

Carbohydrate Metabolism

Background

- ❖ Glucose occupies a central position in the metabolism of plants, animals, and many microorganisms.
- ❖ It is relatively rich in potential energy, and thus a good fuel.
- ❖ The complete oxidation of glucose yields 2,840 kJ/mol.
- ❖ By storing glucose as a high molecular weight polymer such as starch or glycogen, a cell can stockpile large quantities of hexose units while maintaining a relatively low cytosolic osmolarity.
- ❖ When energy demands increase, glucose can be released from these intracellular storage polymers and used to produce ATP either aerobically or anaerobically.
- ❖ Glucose is not only an excellent fuel, it is also a remarkably versatile precursor, capable of supplying a huge array of metabolic intermediates for biosynthetic reactions.

Major Fates of Glucose

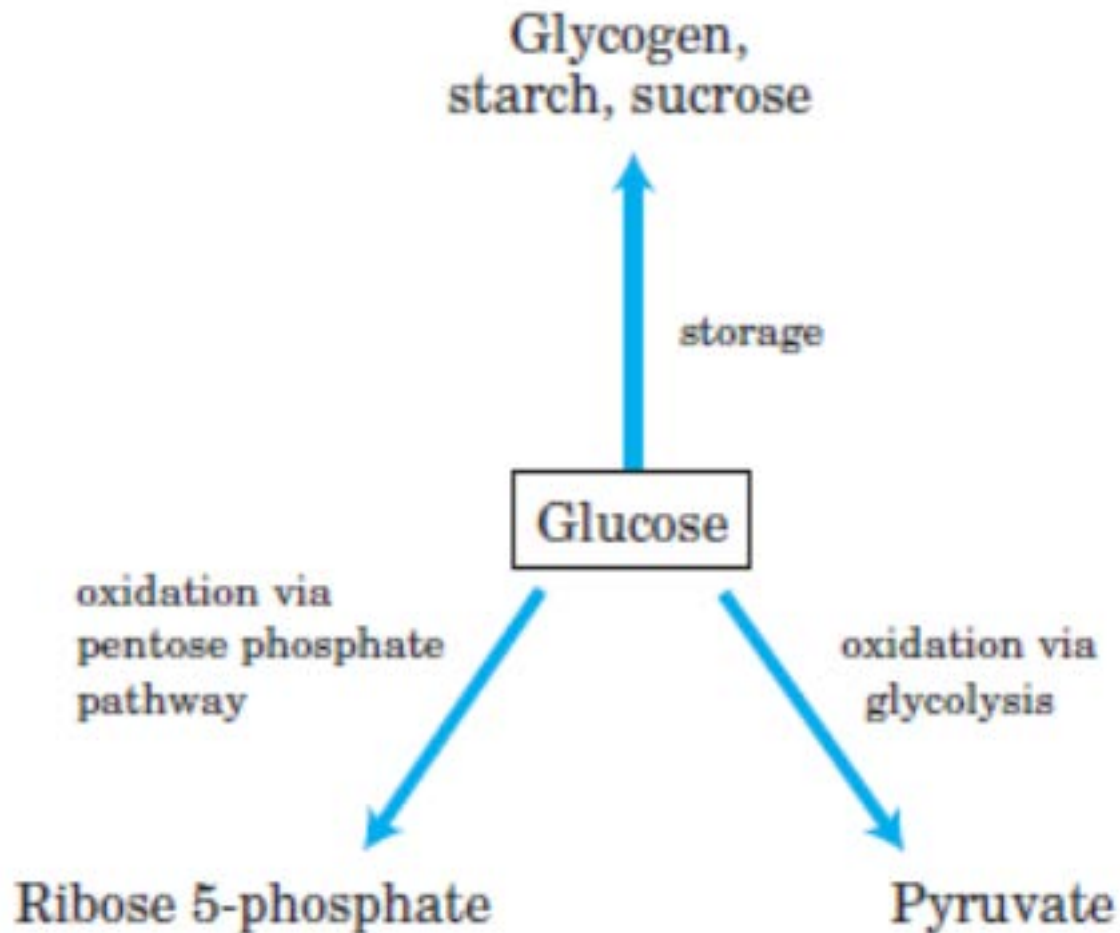
In animals and vascular plants, glucose has three major fates:

It may be stored (as a polysaccharide or as sucrose)

Oxidized to a three-carbon compound (pyruvate) via glycolysis to provide ATP and metabolic intermediates

Oxidized via the pentose phosphate (phosphogluconate) pathway to yield ribose 5-phosphate for nucleic acid synthesis

Major Pathway of Glucose Utilization



Glycolysis

Glycolysis was the first metabolic pathway to be elucidated

In **glycolysis** (from the Greek word *glykys*, meaning “sweet,” and *lysis*, meaning “**splitting**”), a molecule of glucose is degraded in a series of enzyme-catalyzed reactions to yield two molecules of the three-carbon compound pyruvate.

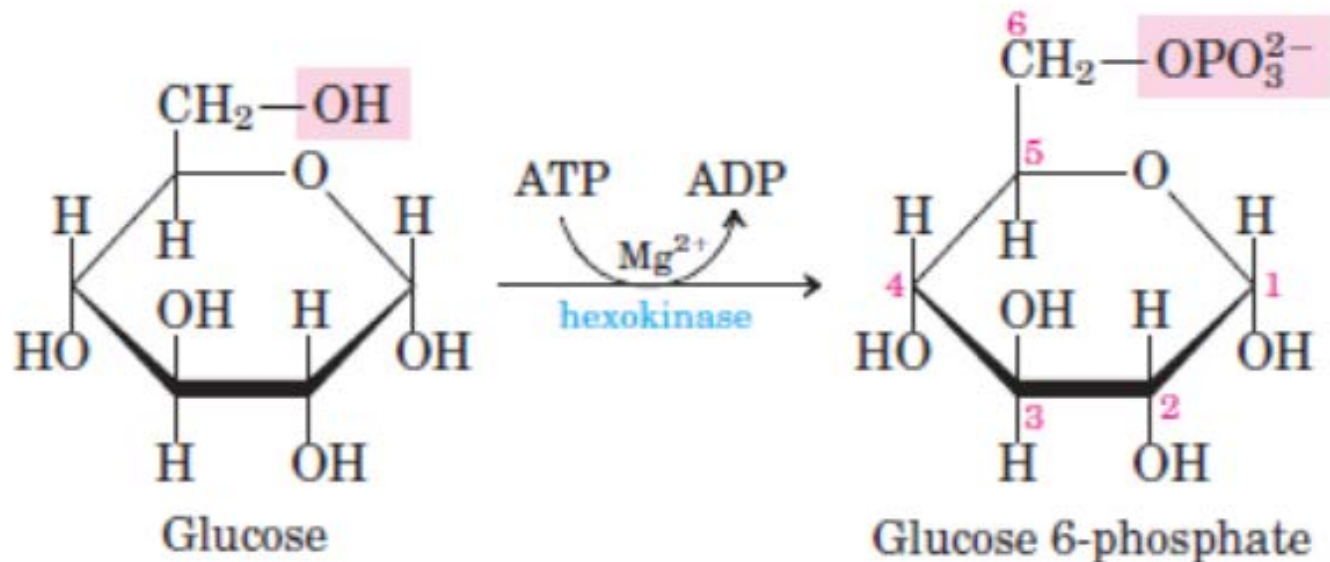
During the sequential reactions of glycolysis, some of the free energy released from glucose is conserved in the form of ATP and NADH.

The breakdown of **the six-carbon glucose into two molecules of the three-carbon pyruvate** occurs in ten steps

the first five of which constitute the *preparatory phase*

And subsequent five step constitute *payoff phase*

① **Phosphorylation of Glucose** In the first step of glycolysis, glucose is activated for subsequent reactions by its phosphorylation at C-6 to yield **glucose 6-phosphate**, with ATP as the phosphoryl donor:

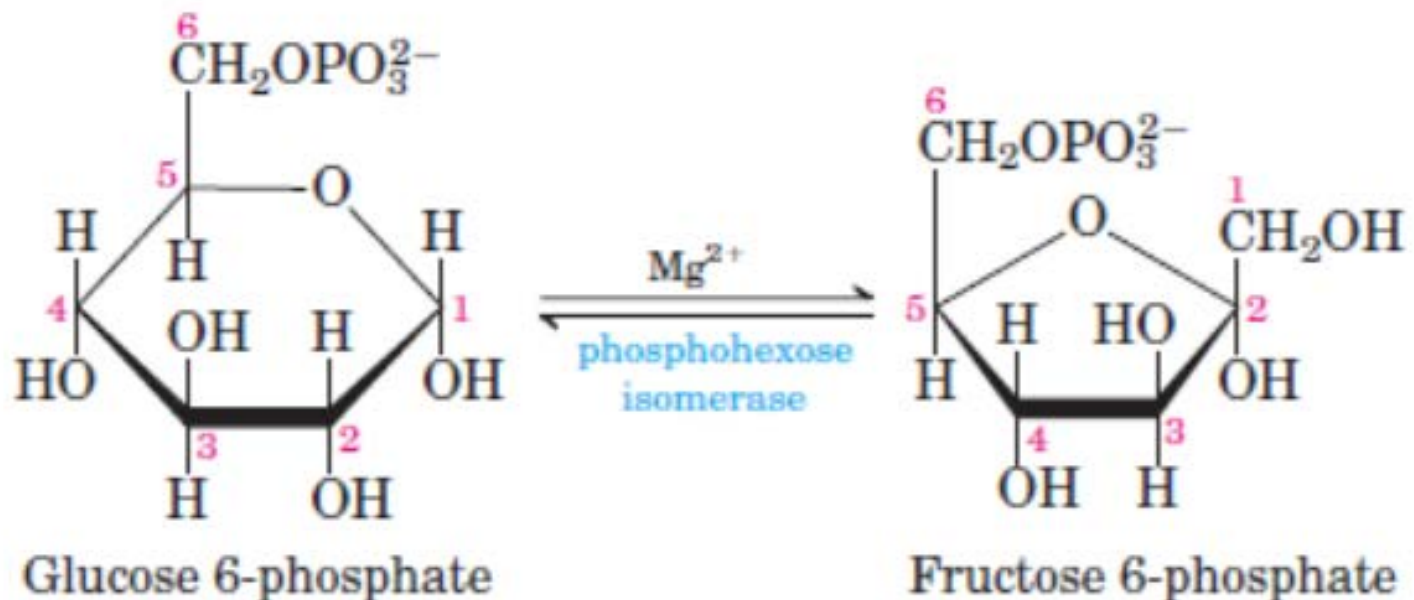


$$\Delta G'^{\circ} = -16.7 \text{ kJ/mol}$$

This reaction, which is irreversible under intracellular conditions, is catalyzed by **hexokinase**. Recall that

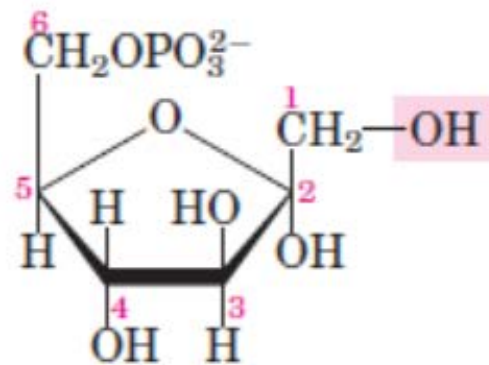
② *Conversion of Glucose 6-Phosphate to Fructose 6-Phosphate*

The enzyme **phosphohexose isomerase** (**phosphoglucose isomerase**) catalyzes the reversible isomerization of glucose 6-phosphate, an aldose, to **fructose 6-phosphate**, a ketose:

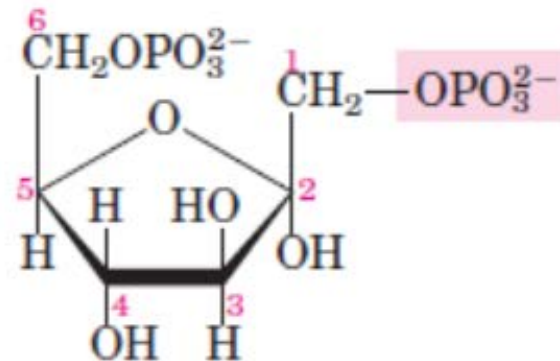
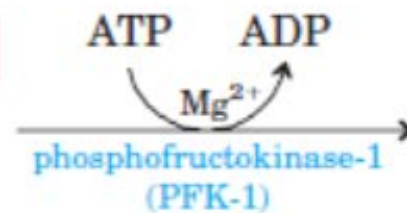


$$\Delta G'^{\circ} = 1.7 \text{ kJ/mol}$$

③ **Phosphorylation of Fructose 6-Phosphate to Fructose 1,6-Bisphosphate** In the second of the two priming reactions of glycolysis, **phosphofructokinase-1 (PFK-1)** catalyzes the transfer of a phosphoryl group from ATP to fructose 6-phosphate to yield **fructose 1,6-bisphosphate**:

