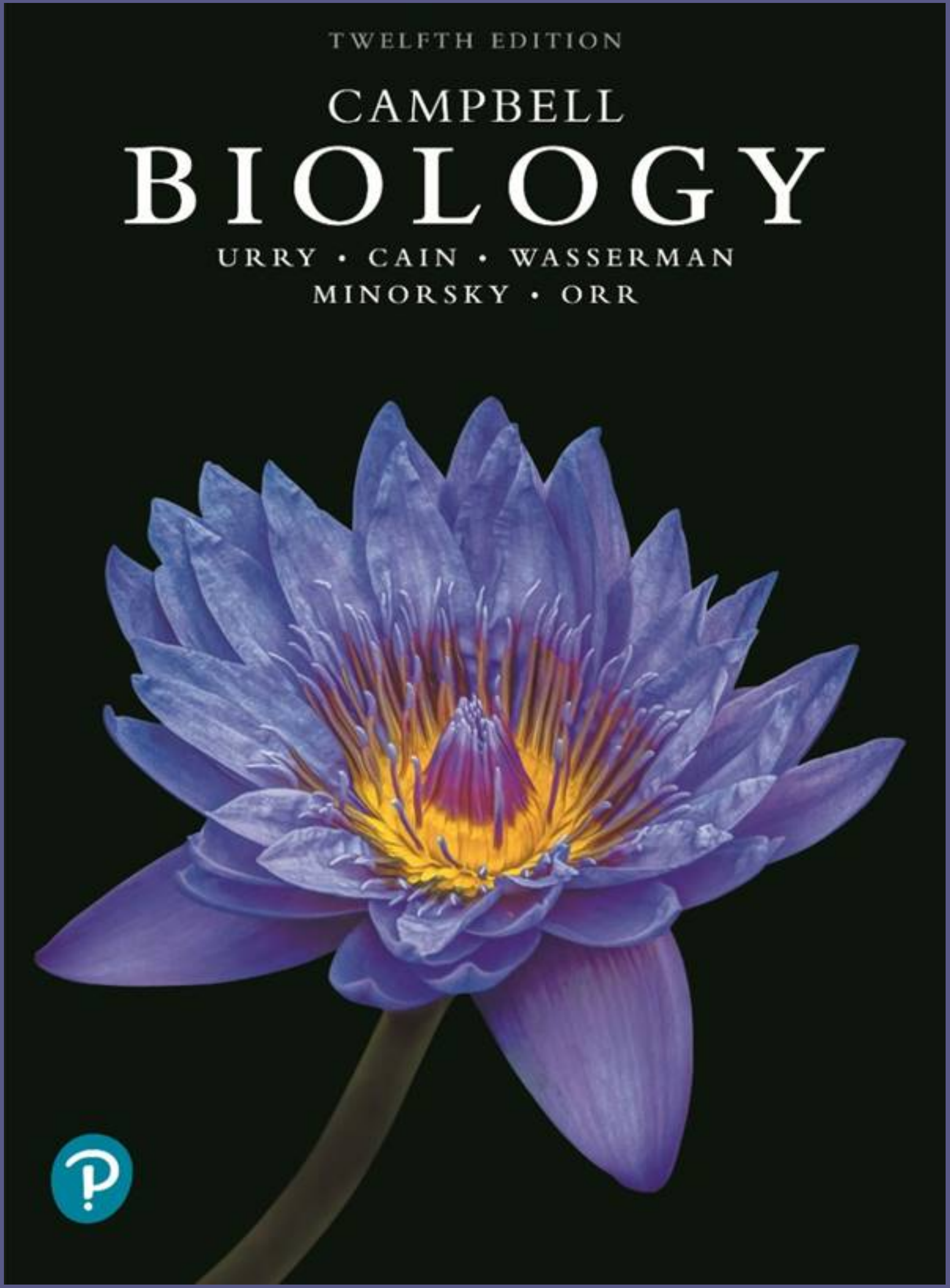


Chapter 8

An Introduction to Metabolism

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

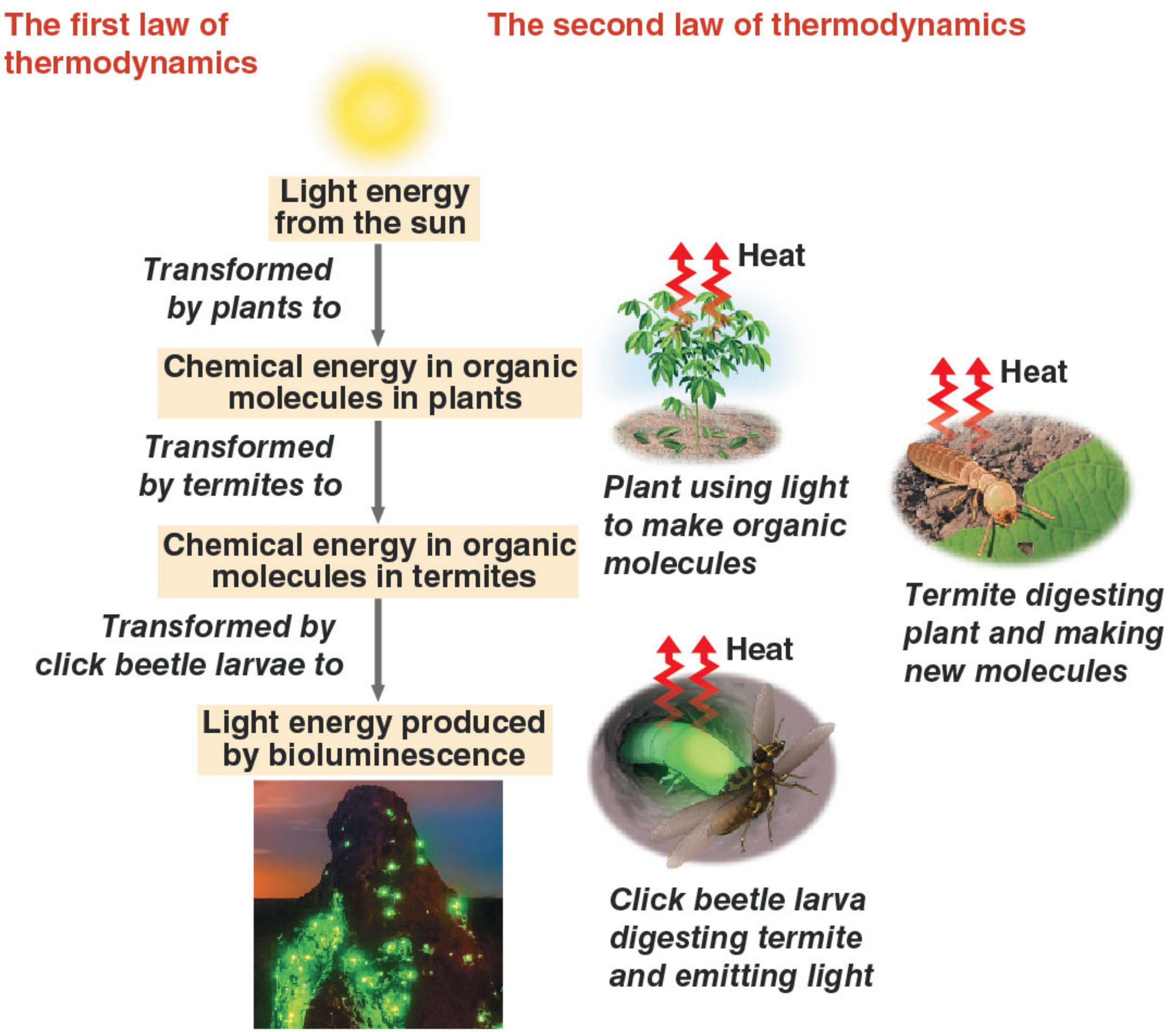
Figure 8.1a

How do the laws of thermodynamics relate to biological processes?

- Energy use by living things demonstrates the first law of thermodynamics
  - Energy can be transferred or transformed, but not created or destroyed
- The conversion of energy to thermal energy released as heat by living things demonstrates the second law of thermodynamics
  - Every energy transfer or transformation increases the entropy (disorder) of the universe

Figure 8.1b

How do the laws of thermodynamics relate to biological processes?



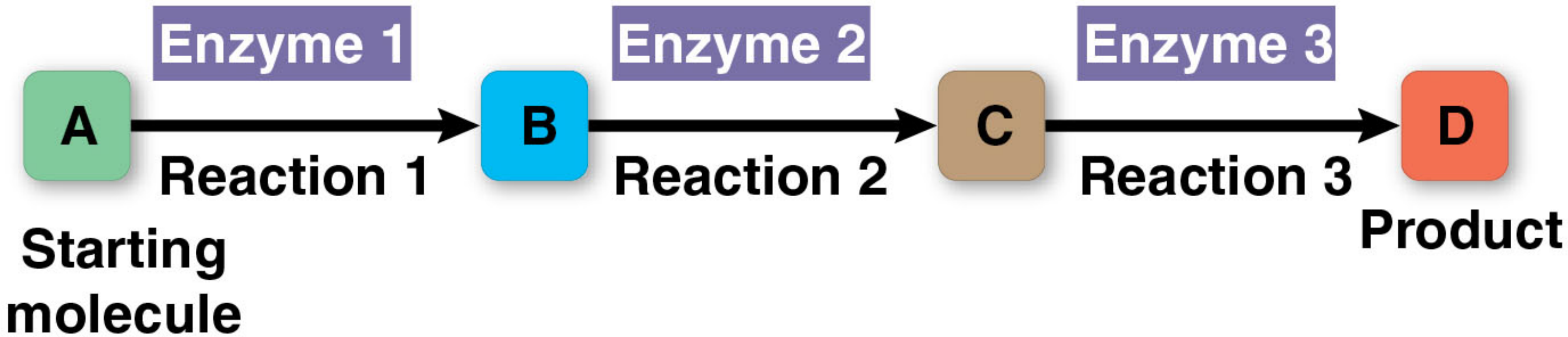
CONCEPT 8.1: An organism's metabolism transforms matter and energy

- **Metabolism** is the totality of an organism's chemical reactions
- It is an emergent property of life that arises from orderly interactions between molecules

Metabolic Pathways

- In a **metabolic pathway**, a specific molecule is altered in a series of steps to produce a product
- Each step is catalyzed by a specific enzyme, a macromolecule that speeds up a specific reaction

Figure 8.UN01



- **Catabolic pathways** release energy by breaking down complex molecules into simpler compounds
- Cellular respiration, the breakdown of glucose in the presence of O_2, is an example of a pathway of catabolism

- **Anabolic pathways** consume energy to build complex molecules from simpler ones
  - For example, the synthesis of protein from amino acids is an anabolic pathway

- Catabolic pathways are described as “downhill” reactions, whereas anabolic pathways are “uphill”
- Living things use energy released from the downhill reactions of catabolic pathways to power the uphill reactions of anabolic pathways
- **Bioenergetics** is the study of how energy flows through living organisms

Forms of Energy

- **Energy**, the capacity to cause change, can be used to do work—move matter against opposing forces, such as gravity and friction
- Energy exists in various forms
- Living cells must transform energy from one form to another to do the work of life

- **Kinetic energy** is energy associated with motion
- Moving objects perform work by imparting motion to other matter
  - For example, water gushing through a dam turns turbines

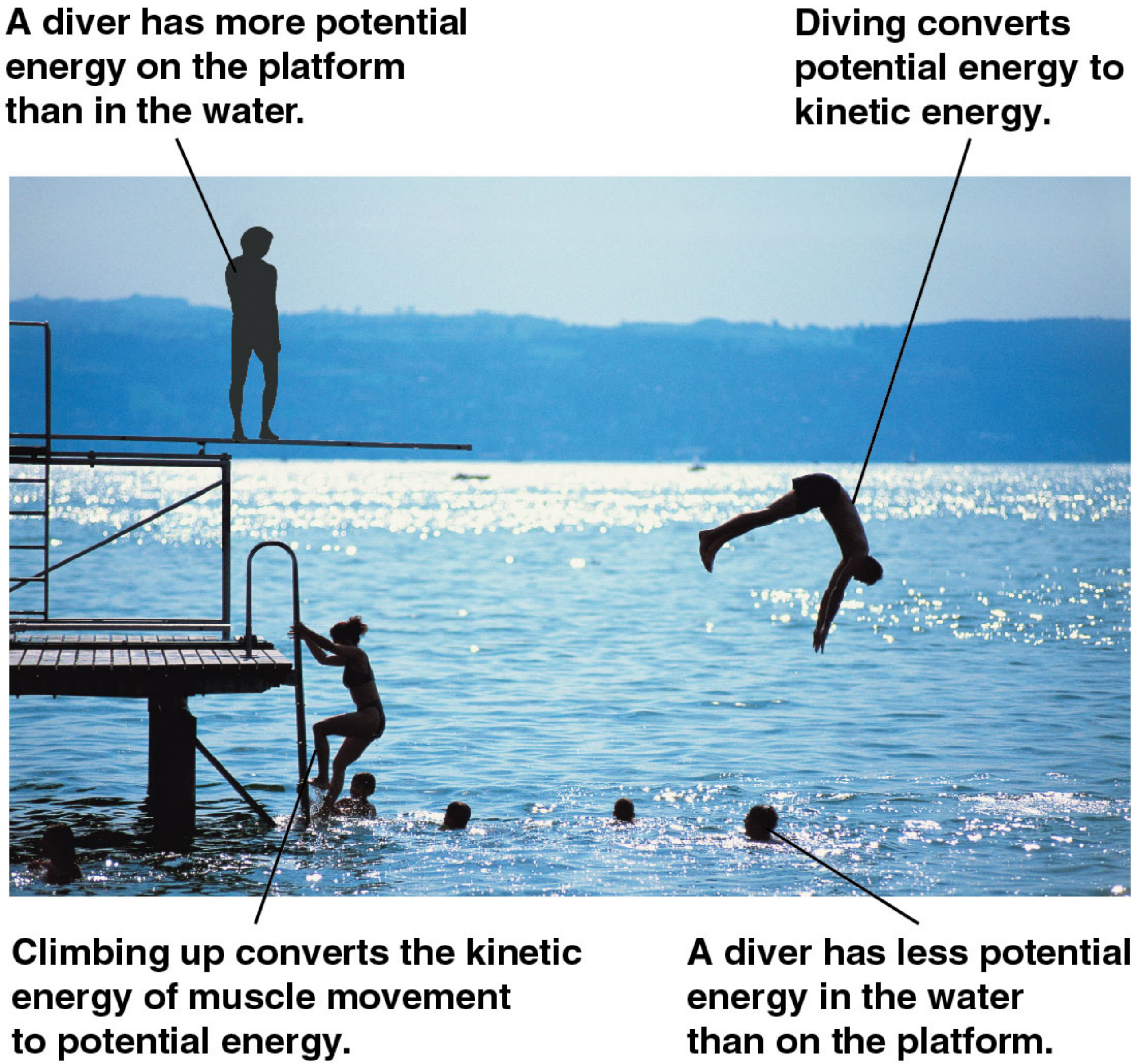
- **Thermal energy** is the kinetic energy associated with random movement of atoms or molecules
- Thermal energy in transfer from one object to another is called **heat**
- Light is another type of energy that can be harnessed to do work, such as photosynthesis

- **Potential energy** is energy that matter possesses because of its location or structure
  - For example, water behind a dam possesses energy because of its altitude above sea level
  - Molecules possess energy due to the arrangement of electrons in bonds between their atoms

- **Chemical energy** is potential energy available for release in a chemical reaction
- Complex molecules, such as glucose, are high in chemical energy because energy is released as they are broken down to simpler products

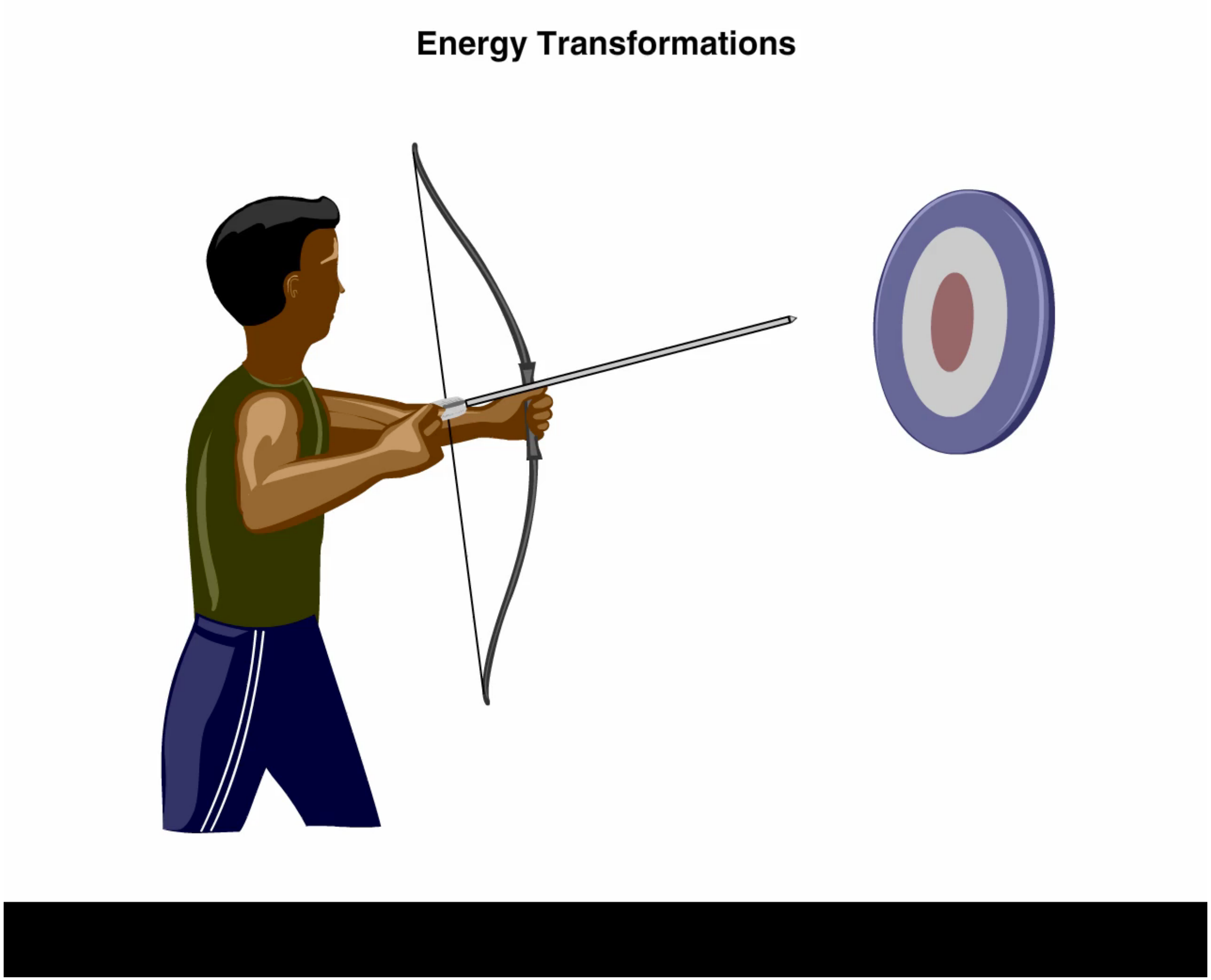
- Energy can be converted from one form to another
  - For example, chemical energy from food is used to perform the work of climbing up to a diving platform
  - The kinetic energy of muscle movement is transformed into potential energy as the diver climbs higher above the water
  - The potential energy is then transformed to kinetic energy as the diver falls back down to the water

Figure 8.2



A diver has more potential energy on the platform than in the water.
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 than on the platform.

Animation: Energy Transformations



The Laws of Energy Transformation

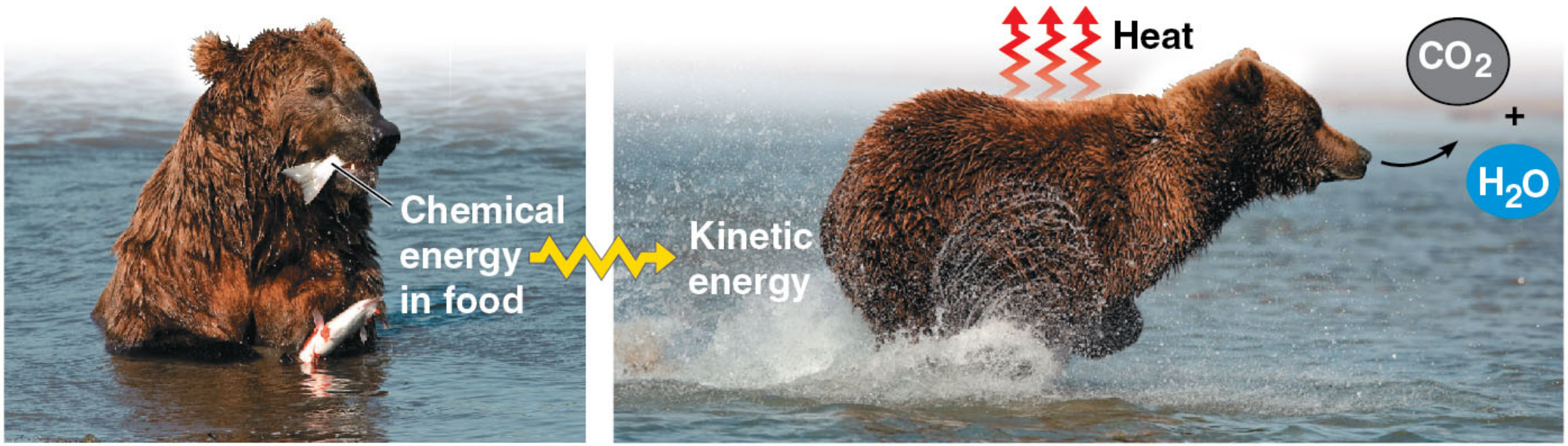
- **Thermodynamics** is the study of energy transformations in a collection of matter
- An isolated system, such as the liquid in a thermos bottle, is unable to exchange energy or matter with its surroundings

- In an open system, energy and matter can be transferred between the system and its surroundings
- Organisms are open systems; they absorb energy from light or food and release heat and metabolic wastes, such as CO_2, to the surroundings

