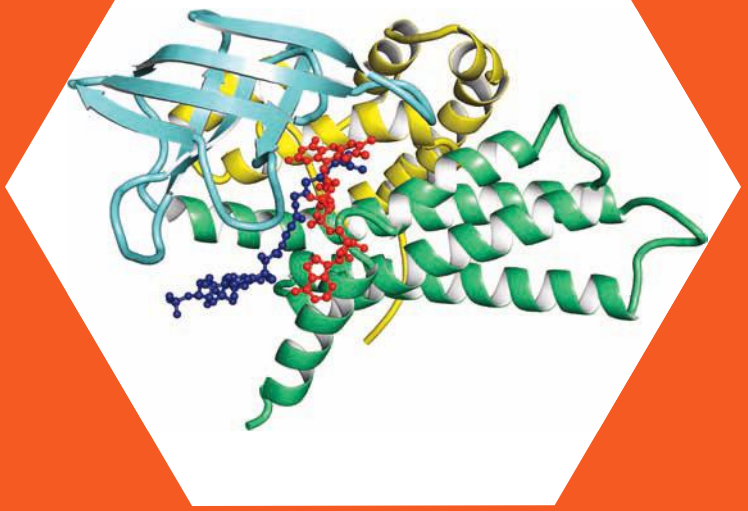
CHAPTER

17



Acyl CoA dehydrogenase is an enzyme that catalyzes the introduction of a C=C double bond into fatty acids during their metabolism.

The Organic Chemistry of Metabolic Pathways

The organic chemical reactions that take place in even the smallest and simplest living organism are more complex than those carried out in any laboratory. Yet all those reactions in living organisms, regardless of their complexity, follow the same rules of reactivity and proceed by the same mechanisms we've seen in the preceding chapters.

A word of caution, though: biological molecules are often much larger and more complicated than the substances we've been dealing with thus far. But don't be intimidated. Keep your focus on the parts of the molecules where changes occur and ignore the parts where nothing changes. The reactions themselves are exactly the same additions, eliminations, substitutions, carbonyl condensations, and so forth, that we've been dealing with all along. By the end of this chapter, it should be clear that the chemistry of living organisms *is* organic chemistry.

OWL

Online homework for this chapter can be assigned in OWL, an online homework assessment tool.

WHY THIS CHAPTER?

To understand the chemistry of living organisms, knowing *what* occurs isn't enough. It's also necessary to understand *how* and *why* organisms use the chemistry they do. In this chapter, we'll look at some of the pathways by which organisms carry out their chemistry, focusing primarily on how they

metabolize fats and carbohydrates. The treatment will be far from complete, but it should give you an idea of how biological processes occur.

17.1 An Overview of Metabolism and Biochemical Energy

The many processes that go on in the cells of living organisms are collectively called **metabolism**. The pathways that break down larger molecules into smaller ones are said to be **catabolic** and usually release energy, while the pathways that put smaller molecules together to synthesize larger biomolecules are **anabolic** and usually absorb energy. Catabolic processes can be divided into the four stages shown in Figure 17.1.

Stage 1 Bulk food is hydrolyzed in the stomach and small intestine to give small molecules.

Stage 2 Fatty acids, monosaccharides, and amino acids are degraded in cells to yield acetyl CoA.

Stage 3 Acetyl CoA is oxidized in the citric acid cycle to give CO_2.

Stage 4 The energy released in the citric acid cycle is used by the electron-transport chain to oxidatively phosphorylate ADP and produce ATP.

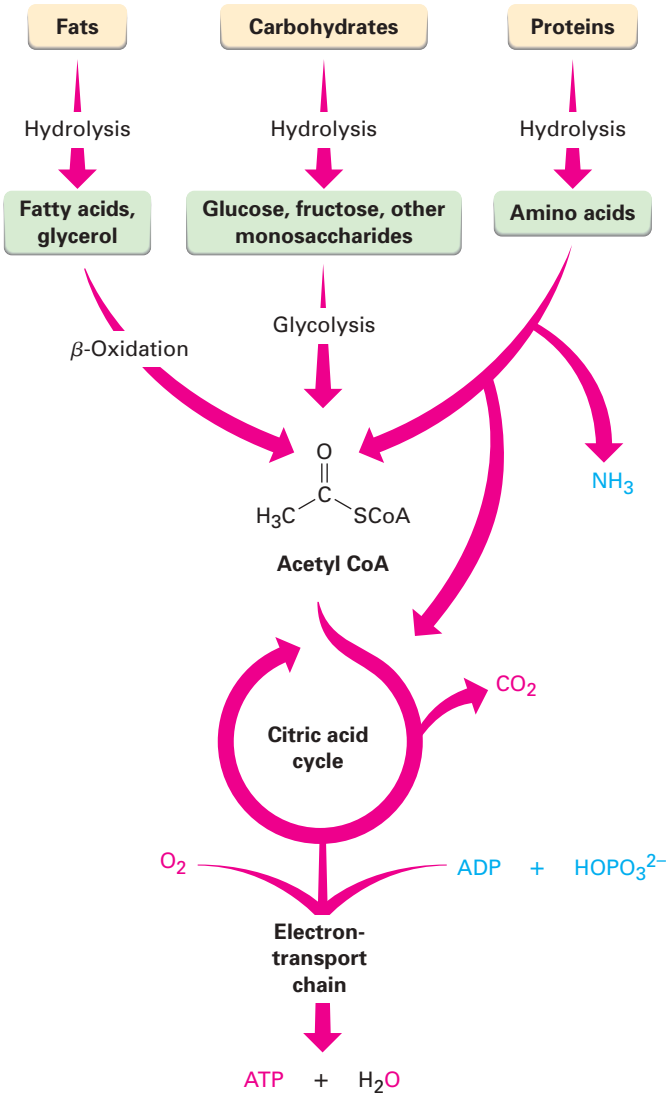
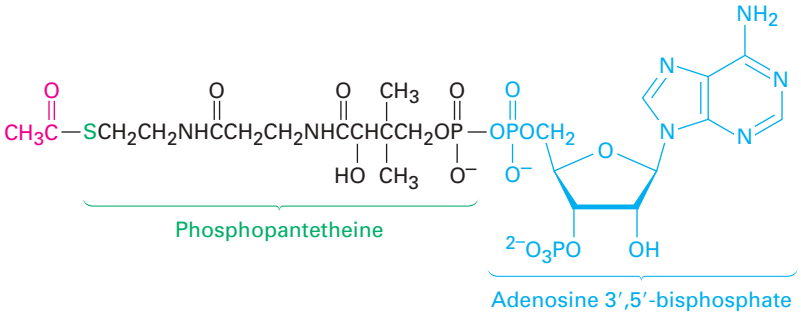


Figure 17.1 An overview of catabolic pathways for the degradation of food and the production of biochemical energy. The ultimate products of food catabolism are CO_2 and H_2O, with the energy released in the citric acid cycle used to drive the synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) plus phosphate ion, $HOPO_3^{2-}$.

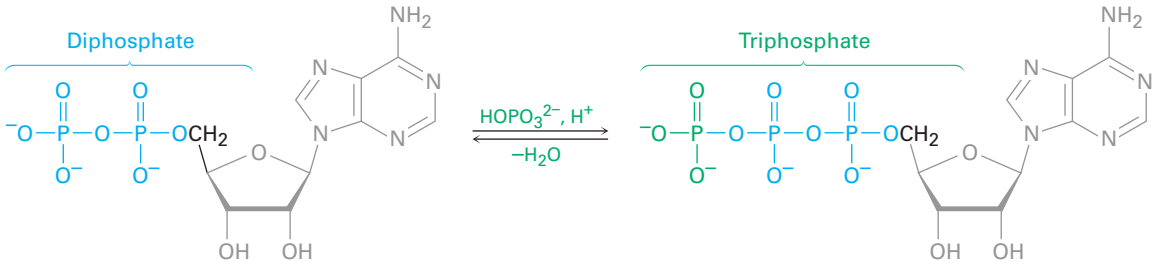
In the first catabolic stage, commonly called digestion, food is broken down in the mouth, stomach, and small intestine by hydrolysis of ester, acetal (glycoside), and amide (peptide) bonds to yield fatty acids, simple sugars, and amino acids. These small molecules are then absorbed by cells and further degraded in the second stage of catabolism to acetyl groups attached by a thioester bond to the large carrier molecule coenzyme A. The resultant compound, acetyl coenzyme A (acetyl CoA), is a key substance in the metabolism of food molecules and in many other biological pathways. As noted in Section 10.12, the acetyl group in acetyl CoA is linked to the sulfur atom of phosphopantetheine, which is itself linked to adenosine 3′,5′-bisphosphate.



Acetyl CoA—a thioester

Acetyl CoA next enters the third stage of catabolism, the *citric acid cycle,* where it is oxidized to yield CO_2. Like most oxidations, this stage releases a large amount of energy, which is used in the fourth stage, the *electron-transport chain,* to make adenosine triphosphate, ATP.

ATP has been called the "energy currency" of the cell. Catabolic reactions buy ATP by using the energy they release to synthesize it from adenosine diphosphate (ADP) plus hydrogen phosphate ion, HPO_4^{2-}. Anabolic reactions then spend ATP by transferring a phosphate group to another molecule, thereby releasing energy and regenerating ADP. Energy production and use thus revolves around the ATP ⇄ ADP interconversion.



Adenosine diphosphate (ADP) **Adenosine triphosphate (ATP)**

How does the body use the ATP it spends? You may recall from your general chemistry course that a chemical reaction must have a favorable equilibrium constant and release energy (actually, *free energy, G*) to occur spontaneously. This means that the free-energy change for the reaction, ΔG, must be negative. If ΔG is positive, the reaction is unfavorable and can't occur spontaneously.

What typically happens for an energetically unfavorable reaction to occur is that it is "coupled" to an energetically favorable reaction so that the overall free-energy change for the two reactions together is favorable. Imagine, for instance, that reaction 1 does not occur to any reasonable extent because it

has a small equilibrium constant and is energetically unfavorable; that is, the reaction has $\Delta G > 0$.

(1) **A** + *m* $\rightleftharpoons$ **B** + *n* $\quad \Delta G > 0$

where **A** and **B** are the biochemically "important" substances, while *m* and *n* are enzyme cofactors, H_2O, or other small molecules

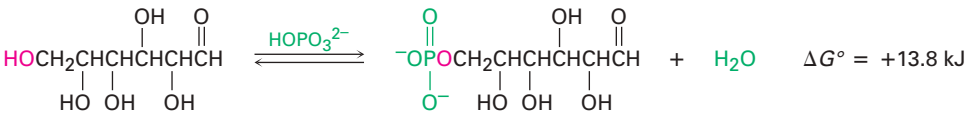
Imagine also that product *n* can react with substance *o* to yield *p* and *q* in a second, energetically favorable reaction that has a large equilibrium constant and $\Delta G << 0$.

(2) *n* + *o* $\rightleftharpoons$ *p* + *q* $\quad \Delta G << 0$

Taking the two reactions together, they share, or are coupled through, the common intermediate *n*, which is a product in the first reaction and a reactant in the second. When even a tiny amount of *n* is formed in reaction 1, it undergoes complete conversion in reaction 2, thereby removing it from the first equilibrium and forcing reaction 1 to continually replenish *n* until reactant **A** has been completely converted to product **B**. That is, the two reactions added together have a favorable $\Delta G < 0$, and we say that the favorable reaction 2 "drives" the unfavorable reaction 1. Because the two reactions are coupled through *n*, the transformation of **A** to **B** becomes favorable.