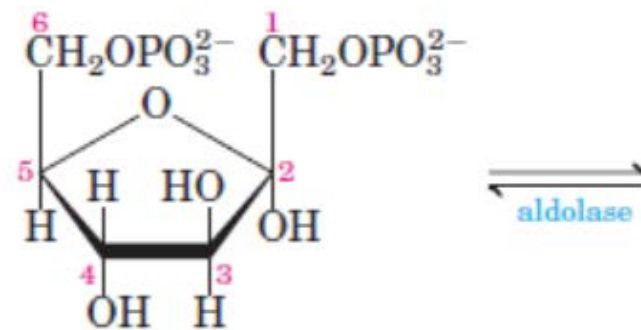


Fructose 6-phosphate

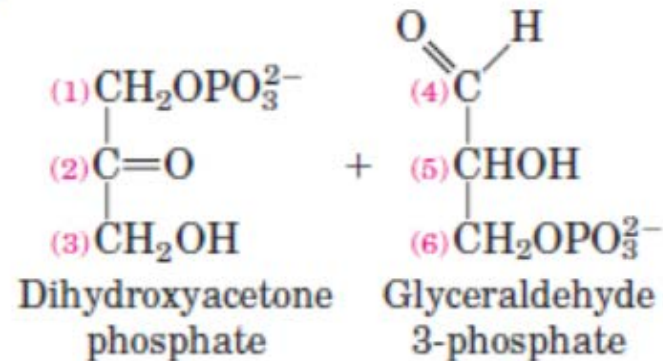


Fructose 1,6-bisphosphate

④ **Cleavage of Fructose 1,6-Bisphosphate** The enzyme **fructose 1,6-bisphosphate aldolase**, often called simply **aldolase**, catalyzes a reversible aldol condensation (p. 485). Fructose 1,6-bisphosphate is cleaved to yield two different triose phosphates, **glyceraldehyde 3-phosphate**, an aldose, and **dihydroxyacetone phosphate**, a ketose:

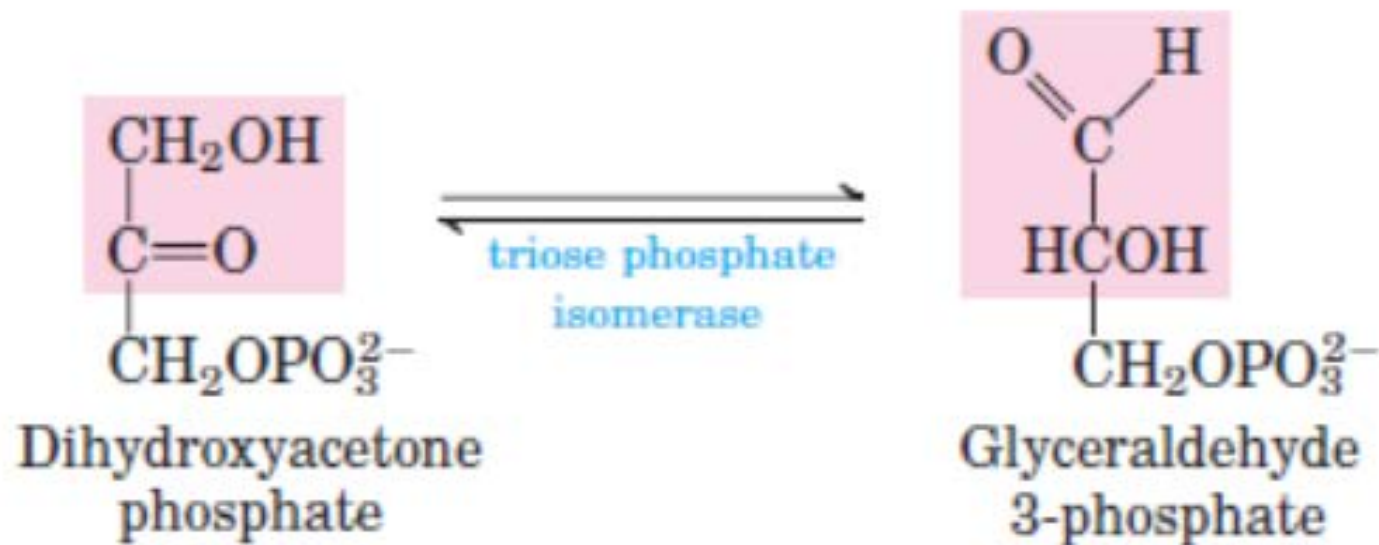


Fructose 1,6-bisphosphate

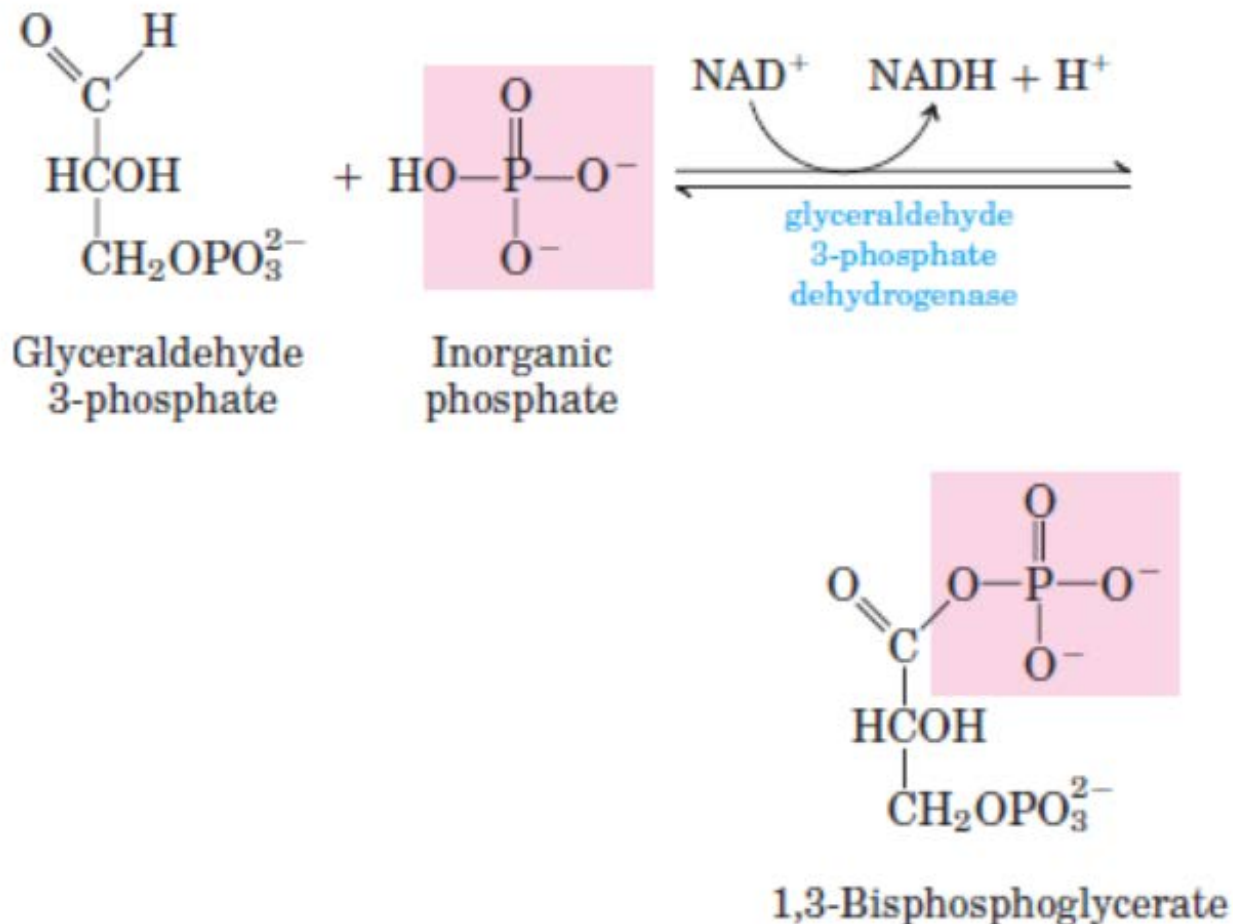


$$\Delta G'^{\circ} = 23.8 \text{ kJ/mol}$$

⑤ **Interconversion of the Triose Phosphates** Only one of the two triose phosphates formed by aldolase, glyceraldehyde 3-phosphate, can be directly degraded in the subsequent steps of glycolysis. The other product, dihydroxyacetone phosphate, is rapidly and reversibly converted to glyceraldehyde 3-phosphate by the fifth enzyme of the sequence, **triose phosphate isomerase**:

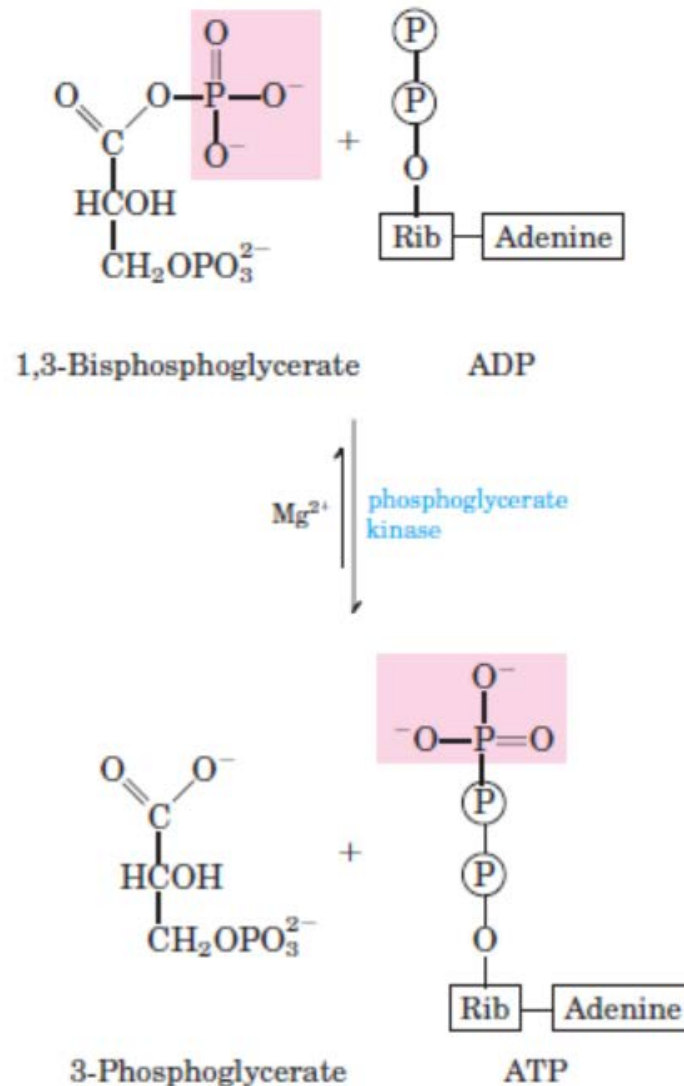


⑥ **Oxidation of Glyceraldehyde 3-Phosphate to 1,3-Bisphosphoglycerate** The first step in the payoff phase is the oxidation of glyceraldehyde 3-phosphate to **1,3-bisphosphoglycerate**, catalyzed by **glyceraldehyde 3-phosphate dehydrogenase**:



