Enzyme definition

Enzymes are protein catalysts that increase the velocity of a chemical reaction and are not consumed during the reaction they catalyze.

[Note: Some types of RNA can act like enzymes, usually catalyzing the cleavage and synthesis of phosphodiester bonds; RNAs with catalytic activity are called ribozymes and are much less commonly encountered than protein catalysts.]

Biologic catalysts

1. Shared properties with chemical catalysts

a. Enzymes are neither consumed nor produced during the course of a reaction.
b. Enzymes do not cause reactions to take place, but they greatly enhance the rate of reactions that would proceed much slower in their absence. They alter the rate but not the equilibrium constants of reactions that they catalyze.

2. Differences between enzymes and chemical catalysts

a. Enzymes are proteins.
b. Enzymes are highly specific and produce only the expected products from the given reactants, or **substrates** (i.e., there are no side reactions).
c. Enzymes may show a high specificity toward one substrate or exhibit a broad specificity, using more than one substrate.
d. Enzymes usually function within a moderate pH and temperature range.

Enzymes execute of two basic functions in biological object.

They are catalytic and regulation.

Catalytic efficiency

Most enzyme-catalyzed reactions are highly efficient, proceeding from 10^3 to 10^8 times faster than uncatalyzed reactions. Typically, each enzyme molecule is capable of transforming 100 to 1000 substrate molecules into product each second. The number of molecules of substrate converted to product per enzyme molecule per second is called the **turnover number.**

Regulation

Enzyme activity can be regulated — that is, enzymes can be activated or inhibited so that the rate of product formation responds to the needs of the cell.

Measures of enzyme activity

1. Specific activity is usually expressed as μmol of substrate transformed to product per minute per milligram of enzyme under optimal conditions of measurement.

2. Turnover number, or k_{cal}, is the number of substrate molecules metabolized per enzyme molecule per unit time with units of min^{-1} or s^{-1}.

Enzyme classification

1. Enzymes are divided into six **major classes** with several subclasses.
    a. **Oxidoreductases** are involved in oxidation and reduction.
    b. **Transferases** transfer functional groups (e.g., amino or phosphate groups).
    c. **Hydrolases** transfer water; that is, they catalyze the hydrolysis of a substrate.
    d. **Lyases** add (or remove) the elements of water, ammonia, or carbon dioxide (CO_2) to (or from) double bonds.
    e. **Isomerases** catalyze rearrangements of atoms within a molecule.
    f. **Ligases** join two molecules.

Six Major Classes of Enzymes and Examples of Their Subclasses

	Classification	Distinguishing Feature
1.	Oxidoreductases	$A_{red} + B_{ox} \rightarrow A_{ox} + B_{red}$
	Oxidases	Use oxygen as an electron acceptor but do not incorporate it into the substrate
	Dehydrogenases	Use molecules other than oxygen (e.g., NAD^+) as an electron acceptor
	Oxygenases	Directly incorporate oxygen into the substrate
	Peroxidases	Use H_2O_2 as an electron acceptor
2.	Transferases	A-B+C → A+B-C
	Methyltransferases	Transfer one-carbon units between substrates
	Aminotransferases	Transfer NH_2 from amino acids to keto acids
	Kinases	Transfer PO_3~ from ATP to a substrate
	Phosphorylases	Transfer PO_3~ from inorganic phosphate (P,) to a substrate
3.	Hydrolases	A-B+H_2O → A-H + B-OH
	Phosphatases	Remove PO_3~ from a substrate
	Phosphodiesterases	Cleave phosphodiester bonds such as those in nucleic acids
	Proteases	Cleave amide bonds such as those in proteins
4.	Lyases	A(XH)-B → A-X+B-H
	Decarboxylases	Produce CO_2 via elimination reactions
	Aldolases	Produce aldehydes via elimination reactions
	Synthases	Link two molecules without involvement of ATP
5.	Isomerases	A⇔Изо-A
	Racemases	Interconvert **L** and **D** stereoisomers
	Mutases	Transfer groups between atoms within a molecule
6.	Ligases	A+B+ATP → A-B+ADP+Pi
	Carboxylases	Use CO_2 as a substrate
	Synthetases	Link two molecules via an ATP-dependent reaction

NOMENCLATURE_OF ENZYMES

Each enzyme is assigned two names. The first is its short, **recommended name,** convenient for everyday use. The second is the more complete **systematic name,** which is used when the enzyme must be identified without ambiguity.

A. Recommended name

Most commonly used enzyme names have the suffix "-ase" attached to the substrate of the reaction, for example, *glucosidase, urease, sucrase;* or to a description of the action performed, for example, *lactate dehydrogenase* and *adenylate cyclase.*

[Note: Some enzymes retain their original trivial names, which give no hint of the associated enzymic reaction, for example, *trypsin* and *pepsin*.]

B. Systematic name

The International Union of Biochemistry and Molecular Biology (IUBMB) developed a system of nomenclature in which enzymes are divided into six major classes, each with numerous subgroups. The suffix "-ase" is attached to a fairly complete description of the chemical reaction catalyzed, for example *D-glyceraldehyde 3-phosphate:NAD oxidoreductase.* The IUBMB names are unambiguous and informative, but are sometimes too cumbersome to be of general use.

