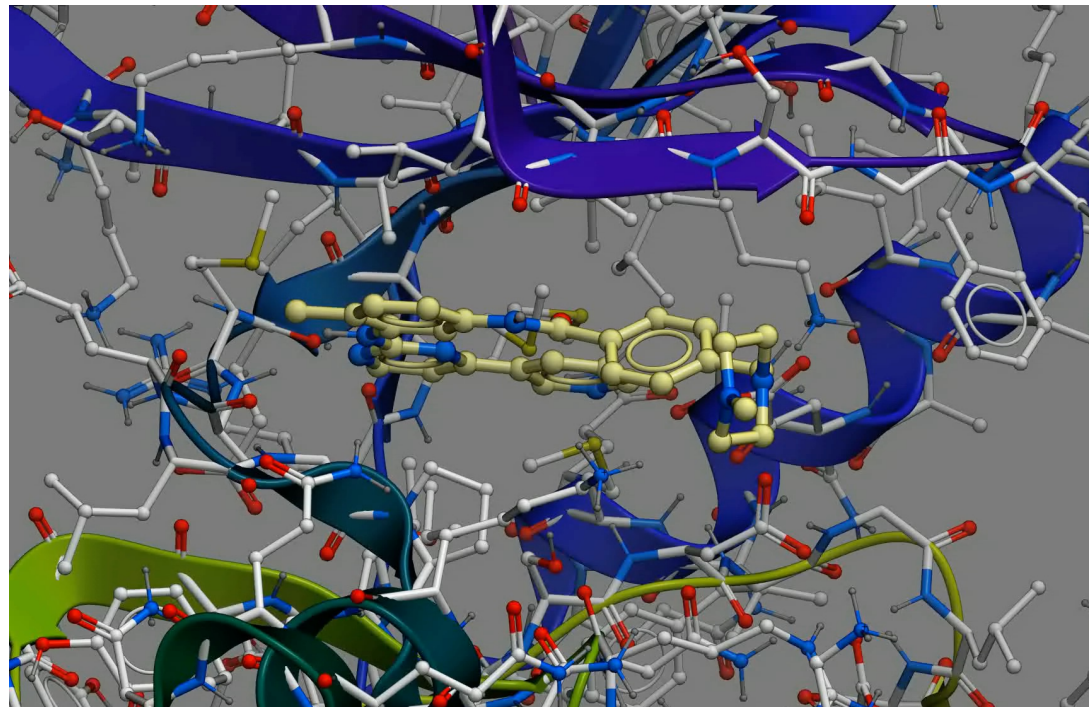


Molecular Interactions

Electrostatics

Charges in Drug Molecules

Formal charges, acid-base equilibrium



Molecular interactions of drugs in 3D

Bonds:

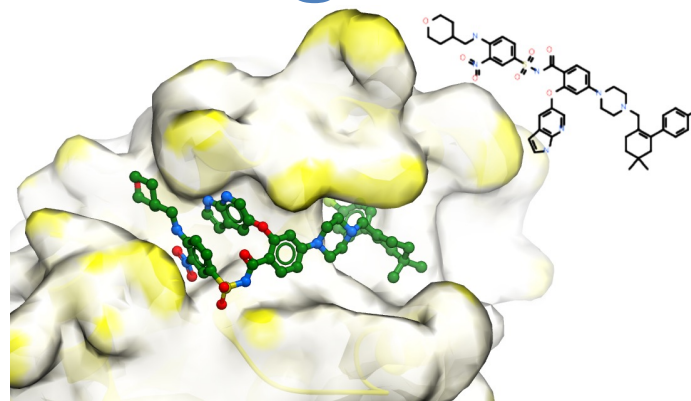
- Covalent
- Non-covalent pairwise interactions

Covalent bonds

- Strong covalent bonds that are *not easily broken by thermal fluctuations* (>40kcal/mol vs thermal 0.6 kcal/mol)
 - Cell *enzymes* can break covalent bonds
 - Covalent drugs have ‘reactive warheads’
- Bond length and bond angles are well defined by the covalent geometry
- Single bonds are *rotatable*

Non-covalent interactions

- Intra-molecular, drug and environment, drug and target



Venetoclax
interacting with its
target, **BCL-2**

Main contributions to molecular energetics

$$G = H - TS$$

- **Quantum effects**
 - covalent bonds (bonding orbitals)
 - atom *repulsion* (Pauli exclusion principle)
- **Electrostatic interactions**
 - Interactions between full charges, dipoles, induced dipoles, hydrogen bonds, attractive part of the Lennard-Jones potential
- **Entropic effects**
 - a part of the hydrophobic effect
 - Conformational entropy changes upon binding
 - .. Concentration-dependent entropies of mixing
- Other energy terms are either subtypes of the main class, or combinations of the main types (e.g. hydrophobic interactions)