The First Law of Thermodynamics

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

Figure 8.3



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

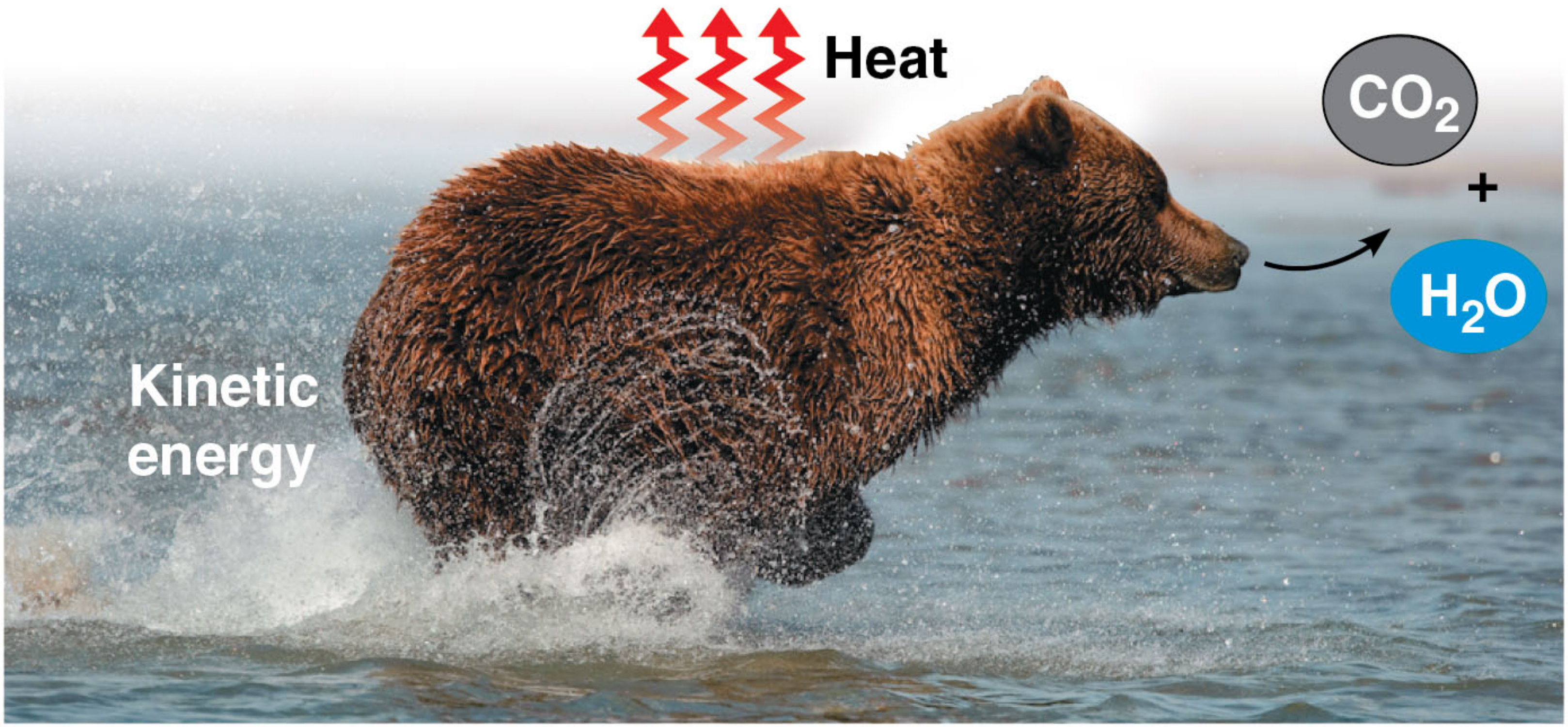
Figure 8.3a

(a) First law of thermodynamics

The Second Law of Thermodynamics

- During every energy transfer or transformation, some energy is converted to thermal energy and lost as heat, becoming unavailable to do work
- According to the **second law of thermodynamics**,
  - Every energy transfer or transformation increases the **entropy** of the universe
  - Entropy is a measure of molecular disorder, or randomness

Figure 8.3b



(b) Second law of thermodynamics

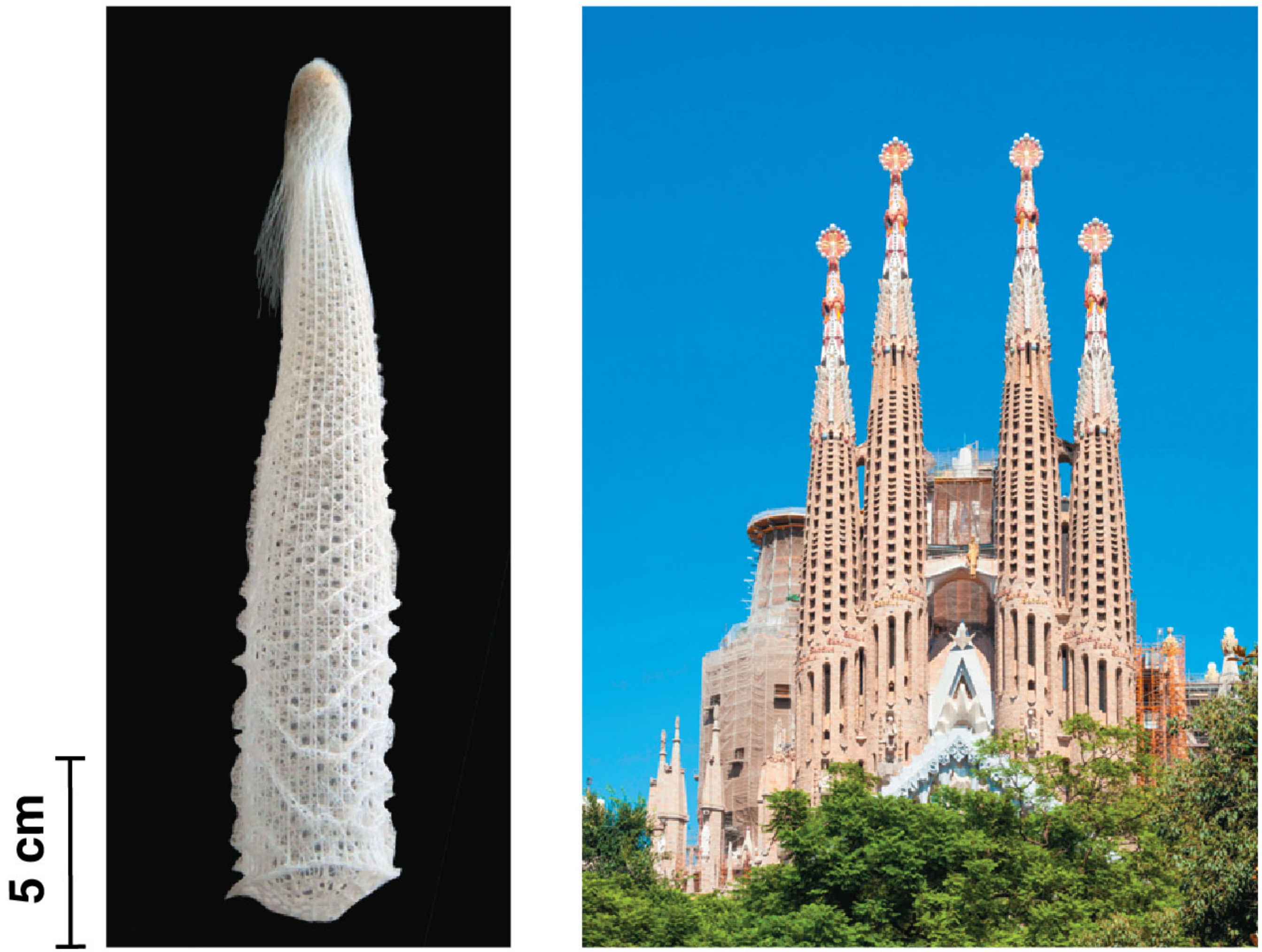
- Living organisms increase the disorder of their surroundings through their metabolism
  - For example, the breakdown of food releases heat and small molecules, such as CO_2

- Processes that increase the entropy of the universe can occur spontaneously
- **Spontaneous processes** occur without energy input; they can happen quickly or slowly
- Processes that decrease entropy are nonspontaneous; they require an input of energy

Biological Order and Disorder

- Cells create ordered structures from less organized starting materials
  - For example, simple molecules are ordered into amino acids, which are assembled into ordered polypeptides
- Complex, ordered structures are also produced from simpler starting materials at the organismal level

Figure 8.4



(a) Glass sponge **(b) La Sagrada Família towers**

- The increase in order within living systems is balanced by the catabolic breakdown of organized forms of matter, releasing heat and small molecules
- At a larger scale, energy flows in to ecosystems as light and exits as heat

- The evolution complex organisms from simpler ancestors does not violate the second law
- Entropy (disorder) may decrease in a particular system, such as an organism, as long as the total entropy of the system and surroundings increases

CONCEPT 8.2: The free-energy change of a reaction tells us whether or not the reaction occurs spontaneously

- Biologists follow the energy and entropy changes during chemical reactions to determine whether they require an input of energy or occur spontaneously

Free-Energy Change, ΔG

- Gibbs free energy, *G*, can be simplified and referred to as free energy
- **Free energy** is the portion of a system's energy that can do work when temperature and pressure are uniform throughout the system, as in a living cell

- Change in free energy during a reaction is related to temperature and changes in enthalpy and entropy

$$\Delta G = \Delta H - T\Delta S$$

  - ΔG = change in free energy
  - ΔH = change in enthalpy (total energy)
  - ΔS = change in entropy
  - T = Temperature in Kelvin (K)

- The ΔG for a process can be used to determine whether it is spontaneous or not
  - ΔG is negative for all spontaneous processes
  - ΔG is zero or positive for nonspontaneous processes
- Every spontaneous process decreases the system's free energy
- Spontaneous processes can be harnessed by the cell to perform work

Free Energy, Stability, and Equilibrium

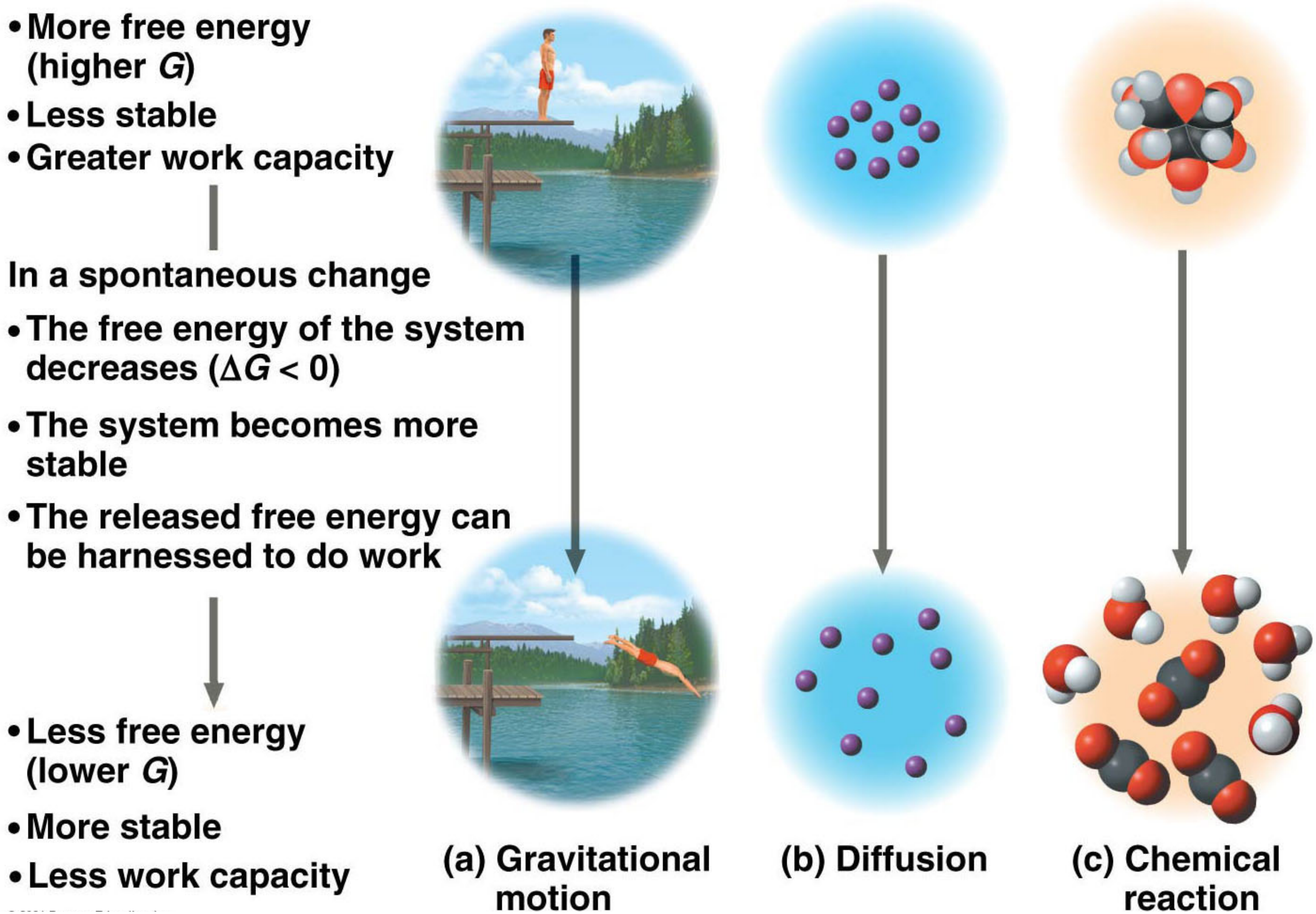
- ΔG represents the difference between free energy of the final state and free energy of the initial state

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

- If a reaction has negative ΔG, the system loses free energy and becomes more stable

- Free energy can be thought of as a measure of a systems stability; unstable systems (higher *G*) tend to become more stable (lower *G*)
  - For example, a diver on a platform is less stable than when floating in the water
  - A drop of concentrated dye is less stable than when it is dispersed randomly through a liquid
  - A glucose molecule is less stable than the simpler molecules into which it can be split

Figure 8.5


• 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

- Equilibrium, the point at which forward and reverse reactions occur at the same rate, describes a state of maximum stability
- Systems never spontaneously move away from equilibrium
- A process is spontaneous and can perform work only when it is moving toward equilibrium

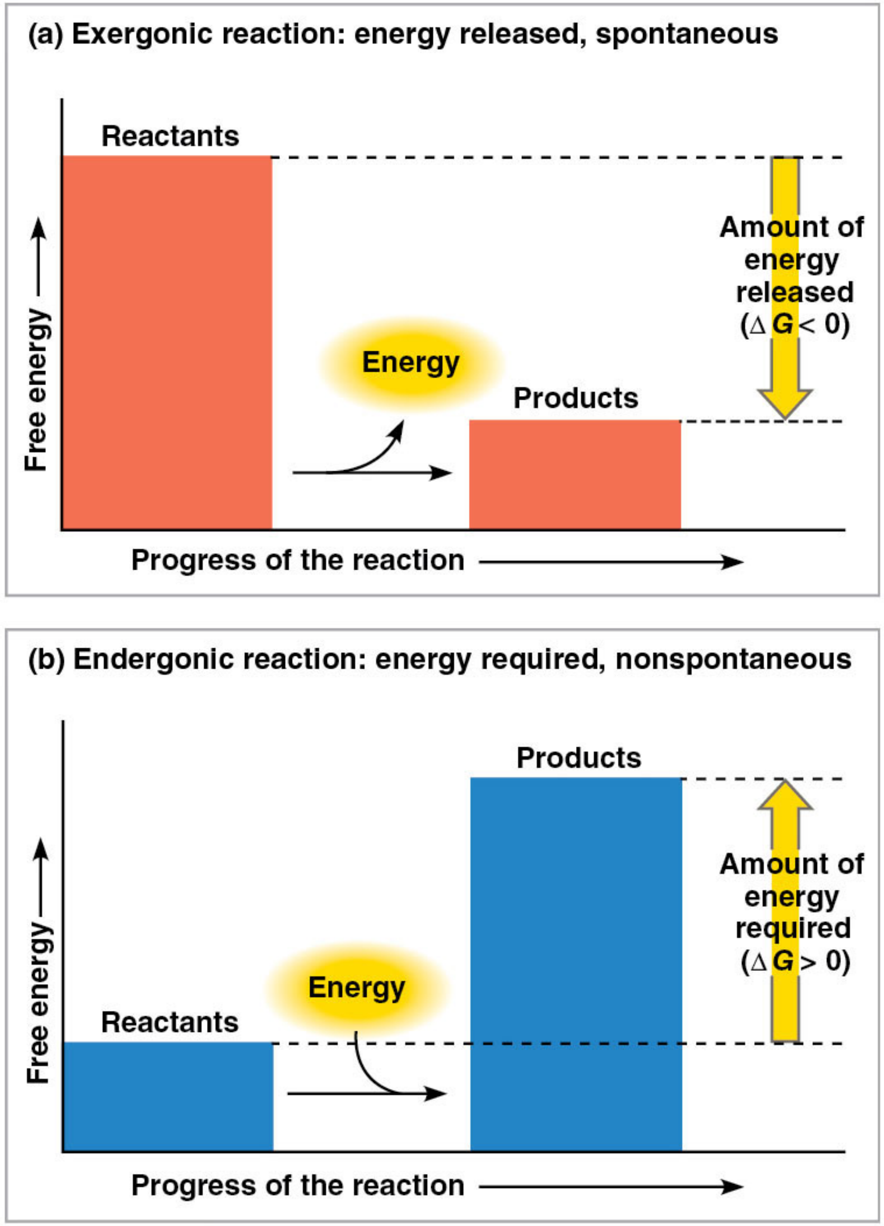
Free Energy and Metabolism

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

Exergonic and Endergonic Reactions in Metabolism

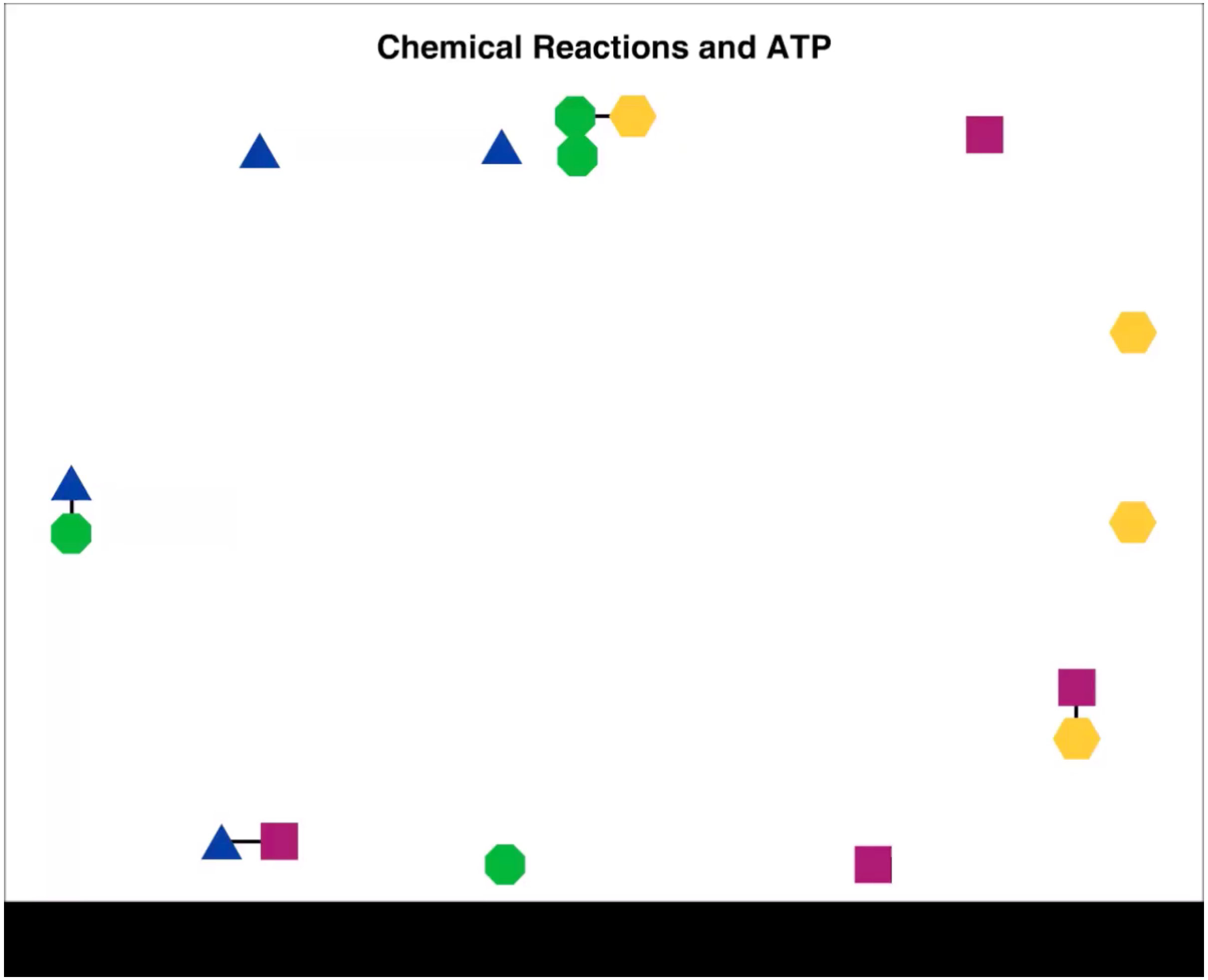
- Chemical reactions can be classified based on their free-energy changes
  - An **exergonic reaction** (“energy outward”) proceeds with a net release of free energy to the surroundings
  - An **endergonic reaction** (“energy inward”) absorbs free energy from the surroundings

Figure 8.6



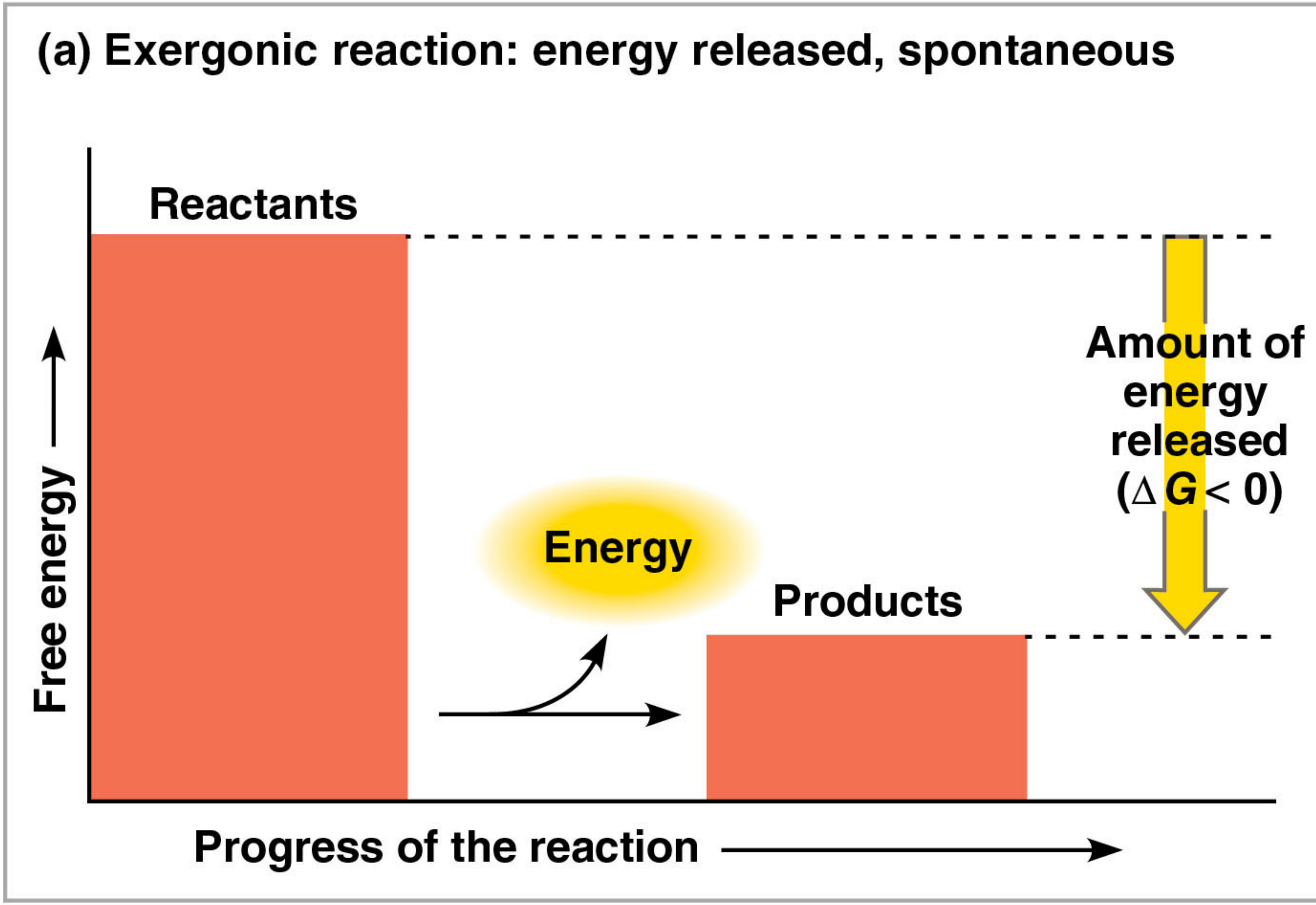
(a) Exergonic reaction: energy released, spontaneous
Reactants
Free energy
Energy
Products
Amount of energy released (Δ G < 0)
Progress of the reaction
(b) Endergonic reaction: energy required, nonspontaneous
Products
Free energy
Energy
Reactants
Amount of energy required (Δ G > 0)
Progress of the reaction

