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Biochemistry 2

Doctor 2018 | Medicine | JU

carbohydrates isomers ketone starch lipid protein amine

◉ Sheet ○ Slides

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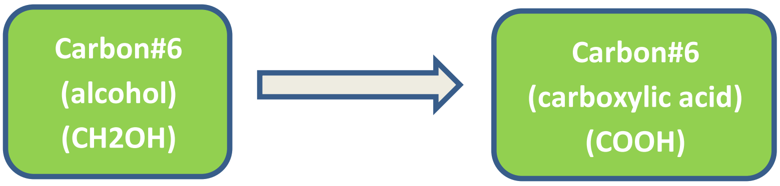
In the last lecture we talked about the metabolism of monosaccharides, now we are going to talk about glucuronic acid, gluconic acid and the pentose phosphate pathway (PPP).

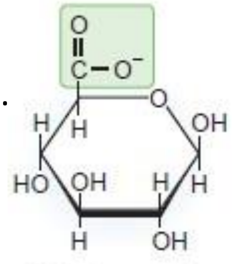
What is glucuronic acid? How is it formed?

Glucuronic acid is a sugar acid derived from glucose, with its sixth carbon atom oxidized to a carboxyl group.

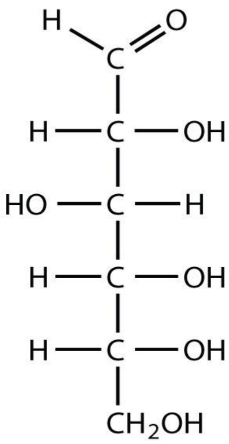


Note:

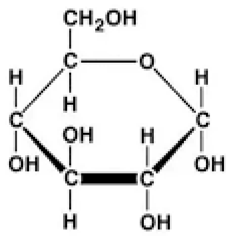
- ✓ **Glucuronate** is the ionized form of glucuronic acid (unprotonated).



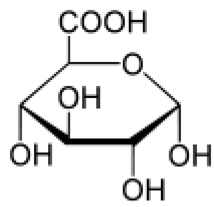
β-D-glucuronate



D-glucose



α-D-glucose



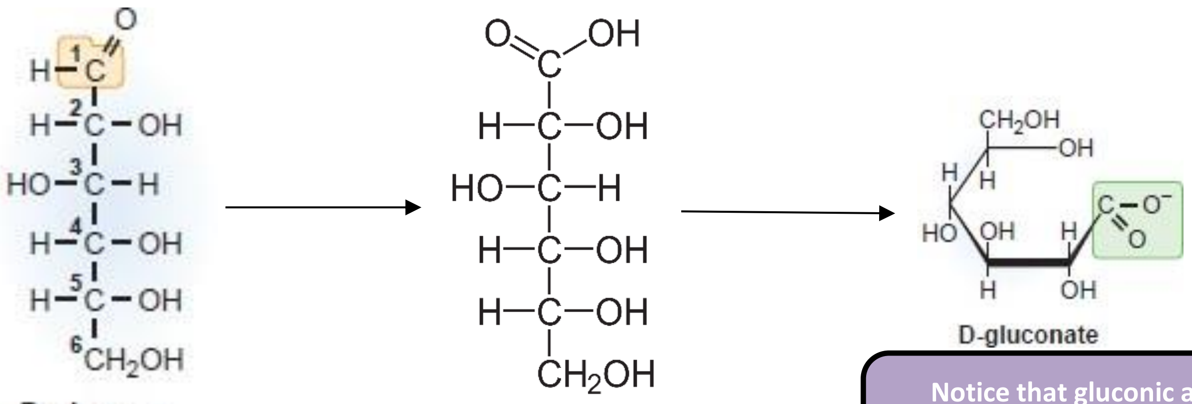
α-D-glucuronic acid

Note:

- ✓ The conversion of glucose from its open chain form into its cyclic form results from the reaction of carbon#1(aldehyde group) with the hydroxyl group on carbon#5 which forms hemiacetal.
- ✓ This reaction is a spontaneous reaction that doesn't require a catalyst and is reversible.

What is gluconic acid? How is it formed?

Gluconic Acid is the carboxylic acid formed by the oxidation of the first carbon of glucose.



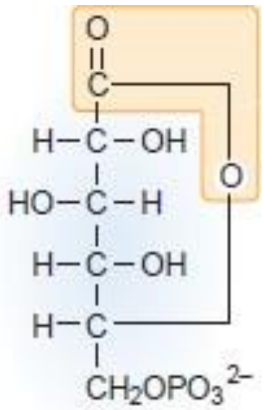
Notice that gluconic acid (gluconate) can't form a ring structure.

Note:

Gluconate is the ionized form of gluconic acid (unprotonated).

When it’s protonated it becomes Gluconic acid.

Gluconic acid cannot exist in a hemiacetal ring form but can form a cyclic structure by forming an intramolecular ester linkage between the carboxyl group on carbon #1 and the hydroxyl group on carbon #5 within the same molecule. This type of cyclic ester is known as a lactone.



