Pentose Phosphate Pathway

- In most animal tissues, the major catabolic fate of glucose 6-phosphate is glycolytic breakdown to pyruvate, much of which is then oxidized via the citric acid cycle, ultimately leading to the formation of ATP.
- Glucose 6-phosphate does have other catabolic fates, however, which lead to specialized products needed by the cell.
- Of particular importance in some tissues is the oxidation of glucose 6-phosphate to pentose phosphates by the **pentose phosphate pathway** (also called the **phosphogluconate pathway or the hexose monophosphate pathway.**
- In this oxidative pathway, NADP is the electron acceptor, yielding NADPH. Rapidly dividing cells, such as those of bone marrow, skin, and intestinal mucosa, use the pentoses to make RNA, DNA, and such coenzymes as ATP, NADH, FADH2, and coenzyme A.
- In other tissues, the essential product of the pentose phosphate pathway is not the pentoses but the electron donor NADPH, needed for reductive biosynthesis or to counter the damaging effects of oxygen radicals.
- Tissues that carry out extensive fatty acid synthesis (liver, adipose, lactating mammary gland) or very active synthesis of cholesterol and steroid hormones (liver, adrenal gland, gonads) require the NADPH provided by the pathway. Erythrocytes and the cells of the lens and cornea are directly exposed to oxygen and thus to the damaging free radicals generated by oxygen.

By maintaining a reducing atmosphere (a high ratio of NADPH to NADP and a high ratio of reduced to oxidized glutathione), they can prevent or undo oxidative damage to proteins, lipids, and other sensitive molecules.

In erythrocytes, the NADPH produced by the pentose phosphate pathway is so important in preventing oxidative damage that a genetic defect in glucose 6-phosphate dehydrogenase, the first enzyme of the pathway, can have serious medical consequences

