Biochemistry

Metabolism

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Nucleotide
Metabolism

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Physiological Function of Nucleotides

-Building blocks of nucleic acids

-High energy donors
- -ATP, GTP
- -UDP-Glc, CDP-Choline...

-Cofactors
- -NAD^+, FAD, CoA, (SAM)

-Metabolic control
- - as allosteric modulators
- -as second messengers (cAMP, cGMP)

Note:
Nucleotide-protein binding is rather strong
(F_0F_1 ATPase; G-proteins; DNA-binding proteins)

Purine and pyrimidine bases of nucleic acids

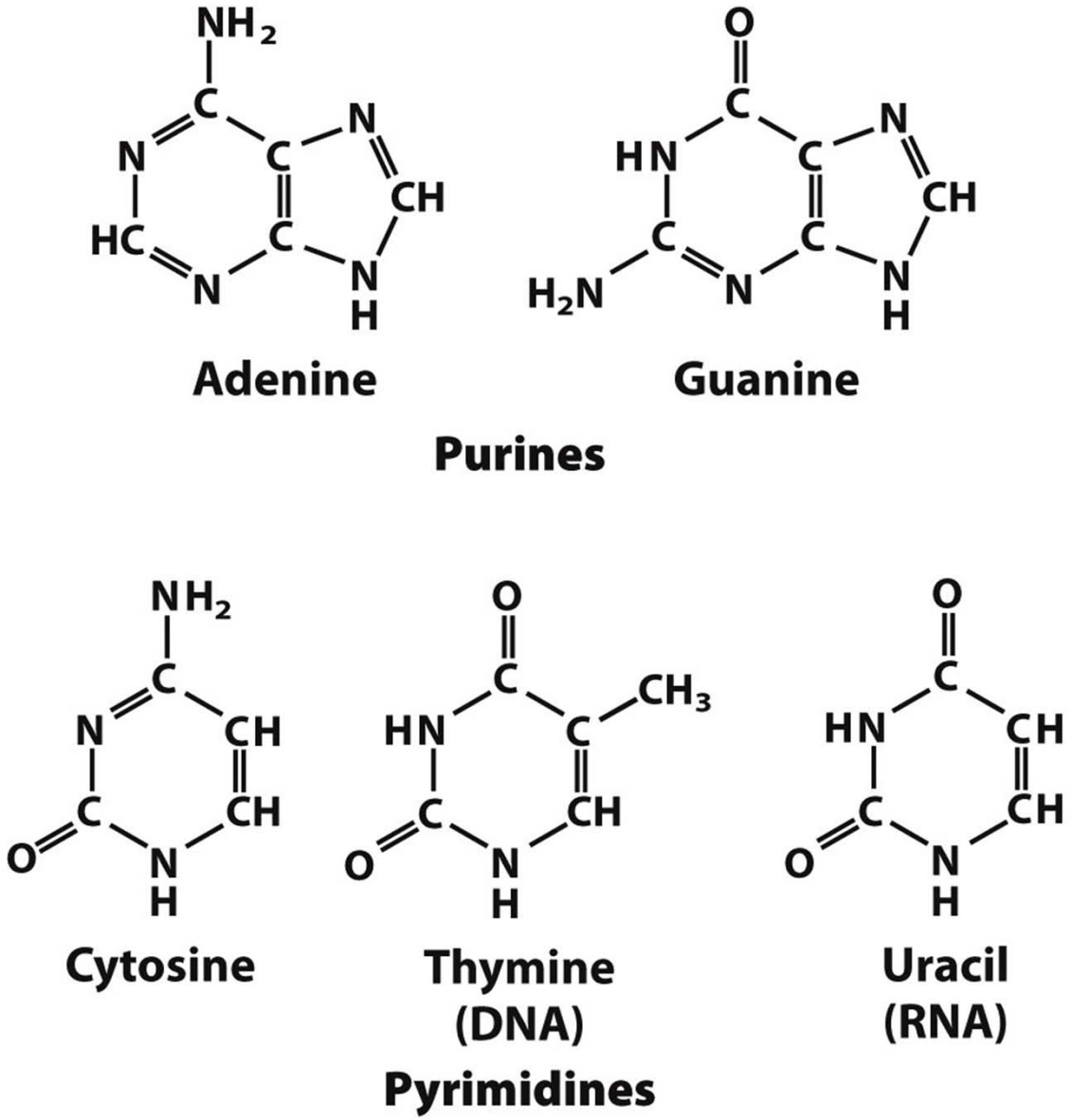


Figure 8-2
Lehninger Principles of Biochemistry, Fifth Edition

Hydrogen-bonding patterns in the base pairs defined by Watson and Crick

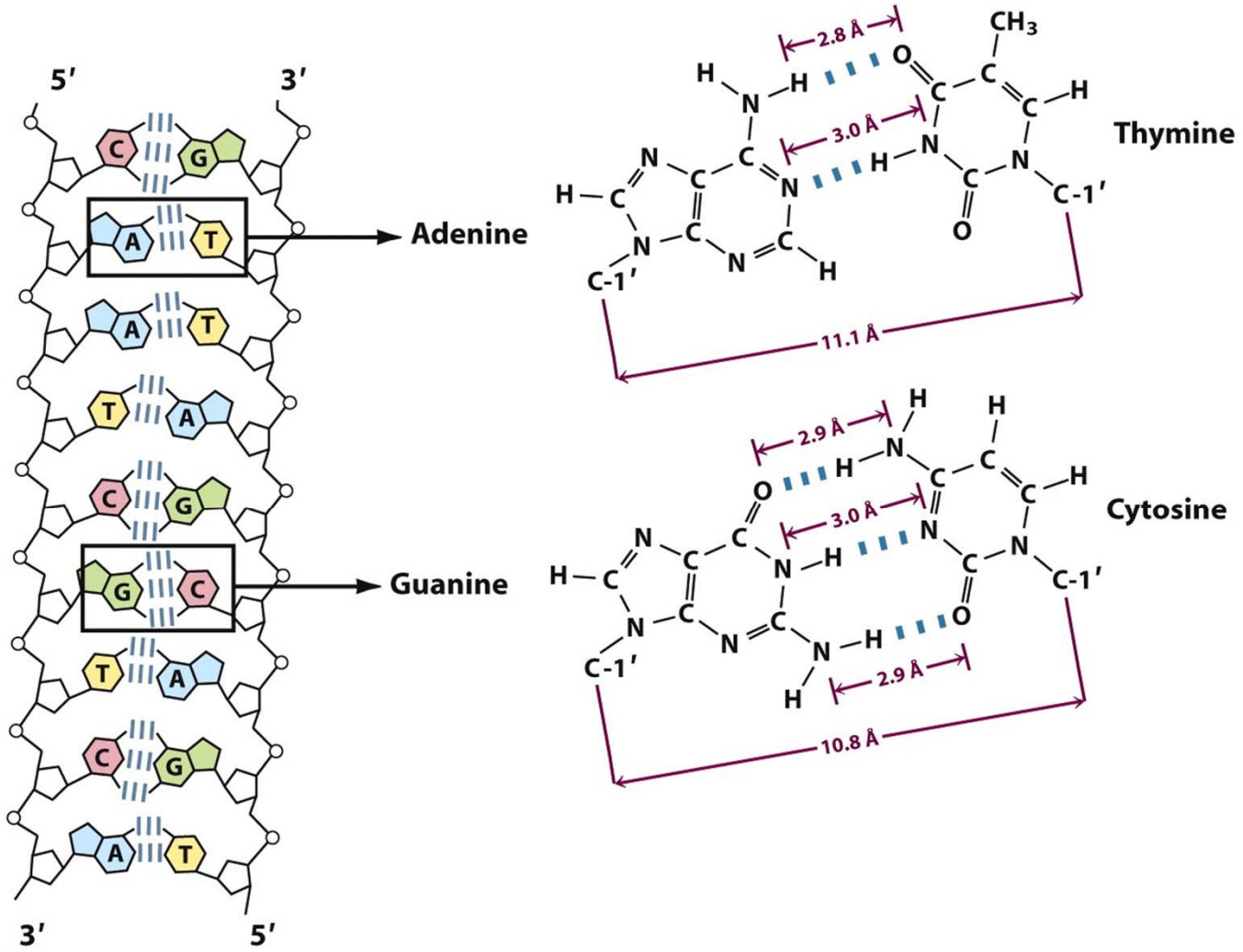
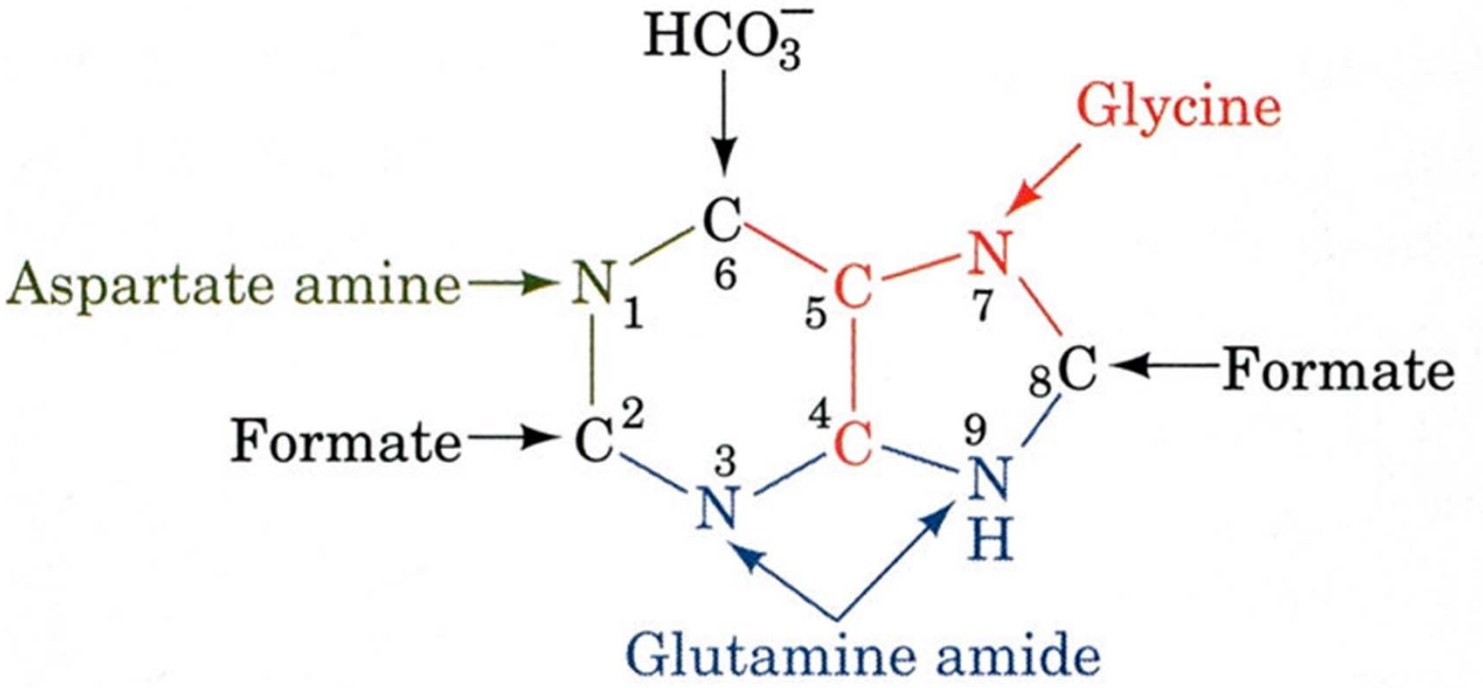


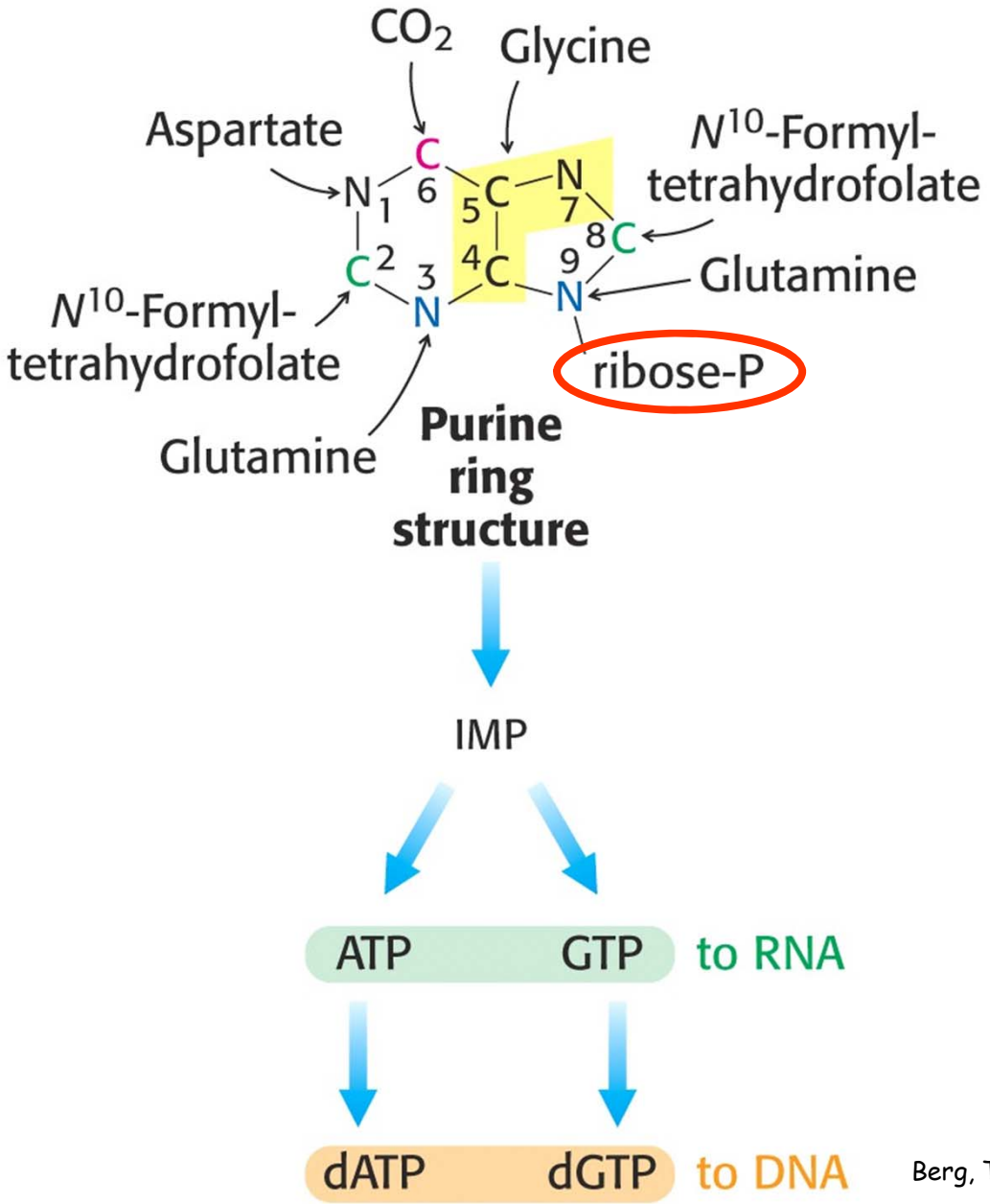
Figure 8-11
Lehninger Principles of Biochemistry, Fifth Edition

