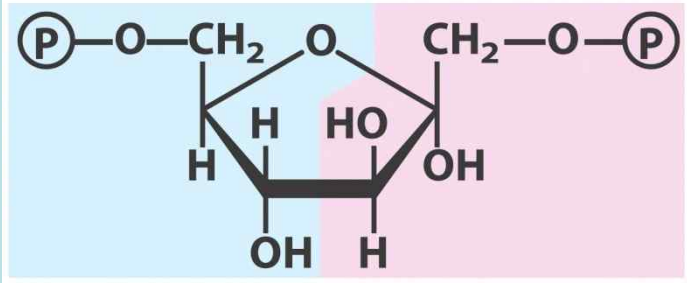
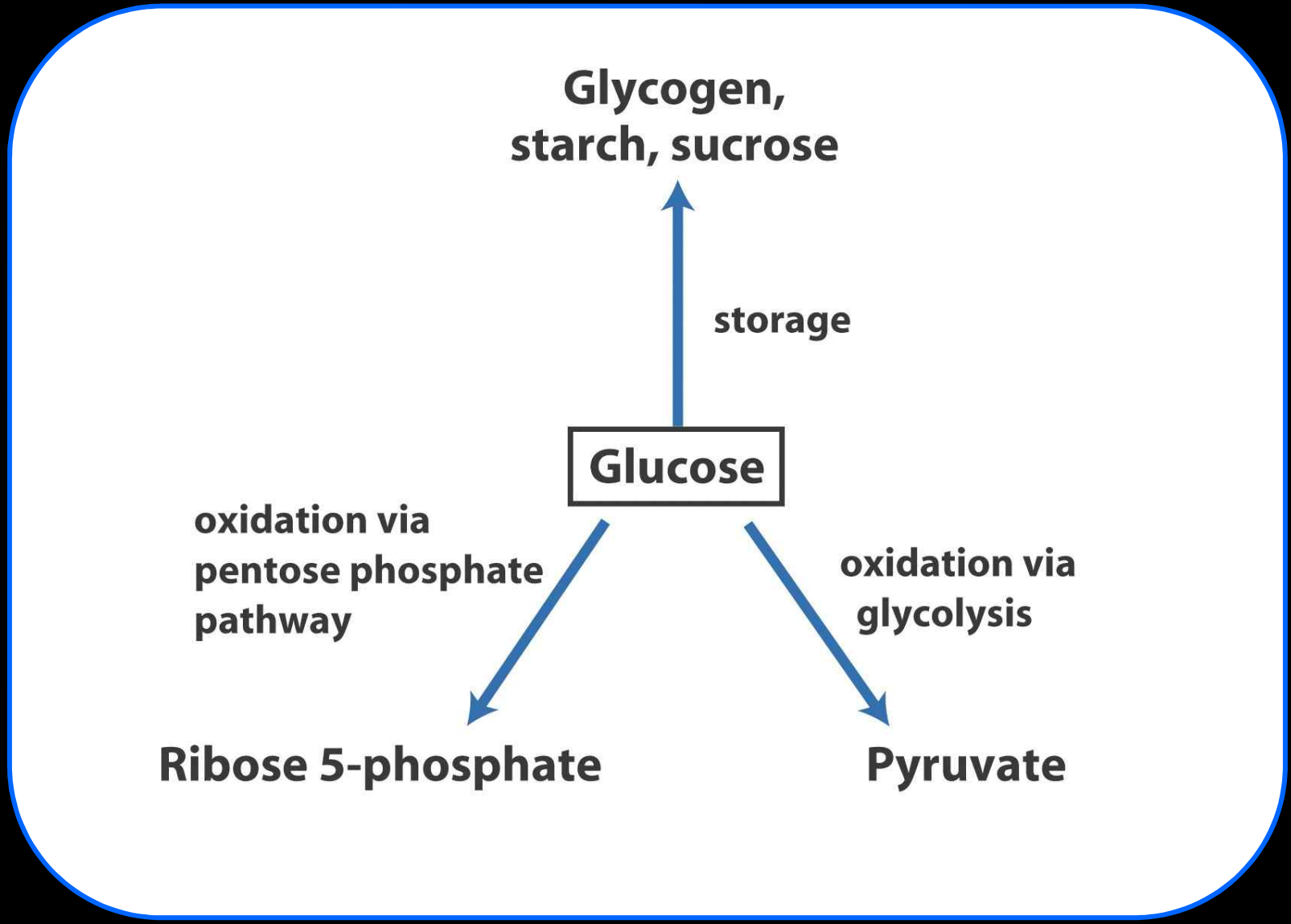


Chapter 14

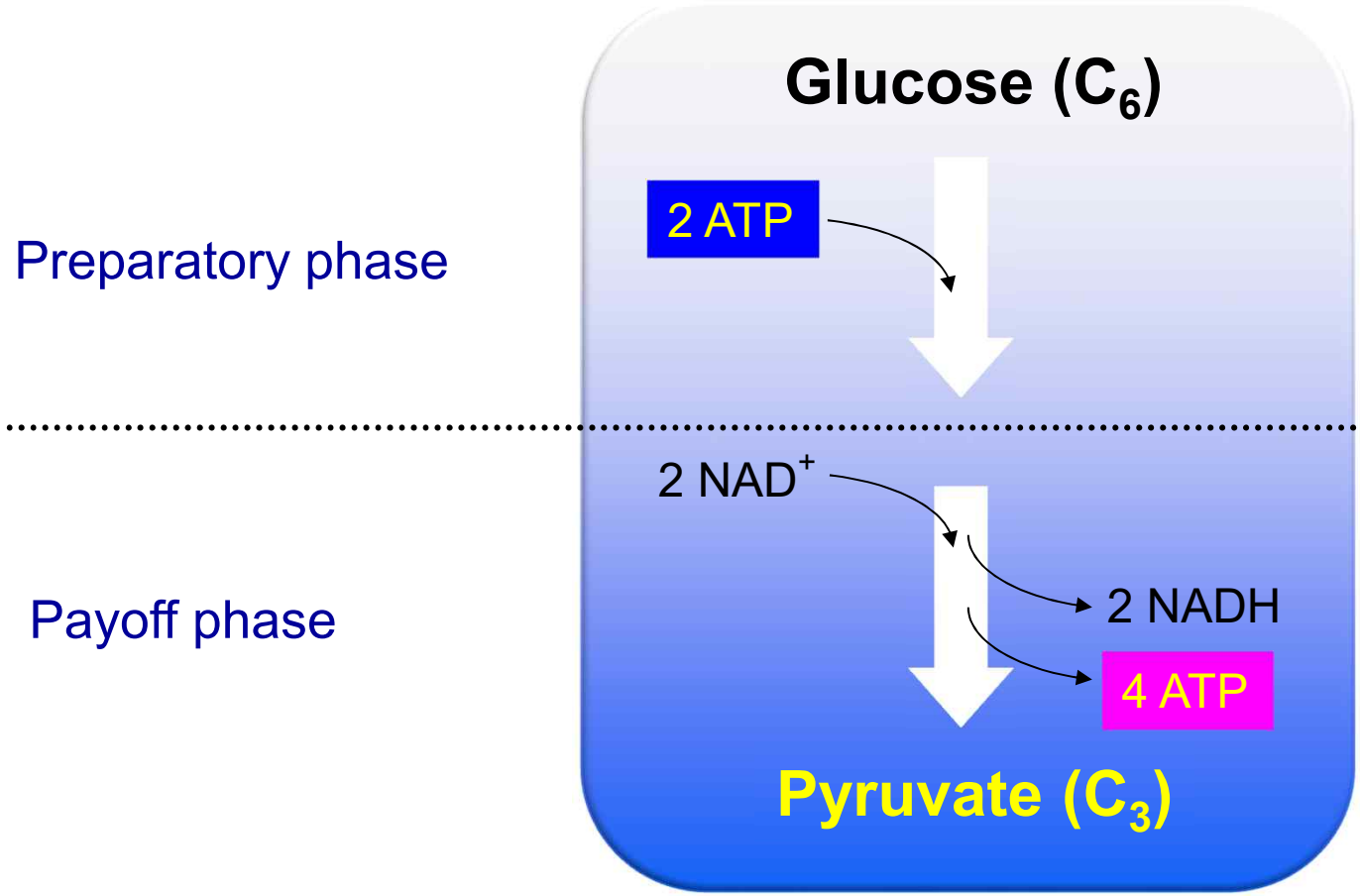
Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway

14.1 Glycolysis
14.2 Feeder pathways for Glycolysis
14.3 Fates of Pyruvate under anaerobic conditions : (Fermentation)
14.4 Gluconeogenesis
14.5 Pentose phosphate pathway of glucose oxidation

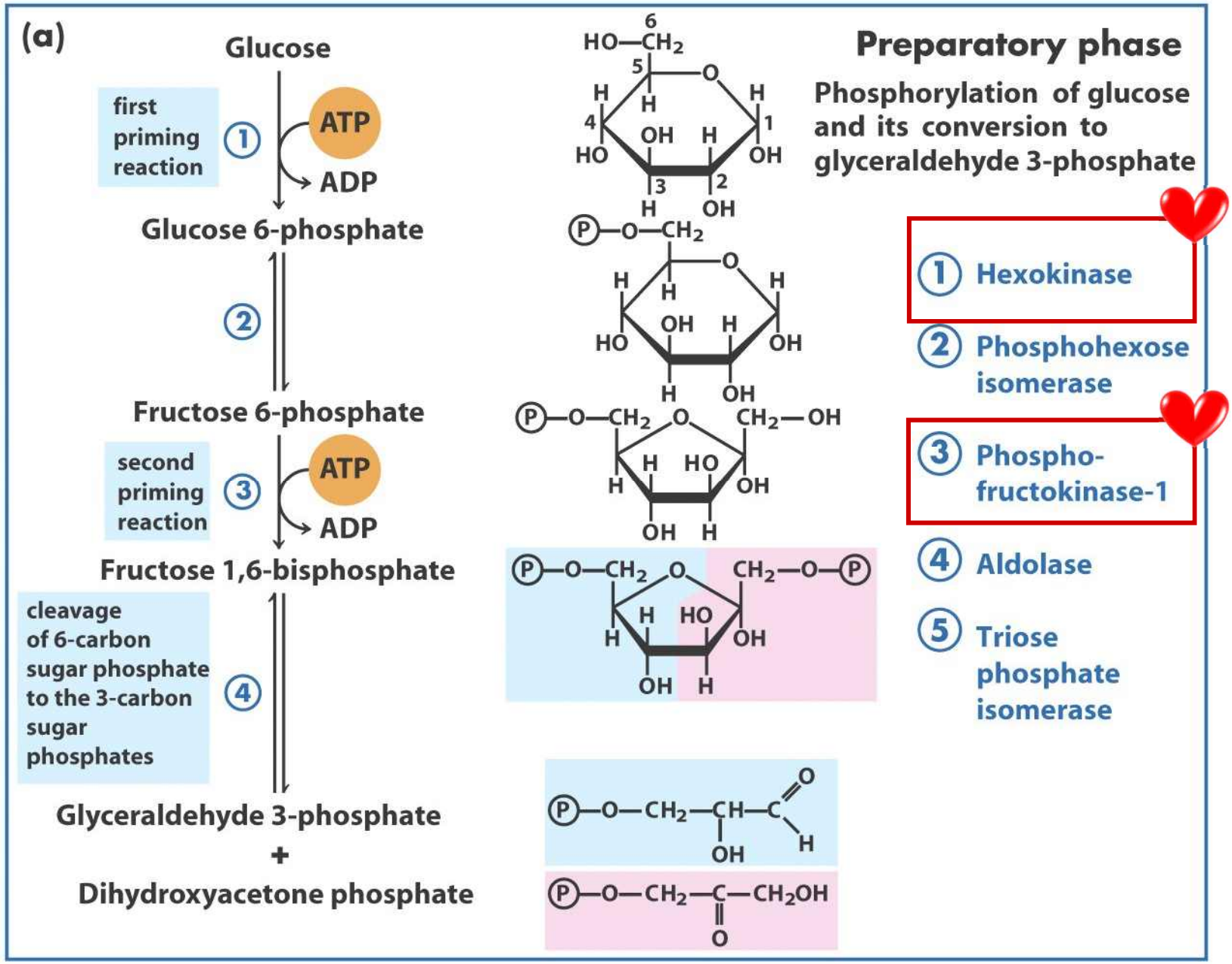
Major pathway of glucose utilization

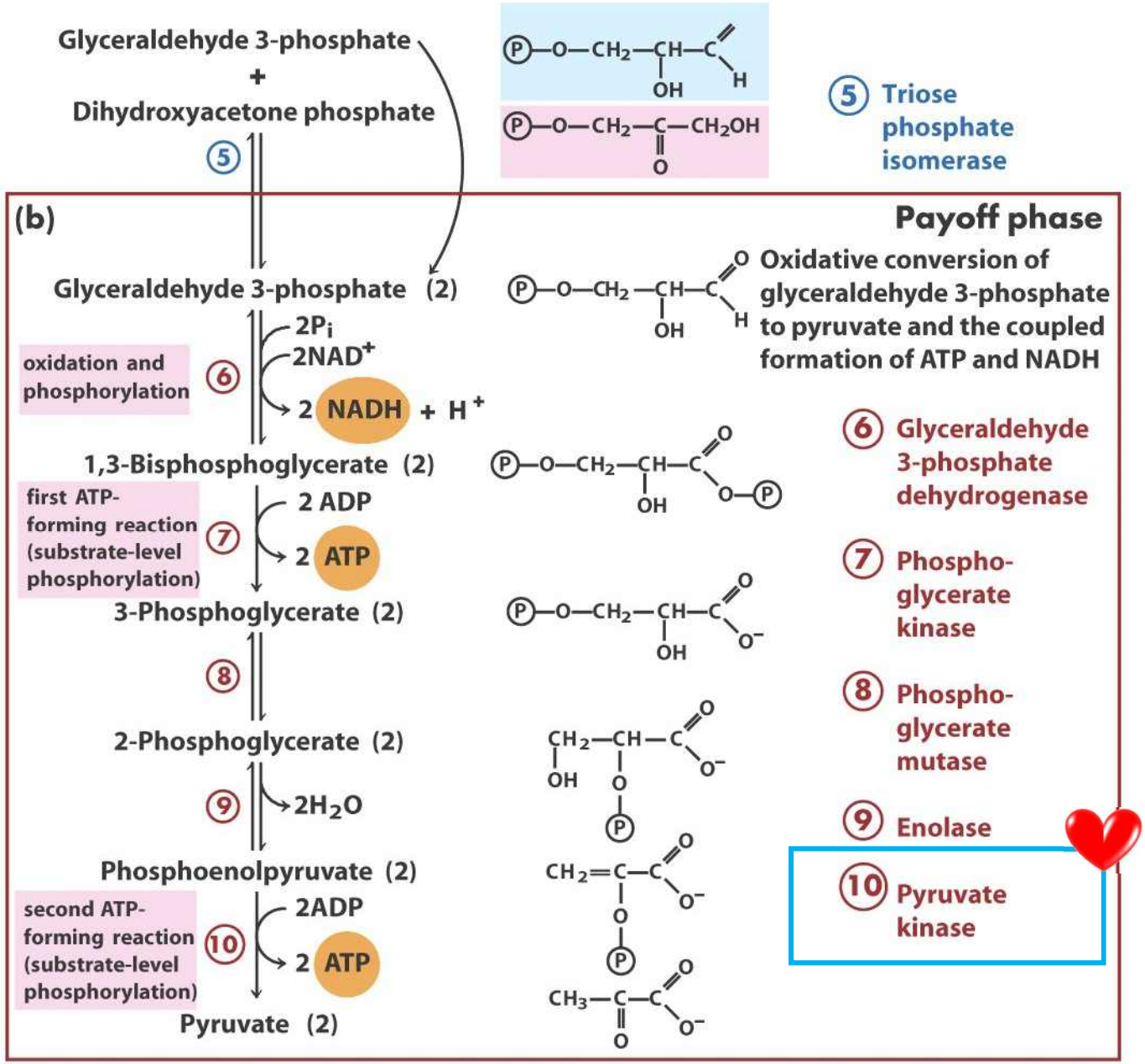


Glycolysis



Glucose + 2 NAD^+ + 2 ATP ⟶ 2 Pyruvate + 2 NADH + 4 ATP


(a)
Glucose
first priming reaction
1
ATP
ADP
Glucose 6-phosphate
2
Fructose 6-phosphate
second priming reaction
3
ATP
ADP
Fructose 1,6-bisphosphate
cleavage of 6-carbon sugar phosphate to the 3-carbon sugar phosphates
4
Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
Preparatory phase
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate
1 Hexokinase
2 Phosphohexose isomerase
3 Phospho-fructokinase-1
4 Aldolase
5 Triose phosphate isomerase


Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
5
5 Triose phosphate isomerase
(b)
Payoff phase
Glyceraldehyde 3-phosphate (2)
Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH
oxidation and phosphorylation
6
2Pi
2NAD+
2 NADH + H+
6 Glyceraldehyde 3-phosphate dehydrogenase
1,3-Bisphosphoglycerate (2)
first ATP-forming reaction (substrate-level phosphorylation)
7
2 ADP
2 ATP
7 Phospho-glycerate kinase
3-Phosphoglycerate (2)
8
8 Phospho-glycerate mutase
2-Phosphoglycerate (2)
9
2H2O
9 Enolase
Phosphoenolpyruvate (2)
second ATP-forming reaction (substrate-level phosphorylation)
10
2ADP
2 ATP
10 Pyruvate kinase
Pyruvate (2)

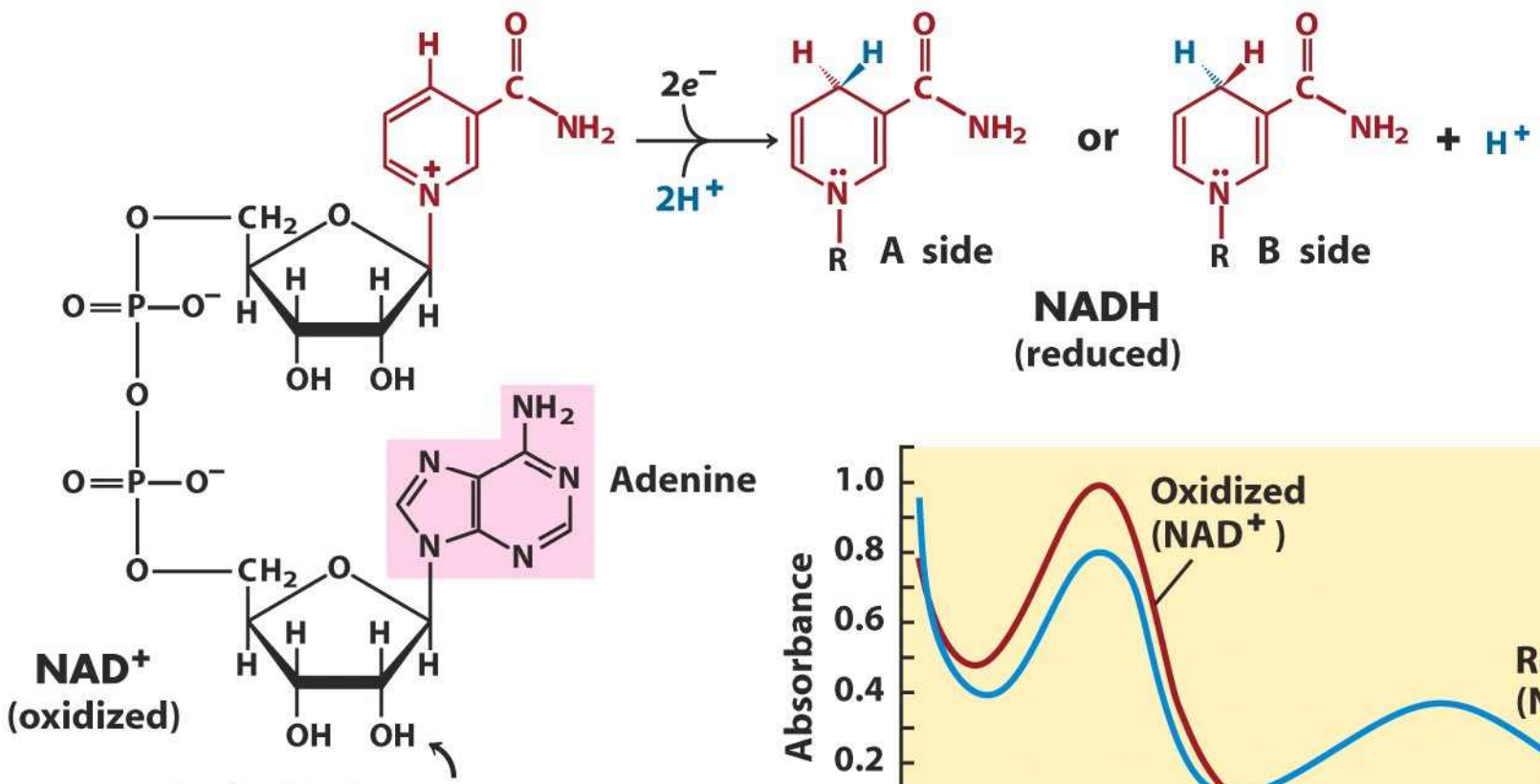
Importance of phosphorylated intermediates

1. The phosphorylated glycolytic intermediates (9) cannot leave the cell. (lack of transporters for phosphorylated sugars in plasma membrane)

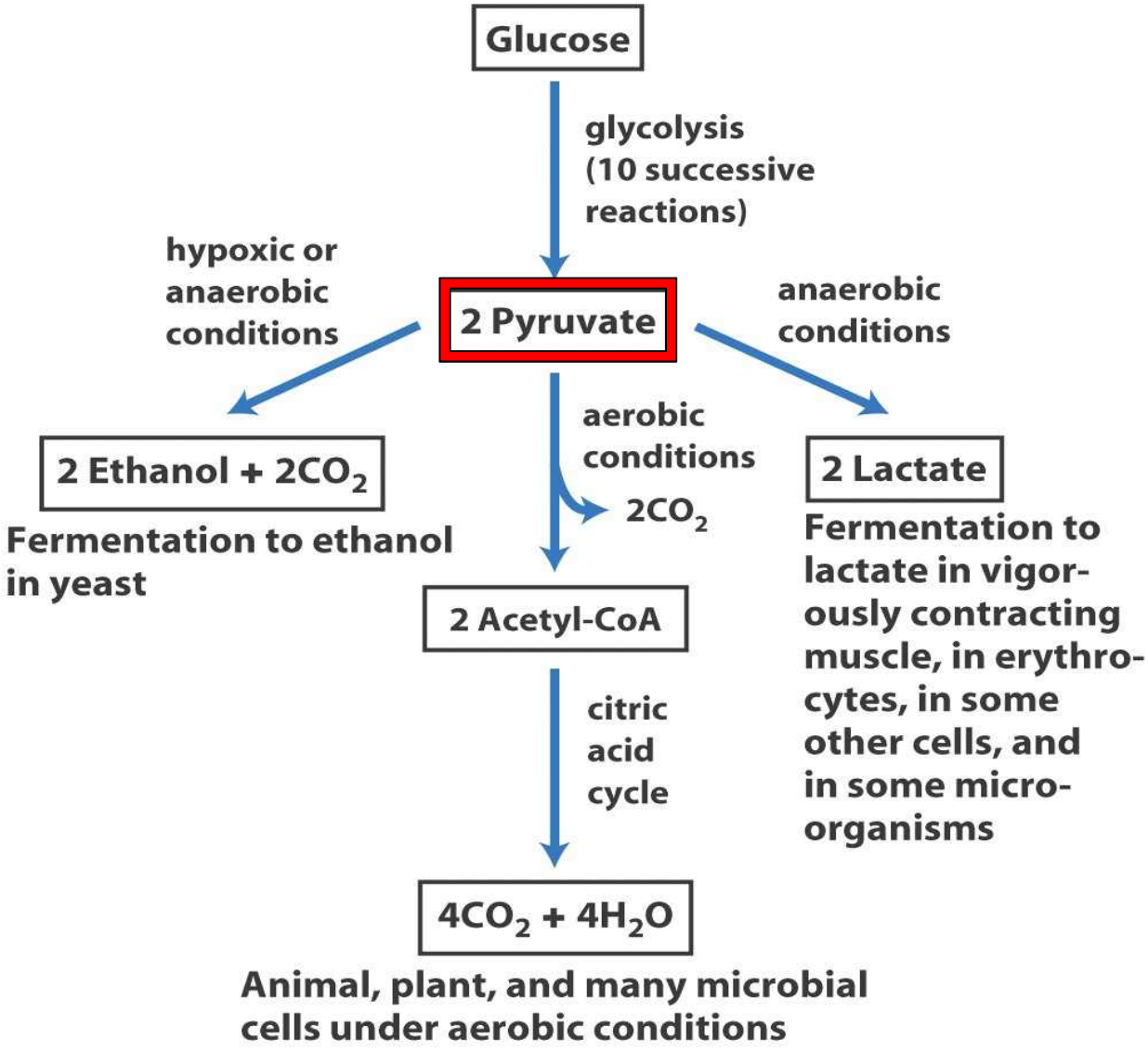
2. Phosphoryl groups are essential components in enzymatic conservation of metabolic E.

