

Physical and Chemical Principles

I. Molecular Transport

1. Diffusion

* Fick's Law:

$$J = -D \nabla n$$

J is the flux

D is the diffusion constant

n is the concentration

Interpretation

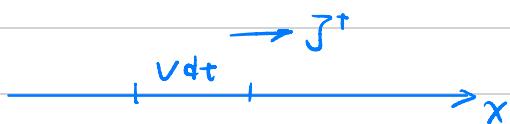
- there is a net flow of particles from high concentration to low concentration
- more molecules in the region of higher conc.
→ more random flow

* 1D diffusion model

molecules can change direction



↳ the rate of direction change is p



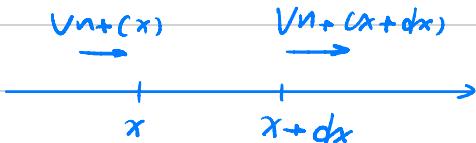
$$J_+ dt = n_+ v dt \Rightarrow J_+ = v n_+$$

$$J_- = -v n_-$$

During time dt , consider a small section dx :

$$J = J_+ + J_- = v(n_+ - n_-)$$

$$\begin{aligned} dn_+ dx = & \underbrace{-n_+ dx p dt}_{+ to -} + \underbrace{n_- dx p dt}_{- to +} \\ & + v n_+ (x) dt - v n_+ (x+dx) dt \\ & \text{charge due to flux} \end{aligned}$$



Dividing by $dx dt$:

$$\frac{dn_+}{dt} = -v \frac{dn_+}{dx} - p n_+ + p n_-$$

$$\Rightarrow \frac{dJ}{dt} = -2Jp - v^2 \frac{d(n_+ - n_-)}{dx}$$

Similarly:

$$\frac{dn_-}{dt} = +v \frac{dn_-}{dx} - p n_- + p n_+$$

Apply steady-state assumption: $J_p \gg \frac{dJ}{dt}$

$$J = -\frac{v^2}{2p} \frac{dn}{dx} \quad \text{with } n = n_+ + n_-$$

— Fick's Law

Summing $\frac{dn+}{dt}$ and $\frac{dn-}{dt}$:

$$\frac{dn}{dt} = -\frac{\partial J}{\partial x} = \frac{v^2}{2P} \frac{\partial^2 n}{\partial x^2}$$

— Diffusion equation

where $D = \frac{v^2}{2P}$

* Reaction-diffusion

$$\frac{dn}{dt} = D \nabla^2 n + P$$

↓
the local production rate per unit volume

* Reaction-diffusion in a membrane

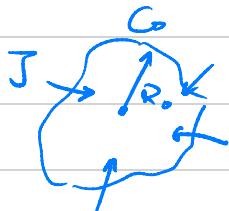
Solution to $D \nabla^2 n + P = 0$ (Steady state):

$$n(z) = \frac{P}{2D} (z_h - z^2) + \frac{C_1 - C_0}{h} z + C_0$$

C_0, C_1 are concentration at $z=0$ and $z=h$

$J(h) - J(0) = Ph \rightarrow$ the rate of particle production in the membrane

Diffusion in a tumor



$$PR^3 \approx JR^2$$

$$J_{\max} \approx D \frac{C_0}{R} \rightarrow R_{\max} \approx \sqrt{\frac{DC_0}{P}}$$

2. Osmotic pressure

* Osmosis definition

Osmosis is the process by which water flows through a semi-permeable membrane due to a differential in concentration of non-permeable solutes on both sides.

Water would flow from low solute concentration to high solute concentration.