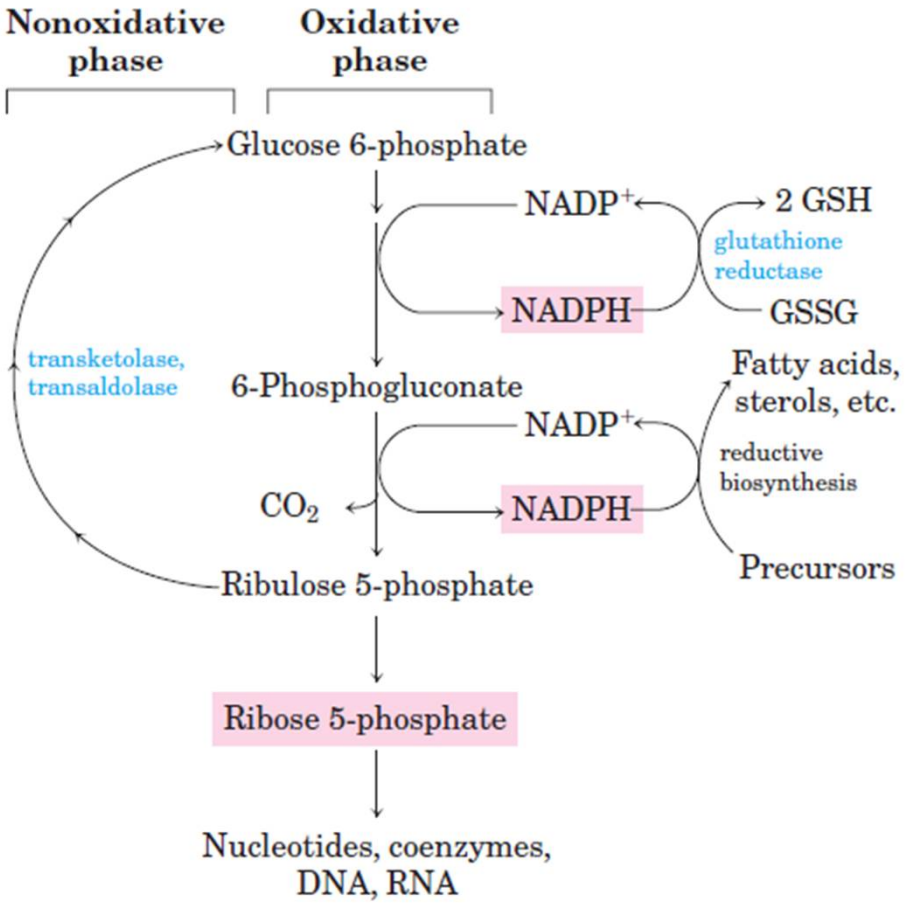
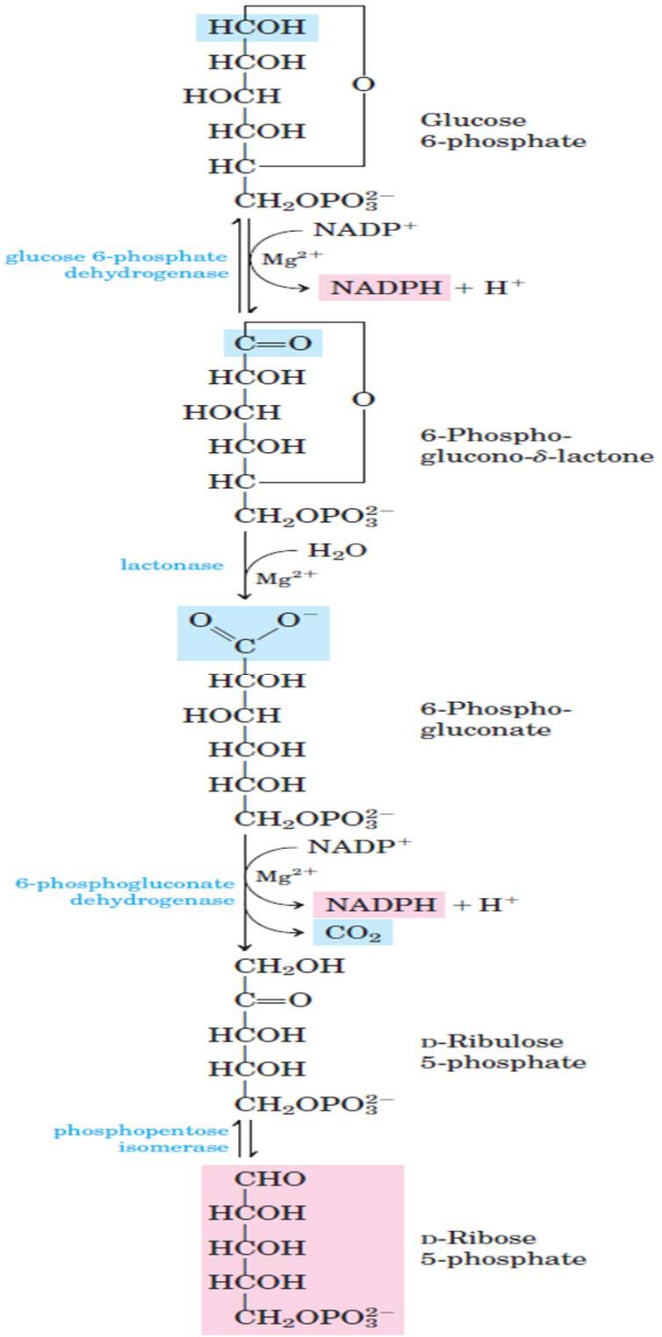


FIGURE 14–20 **General scheme of the pentose phosphate pathway.** NADPH formed in the oxidative phase is used to reduce glutathione, GSSG (see Box 14–3) and to support reductive biosynthesis. The other product of the oxidative phase is ribose 5-phosphate, which serves as precursor for nucleotides, coenzymes, and nucleic acids. In cells that are not using ribose 5-phosphate for biosynthesis, the nonoxidative phase recycles six molecules of the pentose into five molecules of the hexose glucose 6-phosphate, allowing continued production of NADPH and converting glucose 6-phosphate (in six cycles) to CO_2.