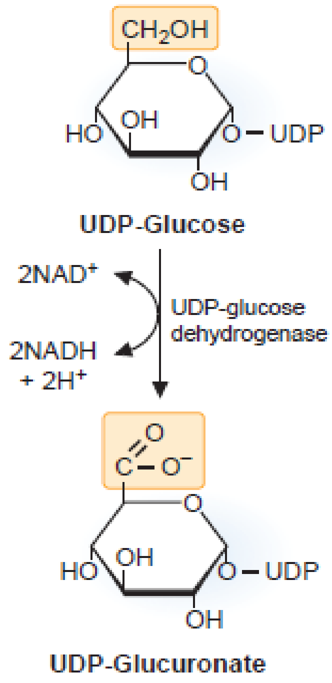
6-Phosphoglucono-δ-lactone

Note:

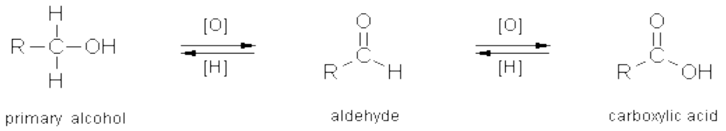
- ✓ Each carbon in the molecule has a name according to its location in regard to the alpha carbon.
- ✓ The first carbon atom that attaches to a functional group is the alpha carbon, the carbon atom next to the α carbon is the beta carbon and so on.
- ✓ In this case the carboxyl group on carbon #1 reacts with the hydroxyl group on carbon #5(delta) forming an ester bond.
- ✓ This forms a delta lactone.
- ✓ In the structure on the left, a phosphate group is present on carbon #6, hence the name 6-Phosphoglucono- δ-lactone.

Formation and uses of glucoronate:

- **Formation :**

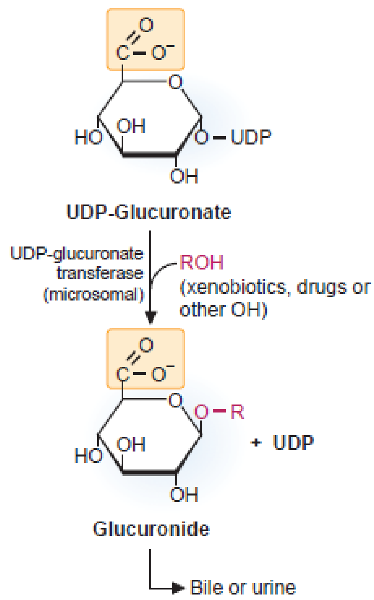


- ➢ Glucose is converted into glucuronate when it's part of UDP-Glucose.
- ➢ Glucose is converted into glucuronate by the oxidation of the alcohol group on carbon #6 into a carboxyl group.
- ➢ Two oxidation steps are involved (since the alcohol group on carbon #6 is a primary alcohol group).



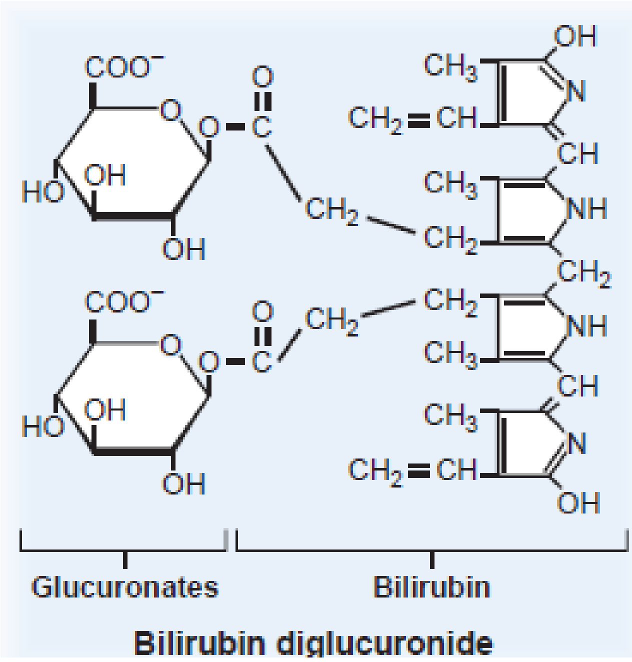
- ➢ The enzyme that catalyzes this reaction is called **UDP-glucose dehydrogenase.**
- ➢ Since two oxidation steps are involved, two NADH molecules are produced.
- ➢ Glucuronate is very soluble in water since it has multiple hydroxyl groups in addition to a negative charge.

- **Function(use) of glucuronate:**



- ➢ Glucuronate can be transferred to many insoluble substances making them soluble in water.
- ➢ This is important in the metabolism of water-insoluble drugs by the liver.
- ➢ **UDP-Glucuronate transferase** catalyzes the transfer of glucuronate from UDP-glucuronate to hydrophobic molecules.
- ➢ The substance produced by linking glucuronate to the hydrophobic molecule is called Glucuronide, which can be excreted by urine or bile.

An important example of the function of Glucuronate is the formation of bilirubin diglucuronide.



