

LECTURE 5 - Pentose Phosphate Pathway

Monday, April 21, 2008
9:41 AM

Metabolism Lecture 5 — PENTOSE PHOSPHATE PATHWAY — Restricted for students enrolled in MCB102, UC Berkeley, Spring 2008 ONLY

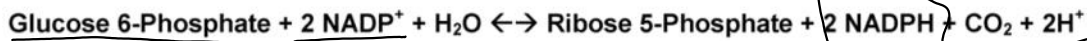
Bryan Krantz: University of California, Berkeley
MCB 102, Spring 2008, Metabolism Lecture 5

Reading: Ch. 14 of *Principles of Biochemistry*, "Glycolysis, Gluconeogenesis, & Pentose Phosphate Pathway."

PENTOSE PHOSPHATE PATHWAY

This pathway produces ribose from glucose, and it also generates 2 NADPH.

Two Phases: [1] Oxidative Phase & [2] Non-oxidative Phase



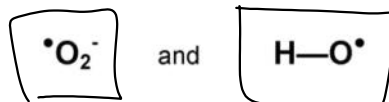
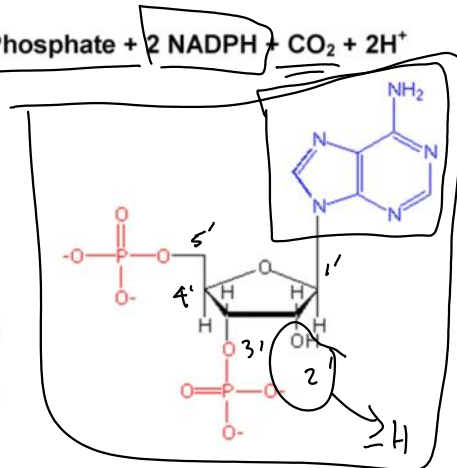
• What are pentoses? Why do we need them?

◦ DNA & RNA

◦ Cofactors in enzymes

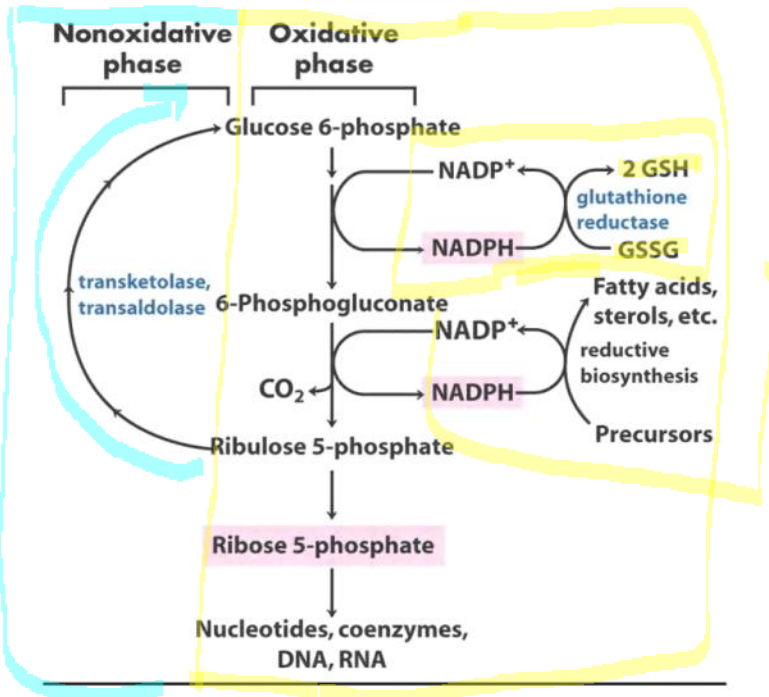
• Where do we get them? Diet and from glucose (and other sugars) via the Pentose Phosphate Pathway.