The Oxidative Phase Produces Pentose Phosphates and NADPH

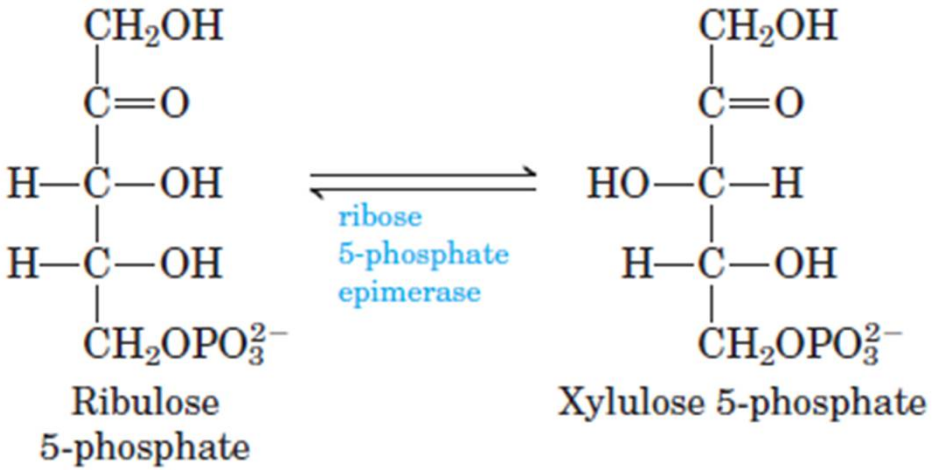
- The first reaction of the pentose phosphate pathway is the oxidation of glucose 6-phosphate by **glucose 6-phosphate dehydrogenase (G6PD)** to form 6-phosphoglucono--lactone, an intramolecular ester.
- NADP is the electron acceptor, and the overall equilibrium lies far in the direction of NADPH formation.
- The lactone is hydrolyzed to the free acid 6-phosphogluconate by a specific **lactonase, then 6-phosphogluconate** undergoes oxidation and decarboxylation by **6-phosphogluconate dehydrogenase** to form the ketopentose ribulose 5-phosphate. This reaction generates a second molecule of NADPH.
- **Phosphopentose isomerase** converts ribulose 5-phosphate to its aldose isomer, ribose 5-phosphate. In some tissues, the pentose phosphate pathway ends at this point, and its overall equation is

$$\text{Glucose 6-phosphate} + 2\text{NADP}^+ + \text{H}_2\text{O} \longrightarrow \text{ribose 5-phosphate} + \text{CO}_2 + 2\text{NADPH} + 2\text{H}^+$$

The net result is the production of NADPH, a reductant for biosynthetic reactions, and ribose 5-phosphate, a precursor for nucleotide synthesis.

The Nonoxidative Phase Recycles Pentose Phosphates to Glucose 6-Phosphate

In tissues that require primarily NADPH, the pentose phosphates produced in the oxidative phase of the pathway are recycled into glucose 6-phosphate. In this nonoxidative phase, ribulose 5-phosphate is first epimerized to xylulose 5-phosphate:



Ribulose 5-phosphate

Xylulose 5-phosphate

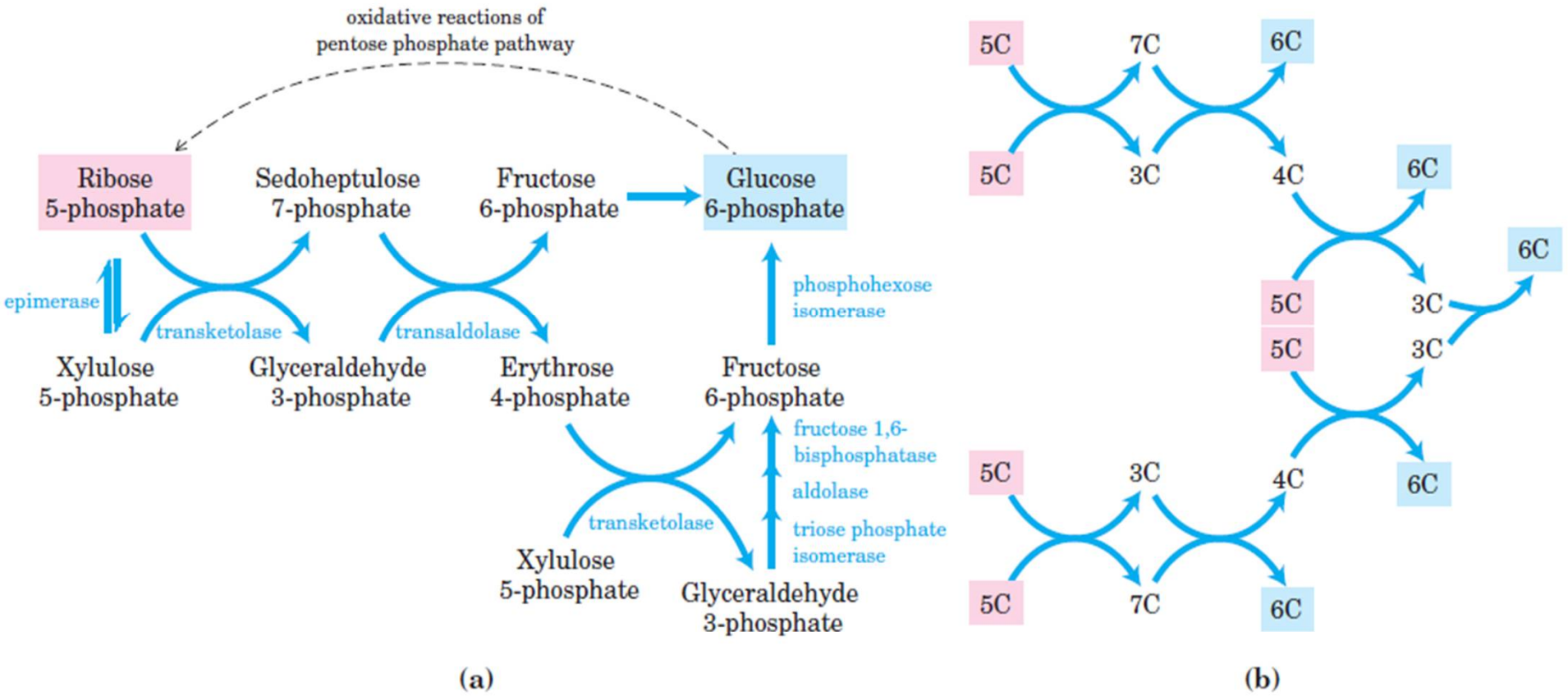
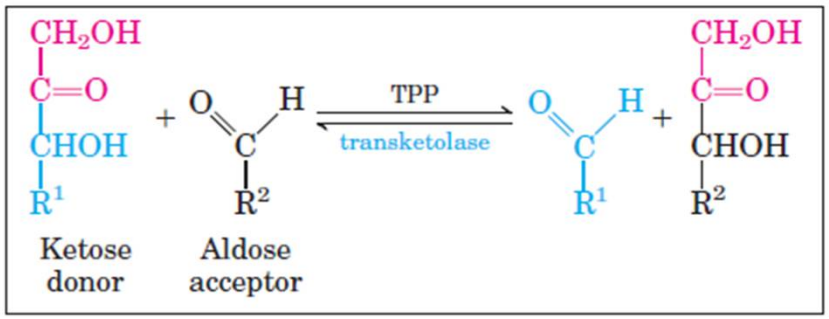
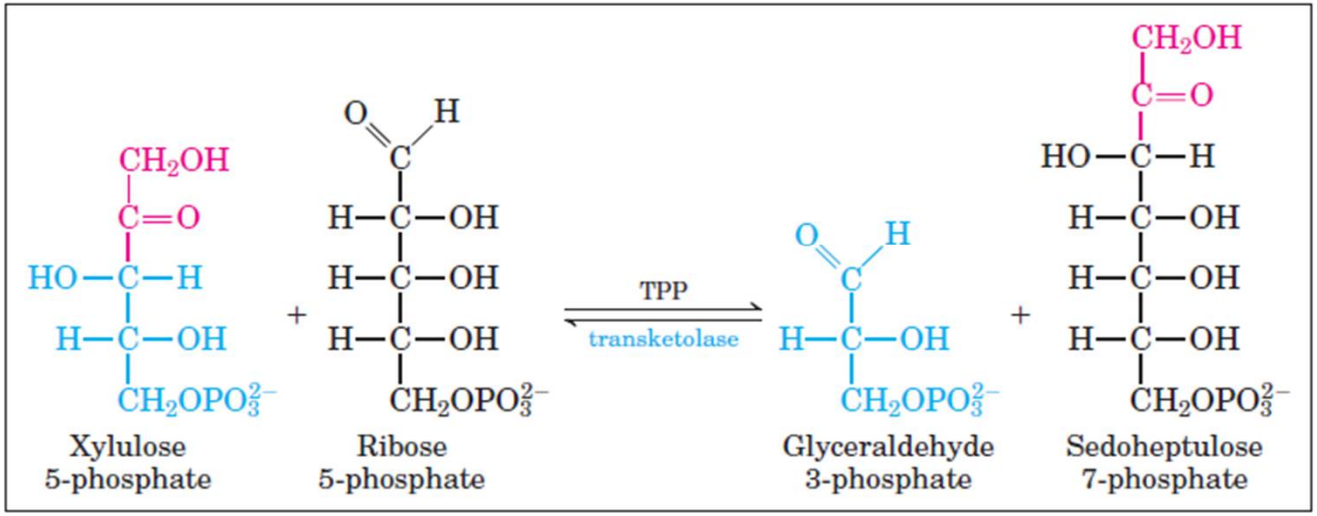


