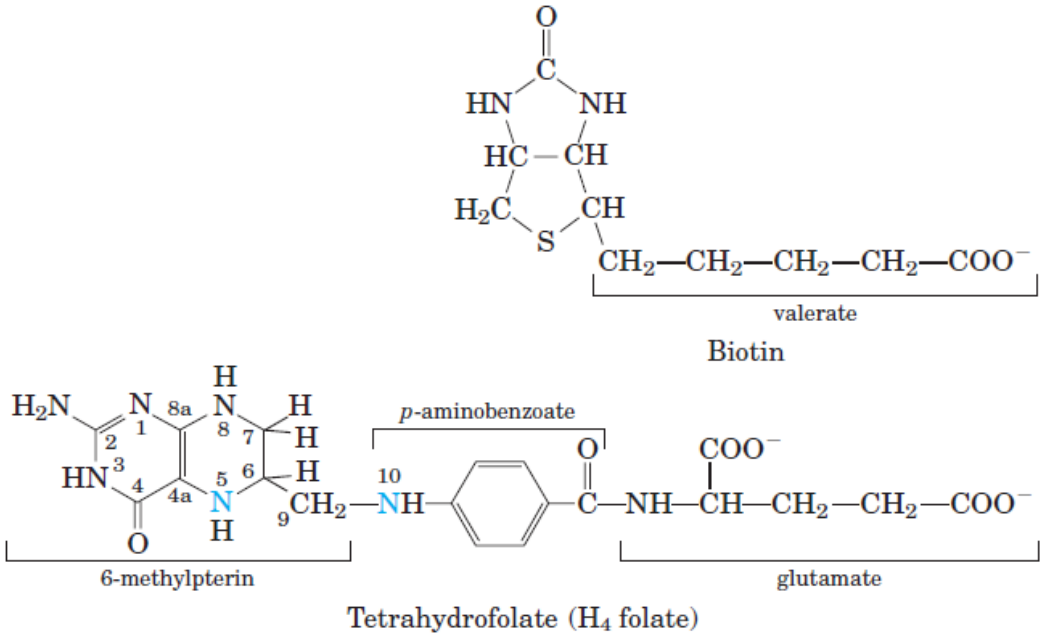
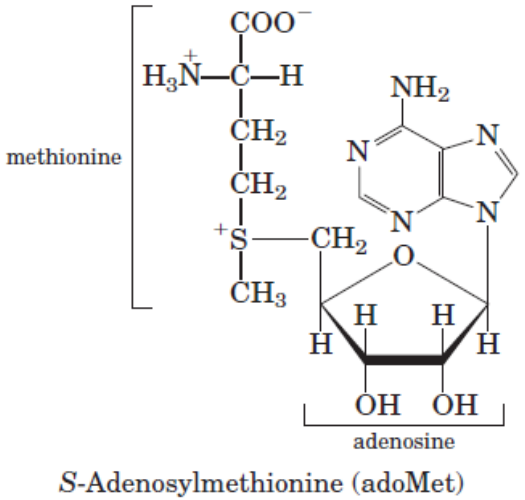
METABOLISM OF 1-CARBON UNITS





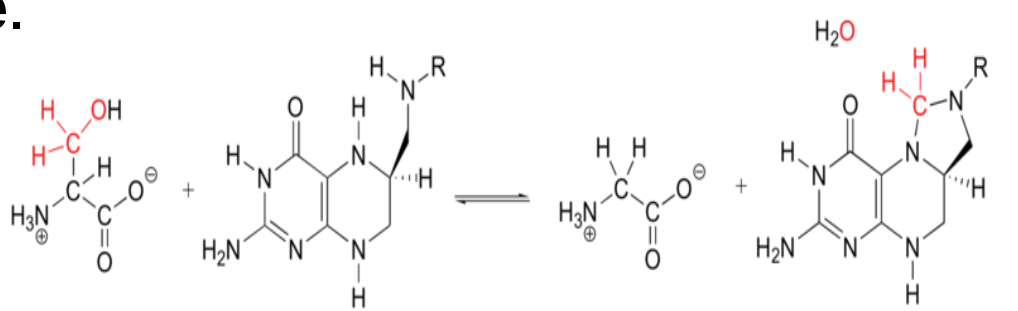
Carbon transfers generally involve one of three cofactors illustrated

- Biotin (vit. B8 or vit. H) transfers carbon in the most oxidized state (CO_2).
- H_4 Folate transfers carbon with multiple oxidation states.
- adoMet transfers carbon in the most reduced state (CH_3)

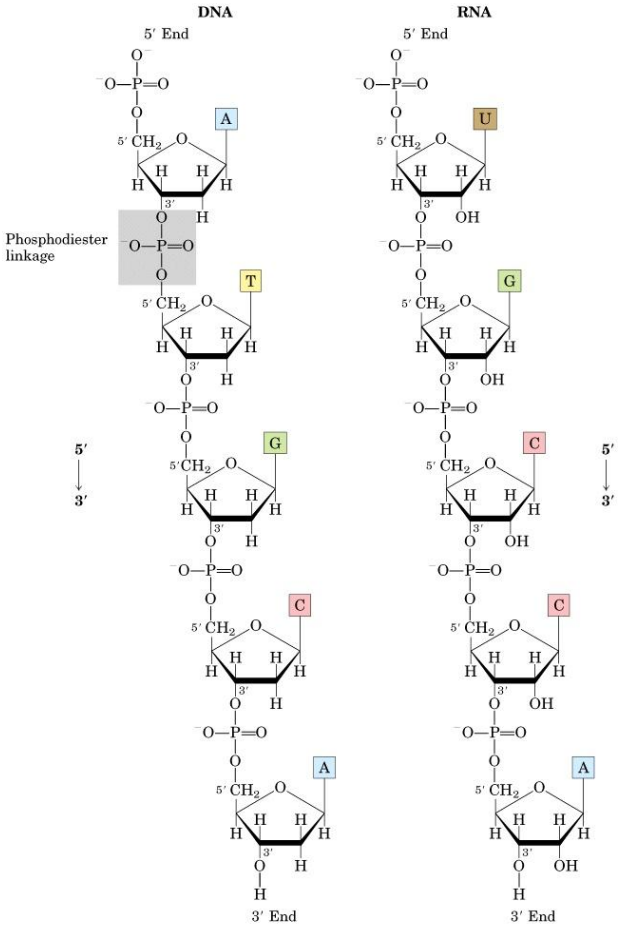
ONE-CARBON UNITS

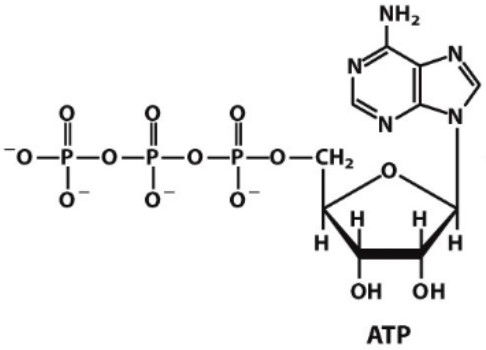
Methyl alcohol	methyl ($-CH_3$)
Formic aldehyde	hydroxymethyl ($-CH_2OH$)
	methylene ($=CH_2$)
Formic acid	formyl ($-CHO$)
	methenyl ($=CH-$)

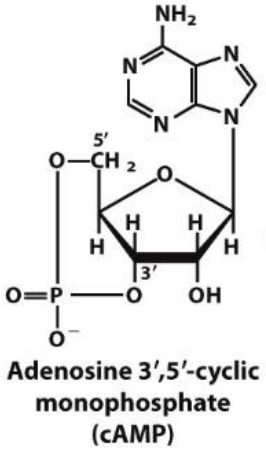
Anyhow methanol, formaldehyde, formic acid have not physiological relevance, thus the **main precursor in cellular reactions is the β C of serine**.