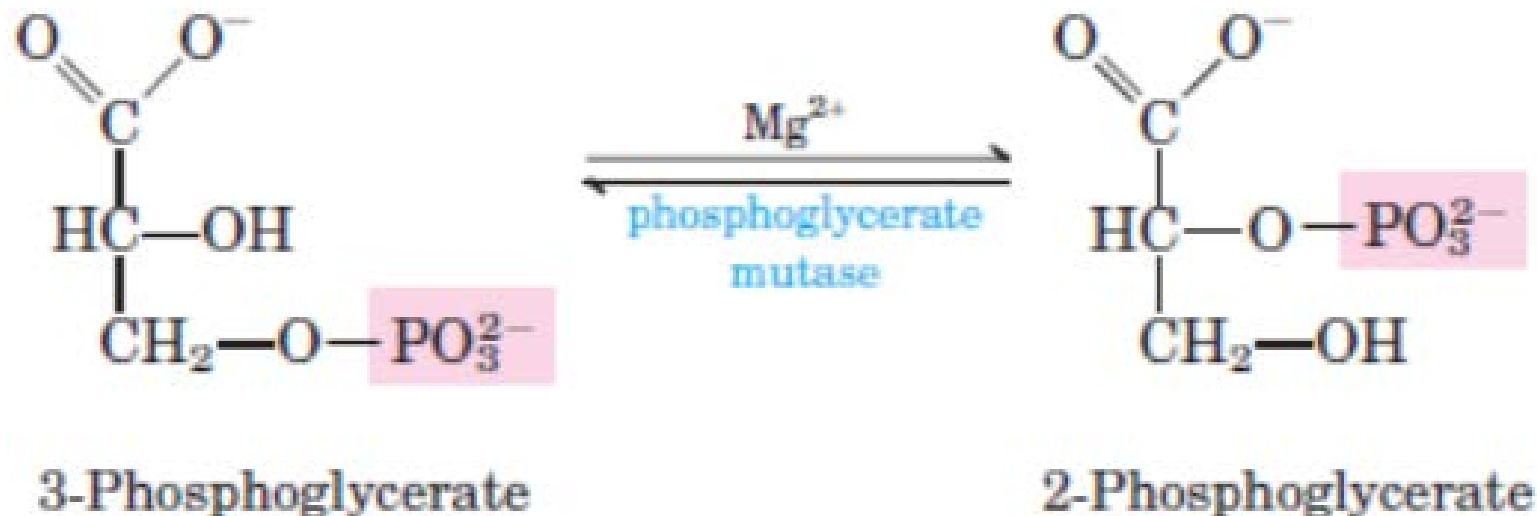
⑦ **Phosphoryl Transfer from 1,3-Bisphosphoglycerate to ADP**

The enzyme **phosphoglycerate kinase** transfers the high-energy phosphoryl group from the carboxyl group of 1,3-bisphosphoglycerate to ADP, forming ATP and **3-phosphoglycerate**:



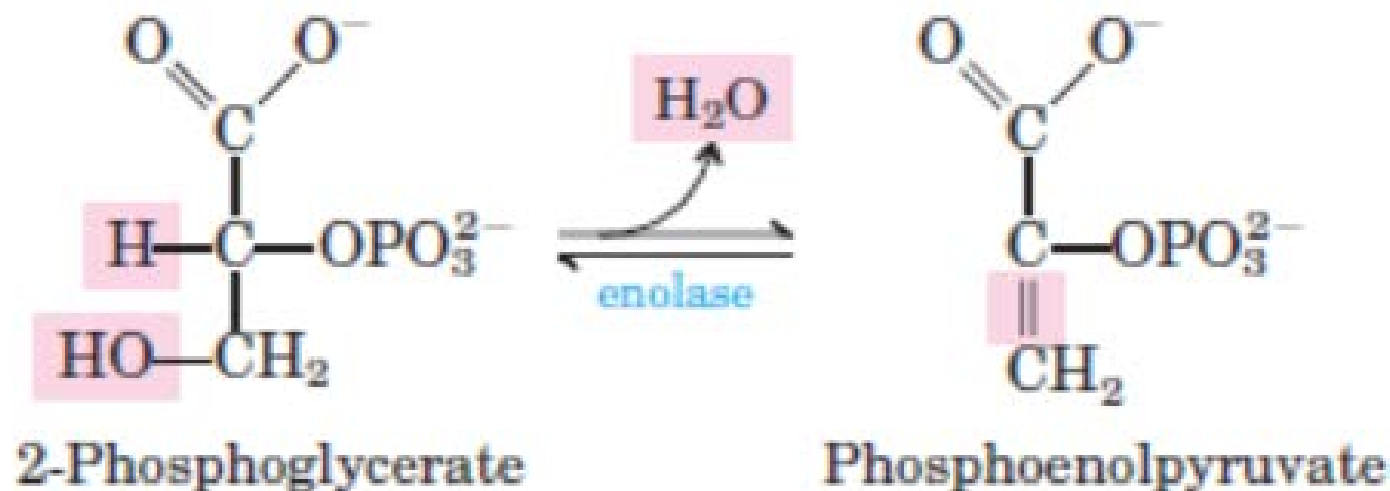
⑧ **Conversion of 3-Phosphoglycerate to 2-Phosphoglycerate**

The enzyme **phosphoglycerate mutase** catalyzes a reversible shift of the phosphoryl group between C-2 and C-3 of glycerate; Mg^{2+} is essential for this reaction:

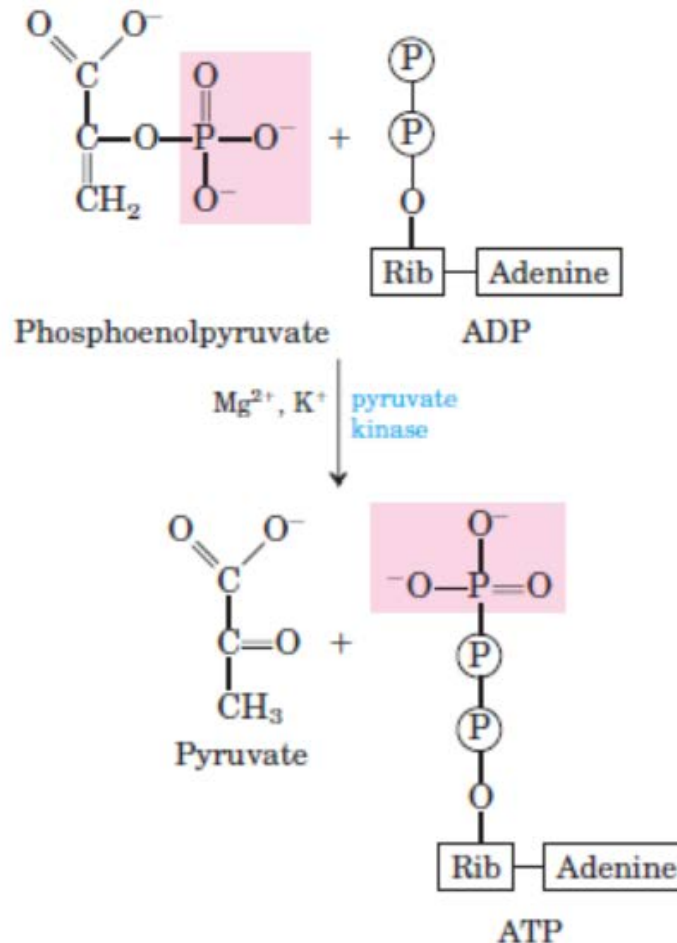


⑨ **Dehydration of 2-Phosphoglycerate to Phosphoenolpyruvate**

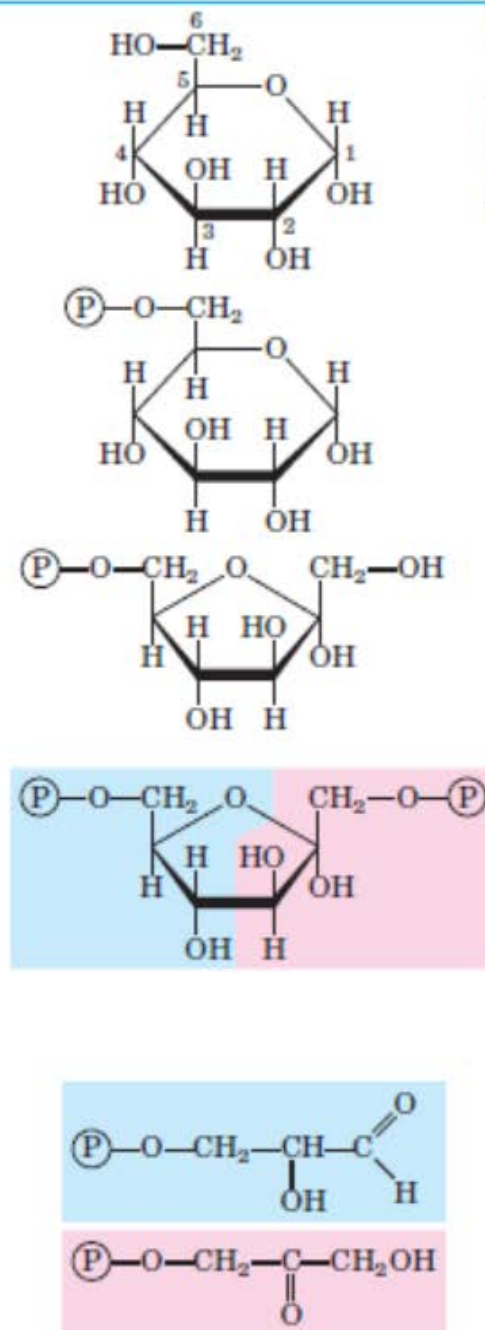
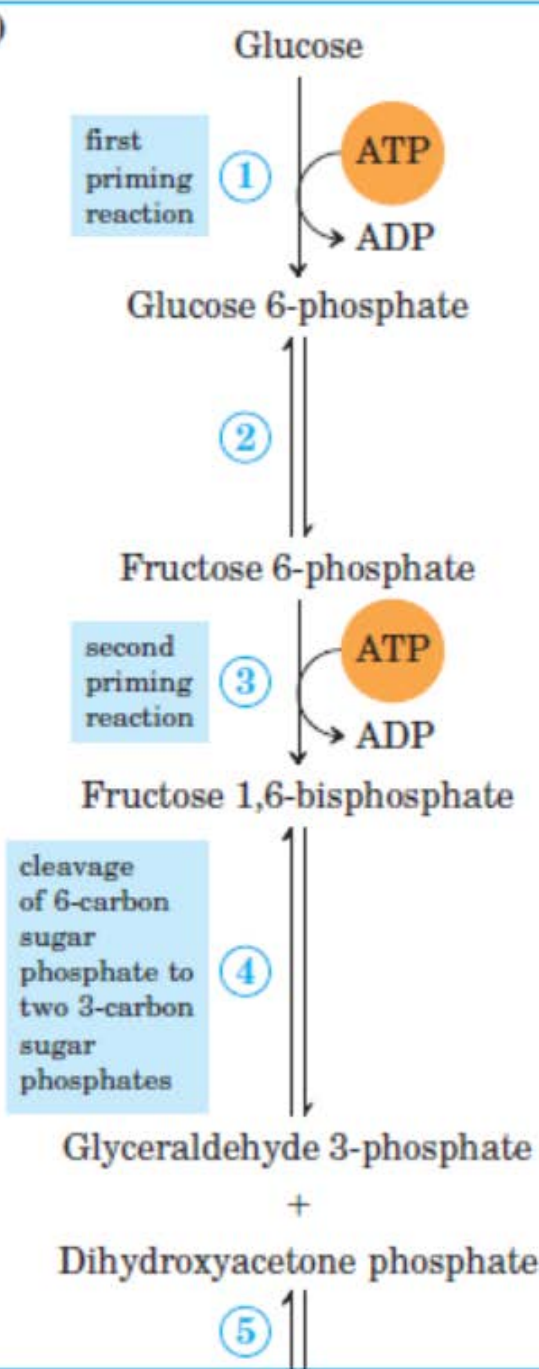
In the second glycolytic reaction that generates a compound with high phosphoryl group transfer potential, **enolase** promotes reversible removal of a molecule of water from 2-phosphoglycerate to yield **phosphoenolpyruvate (PEP)**:



⑩ Transfer of the Phosphoryl Group from Phosphoenolpyruvate to ADP The last step in glycolysis is the transfer of the phosphoryl group from phosphoenolpyruvate to ADP, catalyzed by **pyruvate kinase**, which requires K^+ and either Mg^{2+} or Mn^{2+} :



(a)