The biosynthetic origins of purine ring atoms



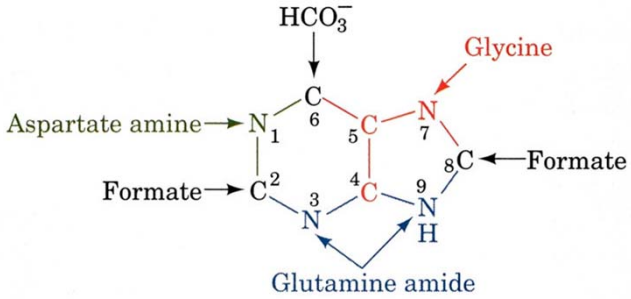
Voet, Voet: Biochemistry

Strategy of purine biosynthesis



Berg, Tymoczko, Stryer: Biochemistry

Purine biosynthesis (I)



α-D-Ribose-5-phosphate

ATP → AMP: 1 ribose phosphate pyrophosphokinase

5-Phosphoribosyl-α-pyrophosphate (PRPP)

→ pyrimidines
Trp, His

Glutamine + H_2O → Glutamate + PP_i: 2 amidophosphoribosyl transferase

→ unique to *de novo* purine biosynthesis
⇒ rate-limiting

β-5-Phosphoribosylamine

Glycine + ATP → ADP + P_i: 3 GAR synthetase

Glycinamide ribotide (GAR)

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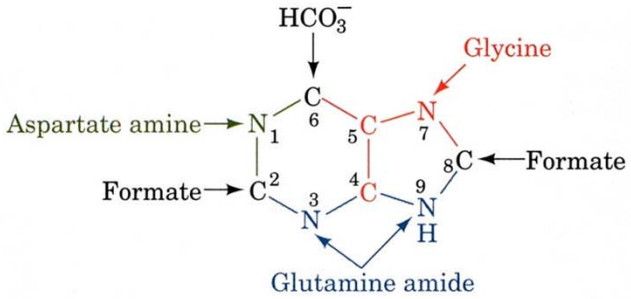
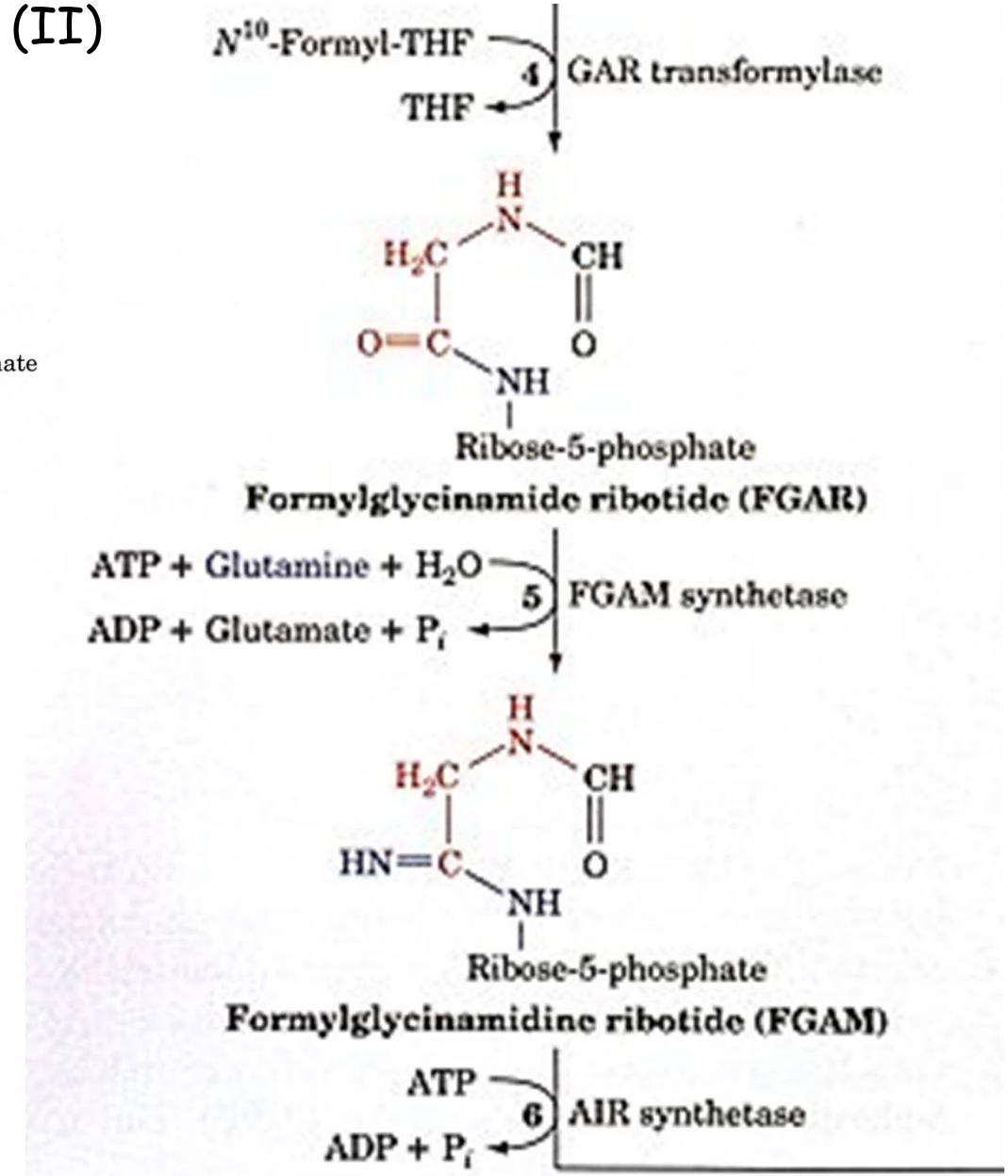
Purine biosynthesis (II)





