

# Review

Drug quantity: Molecular weight, moles, Avogadro, pills, Reactions/Transitions, Energies

- From molecular mass in Da to the mass of 1 mole, e.g. how many moles in a 100mg tablet? What is a mole and the Avogadro number
- Molecules move at temperature **T**: mean velocity  $V = \sqrt{3RT/MolMass}$   
Do not forget that T is Kelvin temperature and  $^{\circ}K = 273.15 + ^{\circ}C$
- Gas constant R in different units convenient for the calculation
- Understanding **reaction (or transition) Equilibrium** and how to calculate an **equilibrium constant K** for any transition or reaction. Example: drug-target dissociation  $K_d: [PL] \rightarrow [P] + [L]$ ,  $K_d = [P][L]/[PL]$ ,  $K_d$  has units of concentration
- Reaction or transition energy changes:  $\Delta G = \Delta H - T\Delta S$ , meaning
  - $\Delta H$  is responsible for the heat: negative – exo, positive – endo
  - Molar amounts  $\Delta H_0$ , or given the concentration or amount how much heat is produced

# Review

- **LogP** definition:  $\text{Log}_{10}\left(\frac{C_{oct}}{C_{wat}}\right)$ 
  - How to convert this ratio to the water to octanol transition energy. Hint:  $K = \left(\frac{C_{oct}}{C_{wat}}\right)$ ;  $\Delta G = -RT \ln K$
- **Radioactive decay, gamma rays, their energy, wavelength, speed-of-light, Planck constant  $h$ , frequency**
- **Boiling and propellants. Propellant-based inhalers**

# Review

- Free Energy  $\Delta G$
- chemical potential  $\mu$  of a component in a mixture:
  - Gas
  - Liquid mixture
  - $\Delta G$  and entropy of mixing.
- The chemical equilibrium
  - K via concentrations and reaction stoichiometry
  - From K, to  $\Delta G^\circ$
  - From K at  $T_1$  and  $T_2$ , to  $\Delta H^\circ$ , Van't Hoff

$$\mu_i = \mu_i^{c_0} + RT \ln \frac{c_i}{c_0}$$

$a_i$  is molar fraction  $x_i$  or concentration  $c_i$  or activity depending on the standard state and ideality

$$K = \prod_{i=1}^n a_i^{\nu_i}, \quad \text{e.g. } K = \frac{[A \bullet B]}{[A][B]}$$

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

$$\ln K = -\frac{\Delta_r H^\circ}{RT} + \frac{\Delta_r S^\circ}{R} \qquad \ln \left( \frac{K_1}{K_2} \right) = -\frac{\Delta H^\circ}{R} \left( \frac{1}{T_1} - \frac{1}{T_2} \right)$$

