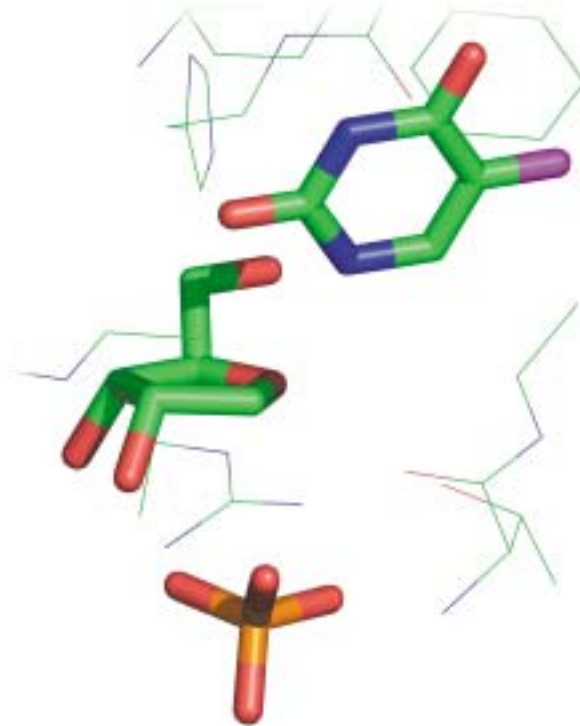


6 Nucleotide Metabolism



Extensive salvage pathways exist to conserve nucleotides, the building blocks for DNA and RNA. The structure shows the ribosyl oxonium ion trapped at the active site of uridine phosphorylase, using fluorouridine and sulfate as alternative substrates.

6.1 Nucleotide Catabolism

Pyrimidines: Cytidine, Uridine, and Thymidine
Purines: Adenosine and Guanosine

6.2 Biosynthesis of Pyrimidine Ribonucleotides

Uridine Monophosphate
Cytidine Triphosphate

6.3 Biosynthesis of Purine Ribonucleotides

Inosine Monophosphate
Adenosine Monophosphate and Guanosine Monophosphate

6.4 Biosynthesis of Deoxyribonucleotides

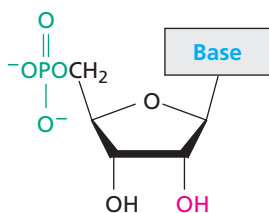
Deoxyadenosine, Deoxyguanosine, Deoxycytidine, and
Thymidine Diphosphates
Thymidine Monophosphate

References

Problems

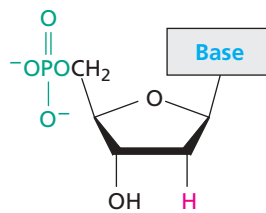
Nucleotides, the last major group of biomolecules that we'll consider, form the building blocks of nucleic acids just as amino acids form the building blocks of proteins. In addition, nucleoside triphosphates are involved as phosphorylating agents in many biochemical pathways and nucleotides are constituents of several important coenzymes, including NAD^+ , FAD, and coenzyme A.

Recall from Section 2.5 and Figure 2.12 that there are four ribonucleotides and four deoxyribonucleotides, each consisting of a cyclic amine (a “base”) bonded to a five-carbon sugar, with the sugar in turn bonded to a phosphate group. In ribonucleotides, two of the amine bases (cytosine and uracil) have a modified pyrimidine ring, and two (adenine and guanine) have a modified purine ring. In deoxyribonucleotides, cytosine, adenine, and guanine are still present but thymine replaces uracil.



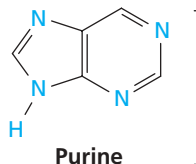
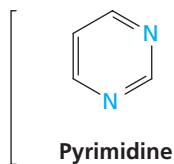
Ribonucleotides

Cytidine monophosphate (CMP)
Uridine monophosphate (UMP)
Adenosine monophosphate (AMP)
Guanosine monophosphate (GMP)



Deoxyribonucleotides

Deoxycytidine monophosphate (dCMP)
Thymidine monophosphate (dTMP or TMP)
Deoxyadenosine monophosphate (dAMP)
Deoxyguanosine monophosphate (dGMP)



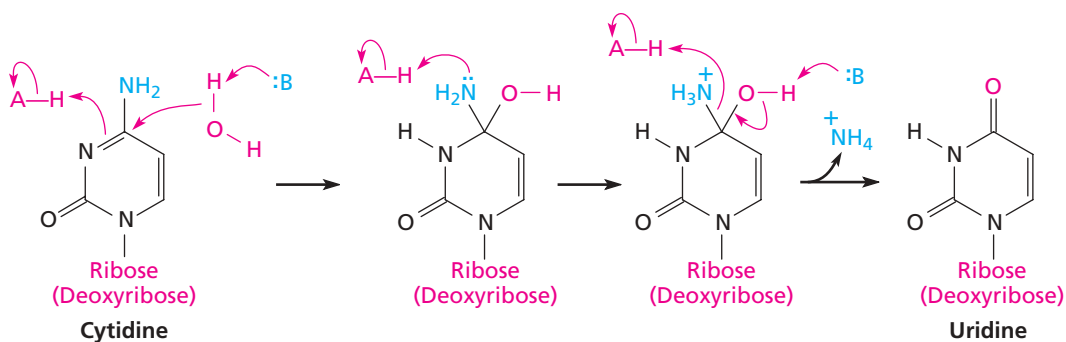
As in previous chapters, we'll look first at the metabolic pathways by which nucleotides are degraded and then cover their biosynthesis.

6.1 Nucleotide Catabolism

Dietary nucleic acids pass through the stomach to the intestines, where they are hydrolyzed to their constituent nucleotides by a variety of different nucleases. Further breakdown by various nucleotidases and phosphatases gives nucleosides, and a third hydrolysis by nucleosidases and nucleoside phosphorylases gives the constituent bases. A fraction of these bases are transported to tissues where they are reused for nucleic acid synthesis, but the rest are catabolized to produce intermediates of other metabolic processes.

Pyrimidines: Cytidine, Uridine, and Thymidine

The catabolism of **cytidine** begins with its hydrolytic deamination to give uridine. The reaction is catalyzed by cytidine deaminase¹ and occurs by nucleophilic addition of water to the C=N double bond, followed by expulsion of ammonia.



Uridine is cleaved by phosphorolysis to give uracil plus ribose 1-phosphate, and the uracil is then catabolized as the free base. Uridine catabolism occurs in six steps, as shown in Figure 6.1.

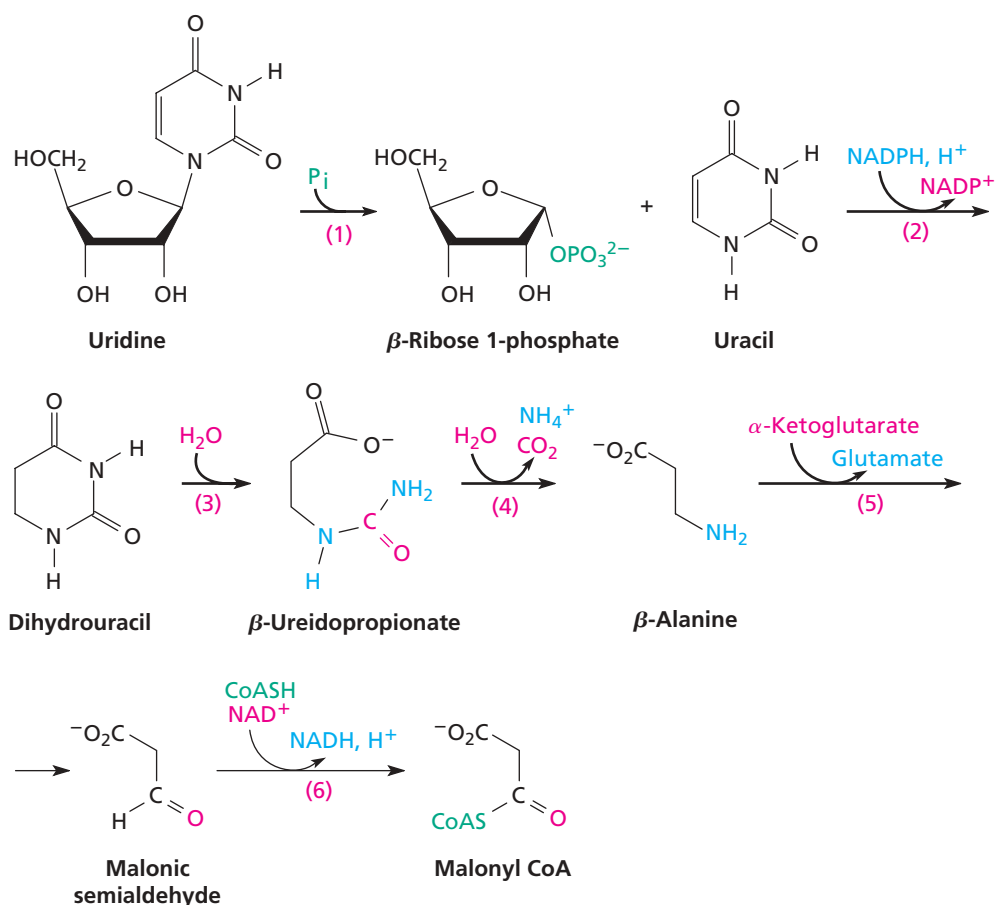


FIGURE 6.1 Pathway for the catabolism of uracil.

Steps 1–2. Phosphorolysis and reduction The phosphorolysis of uridine to give β -ribose 1-phosphate plus uracil is catalyzed by uridine phosphorylase and occurs by an S_N1 -like replacement of uracil by phosphate ion through an oxonium-ion intermediate, analogous to the reaction of inverting glycosidases shown in Figure 4.2. Reduction of the $C=C$ double bond in uracil then gives dihydrouracil in a reaction catalyzed by dihydropyrimidine dehydrogenase.² This reduction is substantially more complex than the result suggests. Rather than react directly with

the substrate, NADPH first reduces a nonactive-site FAD by hydride transfer, and FADH_2 then reduces an active-site FMN (flavin mononucleotide) by a long-range electron transfer mediated by two iron–sulfur clusters. Reduced FMN transfers a hydride ion to the *si* face of the unsaturated carbonyl group in uracil, and protonation of the intermediate anion by Cys-671 also occurs on the *si* face giving dihydrouracil (Figure 6.2).