• Is the Pentose Phosphate Pathway just about making ribose sugars from glucose? (1) Important for biosynthetic pathways using NADPH, and (2) a high cytosolic reducing potential from NADPH is sometimes required to avert oxidative damage by radicals, e.g.,

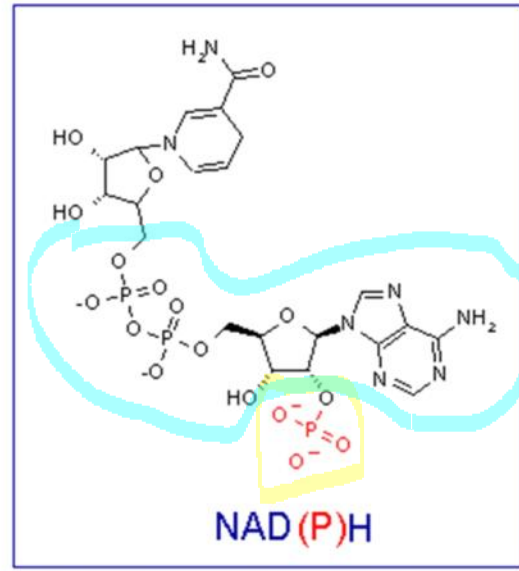


deoxy-
ribose

Two Phases of the Pentose Phosphate Pathway



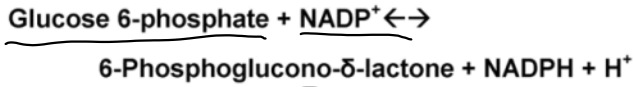
NADPH vs. NADH



PART OF
ATP

Oxidative Phase: Glucose-6-P → Ribose-5-P

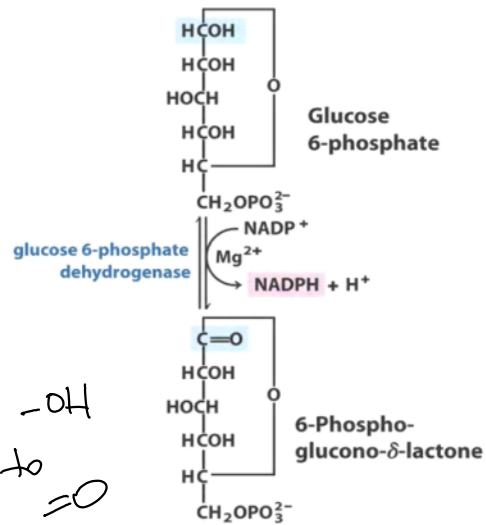
Glucose 6-phosphate dehydrogenase. First enzymatic step in oxidative phase, converting NADP^+ to NADPH.



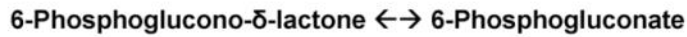
Mechanism. Oxidation reaction of C1 position. Hydride transfer to the NADP^+ , forming a **lactone**, which is an intra-molecular ester.

oxidizing -OH to =O

Energetics. Very favorable reaction in the forward direction for producing NADPH.

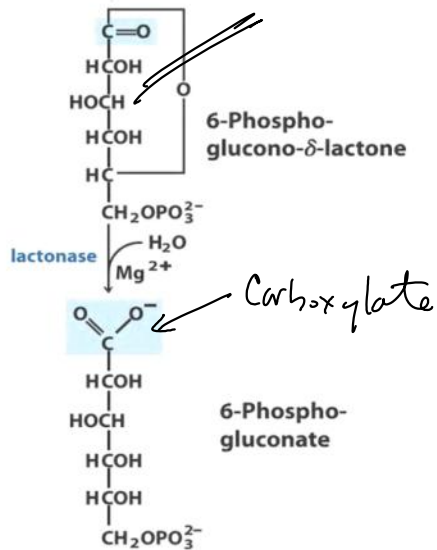


Lactonase. A specific enzyme that targets 6-Phosphoglucono- δ -lactone for hydrolysis.



Mechanism. The lactone is opened by **hydrolysis**, the addition of water to cleave a bond, usually a type of amide or ester. In this case, since the lactone (by definition) is intramolecular, then 6-phosphoglucono- δ -lactone is opened up to the acid form, gluconate.

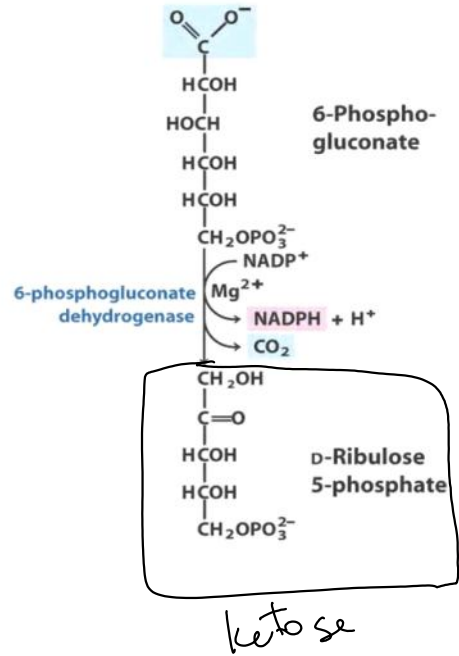
Energetics. Often these types of hydrolysis reactions are very favorable.