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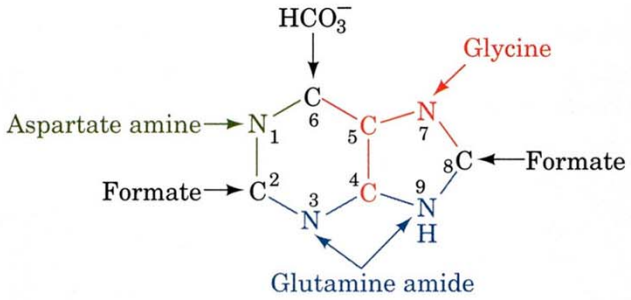
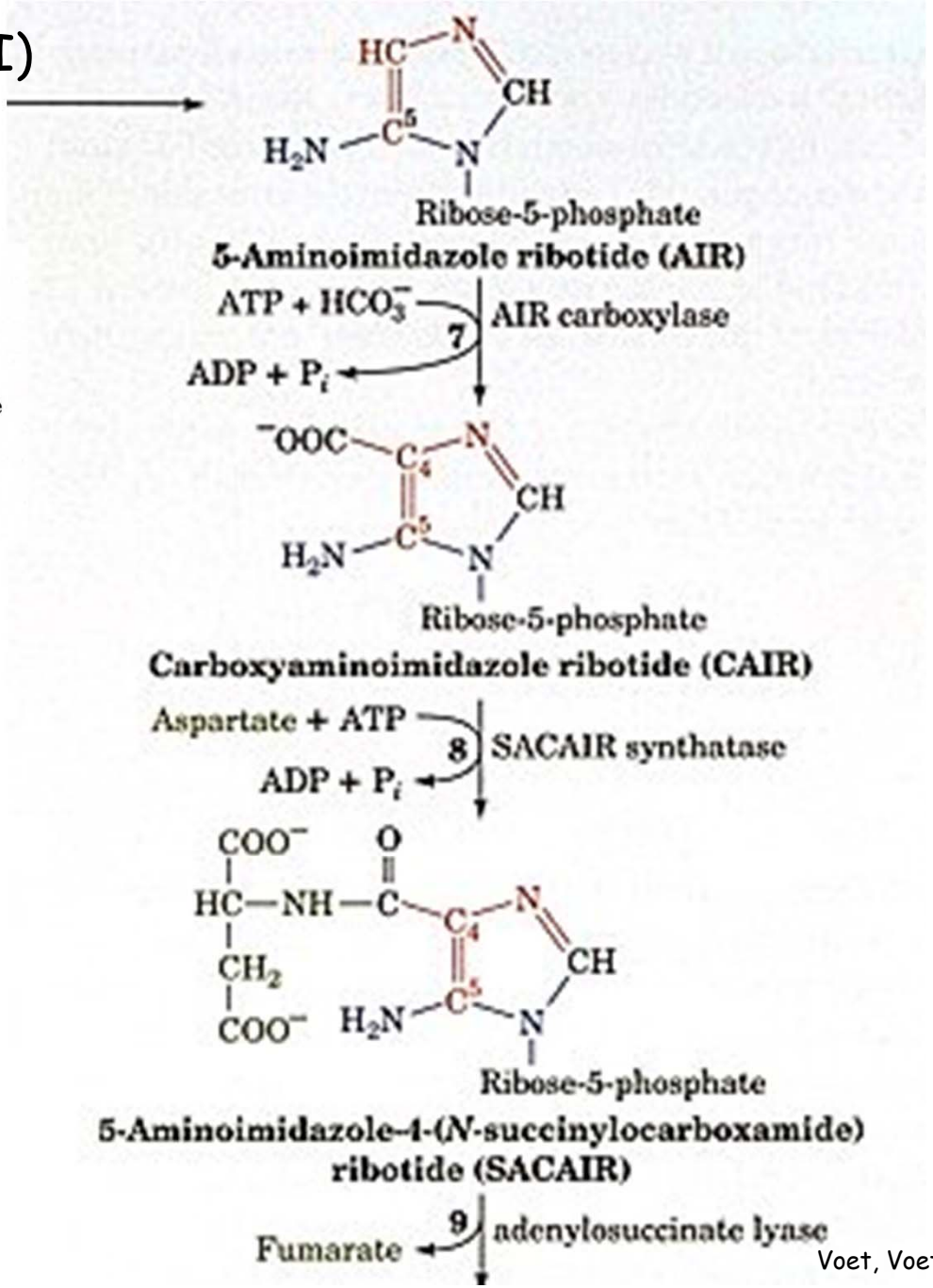
Purine biosynthesis (III)





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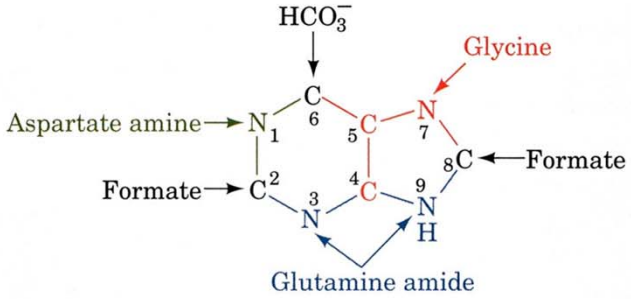
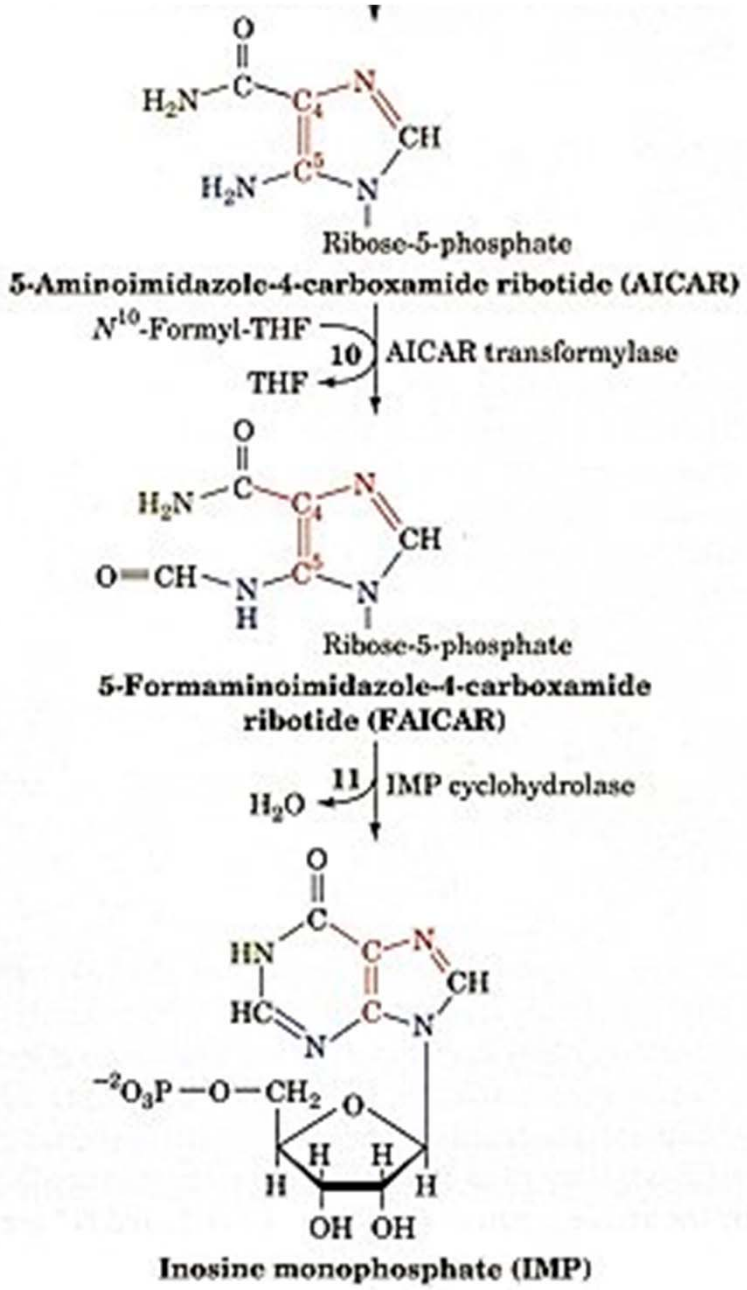
Purine biosynthesis (IV)





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De novo purine biosynthesis

x-ray structures of biosynthetic enzymes:

monomeric enzymes are colored in rainbow order from their N-termini (blue) to their C-termini (red).