Animation: Exergonic and Endergonic Reactions



- In exergonic reactions, the products store less free energy than the reactants
- Because ΔG is negative, exergonic reactions occur spontaneously
- Recall that the term spontaneous means that a reaction is energetically favorable, not that it will occur rapidly

Figure 8.6a

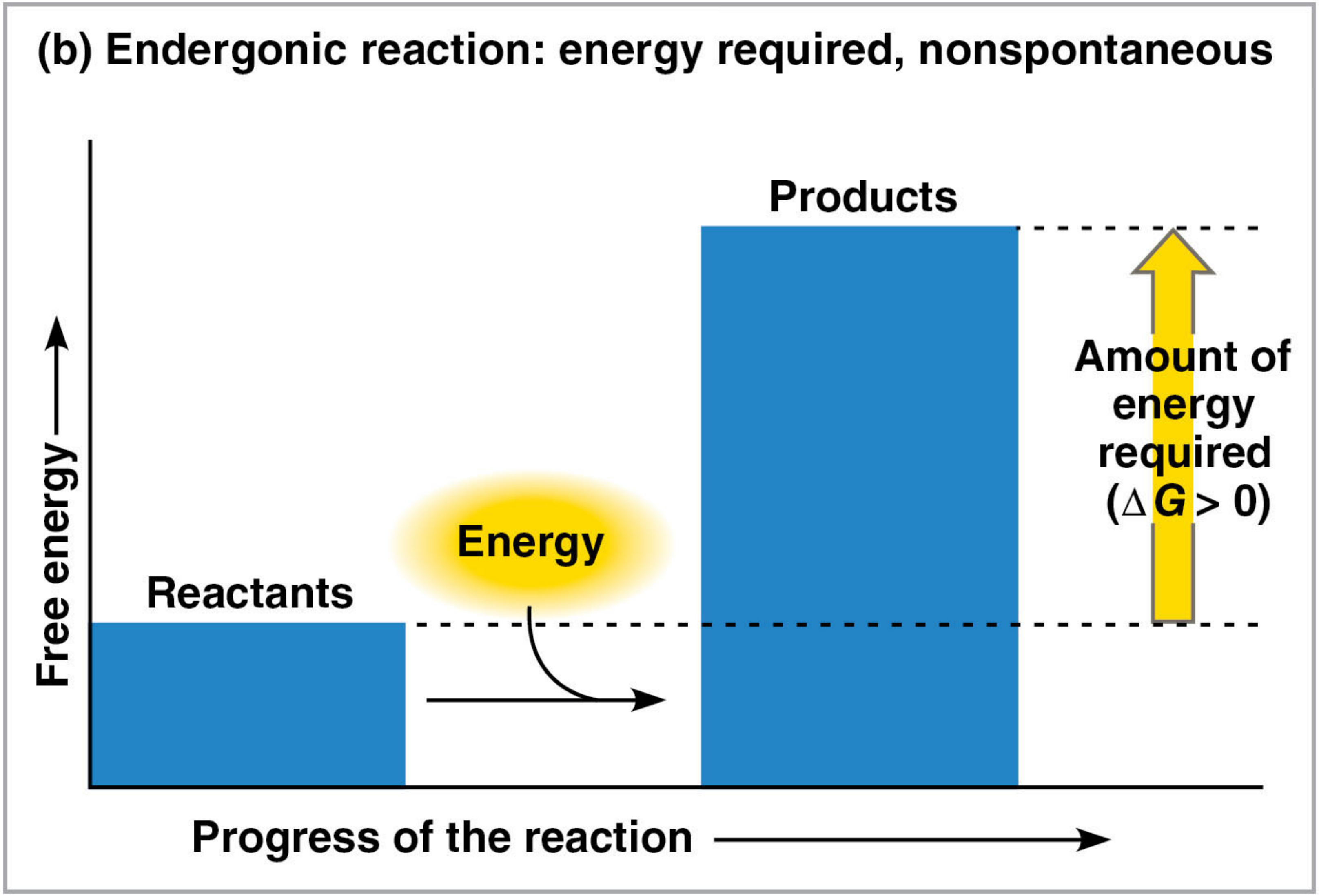

(a) Exergonic reaction: energy released, spontaneous
Reactants
Amount of energy released ($\Delta G < 0$)
Energy
Products
Free energy
Progress of the reaction

- The magnitude of ΔG determines the maximum amount of work an exergonic reaction can perform
  - For example, for each mole of glucose broken down during cellular respiration, 686 kcal of energy is available for work
  - The chemical products of respiration store 686 kcal less free energy per mole than the reactants

- Breaking bonds during a chemical reaction does not release energy; it requires energy
- If the products are of lower free energy than the reactants, potential energy is released when new bonds are formed after the original bonds break

- In endergonic reactions, the products store more free energy than the reactants
- Because ΔG is positive, endergonic reactions are nonspontaneous

Figure 8.6b

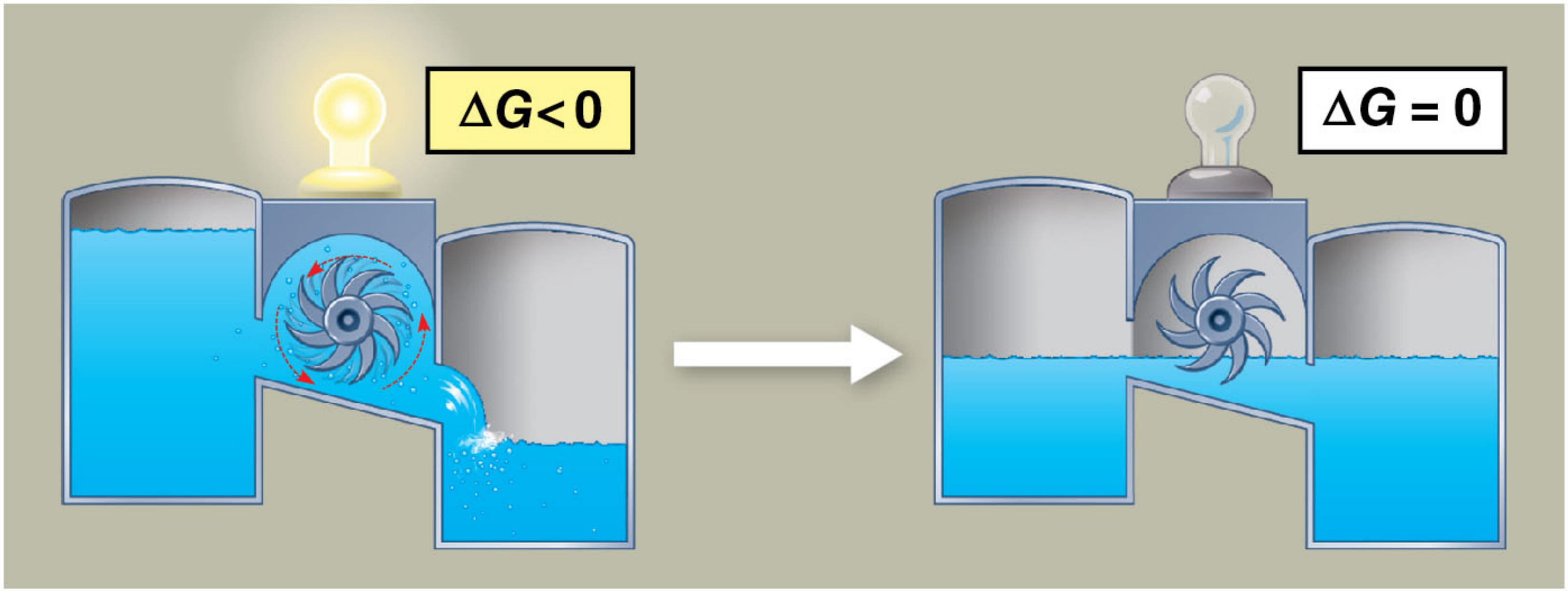

(b) Endergonic reaction: energy required, nonspontaneous
Products
Amount of energy required ($\Delta G > 0$)
Energy
Reactants
Free energy
Progress of the reaction

- The magnitude of Δ*G* determines the quantity of energy required to drive an endergonic reaction
  - For example, to produce glucose and O_2 from CO_2 and H_2O requires an input of 686 kcal/mol
  - The products of photosynthesis store 686 kcal more free energy per mole than the reactants
  - This reaction is powered by converting light energy to chemical energy

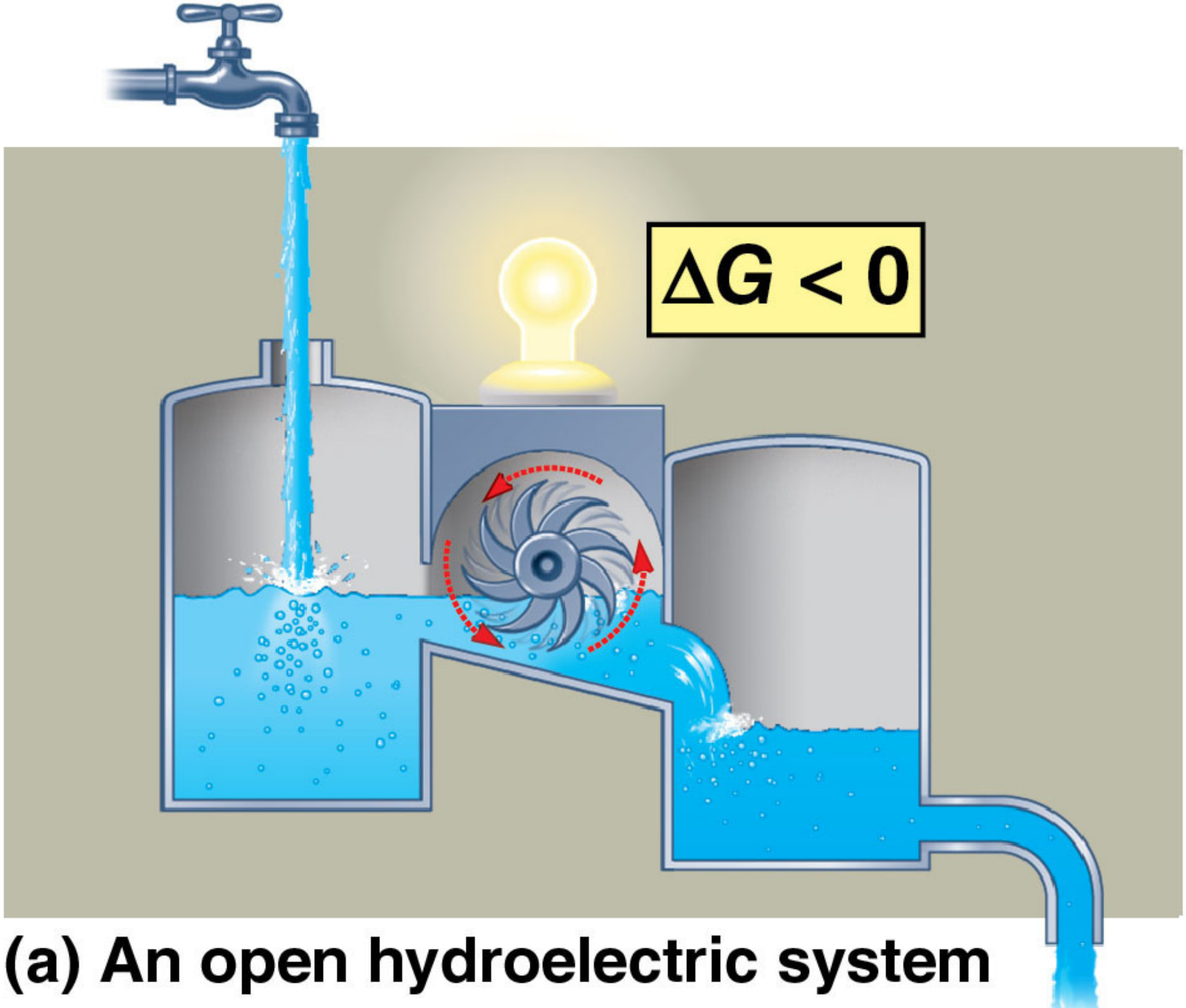
Equilibrium and Metabolism

- Reactions in a closed system, such as an isolated hydroelectric system, eventually reach equilibrium and can then do no work

Figure 8.7



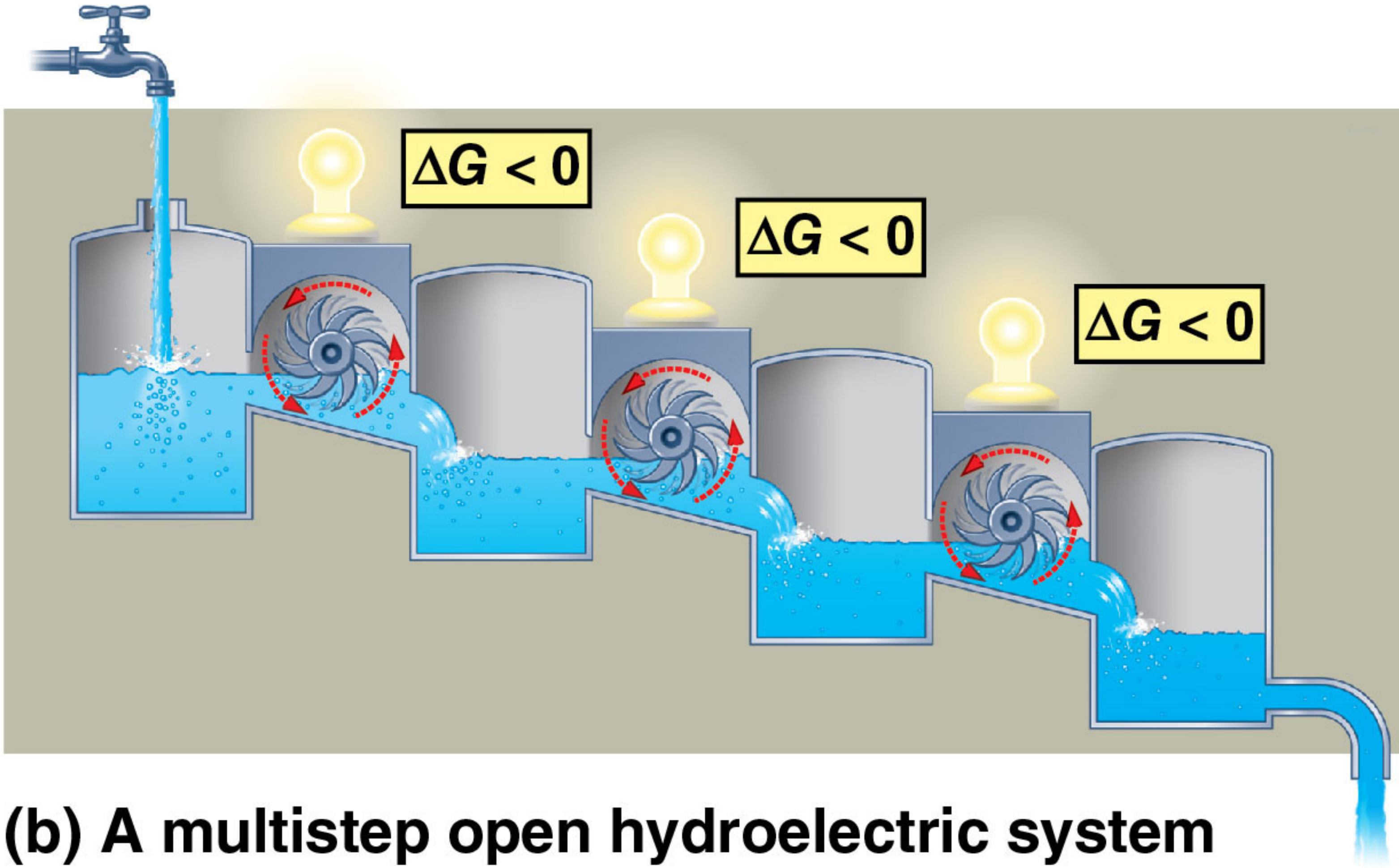
- The chemical reactions of metabolism are reversible, but never reach equilibrium in a living cell
- This is one of the defining features of life
- Like an open hydroelectric system, cells allow materials to flow in and out
- The flow of materials prevents metabolic equilibrium, enabling cells to continue doing work



(a) An open hydroelectric system

- Like a multistep open hydroelectric system, a catabolic pathway in a cell releases free energy in a series of reactions
  - For example, in cellular respiration reactions are “pulled” in one direction because the products of each reaction are the reactants in the next step
  - A steady inflow of glucose and release of waste products ensures that equilibrium is never reached

Figure 8.8b



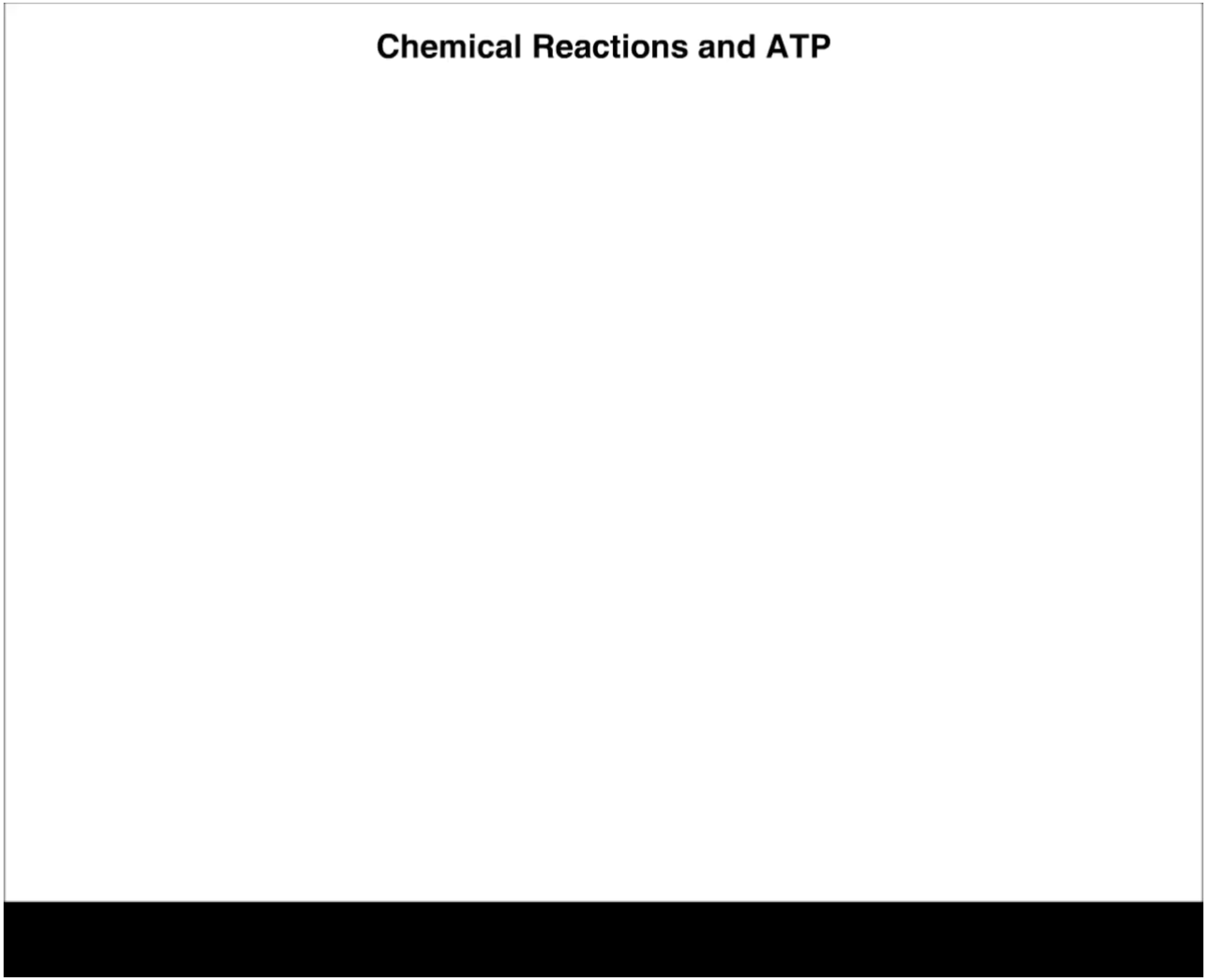
(b) A multistep open hydroelectric system

CONCEPT 8.3: ATP powers cellular work by coupling exergonic reactions to endergonic reactions

- A cell does three main kinds of work:
  - Chemical work—pushing endergonic reactions
  - Transport work—pumping substances across membranes against the direction of spontaneous movement
  - Mechanical work—such as beating cilia or contracting muscle cells

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

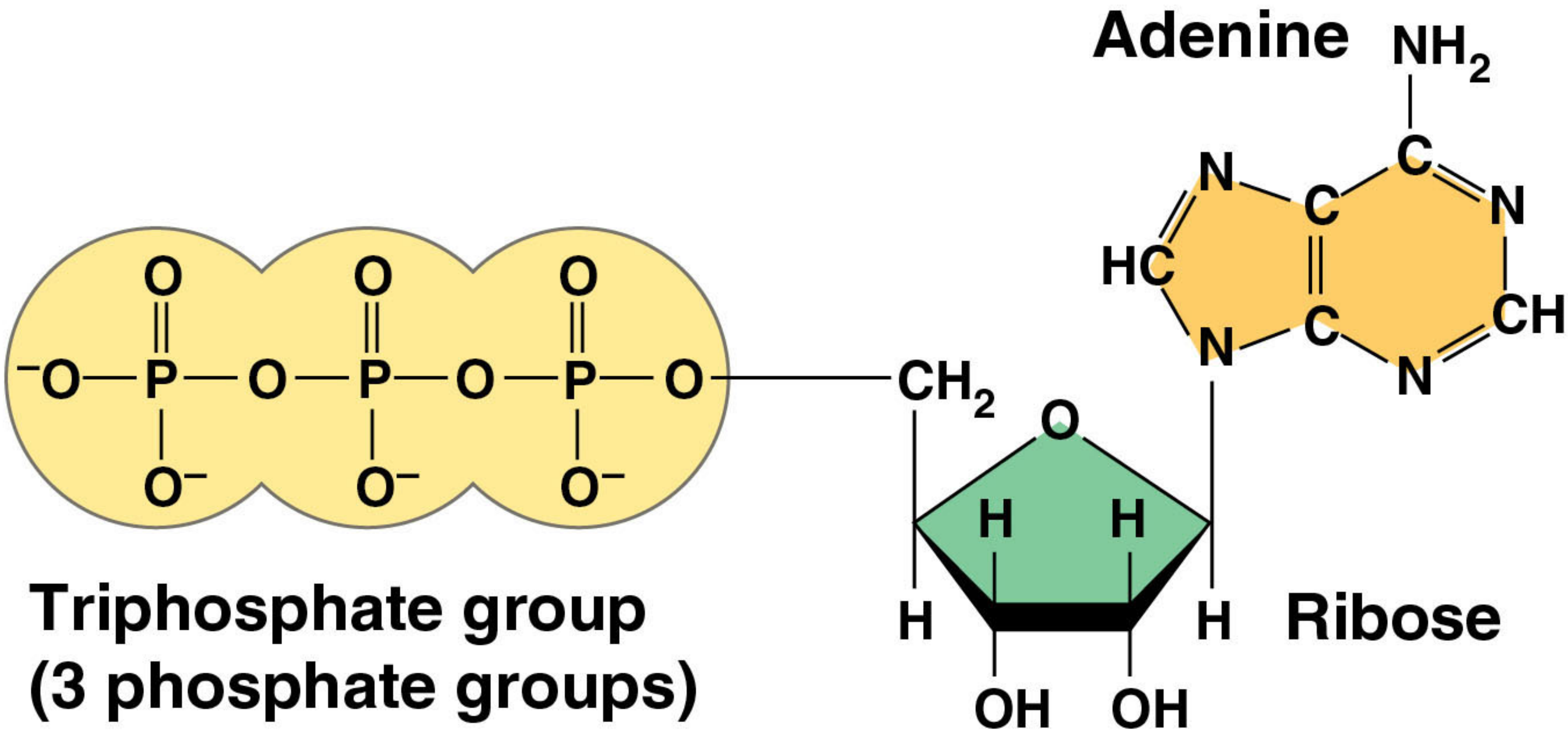
Animation: Energy Coupling



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 energy coupling, ATP functions as one of the nucleoside triphosphates used to make RNA

