Chapter 15

Metabolism is composed of many interconnected reactions
ATP – universal free energy currency
Oxidation of carbon fuels is an important source of energy
Metabolic pathway contain many recurring motifs

Cells extract energy from their environment and use the energy for a host of biological activities including biosynthesis.

The reactions of energy extraction and energy use are called metabolism or intermediary metabolism.

Basic principles govern energy manipulations in all cells:

1. Molecules are degraded or synthesized stepwise in a series of reactions termed metabolic pathways.

2. ATP is the energy currency of life.

3. ATP can be formed by the oxidation of carbon fuels.

4. Although many reactions occur inside a cell, there are a limited number of reaction types involving particular intermediates that are common to all metabolic pathways.

5. Metabolic pathways are highly regulated.

Energy is required to power muscle contraction and cell movement, active transport, and biosynthesis.

Phototrophs obtain energy by capturing sunlight.

Chemotrophs obtain energy through the oxidation of carbon fuels.

Metabolism consists of energy-yielding and energy-requiring reactions

Metabolic pathways can be divided into two types:

1. Catabolic pathways combust carbon fuels to synthesize ATP.

$$\text{Fuel (carbohydrates, fats)} \xrightarrow{\text{Catabolism}} CO_2 + H_2O + \text{useful energy}$$

2. Anabolic pathways use ATP and reducing power to synthesize large biomolecules.

$$\text{Useful energy} + \text{simple precursors} \xrightarrow{\text{Anabolism}} \text{complex molecules}$$

Some pathways, called amphibolic pathways, can function anabolically or catabolically.

Although anabolic and catabolic pathways may have reactions in common, the regulated, irreversible reactions are always distinct.

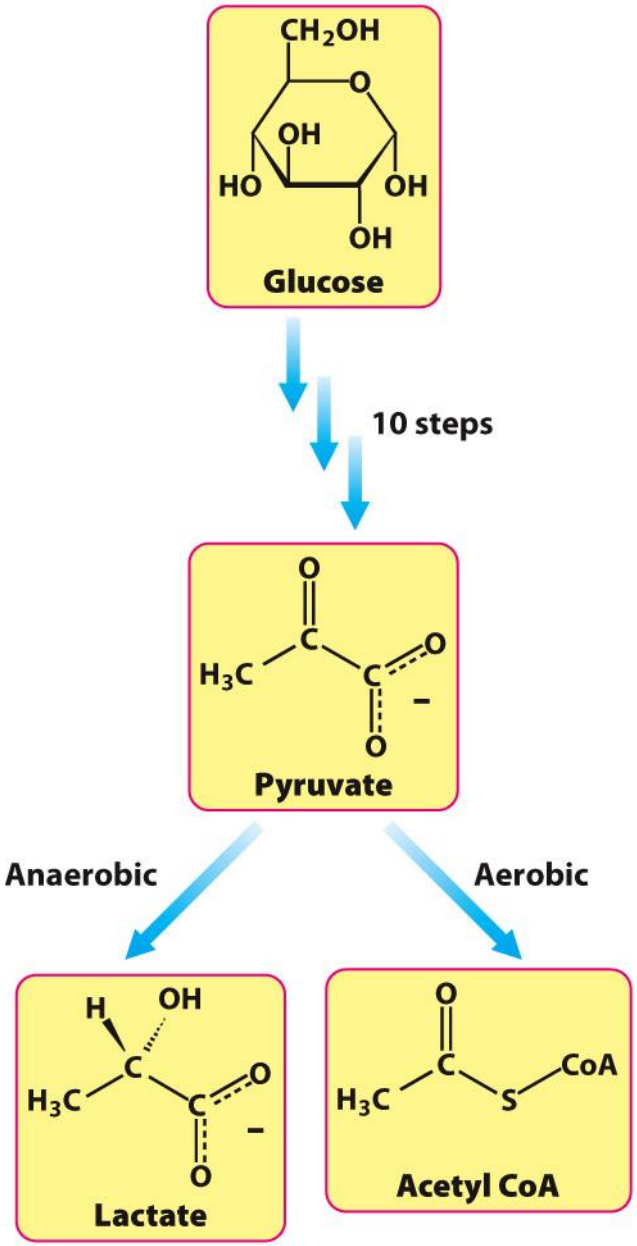

Figure 15.1
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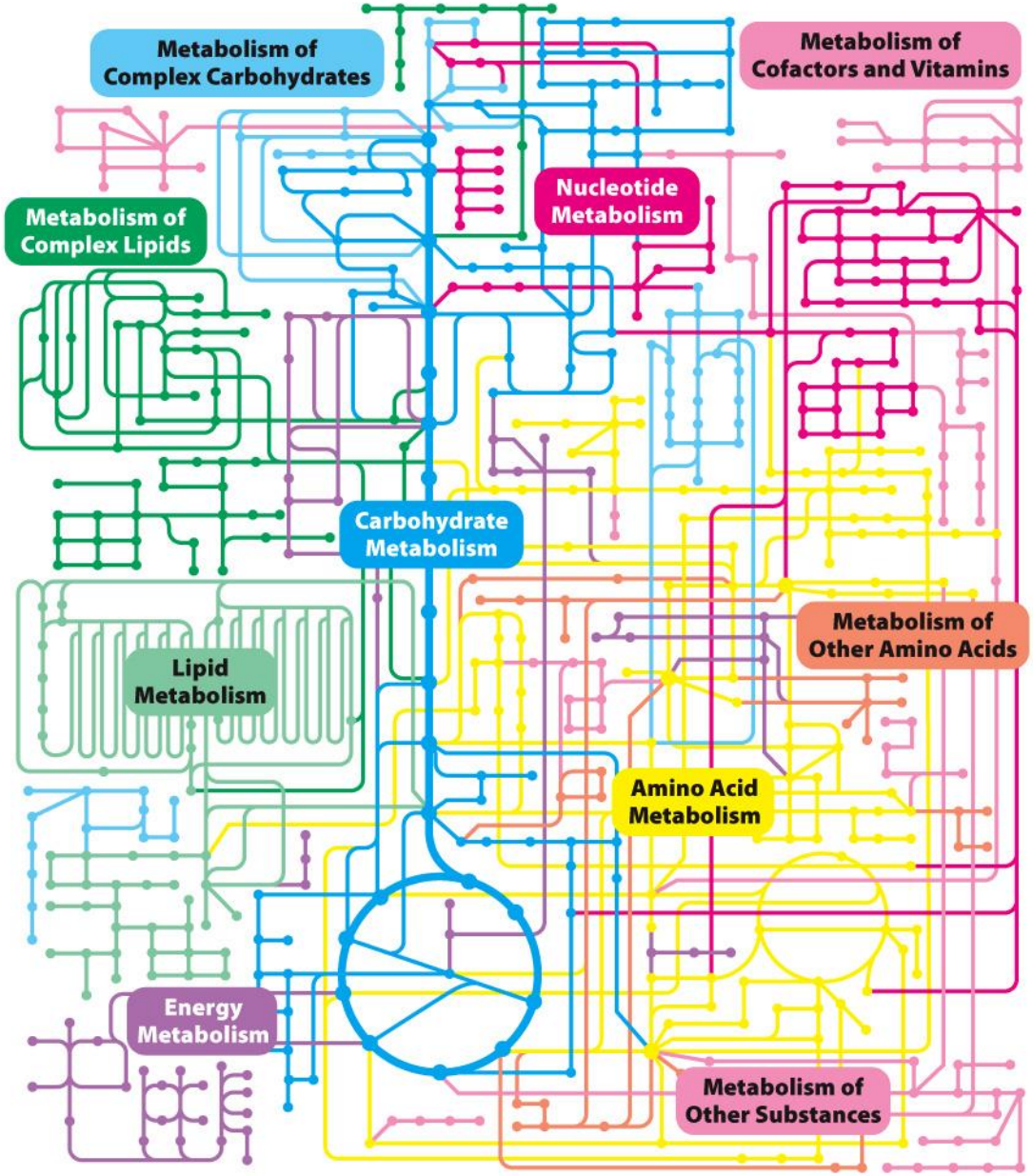

Figure 15.2
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Metabolic pathways. Each node represents a metabolite

Biosynthesis and degradation pathways are almost always distinct. The separation is necessary for energetic reasons.

A thermodynamically unfavorable reaction can be driven by a favorable reaction

In order to construct a metabolic pathway, two criteria must be met:

1. The individual reactions must be specific.

2. The pathway in total must be thermodynamically favorable.

A thermodynamically unfavorable reaction in a pathway can be made to occur by coupling it to a more favorable reaction.

$$\begin{array}{ll} A \rightleftharpoons B + C & \Delta G^{\circ\prime} = +21\ \text{kJ mol}^{-1}\ (+5\ \text{kcal mol}^{-1}) \\ B \rightleftharpoons D & \Delta G^{\circ\prime} = -34\ \text{kJ mol}^{-1}\ (-8\ \text{kcal mol}^{-1}) \\ \hline A \rightleftharpoons C + D & \Delta G^{\circ\prime} = -13\ \text{kJ mol}^{-1}\ (-3\ \text{kcal mol}^{-1}) \end{array}$$

Energy derived from fuels or light is converted into adenosine triphosphate (ATP), the cellular energy currency.

ATP hydrolysis is exergonic

The hydrolysis of ATP is exergonic because the triphosphate unit contains two phosphoanhydride bonds that are unstable.

The energy released on ATP hydrolysis is used to power a host of cellular functions.

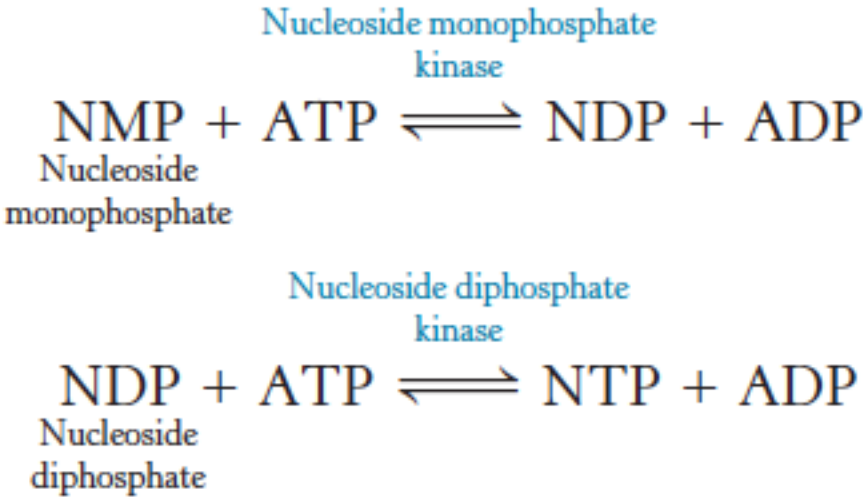
$$\mathrm{ATP} + \mathrm{H_2O} \rightleftharpoons \mathrm{ADP} + \mathrm{P_i} \qquad \Delta G^{\circ\prime} = -30.5\ \mathrm{kJ\ mol^{-1}}\ (-7.3\ \mathrm{kcal\ mol^{-1}})$$

