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6

An Introduction to Metabolism

Lecture Presentations by
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SECOND EDITION

The Energy of Life

- The living cell is a miniature chemical factory where thousands of reactions occur
- The cell extracts energy and applies energy to perform work
- Some organisms even convert energy to light, as in bioluminescence

Figure 6.1

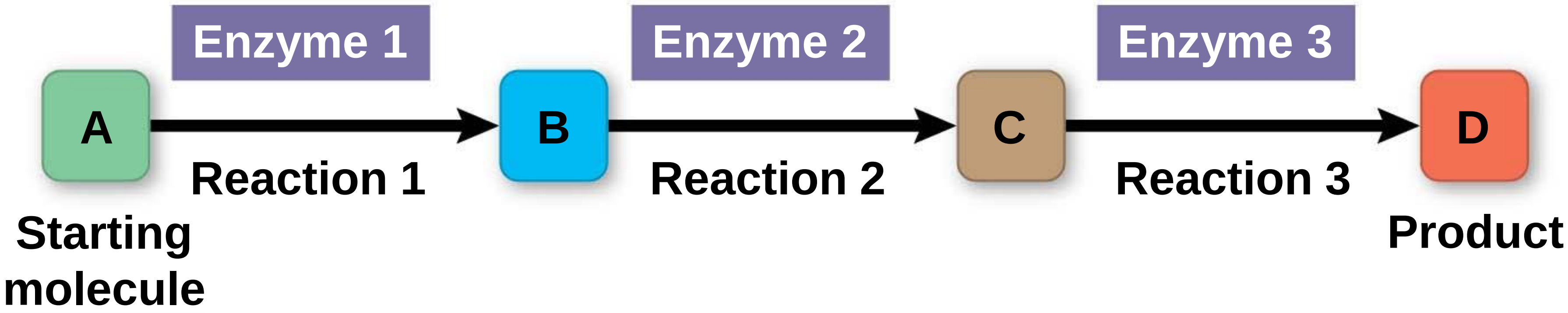
Concept 6.1: An organism’s metabolism transforms matter and energy

- **Metabolism** is the totality of an organism’s chemical reactions
- Metabolism is an emergent property of life that arises from interactions between molecules within the cell

Metabolic Pathways

- A **metabolic pathway** begins with a specific molecule and ends with a product
- Each step is catalyzed by a specific enzyme

Figure 6.UN01



- **Catabolic pathways** release energy by breaking down complex molecules into simpler compounds
- One example of catabolism is cellular respiration, the breakdown of glucose and other organic fuels to carbon dioxide and water

- **Anabolic pathways** consume energy to build complex molecules from simpler ones
- The synthesis of proteins from amino acids is an example of anabolism
- **Bioenergetics** is the study of how energy flows through living organisms

Forms of Energy

- **Energy** is the capacity to cause change
- Energy exists in various forms, some of which can perform work

- **Kinetic energy** is energy associated with motion
- **Thermal energy** is kinetic energy associated with random movement of atoms or molecules
- **Heat** is thermal energy in transfer from one object to another
- Light is another type of energy that can be harnessed to perform work

- **Potential energy** is energy that matter possesses because of its location or structure
- **Chemical energy** is potential energy available for release in a chemical reaction
- Energy can be converted from one form to another

Animation: Energy Concepts

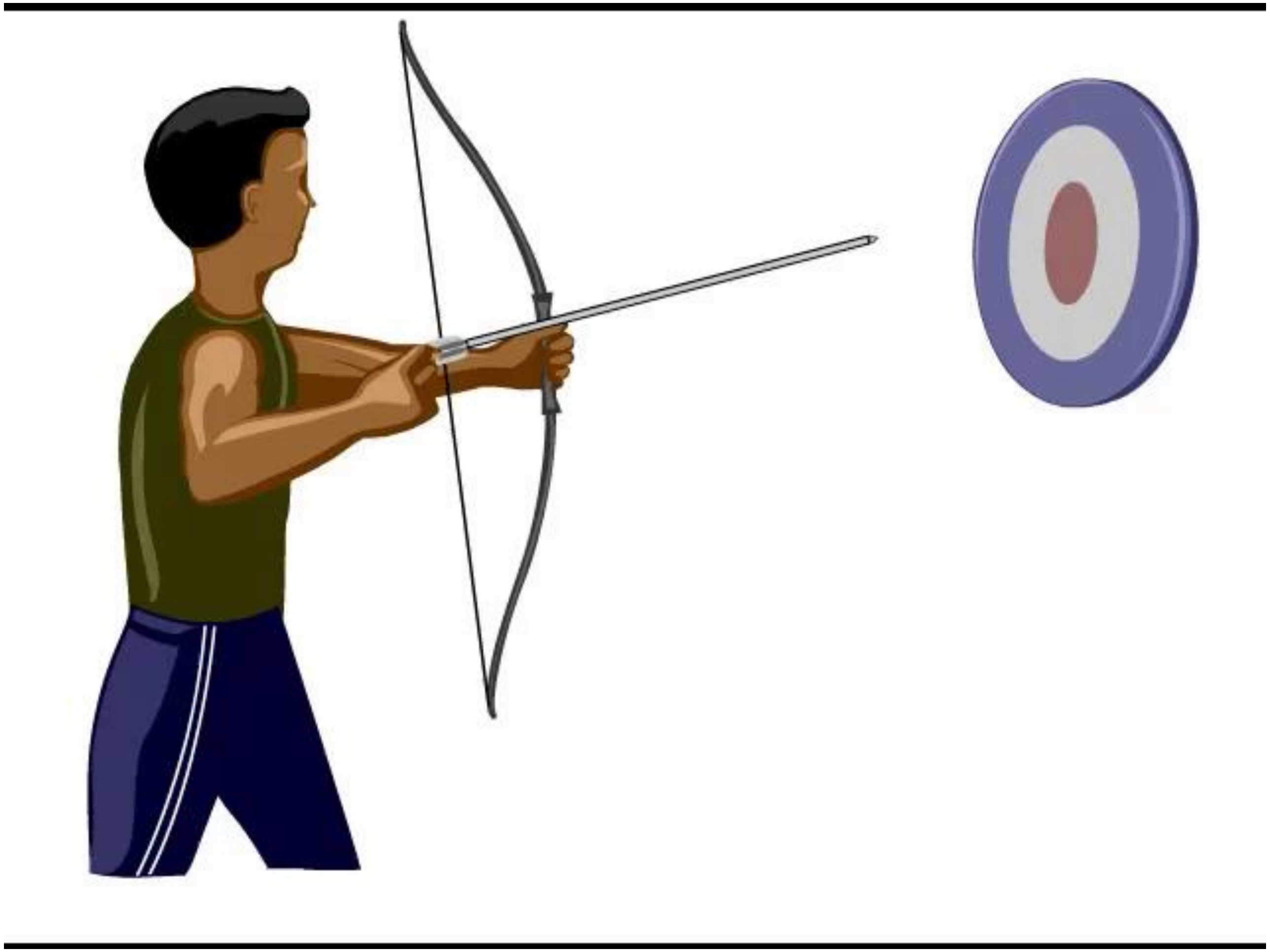
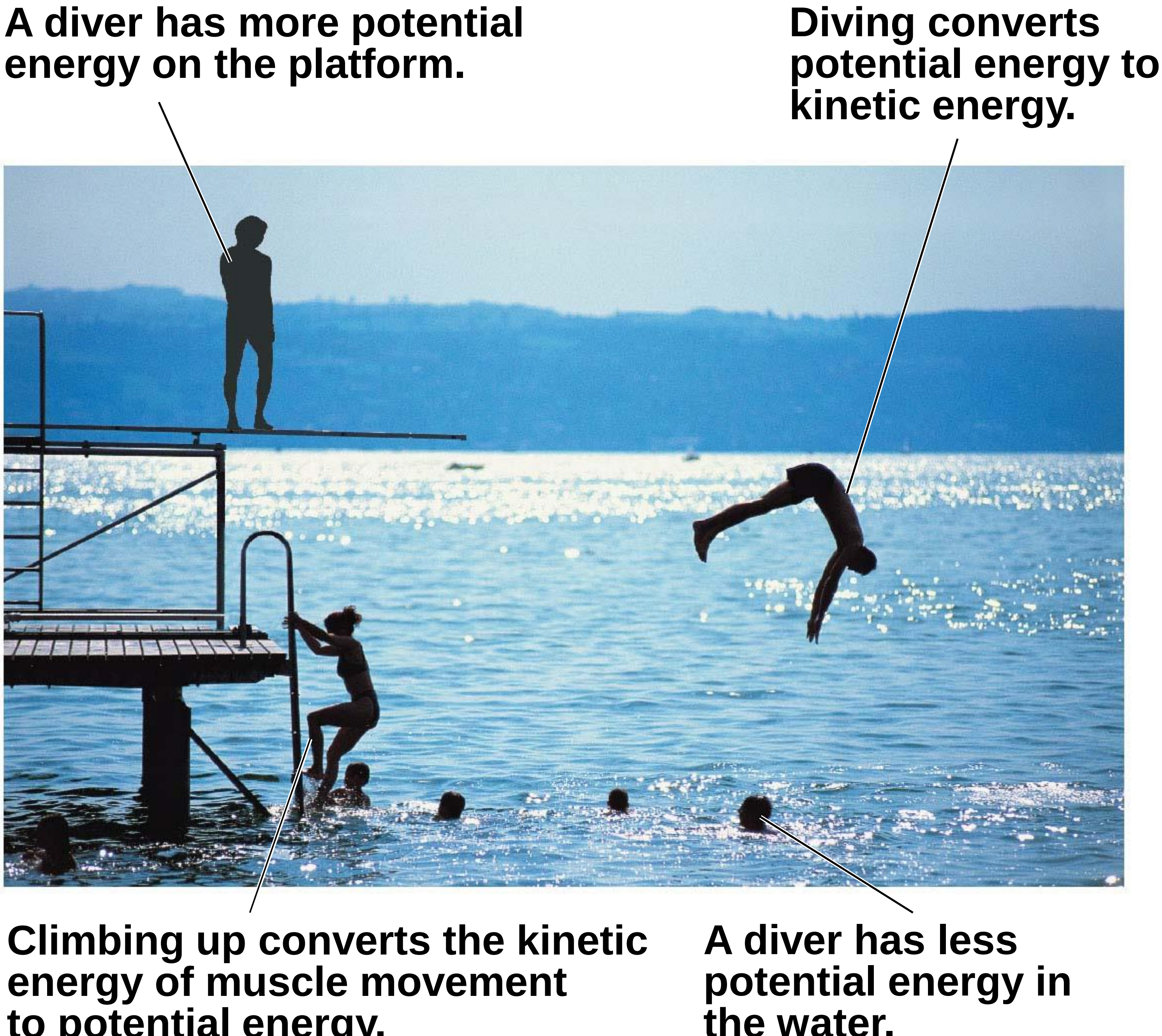


Figure 6.2


A diver has more potential energy on the platform.
Diving converts potential energy to kinetic energy.
Climbing up converts the kinetic energy of muscle movement to potential energy.
A diver has less potential energy in the water.

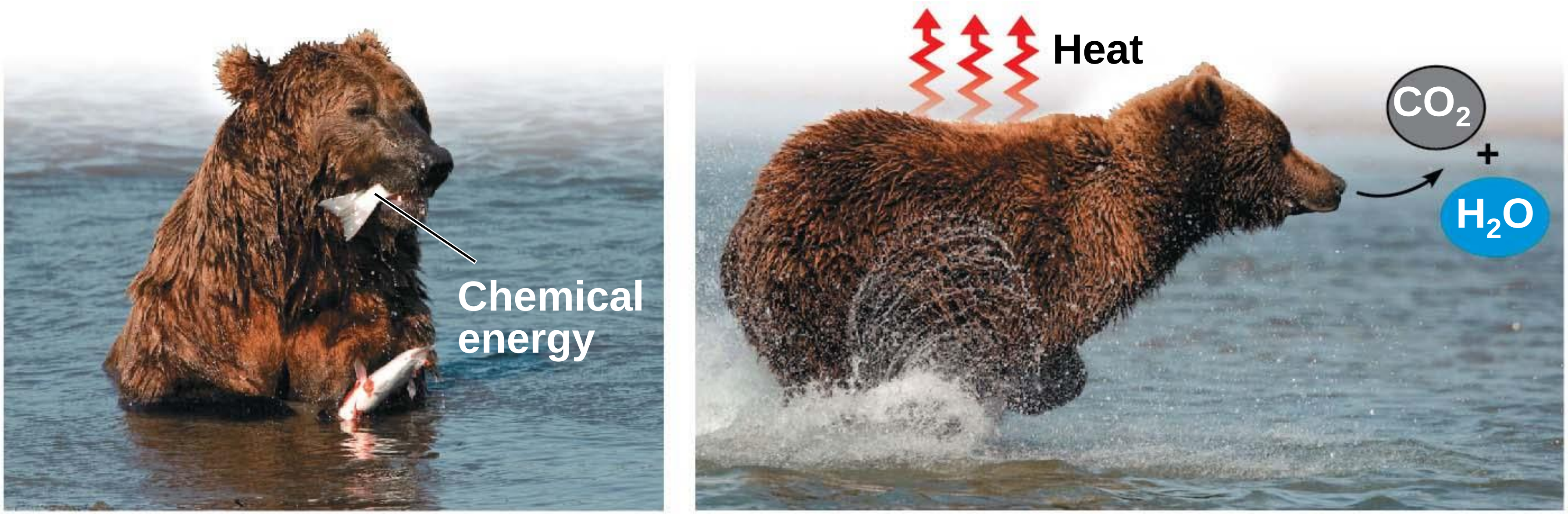
The Laws of Energy Transformation

- **Thermodynamics** is the study of energy transformations
- In an open system, energy and matter can be transferred between the system and its surroundings
- In an isolated system, exchange with the surroundings cannot occur
- Organisms are open systems

The First Law of Thermodynamics

- According to the **first law of thermodynamics**, the energy of the universe is constant
  - *Energy can be transferred and or transformed, but it cannot be created or destroyed*
- The first law is also called the *principle of conservation of energy*

Figure 6.3



(a) First law of thermodynamics **(b) Second law of thermodynamics**

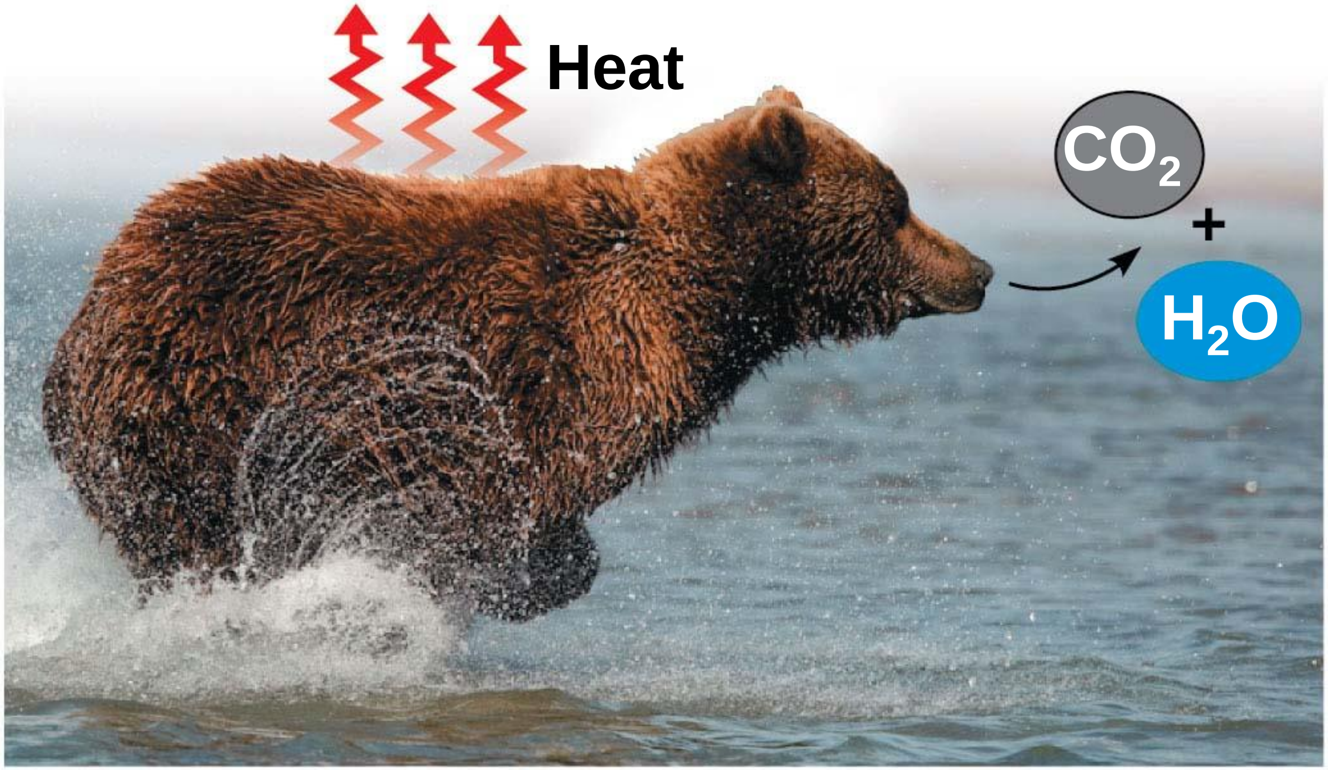
Figure 6.3-1

(a) First law of thermodynamics

The Second Law of Thermodynamics

- During every energy transfer or transformation, some energy is lost as heat
- According to the **second law of thermodynamics**
  - *Every energy transfer or transformation increases the entropy of the universe*
- **Entropy** is a measure of disorder, or randomness

Figure 6.3-2



(b) Second law of thermodynamics

- Living cells unavoidably convert organized forms of energy to heat
- **Spontaneous processes** occur without energy input; they can happen quickly or slowly
  - *For a process to occur spontaneously, it must increase the entropy of the universe*

Biological Order and Disorder

- Cells create ordered structures from less ordered materials
- Organisms also replace ordered forms of matter and energy with less ordered forms
- Energy flows into an ecosystem in the form of light and exits in the form of heat

