Week 5

Catalysis

5.1 Midterm Review and Intro to Catalysts

4/27:

- Example problem 1: Steady-state approximation.
  - Let

$$A \underset{k_a'}{\overset{k_a}{\rightleftharpoons}} B \underset{k_b'}{\overset{k_b}{\rightleftharpoons}} C \underset{k_c'}{\overset{k_c}{\rightleftharpoons}} D$$

    Suppose [A] is maintained at a fixed value and the produce D is removed from the reaction as it is formed. Find the rate at which the product is formed in terms of [A].
  - By hypothesis, we have that at all times t, $[\mathrm{A}] = [\mathrm{A}]_0$ and $[\mathrm{D}] = 0$.
  - The hypotheses also imply that we can apply the steady-state approximation to both B and C.
  - Thus, we have that

$$\begin{aligned}
\frac{\mathrm{d}[\mathrm{C}]}{\mathrm{d}t} = 0 &= k_b[\mathrm{B}] - k_c[\mathrm{C}] - k_b'[\mathrm{C}] \\
[\mathrm{B}] &= \frac{k_b' + k_c}{k_b}[\mathrm{C}]
\end{aligned}$$

    so that

$$\begin{aligned}
\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}t} &= k_a[\mathrm{A}] - k_b[\mathrm{B}] - k_a'[\mathrm{B}] + k_b'[\mathrm{C}] \\
0 &= k_a[\mathrm{A}] - k_b \cdot \frac{k_b' + k_c}{k_b}[\mathrm{C}] - k_a' \cdot \frac{k_b' + k_c}{k_b}[\mathrm{C}] + k_b'[\mathrm{C}] \\
[\mathrm{C}] &= \frac{k_a k_b}{k_b k_c + k_a' k_b' + k_a' k_c}[\mathrm{A}]
\end{aligned}$$

    and therefore

$$\begin{aligned}
\frac{\mathrm{d}[\mathrm{D}]}{\mathrm{d}t} &= k_c[\mathrm{C}] - k_c' \cdot 0 \\
&= \frac{k_a k_b k_c}{k_b k_c + k_a' k_b' + k_a' k_c}[\mathrm{A}]
\end{aligned}$$

- Example problem 2.
  - Consider the reaction

$$\mathrm{HCl} + \mathrm{CH_3CH{=}CH_2} \rightleftharpoons \mathrm{CH_3CHClCH_3}$$

    which proceeds by the mechanism

1. $\text{HCl} + \text{HCl} \rightleftharpoons (\text{HCl})_2$ (equilibrium constant K_1).
2. $\text{HCl} + \text{CH}_3\text{CH}{=}\text{CH}_2 \rightleftharpoons \text{complex}$ (equilibrium constant K_2).
3. $(\text{HCl})_2 + \text{complex} \rightleftharpoons \text{CH}_3\text{CHClCH}_3 + \text{HCl} + \text{HCl}$ (equilibrium constant K_3).

- The equilibrium constants for the two pre-equilibria are

$$K_1 = \frac{[(\text{HCl})_2]_{\text{eq}} c^\circ}{[\text{HCl}]_{\text{eq}}^2} \qquad\qquad K_2 = \frac{[\text{complex}]_{\text{eq}} c^\circ}{[\text{HCl}]_{\text{eq}}[\text{CH}_3\text{CH}{=}\text{CH}_2]_{\text{eq}}}$$

- We can divide the mass-action expression for K_1 by $(c^\circ)^2$ to get each concentration over c° within its exponent.
- The rate of product formation is

$$\begin{aligned}
v &= \frac{\mathrm{d}[\text{CH}_3\text{CHClCH}_3]}{\mathrm{d}t} \\
&= k_r[(\text{HCl})_2][\text{complex}] \\
&\approx k_r[(\text{HCl})_2]_{\text{eq}}[\text{complex}]_{\text{eq}} \\
&= k_r \cdot \frac{K_1[\text{HCl}]_{\text{eq}}^2}{c^\circ} \cdot \frac{K_2[\text{HCl}]_{\text{eq}}[\text{CH}_3\text{CH}{=}\text{CH}_2]_{\text{eq}}}{c^\circ} \\
&= \frac{k_r K_1 K_2}{(c^\circ)^2}[\text{HCl}]_{\text{eq}}^3[\text{CH}_3\text{CH}{=}\text{CH}_2]_{\text{eq}}
\end{aligned}$$

  - There's a key assumption with the steady state and something about being able to apply the equilibrium concentration of the intermediate as the steady-state quantity.
  - This question wants to let you know that an equilibrium constant like K_1 might indicate a steady-state approximation.

