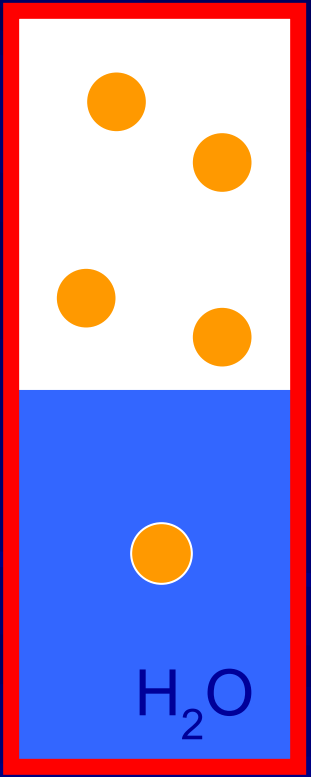
PROTEIN PHYSICS

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:

$S_E = \boldsymbol{k_B} \bullet \mathbf{ln}[M_E]$; M_E=number_of_states(E)

Why k_B? What is k_B?

Because **entropy** $\mathbf{S}_E$ comes to the **free energy**

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

and T is measured in degrees, while

ln[number of states] is dimensionless;

Thus, $\boldsymbol{k_B}$ is energy_unit/degree

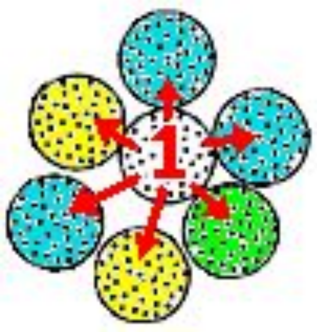
FREE ENERGY:

Probability(E) ~ $M_E \bullet \exp(-E/k_BT) = \exp(-F_E/k_BT)$

Boltzmann

F=E-TS at V=*const*;

G=H-TS=(E+PV)-TS at P=*const* (better for experiment)



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

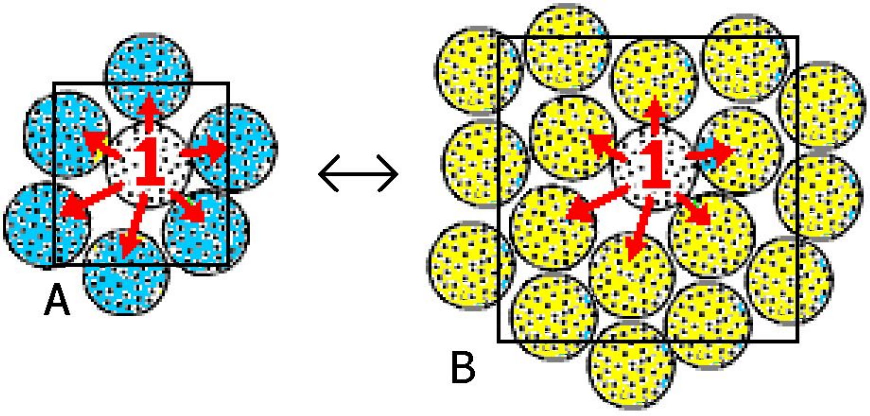
Chemical potential:

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

EQUILIBRIUM for transition

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

chemical potentials in A and B are equal



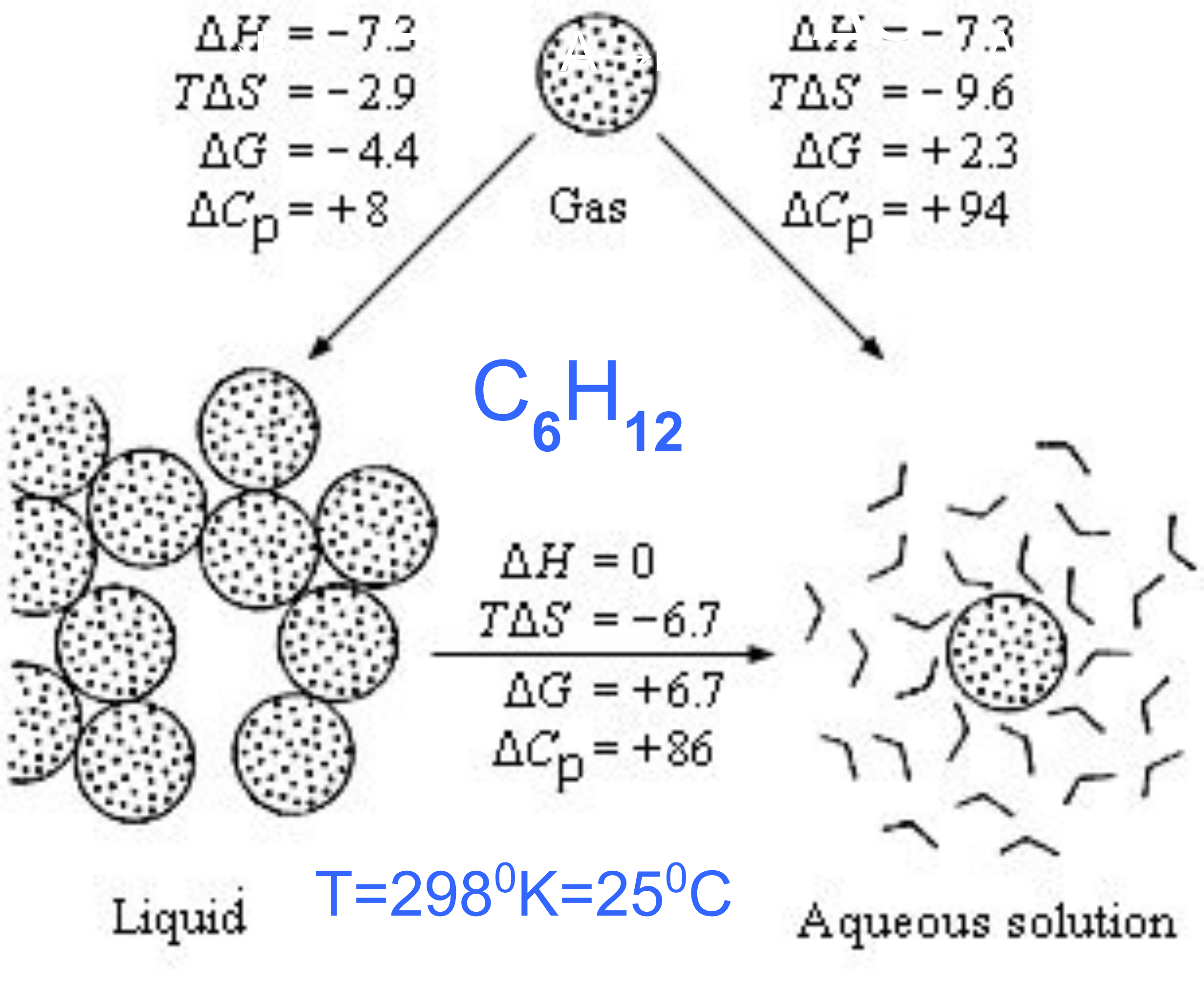
$$\Delta G^{int}_{A \to B} \equiv G^{int}_B - G^{int}_A$$

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

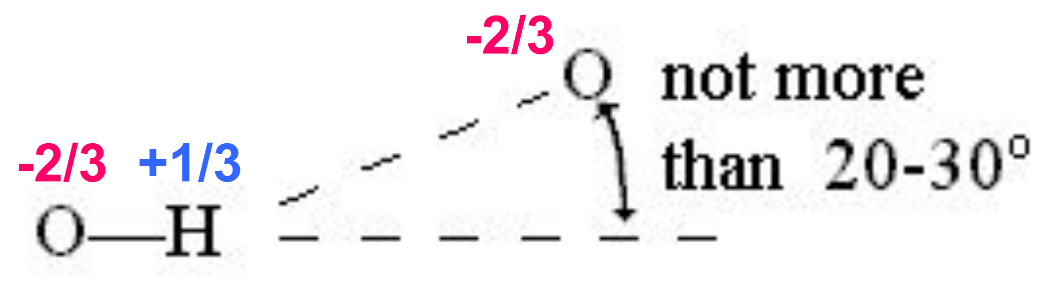
Experiment: $\Delta G^{int}_{A\to B} = k_B T \cdot \ln([C_{1\,in\,A}]/[C_{1\,in\,B}])$