Figure 6.4

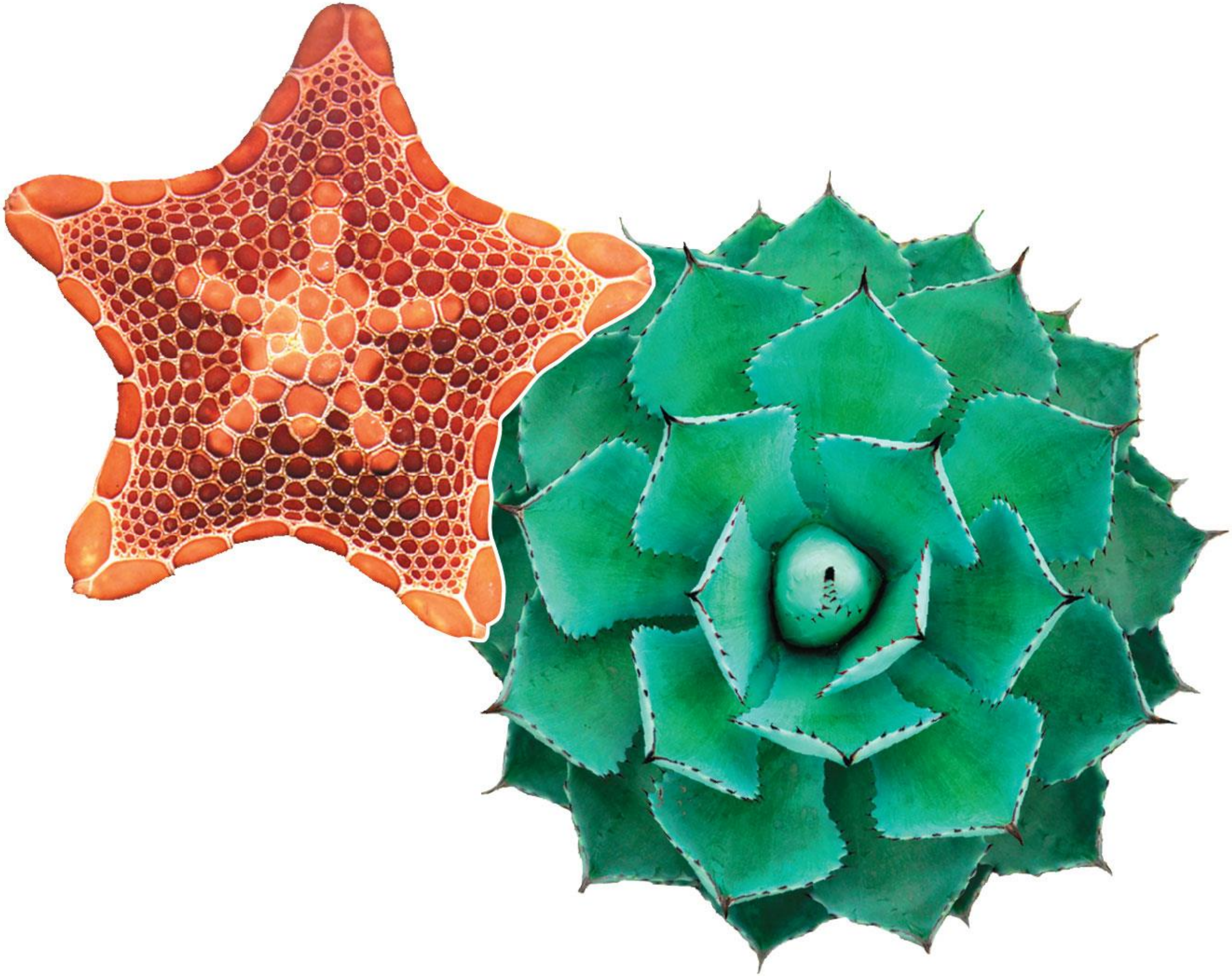


Figure 6.4-1

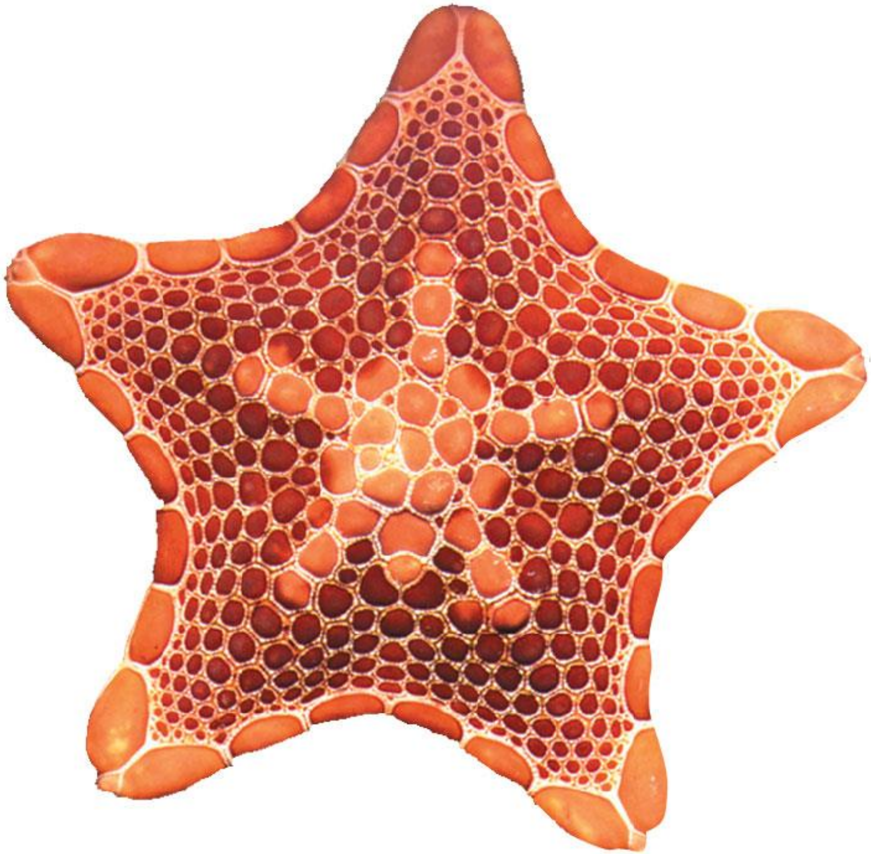
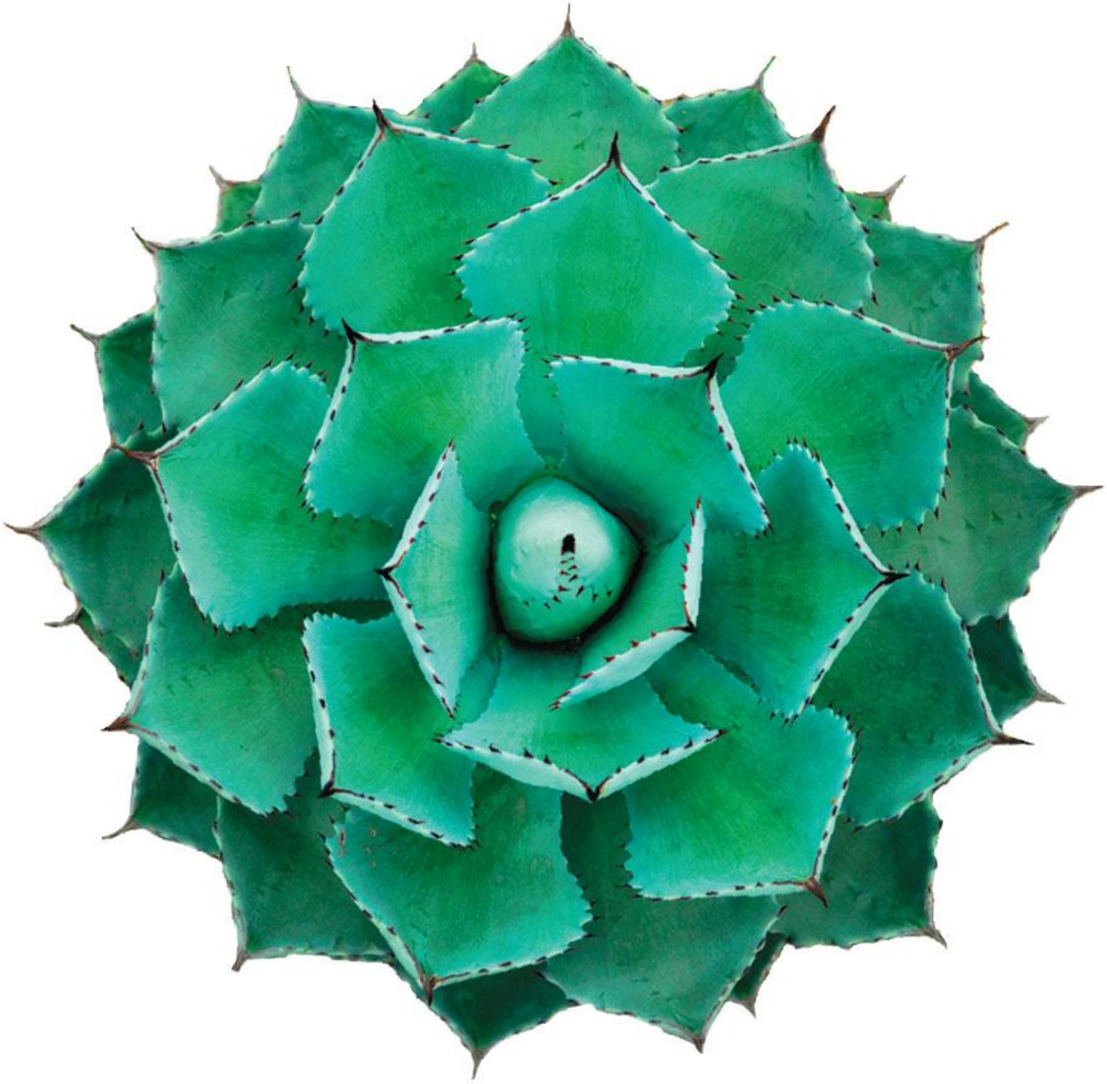


Figure 6.4-2



- The evolution of more complex organisms does not violate the second law of thermodynamics
- Entropy (disorder) may decrease in a system, but the universe’s total entropy increases
- Organisms are islands of low entropy in an increasingly random universe

Concept 6.2: The free-energy change of a reaction tells us whether or not the reaction occurs spontaneously

- Biologists measure changes in free energy to help them understand the chemical reactions of life

Free-Energy Change (ΔG), Stability, and Equilibrium

- A living system's **free energy** is energy that can do work when temperature and pressure are uniform, as in a living cell

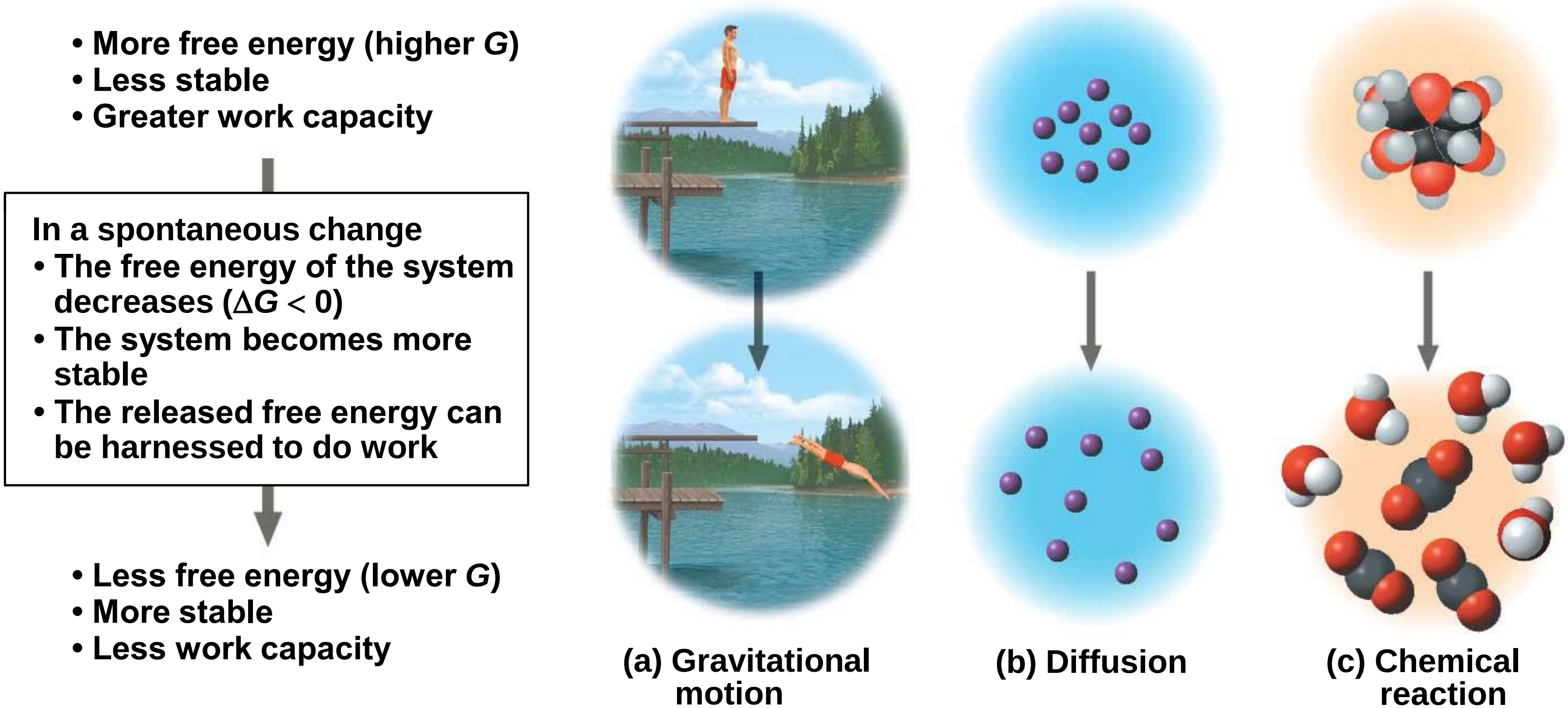
- The change in free energy (ΔG) during a chemical reaction is the difference between the free energy of the final state and the free energy of the initial state

$$\Delta G = G_{\text{final state}} - G_{\text{initial state}}$$

- Only processes with a negative ΔG are spontaneous
- Spontaneous processes can be harnessed to perform work

- Free energy is a measure of a system’s instability, its tendency to change to a more stable state
- During a spontaneous change, free energy decreases and the stability of a system increases

Figure 6.5



• More free energy (higher G)
• Less stable
• Greater work capacity
In a spontaneous change
• The free energy of the system decreases (ΔG < 0)
• The system becomes more stable
• The released free energy can be harnessed to do work
• Less free energy (lower G)
• More stable
• Less work capacity
(a) Gravitational motion
(b) Diffusion
(c) Chemical reaction

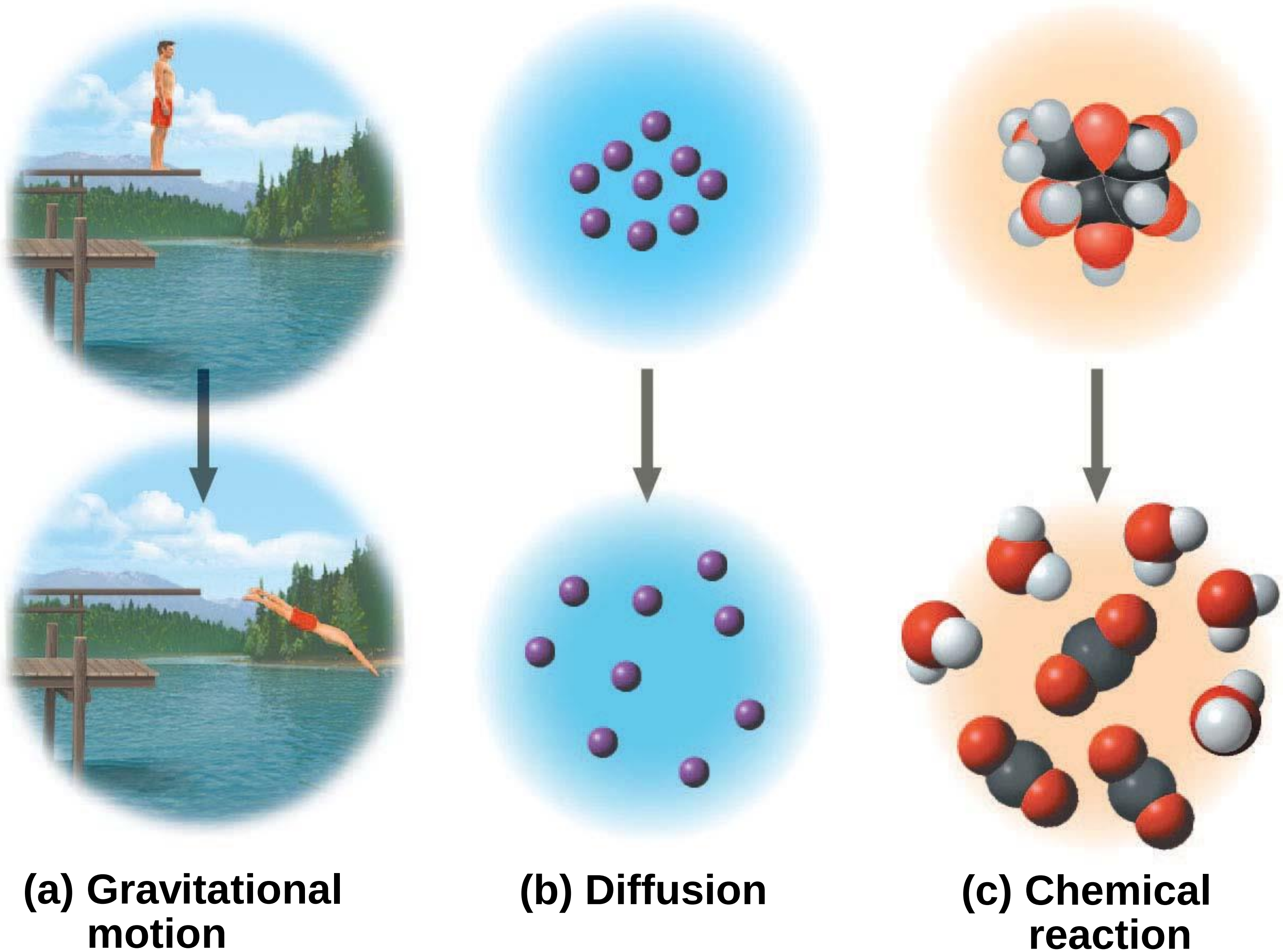
Figure 6.5-1

- More free energy (higher *G*)
- Less stable
- Greater work capacity

In a spontaneous change
- The free energy of the system decreases ($\Delta G < 0$)
- The system becomes more stable
- The released free energy can be harnessed to do work

- Less free energy (lower *G*)
- More stable
- Less work capacity

Figure 6.5-2



- At equilibrium, forward and reverse reactions occur at the same rate; it is a state of maximum stability
  - *A process is spontaneous and can perform work only when it is moving toward equilibrium*

Free Energy and Metabolism

- The concept of free energy can be applied to the chemistry of life's processes

Exergonic and Endergonic Reactions in Metabolism

- An **exergonic reaction** proceeds with a net release of free energy and is spontaneous; ΔG is negative
- The magnitude of ΔG represents the maximum amount of work the reaction can perform

Figure 6.6

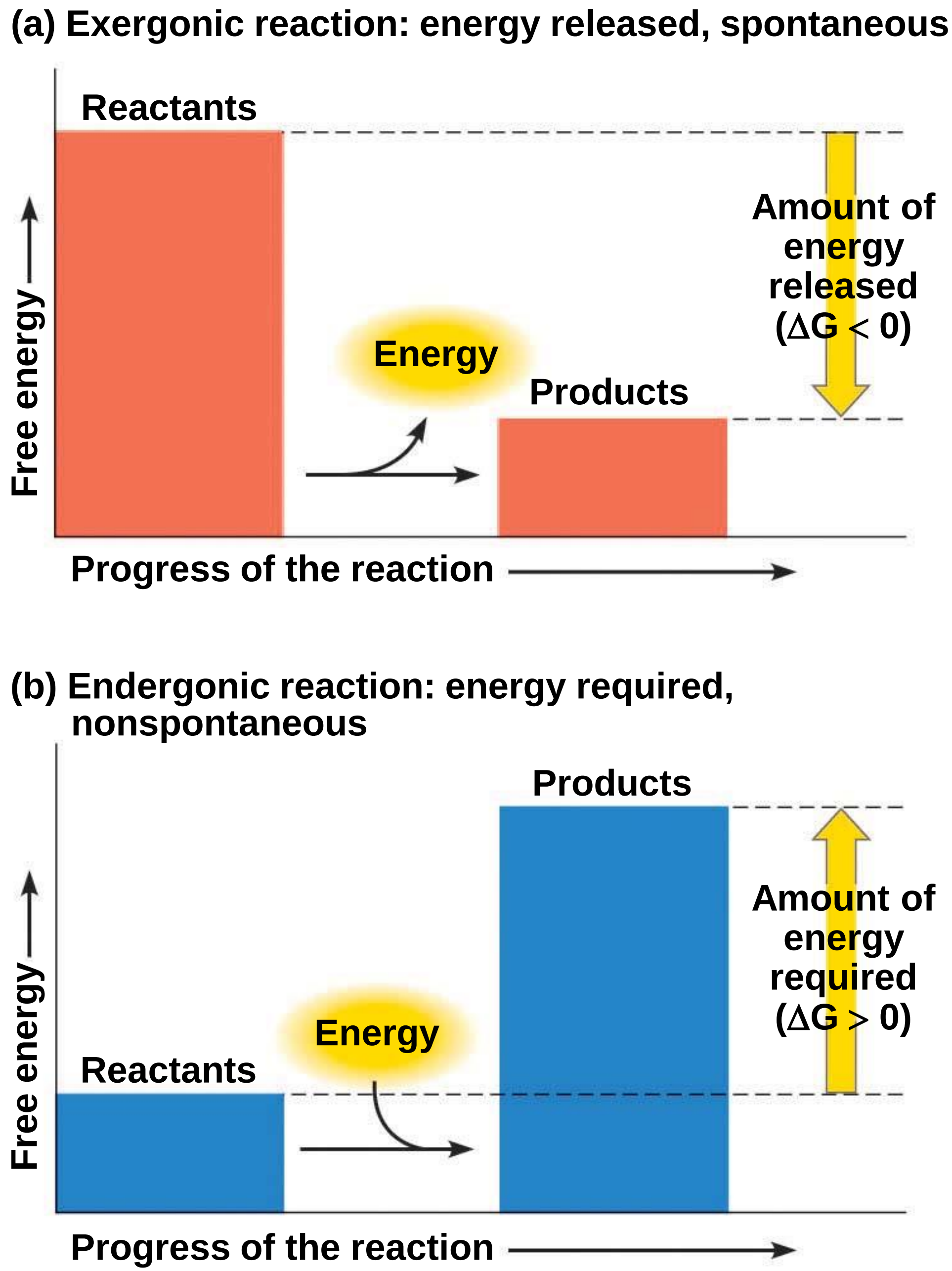
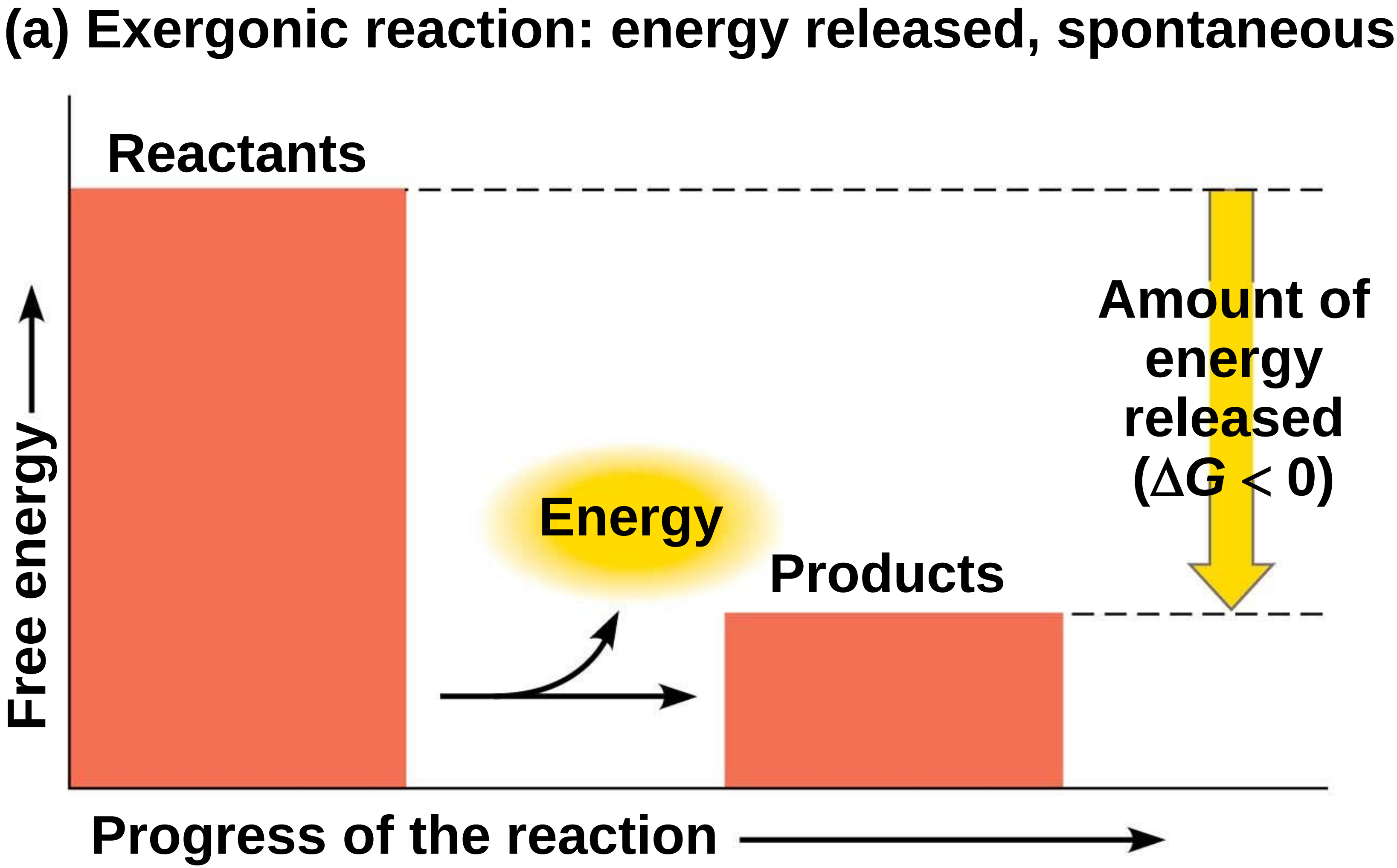
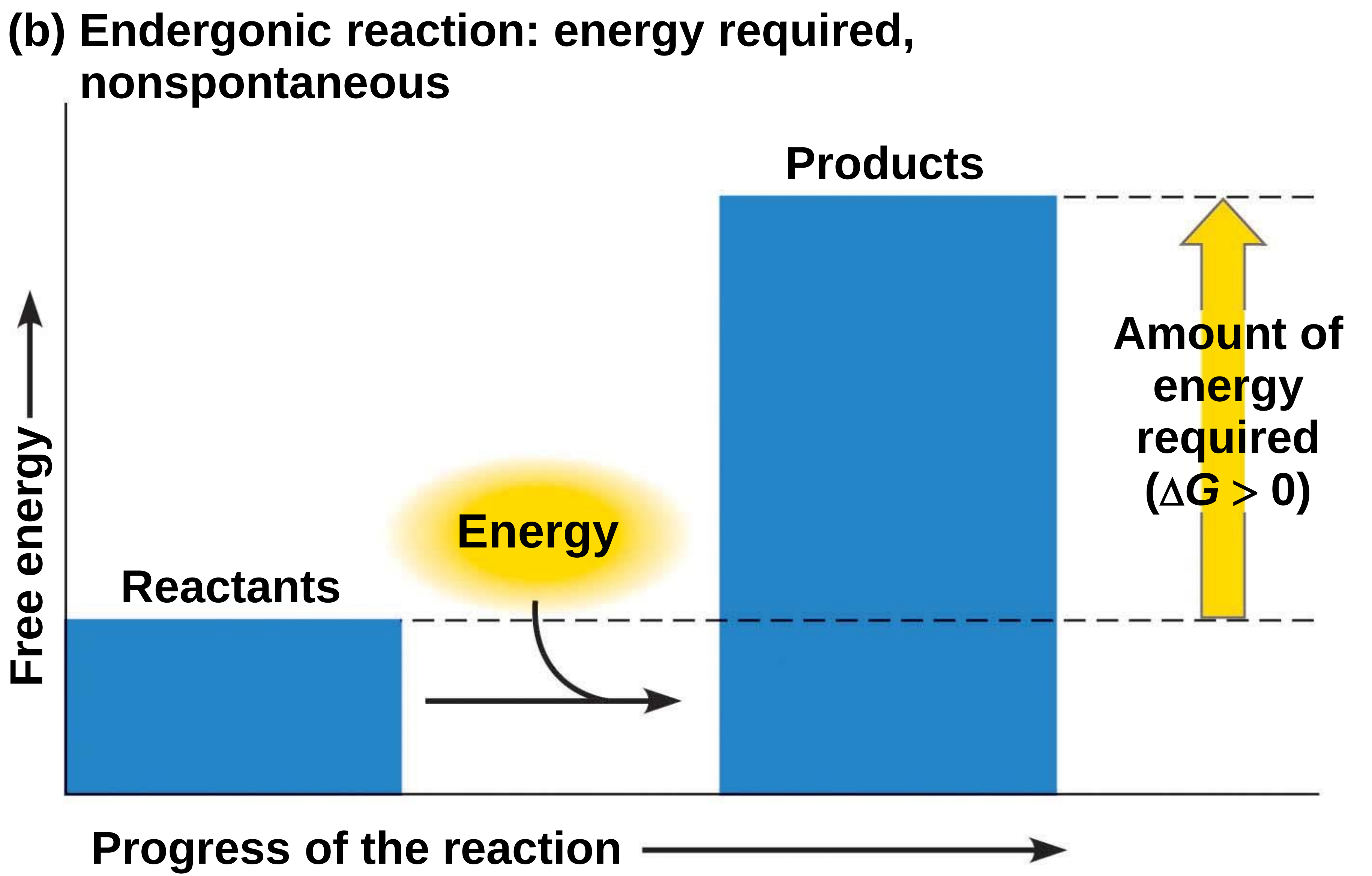