A difference in hydrostatic pressure is need to stop this flow.

$$P_1 - \pi_1 = P_2 - \pi_2$$

$$\Rightarrow \pi_1 - \pi_2 = P_2 - P_1 = \rho g \Delta h$$

π_1 and π_2 are the osmotic pressure

* Osmolarity

Osmotic pressure (*assumption: low solute concentrations)

$$\pi = RT \sum C_i$$
 C_i is the concentration for solute ;

$$\text{Osmolarity} : \frac{\pi}{RT} \quad \text{Unit: osmol (os)}$$

$$Osm = \phi \sum C_i$$

↳ accounts for "non-ideality" of the solutes

tends to 1 at low solute concentrations

* independent of the nature of the solutes

* Hyper / hypo - tonicity

When cells are in contact with a solution, the solution is:

- hypertonic if the cell shrinks
- hypotonic if the cell swells
- isotonic if the cell does not change

* Derivation of the osmotic pressure

Outline:

- find free energy before mixing
 - find variation of internal energy, ΔU (due to changes in link in between solute and water molecules)
 - find variation of entropy ΔS
- ⇒ Get the Gibbs free energy, after mixing on both side of the membrane
- at equilibrium, $\frac{\partial G_1}{\partial n_1} = \frac{\partial G_2}{\partial n_2}$ since $\frac{\partial G}{\partial n_2} = 0$
 - apply the equilibrium condition to get the solution

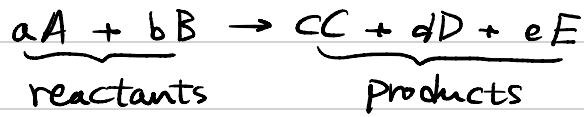
Assumptions:

- all solute molecules are surrounded by water molecule after mixing → the concentration is not too high
- consider only the spatial arrangements for entropy calculation
- ΔV can be neglected in solutions

Note: Gibbs free energy $G = U + PV - TS$

II. Chemical Principles

1. Chemical reactions



a, b, c, d, e represent the quantitative relationship between reactants and products → stoichiometry

Two important aspects:

- * Thermodynamics — for a reaction to occur, it must be thermodynamically favourable
- * Kinetics — how fast the reaction occurs

2. Law of mass action

* Extent of reaction

For a reaction $aA + bB \rightleftharpoons cC$,

Use the extent of reaction ξ to characterise the variation of the chemical concentrations:

$$dn_A = -a d\xi, dn_B = -b d\xi, dn_C = c d\xi$$

* Gibbs free energy of reaction

The system is at the thermodynamical equilibrium if:

$$\boxed{\left. \frac{\delta G}{\delta \xi} \right|_{T,P} = 0}$$

where (from chain rule $\left. \frac{\delta G}{\delta n_i} \right|_{T,P,n_{k\neq i}} \frac{dn_i}{d\xi}$)

$$\boxed{\left. \frac{\delta G}{\delta \xi} \right|_{T,P} = -a \mu_A(P,T) - b \mu_B(P,T) + c \mu_C(P,T)}$$

μ is the chemical potential

* Chemical potential

Chemical potential of solutes:

$$\mu_A = \frac{\partial G}{\partial n_A} \Big|_{T, P, n_B} = \mu_A^{(0)}(P, T) + \lambda + RT \ln(x_A), \quad x_A = \frac{n_A}{n_B + n_A} \approx \frac{n_A}{n_B}$$

$$\mu_A = \underbrace{\mu_A^{(0)}(P, T) + \lambda}_{\boxed{\mu_A^{(0)}(P, T)}} + RT \ln\left(\frac{V}{n_B}\right) + RT \ln([A])$$

$\mu_A^{(0)}(P, T)$ is the standard chemical potential

* Equilibrium Constant

The condition for the equilibrium is

$$\frac{\partial G}{\partial \xi} \Big|_{T, P} = -a\mu_A - b\mu_B + c\mu_C = 0$$

$$\frac{\partial G}{\partial \xi} \Big|_{T, P} = \underbrace{-a\mu_A^{(0)} - b\mu_B^{(0)} + c\mu_C^{(0)}}_{\Delta r G^{(0)}} + RT(-a\ln[A] - b\ln[B] + c\ln[C])$$

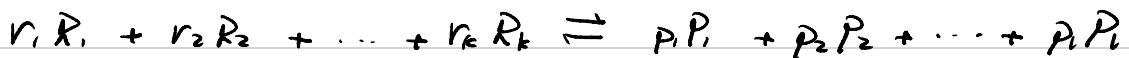
$\Delta r G^{(0)}$ → Gibbs free energy for the reaction