Preparatory phase

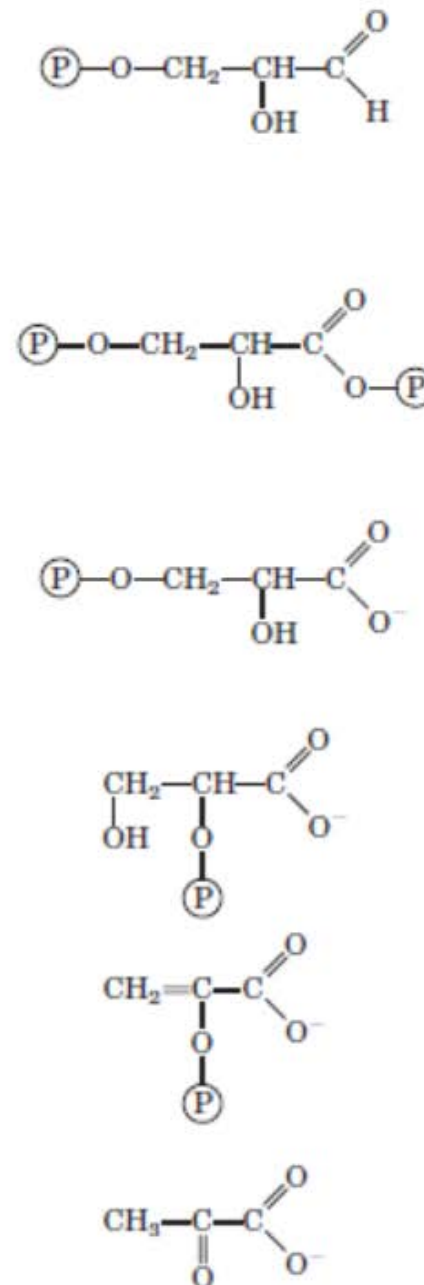
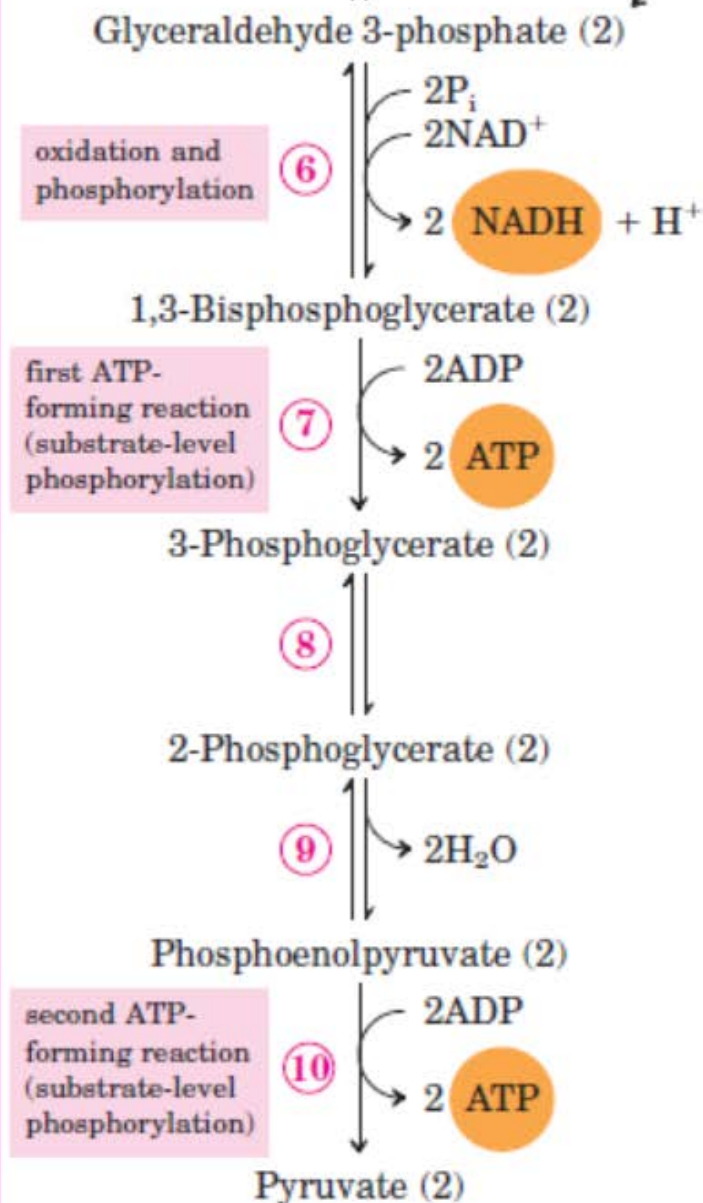
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate

- ① Hexokinase
- ② Phosphohexose isomerase
- ③ Phosphofructokinase-1
- ④ Aldolase
- ⑤ Triose phosphate isomerase

(b)

Payoff phase

Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH



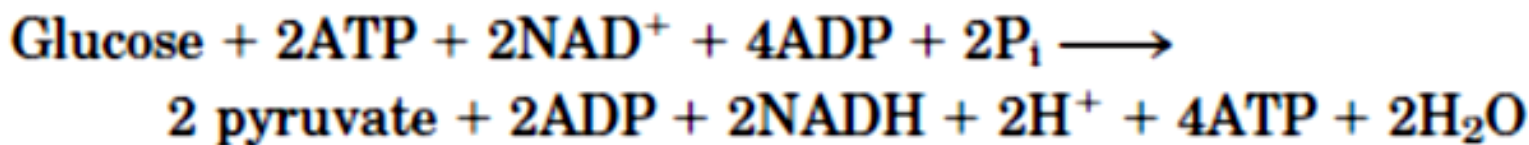
(6) Glyceraldehyde 3-phosphate dehydrogenase

(7) Phosphoglycerate kinase

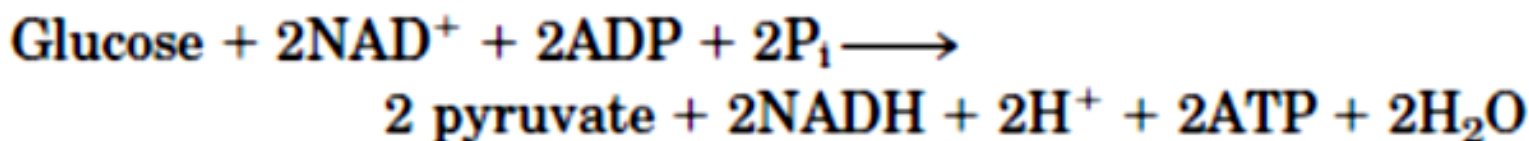
(8) Phosphoglycerate mutase

(9) Enolase

(10) Pyruvate kinase



Canceling out common terms on both sides of the equation gives the overall equation for glycolysis under aerobic conditions:



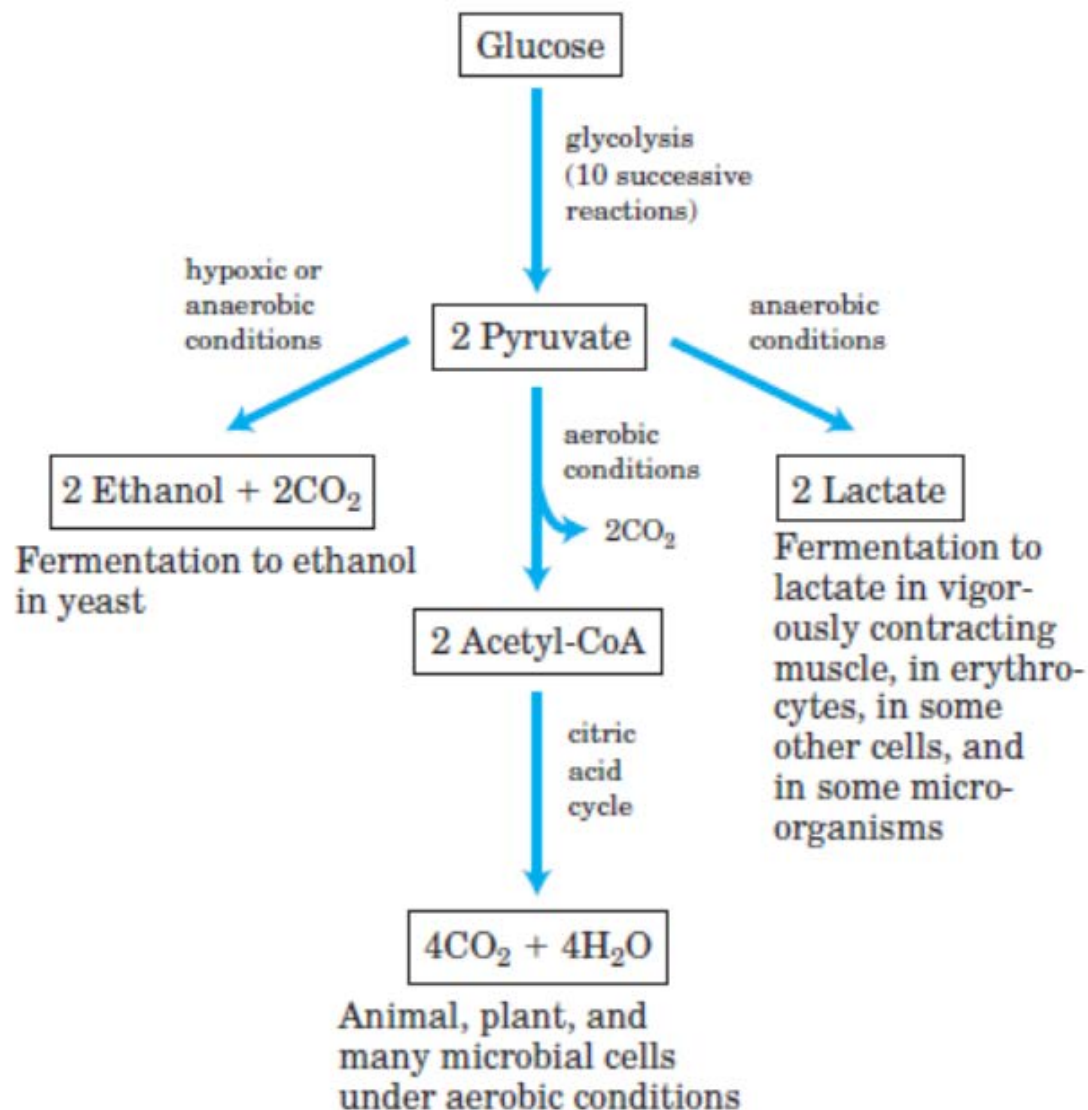
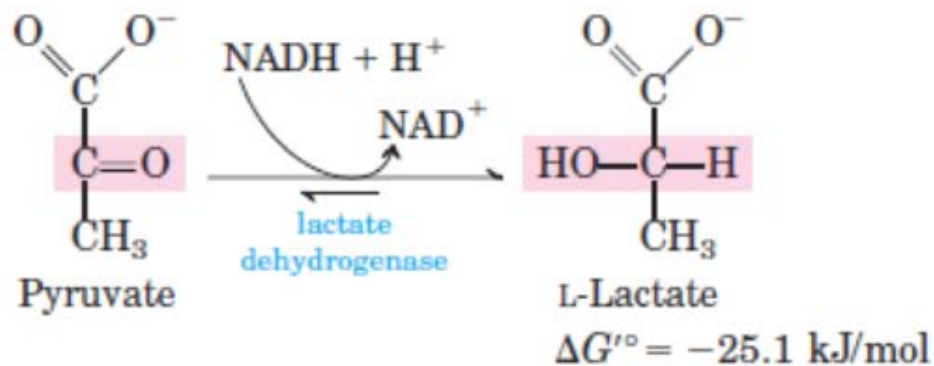


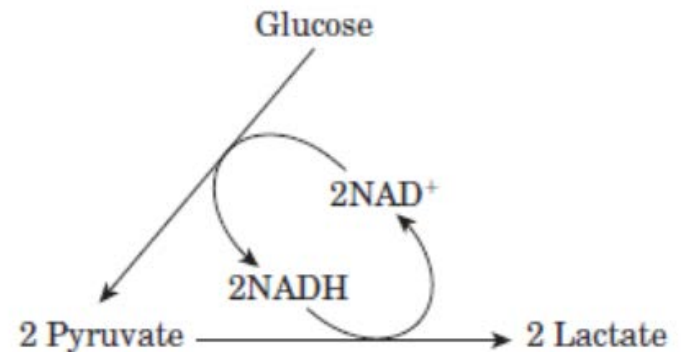
FIGURE 14-3 Three possible catabolic fates of the pyruvate formed in glycolysis. Pyruvate also serves as a precursor in many anabolic reactions, not shown here.

