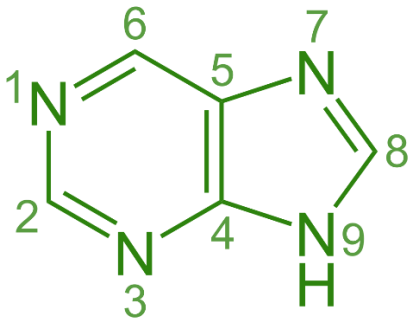
Nucleic acid metabolism and genetic information transfer

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

First Hope

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. 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)

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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):

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Enzymes:

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

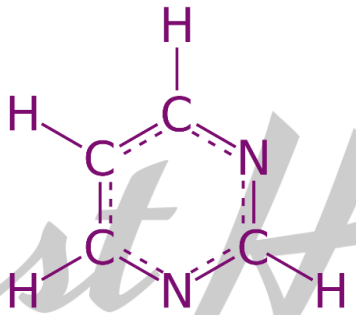
Clinical Note:

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

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



First Hope

Step-by-Step Biosynthesis

1. Formation of Carbamoyl Phosphate

- **Enzyme**: Carbamoyl phosphate synthetase II (CPS II)
- **Reaction**: Glutamine + CO_2 + 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)

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