Boltzmann's factor and probability, p

- If we have two states, A and B, say two rotamers of a drug, the *probability* to find a higher energy state depends *exponentially* on ΔE
- If you have two energies differing by 0.6 kcal/mole the higher energy state will be found **e** (2.71) times less frequently.
- **1.36** kcal/mol – **10** times less

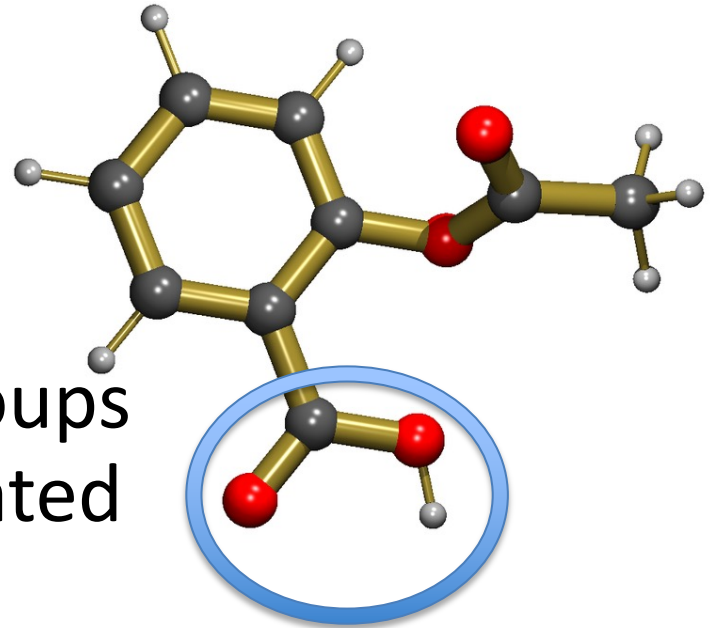
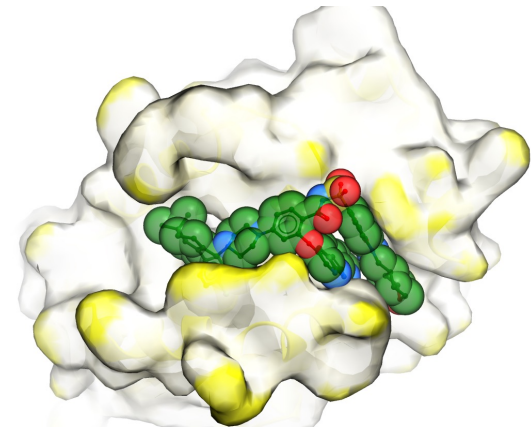
$$\ln K = -\frac{\Delta_r G^o}{RT}$$

$$\frac{[A]}{[B]} = e^{-\frac{G_A - G_B}{RT}}$$

$$p \propto e^{-\frac{\Delta E}{RT}}$$

Non-covalent Interactions

- Drug atoms interact with atoms of the following main molecules:
- Other atoms of the same molecule
- Water molecules
- Lipids
- Receptor atoms
- Acidic or Basic functional groups get protonated or deprotonated depending on pH



Electrostatic Interactions

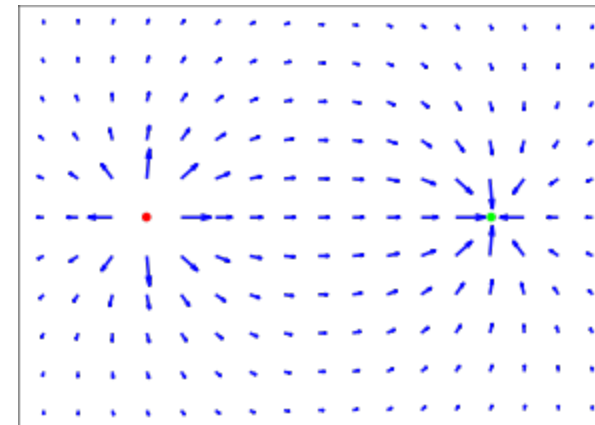
- Charges of interacting molecules may be
 - (i) Formal charges, (ii) partial charges; (iii) induced
- Coulomb's potential energy, in SI units

$$U_{el} = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{\epsilon r}$$

- Energy in Joules, distance in meters, charges in C (1 Coulomb = Ampere x second)
- Like charges repel one another
- Opposite charges attract one another
- The force of repulsion/attraction get weaker as the charges are farther apart.



