CHAPTER 14
Glycolysis, Gluconeogenesis, and the Pentose Phosphate Pathway

p543

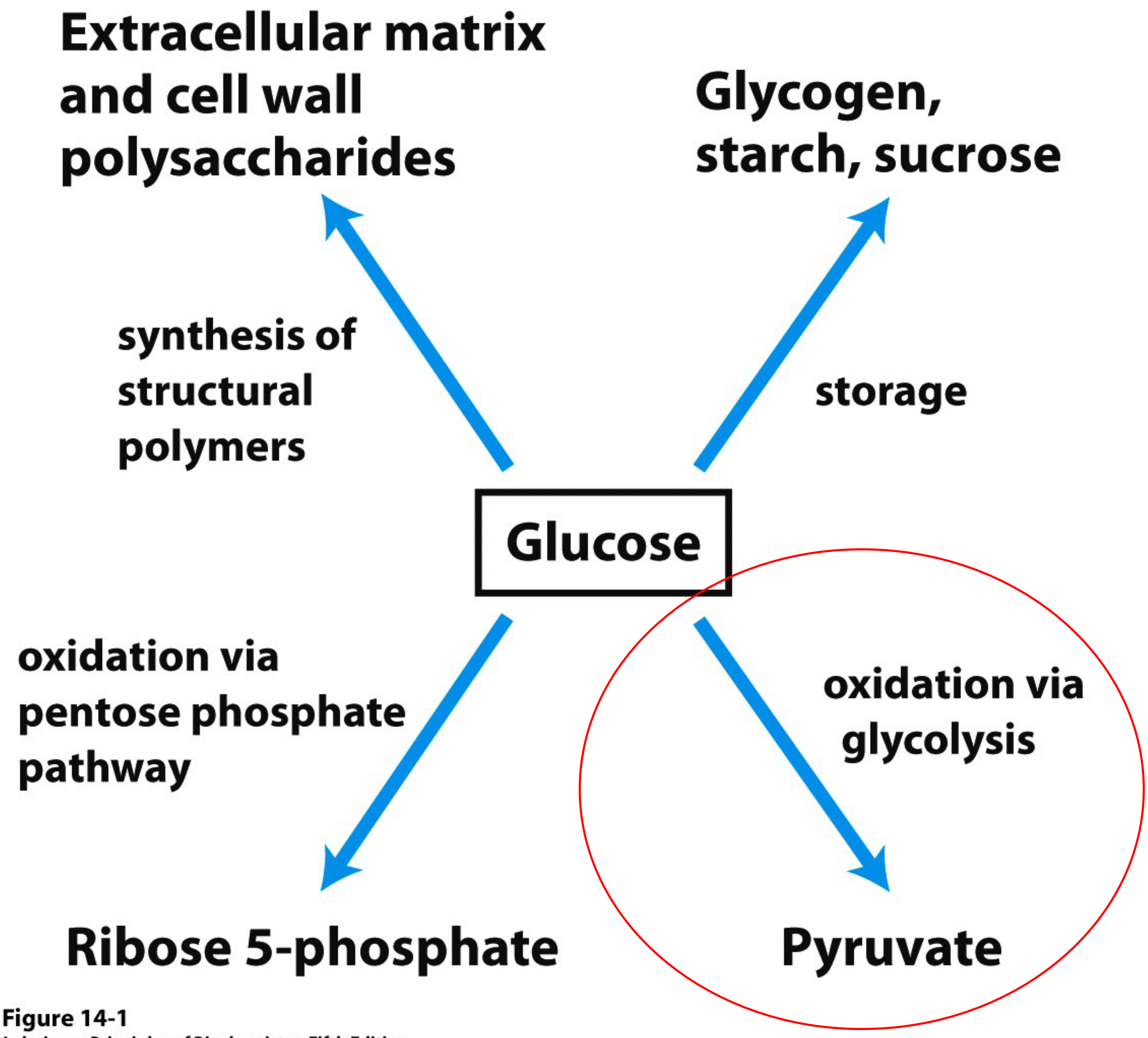


Figure 14-1
Lehninger Principles of Biochemistry, Fifth Edition

14.1 Glycolysis

History

1856年，法国的Louis Paster(巴斯德)证实发酵是由微生物进行的。这是科学史上的一块里程碑。但在那时，认为葡萄糖到乙醇的发酵过于复杂，无法在活细胞外重复这一过程。