⇒ Equilibrium constant K for the reaction is

$$\frac{[C]^c}{[A]^a[B]^b} = \exp\left(-\frac{\Delta r G^{(0)}}{RT}\right) = K(T, P)$$

* Law of mass action

For any chemical reaction:



The constant of equilibrium is

$$K(T, P) = \frac{[P_1]^{p_1} [P_2]^{p_2} \cdots [P_l]^{p_l}}{[R_1]^{r_1} [R_2]^{r_2} \cdots [R_k]^{r_k}}$$

* Particular cases for equilibrium Constants

- Solvent or Solid (precipitate) reactants or products do not appear in the equilibrium constant
- at high concentrations, the expressions for the chemical potential are invalid

precipitation forms
at equilibrium

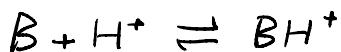
3. Acid and bases

* Definitions

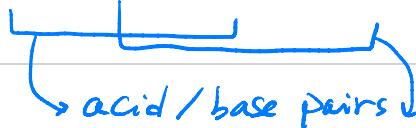
- A acid is a substance that can donate hydrogen ions (protons)



- A base is a substance that can accept hydrogen ions

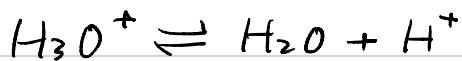


- Acid and bases can react together

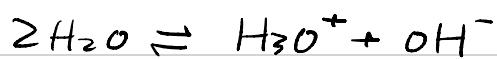


* Acid and bases in water

Water is both acid and base — amphoteric

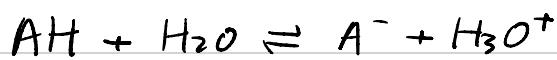


* Dissociation of water



$$K_e = [H_3O^+][OH^-] = 10^{-14} \quad (\text{pH} = -\log_{10}([H_3O^+]))$$

Dissociation constant in water



$$K_a = \frac{[A^-][H_3O^+]}{[AH]}$$

The strength of the acid is quantified by its pK_a

$$pK_a = -\log_{10} K_a$$

• An acid is strong if it completely dissociates in water

→ negative pK_a

• An base is strong if it fully dissociates in water

→ large K_b , where $K_b = K_e/K_a$

• Weak acids or bases only partially react / dissociate with water

4. Kinetics

* Reaction rate

— time derivative of the extent of reaction ξ .

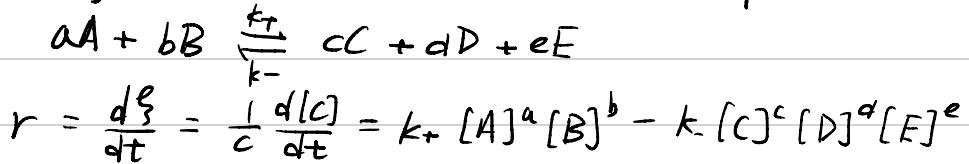


$$r = \frac{d\xi}{dt} = -\frac{1}{a} \frac{d[A]}{dt} = -\frac{1}{b} \frac{d[B]}{dt} = \frac{1}{c} \frac{d[C]}{dt} = \frac{1}{d} \frac{d[D]}{dt} = \frac{1}{e} \frac{d[E]}{dt}$$

* Elementary reactions

— reactions which occur, at the molecular level, in only one step

For elementary reactions, the rate takes the form:



* Kinetics and equilibrium

Thermodynamic equilibrium = rate of all chemical reactions is zero

$$r = k_+ [A]^a [B]^b - k_- [C]^c [D]^d [E]^e = 0$$

$$\frac{[C]^c [D]^d [E]^e}{[A]^a [B]^b} = \frac{k_+}{k_-} = K(T)$$

* Application to gas solubility

Ideal gas law:

$$PV = n k_b T$$

$$PV = N R T$$

$$N = n / N_A, \quad R = k_b N_A$$

k_b : Boltzmann's constant

R : universal gas constant

N_A : Avogadro number

Partial pressure in gas: $P_i = x_i P$

P : total pressure

x_i : mole fraction of the gas

* Gas Solubility

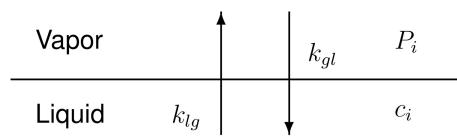
There is exchange of molecule between the gas and the liquid at an interface.