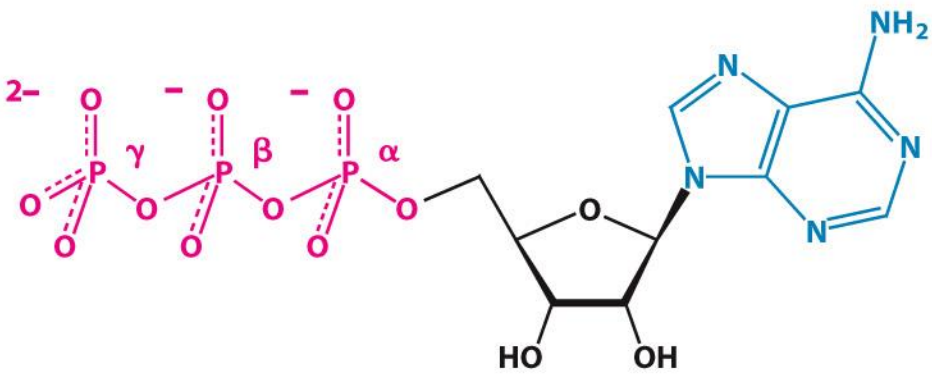
$$\mathrm{ATP} + \mathrm{H_2O} \rightleftharpoons \mathrm{AMP} + \mathrm{PP_i} \qquad \Delta G^{\circ\prime} = -45.6\ \mathrm{kJ\ mol^{-1}}\ (-10.9\ \mathrm{kcal\ mol^{-1}})$$

ATP hydrolysis is exergonic

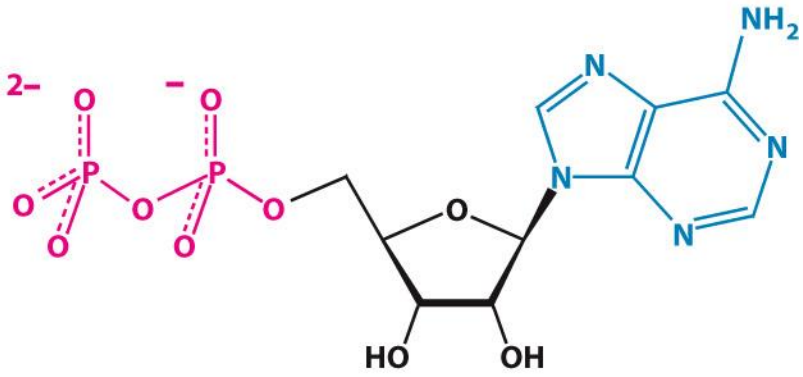
The ATP/ADP cycle is an important means of energy exchange in biological systems.

Enzymes can catalyze the transfer of a terminal phosphoryl group from one nucleotide to another.

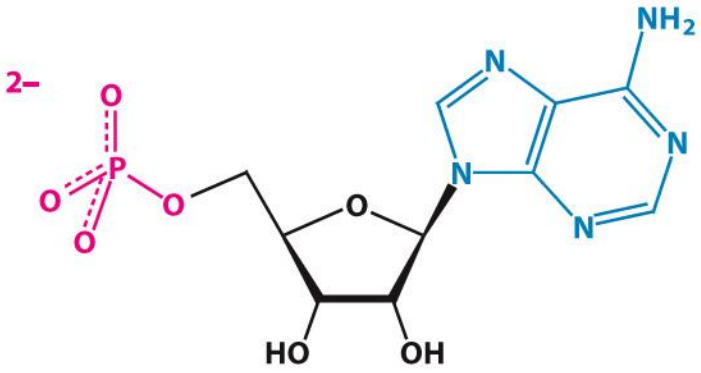




Adenosine triphosphate (ATP)



Adenosine diphosphate (ADP)



Adenosine monophosphate (AMP)

Figure 15.3

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ATP hydrolysis drives metabolism by shifting the equilibrium of coupled reactions

Consider the following endergonic reaction:

$$A \rightleftharpoons B \qquad \Delta G^{\circ\prime} = +16.7\ \text{kJ mol}^{-1}\ (+4\ \text{kcal mol}^{-1})$$

$$K'_{eq} = [B]_{eq}/[A]_{eq} = e^{-\Delta G^{\circ\prime}/2.47} = 1.15 \times 10^{-3}$$

Coupling this reaction with ATP hydrolysis renders the formation of B exergonic.

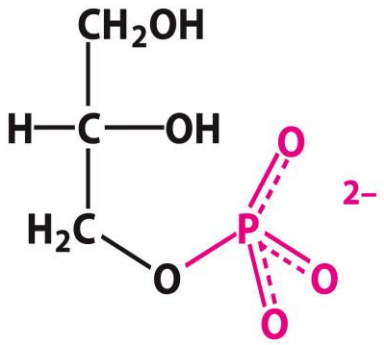
$$A + ATP + H_2O \rightleftharpoons B + ADP + P_i$$
$$\Delta G^{\circ\prime} = -13.8\ \text{kJ mol}^{-1}(-3.3\ \text{kcal mol}^{-1})$$

$$K'_{eq} = \frac{[B]_{eq}}{[A]_{eq}} \times \frac{[ADP]_{eq}[P_i]_{eq}}{[ATP]_{eq}} = e^{13.8/2.47} = 2.67 \times 10^{2}$$

The high phosphoryl potential of ATP results from structural differences between ATP and its hydrolysis products

Phosphoryl-transfer potential—the standard free energy of hydrolysis—is a means of comparing the tendency of organic molecules to transfer a phosphoryl group to an acceptor molecule. ATP has a higher phosphoryl-transfer potential than glycerol 3-phosphate.

$$\text{ATP} + \text{H}_2\text{O} \rightleftharpoons \text{ADP} + \text{P}_\text{i}$$
$$\Delta G^{\circ\prime} = -30.5\ \text{kJ mol}^{-1}\ (-7.3\ \text{kcal mol}^{-1})$$
$$\text{Glycerol 3-phosphate} + \text{H}_2\text{O} \rightleftharpoons \text{glycerol} + \text{P}_\text{i}$$
$$\Delta G^{\circ\prime} = -9.2\ \text{kJ mol}^{-1}\ (-2.2\ \text{kcal mol}^{-1})$$



Glycerol 3-phosphate

The high phosphoryl potential of ATP results from structural differences between ATP and its hydrolysis products

ATP has a high phosphoryl-transfer potential because of four key factors:

1. Resonance stabilization of ADP and Pi

1. Electrostatic repulsion.

2. Increase in entropy.

4. Stabilization by hydration.

Phosphoryl-transfer potential is an important form of cellular energy transformation

ATP has a phosphoryl-transfer potential intermediate between high phosphoryl-potential compounds derived from fuel molecules and acceptor molecules that require the addition of a phosphoryl group for cellular needs.

Creatine phosphate serves as an energy reserve in vertebrate muscle.

$$\text{Creatine phosphate} + \text{ADP} \overset{\text{Creatine kinase}}{\rightleftharpoons} \text{ATP} + \text{creatine}$$

$$K_{eq} = \frac{[\text{ATP}][\text{creatine}]}{[\text{ADP}][\text{creatine phosphate}]} = e^{-\Delta G^{\circ\prime}/2.47} = e^{12.6/2.47} = 162$$

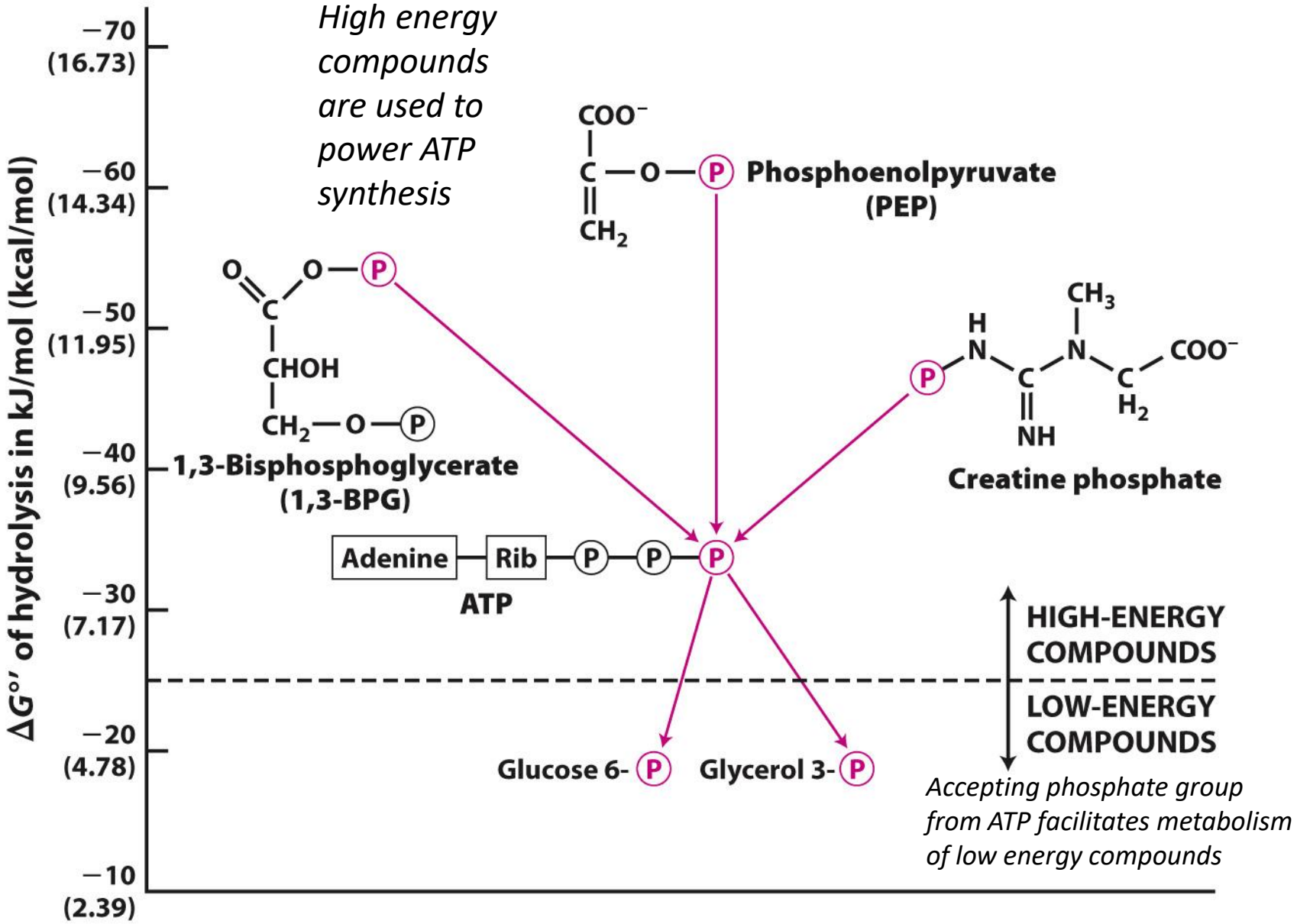


Figure 15.6
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TABLE 15.1 Standard free energies of hydrolysis of some phosphorylated compounds

Compound	kJ mol^{-1}	kcal mol^{-1}
Phosphoenolpyruvate	−61.9	−14.8
1,3-Bisphosphoglycerate	−49.4	−11.8
Creatine phosphate	−43.1	−10.3
ATP (to ADP)	−30.5	− 7.3
Glucose 1-phosphate	−20.9	− 5.0
Pyrophosphate	−19.3	− 4.6
Glucose 6-phosphate	−13.8	− 3.3
Glycerol 3-phosphate	− 9.2	− 2.2