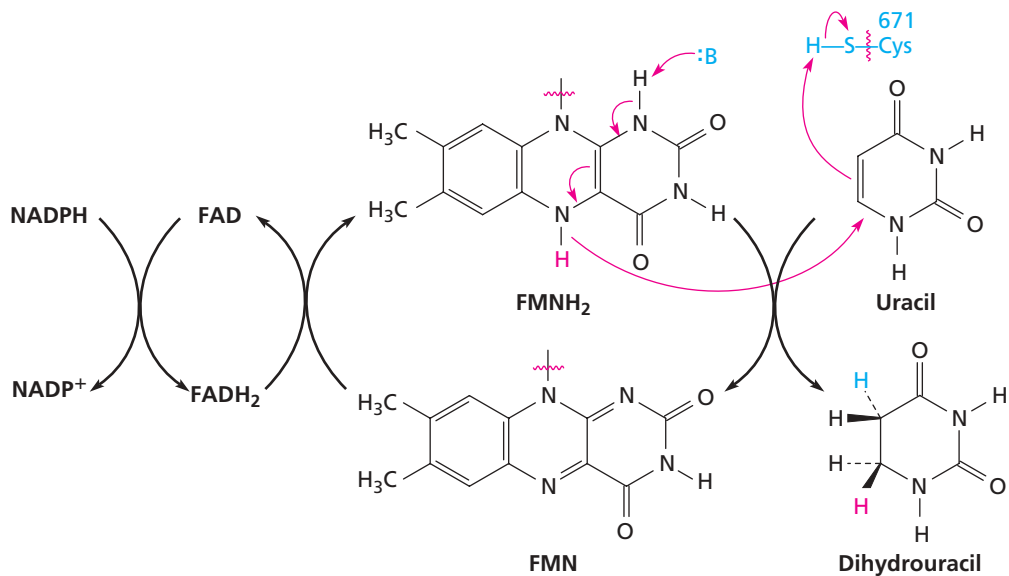


FIGURE 6.2 Mechanism of the reduction of dihydrouracil, catalyzed by dihydropyrimidine dehydrogenase.

An X-ray crystal structure of the active site in the enzyme–substrate complex of dihydropyrimidine dehydrogenase shows the flavin ring, the adjacent uracil substrate, and Cys-671 positioned for protonation (Figure 6.3).

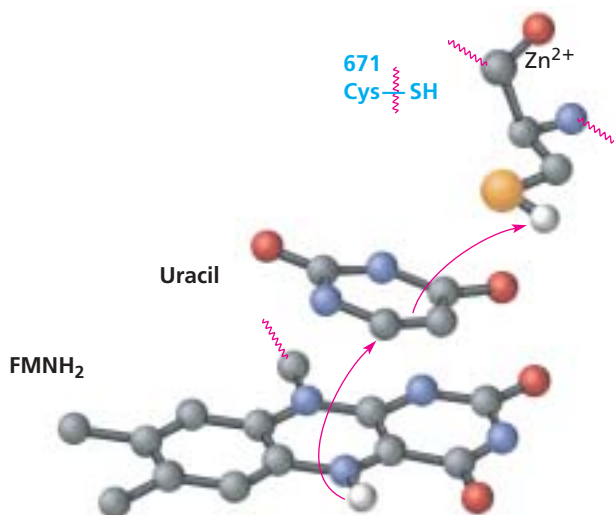
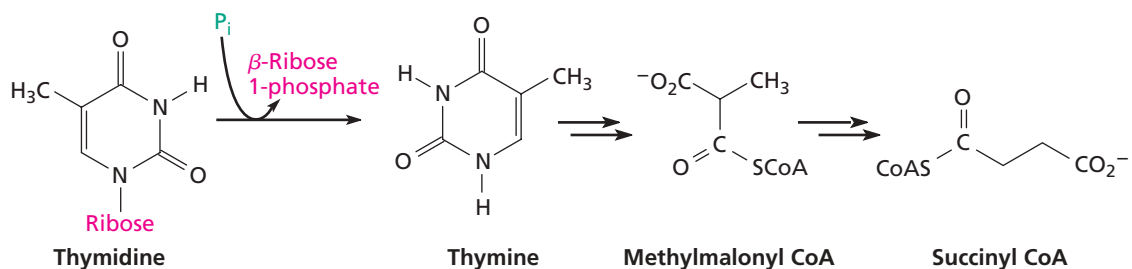


FIGURE 6.3 An X-ray crystal structure of the active site in the enzyme–substrate complex of dihydropyrimidine dehydrogenase. Reduced flavin transfers a hydride ion to uracil, and protonation by Cys-671 gives dihydrouracil.

Steps 3–4. Hydrolysis and decarboxylation Dihydrouracil undergoes hydrolysis by a nucleophilic acyl substitution mechanism to give the open-chain β -ureidopropionate. Further hydrolysis of the urea group yields ammonia and a carbamic acid ($R-NH-CO_2^-$), which decarboxylates to give β -alanine.

Steps 5–6. Transamination and oxidation PLP-dependent transamination of β -alanine by reaction with α -ketoglutarate in the usual way (Section 5.1) is followed by oxidation of the resultant malonic semialdehyde to yield malonyl CoA. Malonyl CoA then either decarboxylates to acetyl CoA or enters the pathway for fatty acid synthesis (Section 3.4, Figure 3.12). As in valine catabolism (Section 5.3), this final oxidation is thought to occur by addition to the aldehyde of a thiol residue on the dehydrogenase enzyme to give a hemithioacetal, followed by oxidation with NAD^+ and nucleophilic acyl substitution by coenzyme A.

Thymidine is cleaved to thymine and then degraded by a pathway analogous in all respects to that of uracil. The final product is methylmalonyl CoA, the same substance produced by threonine catabolism and ultimately converted to succinyl CoA (Section 5.3).



Purines: Adenosine and Guanosine

In mammals, **adenosine** (or deoxyadenosine) is not cleaved directly to adenine. Instead, it is deaminated to give inosine by the same mechanism as that in cytidine catabolism, and inosine is cleaved by purine nucleoside phosphorylase to hypoxanthine. Hypoxanthine is then oxidized to yield xanthine, and a further oxidation produces uric acid, which is excreted in the urine (Figure 6.4).

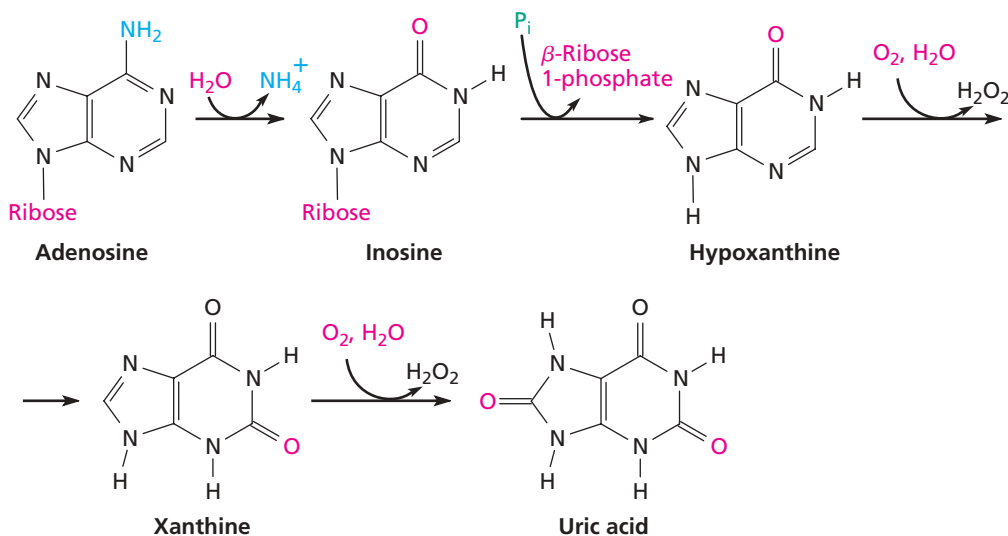


FIGURE 6.4 Pathway for the catabolism of adenosine to uric acid.

Hypoxanthine and xanthine oxidations are both catalyzed by xanthine oxidase,^{3, 4} a complex enzyme that contains FAD, two iron–sulfur clusters, and an oxo–molybdenum(VI) cofactor. Numerous mechanisms have been proposed, but

current evidence³ suggests the process shown in Figure 6.5. In this mechanism, a glutamate residue in the enzyme deprotonates the Mo—OH group, and the resulting anion does a nucleophilic addition to a C=N double bond in hypoxanthine. The nitrogen anion then expels hydride ion, which adds to an S=Mo bond, thereby reducing the molybdenum center from Mo(VI) to Mo(IV). Subsequent hydrolysis of the O—Mo bond gives an enol that tautomerizes to xanthine, and the reduced molybdenum is reoxidized by O₂ in a complex redox pathway. Note that the expulsion of hydride ion by electrons on the neighboring nitrogen atom is analogous to what occurs during NADH reductions (Section 1.9).

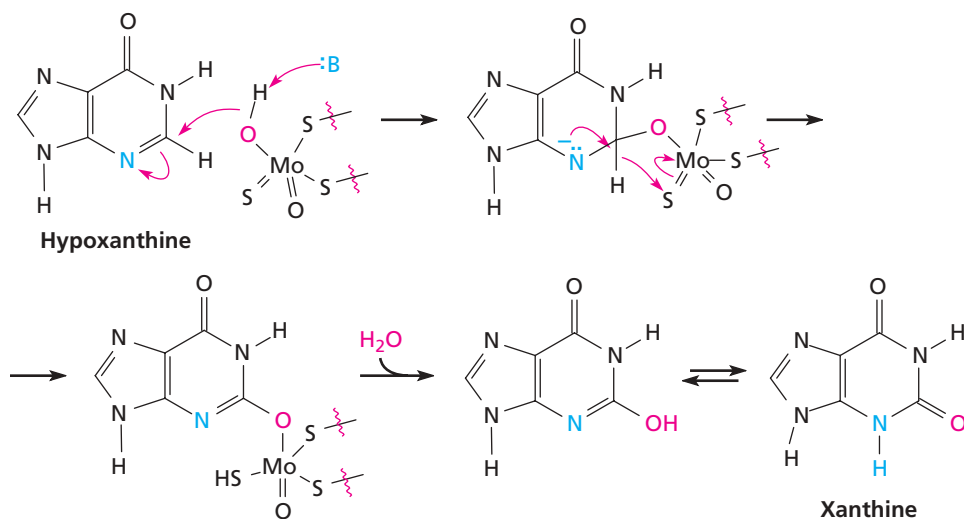
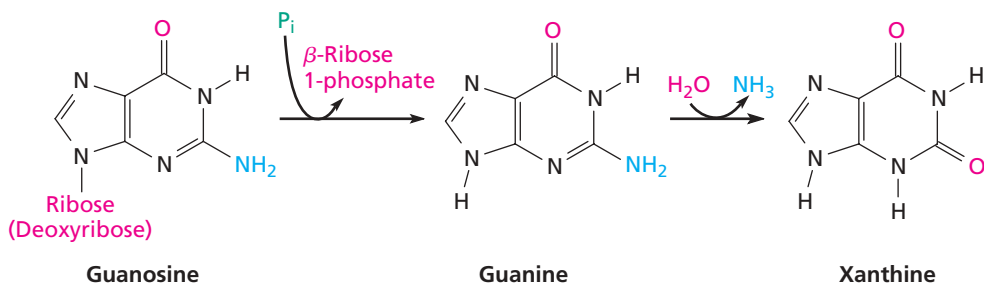


FIGURE 6.5 Proposed mechanism for the oxidation of hypoxanthine to xanthine. A similar process occurs in the subsequent oxidation of xanthine to uric acid.