oligomeric enzymes, all of which consist of identical polypeptide chains, are viewed along a rotation axis with their various chains differently colored. Bound ligands are shown in space-filling form:

- α,β-methylene-ADP = red in catalytic and blue in allosteric site of Enz. 1;
- GAR=cyan and THF-derivative = red in Enz. 4)

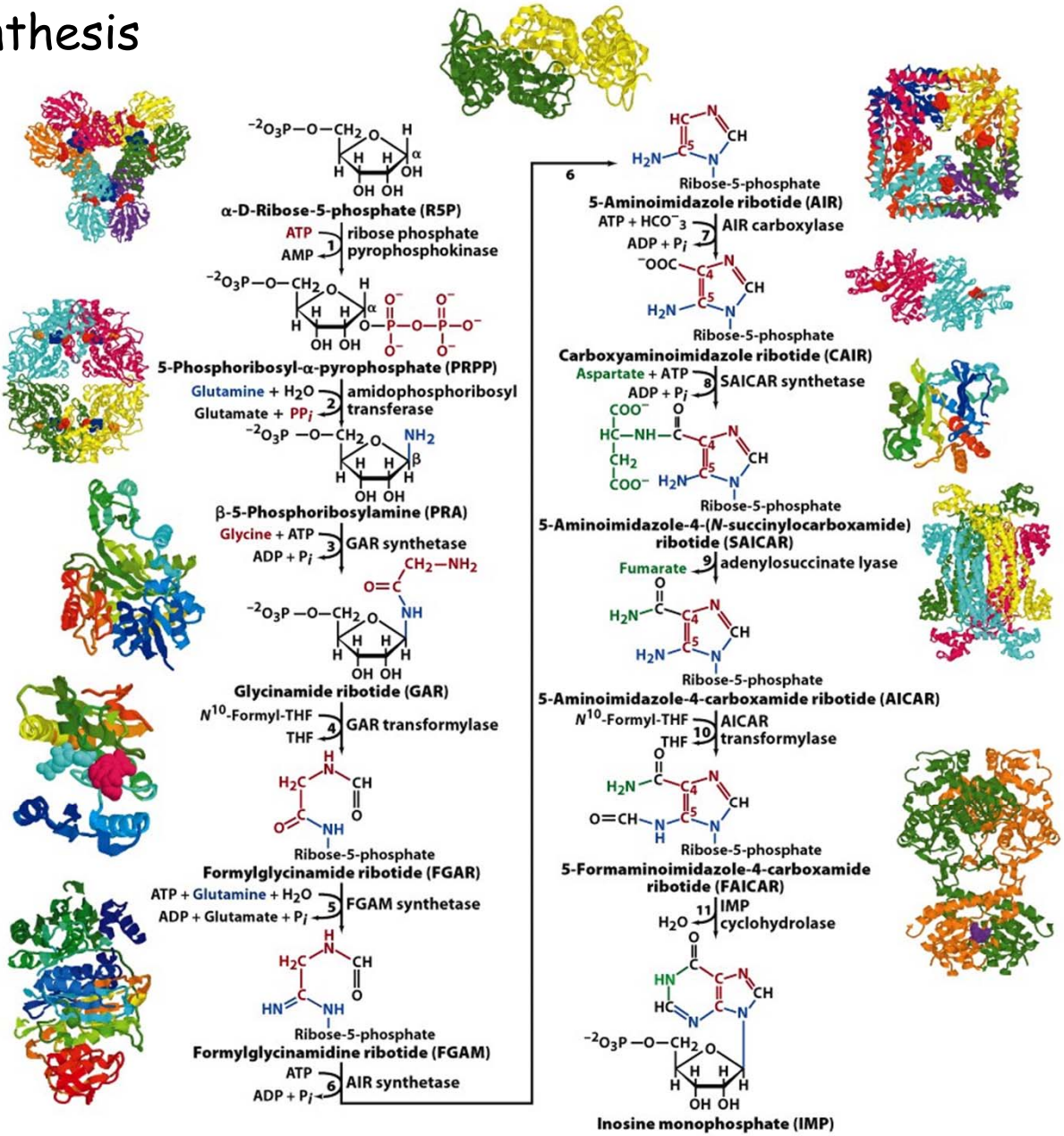

Figure 28-2

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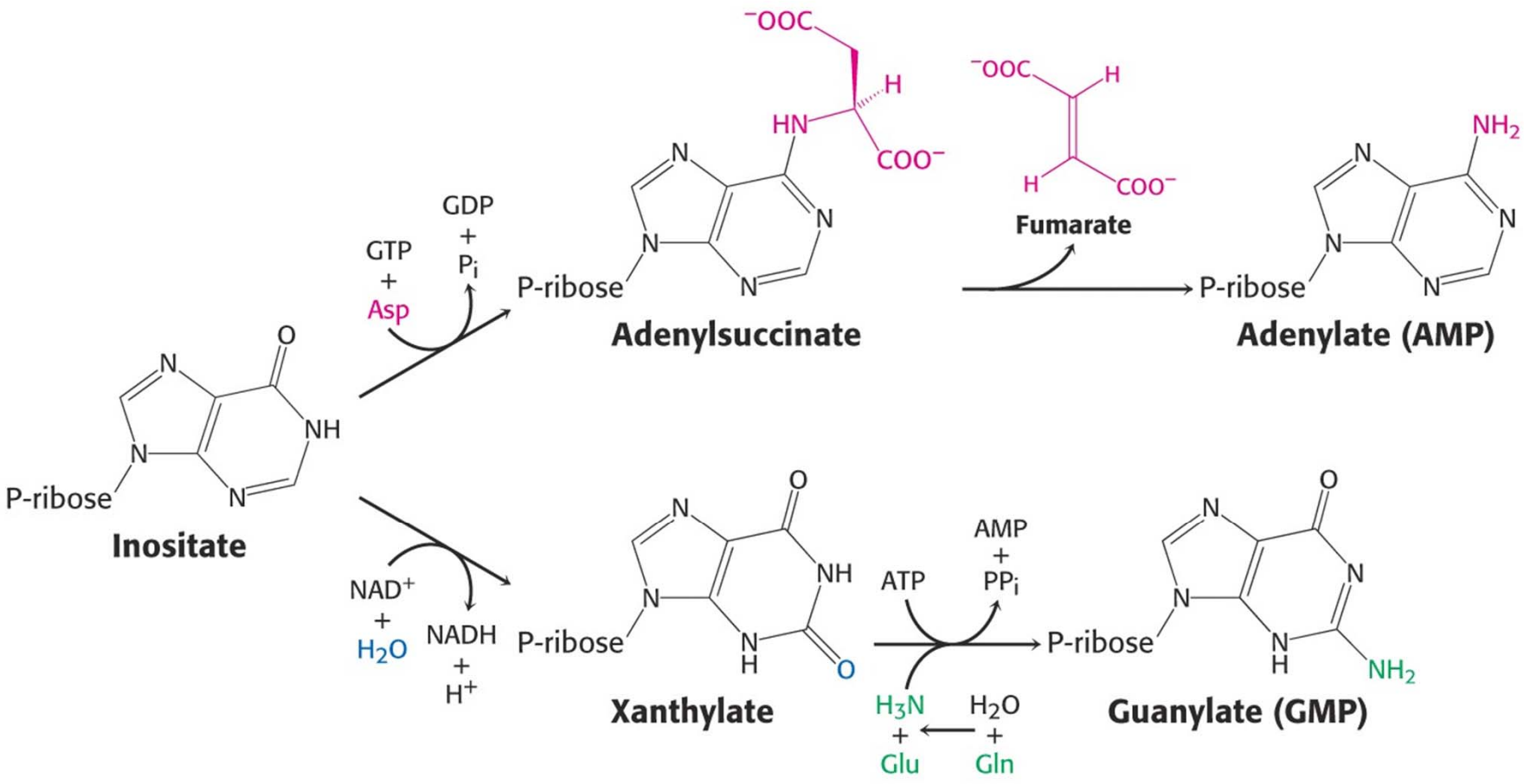
Conversion of IMP to AMP and GMP

