Enzyme Catalysis

Uses either:

1. Amino acid side chains
can act as...
   - Acids/bases
   - Nucleophiles
   - Electrophiles
   - Charge neutralizers
   - Hydrophobic patches
   - Hydrogen bonding groups

2. Cofactors
   - Organic
   - Inorganic
   - Ions
   - Resembles substrate
   - Recyclable
   - Noncovalent interactions
   - Loosely bound

3. Coenzymes
   - Covalently bonded
   - Recyclable when catalysis is over

4. Prosthetic groups
   - Fe
   - Zn+
Enzymes that catalyze the transfer of electrons in a redox reaction:
\[ A^- + B \rightarrow A + B^- \]

1. Oxidoreductases

- **Lactase dehydrogenase**: pyruvate \( \rightarrow \) lactate, using NADH as e- acceptor
- **Dihydrofolate reductase DHFR**: uses NADPH as e- donor

2. Transferases

Enzymes that catalyze the transfer of functional groups, such as an amino group, acetyl group, or phosphate group:
\[ A-X + B \rightarrow A + B-X \]

- **Creatine kinase**: ATP \( \rightarrow \) ADP, transfer of phosphate group
- **Hexokinase**: hexose \( \rightarrow \) hexose phosphate, transfer of phosphate group

3. Hydrolases

Enzymes that catalyze the cleavage of a chemical bond via hydrolysis with the transfer of a functional group to water:
\[ A-B + H_2O \rightarrow A-OH + B-H \]

- **Lactase dehydrogenase**: pyruvate \( \rightarrow \) lactate, using NADH as e- acceptor
- **Dihydrofolate reductase DHFR**: uses NADPH as e- donor

4. Lyases

Enzymes that catalyze the bond cleavage without hydrolysis, often forming a new double bond or ring structure:
\[ ATP \rightarrow cAMP + PP_i \]

- **Fumarase**: hydration/dehydration of fumarate \( \rightarrow \) S-malate

5. Isomerase

Enzymes that catalyze the rearrangement of atoms within a molecule, intramolecular group transfer (isomerization)

- **Triose phosphate isomerase** and **Methylmalonyl CoA mutase**

6. Ligase

Enzymes that catalyze the glue together two molecules using ATP by synthesizing a new bond: \( Ab + C \rightarrow A-C + b \)

- **Triose phosphate isomerase** and **Methylmalonyl CoA mutase**
Acid/base catalysis

- Molecule acts as H+ donor or acceptor in order to stabilize developing charges in the transition state
- With the transfer of a H+, a nucleophile or electrophile is activated so the reaction can proceed
- Histidine is often involved since it has a pKa close to neutral pH that can both accept/donate protons
- There are two different ways:
  - **Specific a/b catalysis:** specifically H+/OH- accelerate the reaction; only dependent on pH, not conc.
    - Specific acid: protonation lowers free energy of transition state, rate of reaction increases with decrease in pH
    - Specific base: abstraction of H+ (or nucleophilic attack) by OH- lowers the free energy of the transition state, rate of reaction increases with increase in pH
  - **General a/b catalysis:** where the side chain of amino acids act as acids/bases; where all species capable of donating/accepting H+ contribute to the acceleration of the reaction including the buffer
- The pKa is can be modified significantly by the environment, to the extent that residues which are basic in solution may act as proton donors, and vice versa. This alteration of pKa is possible through the local environment of the residue:

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Acids</th>
<th>Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophobic environment</td>
<td>↑ pKa</td>
<td>↓ pKa</td>
</tr>
<tr>
<td>Adjacent residues of like charge</td>
<td>↑ pKa</td>
<td>↓ pKa</td>
</tr>
<tr>
<td>Salt bridge (and H bond) formation</td>
<td>↓ pKa</td>
<td>↑ pKa</td>
</tr>
</tbody>
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Nucleophilic catalysis

- Involves the substrate forming a transient covalent bond with residues in the active site or with a cofactor
- This adds an additional covalent intermediate to the reaction to help reduce the energy of later transition states
- The covalent bond must eventually be broken to regenerate the enzyme
- Mechanism found in proteases (e.g. chymotrypsin, trypsin) where an acyl-enzyme intermediate is formed
- Some enzymes utilize non-amino acid cofactors to form covalent intermediates

Electrostatic catalysis

- Residues in the active site form ionic bonds with the intermediate to stabilize the transition state
- Ionic bonds come from acidic/basic amino acid side chains (e.g. + Lys, Arg; – Glu, Asp), or metallic cofactors (Zn+)
- Electrostatic effects give the largest contribution to catalysis

Bond strain

- Affinity of the enzyme to the transition state is greater than to the substrate itself
- Induces structural rearrangements which strain substrate bonds into a position closer to the conformation of the transition state, lowering the energy difference between substrate and transition state to help catalyze the reaction
- Limitations to this exist since enzymes are flexible

Proximity and orientation

- Reduces the entropy of the reactants and thus makes reactions such as ligations more favorable
- Reduction in the overall loss of entropy when two reactants become a single product
- This effect is analogous to an effective increase in concentration of the reagents
- Binding of reagents to the enzyme gives the reaction intramolecular character, which gives a massive rate increase

Charge neutralization

- By neutralizing the charge of the transition state, it facilitates the binding of substrate and/or stabilizes the intermediate

Environmental effects

- Solvent or other molecule in the environment help stabilize the transition state, e.g. electrolytes, polarity, pH