$$\frac{dc_i}{dt} = k_{lg} P_i - k_{gl} c_i$$

At the equilibrium:

$$c_i = (k_{gl}/k_{lg}) P_i = \sigma_i(T) P_i$$

σ is the gas solubility



* Steady-state assumption

Consider a non-elementary reaction



$$\frac{d[A]}{dt} = -k_1[A]$$

$$\frac{d[B]}{dt} = k_1[A] - k_2[B]$$

$$\frac{d[C]}{dt} = k_2[B]$$

Analytical solution:

For $k_1 \neq k_2$, $[A](\infty) = A_0$ and $[B](\infty) = [C](\infty) = 0$

$$[A] = [A]_0 e^{-k_1 t}$$

$$[B] = [A]_0 \frac{k_1}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t})$$

$$[C] = [A]_0 \left(1 + \frac{k_1 e^{-k_1 t} - k_2 e^{-k_2 t}}{k_2 - k_1} \right)$$

Steady-state approximation

Assumption: the concentration of such intermediates is simply constant.

$$\frac{d[B]}{dt} = k_1[A] - k_2[B] = 0$$

$$[B] = \frac{k_1}{k_2} [A]$$

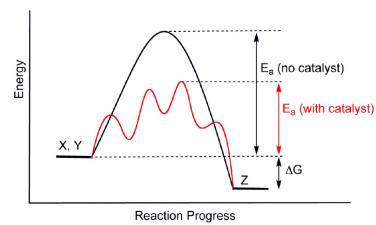
$$\Rightarrow [C] = [A]_0 (1 - e^{-k_1 t})$$

III. Enzyme Kinetics

1. Enzymes

* Catalysts

A catalyst is a compound that controls the rate of a chemical reaction without being consumed or produced by it.



A catalyst does not change the net reaction
→ does not impact equilibrium constant

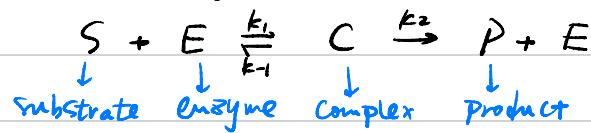
However, the difficult steps that require higher activation energies can be transformed into a succession of much simpler steps.

* Enzymes

Enzymes are proteins that have a catalytic function in the cell.
They transform substrate molecules into products.

2. Michaelis - Menten Kinetics

* Enzyme catalysis reaction



$$\frac{d[S]}{dt} = k_{-1}[C] - k_1[S][E]$$

$$\frac{d[E]}{dt} = (k_{-1} + k_2)[C] - k_1[S][E]$$

$$\frac{d[C]}{dt} = k_1[S][E] - (k_2 + k_{-1})[C]$$

$$\frac{d[P]}{dt} = k_2[C] = V \rightarrow \text{the overall rate of the reaction}$$

* Fast equilibrium assumption

Assuming that the equilibrium is fast implies that $k_1 \gg k_2$

$$\Rightarrow k_1 = \frac{[S][E]}{[C]} = \frac{k_1}{k_2}$$

(ignore the second reaction)

$$E_0 = [E] + [C] \quad \text{total amount of enzyme}$$

$$= \left(\frac{k_1}{[S]} + 1 \right) [C]$$

$$\Rightarrow [C] = E_0 \frac{[S]}{[S] + k_1}$$

$$\Rightarrow V = k_2 E_0 \frac{[S]}{[S] + k_1}$$

* Fast product formation assumption

Assume the transformation from C to P is fast

$$\rightarrow \text{steady state assumption on } C \rightarrow \frac{d[C]}{dt} = 0$$