- Note: Mind the positive and negative signs when constructing differential rate laws!
- The midterm will be posted this Friday (April 29) and will be available until the following Friday (May 6). There will be a timed 2 hour period to take it.
- **Catalyst**: A substance that participates in the chemical reaction but is not consumed in the process.
  - A catalyst affects the mechanism and activation energy of a chemical reaction.
  - A catalyst can give rise to a reaction path with a negligible activation barrier.
  - The exothermicity or endothermicity of the chemical reaction is not altered by the presence of a catalyst.
- **Homogeneous catalysis**: Catalysis in which the catalyst is in the same phase as the reactants and products.
- **Heterogeneous catalysis**: Catalysis in which the catalyst is in a different phase from the reactants and products.
- Imagine that initially, we have the reaction

$$\text{A} \xrightarrow{k} \text{products}$$

  where k is the observed rate constant.
  - When a catalyst is introduced into solution, this mechanism continues, but we now also have the new reaction pathway

$$\text{A} + \text{catalyst} \xrightarrow{k_{\text{cat}}} \text{products} + \text{catalyst}$$

- If each of these competing reactions is an elementary process, then

$$-\frac{\mathrm{d[A]}}{\mathrm{d}t} = k[\mathrm{A}] + k_{\mathrm{cat}}[\mathrm{A}][\mathrm{catalyst}]$$

- In most cases, catalysts enhance reaction rates by many orders of magnitude, and therefore only the rate law for the catalyzed reaction need be considered in analyzing experimental data.

- Reviews the Nobel Prizes in 2020 and 2021 (for CRISPR and asymmetric organocatalysis, respectively).
- An example of homogeneous catalysis.
  - Consider the reaction

$$2\,\mathrm{Ce^{4+}(aq)} + \mathrm{Tl^{+}(aq)} \longrightarrow 2\,\mathrm{Ce^{3+}(aq)} + \mathrm{Tl^{3+}(aq)}$$

  - In the absence of a catalyst,

$$v = k[\mathrm{Tl^+}][\mathrm{Ce^{4+}}]^2$$

    and the mechanism is a termolecular elementary reaction.
  - However, with $\mathrm{Mn^{2+}}$ as the catalyst, we have the mechanism

$$\mathrm{Ce^{4+}(aq)} + \mathrm{Mn^{2+}(aq)} \xRightarrow{k_{\mathrm{cat}}} \mathrm{Mn^{3+}(aq)} + \mathrm{Ce^{3+}(aq)}$$

$$\mathrm{Ce^{4+}(aq)} + \mathrm{Mn^{3+}(aq)} \Longrightarrow \mathrm{Mn^{4+}(aq)} + \mathrm{Ce^{3+}(aq)}$$

$$\mathrm{Mn^{4+}(aq)} + \mathrm{Tl^{+}(aq)} \Longrightarrow \mathrm{Mn^{2+}(aq)} + \mathrm{Tl^{3+}(aq)}$$

    where the step with k_{cat} is the rate-determining step.
    - Thus, for this mechanism, we have that

$$v = k_{\mathrm{cat}}[\mathrm{Ce^{4+}}][\mathrm{Mn^{2+}}]$$

  - The overall rate law for this reaction is therefore

$$v = k[\mathrm{Tl^+}][\mathrm{Ce^{4+}}]^2 + k_{\mathrm{cat}}[\mathrm{Ce^{4+}}][\mathrm{Mn^{2+}}]$$

5.2 Enzymatic Catalysis

4/27:

- Midterm questions:
  - First 10 are T/F. He will test key concepts by making statements that are either true or false.
    - We should expect to spend no more than 30 minutes out of our 2 hours on these.
  - 4 calculation problems.
    - First- and second-order reactions.
    - Collisions.
    - A reaction mechanism problem.
  - Use calculators, do online searches, and use the textbook.
  - Do not talk to your classmates.
  - The midterm will become available Friday at noon.
- Enzymes are protein molecules that catalyze specific biochemical reactions.
  - For example, hexokinase converts glucose and ATP to glucose 6-phosphate, ADP, and $\mathrm{H^+}$.
- **Substrate**: The reactant molecule acted upon by an enzyme.

