

Van t'Hoff Factor

- **Problem:** When the pharmaceutical formulation of drug X, $[X]_2Ca^{2+}$ is dissolved in water, 30% of the molecules dissociated into three ions, 30% into two ions, and 40% did not dissociate. Calculate the van't Hoff factor for the solution.
 - A. 0.3
 - B. 0.4
 - C. 1
 - D. 1.9
 - E. 2
- **Solution:**
 - $3 \times 0.3 + 2 \times 0.3 + 1 \times 0.4 = 0.9 + 0.6 + 0.4 = 1.9$
 - OR: Every 100 molecules will produce $3 \times 30 + 2 \times 30 + 1 \times 40 = 190$ particles.
- **Answer:** the van t'Hoff factor is 1.9 (to be used for calculation of all colligative properties)

Raoult's Law

- **Problem:** The pure water vapor pressure at 47°C is 0.1 bar. Estimate the vapor pressure when 32 g of NaCl (MW = 58 g/mol) is added to 1 L of water. Assume that the salt is not volatile, but it dissociates completely.
 - A. 0.002 bar
 - B. 0.02 bar
 - C. 0.098 bar
 - D. 0.98 bar
- **Solution:**
 - 32 g = 32/58 ~ 0.55 mol of salt
 - Dissolved AND DISSOCIATED in 1L = 55 mol of water; **van t'Hoff factor of 2**
 - Molar fraction of the solute $x \approx 2 \times 0.55 / 55 = 0.02$.
 - Raoult's Law, $\Delta P_w = x_{solute} P_w^* = 0.02 * 0.1 = 0.002$ bar
 - $P_w = P_w^* - \Delta P_w = 0.1 - 0.002 = 0.098$ bar
- **Answer:** The new vapor pressure is ~ 0.098 bar.

Osmotic pressure $\Delta P \sim \Delta M 25$ [atm L/mol]

- **Problem:** The blood glucose level of a diabetic patient is approximately 0.198 g/dL (dL = 0.1L). Given that glucose MW = 180.16 g/mol, calculate the osmotic pressure created by glucose.
 - A. 0.9 mmHg
 - B. 19 mmHg
 - C. 109 mmHg
 - D. 209 mmHg
- **Solution:**
 - no dissociation occurs: **van t'Hoff factor = 1**
 - 0.198 g/dL = 1.98 g/L \sim 11 mM = osmolarity
 - $\Delta P_{osm} = 11 \text{ mOsm/L} \times 25 \text{ L atm/mol} = 0.275 \text{ atm} = 209 \text{ mmHg}$
- **Answer:**
 - 209 mmHg
 - Note that glucose does permeate membranes; the actual ΔP_{osm} due to glucose between plasma and interstitium is lower

Problem solving steps

- Determine the reaction or transition
- Write the chemically balanced equation

- $\Delta G \rightarrow K$

- Write the equilibrium constant
- Find the equilibrium constant using
- If necessary, solve for components

$$K = \exp\left(-\frac{\Delta G^0}{RT}\right)$$

- $K \rightarrow \Delta G$

- Find the equilibrium constant using
- Find ΔG using

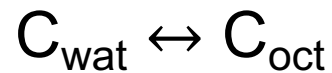
$$\Delta G^0 = -RT \ln K$$

- $[r] \leftrightarrow [p]$

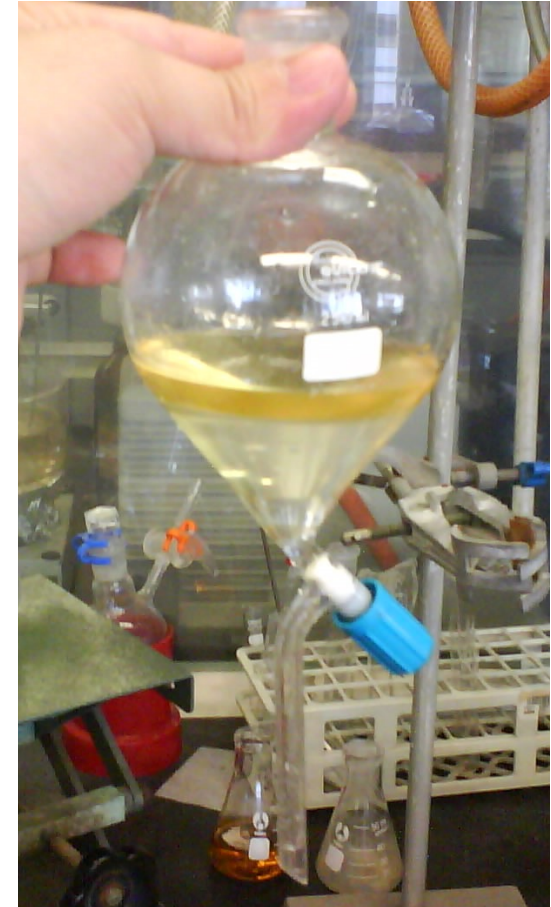
- Use equilibrium constant K definition from concentrations of reactants and products and stoichiometry