Coulomb, Charles Augustin



Units and Constants in Coulomb's formula

- Energy of one mole of interactions:

- Charges in electron units, [eU] (e.g. -1,1,-0.5),
- Distance, r , of d , in Ångstroms,
- Energy, U , in kcal/mol (energy of N_A of interactions)

$$C = 332 \text{ [kcal Å/(mol} \cdot \text{electron_units}^2\text{)]}$$

$$U = C \frac{q_1 q_2}{\epsilon r}$$

- ϵ is dielectric constant of the medium

$\epsilon=1$ for vacuum

- **Example:** +1 and -1 charges at 3.32 Å, $U=$

- -100 kcal/mol in vacuum
- -25 kcal/mol in a membrane ($\epsilon=4$)
- -1.23 kcal/mol in water at $\epsilon=81$
- Let us compare to a drug binding energy for $K_d = 10\text{nM}$:

$$\Delta G_{\text{binding}} = -RT \ln(10^{-5}) = 5 \cdot 0.6 \cdot \ln(10) = -6.9 \text{ kcal/mol}$$

A more accurate calculation in cal/mol:

$R = 0.001987 \text{ kcal/mol K}$

T is in degrees Kelvin at $25 \text{ }^\circ\text{C} = 298.15\text{K}$

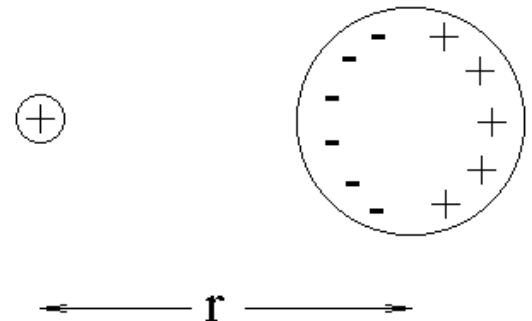
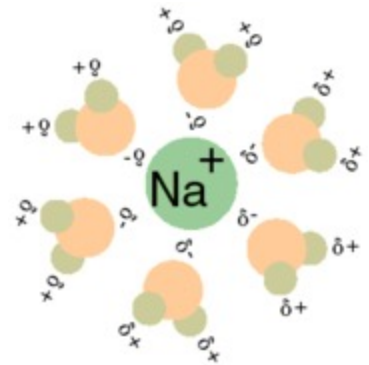
$RT = 0.59 \text{ kcal/mol}$

Polarization, solvation and ϵ

- Electrostatic interactions are *reduced* by ϵ because of the polarization of the media.

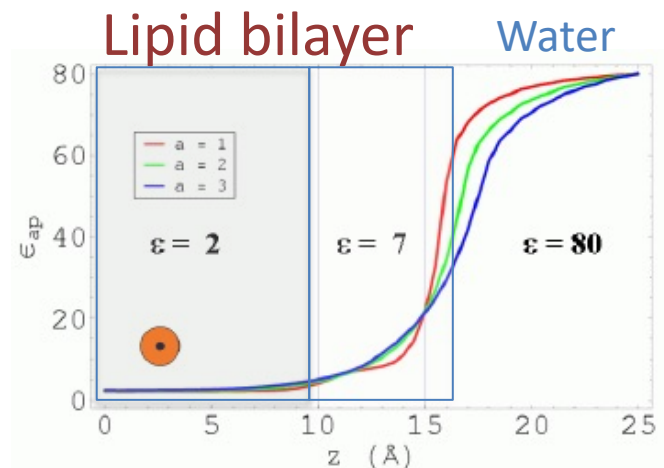
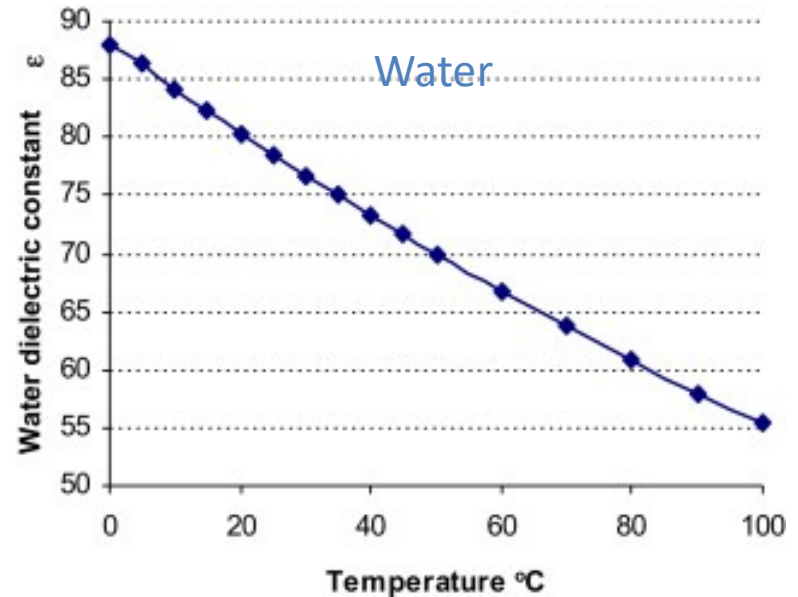
$$U = C \frac{q_1 q_2}{\epsilon r}$$