(1)	**A** + *m* $\rightleftharpoons$ **B** + ~~*n*~~	$\Delta G > 0$
(2)	~~*n*~~ + *o* $\rightleftharpoons$ *p* + *q*	$\Delta G << 0$
Net:	**A** + *m* + *o* $\rightleftharpoons$ **B** + *p* + *q*	$\Delta G < 0$

As an example of two reactions that are coupled, look at the phosphorylation reaction of glucose to yield glucose 6-phosphate plus water, an important step in the breakdown of dietary carbohydrates.



Glucose **Glucose 6-phosphate**

The reaction of glucose with $HOPO_3^{2-}$ does not occur spontaneously because it is energetically unfavorable, with $\Delta G° = +13.8$ kJ/mol. At the same time, however, the reaction of water with ATP to yield ADP plus $HOPO_3^{2-}$ is strongly favorable, with $\Delta G° = -30.5$ kJ/mol. When the two reactions are coupled, glucose reacts with ATP to yield glucose 6-phosphate plus ADP in a reaction that is favorable by about 16.7 kJ/mol (4.0 kcal/mol). That is, ATP drives the phosphorylation reaction of glucose.

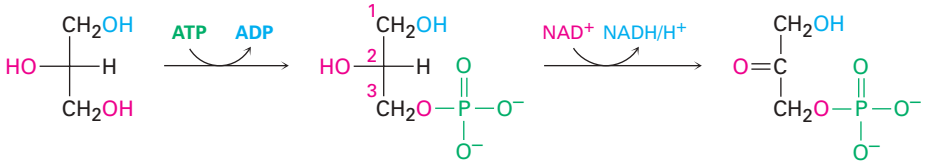
	Glucose + ~~$HOPO_3^{2-}$~~ $\longrightarrow$ Glucose 6-phosphate + ~~H_2O~~	$\Delta G° = +13.8$ kJ/mol
	ATP + ~~H_2O~~ $\longrightarrow$ ADP + ~~$HOPO_3^{2-}$~~ + H^+	$\Delta G° = -30.5$ kJ/mol
Net:	Glucose + ATP $\longrightarrow$ Glucose 6-phosphate + ADP + H^+	$\Delta G° = -16.7$ kJ/mol

It's this ability to drive otherwise unfavorable phosphorylation reactions that makes ATP so useful. The resultant phosphates are much more reactive as leaving groups in nucleophilic substitutions and eliminations than the alcohols they're derived from and are therefore much more chemically useful.

Problem 17.1 One of the steps in fat metabolism is the reaction of glycerol (propane-1,2,3-triol) with ATP to yield glycerol 1-phosphate. Write the reaction, and draw the structure of glycerol 1-phosphate.

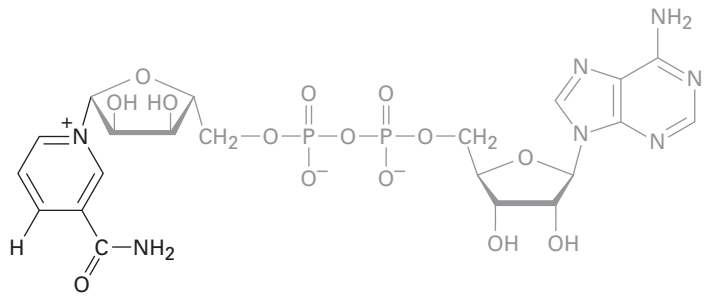
17.2 Catabolism of Fats: β-Oxidation

Let's begin a study of some common metabolic pathways by looking at fat catabolism. The metabolic breakdown of fats and oils (triacylglycerols) begins with their hydrolysis to yield glycerol plus fatty acids. Glycerol is then phosphorylated by reaction with ATP and oxidized to yield dihydroxyacetone phosphate, which enters the carbohydrate catabolic pathway to be discussed in Section 17.3.

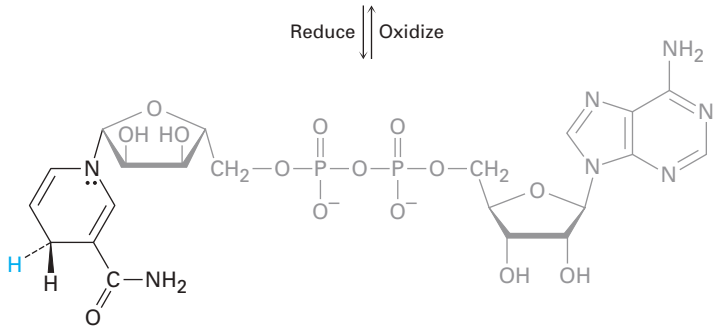


Glycerol | ***sn*-Glycerol 3-phosphate** | **Dihydroxyacetone phosphate (DHAP)**

Note how the preceding reactions are written. It's common practice when writing biochemical transformations to show only the structures of the reactant and product, while abbreviating the structures of coenzymes (Section 15.9) and other substances. Thus, the curved arrow intersecting the usual straight reaction arrow in the first step shows that ATP is also a reactant and that ADP is also a product. The coenzyme nicotinamide adenine dinucleotide (NAD^+) is required in the second step, and reduced nicotinamide adenine dinucleotide (NADH) plus a proton are products. We'll see shortly that NAD^+ is often involved as a biochemical oxidizing agent for converting alcohols to aldehydes or ketones.



Nicotinamide adenine dinucleotide (NAD^+)



Reduced nicotinamide adenine dinucleotide (NADH)

Note also that glyceraldehyde 3-phosphate is written with its phosphate group dissociated, that is, $-OPO_3^{2-}$ rather than $-OPO_3H_2$. As remarked in Section 15.1, it's standard practice in writing biochemical structures to show carboxylic acids and phosphoric acids as their anions because they exist in this form at the physiological pH of 7.3 found in cells.

The fatty acids produced on triacylglycerol hydrolysis are catabolized by a repetitive four-step sequence of enzyme-catalyzed reactions called the **β-oxidation pathway**, shown in Figure 17.2. Each passage along the pathway results in the cleavage of a two-carbon acetyl group from the end of the fatty-acid chain, until the entire molecule is ultimately degraded. As each acetyl group is produced, it enters the citric acid cycle, which we'll see in Section 17.4.

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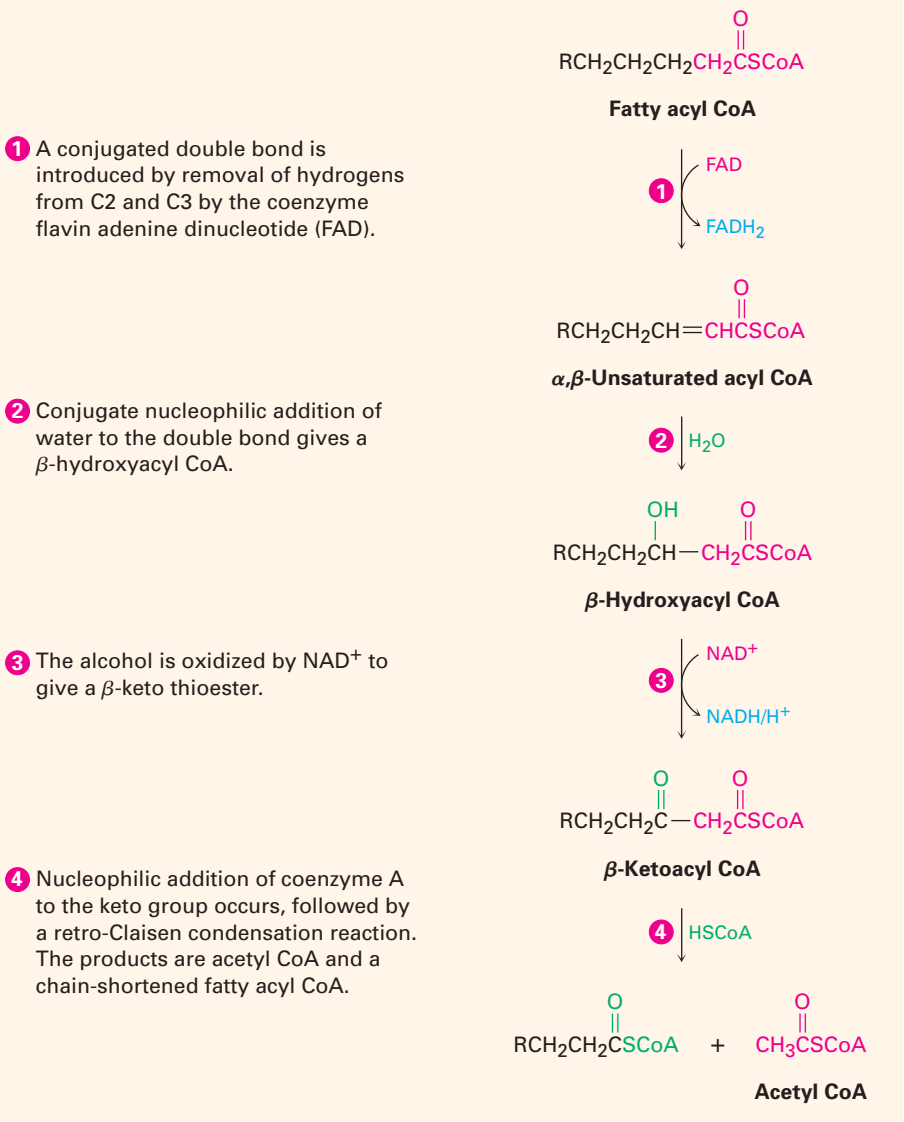
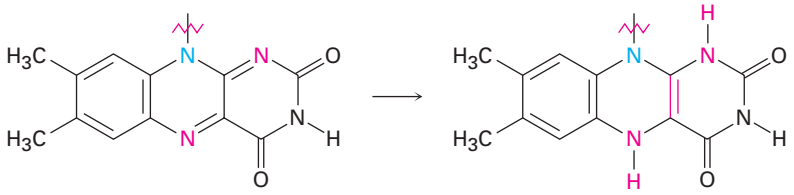
Figure 17.2 The four steps of the β-oxidation pathway, resulting in the cleavage of an acetyl group from the end of the fatty-acid chain. The chain-shortening step is a retro-Claisen reaction of a β-keto thioester. Individual steps are explained in the text.



STEP 1 OF FIGURE 17.2: INTRODUCTION OF A DOUBLE BOND

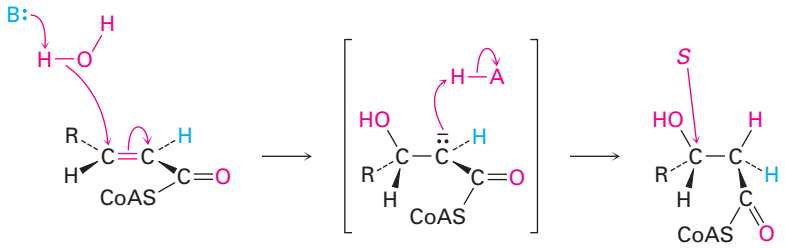
The β-oxidation pathway begins when a fatty acid reacts with coenzyme A to give a fatty acyl CoA. Two hydrogen atoms are then removed from C2 and C3 by an acyl CoA dehydrogenase to yield an α, β-unsaturated acyl CoA. This kind of oxidation—the introduction of a conjugated double bond into a carbonyl compound—occurs frequently in biochemical pathways and is usually carried out by the coenzyme flavin adenine dinucleotide (FAD). Reduced $FADH_2$ is the by-product.