3. Binding E resulting from the binding of phosphate groups to the active sites of enzymes lowers the activation E and increases the specificity of the enzymatic reactions. (most glycolytic enzymes require Mg^{2+})

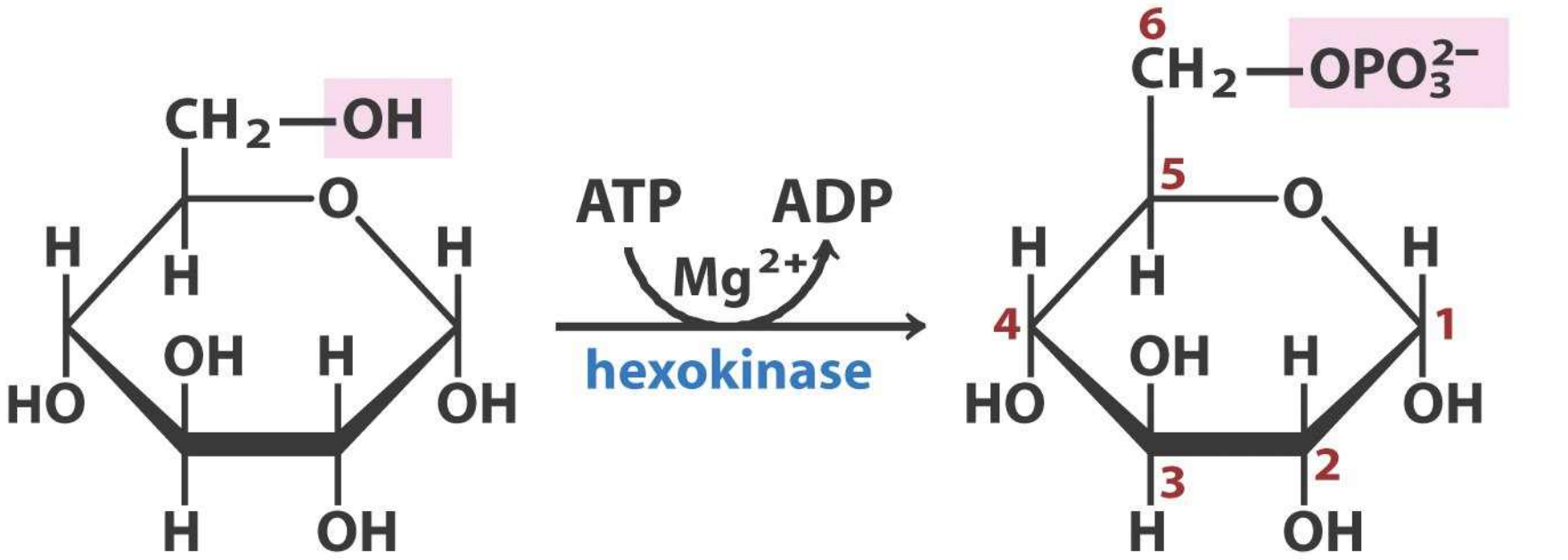
NAD *Nicotinamide Adenine Dinucleotide*



Three possible catabolic fates of the pyruvate formed



1 *Phosphorylation of Glucose*

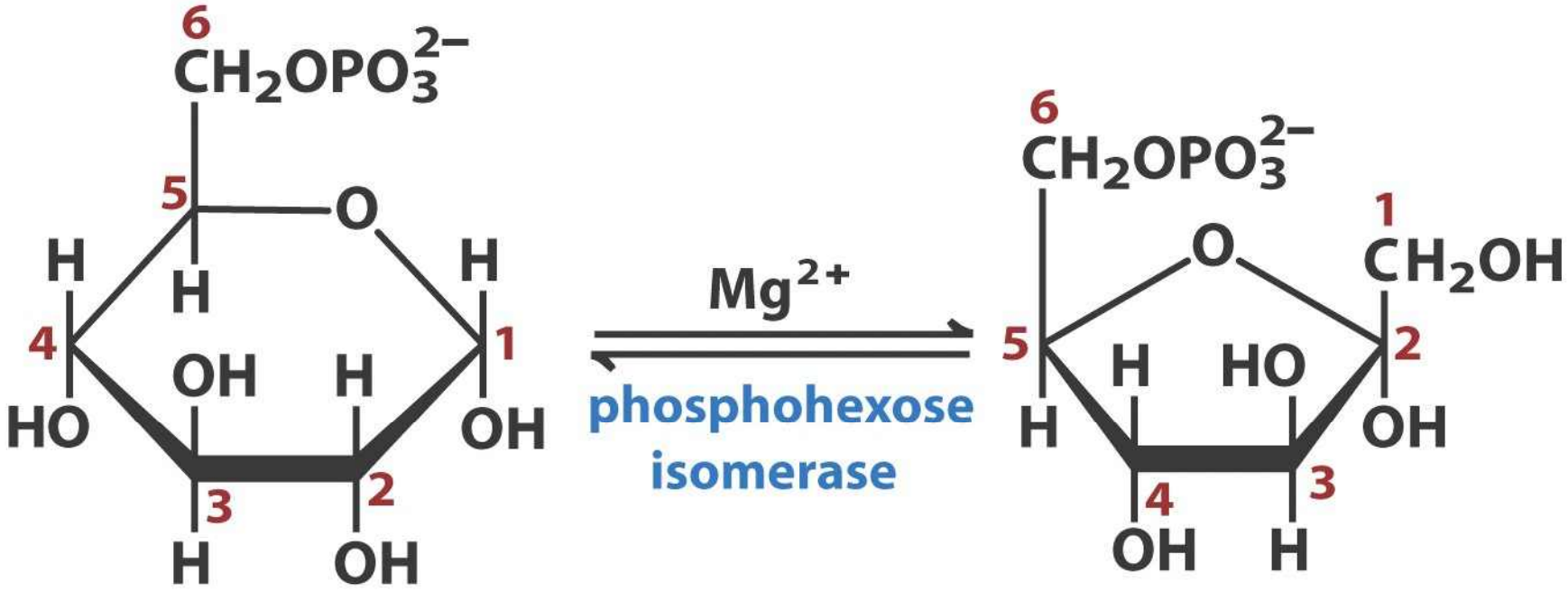


Glucose

Glucose 6-phosphate

$\Delta G'^{\circ} = -16.7$ kJ/mol

2 Conversion of G6P to F6P



Glucose 6-phosphate ⇌ **Fructose 6-phosphate**

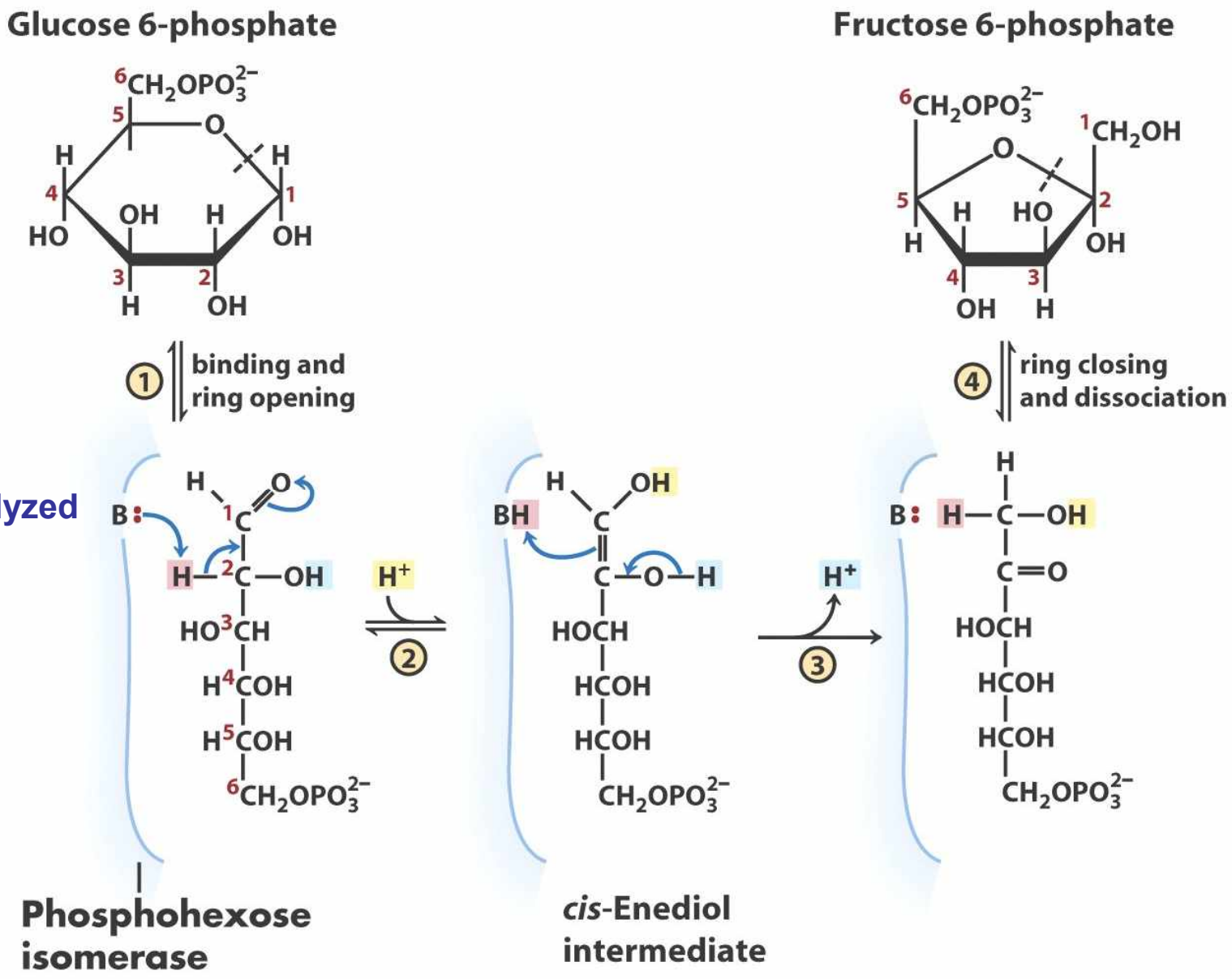
$\Delta G'^{\circ} = 1.7$ kJ/mol

Pyran ring

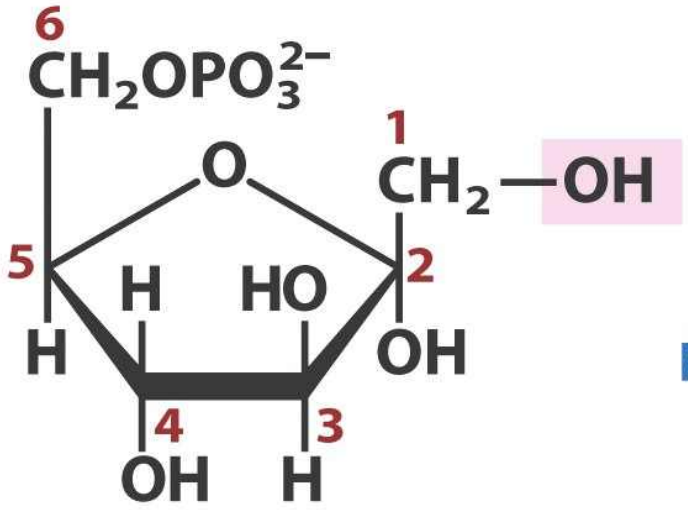
Furan ring

Phosphohexose isomerase reaction

Base-catalyzed reaction



3 *Phosphorylation of F6P to F1,6P*



Fructose 6-phosphate

ATP ADP

Mg^{2+}

PPi

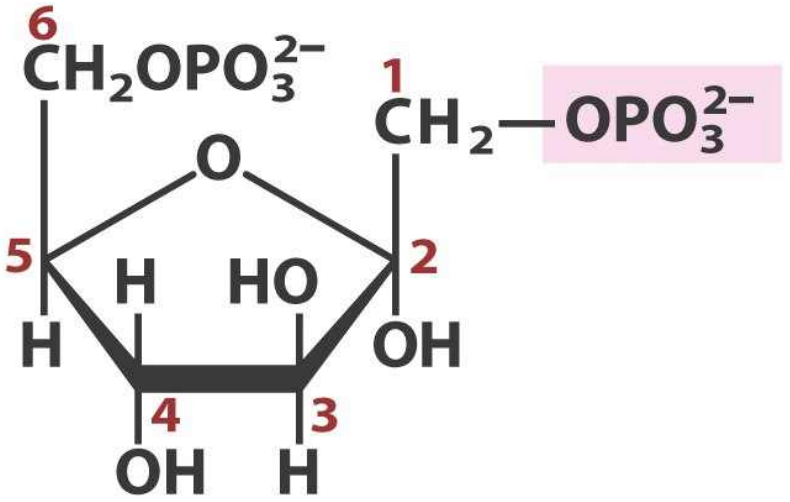
irreversible

phosphofructokinase-1

(PFK-1)

ADP or AMP
F2,6P

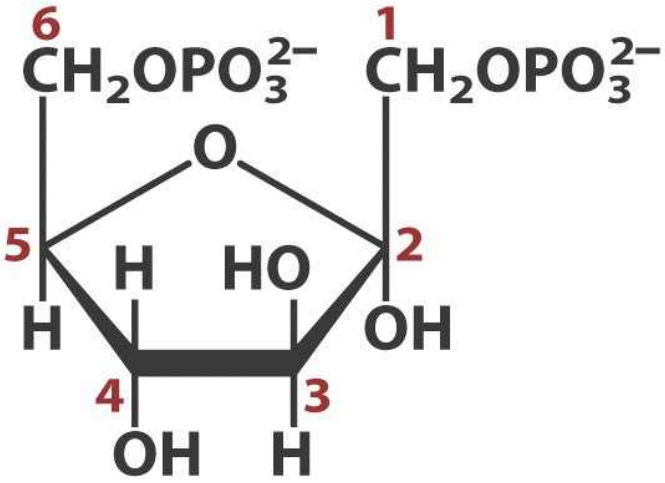
ATP or Citrate



Fructose 1,6-bisphosphate

$\Delta G'^{\circ} = -14.2$ kJ/mol

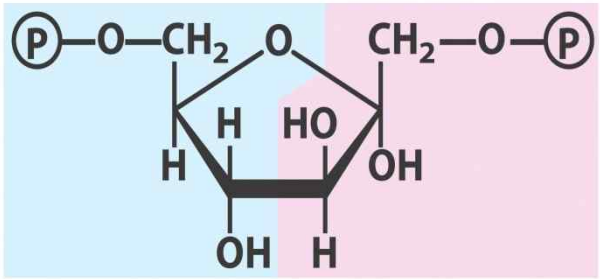
4 *Cleavage of Fructose 1,6-bisphosphate*