Pyruvate Is the Terminal Electron Acceptor in Lactic Acid Fermentation

When animal tissues cannot be supplied with sufficient oxygen to support aerobic oxidation of the pyruvate and NADH produced in glycolysis, NAD^+ is regenerated from NADH by the reduction of pyruvate to **lactate**. As mentioned earlier, some tissues and cell types (such as erythrocytes, which have no mitochondria and thus cannot oxidize pyruvate to CO_2) produce lactate from glucose even under aerobic conditions. The reduction of pyruvate is catalyzed by **lactate dehydrogenase**, which forms the L isomer of lactate at pH 7:

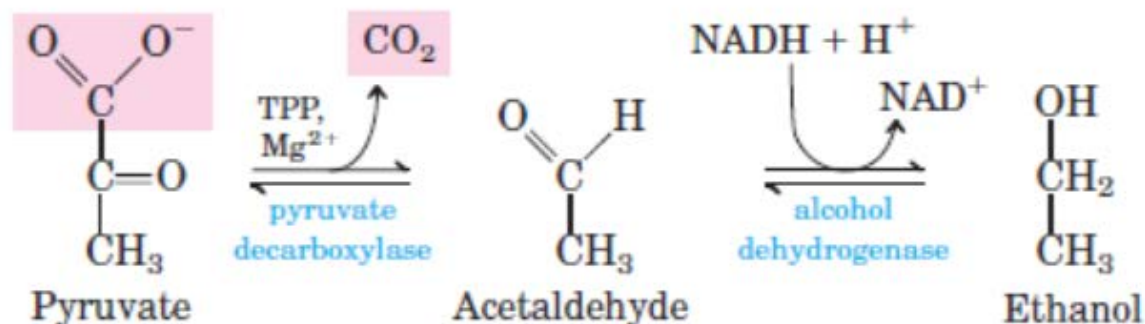


The overall equilibrium of this reaction strongly favors lactate formation, as shown by the large negative standard free-energy change.



Ethanol Is the Reduced Product in Ethanol Fermentation

Yeast and other microorganisms ferment glucose to ethanol and CO_2 , rather than to lactate. Glucose is converted to pyruvate by glycolysis, and the pyruvate is converted to ethanol and CO_2 in a two-step process:



In the first step, pyruvate is decarboxylated in an irreversible reaction catalyzed by **pyruvate decarboxylase**. This reaction is a simple decarboxylation and does not involve the net oxidation of pyruvate. Pyruvate decarboxylase requires Mg^{2+} and has a tightly bound coenzyme, thiamine pyrophosphate, discussed below. In the second step, acetaldehyde is reduced to ethanol through the action of **alcohol dehydrogenase**, with

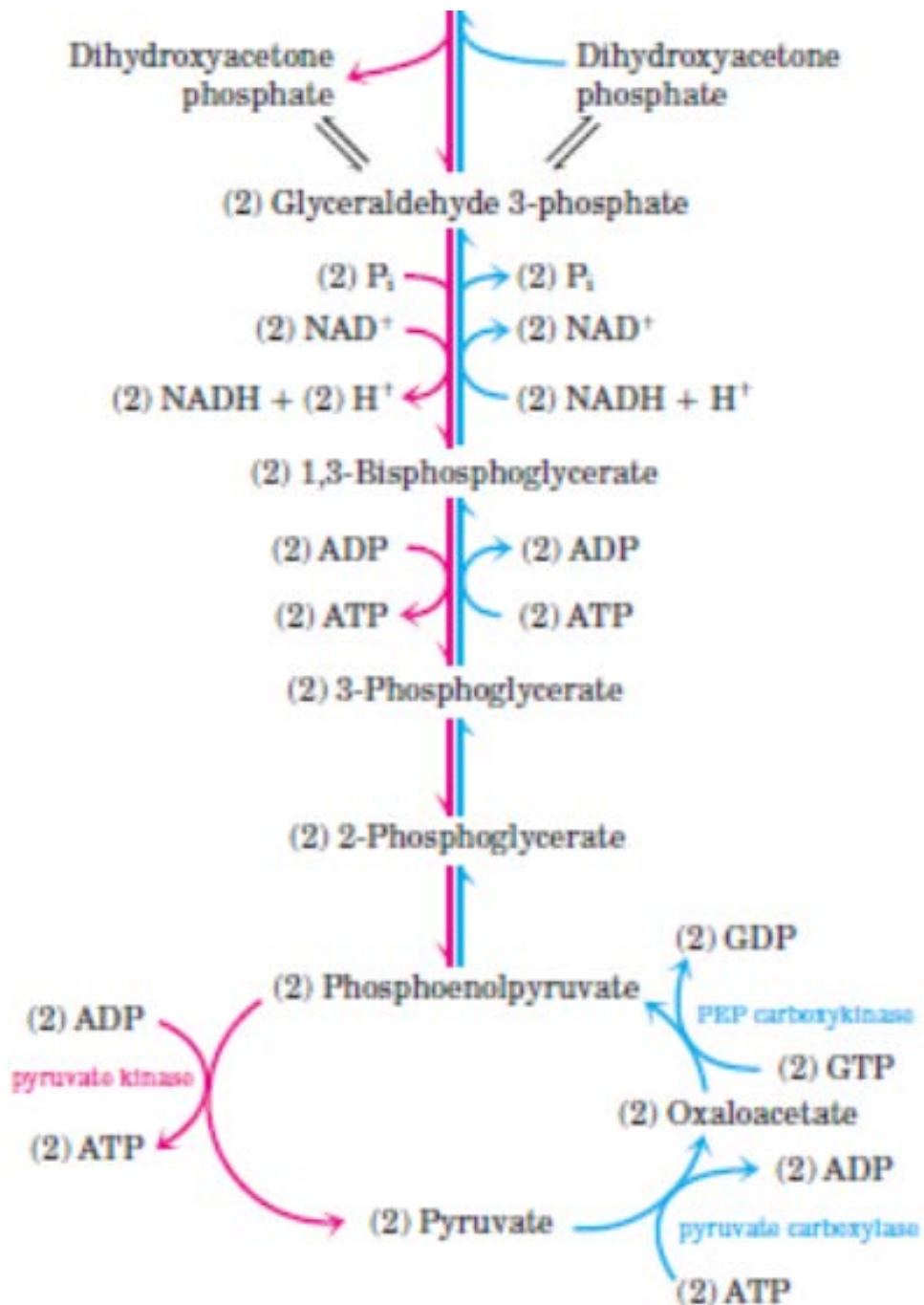
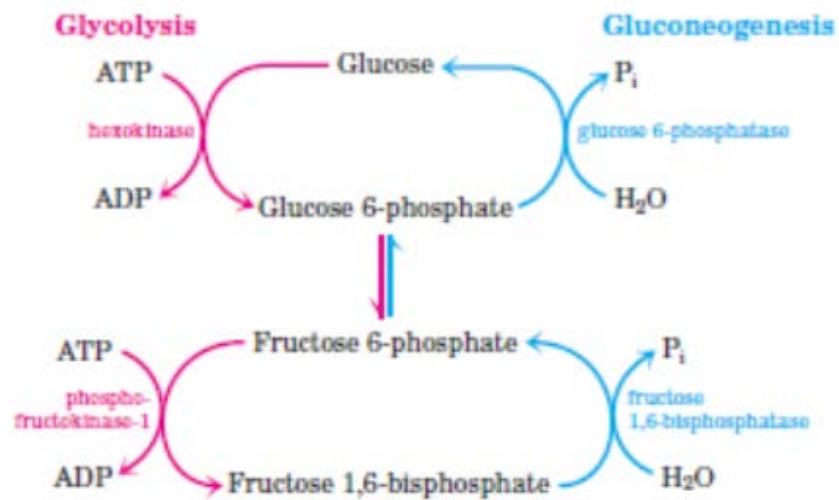
Gluconeogenesis

Formation of glucose from non carbohydrate precursor is known as gluconeogenesis.

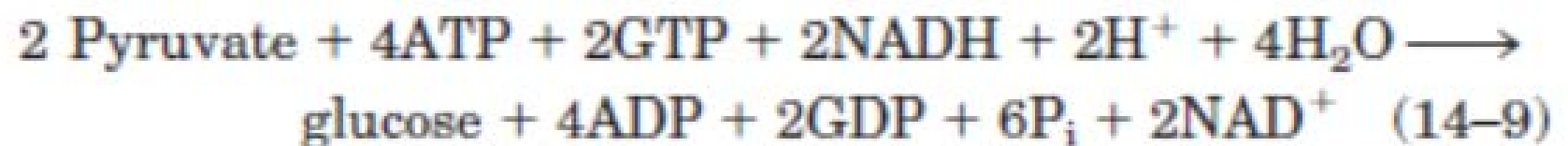
Gluconeogenesis (“formation of new sugar”), converts pyruvate and related three- and four-carbon compounds into glucose.

Gluconeogenesis occurs in all animals, plants, fungi, and microorganisms. The reactions are essentially the same in all tissues and all species.

The important precursors of glucose in animals are three-carbon compounds such as lactate, pyruvate, and glycerol, as well as certain amino acids.



The sum of the biosynthetic reactions leading from pyruvate to free blood glucose (Table 14–3) is



Glycogenolysis

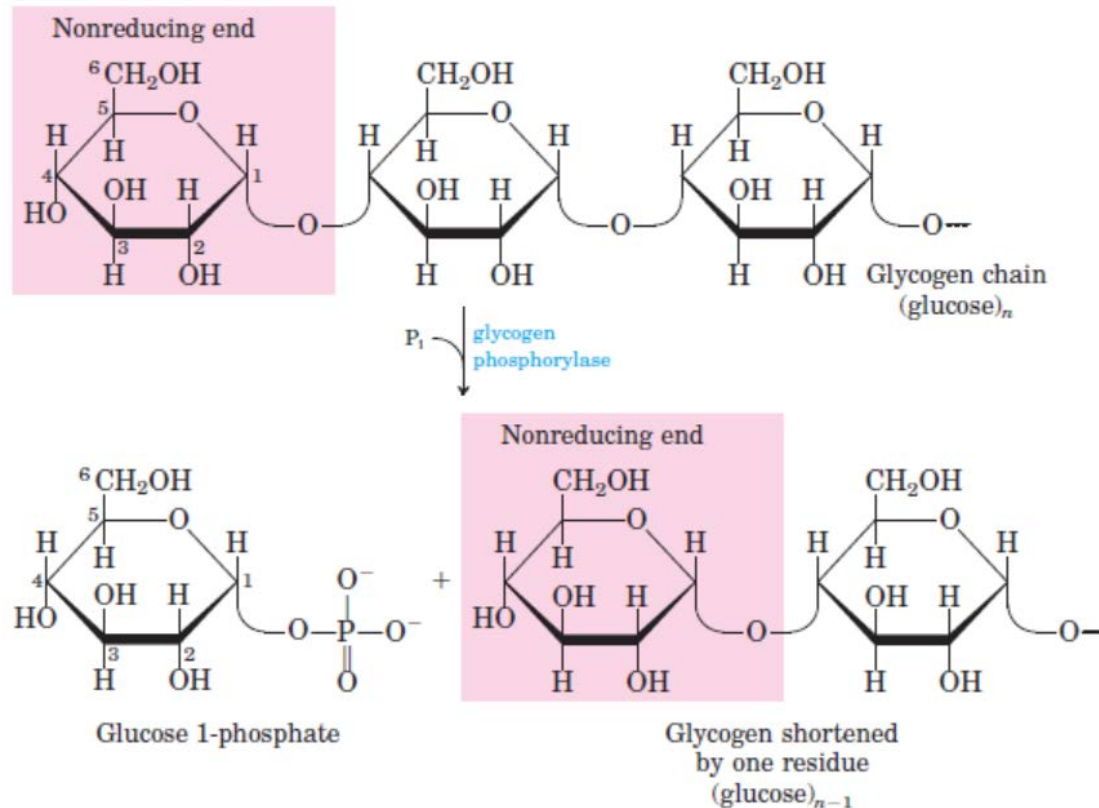
In skeletal muscle and liver, the glucose units of the outer branches of glycogen enter the glycolytic pathway through the action of three enzymes:

Glycogen phosphorylase

Glycogen debranching enzyme

Phosphoglucomutase

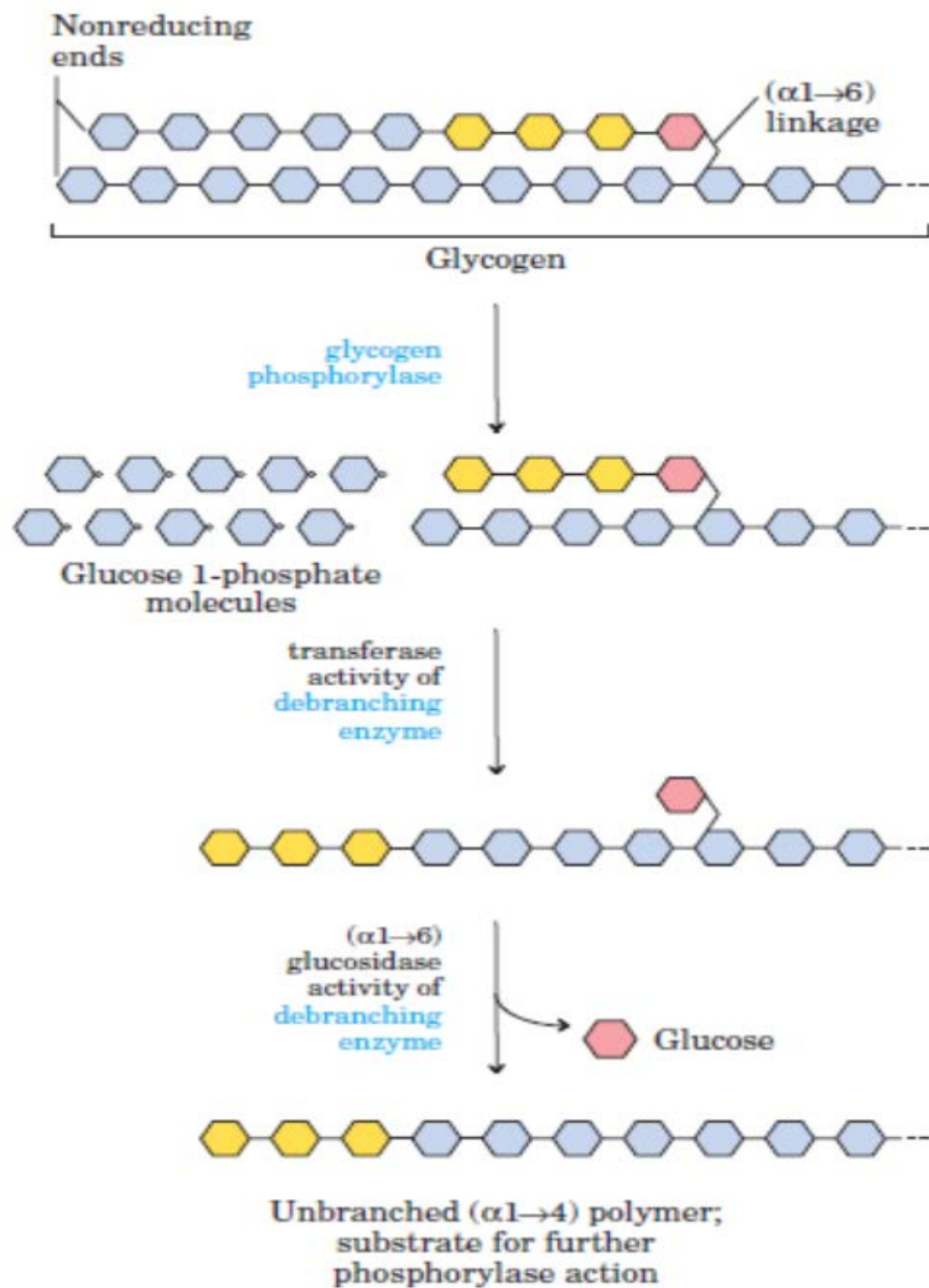
Glycogen phosphorylase catalyzes the reaction in which an (α 1-4) glycosidic linkage between two glucose residues at a non reducing end of glycogen undergoes attack by inorganic phosphate (P_i), removing the terminal glucose residue as D-glucose 1-phosphate



Glycogen phosphorylase acts repetitively on the nonreducing ends of glycogen branches until it reaches a point four glucose residues away from an (α 1-6) branch point, where its action stops.

Further degradation by glycogen phosphorylase can occur only after the **debranching enzyme** catalyzes two successive reactions that transfer branches.

Once these branches are transferred and the glucosyl residue at C-6 is hydrolyzed and glycogen phosphorylase activity continue.



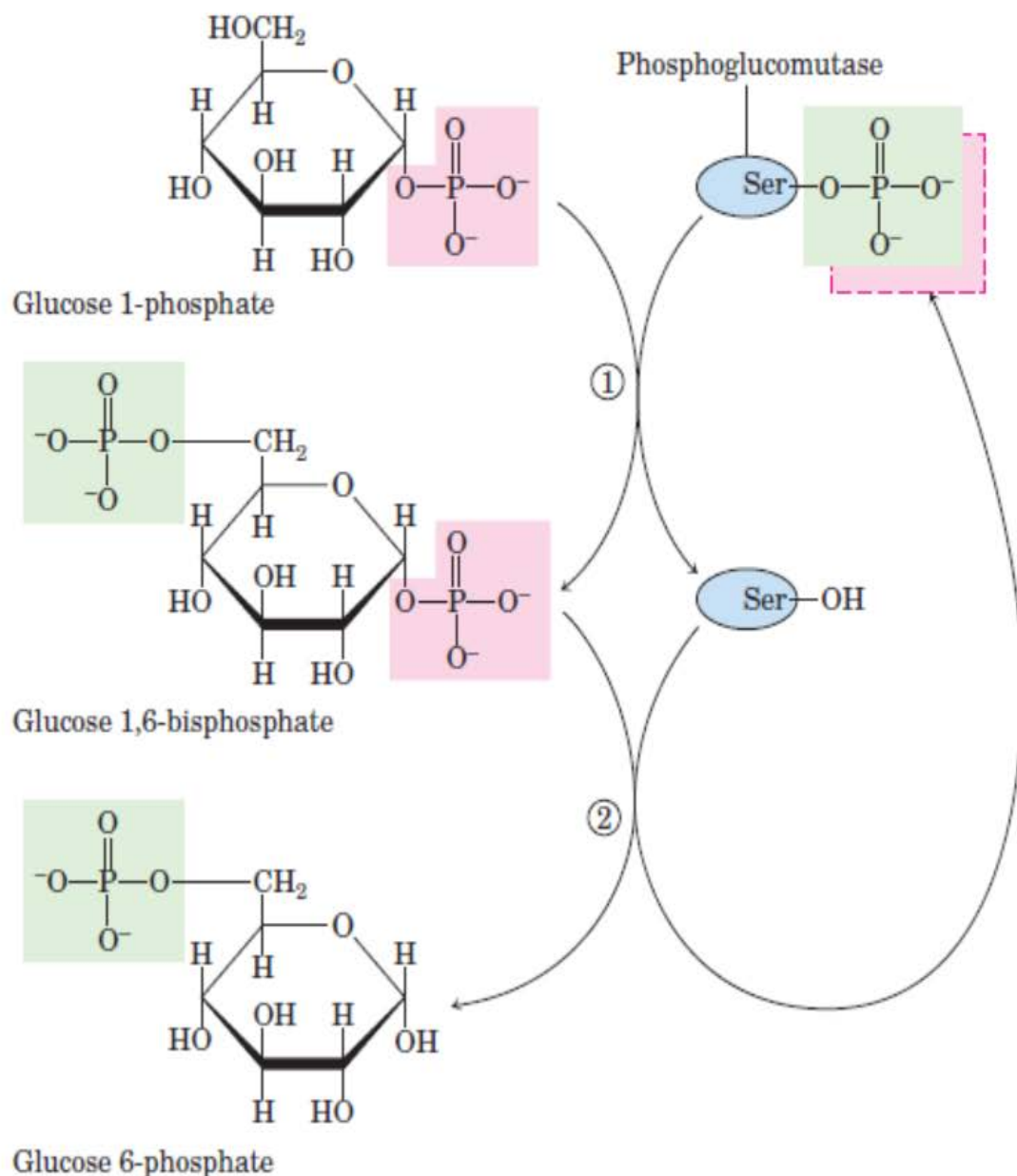
Glucose 1-Phosphate Can Enter Glycolysis or, in Liver, Replenish Blood Glucose

Glucose 1-phosphate, the end product of the glycogen phosphorylase reaction, is converted to glucose 6-phosphate by **phosphoglucomutase**, which catalyzes the reversible reaction



The glucose 6-phosphate formed from glycogen in skeletal muscle can enter glycolysis and serve as an energy source to support muscle contraction. In liver, glycogen breakdown serves a different purpose: to release glucose into the blood when the blood glucose level drops, as it does between meals. This requires an enzyme, glucose 6-phosphatase, that is present in liver and kidney but not in other tissues.

FIGURE 15-5 Reaction catalyzed by phosphoglucomutase. The reaction begins with the enzyme phosphorylated on a Ser residue. In step ①, the enzyme donates its phosphoryl group (green) to glucose 1-phosphate, producing glucose 1,6-bisphosphate. In step ②, the phosphoryl group at C-1 of glucose 1,6-bisphosphate (red) is transferred back to the enzyme, re-forming the phosphoenzyme and producing glucose 6-phosphate.



Glycogenesis

Glycogen synthesis takes place in virtually all animal tissues but is especially prominent in the liver and skeletal muscles.

The starting point for synthesis of glycogen is **glucose 6-phosphate**.

This can be derived from free glucose in a reaction catalyzed by the isozymes **hexokinase I and hexokinase II** in muscle and **hexokinase IV (glucokinase)** in liver.



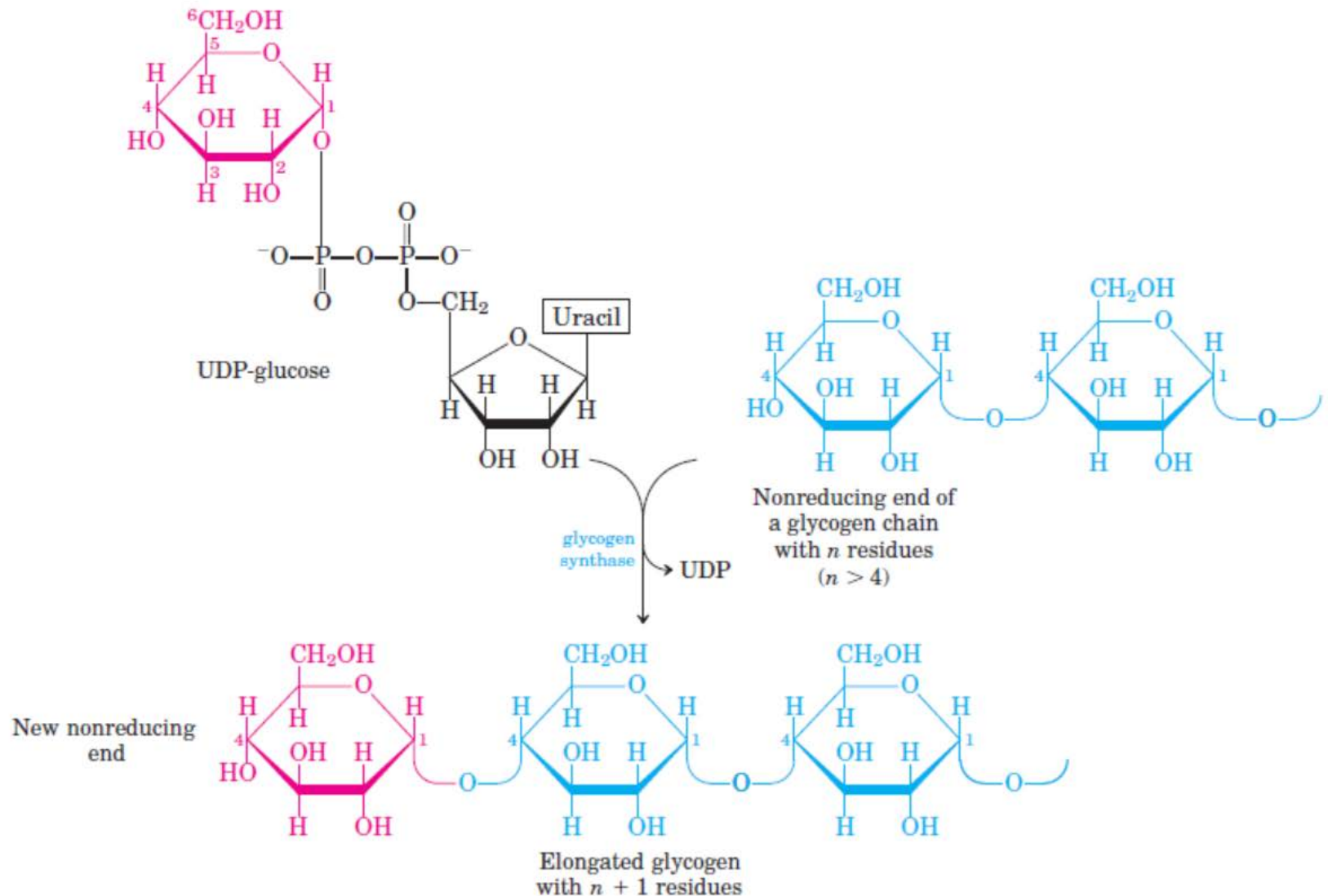
To initiate glycogen synthesis, the glucose 6-phosphate is converted to **glucose 1-phosphate** in the phosphoglucomutase reaction:



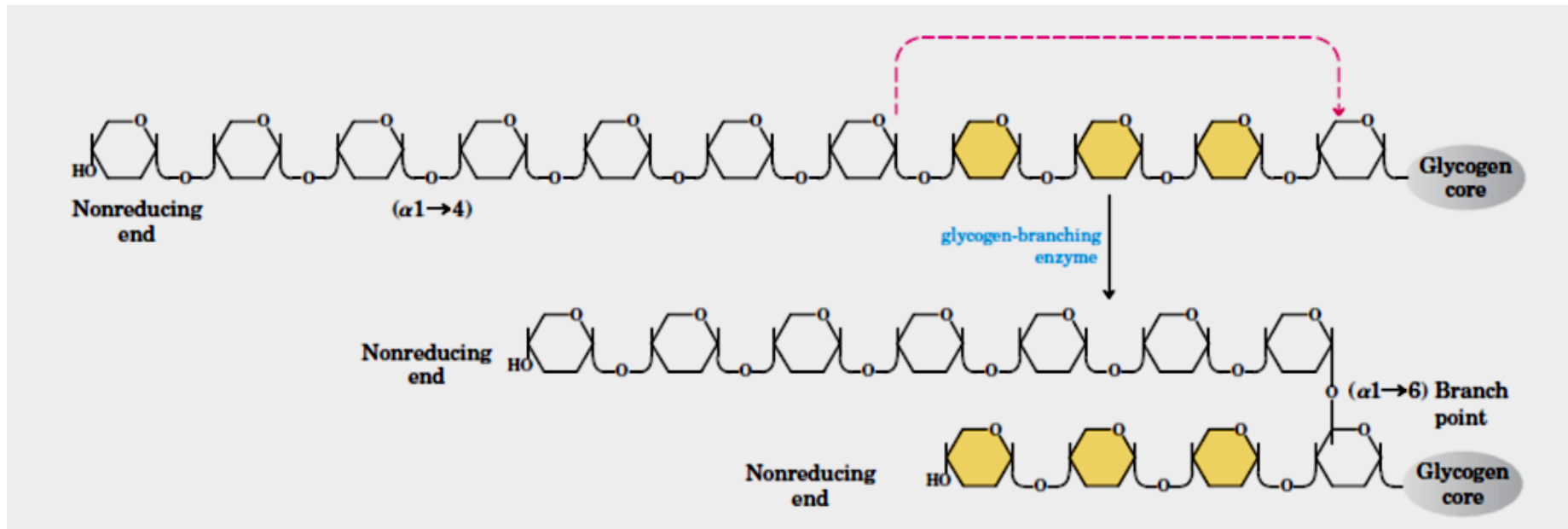
The product of this reaction is converted to UDP-glucose by the action of **UDP-glucose pyrophosphorylase**, in a key step of glycogen biosynthesis:



glycogen synthase, promotes the transfer of the glucose residue from UDP-glucose to a non reducing end of a branched glycogen molecule



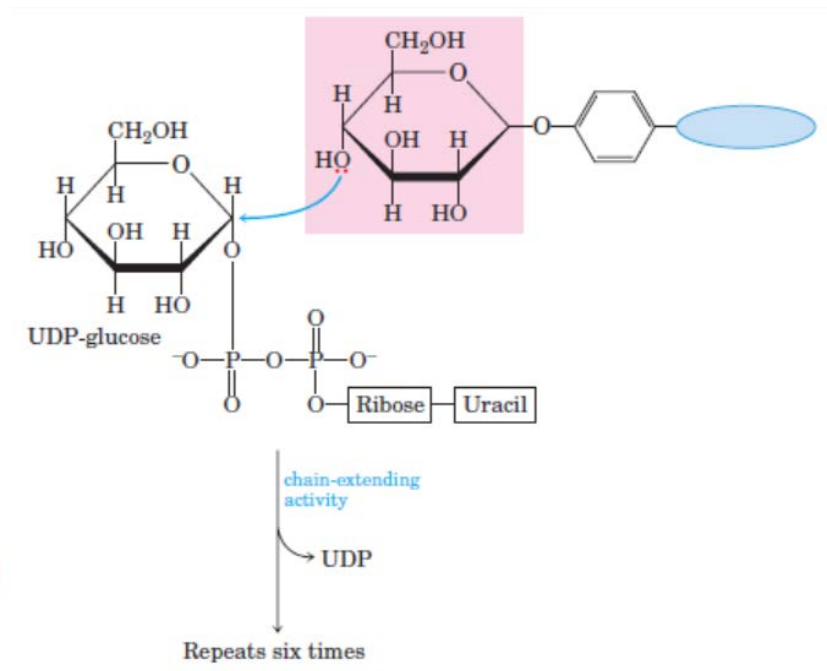
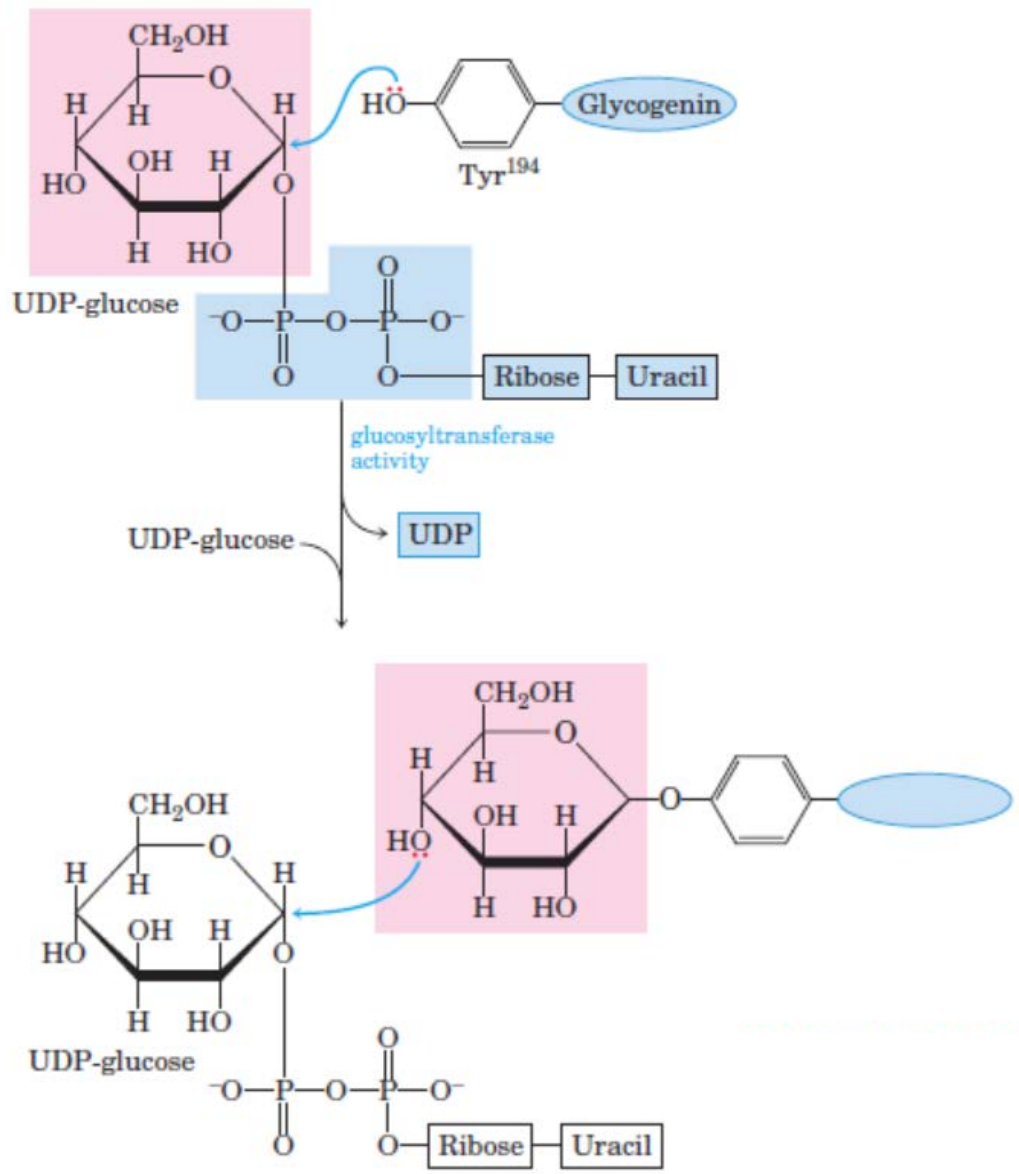
Glycogen synthase cannot make the (α 1-6) bonds found at the branch points of glycogen; these are formed by the glycogen-branching enzyme, also called **amylo (1-4) to (1-6) transglycosylase** or **glycosyl- (4-6)-transferase**



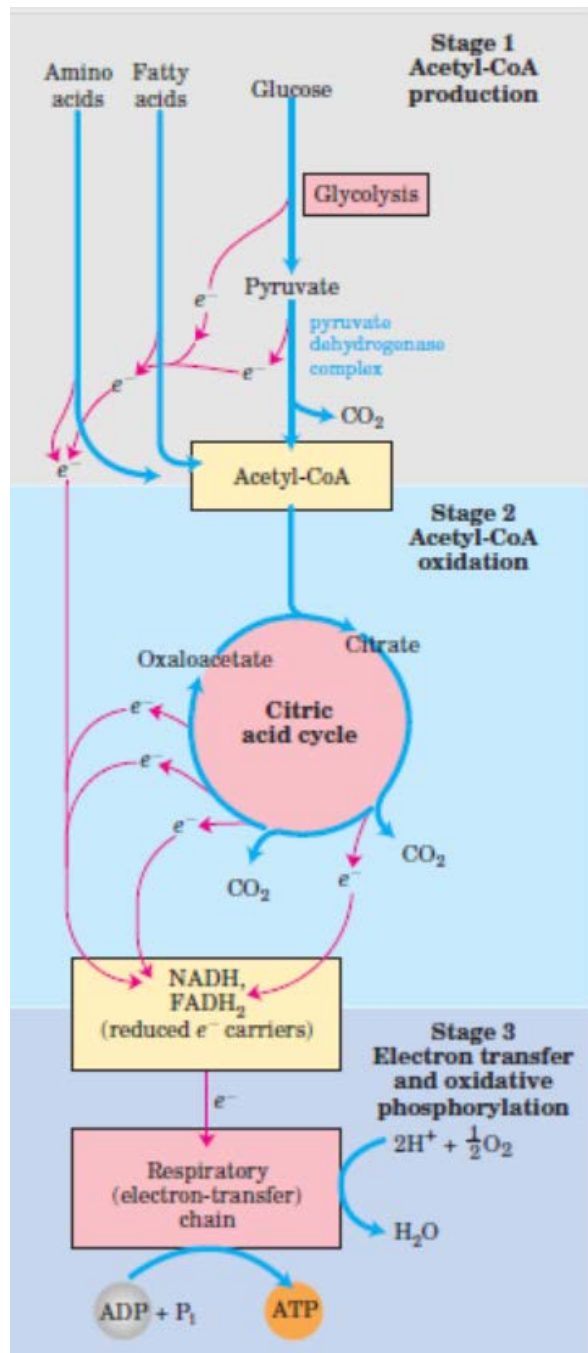
Glycogenin Primes the Initial Sugar Residues in Glycogen

Glycogen synthase cannot initiate a new glycogen chain de novo. It requires a primer, usually a preformed (1-4) polyglucose chain or branch having at least eight glucose residues. How is a *new glycogen molecule* initiated? The intriguing protein **glycogenin** is both the primer on which new chains are assembled and the enzyme that catalyzes their assembly.