Table 15.1
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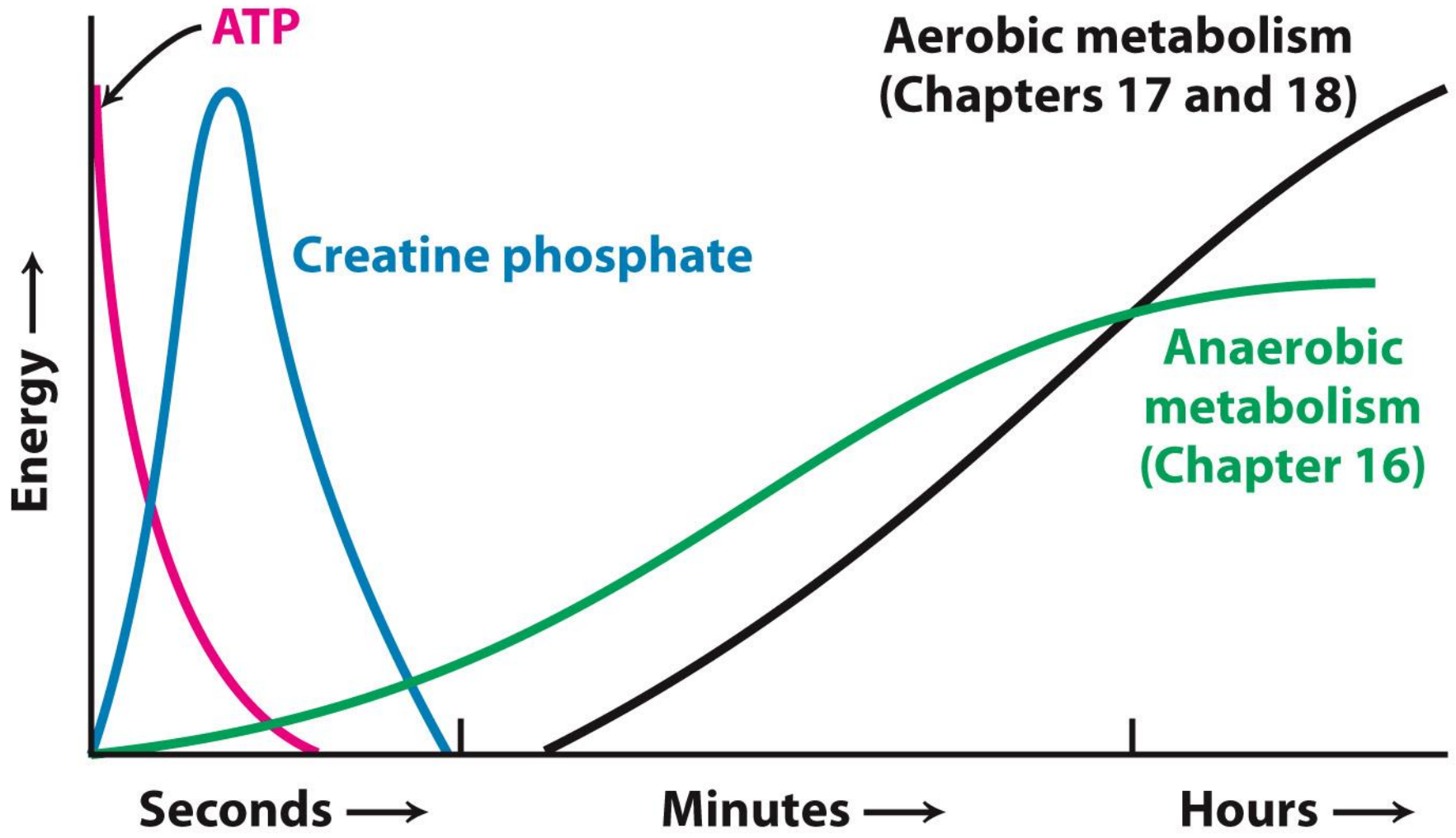

Figure 15.7
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ATP is the immediate donor of free energy for biological activities.

However, the amount of ATP is limited.

Consequently, ATP must be constantly recycled to provide energy to power the cell.

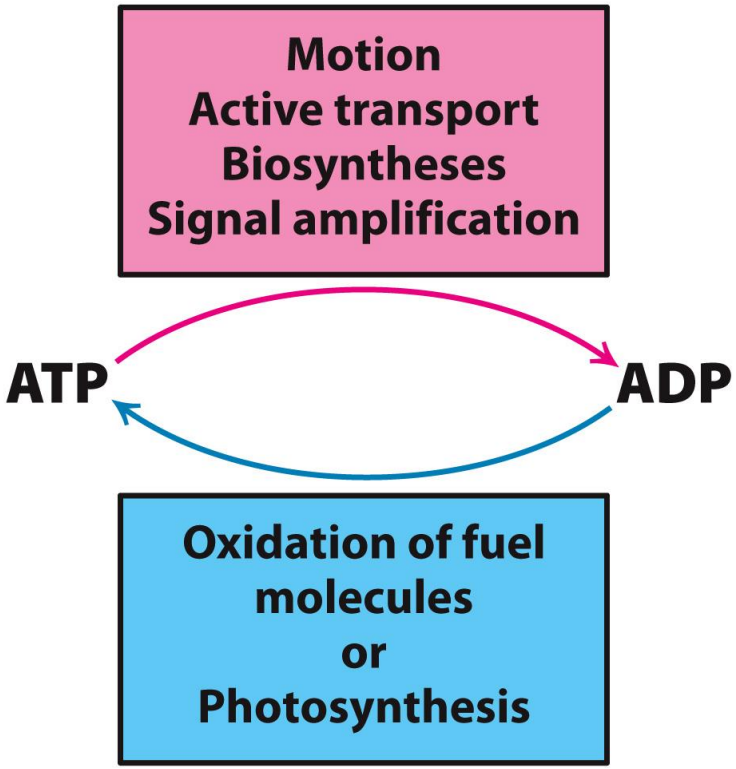

Figure 15.8
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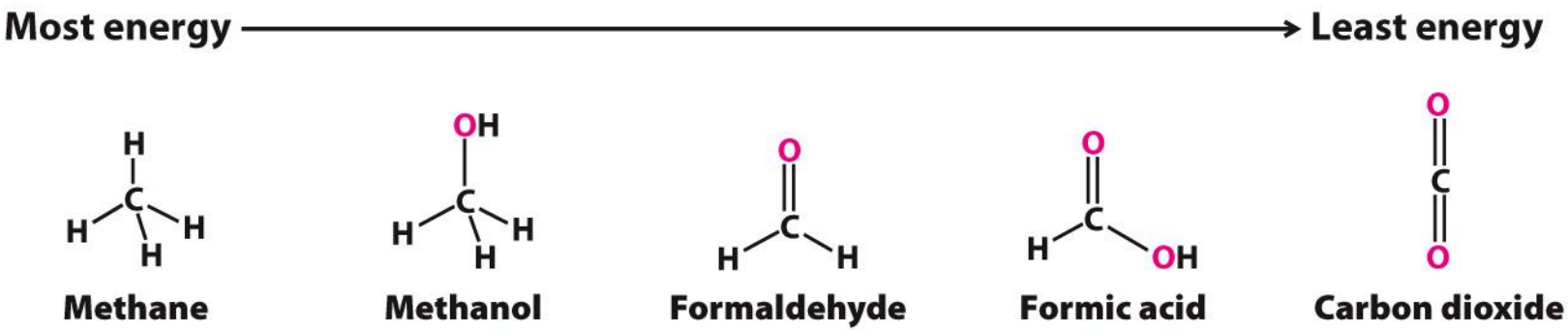
Oxidation reactions involve loss of electrons. Such reactions must be coupled with reactions that gain electrons. The paired reactions are called oxidation-reduction reactions or redox reactions.

The carbon atoms in fuels are oxidized to yield CO_2, and the electrons are ultimately accepted by oxygen to form H_2O.

The more reduced a carbon atom is, the more free energy is released upon oxidation.

Fats are a more efficient food source than glucose because fats are more reduced.



	Methane	Methanol	Formaldehyde	Formic acid	Carbon dioxide
$\Delta G^{\circ\prime}_{\text{oxidation}}$ (kJ mol^{-1})	–820	–703	–523	–285	0
$\Delta G^{\circ\prime}_{\text{oxidation}}$ (kcal mol^{-1})	–196	–168	–125	–68	0

Figure 15.9
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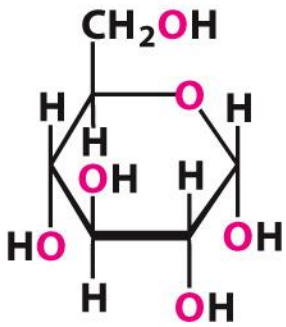
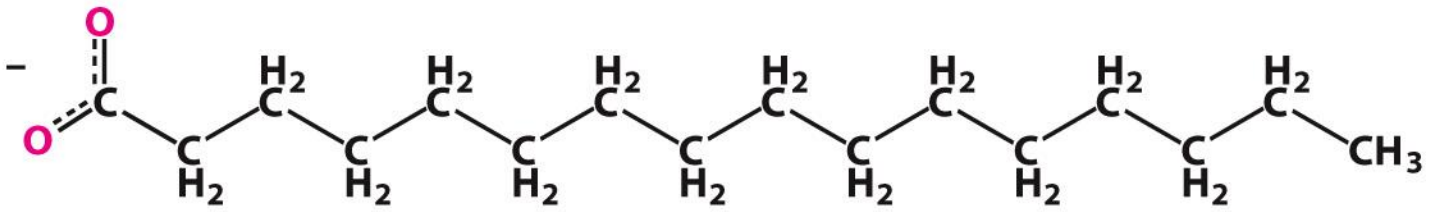


Glucose



Saturated fatty acid

Figure 15.10
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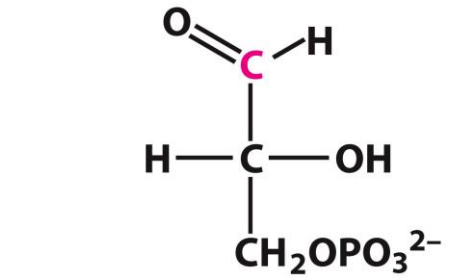
Compounds with high phosphoryl-transfer potential can couple carbon oxidation to ATP synthesis

The essence of catabolism is capturing the energy of carbon oxidation as ATP.

Oxidation of the carbon atom may form a compound with high phosphoryl-transfer potential that can then be used to synthesize ATP.

The energy released when carbon 1 (shown in red) of glyceraldehyde 3-phosphate is oxidized can be captured first as1,3-bisphosphoglycerate and then as ATP.



Glyceraldehyde 3-phosphate (GAP)

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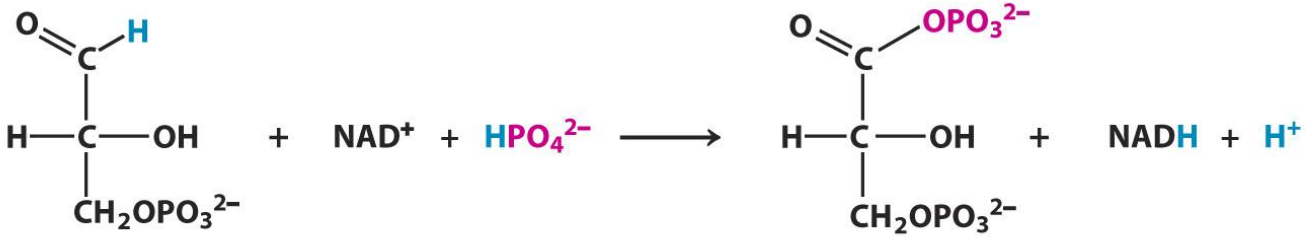

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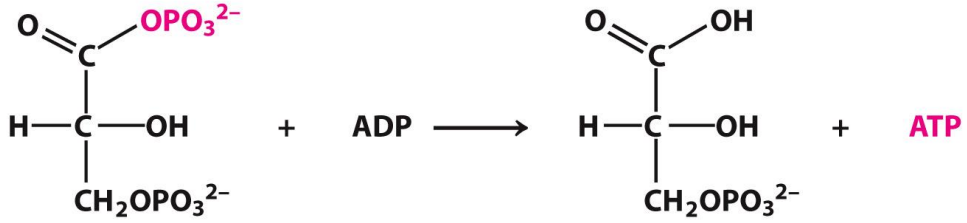

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Ion gradients across membranes provide an important form of cellular energy that can be coupled to ATP synthesis

Ion gradients can couple endergonic reactions with exergonic reactions.