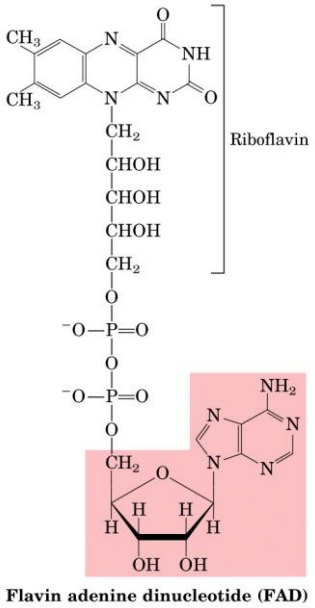


Nucleotides in context





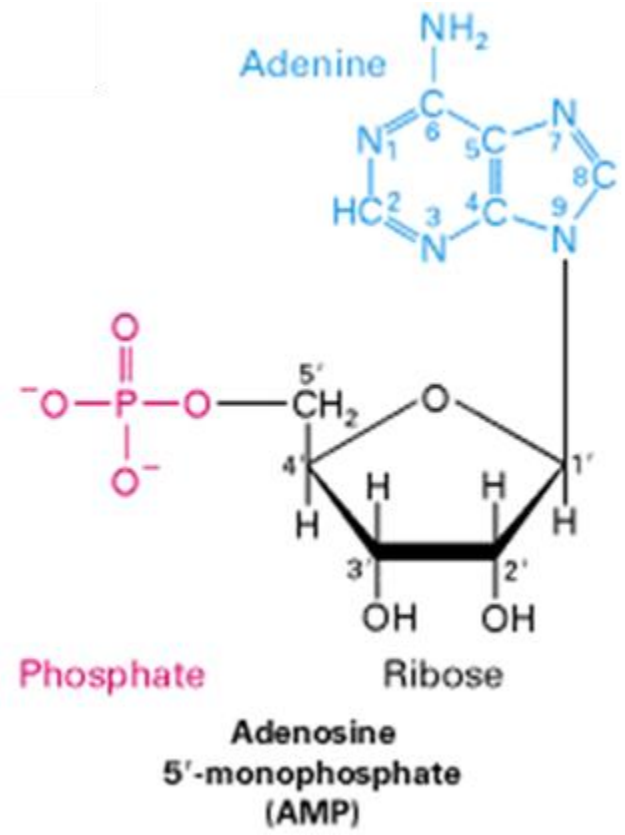




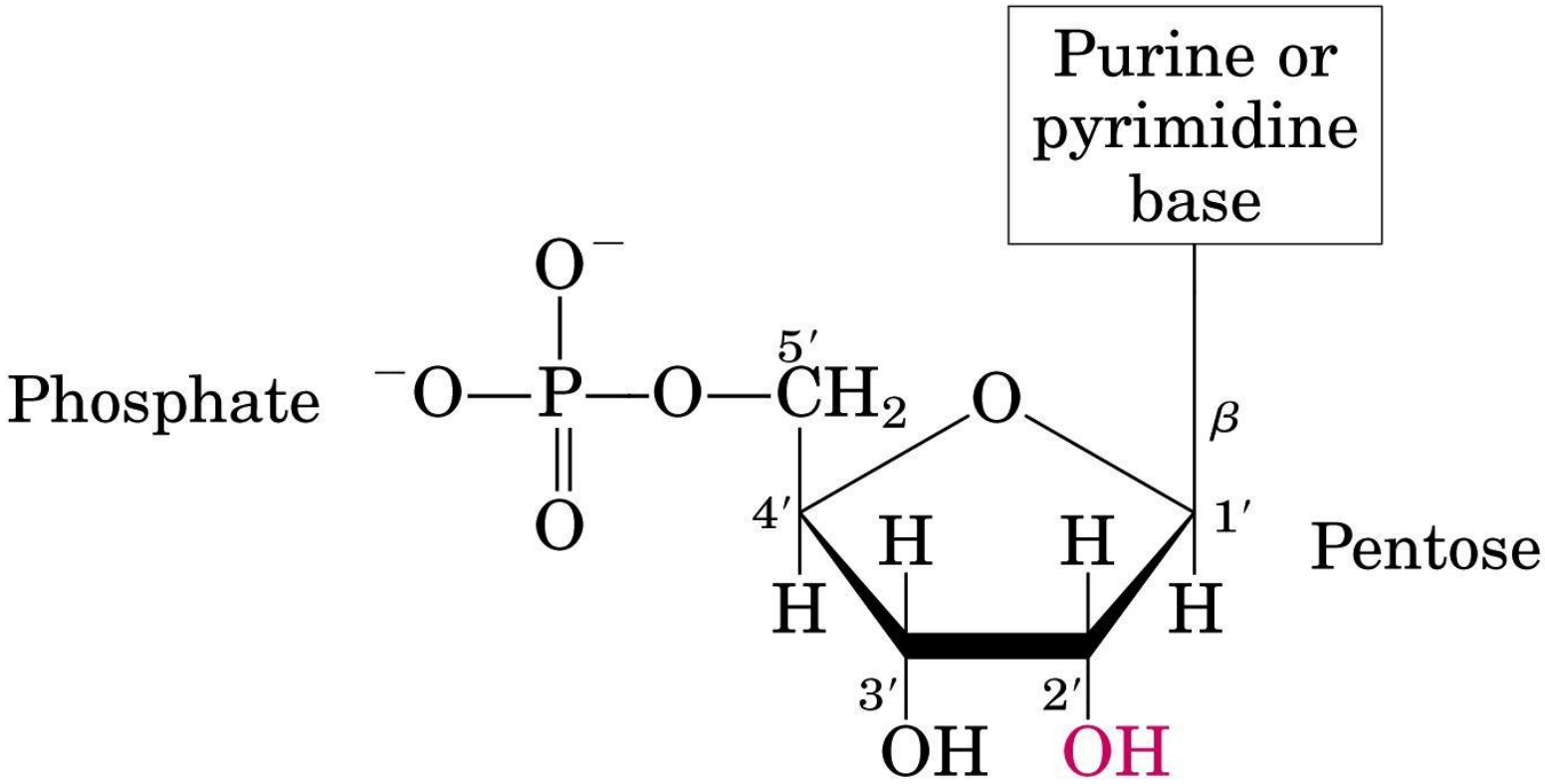
A nucleotide is made up of:

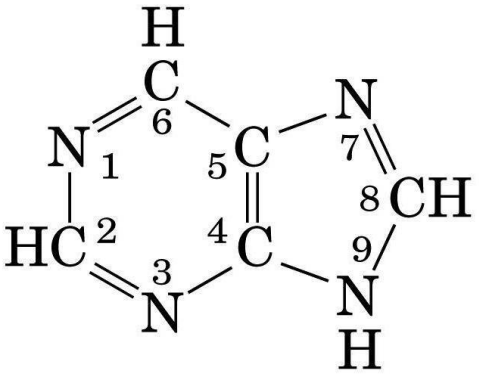
- phosphoric acid;
- a pentose sugar;
- a heterocyclic base.

A nucleoside is the form non-esterified with the phosphate group.

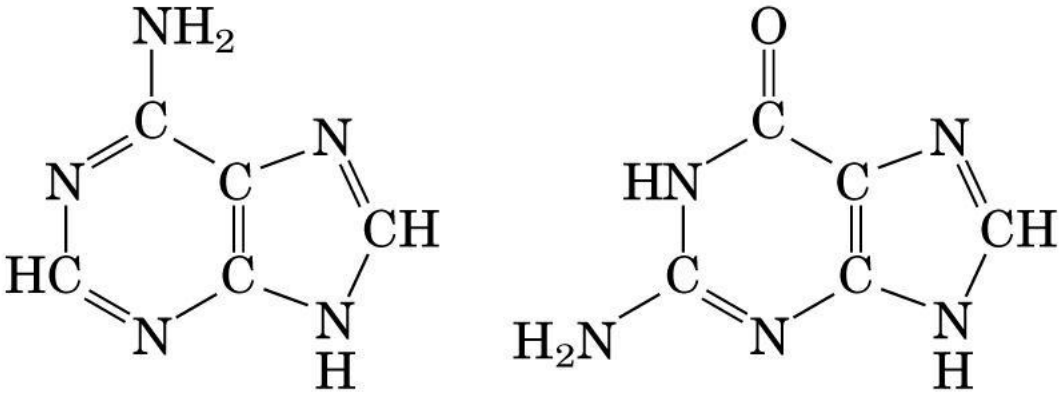


The heterocyclic nitrogenous base linked to D-(deoxy)ribose-5-phosphate is alternatively pyrimidine or purine, depending on the single or double ring – respectively.