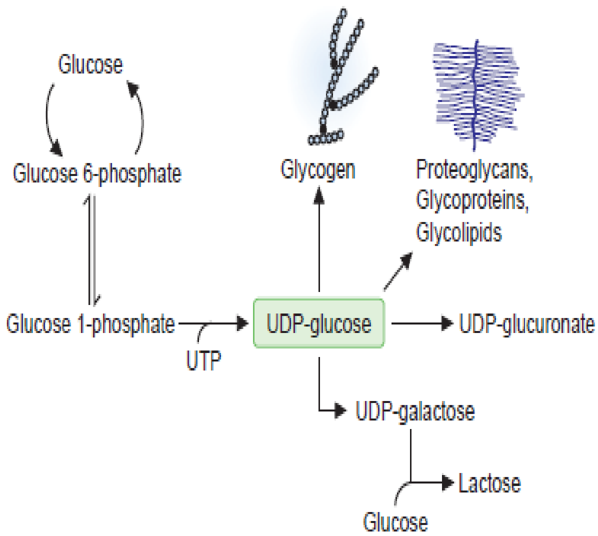
- ✓ **Bilirubin** is a compound obtained from the degradation of Heme.
- ✓ Bilirubin consists of an open chain tetrapyrrole formed by the cleavage of the cyclic structure of heme.
- ✓ It's mostly insoluble (since it contains an insoluble tetrapyrrole chain) although it has two polar propionic acid side-chains (they aren't sufficient to make it soluble).
- ✓ Once bilirubin is produced in the blood, it gets carried to the liver in order to be excreted.
- ✓ In the liver, bilirubin (insoluble) binds to two Glucuronic acid molecules forming bilirubin diglucuronide (soluble) which can be excreted through bile.
- ✓ The binding occurs between carbon #1 in glucuronic acid and the two propionic acid side-chains of bilirubin as shown in the figure above.
- ✓ High level of bilirubin can be very harmful.

Example mentioned by the doctor:

The majority of newborn infants in their first postnatal week have a yellowish colored skin (**Jaundice**) due to the increased level of bilirubin in their body, that is mainly because their liver isn't mature enough to remove bilirubin by conjugating it with glucuronic acid.

- UDP-glucose has many functions:

1. Glycogen synthesis
2. Formation of Lactose by exchanging glucose with galactose
3. Formation of UDP-glucuronate
4. Formation of large molecules that require carbohydrates
   e.g. Proteoglycans, Glycoproteins, Glycolipids



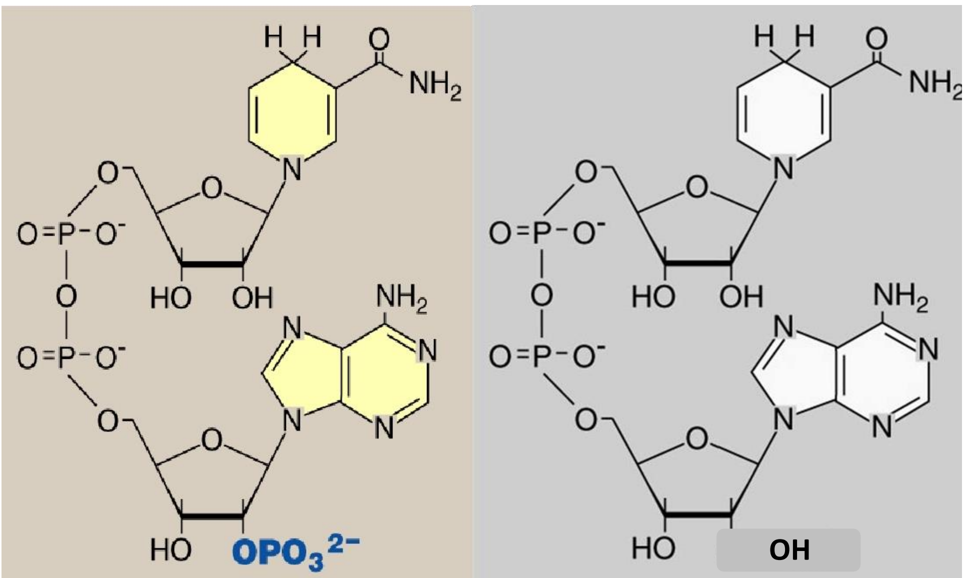
Pentose Phosphate Pathway (Hexose Monophosphate Shunt)

- There are two main functions of the pentose phosphate pathway:
    1. The production of **NADPH**.
    2. Metabolism of five-carbon sugars (Pentoses).
        - Ribose 5-phosphate (nucleotide biosynthesis)
        - Metabolism of pentoses

So far, we have learnt a lot about NADH, from the reactions that produce NADH to the oxidation of NADH by the oxidative phosphorylation process to produce energy.

Well, what about NADPH? How does it differ from NADH?

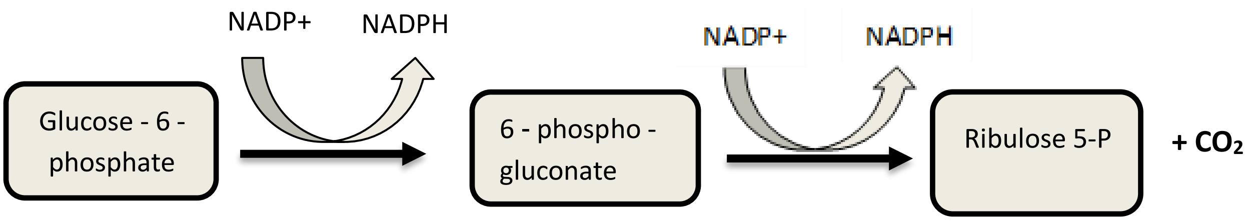
- ✓ Obviously, they differ by the presence of an additional phosphate group on one of the ribose units in NADPH.
- ✓ Though, they both have the same reduction potential.
- ✓ NADPH has many important distinct functions :
    1. NADPH dependent biosynthesis of fatty acids
- Liver, lactating mammary glands, adipose tissue
    2. NADPH dependent biosynthesis of steroid hormones
- Testes, ovaries, placenta, and adrenal cortex
    3. Maintenance of Glutathione (GSH) in the reduced form in the RBCs