Guanosine (or deoxyguanosine) is cleaved by purine nucleoside phosphorylase to guanine, which is then hydrolytically deaminated to yield xanthine by the same mechanism as in cytidine deamination.



6.2 Biosynthesis of Pyrimidine Ribonucleotides

Uridine Monophosphate

Uridine monophosphate (UMP) is biosynthesized in a six-step pathway from aspartate, bicarbonate, and ammonia, which itself comes from the amide nitrogen of glutamine (Figure 6.6).

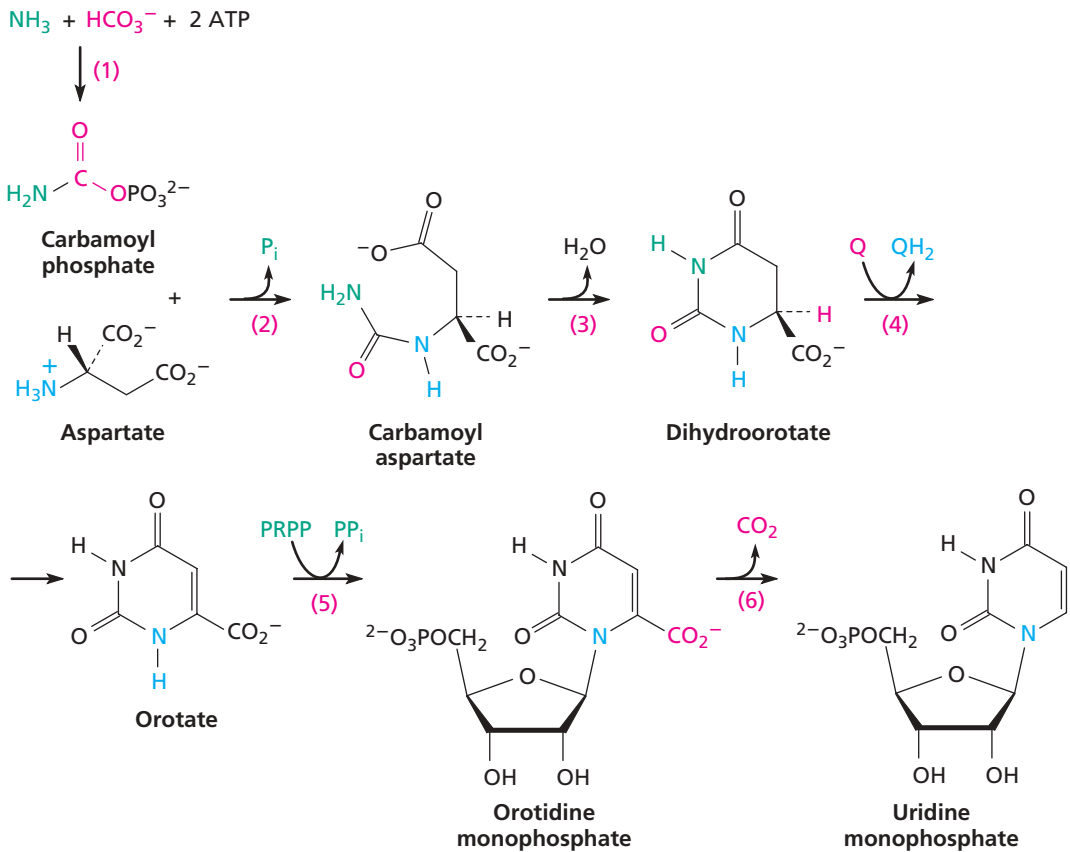
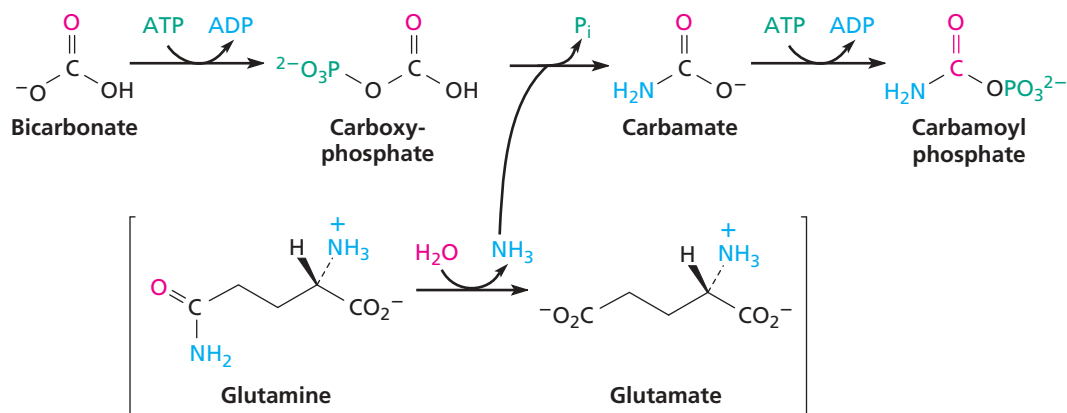


FIGURE 6.6 Pathway for the biosynthesis of uridine monophosphate (UMP) from carbamoyl phosphate and aspartate.

Step 1. Carbamoyl phosphate synthesis UMP biosynthesis begins with formation of carbamoyl phosphate, catalyzed by carbamoyl phosphate synthetase II.⁵ The reaction is identical to that occurring in the urea cycle (Section 5.2) except that the ammonia used for pyrimidine synthesis comes from hydrolysis of glutamine within the synthetase enzyme rather than from free ammonia as in the urea cycle.



Steps 2–3. Reaction with aspartate and cyclization Carbamoyl phosphate reacts with aspartate in a nucleophilic acyl substitution reaction with phosphate as the leaving group to give carbamoyl aspartate. Cyclization then forms dihydroorotate. The cyclization is catalyzed by dihydroorotase⁶ and is mechanistically interesting because it accomplishes the formation of an amide bond between a poor nucleophile (a urea-like nitrogen) and a poor electrophile (a carboxylate). What evidently happens is that the carboxylate is activated by coordination to two Lewis-acidic Zn^{2+} ions, and both reacting centers are surrounded by various charged groups within the enzyme that electrostatically stabilize the reaction intermediates. Deprotonation of the urea —NH_2 by an aspartate residue and concurrent addition to the carboxylate carbonyl group in a nucleophilic acyl substitution reaction gives the product. Figure 6.7 shows both the mechanism and an X-ray crystal structure of the substrate bound in the active site.

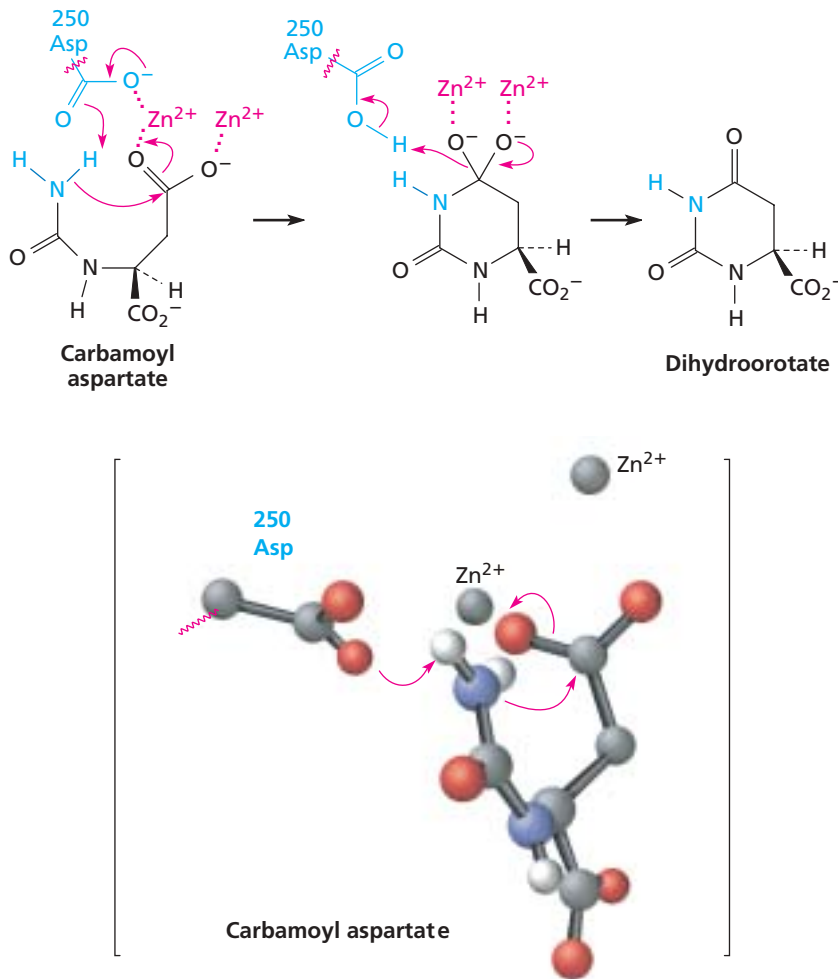


FIGURE 6.7 Mechanism of the cyclization of carbamoyl aspartate to dihydroorotate, along with an X-ray crystal structure of the substrate bound in the active site.

Step 4. Dehydrogenation Introduction of a double bond into dihydroorotate to give orotate is catalyzed by dihydroorotate dehydrogenase^{7, 8} a flavin-dependent enzyme that, in humans, uses coenzyme Q, also called ubiquinone, as the ultimate electron acceptor. The reaction occurs by base abstraction of the *pro-S* hydrogen at C5 and donation of hydride ion from C6 to FMN. The FMNH₂ is then reoxidized

by coenzyme Q. As shown in Figure 6.8, CoQ is a benzoquinone with a long hydrocarbon tail that allows it to dissolve readily in lipid membranes. Its function is to act as a redox agent in the transport of electrons between enzymes embedded in the inner mitochondrial membrane.

