Pentose Phosphate Pathway
Aka the Hexose Monophosphate Shunt

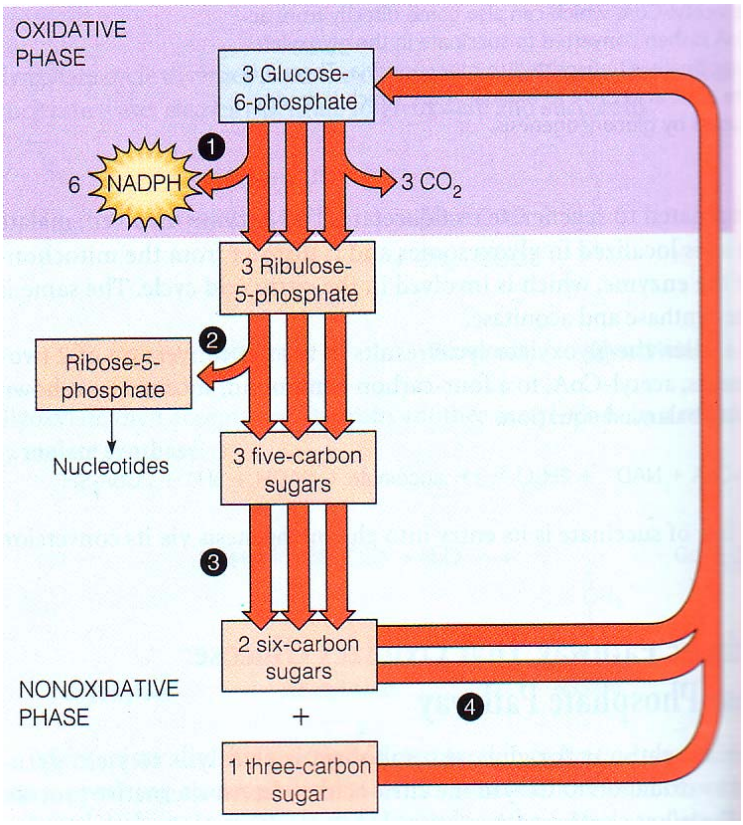
January 29, 2003

Bryant Miles

In most animal tissues, glucose is catabolized via the glycolytic pathway into two molecules of pyruvate. Pyruvate is then oxidized via the citric acid cycle to generate ATP. There is another metabolic fate for glucose used to generate NADPH and specialized products needed by the cell. This pathway is called the **pentose phosphate pathway**. Some text books call it the hexose monophosphate shunt, still others call it the phosphogluconate pathway. We will call it in this class the pentose phosphate pathway.

The pentose phosphate pathway produces NADPH which is the universal reductant in anabolic pathways. In mammals the tissues requiring large amounts of NADPH produced by this pathway are the tissues that synthesize fatty acids and steroids such as the mammary glands, adipose tissue, adrenal cortex and the liver. Tissues less active in fatty acid synthesis such as skeletal muscle are virtually lacking the pentose phosphate pathway.

The second function of the pentose phosphate pathway is to generate pentoses, particularly ribose which is necessary for the synthesis of nucleic acids.



It is convenient to think of the pentose phosphate pathway as operating in two phases. The first phase is the oxidative phase. Two of the first three reactions of the first phase generate NADPH. The second phase is the nonoxidative phase.

In the first step glucose-6-phosphate is oxidized into ribulose-5-phosphate, CO_2. During the oxidation of glucose-6-phosphate $NADP^+$ is reduced into NADPH.

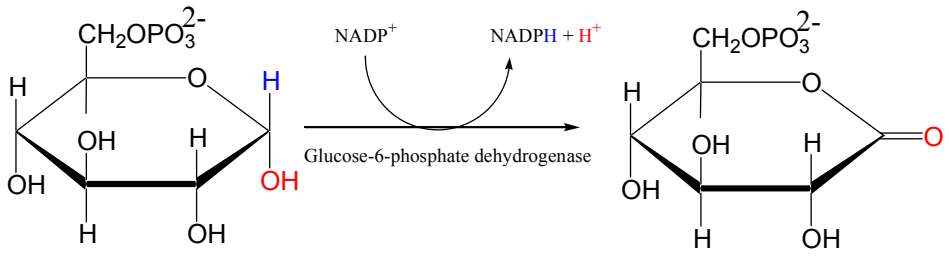
The second step of the pathway coverts the ribulose 5-phosphate into other pentose-5-phosphates including ribose-5-phosphate used to synthesize nucleic acids.

The third step includes a series of reactions that convert three of the pentose-5-phosphates into two molecules of hexoses and one triose.

In the fourth step, some of these sugars are converted into glucose-6-phosphate so the cycle can be be repeated. The direction of the pathway varies to meet different metabolic conditions.