$$\Rightarrow k_1 [S][E] = (k_2 + k_1)[C]$$

$$\frac{[S][E]}{[C]} = \frac{k_2 + k_1}{k_1} = K_m \quad \rightarrow \text{the Michaelis Constant}$$

$$\Rightarrow [C] = E_0 \frac{[S]}{[S] + K_m}$$

$$\Rightarrow V = k_2 E_0 \frac{[S]}{[S] + K_m}$$

* Michaelis - Menten equation

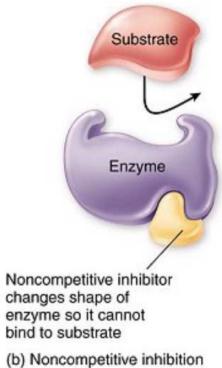
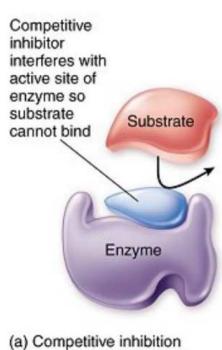
$$V = V_{\max} \frac{[S]}{[S] + K_m}$$

The maximum reaction is achieved when the substrate concentration is very high \rightarrow all of the enzyme molecules are bound into complexes $([C] \approx E_0)$

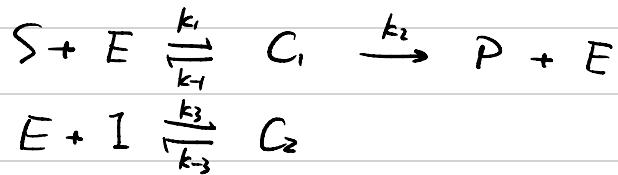
$$\text{Rearrange: } \frac{1}{V} = \frac{1}{V_{\max}} + \frac{K_m}{V_{\max}} \frac{1}{[S]}$$

plot of $\frac{1}{V}$ vs. $\frac{1}{[S]}$ is a straight line

3. Inhibitors and activators



* Competitive inhibition



Rate constants:

$$K_m = \frac{[S][E]}{[C_1]} = \frac{k_2 + k_1}{k_1}$$

$$k_2 = \frac{[I][E]}{[C_2]} = \frac{k_3}{k_4}$$

Conservation:

$$E_0 = [E] + [C_1] + [C_2]$$

$$\Rightarrow [C_1] = \frac{[S] E_0 k_2}{[S] k_2 + [I] K_m + k_2 K_m}$$

$$[C_2] = \frac{[I] E_0 K_m}{[S] k_2 + [I] K_m + k_2 K_m}$$

$$\Rightarrow V = \frac{V_{max} [S]}{[S] + K'_m}$$

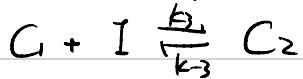
with

$$V_{max} = k_2 E_0$$

$$K'_m = K_m (1 + [I]/k_2)$$

→ Competitive inhibition leads to an effective increase of K_m

* Uncompetitive inhibition



$$\Rightarrow V = \frac{V_{max} [S]}{[S] (1 + [I]/K_m) + K_m}$$

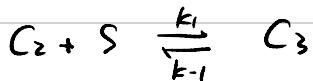
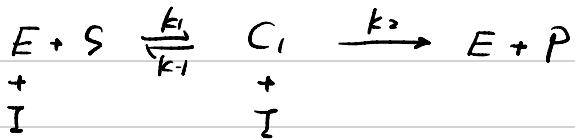
$$V = \frac{V_{max} [S]}{[S] + K_m}$$

with

$$K_m = \frac{K_m}{1 + [I]/K_2}$$

$$V_{max} = \frac{V_{max}}{1 + [I]/K_2}$$

* Non-competitive inhibition



Assumption: fast equilibrium

$$\Rightarrow V = \frac{V_{max} [S]}{[S] + K_m}$$

with

$$V_{max} = \frac{V_{max}}{1 + [I]/K_2}$$

$$K_m = \frac{k_1}{k_2} \quad \text{and} \quad K_2 = \frac{k_3}{k_2}$$