Uncatalyzed

$\Delta \Delta G_{\text{cat}}^{\dagger}$ (the reduction in $\Delta G^{\dagger}$ by the catalyst)

Catalyzed

Reactions:

$A + B \iff P + Q$

Reaction coordinate

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<table>
<thead>
<tr>
<th>Classification</th>
<th>Type of Reaction Catalyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oxidoreductases</td>
<td>Oxidation–reduction reactions</td>
</tr>
<tr>
<td>2. Transferases</td>
<td>Transfer of functional groups</td>
</tr>
<tr>
<td>3. Hydrolases</td>
<td>Hydrolysis reactions</td>
</tr>
<tr>
<td>4. Lyases</td>
<td>Group elimination to form double bonds</td>
</tr>
<tr>
<td>5. Isomerases</td>
<td>Isomerization</td>
</tr>
<tr>
<td>6. Ligases</td>
<td>Bond formation coupled with ATP hydrolysis</td>
</tr>
</tbody>
</table>
Pyruvate is reduced to lactate in anaerobic metabolism in muscle cells.
Transferases and hydrolases catalyze group transfer reactions

Acyl transfer:

\[
\begin{align*}
\text{O} & \quad \text{C} & \quad \text{X} \\
\text{R} & \quad \text{Y} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{C} & \quad \text{X} \\
\text{Y} & \quad \text{O}^- \\
\end{align*}
\]

Tetrahedral intermediate

\[
\begin{align*}
\text{R} & \quad \text{C} & \quad \text{Y} \\
\text{X}^- & \quad \text{O} \\
\end{align*}
\]
Hexokinase catalyzes a phosphoryl transfer from ATP to glucose

\[
\text{ATP} \rightarrow \text{ADP} + \text{Glucose 6-phosphate, a phosphate ester}
\]
Glycosidases are hydrolases, catalyzing hydrolysis of glycosidic bonds.
Lyases catalyze eliminations and the formation/breaking of carbon-carbon bonds.
Lyases catalyze eliminations and the formation/breaking of carbon-carbon bonds.

**Aldol condensation**

\[
\begin{align*}
\text{R}_1\text-C\text-C\text-H & \xrightarrow{\text{H}^+} \text{R}_1\text-C\text-C\text-C\text-OH \\
\text{H} & \xrightarrow{\text{H}^+} \text{H}
\end{align*}
\]

**Claisen ester condensation**

\[
\begin{align*}
\text{CoA-S-C-C-O} & \xrightarrow{\text{H}^+} \text{CoA-S-C-C-OH} \\
\text{H} & \xrightarrow{\text{H}^+} \text{H}
\end{align*}
\]

**Decarboxylation of a β-keto acid**

\[
\begin{align*}
\text{R-C-C-O} & \xrightarrow{\text{H}^+} \text{R-C-C-H} + \text{CO}_2 \\
\text{R} & \xrightarrow{\text{H}^+} \text{R}
\end{align*}
\]
Isomerases catalyze isomerizations or internal rearrangements.

Figure 4-7b
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Ligases couple ATP (or NTP) hydrolysis with bond formation

\[
\text{CH}_2-\text{COO}^- \\ \text{CH}_2 \\ C-S-\text{CoA} \\ \text{O} \\
\text{Succinyl-CoA}
\] 

\[\text{GDP} + P_i \rightarrow \text{GTP} \rightarrow \text{CoA-SH} \rightarrow \text{COO}^- \\ \text{CH}_2 \\ \text{CH}_2 \\ \text{COO}^- \\
\text{Succinyl-CoA synthetase} \\
\text{Succinate}
\]

\[\Delta G^\circ = -2.9 \text{ kJ/mol}\]
Enzymes can dramatically enhance reaction rates

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Nonenzymatic Reaction Rate (s⁻¹)</th>
<th>Enzymatic Reaction Rate (s⁻¹)</th>
<th>Rate Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase</td>
<td>$1.3 \times 10^{-1}$</td>
<td>$1 \times 10^6$</td>
<td>$7.7 \times 10^6$</td>
</tr>
<tr>
<td>Chorismate mutase</td>
<td>$2.6 \times 10^{-5}$</td>
<td>50</td>
<td>$1.9 \times 10^6$</td>
</tr>
<tr>
<td>Triose phosphate isomerase</td>
<td>$4.3 \times 10^{-6}$</td>
<td>4300</td>
<td>$1.0 \times 10^9$</td>
</tr>
<tr>
<td>Carboxypeptidase A</td>
<td>$3.0 \times 10^{-9}$</td>
<td>578</td>
<td>$1.9 \times 10^{11}$</td>
</tr>
<tr>
<td>AMP nucleosidase</td>
<td>$1.0 \times 10^{-11}$</td>
<td>60</td>
<td>$6.0 \times 10^{12}$</td>
</tr>
<tr>
<td>Staphylococcal nuclease</td>
<td>$1.7 \times 10^{-13}$</td>
<td>95</td>
<td>$5.6 \times 10^{14}$</td>
</tr>
</tbody>
</table>


