Biosynthesis of Nucleotides

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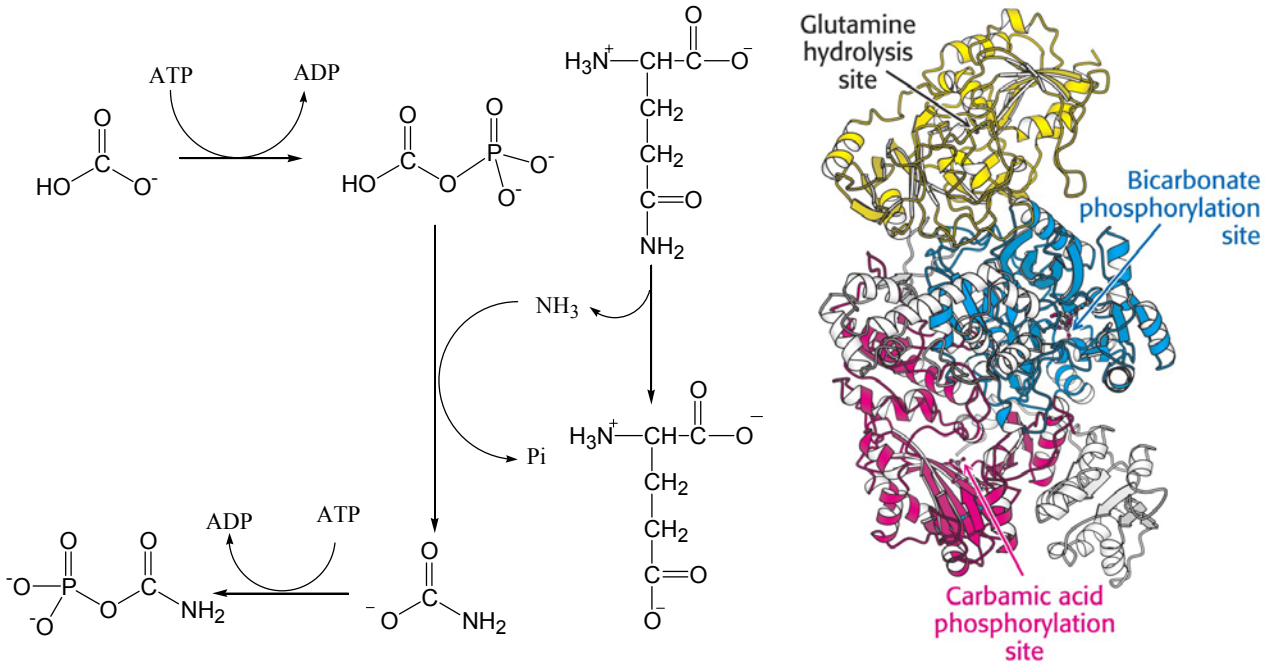
Nucleotides play a variety of crucial roles in cells. They are the precursors of DNA and RNA. Nucleoside triphosphates are carriers of metabolic energy. Let's begin by looking at the de novo biosynthesis of pyrimidines.

I. Pyrimidine Biosynthesis.

The pyrimidine ring is synthesized first and then attached to ribose to form the pyrimidine nucleotide. Pyrimidines are synthesized from bicarbonate, aspartate and ammonia.

Carbamoyl Phosphate Synthetase II.

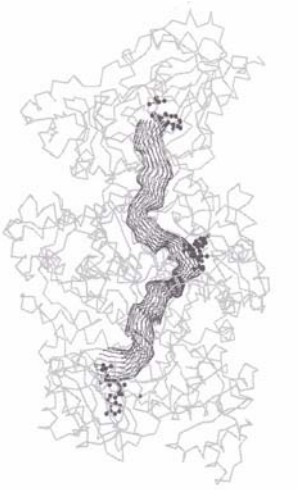
Remember carbamoyl phosphate synthetase I? This enzyme is found in the mitochondria of the liver and uses 2 molecules of ATP to take bicarbonate and ammonia and form carbamoyl phosphate. CPS I uses ammonia as the nitrogen source. CPS II catalyzes the same reaction, but the nitrogen source comes from the hydrolysis of glutamine. The subunit that hydrolyzes glutamine to pruduce the ammonia for biosynthesis is called a glutamine amidotransferase.



The crystal structure of this enzyme is shown above. This enzyme has three active sites. The first one is in the yellow subunit which catalyzes the hydrolysis of glutamine to produce glutamate and ammonia. The second active site is shown in Blue this site activates bicarbonate with ATP to form carboxyphosphate which then reacts with the nascent ammonia to form the carbamate. The third active site is shown in red. This site catalyzes the phosphorylation of carbamate to form carbamoyl phosphate. These three active sites are separated from each other by 45 Å. How are the intermediates shuttled from one active site to the next?