In animals, 90% of ATP is generated when the energy of a proton gradient is coupled with ATP synthesis in the process of oxidative phosphorylation.

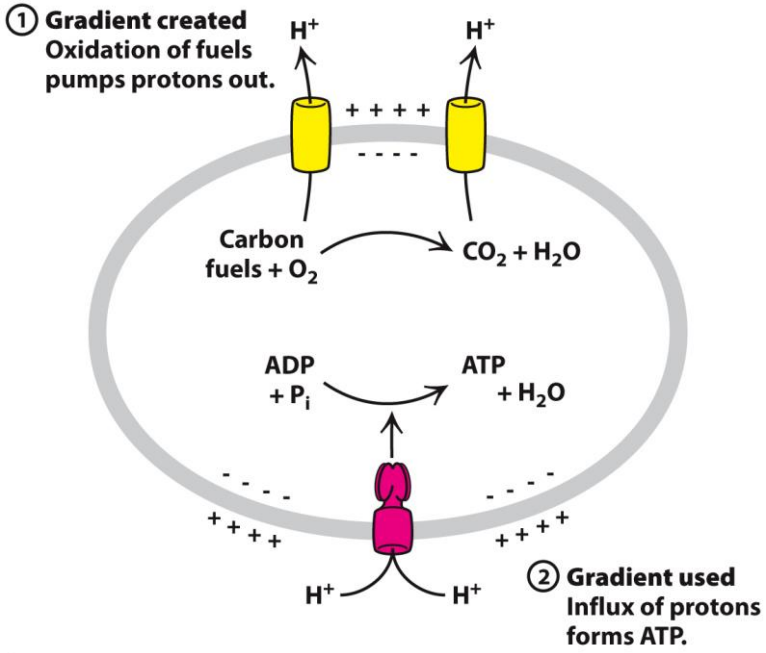

Figure 15.11
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Phosphates play a prominent role in biochemical processes

Phosphates are important chemicals in biochemical reactions because they are thermodynamically unstable while being kinetically stable. The kinetic stability is due to the negative charges that resist hydrolysis.

The combination of thermodynamic instability and kinetic stability allows the enzyme-catalyzed use of phosphate esters for energy transformations as well as regulation.

The generation of energy from food occurs in three stages:

1. Large molecules in food are broken down into smaller molecules in the process of digestion.

2. The many small molecules are processed into key molecules of metabolism, most notably acetyl CoA.

3. ATP is produced from the complete oxidation of the acetyl component of acetyl CoA.

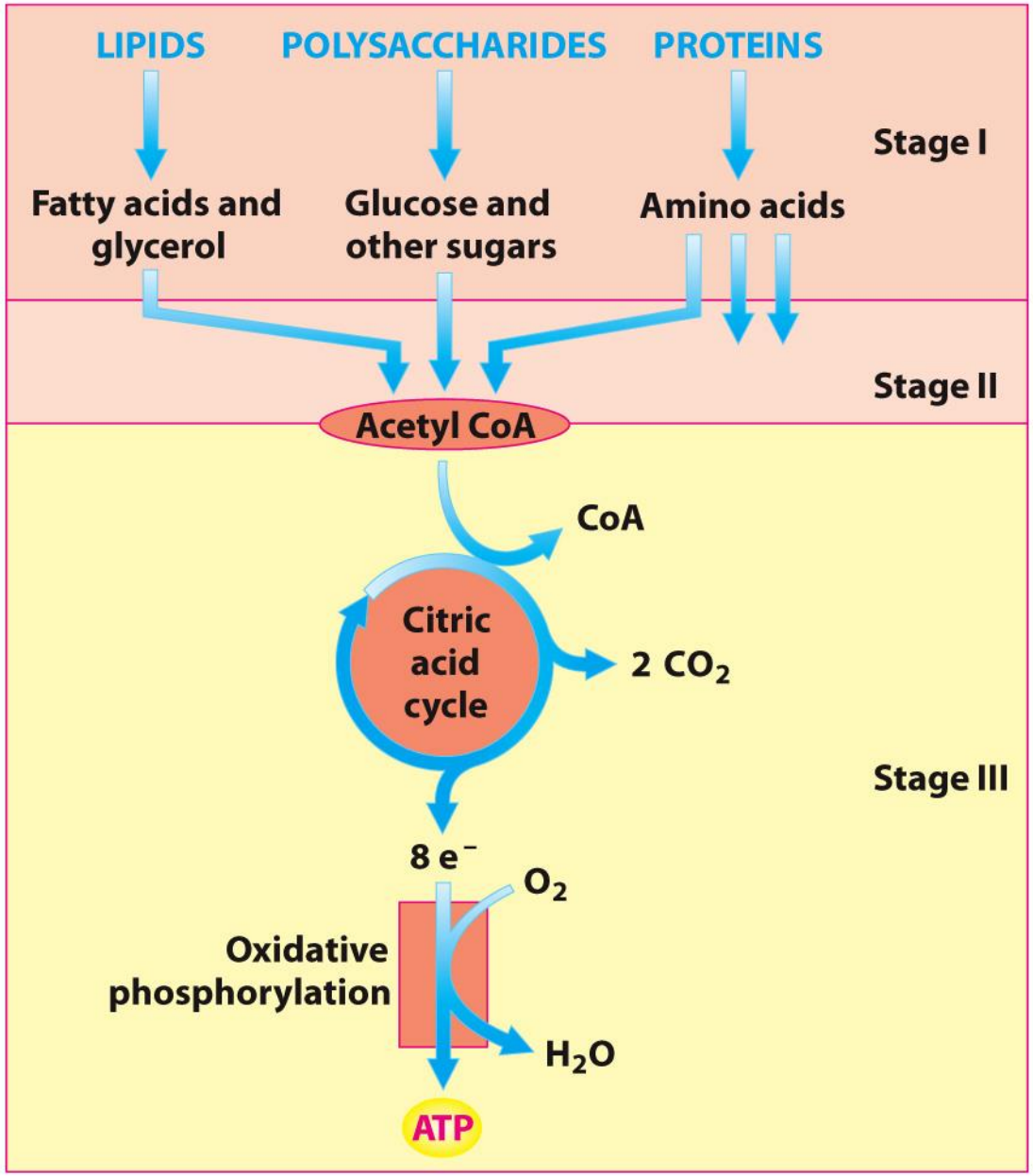

Figure 15.12
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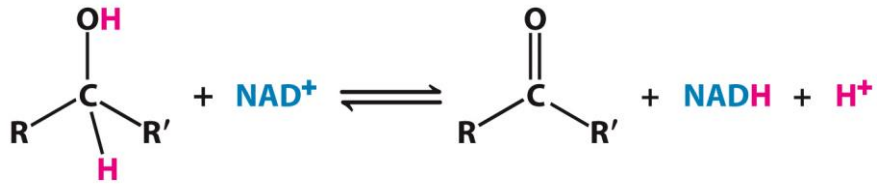
Activated carriers exemplify the modular design and economy of metabolism

ATP is an activated carrier of phosphoryl groups. Other activated carriers are common in biochemistry, and they often are derived from vitamins.

NADH/NAD^+ and $FADH_2$/FAD are activated carriers of electrons for fuel oxidation.

NADH/NAD^+ participate in reactions such as the following:



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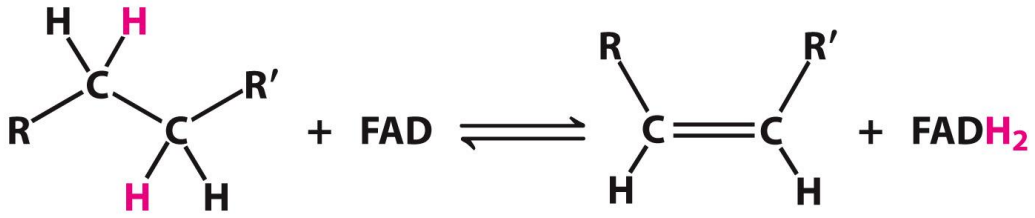
$FADH_2$/FAD participate in reactions such as the following:



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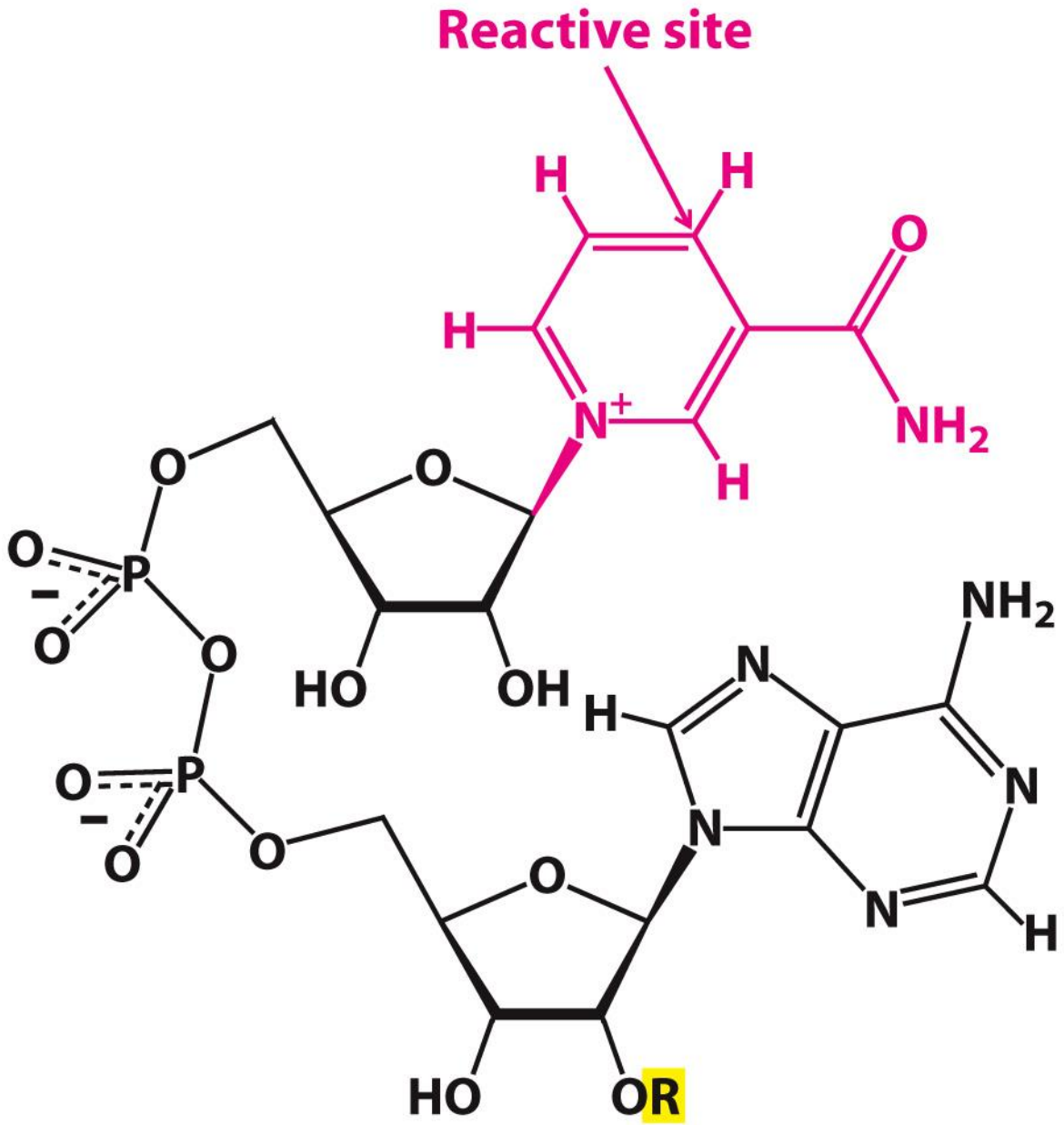