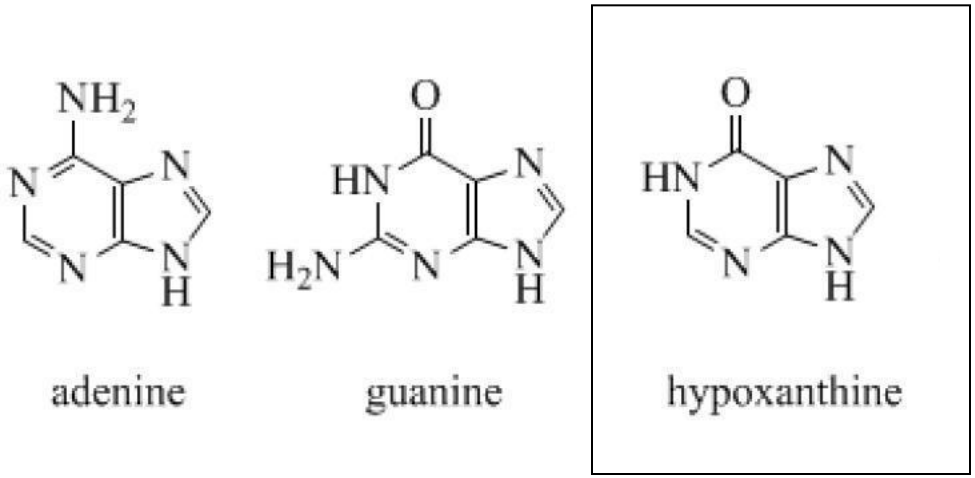




Purines in nucleic acids are usually adenine and guanine.

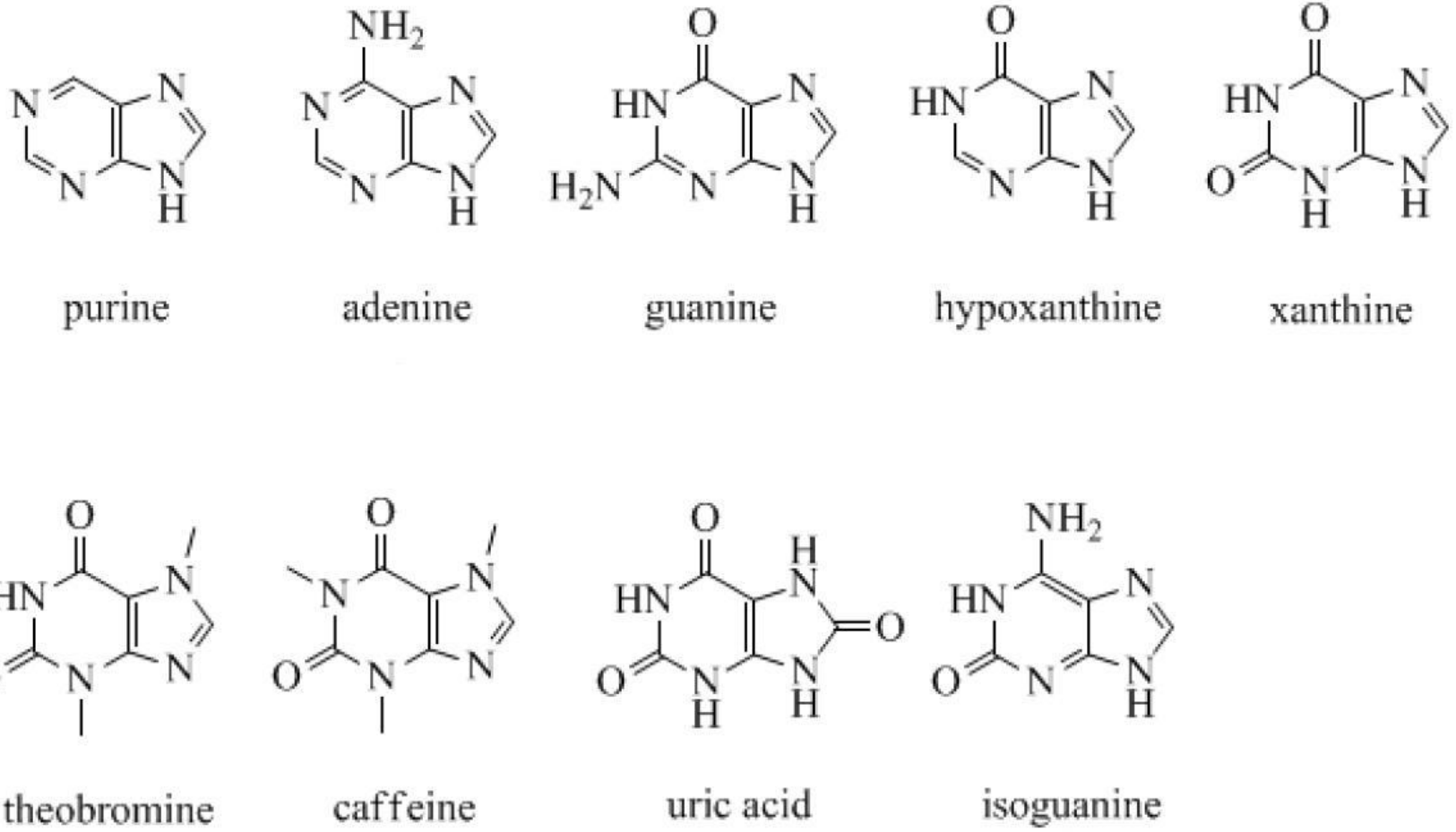


Purines

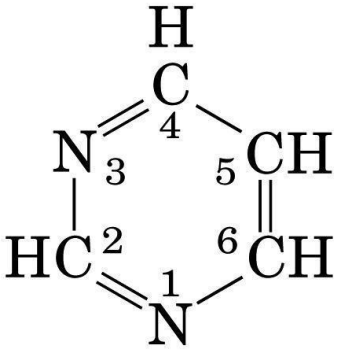


Hypoxanthine is an occasional constituent of nucleic acids, where the nucleotide that contains it – inosine – can become part of the transfer RNA, at the anticodon level.

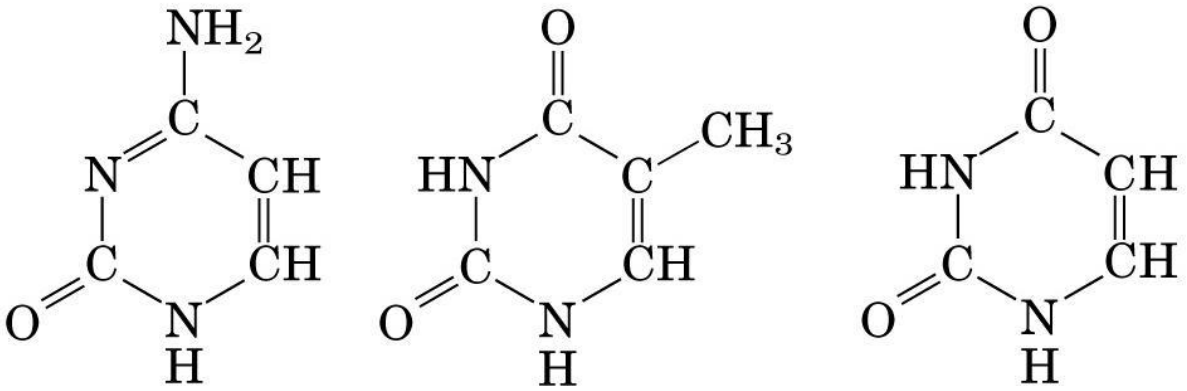
Hypoxanthine is also a product of spontaneous deamination of adenine and as such, due to its remarkable similarity to guanine, it can induce errors in DNA replication and transcription.