(a) Exergonic reaction: energy released, spontaneous
Reactants
Amount of energy released ($\Delta G < 0$)
Energy
Products
Free energy
Progress of the reaction
(b) Endergonic reaction: energy required, nonspontaneous
Products
Amount of energy required ($\Delta G > 0$)
Energy
Reactants
Free energy
Progress of the reaction

Figure 6.6-1


(a) Exergonic reaction: energy released, spontaneous
Reactants
Amount of energy released ($\Delta G < 0$)
Energy
Products
Free energy
Progress of the reaction

- An **endergonic reaction** absorbs free energy from its surroundings and is nonspontaneous; ΔG is positive
- The magnitude of ΔG is the quantity of energy required to drive the reaction

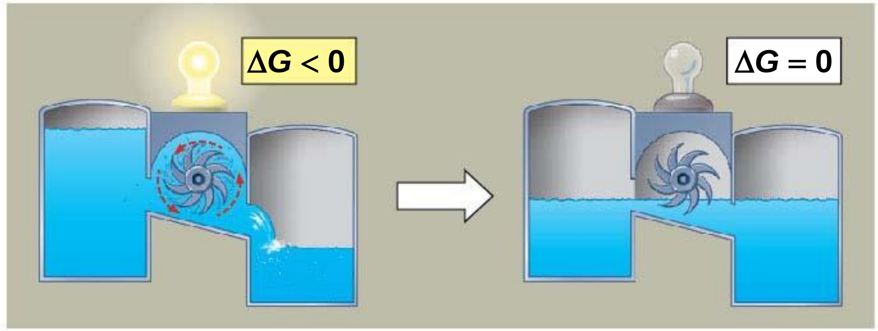
Figure 6.6-2


(b) Endergonic reaction: energy required, nonspontaneous
Products
Amount of energy required ($\Delta G > 0$)
Energy
Reactants
Free energy
Progress of the reaction

Equilibrium and Metabolism

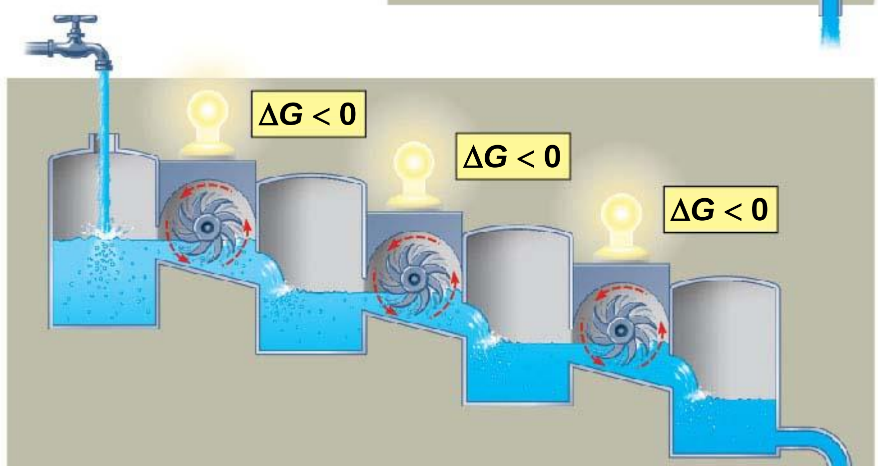
- Hydroelectric systems can serve as analogies for chemical reactions in living systems
- Reactions in an isolated system eventually reach equilibrium and can then do no work

Figure 6.7

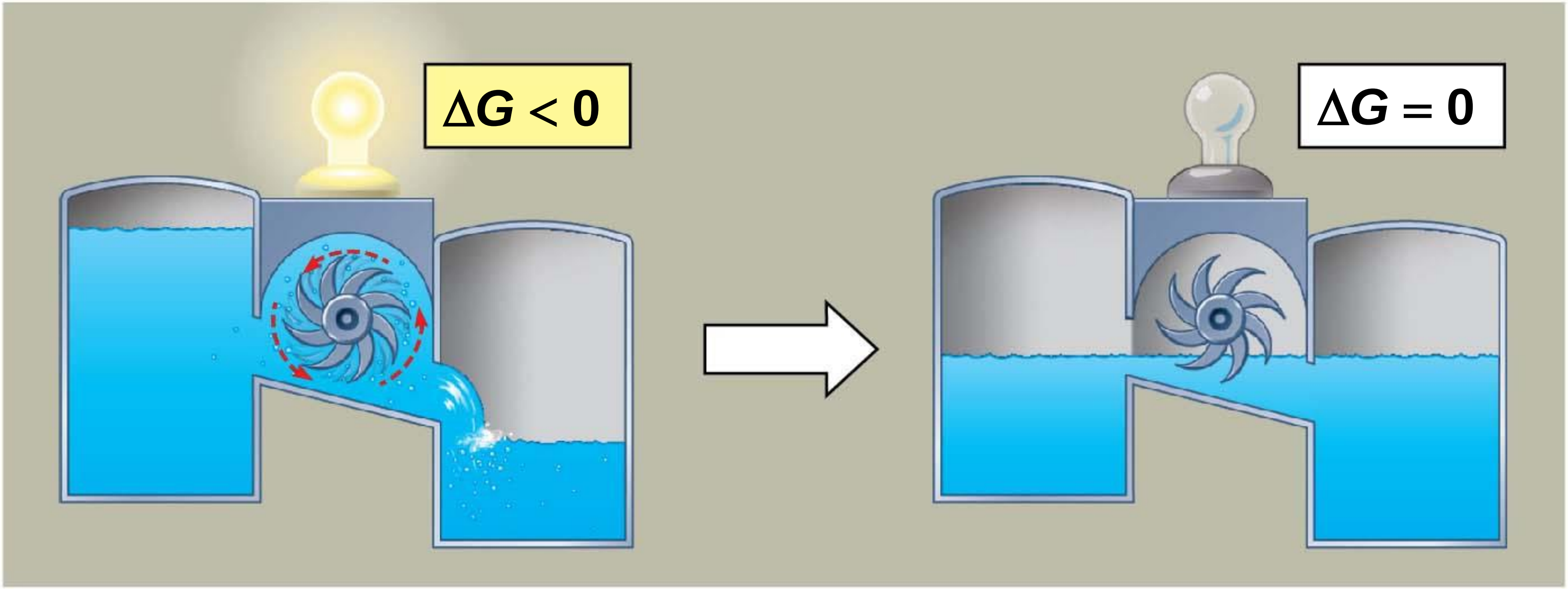


(a) An isolated hydroelectric system

(b) An open hydroelectric system



(c) A multistep open hydroelectric system

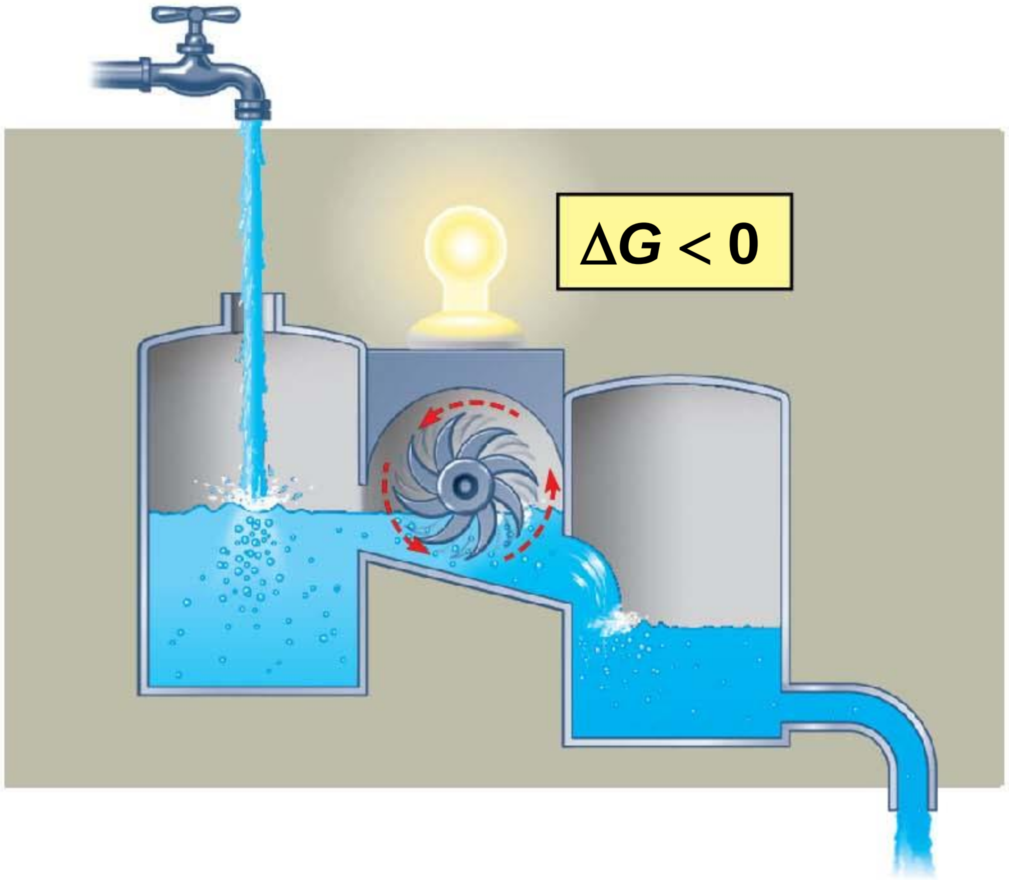


(a) An isolated hydroelectric system

- Cells are not in equilibrium; they are open systems experiencing a constant flow of materials

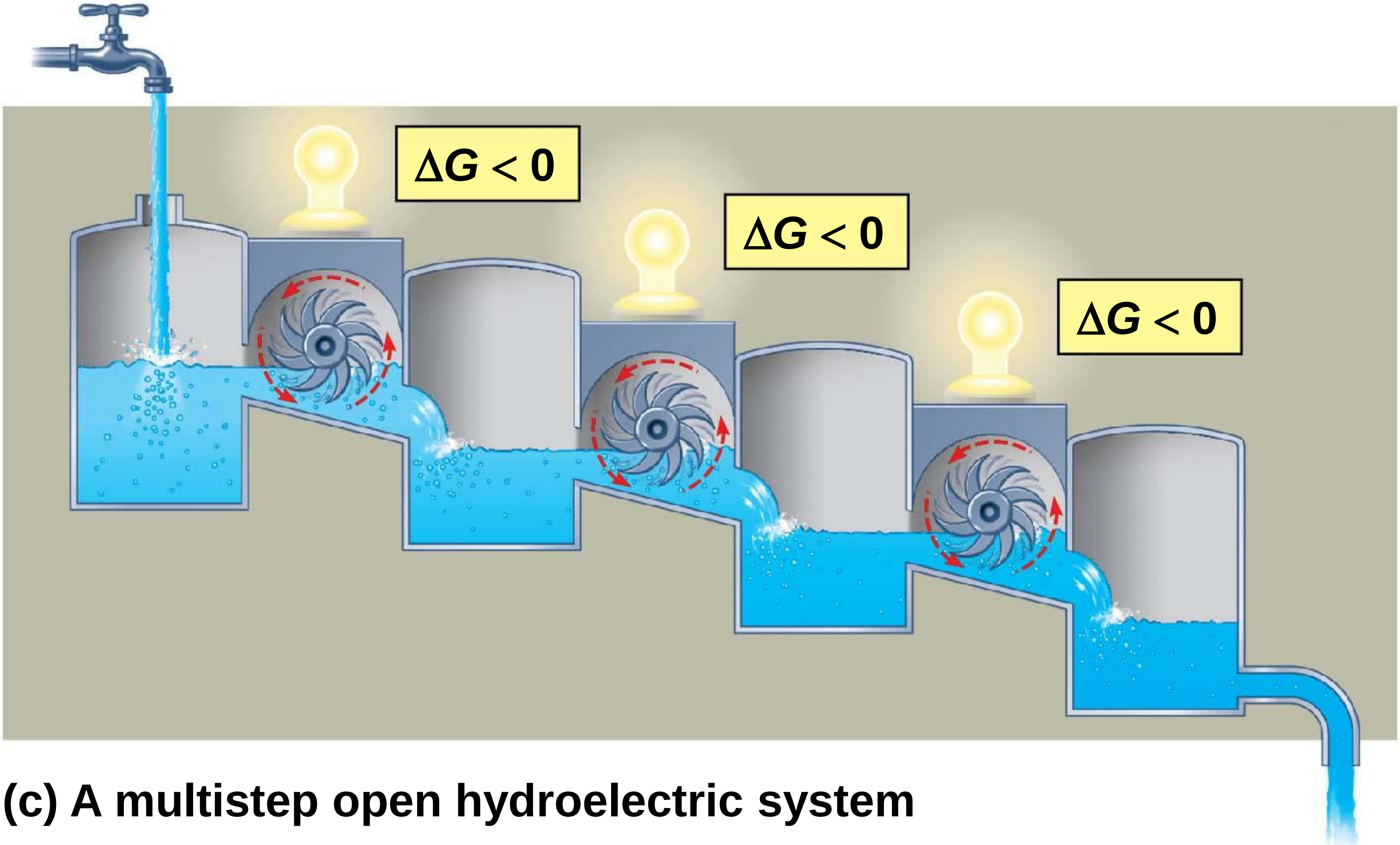
Figure 6.7-2

(b) An open hydroelectric system



- A catabolic pathway in a cell releases free energy in a series of reactions
- The product of each reaction is the reactant for the next, preventing the system from reaching equilibrium

Figure 6.7-3



(c) A multistep open hydroelectric system

Concept 6.3: ATP powers cellular work by coupling exergonic reactions to endergonic reactions

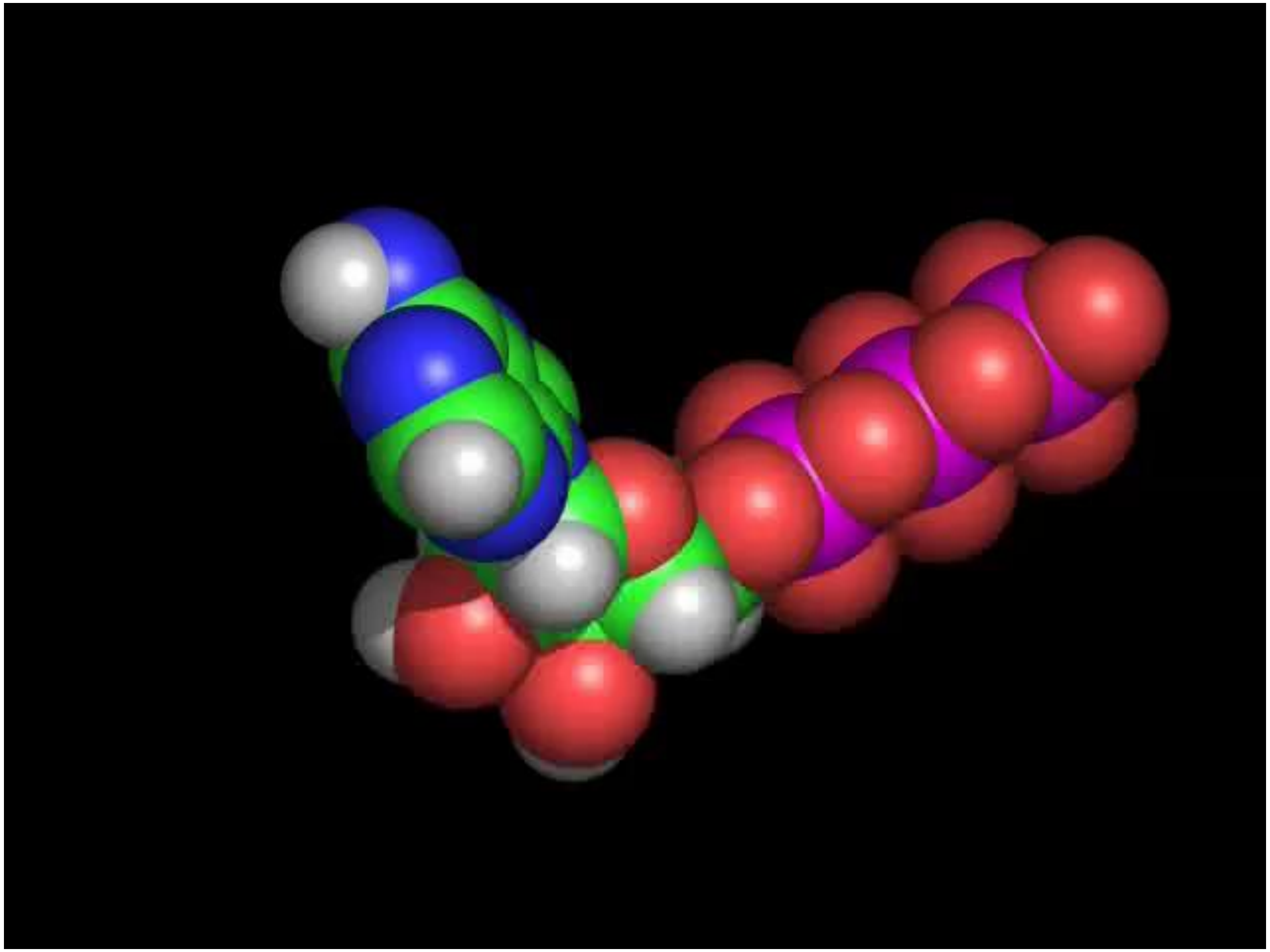
- A cell does three main kinds of work
  - Chemical
  - Transport
  - Mechanical

- To do work, cells manage energy resources by **energy coupling**, the use of an exergonic process to drive an endergonic one
- Most energy coupling in cells is mediated by ATP

The Structure and Hydrolysis of ATP

- **ATP** (**adenosine triphosphate**) is composed of ribose (a sugar), adenine (a nitrogenous base), and three phosphate groups
- In addition to its role in energy coupling, ATP is also used to make RNA