aldolase

Class I : animals, plants
ClassII : fungi, bacteria

Fructose 1,6-bisphosphate



(1) $CH_2OPO_3^{2-}$
(2) C=O
(3) CH_2OH

Dihydroxyacetone phosphate

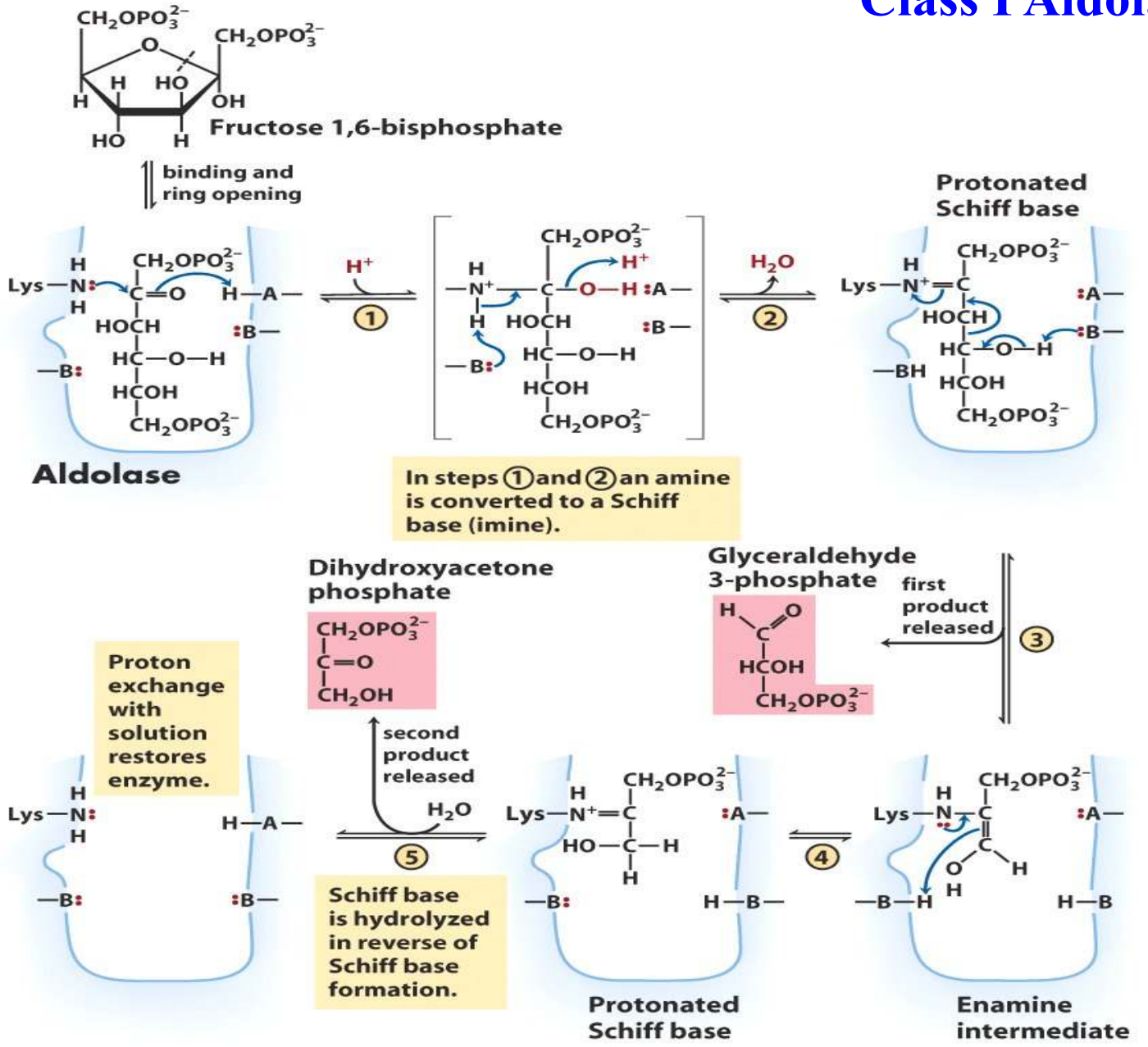
+

(4) C
(5) CHOH
(6) $CH_2OPO_3^{2-}$

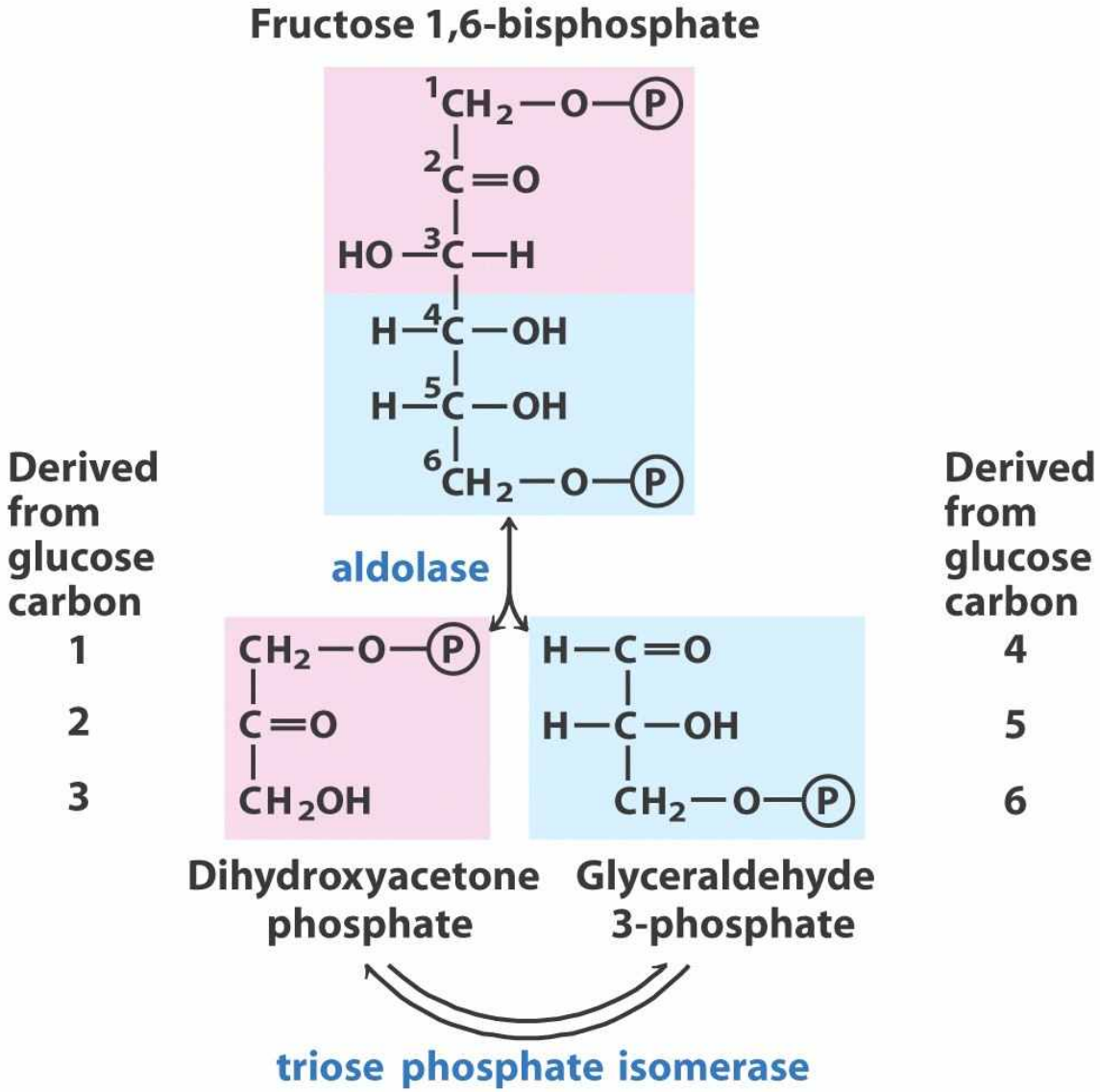
Glyceraldehyde 3-phosphate

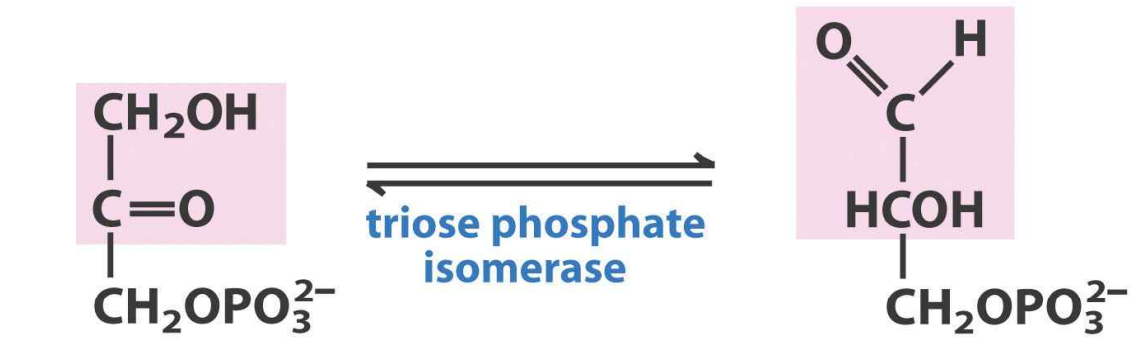
$\Delta G'^{\circ} = 23.8$ kJ/mol

Class I Aldolase reaction



5 Interconversion of the Triose Phosphate





Dihydroxyacetone phosphate

Glyceraldehyde 3-phosphate

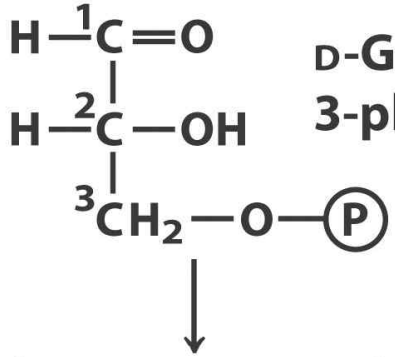
$\Delta G'^{\circ} = 7.5$ kJ/mol

Derived from glucose carbons

4 or 3

5 or 2

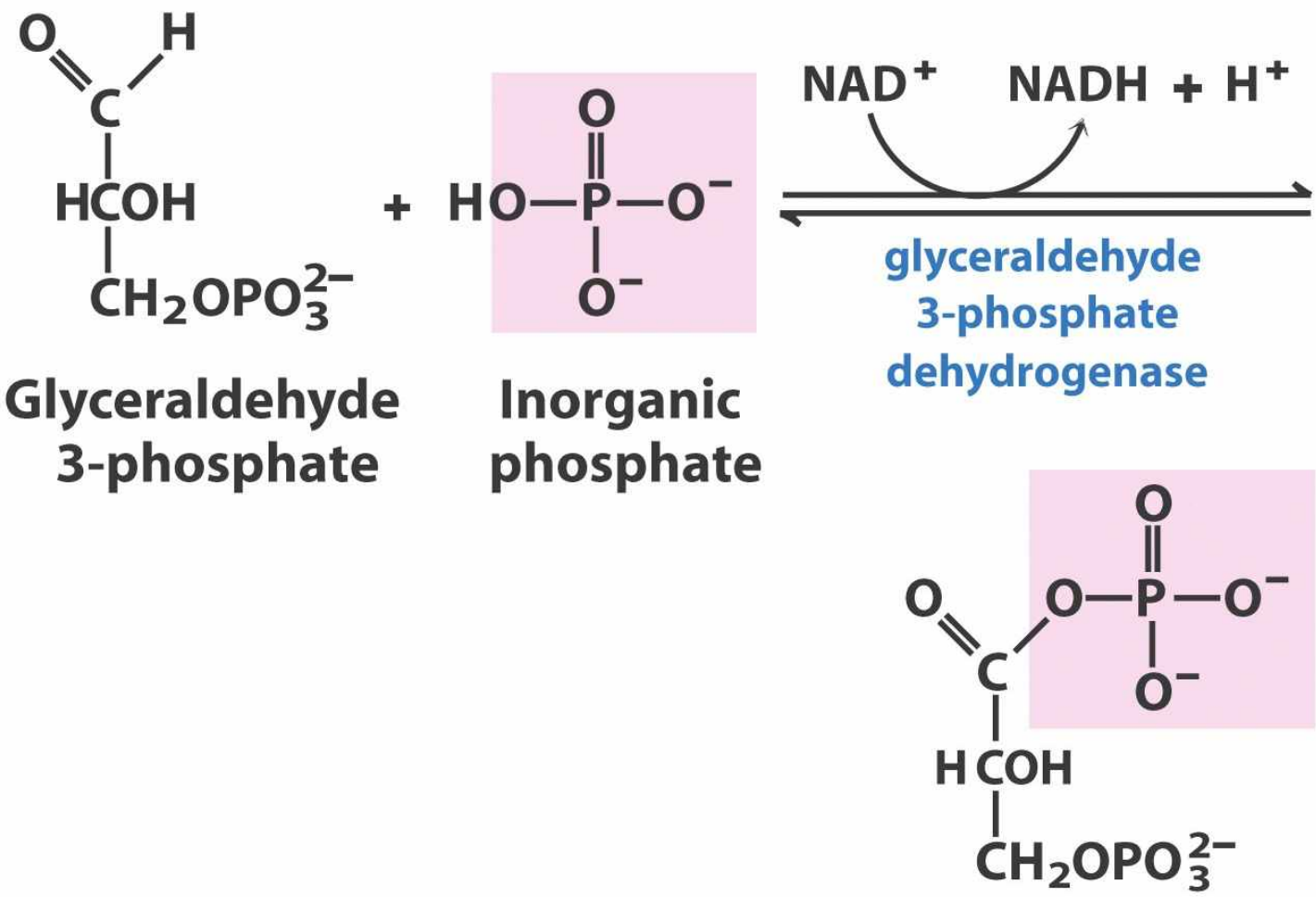
6 or 1



D-Glyceraldehyde 3-phosphate

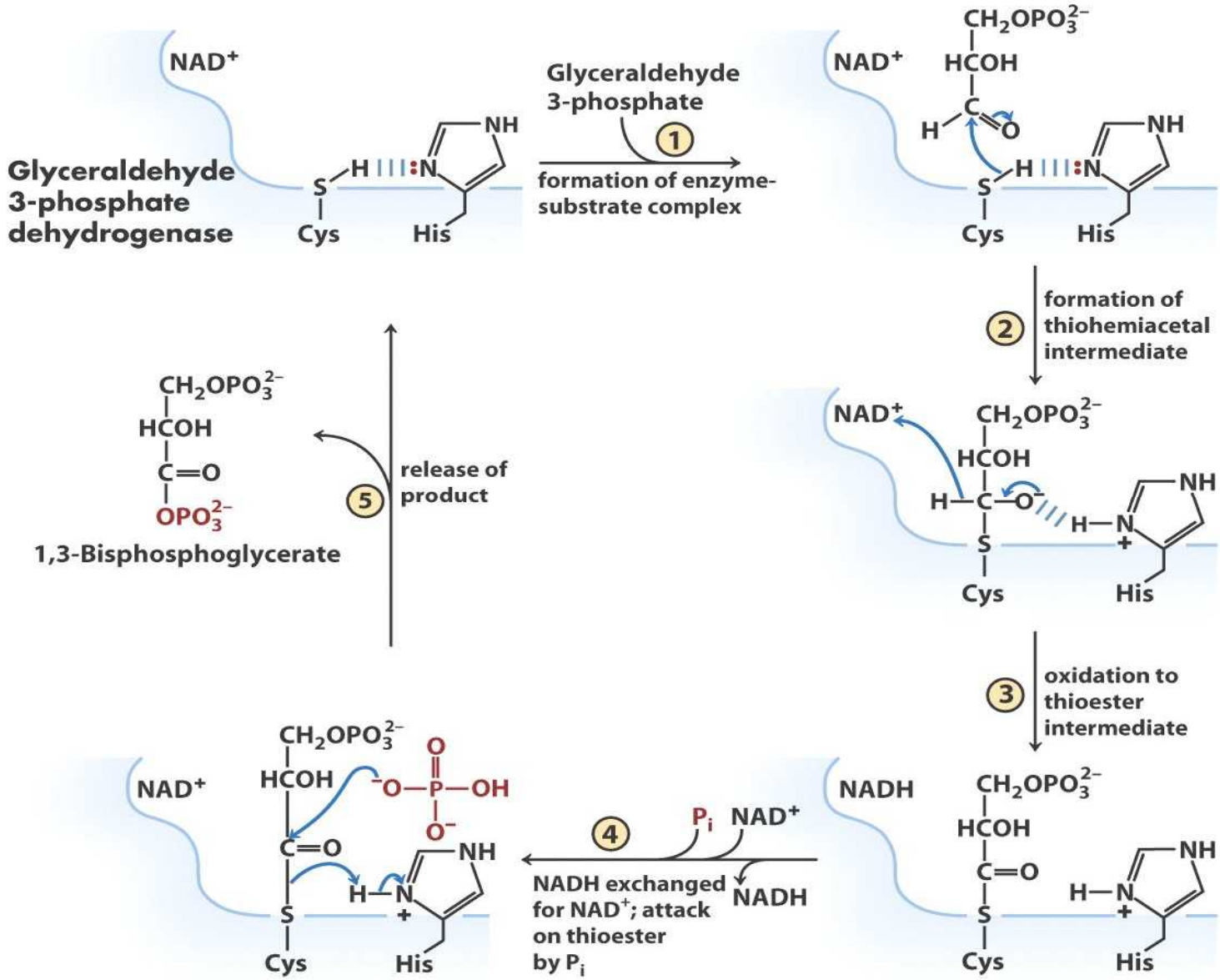
Subsequent reactions of glycolysis

6 *Oxidation of G3P to 1,3-bisphosphoglycerate*

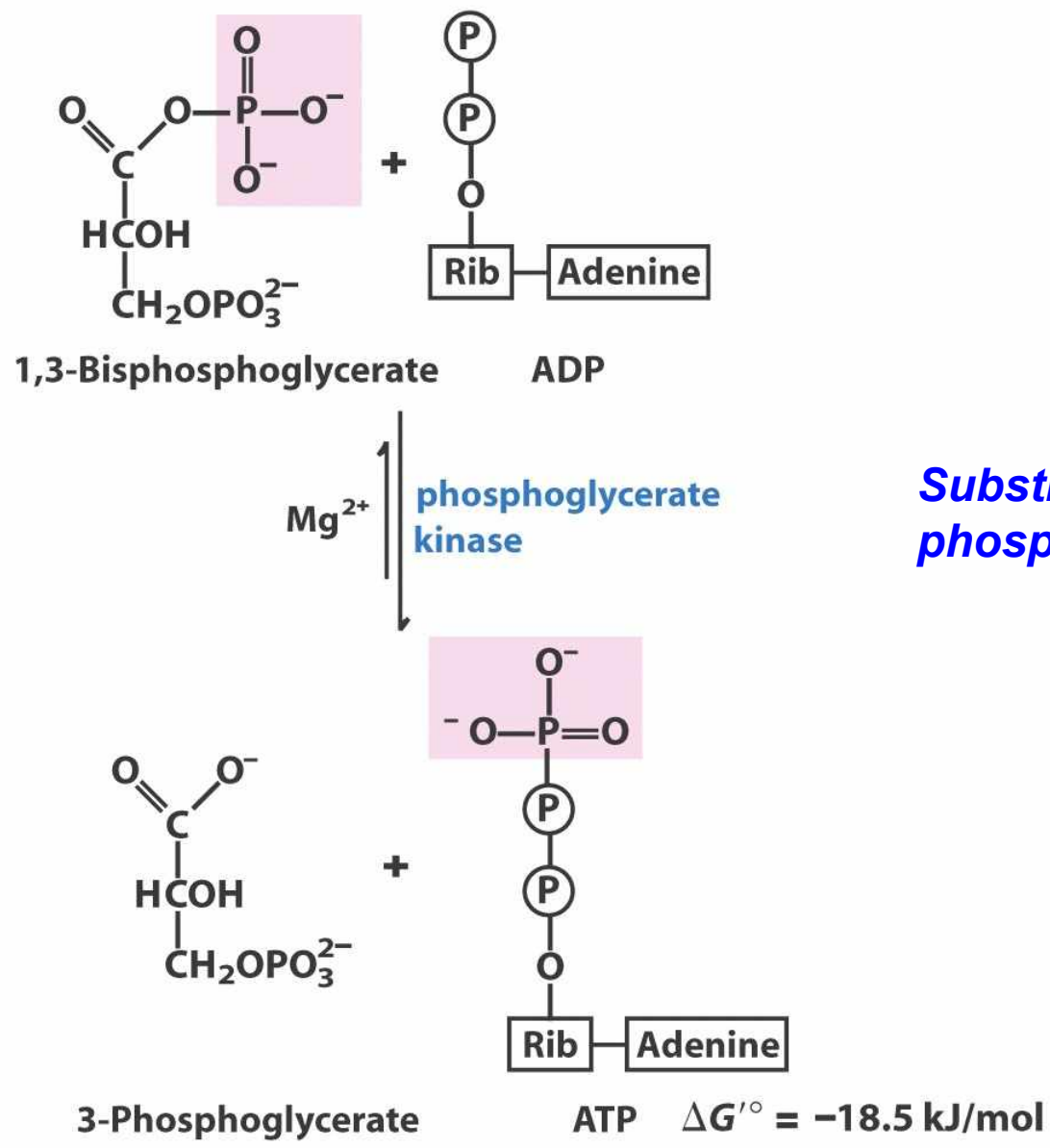


$\Delta G'^{\circ} = 6.3$ kJ/mol

Glyceraldehyde 3-phosphate dehydrogenase reaction

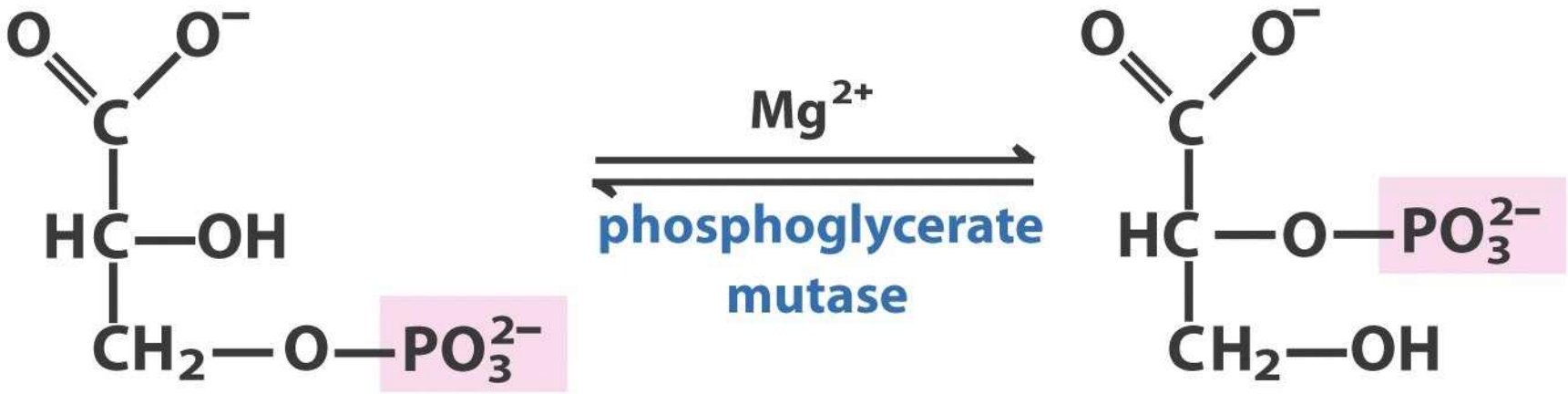


7 *Phosphoryl transfer from 1,3-bisphosphoglycerate*



Substrate-level phosphorylation

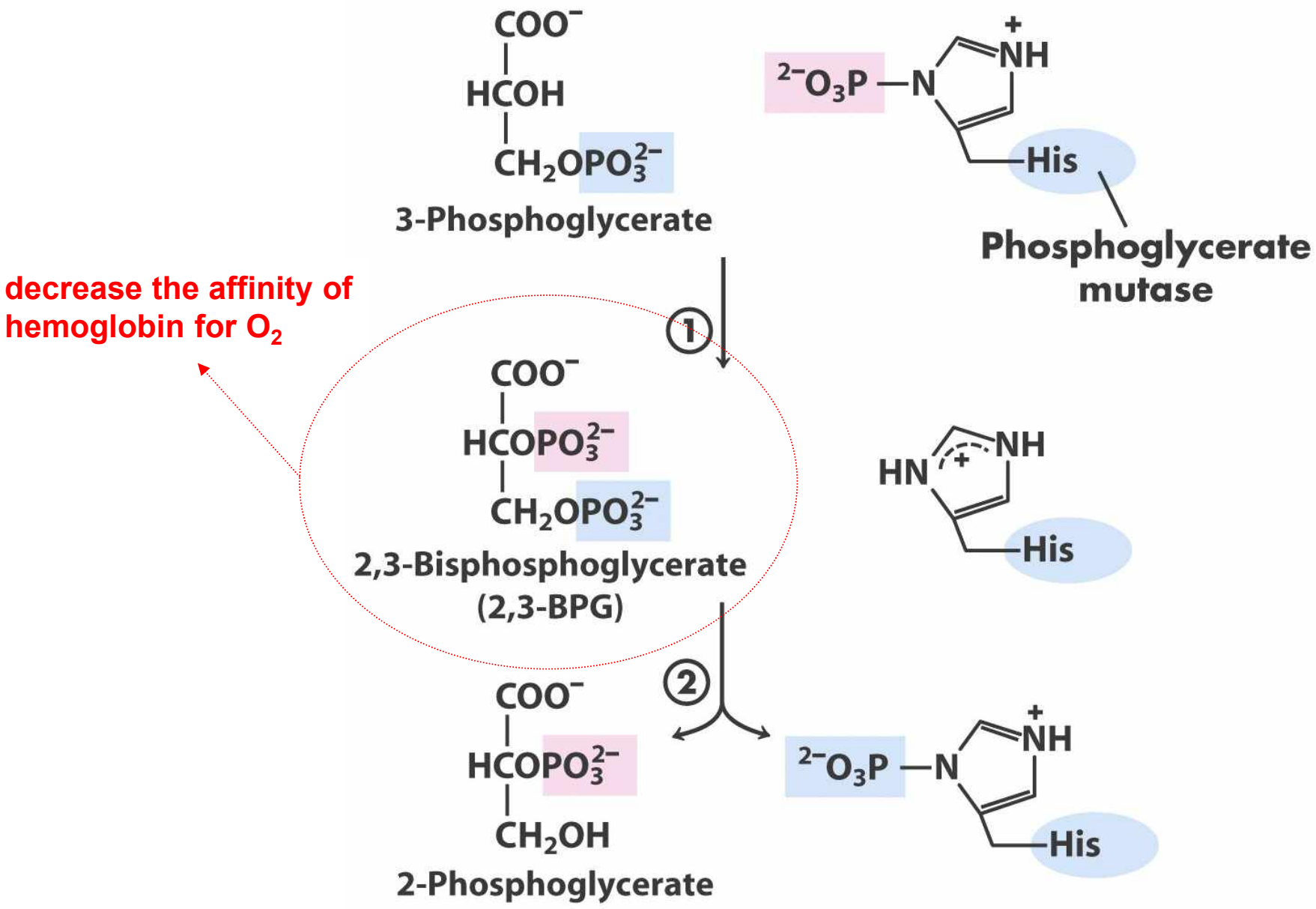
8 *Conversion of 3-phosphoglycerate to 2-phosphoglycerate*



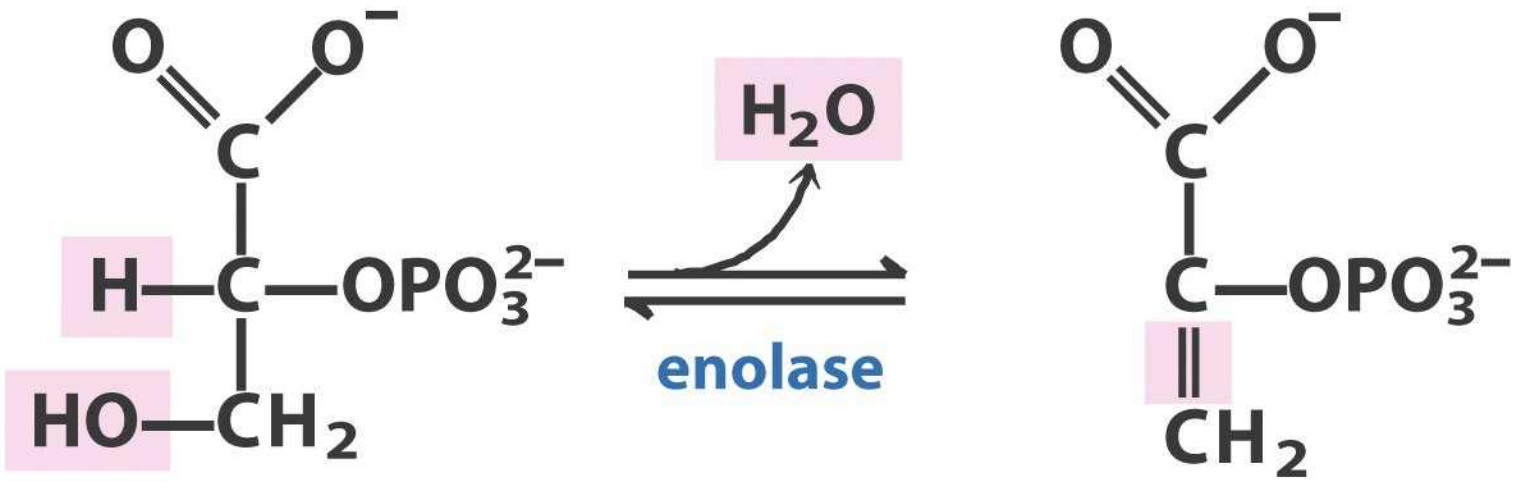
3-Phosphoglycerate **2-Phosphoglycerate**

$\Delta G'^{\circ} = 4.4$ kJ/mol

Phosphoglycerate mutase reaction (2 step)