- **Active site**: The region of the enzyme where the substrate reacts.
- **Lock-and-key model**: The active site and substrate have complementary three-dimensional structures and dock without the need for major atomic rearrangements.
- **Induced fit model**: Binding of the substrate induces a conformation change in the active site. The substrate fits well in the active site after the conformational change has taken place.
- The Michaelis-Menten Mechanism is a reaction mechanism for enzyme catalysis.
- Intuition.
  - Imagine we have a solution of enzymes and substrate molecules.
  - Limiting factors of an enzymatically catalyzed reaction.
    - The enzyme-substrate affinity.
    - The turnover number.
  - If the substrate concentration is low (i.e., $[\mathrm{S}]_0 \ll [\mathrm{E}]_0$) and the enzyme-substrate affinity is strong (but not so strong that the enzyme-substrate complex is energetically favorable), then we expect $v_{\text{initial}} \propto [\mathrm{S}]_0$ because we'd think that all of the substrate will immediately be absorbed and transformed.
  - If the substrate concentration is large (i.e., $[\mathrm{S}]_0 \gg [\mathrm{E}]_0$) and the enzyme-substrate affinity is strong, then we expect $v_{\text{initial}} \propto [\mathrm{E}]_0$ and, importantly, $v_{\text{initial}} \not\propto [\mathrm{S}]_0$.
- Mathematical derivation.
  - Experimental studies reveal that the rate law for many enzyme-catalyzed reactions has the form

$$-\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = \frac{k[\mathrm{S}]}{K_m + [\mathrm{S}]}$$

    - This is the final goal of the derivation.
  - The mechanism is

$$\mathrm{S} + \mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{P} + \mathrm{E}$$

  - Thus,

$$\begin{aligned}
-\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} &= k_1[\mathrm{E}][\mathrm{S}] - k_{-1}[\mathrm{ES}] \\
-\frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} &= (k_2 + k_{-1})[\mathrm{ES}] - k_1[\mathrm{E}][\mathrm{S}] - k_{-2}[\mathrm{E}][\mathrm{P}] \\
\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} &= k_2[\mathrm{ES}] - k_{-1}[\mathrm{E}][\mathrm{P}]
\end{aligned}$$

  - Note that

$$[\mathrm{E}]_0 = [\mathrm{ES}] + [\mathrm{E}]$$

  - Plugging that equation into the rate law for the enzyme-substrate complex and applying the steady-state approximation yields

$$\begin{aligned}
-\frac{\mathrm{d}[\mathrm{ES}]}{\mathrm{d}t} = 0 &= [\mathrm{ES}](k_1[\mathrm{S}] + k_{-1} + k_2 + k_{-1}[\mathrm{P}]) - k_1[\mathrm{S}][\mathrm{E}]_0 - k_2[\mathrm{P}][\mathrm{P}]_0 \\
[\mathrm{ES}] &= \frac{k_1[\mathrm{S}] + k_{-1}[\mathrm{P}]}{k_1[\mathrm{S}] + k_{-2}[\mathrm{P}] + k_{-1} + k_2}[\mathrm{E}]_0
\end{aligned}$$

- Substituting this and the original expression for $[\mathrm{E}]_0$ into the rate law for the substrate yields

$$v = -\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = \frac{k_1 k_2[\mathrm{S}] + k_{-1}k_{-2}[\mathrm{P}]}{k_1[\mathrm{S}] + k_{-2}[\mathrm{P}] + k_{-1} + k_2}[\mathrm{E}]_0$$

- If the experimental measurements of the reaction rate are taken during the time period when only a small percentage (1-3%) of the substrate is converted to product, then

$$[\mathrm{S}] \approx [\mathrm{S}]_0$$

and

$$[\mathrm{P}] \approx 0$$

- Using this approximation simplifies the above rate law to

$$v = -\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = \frac{k_1 k_2[\mathrm{S}]_0[\mathrm{E}]_0}{k_1[\mathrm{S}]_0 + k_{-1} + k_2} = \frac{k_2[\mathrm{S}]_0[\mathrm{E}]_0}{K_m + [\mathrm{S}]_0}$$

where $K_m = (k_{-1} + k_2)/k_1$ is the **Michaelis constant**.