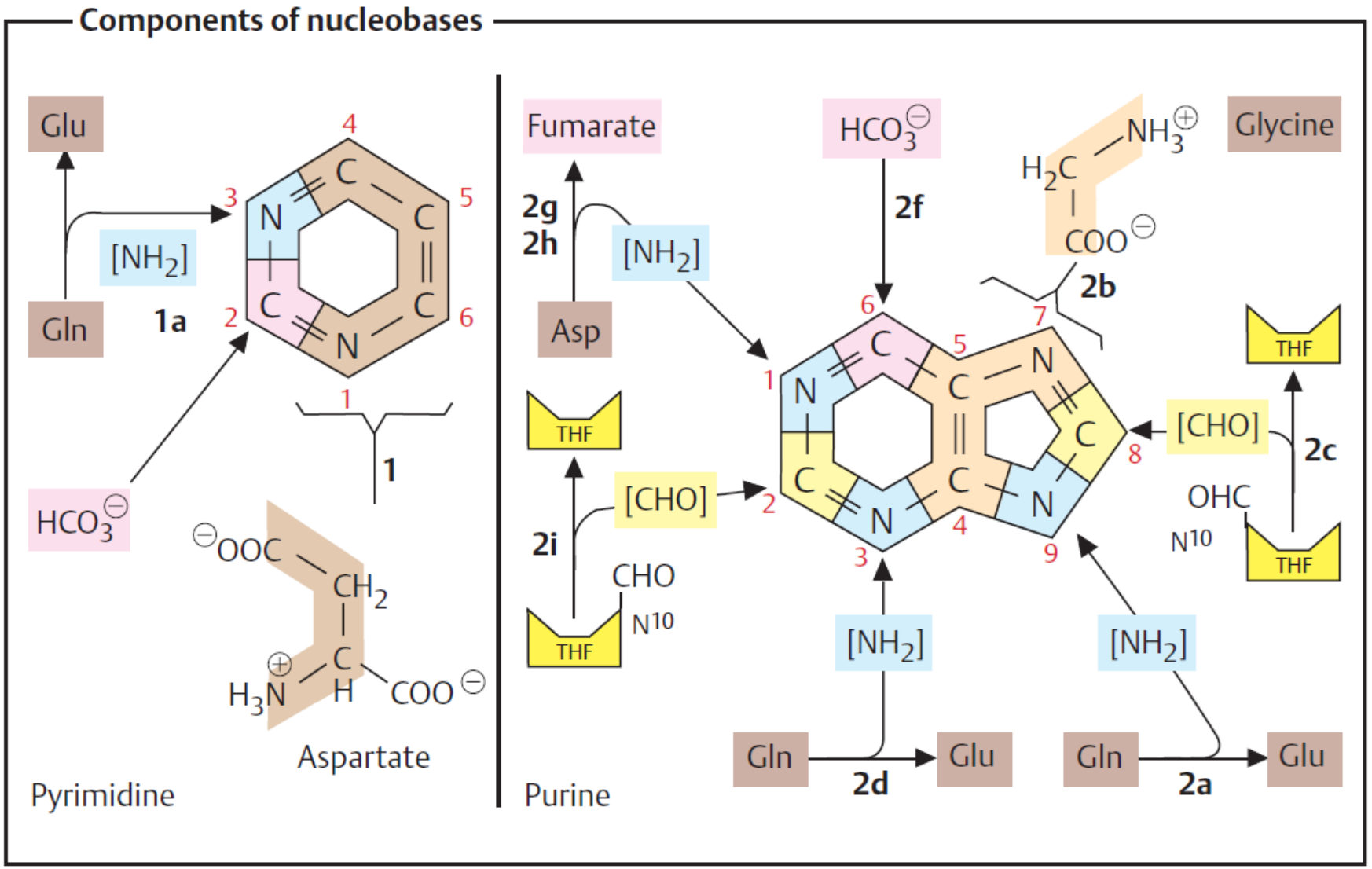
In addition to the progenitor, the purine “family” also includes numerous heterocyclic compounds with which we are somewhat familiar. For example, caffeine and theobromine, for their effect on the nervous system…



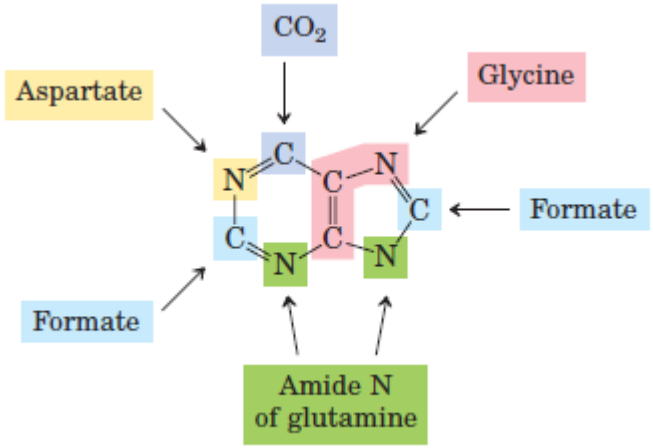
Pyrimidines in nucleic acids are usually:
cytosine and thymine in DNA;
cytosine and uracil in RNA.