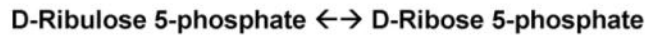
6-Phosphogluconate dehydrogenase. Performs oxidative decarboxylation converting the 6-carbon skeleton to a pentose.



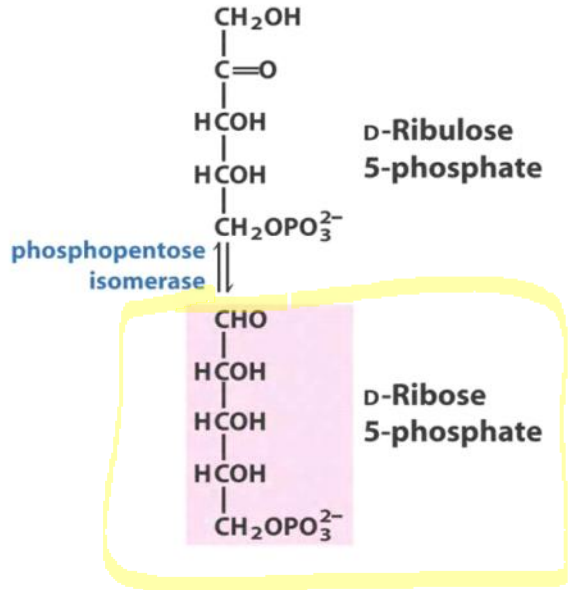
Mechanism. The C1 carboxylate is removed as the C3 position is oxidized to a ketone, making 5-carbon ketose, ribulose.



Phosphopentose Isomerase.



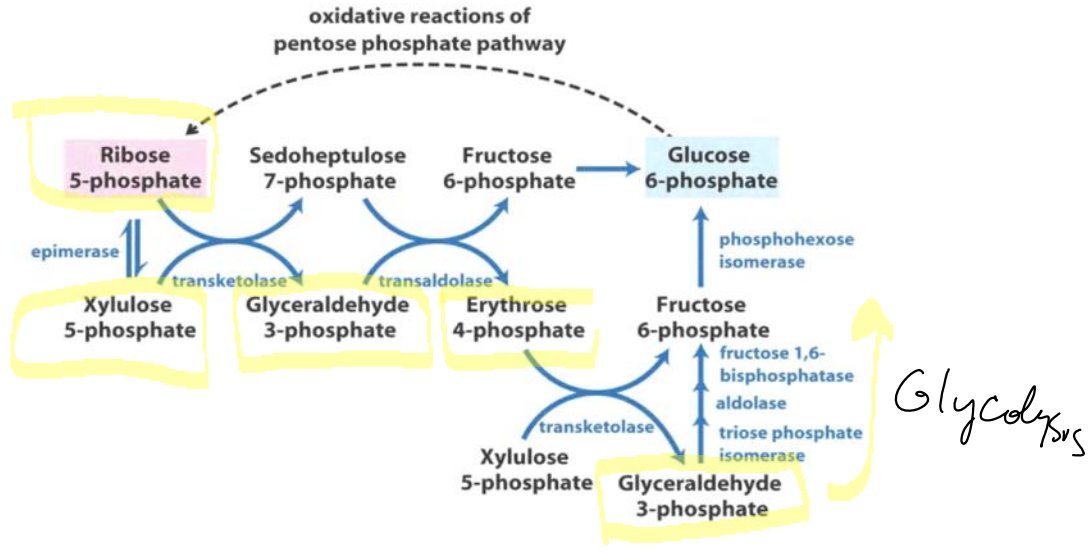
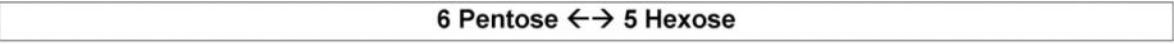
Mechanism. Typical ketose to aldose conversion. Another example of a **general acid base catalyzed reaction.**



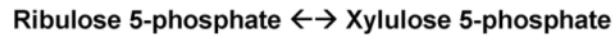
Non-oxidative Phase: Recycling Pentose Phosphates to Glucose 6-Phosphate

What if the cell needs much more NADPH than it needs pentose? D-ribose 5-phosphate has to be converted back to glucose 6-phosphate in multiple enzyme catalyzed steps.

