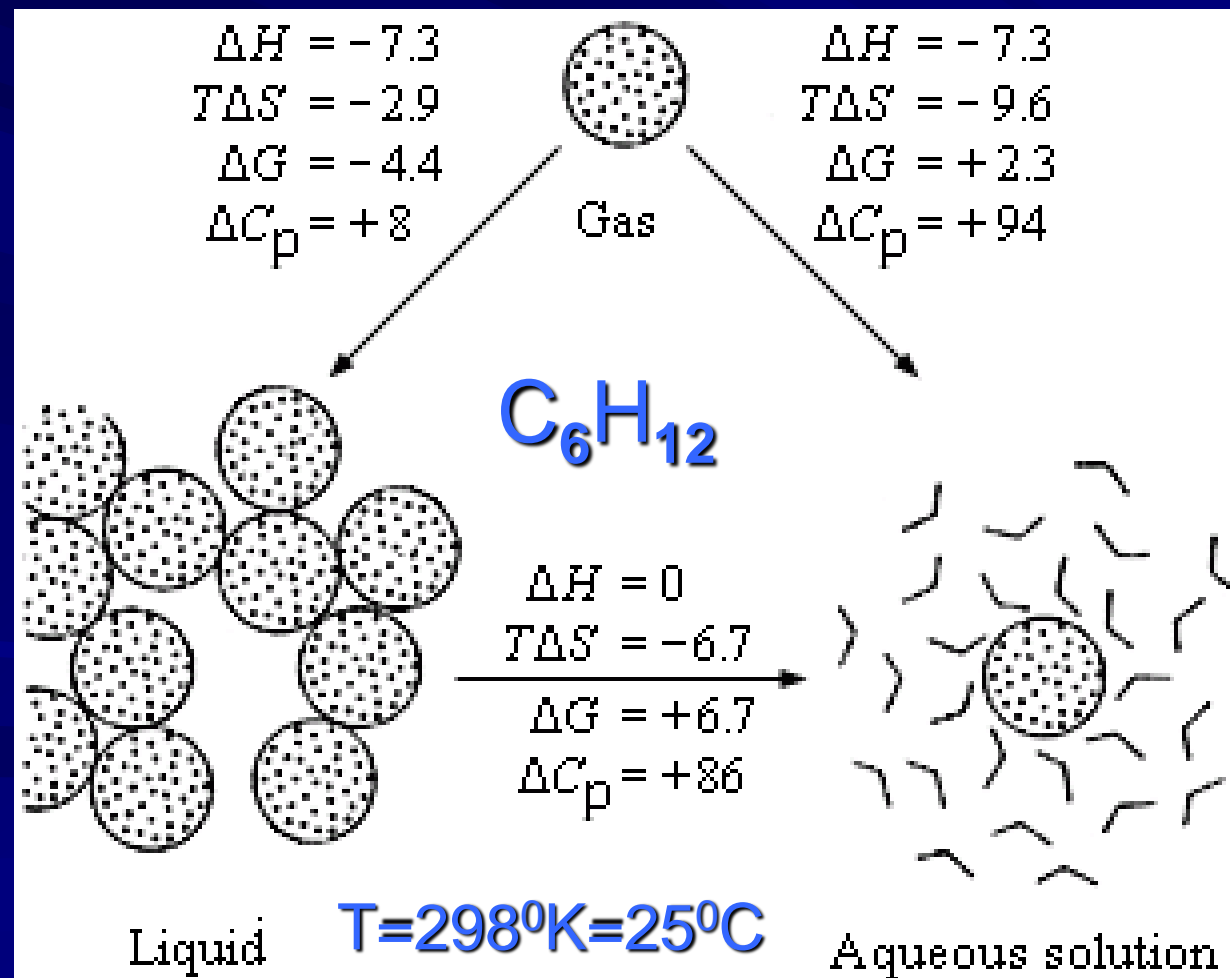
$$\Delta G^{\text{int}}_{A \rightarrow B} = k_B T \cdot \ln([C_{\text{inA}}]/[C_{\text{inB}}])$$



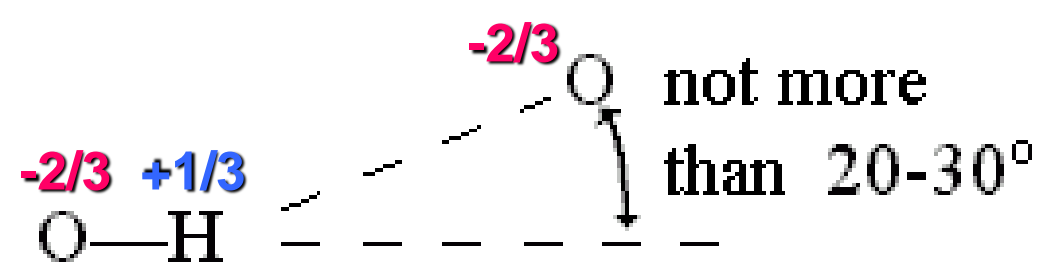
Experiment: $\Delta G^{\text{int}}_{A \rightarrow B} = k_B T \cdot \ln([C_{1 \text{ in } A}]/[C_{1 \text{ in } B}])$

$$\Delta S^{\text{int}}_{A \rightarrow B} = -d(\Delta G^{\text{int}}_{A \rightarrow B})/dT$$

$$\Delta H^{\text{int}}_{A \rightarrow B} = \Delta G^{\text{int}}_{A \rightarrow B} + T\Delta S^{\text{int}}_{A \rightarrow B}$$

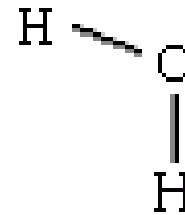


[C] of C_6H_{12}
in H_2O :
50 times **less**
than in gas;
100000 times
less than in
liquid C_6H_{12}



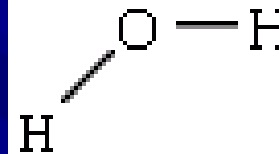
H-bond: directed

Loss: S



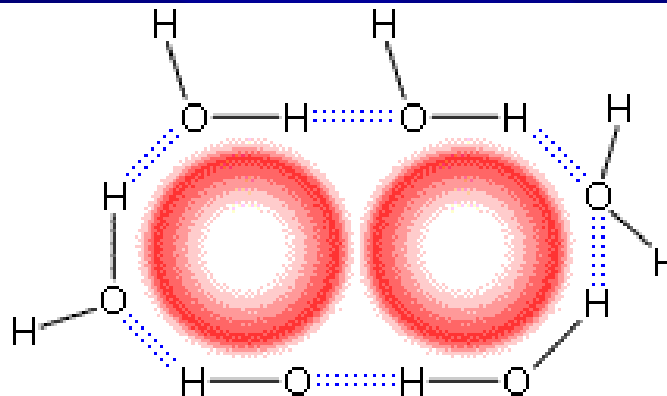
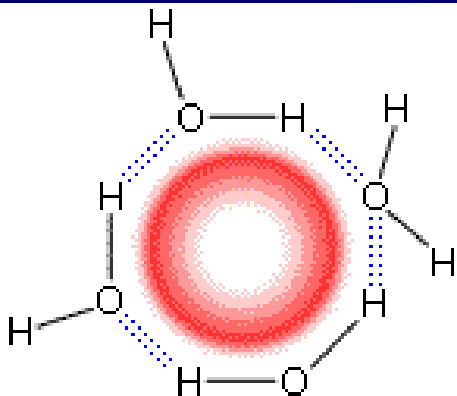
usual case