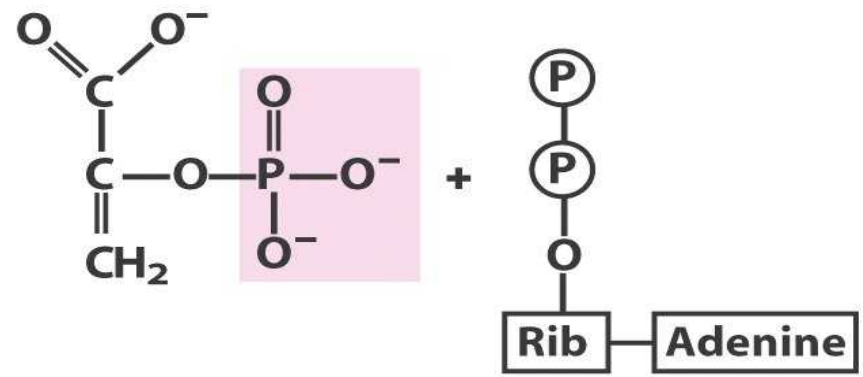
9 *Dehydration of 2-phosphoglycerate to PEP*



2-Phosphoglycerate **Phosphoenolpyruvate**

$\Delta G'^{\circ} = 7.5$ kJ/mol

10 *Phosphoryl transfer from PEP to ADP*

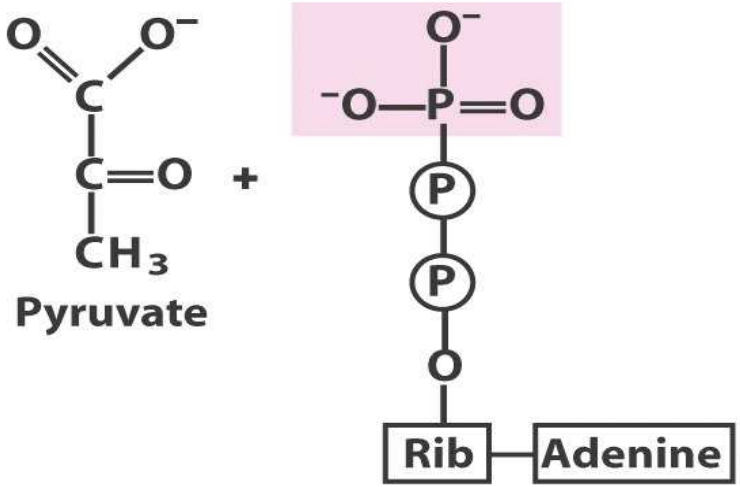


Phosphoenolpyruvate ADP

Mg^{2+}, K^+ | pyruvate kinase

irreversible

Substrate-level phosphorylation



Pyruvate ATP

Phosphoenolpyruvate hyrolysis : -61.9 kJ/mol

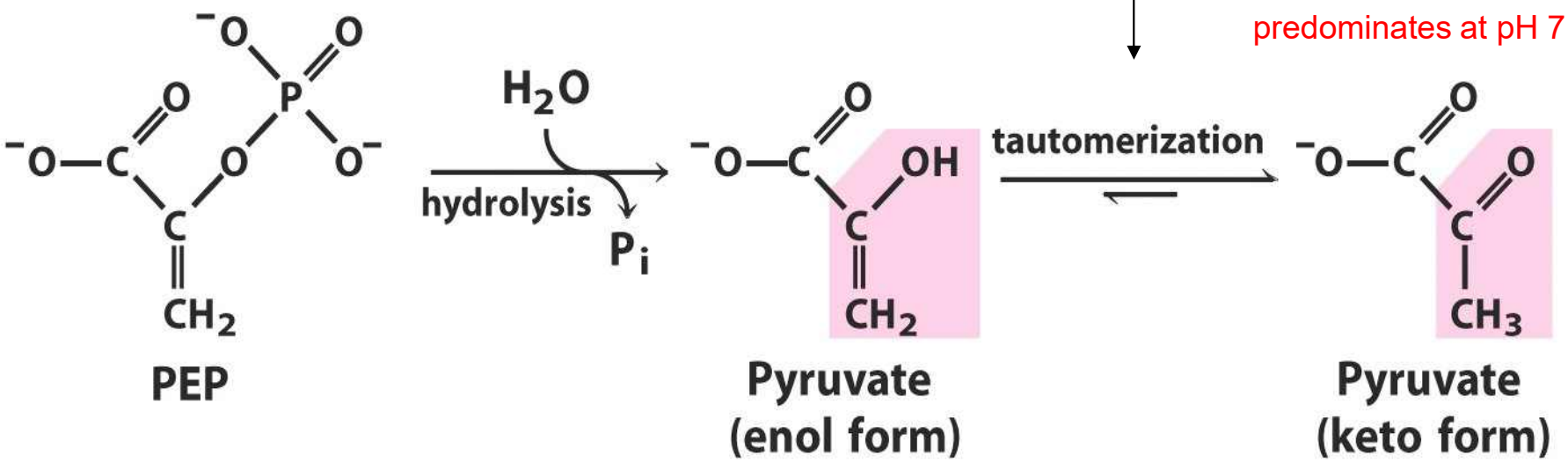
→ **ATP synthesis : -30.5 kJ/mol**

$\Delta G'^{\circ} = -31.4$ kJ/mol

Tautomerization of Pyruvate

Tautomerization is not possible in PEP, and thus the products of hydrolysis are stabilized relative to the reactants

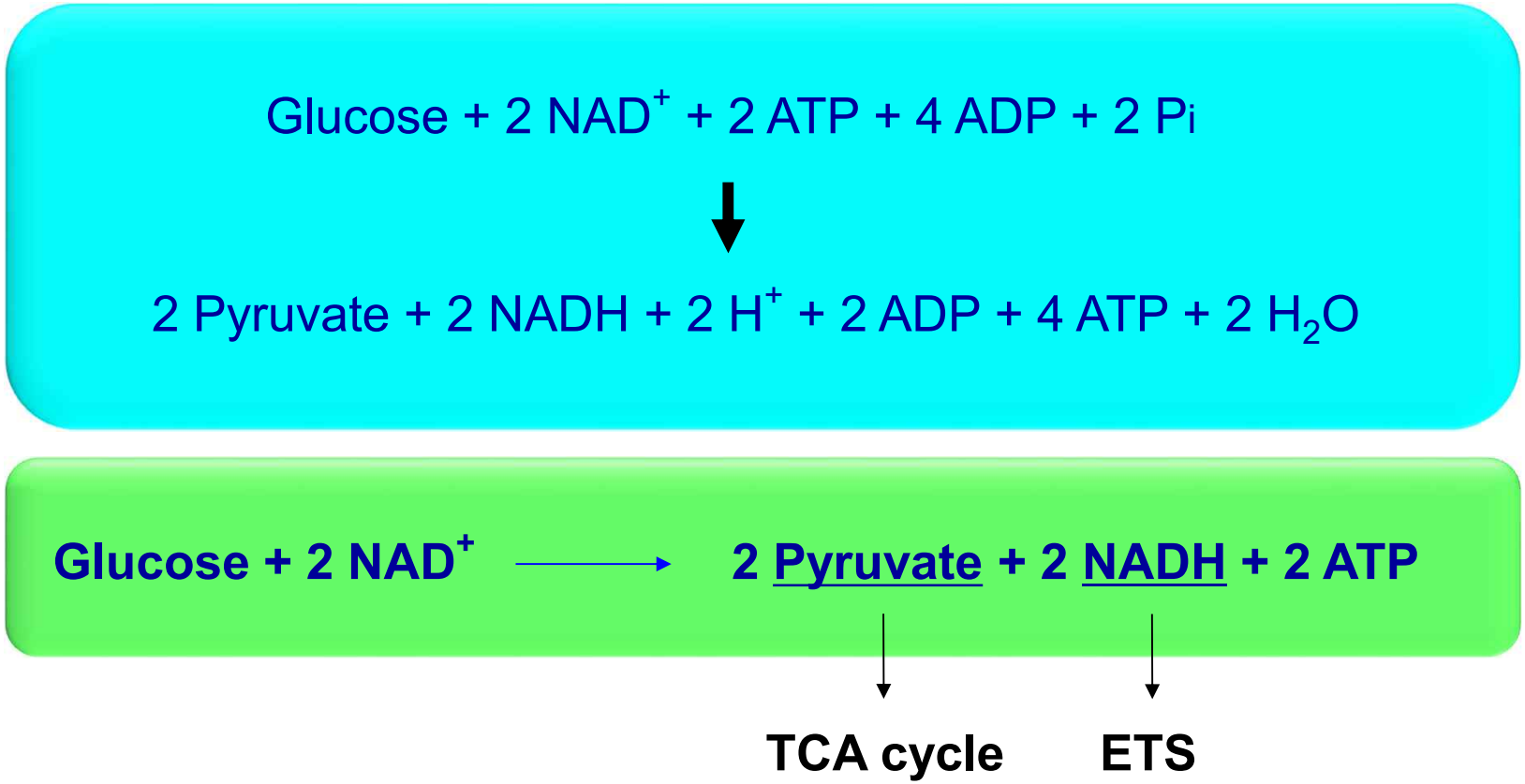
predominates at pH 7



$$PEP^{3-} + H_2O \longrightarrow pyruvate^{-} + P_i^{2-}$$

$$\Delta G'^{\circ} = -61.9\ kJ/mol$$

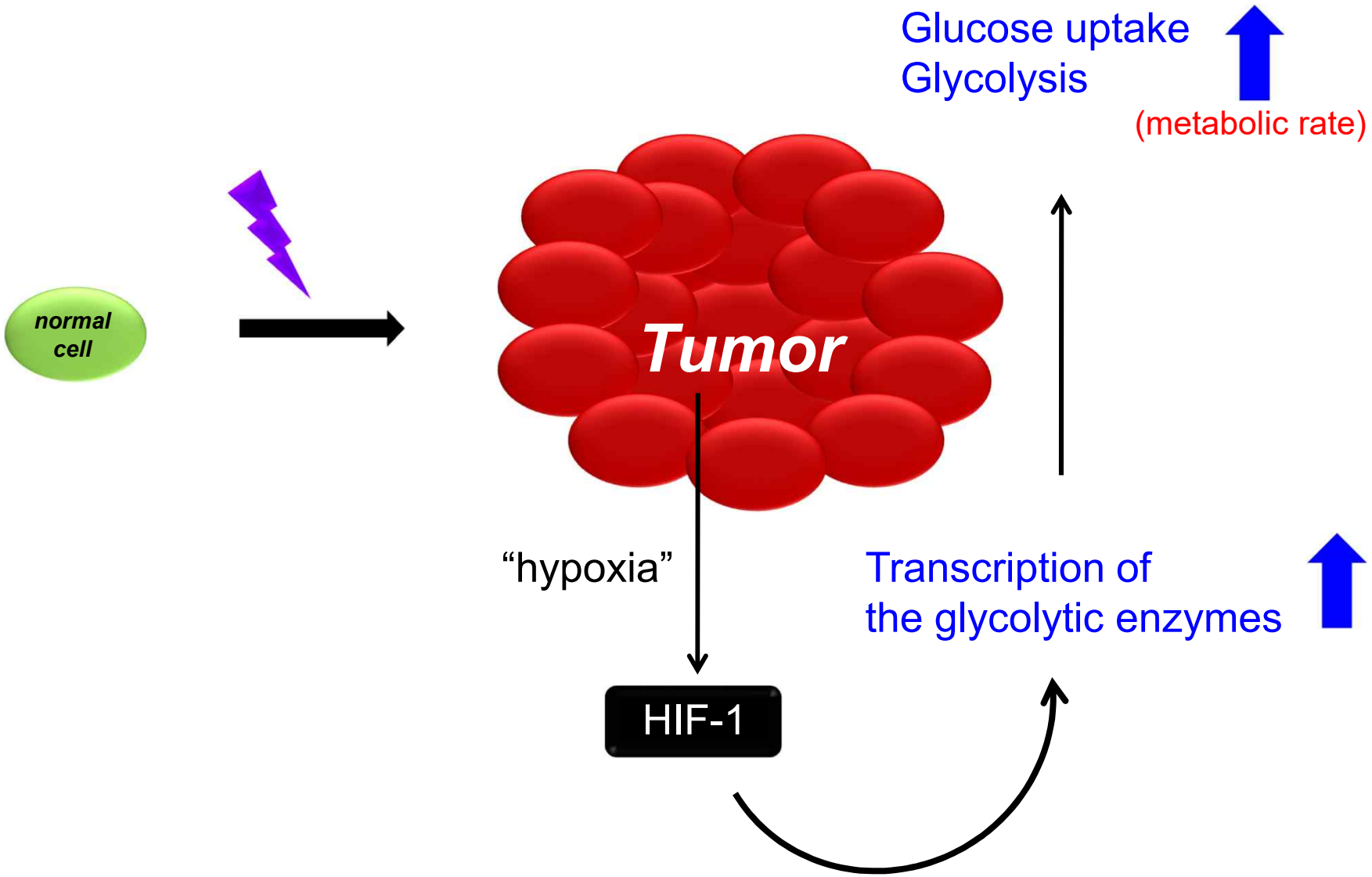
The overall balance for glycolysis



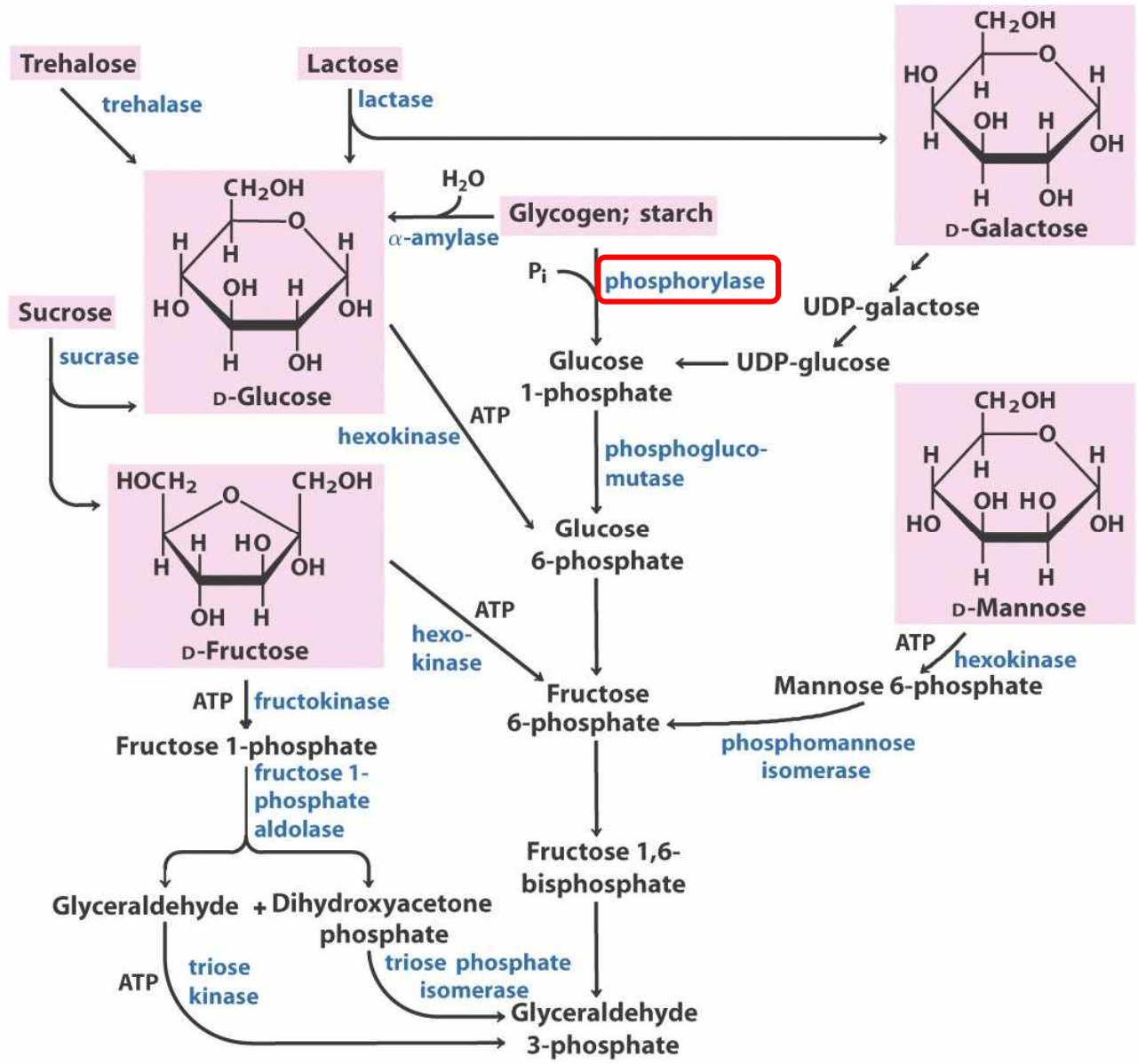
The Rate of Glycolysis : ATP consumption, NADH regeration
allosteric regulation of glycolytic enzymes
(Hexokinase, PFK-1, Pyruvate kinase)
Hormone regulation (glucagon, insulin, epinephrin)

Cancerous tissue

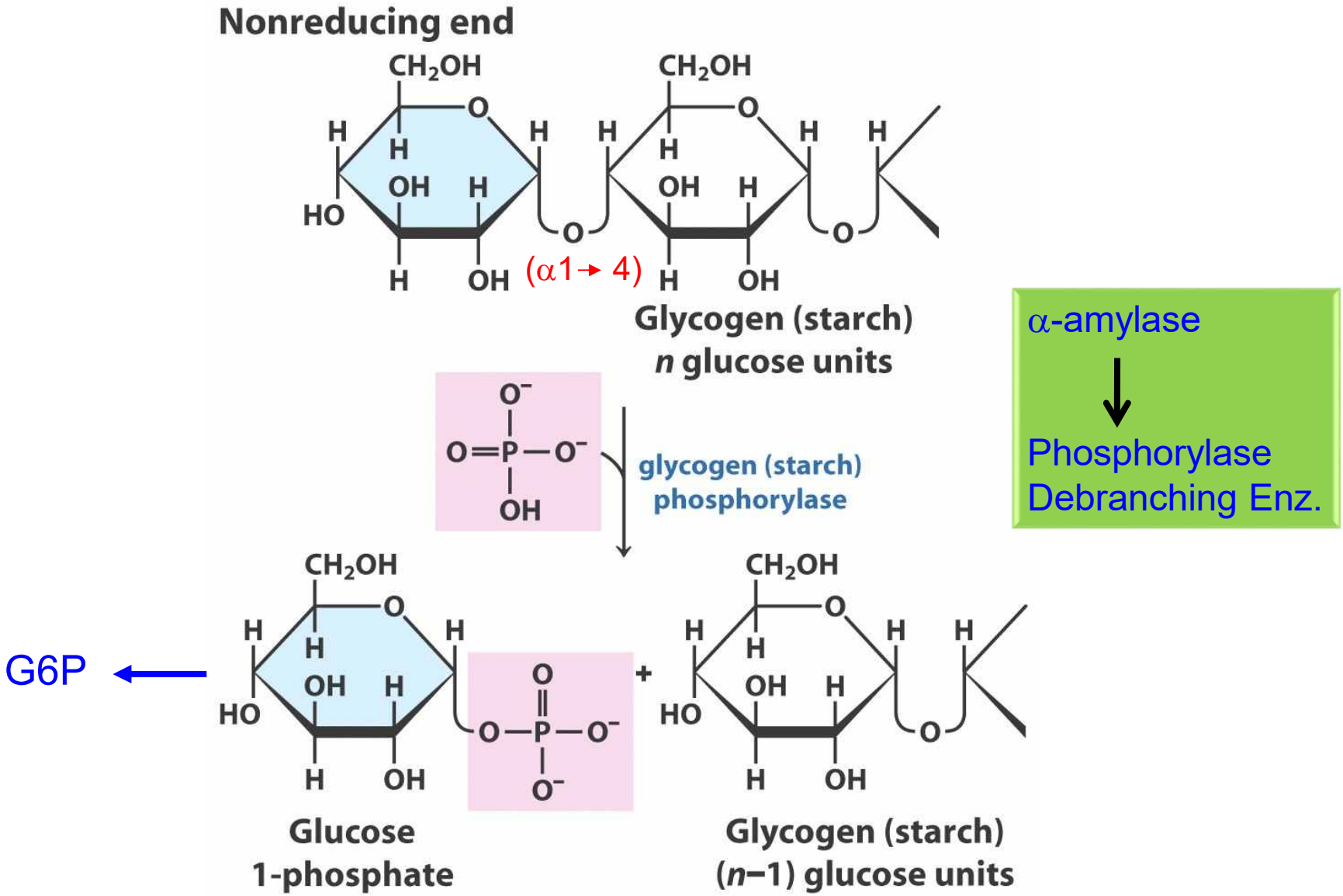
PET (positron emmision tomography)