Video: ATP Space-filling Model



Video: ATP Stick Model

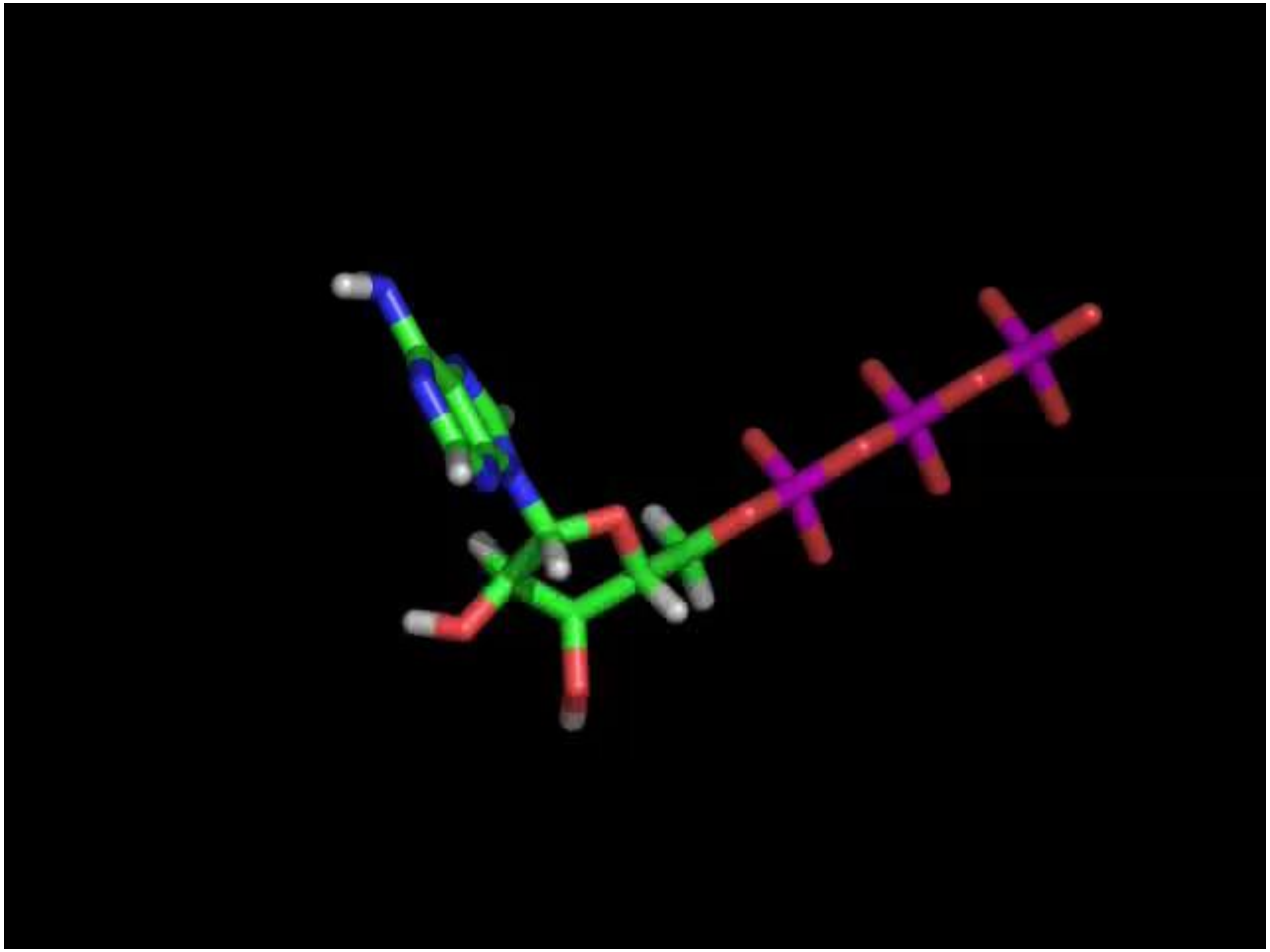
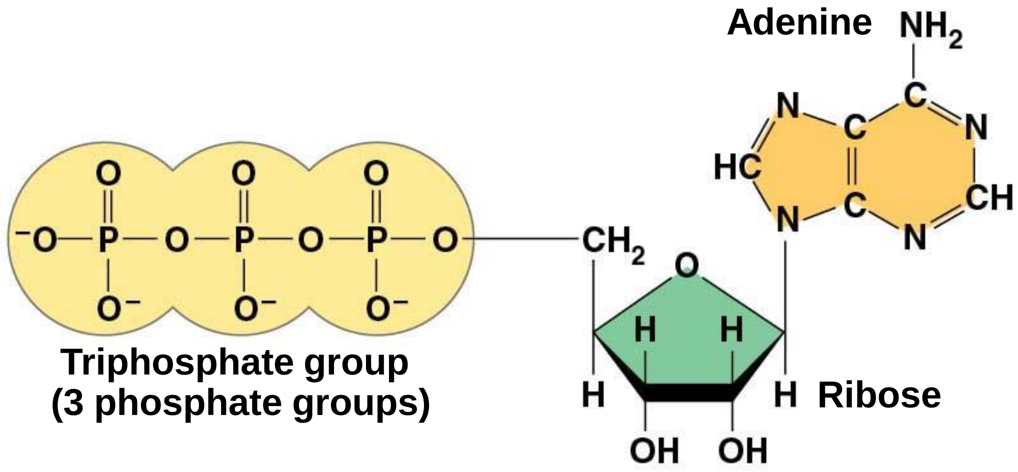
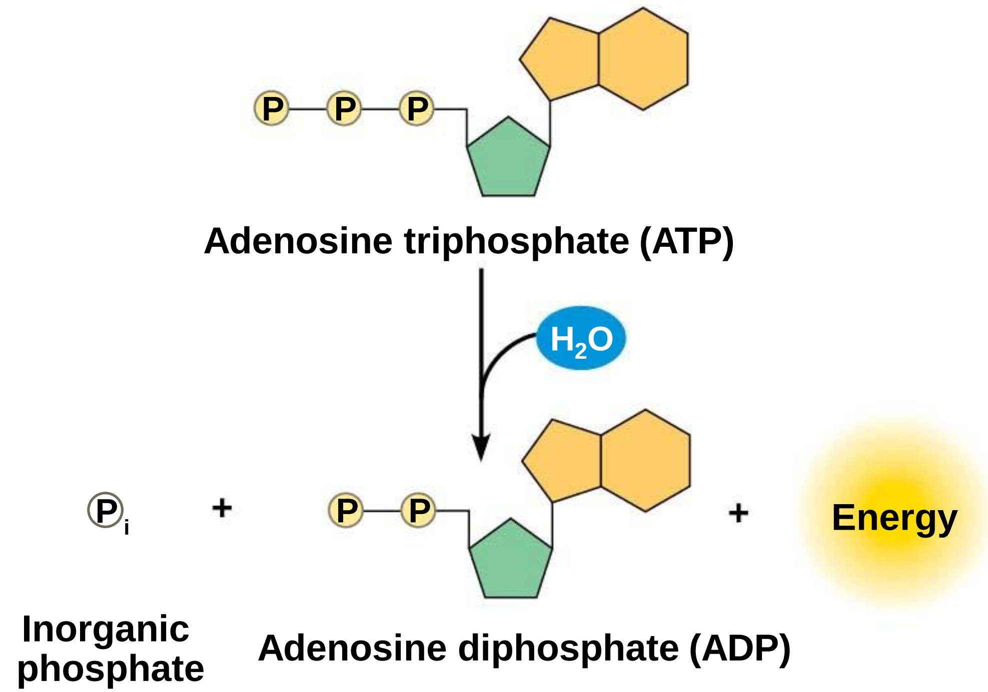


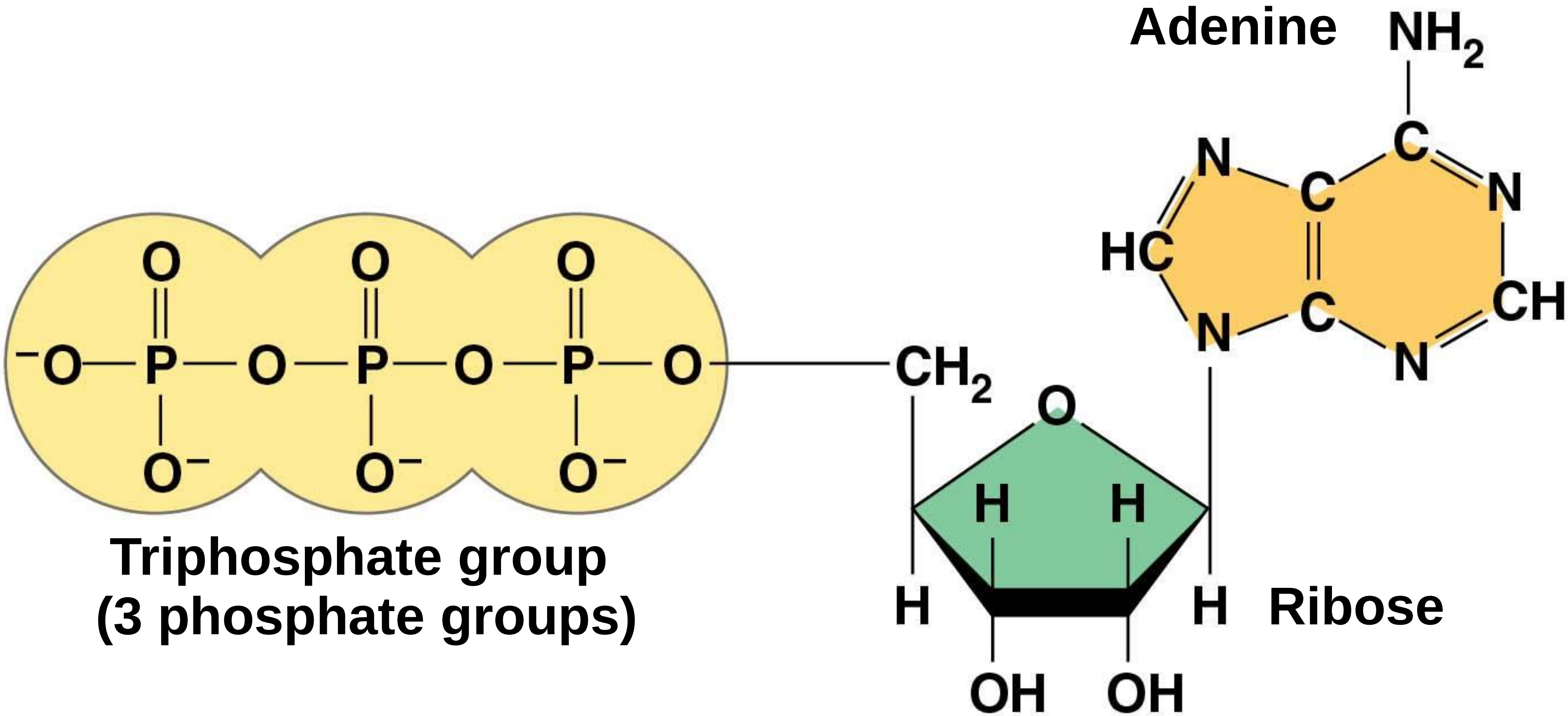
Figure 6.8



(a) The structure of ATP



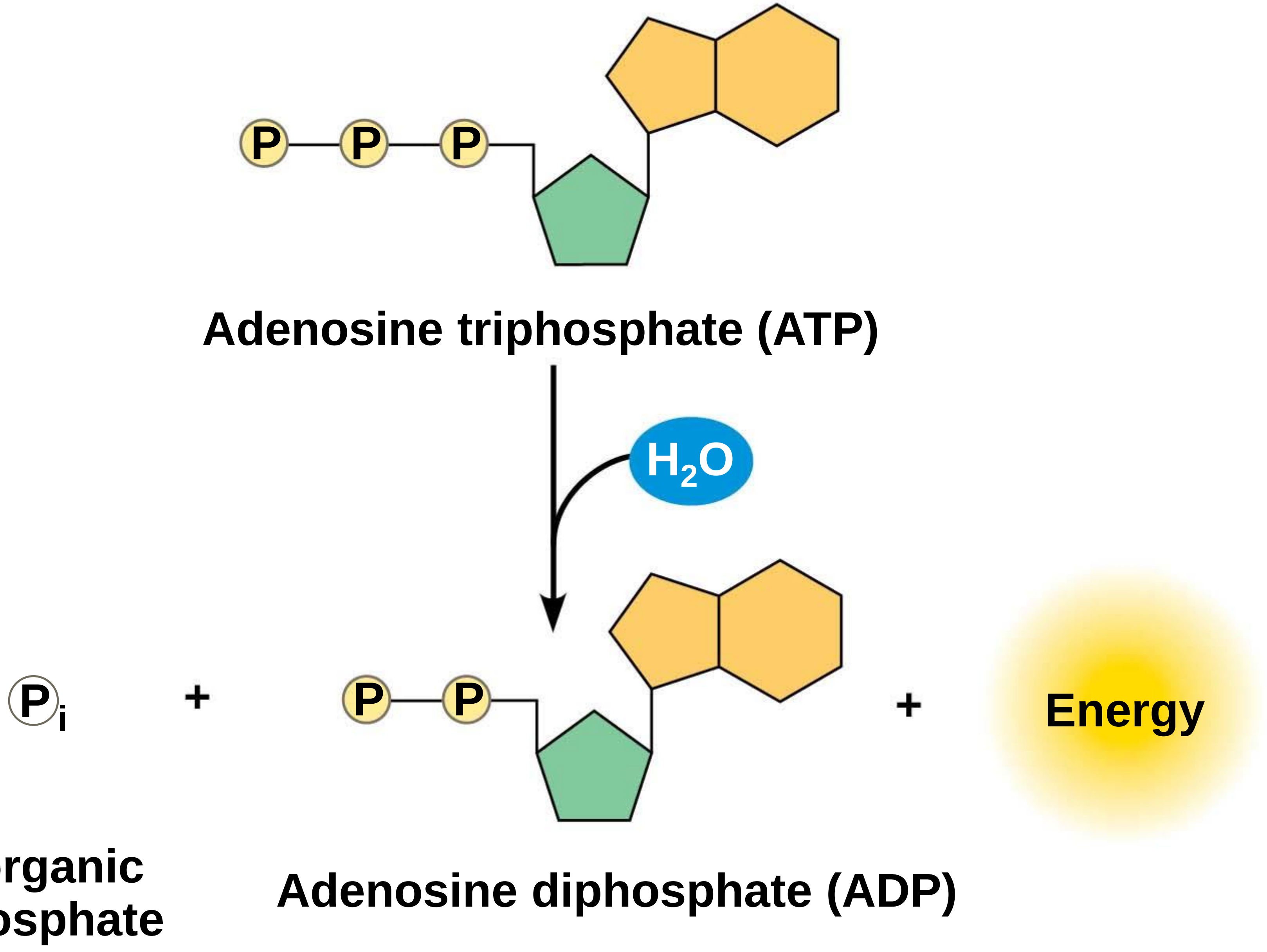
(b) The hydrolysis of ATP



(a) The structure of ATP

- The bonds between the phosphate groups of ATP can be broken by hydrolysis
- Energy is released from ATP when the terminal phosphate bond is broken
- This release of energy comes from the chemical change to a state of lower free energy, not from the phosphate bonds themselves

Figure 6.8-2



(b) The hydrolysis of ATP

- ATP hydrolysis releases a lot of energy due to the repulsive force of the three negatively charged phosphate groups
- The triphosphate tail of ATP is the chemical equivalent of a compressed spring

How the Hydrolysis of ATP Performs Work

- The three types of cellular work (mechanical, transport, and chemical) are powered by the hydrolysis of ATP
- In the cell, the energy from the exergonic reaction of ATP hydrolysis can be used to drive endergonic reactions

- ATP drives endergonic reactions by phosphorylation, transferring a phosphate group to some other molecule, such as a reactant
- The recipient molecule is now called a **phosphorylated intermediate**
- Overall, the coupled reactions are exergonic

Figure 6.9

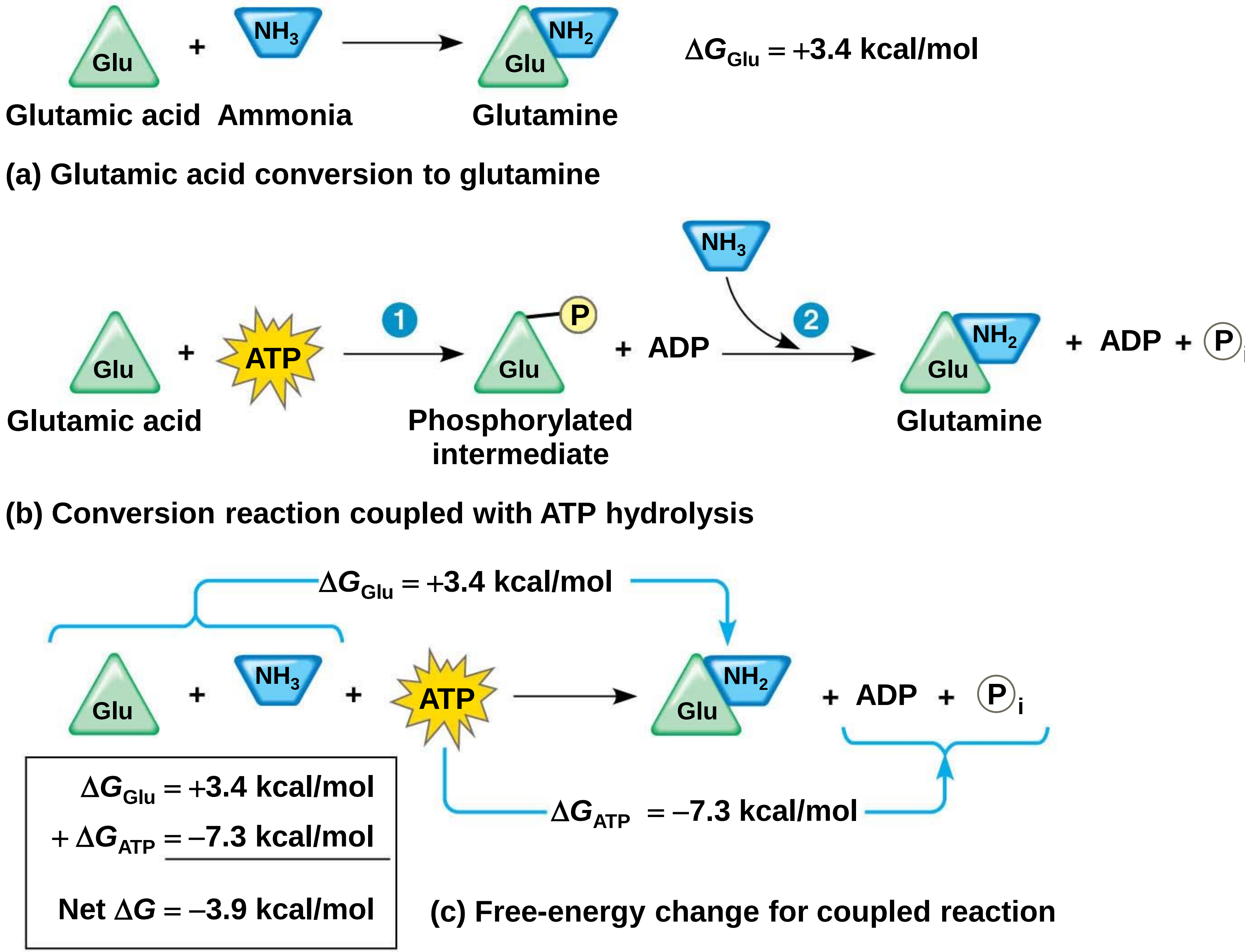

Glu
+
NH3
Glu
NH2
ΔGGlu = +3.4 kcal/mol
Glutamic acid
Ammonia
Glutamine
(a) Glutamic acid conversion to glutamine
Glu
+
ATP
1
Glu
P
+ ADP
NH3
2
Glu
NH2
+ ADP + P i
Glutamic acid
Phosphorylated intermediate
Glutamine
(b) Conversion reaction coupled with ATP hydrolysis
ΔGGlu = +3.4 kcal/mol
Glu
+
NH3
+
ATP
Glu
NH2
+ ADP + P i
ΔGATP = –7.3 kcal/mol
ΔGGlu = +3.4 kcal/mol
+ ΔGATP = –7.3 kcal/mol
Net ΔG = –3.9 kcal/mol
(c) Free-energy change for coupled reaction

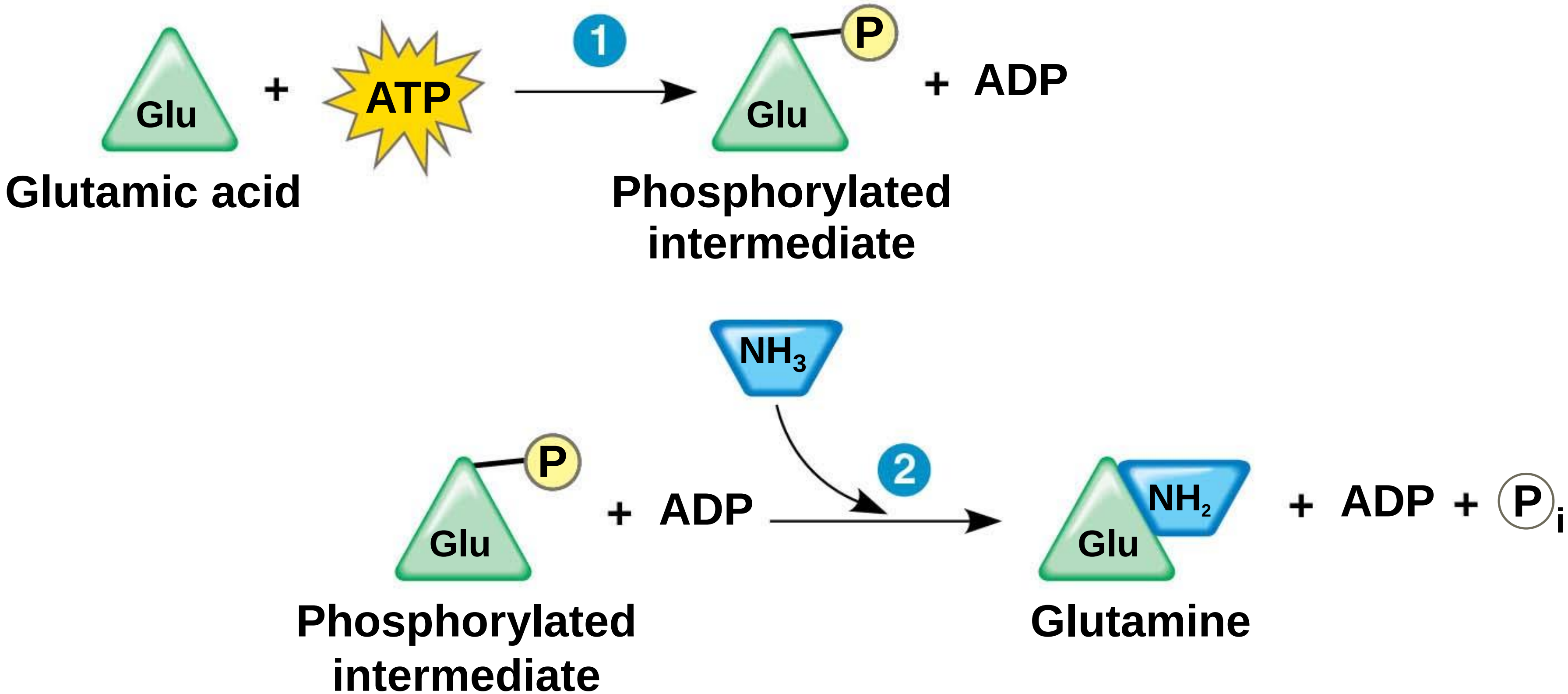
Figure 6.9-1

Glutamic acid Ammonia Glutamine

$\Delta G_{Glu} = +3.4$ kcal/mol

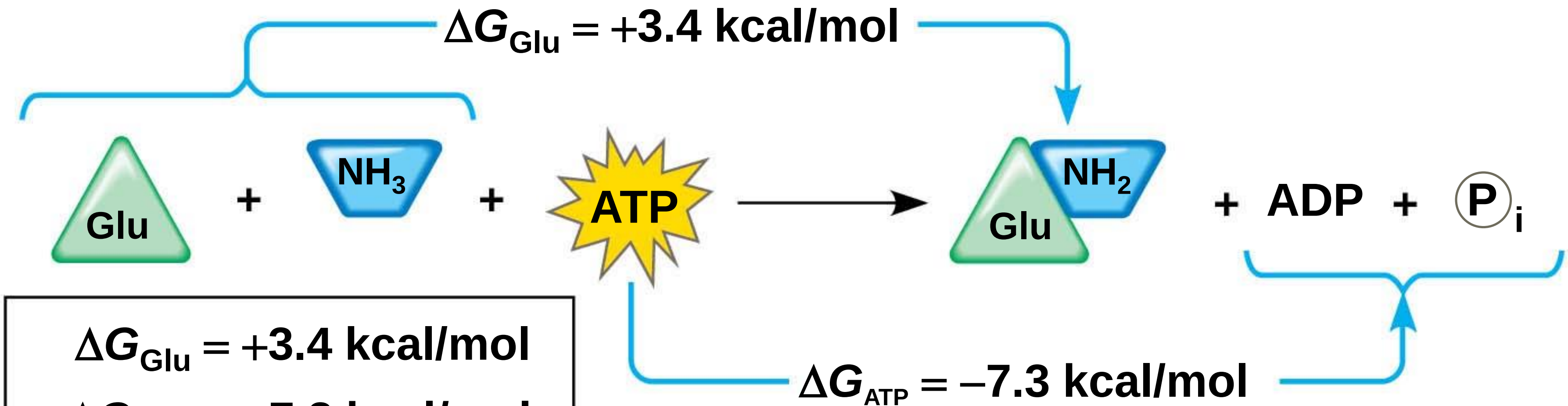
(a) Glutamic acid conversion to glutamine