Loss: LARGE E

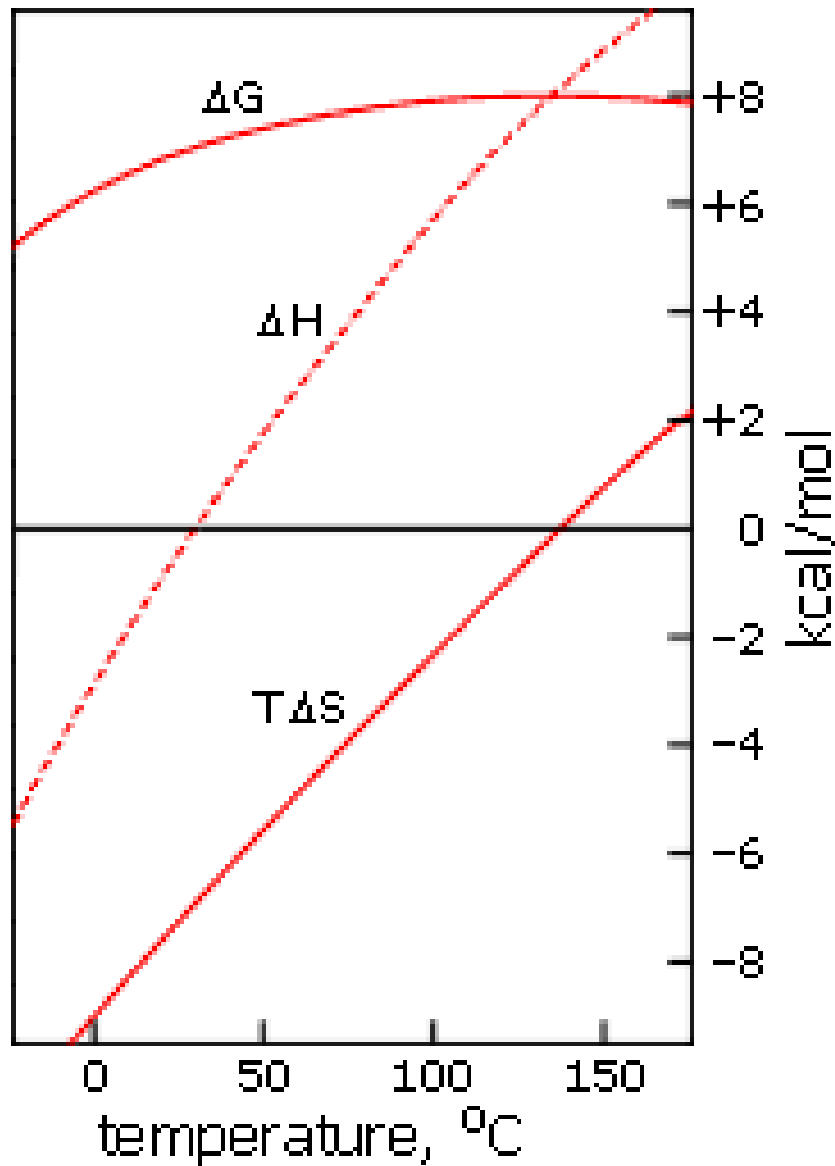


Non-polar body

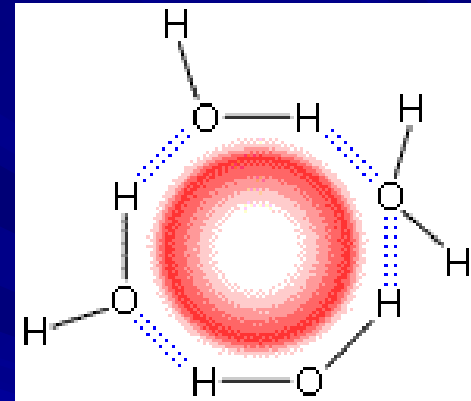
rare case

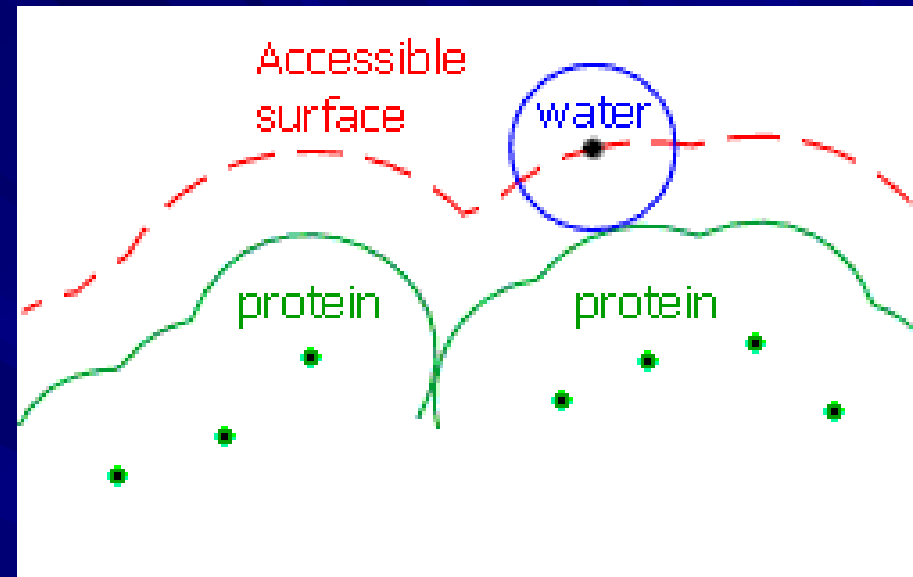
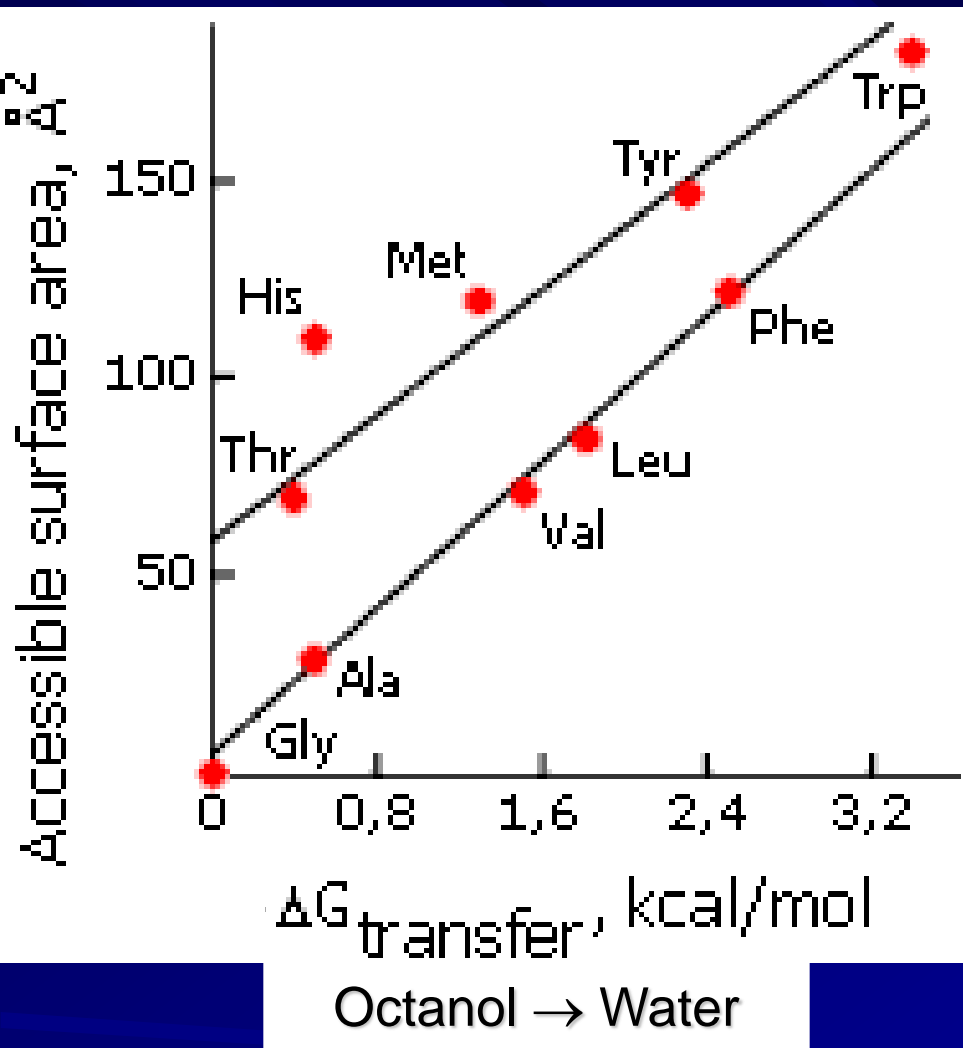