Figure 8.9a

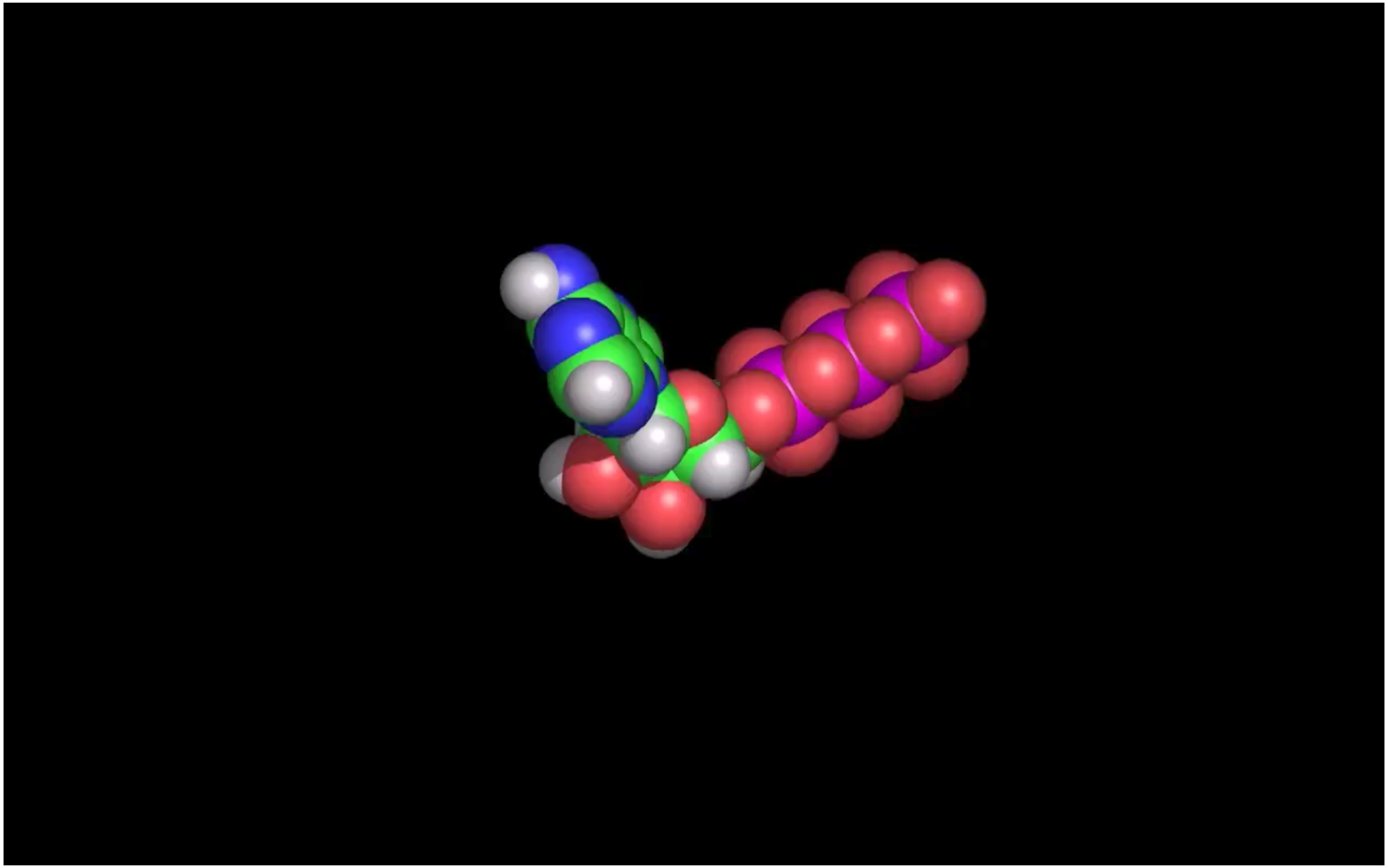


(a) The structure of ATP

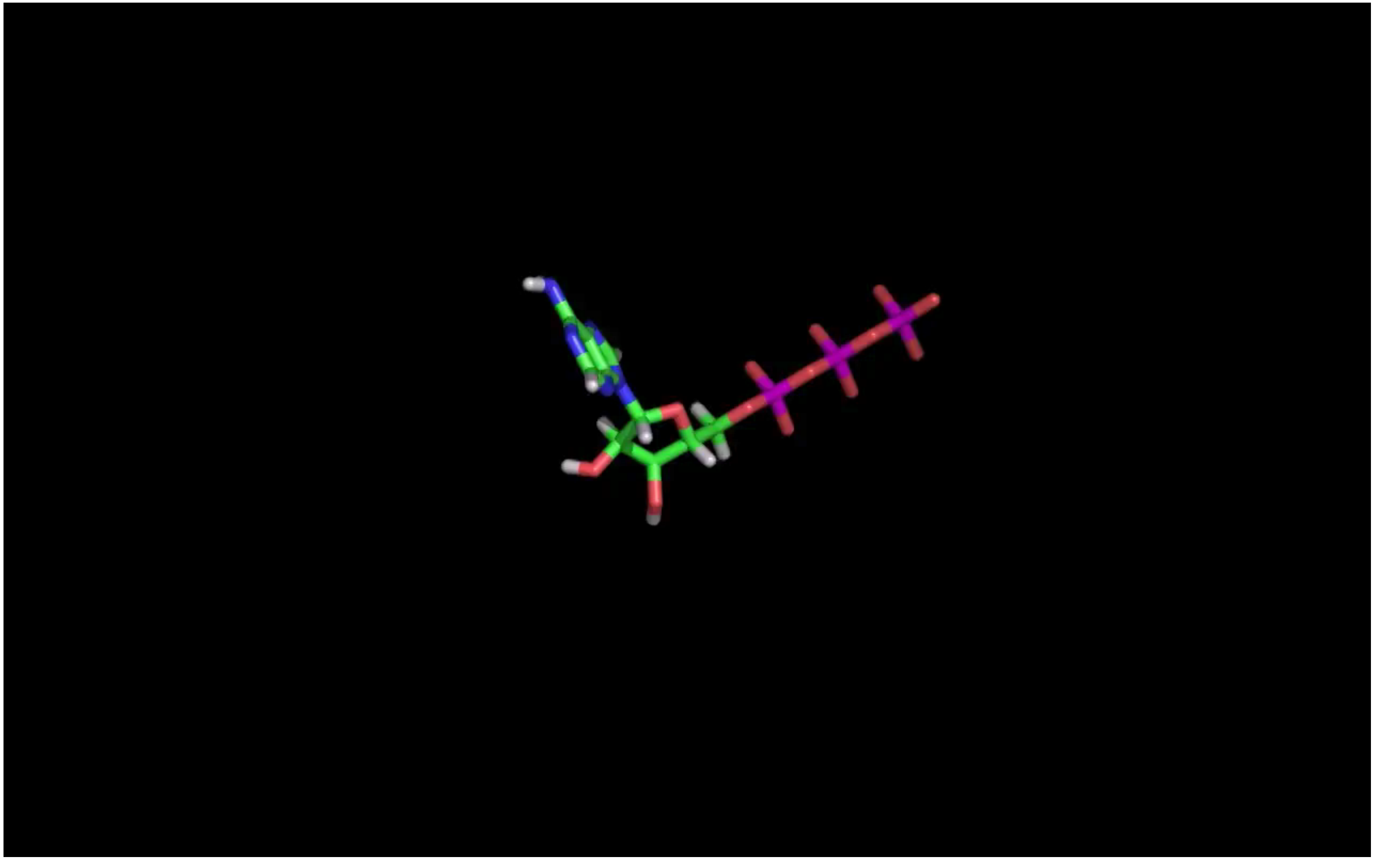
Animation: The Structure of ATP

[redacted]

Animation: Space Filling Model of ATP

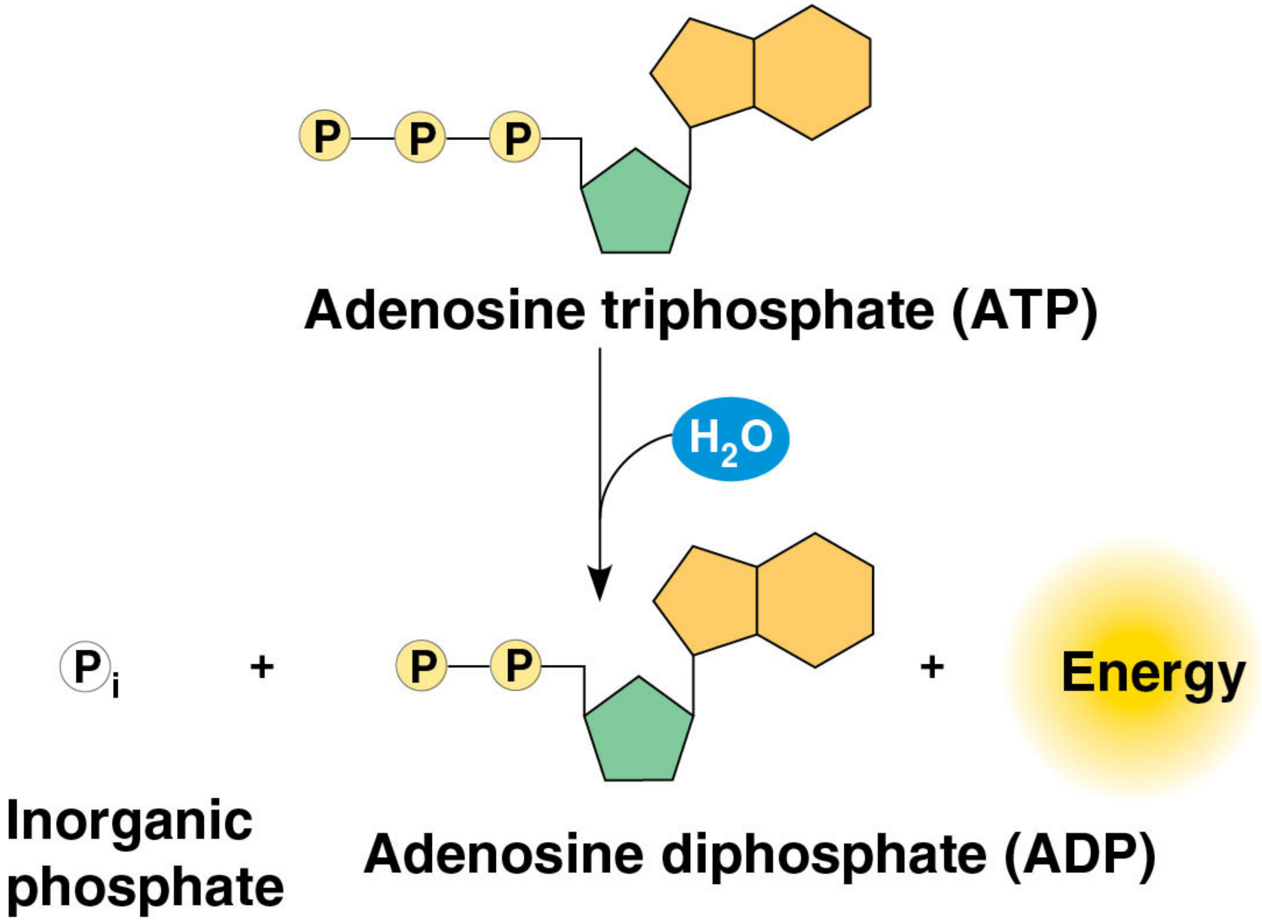


Animation: Stick Model of ATP



- Energy is released from ATP when the terminal phosphate bond is broken by hydrolysis, the addition of a water molecule
- The energy does not come directly from the phosphate bonds, but from the chemical change to a state of lower free energy in the products

Figure 8.9b



(b) The hydrolysis of ATP

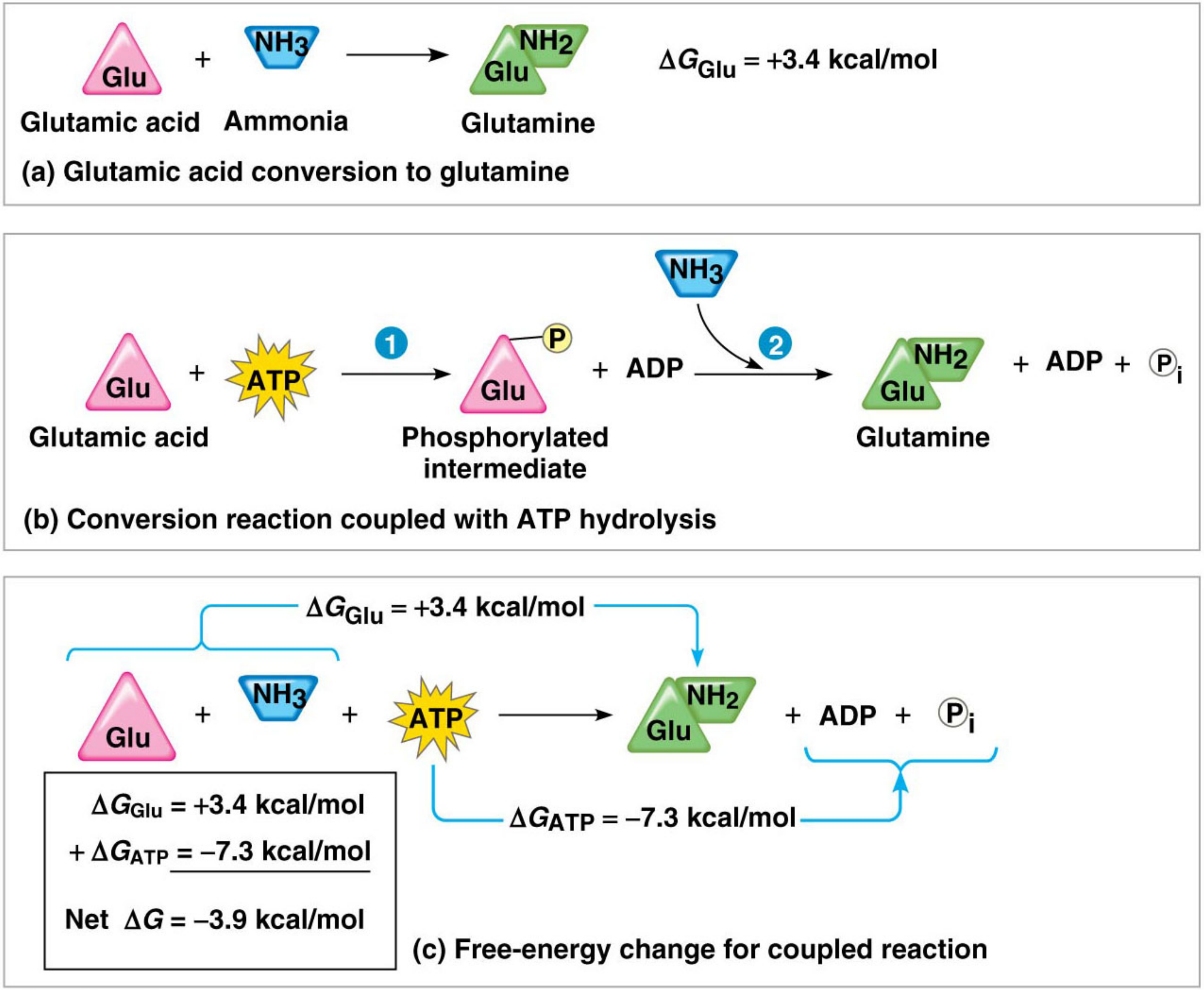
- ATP releases more energy with the loss of a phosphate than most other molecules could deliver
- Repulsion between the negative charges of the three phosphate groups creates a lot of potential energy
- The triphosphate tail is the chemical equivalent of a compressed spring

How ATP Provides Energy That Performs Work

- Cellular work (mechanical, transport, and chemical) is powered by ATP hydrolysis
- In the cell, energy from the exergonic hydrolysis of ATP is used to drive endergonic reactions
- Overall, the coupled reactions are exergonic

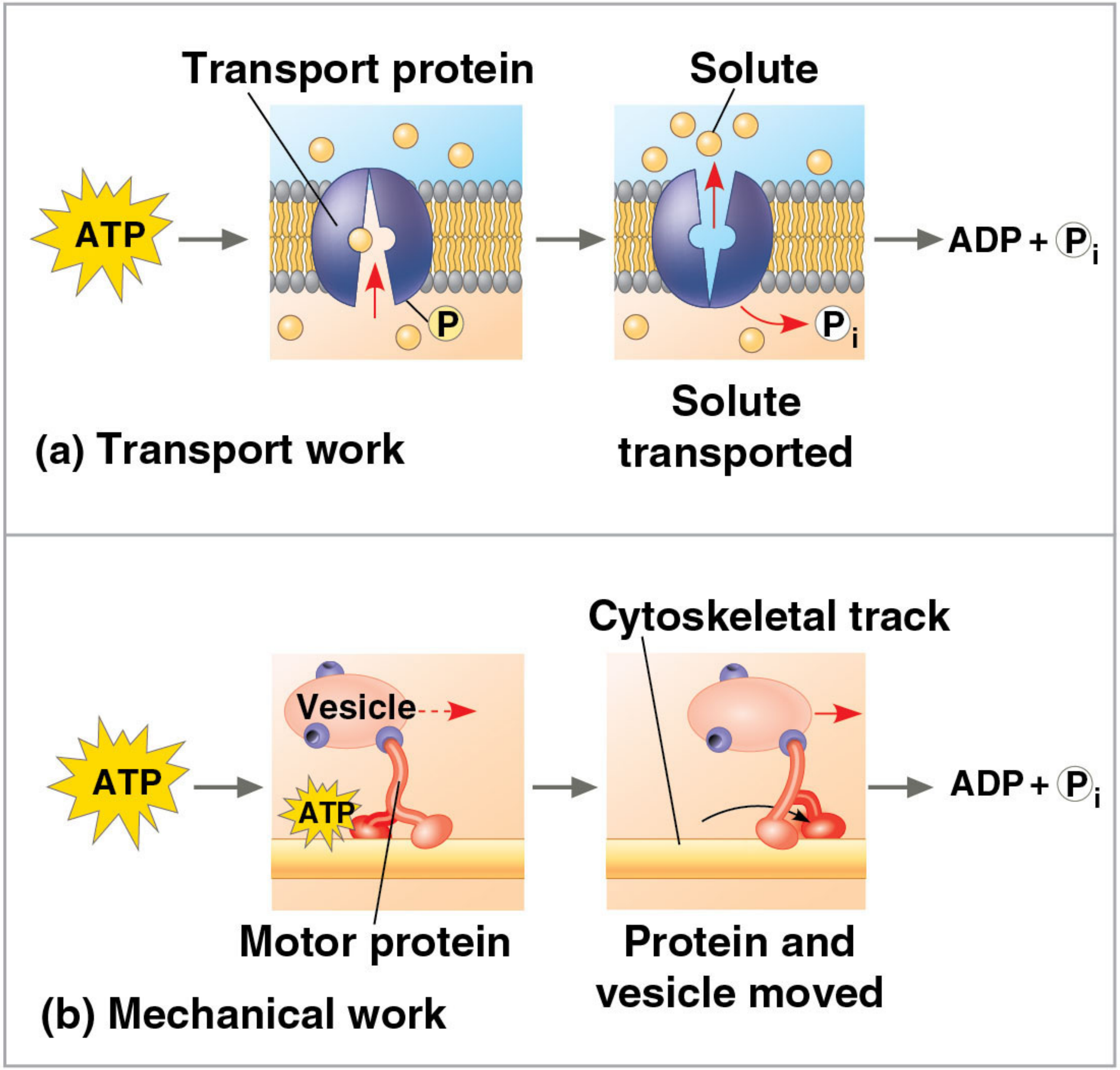
- Phosphorylation, transfer of a phosphate group from ATP to another molecule, is typically used to power endergonic reactions
- The recipient molecule, a **phosphorylated intermediate**, is more reactive (less stable, with more free energy) that the original molecule

Figure 8.10


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

- Transport and mechanical work in the cell are also nearly always powered by ATP hydrolysis
- ATP hydrolysis causes a change in protein shape and binding ability

Figure 8.11

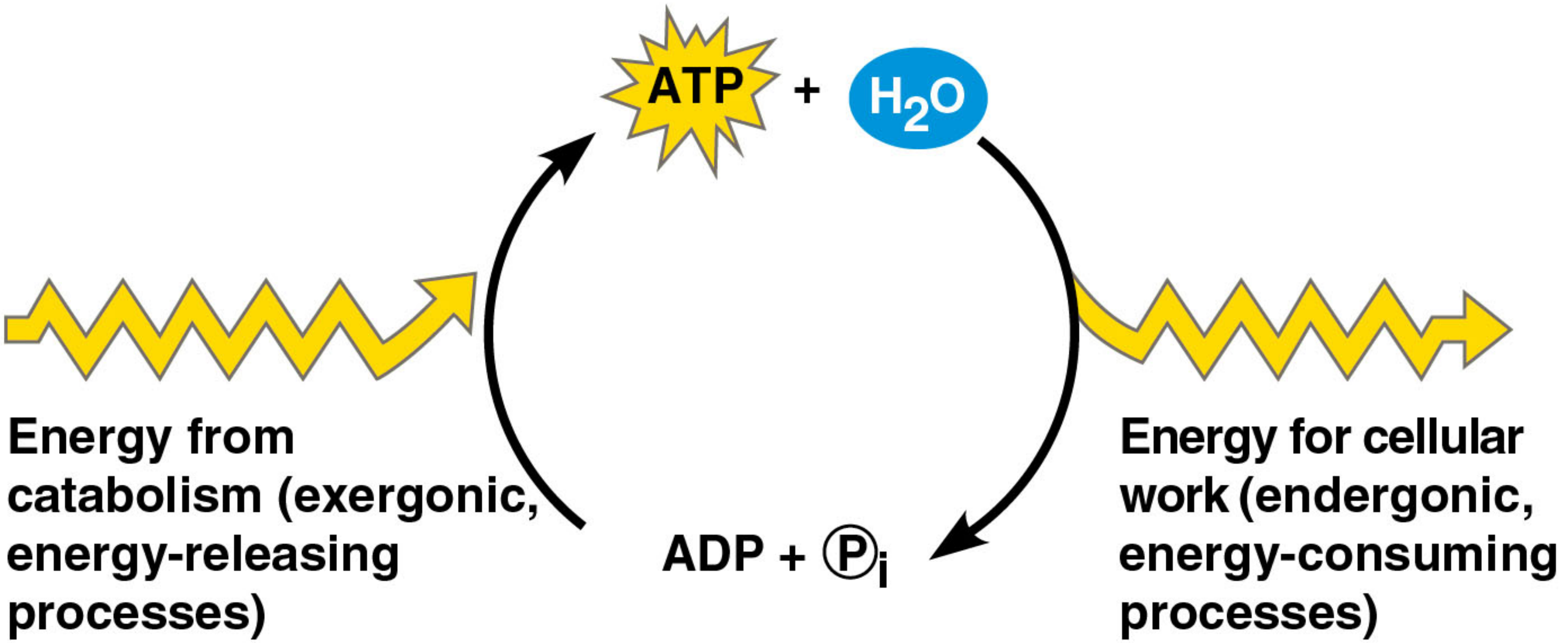


Transport protein
Solute
ATP
P
$ADP + P_i$
P_i
Solute transported
(a) Transport work
Cytoskeletal track
Vesicle
ATP
ATP
$ADP + P_i$
Motor protein
Protein and vesicle moved
(b) Mechanical work