Figure 15.13
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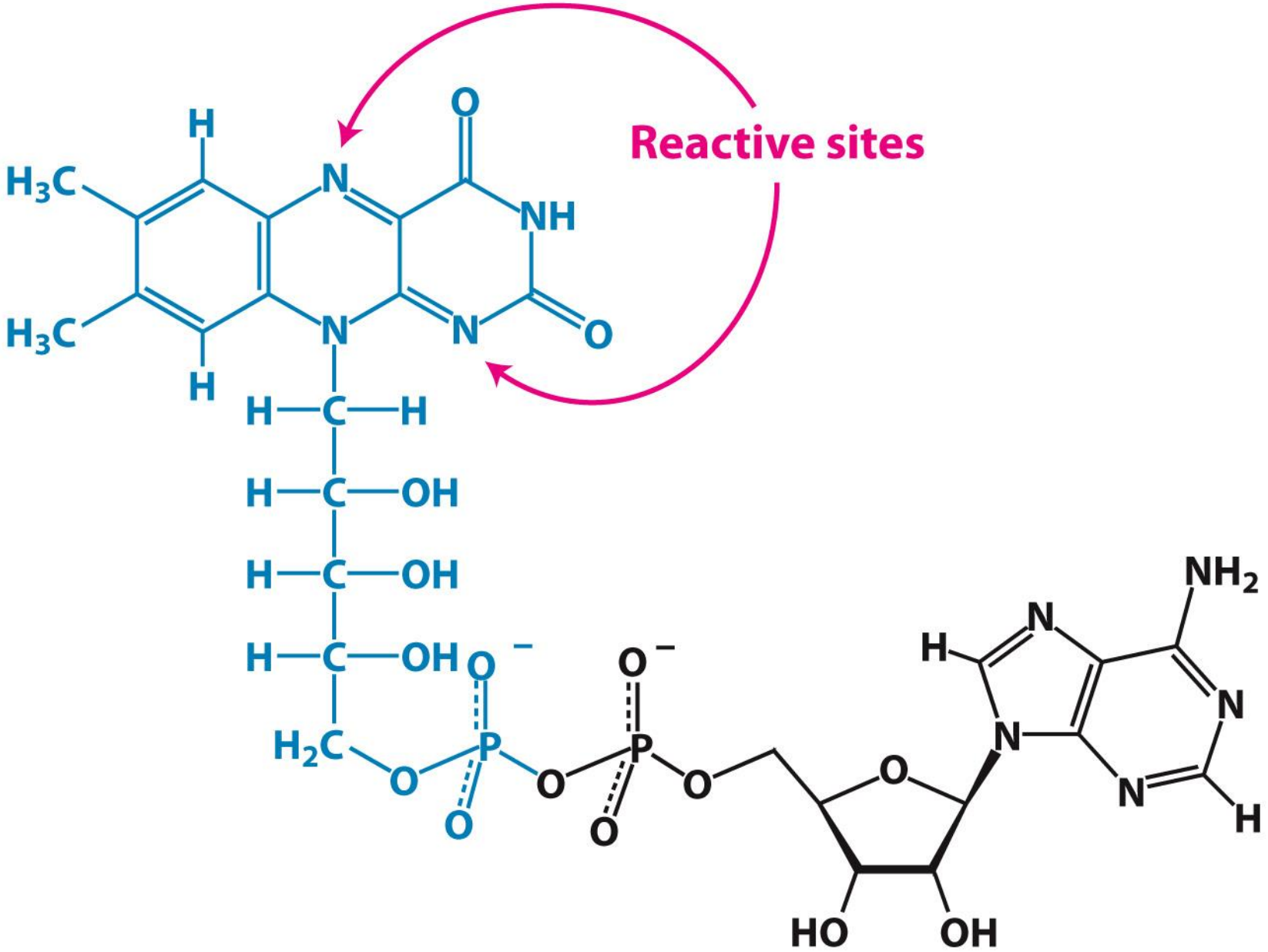

Figure 15.14
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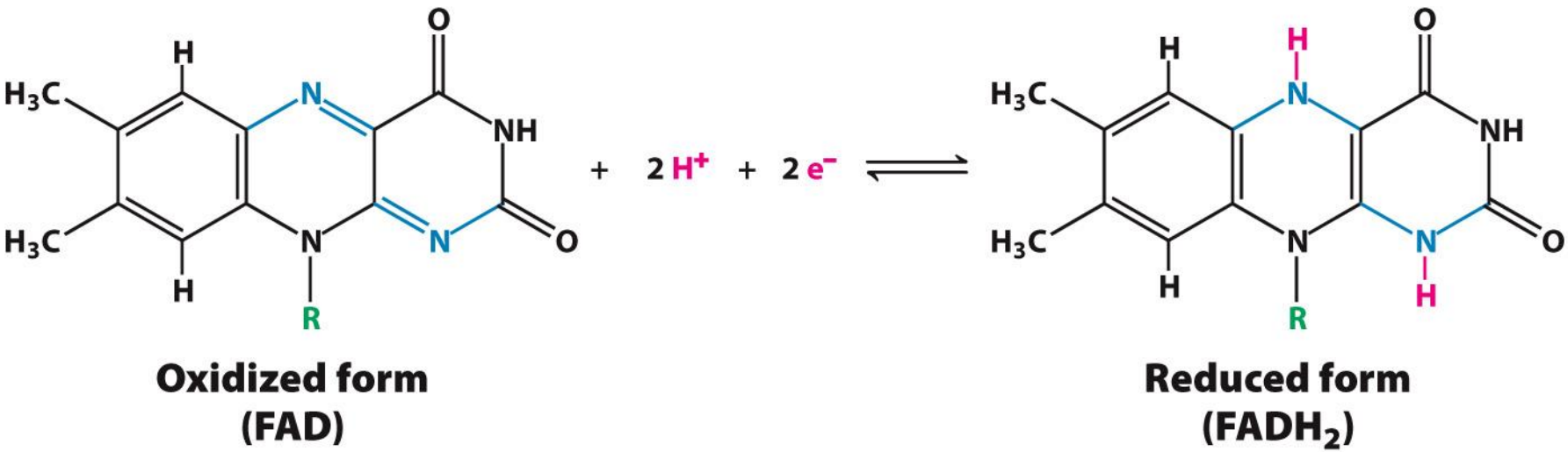

Figure 15.15
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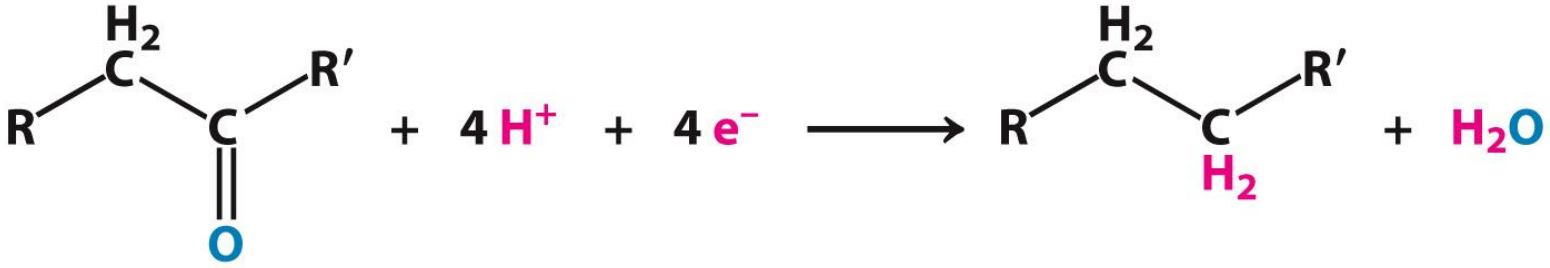
NADPH/$NADP^+$ is the electron carrier for reductive biosynthesis. Two molecules of NADPH are required for the reduction of a keto group to a methylene group in fatty acid synthesis. Whereas NADH is used for generation of ATP.



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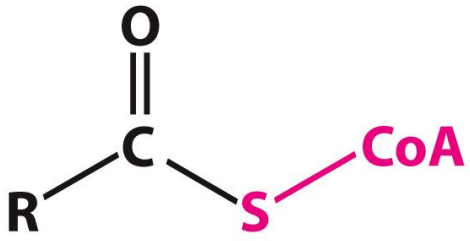
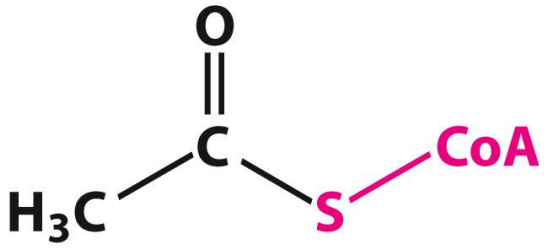
Coenzyme A (CoA or CoASH) is an activated carrier of acyl groups such as the acetyl group.



Acyl CoA



Acetyl CoA

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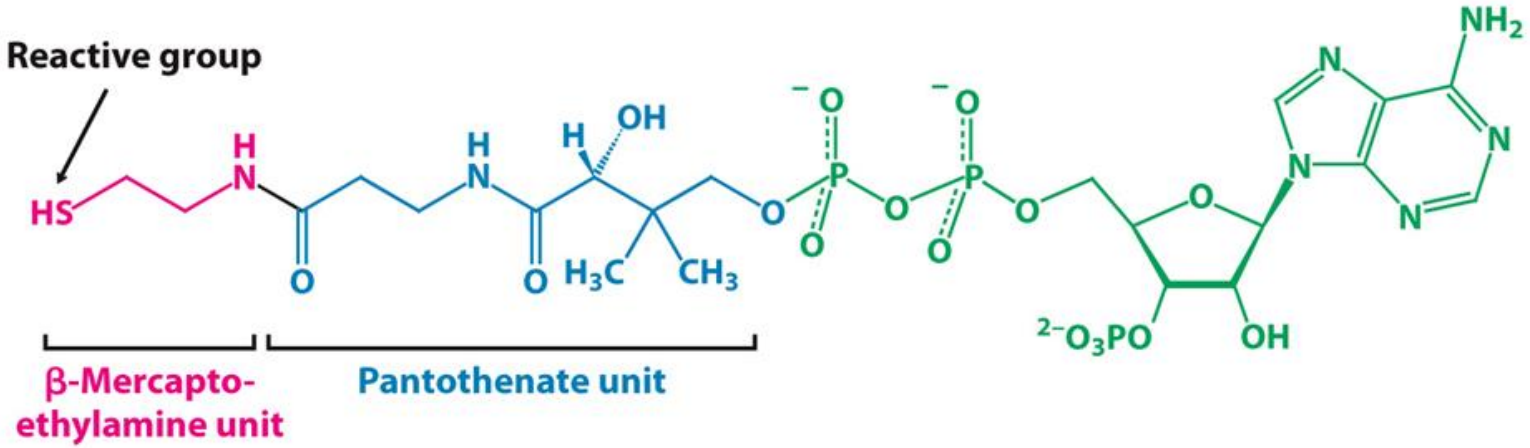

Figure 15.16
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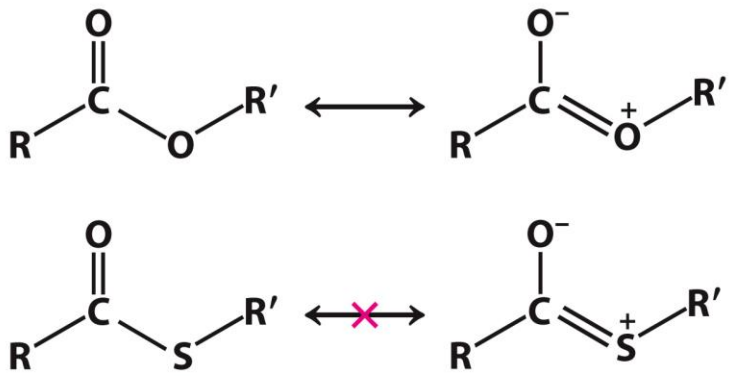
The transfer of the acyl group is exergonic because the thioester is unstable.

$$\text{Acetyl CoA} + H_2O \rightleftharpoons \text{acetate} + \text{CoA} + H^+$$

$$\Delta G^{\circ\prime} = -31.4\ \text{kJ mol}^{-1}(-7.5\ \text{kcal mol}^{-1})$$



Oxygen esters are stabilized by resonance structures not available to thioesters.