Flavin adenine dinucleotide (FAD) **Reduced flavin adenine dinucleotide ($FADH_2$)**

STEP 2 OF FIGURE 17.2: CONJUGATE ADDITION OF WATER

The α, β-unsaturated acyl CoA produced in step 1 reacts with water by a conjugate nucleophilic addition pathway (Section 9.10) to yield a β-hydroxyacyl CoA in a process catalyzed by enoyl-CoA hydratase. Water adds to the β carbon of the double bond, yielding an enolate ion intermediate, which is then protonated.



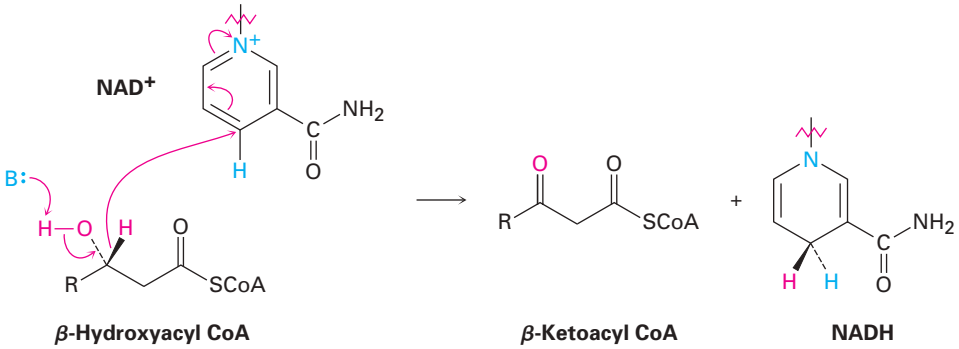
(3*S*)-Hydroxyacyl CoA

STEP 3 OF FIGURE 17.2: ALCOHOL OXIDATION

The β-hydroxyacyl CoA from step 2 is oxidized to a β-ketoacyl CoA in a reaction catalyzed by L-3-hydroxyacyl-CoA dehydrogenase. As in the oxidation of glycerol 1-phosphate to dihydroxyacetone phosphate mentioned at the beginning of this section, the alcohol oxidation requires NAD^+ as a coenzyme and yields reduced NADH as by-product.

The mechanism of the alcohol oxidation is similar in some respects to that of the conjugate nucleophilic addition reaction in step 2. Thus, a hydride ion expelled from the alcohol acts as a nucleophile and adds to the C=C—C=N^+

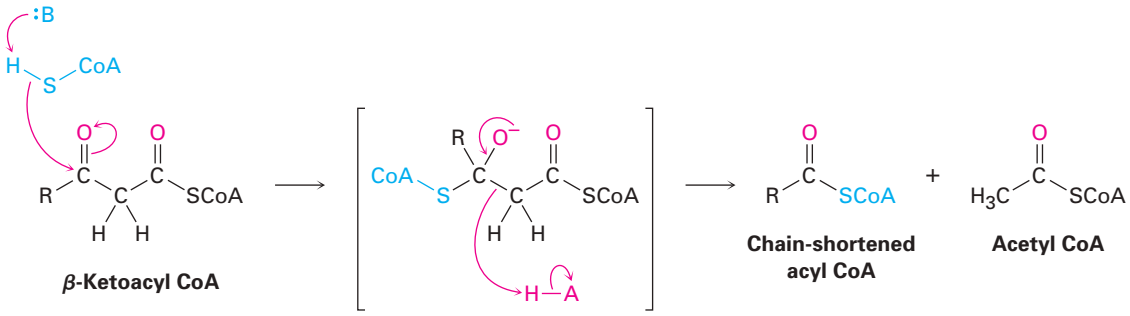
part of NAD^+ in much the same way that water acts as a nucleophile and adds to the C=C—C=O part of the unsaturated acyl CoA.



STEP 4 OF FIGURE 17.2: CHAIN CLEAVAGE

Acetyl CoA is split off from the acyl chain in the final step of β-oxidation, leaving behind an acyl CoA that is two carbon atoms shorter than the original. The reaction is catalyzed by β-ketoacyl-CoA thiolase and is the exact reverse of a Claisen condensation reaction (Section 11.10). In the *forward* direction, a Claisen condensation joins two esters together to form a β-keto ester product. In the *reverse* direction, a retro-Claisen reaction splits a β-keto ester (or β-keto thioester in this case) to form two esters (or two thioesters).

The reaction occurs by nucleophilic addition of coenzyme A to the keto group of the β-keto acyl CoA to yield an alkoxide ion intermediate. Cleavage of the C2–C3 bond follows, with expulsion of an acetyl CoA enolate ion that is immediately protonated. The chain-shortened acyl CoA then enters another round of the β-oxidation pathway for further degradation.



Look at the catabolism of myristic acid shown in Figure 17.3 to see the overall result of the β-oxidation pathway. The first passage converts the C_{14} myristoyl CoA into the C_{12} lauroyl CoA plus acetyl CoA; the second passage converts lauroyl CoA into the C_{10} caproyl CoA plus acetyl CoA; the third passage converts caproyl CoA into the C_8 capryloyl CoA; and so on. Note that the last passage produces two molecules of acetyl CoA because the precursor has four carbons.

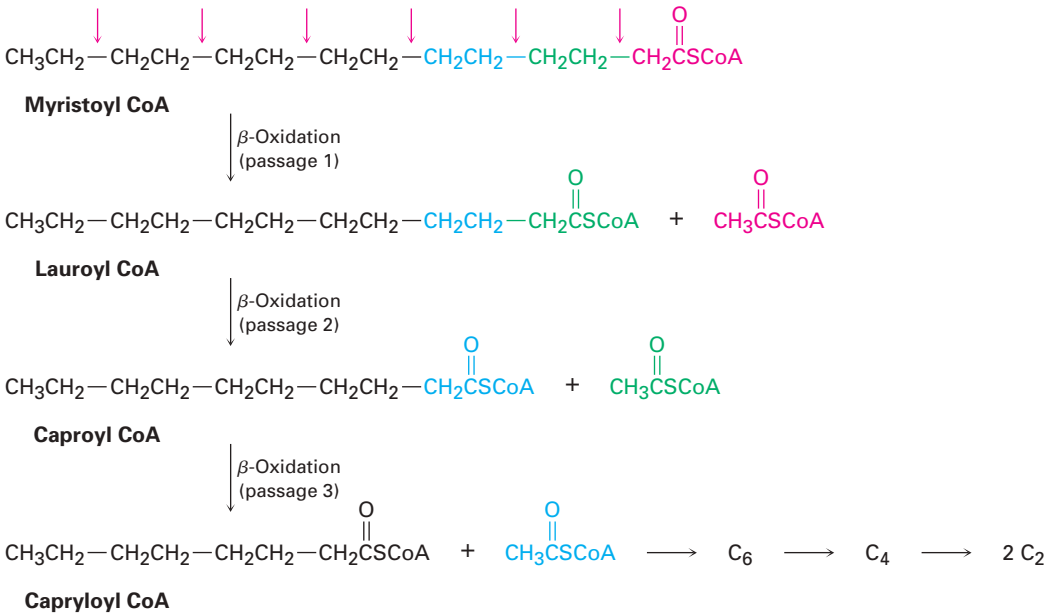


Figure 17.3 Catabolism of the C_{14} myristic acid in the β-oxidation pathway yields seven molecules of acetyl CoA after six passages.

Most fatty acids have an even number of carbon atoms, so none are left over after β-oxidation. Those fatty acids with an odd number of carbon atoms or with double bonds require additional steps for degradation, but all carbon atoms are ultimately released for further oxidation in the citric acid cycle.

Problem 17.2 Write the equations for the remaining passages of the β-oxidation pathway following those shown in Figure 17.3.

Problem 17.3 How many molecules of acetyl CoA are produced by catabolism of the following fatty acids, and how many passages of the β-oxidation pathway are needed?

(a) Palmitic acid, $CH_3(CH_2)_{14}CO_2H$
(b) Arachidic acid, $CH_3(CH_2)_{18}CO_2H$

17.3 Catabolism of Carbohydrates: Glycolysis

Glucose is the body's primary short-term energy source. Its catabolism begins with **glycolysis**, a series of ten enzyme-catalyzed reactions that break down glucose into 2 equivalents of pyruvate, $CH_3COCO_2^-$. The steps of glycolysis, also called the *Embden–Meyerhoff pathway* after its discoverers, are summarized in Figure 17.4.

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Figure 17.4 The ten-step glycolysis pathway for catabolizing glucose to pyruvate. Individual steps are described in the text.