Figure 6.9-2



(b) Conversion reaction coupled with ATP hydrolysis

Figure 6.9-3

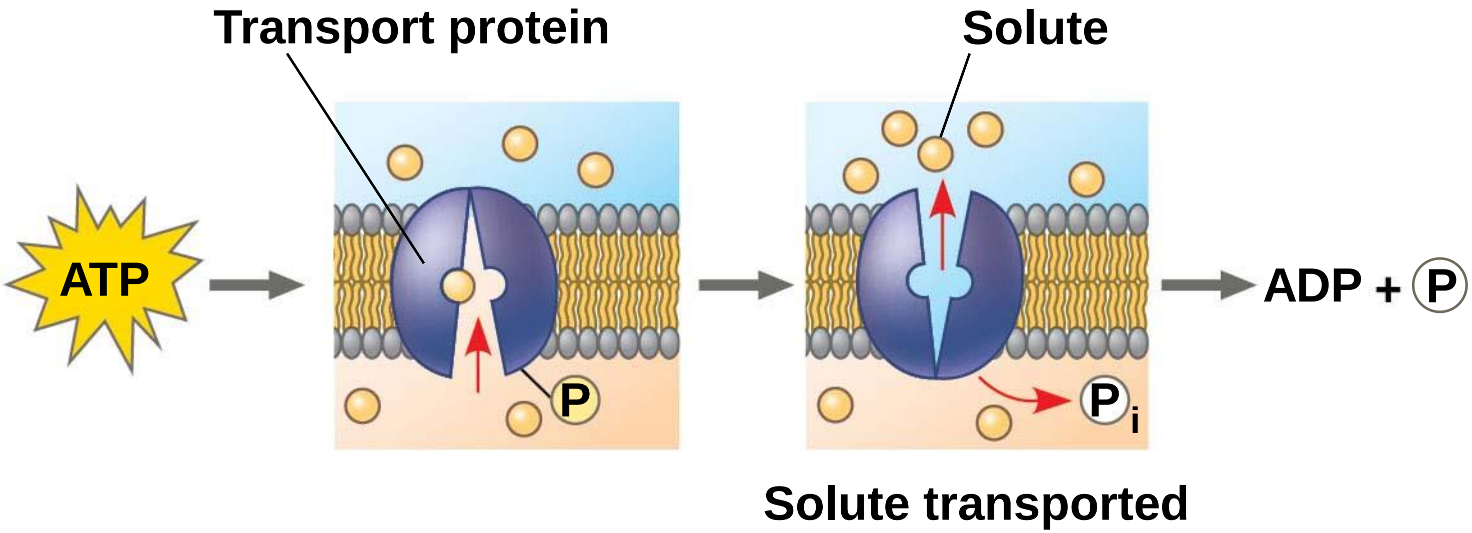


$$\Delta G_{Glu} = +3.4 \text{ kcal/mol}$$
$$+\,\Delta G_{ATP} = -7.3 \text{ kcal/mol}$$
$$\text{Net } \Delta G = -3.9 \text{ kcal/mol}$$

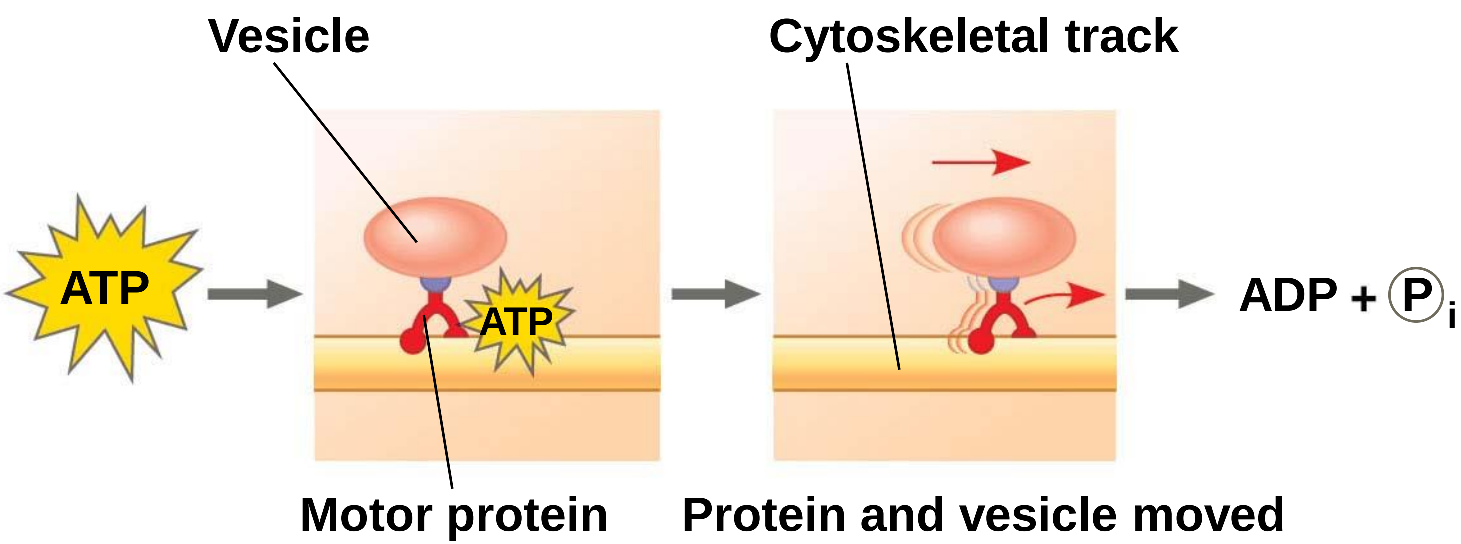
(c) Free-energy change for coupled reaction

- Transport and mechanical work in the cell are powered by ATP hydrolysis
- ATP hydrolysis leads to a change in a protein's shape and often its ability to bind to another molecule

Figure 6.10



(a) Transport work: ATP phosphorylates transport proteins.

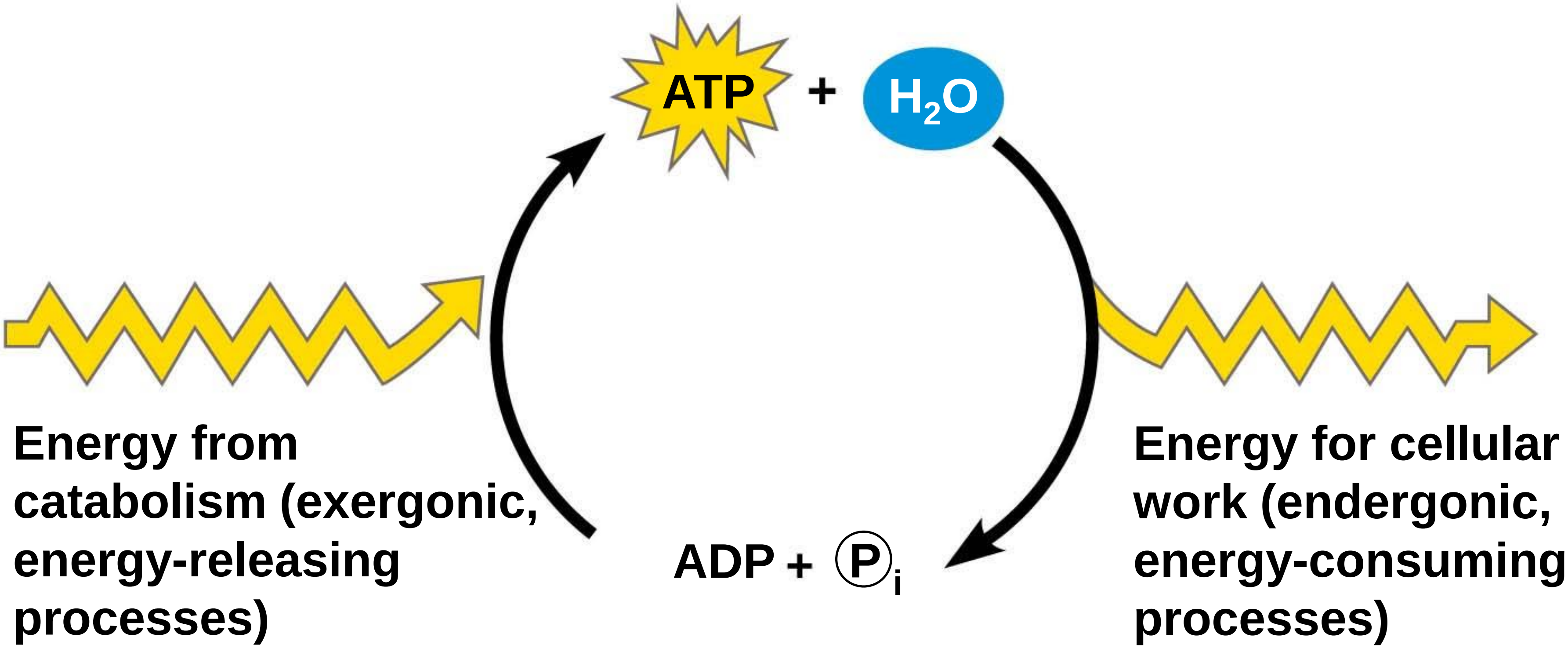


(b) Mechanical work: ATP binds noncovalently to motor proteins and then is hydrolyzed.

The Regeneration of ATP

- ATP is a renewable resource that is regenerated by addition of a phosphate group to adenosine diphosphate (ADP)
- The energy to phosphorylate ADP comes from catabolic reactions in the cell
- The ATP cycle is a revolving door through which energy passes during its transfer from catabolic to anabolic pathways

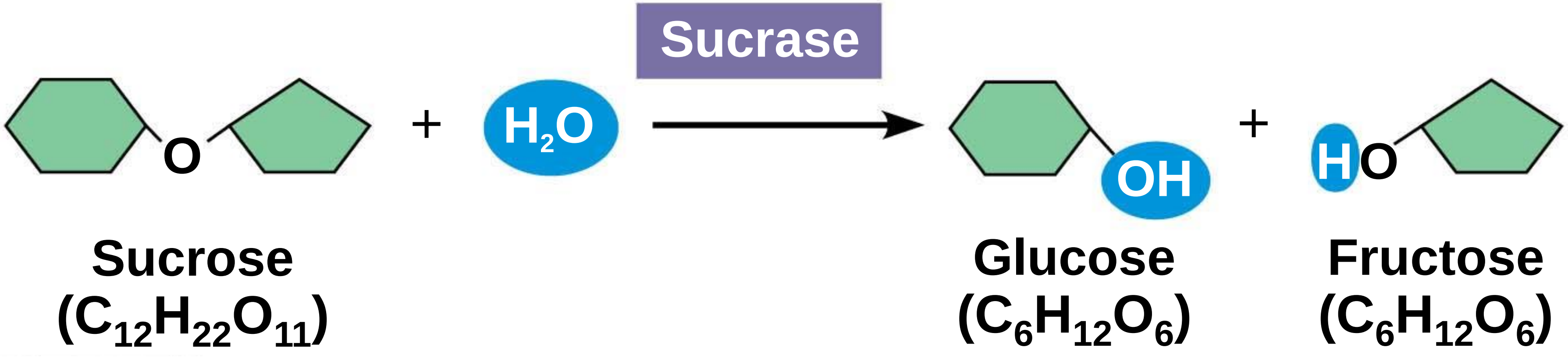
Figure 6.11


ATP + H_2O
Energy from catabolism (exergonic, energy-releasing processes)
Energy for cellular work (endergonic, energy-consuming processes)
ADP + Ⓟ$_i$

Concept 6.4: Enzymes speed up metabolic reactions by lowering energy barriers

- A **catalyst** is a chemical agent that speeds up a reaction without being consumed by the reaction
- An **enzyme** is a catalytic protein
- Hydrolysis of sucrose by the enzyme sucrase is an example of an enzyme-catalyzed reaction

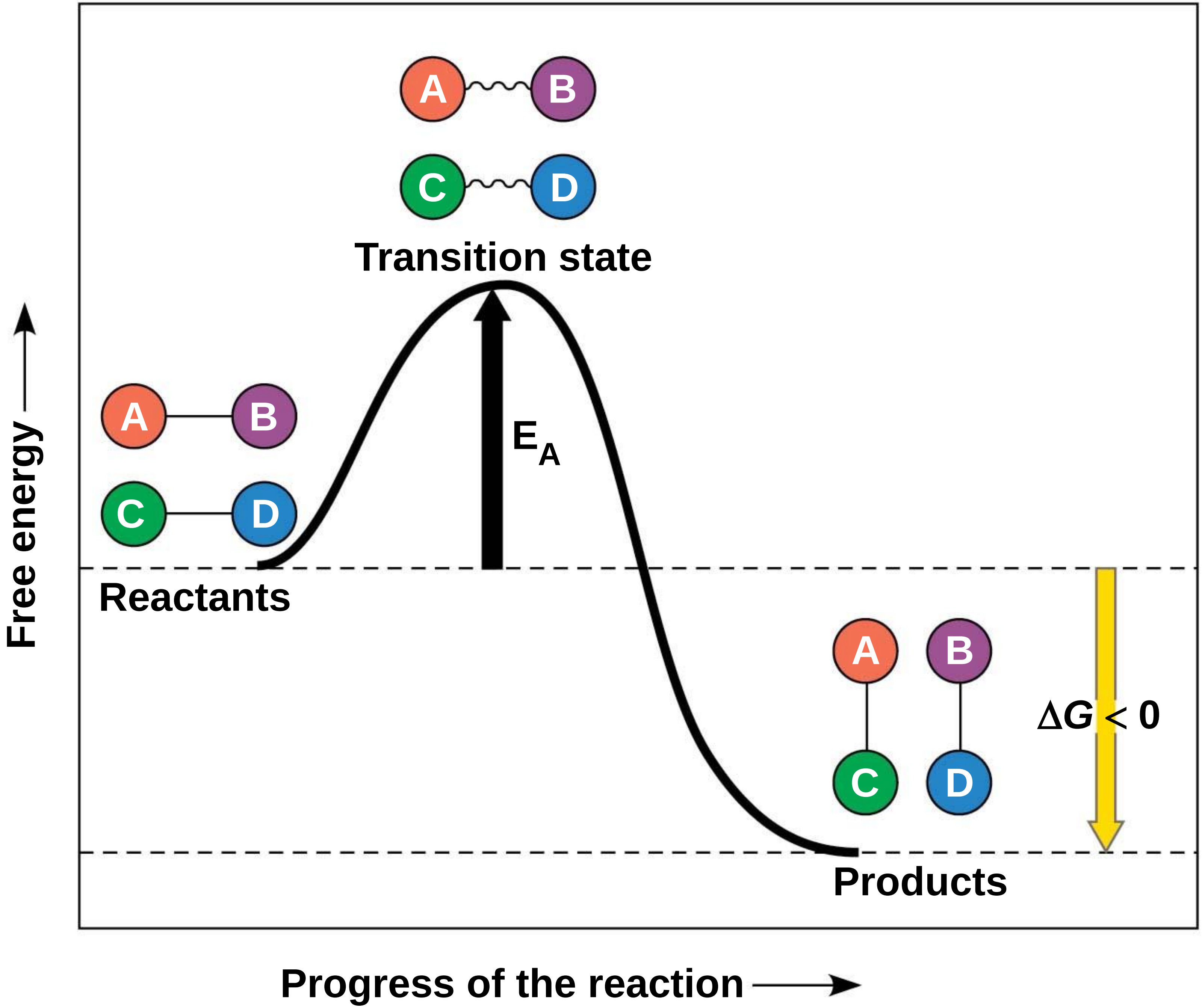
Figure 6.UN02



The Activation Energy Barrier

- Every chemical reaction between molecules involves bond breaking and bond forming
- The initial energy needed to start a chemical reaction is called the free energy of activation, or **activation energy** (E_A)
- Activation energy often occurs in the form of heat that reactant molecules absorb from the surroundings

Figure 6.12


A
B
C
D
Transition state
E A
A
B
C
D
Reactants
A
B
C
D
ΔG < 0
Products
Free energy
Progress of the reaction

How Enzymes Speed Up Reactions

- Instead of relying on heat, organisms carry out **catalysis** to speed up reactions
- A catalyst (for example, an enzyme) can speed up a reaction by lowering the E_A barrier without itself being consumed
- Enzymes do not affect the change in free energy (ΔG); instead, they hasten reactions that would occur eventually

Animation: How Enzymes Work

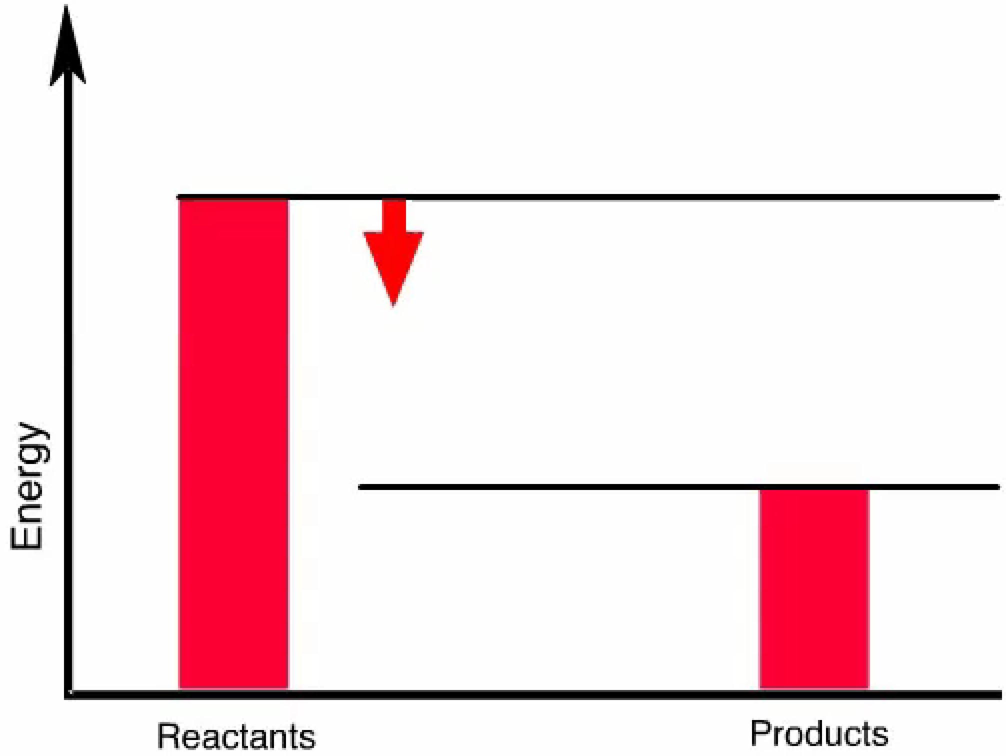
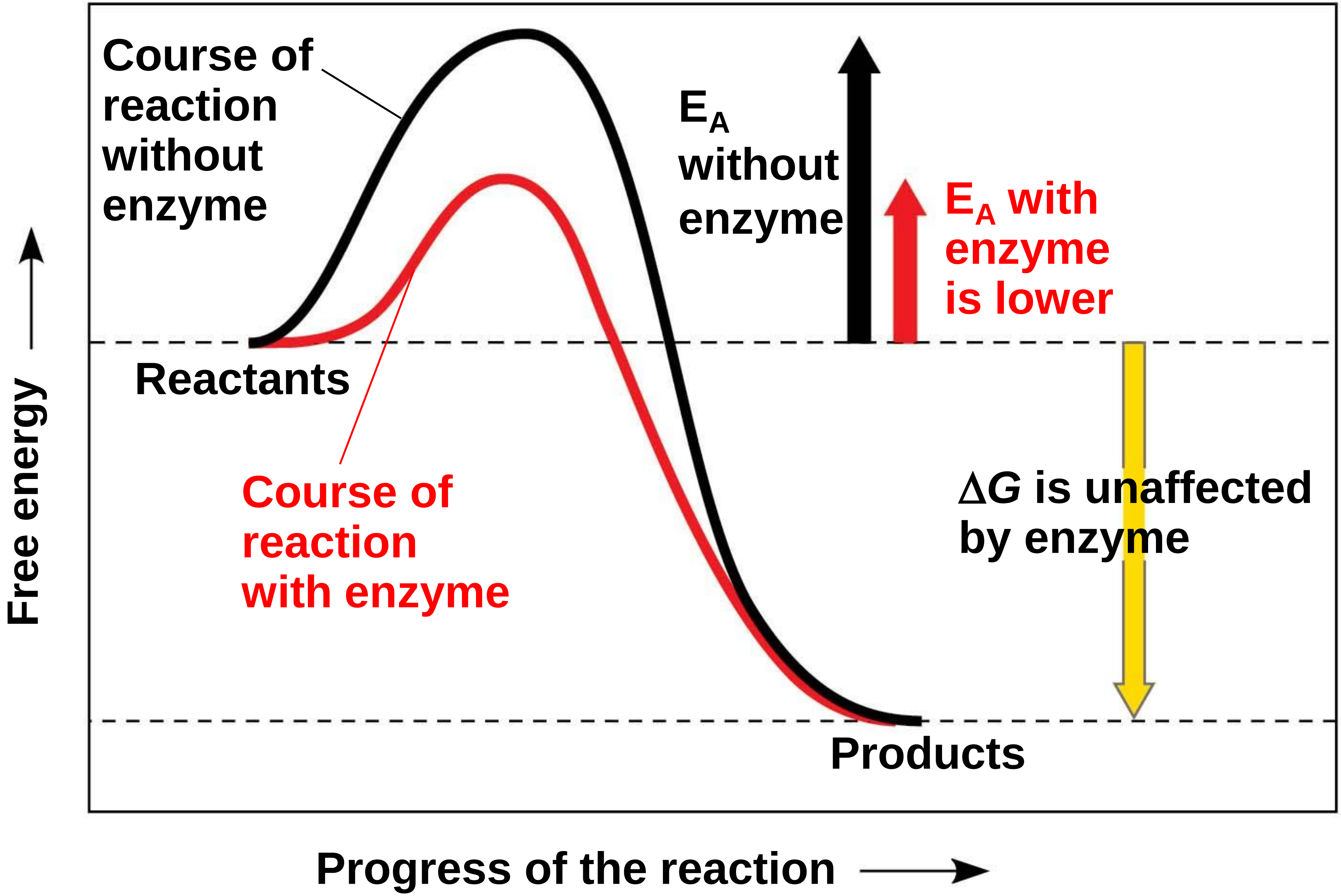


