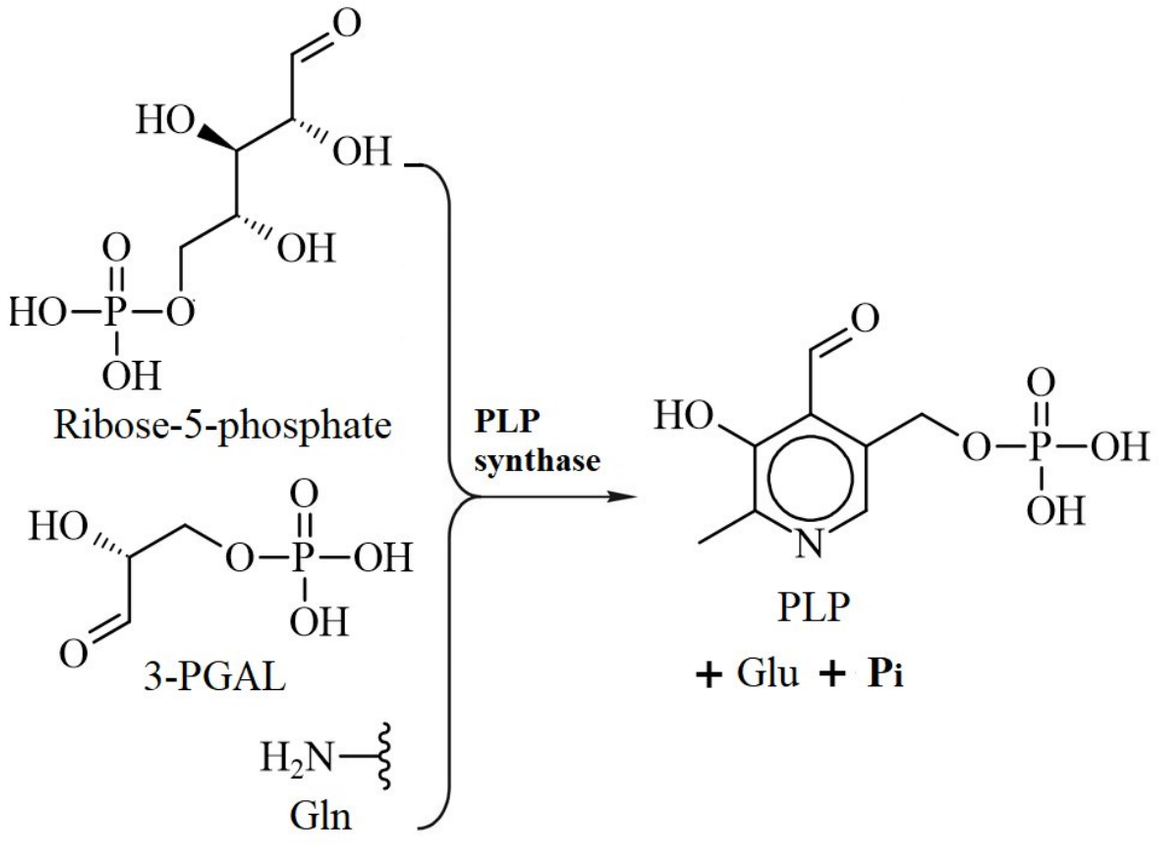
Pyridoxal phosphate

Pyridoxal phosphate (PLP)the active form of vitamin B6, functions as a versatile coenzyme in numerous enzymatic reactions, primarily involving amino acid metabolism. Its function arises from its ability to form a covalent intermediate with the substrate and act as an electron sink, stabilizing highly reactive carbanionic intermediates through a conjugated pi-system.

Structure

Pyridoxal phosphate (PLP), or pyridoxal 5'-phosphate (P5P), is a derivative of the vitamin B6 vitamers (pyridoxine, pyridoxal, and pyridoxamine).



- Chemical Structure: It is (4-Formyl-5-hydroxy-6-methylpyridin-3-yl)methyl dihydrogen phosphate, with the chemical formula $C_8H_{10}NO_6P$.
- Key Functional Groups: The structure features a pyridine ring, a hydroxyl group, a methyl group, a hydroxymethyl group linked to a phosphate group, and a reactive aldehyde group.
- Active Site Binding: In most PLP-dependent enzymes, the aldehyde group of PLP initially forms a covalent Schiff-base linkage (internal aldimine) with the

-amino group of a specific lysine residue in the active site.