- **$\epsilon=80$** in water at 300K.
- Electronic polarization, dipole relaxation. Water is a strong dipole
- In the hydrocarbon layer of membranes $\epsilon \sim 2$ to 4
- in proteins $\epsilon \sim 4$ to 10



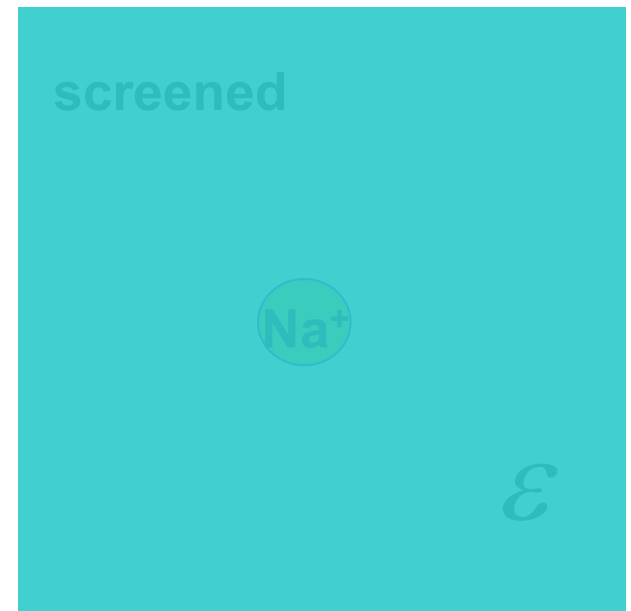
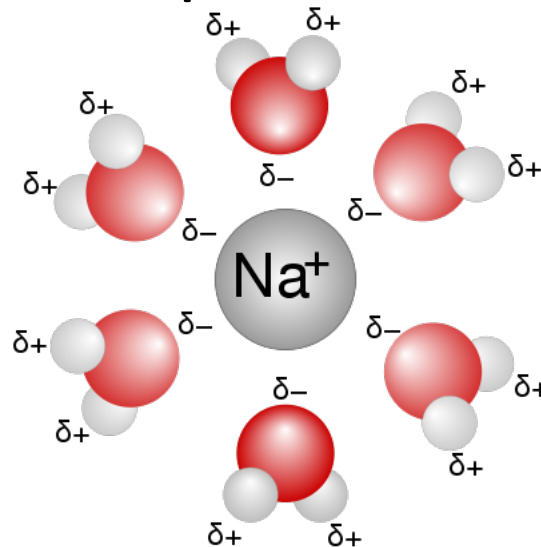
Dielectric constants at 25C

- Water 78.5 at 25C, 80.1 at 20C, etc. depends on T
- Methanol 33.0
- Ethanol 24.3
- Ammonia 16.9
- Benzene 2.3
- Cyclohexane 2.0
- Methane _{100K} 1.8



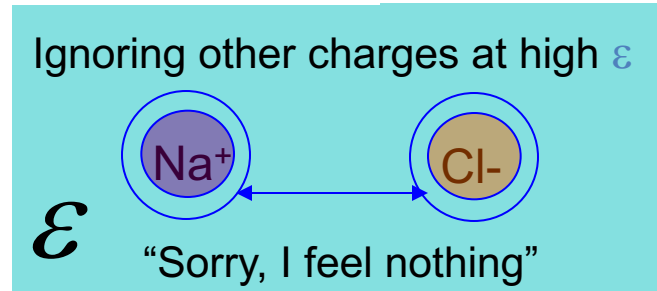
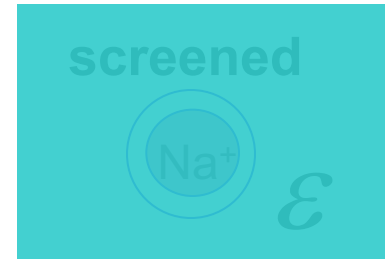
A Charge in a fog