“hydrophobic bond”



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





20-25 cal/mol per Å² of molecular accessible non-polar surface



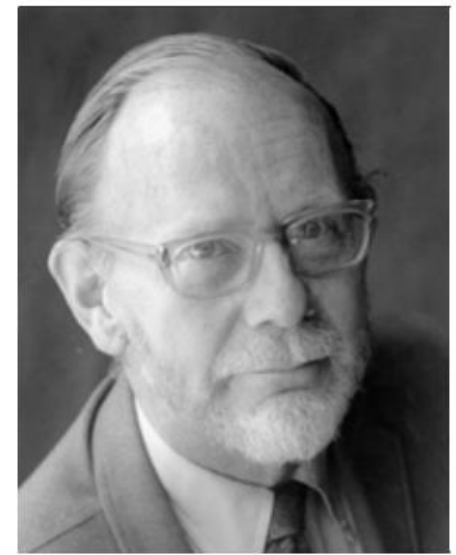
Семён Ефимович **Бреслер**
(1911 – 1983)

Hypothesis on a role of hydrophobic effect in protein folding



Давид Львович **Талмуд**
(1900 - 1973)

Hydrophobic
effect
&
denaturation
of proteins



**WALTER
KAUZMANN**

1916-2009



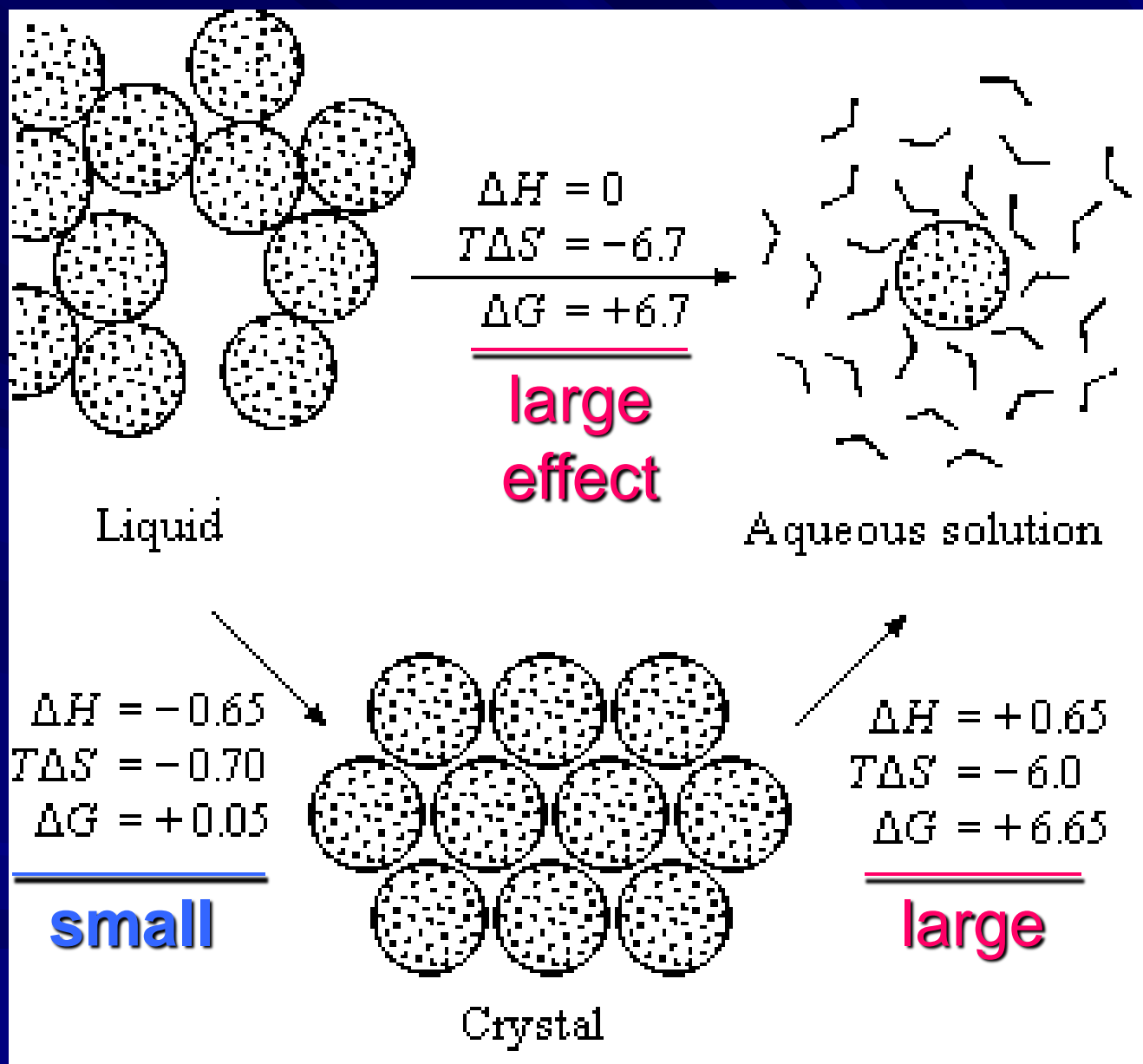
Charles **Tanford**
(1921 - 2009)

General physical
features of
Hydrophobic
effect



Cyrus Homi **Chothia**,
1942

Hydrophobic
effect
&
amino acid
water-accessible
surface



Electrostatics in uniform media:

potential $\varphi_1 = q_1/\epsilon r$

Interaction of two charges:

$$U = \varphi_1 q_2 = \varphi_2 q_1 = q_1 q_2 / \epsilon r$$

$\epsilon = 1$ vacuum

$\epsilon \approx 3$ protein

$\epsilon \approx 80$ water

Protein/water interface

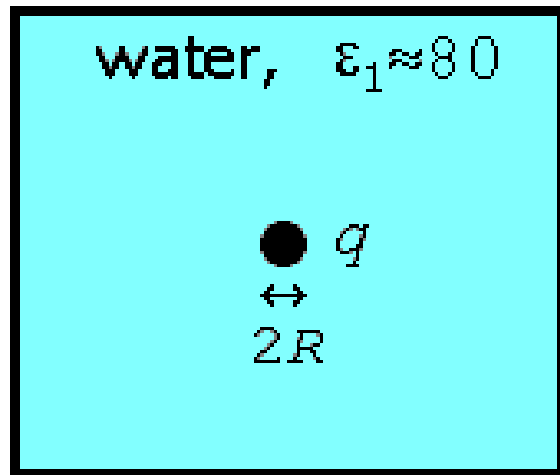
In non-uniform media: $\epsilon_{\text{eff}} = ?$

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

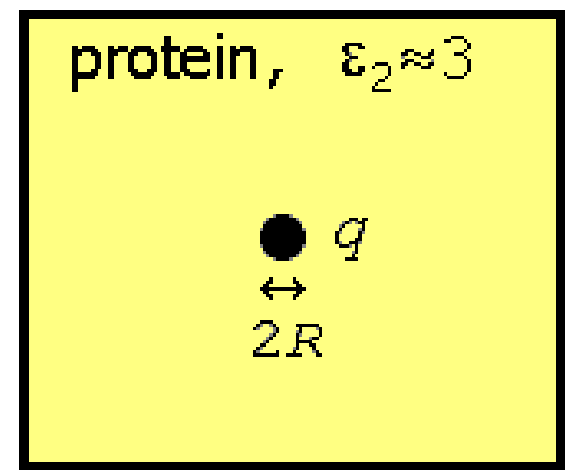
Charles-Augustin de Coulomb



(1736-1806)