FIGURE 14–22 Nonoxidative reactions of the pentose phosphate pathway. (a) These reactions convert pentose phosphates to hexose phosphates, allowing the oxidative reactions (see Fig. 14–21) to continue. The enzymes transketolase and transaldolase are specific to this pathway; the other enzymes also serve in the glycolytic or gluconeogenic pathways. (b) A schematic diagram showing the pathway from six pentoses (5C) to five hexoses (6C). Note that this involves two sets of the interconversions shown in (a). Every reaction shown here is reversible; unidirectional arrows are used only to make clear the direction of the reactions during continuous oxidation of glucose 6-phosphate. In the light-independent reactions of photosynthesis, the direction of these reactions is reversed (see Fig. 20–10).

- In a series of rearrangements of the carbon skeletons, six five-carbon sugar phosphates are converted to five six-carbon sugar phosphates, completing the cycle and allowing continued oxidation of glucose 6-phosphate with production of NADPH.
- Continued recycling leads ultimately to the conversion of glucose 6-phosphate to six CO2. Two enzymes unique to the pentose phosphate pathway act in these interconversions of sugars: transketolase and transaldolase.



(a)



(b)

FIGURE 14–23 The first reaction catalyzed by transketolase. (a) The general reaction catalyzed by transketolase is the transfer of a two-carbon group, carried temporarily on enzyme-bound TPP, from a ketose donor to an aldose acceptor. (b) Conversion of two pentose phosphates to a triose phosphate and a seven-carbon sugar phosphate, sedoheptulose 7-phosphate.

Transketolase catalyzes the transfer of a two-carbon fragment from a ketose donor to an aldose acceptor (Fig. 14–23a). In its first appearance in the pentose phosphate pathway, transketolase transfers C-1 and C-2 of xylulose 5-phosphate to ribose 5-phosphate, forming the seven-carbon product sedoheptulose 7-phosphate (Fig. 14–23b).

The remaining three-carbon fragment from xylulose is glyceraldehyde 3-phosphate.

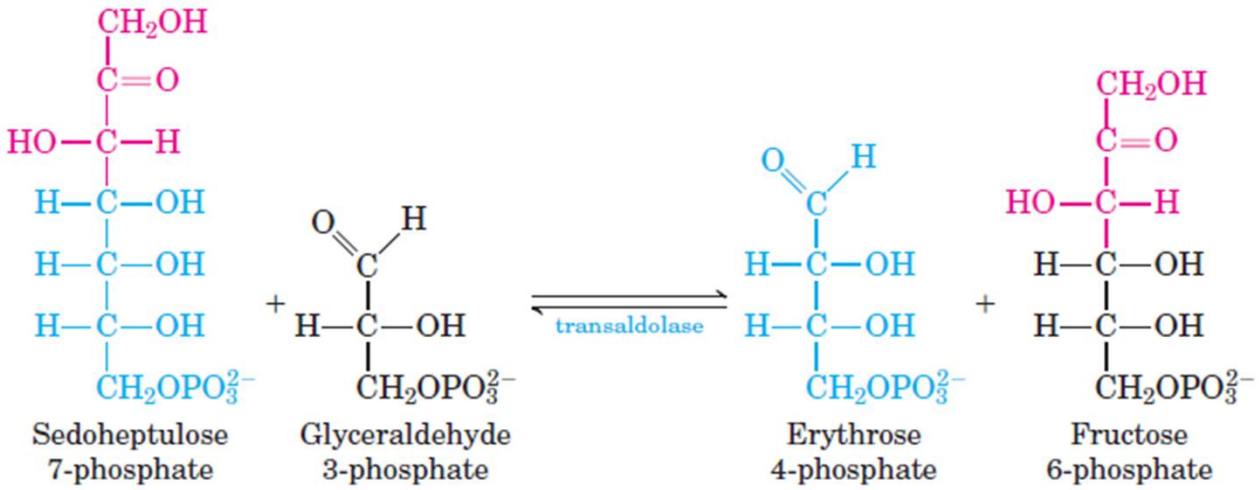


FIGURE 14–24 The reaction catalyzed by transaldolase.