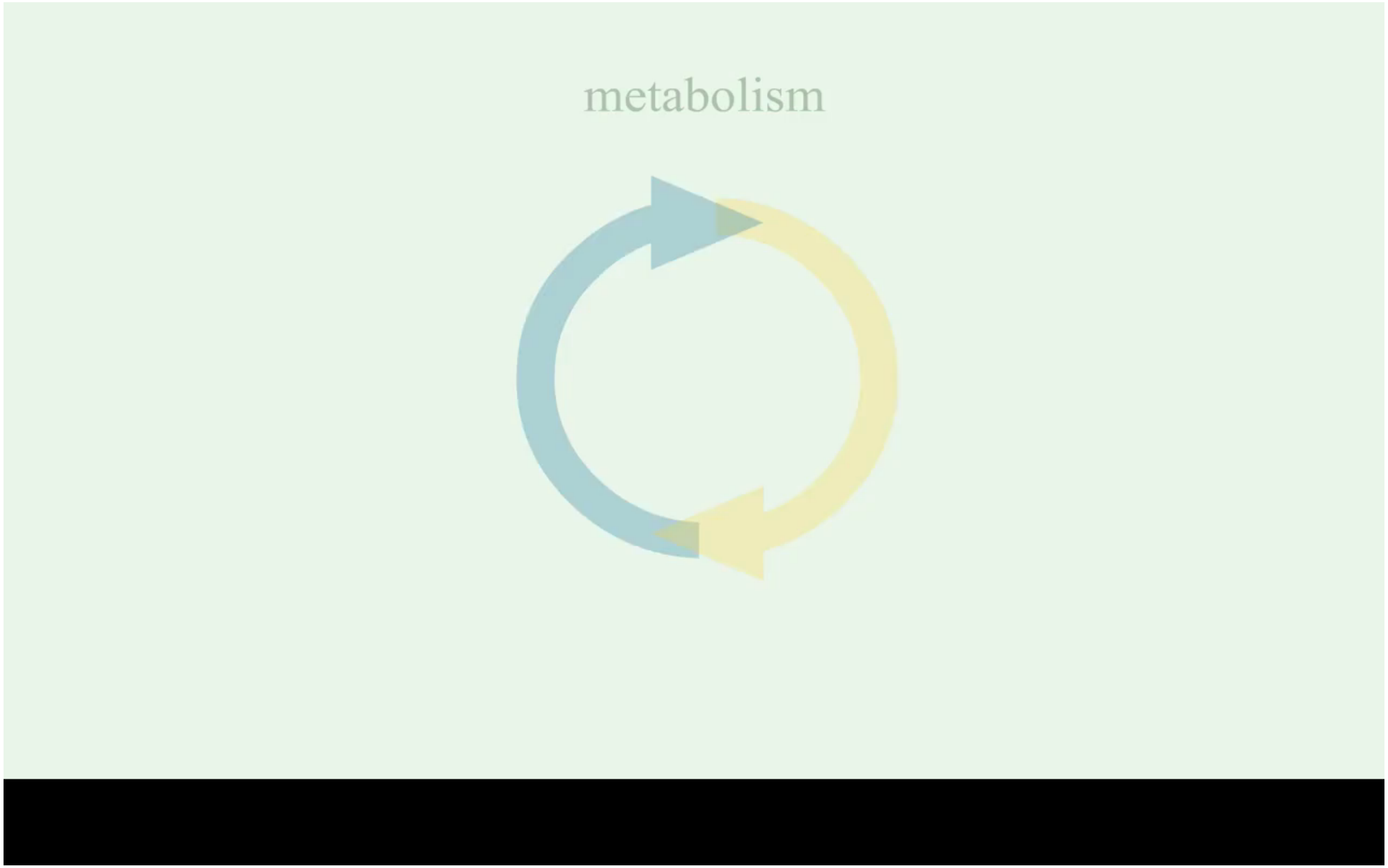
The Regeneration of ATP

- ATP is regenerated by addition of a phosphate group to adenosine diphosphate (ADP)
- Free energy needed to phosphorylate ADP comes from exergonic breakdown reactions (catabolism)
- The shuttling of inorganic phosphate and energy is called the ATP cycle; it couples energy-yielding processes to energy-consuming ones

Figure 8.12


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

Animation: Metabolism Overview

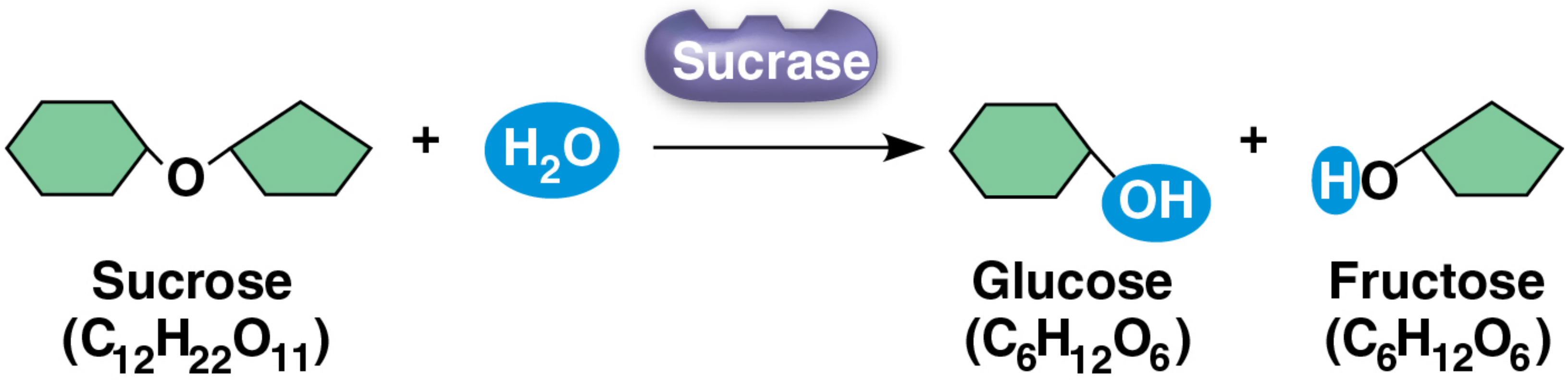


CONCEPT 8.4: Enzymes speed up metabolic reactions by lowering energy barriers

- Spontaneous reactions do not need added energy, but they can be slow enough to be imperceptible
  - For example, the hydrolysis of sucrose to glucose and fructose is spontaneous
  - At room temperature, a solution of sucrose in sterile water would sit for years without appreciable hydrolysis

- A **catalyst** is a chemical agent that speeds up a reaction without being consumed by the reaction
- An **enzyme** is a macromolecule (typically protein) that acts as a catalyst to speed up a specific reaction
  - For example, adding the enzyme sucrase to a sucrose solution at room temperature will catalyze the complete hydrolysis of sucrose within seconds

Figure 8.UN02



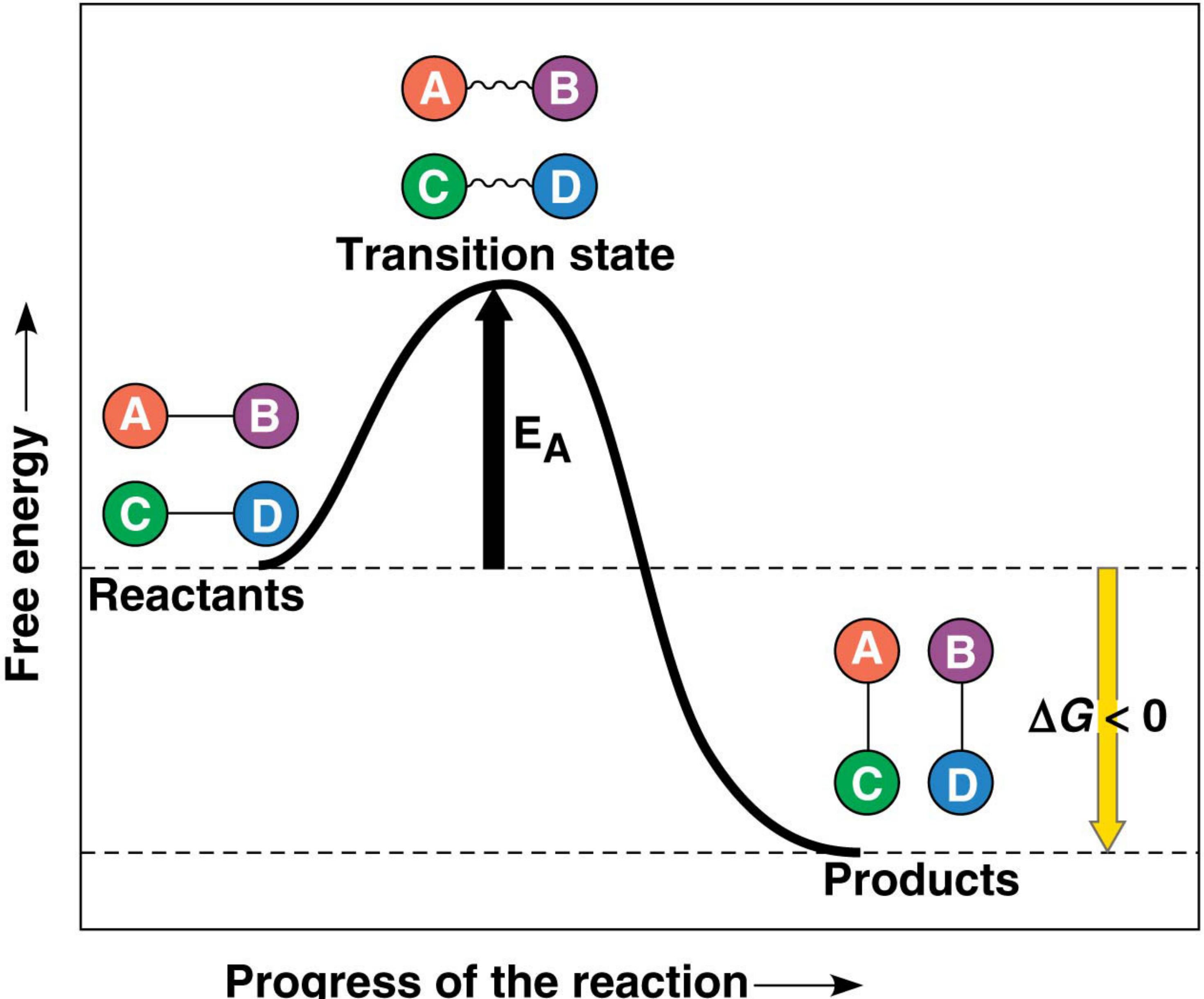
The Activation Energy Barrier

- Every chemical reaction between molecules involves bond breaking and bond forming
- A molecule must be contorted into a highly unstable state before bonds can break to start the reaction
- To reach this state, the molecule must absorb energy from its surroundings

- The initial energy needed to break the bonds of the reactants is called the **activation energy** (E_A)
- Heat in the form of thermal energy absorbed from the surroundings often supplies activation energy
- Molecules become unstable when enough energy is absorbed to break bonds; this is the transition state

- As atoms settle into new, more stable bonds, energy is released to the surroundings
- In an exergonic reaction, the formation of new bonds releases more energy than was invested in breaking the old bonds

Figure 8.13


A
B
C
D
Transition state
A
B
C
D
E_A
Reactants
A
B
C
D
$\Delta G < 0$
Products
Free energy
Progress of the reaction

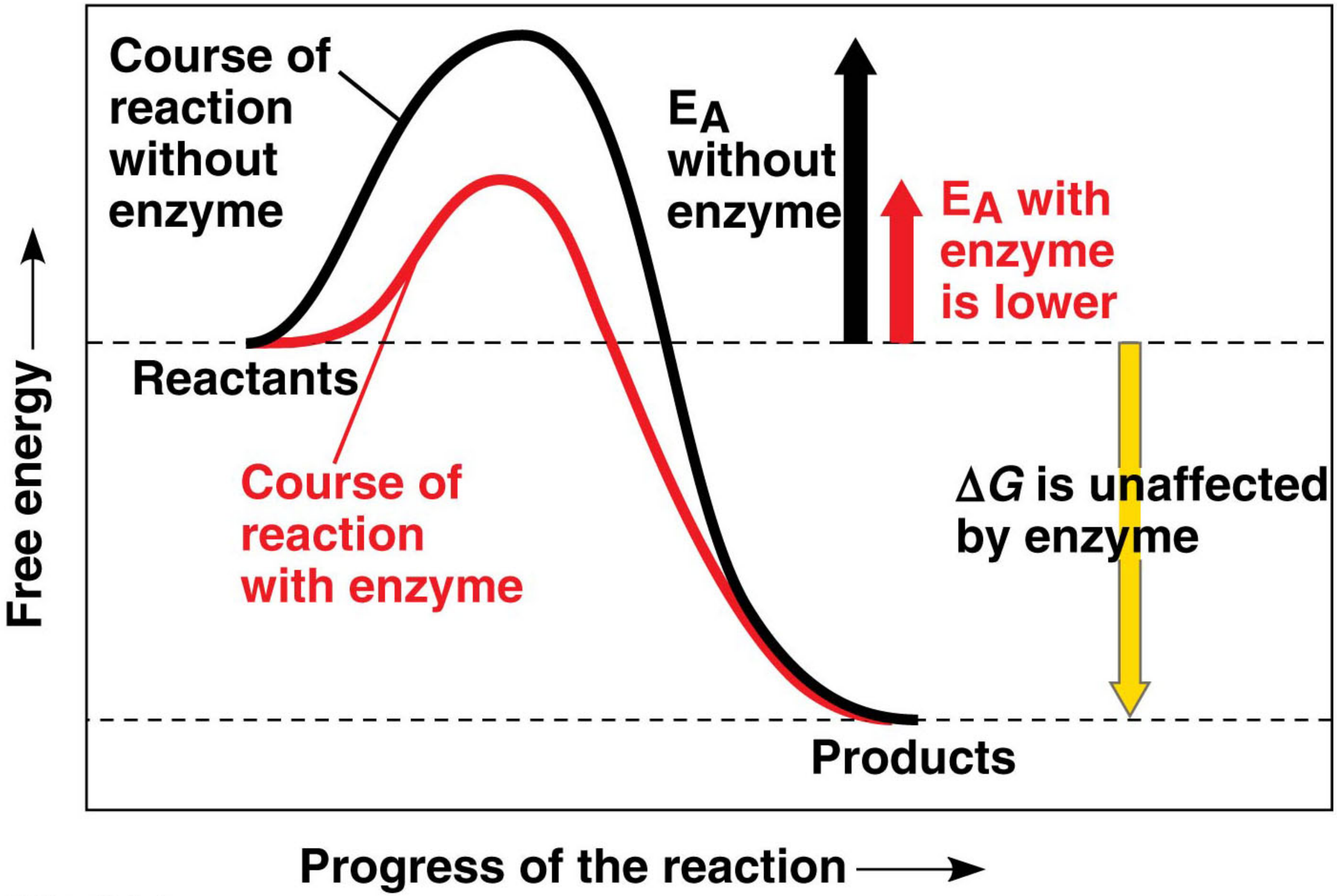
- The activation energy provides a barrier that determines the rate of spontaneous reactions
- For some reactions, E_A is low enough that thermal energy at room temperature is sufficient to overcome the activation barrier
- Most reactions have high E_A, and need additional energy (usually heat) to reach the transition state

How Enzymes Speed Up Reactions

- Adding heat is not a useful way to speed reactions in cells because it can cause proteins to denature
- Heat is also impractical because it would speed up all reactions, not just those that are needed
- Instead, organisms carry out **catalysis**, the process by which a catalyst selectively speeds up a reaction without itself being consumed

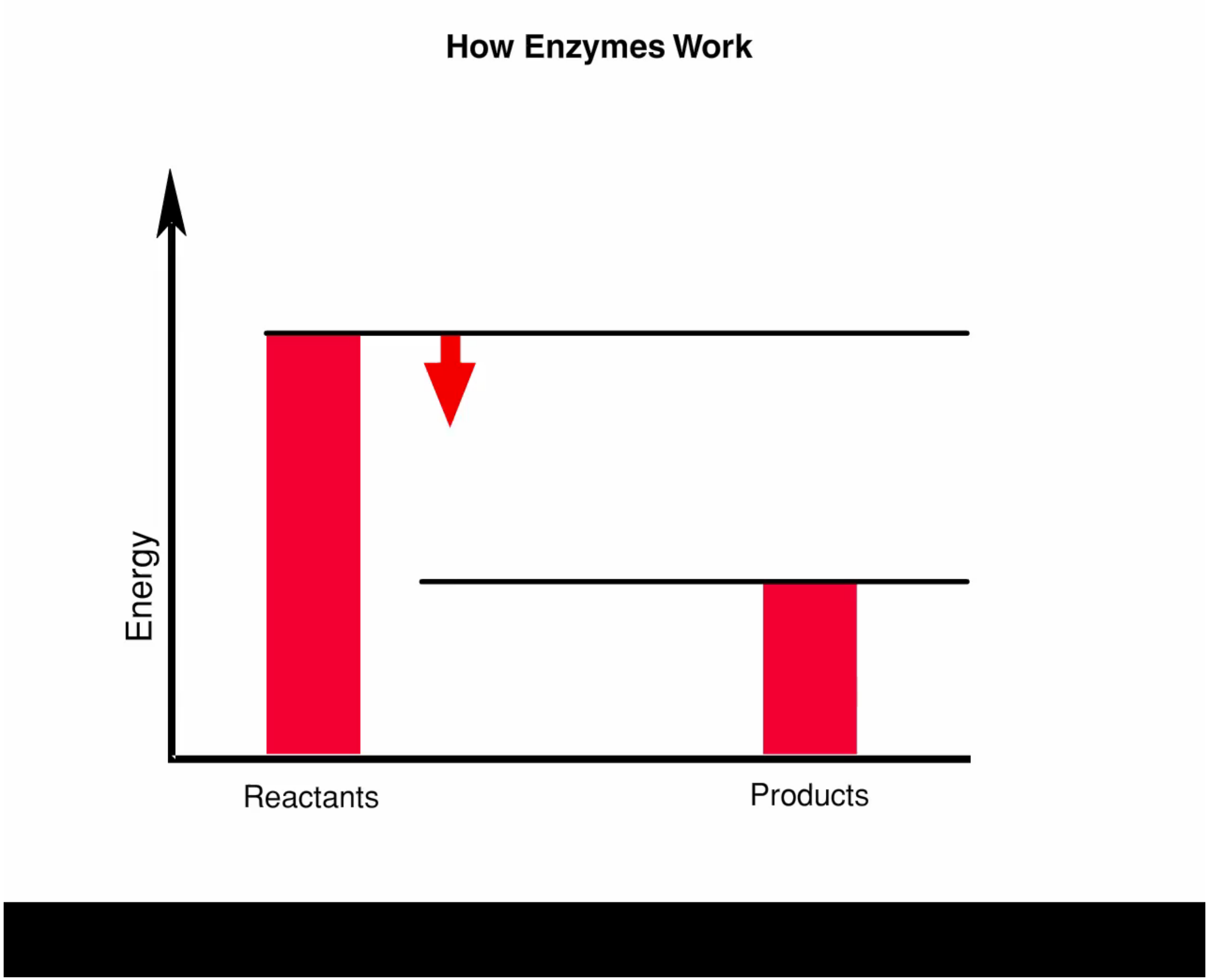
- An enzyme catalyzes a reaction by lowering the E_A barrier enough for the reaction to occur at moderate temperatures
- An enzyme cannot change ΔG; it only speeds up a reaction that would eventually occur anyway

Figure 8.14



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

Animation: How Enzymes Work



Substrate Specificity of Enzymes

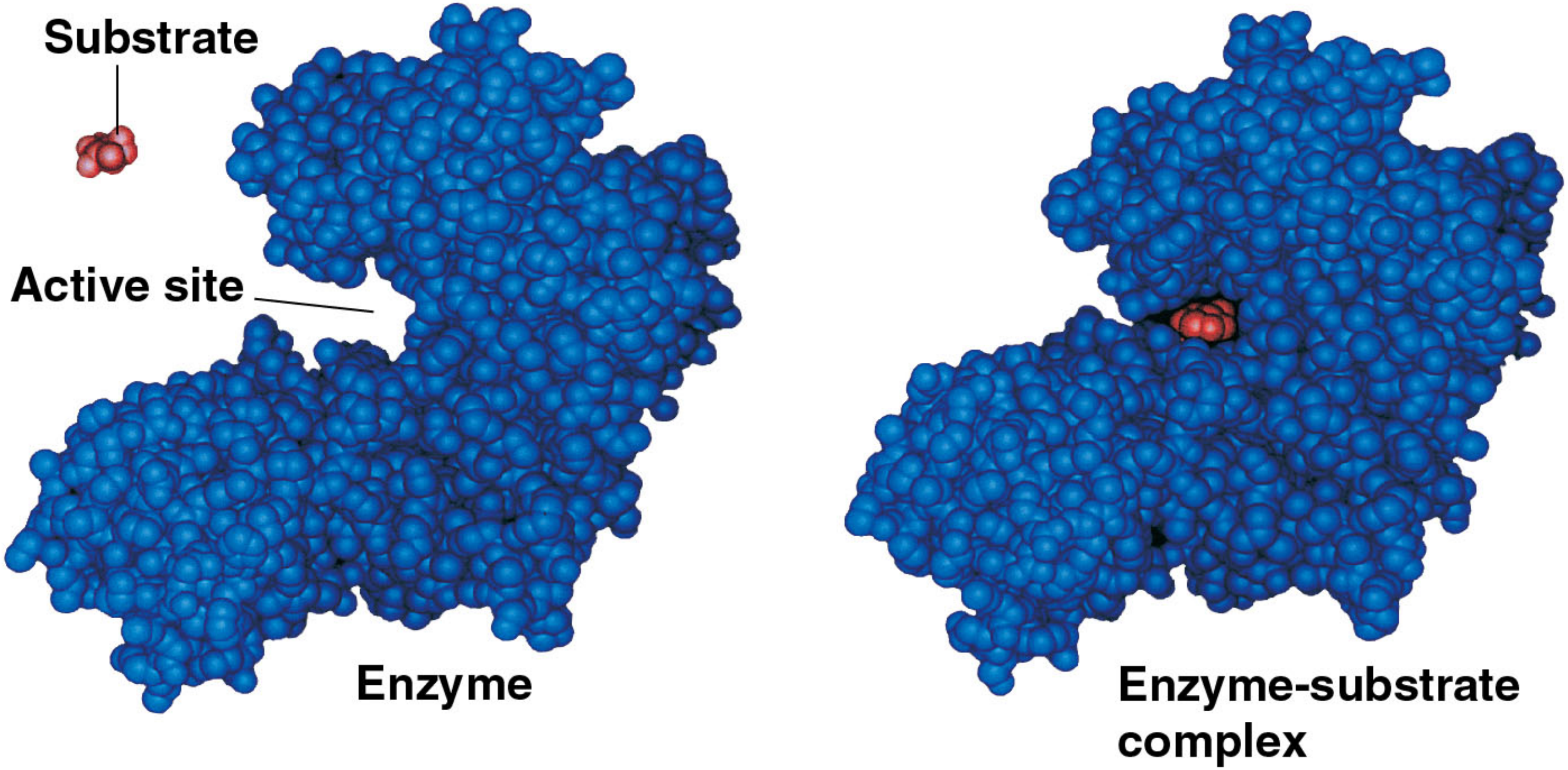
- The reactant that an enzyme acts on is called the enzyme's **substrate**
- The enzyme binds to its substrate, forming an **enzyme-substrate complex**
- While bound, the catalytic activity of the enzyme converts substrate to product

- Most enzyme names end in -*ase*
  - For example, the enzyme sucrase catalyzes the hydrolysis of sucrose into glucose and fructose
- Each enzyme catalyzes a specific reaction and can recognize its specific substrate among even closely related compounds