- Dipoles reorient,
- electron density flows to compensate the charge
- Le Chatelier principle

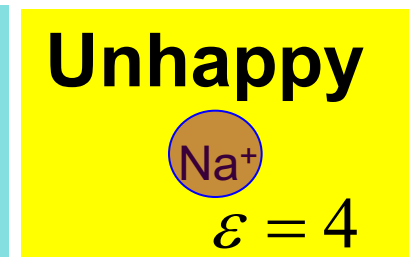
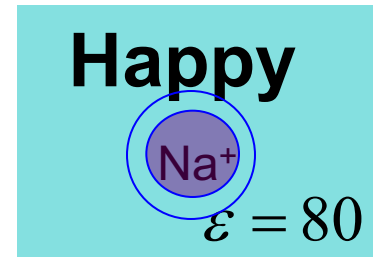


Three consequences of high ϵ

- Charged atoms are almost completely “screened” in water ($U_w = U_{\text{vacuum}}/80 = U_{\text{fat}}/40$)
- Direct charge-charge interaction is **weak** in water
- $(\text{Na}^+)(\text{Cl}^-)$: $d=2.5\text{\AA}$, $E= -1.7\text{kcal/mol}$
- Charged (and polar) atoms are extremely **happy** in water (low energy) and do not want to go to media with smaller ϵ .



charge is screened



Solvation Energy of Charges. Born formula

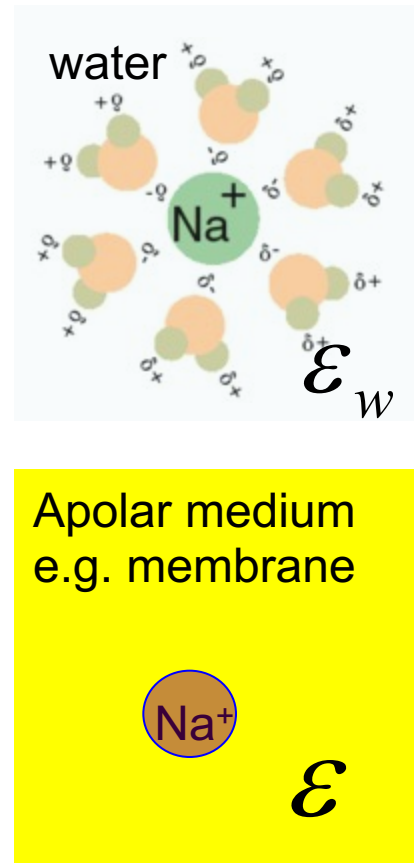
- **Born formula** for the solvation energy of a charge with radius r_q , $C=332$
- The solvation energy difference of the ion:

$$U_{\text{Solv}}^{\text{Solvent to Water}} = \frac{C}{2} \frac{q^2}{r_q} \left(\frac{1}{\epsilon_w} - \frac{1}{\epsilon} \right)$$

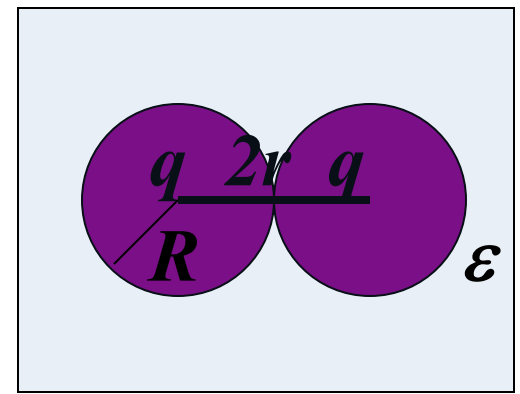
when moved from *apolar solvent* to *water* (U_{Solv} is *negative*)

$U_{\text{desolv}} = -U_{\text{Solv}}$ and is positive

If $\epsilon = 2$ and $r = 2\text{\AA}$, $U = -332./8. \sim -40 \text{ kcal/mol}$