Reaction: phase partition, LogP

- **Reaction** of spontaneous transfer of the compound from non-polar to polar phase



- **Constant:** $K = C_{\text{oct}}/C_{\text{H}_2\text{O}}$
- LogP definition (LogP needs to be in a narrow range for compound permeability)
 $\log P = \log_{10} (C_{\text{oct}}/C_{\text{H}_2\text{O}})$: experimental
- $K = 10^{\log P}$
- May need to use *molar amt = conc x volume*



Phase Partition Equilibrium I

- **Problem:** 4.02 mmol of a compound with $\log P = 2.3$ is added to a container with **0.5L** octanol and **0.5L** water. Find the concentrations of the compound in water and octanol after the system equilibrates.

- **Solution:**

- ❖ Reaction: Compound in $\text{H}_2\text{O} \rightleftharpoons$ Compound in Octanol

- ❖ $\log P = 2.3 \Rightarrow K = C_{\text{oct}} / C_{\text{H}_2\text{O}} = 10^{2.3} \approx 200$, so $C_{\text{oct}} \approx 200 \times C_{\text{H}_2\text{O}}$

	Molar amount	Concentration	Volume
Water	x [mol]	$x / 0.5 \text{ L} = 2x$ [M]	0.5 L
Octanol	200x [mol]	200 \times $C_{\text{H}_2\text{O}} = 400x$ [M]	0.5 L

- ❖ $200x + x = 4.02 \text{ mmol} \Rightarrow 201x = 4.02 \times 10^{-3} \text{ mol} \Rightarrow x = 20 \mu\text{mol}$

- ❖ 20 μmol in water, 4 mmol in octanol

- ❖ Concentrations: 20 $\mu\text{mol} / 0.5 \text{ L} = 40 \mu\text{M}$ in water, 4 mmol / 0.5 L = 8 mM in octanol (*sanity check, please?*)

- **Answer:** 40 μM and 8 mM

Phase Partition Equilibrium II

- **Problem:** 12.3 μmol of a compound with $\log P = 2.3$ is added to a container with **0.5L** octanol and **2.5L** water. Find the concentrations of the compound in water and octanol after the system equilibrates.

- **Solution:**

- ❖ Reaction: Compound in $\text{H}_2\text{O} \rightleftharpoons$ Compound in Octanol

- ❖ $\log P = 2.3 \Rightarrow K = C_{\text{oct}} / C_{\text{H}_2\text{O}} = 10^{2.3} \approx 200$ and $C_{\text{oct}} \approx 200 \times C_{\text{H}_2\text{O}}$

	Molar amount	Concentration	Volume
Water	x mol	$x / 2.5 \text{ L} = 0.4x \text{ M}$	2.5 L
Octanol	$200 \times (0.5/2.5) = 40x$ mol	$200 \times C_{\text{H}_2\text{O}} = 80x \text{ M}$	0.5 L

- ❖ $40x + x = 12.3 \mu\text{mol} \Rightarrow 41x = 12.3 \times 10^{-6} \text{ mol} \Rightarrow x = 0.3 \mu\text{mol}$

- ❖ 0.3 μmol in water, 12 μmol in octanol

- ❖ Concentrations: 0.3 $\mu\text{mol} / 2.5 \text{ L} = 0.12 \mu\text{M}$ in water, 12 $\mu\text{mol} / 0.5 \text{ L} = 24 \mu\text{M}$ in octanol (*sanity check, please?*)

- **Answer:** 0.12 μM and 24 μM

Phase Partition, K to ΔG

- **Problem:** 4.6 mmol of a compound was added to a container with **1L** octanol and **3L** water. After the system equilibrated, the aqueous concentration of the compound was found to be 0.2 mM. Find the compound logP and molar ΔG of its transition from octanol to water.
- **Solution:**