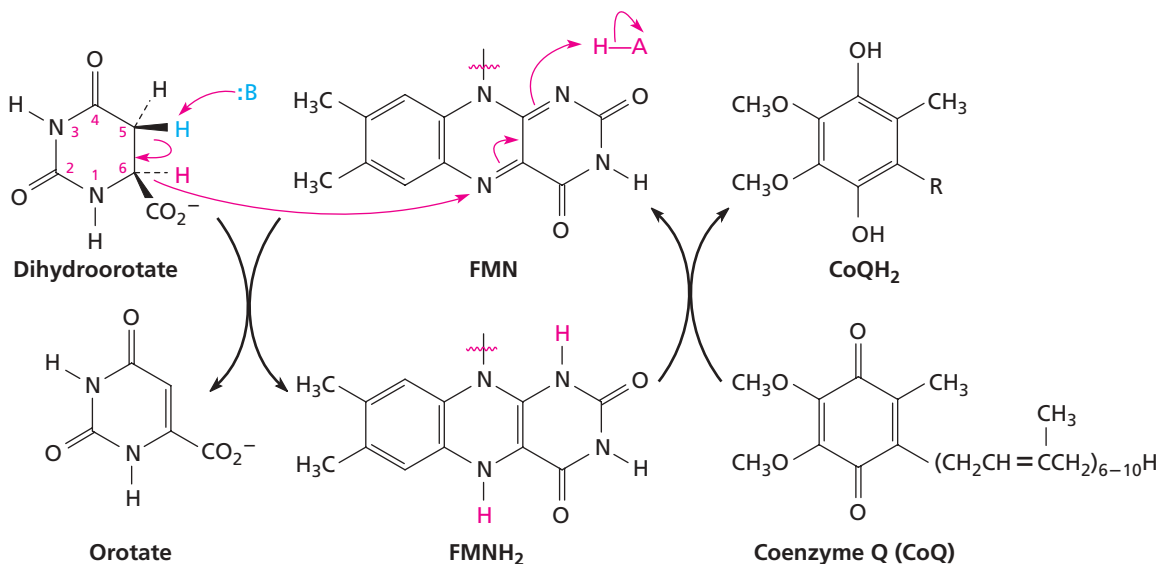


FIGURE 6.8 Mechanism of the dehydrogenation of dihydroorotate to orotate.

Step 5. Ribonucleotide formation Orotate reacts with 5-phosphoribosyl α -diphosphate (PRPP) to give the ribonucleotide orotidine monophosphate (OMP). This ribonucleotide formation takes place by a nucleophilic substitution reaction, catalyzed by orotate phosphoribosyltransferase.⁹ Although the reaction occurs with an inversion of stereochemistry, the likely mechanism involves spontaneous, $\text{S}_{\text{N}}1$ -like loss of diphosphate ion to give an oxonium-ion intermediate, much like what occurs in the hydrolysis of a polysaccharide catalyzed by an inverting glycosidase (Section 4.1, Figure 4.2). The 5-phosphoribosyl α -diphosphate precursor is formed from α -D-ribose 5-phosphate by reaction with ATP in the presence of PRPP synthetase (Figure 6.9).

Step 6. Decarboxylation The final step in UMP biosynthesis is the decarboxylation of OMP, catalyzed by orotidine monophosphate decarboxylase.¹⁰ This enzyme contains no cofactors and holds the distinction of having the greatest

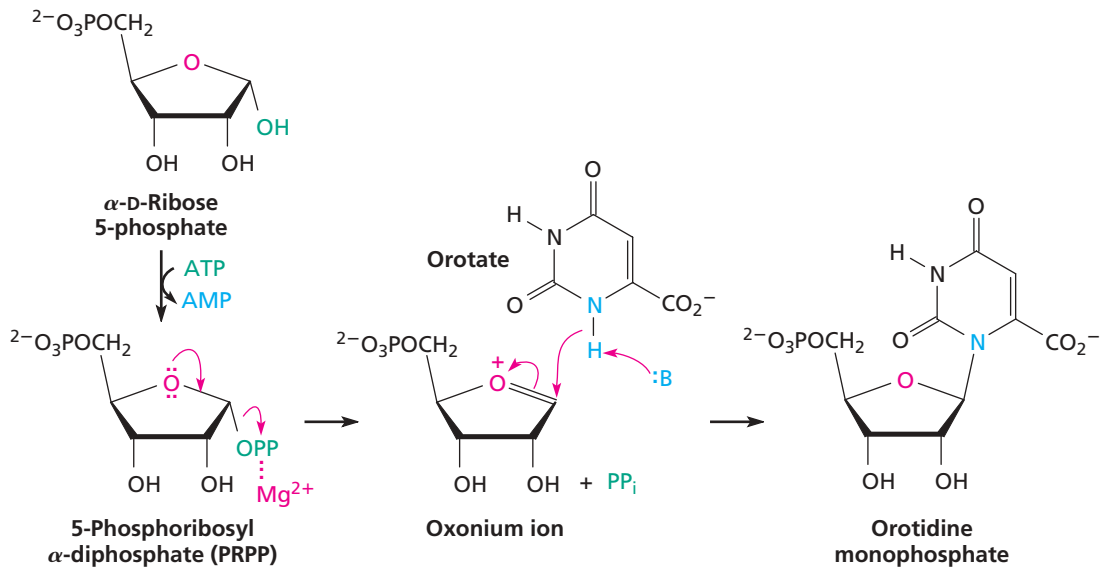
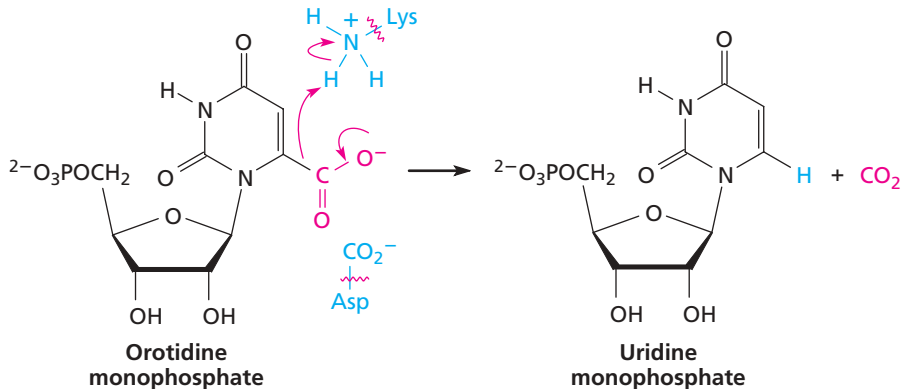


FIGURE 6.9 Mechanism of the formation of orotidine monophosphate.

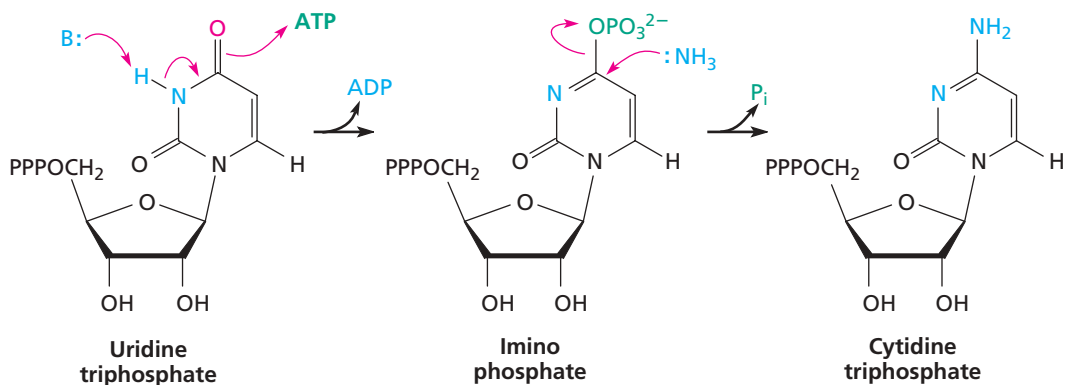
experimentally determined rate acceleration known for any enzyme, a factor of $2 \times 10^{23} \text{ M}^{-1}$ for the catalyzed versus uncatalyzed reaction! Mechanistically, the decarboxylation is unusual because the substrate is not a β keto acid and has no obvious electron sink nearby to accept electrons as CO_2 leaves. It's thought instead that the decarboxylation occurs in a single step, driven by electrostatic interactions between the substrate and charged residues in the active site. An aspartate residue held near the carboxylate destabilizes the ground state, while a protonated lysine stabilizes the transition state and provides a proton as CO_2 departs.



Cytidine Triphosphate

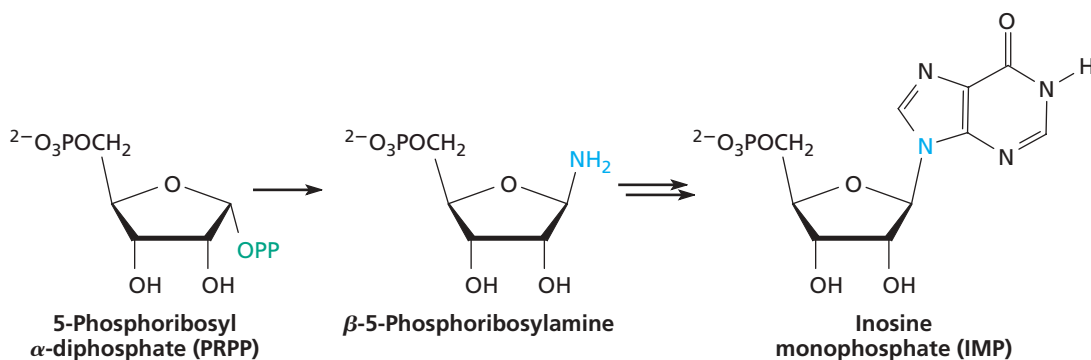
Following its synthesis from orotate, uridine monophosphate is converted into the corresponding triphosphate (UTP) by two sequential reactions with ATP. Uridine triphosphate is then converted into **cytidine triphosphate** by a reaction that is essentially the reverse of the cytidine \rightarrow uridine conversion seen in cytidine catabolism (Section 6.1). The primary difference between the two processes is that the cytidine \rightarrow uridine conversion requires no ATP while the uridine \rightarrow cytidine conversion is coupled to ATP hydrolysis for energetic reasons. Catalyzed by CTP synthase,¹¹ glutamine is first hydrolyzed to glutamate plus ammonia at one site in the enzyme, a process similar to what occurs in carbamoyl phosphate synthesis (Section 6.2). The ammonia then moves through a channel in the enzyme to the next reaction site.

In the second site, uridine triphosphate is phosphorylated on the pyrimidine oxygen by ATP, and the resultant imino phosphate undergoes nucleophilic acyl substitution by addition of NH_3 to the $\text{C}=\text{N}$ double bond followed by elimination of P_i .



6.3 Biosynthesis of Purine Ribonucleotides

As we've just seen, pyrimidine nucleotides are synthesized by an initial multistep formation of the pyrimidine base, followed by attachment of phosphoribose to the base. Purine nucleotides, in contrast, are formed by the initial attachment of an —NH_2 group to the phosphoribose, followed by multistep formation of the purine base. Inosine monophosphate (IMP) is the first fully formed purine ribonucleotide, with adenosine monophosphate (AMP) and guanosine monophosphate (GMP) then derived from it.



Inosine Monophosphate

The biosynthetic pathway for inosine monophosphate is shown in Figure 6.10. The pathway has 11 steps starting from 5-phosphoribosyl α -diphosphate, which is itself prepared by reaction of α -D-ribose 5-phosphate with ATP, as noted in the previous section.