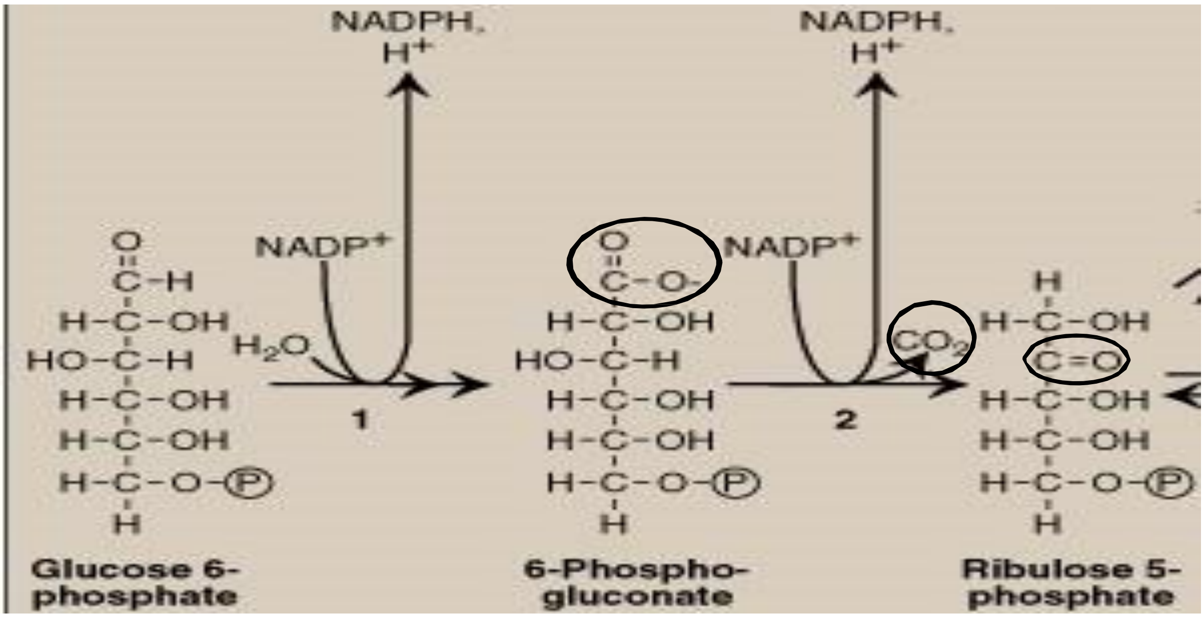


The pentose phosphate pathway includes two phases:

1) The Oxidative Phase (irreversible): two irreversible oxidative reactions (oxidation-reduction reactions).
2) The Non-Oxidative Phase (reversible).

- **The oxidative phase ((Irreversible)) :**





First reaction: the oxidation of **glucose – 6 – phosphate** into **6 – Phospho – gluconate (gluconic acid)** with the production of **1 NADPH** molecule.

- This reaction is the rate-limiting reaction and it is regulated.
- **Catalyzed by G6PD: Glucose-6 Phosphate Dehydrogenase**

Second reaction: oxidation of **6 – Phospho – gluconate** with **decarboxylation** to produce **Ribulose 5 – phosphate (ketone)**, **1 NADPH** and a **CO_2** molecule.

Oxidative decarboxylation reaction:

- Oxidation of carbon #3 into a ketone group.
- Decarboxylation of carbon #1 as a CO_2 molecule.
- **Catalyzed by 6-PGD: 6-phosphogluconate Dehydrogenase**

Net Reaction:

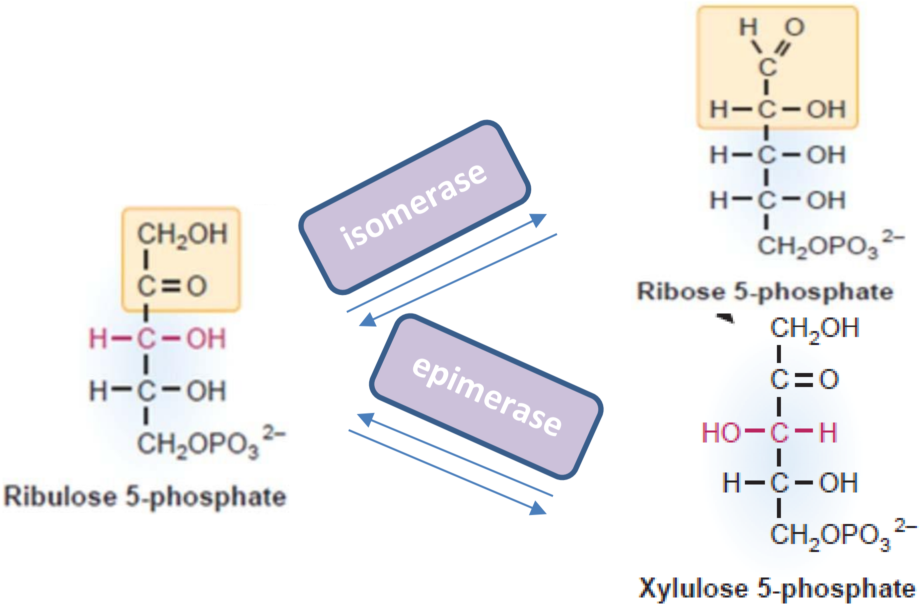
Glc.6 Phosphate + 2 $NADP^+$ ⟶ Ribulose 5-Phosphate + CO2 + 2 NADPH