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

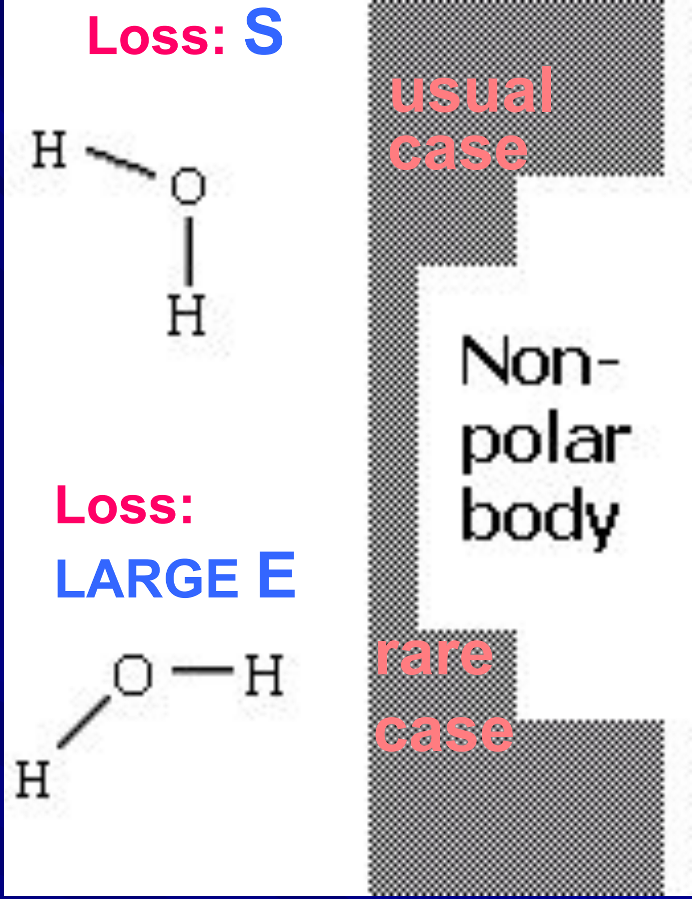
$\Delta H^{int} = \Delta G^{int}_{A\to} + T\Delta S^{int}$

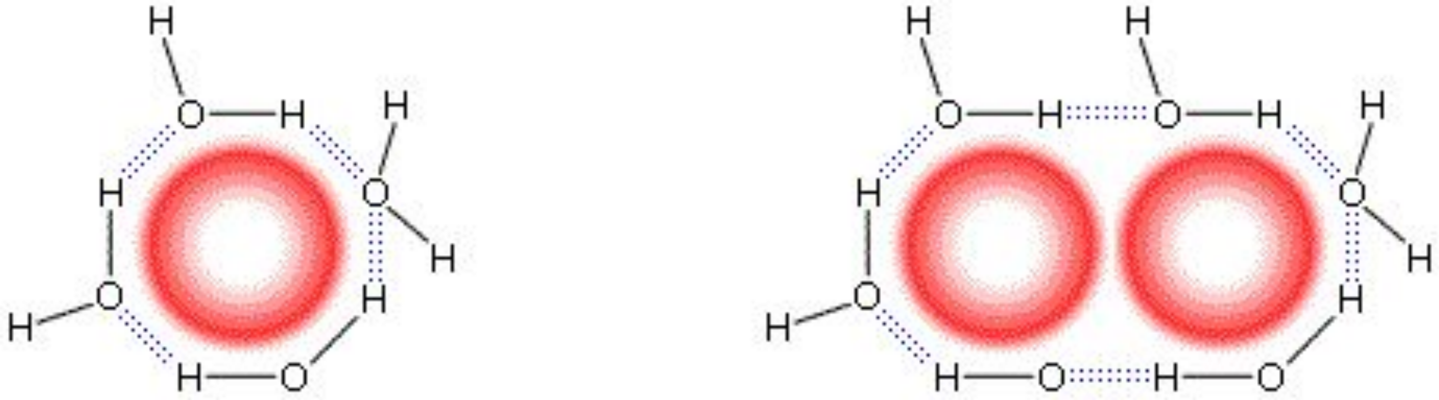


[C] of C_6H_{12} in H_2O:
50 times **less** than in gas;
100000 times **less** than in liquid C_6H_{12}