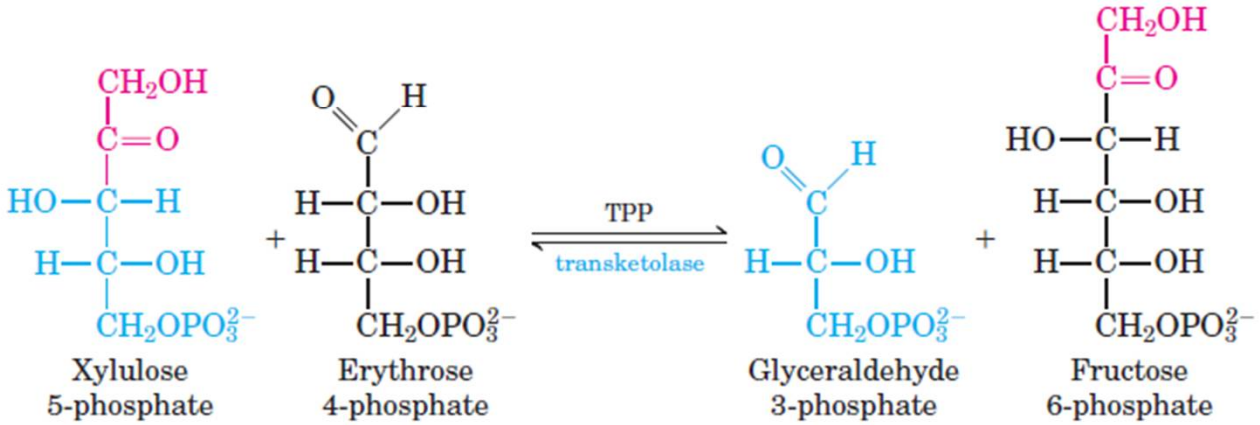
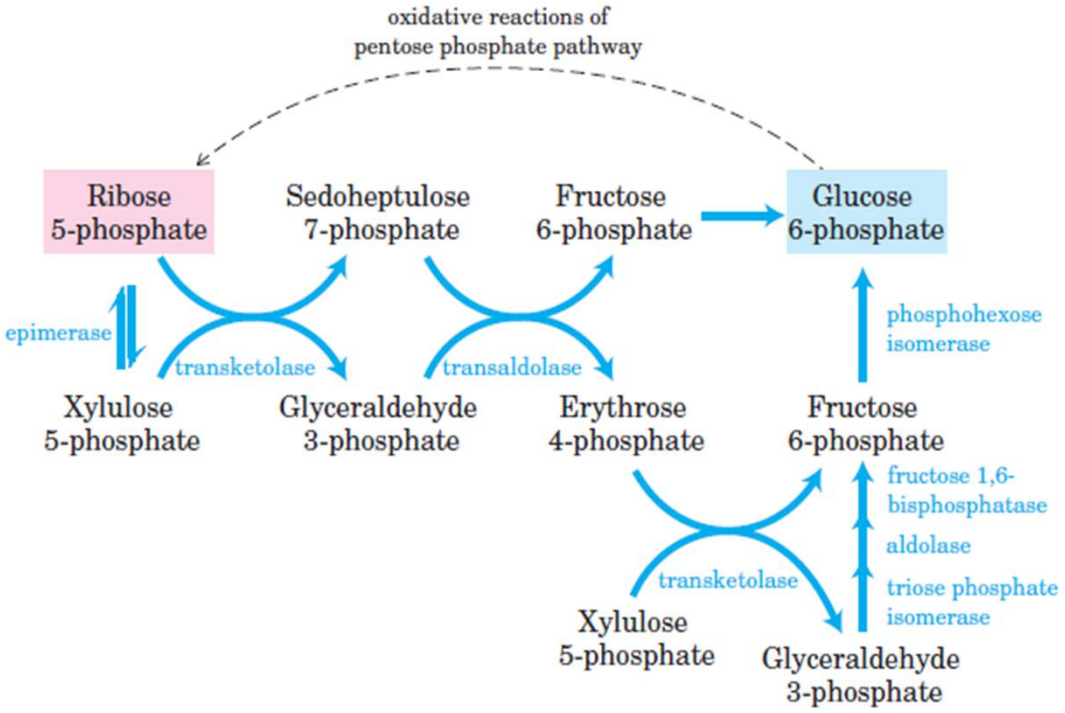