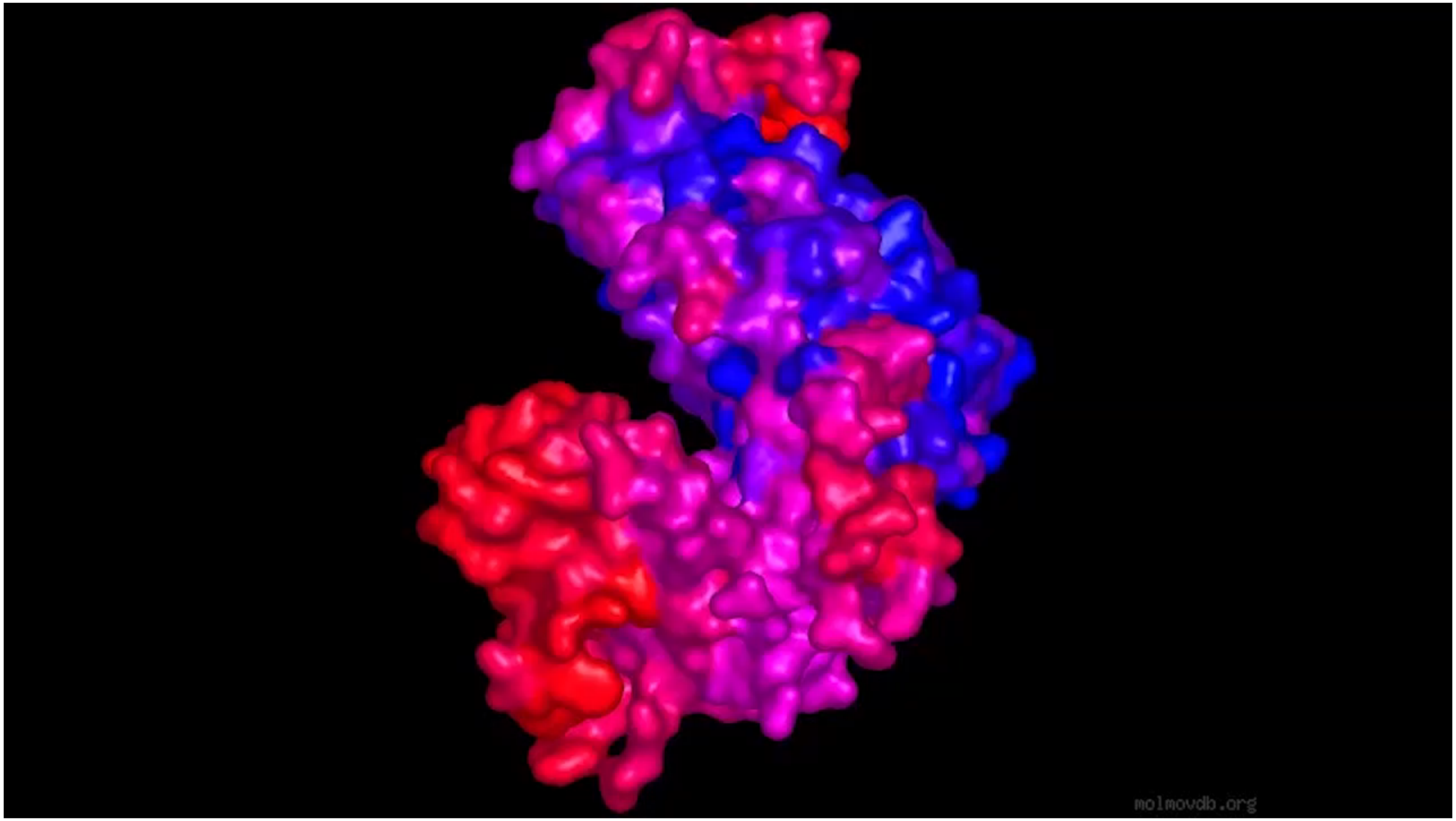
- The **active site** is the region on the enzyme, often a pocket or groove, that binds to the substrate
- The complementary fit between the shape of the active site and the shape of the substrate is responsible for enzyme specificity

- When the substrate enters the active site, the enzyme changes shape slightly, tightening around the substrate like a handshake
- This **induced fit** results from interactions between chemical groups on the substrate and the active site
- It brings the chemical groups of the active site into positions that enhance catalysis of the reaction

Figure 8.15



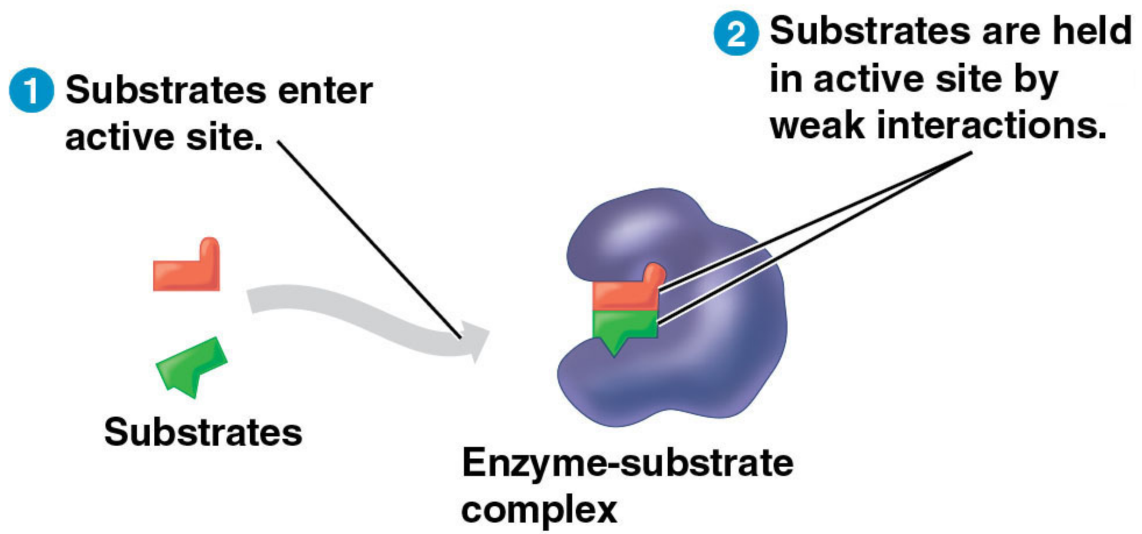
Video: Closure of Hexokinase Via Induced Fit



Catalysis in the Enzyme's Active Site

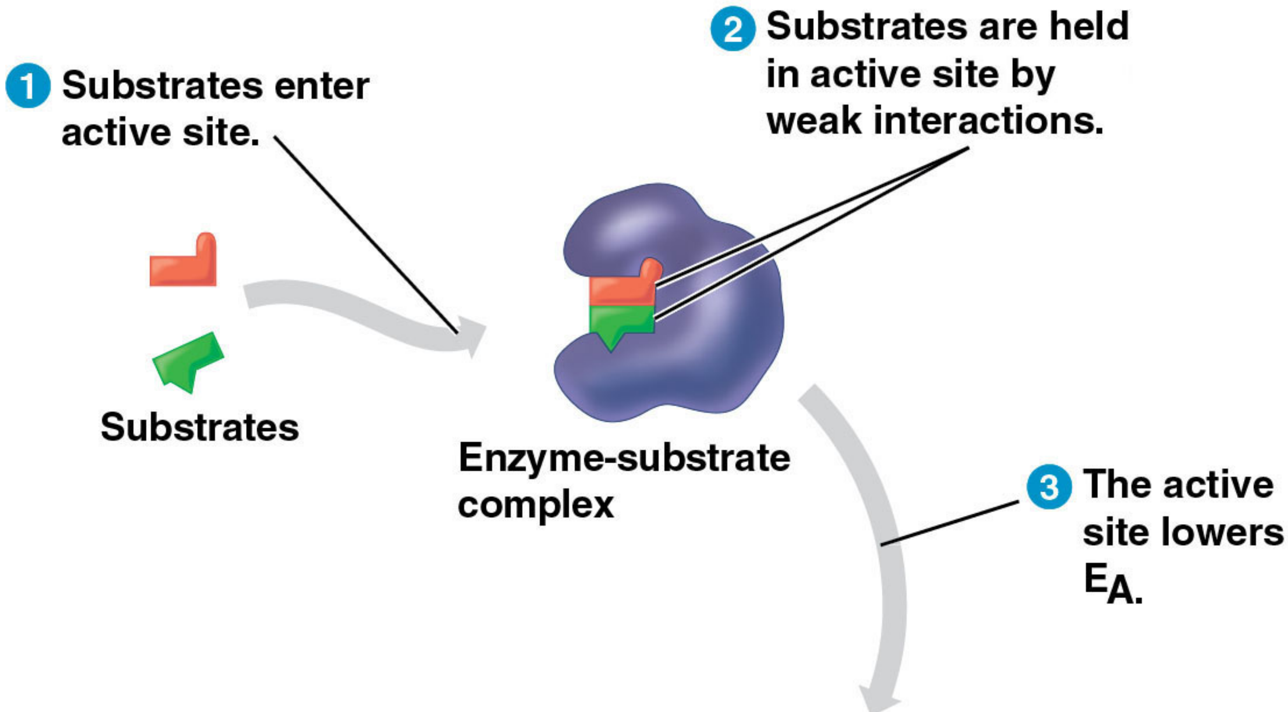
- The substrate is typically held in the enzyme's active site by weak bonds, such as hydrogen bonds
- The conversion of substrate to product happens rapidly, and product is released from the active site
- Because enzymes emerge from reactions in their original form, small amounts can have huge metabolic impacts

Figure 8.16-1



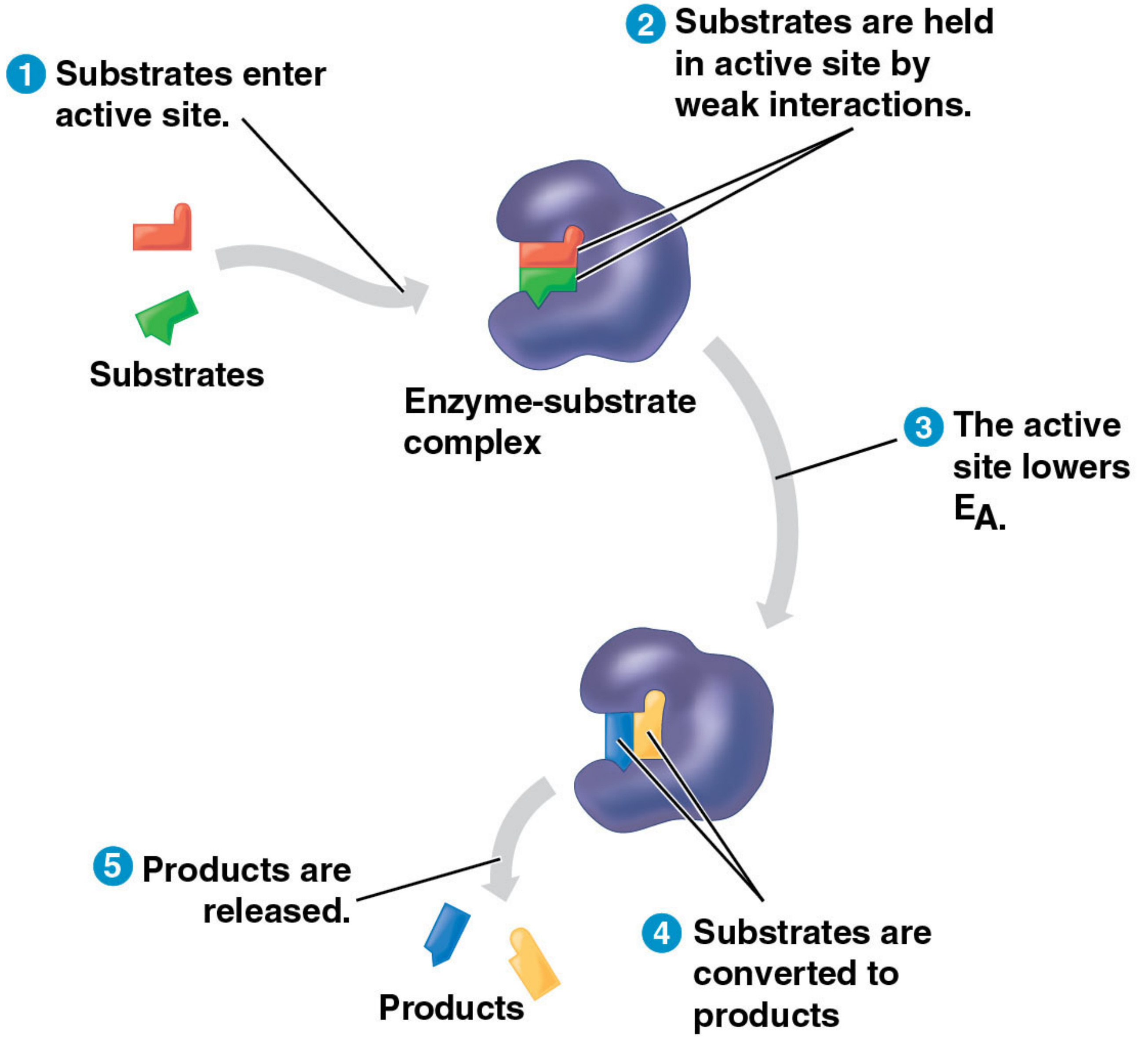
1 Substrates enter active site.
2 Substrates are held in active site by weak interactions.
Substrates
Enzyme-substrate complex

Figure 8.16-2



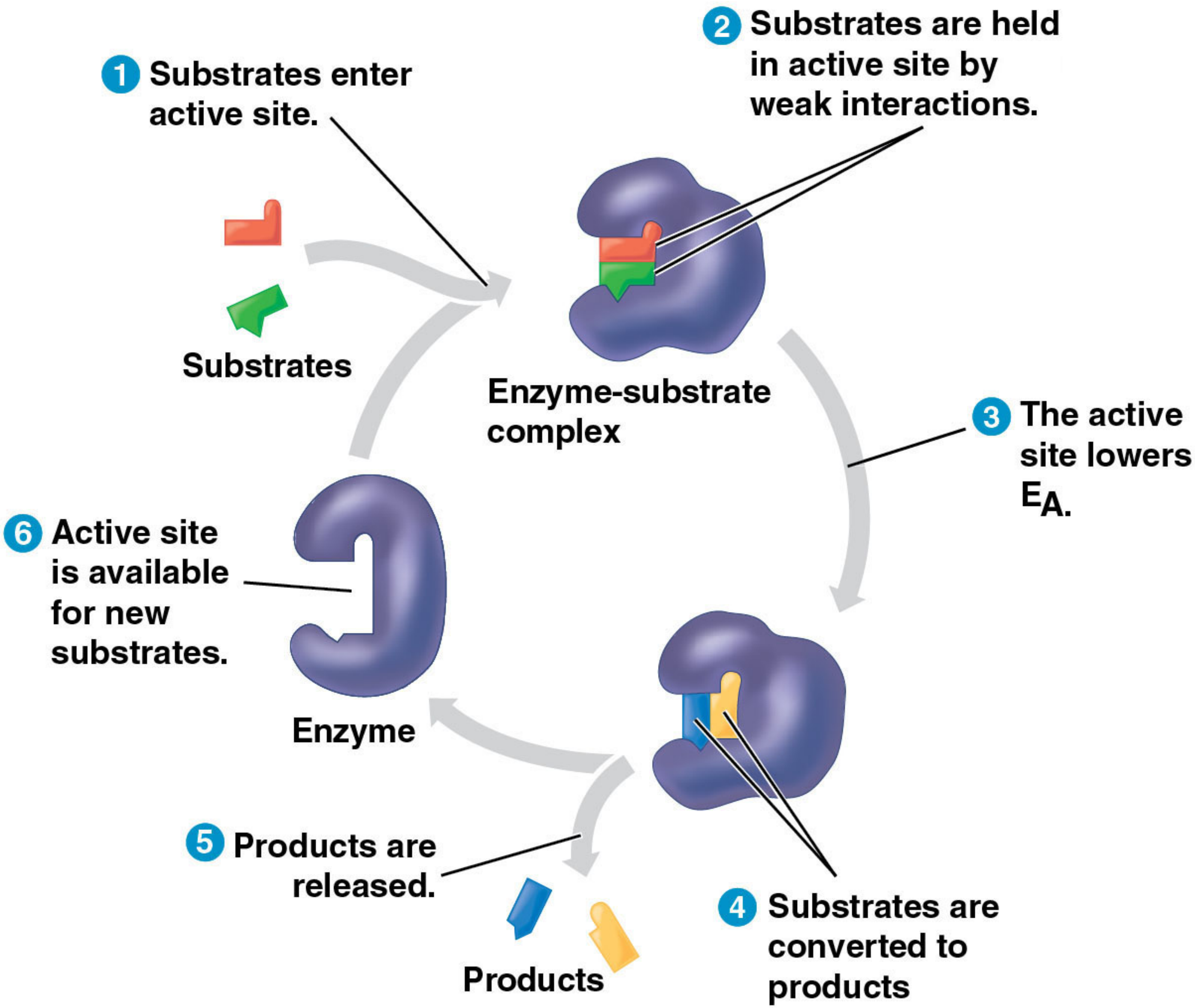
1 Substrates enter active site.
2 Substrates are held in active site by weak interactions.
Substrates
Enzyme-substrate complex
3 The active site lowers E_A.

Figure 8.16-3



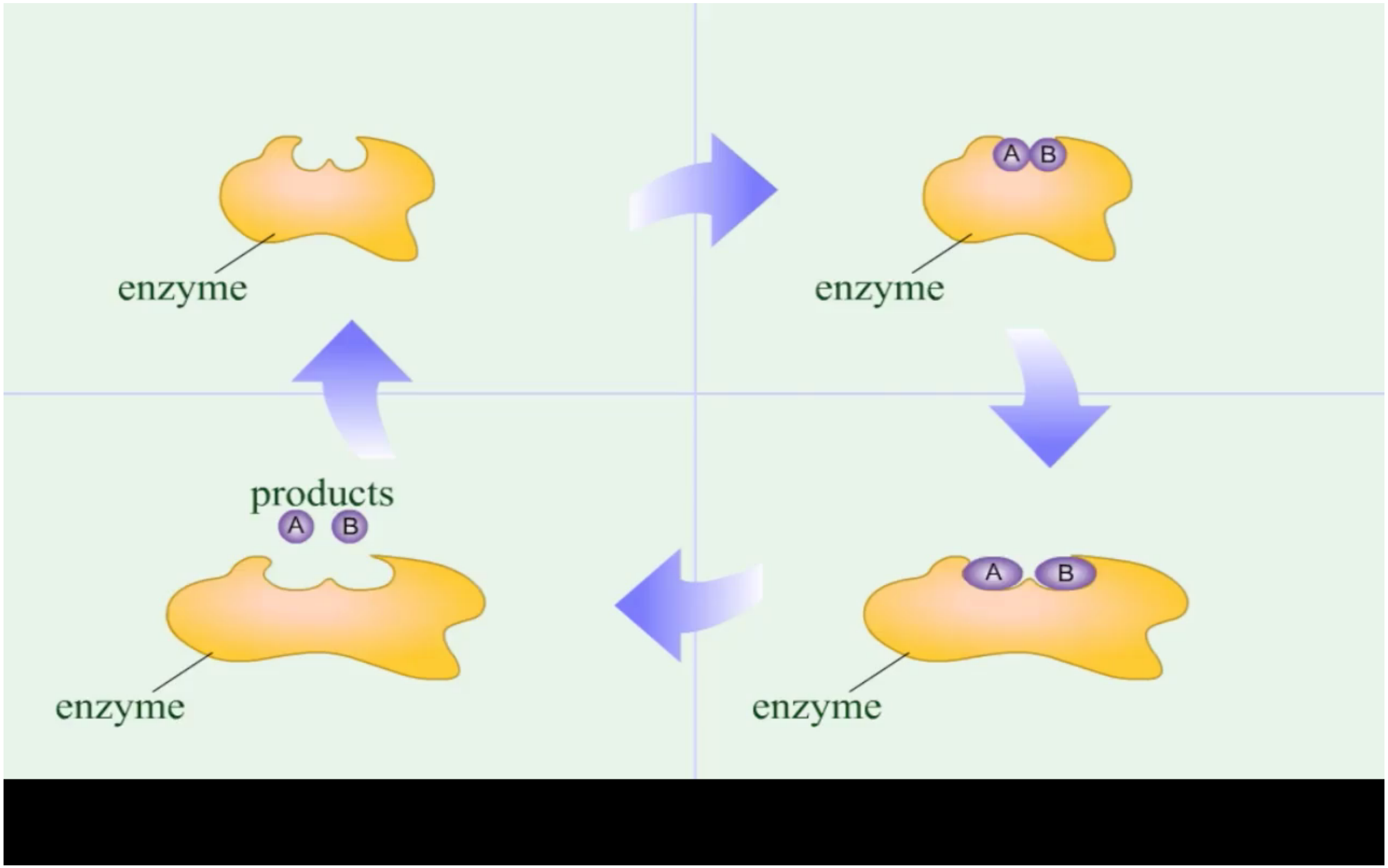
1 Substrates enter active site.
2 Substrates are held in active site by weak interactions.
Substrates
Enzyme-substrate complex
3 The active site lowers E_A.
5 Products are released.
Products
4 Substrates are converted to products

Figure 8.16-4



1 Substrates enter active site.
2 Substrates are held in active site by weak interactions.
Substrates
Enzyme-substrate complex
3 The active site lowers E_A.
6 Active site is available for new substrates.
Enzyme
5 Products are released.
Products
4 Substrates are converted to products

Animation: Enzymes: Steps in a Reaction



- Enzymes use a variety of mechanisms to lower E_A
  - Substrates may be oriented to facilitate the reaction
  - Substrates may be stretched to make the bonds easier to break
  - The active site may provide a microenvironment that favors the reaction
  - Amino acids in the active site may participate in the reaction

- The rate of an enzyme-catalyzed reaction can be sped up by increasing substrate concentration
- When all enzyme molecules have their active sites engaged, the enzyme is saturated
- If the enzyme is saturated, the reaction rate can only be sped up by adding more enzyme

Effects of Local Conditions on Enzyme Activity

- Enzyme activity can be affected by general environmental factors, such as temperature and pH
- It can also be affected by chemicals that specifically influence the enzyme