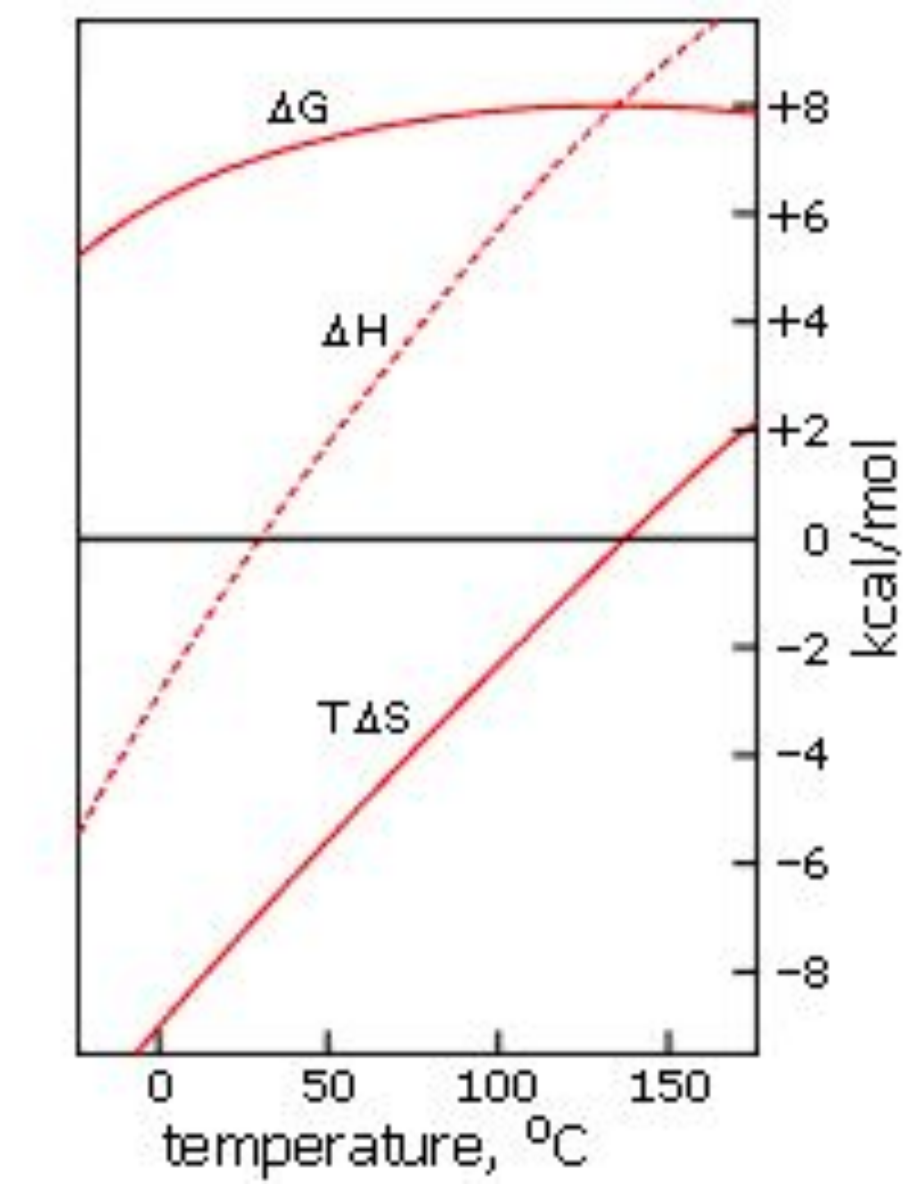


H-bond: directed

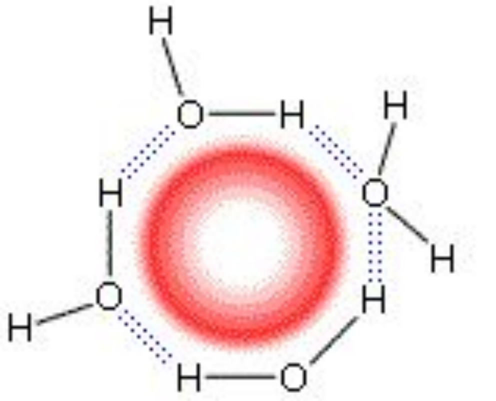


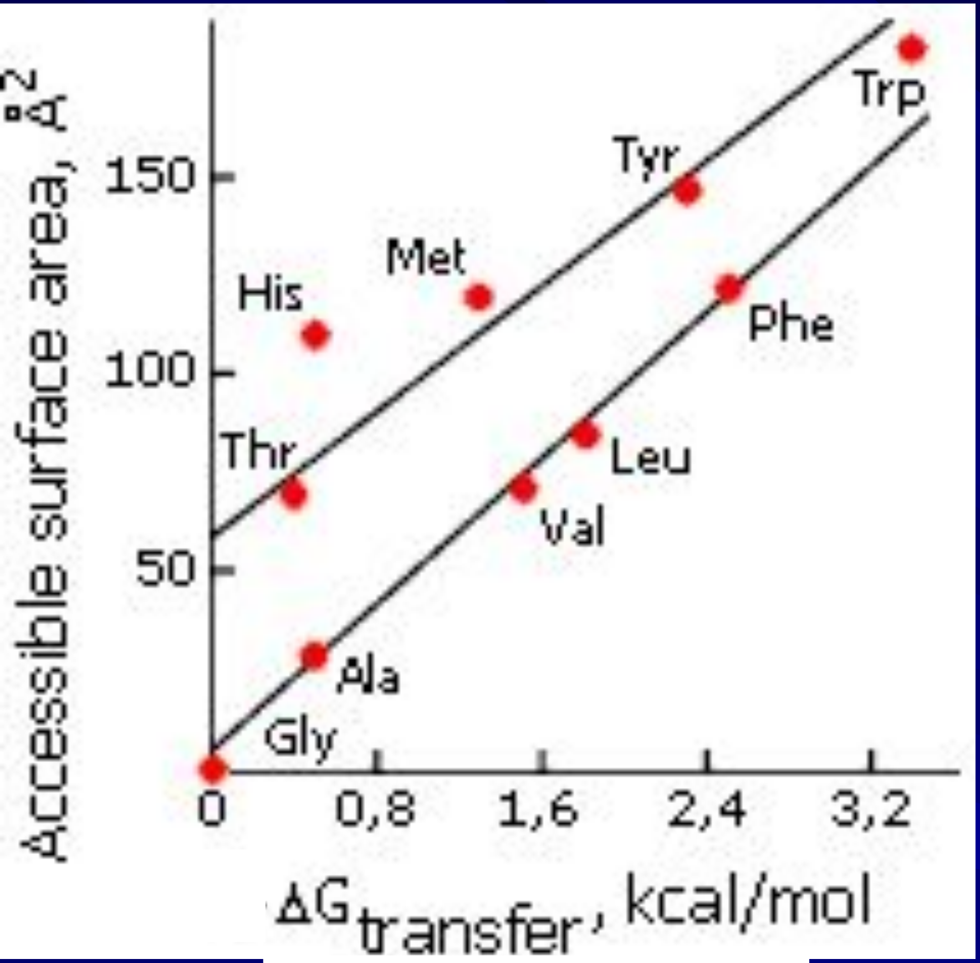


“hydrophobic bond”

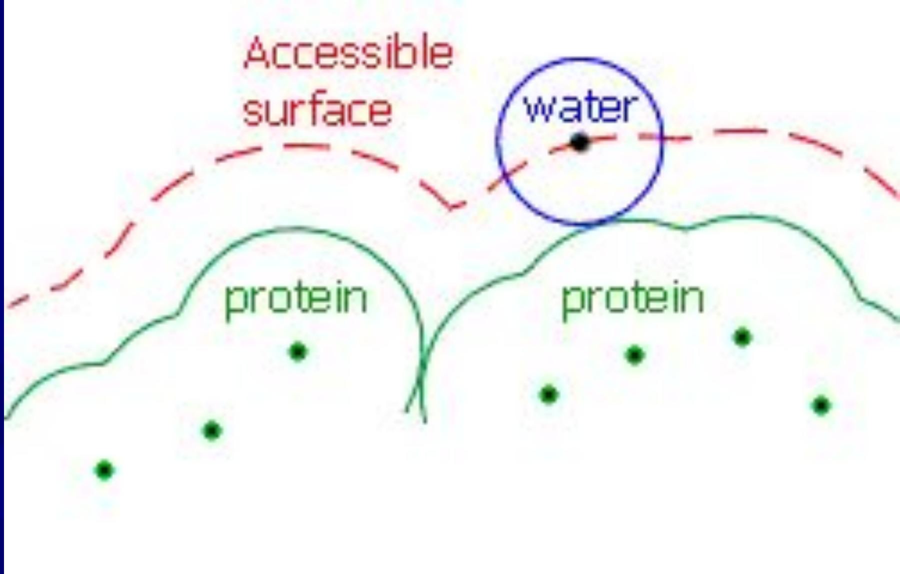


High heat capacity d(ΔH)/dT: Melting of "iceberg"





Octanol → Water



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

Семён Ефимович **Бреслер**

(1911 – 1983)

Давид Львович **Талмуд**

(1900 - 1973)

Hypothesis on a role of hydrophobic effect in protein folding

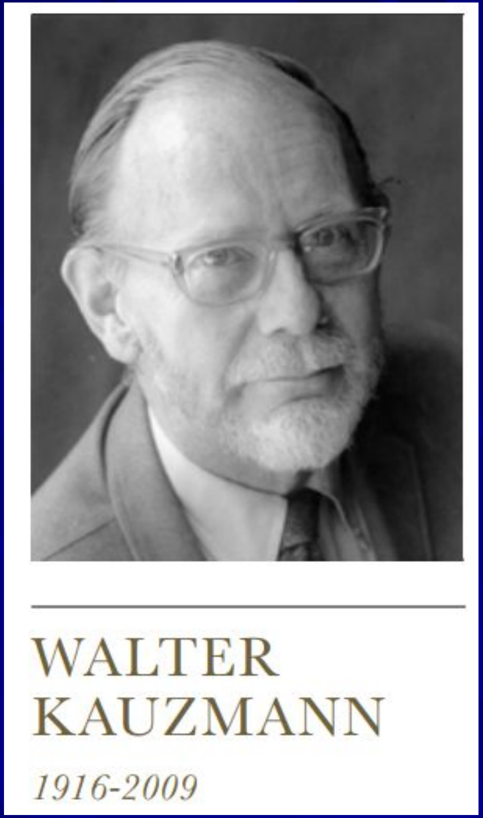
Hydrophobic

effect

&

denaturation

of proteins



Charles **Tanford**

(1921 - 2009)

General physical

features of

Hydrophobic

effect

Cyrus Homi **Chothia**,

1942

Hydrophobic

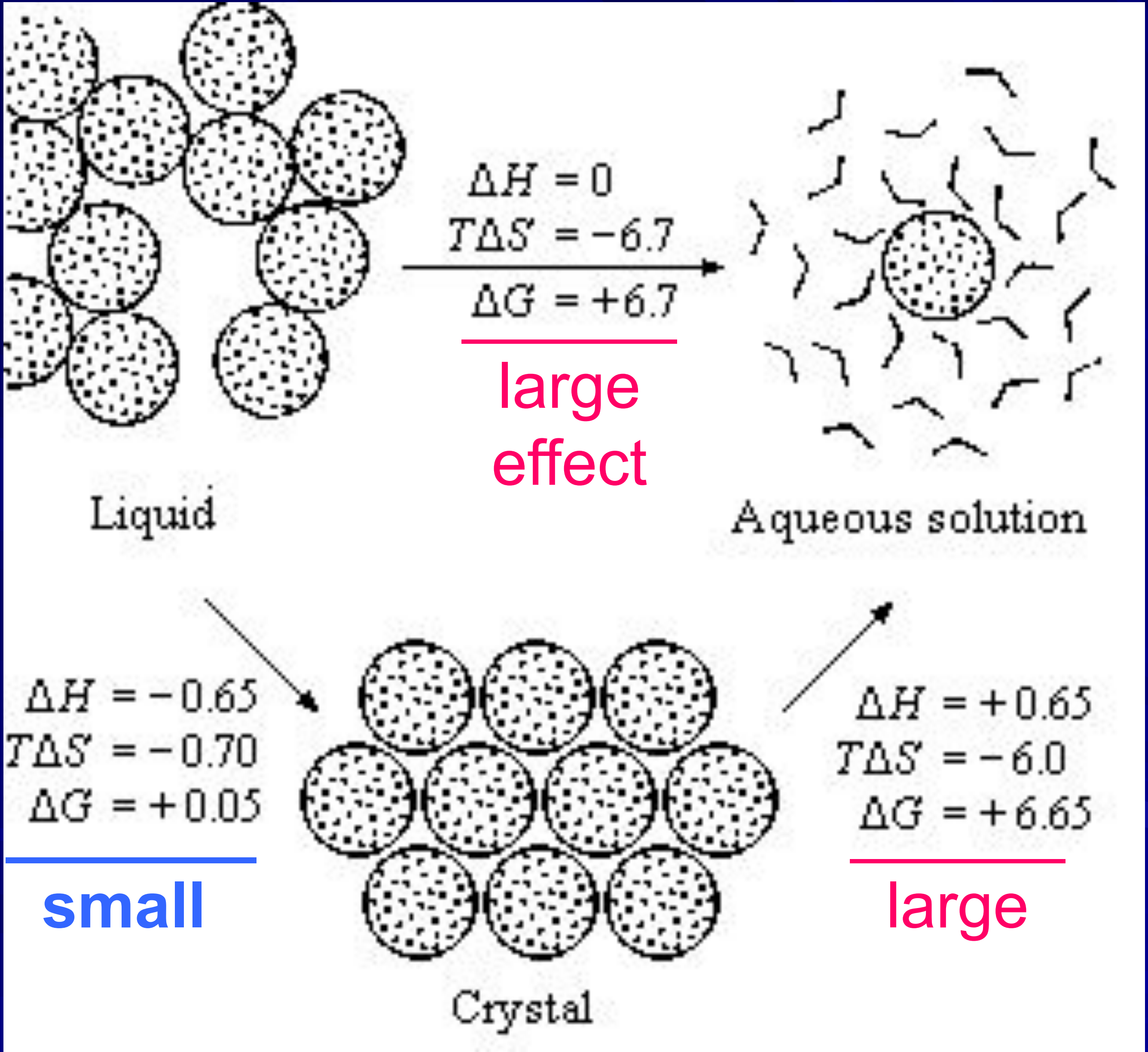
effect

&

amino acid

water-accessible

surface



large effect

small

large

Electrostatics in uniform media:

potential $\phi_1 = q_1/\varepsilon r$

Interaction of two charges:

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

$\varepsilon = 1$ vacuum
$\varepsilon \approx 3$ protein
$\varepsilon \approx 80$ water

Protein/water interface

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

At atomic distances: $\varepsilon_{eff} = ?$

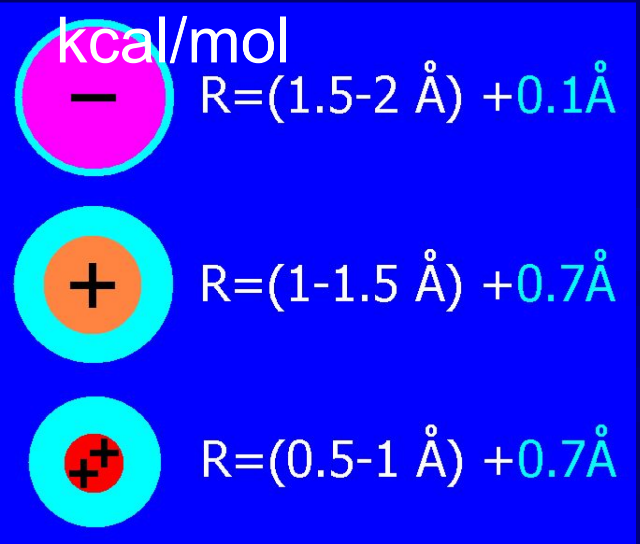
Charles-Augustin de Coulomb

(1736-1806)

CHARGE inside PROTEIN

$$\Delta U_{1 \Rightarrow 2} = q^2/2\varepsilon_2 R - q^2/2\varepsilon_1 R$$

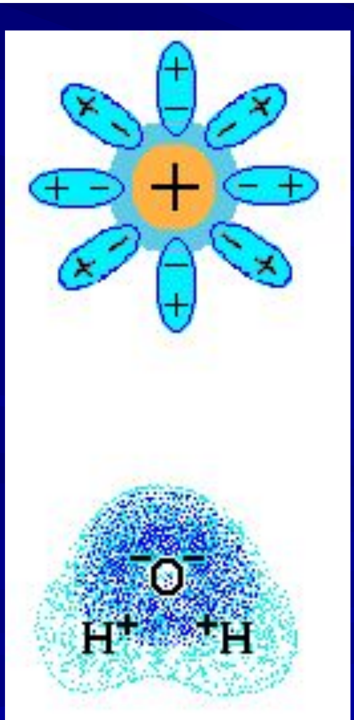
Water => vacuum:
$\Delta U \approx +100$ kcal/mol



R=(1.5-2 Å) +0.1Å

R=(1-1.5 Å) +0.7Å

R=(0.5-1 Å) +0.7Å



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

$R \approx 1.5 - 2$ Å
$\Delta U \approx +30 - 40$ kcal/mol

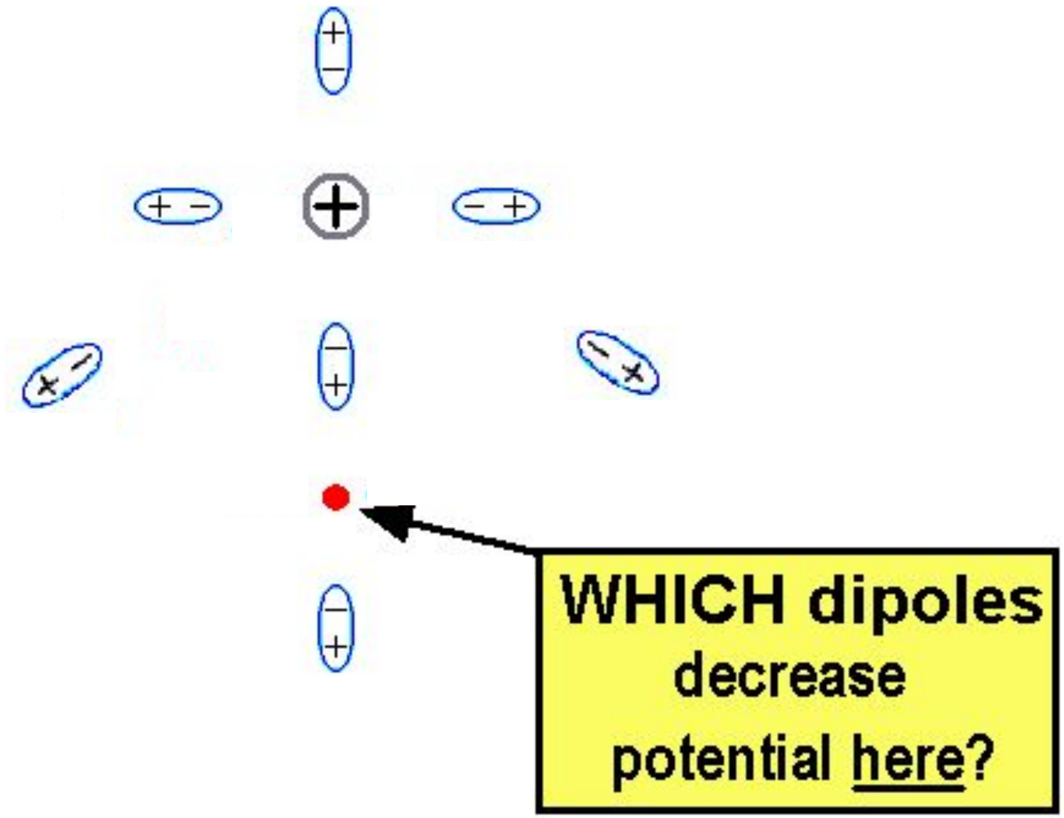
CHARGE inside PROTEIN:
VERY BAD

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

KNOWN:

molecules (dipoles) decrease potential:

$U \sim 1/\varepsilon r$



WHICH dipoles decrease potential here?

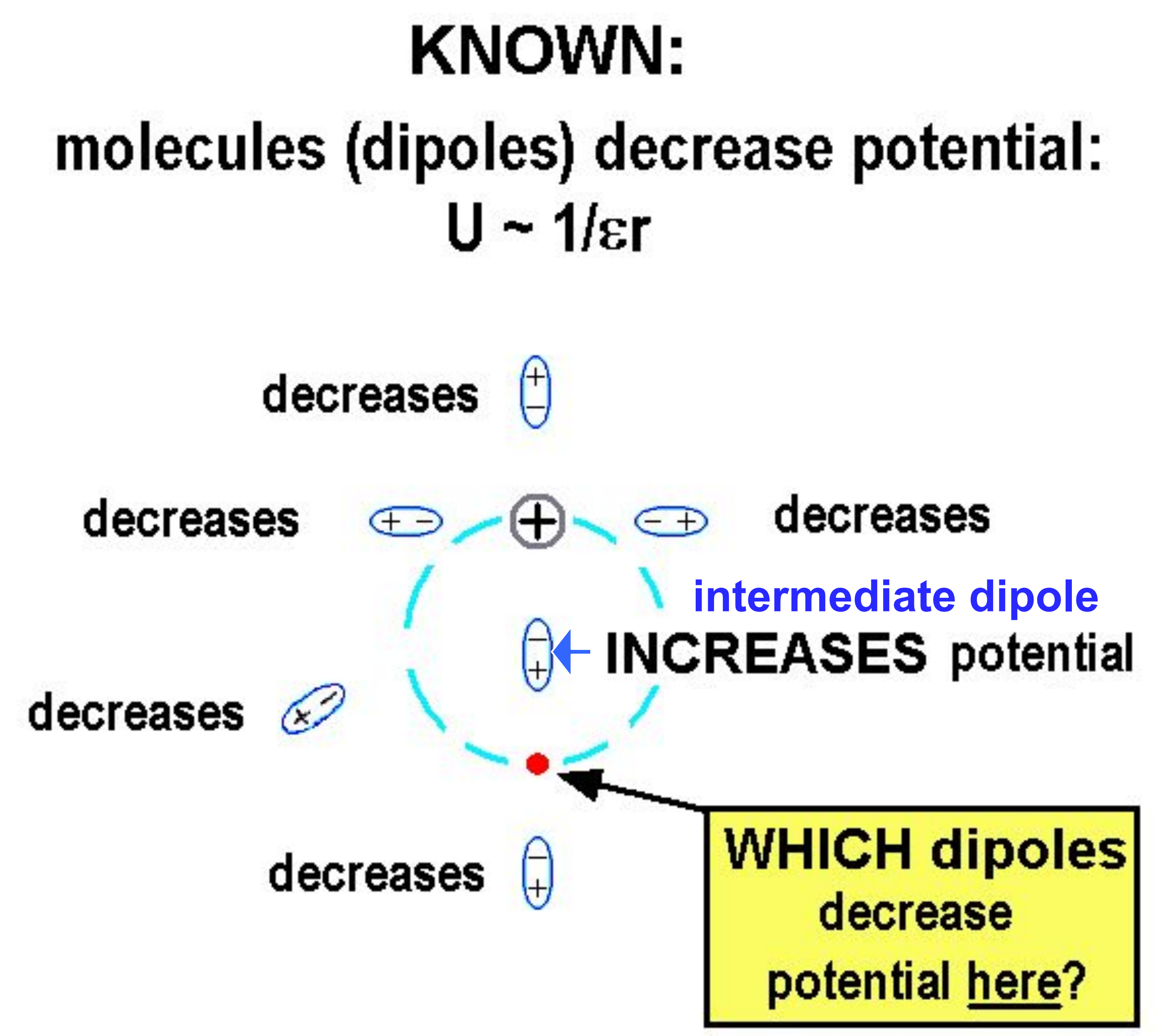
Non-uniform media: $\varepsilon_{eff} = ?$