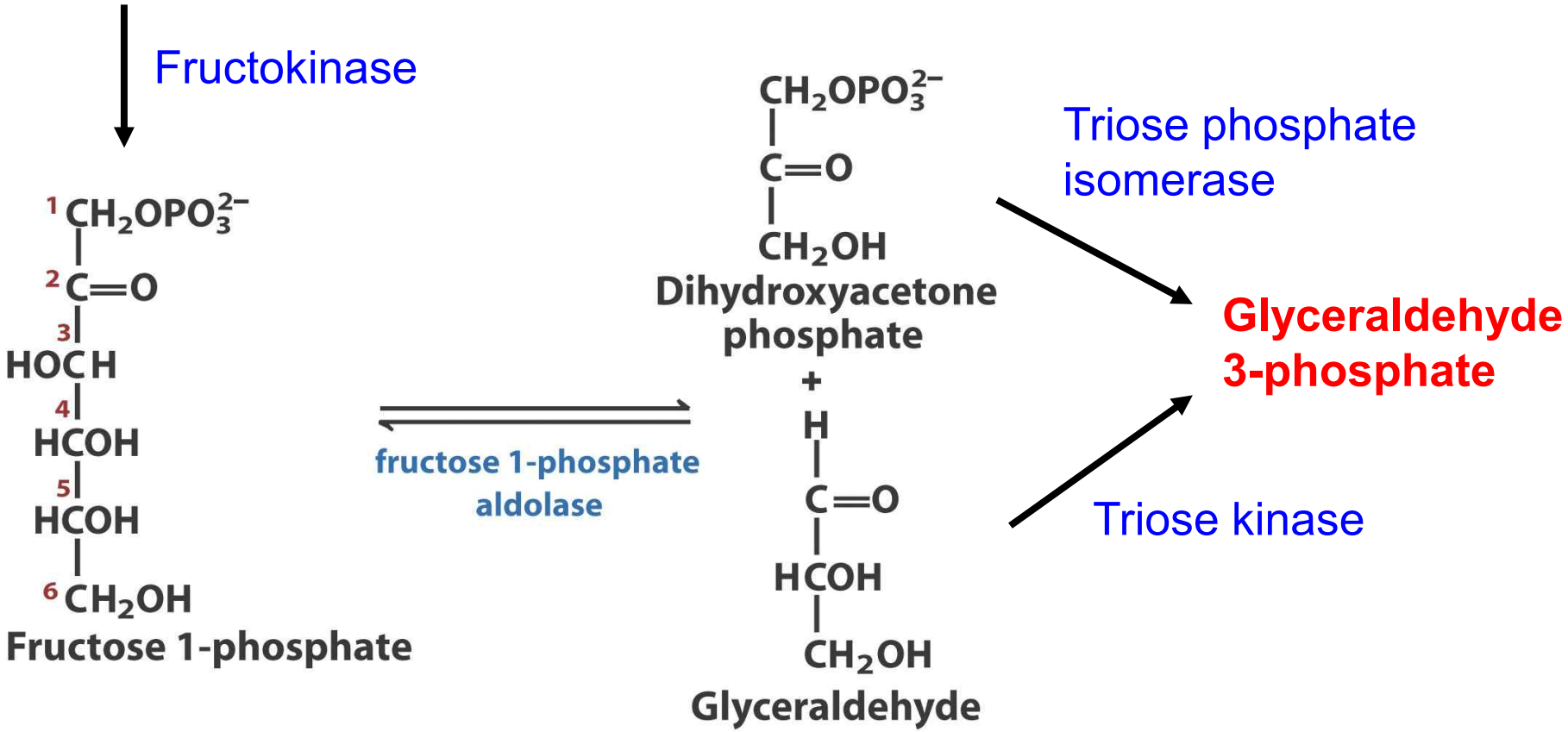
Feeder pathways for glycolysis



Glycogen breakdown by glycogen phosphorylase

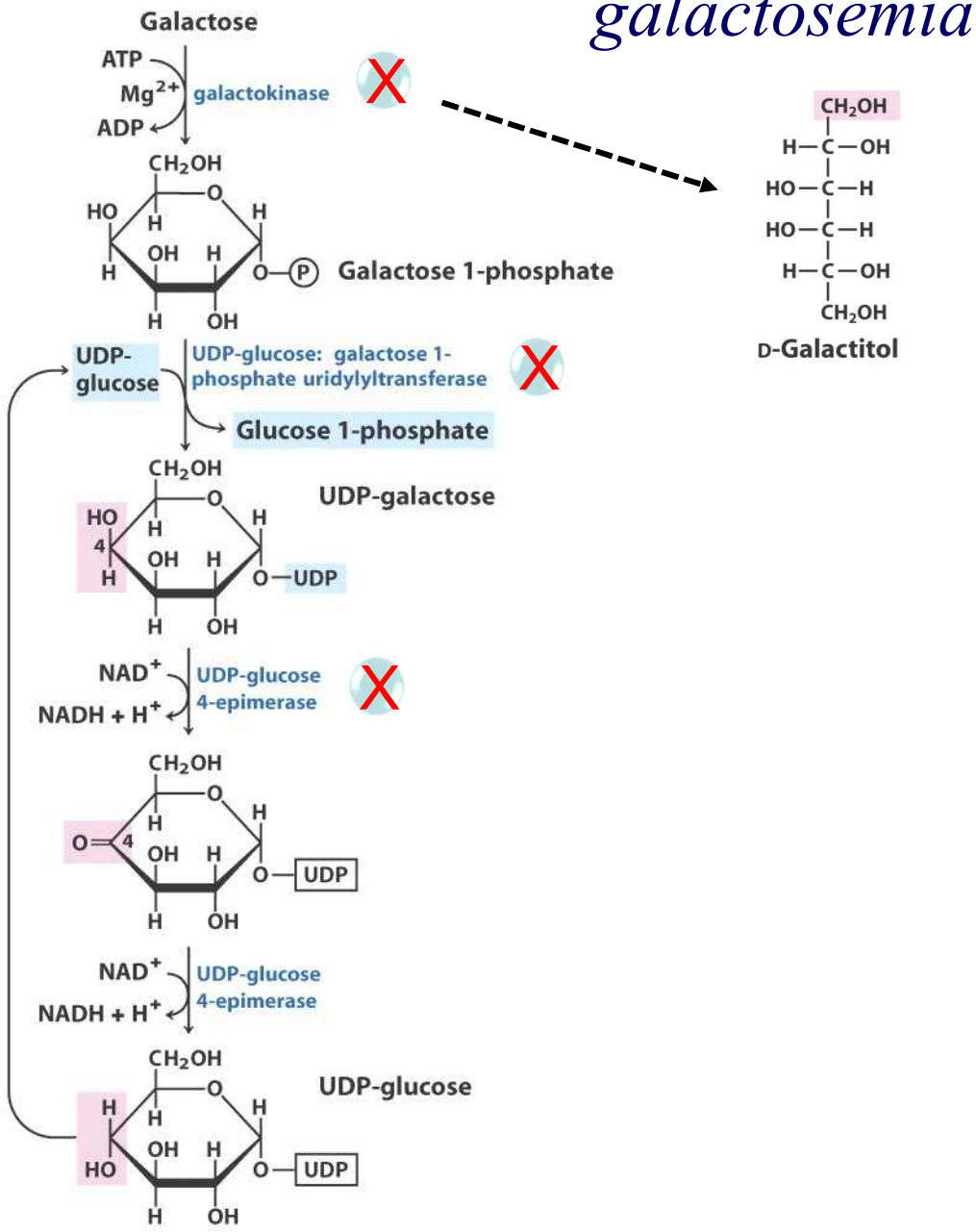


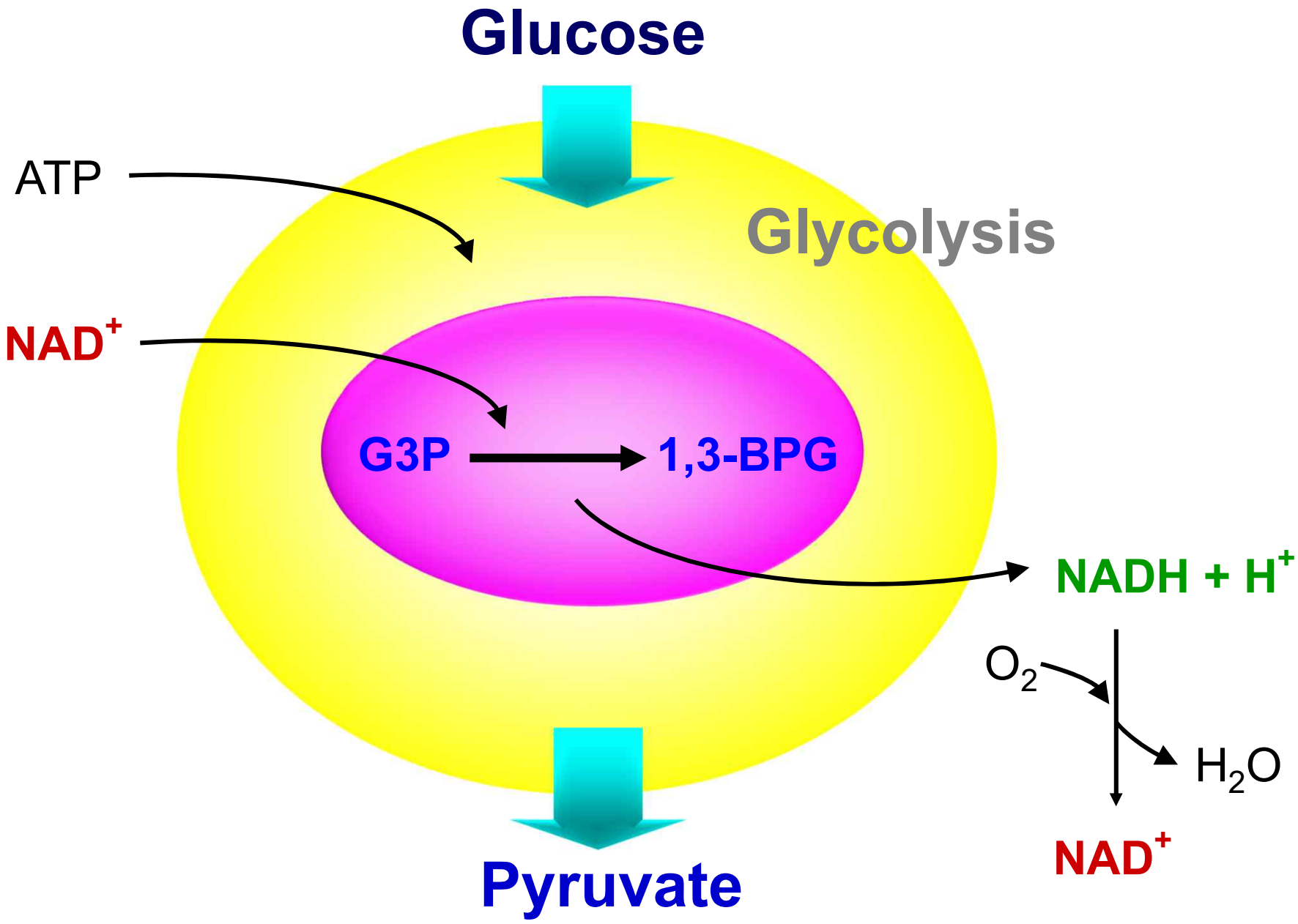
Fructose breakdown



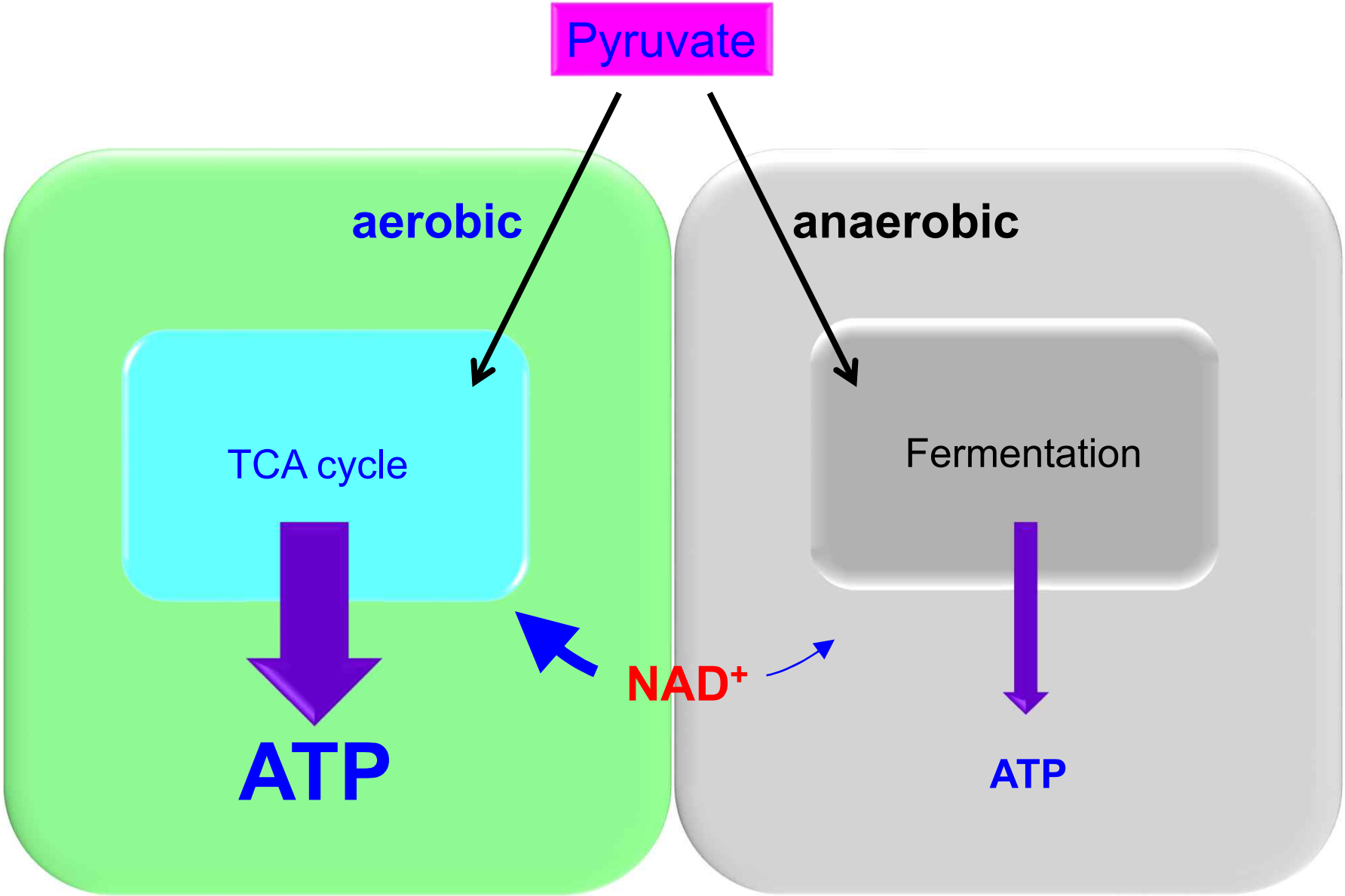
Conversion of galactose to glucose 1-phosphate

galactosemia

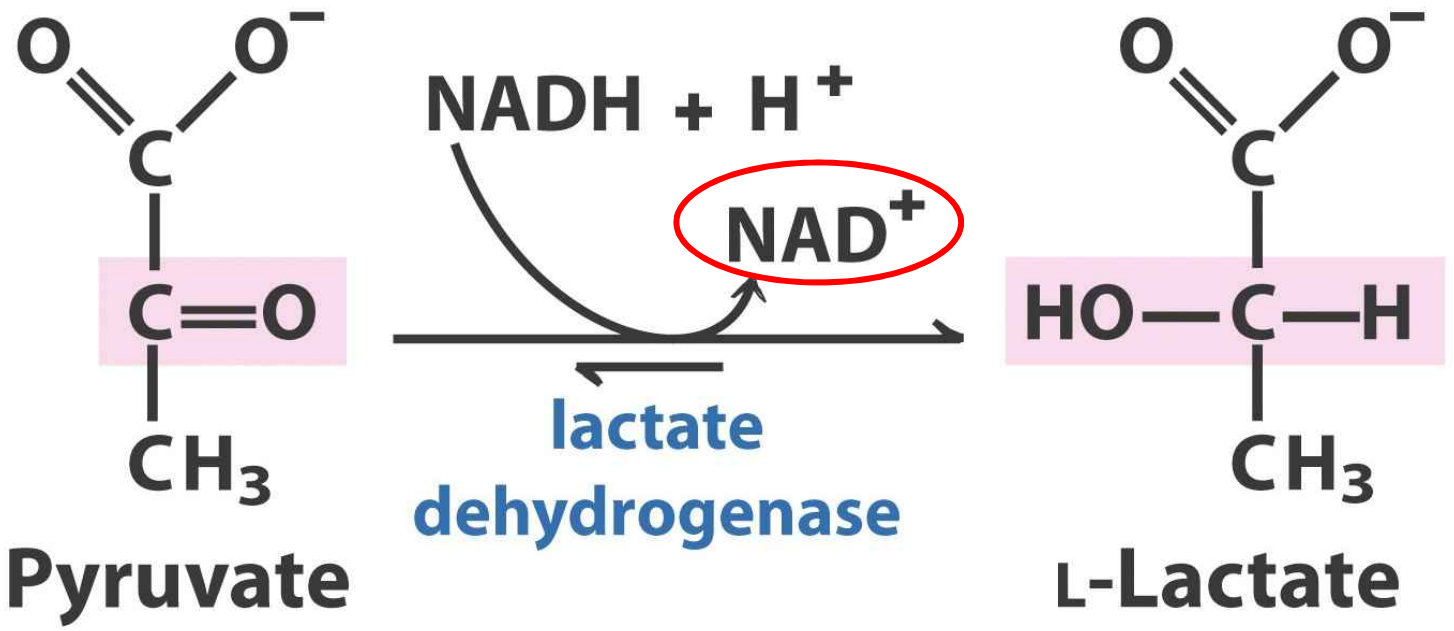



Glucose
ATP
Glycolysis
NAD+
G3P
1,3-BPG
NADH + H+
O2
H2O
NAD+
Pyruvate

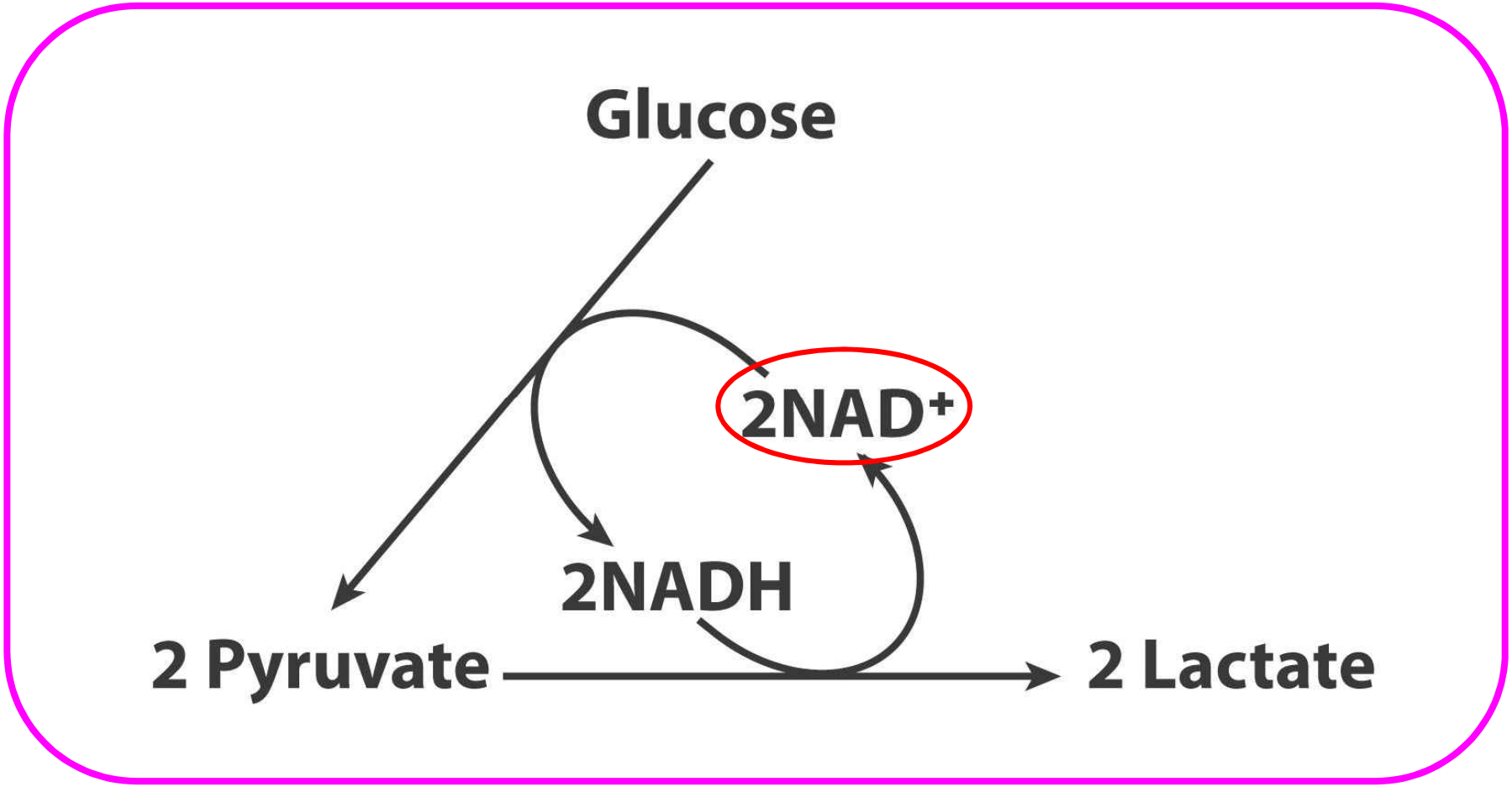
Fates of Pyruvate !!