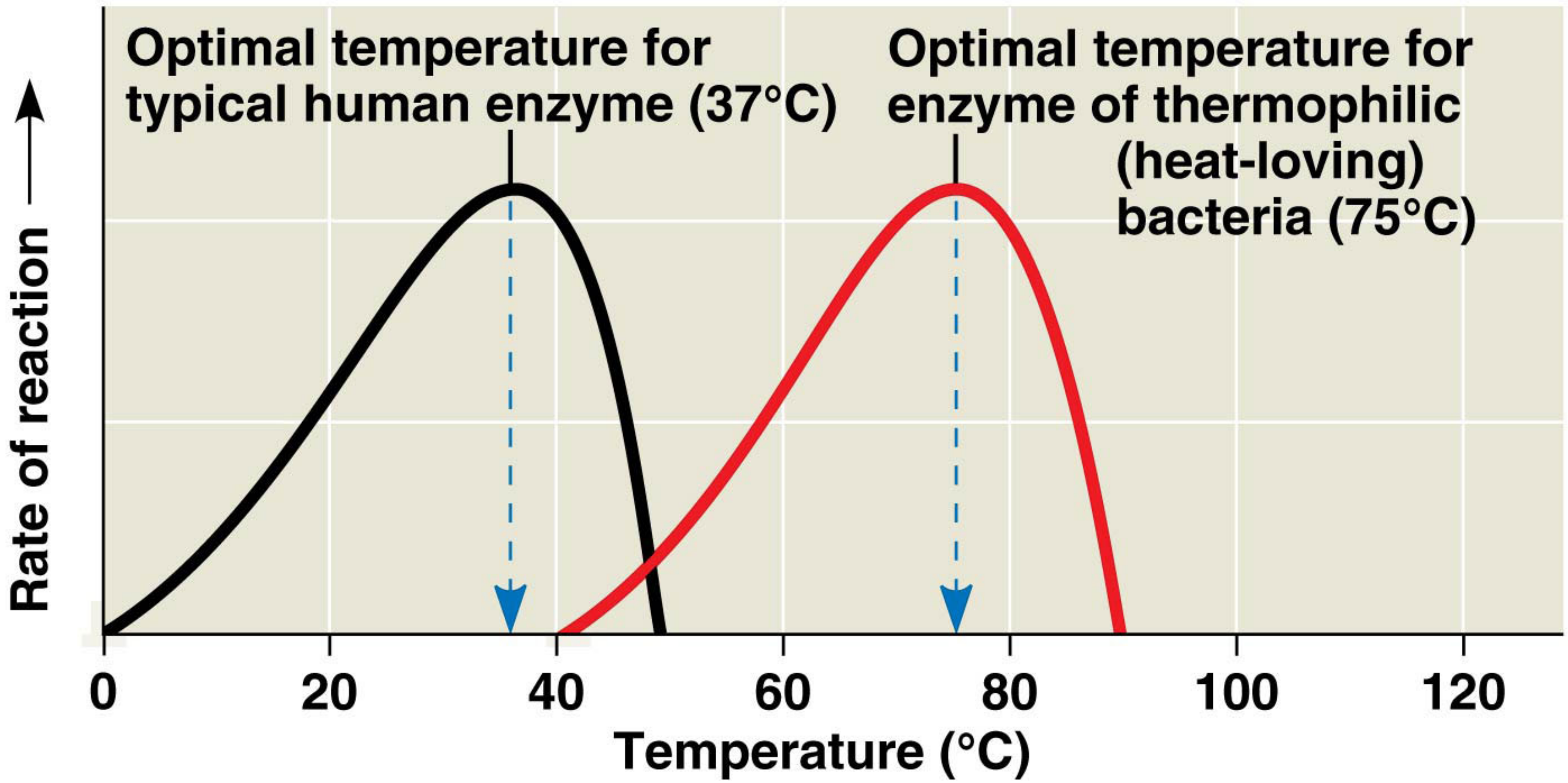
Effects of Temperature and pH

- Each enzyme has an optimal temperature at which it catalyzes its reaction at the maximum possible rate
- Up to this point, the reaction rate increases with increasing temperature; beyond this point the rate of reaction begins to drop
- Enzymes begin to denature at temperatures beyond their optimum

- The optimal temperature of an enzyme is dependent on the environment in which it typically functions
  - For example, the optimal temperature for human enzymes is about 37°C, whereas the optimal temperature for thermophilic bacteria is about 75°C

Figure 8.17

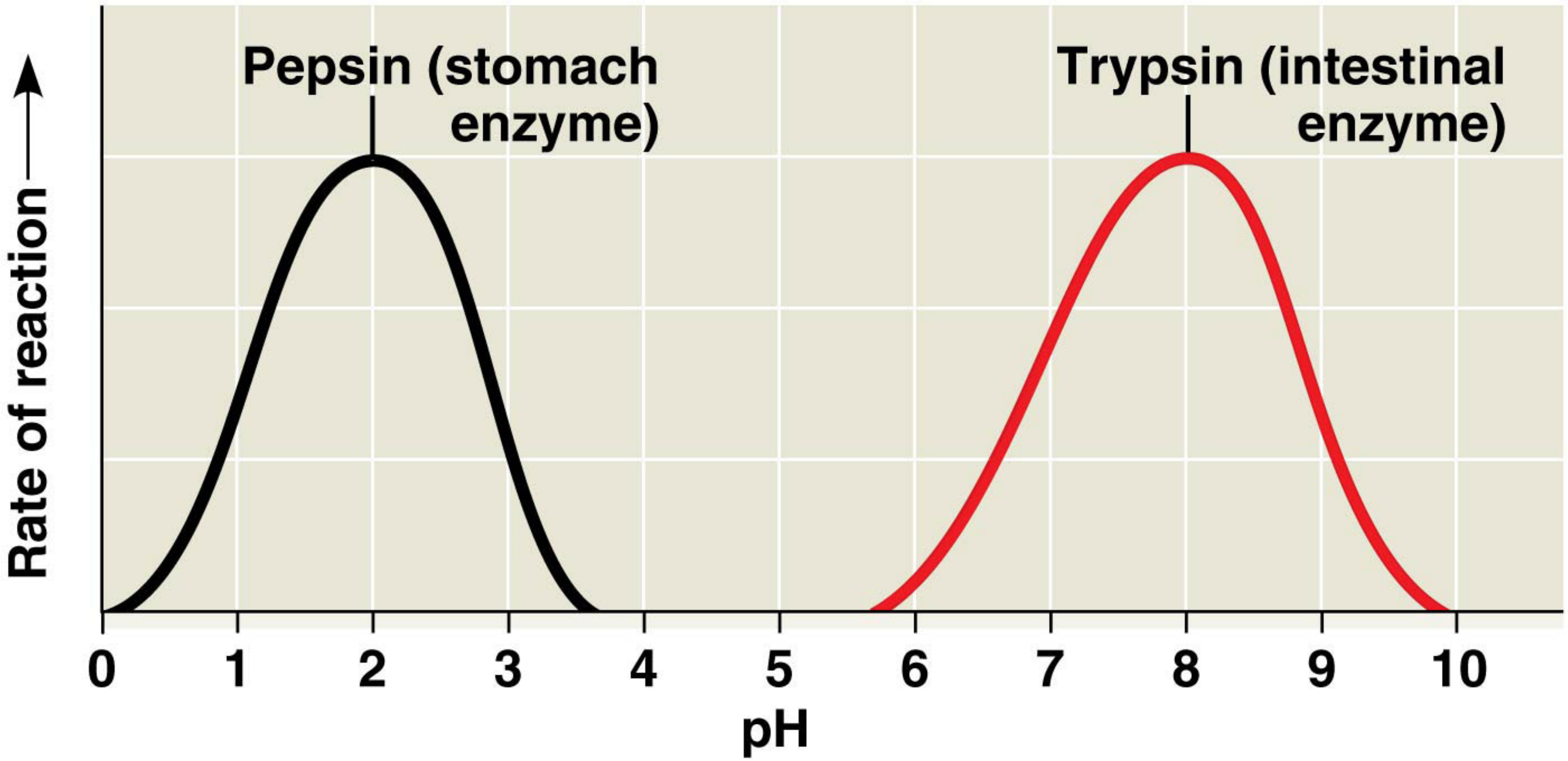
Figure 8.17a



(a) Optimal temperature for two enzymes

- Each enzyme has an optimal pH that is dependent on the environment in which it is typically active
  – For example, the optimal pH for pepsin—a human stomach enzyme—is 2, whereas the optimal pH for trypsin—an intestinal enzyme—is 8

Figure 8.17b



(b) Optimal pH for two enzymes

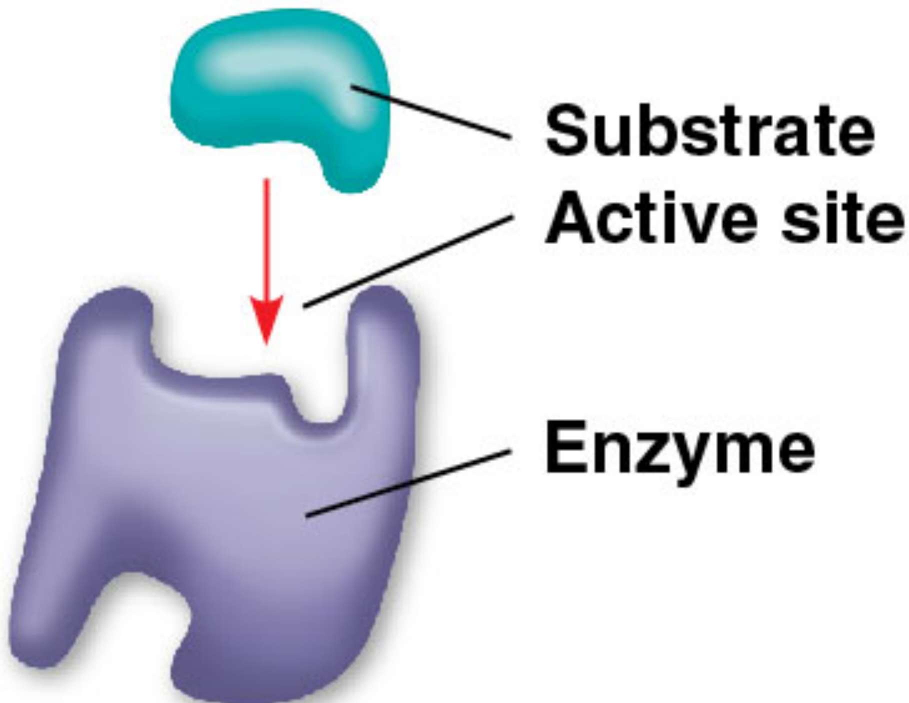
Cofactors

- **Cofactors** are nonprotein helpers that bind to the enzyme permanently, or reversibly with the substrate
- Inorganic cofactors include metal atoms such as zinc, iron, and copper in ionic form
- Organic cofactors are called **coenzymes**
- Most vitamins either act as coenzymes or provide the raw materials needed to make them

Enzyme Inhibitors

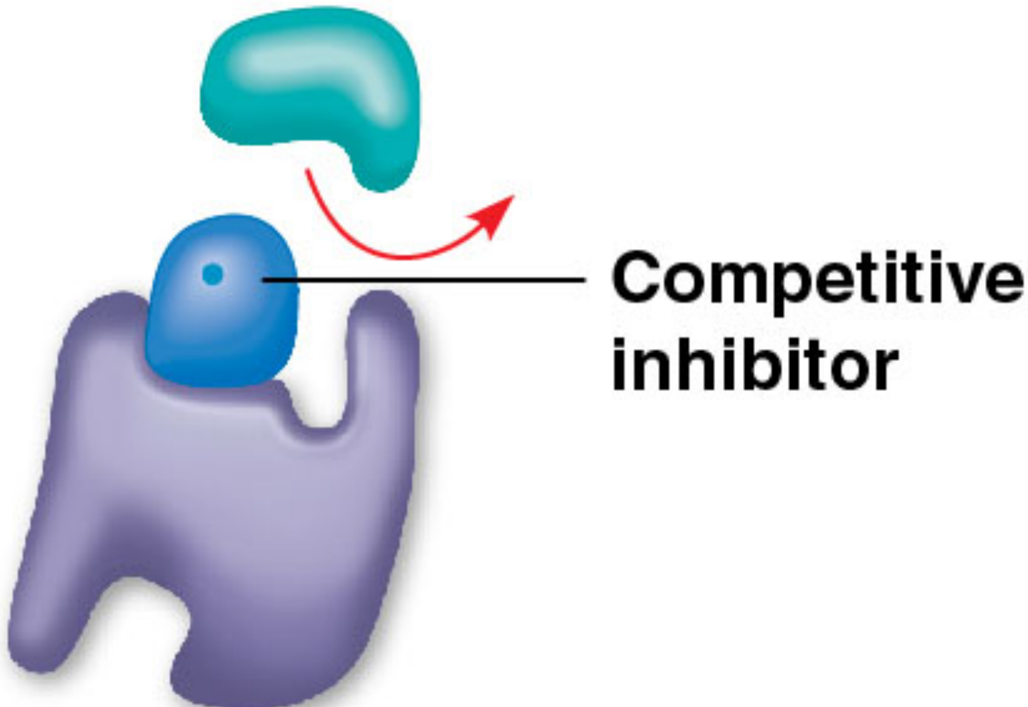
- Certain chemicals selectively inhibit the action of specific enzymes
- If an inhibitor forms covalent bonds with the enzyme, then the inhibition is usually irreversible
- Many inhibitors bind to the enzyme by weak interactions, resulting in reversible inhibition

- **Competitive inhibitors** closely resemble the substrate, and can bind to the enzyme's active site
- Enzyme productivity is reduced because the inhibitor blocks the substrate from entering the active site
- Increasing substrate concentration can overcome this type of inhibition



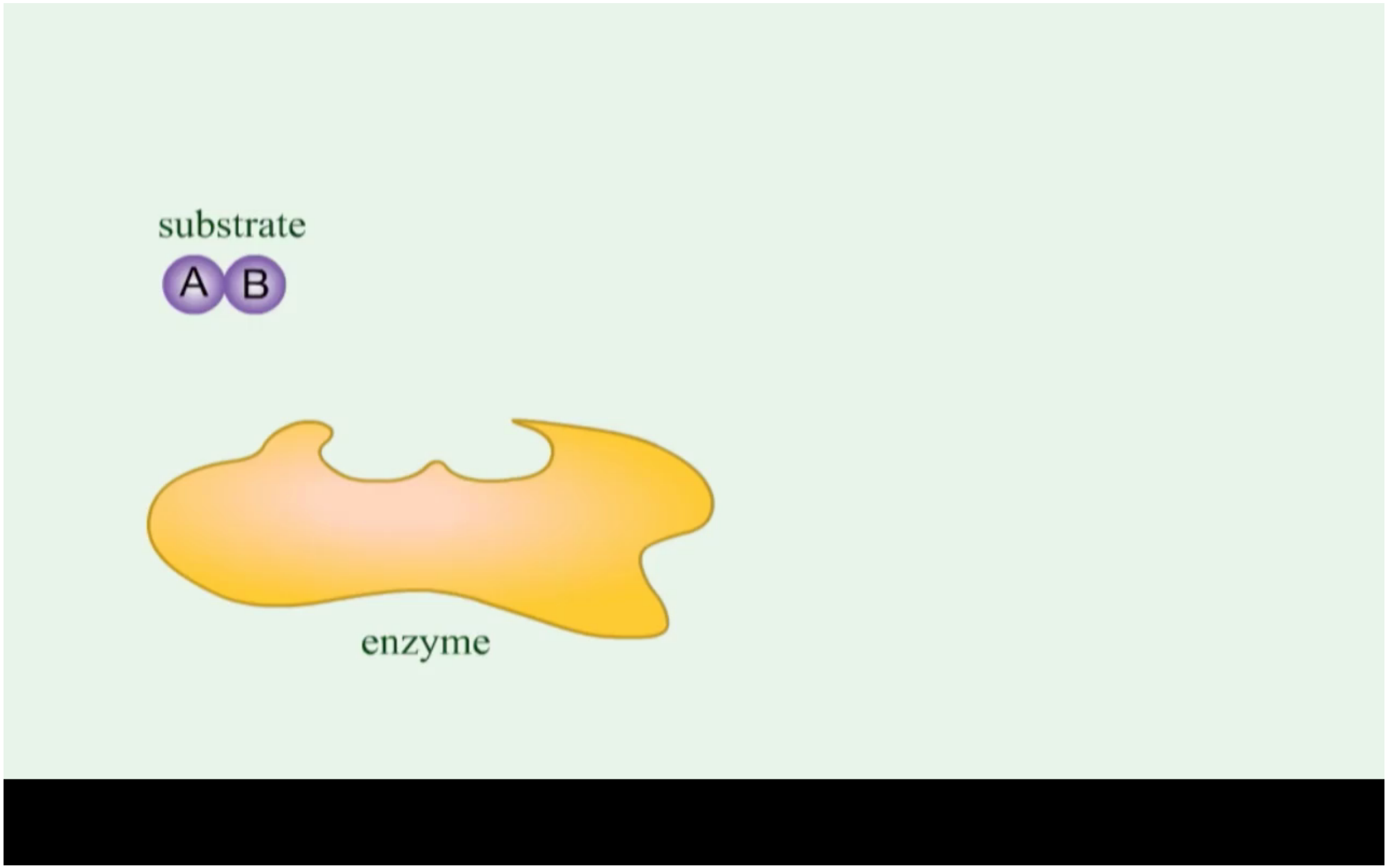
(a) Normal binding

Figure 8.18b



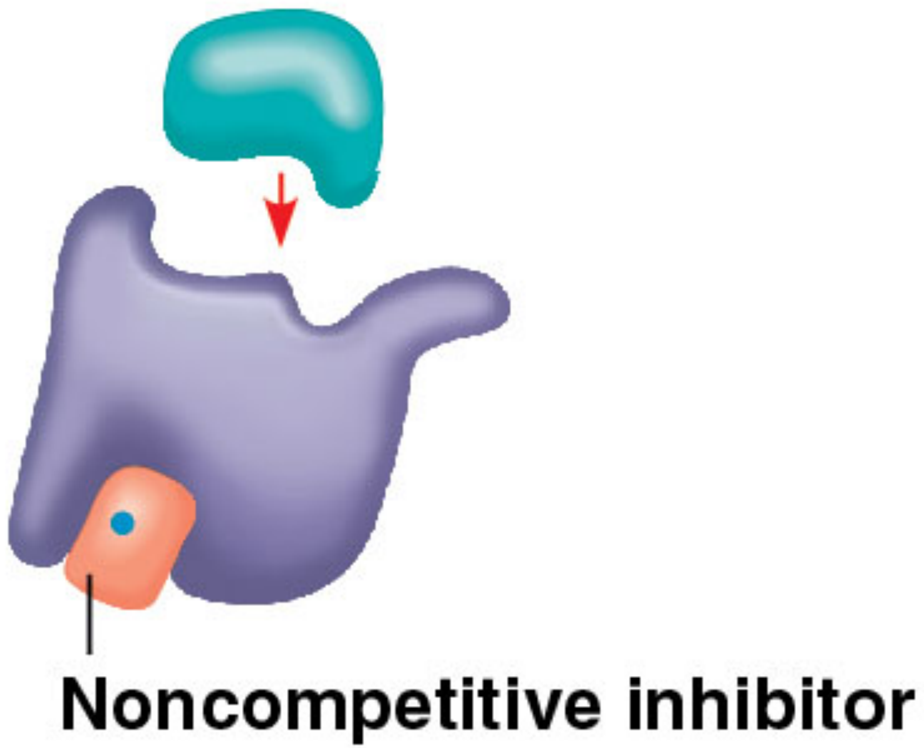
(b) Competitive inhibition

Animation: Enzymes: Competitive Inhibition



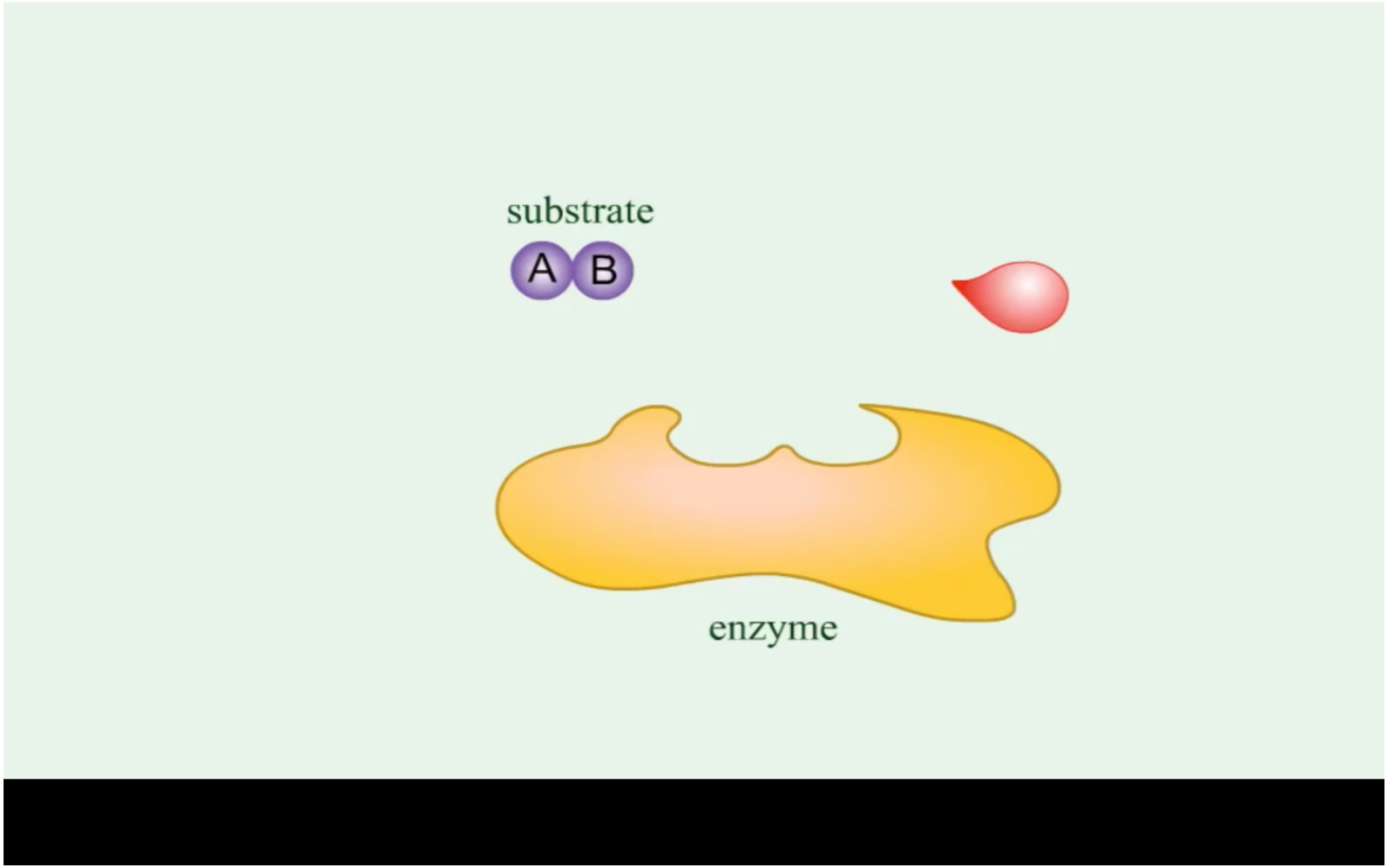
- **Noncompetitive inhibitors** bind to another part of the enzyme, away from the active site
- Binding of the inhibitor causes the enzyme to change shape, making the active site less effective at catalyzing the reaction

Figure 8.18c



(c) Noncompetitive inhibition

Animation: Enzymes: Noncompetitive Inhibition



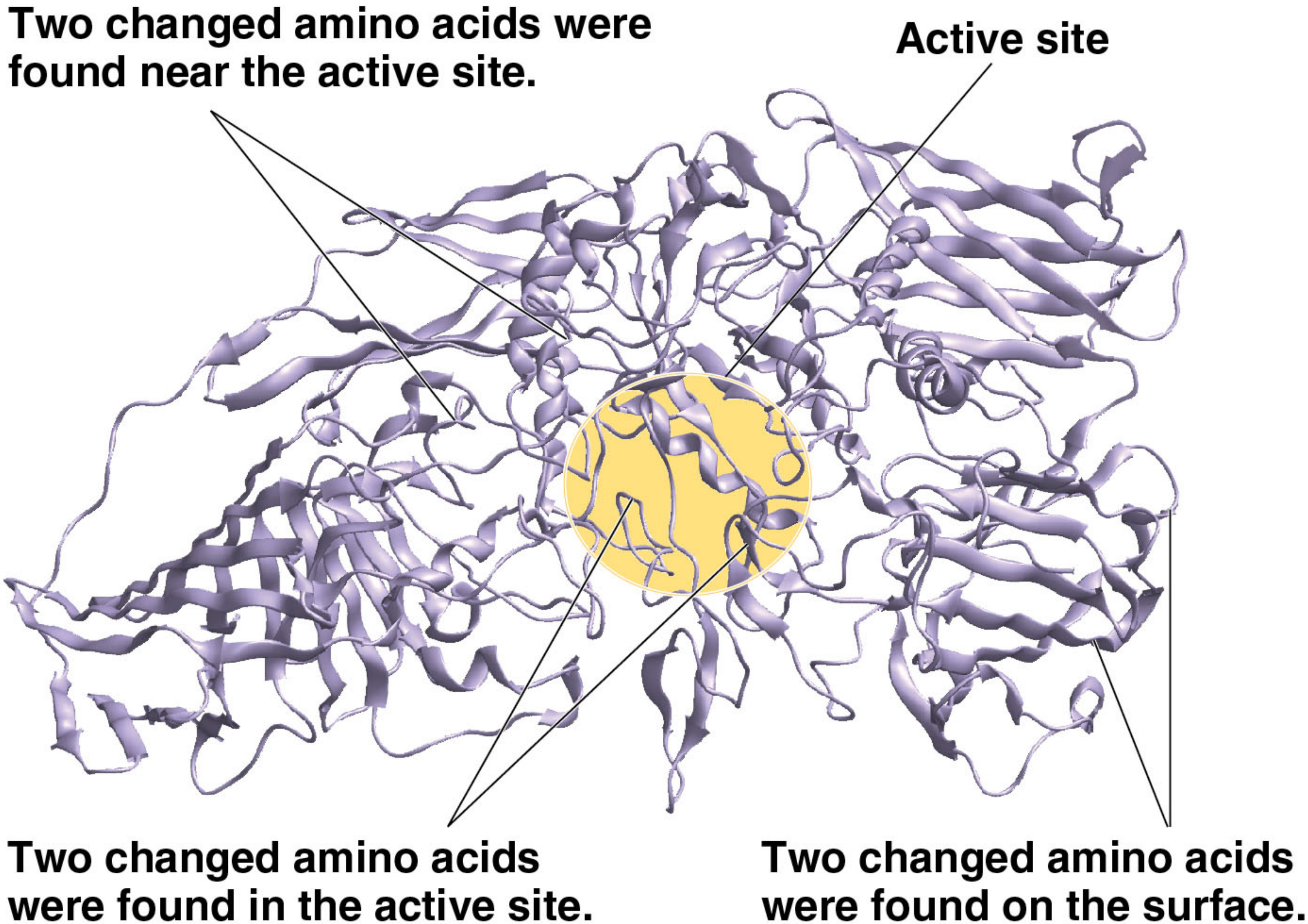
- Toxins and poisons are often irreversible enzyme inhibitors
  - For example, sarin gas was used in a chemical attack in Syria in 2017, killing and injuring hundreds
  - Sarin binds covalently to the active site of acetylcholinesterase, an enzyme important in the nervous system
- Other examples include pesticides and antibiotics

The Evolution of Enzymes

- Enzymes are proteins encoded by genes
- Changes in genes (mutations) lead to changes in the amino acid composition of the enzyme
- Altered amino acids, particularly at the active site, can result in novel enzyme activity or altered substrate specificity

- If a mutation results in a new enzyme function that is beneficial to the organism, natural selection will favor the mutated allele
  - For example, repeated mutation and selection on the β-galactosidase enzyme in *E. coli* resulted in a change of sugar substrate under lab conditions

Figure 8.19


Two changed amino acids were found near the active site.
Active site
Two changed amino acids were found in the active site.
Two changed amino acids were found on the surface.