A skeletal outline of the IUB system is presented below.
(1) Reactions and the enzymes that catalyze them form six classes, each having 4-13 subclasses.
(2) The enzyme name has two parts. The first names the substrate or substrates. The second, ending in *-ase*, indicates the type of reaction catalyzed.
(3) Additional information, if needed to clarify the reaction, may follow in parentheses; eg, the enzyme catalyzing

L-malate + NAD^+ = pyruvate + CO_2 + NADH + H^+

is designated **1.1.1.37 L-malate:NAD^+ oxidoreductase** (decarboxylating).

(4) Each enzyme has a code number (EC) that characterizes the reaction type as to class (first digit), subclass (second digit), and subsubclass (third digit). The fourth digit is for the specific enzyme.
Thus, **EC 2.7.1.1** denotes **class 2** (a transferase), **subclass 7** (transfer of phosphate), **subsubclass 1** (an alcohol is the phosphate acceptor).
The final digit denotes **hexokinase**, or **ATP:D-hexose 6-phosphotransferase**, an enzyme catalyzing phosphate transfer from ATP to the hydroxyl group on carbon 6 of glucose.

Enzyme structure

Active sites

Enzyme molecules contain a special pocket or cleft called the active site. The active site contains amino acid side chains that create a three-dimensional surface complementary to the substrate.
The active site binds the substrate, forming an enzyme-substrate (ES) complex. ES is converted to enzyme-product (EP), which subsequently dissociates to enzyme and product

Cofactors

Some enzymes associate with a nonprotein cofactor that is needed for enzymic activity. Commonly encountered cofactors include metal ions (for example, Zn^{2+}, Fe^{2+}) and organic molecules, known as **coenzymes,** that are often derivatives of vitamins (for example, NAD^{+}, FAD, coenzyme A.
Holoenzyme refers to the enzyme with its cofactor.
Apoenzyme refers to the protein portion of the holoenzyme. In the absence of the appropriate cofactor, the apoenzyme typically does not show biologic activity.
A prosthetic group is a tightly bound coenzyme that does not dissociate from the enzyme.
Most of enzymes can contain additional active site for interaction with regulated molecule. It is called allosteric site.

Allosteric binding sites

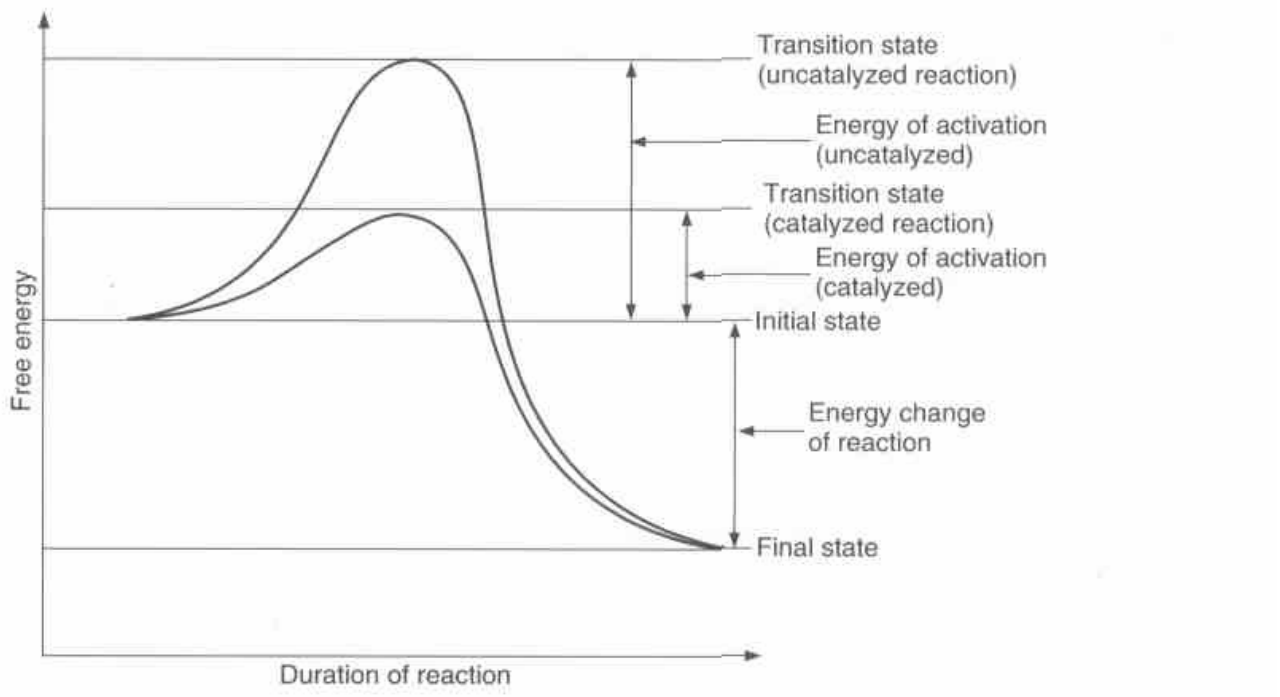
Allosteric enzymes are regulated by molecules called **effectors** (also modifiers or modulators) that bind noncovalently at a site other than the active site. The presence of an allosteric effector can alter the affinity of the enzyme for its substrate or modify the maximal catalytic activity of the enzyme or both. Effectors that inhibit enzyme activity are termed **negative effectors,** whereas those that increase enzyme activity are called positive effector.