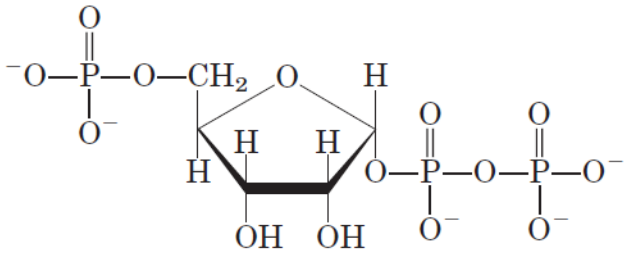


Pyrimidines

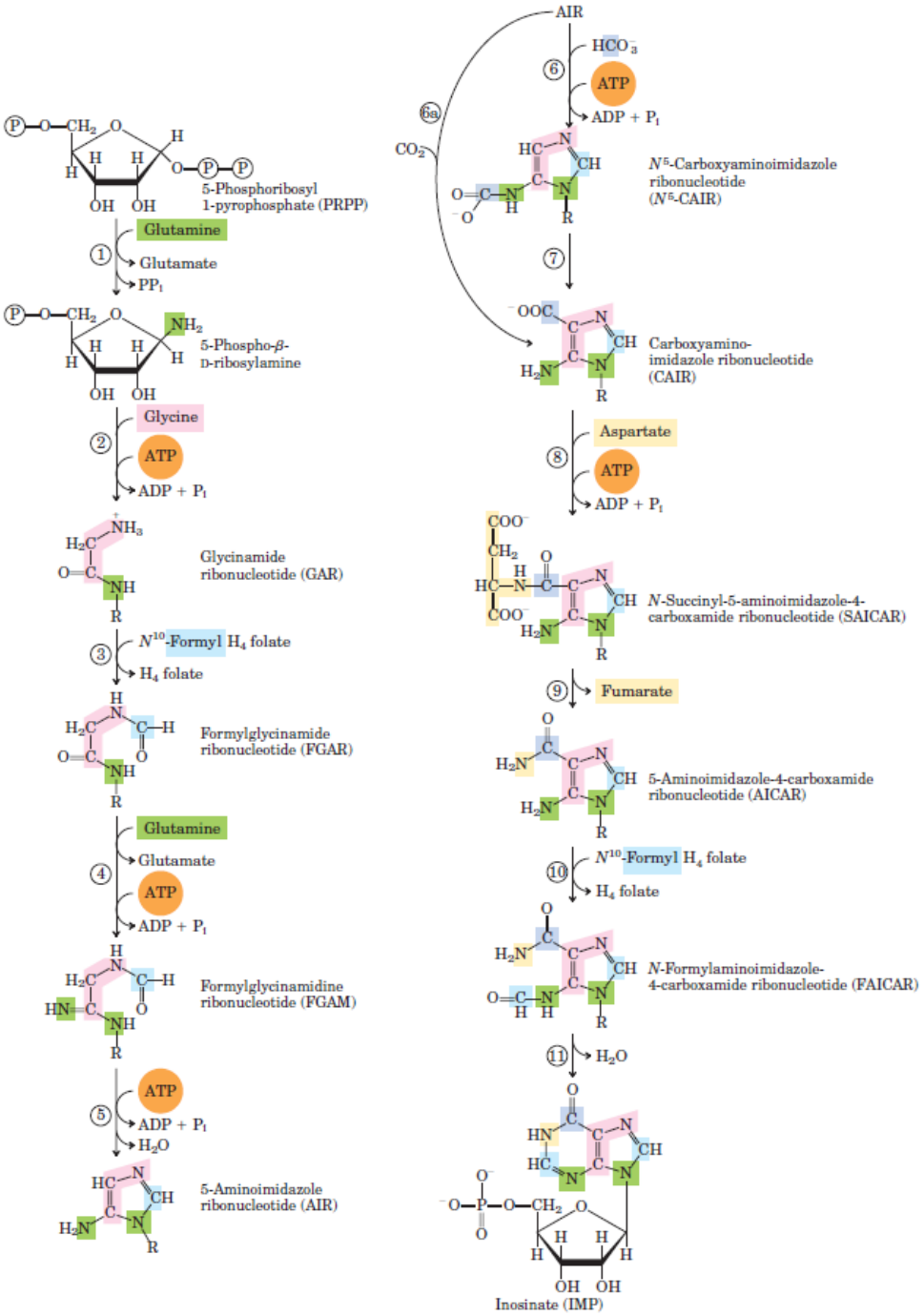


Origin of the ring atoms of purines





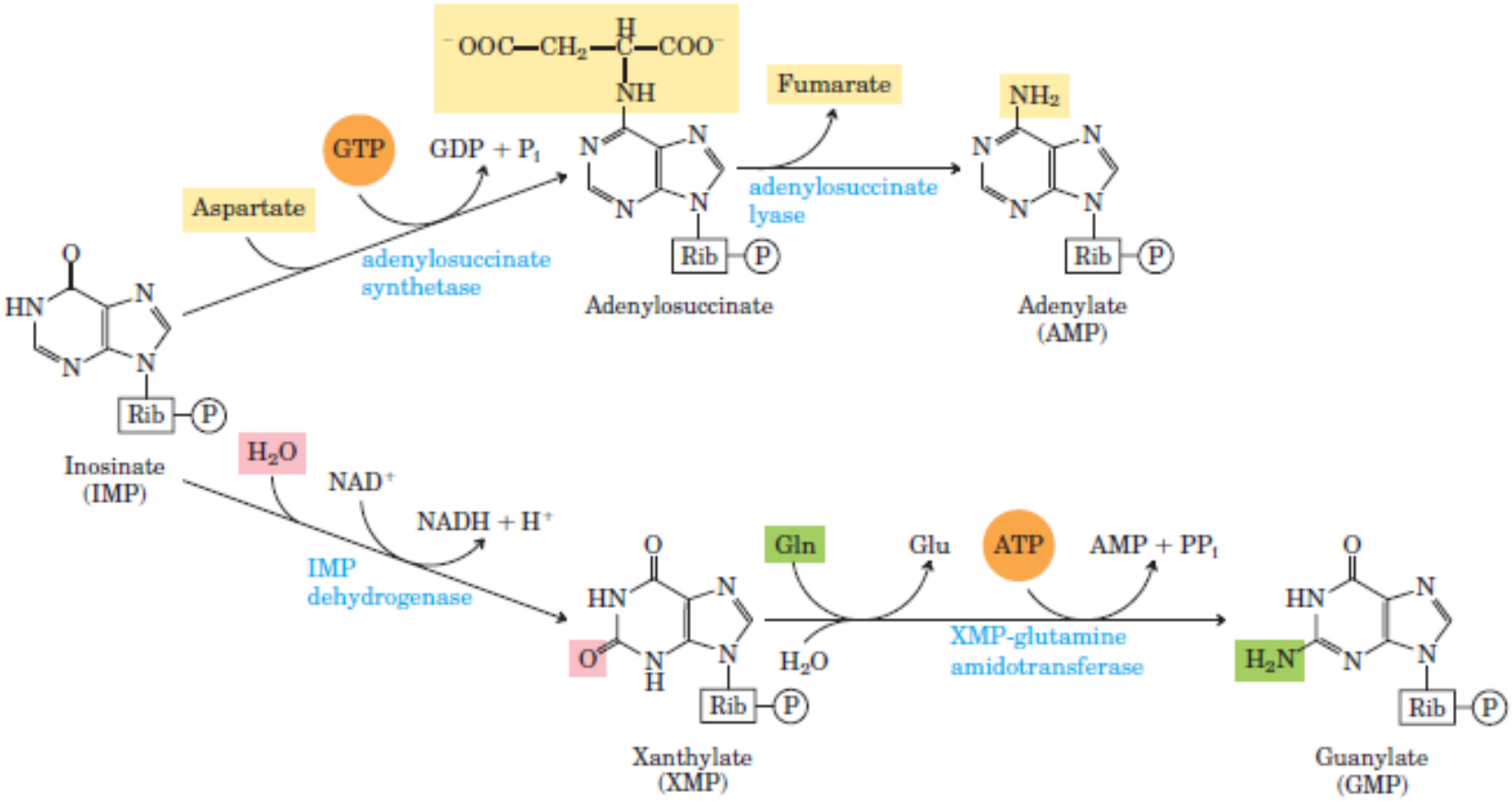
5-phosphoribosyl-1-pyrophosphate (PRPP) is synthesized from ribose 5-phosphate derived from the pentose phosphate pathway, in a reaction catalyzed by ribose phosphate pyrophosphokinase.

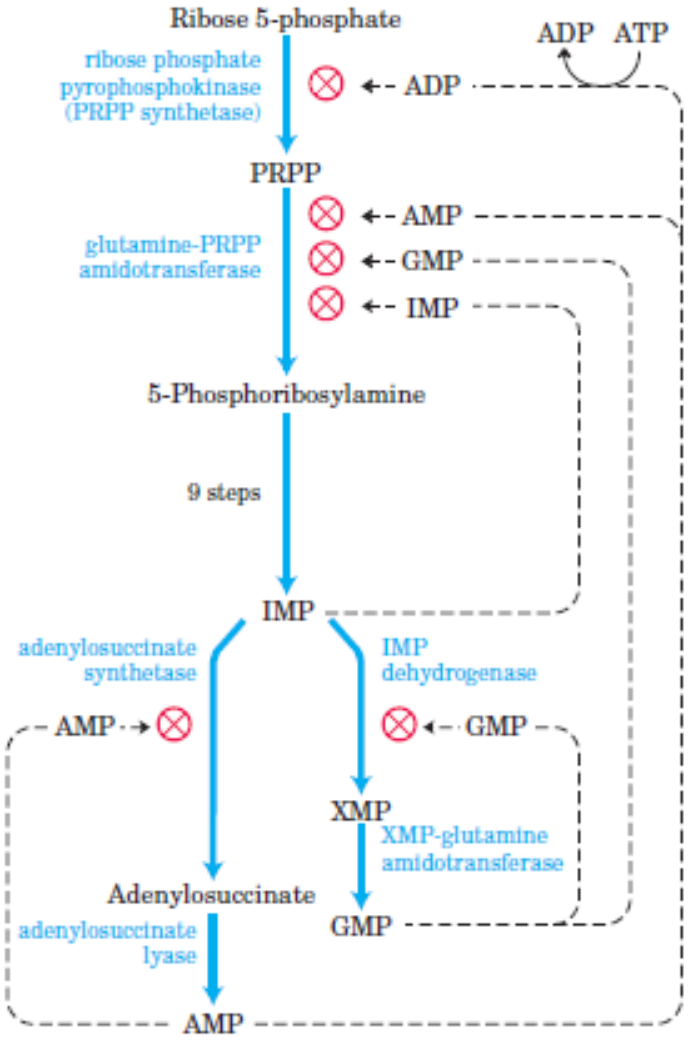


De novo synthesis of purine nucleotides: construction of the purine ring of inosinate (IMP)

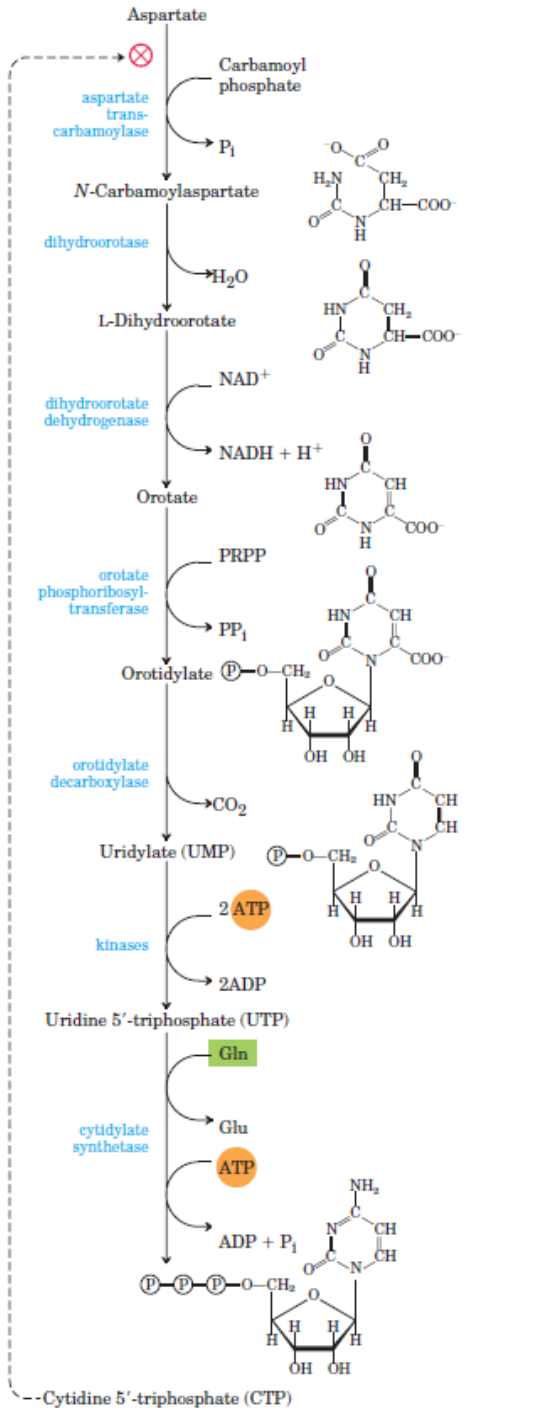
Each addition to the purine ring is shaded. After step 2 , R symbolizes the 5-phospho-D-ribosyl group on which the purine ring is built. Formation of 5-phosphoribosylamine (step 1) is the first committed step in purine synthesis.