# Binding Reaction: Protein + Ligand

$K_a$ , subscript 'a' means association/binding

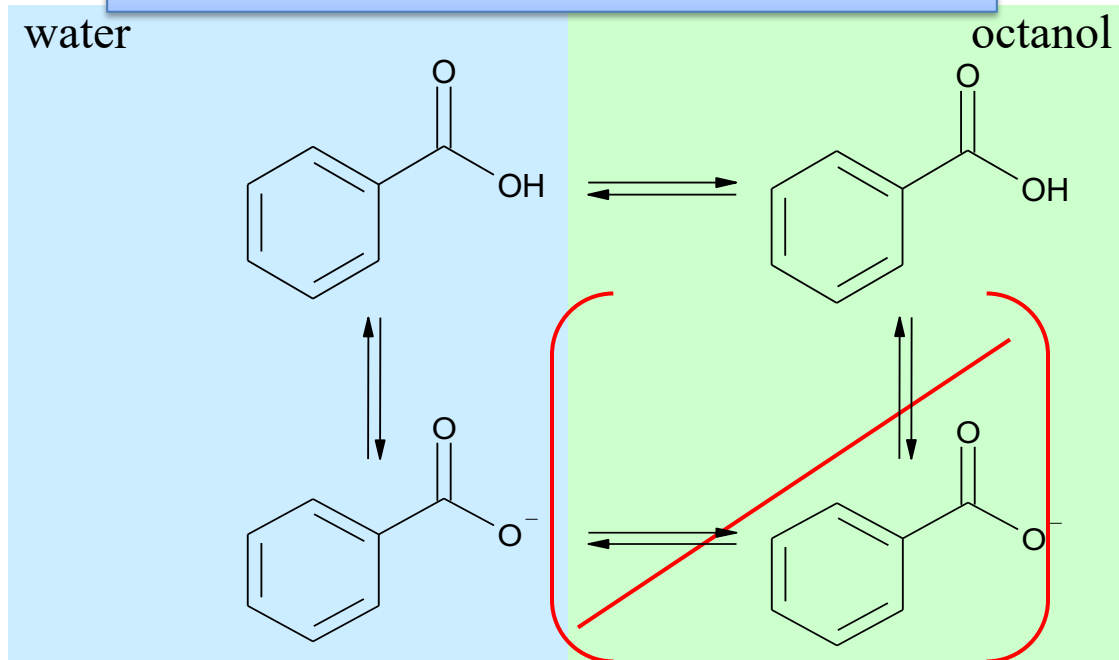
- $PL \leftrightarrow P + L$ ;  $K_{\text{dissociation}} = [P][L]/[PL]$  ;  $K_a = 1/K_d$
- $x = [PL]$ ;  $(P_0 - x)(L_0 - x) = x \cdot K_d$
- $x = \frac{1}{2} \cdot ( P_0 + L_0 + K_d - ( (P_0 + L_0 + K_d)^2 - 4P_0 L_0 )^{1/2} )$
- $P_0 \ll K_d$  :  $[PL]/[P] \approx L_0 / K_d$  (50% inh. @  $L_0 = K_d$  )

**Target Fraction:**  $[PL]/[P_0] = L_0 / (K_d + L_0)$

- $[PL] \ll P_0$  (protein in excess) :  $[PL]/[L] \approx P_0 / K_d$  ,  
fraction\_drug\_bound  $\approx P_0 / (P_0 + K_d)$

# LogD depends on $\text{Log}P$ of the neutral form and $\text{pH}-\text{p}K_a$

$\text{p}K_a = 4.2$ ;  $\text{Log}D (\text{pH}=7.2) \approx 1.87 - 3 = -1.13$



$$\log P = \log \frac{[AH]_{oct}}{[AH]_{wat}}$$

$$\log D = \log \frac{[AH]_{oct} + [A^-]_{oct}}{[AH]_{wat} + [A^-]_{wat}}$$

LogD is *apparent* LogP

$$\log D = \log P - \log(1 + 10^{\text{pH}-\text{p}K_a}) \quad \text{for acids}$$

$$\approx \log P - (\text{pH} - \text{p}K_a) \quad (\text{for } \text{pH} > \text{p}K_a + 1, \text{ charged form dominates})$$

$$\log D = \log P - \log(1 + 10^{-(\text{pH}-\text{p}K_a)}) \quad \text{for bases}$$

$$\approx \log P + (\text{pH} - \text{p}K_a) \quad (\text{for } \text{pH} < \text{p}K_a - 1, \text{ charged form dominates})$$

# Review. Mixtures, Osmosis

- Chemical potential of the same molecule in different phases or compartments (osmosis) *must be equal*
- Chemical potential of water is lower (better) in solution if  $x_{\text{solute}}$  is small:
- Osmotic pressure:  $P_{\text{osm}} = MRT$ , where  $M$  is molarity corrected by dissociation,  $i$ ,  $M = iM_0$
- Osmosis: semi permeable membranes.
- **Osmolarity and Tonicity**: counting solutes that can not cross the membrane and taking dissociation into account ( $i$ , van't Hoff's factor).
- Boiling point elevation
- Freezing point depression ( $K_f$  does not depend on solutes!).  $K_f = 1.858 \text{ K kg/mol}$
- Water pressure reduction: **Raoult's law**
- Gas dissolution in water: **Henry's law**
- The effects are entropic and to the first approximation do not depend on the nature of solutes (**colligative** properties)

$$\mu_{w\_in\_solution} = \mu_{w\_pure} + RT \ln(x_w)$$

$$\Delta\mu_w = RT \ln(1 - x_{\text{solute}}) \approx -RT x_{\text{solute}}$$

$$\Delta S_w \approx R x_{\text{solute}}$$

$$P_{\text{osm}} = \frac{\Delta n_{\text{sol}}}{V} RT = i \Delta M RT$$

$$\Delta T_{\text{boiling}} = K_b x_{\text{solute}}$$

$$\Delta T_{\text{freezing}} = K_f x_{\text{solute}}$$

$$P_{w\_vap\_solution} = P_{w\_vap\_pure} x_{\text{water}}$$

$$P_{\text{solute\_in\_gas}} = K_{\text{Henry}}^{\text{solute}} x_{\text{solute\_in\_water}}$$