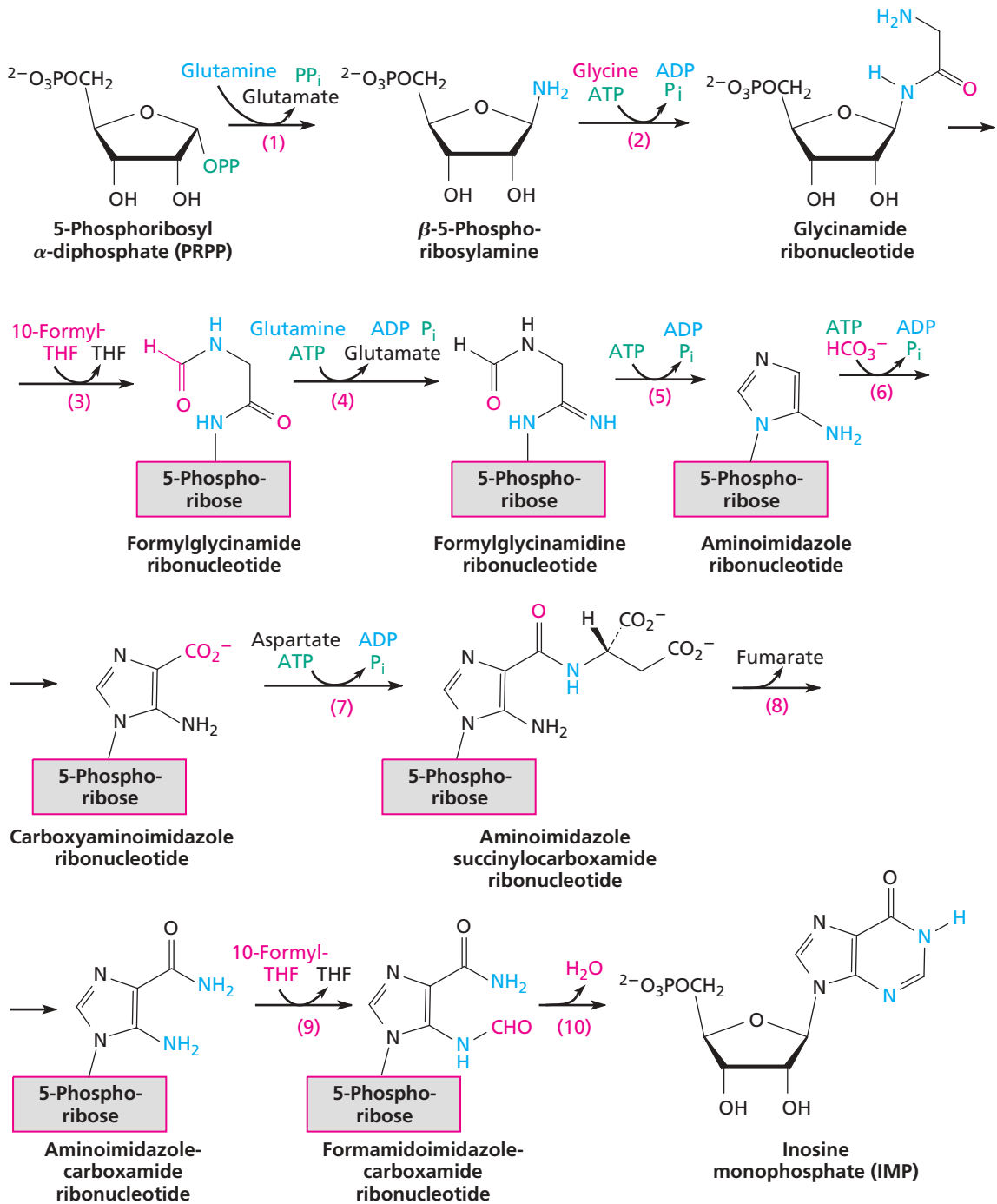
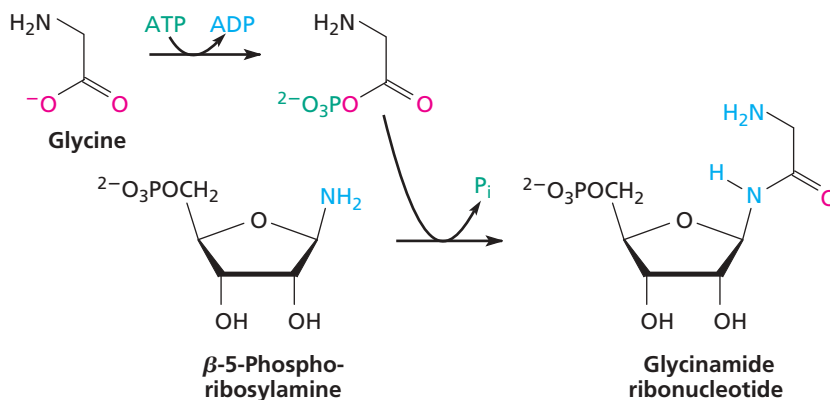


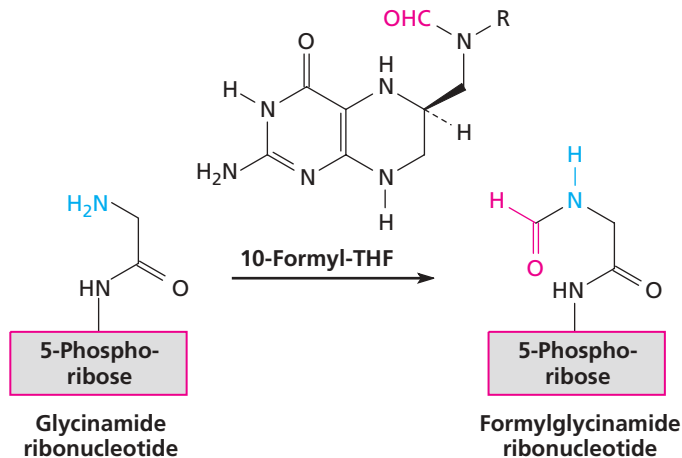
FIGURE 6.10 Pathway for the biosynthesis of the purine ribonucleotide inosine monophosphate (IMP).

Step 1. Amine formation 5-Phosphoribosyl α -diphosphate is converted to β -5-phosphoribosylamine by glutamine PRPP amidotransferase.¹² As in carbamoyl phosphate synthesis (Section 6.2), glutamine is first hydrolyzed to ammonia at one site in the enzyme, and the ammonia then moves through a channel to a second site where it reacts with 5-phosphoribosyl α -diphosphate. Reaction with the ribosyl diphosphate takes place through an oxonium-ion intermediate and occurs with a net inversion of configuration, as in the synthesis of orotidine monophosphate (Figure 6.9).

Step 2. Glycinamide formation Glycine and β -5-phosphoribosylamine react to form the amide glycinamide ribonucleotide (GAR) in a reaction catalyzed by GAR synthetase.¹³ The reaction occurs by initial formation of a glycyl phosphate, followed by nucleophilic acyl substitution with the ribosylamine. This mechanism is similar to that seen in the biosynthesis of glutamine from glutamate (Section 5.4).



Step 3. Formylation Formylation of the amino group in glycinamide ribonucleotide is catalyzed by GAR transformylase¹⁴ and occurs by transfer of a formyl group from 10-formyltetrahydrofolate in a nucleophilic acyl substitution reaction.



Step 4. Glycinimidine formation Formylglycinamide ribonucleotide is converted to formylglycinimidine ribonucleotide by reaction with ATP and ammonia (an amidine has the structure $R_2N-C=NH$). The reaction is catalyzed by formylglycinimidine (FGAM) synthetase and takes place by the mechanism shown in Figure 6.11. The process is very similar to what occurs in the conversion of uridine triphosphate to cytidine triphosphate (Section 6.2).

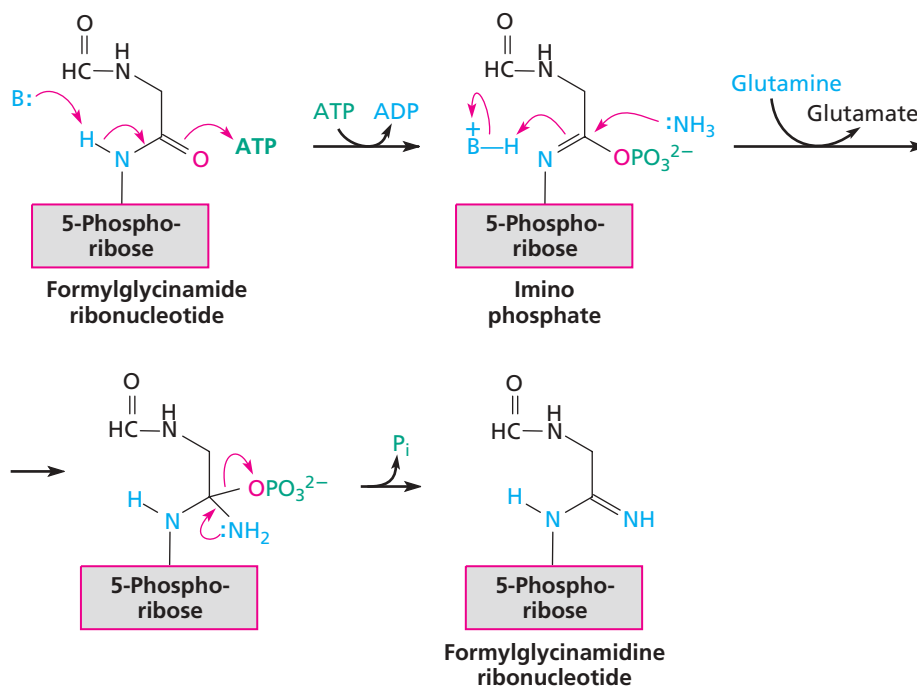
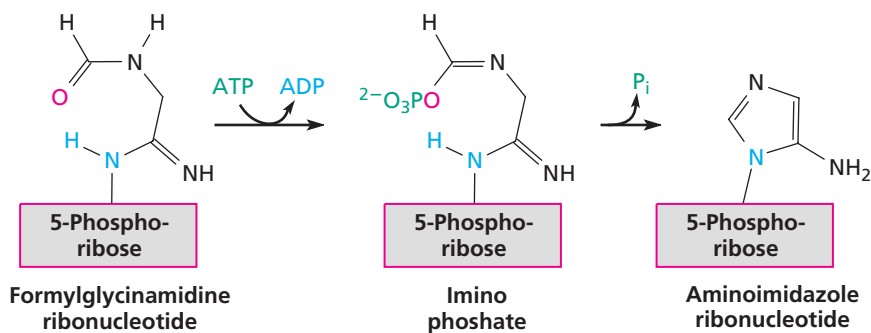


FIGURE 6.11 Mechanism of formylglycinamide formation in step 4 of inosine biosynthesis.