  - The Michaelis constant tells you the ratio of dissociation of the enzyme-substrate complex to the formation of the enzyme-substrate complex. In other words, it provides information on the enzyme-substrate affinity.
  - Note that k_{-2} is not present in the denominator of the Michaelis constant because for a good enzyme, k_{-2} should be very small.
  - The unit of K_m should be concentration.
  - When $K_m = [\mathrm{S}]_0$, $v = v_{\max}/2$

- An enzyme-catalyzed reaction is first order in the substrate at low substrate concentrations ($K \gg [\mathrm{S}]_0$) and then becomes zero order in the substrate at high substrate concentrations ($K \ll [\mathrm{S}]_0$).
- Thus, at low substrate concentrations, the above equation holds, but at high substrate concentrations,

$$-\frac{\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = k_2[\mathrm{E}]_0 \qquad\qquad v_{\max} = k_2[\mathrm{E}]_0$$

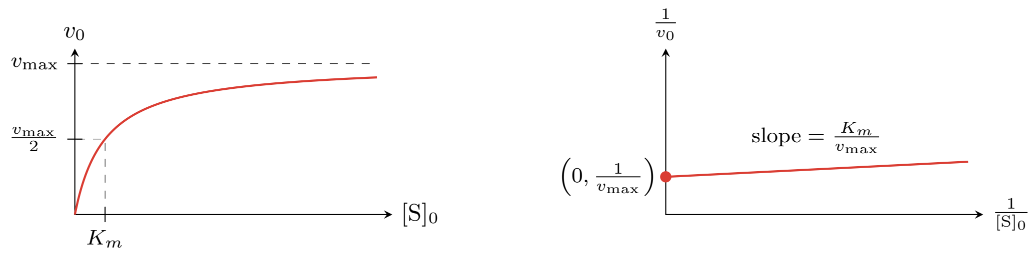
resulting in the **Lineweaver-Burk plot**, canonically represented by the second of the two equivalent forms below.

$$v = \frac{v_{\max}}{1 + K_m/[\mathrm{S}]_0} \qquad\qquad \frac{1}{v} = \frac{1}{v_{\max}} + \frac{K_m}{v_{\max}}\frac{1}{[\mathrm{S}]_0}$$

5.3 Measuring Catalytic Efficiency and Correcting Collision Theory

4/29:

- Everything on the midterm comes from Tian's lecture notes. Thus, he recommends we go through them before taking the midterm.
  - The T/F will be 20-30% of the grade.
  - There will be some integration on the calculation problems, but they'll be pretty easy. All formulas that will appear have been covered in class.
  - The midterm will cover up to Monday's class (this week).
- Consider the substrate concentration $[\mathrm{S}]_0$ vs. the initial rate v_0.
  - Normal plot (Figure 5.1a).
    - As $[\mathrm{S}] \to \infty$, v_0 approaches an asymptote line defined by $v_{\max} = k_2[\mathrm{E}]_0$.



(a) Normal plot.

(b) Reciprocal plot.

Figure 5.1: Plotting v_0 vs. $[\mathrm{S}]_0$.

- At the beginning (low [S]), the paradigm is almost linear (thus, the reaction is first order wrt. substrate concentration here).
- Note that we make use of the assumptions that $[\mathrm{P}] \approx 0$ and $[\mathrm{S}] \approx [\mathrm{S}]_0$.
- Where we have $v_{\max}/2$ on the v_0-axis, we have K_m (the Michaelis constant) on the $[\mathrm{S}]_0$ axis.

– Reciprocal plot (Figure 5.1b).