Biosynthesis of AMP and GMP from IMP





Negative feedback rgulatory mechanisms in the biosynthesis of adenine and guanine nucleotides



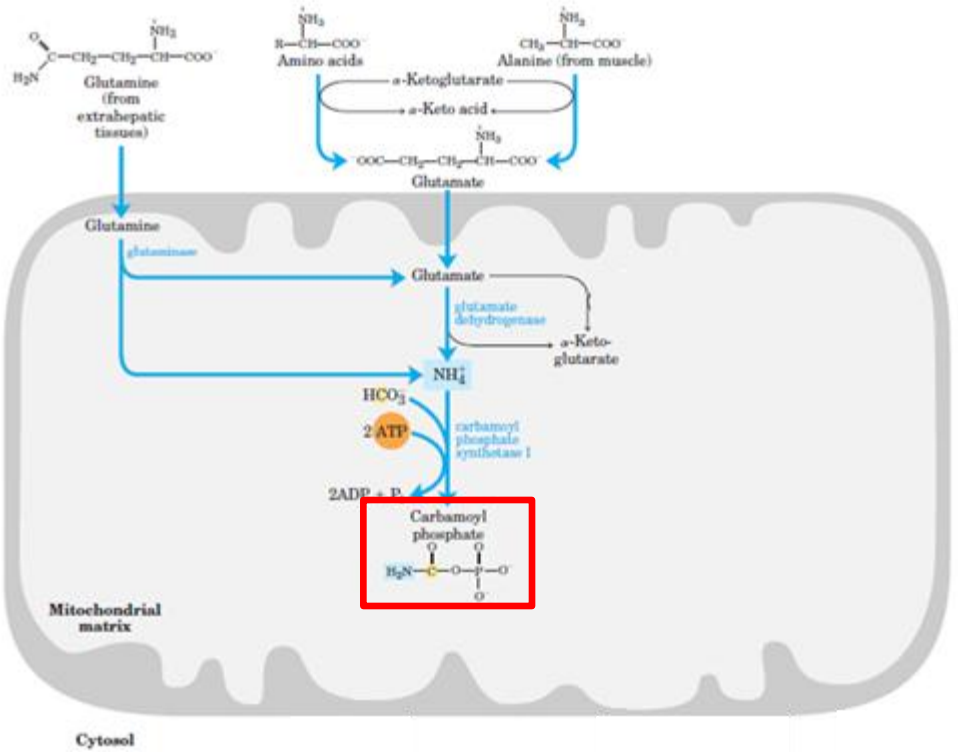
De novo synthesis of pyrimidine nucleotides: biosynthesis of UTP and CTP via orotidylate

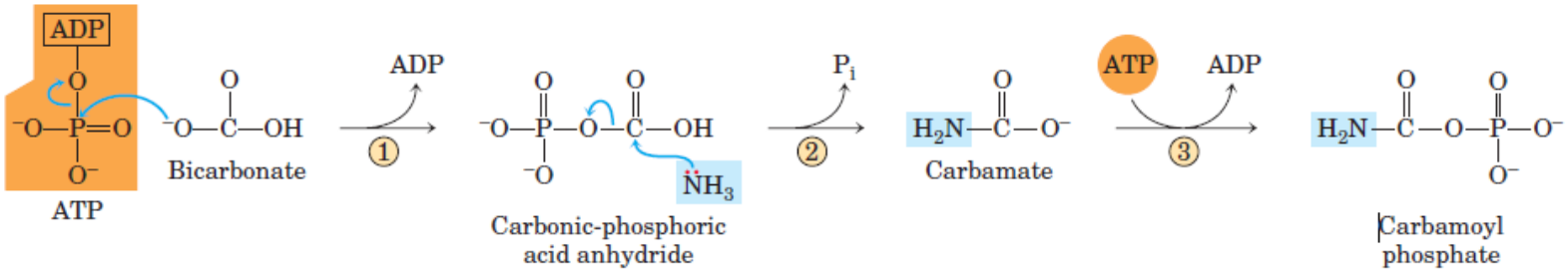
The pyrimidine is constructed from carbamoyl phosphate and aspartate.
The ribose 5-phosphate is then added to the completed pyrimidine ring by orotate phosphoribosyltransferase.
The first step in this pathway is the synthesis of carbamoyl phosphate from CO_2 and NH_4^+, catalyzed in eukaryotes by carbamoyl phosphate synthetase II.

Whatever its source, the NH_4^+ generated in liver mitochondria is immediately used, together with CO_2 (as HCO_3^-) produced by mitochondrial respiration, to form carbamoyl phosphate in the matrix.

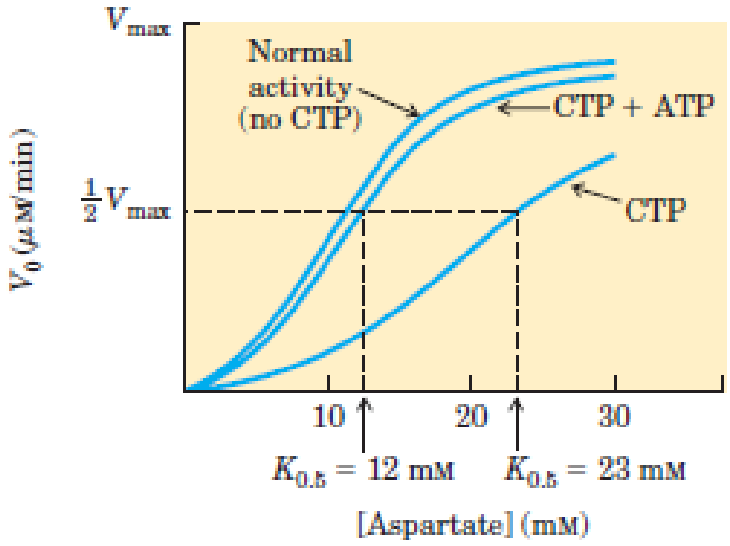
This ATP-dependent reaction is catalyzed by carbamoyl phosphate synthetase I, a regulatory enzyme.

Note that the mitochondrial form of this enzyme is distinct from a cytosolic (II) form, which has a separate function in pyrimidine biosynthesis.





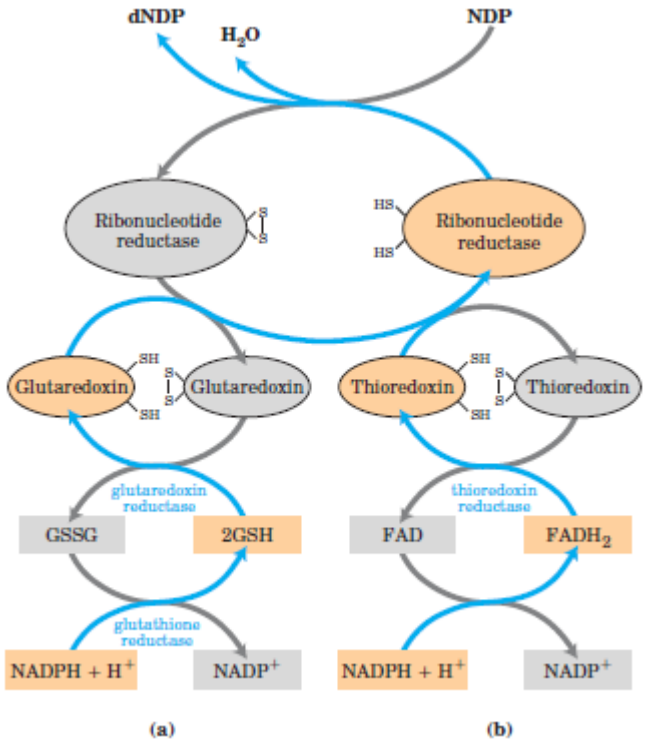
In the reaction catalyzed by carbamoyl phosphate synthetase I, a nitrogen enters from ammonia. The terminal phosphate groups of **two molecules of ATP are used** to form one molecule of carbamoyl phosphate. In other words, this reaction has two activation steps (1 and 3).