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Transfer of acyl group is important in synthesis of lipids and oxidation of fatty acids.

Two characteristics are common to activated carriers:

1. The carriers are kinetically stable in the absence of specific catalysts.

2. The metabolism of activated groups is accomplished with a small number of carriers.

The existence of recuring set of activated carries illustrates modular design of metabolism

TABLE 15.2 Some activated carriers in metabolism

Carrier molecule in activated form	Group carried	Vitamin precursor
ATP	Phosphoryl	
NADH and NADPH	Electrons	Nicotinate (niacin) (vitamin B_3)
$FADH_2$	Electrons	Riboflavin (vitamin B_2)
$FMNH_2$	Electrons	Riboflavin (vitamin B_2)
Coenzyme A	Acyl	Pantothenate (vitamin B_5)
Lipoamide	Acyl	
Thiamine pyrophosphate	Aldehyde	Thiamine (vitamin B_1)
Biotin	CO_2	Biotin (vitamin B_7)
Tetrahydrofolate	One-carbon units	Folate (vitamin B_9)
S-Adenosylmethionine	Methyl	
Uridine diphosphate glucose	Glucose	
Cytidine diphosphate diacylglycerol	Phosphatidate	
Nucleoside triphosphates	Nucleotides	

Note: Many of the activated carriers are coenzymes that are derived from water-soluble vitamins.

Table 15.2
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Many activated carriers are derived from vitamins

The B vitamins function as coenzymes.

Vitamins A, C, D, E, and K play a variety of roles, but do not serve a coenzymes.

TABLE 15.3 The B vitamins

Vitamin	Coenzyme	Typical reaction type	Consequences of deficiency
Thiamine (B_1)	Thiamine pyrophosphate	Aldehyde transfer	Beriberi (weight loss, heart problems, neurological dysfunction)
Riboflavin (B_2)	Flavin adenine dinucleotide (FAD)	Oxidation–reduction	Cheliosis and angular stomatitis (lesions of the mouth), dermatitis
Pyridoxine (B_6)	Pyridoxal phosphate	Group transfer to or from amino acids	Depression, confusion, convulsions
Nicotinic acid (niacin) (B_3)	Nicotinamide adenine dinucleotide (NAD^+)	Oxidation–reduction	Pellagra (dermatitis, depression, diarrhea)
Pantothenic acid (B_5)	Coenzyme A	Acyl-group transfer	Hypertension
Biotin (B_7)	Biotin–lysine adducts (biocytin)	ATP-dependent carboxylation and carboxyl-group transfer	Rash about the eyebrows, muscle pain, fatigue (rare)
Folic acid (B_9)	Tetrahydrofolate	Transfer of one-carbon components; thymine synthesis	Anemia, neural-tube defects in development
B_{12}	5′-Deoxyadenosyl cobalamin	Transfer of methyl groups; intramolecular rearrangements	Anemia, pernicious anemia, methylmalonic acidosis

Table 15.3
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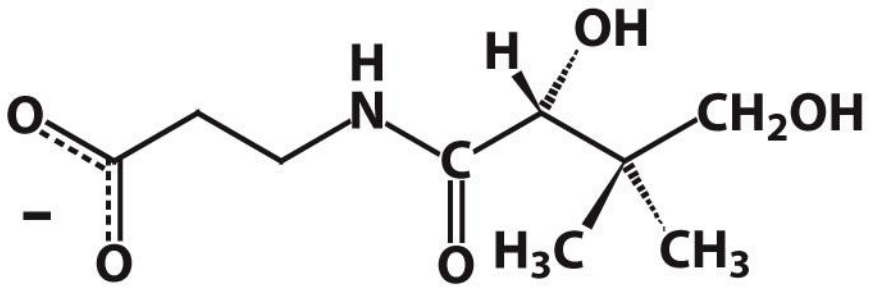
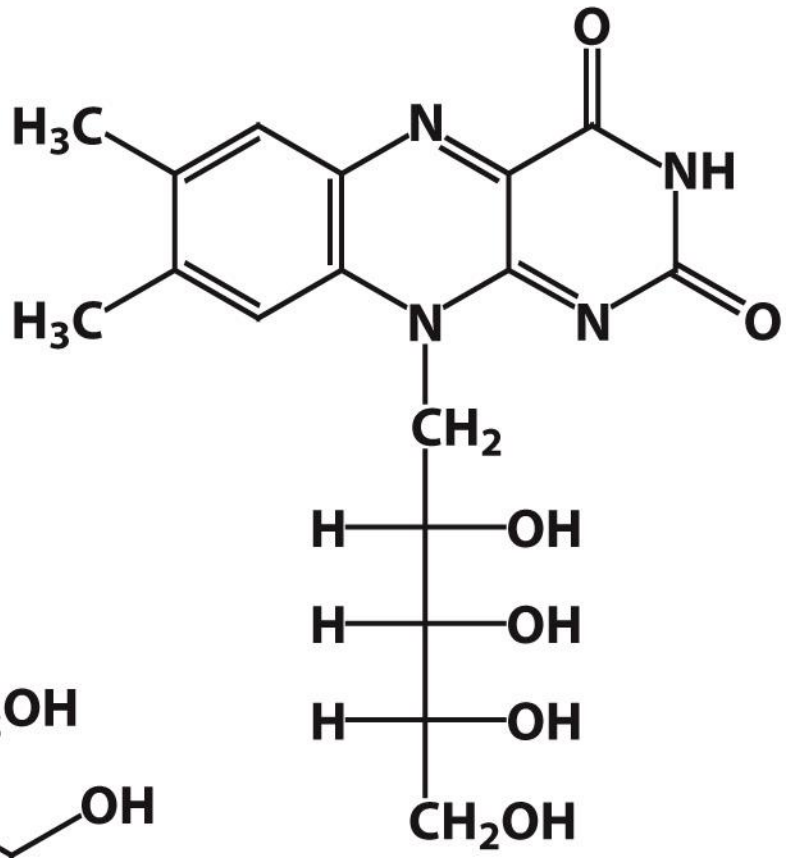
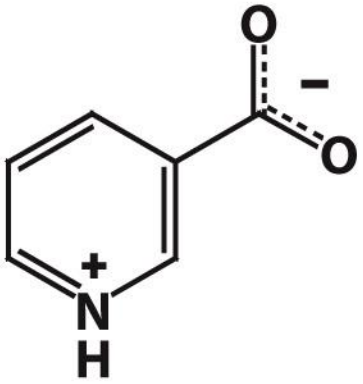


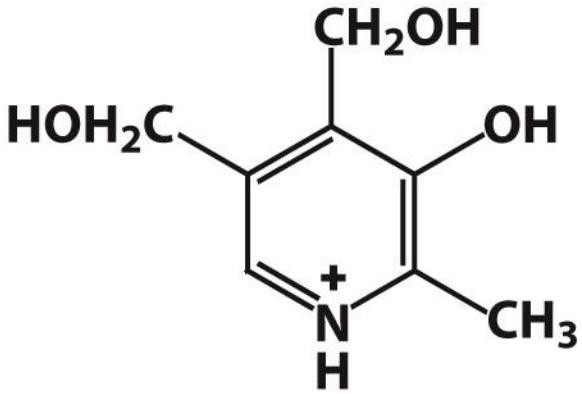
Vitamin B_5
(Pantothenate)



Vitamin B_2
(Riboflavin)



Vitamin B_3
(Niacin)



Vitamin B_6
(Pyridoxine)

Figure 15.17
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TABLE 15.4 Noncoenzyme vitamins

Vitamin	Function	Deficiency
A	Roles in vision, growth, reproduction	Night blindness, cornea damage, damage to respiratory and gastrointestinal tract
C (ascorbic acid)	Antioxidant	Scurvy (swollen and bleeding gums, subdermal hemorrhaging)
D	Regulation of calcium and phosphate metabolism	Rickets (children): skeletal deformities, impaired growth Osteomalacia (adults): soft, bending bones
E	Antioxidant	Lesions in muscles and nerves (rare)
K	Blood coagulation	Subdermal hemorrhaging

Table 15.4
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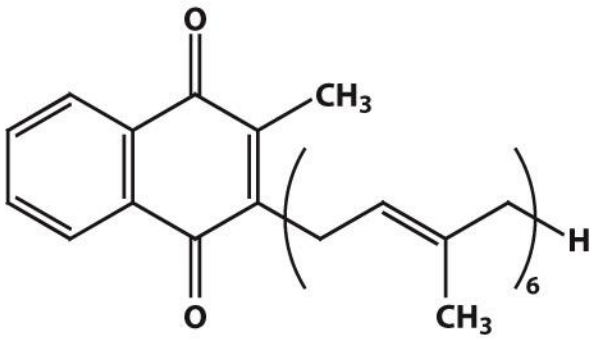
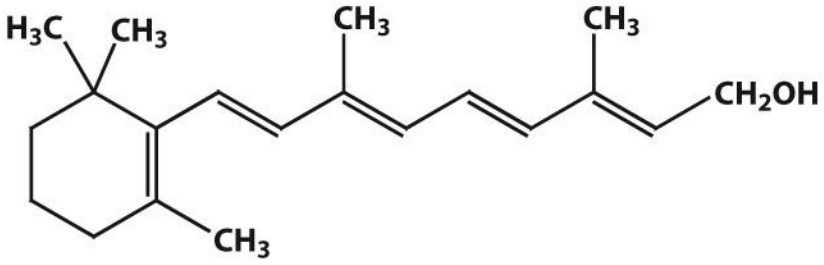
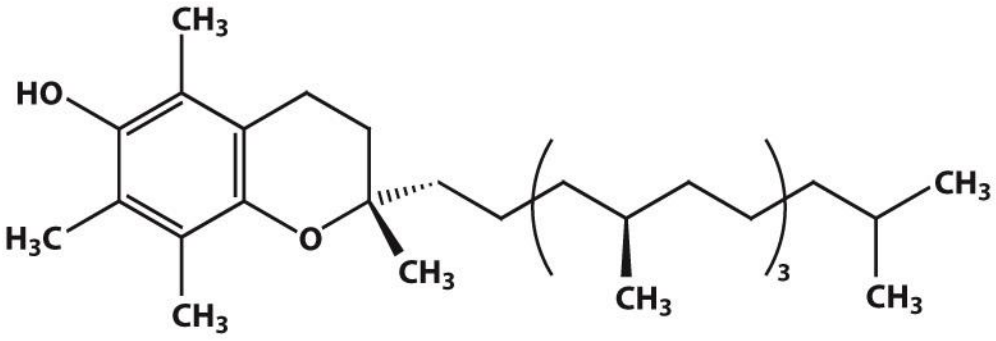