Mnemonic device for the Born formula



- Field energy: What is the Coulomb energy of interaction of **ion with itself**?

$$U = C \frac{q^2}{\epsilon(2r_q)}$$

- To move an ion from media (or vacuum) to water :

$$U_{m \rightarrow w} = U_w - U_m = \frac{Cq^2}{2r_q} \left(\frac{1}{\epsilon_w} - \frac{1}{\epsilon_m} \right)$$

- If the first medium is *vacuum*, then $\epsilon_m = 1$

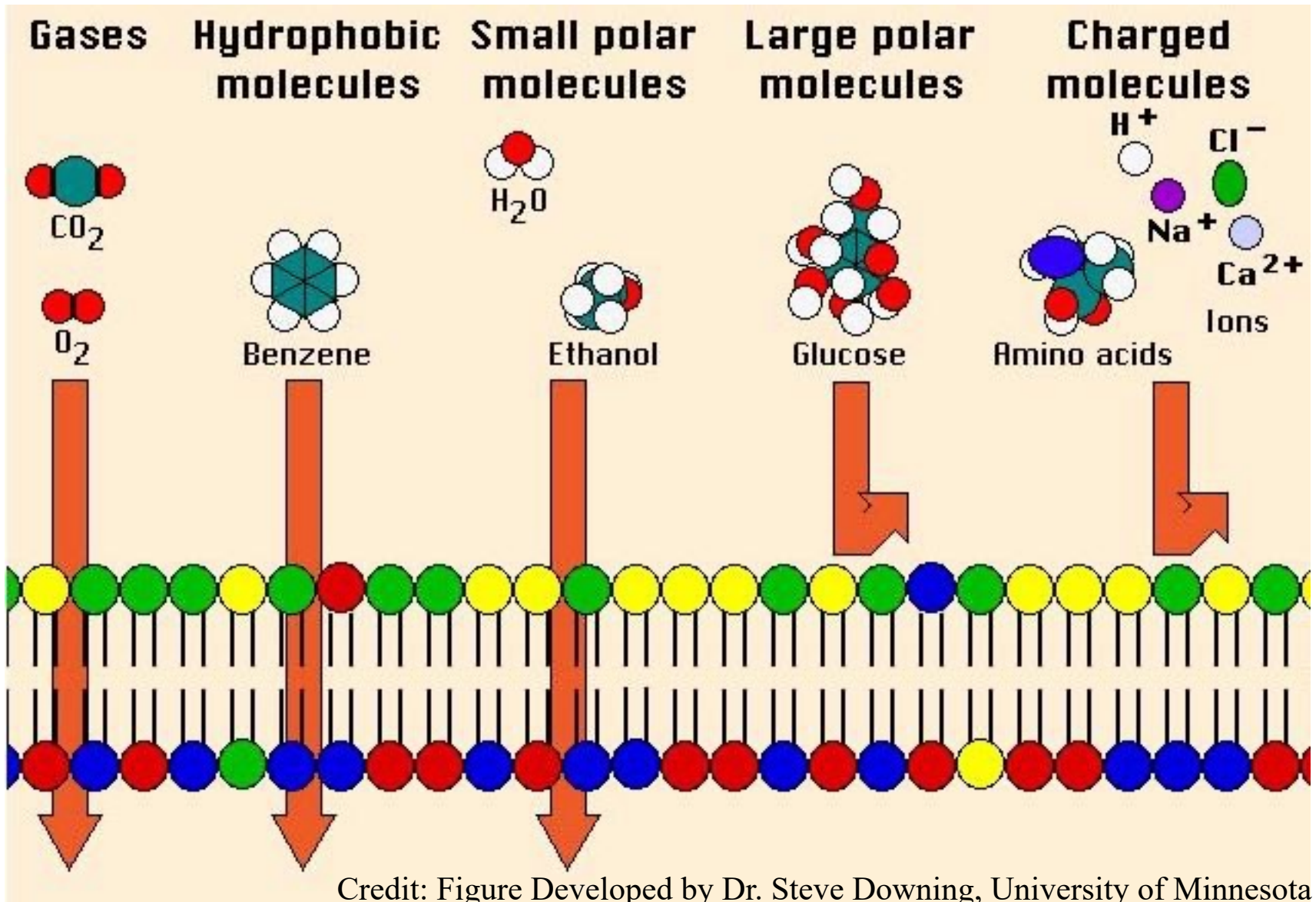
$$U_{\text{vacuum} \rightarrow \text{water}}^{\text{solv}} = \frac{Cq^2}{2r_q} \left(\frac{1}{\epsilon_w} - 1 \right)$$

