

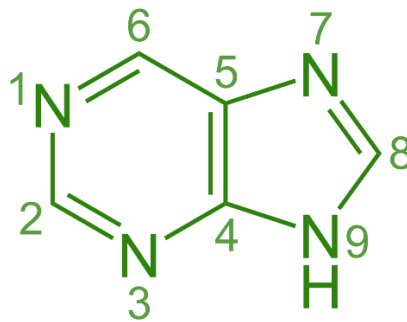
Nucleic acid metabolism

Metabolism of purine nucleotides

Biosynthesis of Purine Nucleotide

Overview

- Purine nucleotides include **adenosine monophosphate (AMP)** and **guanosine monophosphate (GMP)**.
- The purine ring is **built step-by-step directly onto the ribose sugar**, using atoms from multiple precursors.



- **Starting molecule:** Ribose-5-phosphate (from Pentose Phosphate Pathway)
 - **Activated form:** 5-Phosphoribosyl-1-pyrophosphate (PRPP)
 - **Final product of de novo pathway:** Inosine monophosphate (IMP), the precursor to AMP and GMP

Step-by-Step Biosynthesis

1. Formation of PRPP

- **Enzyme:** PRPP synthetase
- **Reaction:** Ribose-5-phosphate + ATP → PRPP
- **Regulation:** Feedback-inhibited by purine nucleotides (AMP, GMP)

2. Formation of 5-Phosphoribosylamine

- **Enzyme:** Glutamine-PRPP amidotransferase
- **Reaction:** PRPP + Glutamine → 5-Phosphoribosylamine + Glutamate + PPI
- **Regulation:** Major control step, inhibited by AMP, GMP, IMP

3–10. Stepwise Formation of IMP

- The atoms of the purine ring come from:

Atom in Purine	Source
N1	Aspartate

C2, C8	Formate (via N10-formyl-THF)
N3, N9	Glutamine
C4, C5, N7	Glycine
C6	CO ₂

Key intermediates:

- Glycine addition
- Formylation
- Cyclization
- Amidation
- Another formylation
- Final ring closure

Final product:

- Inosine monophosphate (IMP)

Conversion of IMP to AMP and GMP

IMP → AMP

- **Enzymes:** Adenylosuccinate synthetase → Adenylosuccinate lyase
- **Requires:** Aspartate and GTP
- **Product:** AMP

IMP → GMP

- **Enzymes:** IMP dehydrogenase → GMP synthetase
- **Requires:** Glutamine and ATP
- **Product:** GMP

Regulation of Purine Biosynthesis

Level	Control
PRPP synthetase	Inhibited by purine nucleotides
Glutamine-PRPP amidotransferase	Inhibited by AMP, GMP, IMP
AMP/GMP Branches	Cross-inhibit each other (GTP drives AMP synthesis and vice versa)

Salvage Pathway for Purines

- Reuses free purine bases (adenine, guanine, hypoxanthine):

Enzymes:

- Hypoxanthine-Guanine Phosphoribosyltransferase (HGPRT)
- Adenine Phosphoribosyltransferase (APRT)

Clinical Note:

- Deficiency of HGPRT leads to **Lesch-Nyhan syndrome**

Purine Catabolism

- Purines are broken down to **uric acid** and excreted in urine.

Pathway:

- AMP → Inosine → Hypoxanthine → Xanthine → Uric Acid
- GMP → Guanine → Xanthine → Uric Acid

Enzyme of interest:

- **Xanthine oxidase**
 - Converts hypoxanthine → xanthine → uric acid

Clinical relevance:

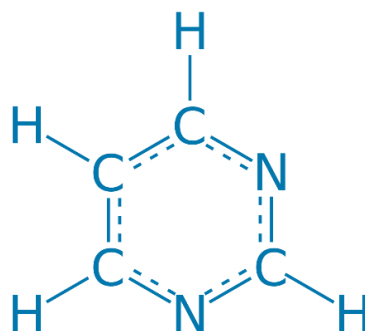
- **Gout:** Accumulation of uric acid crystals in joints (monosodium urate)
 - Painful inflammation, especially in big toe
 - Treated with **allopurinol** (xanthine oxidase inhibitor)

Metabolism of pyrimidine nucleotides

Biosynthesis of Pyrimidine Nucleotide

Overview

- Pyrimidines include **cytidine (CMP)**, **uridine (UMP)**, and **thymidine (TMP)** nucleotides.
 - Unlike purines, the pyrimidine ring is **synthesized first, then attached to PRPP**
 - Final products: UMP → CMP and TMP



Step-by-Step Biosynthesis

1. Formation of Carbamoyl Phosphate

- **Enzyme:** Carbamoyl phosphate synthetase II (CPS II)
- **Reaction:** Glutamine + CO₂ + 2 ATP → Carbamoyl phosphate
- **Location:** Cytosol (not to be confused with CPS I of the urea cycle)
- **Regulation:** Inhibited by UTP, activated by PRPP

2. Formation of Carbamoyl Aspartate

- **Enzyme:** Aspartate transcarbamoylase (ATCase)
- **Reaction:** Carbamoyl phosphate + Aspartate → Carbamoyl aspartate

3. Formation of Dihydroorotate

- **Enzyme:** Dihydroorotase

4. Oxidation to Orotate

- **Enzyme:** Dihydroorotate dehydrogenase
- **Location:** Mitochondria (only mitochondrial step in this pathway)
- **Reaction:** Dihydroorotate → Orotate

5. Addition of PRPP

- **Enzyme:** Orotate phosphoribosyltransferase
- **Reaction:** Orotate + PRPP → Orotidine monophosphate (OMP)

6. Decarboxylation to UMP

- **Enzyme:** Orotidylate decarboxylase
- **Product:** UMP

UMP → CMP and TMP

UMP → UDP → CTP

- UDP is phosphorylated to UTP
- **Enzyme:** CTP synthetase
- **Requires:** Glutamine and ATP → CTP

UDP → dUMP → dTMP

- UDP is reduced to dUDP by **ribonucleotide reductase**, then converted to dUMP
- **Enzyme:** Thymidylate synthase
- **Reaction:** dUMP → dTMP
- **Requires:** N⁵,N¹⁰-methylene-THF (tetrahydrofolate derivative)

Regulation of Pyrimidine Biosynthesis

Level	Control
CPS II	Inhibited by UTP, activated by PRPP
ATCase (bacteria)	Feedback inhibition by CTP
Ribonucleotide reductase	Regulated by dNTP levels

Salvage Pathway for Pyrimidines

- Pyrimidine bases (e.g., uracil, cytosine, thymine) can be reused
- **Enzymes:** Pyrimidine nucleoside phosphorylases
- Less efficient/important than purine salvage

Pyrimidine Catabolism

- Pyrimidines are broken down into **water-soluble products** (unlike purines → uric acid).

Pathway:

- Cytosine, Uracil → **β-alanine**
- Thymine → **β-aminoisobutyric acid**
- All are excreted via the urine

Protein synthesis

What is Translation?

- **Translation** is the biological process by which **ribosomes synthesize proteins** using **messenger RNA (mRNA)** as a template.
- It is the **second step of gene expression**, following transcription.
 - It occurs in the **cytoplasm** of both prokaryotic and eukaryotic cells.
 - It involves three main types of RNA:
 - **mRNA** (messenger RNA): Carries genetic code
 - **tRNA** (transfer RNA): Brings amino acids
 - **rRNA** (ribosomal RNA): Part of the ribosome's structure and catalytic machinery

Major Components of Translation

Component	Function
mRNA	Template with codons that specify amino acids



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