Running through the interior of this enzyme there is a channel completely protected from the solvent that connects all three active sites together. Ammonia is channel form the glutaminase domain to the

carboxyphosphate domain to form carbamate. Carbamate is then channeled to the second ATP site to form carbamoyl phosphate. Each of these three reactions is synchronized such that for every glutamine hydrolyzed one carbamoyl phosphate is produced.



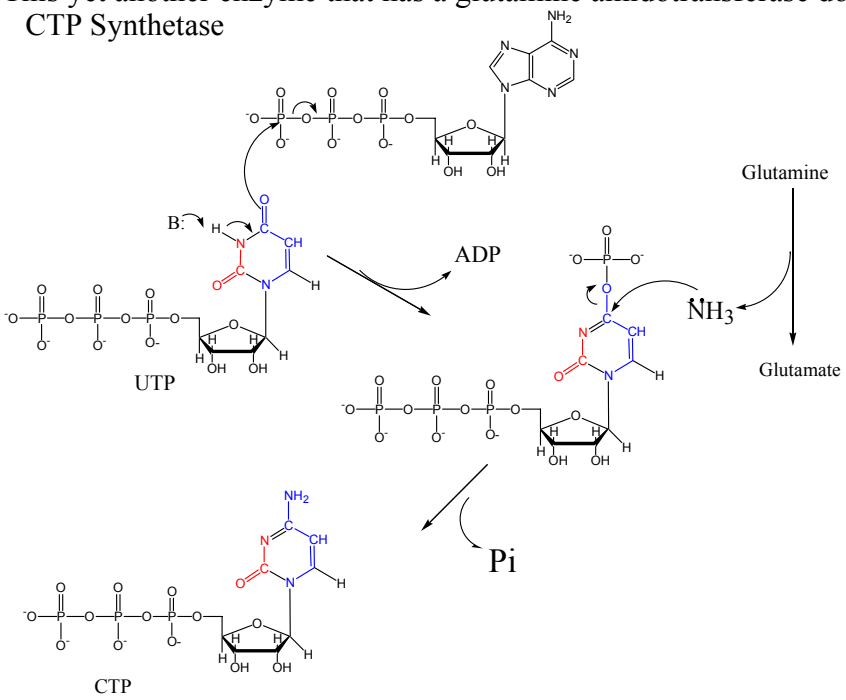
The channel running through carbamoyl phosphate synthetase connecting the three active sites is shown to the left.

The carbamoyl phosphate produced in this reaction reacts with aspartate in a reaction catalyzed by aspartate transcarbamylase to form carbamoylaspartate.

Cytosine Biosynthesis.

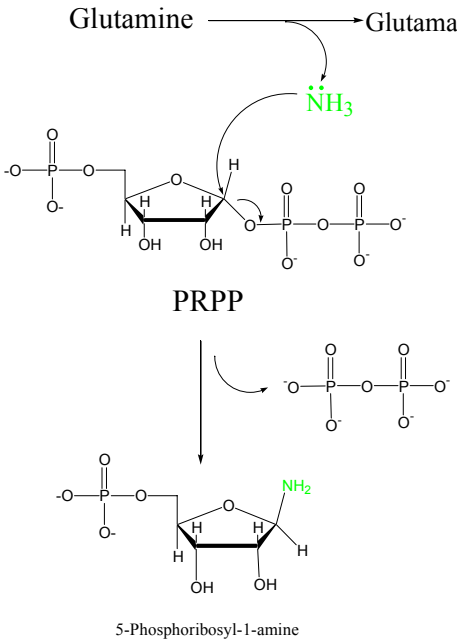
This yet another enzyme that has a glutamine amidotransferase domain.

CTP Synthetase



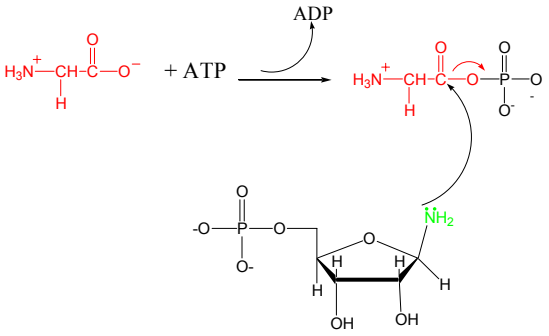
II. Purine Biosynthesis

Glutamine phosphoribosyl amidotransferase



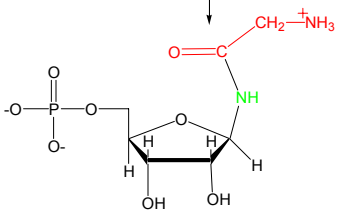
Purine are synthesized from PRPP. PRPP is the foundation upon which the purines are built. The first step of purine biosynthesis is the displacement of the pyrophosphate group of PRPP by ammonia to form 5-phosphoribosyl amine. The enzyme involved is glutamine phosphoribosyl amidotransferase. This enzyme also has a glutamine amidotransferase domain to produce the ammonia for biosynthesis.