Even simpler for water-to-fat transfers

- Transfer *from water to a medium* with $\epsilon=4$ (e.g. membrane, or protein interior) is **energetically unfavorable**:
- r_q is the Born radius of an ion, and Z is its charge in electron units:

$$U_{transfer}^{molar} = 40 \frac{Z^2}{r_q} [kcal / mol]$$

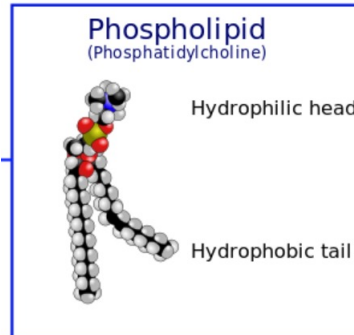
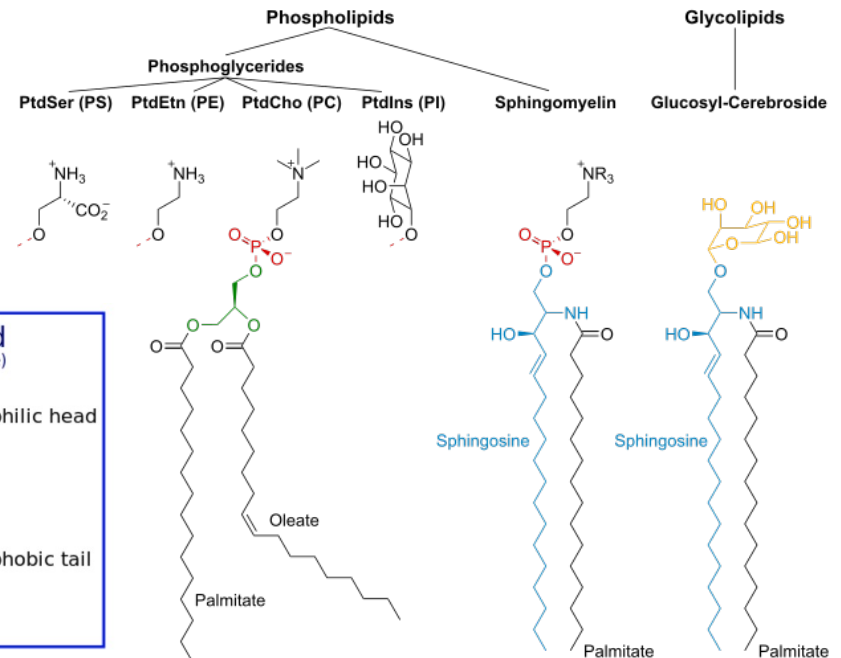
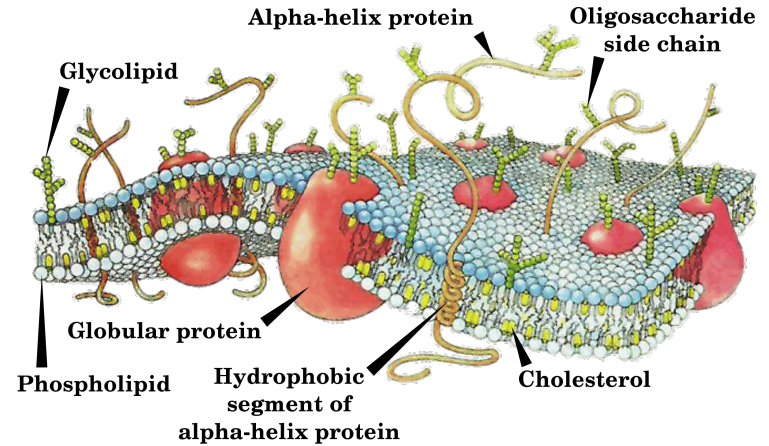
Passive transport of small molecules