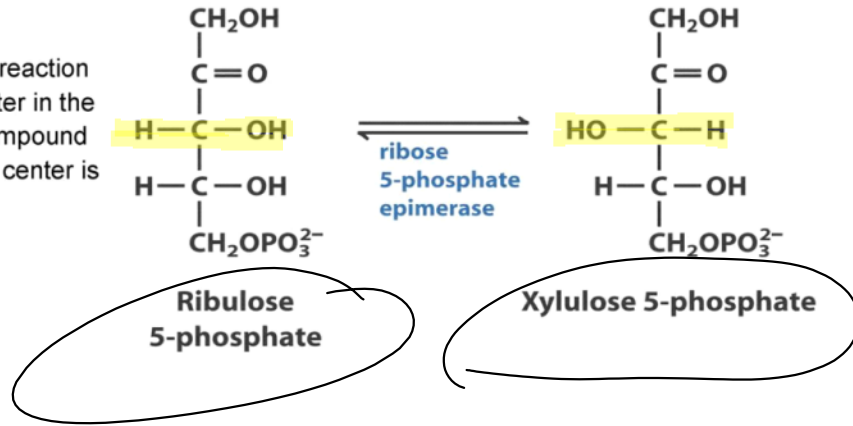
The recycling of 5-carbon skeletons as expected for the stoichiometry below is complex:



Ribulose 5-Phosphate Epimerase.



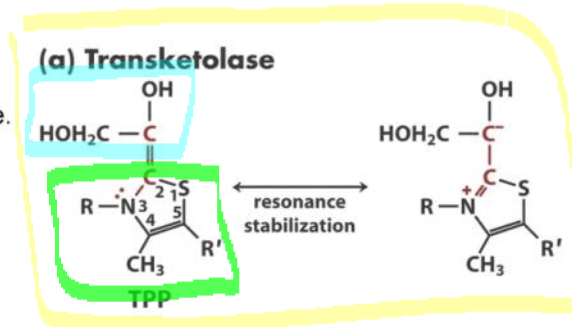
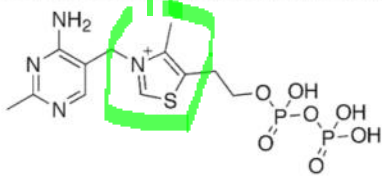
Mechanism. Epimerization reaction is the flipping of a stereo center in the substrate. An epimer of a compound occurs when only *one* stereo center is flipped.



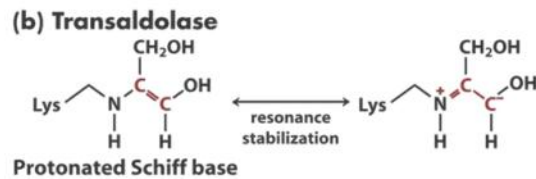
Transketolase & Transaldolase

A myriad of steps are required to transform pentoses back to glucose, but besides the epimerase, only two other *new* enzymes are needed: **[1] transketolase** and **[2] transaldolase**.

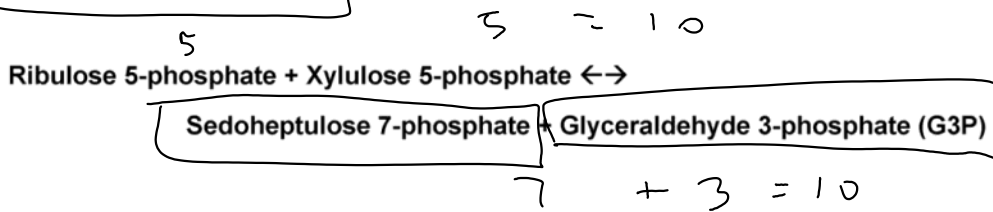
Transketolase. This enzyme uses a cofactor, called **thiamine pyrophosphate (TPP)**. TPP is used to stabilize a 2-carbon carbanion intermediate.