Step 5. Imidazole formation Closure of the imidazole ring in step 5 is catalyzed by aminoimidazole (AIR) synthetase,¹⁵ an ATP-dependent enzyme whose mechanism is analogous to that of FGAM synthetase in step 4 (Figure 6.11). Following ring closure, a tautomerization of the imine to an enamine occurs.



Step 6. Carboxylation Aminoimidazole ribonucleotide undergoes carboxylation by reaction with HCO_3^- in a process catalyzed by AIR carboxylase.^{16, 17} Unlike most other carboxylations, however, the reaction does not require biotin (Section 3.4, Figure 3.14). Instead, the reaction takes place by nucleophilic addition of the amino group to carboxyphosphate (Section 3.4, Figure 3.13) to give an *N*-carboxyaminoimidazole ring, followed by loss of CO_2 and immediate readdition (Figure 6.12). The amino group of AIR thus serves the same purpose as biotin.

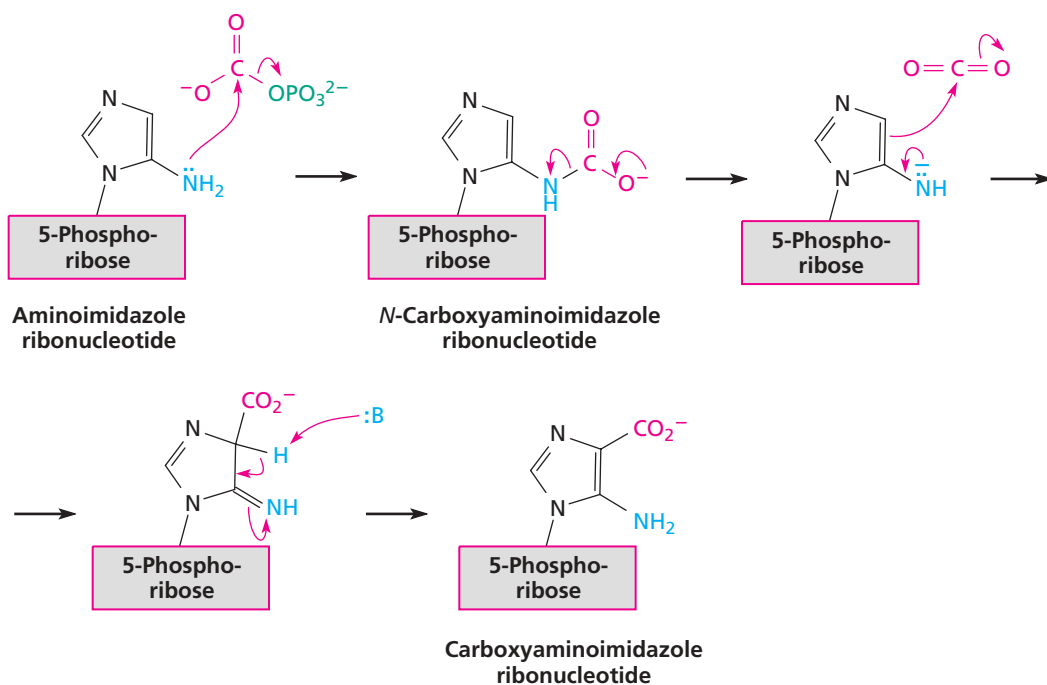


FIGURE 6.12 Mechanism of the carboxylation of aminoimidazole ribonucleotide.

Steps 7–8. Succinylcarboxamide formation and fumarate elimination Carboxyaminoimidazole ribonucleotide reacts with aspartate in step 7 to form an amide. The reaction is catalyzed by aminoimidazole succinylcarboxamide ribonucleotide (SAICAR) synthetase,¹⁸ requires ATP as cofactor, and is mechanistically analogous to glycinamide formation in step 2. SAICAR then undergoes elimination of fumarate in an E1cB reaction to give aminoimidazole carboxamide ribonucleotide (AICAR), a process catalyzed by adenylosuccinate lyase.¹⁹ Note the similarity of steps 7 and 8 in inosine synthesis to steps 2 and 3 in the urea cycle (Section 5.2), in which citrulline is converted to arginine.

Step 9. Formylation The final atom needed for purine synthesis is added in step 9 by formylation of AICAR. The reaction is catalyzed by AICAR transformylase²⁰ and takes place by transfer of a formyl group from 10-formyltetrahydrofolate by a pathway analogous to that in step 3.

Step 10. Cyclization to form IMP The route for inosine monophosphate biosynthesis concludes with the cyclization of formamidoimidazole carboxamide ribonucleotide (FAICAR) in a reaction catalyzed by IMP cyclohydrolase.²¹ Unlike the cyclization reaction in step 5, which forms the imidazole ring, this final cyclization occurs directly and does not require ATP.

Adenosine Monophosphate and Guanosine Monophosphate

Adenosine monophosphate and guanosine monophosphate are both derived from inosine monophosphate by straightforward transformations of the sort we've already encountered (Figure 6.13).

Adenosine monophosphate is synthesized in a two-step sequence from IMP: initial reaction with aspartate to yield adenylosuccinate, followed by loss of fumarate. The first step is catalyzed by adenylosuccinate synthetase,²² requires

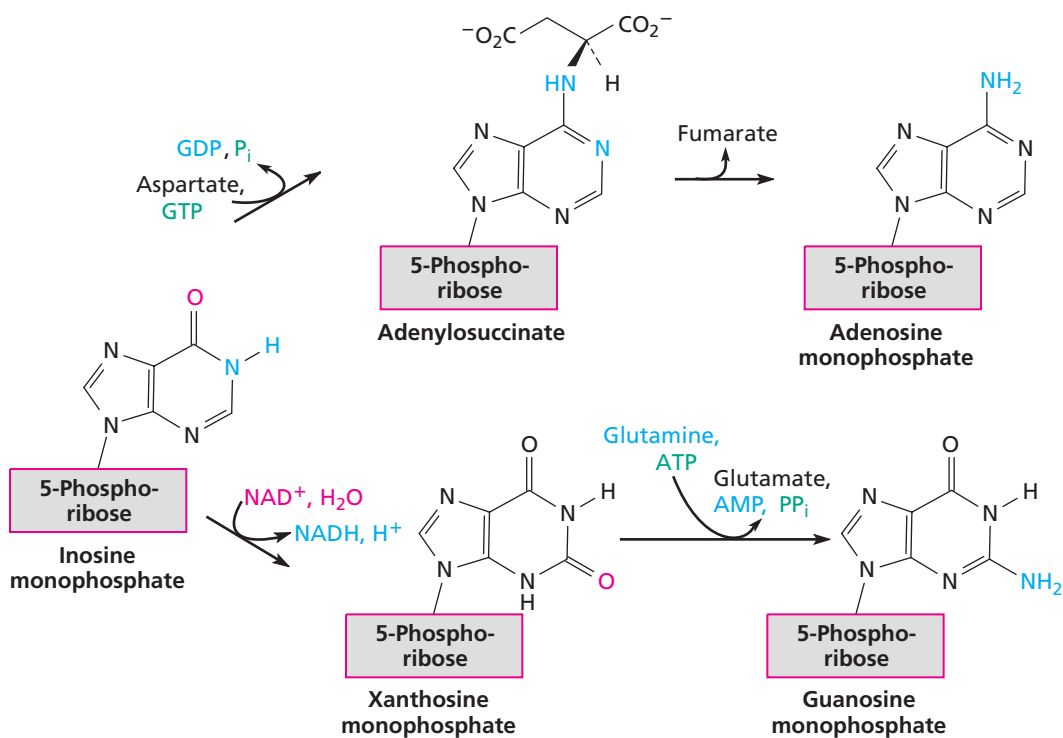


FIGURE 6.13 Pathway for the conversion of inosine monophosphate to adenosine monophosphate and guanosine monophosphate.

GTP as coenzyme, and is mechanistically analogous to the second step in the urea cycle in which citrulline reacts with aspartate to give argininosuccinate (Section 5.2, Figure 5.3). The second step is mechanistically similar to the eighth step in IMP synthesis and is catalyzed by the same adenylosuccinate lyase enzyme.²⁰

Guanosine monophosphate is also synthesized from IMP in two steps: oxidation and hydrolysis to form xanthosine monophosphate (XMP), and amination. The oxidation is catalyzed by IMP dehydrogenase²³ and uses NAD^+ as coenzyme. As shown in Figure 6.14, a thiol group on the enzyme first reacts with the purine ring in a conjugate addition reaction, and the tetrahedral intermediate transfers hydride ion to NAD^+ . Addition of water then replaces the thiol by —OH , and tautomerization of the product gives XMP. Conversion of XMP to GMP in the second step is catalyzed by GMP synthetase²⁴ and is mechanistically analogous to the conversion of UTP to CTP that we saw in Section 6.2.

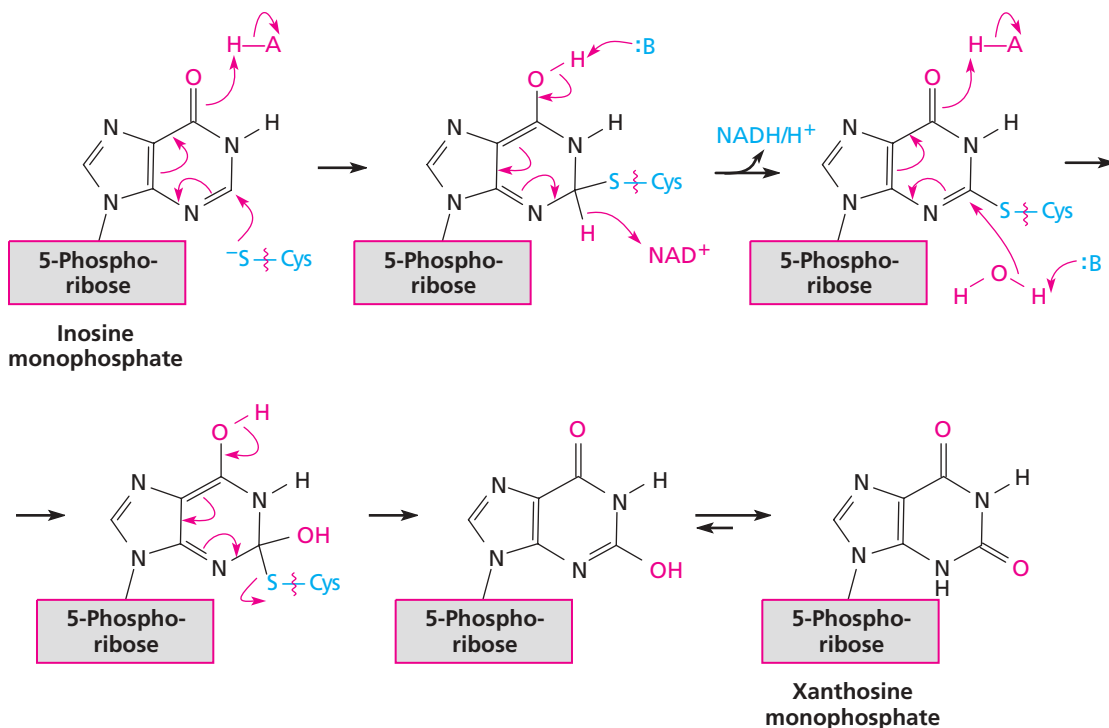


FIGURE 6.14 Mechanism of the oxidation of inosine monophosphate to xanthosine monophosphate.