Credit: Figure Developed by Dr. Steve Downing, University of Minnesota

Cell Membrane: Phospholipids, Glycolipids, Sterols and Proteins

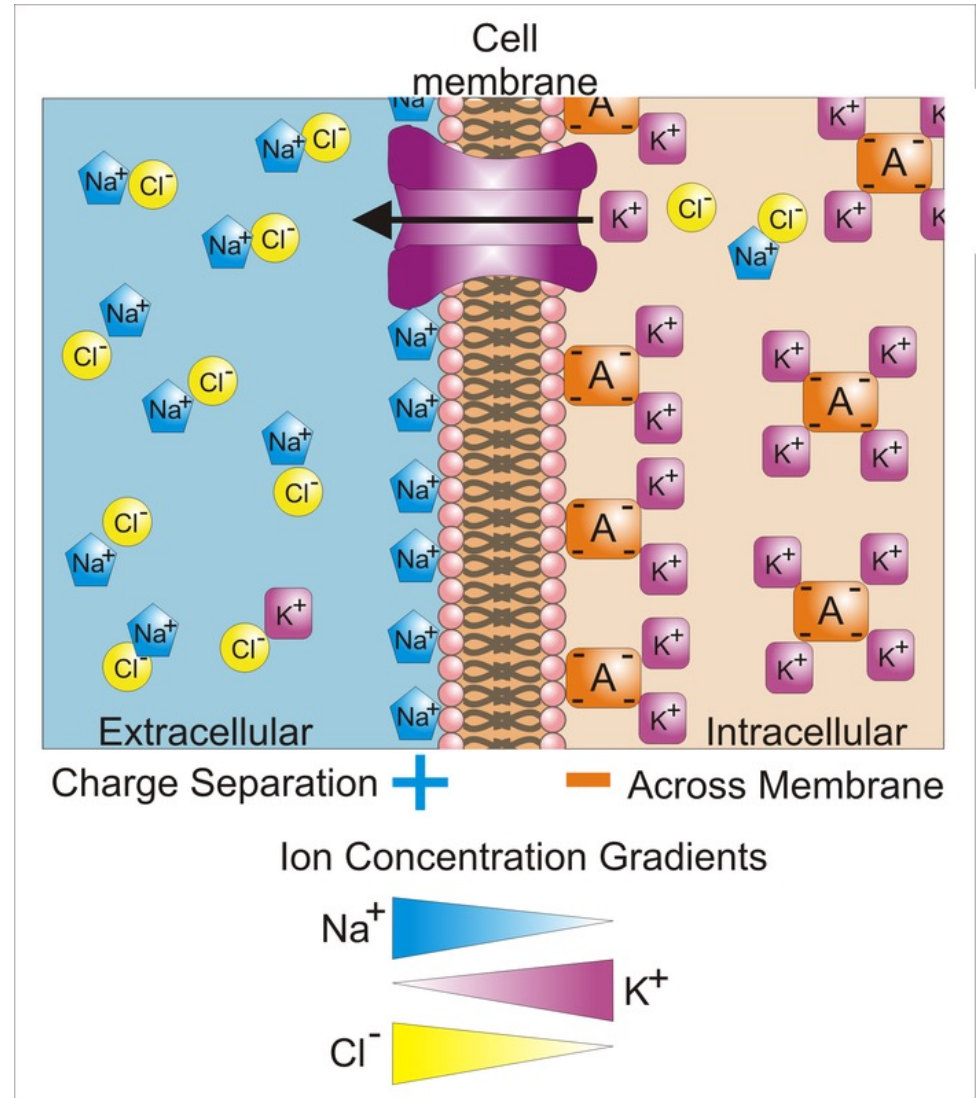
- Passive drug permeation is affected by the number of charged or polar atoms



Membrane Potential: -40 mV to -70 mV

Concentration gradient and Voltage

- Concentration gradients are created by **selective ion transporters**
- Ion gradient leads to a **voltage** called the **membrane potential** in the range -40 mV to -80 mV
- Positively charged drugs may have cell permeation benefit



Example: Ion solvation

- **Problem:** Estimate the ion *desolvation* energy (i.e. the solvation energy change) when a mole of magnesium ions with formal charge of +2 and the Born radius of 1.73 Å is transferred from water to a membrane (assume the dielectric constant of 2). $C = 332 \text{ (kcal Å)} / (\text{mol eu}^2)$.
 - A. -187.1 kcal/mol
 - B. -23.2 kcal/mol
 - C. -470 cal/mol
 - D. 23.2 kcal/mol
 - E. 187.1 kcal/mol
 - F. 470 cal/mol
- **Solution:**

$$E = C \frac{q^2}{2r_q} \times \left(\frac{1}{\epsilon_{to}} - \frac{1}{\epsilon_{from}} \right) = 332 \times \frac{2^2}{2 \times 1.73} \times \left(\frac{1}{2} - \frac{1}{80} \right)$$

$$E = 332 \times \frac{4}{3.46} \times 0.49 = 187.1 \text{ kcal/mol}$$