BME2105 Introduction to Biomedical Engineering
Molecular and Cellular Systems
Lecture 9- Chemical Kinetics and Equilibria

Unimolecular reaction as a general framework – first order:

$$A \xrightarrow{k} B$$

A = reagent
B = product
k = rate constant, a mix of energetic and physical factors

The reaction rate for this elementary reaction is defined as the rate of conversion of A to B, which is equivalent to either the rate of loss of A or rate of generation of B.

Note that in the following, I'll adopt K&S notation of lower case letters for species concentrations.

The Law of Mass Action relates the reaction to the players in this reaction.

$$\text{for } A + B + C + C \xrightarrow{k} D$$

$$\text{rate of reaction} = [A]*[B]*[C]^2 * k$$

In this simple case,

$$\frac{d[A]}{dt} = \frac{da}{dt} = -[A]k = [B]k = -ak = bk$$

From this, we get for a starting concentration of A of $[A]_0$, or a_0,

$$[A](t) = [A]_0 * \exp(-kt)$$

This is not a very useful chemical reaction in biology, as it is unregulated. This is found more often in decay processes.

As a first level of complexity, add the reverse reaction

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$$

This reaction is first order in both forward and reverse. An isomerization reaction, for example

$$\frac{da}{dt} = -k_1 a + k_{-1} b$$

$$\frac{db}{dt} = k_1 a - k_{-1} b$$

$$a + b = a_0$$

Solve, looking at the expression for a, and using the third relation

$$\frac{da}{dt} = -k_1 a + k_{-1}(a_0 - a) = -(k_1 + k_{-1})a + k_{-1} a_0$$

$$a' = a - \frac{k_{-1}}{(k_1 + k_{-1})} a_0$$

which leads to

$$\frac{da'}{dt} = -(k_1 + k_{-1})\left(a' + \frac{k_{-1}}{(k_1 + k_{-1})}a_0\right) + k_{-1}a_0 = -(k_1 + k_{-1})a'$$

or....

$$a'(t) = C\exp(-(k_1 + k_{-1})t)$$

or...

$$a(t) = C\exp(-(k_1 + k_{-1})t) + \frac{k_{-1}}{(k_1 + k_{-1})}a_0$$

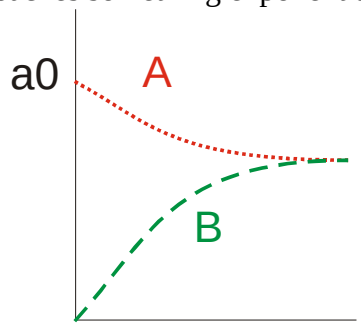
use the bc that at t=0,a=a_0

$$a_0 = C + \frac{k_{-1}}{(k_1 + k_{-1})}a_0$$

$$(k_1 + k_{-1})a_0 = (k_1 + k_{-1})C + k_{-1}a_0$$

$$C = \frac{k_1}{(k_1 + k_{-1})}a_0$$

Not the most informative, but let's try to draw out. We know that a graph of [A] vs. t starts at [A]=a_0. It also approaches something exponentially.



$$a(t = \text{long}) = \frac{k_{-1}}{(k_1 + k_{-1})}a_0$$

$$b = a_0 - a$$

$$b(t = \text{long}) = a_0\left(1 - \frac{k_{-1}}{(k_1 + k_{-1})}\right) = a_0\left(\frac{k_1}{(k_1 + k_{-1})}\right)$$

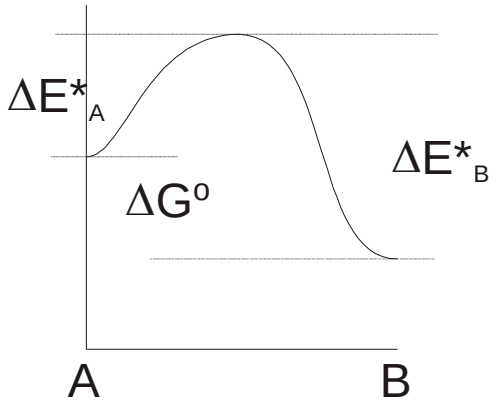
or.....

$$\left.\frac{b}{a}\right|_{t=\text{long}} = \frac{k_1}{k_{-1}} = K_{eq}$$

and this condition is called equilibrium.

- Note that we could have gotten here by setting da/dt=0 and solving.
- At equilibrium, it is not that A does not become B, and vice versa, but net changes are zero.
- Equilibrium is the long term, and the trajectory of how we got there is the kinetics.

Focus for a moment on rate constants and the relation to [A]/[B] final ratio.



This graph is a general diagram of what's going on. Two rates, forward and reverse.

- Rate constant in either direction is related to energy needed to go uphill
- Thus, as drawn, A->B is faster than B->A
- Thus, equilibrium favors B. Correspondingly, $K_{eq} > 1$
- Conversely $K_{eq} < 1$ favors A

for the most part, these are empirical; we won't derive them, it is important to have a feeling of some of the terms. Clearly, energy barrier is a big one. Other factors include rigidity of the molecule, and, when more than one molecule is being considered, the geometry of interactions between molecules.

Temperature is another big one. Fundamentally, raising temperature raises reaction rate.