Extra note: Glucose 6-phosphate dehydrogenase (G6PD) catalyzes an irreversible oxidation of glucose 6-phosphate to 6-phosphogluconolactone which is then hydrolyzed by 6-phosphogluconolactone hydrolase into 6-phosphogluconate. (The oxidative portion of the pentose phosphate pathway consists of three reactions two of which are irrevirsble oxidative reactions)

- **The non-oxidative phase (Reversible) :**

After production of Ribulose 5-Phosphate, the reversible reactions of the second phase permit **Ribulose 5-phosphate** (produced by the oxidative portion of the pathway) to be **converted either to:**

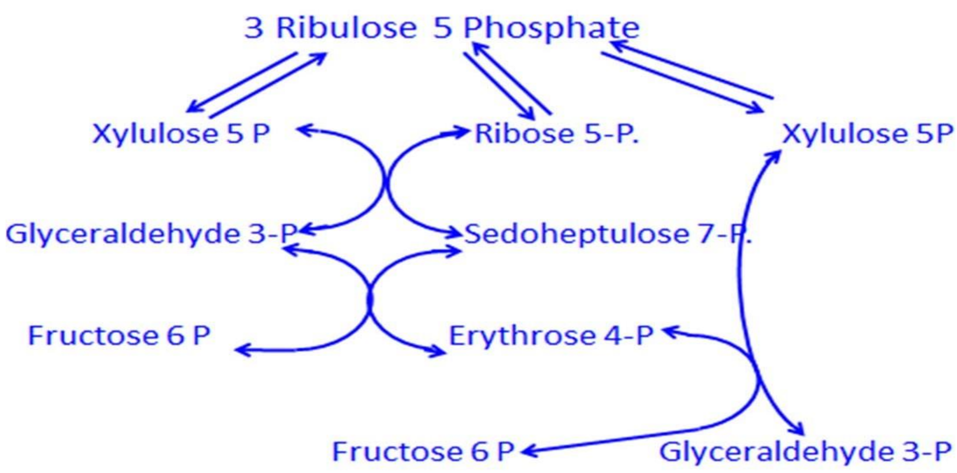
- **Ribose 5-phosphate** (needed for nucleotide (DNA, RNA) synthesis)
- Or to **Xylulose 5-phosphate** to produce intermediates of glycolysis (fructose 6-phosphate and glyceraldehyde 3-phosphate)



Looking at the structure of Ribose 5-p and Ribulose 5-p we notice that they are isomers thus the enzyme catalyzing the conversion of ribulose 5-p to ribose 5-p is called **isomerase.**

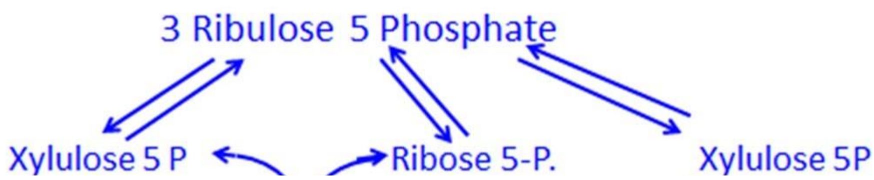
Looking at the structure of Ribulose 5-p and Xylulose 5-p we notice that they are epimers at carbon #3 thus the enzyme catalyzing the conversion of ribulose 5-p to Xylulose 5-p is called **epimerase.**

The Non-oxidative Phase (reversible)



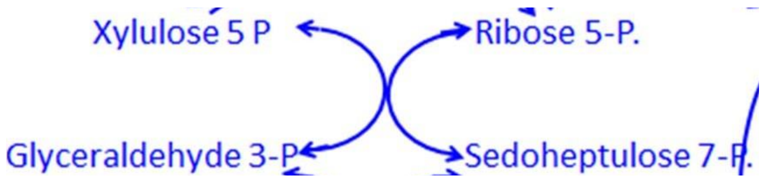
Steps:

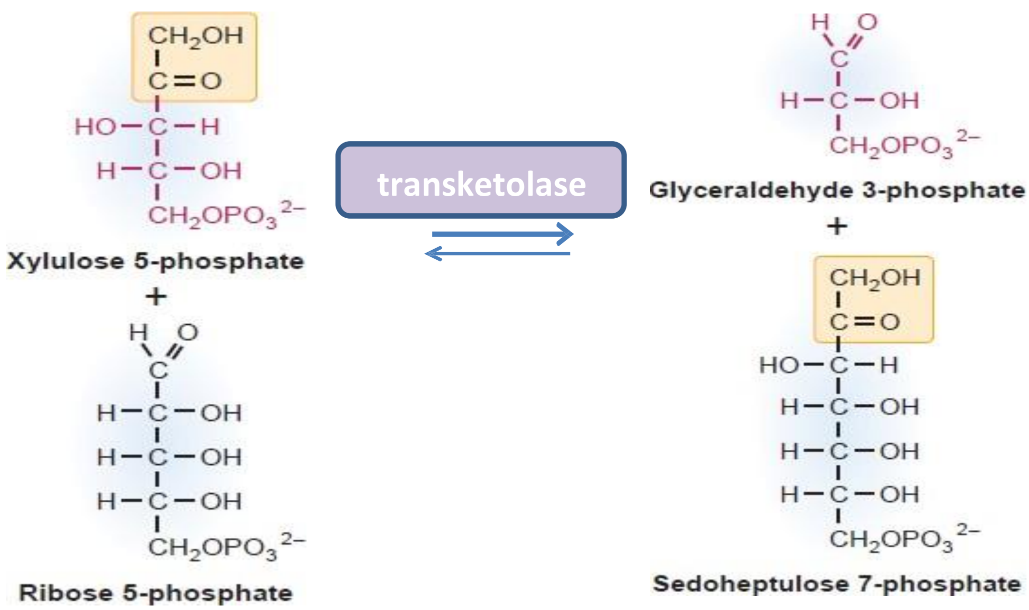
1) The non-oxidative phase stars with **three** ribulose 5-phosphate molecules , **two** are converted into Xylulose 5-P and **one** is converted to Ribose 5-P.