- Note that a plot of v_0 vs. $[\mathrm{S}]_0$ is nonlinear but a plot of $1/v_0$ vs. $1/[\mathrm{S}]_0$ is linear.
- This reciprocal plot (the Lineweaver-Burk plot) gives $v_{\max}$ (via the y-intercept) and K_m via this information and the slope.
- Note that

$$\begin{aligned} \frac{1}{v_0} &\propto \frac{K_m}{v_{\max}} \frac{1}{[\mathrm{S}]_0} \\ &= \frac{(k_{-1}+k_2)/k_1}{k_2[\mathrm{E}]_0} \frac{1}{[\mathrm{S}]_0} & &= \frac{k_{-1}+k_2}{k_1 k_2} \frac{1}{[\mathrm{E}]_0[\mathrm{S}]_0} \end{aligned}$$

- Evaluating the performance of a catalyst.

$$\frac{k_{-1}+K_2}{k_1 k_2} = \frac{K_m}{v_{\max}} \cdot [\mathrm{E}]_0$$

– K_m is relevant to the enzyme-substrate affinity.

– $v_{\max}$ tells us about conversion from the ES with a focus on the second elementary step.

- An alternate form of the Lineweaver-Burk plot is

$$\frac{1}{v_0} = \frac{1}{v_{\max}} + \frac{k_2+k_{-1}}{k_1 k_2} \frac{1}{[\mathrm{E}]_0[\mathrm{S}]_0}$$

– Regrouping the terms, we have

$$\frac{1}{v_0} = \frac{1}{v_{\max}} + \frac{k_2+k_{-1}}{k_2} \frac{1}{k_1[\mathrm{S}]_0[\mathrm{E}]_0} = \frac{1}{v_{\max}} + \frac{k_2+k_{-1}}{k_2} \frac{1}{v_{f1}}$$

where v_{f1} is the forward reaction rate for the first elementary step.

- **Turnover number**: The number of catalytic cycles that each active site undergoes per unit time. *Given by*

$$\mathrm{TON} = \frac{v_{\max}}{n[\mathrm{E}]_0} = \frac{k_2[\mathrm{E}]_0}{n[\mathrm{E}]_0} = \frac{k_2}{n}$$

– Indicates how fast the ES complex proceeds to $\mathrm{E}+\mathrm{P}$.

– k_2/n is the number of active sites per enzyme.

- **Catalytic efficiency**: The following quantity. *Given by*

$$\frac{\text{TON}}{K_m}$$

- Consider the reaction

$$\text{A}\,(\text{g}) + \text{B}\,(\text{g}) \overset{k}{\Longrightarrow} \text{products}$$

  - The rate of the general bimolecular elementary gas-phase reaction is

$$v = -\frac{\text{d}[\text{A}]}{\text{d}t} = k[\text{A}][\text{B}]$$

  - Using the naïve assumption that every collision between the hard spheres A and B yields products,

$$v = Z_{\text{AB}} = \sigma_{\text{AB}} \langle u_r \rangle \rho_{\text{A}} \rho_{\text{B}}$$

  - Moreover,

$$k = \sigma_{\text{AB}} \langle u_r \rangle$$

  - Unfortunately, this is not accurate. We make our first improvement to collision theory by taking into account the dependence of the reaction rate on the relative speed, or energy, of the collision. Thus, we average over all possible collision speeds.

$$k = \int_0^\infty \text{d}u_r \, f(u_r) k(u_r) = \int_0^\infty \text{d}u_r \, u_r f(u_r) \sigma_r(u_r)$$

  - Since $f(u_r)$ is the distribution of relative speeds in the gas sample, we have that

$$u_r f(u_r) \, \text{d}u_r = \left(\frac{\mu}{k_{\text{B}} T} \right)^{3/2} \left(\frac{2}{\pi} \right)^{1/2} u_r^3 \text{e}^{-\mu u_r^2 / 2k_{\text{B}} T} \, \text{d}u_r$$

  - To compare this with the traditional Arrhenius form of k, we need to change the dependent variable from u_r to E, which we can do via

$$E_r = \frac{1}{2} \mu u_r^2 \qquad u_r = \sqrt{\frac{2E_r}{\mu}} \qquad \text{d}u_r = \sqrt{\frac{1}{2\mu E_r}} \, \text{d}E_r \qquad E_a = k_{\text{B}} T^2 \frac{\text{d} \ln k}{\text{d}T}$$