KNOWN:

molecules (dipoles) decrease potential:

$U \sim 1/\varepsilon r$

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



KNOWN:

molecules (dipoles) decrease potential:

$U \sim 1/\varepsilon r$

decreases

decreases

decreases

intermediate dipole

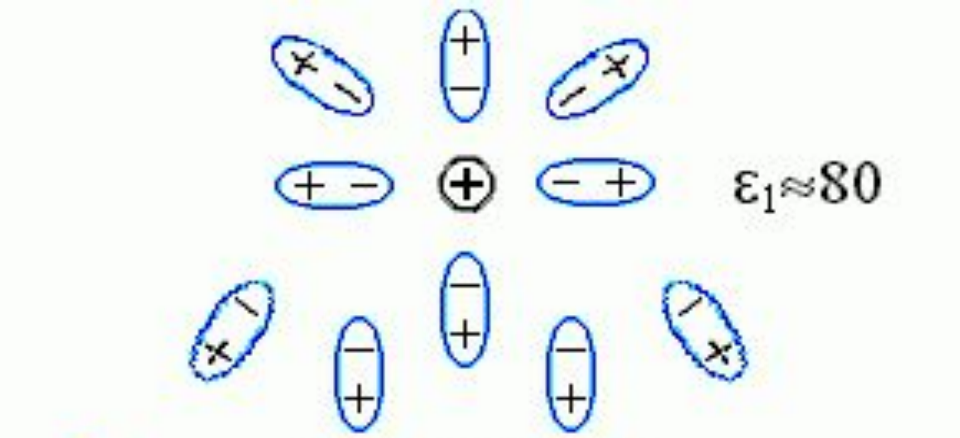
INCREASES potential

decreases

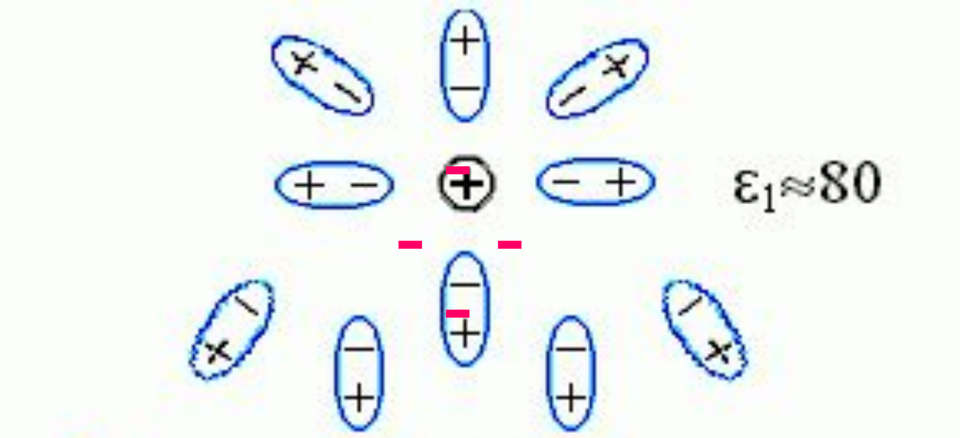
decreases

WHICH dipoles decrease potential here?