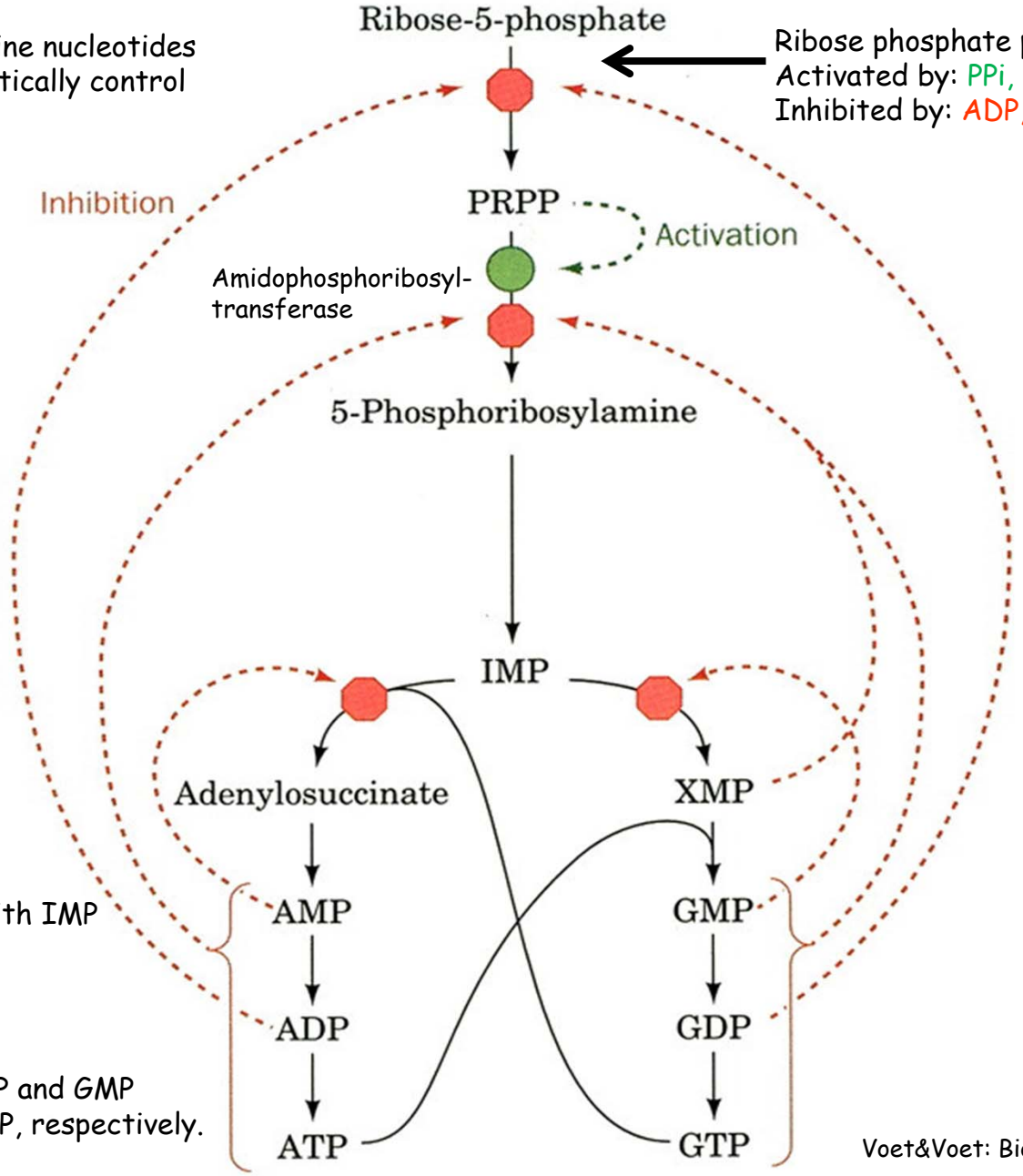


NMP kinases are base-specific but do not discriminate between NMP and dNMP.
NDP kinases are non specific regarding both, the bases and the sugar.

Berg, Tymoczko, Stryer: Biochemistry

Control of purine-biosynthesis

Levels of adenine and guanine nucleotides independently but synergistically control the rate of IMP formation

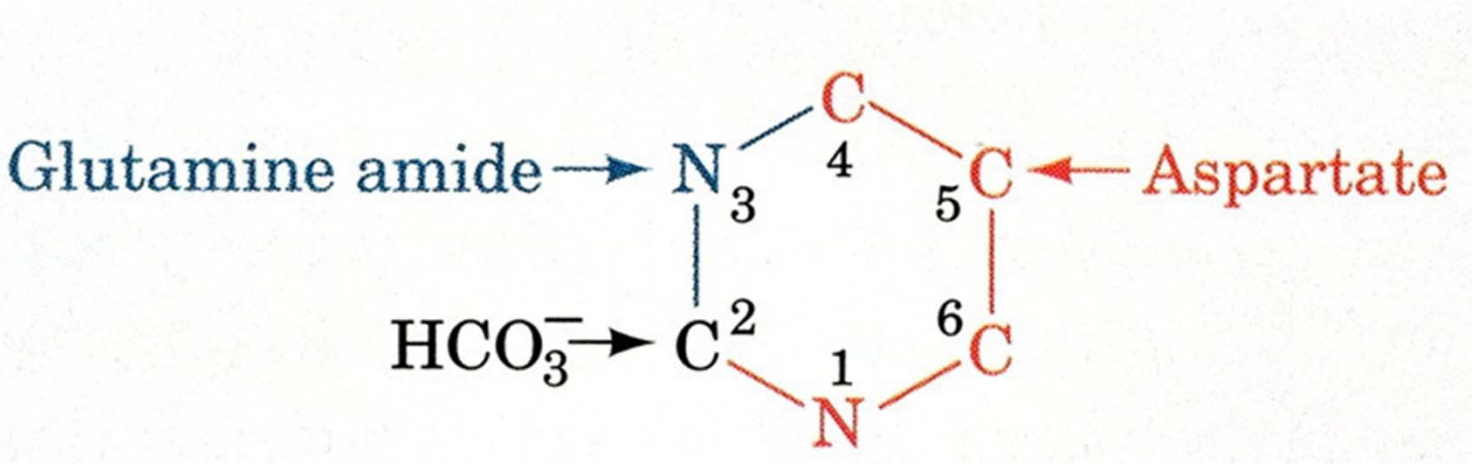


AMP and GMP compete with IMP

Reciprocal control of AMP and GMP formation by GTP and ATP, respectively.