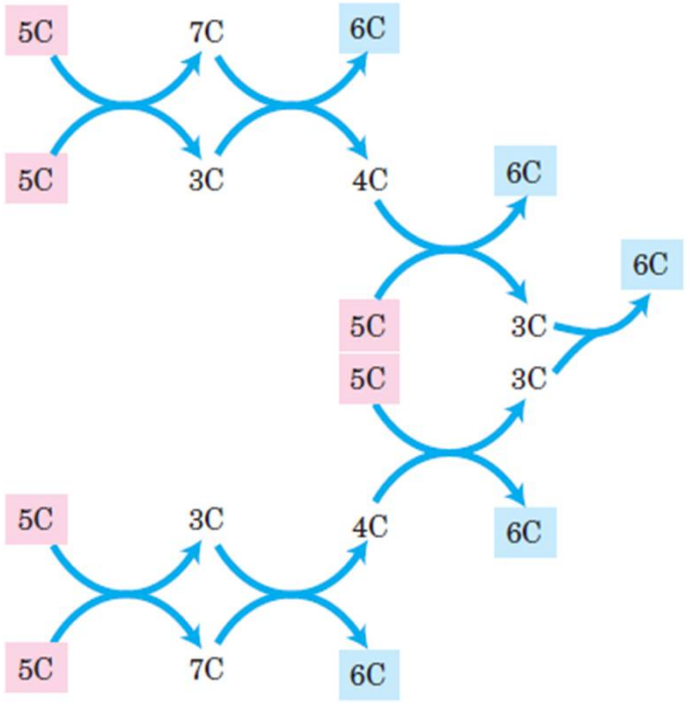
FIGURE 14–25 The second reaction catalyzed by transketolase.

Next, **transaldolase** catalyzes a reaction similar to the aldolase reaction of glycolysis: a three-carbon fragment is removed from sedoheptulose 7-phosphate and condensed with glyceraldehyde 3-phosphate, forming fructose 6-phosphate and the tetrose erythrose 4-phosphate (Fig. 14–24).

Now transketolase acts again, forming fructose 6-phosphate and glyceraldehyde 3-phosphate from erythrose 4-phosphate and xylulose 5-phosphate (Fig. 14–25).

- Two molecules of glyceraldehyde 3-phosphate formed by two iterations of these reactions can be converted to a molecule of fructose 1,6-bisphosphate as in gluconeogenesis, and finally FBPase-1 and phosphohexose isomerase convert fructose 1,6-bisphosphate to glucose 6-phosphate. The cycle is complete: six pentose phosphates have been converted to five hexose phosphates.