2) One of the two **Xylulose 5-P** (pentose, ketose) molecules donates **two carbons** to **Ribose 5-P** (aldose) which results in the formation of :

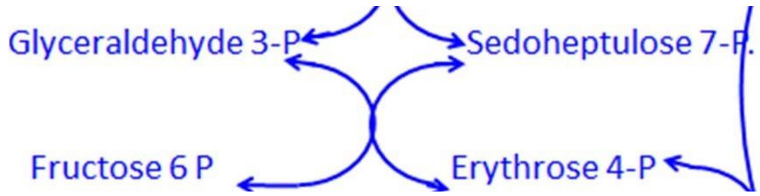
- Glyceraldehyde 3-P (triose)
- Sedoheptulose 7-P (heptose)

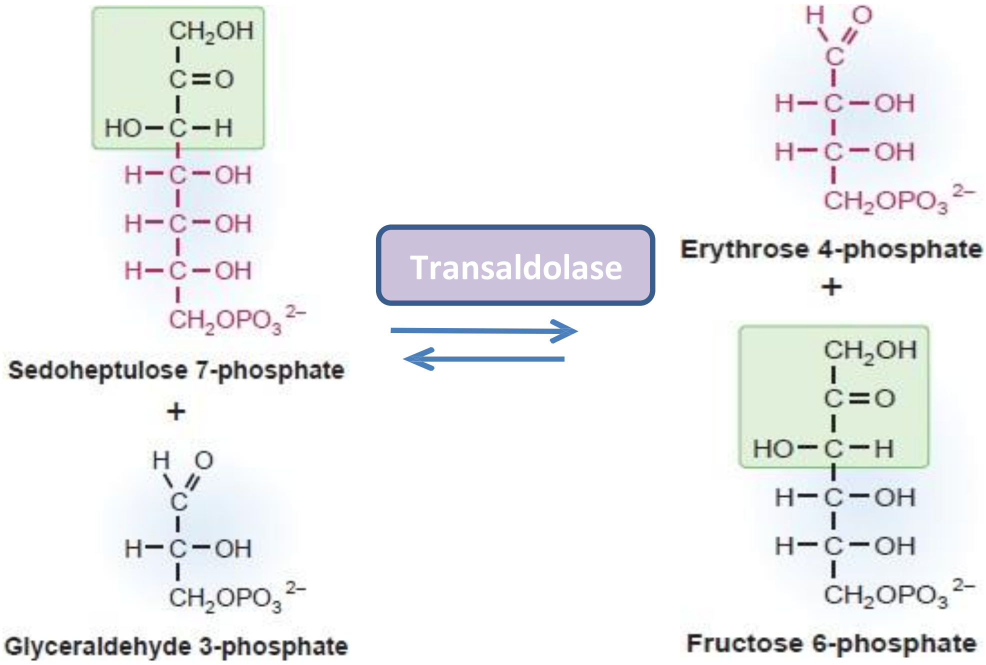




3) **Sedoheptulose 7-P** (ketose) donates **3 carbons** to **Glyceraldehyde 3-P** (aldose) which results in the formation of:

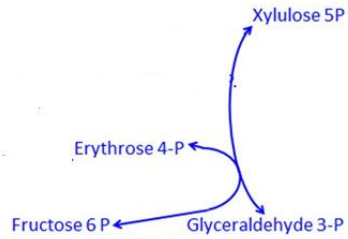
- Fructose 6-P (hexose)
- Erythrose 4-P (tetrose)