Figure 6.13



Course of reaction without enzyme
E$_A$ without enzyme
E$_A$ with enzyme is lower
Reactants
Course of reaction with enzyme
ΔG is unaffected by enzyme
Products
Free energy
Progress of the reaction

Substrate Specificity of Enzymes

- Enzymes are very specific for the reactions they catalyze
- The reactant that an enzyme acts on is called the enzyme's **substrate**
- The enzyme binds to its substrate, forming an **enzyme-substrate complex**
- The **active site** is the region on the enzyme where the substrate binds

- Enzyme specificity results from the complementary fit between the shape of the enzyme's active site and the shape of the substrate
- Enzymes change shape due to chemical interactions with the substrate
- This **induced fit** of the enzyme to the substrate brings chemical groups of the active site together

Video: Enzyme Induced Fit

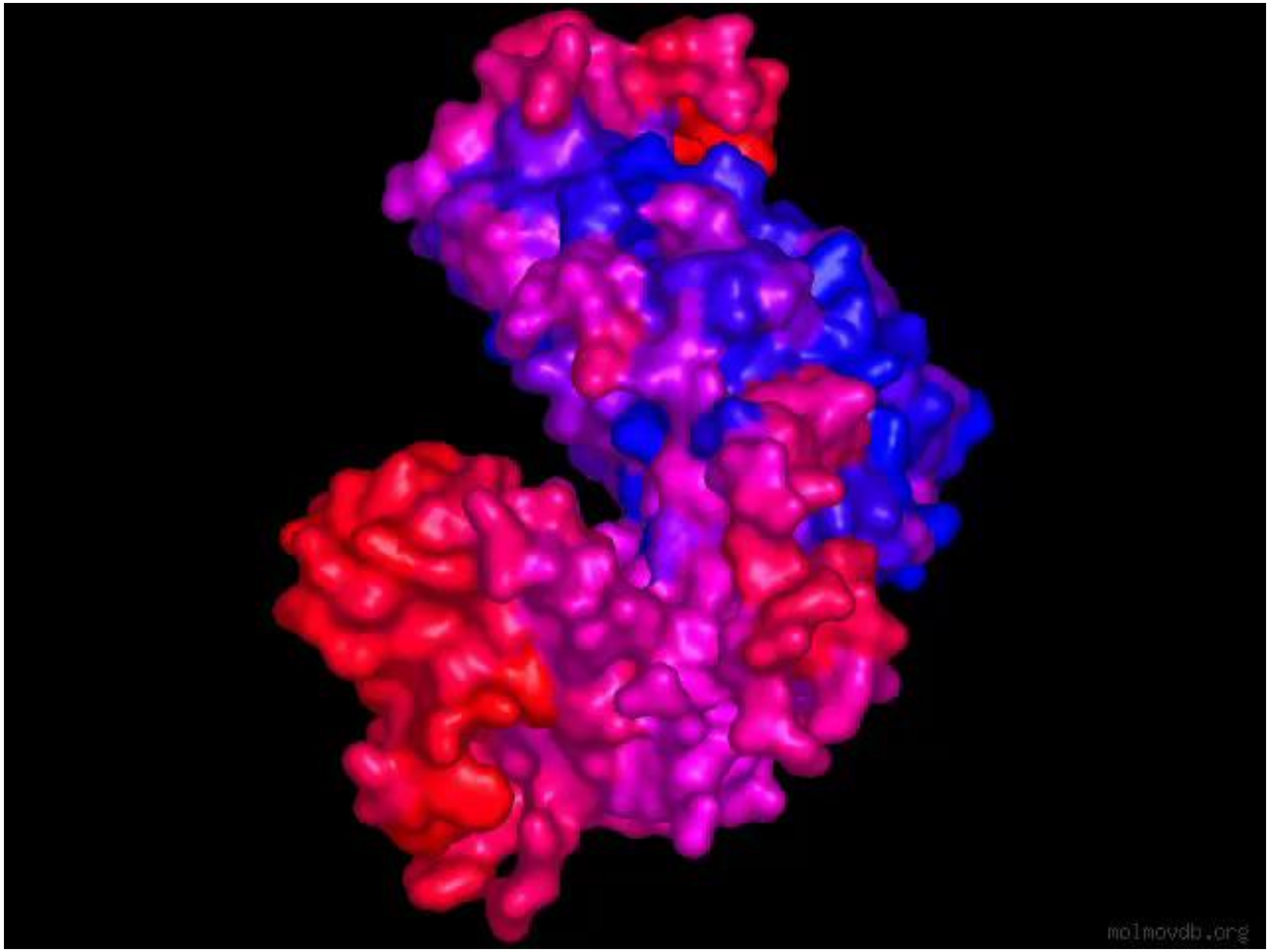
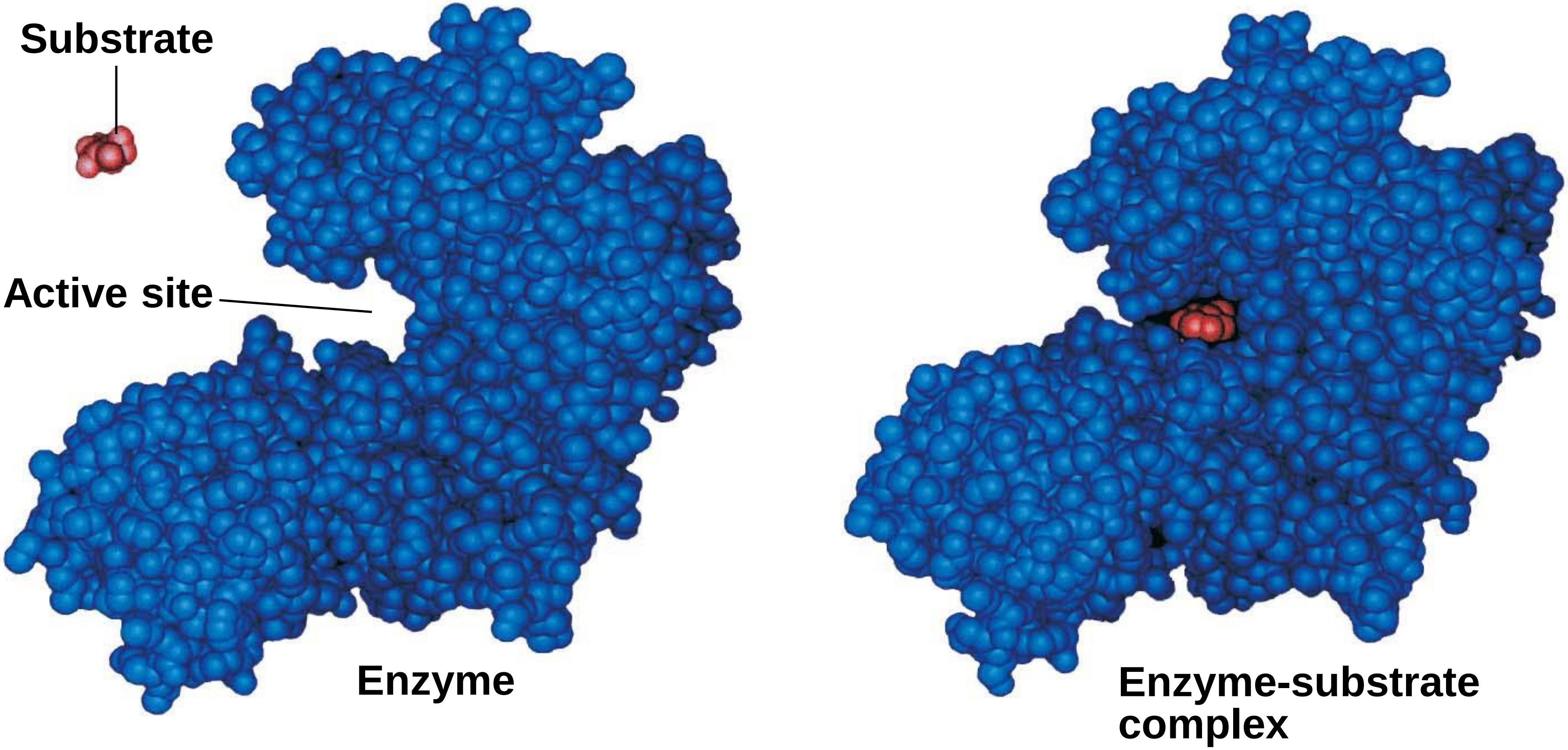


Figure 6.14



Catalysis in the Enzyme's Active Site

- In an enzymatic reaction, the substrate binds to the active site of the enzyme
- The active site can lower an E_A barrier by
  - Orienting substrates correctly
  - Straining substrate bonds
  - Providing a favorable microenvironment
  - Covalently bonding to the substrate

Figure 6.15-s1

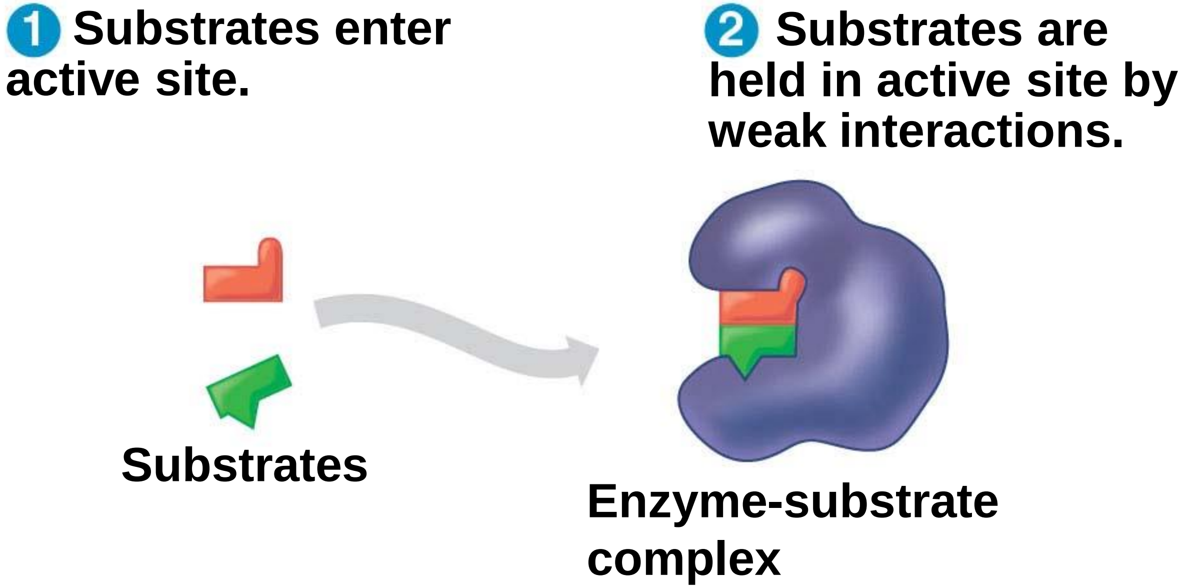
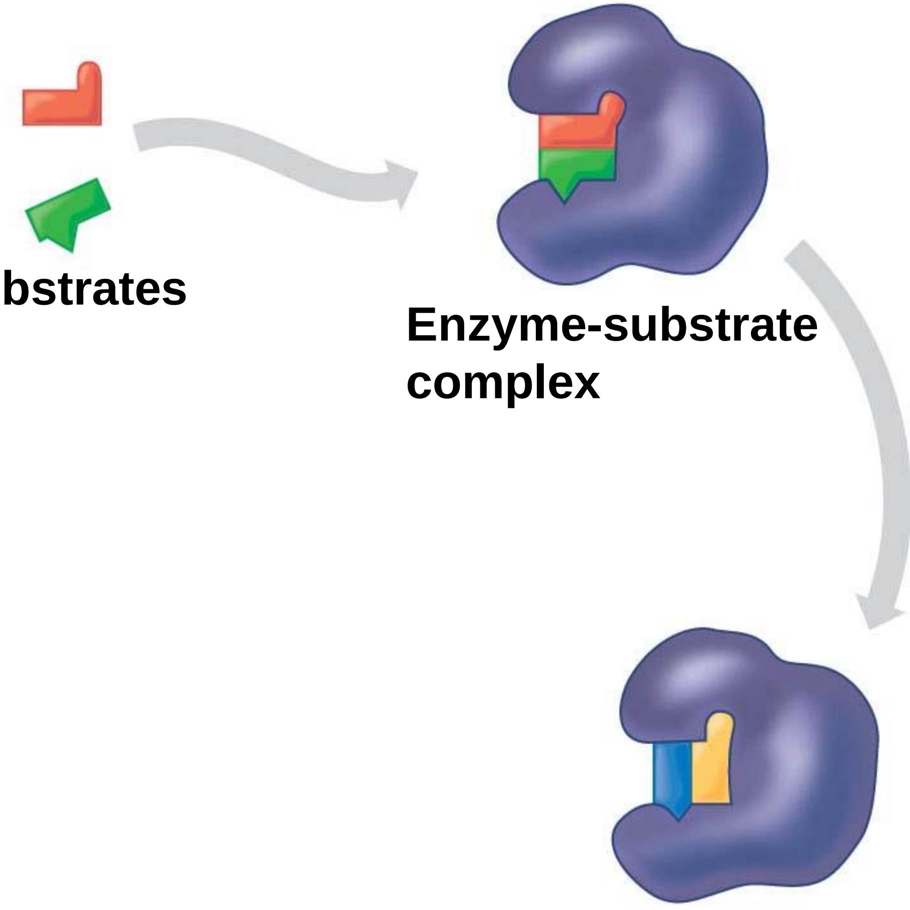


Figure 6.15-s2

1 **Substrates enter active site.**

2 **Substrates are held in active site by weak interactions.**



3 **Substrates are converted to products.**

Figure 6.15-s3

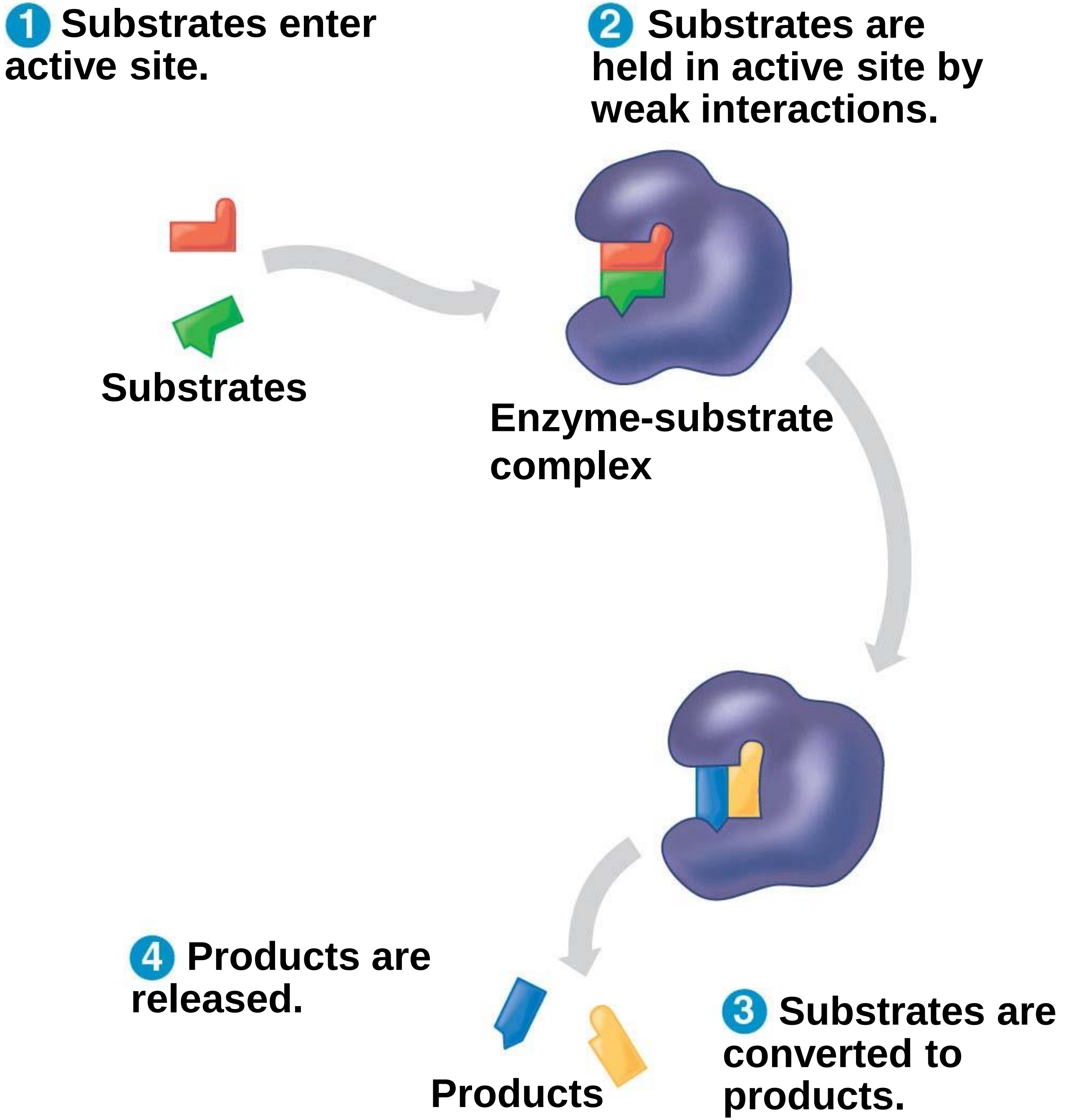
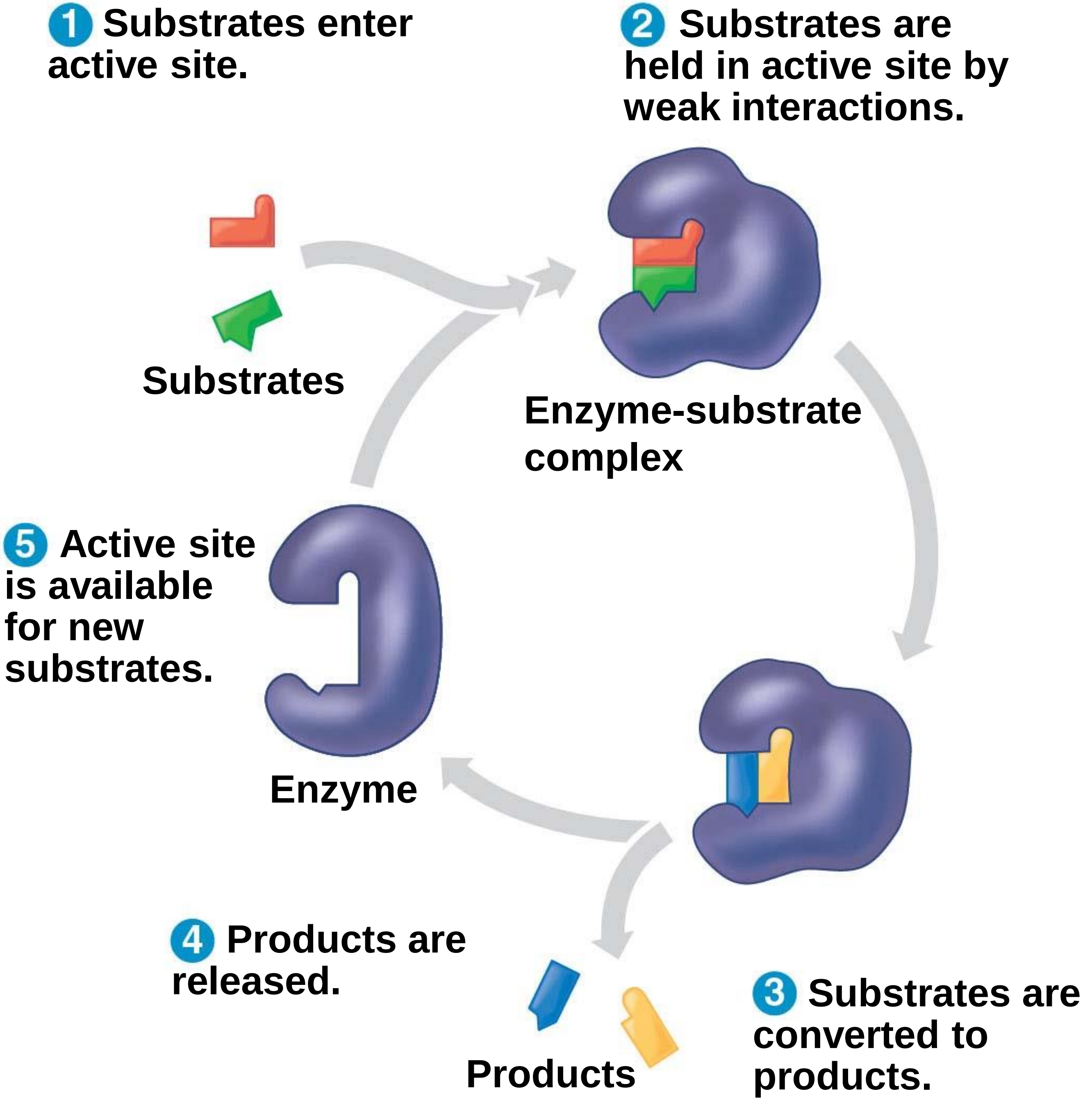


Figure 6.15-s4



- The rate of enzyme catalysis can usually be sped up by increasing the substrate concentration in a solution
- When all enzyme molecules in a solution are bonded with substrate, the enzyme is saturated
- At enzyme saturation, reaction speed can only be increased by adding more enzyme

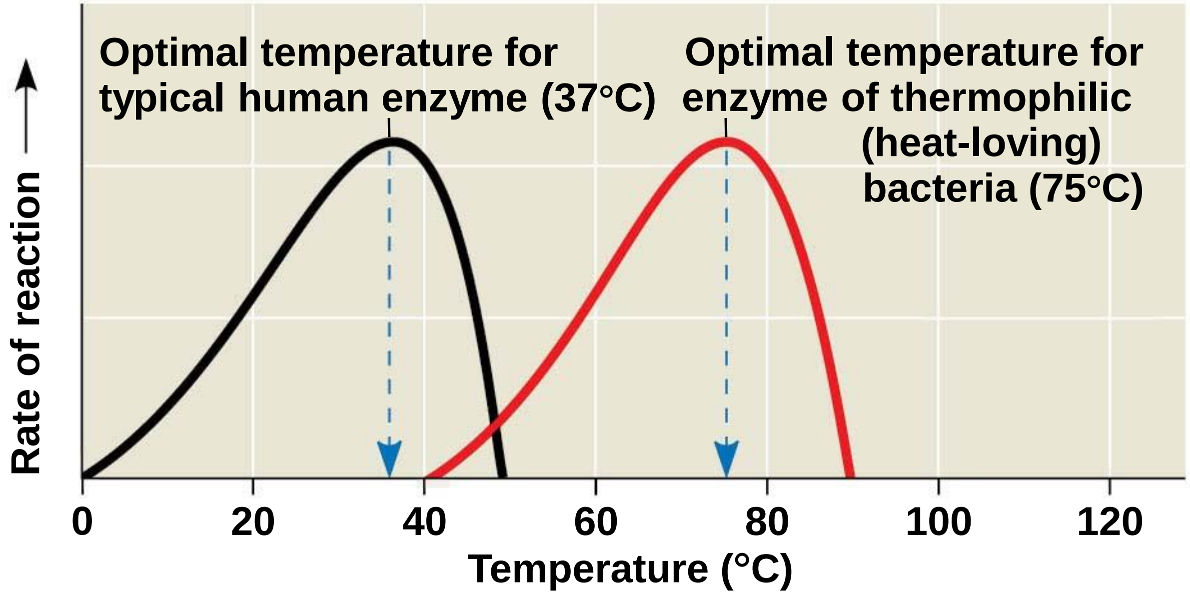
Effects of Local Conditions on Enzyme Activity