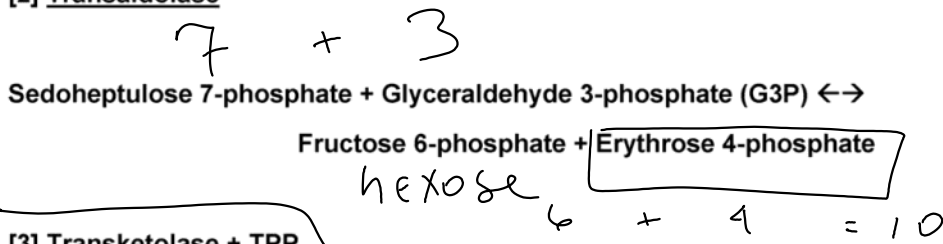
Transaldolase. This enzyme forms a **protonated Schiff base intermediate** with a **ketose**, stabilizing a 3-carbon **carbanion** intermediate, allowing an aldehyde based sugar to react with the enzyme-linked ketose. The mechanism is similar to aldolase.



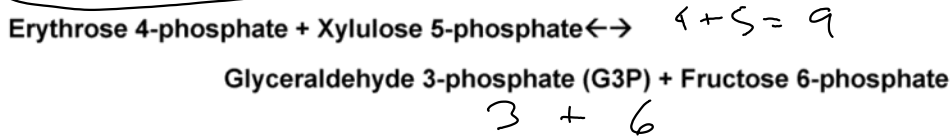
[1] Transketolase + TPP



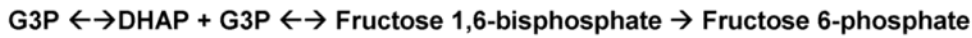
[2] Transaldolase



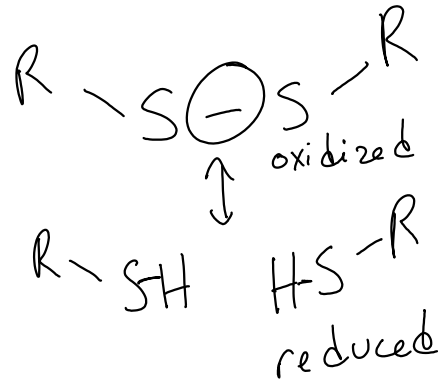
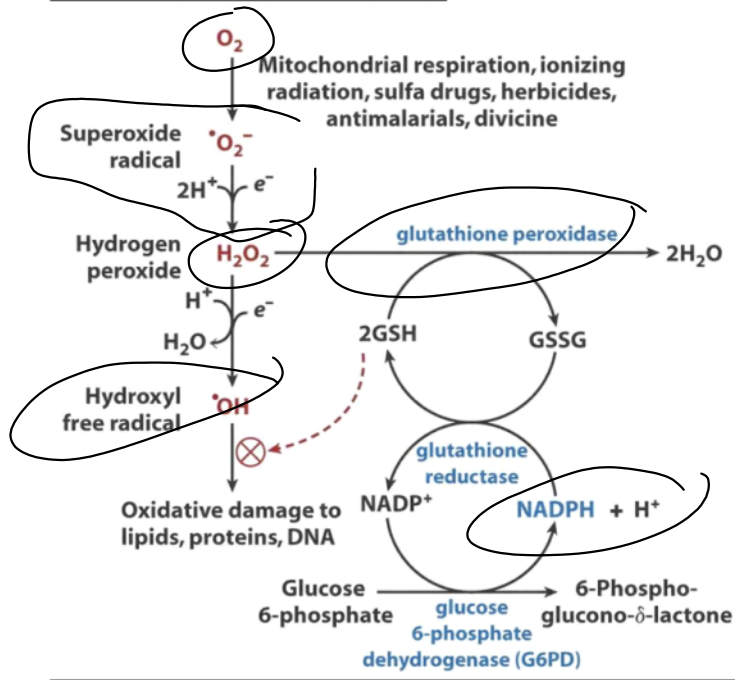
[3] Transketolase + TPP



[4] Reversal of Glycolysis



Protection from Radical Damage



Regulation of the Pentose Phosphate Pathway.

How is this pentose phosphate pathway regulated? NADPH which is generated in the oxidative branch of the pathway can feed back and inhibit the pathway. Glucose 6-phosphate can still be utilized by glycolysis.