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How do they do it?
Enzymes use several catalytic mechanisms (often together) to enhance reaction rates

- **Proximity and orientation effects**: the enzyme specifically binds and positions substrates (with respect to each other and to enzyme functional groups) to maximize reactivity
- **Electrostatic catalysis**: the enzyme uses charge-charge interactions in catalysis
- **Preferential binding of transition state**: binding interactions between the enzyme and TS are maximized; they are greater than those in the enzyme-substrate or enzyme-product complexes
- **General acid and general base catalysis**: functional groups of the enzyme donate &/or accept protons
- **Covalent catalysis**: the enzyme forms a covalent bond with the substrate
- **Metal-ion catalysis**: the enzyme uses a metal ion to aid catalysis
Enzymes bind their substrates with geometric and electronic complementarity
Enzymes are stereoselective (ex: aconitase)

Citrate

\[
\text{HO} - \overset{\text{aconitase}}{\text{C}} - \text{COO}^- \quad \overset{\text{aconitase}}{\text{H}} - \text{C} - \text{COO}^-
\]

Isocitrate
Binding complementarity positions substrates to maximize reaction rates

$sp^2-p$ hybridization at carbon

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Enzymes use several catalytic mechanisms (often together) to enhance reaction rates

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Figure 6-5a
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Enzyme complementary to substrate

Magnets

ES

Free energy, $G$

Reaction coordinate

$\Delta G_{\text{uncat}}^+$

$\Delta G_{\text{cat}}^+$

$\Delta G_M$
Enzyme complementary to transition state

Figure 6-5c
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(a) No enzyme

Substrate (metal stick) → Transition state (bent stick) → Products (broken stick)

(b) Enzyme complementary to substrate

ES → Magnets

(c) Enzyme complementary to transition state

ES → Transition state → E

Figure 6-5
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Acid-base and covalent catalysis rely on nucleophile-electrophile chemistry
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Proteins use cofactors to expand their range of functions

- Cofactors
  - Metal ions
  - Coenzymes
    - Cosubstrates
    - Prosthetic groups
<table>
<thead>
<tr>
<th>Ions</th>
<th>Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Cu}^{2+}$</td>
<td>Cytochrome oxidase</td>
</tr>
<tr>
<td>$\text{Fe}^{2+}$ or $\text{Fe}^{3+}$</td>
<td>Cytochrome oxidase, catalase, peroxidase</td>
</tr>
<tr>
<td>$\text{K}^+$</td>
<td>Pyruvate kinase</td>
</tr>
<tr>
<td>$\text{Mg}^{2+}$</td>
<td>Hexokinase, glucose 6-phosphatase, pyruvate kinase</td>
</tr>
<tr>
<td>$\text{Mn}^{2+}$</td>
<td>Arginase, ribonucleotide reductase</td>
</tr>
<tr>
<td>Mo</td>
<td>Dinitrogenase</td>
</tr>
<tr>
<td>$\text{Ni}^{2+}$</td>
<td>Urease</td>
</tr>
<tr>
<td>Se</td>
<td>Glutathione peroxidase</td>
</tr>
<tr>
<td>$\text{Zn}^{2+}$</td>
<td>Carbonic anhydrase, alcohol dehydrogenase, carboxypeptidases A and B</td>
</tr>
</tbody>
</table>
Carbonic anhydrase uses Zn\(^{2+}\) for catalysis
Enzymes use several catalytic mechanisms (often together) to enhance reaction rates

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Self test: Identify the enzyme class and catalytic mechanisms used.
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2',3'-Cyclic nucleotide

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Self test: Identify the enzyme class and catalytic mechanisms used.

Acetoacetate  

\[
\text{CH}_3\text{CCH}_2\text{COO}^- \quad \xrightarrow{\text{CO}_2} \quad \left[\text{CH}_3\text{C}\equiv\text{CH}_2\right] \quad \xrightarrow{\text{H}^+} \quad \text{CH}_3\text{CCH}_3
\]

Enolate  

\[
\text{CH}_3\text{C}\equiv\text{CH}_2 \quad \xrightarrow{\text{RNH}_2} \quad \text{R}\text{N}+\text{H} \quad \xrightarrow{\text{CO}_2} \quad \text{R}\text{N}+\text{H} \quad \xrightarrow{\text{H}^+} \quad \text{CH}_3\text{CCH}_3
\]

Acetone  

\[
\text{RNH}_2 \quad \xrightarrow{\text{OH}^-} \quad \text{R}\text{N}+\text{H} \quad \xrightarrow{\text{OH}^-} \quad \text{CH}_3\text{CCH}_3
\]

Schiff base (imine)
Self test: Identify the enzyme class and catalytic mechanisms used.

\[
\text{p-Nitrophenylacetate} \quad \rightarrow \quad \text{N-Acetylimidazolium} + \text{p-Nitrophenolate}
\]
Self test: Identify the enzyme class and catalytic mechanisms used.

L-Proline  Planar transition state  D-Proline

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