Allosteric regulation of aspartate transcarbamoylase by CTP and ATP

Addition of 0.8 mM CTP, the allosteric inhibitor of ATCase, increases the $K_{0.5}$ for aspartate (lower curve) and the rate of conversion of aspartate to *N*-carbamoylaspartate. ATP at 0.6 mM fully reverses this effect

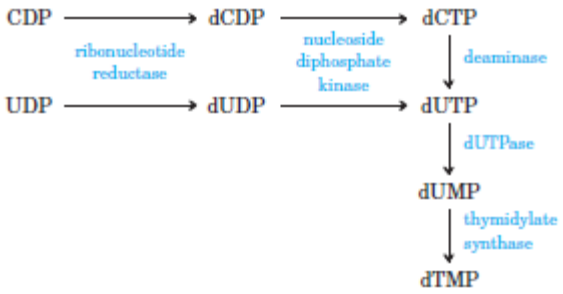
Reduction of ribonucleotides to deoxyribonucleotides by ribonucleotide reductase

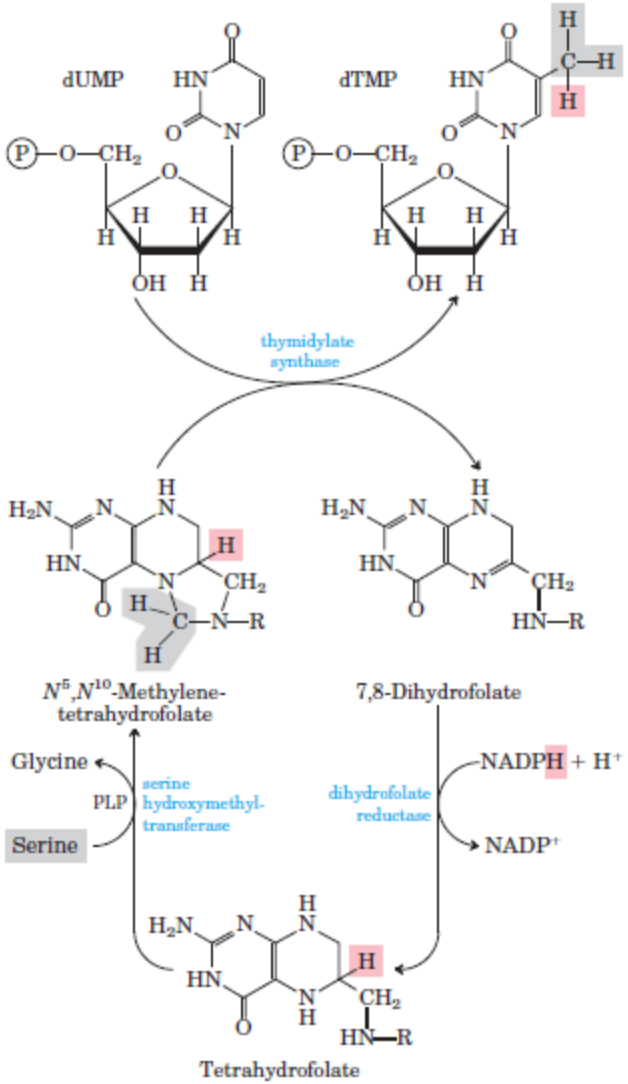


Electrons are transmitted (blue arrows) to the enzyme from NADPH by:
(a) glutaredoxin or
(b) thioredoxin.

The sulfide groups in glutaredoxin reductase are contributed by two molecules of bound glutathione (GSH; GSSG indicates oxidized glutathione).
Thioredoxin reductase is a flavoenzyme, with FAD as prosthetic group.

Biosynthesis of thymidylate (dTMP)

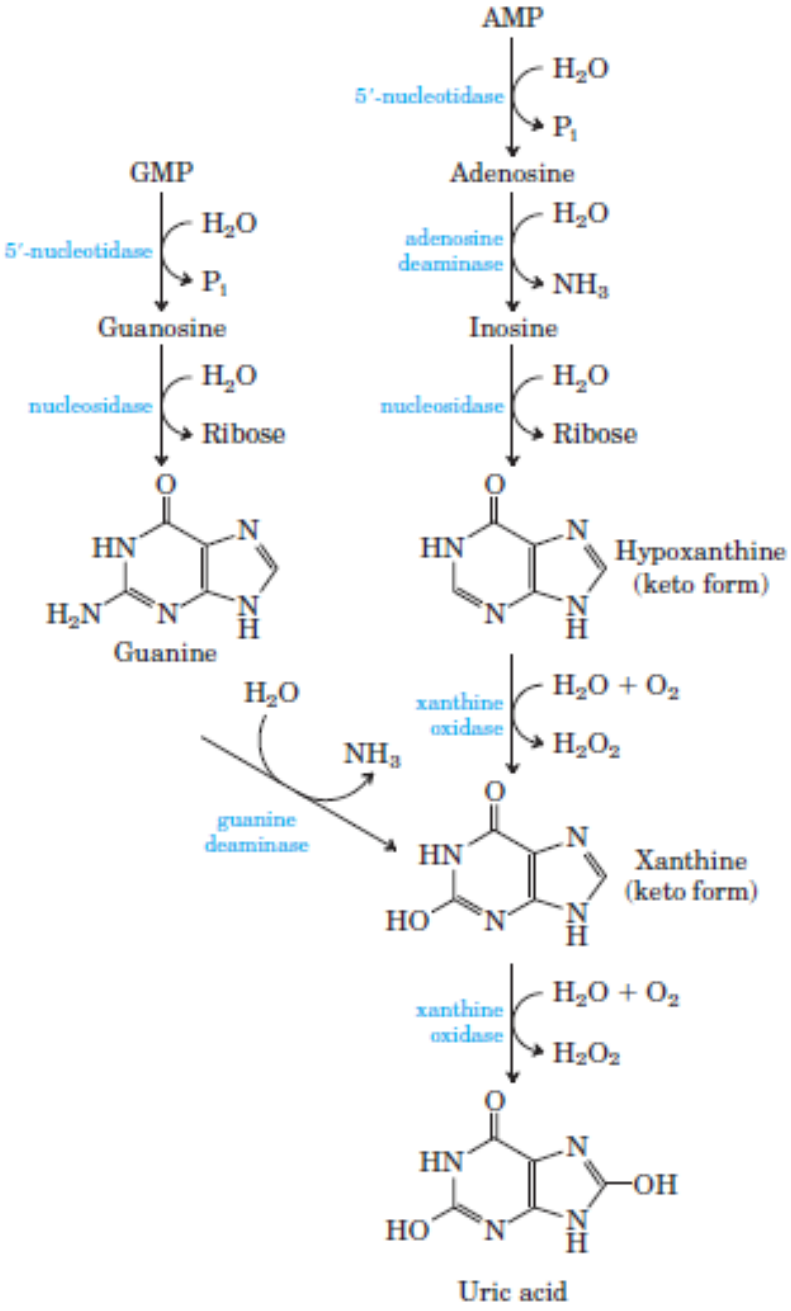




Conversion of dUMP to dTMP by thymidylate synthase and dihydrofolate reductase

Serine hydroxymethyltransferase is required for regeneration of the *N*5,*N*10-methylene form of tetrahydrofolate.