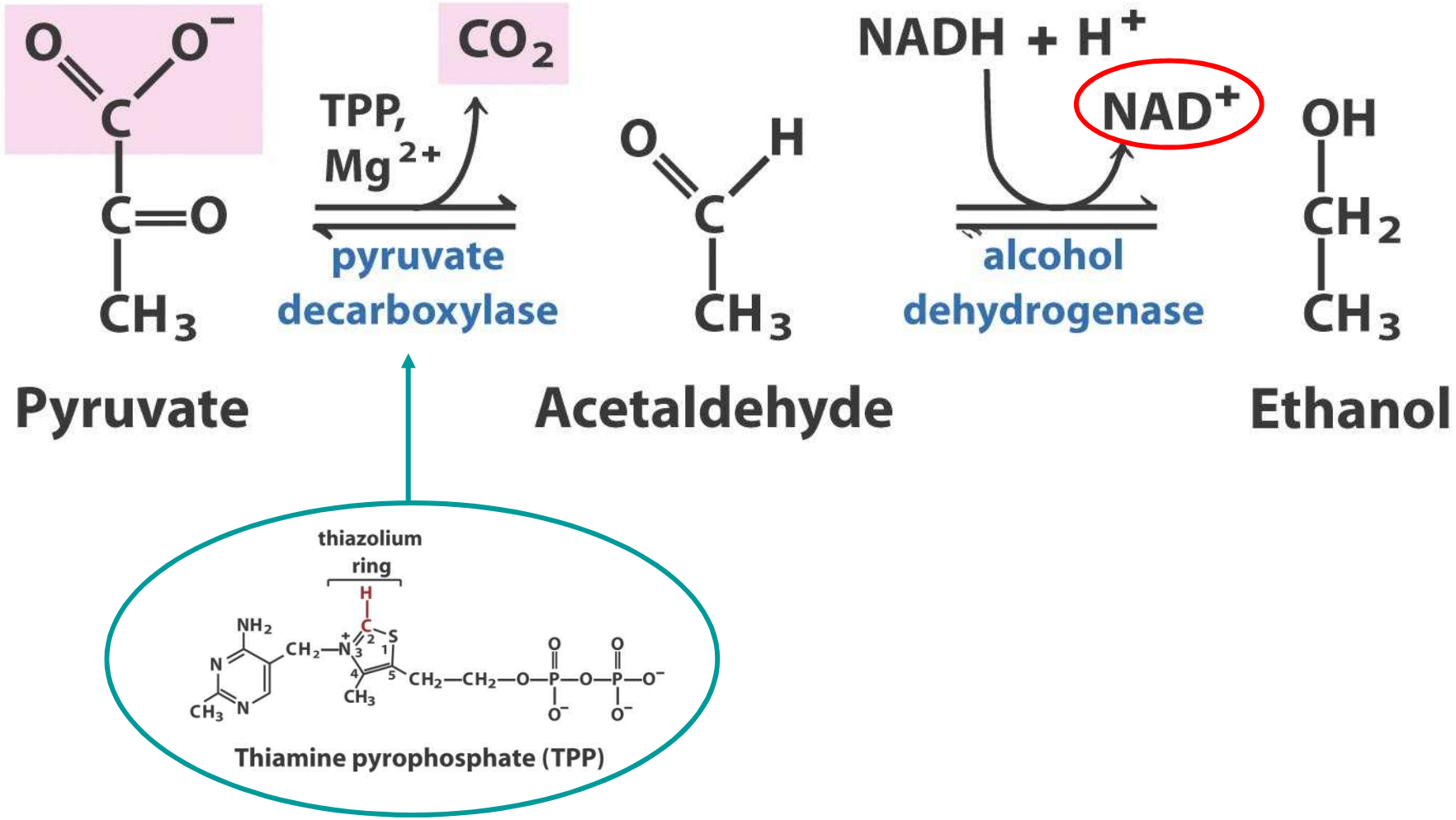
Lactic acid fermentation



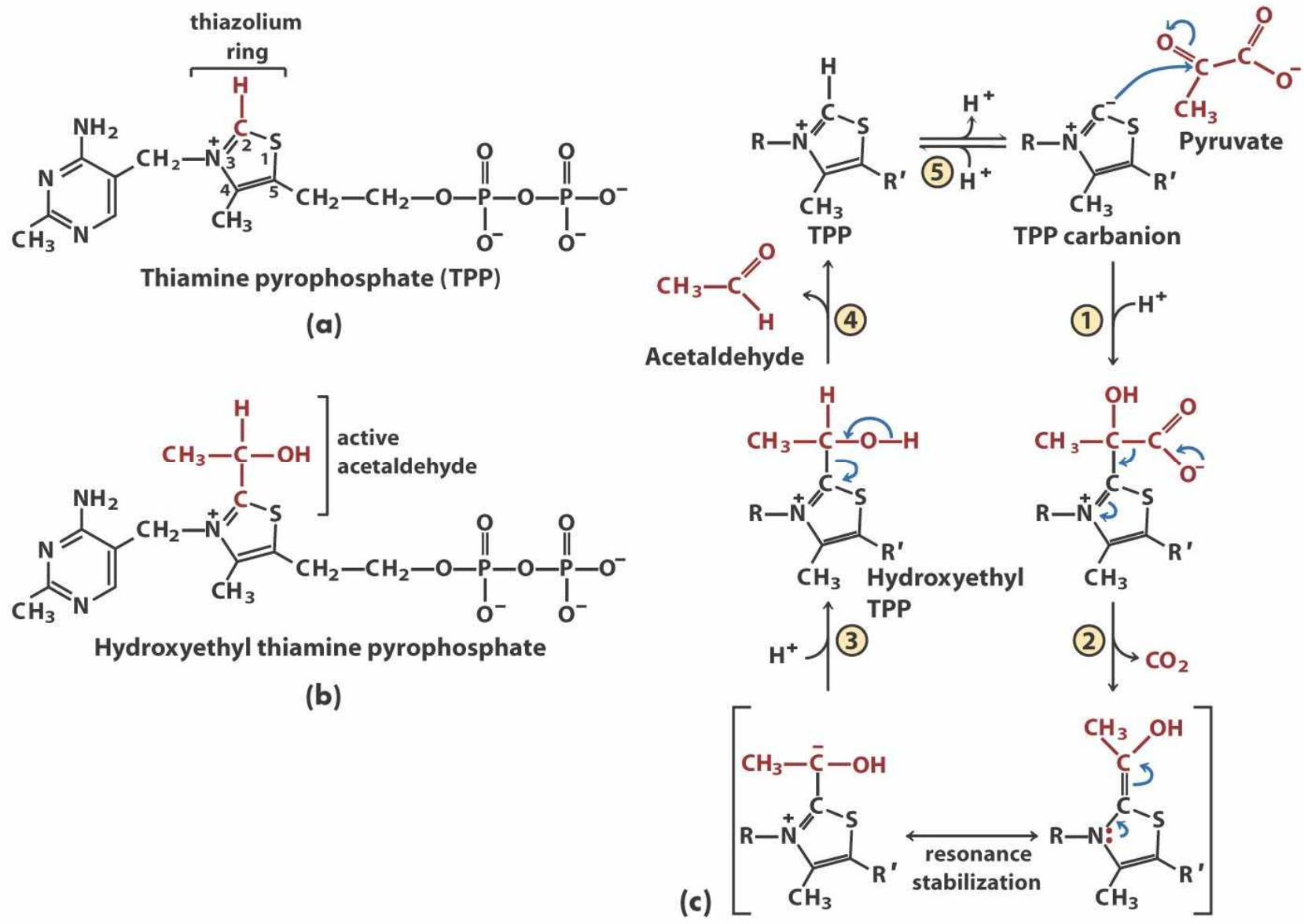
$\Delta G'^{\circ} = -25.1$ kJ/mol


Glucose
2NAD+
2NADH
2 Pyruvate
2 Lactate

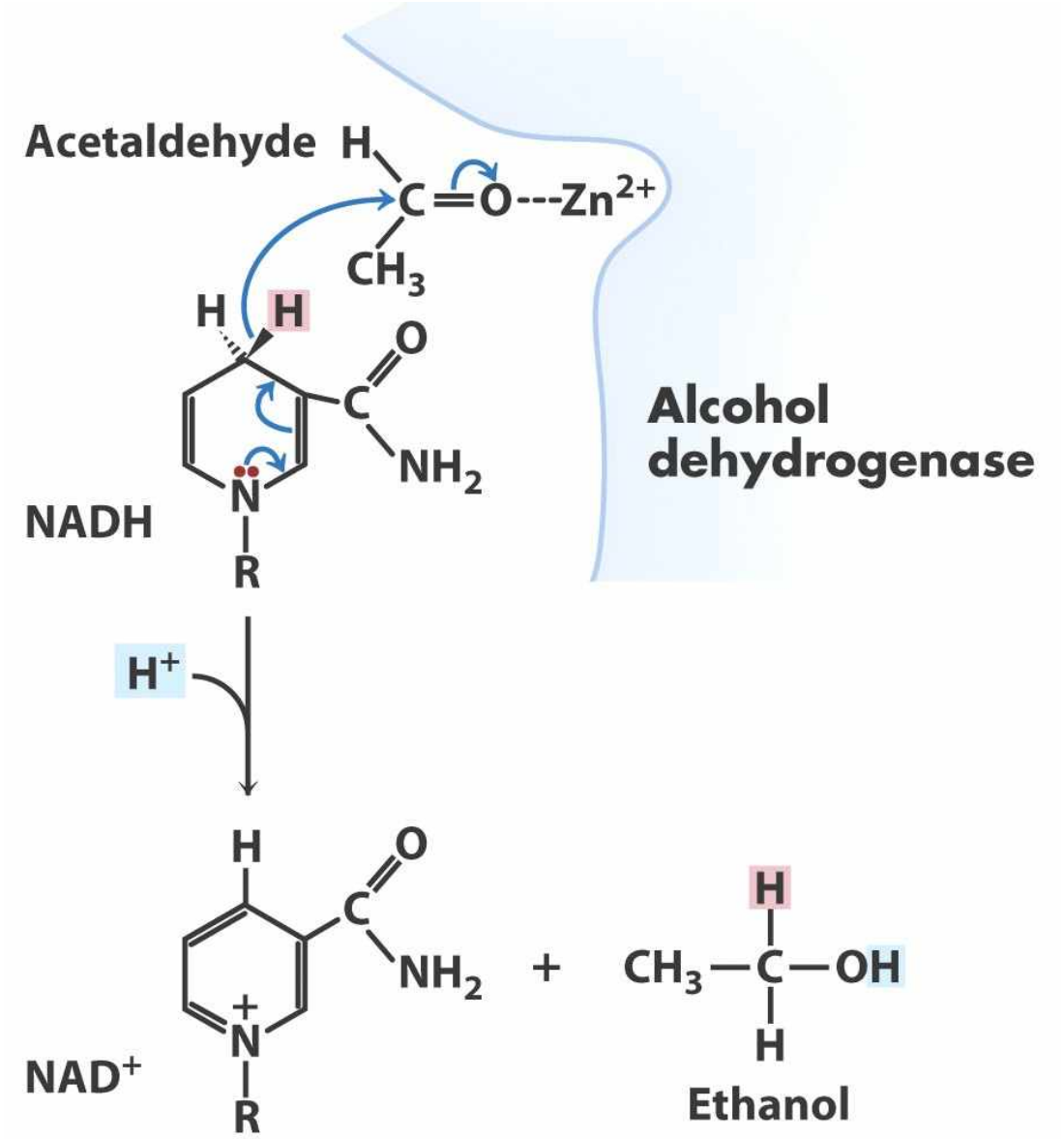
Alcohol fermentation



TPP and its role in pyruvate decarboxylase

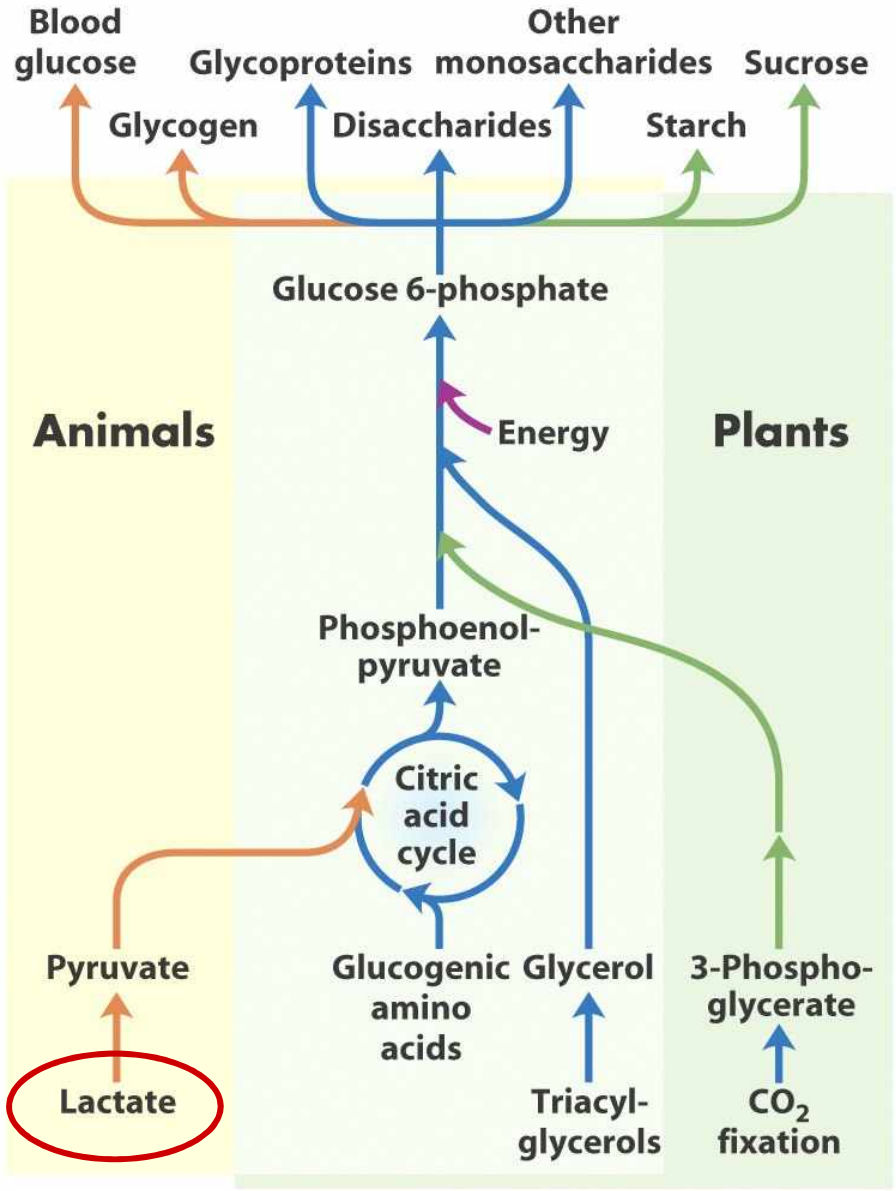


Alcohol dehydrogenase reaction



Carbohydrate synthesis from simple precursors

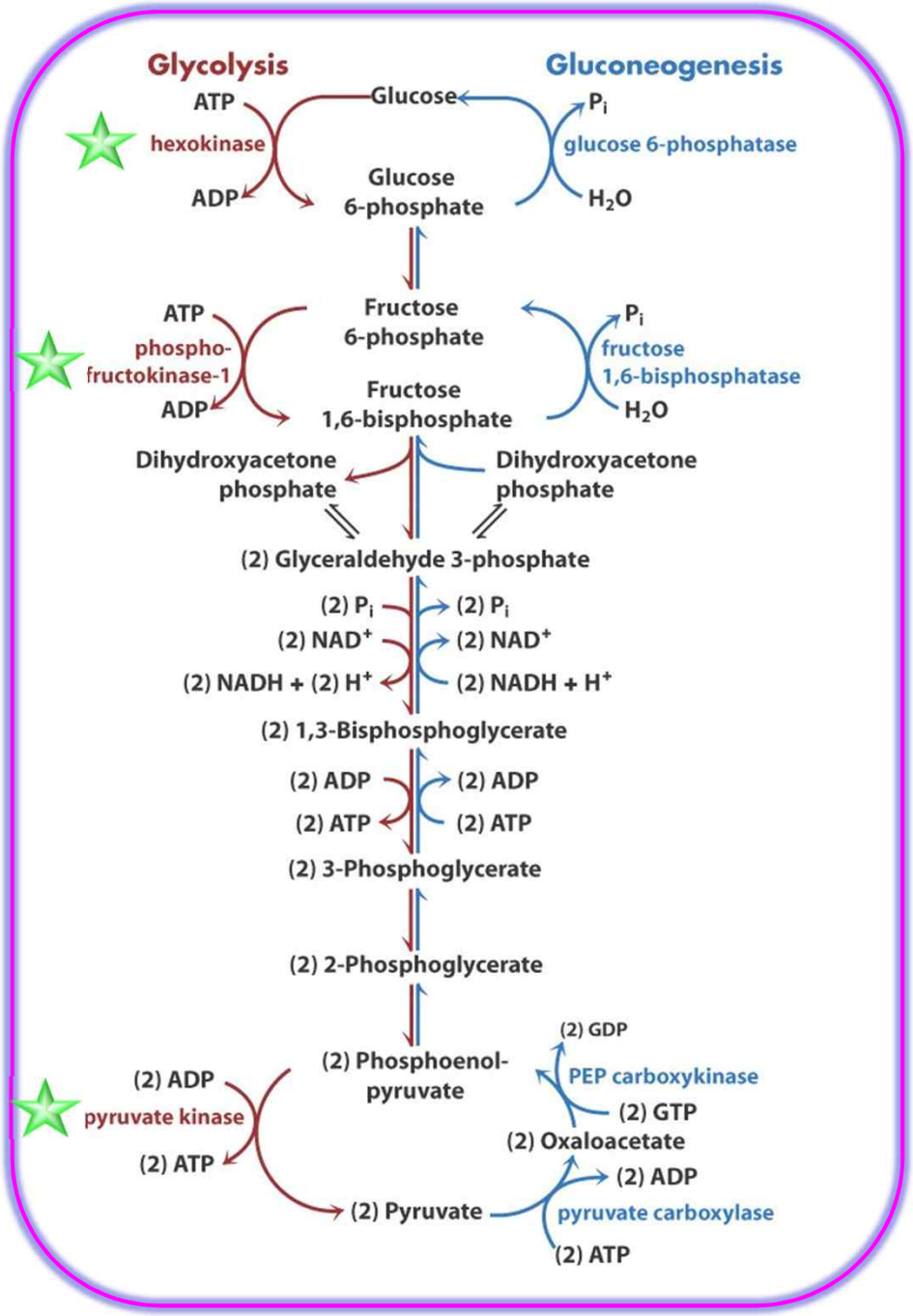
(Gluconeogenesis)

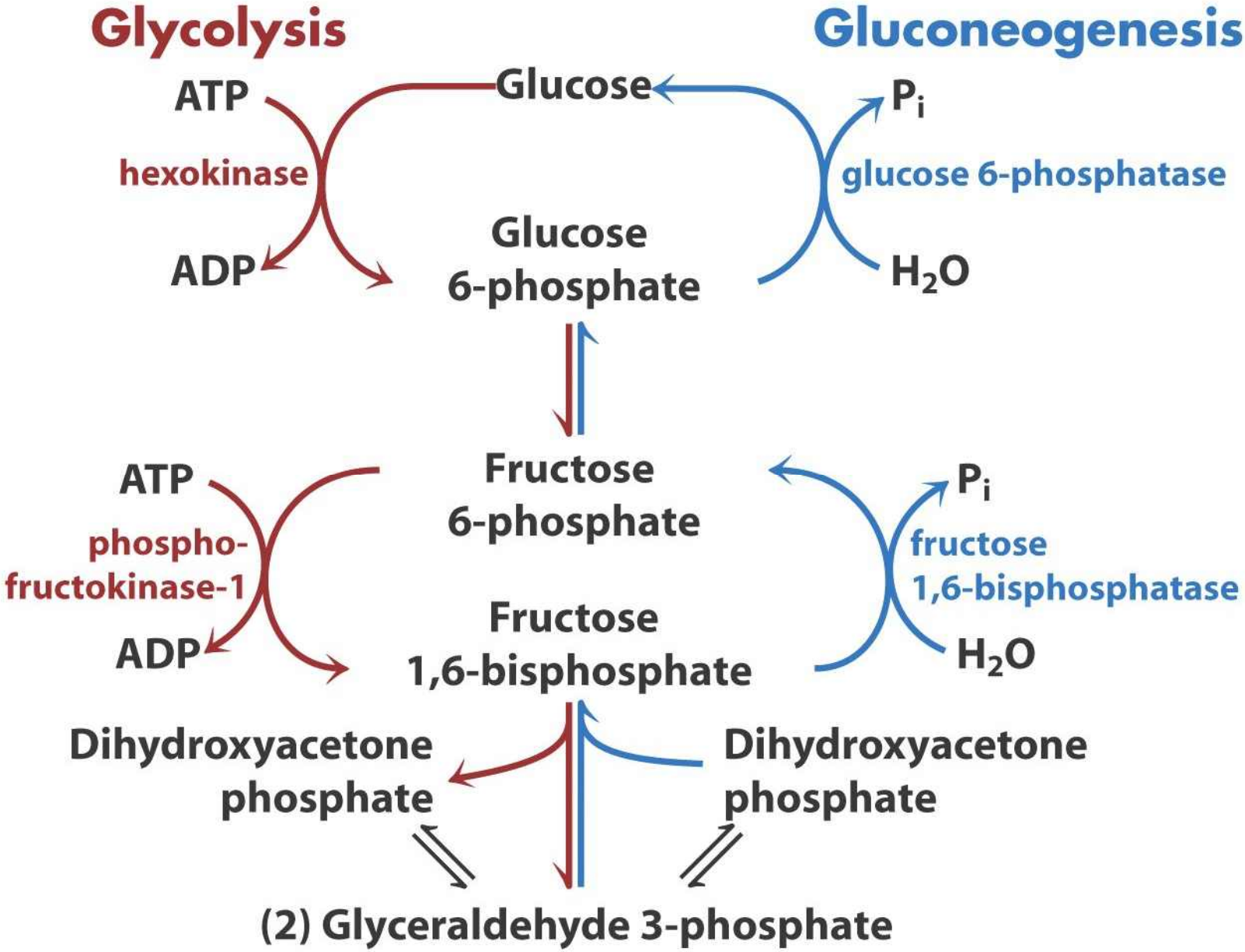


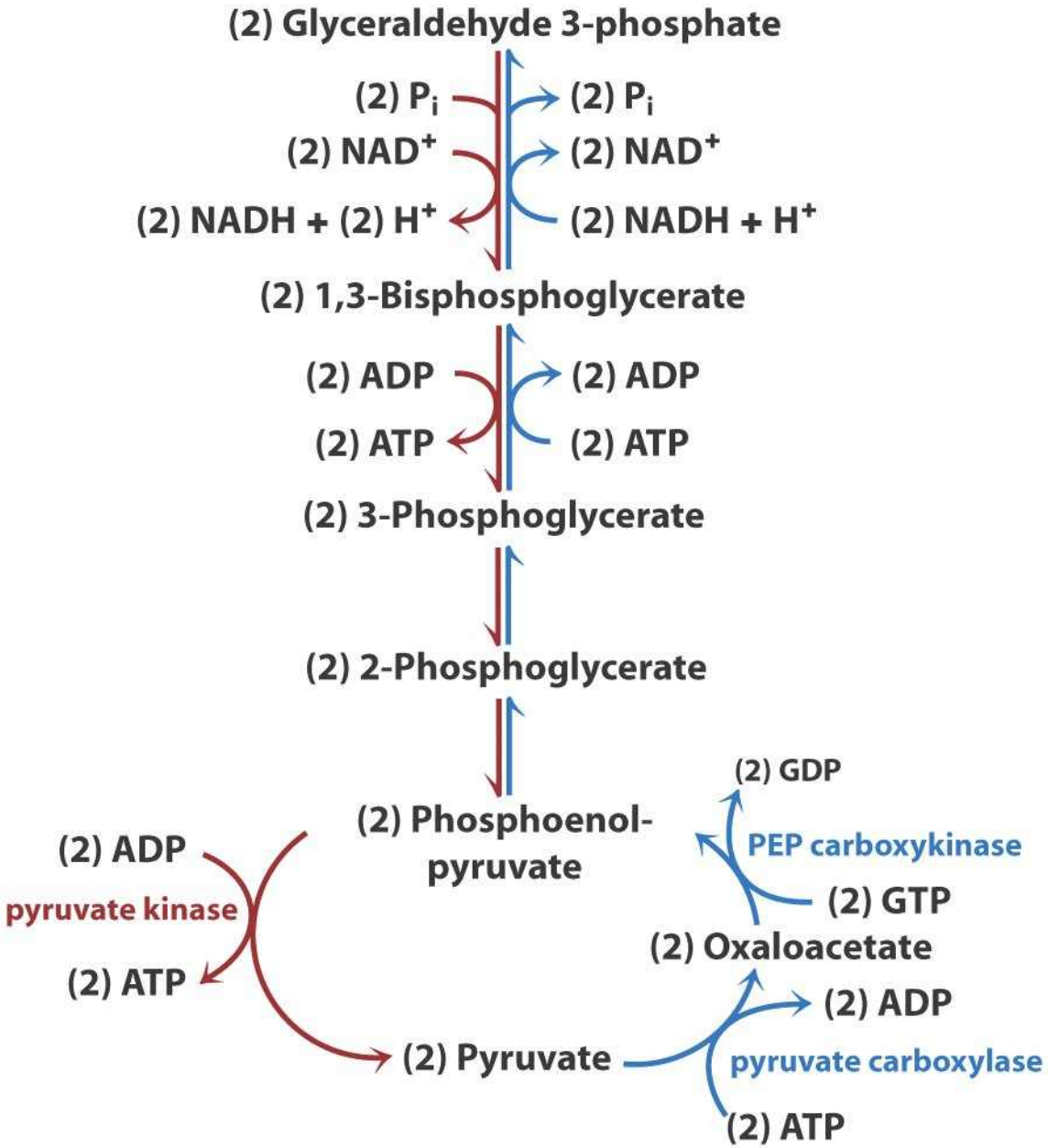
* brain: ~120 g of glucose/day

Opposing pathways of glycolysis and gluconeogenesis

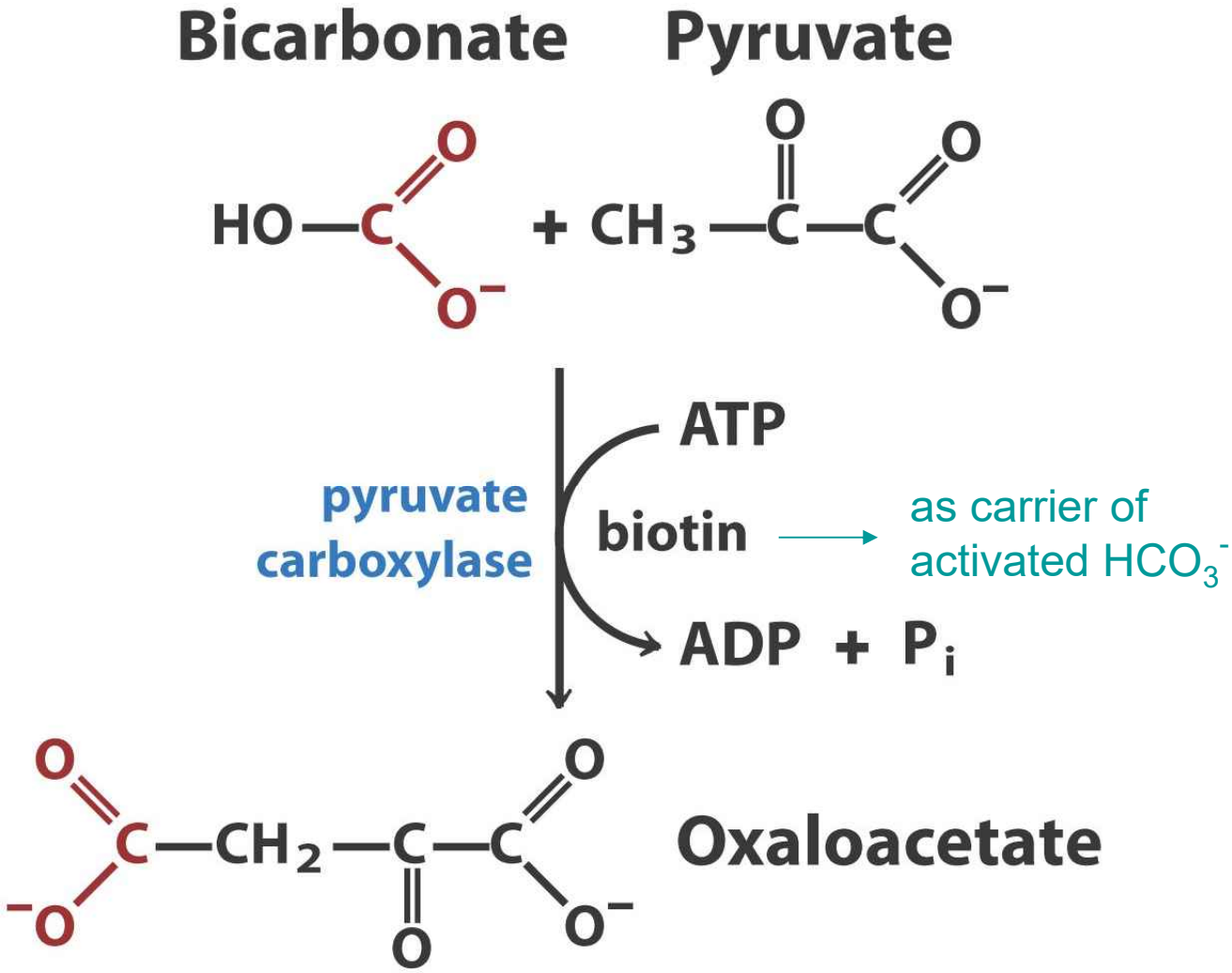
mainly in the liver (mammals)