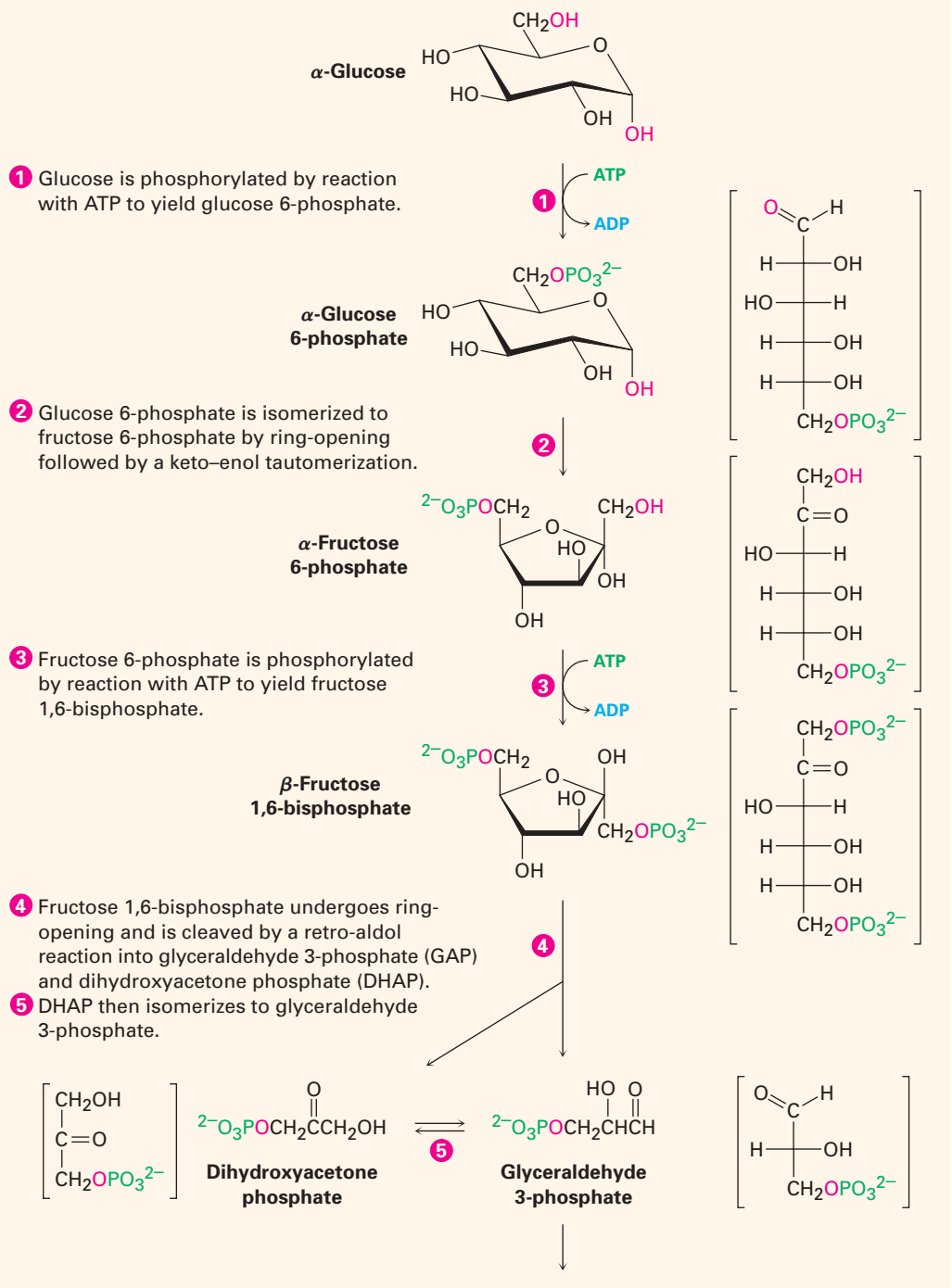

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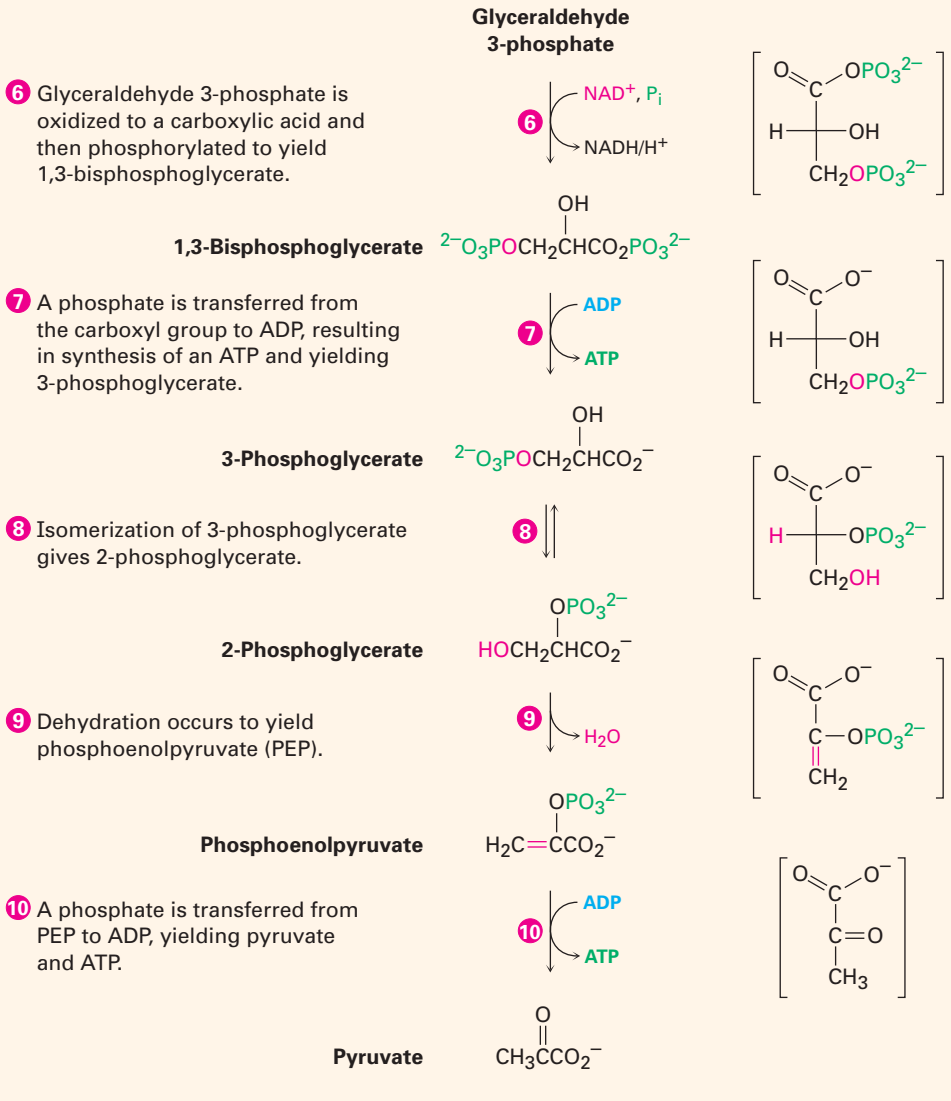
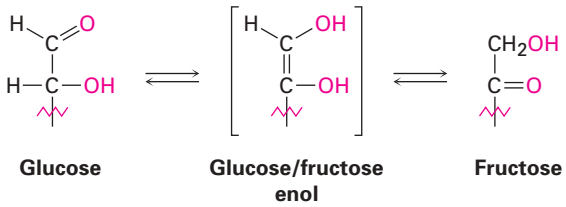
Figure 17.4 Continued.



STEPS 1–3 OF FIGURE 17.4: PHOSPHORYLATION AND ISOMERIZATION

Glucose, produced by digestion of dietary carbohydrates, is phosphorylated in step 1 by reaction with ATP in a reaction catalyzed by hexokinase. The glucose 6-phosphate that results is then isomerized in step 2 by glucose-6-phosphate isomerase to give fructose 6-phosphate. The isomerization

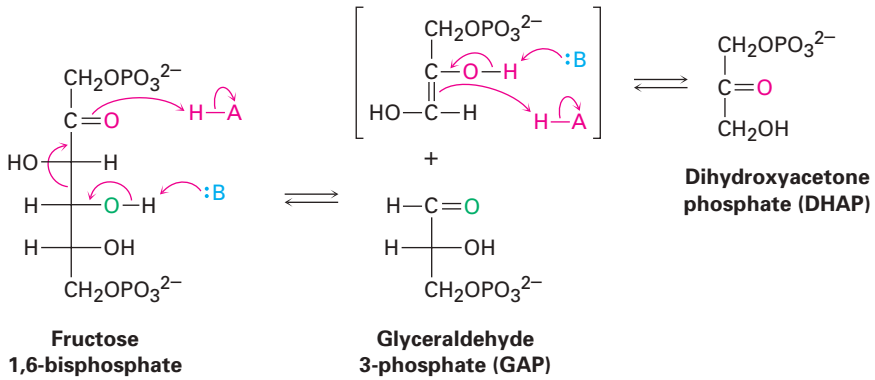
takes place by initial opening of the glucose hemiacetal ring to the open-chain form, followed by keto–enol tautomerization (Section 11.1) to an enol that is common to both glucose and fructose.



Fructose 6-phosphate is converted in step 3 to fructose 1,6-bisphosphate by a phosphofructokinase-catalyzed phosphorylation reaction with ATP (recall that the prefix *bis-* means "two"). The result is a molecule ready to be split into the two three-carbon intermediates that will ultimately become two molecules of pyruvate.

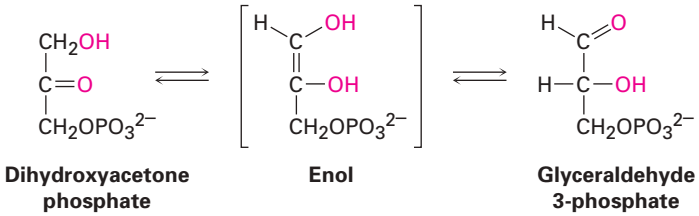
STEPS 4–5 OF FIGURE 17.4: CLEAVAGE AND ISOMERIZATION

Fructose 1,6-bisphosphate is cleaved in step 4 into two 3-carbon pieces, dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (GAP). The bond between C3 and C4 of fructose 1,6-bisphosphate breaks, and a C=O group is formed at C4. Mechanistically, the cleavage is the reverse of an aldol reaction (Section 11.8) and is carried out by an aldolase enzyme. (A *forward* aldol reaction joins two aldehydes or ketones to give a β-hydroxy carbonyl compound, while a *retro*-aldol reaction cleaves a β-hydroxy carbonyl compound into two aldehydes or ketones.)



Glyceraldehyde 3-phosphate continues on in the glycolysis pathway, but dihydroxyacetone phosphate is first isomerized in step 5 by triose phosphate isomerase. As in the glucose-to-fructose conversion of step 2, the isomerization of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate takes place by keto–enol tautomerization through a common enol. The net result

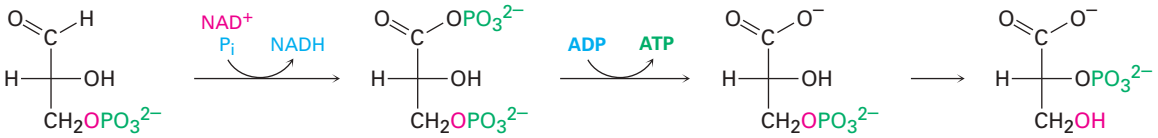
of steps 4 and 5 is the production of two glyceraldehyde 3-phosphate molecules, both of which pass down the rest of the pathway. Thus, each of the remaining five steps of glycolysis takes place twice for every glucose molecule that enters at step 1.



Dihydroxyacetone phosphate **Enol** **Glyceraldehyde 3-phosphate**

STEPS 6–8 OF FIGURE 17.4: OXIDATION AND PHOSPHORYLATION

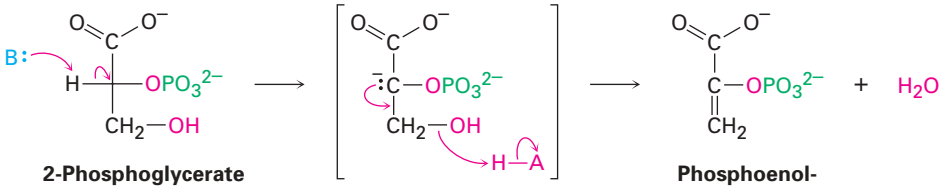
Glyceraldehyde 3-phosphate is oxidized and phosphorylated in step 6 to give 1,3-bisphosphoglycerate. The reaction requires the coenzyme NAD^+ in the presence of phosphate ion (HPO_4^{2-}, abbreviated P_i) and is catalyzed by glyceraldehyde-3-phosphate dehydrogenase. Transfer of a phosphate group from the carboxyl of 1,3-bisphosphoglycerate to ADP in step 7 then yields 3-phosphoglycerate, which is isomerized to 2-phosphoglycerate in step 8. The phosphorylation is catalyzed by phosphoglycerate kinase, and the isomerization is catalyzed by phosphoglycerate mutase.