MECHANISM OF ENZYME CATALYSIS

A. Chemical reactions

1. Free-energy changes that occur during a chemical reaction when the reaction is catalyzed (lower curve) and uncatalyzed (upper curve) are illustrated in Fig.

2. Energy of activation is required to sufficiently energize a substrate molecule to reach a **transition state** in which there is a high probability that a chemical bond will be made or broken to form the product. Enzymes increase the rate of reaction by decreasing the energy of activation.



Specificity

The specificity of an enzyme is determined by the functional groups of the substrate, the functional groups of the enzyme, and the physical proximity of these functional groups.

Two theories have been proposed to explain the specificity of enzyme action.

- **Lock and key theory.** The enzyme active site is complementary in conformation to the substrate, so that enzyme and substrate recognize one another.
- **Induced-fit theory.** The enzyme changes shape on binding substrate, so that the conformation of substrate and enzyme is only complementary after binding.

CATALYTIC MECHANISM OF CHYMOTRYPSIN

Chymotrypsin hydrolyzes specific peptide bonds of denatured proteins.

Proteolysis in the absence of chymotrypsin. The scissile bond is shown in blue.

A. The carbonyl carbon, which carries a partial positive charge, is attacked by a hydroxyl group from water.
B. An unstable tetrahedral oxyanion intermediate is formed, which is the transition state complex.
C. As the electrons return to the carbonyl carbon, the remaining proton from water adds to the leaving group to form an amine.

catalytic mechanism of chymotrypsin (step by step)

1. Substrate binding
2. Histidine activates serine for nucleophilic attack
3. The oxyanion tetrahedral intermediate is stabilized by hydrogen bonds
4. Cleavage of the peptide bond
5. The covalent acyl -enzyme intermediate
6. Water attacks the carbonyl carbon
7. Second oxyanion tetrahedral intermediate
8. Acid catalysis breaks the acyl-enzyme covalent bond
9. The product is free to dissociate

Some General Strategies of Enzymatic Catalysis

Proximity and orientation

Transition state stabilization

Acid-base catalysis

Nucleophilic catalysis

Electrophilic catalysis

Covalent catalysis

Coenzymes Can Be Classified According to the Group Whose Transfer They Facilitate

BASED ON THE ABOVE CONCEPT, WE MIGHT CLASSIFY COENZYMES AS FOLLOWS:

1.For transfer of groups other than hydrogen-

- Sugar phosphates
- CoA-SH
- Thiamin pyrophosphate
- Pyridoxal phosphate
- Folate coenzymes
- Biotin
- Cobamide (B_{12}) coenzymes
- Lipoic acid

2.For transfer of hydrogen-

- NAD+ NADP+
- FMN, FAD
- Lipoic acid
- Coenzyme Q

COENZYMES

The functional group of thiamine pyrophosphate (shown in blue) participates in formation of a covalent intermediate.

A. base on the enzyme (B:) abstracts a proton from thiamine, creating a carbanion (general acid-base catalysis).

B. The carbanion is a strong nucle-ophile, and attacks the positively charged keto group on the substrate.

C. A covalent intermediate is formed, which is stabilized by resonance forms. The uncharged intermediate is the stabilized transition state complex.

CoA and biotin are activation transfer coenzymes.

A. Coenzyme A (CoA or CoASH) and phosphopantetheine are synthesized from the vitamin pantothenate (pantothenic acid). The active sulfhydryl group, shown in blue, is where acyl (e.g., acetyl, succmyl, or fatty acyl) groups bind to form thioesters.

B. Biotin activates and transfers CO_2 to compounds in carboxylation reactions. The reactive N is shown in blue. The covalent attachment to a lysine residue of a carboxylase enzyme gives it a long flexible arm.

Reactive sites of pyridoxal phosphate.

Pyridoxal phosphate contains a reactive aldehyde which forms a covalent intermediate with amino groups of amino acids (a Schiff base). The positively charged pyridine ring is a strong electron-withdrawing group which pulls electrons into it from the bonds around the amino acid α-carbon (electrophilic catalysis).

NAD^+ accepts a hydride ion, shown in blue. NAD^+-dependent dehydrogenases catalyze the transfer of a hydride ion (H**:-**) from a carbon to NAD+ in oxidation reactions such as the oxidation of alcohols to ketones or aldehydes to acids. The positively charged pyridine ring nitrogen of NAD^+ increases the electrophilicity of the carbon opposite it in the ring. This carbon then accepts the negatively charged hydride ion. The alcoholic proton is released into water. NADP functions by the same mechanism, but is usually involved in pathways of reductive synthesis.