$$\phi = q/\varepsilon_1 r$$



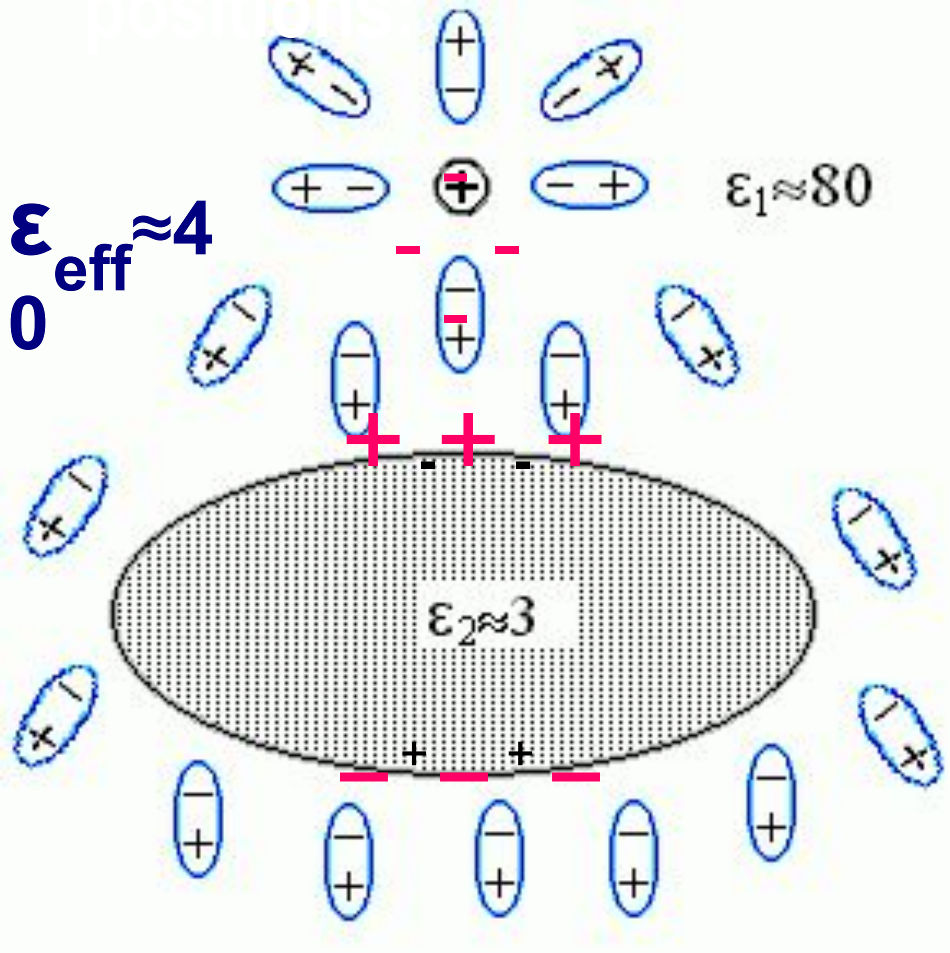
$$\phi = (q/\varepsilon_1)/r$$



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

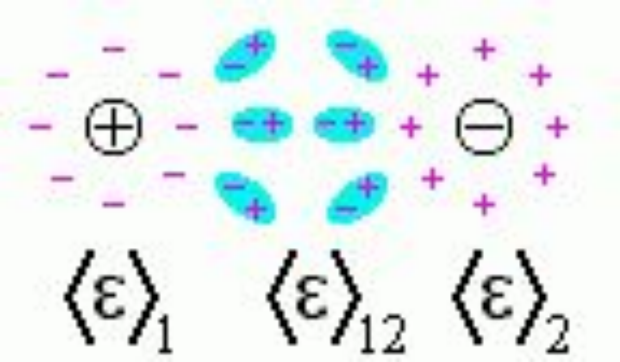
$$\vec{E} = -d\varphi/d\vec{r}$$

$\varepsilon_{eff} \approx 40$



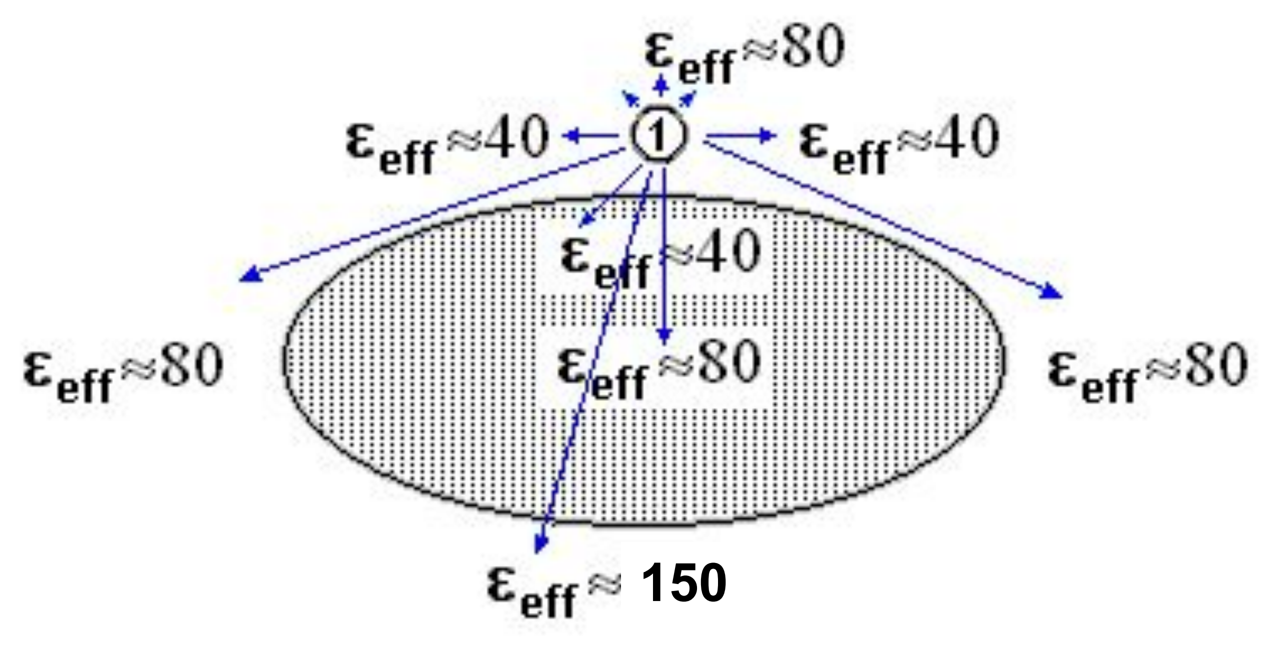
$$U = q_1 q_2/\varepsilon_{eff} r =$$

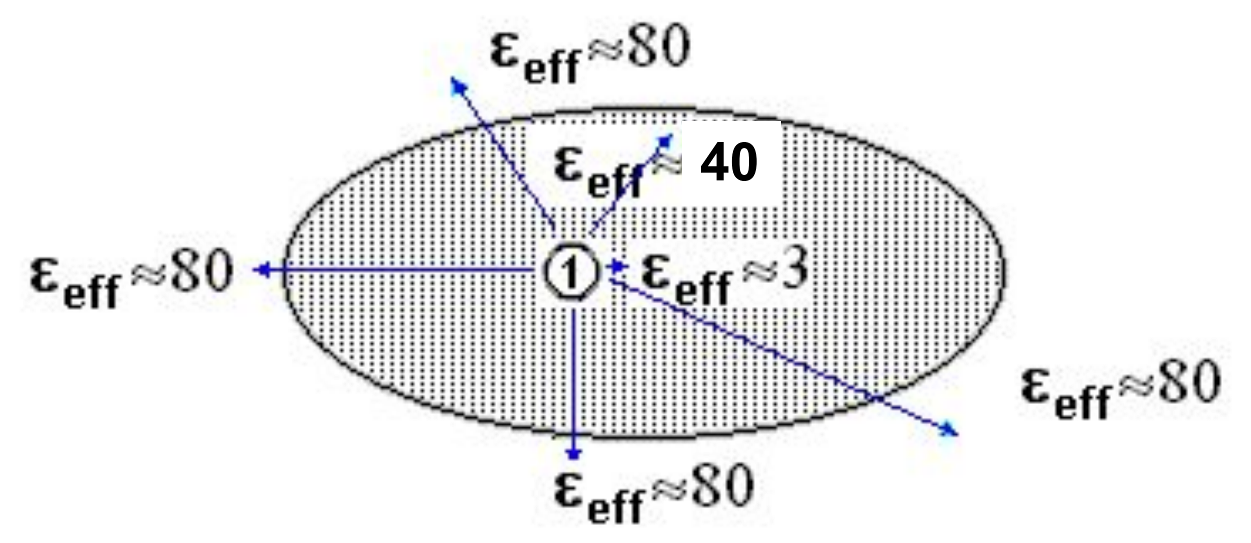
$$(q_1/\langle\varepsilon\rangle_1)\cdot(\langle\varepsilon\rangle_{12}/r)\cdot(q_2/\langle\varepsilon\rangle_2)$$



Good estimate for non-uniform media

$\varepsilon_{eff} \approx 150$!!



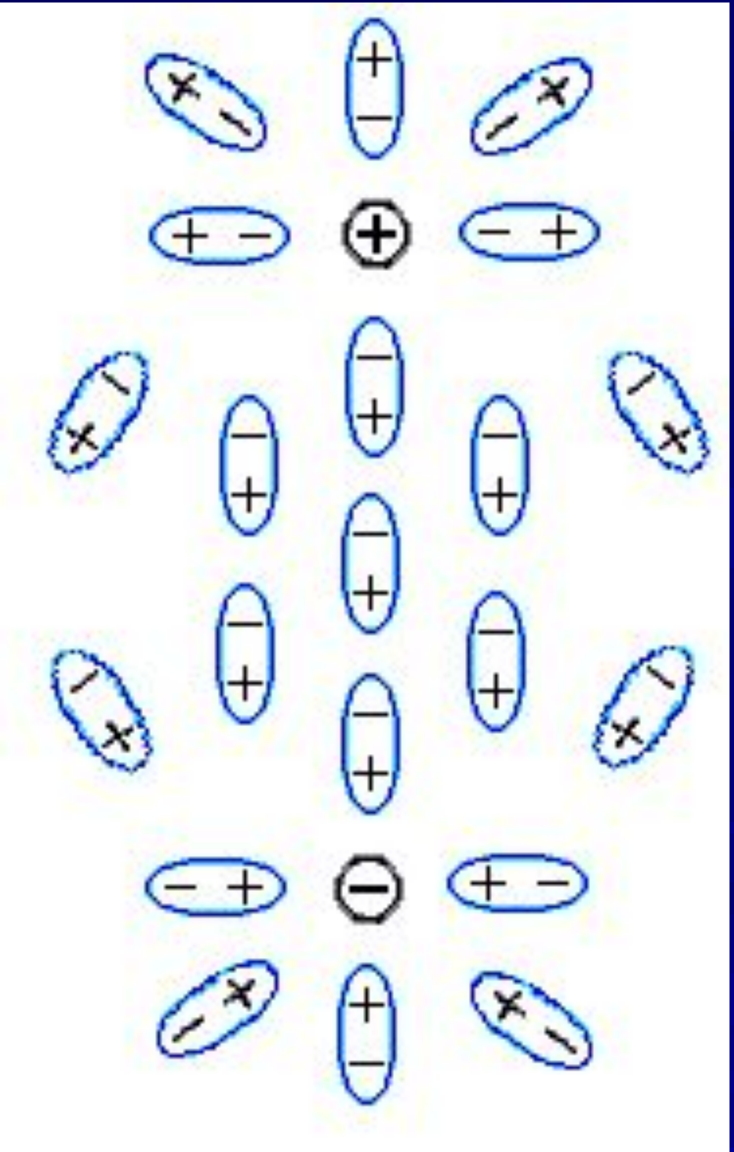


$\varepsilon_{effective}$ in non-uniform media

Large distance: Atomic distance:

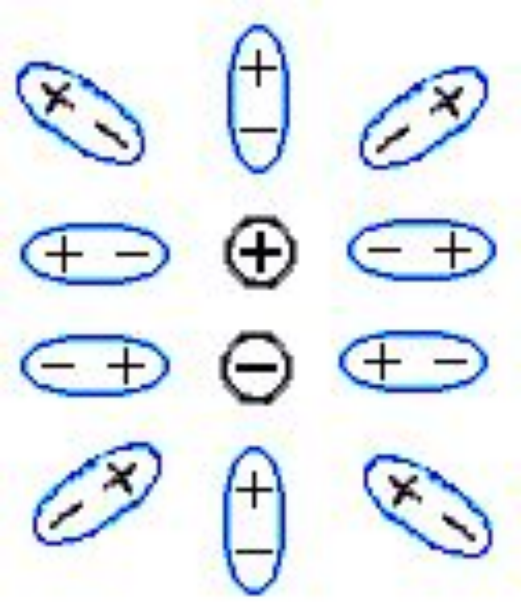
$\varepsilon_{eff} = \varepsilon = 80$

$\varepsilon_{eff} = ?$



intermediate "vacuum", ε~1? but the absence

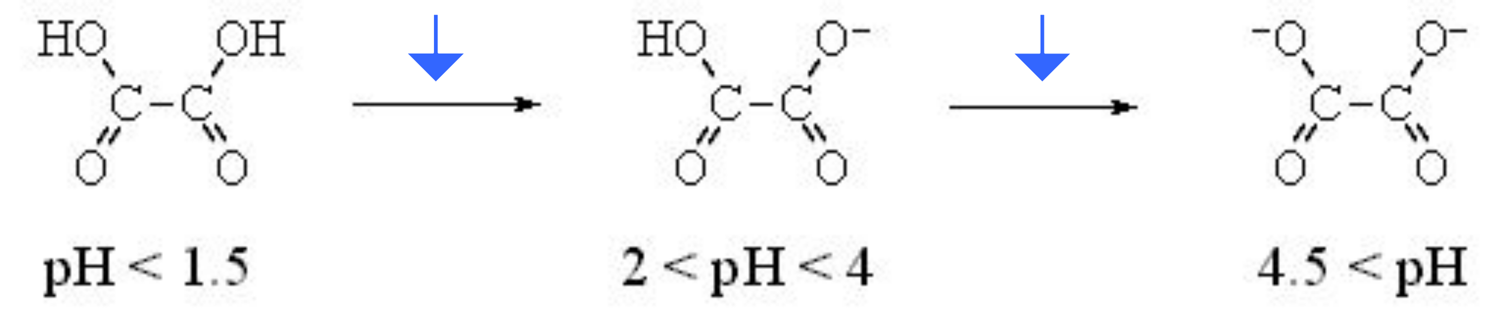
of intermediate dipoles can only increase interaction…