Glycinamide Ribonucleotide synthetase



5-Phosphoribosyl-1-amine

Pi

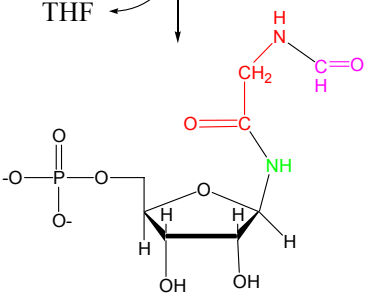


Glycinamide Ribonucleotide

N^{10}-Formyl-THF

Glycinamide Ribonucleotide Transformylase

THF

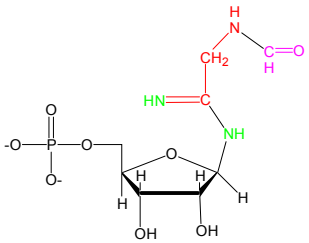


Formylglycinamide Ribonucleotide

ATP +Gln + H_2O

FGAM Synthetase

ADP + Pi + Glu

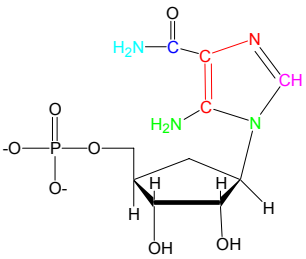


Formylglycinamidine Ribonucleotide

ATP

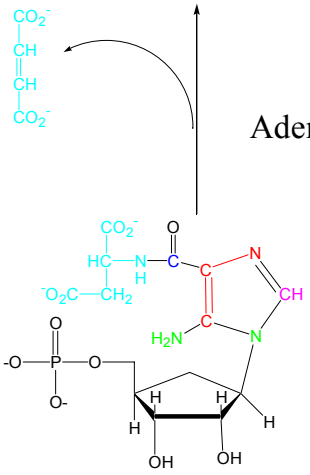
ADP + Pi

AIR Synthetase



5-Aminoimidazole-4-carboxamide ribonucleotide

Adenylosuccinate lyase

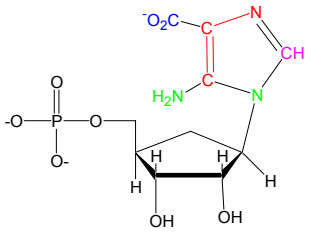


N-Succinyl-5-aminoimidazole-4-carboxamide ribonucleotide

ADP + Pi

SAICAR Synthetase

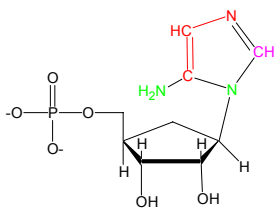
Aspartate + ATP



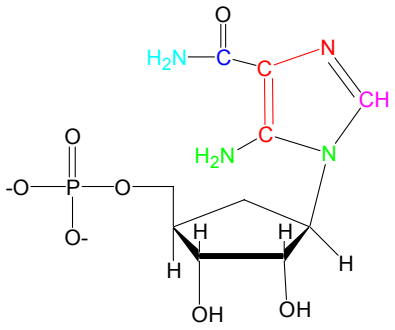
ADP + Pi

AIR Carboxylase

ATP + HCO_3^-



5-Amidoimidazole Ribonucleotide

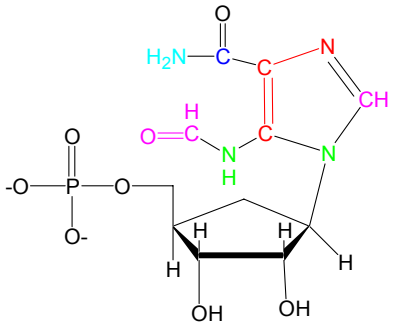


5-Aminoimidazole-4-carboxamide ribonucleotide

N^{10}-Formyl-THF

AICAR Transformylase

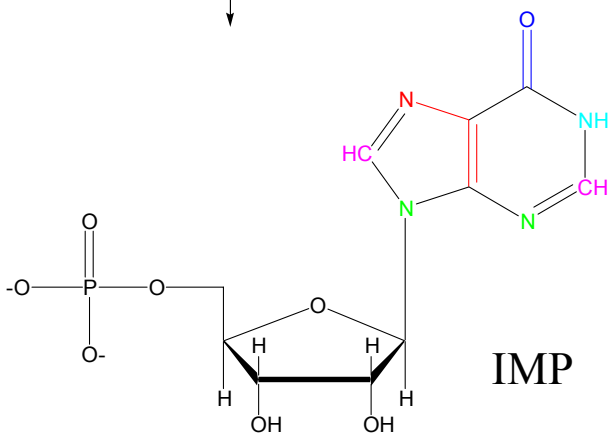
THF



N-Formylaminoimidazole-4-carboxamide FAICAR

IMP Synthase

H_2O



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