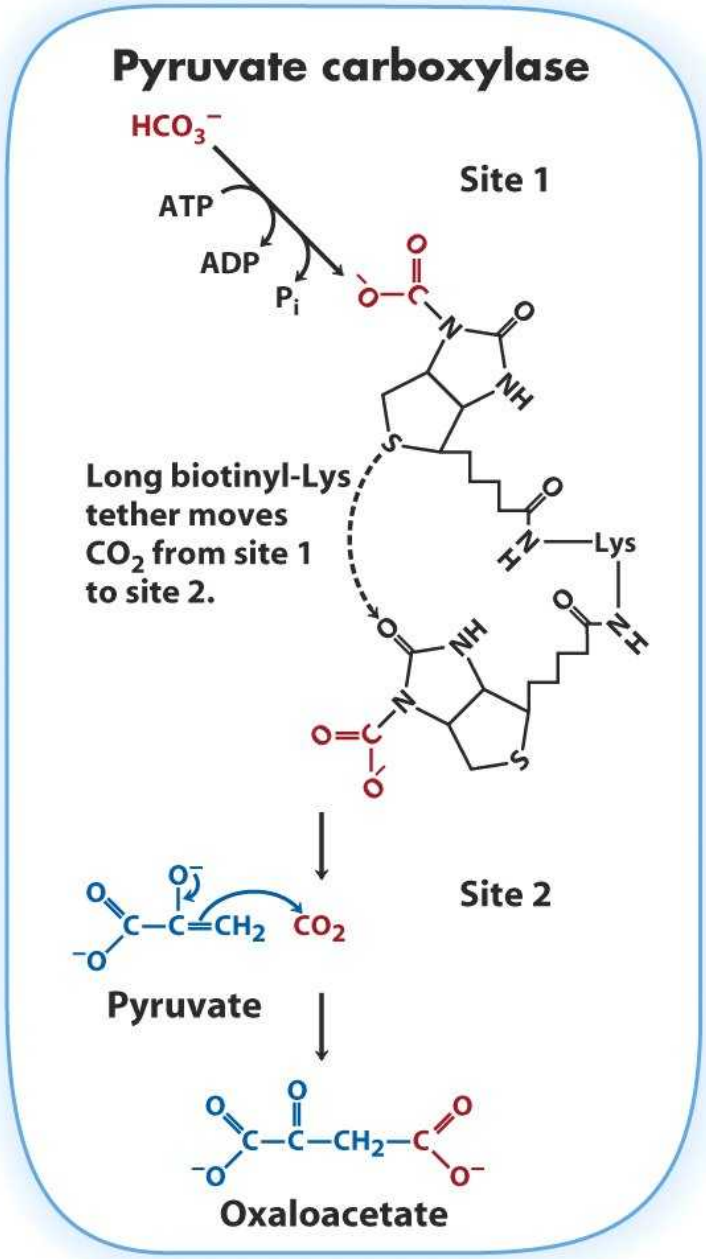

Glycolysis
Gluconeogenesis
ATP
Glucose
P_i
hexokinase
glucose 6-phosphatase
ADP
Glucose
6-phosphate
H_2O
ATP
Fructose
6-phosphate
P_i
phospho-
fructokinase-1
fructose
1,6-bisphosphatase
ADP
Fructose
1,6-bisphosphate
H_2O
Dihydroxyacetone
phosphate
Dihydroxyacetone
phosphate
(2) Glyceraldehyde 3-phosphate


(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) P_i
(2) NAD^+
(2) NAD^+
(2) NADH + (2) H^+
(2) NADH + H^+
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ADP
(2) ATP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) Phosphoenol-pyruvate
(2) GDP
PEP carboxykinase
(2) GTP
(2) ADP
pyruvate kinase
(2) ATP
(2) Oxaloacetate
(2) ADP
(2) Pyruvate
pyruvate carboxylase
(2) ATP

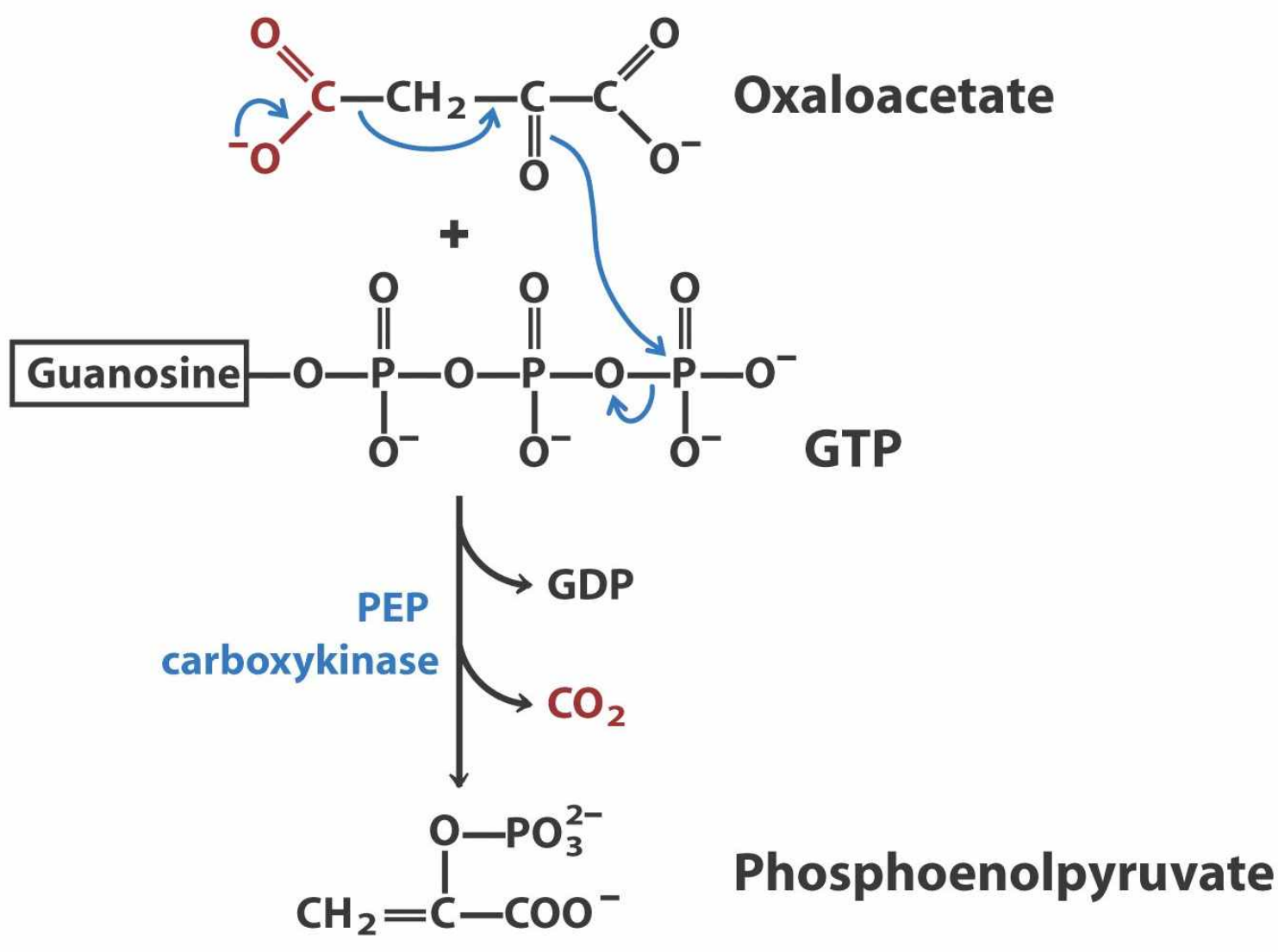
Synthesis of PEP from pyruvate (Step 1)

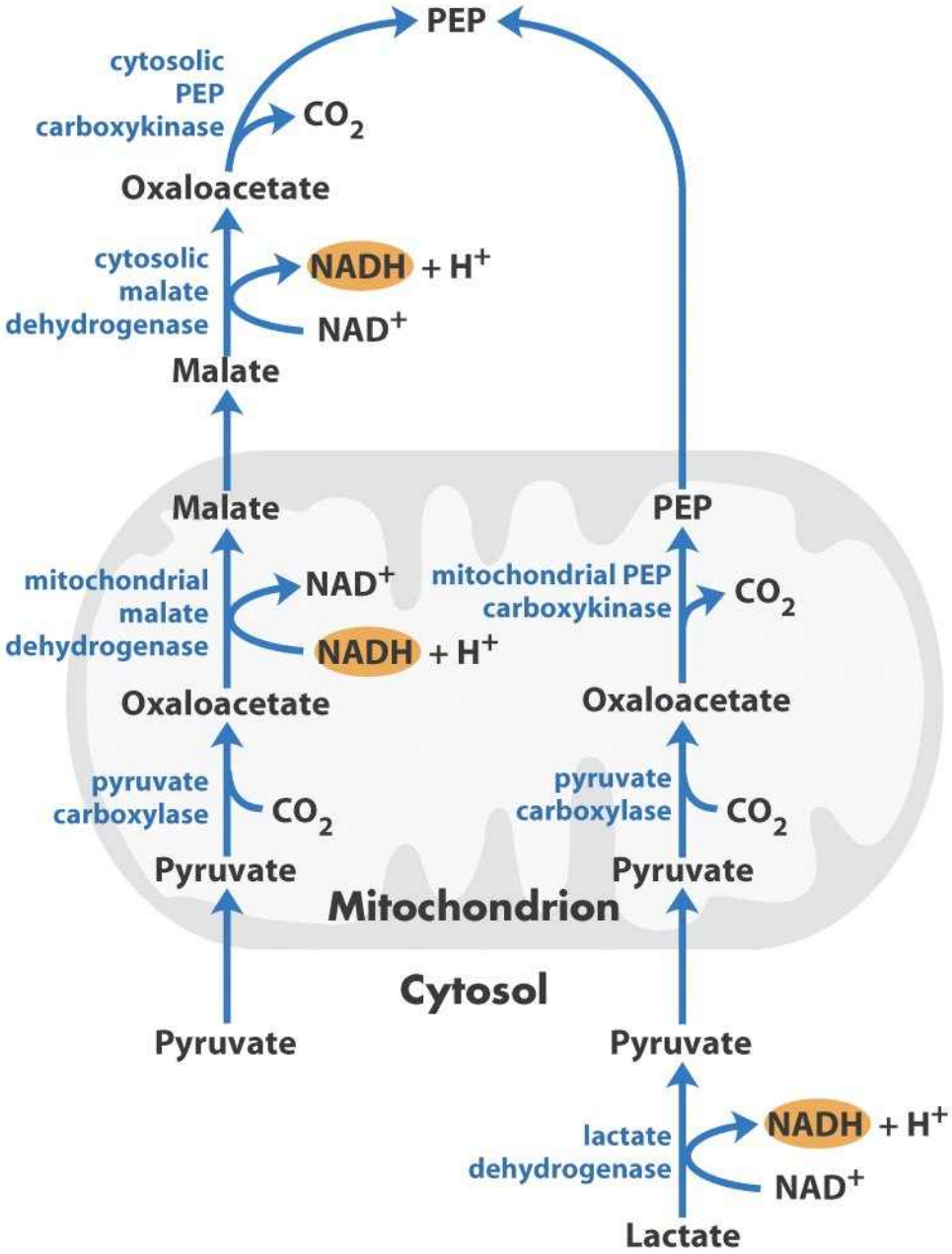


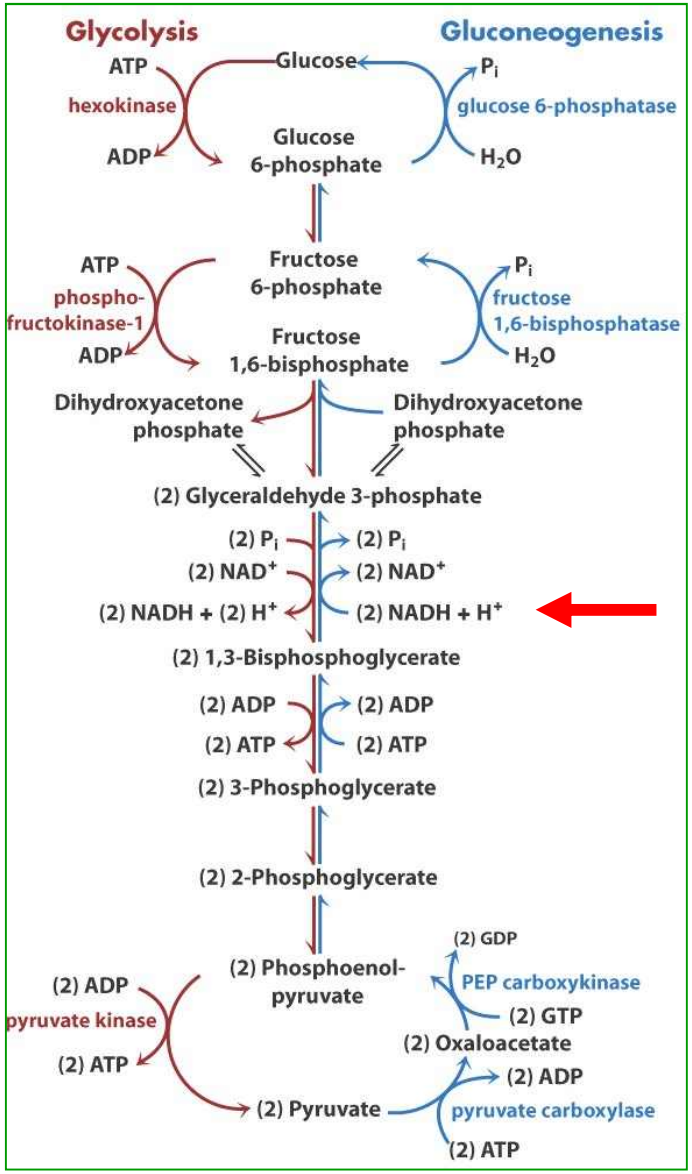
Role of biotin in the pyruvate carboxylase reaction



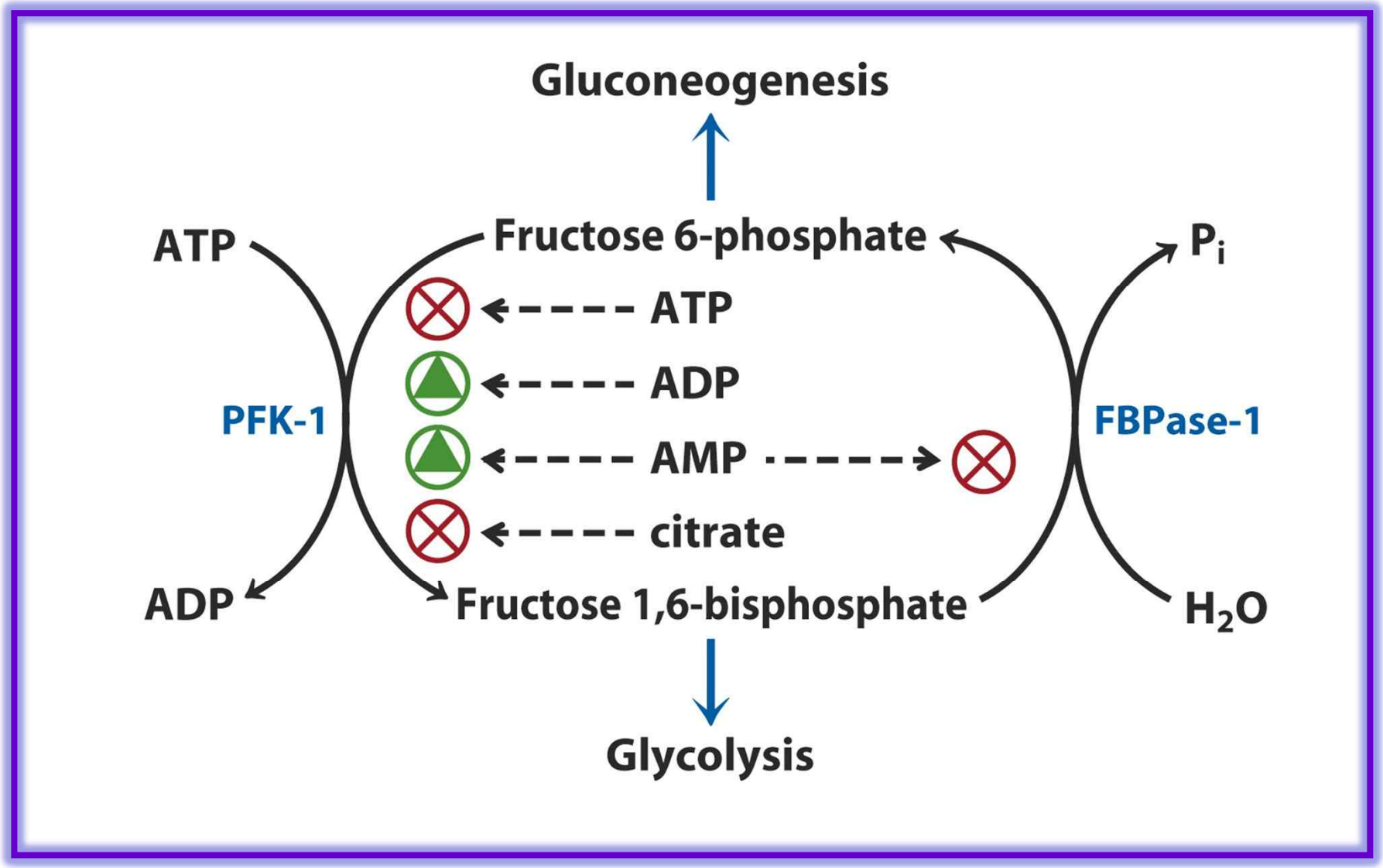
Synthesis of PEP from pyruvate (Step 2)



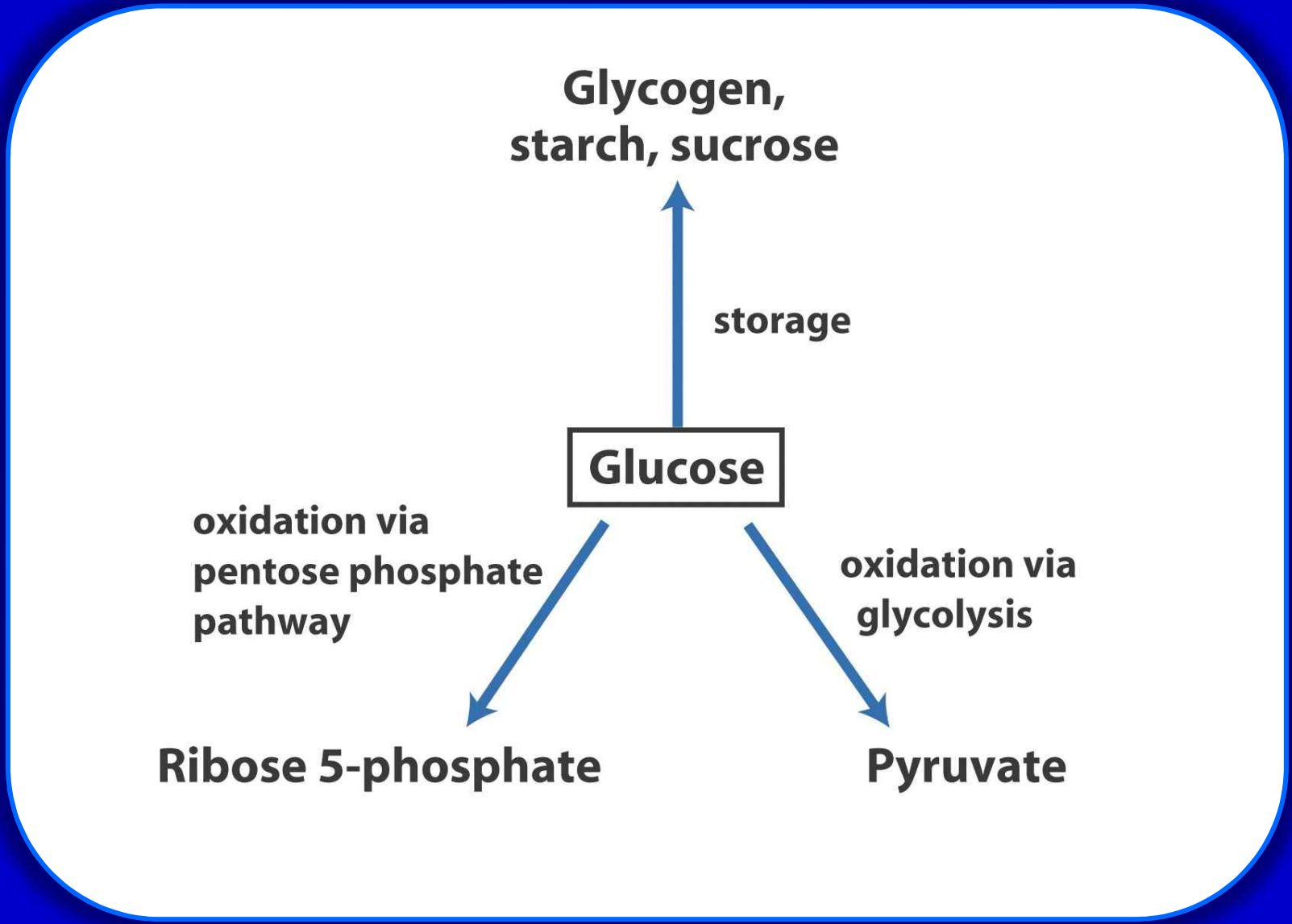

PEP
cytosolic PEP carboxykinase
CO_2
Oxaloacetate
cytosolic malate dehydrogenase
NADH + H^+
NAD^+
Malate
Malate
mitochondrial malate dehydrogenase
NAD^+
NADH + H^+
Oxaloacetate
pyruvate carboxylase
CO_2
Pyruvate
PEP
mitochondrial PEP carboxykinase
CO_2
Oxaloacetate
pyruvate carboxylase
CO_2
Pyruvate
Mitochondrion
Cytosol
Pyruvate
Pyruvate
lactate dehydrogenase
NADH + H^+
NAD^+
Lactate