	Molar amount	Concentration	Volume
Water	$0.2 \text{ mM} \times 3\text{L} = 0.6 \text{ mmol}$	0.2 mM	3L
Octanol	$4.6 - 0.6 = 4 \text{ mmol}$	$4 \text{ mmol} / 1\text{L} = 4\text{mM}$	1L

$$\log P = \log C_{\text{oct}} / C_{\text{H}_2\text{O}} = \log (4\text{mM} / 0.2 \text{ mM}) = \log 20 \sim 1.3$$

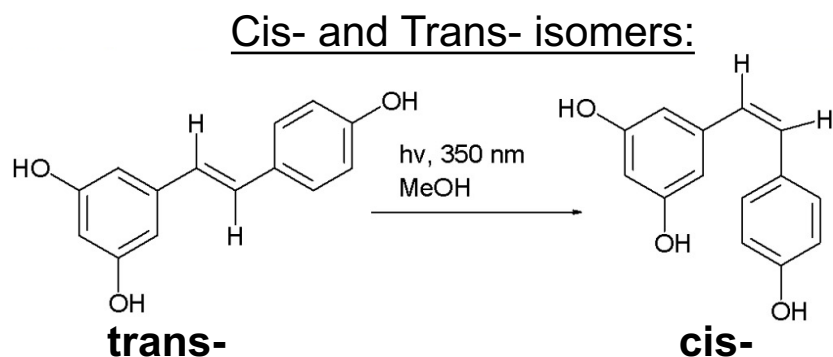
$$\Delta G^0 = -RT \ln C_{\text{H}_2\text{O}}/C_{\text{oct}}$$

$$\Delta G^0 = -0.6 \ln 1/20 = 0.6 \ln 20 = 0.6 \times 3 = 1.8 \text{ kcal/mol (sanity check?)}$$

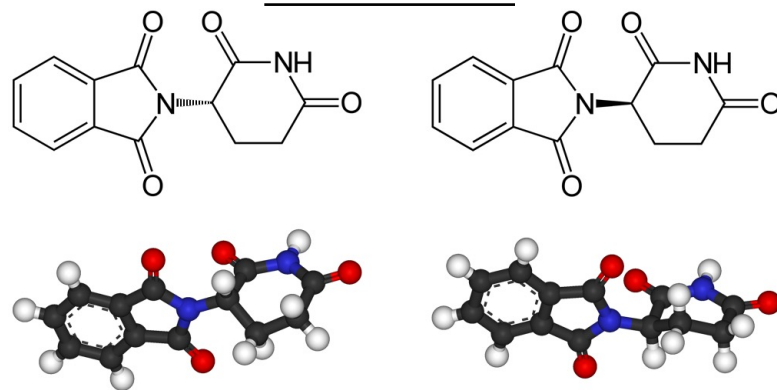
- **Answer:** $\log P = 1.3$, ΔG^0 (octanol \Rightarrow water) = 1.8 kcal/mol
- **Useful hint:** $\ln 20 \sim 3$.

Drug stereo-isomers: conformational transition

- Compound has two distinct stereo-isomers, e.g.:
(if there is a chiral center) (S) and (R)
(if there is a double bond) cis- and trans-
“state A and state B”
- **Reaction** of spontaneous transition:
 $A \rightleftharpoons B$
- $K = C_B/C_A$ (ratio of two concentrations)



Enantiomers:



(S)-thalidomide
Teratogenic

(R)-thalidomide
Safe, effective against
morning sickness

Problem: Isomerisation, ΔG to K

- The Gibbs free energies of formation of two stereoisomers, X and Y, of a compound at $T = 300\text{K}$ are $G_f(X) = 93.2 \text{ kcal/mol}$ and $G_f(Y) = 96.2 \text{ kcal/mol}$. Estimate the molar fraction of [Y] in the (*equilibrium*) racemic mixture at this temperature.

- Solution:**

Reaction $Y \rightleftharpoons X$

$$\Delta G = G_f(X) - G_f(Y) = -3 \text{ kcal/mol}$$

Find the equilibrium constant, $K = [X]/[Y]$

$$K = \exp(-\Delta G / RT) = \exp(3 / 0.6) = \exp 5 \sim 149$$

$[X]/[Y] \sim 149/1$ (*sanity check, please?*)

Molar fraction of Y is $[Y]/([Y]+[X]) \sim 1 / 150$

$$K = \exp\left(-\frac{\Delta G^0}{RT}\right)$$

Answer: $\sim 1/150$