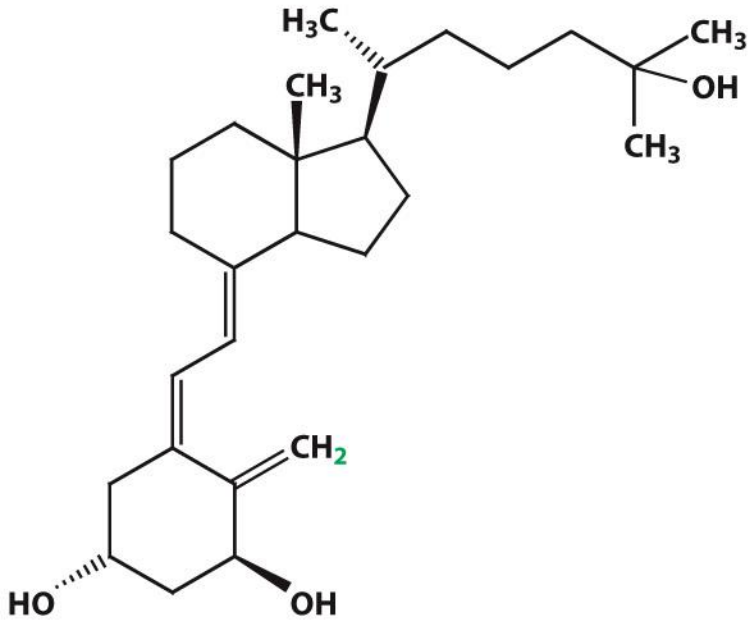
Vitamin K



Vitamin A (Retinol)



Vitamin E (α-Tocopherol)



1,25-Dihydroxyvitamin D_3 (Calcitriol)

Figure 15.18
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Key reactions are reiterated throughout metabolism

Although thousands of reactions constitute metabolism, there are only six types of reactions.

1. Oxidation-reduction reactions in citric acid cycle

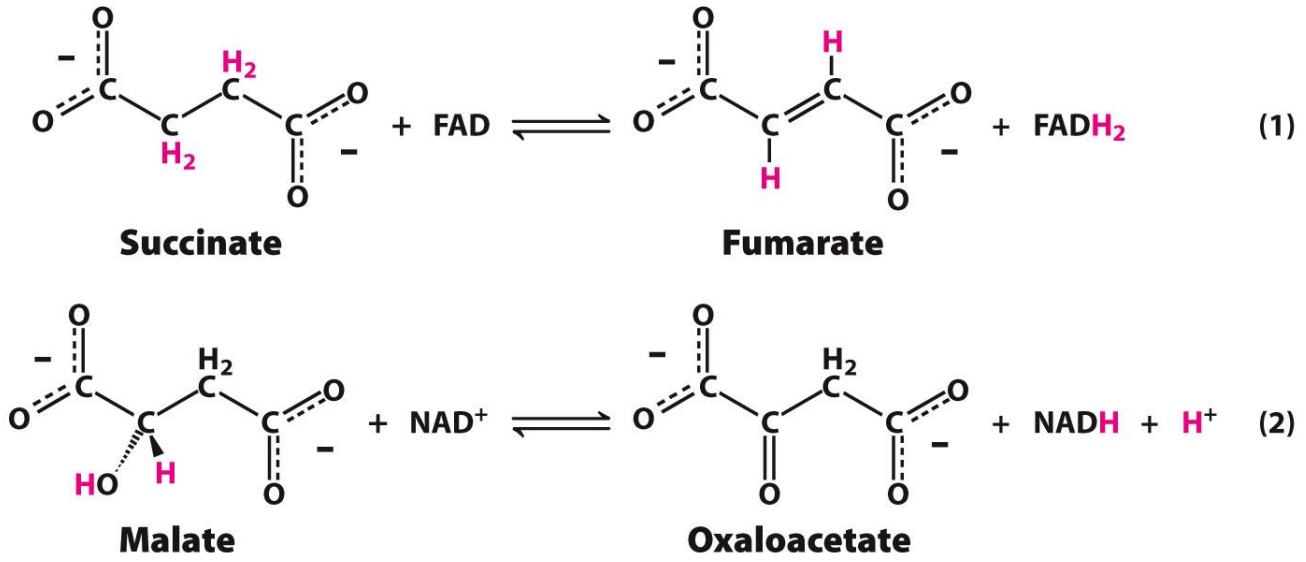

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TABLE 15.5 Types of chemical reactions in metabolism

Type of reaction	Description
Oxidation–reduction	Electron transfer
Ligation requiring ATP cleavage	Formation of covalent bonds (i.e., carbon–carbon bonds)
Isomerization	Rearrangement of atoms to form isomers
Group transfer	Transfer of a functional group from one molecule to another
Hydrolytic	Cleavage of bonds by the addition of water
Carbon bond cleavage by means other than hydrolysis or oxidation	Two substrates yielding one product or vice versa. When H_2O or CO_2 are a product, a double bond is formed.

Table 15.5
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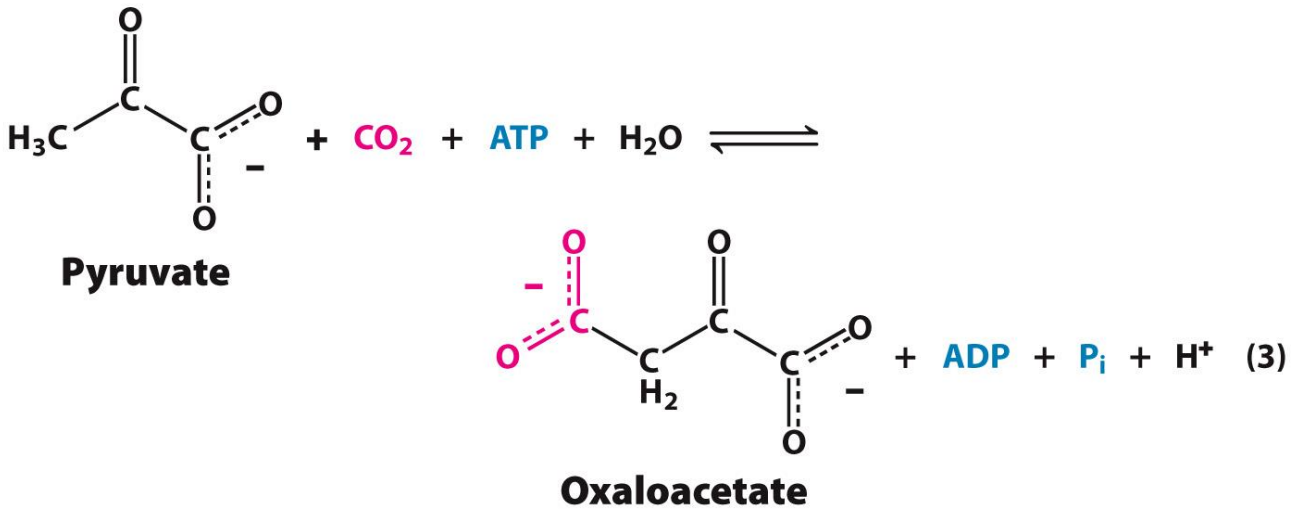
2. Ligation reactions – bond formation using free energy from ATP



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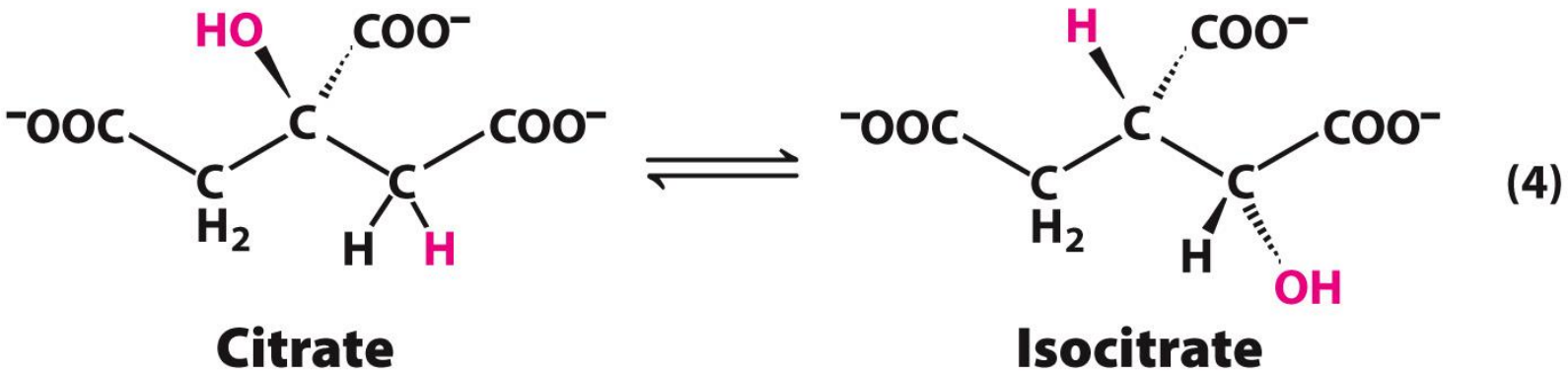
3. Isomerization reactions in citric acid cycle



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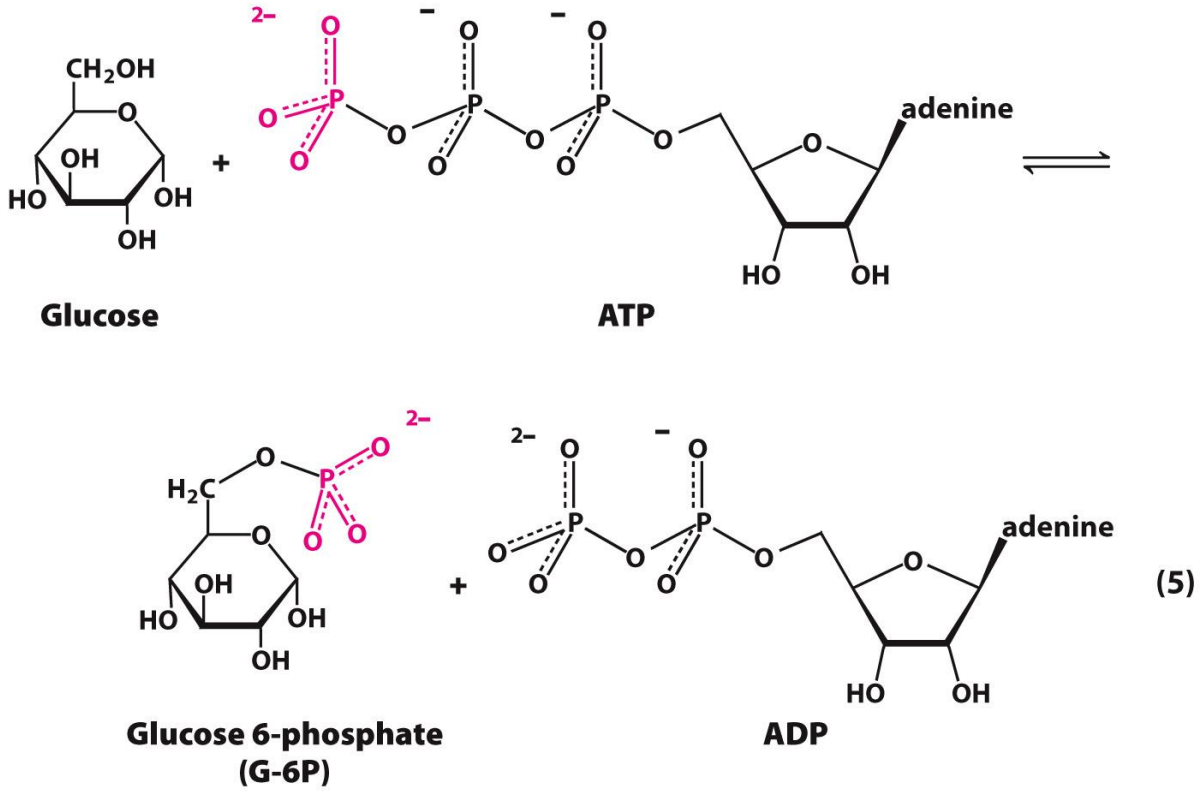
4. Group-transfer reactions (initial step of glycolysis).