Glyceraldehyde 3-phosphate **1,3-Bisphospho-glycerate** **3-Phospho-glycerate** **2-Phospho-glycerate**

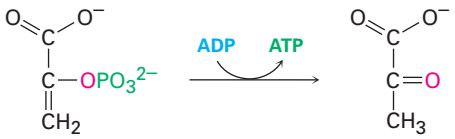
STEPS 9–10 OF FIGURE 17.4: DEHYDRATION AND DEPHOSPHORYLATION

Like most β-hydroxy carbonyl compounds produced in aldol reactions (Section 11.9), 2-phosphoglycerate undergoes a ready dehydration in step 9 by an E1cB mechanism (Section 7.8). The process is catalyzed by enolase, and the product is phosphoenolpyruvate, abbreviated PEP.



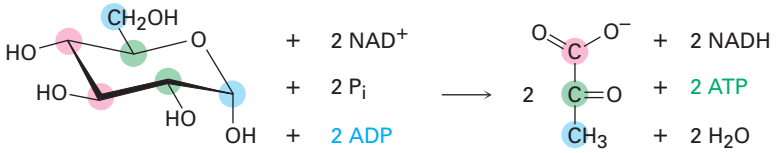
2-Phosphoglycerate **Phosphoenol-pyruvate (PEP)**

Transfer of the phosphate group to ADP in step 10 then generates ATP and gives pyruvate, a reaction catalyzed by pyruvate kinase.



Phosphoenol-pyruvate **Pyruvate**

The overall result of glycolysis is



Glucose **Pyruvate**

Pyruvate can undergo several further transformations, depending on the conditions and on the organism. Most commonly, pyruvate is converted to acetyl CoA through a complex, multistep sequence of reactions that requires three different enzymes and four different coenzymes. All the individual steps are well understood and have simple laboratory analogies, although their explanations are a bit outside the scope of this book.

Problem 17.4 Identify the steps in glycolysis in which ATP is produced.

Problem 17.5 Look at the entire glycolysis pathway shown in Figure 17.4 and make a list of the kinds of organic reactions that take place—nucleophilic acyl substitutions, aldol reactions, E1cB reactions, and so forth.

17.4 The Citric Acid Cycle

The first two stages of catabolism result in the conversion of fats and carbohydrates into acetyl groups that are bonded through a thioester link to coenzyme A. Acetyl CoA now enters the third stage of catabolism, the **citric acid cycle**, also called the *tricarboxylic acid (TCA) cycle* or *Krebs cycle* after Hans Krebs, who unraveled its complexities in 1937. The overall result of the cycle is the conversion of an acetyl group into two molecules of CO_2 plus reduced coenzymes by the eight-step sequence of reactions shown in Figure 17.5.

MECHANISM

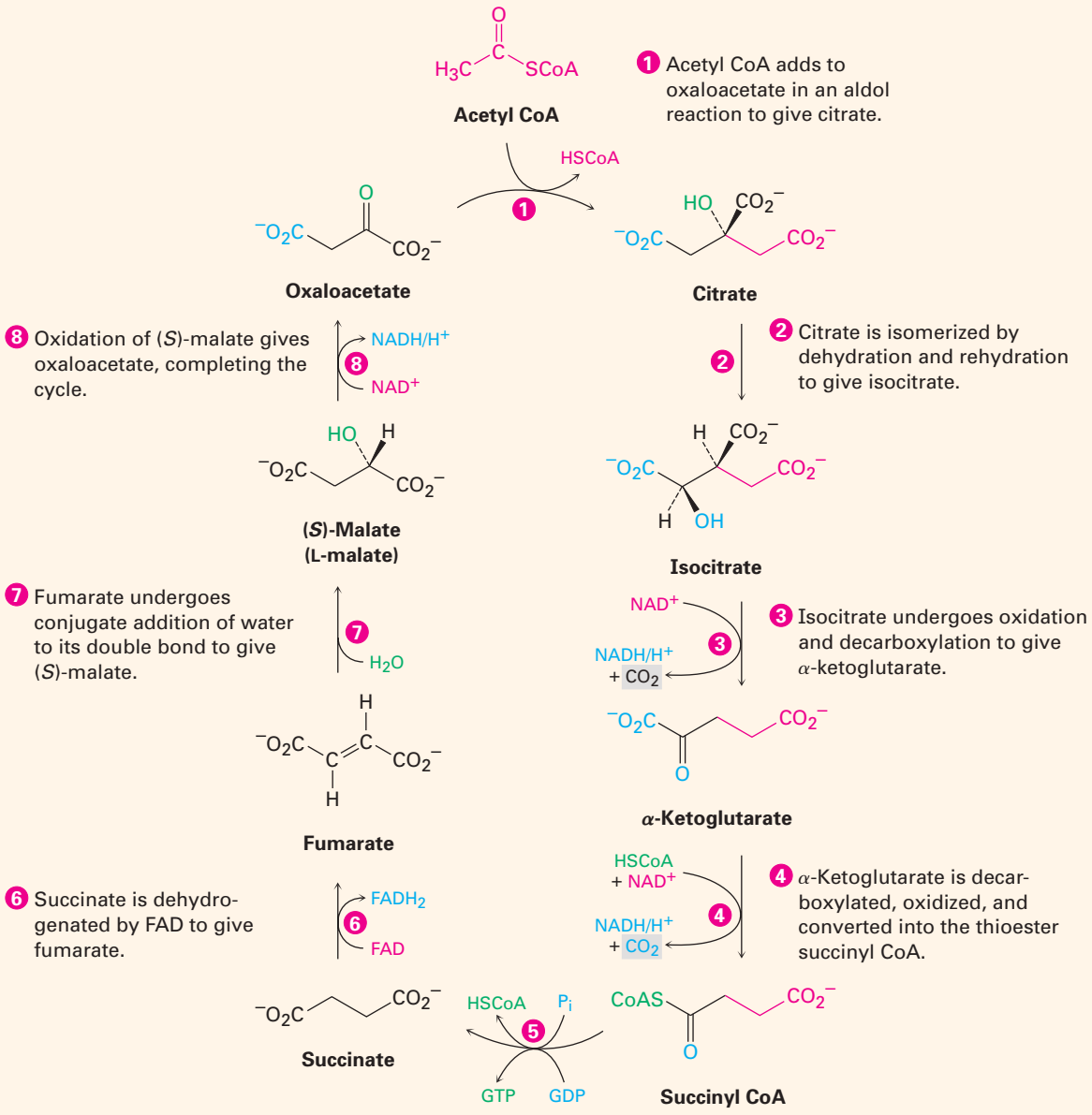
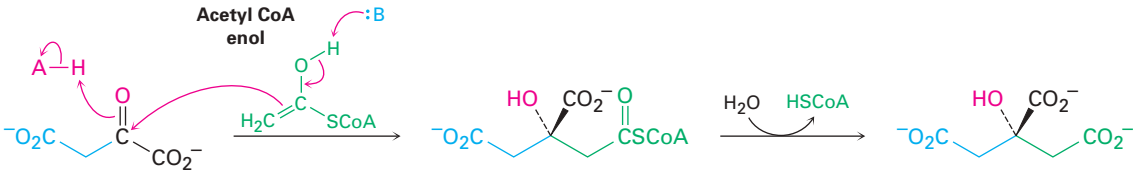


Figure 17.5 The citric acid cycle is an eight-step series of reactions that results in the conversion of an acetyl group into two molecules of CO_2 plus reduced coenzymes. Individual steps are explained in the text.

As its name implies, the citric acid *cycle* is a closed loop of reactions in which the product of the last step (oxaloacetate) is a reactant in the first step. The intermediates are constantly regenerated and flow continuously through the cycle, which operates as long as the oxidizing coenzymes NAD^+ and FAD are available. To meet this condition, the reduced coenzymes NADH and $FADH_2$ must be reoxidized via the electron-transport chain, which in turn relies on oxygen as the ultimate electron acceptor. Thus, the citric acid cycle is also dependent on the availability of oxygen and on the operation of the electron-transport chain.

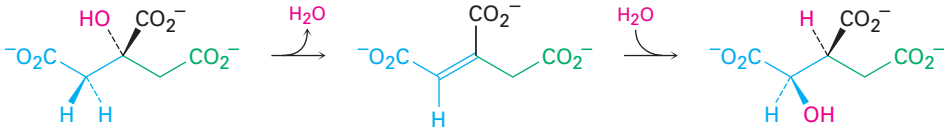
STEPS 1–2 OF FIGURE 17.5: ADDITION TO OXALOACETATE

Acetyl CoA enters the citric acid cycle in step 1 by nucleophilic addition to the ketone carbonyl group of oxaloacetate to give (*S*)-citryl CoA. The addition is an aldol reaction and is catalyzed by citrate synthase, as discussed in detail in Section 15.10. (*S*)-Citryl CoA is then hydrolyzed to citrate by a typical nucleophilic acyl substitution reaction with water, catalyzed by the same citrate synthase enzyme.



Oxaloacetate **(*S*)-Citryl CoA** **Citrate**

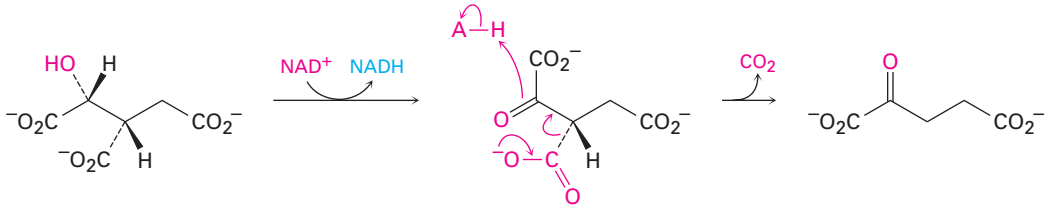
Citrate, a tertiary alcohol, is next converted into its isomer, isocitrate, a secondary alcohol. The isomerization occurs in two steps, both of which are catalyzed by the same aconitase enzyme. The initial step is an E1cB dehydration of the same sort that occurs in step 9 of glycolysis (Figure 17.4). The second step is a conjugate nucleophilic addition of water of the same sort that occurs in step 2 of the β-oxidation pathway (Figure 17.2). Note that the dehydration of citrate takes place specifically *away* from the carbon atoms of the acetyl group that added to oxaloacetate in step 1.



Citrate ***cis*-Aconitate** **Isocitrate**

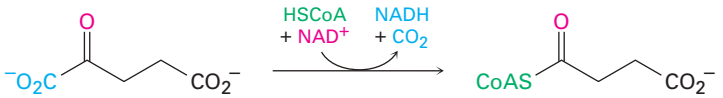
STEPS 3–4 OF FIGURE 17.5: OXIDATION AND DECARBOXYLATION

Isocitrate, a secondary alcohol, is oxidized by NAD^+ in step 3 to give the ketone oxalosuccinate, which loses CO_2 to give α-ketoglutarate. Catalyzed by isocitrate dehydrogenase, the decarboxylation is a typical reaction of a β-keto acid just like that in the malonic ester synthesis (Section 11.6).