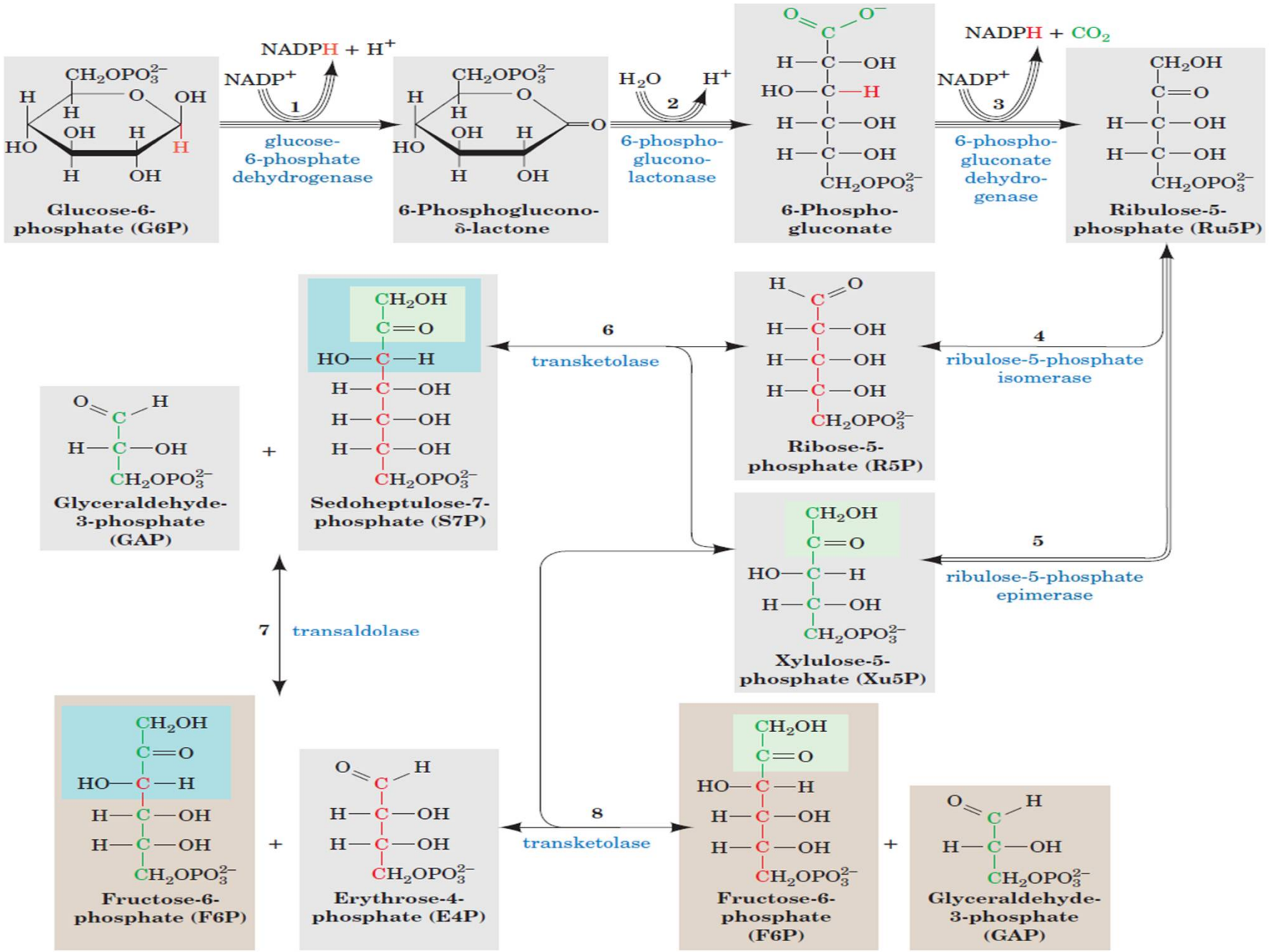

Glucose-6-phosphate (G6P)
NADP+
NADPH + H+
1
glucose-6-phosphate dehydrogenase
6-Phosphogluconono-δ-lactone
H2O
H+
2
6-phospho-gluconono-lactonase
6-Phospho-gluconate
NADP+
NADPH + CO2
3
6-phospho-gluconate dehydro-genase
Ribulose-5-phosphate (Ru5P)
4
ribulose-5-phosphate isomerase
Ribose-5-phosphate (R5P)
6
transketolase
Sedoheptulose-7-phosphate (S7P)
Glyceraldehyde-3-phosphate (GAP)
5
ribulose-5-phosphate epimerase
Xylulose-5-phosphate (Xu5P)
7
transaldolase
Fructose-6-phosphate (F6P)
Erythrose-4-phosphate (E4P)
8
transketolase
Fructose-6-phosphate (F6P)
Glyceraldehyde-3-phosphate (GAP)

Table 20.3 Pentose phosphate pathway

Reaction	Enzyme
Oxidative phase	
Glucose 6-phosphate + $NADP^+ \longrightarrow$ 6-phosphoglucono-δ-lactone + NADPH + H^+	Glucose 6-phosphate dehydrogenase
6-Phosphoglucono-δ-lactone + $H_2O \longrightarrow$ 6-phosphogluconate + H^+	Lactonase
6-Phosphogluconate + $NADP^+ \longrightarrow$ ribulose 5-phosphate + CO_2 + NADPH + H^+	6-Phosphogluconate dehydrogenase
Nonoxidative Phase	
Ribulose 5-phosphate $\rightleftharpoons$ ribose 5-phosphate	Phosphopentose isomerase
Ribulose 5-phosphate $\rightleftharpoons$ xylulose 5-phosphate	Phosphopentose epimerase
Xylulose 5-phosphate + ribose 5-phosphate $\rightleftharpoons$ sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate	Transketolase
Sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate $\rightleftharpoons$ fructose 6-phosphate + erythrose 4-phosphate	Transaldolase
Xylulose 5-phosphate + erythrose 4-phosphate $\rightleftharpoons$ fructose 6-phosphate + glyceraldehyde 3-phosphate	Transketolase