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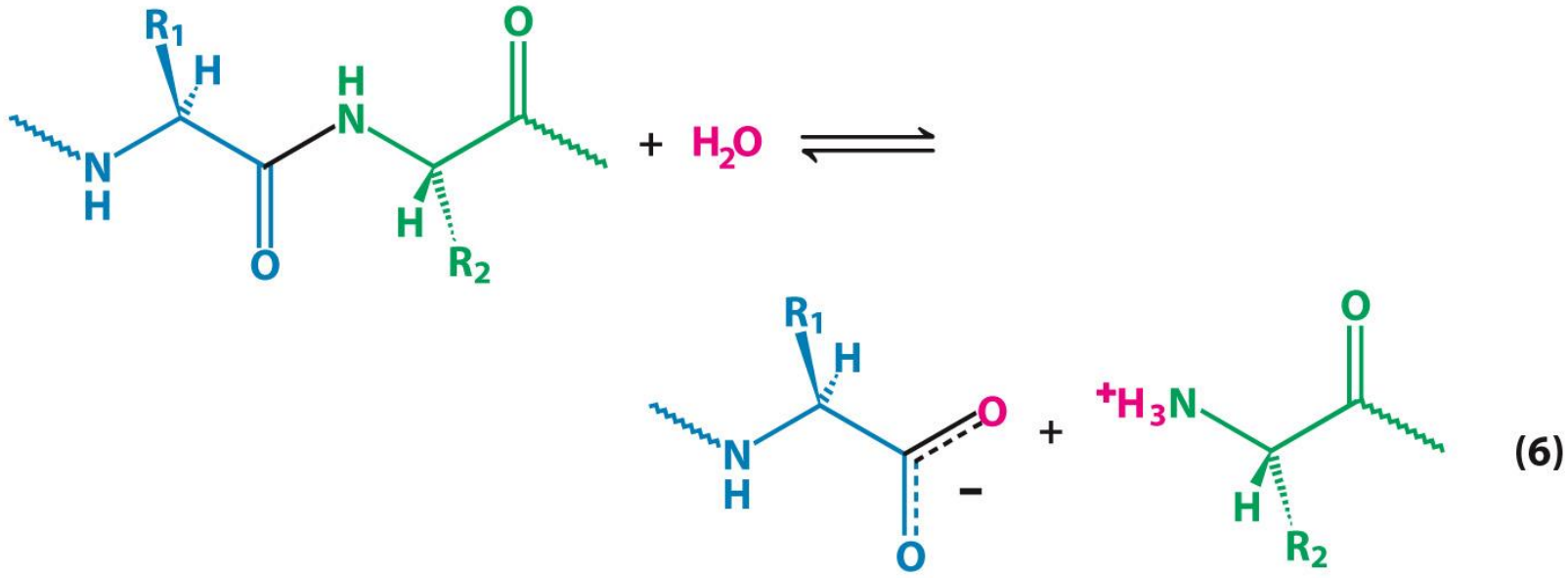
5. Hydrolytic reactions.



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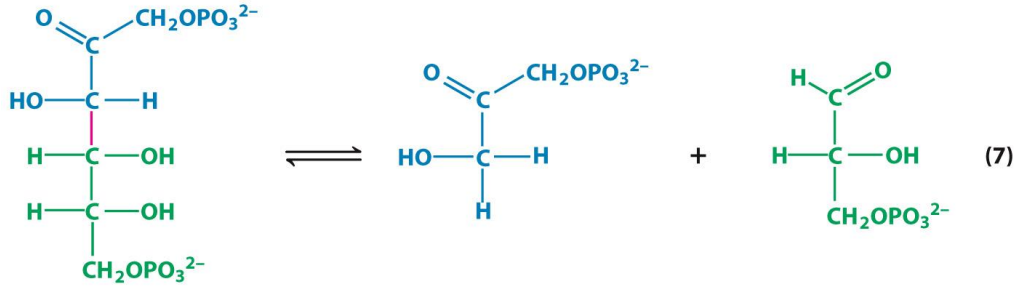
6. Reactions in which carbon bonds are cleaved by means other than hydrolysis or oxidation. In these reactions, two substrates yield one product or vice versa. These reactions are catalyzed by lyases.



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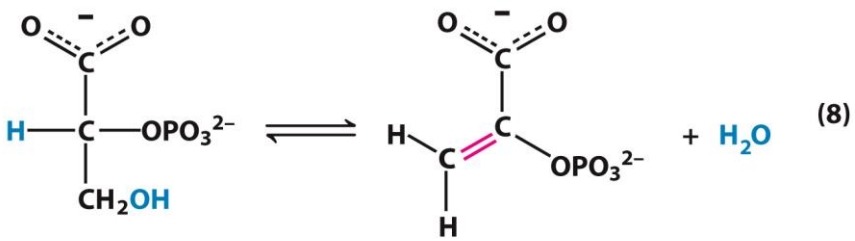

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Metabolic processes are regulated in three principal ways

Metabolic pathways must be regulated to create homeostasis or a stable biochemical environment.

To maintain homeostasis, the levels of available nutrients must be constantly monitored and metabolism adjusted to meet the biochemical needs of the cell.

Homeostasis is maintained by three crucial regulatory strategies.

1. The quantity of enzyme present can be regulated at the level of gene transcription.

2. Catalytic activity is regulated allosterically or by covalent modification. Hormones coordinate metabolic activity, often by instigating the covalent modification of allosteric enzymes.

The energy status of the cell is often an important regulator of enzyme activity. Two common means are used to assess energy status: energy charge and phosphorylation potential.

$$\text{Energy charge} = \frac{[\text{ATP}] + \frac{1}{2}[\text{ADP}]}{[\text{ATP}] + [\text{ADP}] + [\text{AMP}]}$$

$$\text{Phosphorylation potential} = \frac{[\text{ATP}]}{[\text{ADP}] + [\text{P}_i]}$$

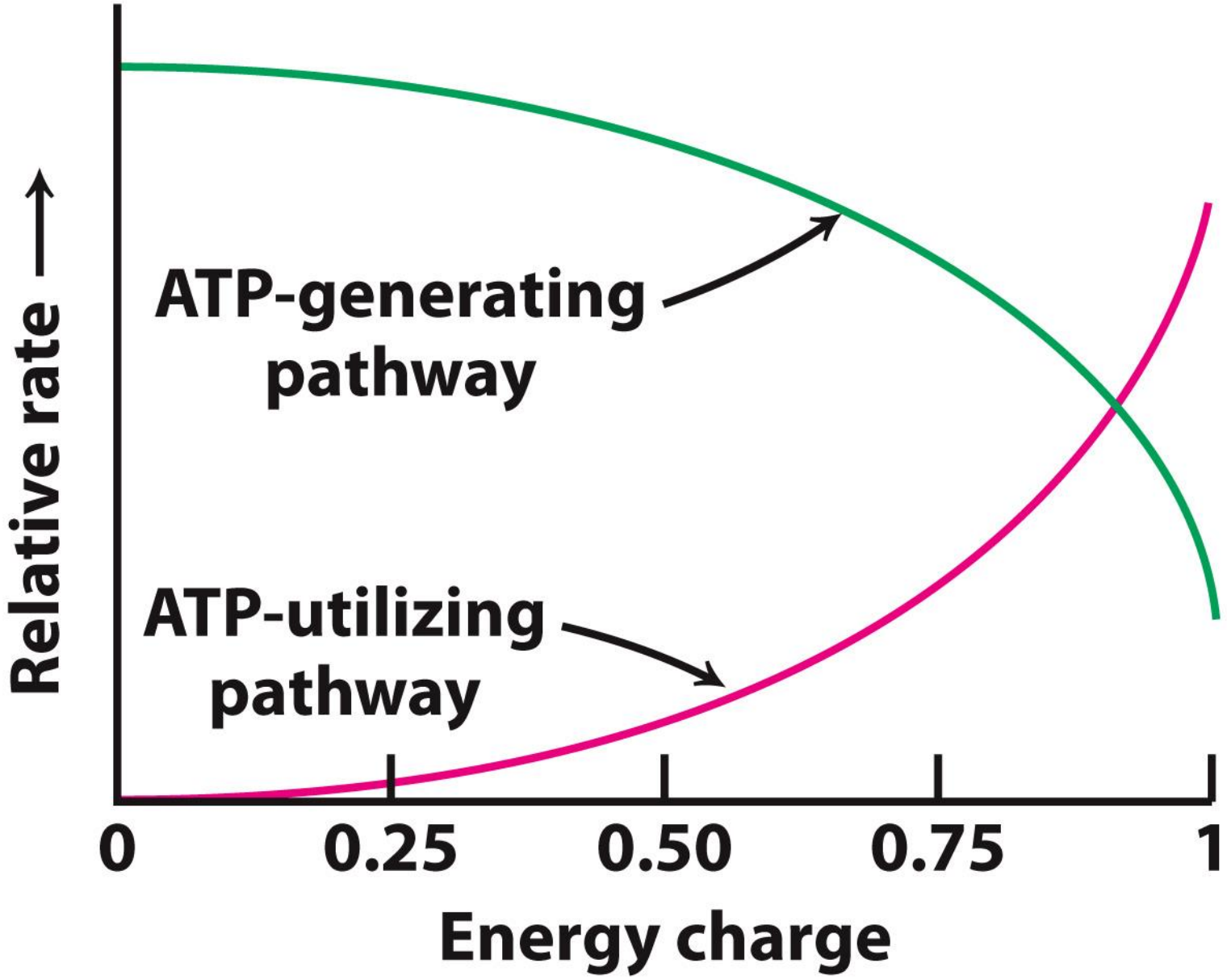

Figure 15.20
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Metabolic processes are regulated in three principal ways

3. Opposing reactions, such as fatty acid synthesis and degradation, may occur in different cellular compartments.

Controlling the flux of substrates between compartments is used to regulate metabolism.

Aspects of metabolism may have evolved from an RNA world

The fact that ATP, NADH, $FADH_2$ and coenzyme A all contain adenosine diphosphate units may be a reflection of the role of RNA in early metabolism.

In the postulated RNA world, RNA served both as a catalyst and an information storage molecule.