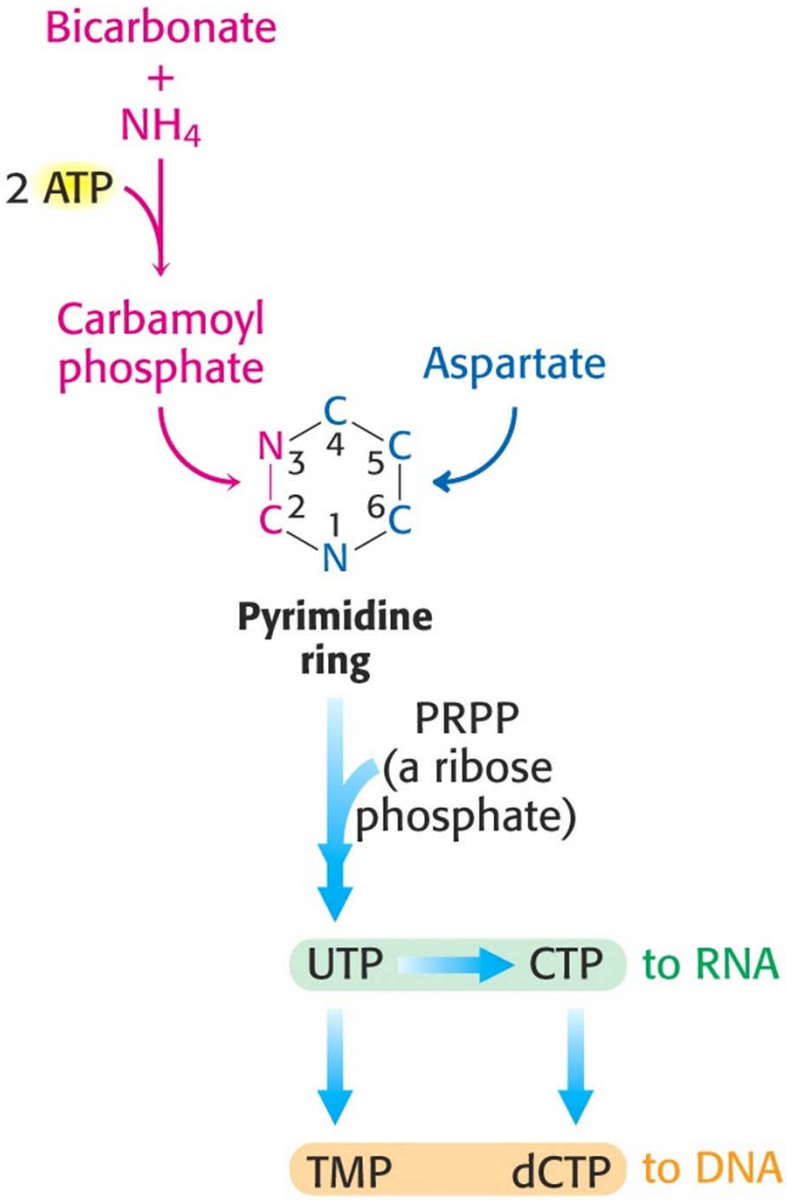
Voet&Voet: Biochemistry

The biosynthetic origins of pyrimidine ring atoms



Voet, Voet: Biochemistry

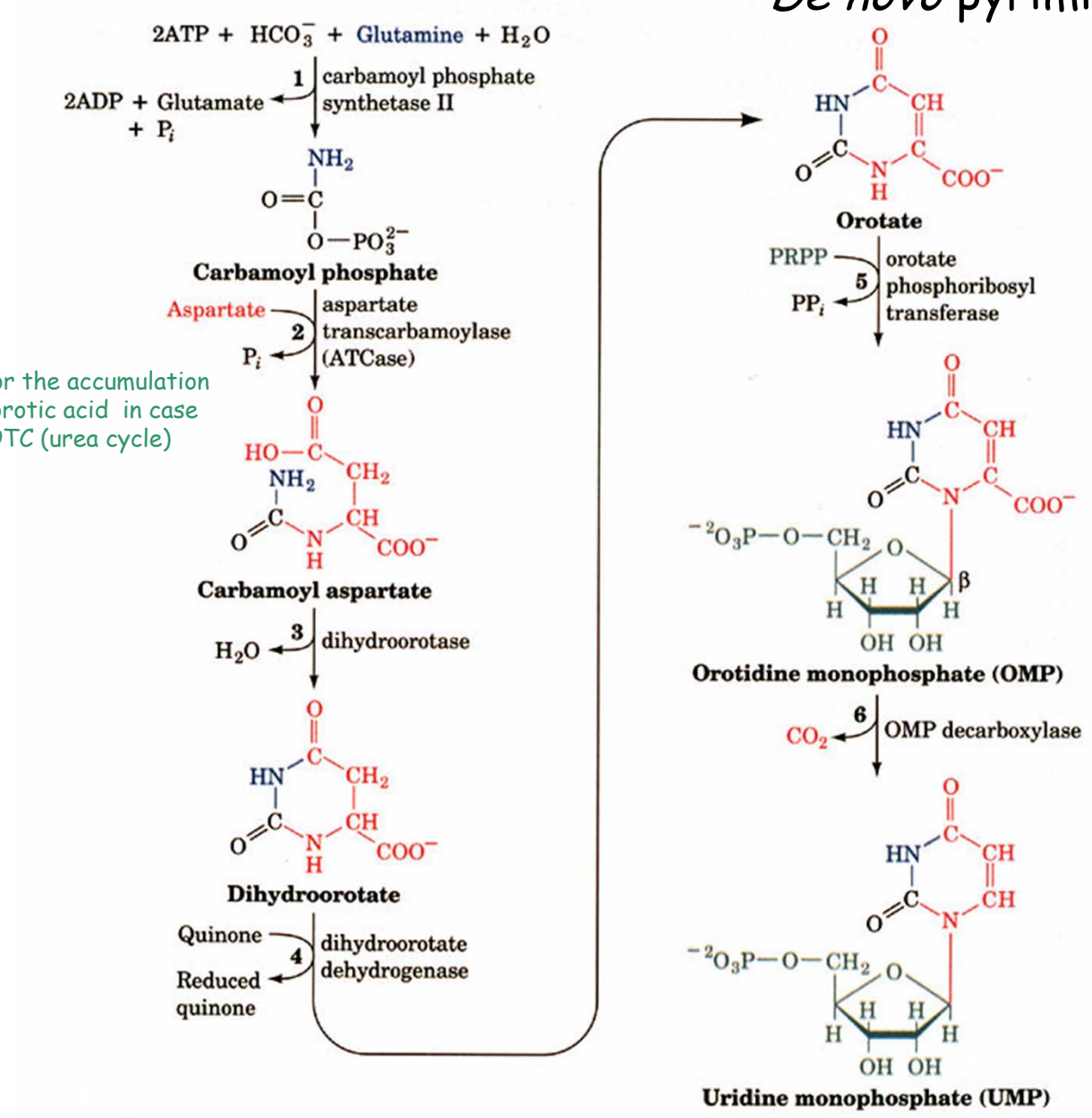
Strategy of pyrimidine biosynthesis



Berg, Tymoczko, Stryer: Biochemistry

De novo pyrimidine biosynthesis

Explanation for the accumulation of uracil and orotic acid in case of deficient OTC (urea cycle)