Isocitrate **Oxalosuccinate** **α-Ketoglutarate**

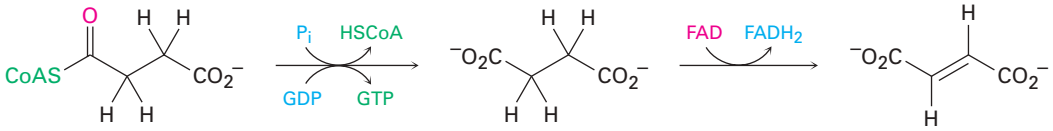
The transformation of α-ketoglutarate to succinyl CoA in step 4 is a multistep process analogous to the transformation of pyruvate to acetyl CoA that we saw in the previous section. Like the pyruvate conversion, the α-ketoglutarate conversion requires a number of different enzymes and coenzymes.



α-Ketoglutarate **Succinyl CoA**

STEPS 5–6 OF FIGURE 17.5: HYDROLYSIS AND DEHYDROGENATION

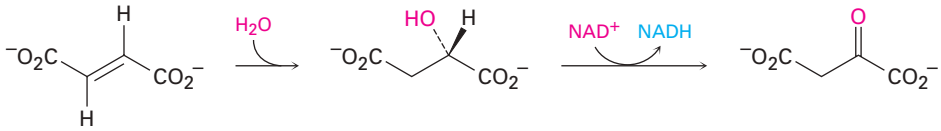
Succinyl CoA is hydrolyzed to succinate in step 5. The reaction is catalyzed by succinyl CoA synthetase and is coupled with phosphorylation of guanosine diphosphate (GDP) to give guanosine triphosphate (GTP). Succinate is then dehydrogenated by FAD and succinate dehydrogenase to give fumarate—a process analogous to that of step 1 in the β-oxidation pathway.



Succinyl CoA **Succinate** **Fumarate**

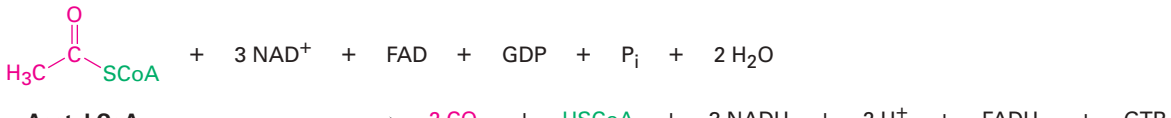
STEPS 7–8 OF FIGURE 17.5: REGENERATION OF OXALOACETATE

The final two steps in the citric acid cycle are the conjugate nucleophilic addition of water to fumarate to yield (*S*)-malate (L-malate) and the oxidation of malate by NAD^+ to give oxaloacetate. The addition is catalyzed by fumarase and is mechanistically similar to the addition of water to *cis*-aconitate in step 2. The oxidation is catalyzed by malate dehydrogenase. At this point, the citric acid cycle has returned to the beginning, ready to revolve again.



Fumarate **(*S*)-Malate** **Oxaloacetate**

The overall result of the citric acid cycle is



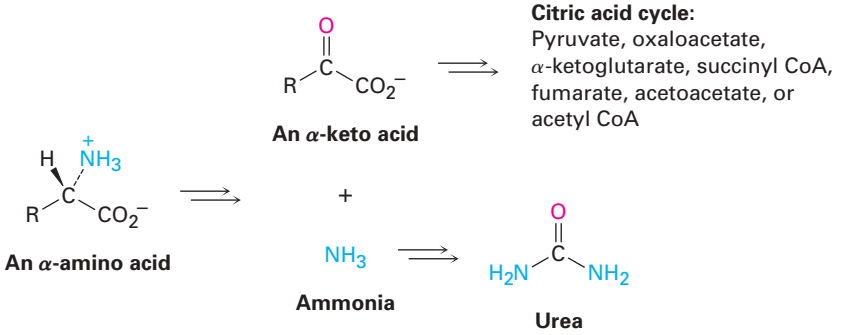
Acetyl CoA

Problem 17.6 Which of the substances in the citric acid cycle are tricarboxylic acids, thus giving the cycle its alternate name?

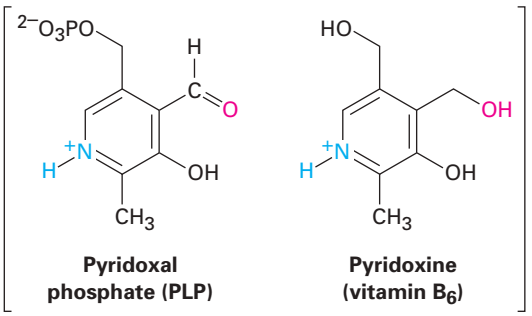
Problem 17.7 Write mechanisms for the reactions in step 2 of the citric acid cycle, the dehydration of citrate and the addition of water to aconitate.

17.5 Catabolism of Proteins: Transamination

The catabolism of proteins is more complex than that of fats and carbohydrates because each of the 20 amino acids is degraded through its own unique pathway. The general idea, however, is that the amino nitrogen atom is removed and the substance that remains is converted into a compound that enters the citric acid cycle.



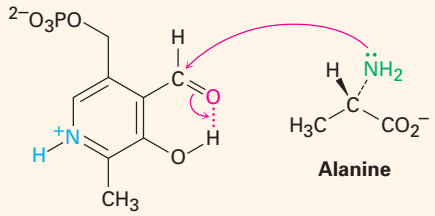
Most amino acids lose their nitrogen atom by a **transamination** reaction in which the $-NH_2$ group of the amino acid changes places with the keto group of α-ketoglutarate. The products are a new α-keto acid and glutamate. The overall process occurs in two parts, is catalyzed by various aminotransferases, and involves participation of the coenzyme pyridoxal phosphate (PLP), a derivative of pyridoxine (vitamin B_6).



As shown in Figure 17.6 for the reaction of alanine, the key step in transamination is nucleophilic addition of an amino acid $-NH_2$ group to the pyridoxal phosphate aldehyde group to yield an imine (Section 9.9), frequently called a *Schiff base* in biological chemistry. Loss of a proton from the α position then results in tautomerization to give a different imine, which is hydrolyzed (the exact reverse of imine formation) to yield pyruvate and pyridoxamine phosphate (PMP), a nitrogen-containing derivative of pyridoxal phosphate. Pyruvate is then converted into acetyl CoA (Section 17.3), which enters the citric acid cycle for further catabolism.

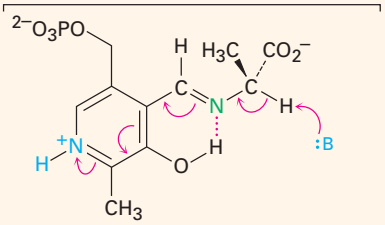
MECHANISM

Figure 17.6 Mechanism of the transamination of alanine by pyridoxal phosphate (PLP) to give pyruvate.



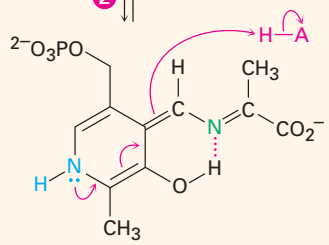
Pyridoxal phosphate (PLP)

1 Alanine reacts with pyridoxal phosphate by nucleophilic addition of its $-NH_2$ to the carbonyl group, giving an imine.



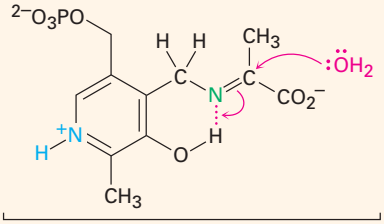
PLP–alanine imine

2 Deprotonation of the acidic α carbon of alanine gives an α-keto acid imine . . .



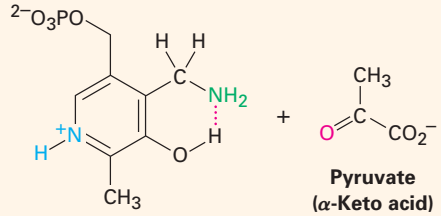
α-Keto acid imine

3 . . . that is reprotonated on carbon. The result of this deprotonation/reprotonation sequence is tautomerization of the imine C=N bond.



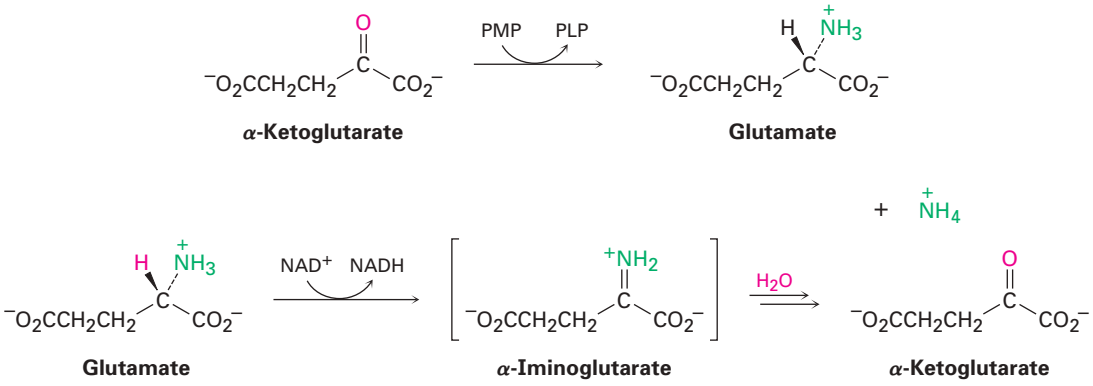
α-Keto acid imine tautomer

4 Hydrolysis of the imine gives the transamination products pyridoxamine phosphate (PMP) and pyruvate, an α-keto acid.



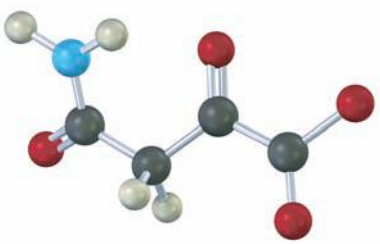
Pyridoxamine phosphate (PMP)

The pyridoxamine phosphate formed by transamination transfers its nitrogen atom to α-ketoglutarate by the reverse of the steps in Figure 17.6, thereby forming glutamate and regenerating pyridoxal phosphate for further use. Glutamate, which now contains the nitrogen atom of the former amino acid, next undergoes an oxidation to an imine and subsequent hydrolysis to yield ammonium ion plus regenerated α-ketoglutarate. The oxidation of the amine to an imine is similar to the oxidation of a secondary alcohol to a ketone, and is carried out by NAD^+.



Problem 17.8 Show the structure of the α-keto acid formed by transamination of leucine.

Problem 17.9 From what amino acid was the following α-keto acid derived?



17.6 Some Conclusions about Biological Chemistry

As promised in the chapter introduction, the past few sections have been a fast-paced tour of a large number of reactions. Following it all undoubtedly required a lot of work and some page-turning to look at earlier sections.

After examining the various metabolic pathways, perhaps the main conclusion about biological chemistry is the remarkable similarity between the mechanisms of biological reactions and the mechanisms of laboratory reactions. In all the pathways described in this chapter, terms like *imine formation, aldol reaction, nucleophilic acyl substitution reaction, E1cB reaction,* and *Claisen reaction* appear constantly.

Biological reactions aren't mysterious; there are clear, understandable reasons for the reactions carried out within living organisms. Biological chemistry *is* organic chemistry. Understanding how nature works and how living organisms function is a fascinating field of study.