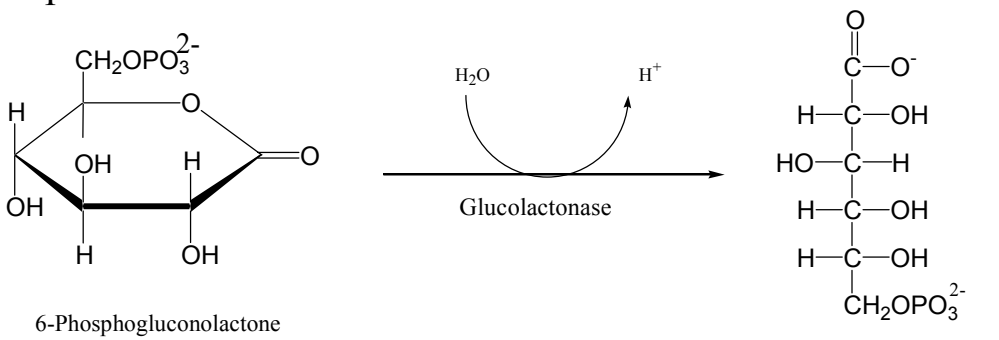
Oxidative Phase: The oxidative phase of the pentose phosphate pathway is composed of three steps.

Step 1



6-Phosphogluconolactone

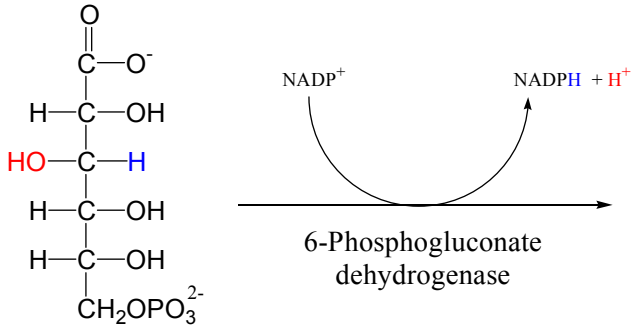
Step 2:



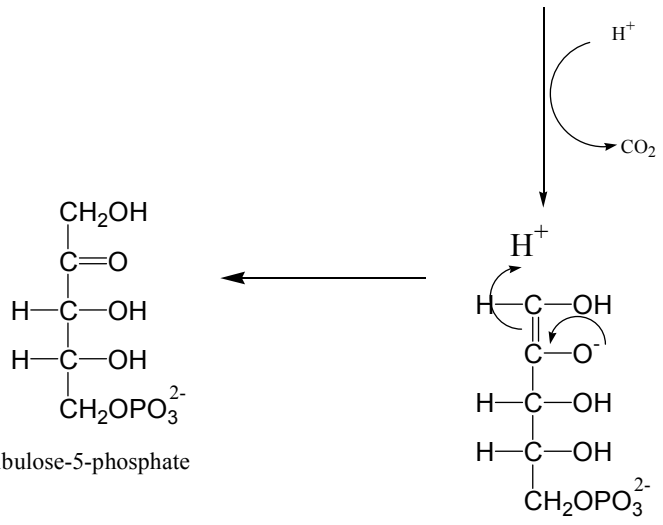
6-Phosphogluconolactone

6-Phosphogluconate

Step 3



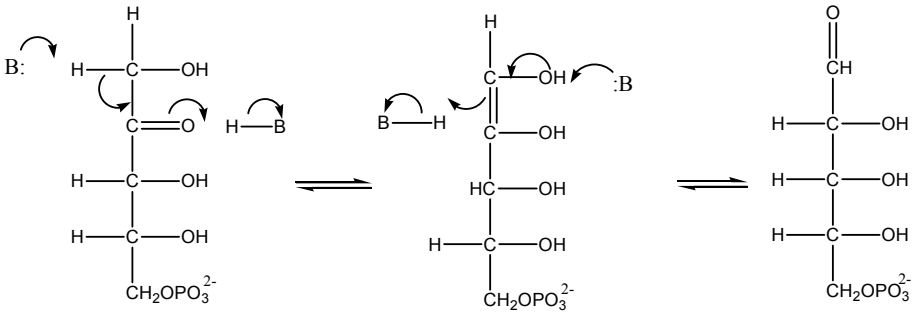
6-Phosphogluconate



Ribulose-5-phosphate

Nonoxidative Phase: The nonoxidative phase of the pentose phosphate pathway is composed of 5 steps but only 4 types of reactions.