(a)



TCA (tricarboxylic acid) Cycle
or
Citric Acid Cycle
or
Krebs Cycle

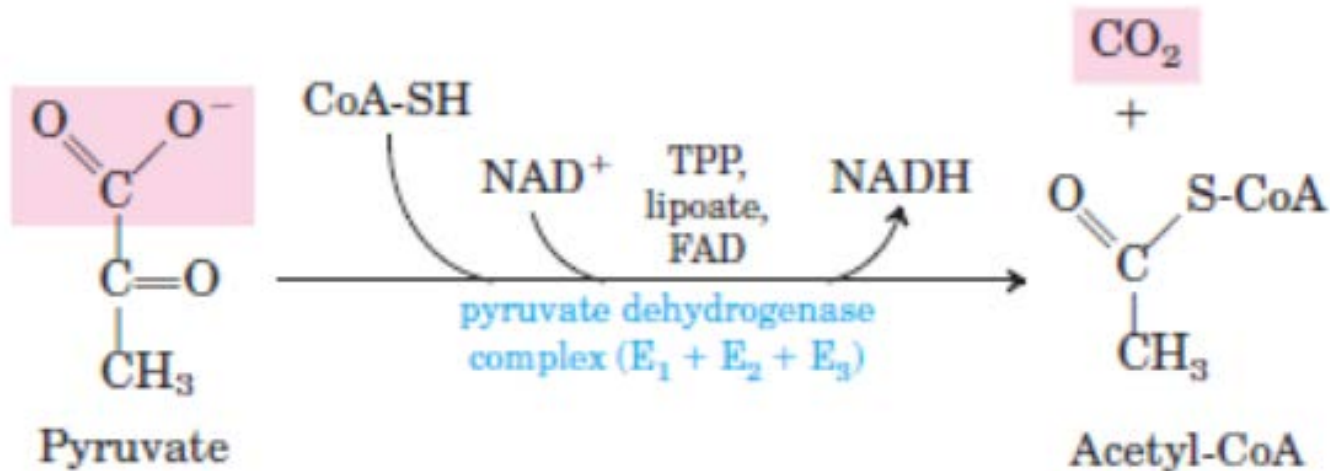


Catabolism of proteins, fats, and carbohydrates in the three stages of cellular respiration.

Stage 1: oxidation of fatty acids, glucose, and some amino acids yields acetyl-CoA. **Stage 2: oxidation of acetyl groups** in the citric acid cycle includes four steps in which electrons are abstracted. **Stage 3: electrons carried by NADH and FADH₂ are funneled into a chain of mitochondrial (or, in bacteria, plasma membrane-bound) electron carriers**—the respiratory chain—ultimately reducing O₂ to H₂O. This electron flow drives the production of ATP.

Production of Acetyl-CoA

- **Pyruvate** is oxidized to **Acetyl-CoA** and **CO₂**
- The overall reaction catalyzed by the **pyruvate dehydrogenase complex** is an **oxidative decarboxylation**
- An irreversible oxidation process in which the carboxyl group is removed from pyruvate as a molecule of CO₂



The combined dehydrogenation and decarboxylation of pyruvate to the acetyl group of acetyl-CoA requires the sequential action of three different enzymes and five different coenzymes or prosthetic Groups

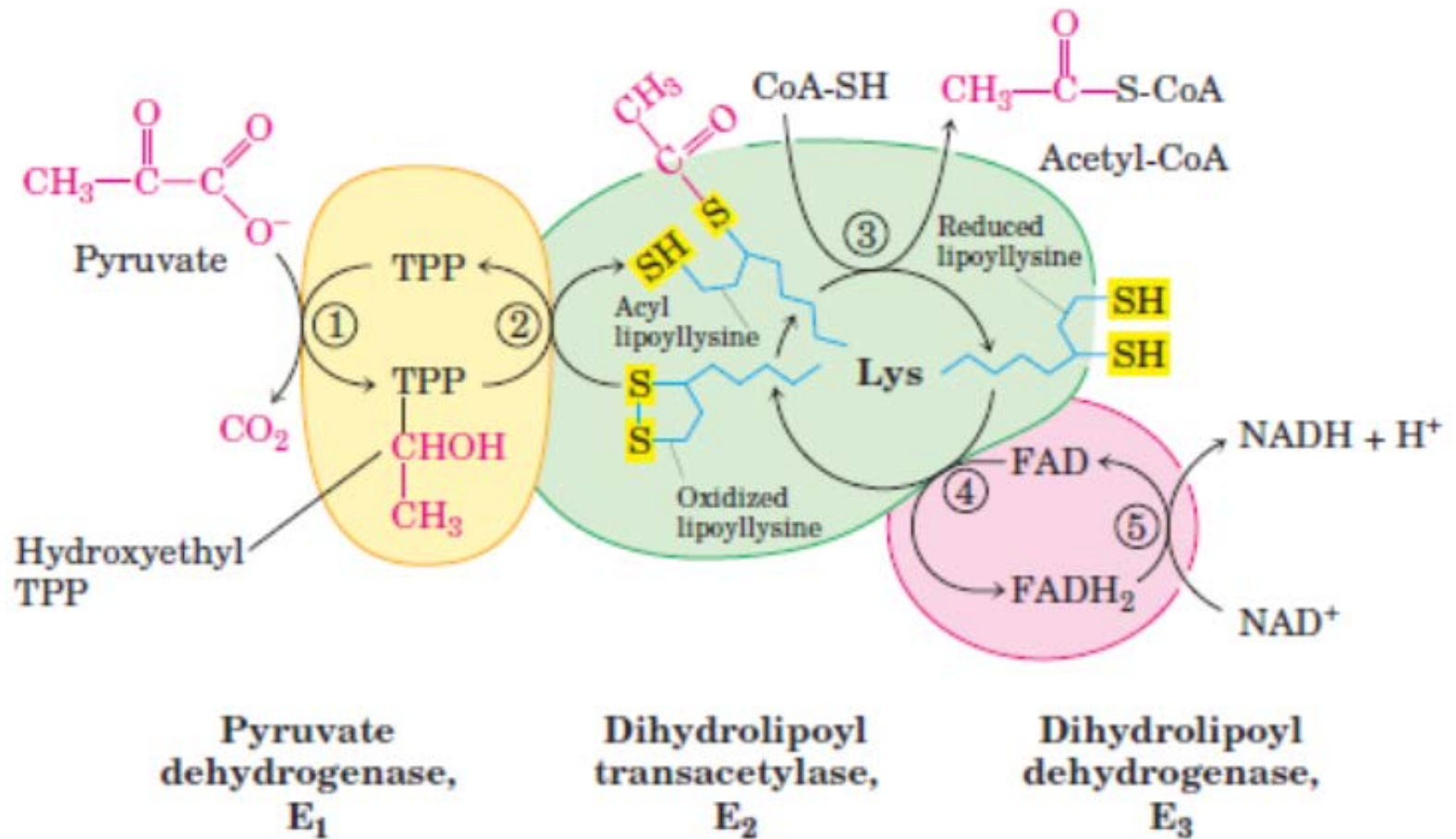
Enzymes

- **E1 (pyruvate dehydrogenase)**
- **E2 (dihydrolipoyl transacetylase)**
- **E3 (dihydrolipoyl dehydrogenase)**

Coenzyme

- **Thiamine pyrophosphate (TPP)**
- **Flavin adenine dinucleotide (FAD)**
- **Coenzyme A (CoA)**
- **Nicotinamide adenine dinucleotide (NAD)**
- **Lipoic acid**

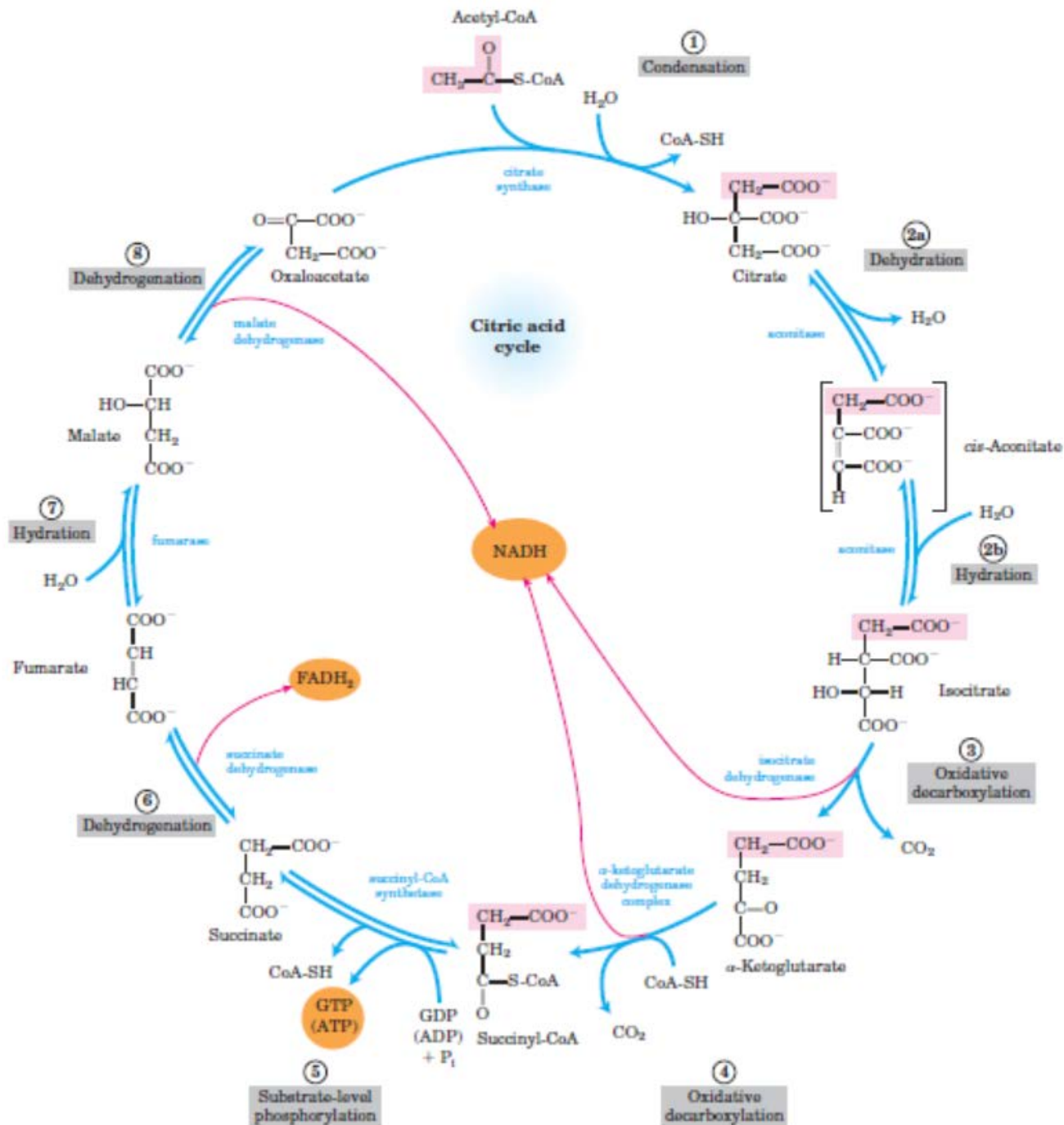
Oxidative decarboxylation of pyruvate to acetyl-CoA by PDH complex



TCA Cycle

- Acetyl-CoA enters the citric acid cycle (in the mitochondria of eukaryotes, the cytosol of prokaryotes) as citrate synthase catalyzes its condensation with oxaloacetate to form citrate.
- In seven sequential reactions, including two decarboxylations, the citric acid cycle converts citrate to oxaloacetate and releases two CO₂. The pathway is cyclic in that the intermediates of the cycle are not used up; for each oxaloacetate consumed in the path, one is produced.
- For each acetyl-CoA oxidized by the citric acid cycle, the energy gain consists of three molecules of NADH, one FADH₂, and one nucleoside triphosphate (either ATP or GTP).
- Besides acetyl-CoA, any compound that gives rise to a four- or five-carbon intermediate of the citric acid cycle—for example, the breakdown products of many amino acids—can be oxidized by the cycle.
- The citric acid cycle is amphibolic, serving in both catabolism and anabolism; cycle intermediates can be drawn off and used as the starting material for a variety of biosynthetic products.

TCA Cycle



Regulation of metabolite flow from the PDH complex through the citric acid cycle