Biological Function

Role in human body

Pyridoxal phosphate has numerous roles in human body. A few examples below:

- Metabolism and biosynthesis of serotonin. Pyridoxal phosphate is a cofactor of aromatic L-amino acids decarboxylase. This allows for conversion of 5-hydroxytryptophan (5-HTP) into serotonin (5-HT). This reaction takes place in serotonergic neurons.
- Metabolism and biosynthesis of histamine. Pyridoxal phosphate is a cofactor of L-histidine decarboxylase. This allows for conversion of histidine into histamine. This reaction takes place in Golgi apparatus in mast cells and in basophils. Next, histamine is stored in granularity in mast cells as a complex with acid residues of heparin proteoglycan while in basophils as a complex with chondroitine sulfate.
- Metabolism and biosynthesis of GABA (γ-aminobutyric acid). Pyridoxal phosphate is a cofactor of glutamic acid decarboxylase (GAD). This allows for conversion of glutamate into GABA. Reaction takes place in cytoplasm of termination of GABA-ergic neurons, therefore vitamin B_6 deficiency may cause epileptic seizures in children. Pyridoxal phosphate also participates in the oxidative deamination of GABA, where it is a cofactor of GABA aminotransferase.
- Metabolism of ornithine. Pyridoxal phosphate is a cofactor of ornithine carboxylase.
- Transamination. Pyridoxal phosphate takes part in decomposition and synthesis of amino acids, fats, and carbohydrates, and in the biosynthesis of hormones, neurotransmitters, and heme.[9][10]

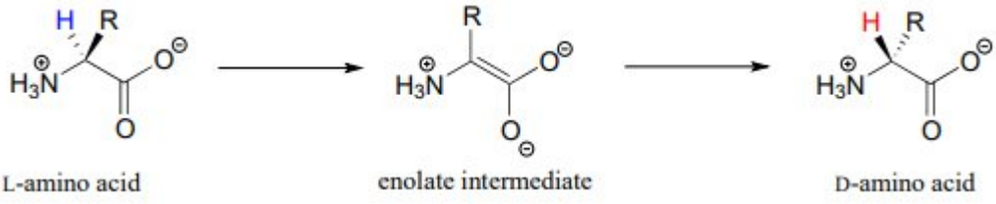
PLP is a coenzyme for over 140 known enzymatic activities, mainly involved in the metabolism of amino acids, carbohydrates, and lipids. Its primary function is as an electrophilic catalyst, stabilizing carbanion intermediates by delocalizing the negative charge across its conjugated ring system.

The versatility of PLP allows it to facilitate a wide array of reactions at the the α- , β - ,γ- carbons of amino acids, including:

- Transamination: The reversible transfer of an amino group between an amino acid and an α- keto acid. In this process, the PLP coenzyme is temporarily converted to pyridoxamine phosphate (PMP) as it acts as a temporary "storage space" for the amino group.
- Decarboxylation: The removal of a carboxyl group ($-COO^-$) from an amino acid to form an amine, which is an essential step in the synthesis of neurotransmitters such as serotonin, dopamine, histamine, and GABA.

- Racemization: The interconversion of L- and D-amino acids.

PLP-dependent amino acid racemization we saw an example of a PLP-independent amino acid racemization reaction, in which the negatively-charged intermediate was simply the enolate form of a carboxylaten:



Many other amino acid racemase reactions, however, require the participation of PLP.

- Elimination and Substitution: Reactions involving the cleavage of bonds at the β - ,γ- carbons of amino acids.
- Other Roles: PLP is also a cofactor for glycogen phosphorylase, where its phosphate group (not the aldehyde) is involved in breaking down glycogen during glycogenolysis to release glucose-1-phosphate. It is also essential for the condensation reaction in heme synthesis.

The specific reaction pathway is determined by how the enzyme's active site orientates the substrate-PLP intermediate (external aldimine), ensuring that the specific bond to be broken is correctly aligned with the coenzyme's pi-orbitals for maximum stabilization (Dunathan stereoelectronic hypothesis).