Step 4: Phosphopentose isomerase

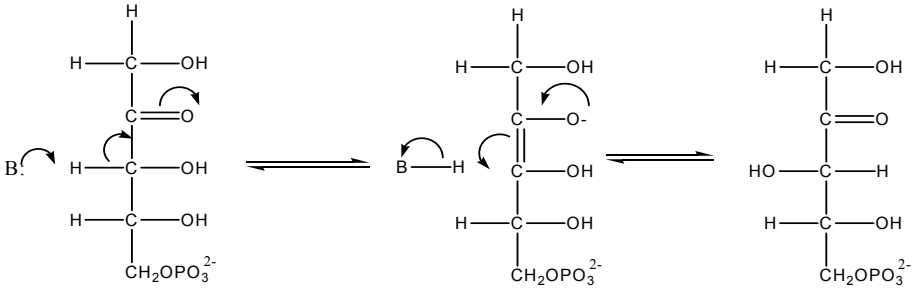


Ribulose-5-phosphate | Enediol intermediate | Ribose-5-phosphate

Net reaction to this point.

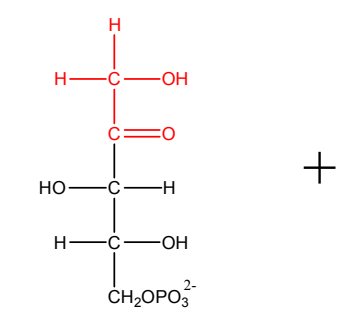
Glucose-6-phosphate + $2NADP^+$ → ribose-5-phosphate + CO_2 + 2NADPH + $2H^+$