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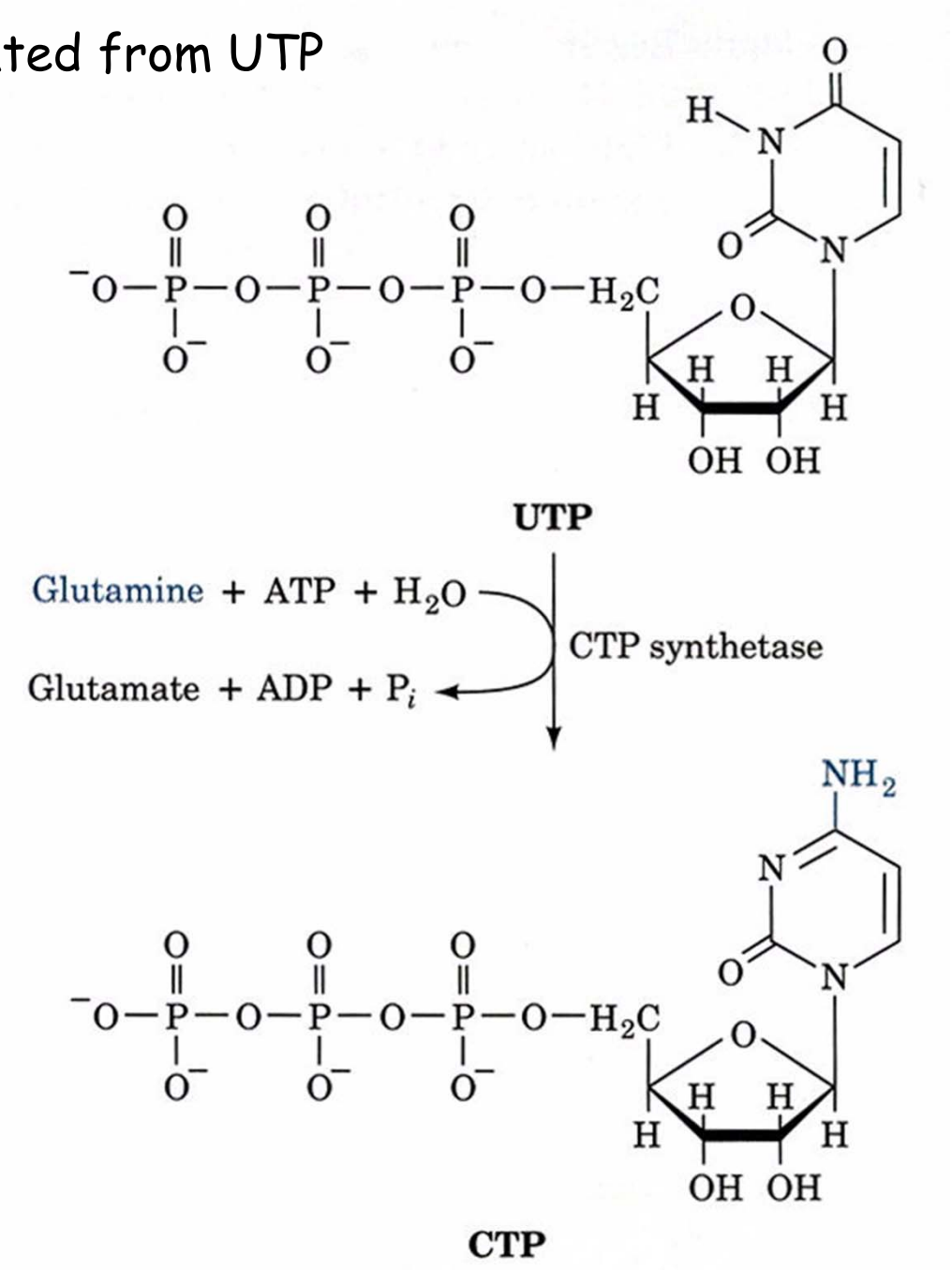
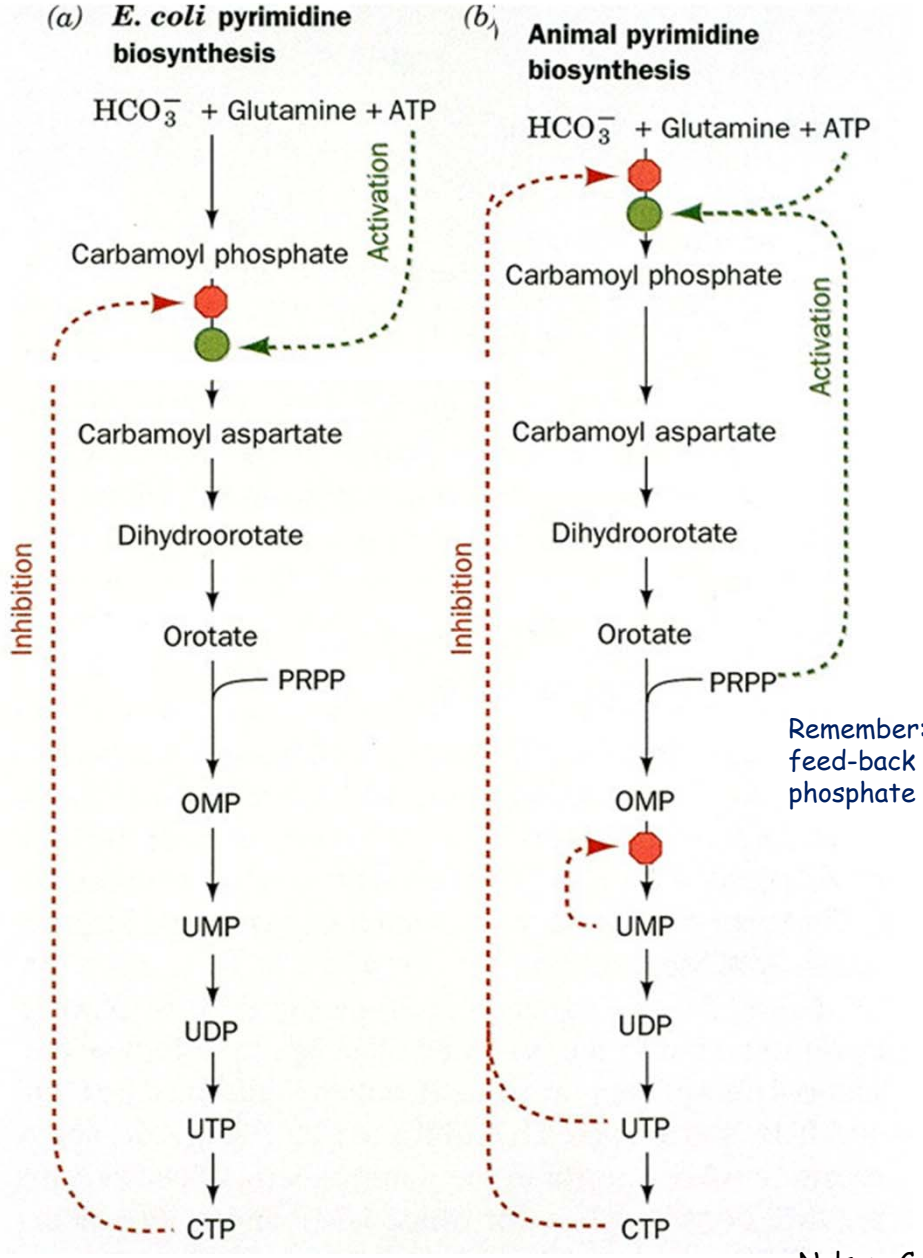
CTP is generated from UTP



Voet, Voet: Biochemistry

Control of pyrimidne biosynthesis



Remember: ADP and GDP are feed-back inhibitors of ribose phosphate pyrophosphokinase

Pathology:
Orotate aciduria, due to defect of orotate phosphoribosyl transferase.

Nelson, Cox: Lehninger Biochemistry