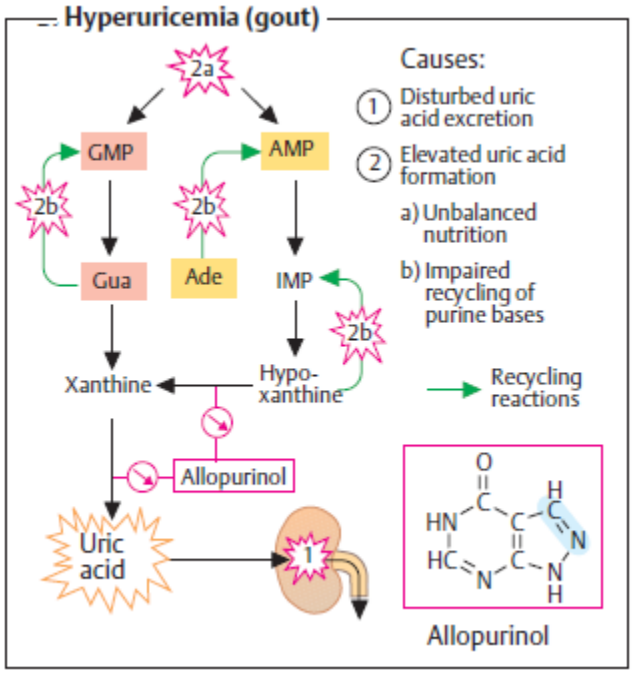
In the synthesis of dTMP, all three hydrogens of the added methyl group are derived from *N*5,*N*10-methylenetetrahydrofolate (pink and gray).

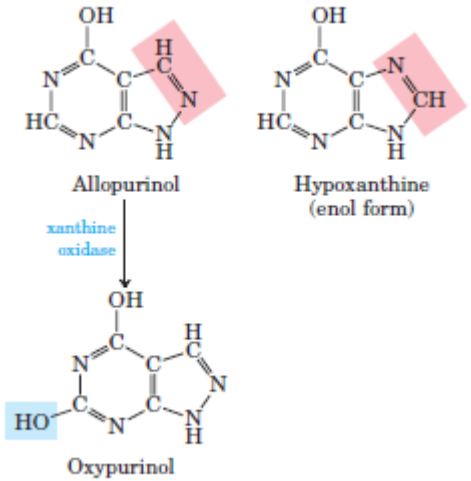


Catabolism of purine nucleotides

Primates excrete much more nitrogen as urea via the urea cycle than as uric acid from purine degradation.

Free purines can be salvaged and rebuilt into nucleotides.
Genetic deficiencies (*hypoxanthine-guanine phosphoribosyltransferase*) cause serious disorders such as Lesch-Nyhan syndrome.

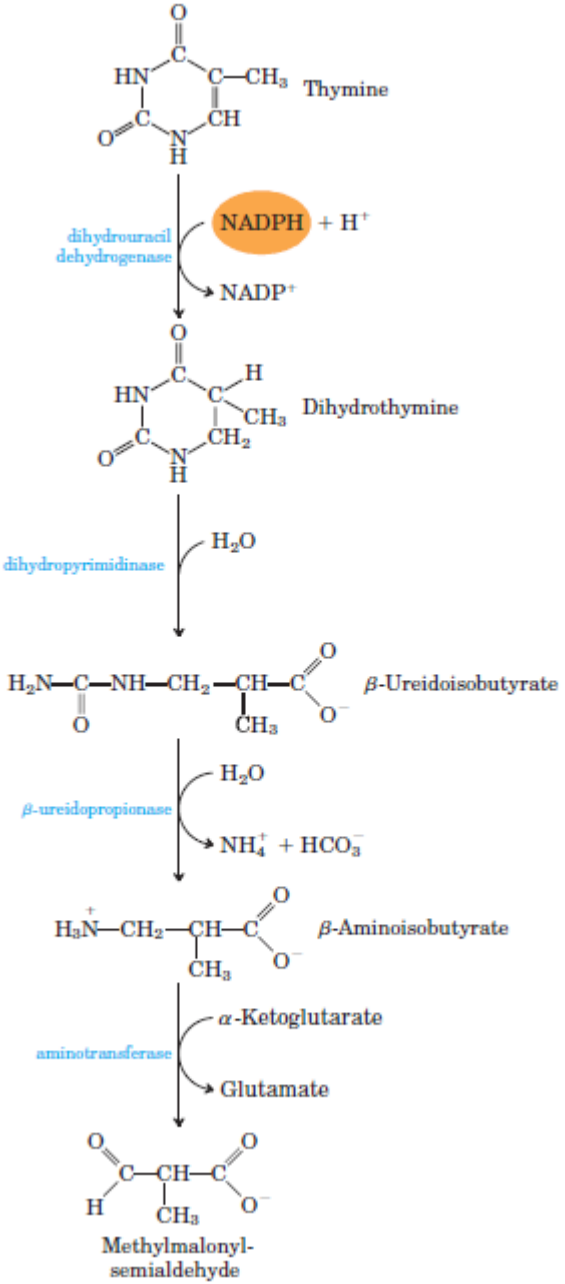


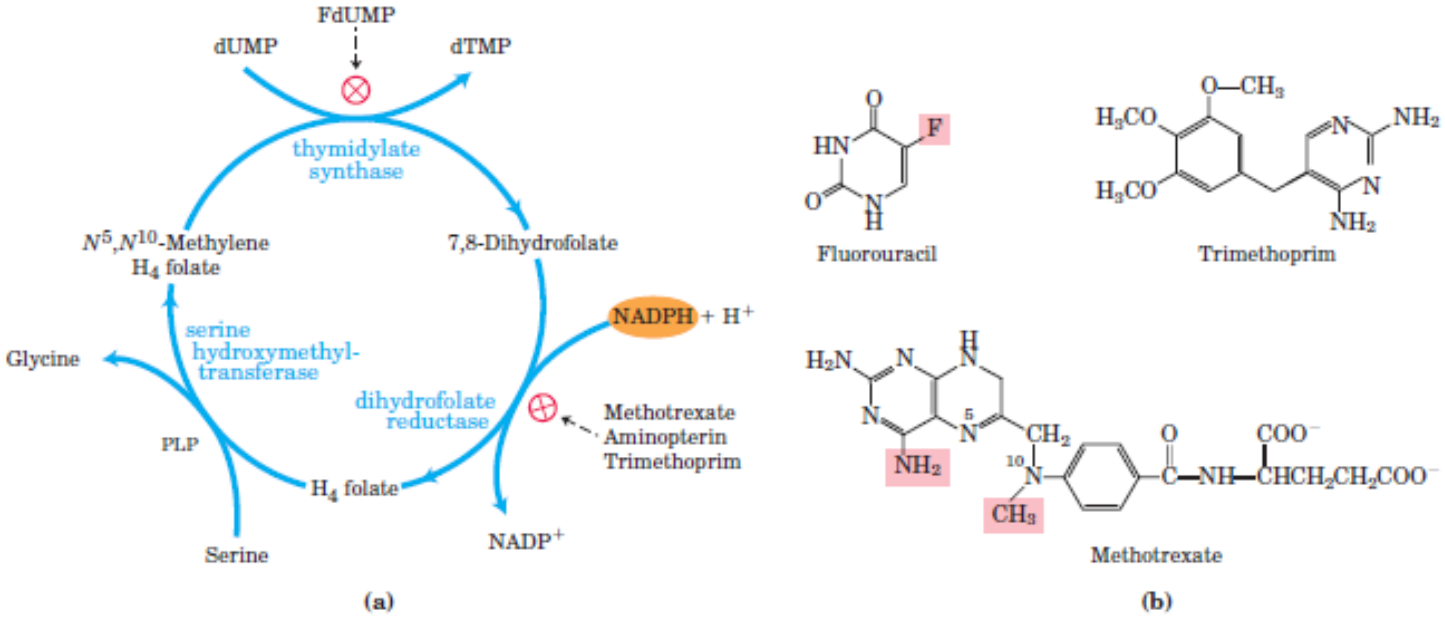


Catabolism of a pyrimidine

Shown here is the pathway for thymine.

The methylmalonylsemialdehyde is further degraded to succinyl-CoA.





Thymidylate synthesis and folate metabolism as targets of chemotherapy

(a) During thymidylate synthesis, *N*5,*N*10-methylenetetrahydrofolate is converted to 7,8-dihydrofolate; the *N*5,*N*10-methylenetetrahydrofolate is regenerated in two steps. This cycle is a major target of several chemotherapeutic agents.

(b) Fluorouracil and methotrexate are important chemotherapeutic agents. In cells, fluorouracil is converted to FdUMP, which inhibits thymidylate synthase. Methotrexate, a structural analog of tetrahydrofolate, inhibits dihydrofolate reductase; the shaded amino and methyl groups replace a carbonyl oxygen and a proton, respectively, in folate. Another important folate analog, aminopterin, is identical to methotrexate except that it lacks the shaded methyl group. Trimethoprim, a tight-binding inhibitor of bacterial dihydrofolate reductase, was developed as an antibiotic.