INTERLUDE

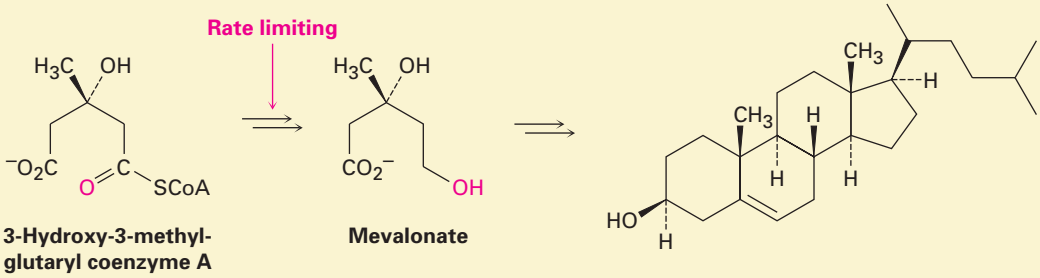
Statin Drugs

The buildup of cholesterol deposits inside arteries can cause coronary heart disease, a leading cause of death for both men and women.

Let's end this text by looking at a remarkable example of how organic and biological chemistry are changing modern medicine. Coronary heart disease—the buildup of cholesterol-containing plaques on the walls of heart arteries—is the leading cause of death for both men and women above age 20. It's estimated that up to one-third of women and one-half of men will develop the disease at some point in their lives.

The onset of coronary heart disease is directly correlated with blood cholesterol levels, and the first step in disease prevention is to lower those levels. It turns out that only about 25% of your blood cholesterol comes from what you eat; the remaining 75% (about 1000 mg each day) is biosynthesized in your liver from dietary fats and carbohydrates. Thus, any effective plan for lowering your cholesterol level means limiting the amount that your body makes, which in turn means understanding and controlling the metabolic pathway for cholesterol biosynthesis.

As you might imagine, that pathway is somewhat complex, but the chemical details of the more than 20 steps have all been worked out. Cholesterol arises from the simple precursor acetyl CoA, and the rate-limiting step in the pathway is the reduction of 3-hydroxy-3-methylglutaryl CoA (abbreviated HMG-CoA) to mevalonate, brought about by the enzyme HMG-CoA reductase. If that enzyme could be stopped from functioning, cholesterol biosynthesis would also be stopped.



3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)

Mevalonate

Cholesterol

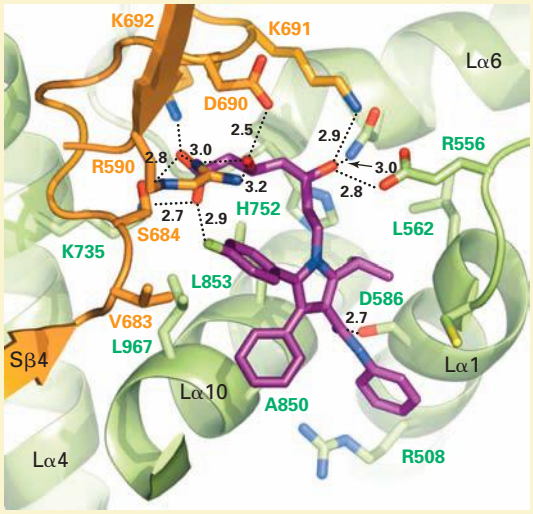
To find a drug that blocks HMG-CoA reductase, chemists did two experiments on a large number of potential drug candidates isolated from soil microbes. In one experiment, the drug candidate and mevalonate were added to liver extract; in the second experiment, only the drug candidate was added without mevalonate. If cholesterol was produced in the presence of mevalonate but was not produced in the absence of mevalonate, it meant that the drug candidate blocked mevalonate synthesis.

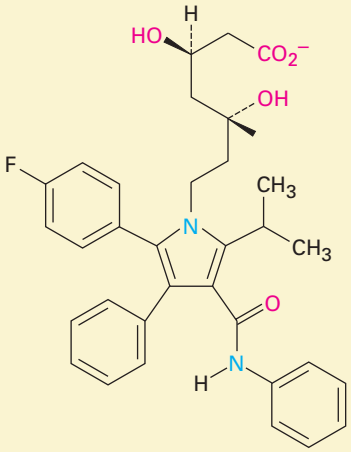
The drugs that block HMG-CoA reductase, and thus control cholesterol synthesis in the body, are called *statins*. They are the most widely prescribed drugs in the world, with an estimated $14.6 billion in annual sales. So effective are they that in the 10-year period following their introduction

continued

INTERLUDE

in 1994, the death rate from coronary heat disease decreased by 33% in the United States. Atorvastatin (Lipitor), simvastatin (Zocor), rosuvastatin (Crestor), pravastatin (Pravachol), and lovastatin (Mevacor) are examples. An X-ray crystal structure of the active site in the HMG-CoA reductase enzyme is shown in the accompanying graphic, along with a molecule of atorvastatin (blue) that is tightly bound in the active site and stops the enzyme from functioning. A good understanding of organic chemistry certainly paid off in this instance.





Atorvastatin (Lipitor)

Summary and Key Words

anabolism 572
β-oxidation pathway 576
catabolism 572
citric acid cycle 584
glycolysis 579
metabolism 572
transamination 588

Metabolism is the sum of all chemical reactions in the body. Reactions that break down larger molecules into smaller ones are **catabolic** and reactions that build up larger molecules from smaller ones are called **anabolic**. Although the details of specific biochemical pathways are sometimes complex, all the reactions that occur follow the normal rules of organic chemical reactivity.

The catabolism of fats begins with hydrolysis to give glycerol and fatty acids. The fatty acids are degraded in the four-step ***β*-oxidation pathway** by removal of two carbons at a time, yielding acetyl CoA. Catabolism of carbohydrates begins with the hydrolysis of glycoside bonds to give glucose, which is degraded in the ten-step **glycolysis** pathway. Pyruvate, the initial product of glycolysis, is then converted into acetyl CoA. The acetyl groups produced by degradation of fats and carbohydrates next enter the eight-step **citric acid cycle**, where they are further degraded into CO_2. The cycle is a closed loop of reactions in which the product of the final step (oxaloacetate) is a reactant in the first step. The intermediates are constantly regenerated and flow continuously through the cycle, which operates as long as the oxidizing coenzymes NAD^+ and FAD are available.

Catabolism of proteins is more complex than that of fats or carbohydrates because each of the 20 different amino acids is degraded by its own unique pathway. In general, though, the amino nitrogen atoms are removed and the substances that remain are converted into compounds that enter the citric acid cycle. Most amino acids lose their nitrogen atom by **transamination**, a reaction in which the $-NH_2$ group of the amino acid changes places with the keto group of an α-keto acid such as α-ketoglutarate. The products are a new α-keto acid and glutamate.

The energy released in all catabolic pathways is used in the electron-transport chain to make molecules of adenosine triphosphate (ATP), the final result of food catabolism. ATP couples with and drives many otherwise unfavorable reactions.

Exercises

Visualizing Chemistry

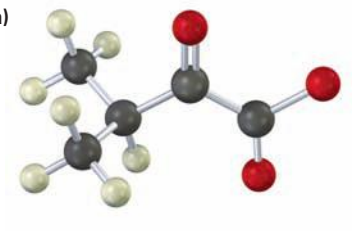
(Problems 17.1–17.9 appear within the chapter.)

OWL

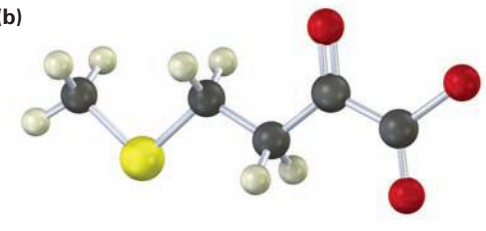
Interactive versions of these problems are assignable in OWL.

17.10 Identify the amino acid that is a catabolic precursor of each of the following α-keto acids:

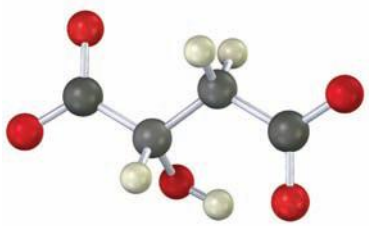
(a)



(b)



17.11 Identify the following intermediate in the citric acid cycle, and tell whether it has *R* or *S* stereochemistry:



Additional Problems

General Metabolism

17.12 What chemical events occur during the digestion of the following kinds of food molecules?
(a) Fats **(b)** Complex carbohydrates **(c)** Proteins

17.13 What is the difference between digestion and metabolism? Between anabolism and catabolism?

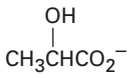
17.14 Draw the structure of adenosine monophosphate (AMP), an intermediate in some biochemical pathways.

17.15 What general kind of reaction does ATP carry out?

17.16 What general kind of reaction does NAD^+ carry out?

17.17 What general kind of reaction does FAD carry out?

17.18 Lactate, a product of glucose catabolism in oxygen-starved muscles, can be converted into pyruvate by oxidation. What coenzyme do you think is needed? Write the equation in the normal biochemical format using a curved arrow.



Lactate

17.19 How many moles of acetyl CoA are produced by catabolism of the following substances?
(a) 1.0 mol glucose **(b)** 1.0 mol palmitic acid ($C_{15}H_{31}CO_2H$)
(c) 1.0 mol maltose

17.20 How many grams of acetyl CoA (mol wt = 809.6 amu) are produced by catabolism of the following substances?
(a) 100.0 g glucose **(b)** 100.0 g palmitic acid **(c)** 100.0 g maltose

17.21 Which of the substances listed in Problem 17.20 is the most efficient precursor of acetyl CoA on a weight basis?

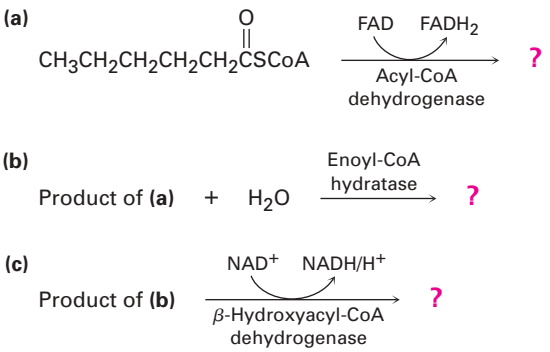
METABOLIC PATHWAYS

17.22 What substance is the starting point of the citric acid cycle, reacting with acetyl CoA in the first step and being regenerated in the last step?

17.23 List the sequence of intermediates involved in the catabolism of glycerol from hydrolyzed fats to yield acetyl CoA.

17.24 Write the equation for the final step in the β-oxidation pathway of any fatty acid with an even number of carbon atoms.

17.25 Show the products of each of the following reactions:

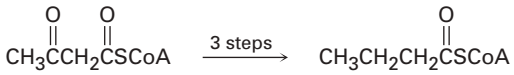


17.26 What is the structure of the α-keto acid formed by transamination of each of the following amino acids?
(a) Valine **(b)** Phenylalanine **(c)** Methionine

17.27 What enzyme cofactor is associated with transamination?

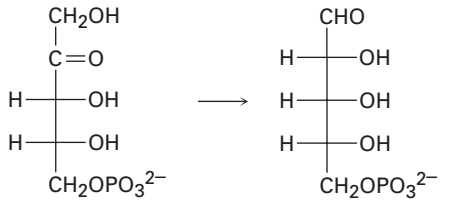
General Problems

17.28 Fatty acids are synthesized in the body by a sequence that begins with acetyl CoA. The first step is the condensation of two acetyl CoA molecules to yield acetoacetyl CoA, which undergoes three further enzyme-catalyzed steps, yielding butyryl CoA. Based on the kinds of reactions that occur in the β-oxidation pathway, what do you think are the three further steps of fatty-acid biosynthesis?