6.4 Biosynthesis of Deoxyribonucleotides

Deoxyadenosine, Deoxyguanosine, Deoxycytidine, and Deoxyuridine Diphosphates

The deoxyribonucleoside diphosphates dADP, dGDP, dCDP, and dUDP arise biosynthetically through deoxygenation of the corresponding ribonucleoside diphosphates catalyzed by ribonucleotide reductase.^{25, 26} Three classes of ribonucleotide reductases are known and are used by different organisms. All are metalloenzymes that use an active-site thiyl radical, but they differ in their mechanisms of radical generation and the nature of the metal species at their active sites. The mechanism of the deoxygenation reaction catalyzed by the non-heme Fe(III) enzyme in eukaryotes is shown in Figure 6.15.

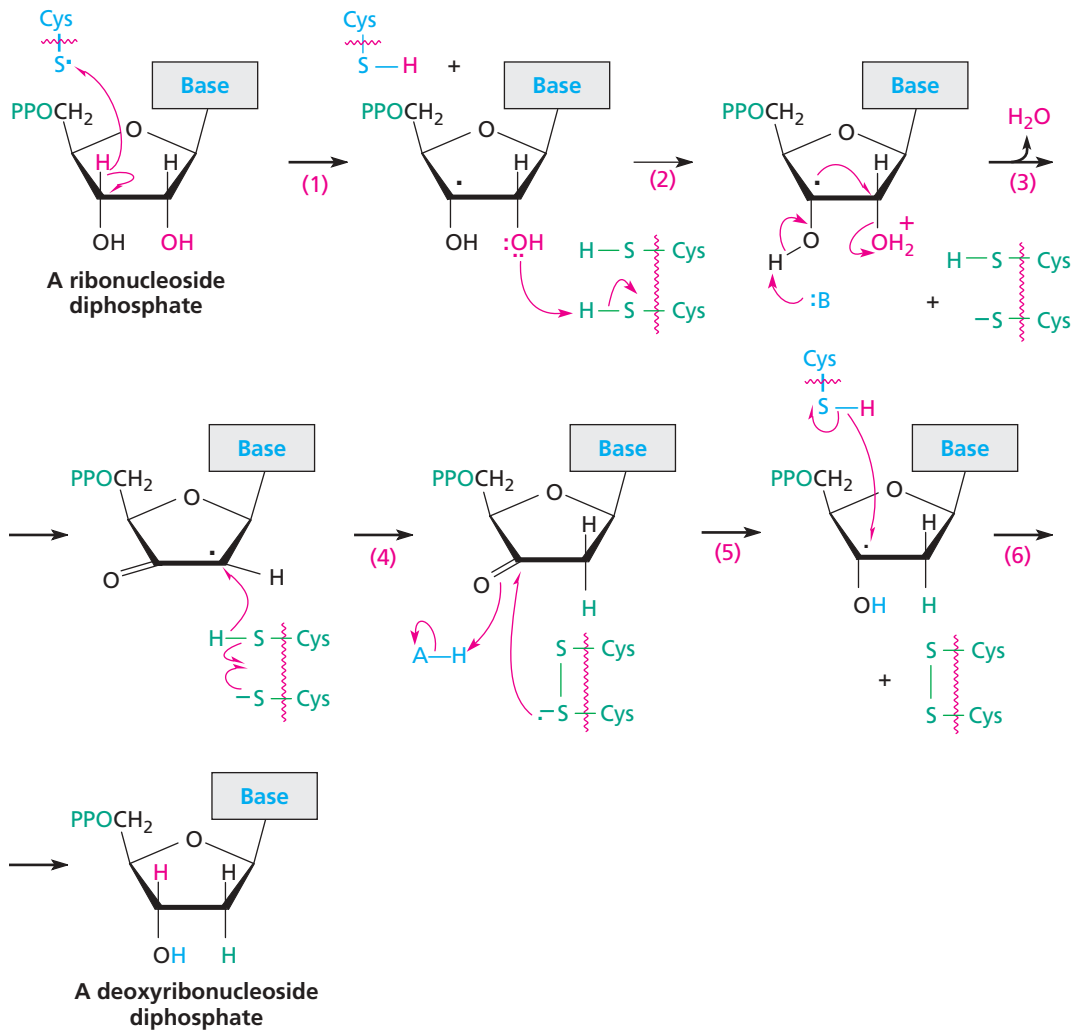


FIGURE 6.15 Mechanism of reduction of ribonucleoside diphosphates to deoxyribonucleoside diphosphates in a reaction catalyzed by ribonucleotide reductase.

Step 1. Hydrogen abstraction Ribonucleotide reduction begins with abstraction of the hydrogen atom at C3' by a thiyl radical center on a cysteine residue in the enzyme.

Steps 2–3. Dehydration The radical is protonated on the —OH group at C2 by one of a pair of cysteine residues, and the protonated alcohol loses water in an S_N1 -like reaction. At the same time, the —OH group at C3 is deprotonated by a glutamate residue acting as a base, giving a neutral α keto radical as product.

Step 4. Hydrogen addition The α keto radical is reduced by addition of a hydrogen atom to the radical center at C2, yielding a neutral ketone. The second of the pair of cysteine residues is the hydrogen-atom donor, and the reaction occurs with formation of a sulfur anion–radical containing a disulfide bond between the two cysteines.

Step 5. Electron transfer The sulfur anion–radical transfers an electron to the nearby carbonyl group at C3, and the carbonyl oxygen is protonated to give a hydroxy radical.

Step 6. Hydrogen addition The hydrogen atom abstracted from C3 by a cysteine residue in the first step is re-added from the same side of the ribose ring in the final step to give the deoxyribonucleotide product. Following this final step, the disulfide produced in step 5 is reduced back to a thiol pair to regenerate active enzyme.

Thymidine Monophosphate

Thymidine monophosphate (dTMP or just TMP), the only DNA monomer without a direct RNA counterpart, is biosynthesized from deoxyuridine monophosphate (dUMP) in a complex process catalyzed by thymidylate synthase.^{27, 28} 5,10-Methylenetetrahydrofolate (Figure 5.6) is the methyl donor, and the mechanism of the reaction is shown in Figure 6.16. An X-ray crystal structure of the enzyme–substrate active site is shown in Figure 6.17.

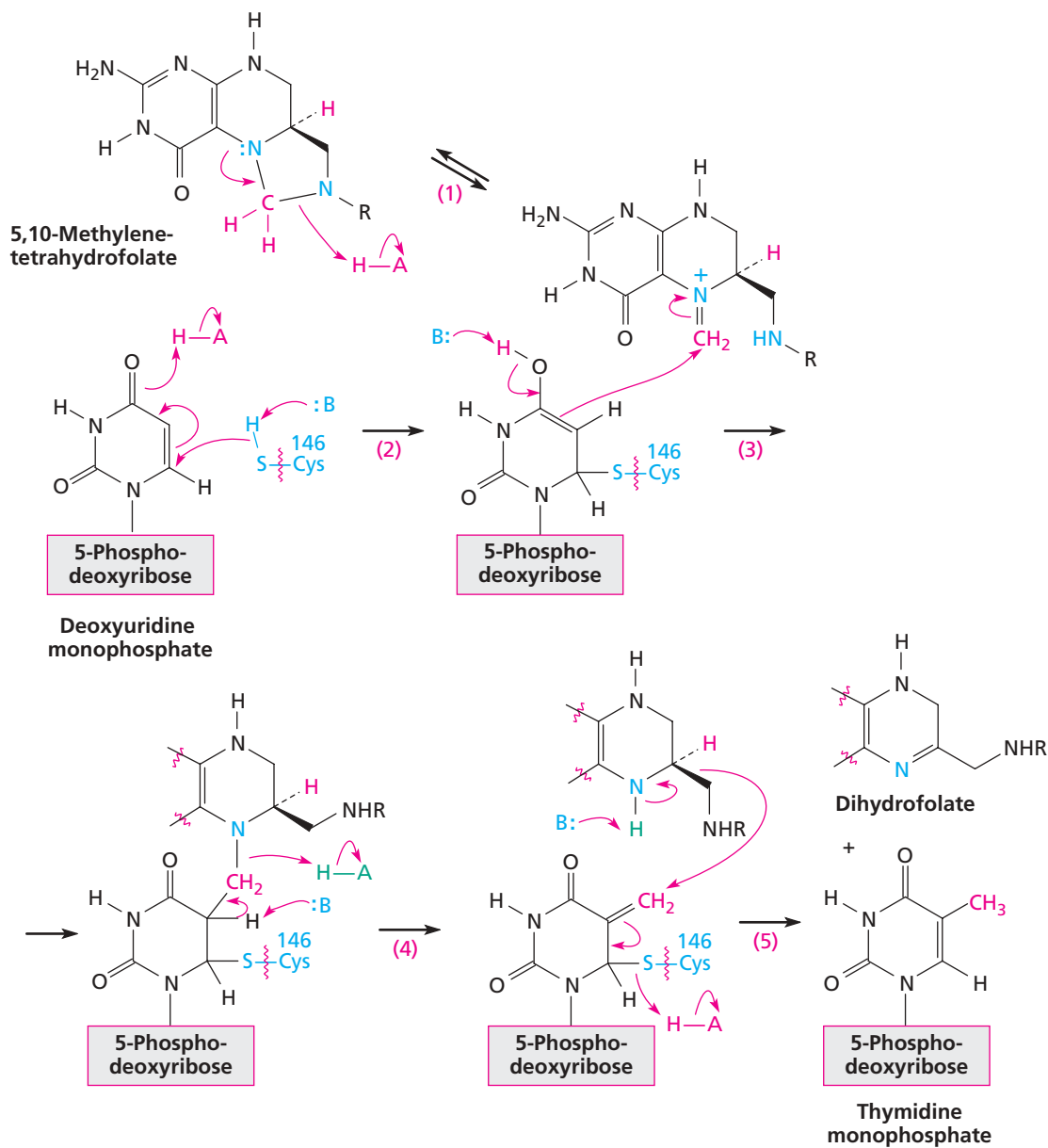


FIGURE 6.16 Mechanism of the biosynthesis of thymidine monophosphate (dTMP) from deoxyuridine monophosphate (dUMP), catalyzed by thymidylate synthase.