CONCEPT 8.5: Regulation of enzyme activity helps control metabolism

- Chemical chaos would result if a cell’s metabolic pathways were operating simultaneously
- Cells can regulate metabolic pathways by switching on or off the genes that encode specific enzymes, or by regulating the activity of existing enzymes

Allosteric Regulation of Enzymes

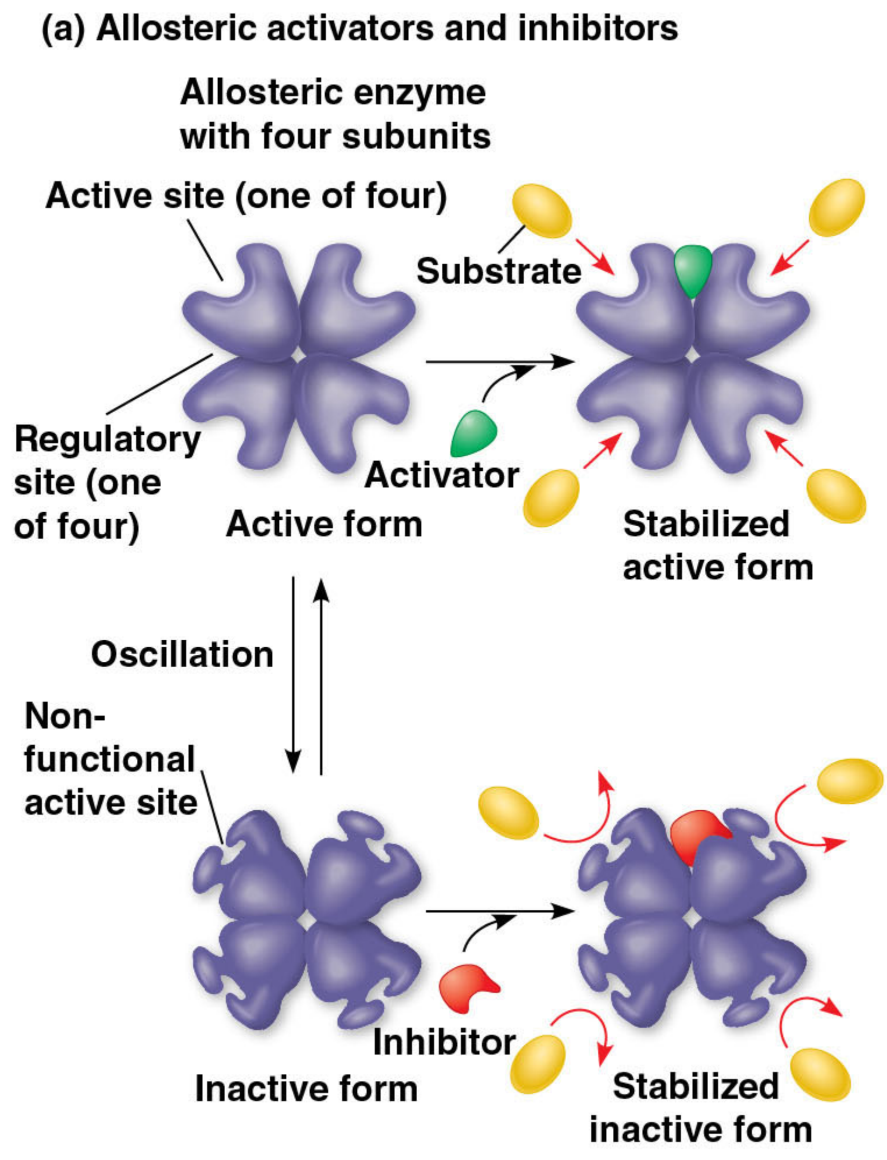
- **Allosteric regulation** occurs when a regulatory molecule binds to a protein at one site and affects the protein's function at another site
- This type of regulation may either inhibit or stimulate enzyme activity

Allosteric Activation and Inhibition

- Most allosterically regulated enzymes are made from polypeptide subunits, each with its own active site
- The complex oscillates between two shapes, one catalytically active and the other inactive

- An activating or inhibiting molecule may bind to a regulatory site, often located where the subunits join
- The binding of an activator stabilizes the shape that has functional active sites, whereas the binding of an inhibitor stabilizes the inactive form of the enzyme

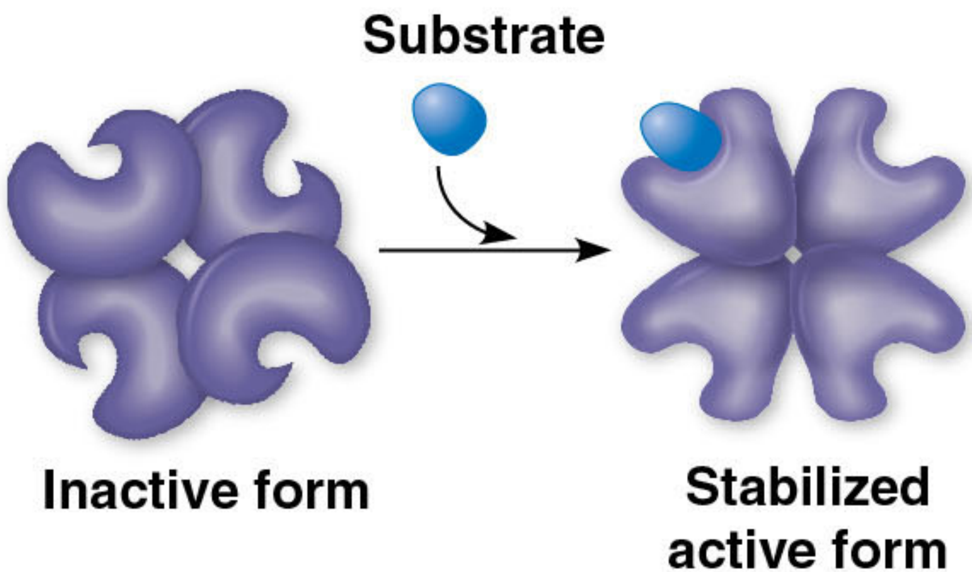
Figure 8.20a



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

- In **cooperativity**, substrate binding to one active site triggers a shape change in the enzyme that stabilizes the active form for all other sites
- This mechanism amplifies the response by priming the enzyme to act on additional substrate molecules more readily

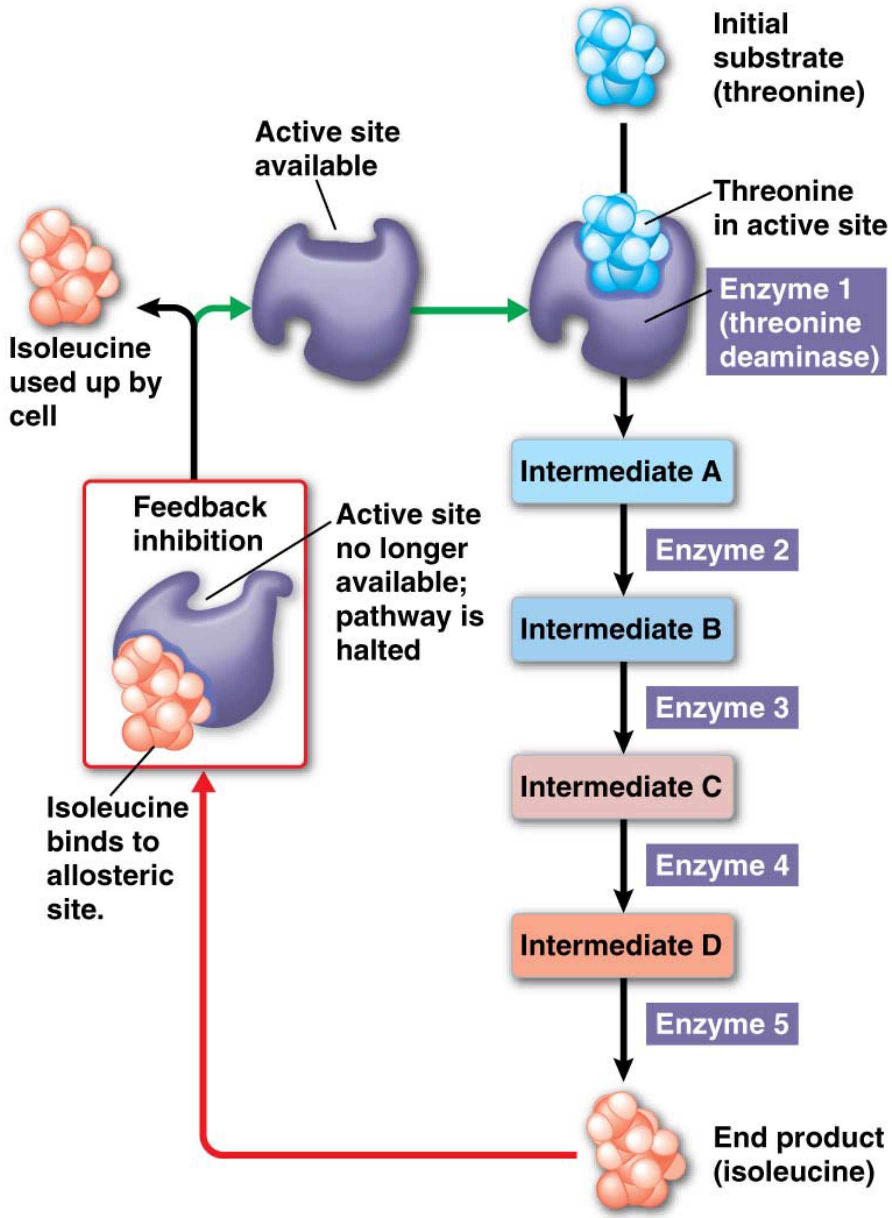
(b) Cooperativity: another type of allosteric activation



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 8.21



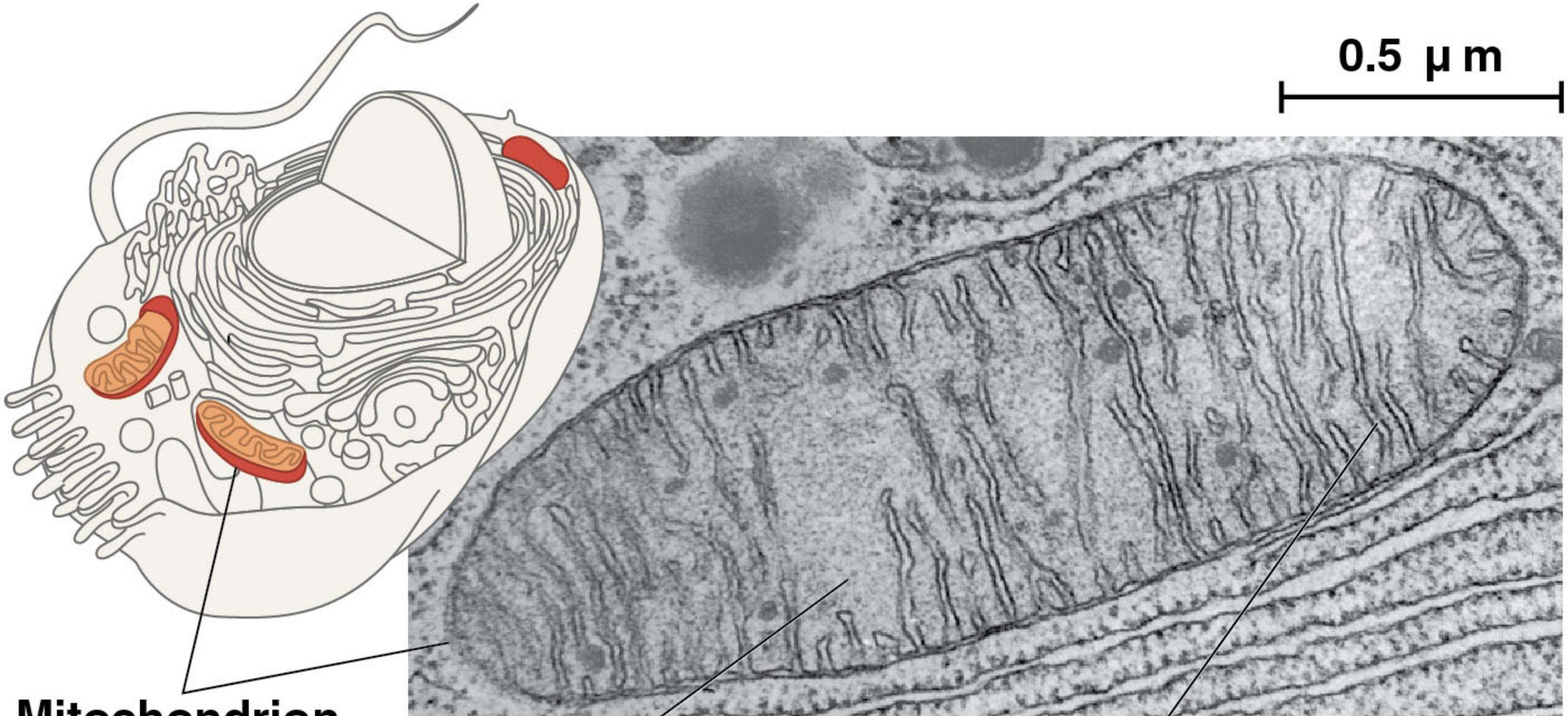
Initial substrate (threonine)
Active site available
Threonine in active site
Enzyme 1 (threonine deaminase)
Isoleucine used up by cell
Intermediate A
Enzyme 2
Feedback inhibition
Active site no longer available; pathway is halted
Intermediate B
Enzyme 3
Intermediate C
Isoleucine binds to allosteric site.
Enzyme 4
Intermediate D
Enzyme 5
End product (isoleucine)

Localization of Enzymes Within the Cell

- Compartmentalization of the cell helps to bring order to metabolic pathways
- In some cases, the enzymes for several steps in a metabolic pathway form a multienzyme complex
- Some enzymes have fixed locations and act as structural components of particular membranes

- In eukaryotic cells, some enzymes reside within specific organelles
  - For example, enzymes for the second and third stages of cellular respiration are located within mitochondria

Figure 8.22



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

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

Figure 8.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 8.UN03b

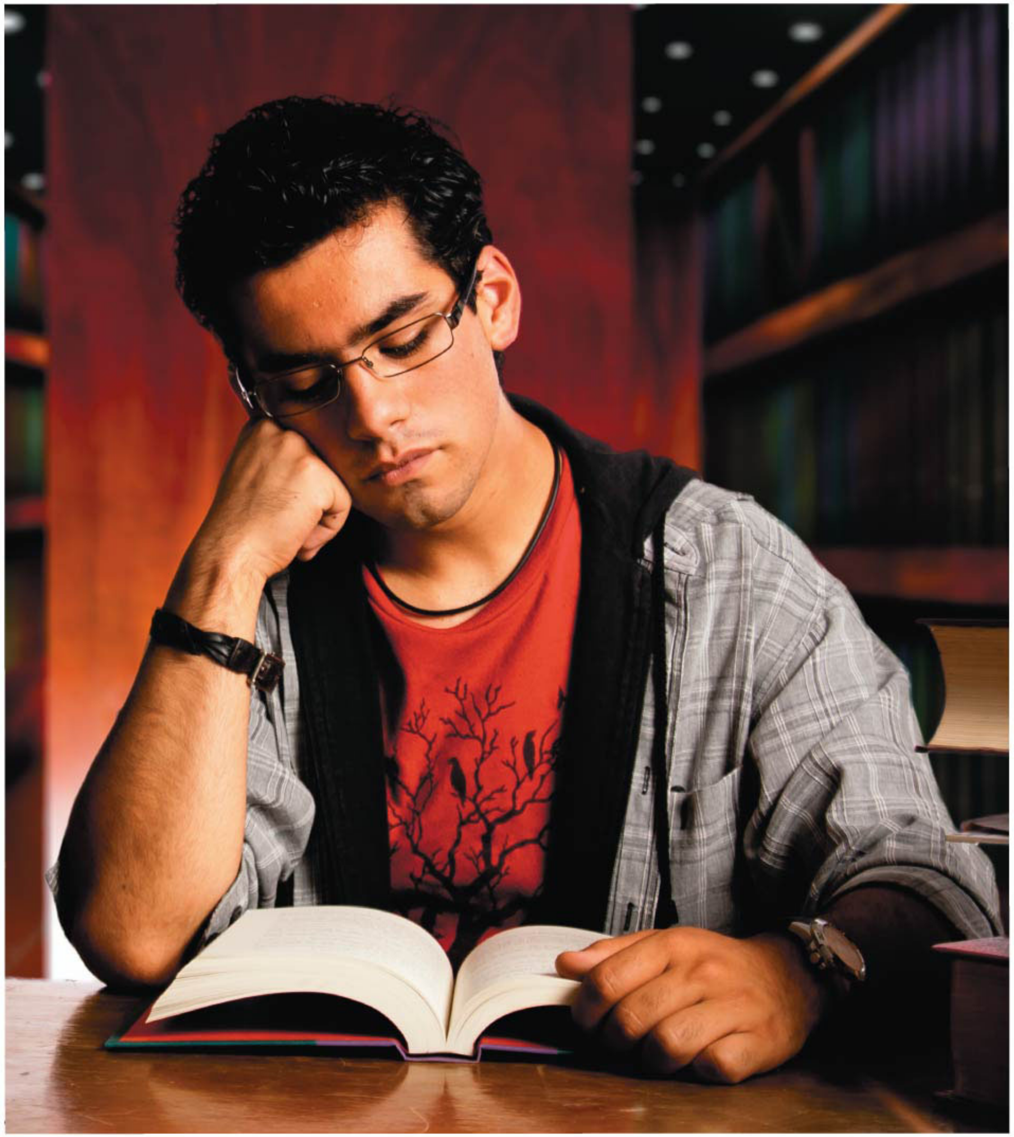


Figure 8.UN04

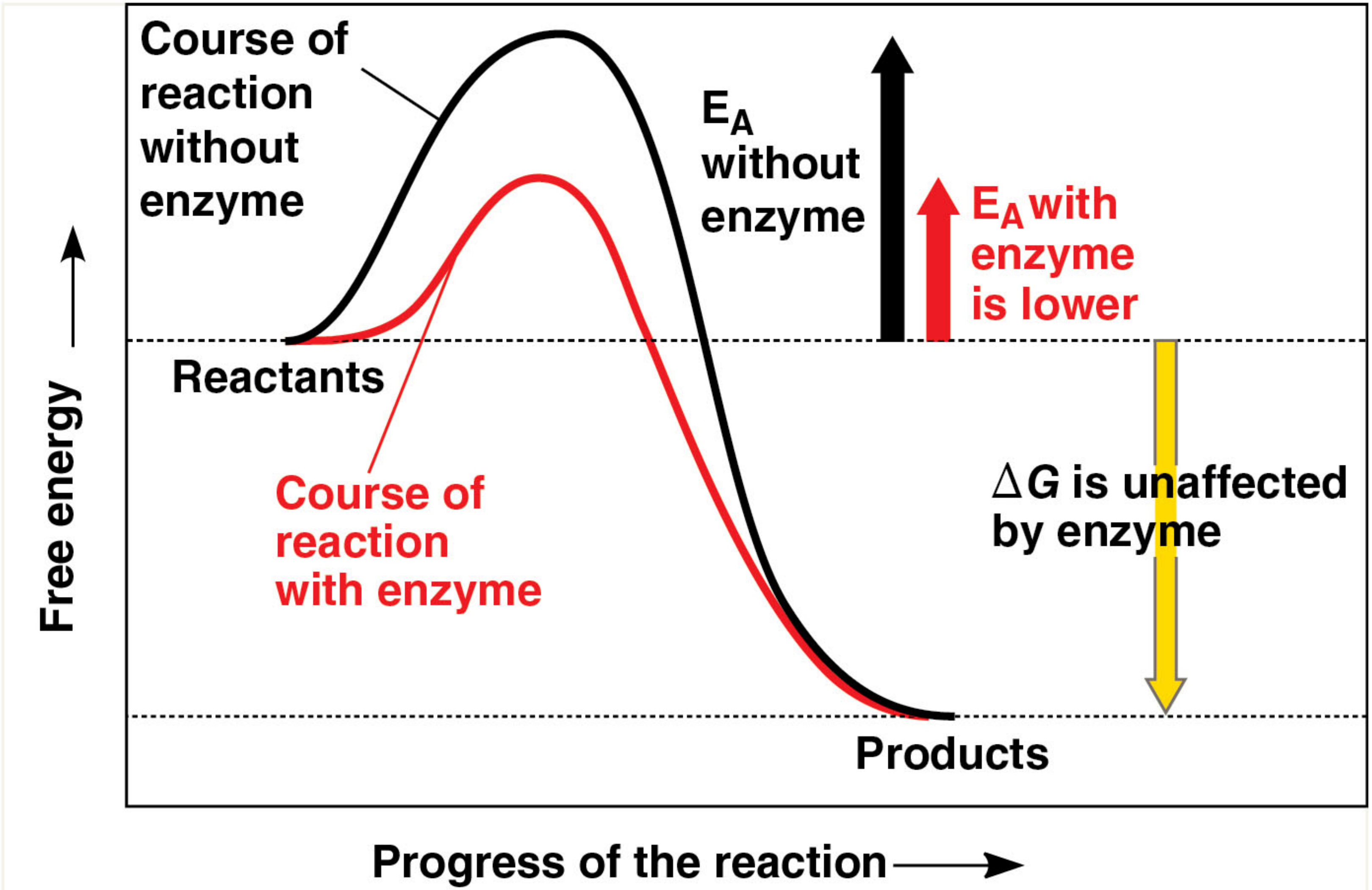


Figure 8.UN05