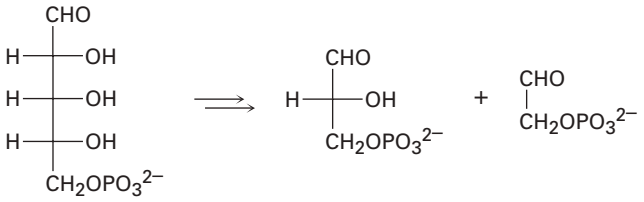
Acetoacetyl CoA **Butyryl CoA**

17.29 In the *pentose phosphate* pathway for degrading sugars, ribulose 5-phosphate is converted to ribose 5-phosphate. Propose a mechanism for the isomerization.



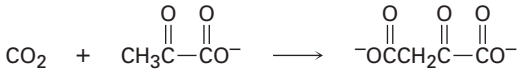
Ribulose 5-phosphate **Ribose 5-phosphate**

17.30 Another step in the pentose phosphate pathway for degrading sugars (see Problem 17.29) is the conversion of ribose 5-phosphate to glyceraldehyde 3-phosphate. What kind of organic process is occurring? Propose a mechanism for the conversion.



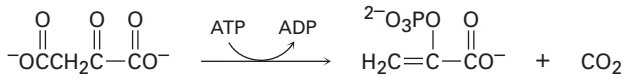
Ribose 5-phosphate **Glyceraldehyde 3-phosphate**

17.31 One of the steps in the *gluconeogenesis* pathway for synthesizing glucose in the body is the reaction of pyruvate with CO_2 to yield oxaloacetate. Tell what kind of reaction is occurring, and suggest a mechanism.



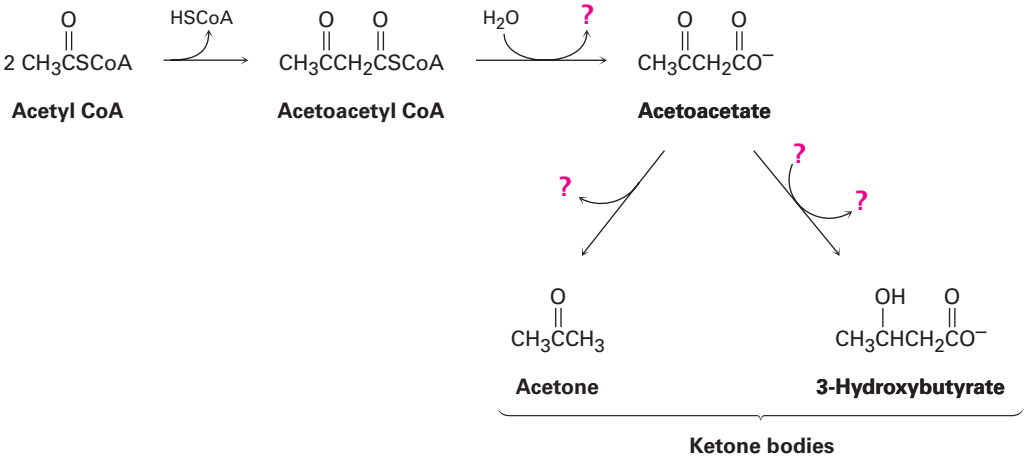
Pyruvate **Oxaloacetate**

17.32 Another step in gluconeogenesis (see Problem 17.31) is the conversion of oxaloacetate to phosphoenolpyruvate by decarboxylation and phosphorylation. Tell what kind of reaction is occurring, and suggest a mechanism.



Oxaloacetate **Phosphoenolpyruvate**

17.33 The primary fate of acetyl CoA under normal metabolic conditions is degradation in the citric acid cycle to yield CO_2. When the body is stressed by prolonged starvation, however, acetyl CoA is converted into compounds called *ketone bodies,* which can be used by the brain as a temporary fuel. The biochemical pathway for the synthesis of ketone bodies from acetyl CoA is shown. Fill in the missing information represented by the four question marks.



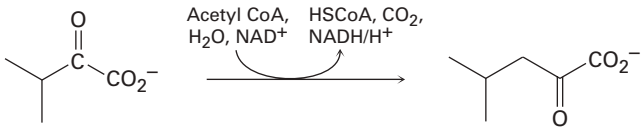
Acetyl CoA **Acetoacetyl CoA** **Acetoacetate**

Acetone **3-Hydroxybutyrate**

Ketone bodies

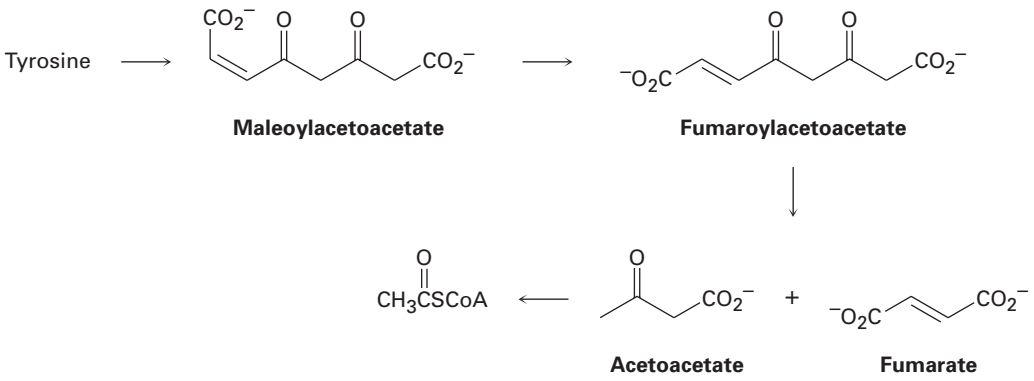
17.34 The initial reaction in Problem 17.33, conversion of two molecules of acetyl CoA to one molecule of acetoacetyl CoA, is a Claisen reaction. Assuming there is a base present, show the mechanism of the reaction.

17.35 The amino acid leucine is biosynthesized from α-ketoisocaproate, which is itself prepared from α-ketoisovalerate by a multistep route that involves (1) aldol-like reaction with acetyl CoA, (2) hydrolysis, (3) dehydration, (4) hydration, (5) oxidation, and (6) decarboxylation. Show the steps in the transformation.



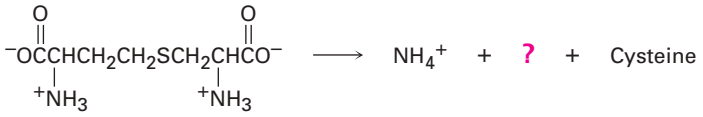
***α*-Ketoisovalerate** ***α*-Ketoisocaproate**

17.36 The amino acid tyrosine is metabolized by a series of steps that include the following transformations. Propose a mechanism for the conversion of fumaroylacetoacetate into fumarate plus acetoacetate.



17.37 Propose a mechanism for the conversion of acetoacetate into acetyl CoA (Problem 17.36).

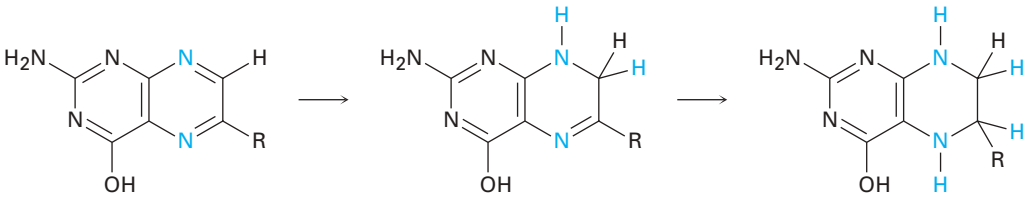
17.38 The amino acid cysteine, $C_3H_7NO_2S$, is biosynthesized from a substance called cystathionine by a multistep pathway.



(a) The first step is a transamination. What is the product?
(b) The second step is an E1cB reaction. Show the products and the mechanism of the reaction.
(c) The final step is a double-bond reduction. What is the product represented by the question mark in the equation?

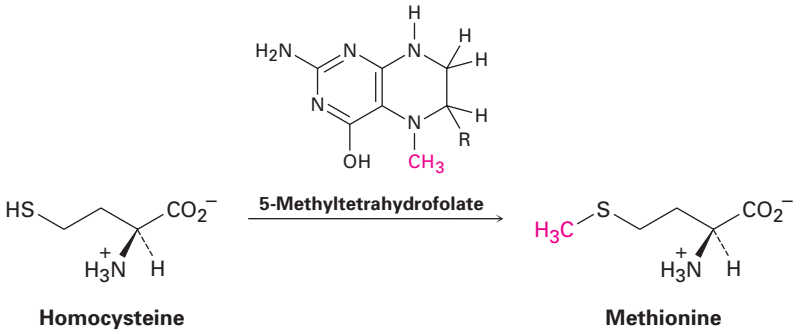
IN THE MEDICINE CABINET

17.39 Many drugs function by interfering with metabolic pathways. The anticancer drug methotrexate, for instance, inhibits the dihydrofolate reductase enzyme that catalyzes the following reactions:



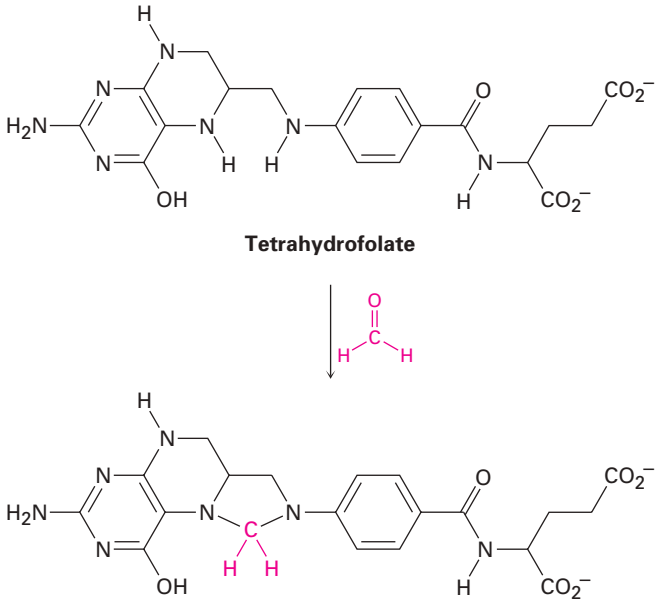
What cofactor is likely to be involved in these reductions? Propose a mechanism.

17.40 Methylation of tetrahydrofolate produces a cofactor called 5-methyltetrahydrofolate that is used in the conversion of homocysteine to methionine. Propose a mechanism for this reaction.



Homocysteine **Methionine**

17.41 In addition to transferring a methyl group, tetrahydrofolate can also transfer a formaldehyde group, a process that is critical for the biosynthesis of thymidine. Draw a mechanism for incorporation of formaldehyde into tetrahydrofolate.



Tetrahydrofolate