Step 5: Phosphopentose Epimerase

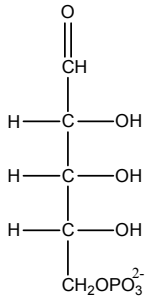


Ribulose-5-phosphate | Enediolate intermediate | Xylulose-5-phosphate

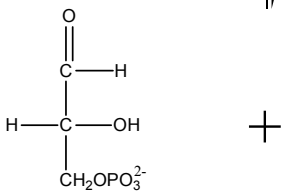
Step 6: Transketolase



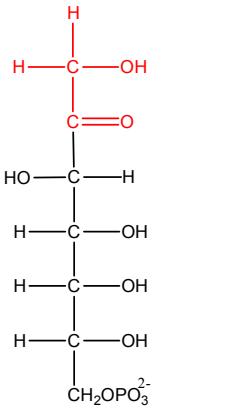
Xylulose-5-phosphate



Ribose-5-phosphate



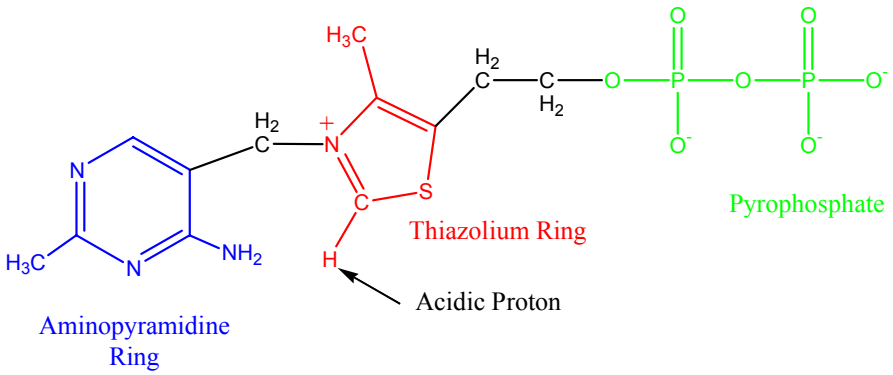
Glyceraldehyde-3-phosphate

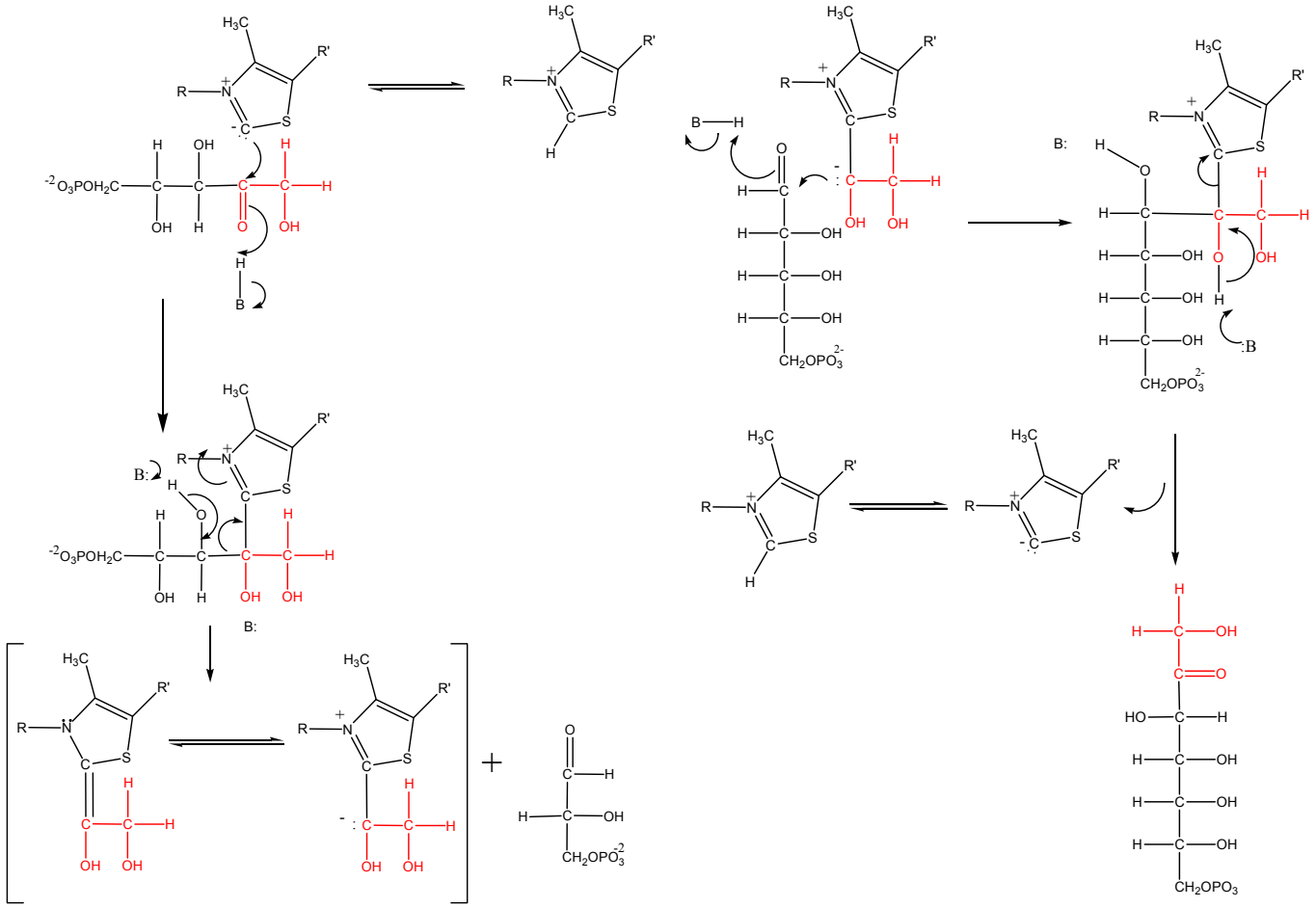


Sedoheptulose-7-phosphate

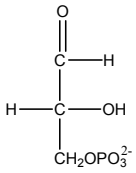
Transketolase: Requires thiamine pyrophosphate as a cofactor.