- An enzyme's activity can be affected by
  - General environmental factors, such as temperature and pH
  - Chemicals that specifically influence the enzyme

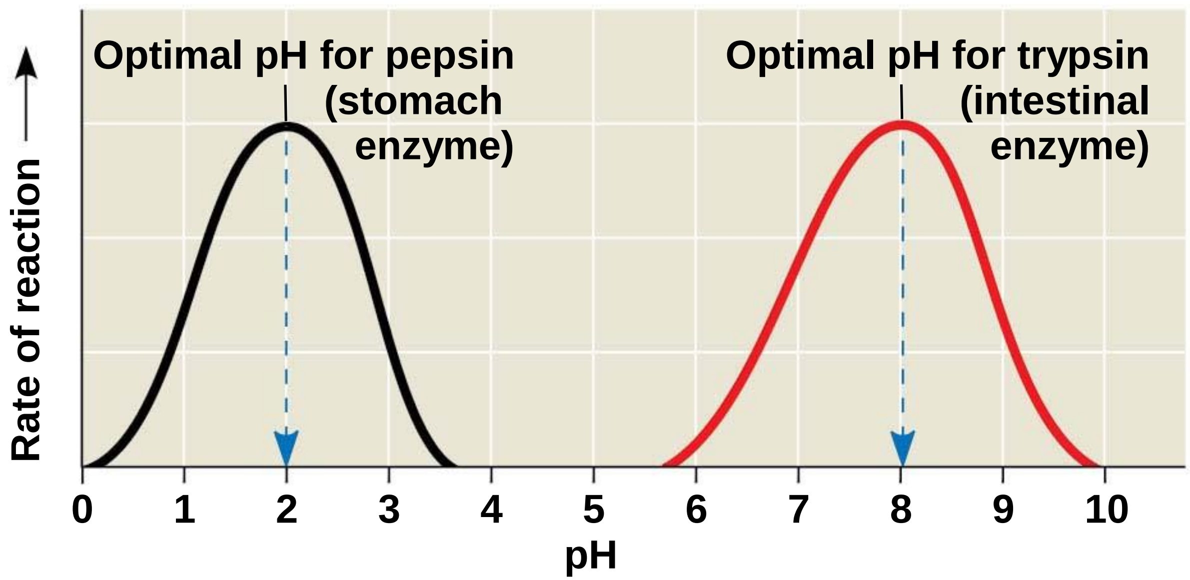
Effects of Temperature and pH

- Each enzyme has an optimal temperature and pH at which its reaction rate is the greatest

Figure 6.16

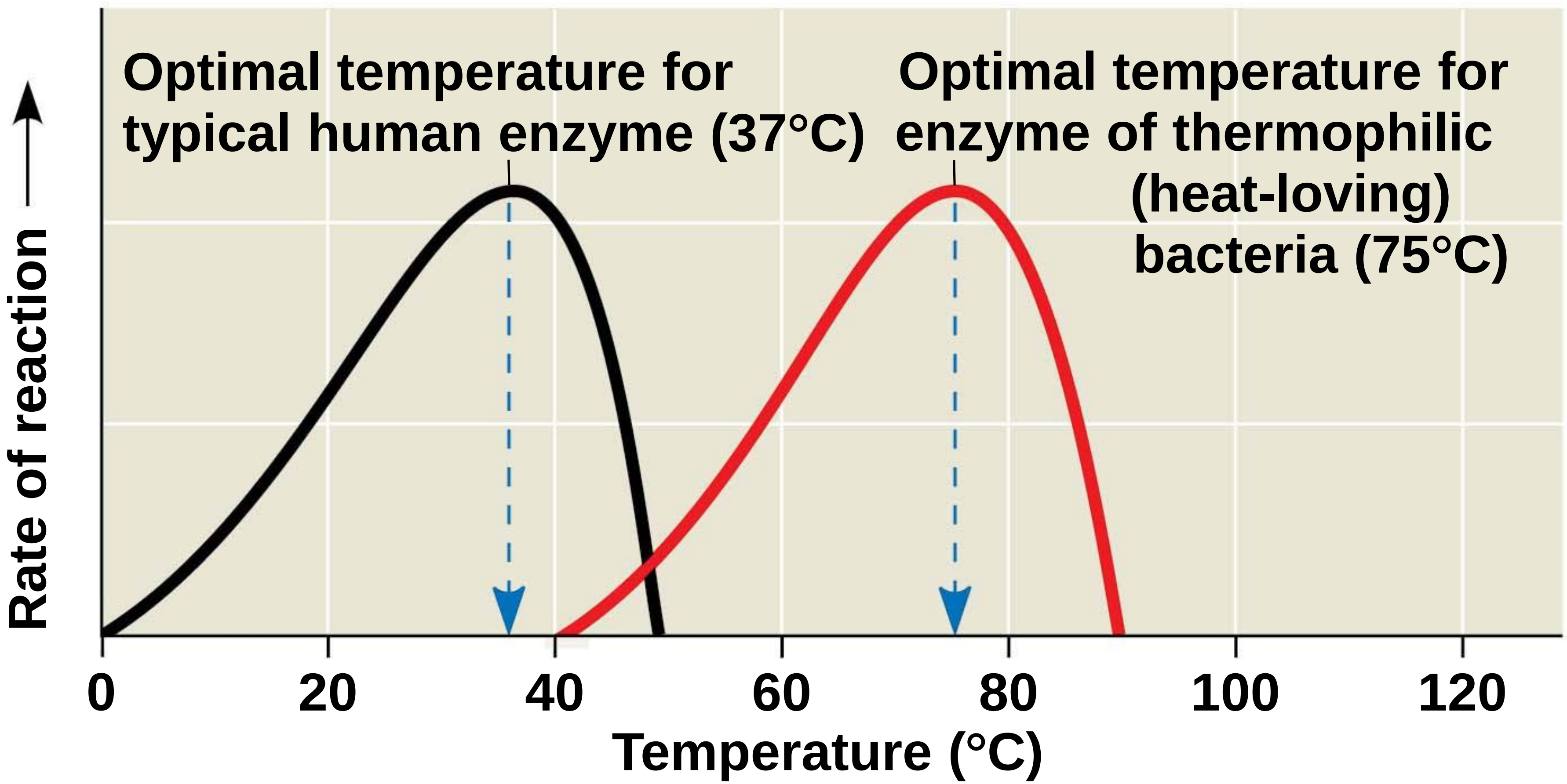


(a) Optimal temperature for two enzymes



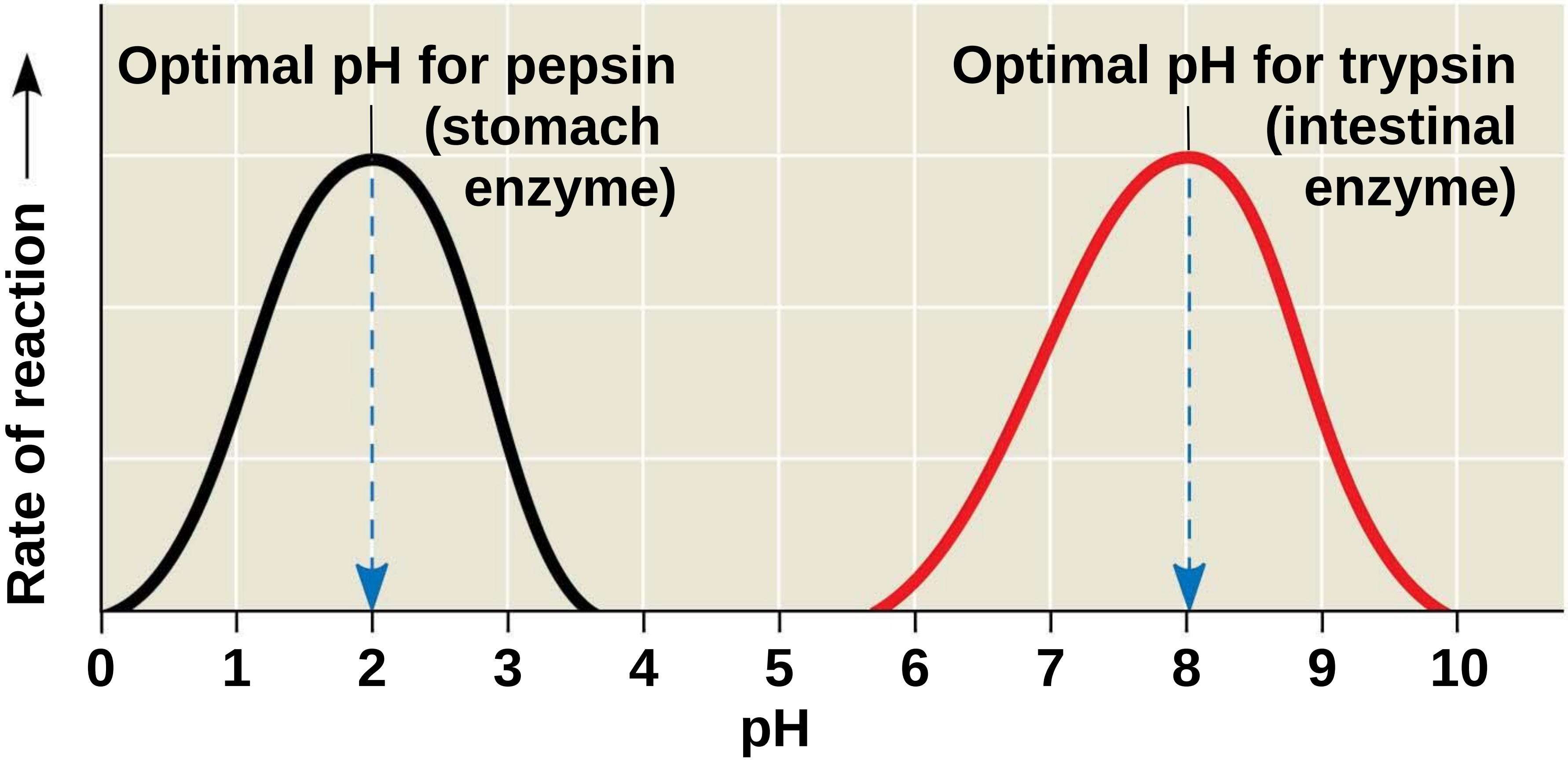
(b) Optimal pH for two enzymes

Figure 6.16-1



(a) Optimal temperature for two enzymes

Figure 6.16-2



(b) Optimal pH for two enzymes

Figure 6.16-3

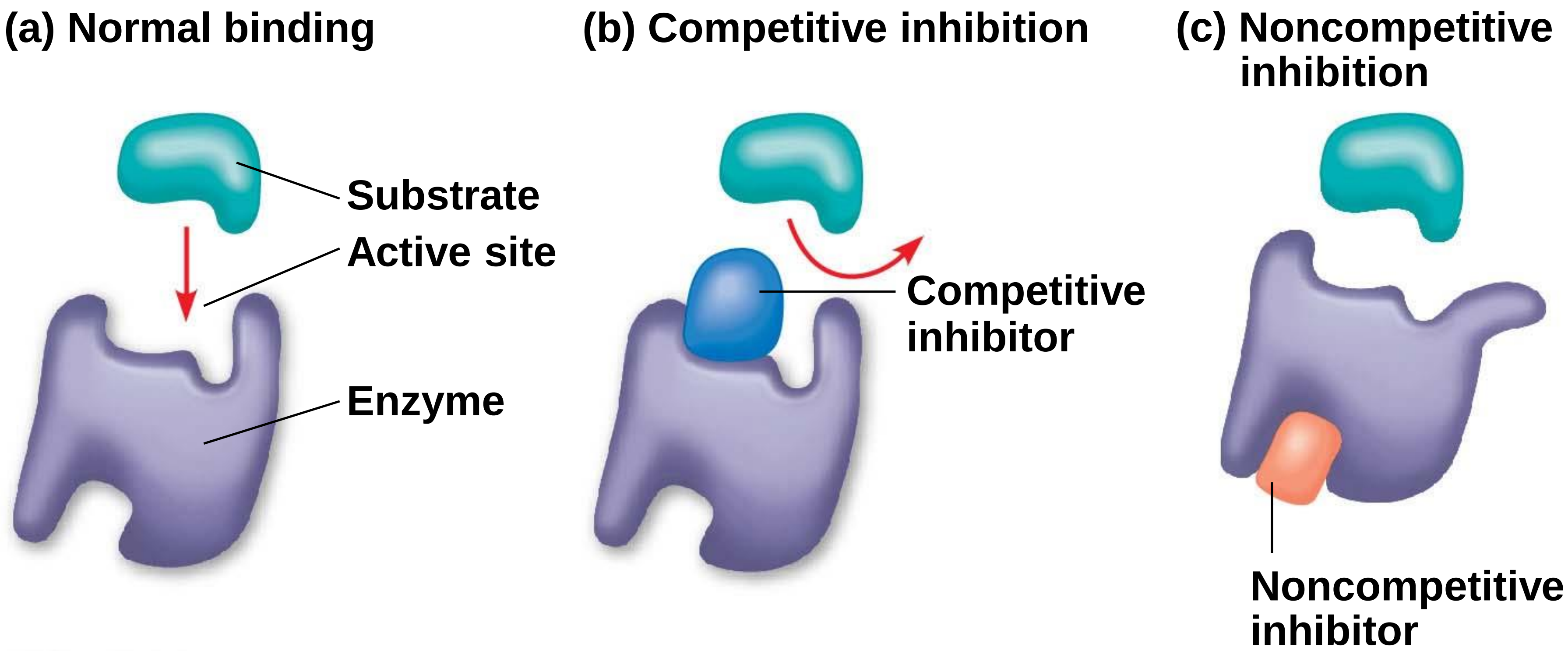
Cofactors

- **Cofactors** are nonprotein enzyme helpers
- Cofactors may be inorganic (such as a metal in ionic form) or organic
- An organic cofactor is called a **coenzyme**
- Most vitamins act as coenzymes or as the raw materials from which coenzymes are made

Enzyme Inhibitors

- **Competitive inhibitors** bind to the active site of an enzyme, competing with the substrate
- **Noncompetitive inhibitors** bind to another part of an enzyme, causing the enzyme to change shape and making the active site less effective
- Examples of inhibitors include toxins, poisons, pesticides, and antibiotics

Figure 6.17


(a) Normal binding
Substrate
Active site
Enzyme
(b) Competitive inhibition
Competitive inhibitor
(c) Noncompetitive inhibition
Noncompetitive inhibitor

The Evolution of Enzymes

- Most enzymes are proteins encoded by genes
- Changes (mutations) in genes lead to changes in amino acid composition of an enzyme
- Altered amino acids in enzymes may alter their activity or substrate specificity
- Under new environmental conditions a novel form of an enzyme might be favored

Concept 6.5: Regulation of enzyme activity helps control metabolism

- Chemical chaos would result if a cell's metabolic pathways were not tightly regulated
- A cell does this by switching on or off the genes that encode specific enzymes or by regulating the activity of enzymes

Allosteric Regulation of Enzymes

- **Allosteric regulation** may either inhibit or stimulate an enzyme's activity
- Allosteric regulation occurs when a regulatory molecule binds to a protein at one site and affects the protein's function at another site

Allosteric Activation and Inhibition

- Most allosterically regulated enzymes are made from polypeptide subunits
- Each enzyme has active and inactive forms
- The binding of an activator stabilizes the active form of the enzyme
- The binding of an inhibitor stabilizes the inactive form of the enzyme

Figure 6.18

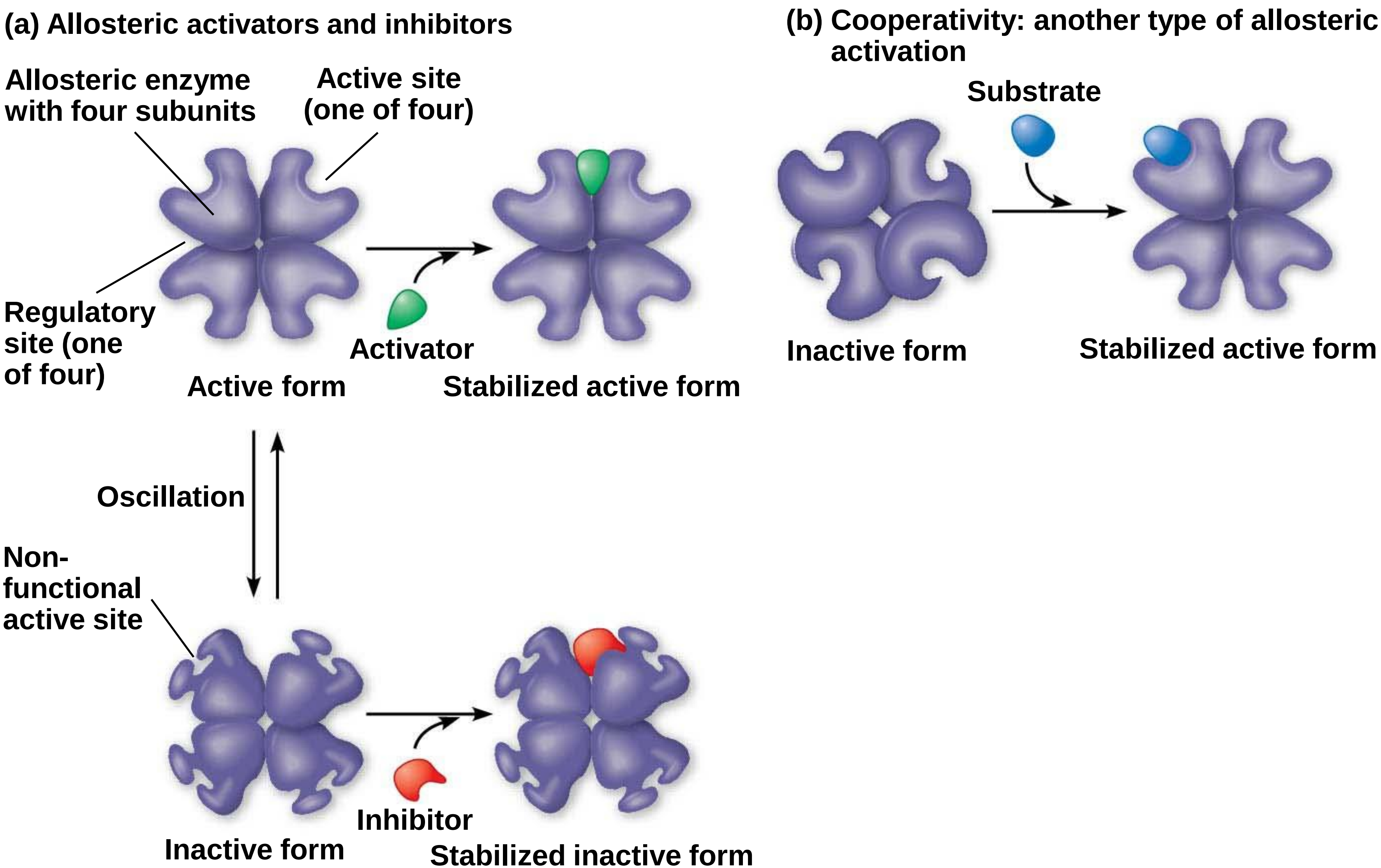
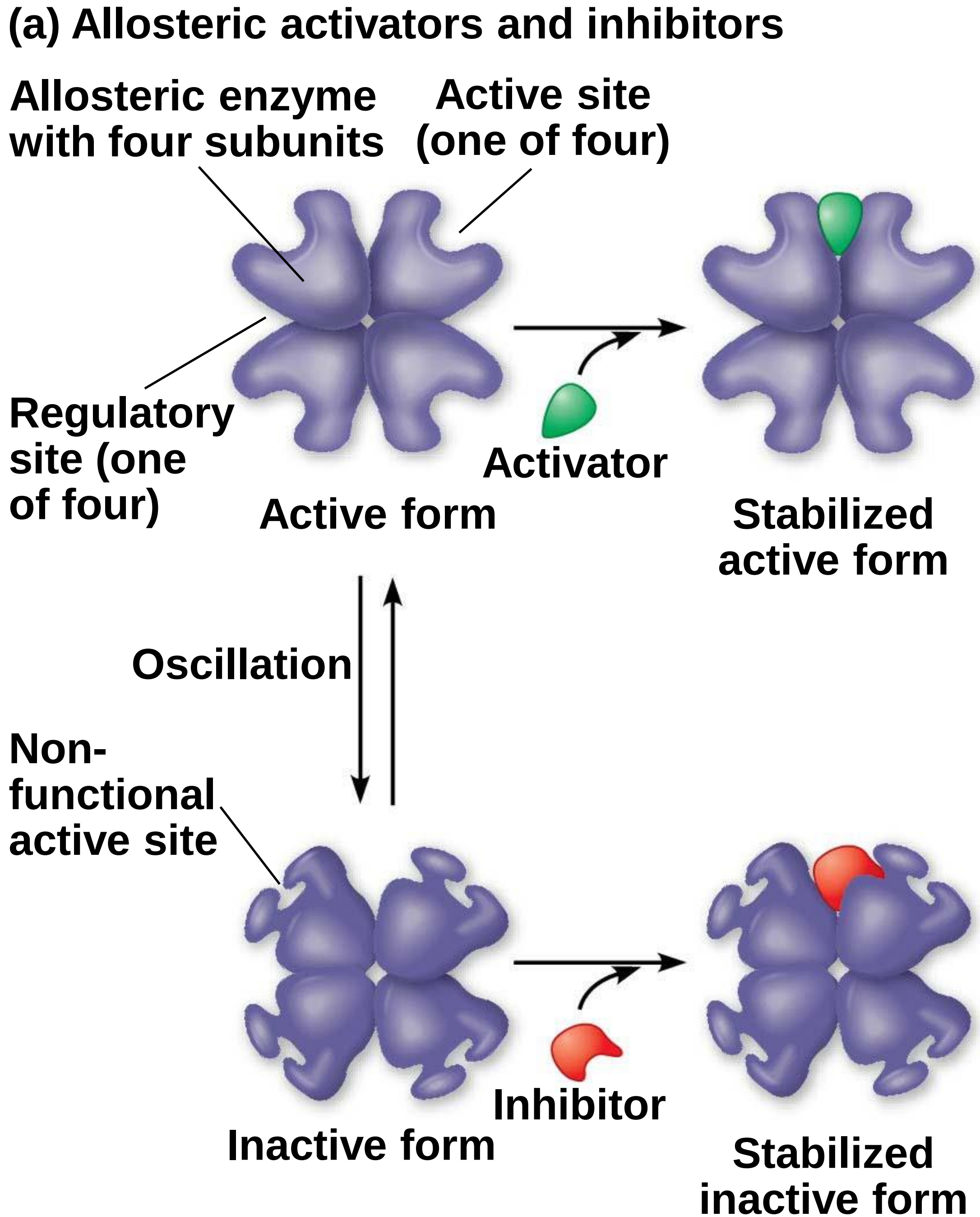
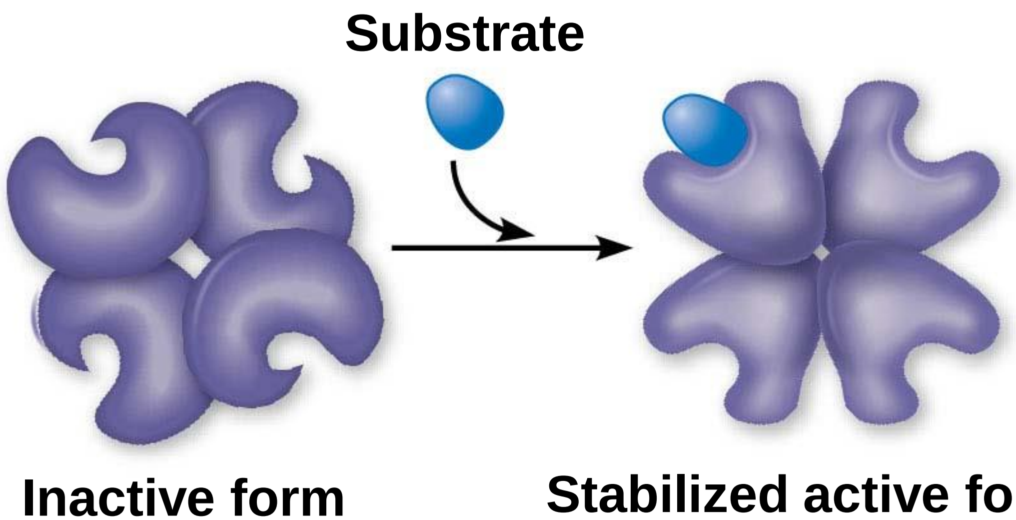