Glycolysis
Gluconeogenesis
ATP
Glucose
P_i
hexokinase
glucose 6-phosphatase
ADP
Glucose 6-phosphate
H_2O
ATP
Fructose 6-phosphate
P_i
phospho-fructokinase-1
fructose 1,6-bisphosphatase
ADP
Fructose 1,6-bisphosphate
H_2O
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) P_i
(2) NAD^+
(2) NAD^+
(2) NADH + (2) H^+
(2) NADH + H^+
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ADP
(2) ATP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) GDP
(2) Phosphoenol-pyruvate
PEP carboxykinase
(2) ADP
pyruvate kinase
(2) GTP
(2) ATP
(2) Oxaloacetate
(2) ADP
(2) Pyruvate
pyruvate carboxylase
(2) ATP

Glycolysis and Gluconeogenesis are regulated reciprocally (Chpt. 15)

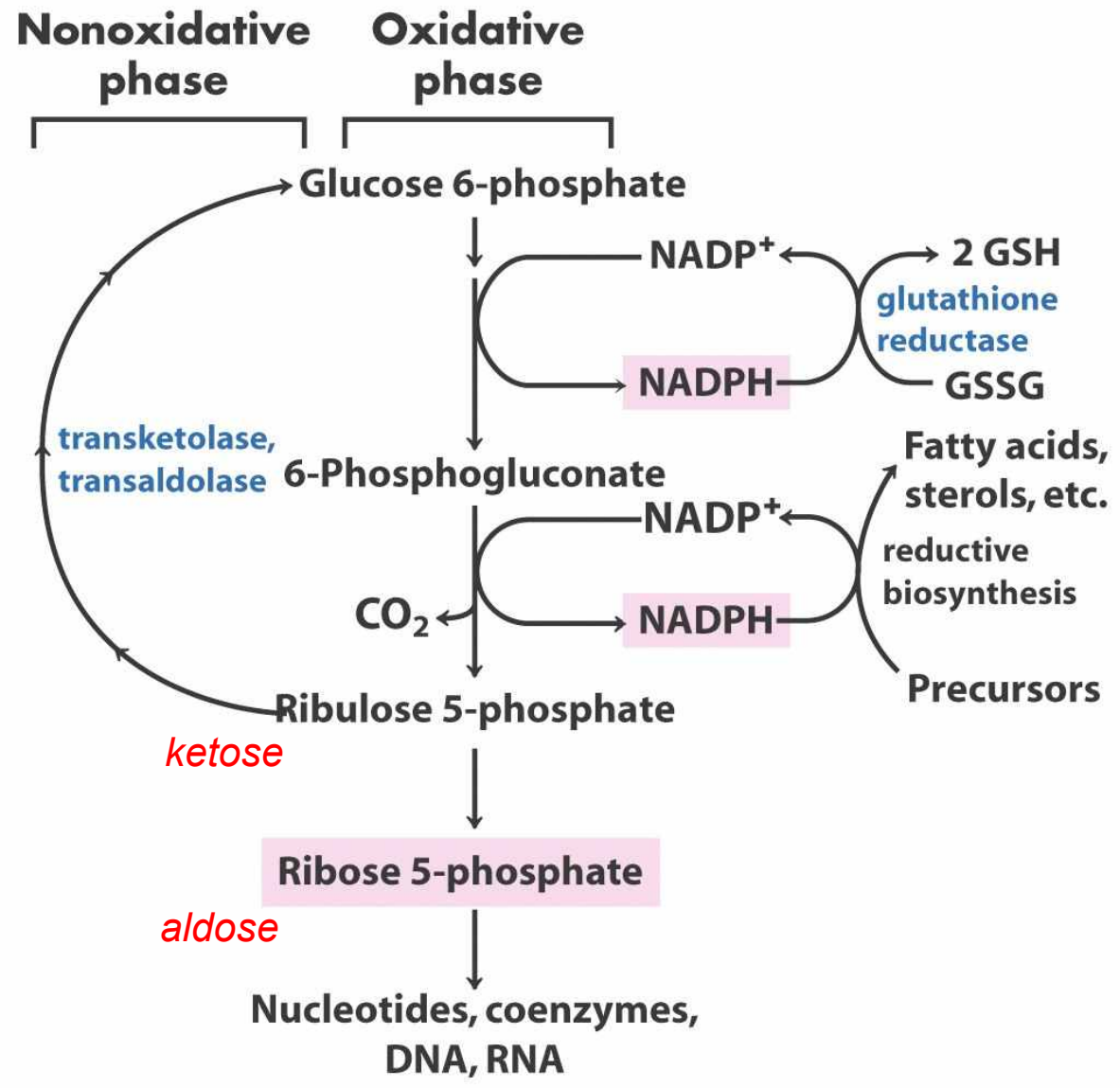


Major pathway of glucose utilization

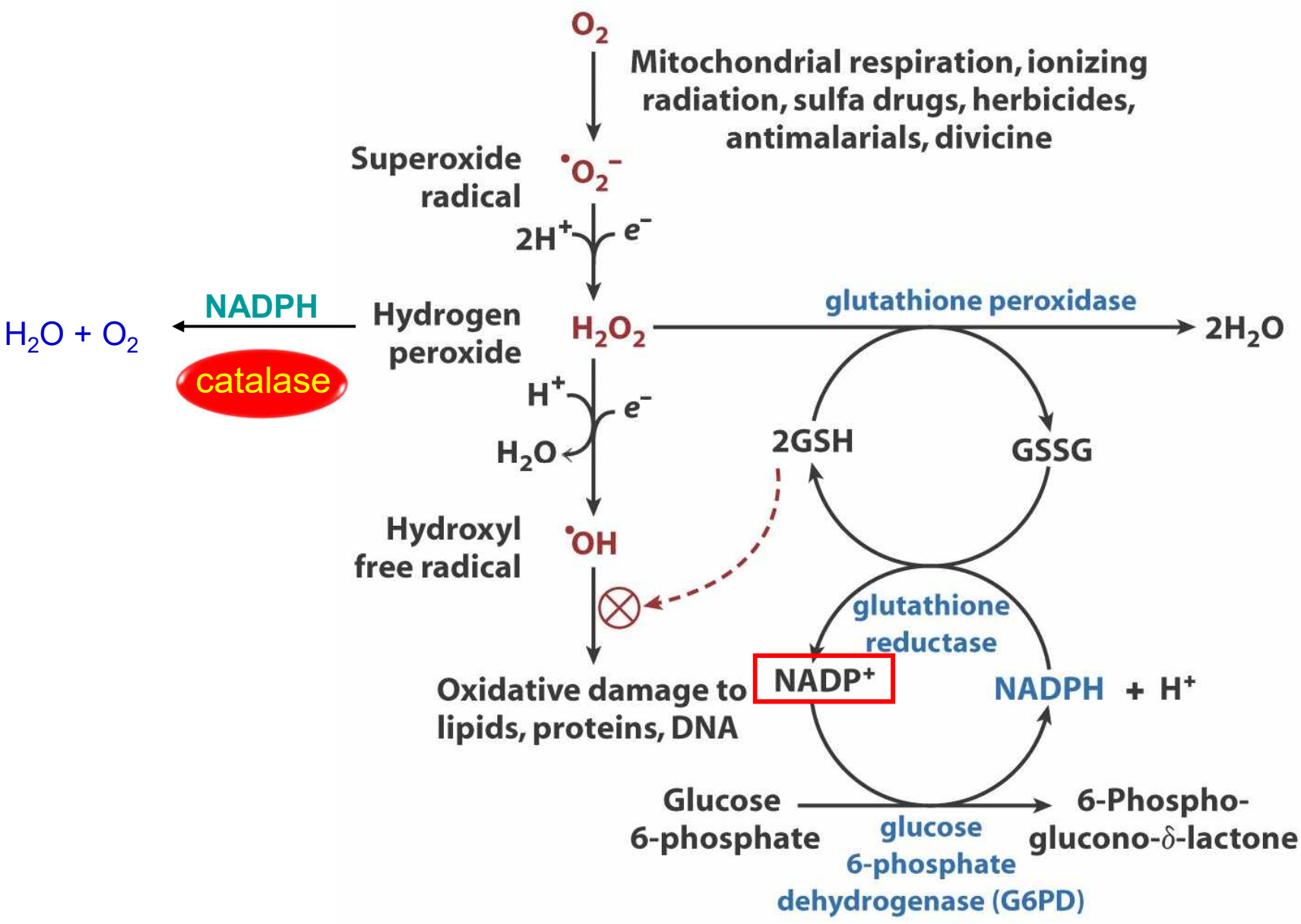


General scheme of the pentose phosphate pathway

(phosphogluconate pathway, hexose monophosphate pathway)

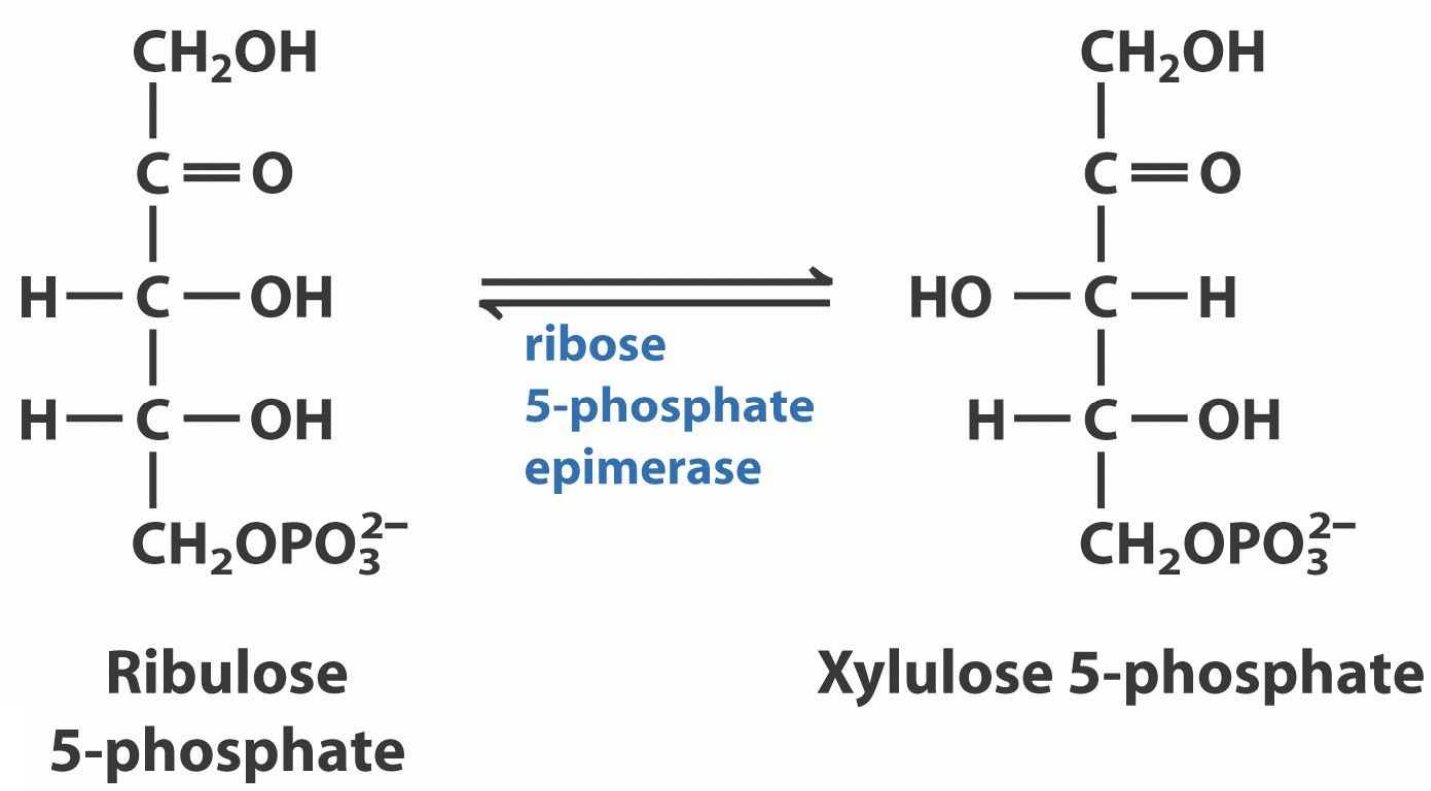


Role of NADPH and glutathione



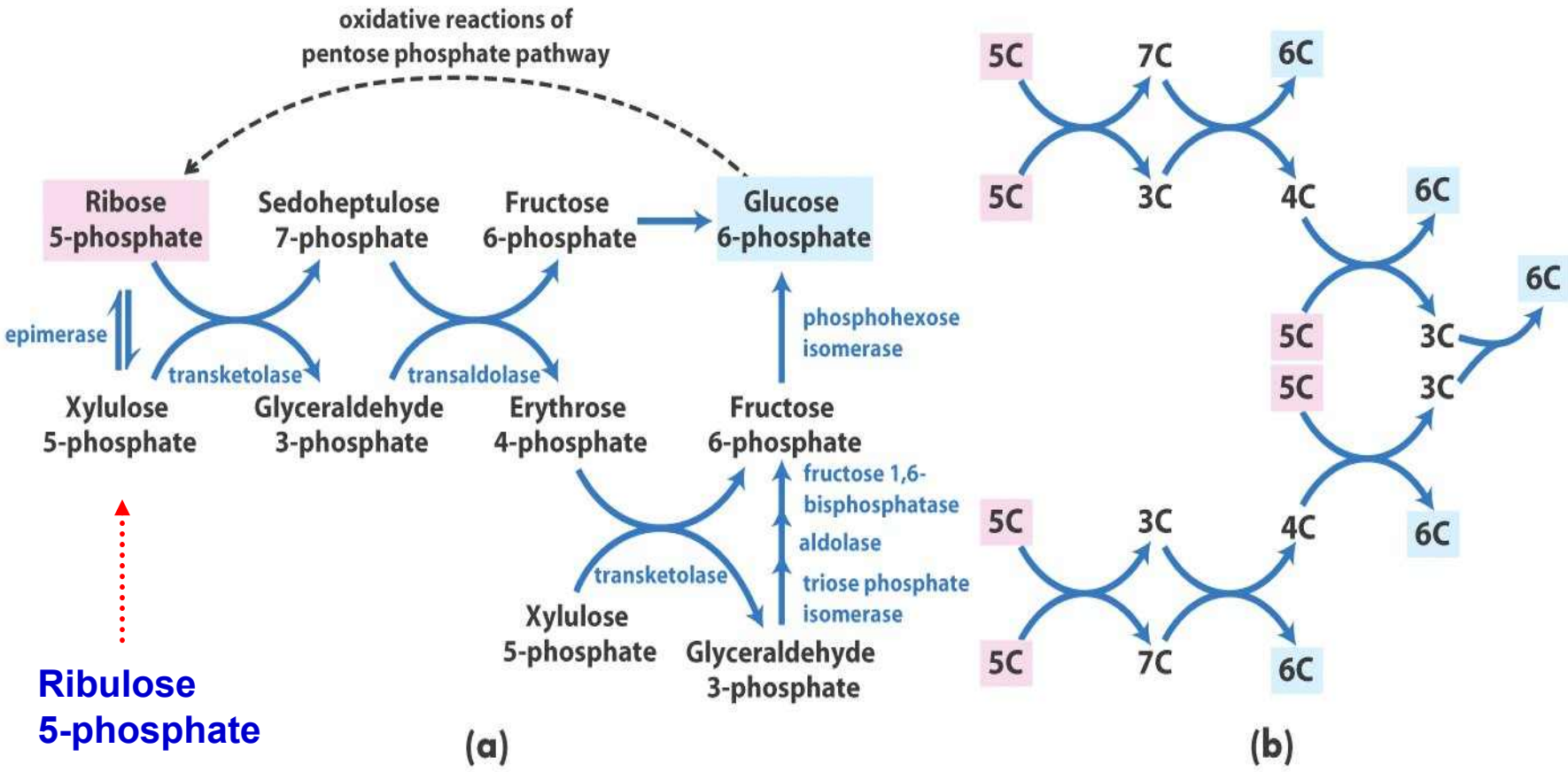
In nonoxidative phase,

Ribulose 5-phosphate is epimerized to xylulose 5-phosphate

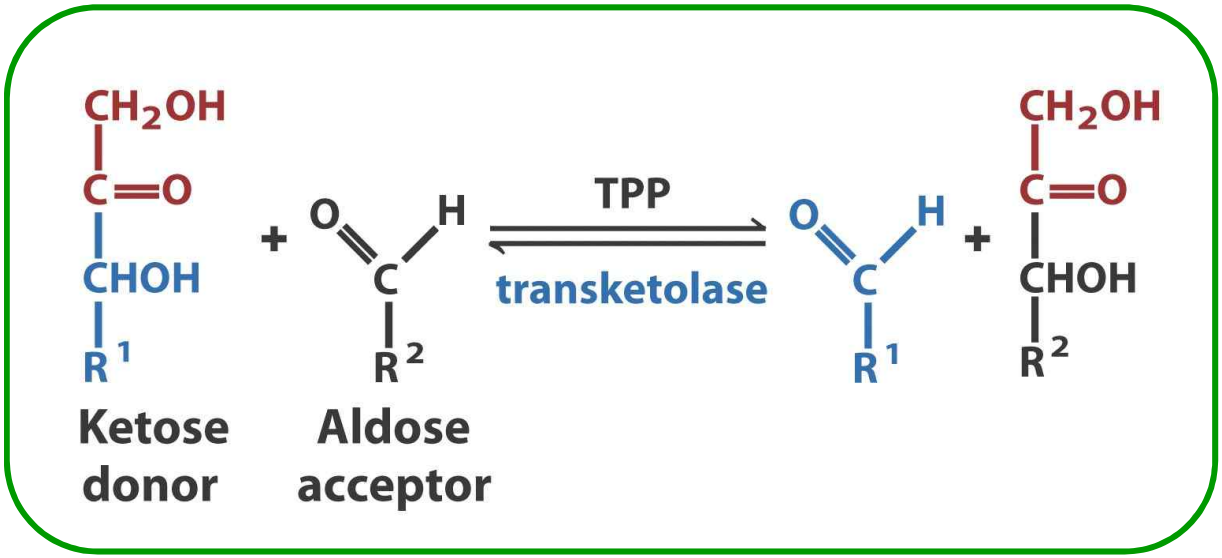


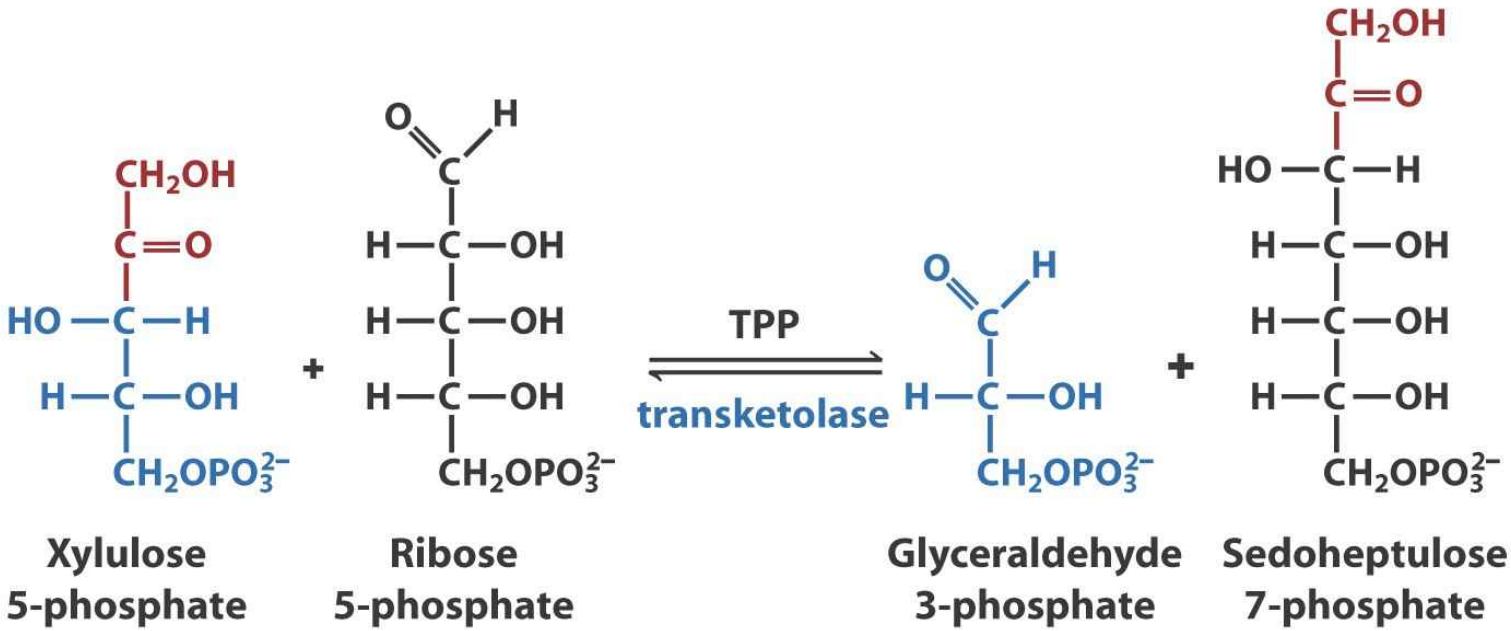
epimer : two sugars that differ only in the configuration around one carbon atom !!

Nonoxidative reactions of the pentose phosphate pathway



Transketolase reaction





Role of NADPH in regulating G6P partitioning between glycolysis and pentose phosphate pathway