Thiamine pyrophosphate

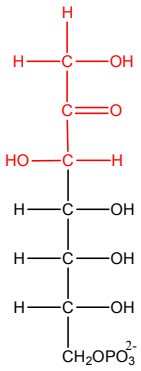




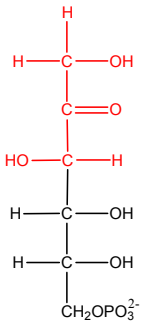
Step 7: TRANSALDOLASE



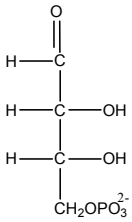
Glyceraldehyde-3-phosphate



Sedoheptulose-7-phosphate

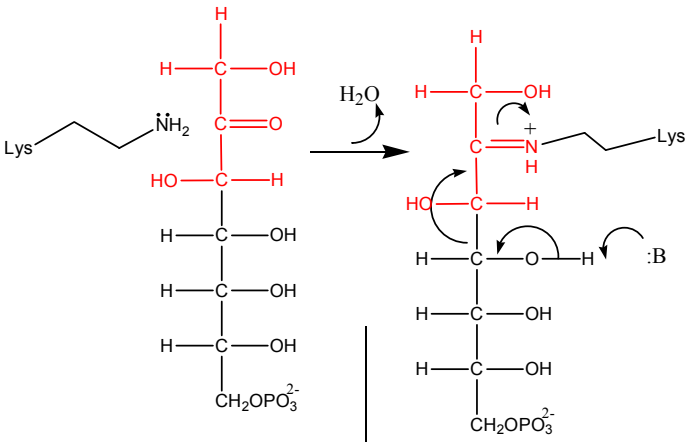


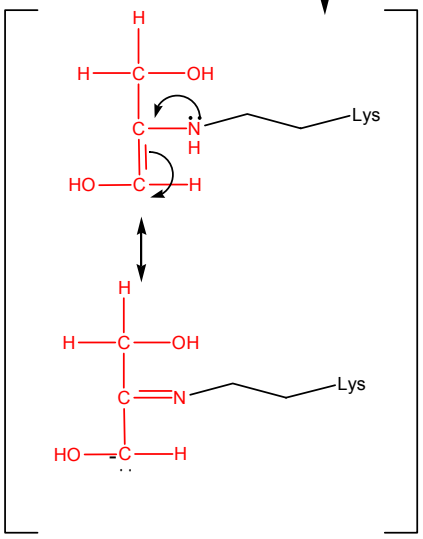
Fructose-6P

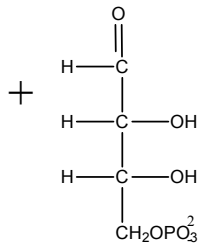


erythrose-4P

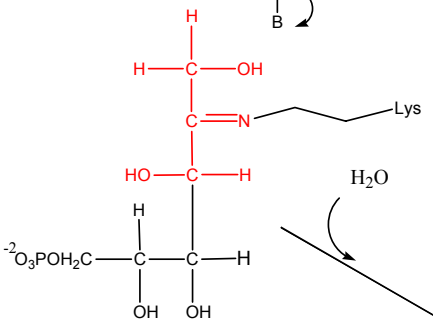
Transaldolase involves Shiff base formation:

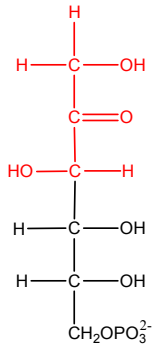






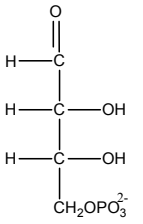
Erythrose-4P



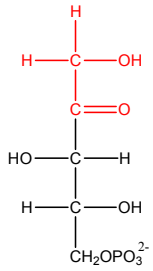


Fructose-6P

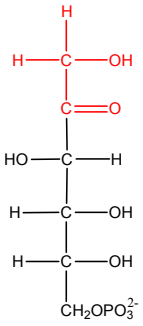
Step 8: Another job for transketolase



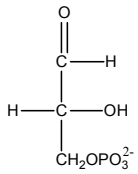
erythrose-4P



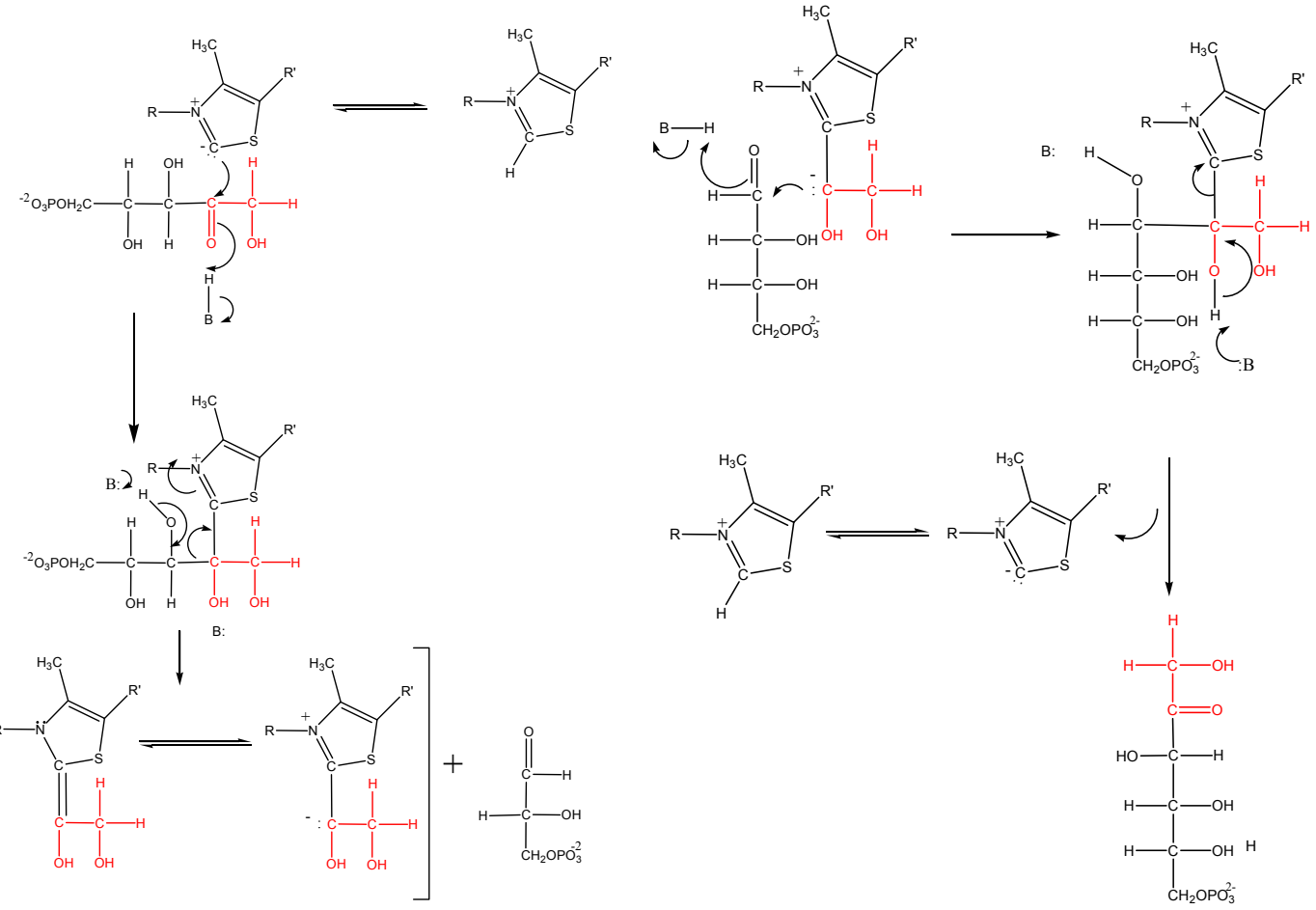
Xylulose-5-phosphate



Fructose-6P



Glyceraldehyde-3-phosphate



Putting it all together.
Oxidative phase:

$3\text{Glucose-6-phosphate} + 6NADP^+ \rightarrow 2\ \text{Xylulose-5p} + \text{ribose-5P} + 3CO_2 + 6NADPH + 6H^+$

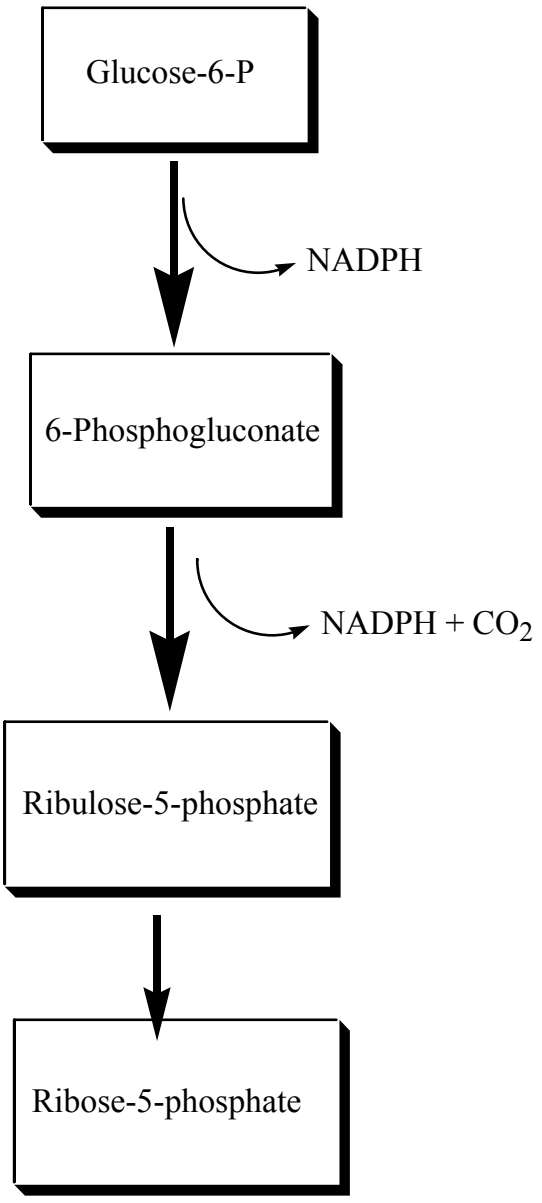
Rearrangements of the nonoxidative phase:

$2\ \text{Xylulose-5P} + \text{ribose-5P} \rightarrow 2\ \text{Frucose-6P} + \text{Glyceraldehyde-3P}$