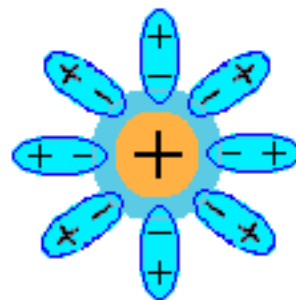
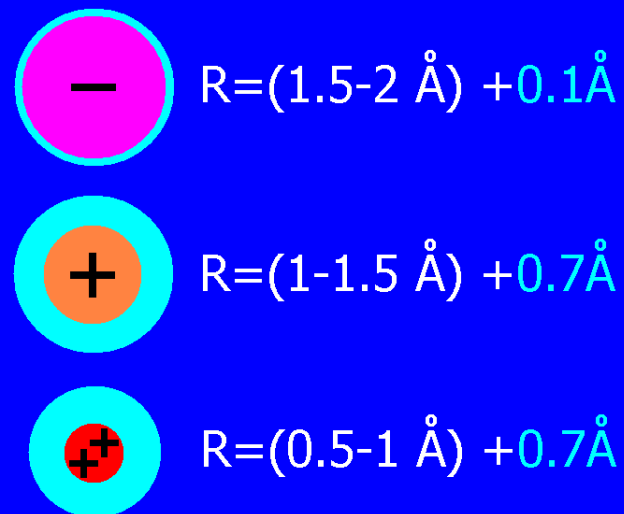


**CHARGE
inside
PROTEIN**



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

Water \Rightarrow vacuum:
 $\Delta U \approx +100$ kcal/mol



Water \Rightarrow PROTEIN
($\epsilon \approx 3$)

$R \approx 1.5 - 2 \text{ \AA}$
 $\Delta U \approx +30 - 40$ kcal/mol

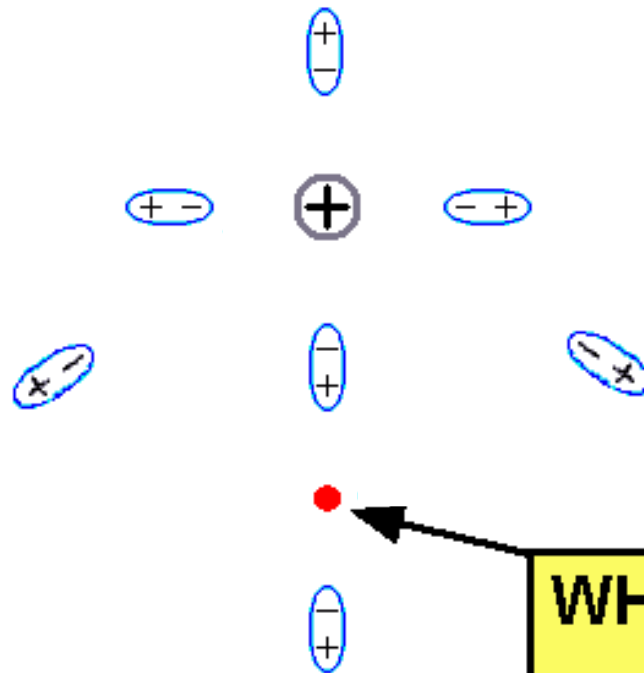
CHARGE inside
PROTEIN:
VERY BAD

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:

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

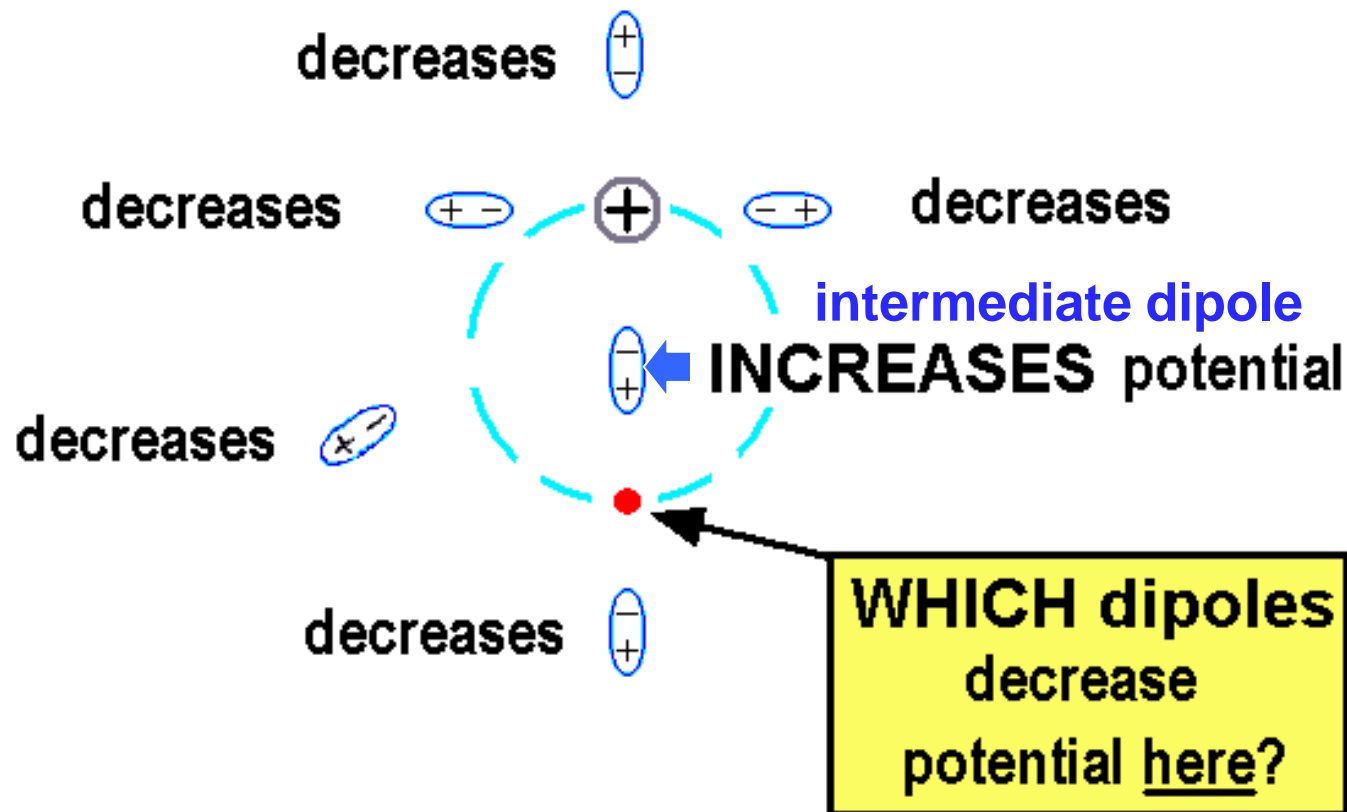


Non-uniform media: $\epsilon_{\text{eff}} = ?$

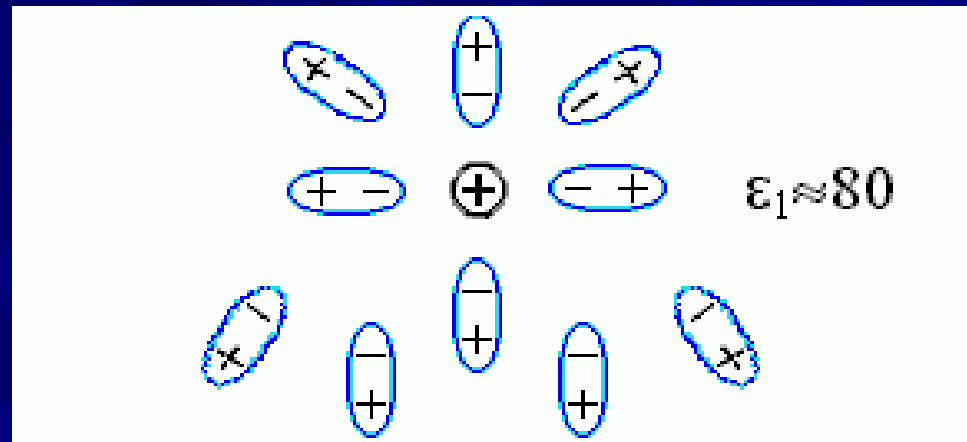
KNOWN:

molecules (dipoles) decrease potential:

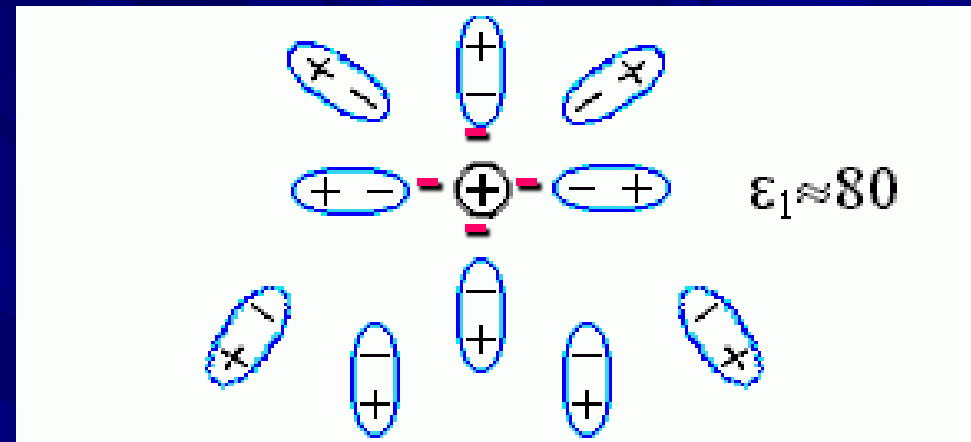
$$U \sim 1/\epsilon r$$



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

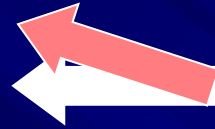


$$\phi = (q/\epsilon_1)/r$$



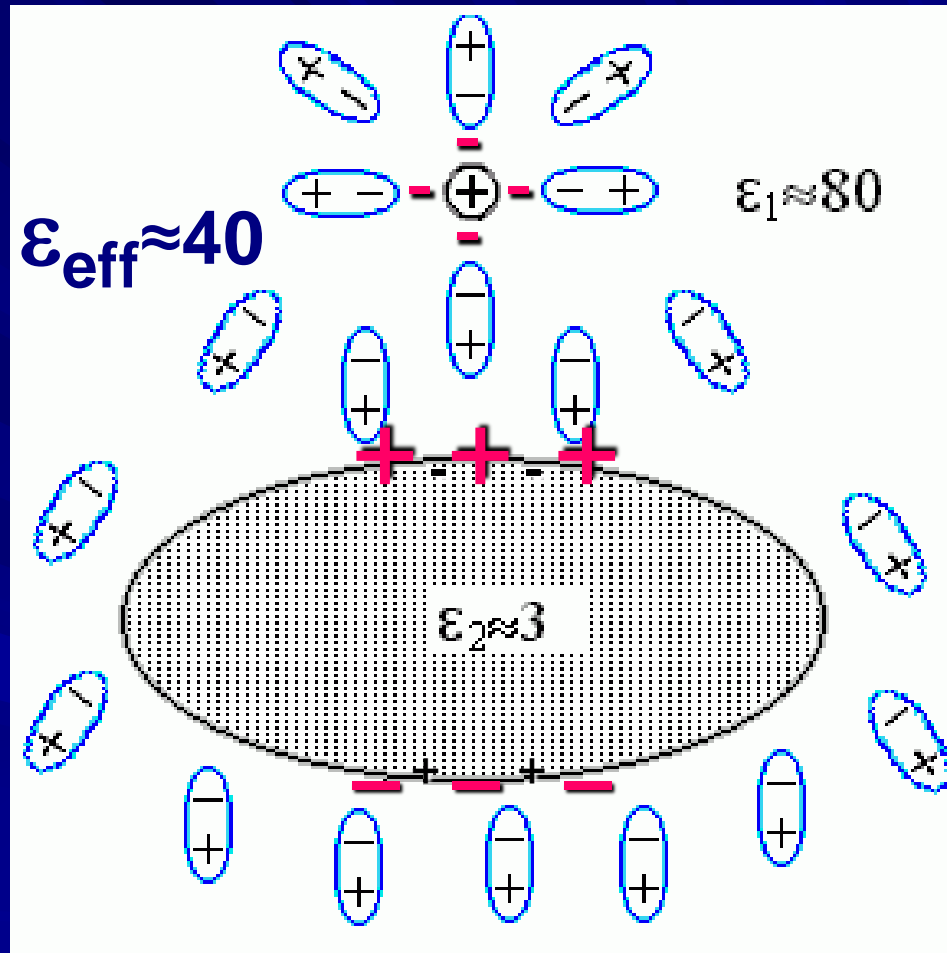
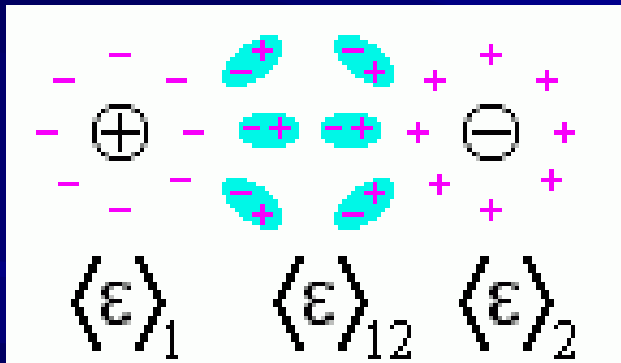
$\phi = q/r\epsilon_{\text{eff}}$ in positions:

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



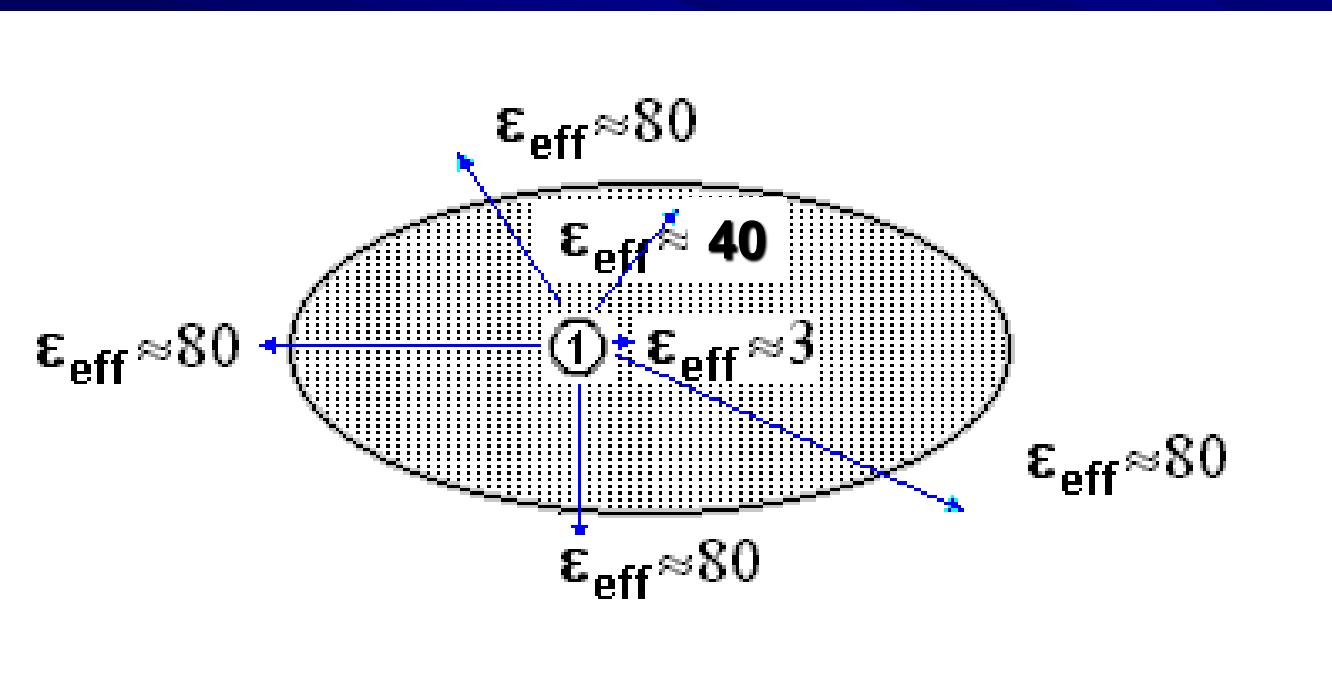
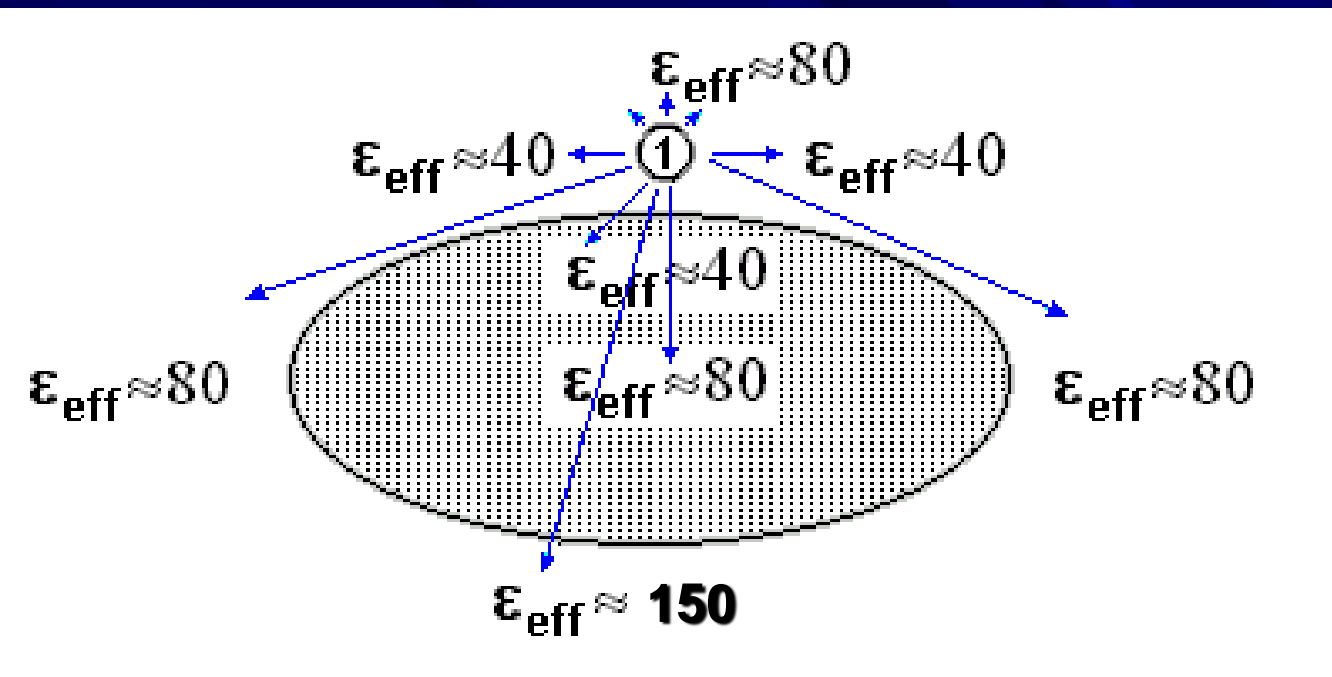
$$U = q_1 q_2 / \epsilon_{\text{eff}} r =$$

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



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

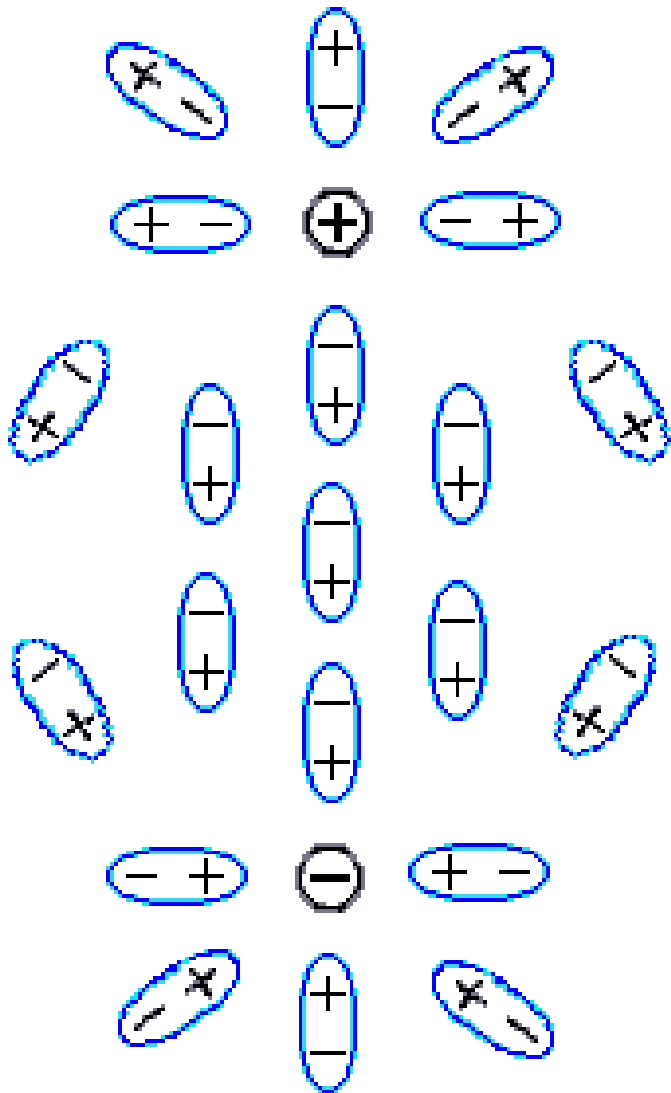
Good estimate for
non-uniform media



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

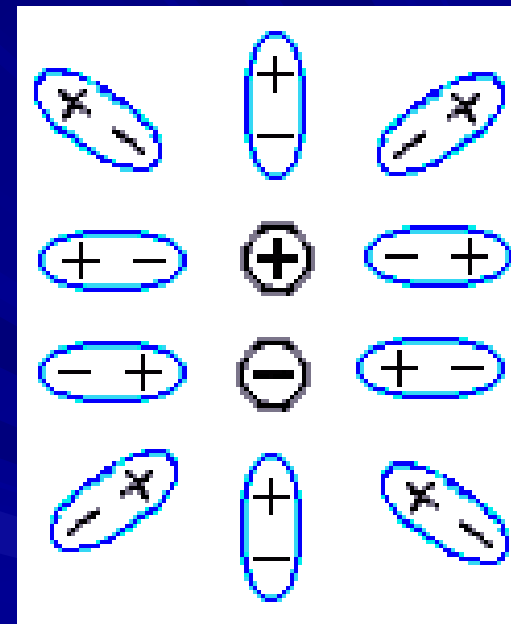
Large distance:

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



Atomic distance:

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

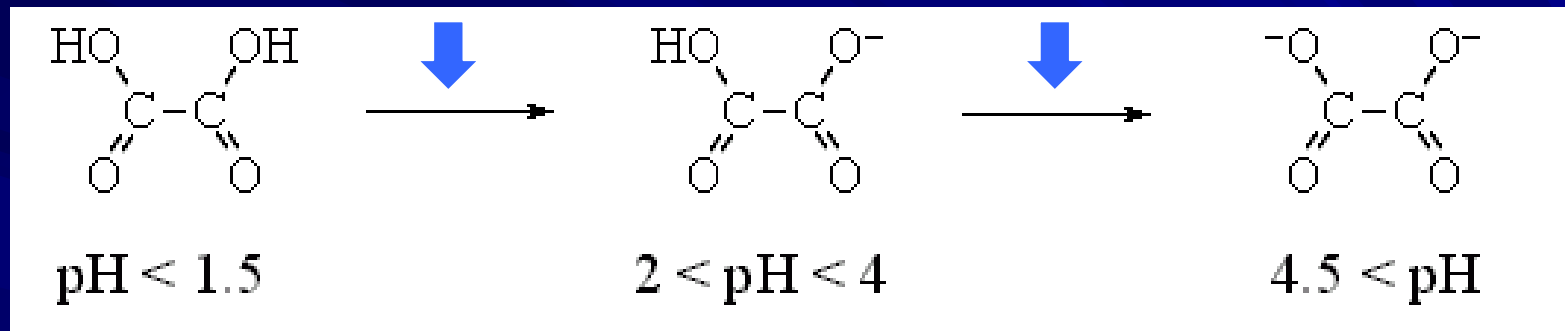


intermediate
“vacuum”, $\epsilon \sim 1$?
but the absence
of intermediate
dipoles can
only increase
interaction...

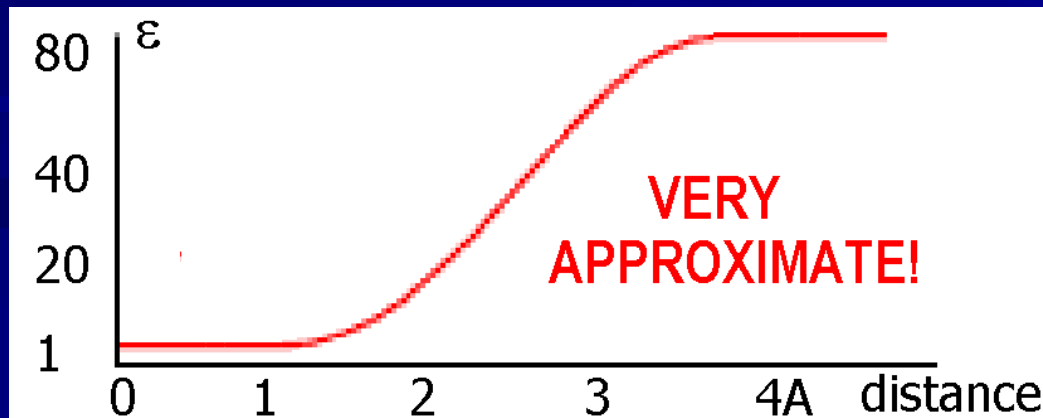
At atomic distances in water:

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

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



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

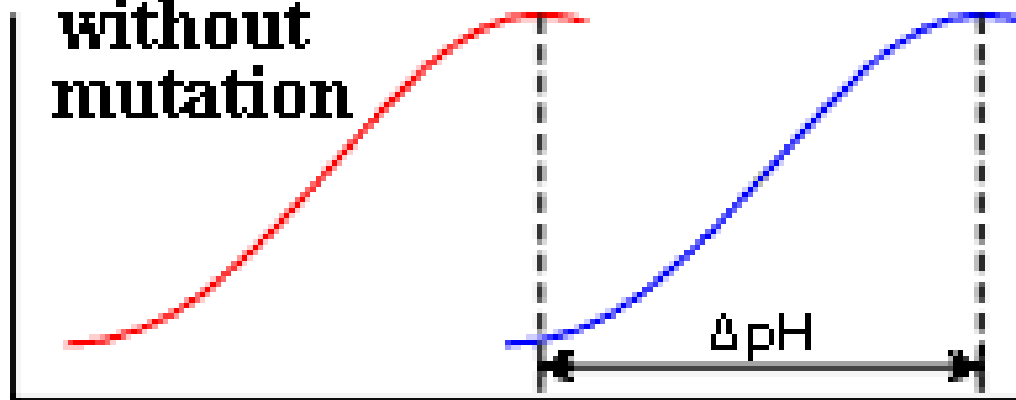


Protein engineering experiments:

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

Activity

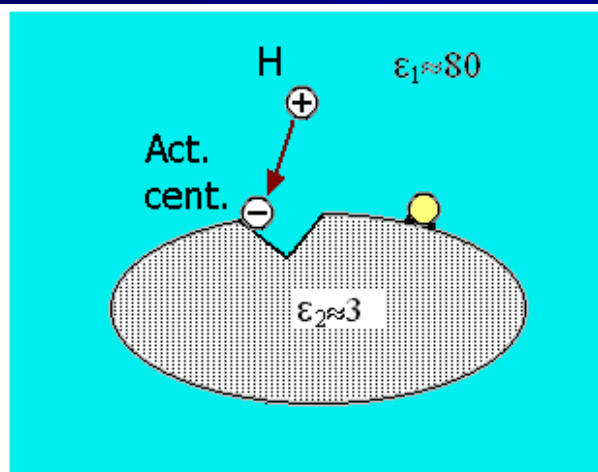
without
mutation



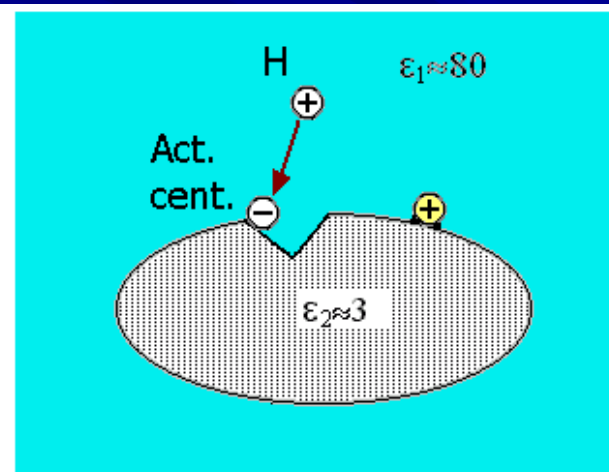
with
mutation



pH



without mutation



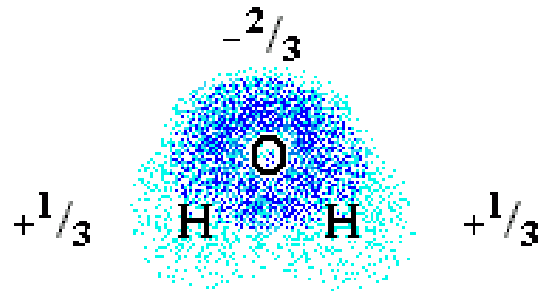
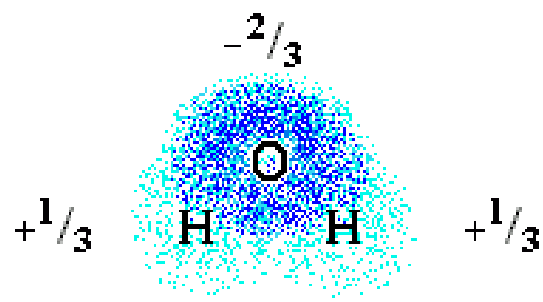
with mutation



Sir Alan Roy **Fersht**, 1943

Protein engineering

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

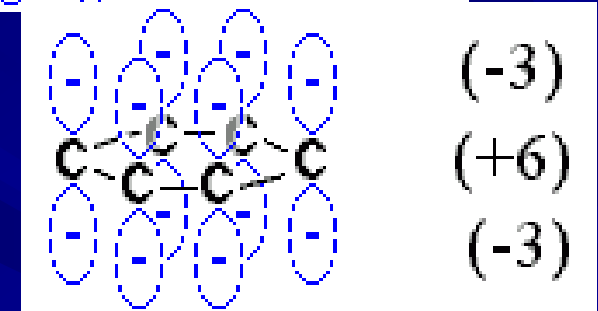
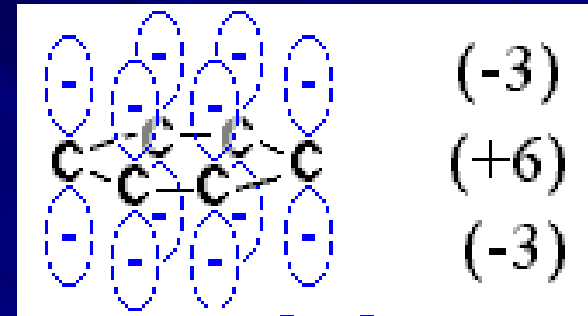


Also: charge-dipole, dipole-quadrupole, etc.