# Review of Energy Contributions to the non-covalent Binding Energy

- q-q: **Coulomb**: (+) or (-) , strong in non-polar medium and weak in water. Long range ( $r^{-1}$ ).  $C=332$  (kcal/mol)Å(eu)<sup>-2</sup>
- q-water: *Ion and dipole Solvation*. Large (-):.
- D-H..A: **Hbonds**. Medium, short range.
- A-A: **Van der Waals** interaction Weak (-0.2 kcal/mol), but many. Short range ( $r^{-6}$ ).
- Apolar-Apolar **Hydrophobic** energy, water entropy contribution

$$E_{el} = C \frac{q_1 q_2}{\epsilon r}$$

$$E_{w-m}^{solv} = \frac{Cq^2}{2r_q} \left( \frac{1}{\epsilon_w} - \frac{1}{\epsilon_m} \right)$$

$$E_{hb} = f(r_{HA}, \alpha_{ALP_{HD}})$$

$$E_{vw} = \frac{A}{r^{12}} - \frac{B}{r^6}$$

$$E_{hp} = \sigma \cdot Area$$

# H.H.: a quantitative picture

- Most drugs are weak acids or weak bases
- It is not all or nothing, there are always several species at different concentrations

$$\log\left(\frac{[A^-]}{[HA]}\right) = pH - pK_a$$

$$\log\left(\frac{[B]}{[BH^+]}\right) = pH - pK_a$$

$$K_a = \frac{[H^+][Base]}{[Acid]},$$

$$pK_a = -\log(K_a)$$

$$pH = -\log([H^+])$$

Drug Solutions (acidic and basic)

$$pH = \frac{1}{2} pK_a - \frac{1}{2} \log c$$

$$pH = 7 + \frac{1}{2} pK_a + \frac{1}{2} \log c$$



# Kinetics and Diffusion

$$k = Ae^{-\frac{G_{activation}}{RT}}$$

$$[A] = [A]_0 - kt$$

$$J = -D \frac{dC}{dx} \approx \Delta C$$

$$[A] = [A]_0 e^{-kt}$$

$$\frac{1}{[A]} - \frac{1}{[A]_0} = k_2 t$$

- [Drug] = Flux(J) • Area(A) • Time

$$K_{eq} = \frac{[B]}{[A]} = \frac{k_f}{k_r}$$

$$K_{bind} = \frac{[PL]}{[P][L]} = \frac{k_{on}}{k_{off}}$$

$$K_d = \frac{[P][L]}{[PL]} = \frac{k_{off}}{k_{on}}$$

# Methods

- Braggs Law of Diffraction
- The diffraction condition for a crystal

$$2d \cdot \sin \theta = n\lambda$$

- $\lambda$  is the wavelength of gamma-rays (  $\sim 1.5\text{\AA}$  )
- $d$  is the distance between planes,
- $\theta$  is the angle of diffraction
- and  $n$  is an integer known as the *order* of the diffracted beam

$$\mathbf{F} = q(\mathbf{E} + \mathbf{v} \times \mathbf{B}) \quad \text{Lorentz force} \quad \frac{m\mathbf{v}^2}{R} = q\mathbf{v}B$$

$$(m/q)\mathbf{a} = \mathbf{E} + \mathbf{v} \times \mathbf{B}$$

$$R = \frac{m}{q} \frac{\mathbf{v}}{B}$$

# The Finals



- **20** problems, 2hours, do the easy ones first
- Start submitting no later than 11:45 to avoid missing the submission deadline
- If your laptop fails or you do not have one, use your friend's device, or my laptop to enter the answers
- The worst-case scenario: you will have a chance to retake