Step 1. Preliminary equilibrium 5,10-Methylenetetrahydrofolate undergoes reversible opening of the five-membered ring in a preliminary equilibrium to give an iminium ion.

Steps 2–3. Addition of cysteine and reaction with methylene-THF A cysteine residue (Cys-146) in the enzyme adds to the double bond in the uracil ring of dUMP in a conjugate addition reaction. The enol product then adds to the iminium ion of 5,10-methylene-THF.

Step 4. Elimination of THF Base-catalyzed elimination of tetrahydrofolate from the adduct generates a new unsaturated carbonyl group on the uracil ring.

Step 5. Reduction Tetrahydrofolate transfers a hydride ion to the uracil ring in a conjugate addition reaction, and the resulting enolate ion expels the cysteine thiolate ion, forming dTMP plus dihydrofolate (DHF). The dihydrofolate is converted back to 5,10-methylenetetrahydrofolate by a two-step pathway that involves initial reduction of DHF to THF by NADPH, followed by transfer of the serine $\text{—CH}_2\text{OH}$ group (Figure 5.6).

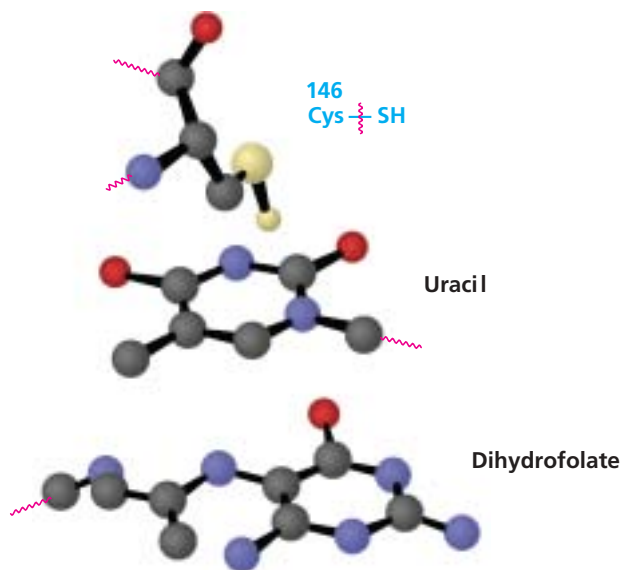


FIGURE 6.17 An X-ray crystal structure of the active site in the enzyme–substrate complex of thymidylate synthase. Cys-146 adds to the double bond of the uracil ring, and a methylene group is transferred from methylene-THF.

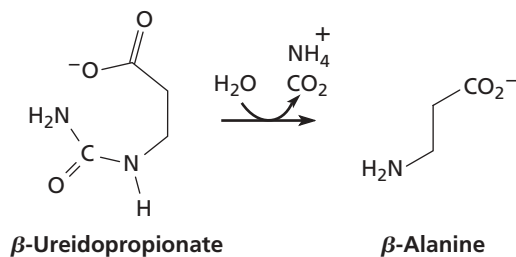
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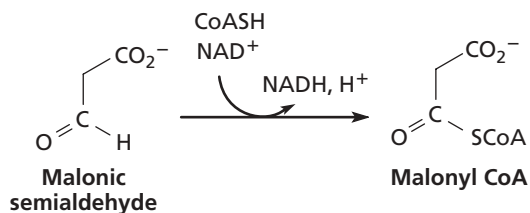
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Problems

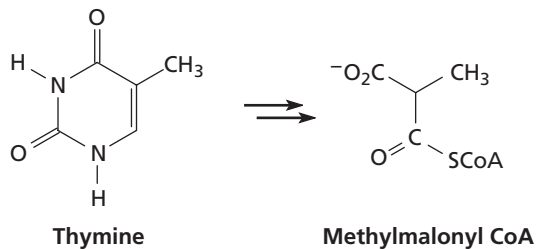
- 6.1 Write a mechanism for hydrolysis of β -ureidopropionate to give β -alanine, a step in uracil catabolism (Figure 6.1).



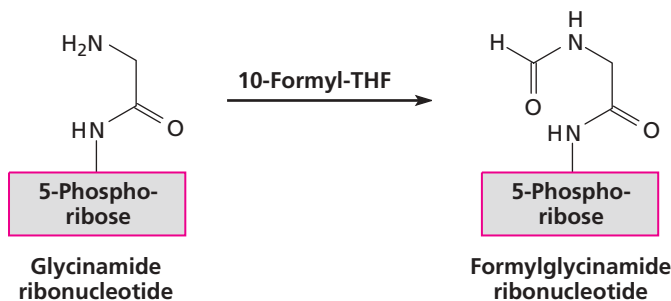
- 6.2 Write a mechanism for the oxidation of malonic semialdehyde to give malonyl CoA, the final step in uracil catabolism (Figure 6.1).



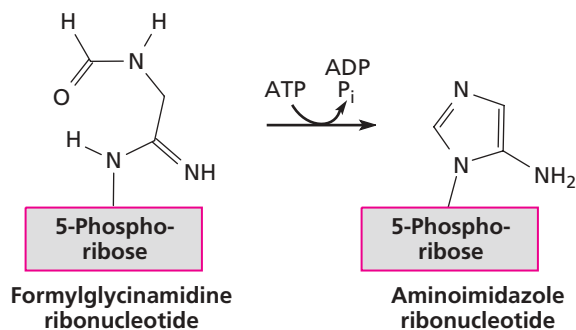
- 6.3 Show the steps and identify the intermediates in the catabolism of thymine to give methylmalonyl CoA.



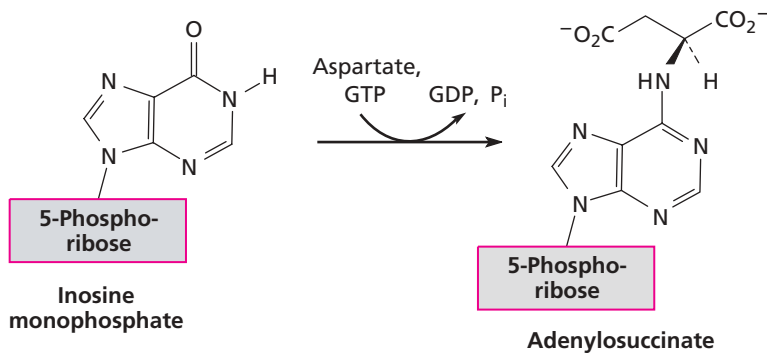
- 6.4 Write a mechanism for the formylation of glycinamide ribonucleotide, the third step in inosine biosynthesis (Figure 6.10).



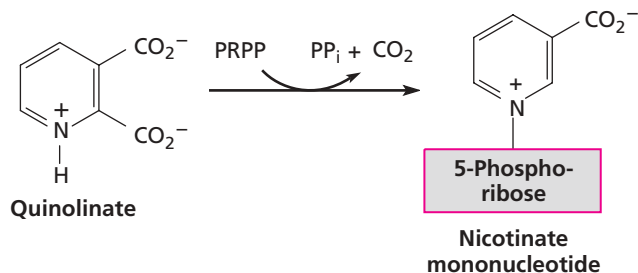
- 6.5 Write a mechanism for the formation of aminoimidazole ribonucleotide from formylglycinamide ribonucleotide, the fifth step in inosine biosynthesis (Figure 6.10).



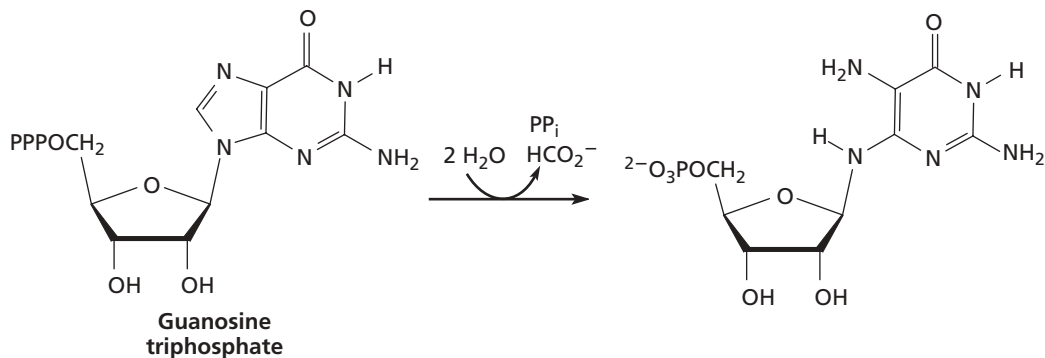
- 6.6 Write a mechanism for the formation of adenylosuccinate from inosine monophosphate.



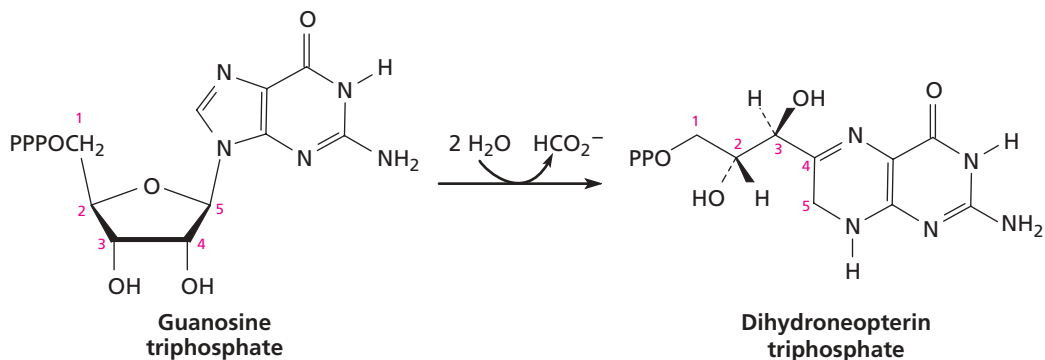
- 6.7 One route for the biosynthesis of NAD^+ involves the following reaction of quinolinate. Propose a mechanism for the reaction.



- 6.8 Guanosine triphosphate is converted by GTP cyclohydrolase II into the following monophosphate. Propose a mechanism.



- 6.9 Guanosine triphosphate is converted by GTP cyclohydrolase I into dihydroneopterin triphosphate. Propose a mechanism.



- 6.10** Retrieve the PDB coordinate file for dihydropyrimidine dehydrogenase (Figure 6.3), and display the structure using the Swiss PDB viewer. (The PDB code is 1GTH.) What is the distance between the C4 carbon of NADPH and the C6 carbon of the pyrimidine substrate? How is the hydride equivalent transferred over this long distance?
- 6.11** Retrieve the PDB coordinate file for thymidylate synthase (Figure 6.17), and display the structure using the Swiss PDB viewer. (The PDB code is 1B02.) Draw the structure of the adduct of 5-fluoro-2'-deoxyuridine-5'-monophosphate with 5,10-methylene-5,6,7,8-tetrahydrofolate, and propose a mechanism for its formation.