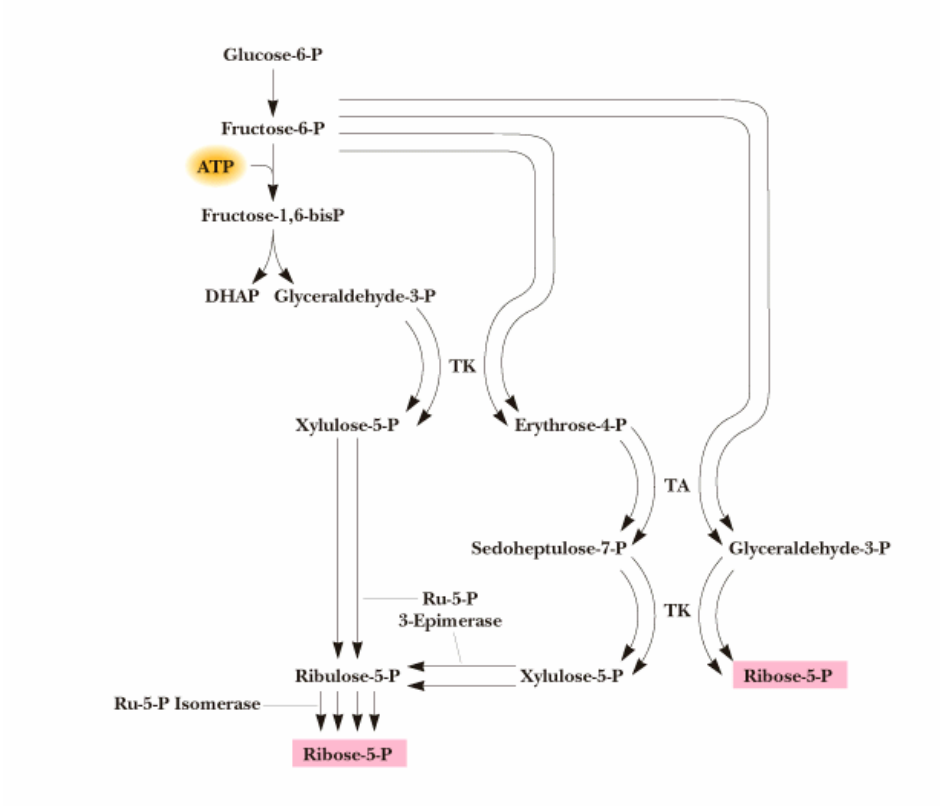
The sum of these two phases:
$3\text{Glucose-6-phosphate} + 6NADP^+ \rightarrow 2\ \text{Frucose-6P} + \text{Glyceraldehyde-3P} + 3CO_2 + 6NADPH + 6H^+$

Tailoring the pentose phosphate pathway to meet specific needs of the cell.
1.) If the cell requires both ribose-5-P and NADPH

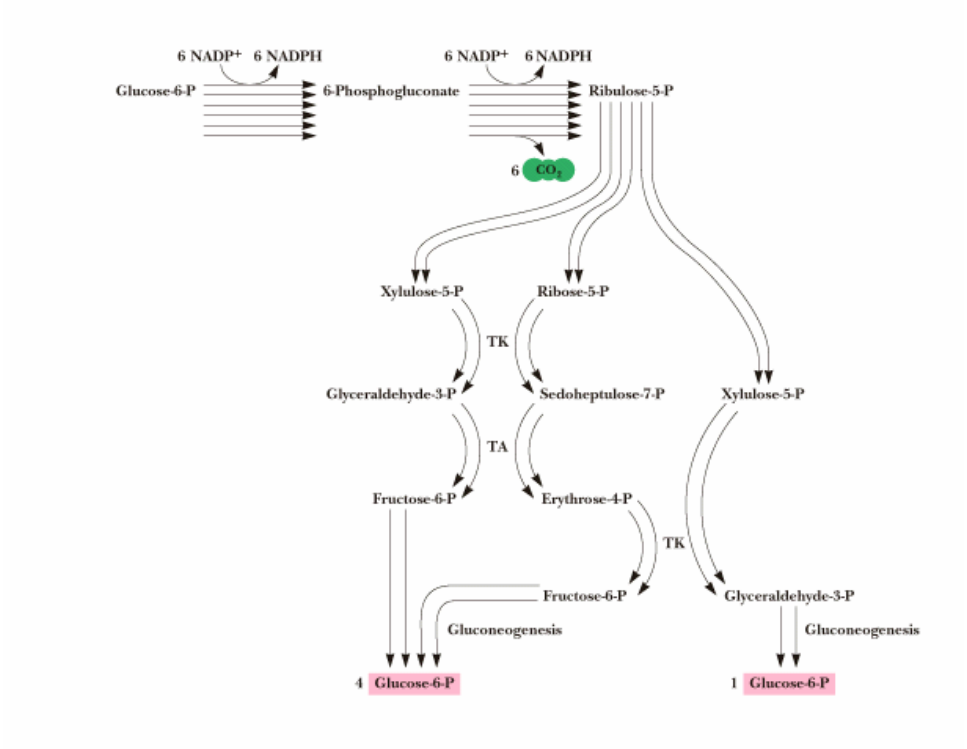
Both NADPH and Ribose-5P needed.



