II.B.2. Protein Function—Enzymes, continued

Enzyme catalysis:

Transition-State Theory:

Enzymes catalyze reactions by lowering $E_A$.

* HOW they do this depends on the reaction and enzyme.

“Lock and Key” vs. “Induced Fit” Models

- Old view of enzyme-substrate interaction called “lock and key” model: The substrate molecule (key) as a perfect fit for a cleft/space on the surface of the enzyme molecule (lock). This model was used to explain the high specificity of enzymatic reactions
- New view of enzyme-substrate interaction called “induced fit” model: Yes, substrate fits well on/into enzyme, but it is the transition state, not the substrate itself, that is the perfect fit “key” to the enzyme “lock.” In this model, achieving that “perfect fit” in the transition state is part of the force driving the reaction forward.

“Induced fit” model works well with transition-state theory—if transition state fits best into enzyme “pocket”, then “fit” can be partly responsible for the lowering of $E_A$ by the enzyme. BUT: This is only part of the story.

Types of catalytic mechanisms:

1. General Acid/Base Catalysis
2. Metal Ion Catalysis
3. Covalent Catalysis
4. Proximity Catalysis
5. Low-barrier Hydrogen Bond Catalysis

1. General Acid/Base Catalysis:

Reaction 1: lysozyme can catalyze hydrolysis of ester bond

Uncatalyzed: Unfavorable transition state, because of unstable positive and negative charges
Catalyzed by acetate ion: Now, both O are $\delta^-$.

- Enzymes can assume the same role as acetate ion—serving to stabilize the charge of the transition state by donating a base (accepting an H from the transition state).
- This type of catalysis is “General Base Catalysis”

Reaction 2: Lysozyme can also catalyze the hydrolysis of acetals

Uncatalyzed:

Catalyzed by acetic acid:

“General Acid Catalysis”

- These are “general” because the acid can be any acid, and the base, any base. In “Specific” acid or base hydrolysis, the donated group has to be just the H$^+$ ion (specific acid) or OH$^-$ ion (specific base).
2. Metal Ion Catalysis

Reaction 1: carboxypeptidase can cleave peptide bonds through a tetrahedral transition state

- Metal ion (Zn\(^{2+}\)) coordinated to the enzyme stabilizes the negative charge on the transition state.
- “Electrophilic metal ion catalysis”

Reaction 2: carbonic anhydrase catalyzes formation of bicarbonate from carbon dioxide

Step 1: formation of zinc-bound hydroxyl

Step 2: polarization of CO\(_2\) and attack by zinc-bound hydroxyl (potent nucleophile)

- Here, metal ion provides source of OH\(^-\) at neutral pH

3. Covalent Catalysis

- Make transient covalent bond during transition step
- Many different types of intermediates—one common one is Schiff base formation

Example:
Schiff bases can be protonated at neutral pH:

\[
\begin{align*}
\text{R-N=CH}_3 & \quad \text{H}^+ \quad \text{H-N=CCH}_3 \\
\end{align*}
\]

Protonated Schiff bases can act as electron sink (stabilize formation of a – charge on one of the α Cs):

\[
\begin{align*}
\text{R-N=CCH}_3 & \quad -\text{H}^+ \quad \text{R-N=CCH}_3 \\
\end{align*}
\]

- This type of Schiff base formation used by acetoacetate decarboxylase to cleave acetoacetate to acetone and carbon dioxide, using the NH₂ of a lys residue
- This type of Schiff base formation is a type of electrophilic catalysis
- Schiff base formation also leave the carbonyl C (the C that used to have the carbonyl) susceptible to nucleophilic attack (the positively-charged N double-bonded to the C is strongly e⁻ withdrawing).
- Many other types of covalent catalysis—both electrophilic and nucleophilic catalysis

4. Proximity Catalysis

- Easiest to understand: Enzyme brings two substrates close together, in the correct orientation to react.
- aka “Entropy Reduction”
- May be combined with other types of catalysis

5. Low Barrier Hydrogen Bond Catalysis

- Difficult to understand
- Think of as a method for doing other types of catalysis

\[
\text{H-} \quad \text{O} \quad \text{H} \quad \text{H}\quad \text{O} \quad \text{H} \\
\text{squeeze} \quad \text{H-bond} \quad \text{H-} \quad \text{O} \quad \text{H}\quad \text{H}\quad \text{O} \quad \text{H} \\
\text{strong} \quad \text{weak} \quad \text{same strength}
\]

- If the enzyme forces a hydrogen bond to be about the same bond length as a normal bond, it will also have roughly the same bond strength
- Now the bond can go either way— the energy barrier to moving the O (or an H) is reduced by a simple spatial compression of the hydrogen bond