$k=Ae^{-E/RT}$; Arrhenius equation

Binding – second order reaction:

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

$$\frac{da}{dt} = -abk_1 + ck_{-1}$$

$$\frac{db}{dt} = -abk_1 + ck_{-1}$$

$$\frac{dc}{dt} = +abk_1 - ck_{-1}$$

Consider the situation in which we are following A in the context of binding some ligand C

$$[A] + [C] = [A]_0$$

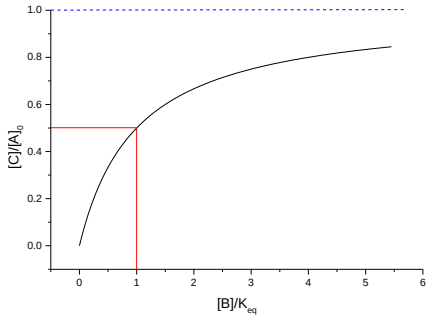
Now, substituting in $[A]=[A]_0-[C]$
and using the relation

$$\frac{d[C]}{dt} = 0 \Rightarrow [C]k_{-1} = k_1(([A]_0 - [C])*[B])$$

and solve for C,

$$[C] = [A]_0 \frac{[B]}{K_{eq} + [B]}; K_{eq} = \frac{k_{-1}}{k_1}$$

and this looks like:



Things to note:

- $[B]/K_{eq}=1$ -> $[C]/[A]_0=0.5$
- K_{eq} is called equilibrium constant, note that it is different than the Mass Action reaction constant.

Buffers:

Important throughout physiology and molecular biology. We'll return to this in a bit, but for now, we'll treat buffers in general on the way to enzymatic reactions.

Start with the Brønsted treatment of acids and bases, in which an acid can donate a proton and a base can accept a proton.

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

Solution	**pH**
gastric secretions	0.7
Soda	2
Cytosol of a cell	7.2
Pancreatic fluid	8.1

Clearly, control over pH is important for protein/system function

General Theme:

$$HA \leftrightarrow H^+ + A^-$$

For strong acids and bases, this dissociation is essentially complete. For weak acids and bases at equilibrium, the balance between dissociated and associated states follows the LeChatlier Principle: a system at equilibrium reacts to an input by minimizing the effect of that input.

Consider being at low pH, at which weak acid is protonated ([HA]). As one adds a strong base, pH rises, removing H^+ from the solution (by binding to OH^-). On balance, H^+ is replenished by action of HA dissociation. Same thing happens in reverse.

In short, if you are in a realm where a weak acid/base is present in both protonated and deprotonated forms in significant fractions, addition of strong base or strong acid will result in a change of pH change of much less than the unbuffered case.

Quite often buffer salts have multiple dissociations, and may salts are multivalent, but leave this complication out.

Quantitatively:

$$HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H^+ + A^-$$

.

$$[HA] + [A^-] = \text{constant}$$

$$\frac{d[HA]}{dt} = 0 \Rightarrow k_1[HA] = k_{-1}[H^+][A^-]$$

$$Ka = \frac{[H^+][A^-]}{[HA]} = \frac{k_1}{k_{-1}} = \text{dissociation constant}$$

Note that Ka is a dissociation constants; the "a" indicates that it is specific for an acid.

Henderson-Hasselbach equation:

$$pKa = -\log\left(\frac{[H^+][A^-]}{[HA]}\right) = -\log[H^+] - \log\left(\frac{[A^-]}{[HA]}\right)$$

switch left and right sides

$$pH = pKa + \log\frac{[A^-]}{[HA]}$$

Buffer characteristics

Buffer strength defined as the concentration of protonated and deprotonated forms of weak acid.

Buffer power (β) defined as the amount of strong base needed to produce a given change in pH.

$$\beta \equiv \frac{\Delta|\text{strong base}|}{\Delta\text{pH}} = -\frac{\Delta|\text{strong acid}|}{\Delta\text{pH}}\text{; units of conc./pH unit}$$

Again, this concept is important throughout physiology, with strong relations in acid/base chemistry of blood. This is described in Chapter 27. We'll need the acid/base part of it, the rest of the chapter is good reading. We'll return to these concepts after treating enzymatic reactions.

Example of pH calculation

Consider a buffer solution containing 10 mM of the monovalent salt HEPES, pKa = 7.55.

HEPES: 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid N-(2-Hydroxyethyl)piperazine-N′-(2-ethanesulfonic acid)

.1 ml of 1 M HCl is added to 100 ml of this buffer which has an initial pH of 7.2. What is the pH of this solution after it has come to equilibrium (long enough to come close)? Compare this to the change in pH in the absence of a buffer salt. What is the buffer strength?

Approach is to recognize that H+ is present as either H^+ or HA. Keep track of the sum of these two before and after addition of strong acid. This total will be denoted H_T.

Note that A^- and HA will be shifting, so easier to get things in terms of $[A]_0$.

So:

- $H_T = [H^+]+[HA] = 10\text{^}(-pH)+[HA]$
- $[A]_0 = [HA]+[A^-]$; $Ka/[H^+]=[A^-]/[HA] \Rightarrow [A]_0=[HA](1+Ka/[H^+])$
- $H_T = [H^+]+[A]_0/(1+Ka/[H^+])$; $[H^+]=10\text{^}(-pH)$
- at pH 7.2, H_T = 6.91 mM.
- Added acid brings conc. to (6.91mM*100ml + 1000mM*0.1ml)/(100.1ml)=7.90 mM.
- Working backwards $[H^+]^2+(Ka+A_0-H_T)[H^+]-H_TK=0$; use quadratic eqn.
- to get pH=6.97, so drop of 0.23 pH units.
- In absence of buffer, pH=3
- Buffer strength = -1E-3 M / (6.97-7.2)=4.3 mM/pH.