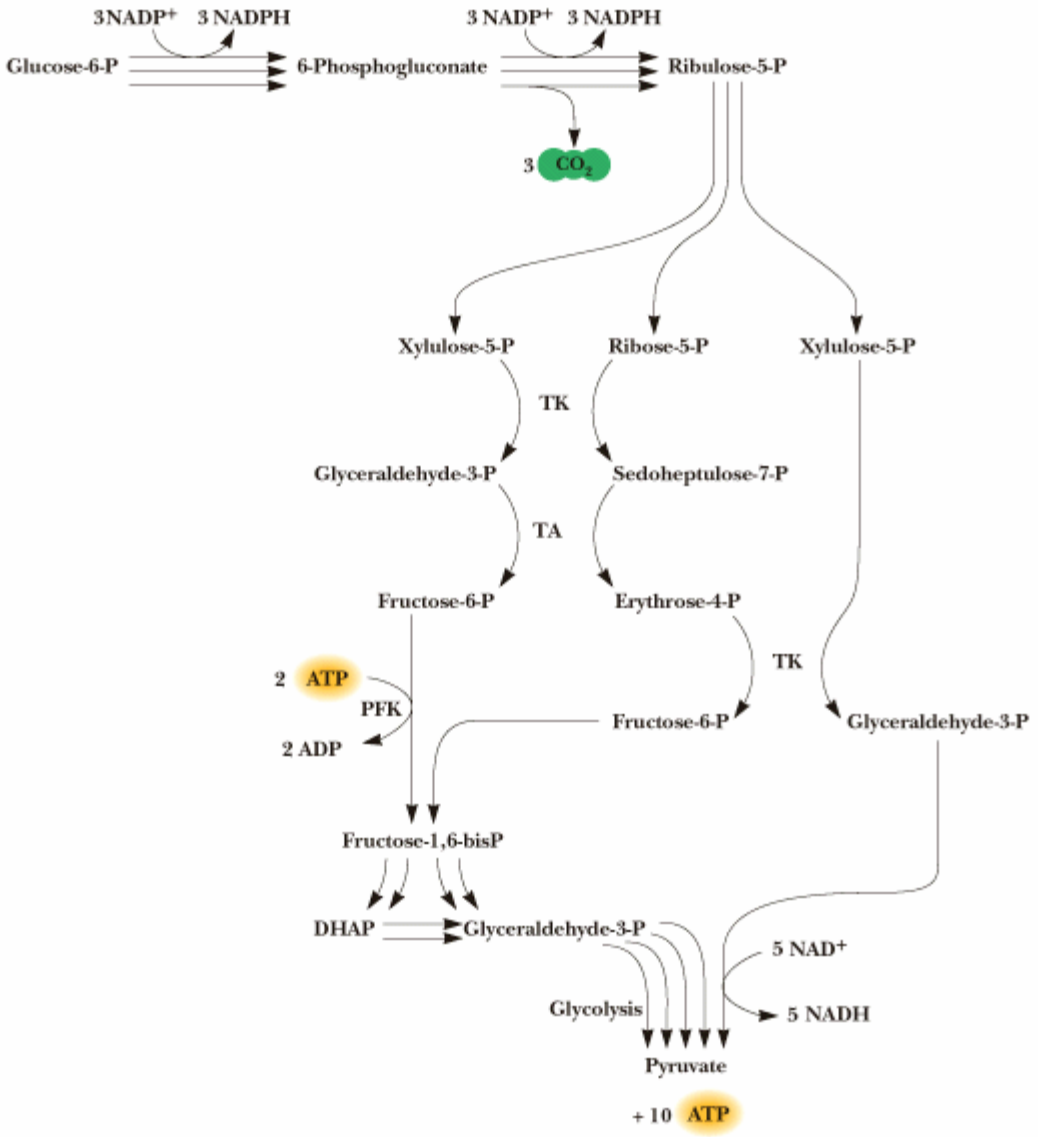
2.) More ribose-5 phosphate needed than NADPH.



3.) More NADPH needed than Ribose-5-phosphate.



4.) Both NADPH and ATP are needed but not ribose-5-phosphate.



Regulation

The first step of the phosphopentose pathway is the irreversible committed step. This reaction is catalyzed by glucose-6-phosphate dehydrogenase. This step is of course allosterically regulated. The product of this reaction NADPH is a strong inhibitor. So when the cytosol concentration of NADPH is high, the enzyme's activity is low. It is also allosterically regulated by fatty acid acyl esters of coenzyme A. The transcription of the gene for this enzyme is under hormonal regulation.