At atomic distances in water:

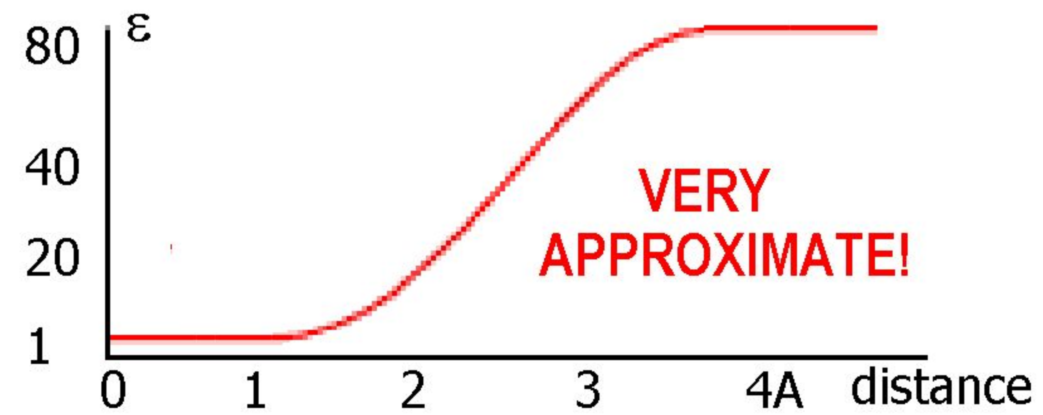
1) ε=80 is not a bad approximation (much better than ε = 1 or 3 !!)
(salt does not dissolve, if ε<50 at 3Å!)

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



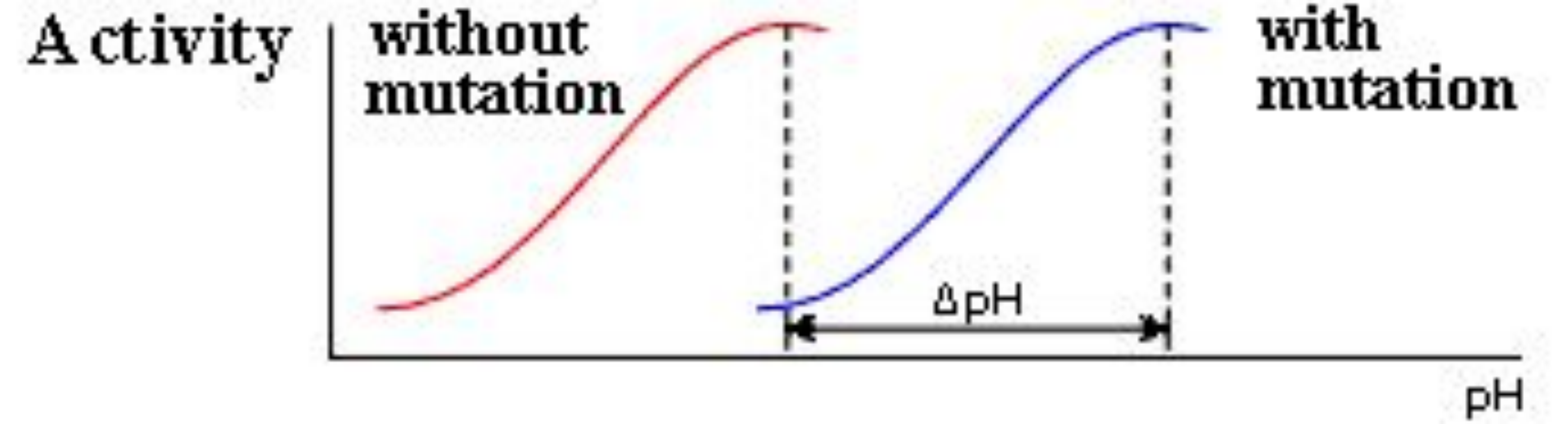
ΔG_{el} = 2.5 × ln(10) × RT ≈ 6RT ≈ 3.5 kcal/mol at ≈2.5Å

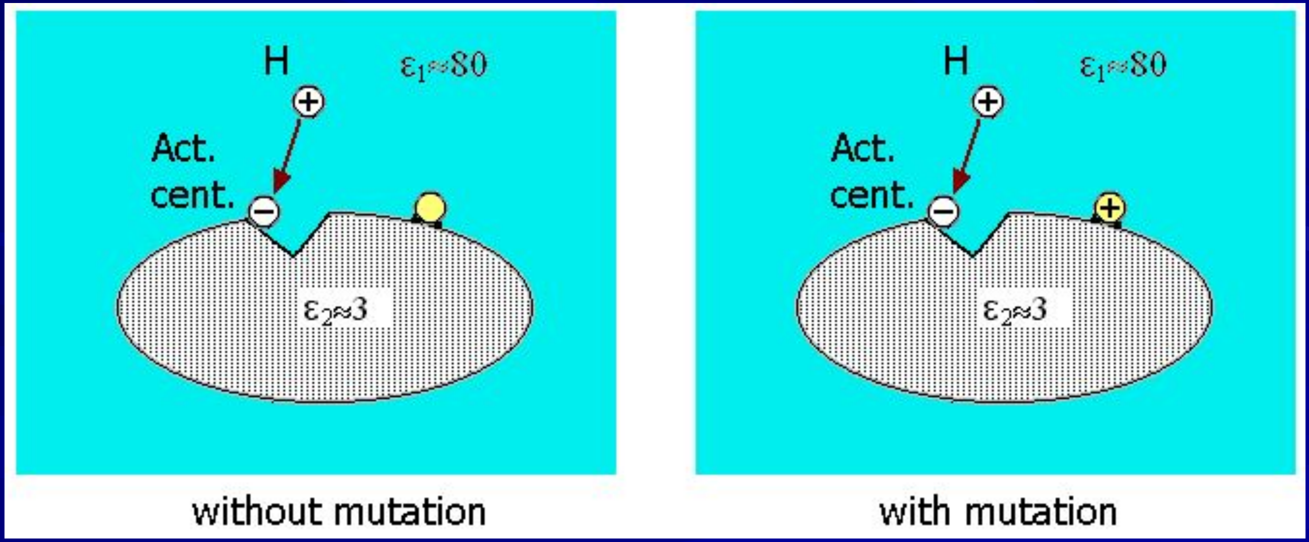
ε ≈ 30-40 at ≈ 2.5Å!



Protein engineering experiments:

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





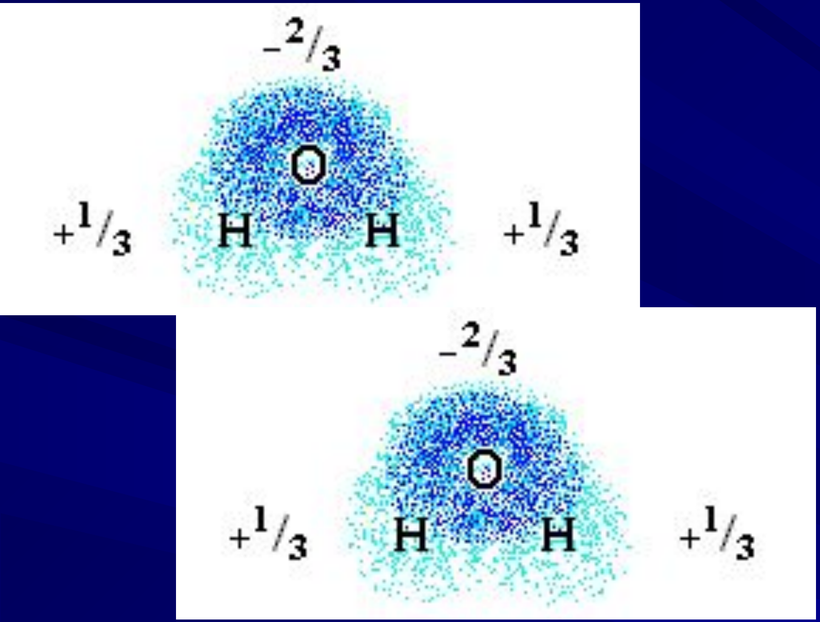
without mutation

with mutation

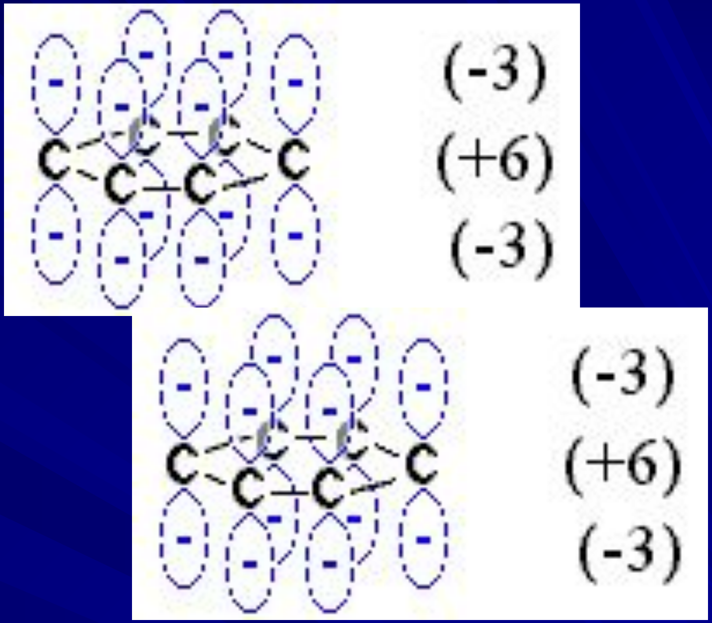
Sir Alan Roy **Fersht**, 1943

Protein engineering

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



Quadruple interactions



$(HO)^{-1/3}\text{-}H^{+1/3}::::::(OH)^{-1/3}\text{-}H^{+1/3}$

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

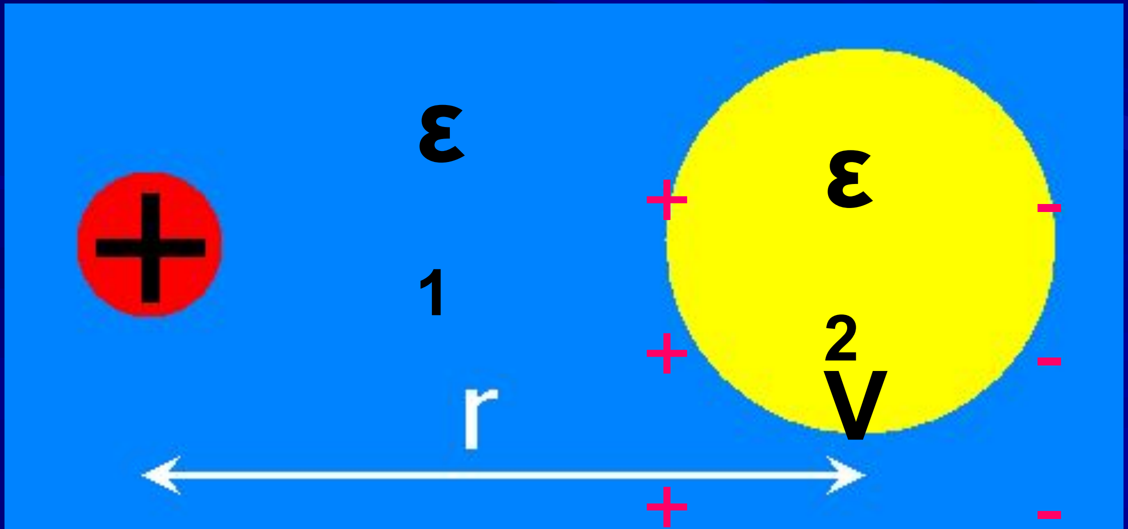
Potentials:

$\phi_{dipole} \sim 1/\varepsilon r^2$ $\qquad$ $\phi_{quadruple} \sim 1/\varepsilon r^3$

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

$U \sim q \cdot [1/\varepsilon_2 - 1/\varepsilon_1] \cdot [\varepsilon_2 /(\varepsilon_1+\varepsilon_2 /2)] \cdot V \cdot (1/r^4)$ at large r

In water: repulsion of charges from non-polar molecules (since here $\varepsilon_1 >> \varepsilon_2$);
in vacuum (where $\varepsilon_1 < \varepsilon_2$) : just the opposite!



Debye-Hückel screening of electrostatic by ions:

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

in water: $D = 3Å\cdot I^{-1/2}$;

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

Usually: $I \approx 0.1$ [mol/liter]; $D \approx 8Å$.

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

Electrostatics is T-dependent;

$U = (1/\varepsilon)\cdot(q_1q_2/r)$

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

$TS = T\cdot(-dU/dT) = -T\cdot[d(1/\varepsilon)/dT]\cdot(q_1q_2/r) =$

$= [d\ln(\varepsilon)/d\ln T]\cdot U$

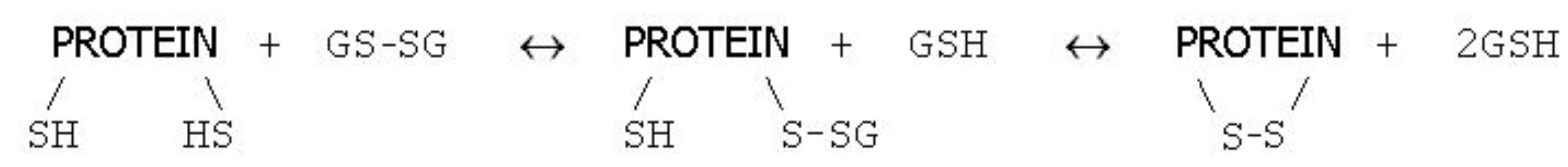
in water: when T grows from 273° to 293°K (by 7%),

ε decreases from 88 to 80 (by 10%):

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

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

S-S bonds (Cys-Cys)



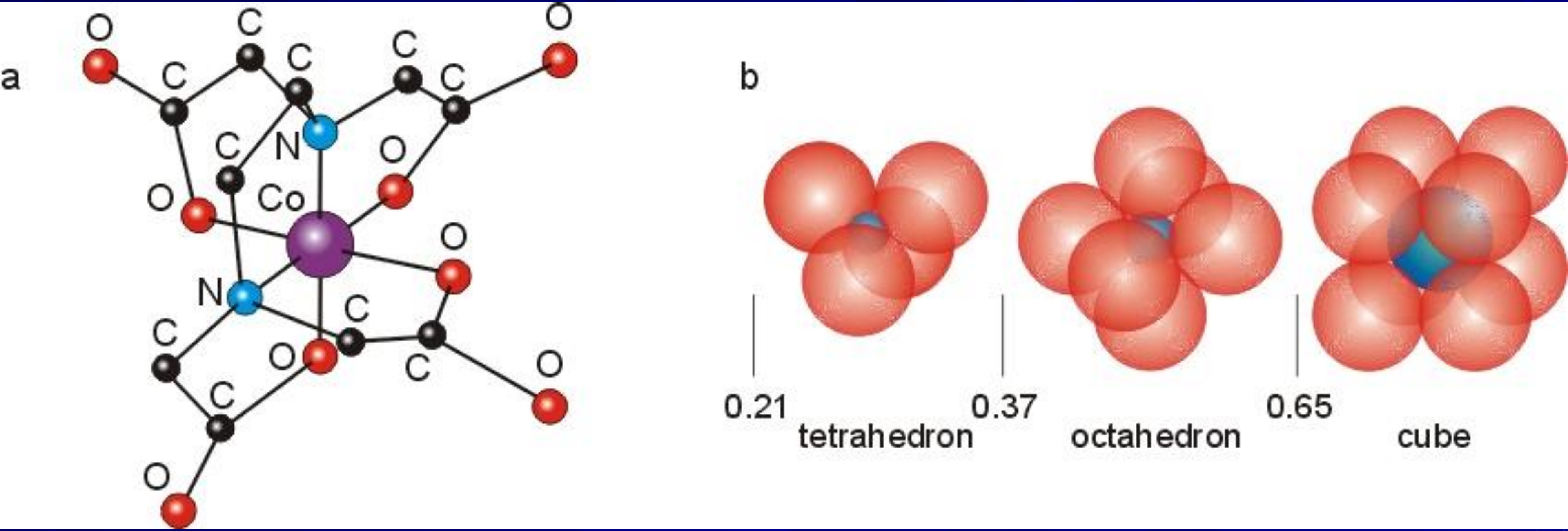
$$\underset{\text{SH}\qquad\text{HS}}{\text{PROTEIN}} + \text{GS-SG} \leftrightarrow \underset{\text{SH}\qquad\text{S-SG}}{\text{PROTEIN}} + \text{GSH} \leftrightarrow \underset{\text{S-S}}{\text{PROTEIN}} + 2\text{GSH}$$

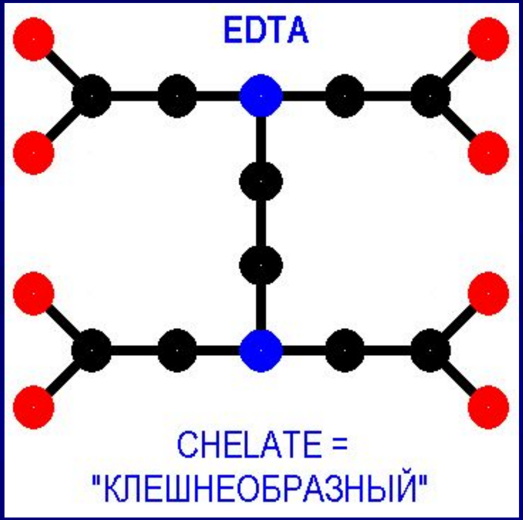
exchange:

entropic force

S-S bond is not stable
within a cell

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





exchange:

entropic

force