Potentials:

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

Quadrupole interactions

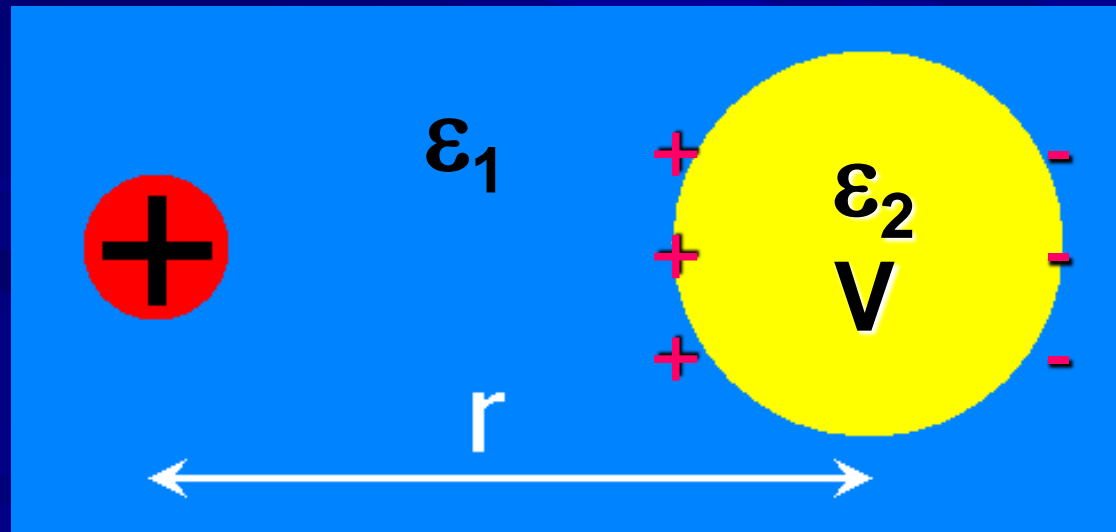


$$\Phi_{\text{quadrupole}} \sim 1/\epsilon r^3$$

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

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

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;

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

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

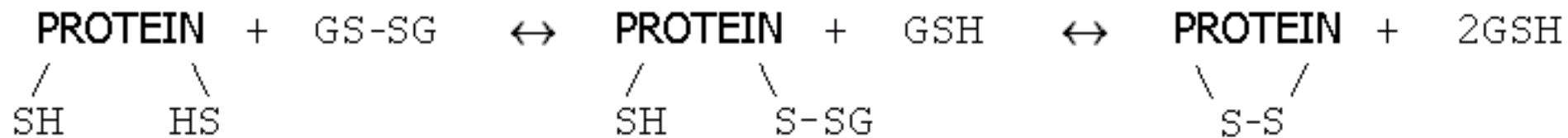
$$\begin{aligned} TS &= T \cdot (-dU/dT) = -T \cdot [d(1/\epsilon)/dT] \cdot (q_1 q_2 / r) = \\ &= [d\ln(\epsilon)/d\ln T] \cdot U \end{aligned}$$

**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)

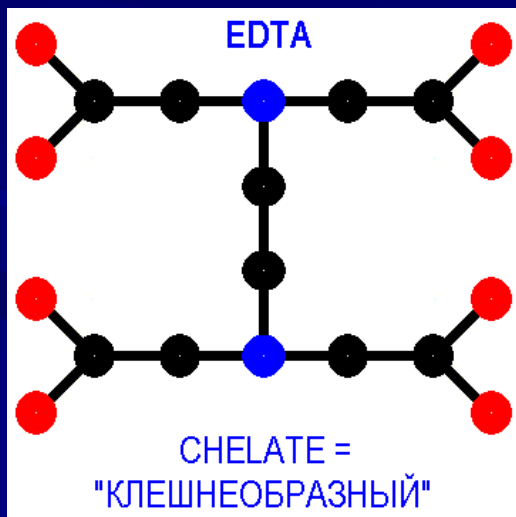
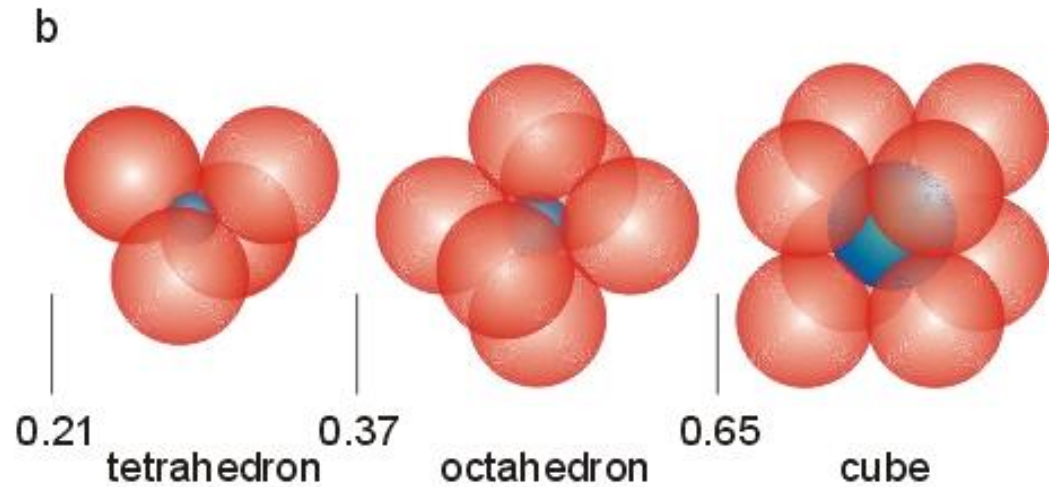
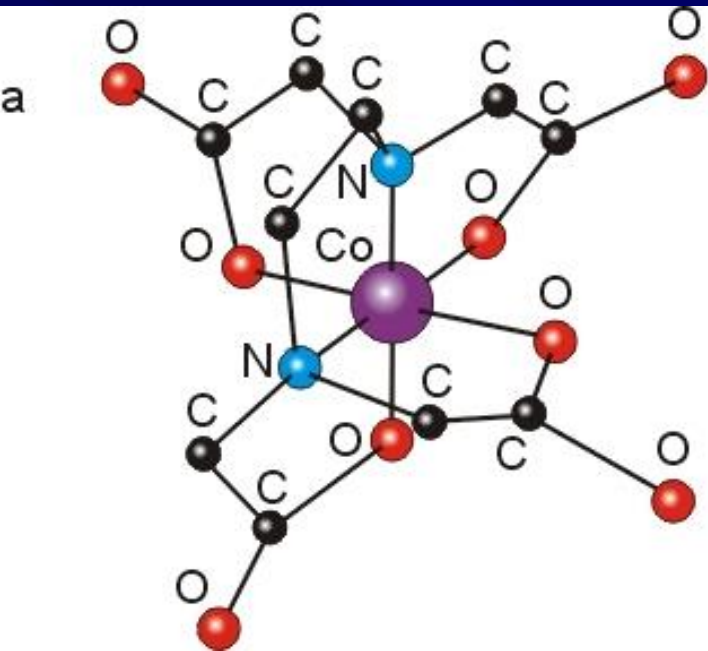


exchange:

entropic force

S-S bond is not stable
within a cell

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



exchange:
entropic force