(a) Allosteric activators and inhibitors
Allosteric enzyme with four subunits
Active site (one of four)
Regulatory site (one of four)
Active form
Activator
Stabilized active form
Oscillation
Non-functional active site
Inactive form
Inhibitor
Stabilized inactive form
(b) Cooperativity: another type of allosteric activation
Substrate
Inactive form
Stabilized active form

Figure 6.18-1


(a) Allosteric activators and inhibitors
Allosteric enzyme with four subunits
Active site (one of four)
Regulatory site (one of four)
Activator
Active form
Stabilized active form
Oscillation
Non-functional active site
Inhibitor
Inactive form
Stabilized inactive form

- **Cooperativity** is a form of allosteric regulation that can amplify enzyme activity
- One substrate molecule primes an enzyme to act on additional substrate molecules more readily
- Cooperativity is allosteric because binding by a substrate to one active site affects catalysis in a different active site

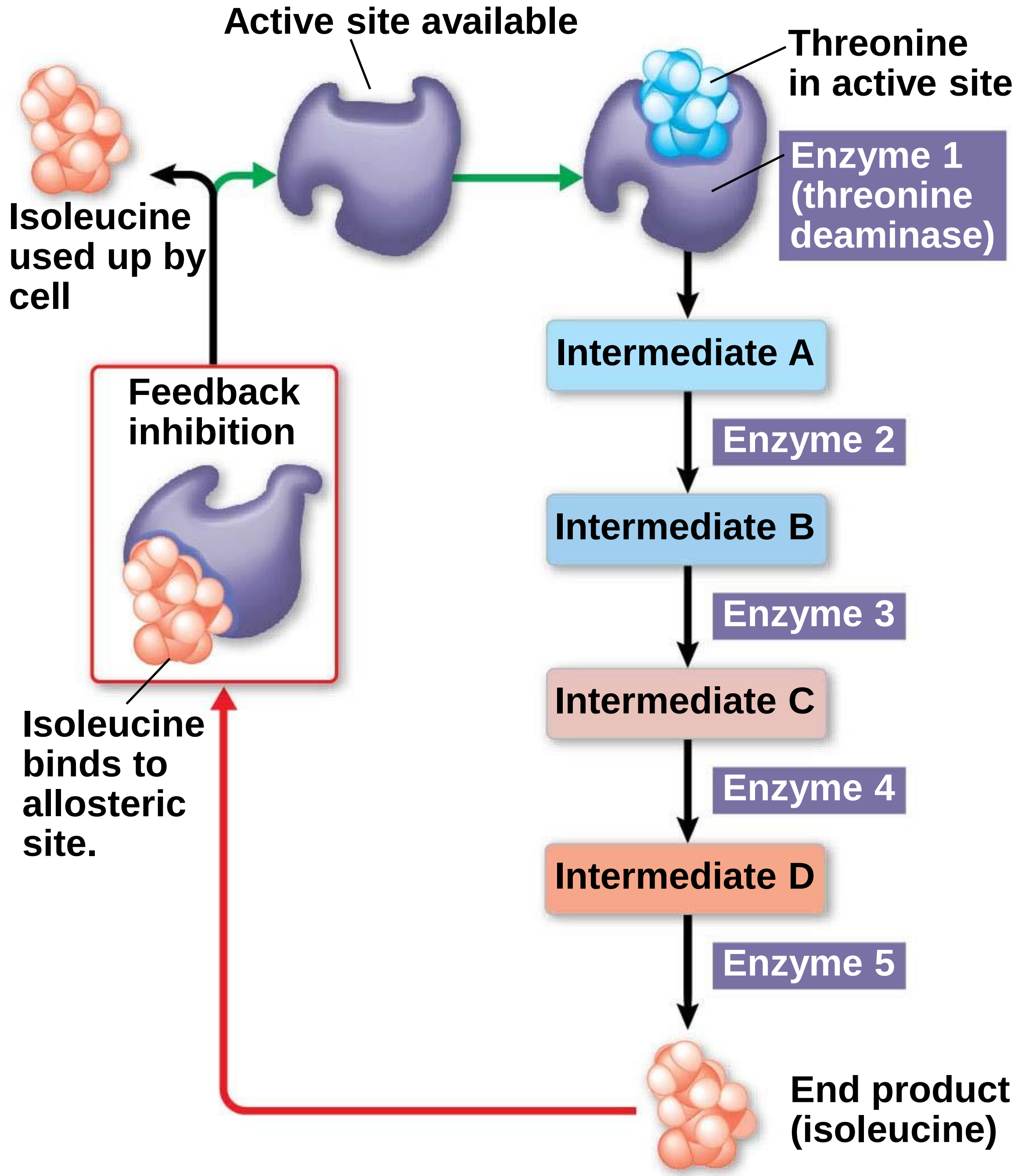
(b) Cooperativity: another type of allosteric activation



Feedback Inhibition

- In **feedback inhibition**, the end product of a metabolic pathway shuts down the pathway
- Feedback inhibition prevents a cell from wasting chemical resources by synthesizing more product than is needed

Figure 6.19

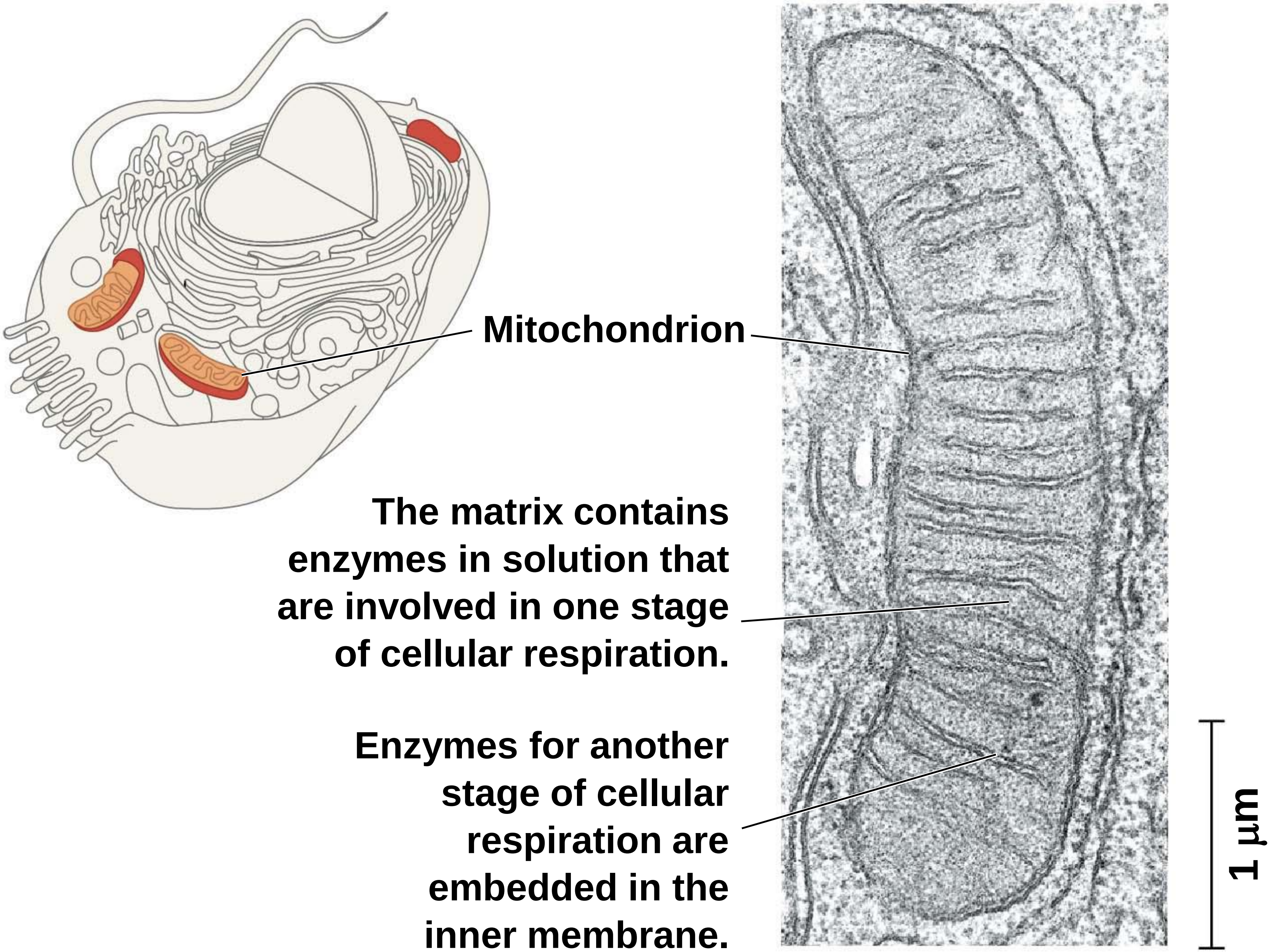


Active site available
Threonine in active site
Enzyme 1 (threonine deaminase)
Isoleucine used up by cell
Intermediate A
Enzyme 2
Feedback inhibition
Intermediate B
Enzyme 3
Isoleucine binds to allosteric site.
Intermediate C
Enzyme 4
Intermediate D
Enzyme 5
End product (isoleucine)

Organization of Enzymes Within the Cell

- Structures within the cell help bring order to metabolic pathways
- Some enzymes act as structural components of membranes
- In eukaryotic cells, some enzymes reside in specific organelles; for example, enzymes for cellular respiration are located in mitochondria

Figure 6.20



Mitochondrion
The matrix contains enzymes in solution that are involved in one stage of cellular respiration.
Enzymes for another stage of cellular respiration are embedded in the inner membrane.
1 µm

Mitochondrion

The matrix contains enzymes in solution that are involved in one stage of cellular respiration.

Enzymes for another stage of cellular respiration are embedded in the inner membrane.

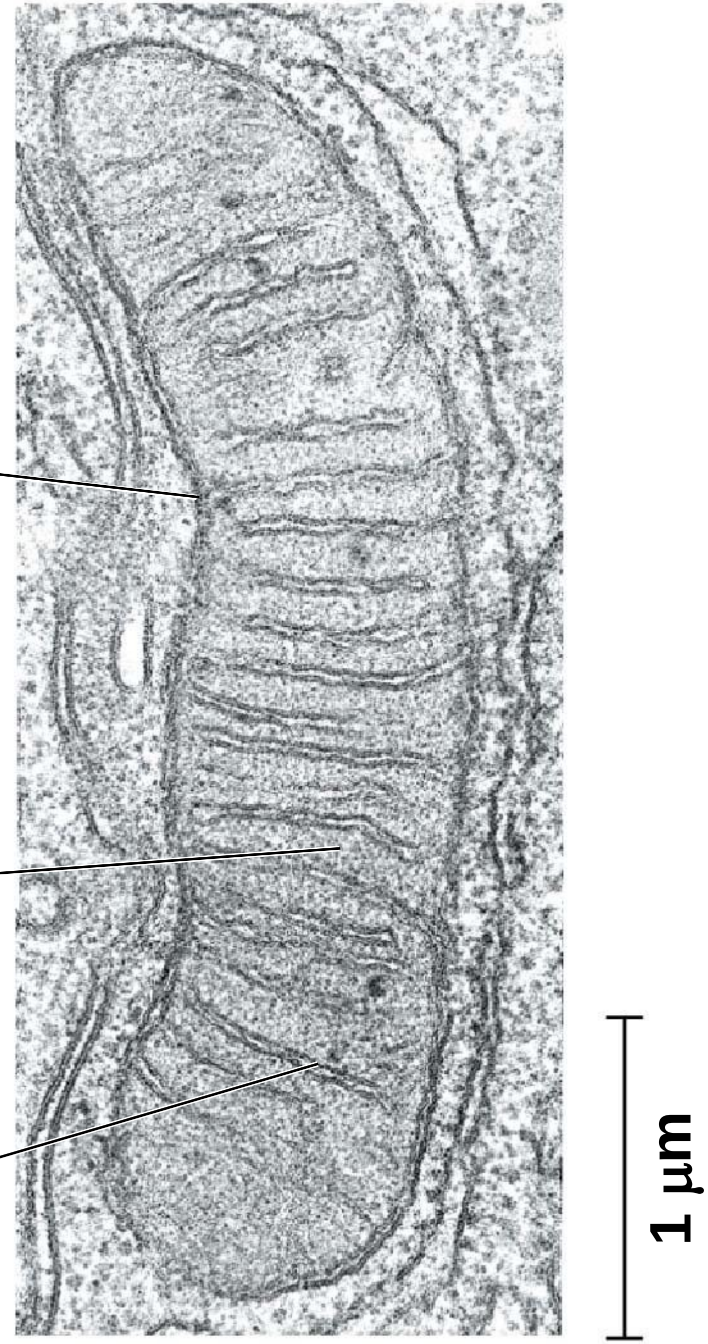


Figure 6.UN03a

Time (min)	Concentration of Ⓟ$_i$ (μmol/mL)
0	0
5	10
10	90
15	180
20	270
25	330
30	355
35	355
40	355

Data from S. R. Commerford et al., Diets enriched in sucrose or fat increase gluconeogenesis and G-6-Pase but not basal glucose production in rats, *American Journal of Physiology—Endocrinology and Metabolism* 283:E545–E555 (2002).

Figure 6.UN03b

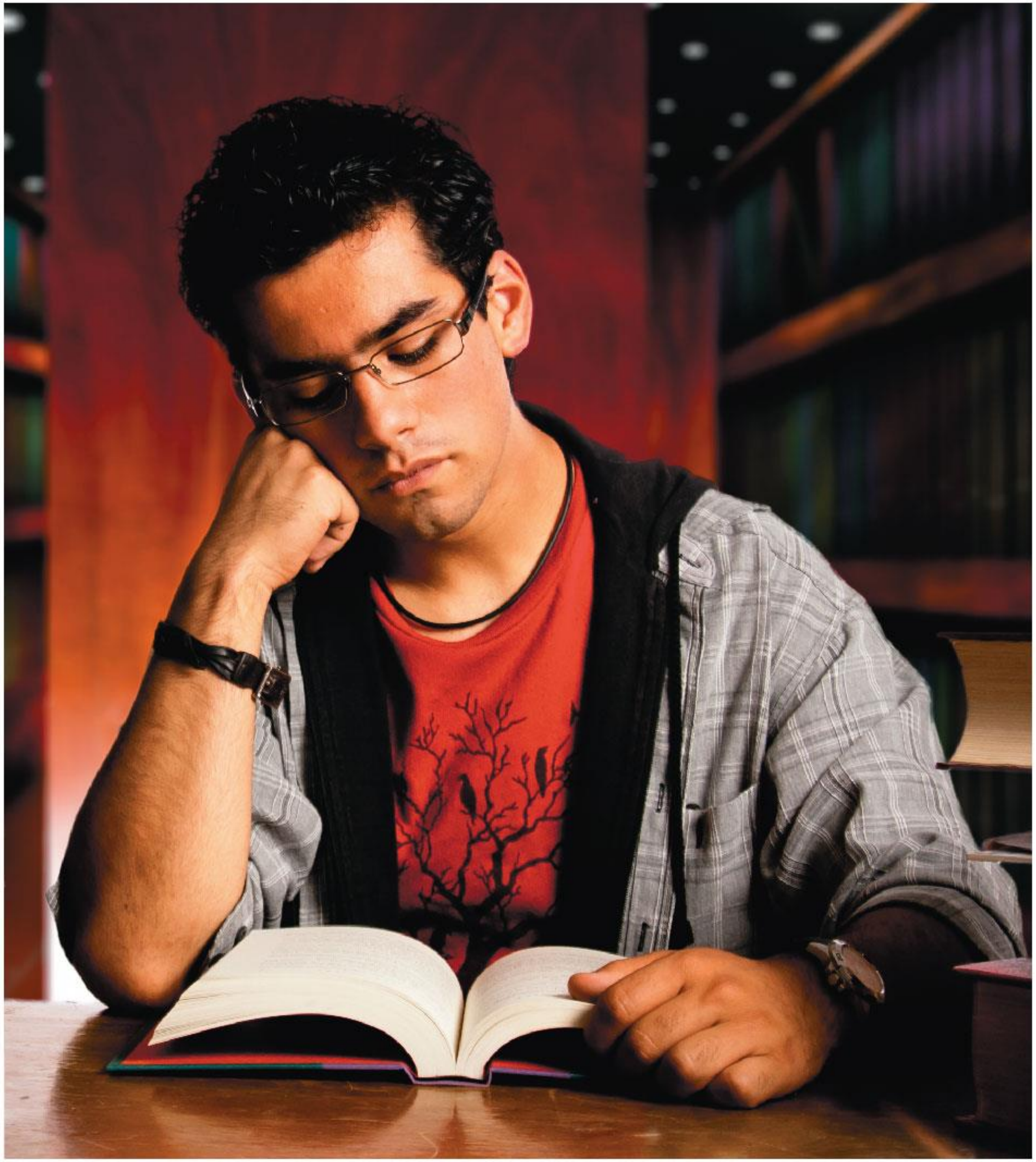


Figure 6.UN04

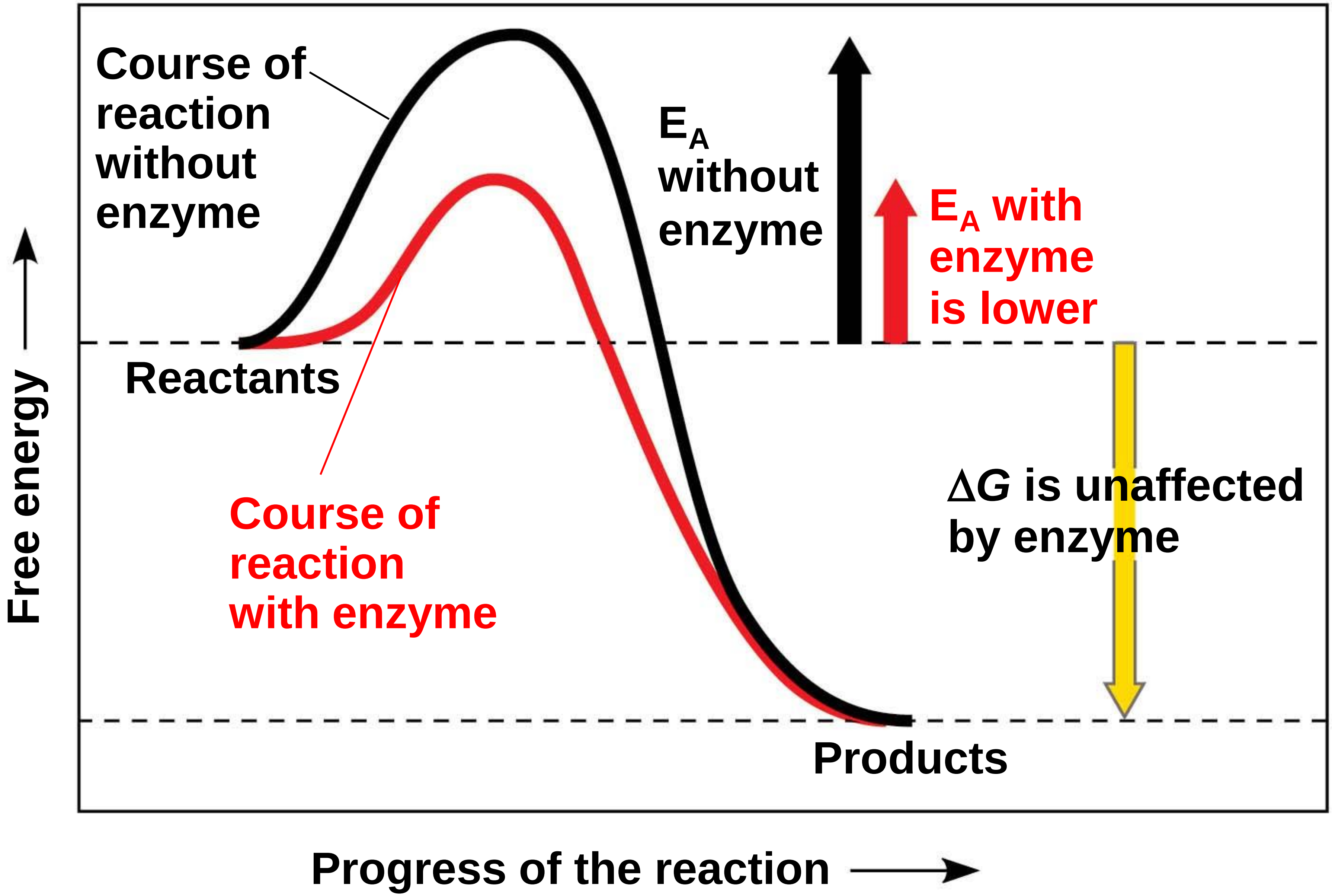


Figure 6.UN05