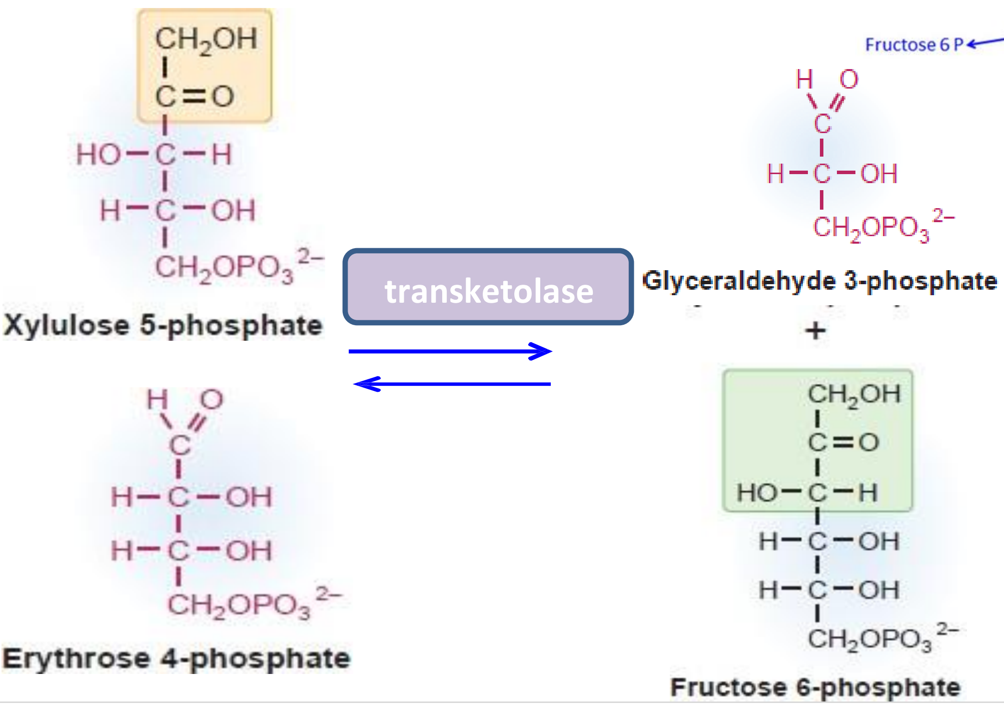




4) The second **Xylulose 5-P** (ketose) molecule donates **two carbons** to **Erythrose 4-P** (aldose) which results in the formation of :

- Fructose 6-P
- Glyceraldehyde 3-P





Summary of the non-oxidative reactions:

- All of the previous reactions are reversible reactions.
- All of the previous reactions include transfer of a 2 or 3 carbon fragment from ketose (donor) to aldose (acceptor).
- Ketose + aldose $\rightleftharpoons$ ketose + aldose
- The reactions that involve a transfer of a 2-carbon fragment are catalyzed by **Transketolase** (2C).
- The reactions that involve a transfer of a 3-carbon fragment are catalyzed by **Transaldolase** (3C).
- After the rearrangement of the sugars the final products are:

  3 pentose phosphate $\rightleftharpoons$ 2 hexose phosphate + 1 triose phosphate

  3 Ribulose 5-phosphate $\rightleftharpoons$ 2 Fructose 6-phoshate + 1 Glyceraldehyde 3-P

- If we multiply the previous reaction by 2 (as if we started with 6 Ribulose 5-P)

  6 Ribulose 5-phosphate $\rightleftharpoons$ 4 Fructose 6-phospate + 2 Glyceraldehyde 3-P

  2 Glyceraldehyde 3-P can be converted to Fructose 6-phophate in gluconeogenesis resulting with 5 Fructose 6-phosphate

  Adding both phases of the reaction, the final result is:

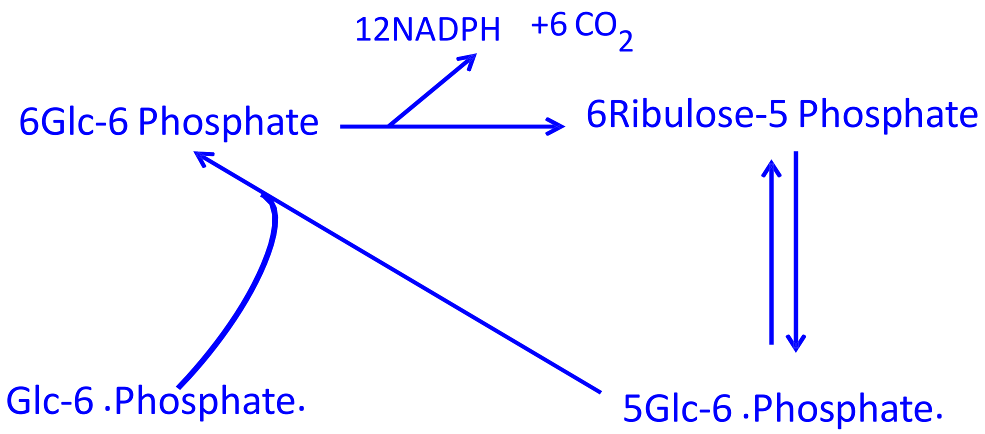
3Glucose 6-P + 6NADP$^+$ $\longrightarrow$ 2Glucose 6-P + GA3-P + 3CO2 + 6 NADPH

X2

6Glucose 6-P + 12NADP$^+$ $\longrightarrow$ 4Glucose 6-P + 2 GA3P + 6CO$_2$ + 12 NADPH

Glucose 6-p

6Glucose 6-P + 12NADP$^+$ $\longrightarrow$ 5Glucose 6-p + 6CO$_2$ + 12NADPH



Notes about the figure above:

1) In the oxidative phase, **6 Glucose 6-P** molecules are converted to **6 Ribulose 5-P** producing **12 NADPH** molecules + **6 CO2** molecules **(2 NADPH per 1 Glucose 6-p).**
2) In the non-oxidative phase, **6 Ribulose 5-P** are converted to **5 Glucose 6-P.**
3) **Addition** of another **Glucose 6-p** to the **5 produced** in the non-oxidative phase results in the formation of **a cycle.**
4) In cells that depend on NADPH (like RBC's) the cycle keeps going on.
5) **12 NADPH** molecules are **produced per cycle (per 1 glucose molecule)**.
   Note: if we simplify the equation below we conclude that 12 NADPH moecules are produced per 1 Glucose molecule.
   $6 \text{ Glucose} - 6 - P \quad + \quad 12 \text{ NADP}^+ \longrightarrow 5 \text{ Glucose} - 6 - P + 6\ CO_2 + 12 \text{ NADPH}$

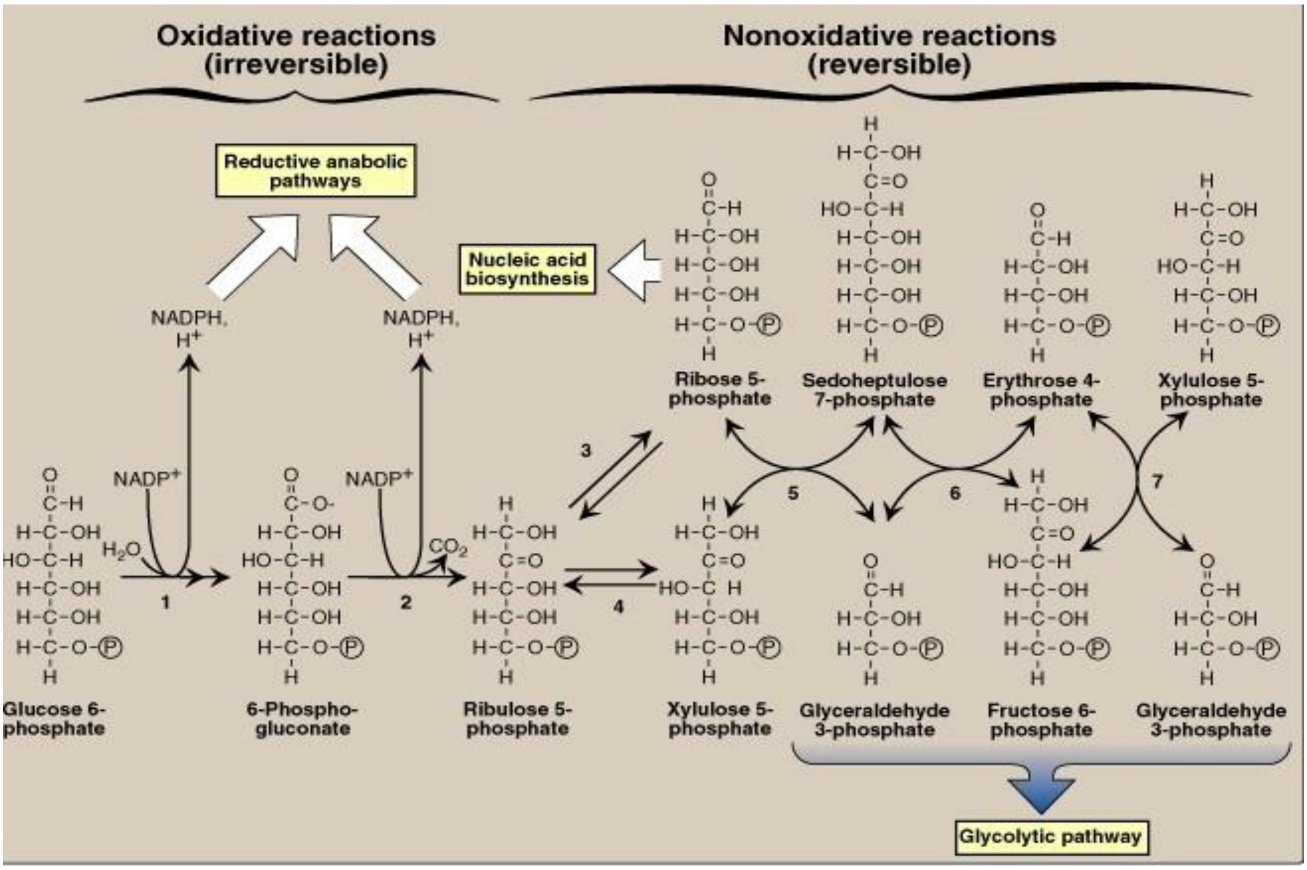
NADH vs NADPH

- ✓ Enzymes can specifically use one NOT the other.
- ✓ NADPH and NADH have different roles.
- ✓ NADPH exists mainly in the reduced form (NADPH).

  Why? It is needed for biosynthesis not producing energy.
- ✓ NADH exists mainly in the oxidized form (NAD^+).

  Why? To keep glycolysis going on.
- ✓ In the cytosol of hepatocyte

- $NADP^+/NADPH \approx 1/10$
- $NAD^+/NADH \approx 1000/1$



Oxidative reactions (irreversible)
Nonoxidative reactions (reversible)
Reductive anabolic pathways
Nucleic acid biosynthesis
NADPH, H+
NADP+
H2O
CO2
Glucose 6-phosphate
6-Phospho-gluconate
Ribulose 5-phosphate
Ribose 5-phosphate
Sedoheptulose 7-phosphate
Erythrose 4-phosphate
Xylulose 5-phosphate
Glyceraldehyde 3-phosphate
Fructose 6-phosphate
Glycolytic pathway

The End.