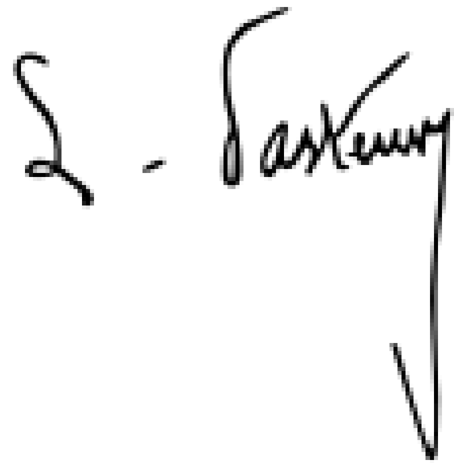
1896年，德国科学家Hans Buchner (older brother)和Eduard Buchner（毕希纳）发现发酵可在无细胞条件下进行。

1905年，Harden和Young发现将无机磷酸加入酵母抽提物后，可以激活和延长葡萄糖发酵。在发酵过程中，无机磷酸从反应培养基中消逝。他们认为发酵是通过形成一个或多个糖磷酸酯进行工作的。

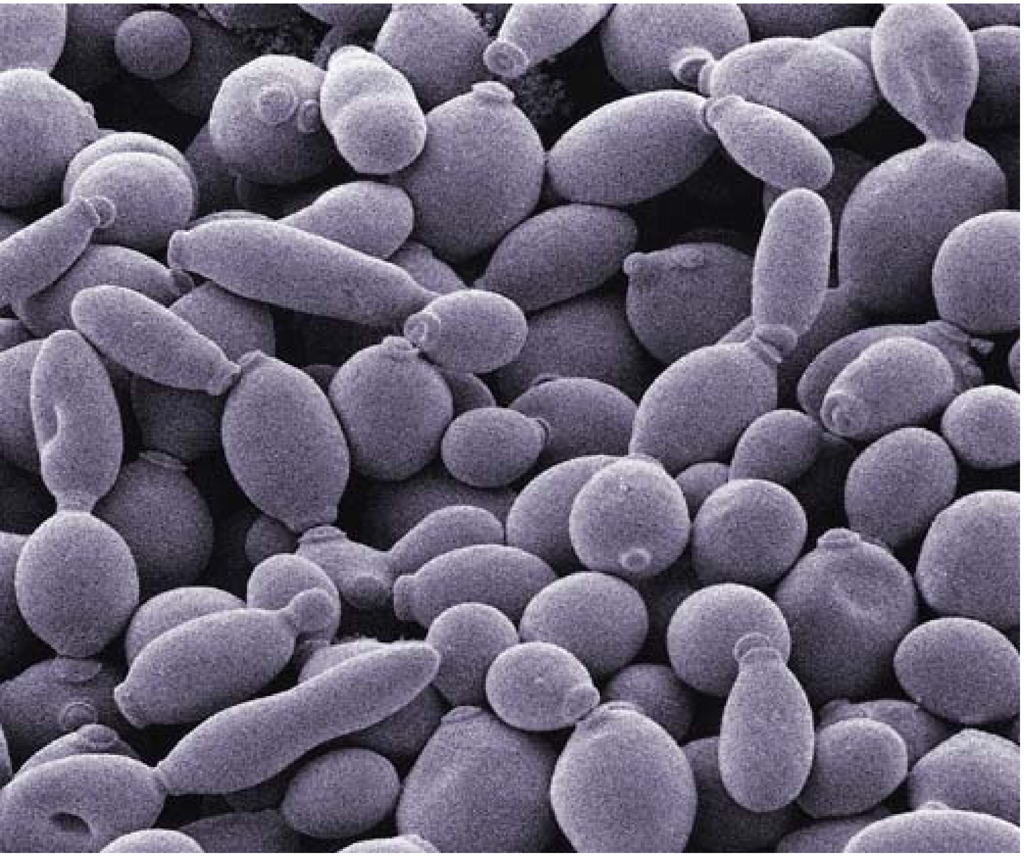
1930年前后，德国的Embden和Meyerhof等将发酵中每一步反应加以分离，鉴定了导致葡萄糖到丙酮酸的10步反应

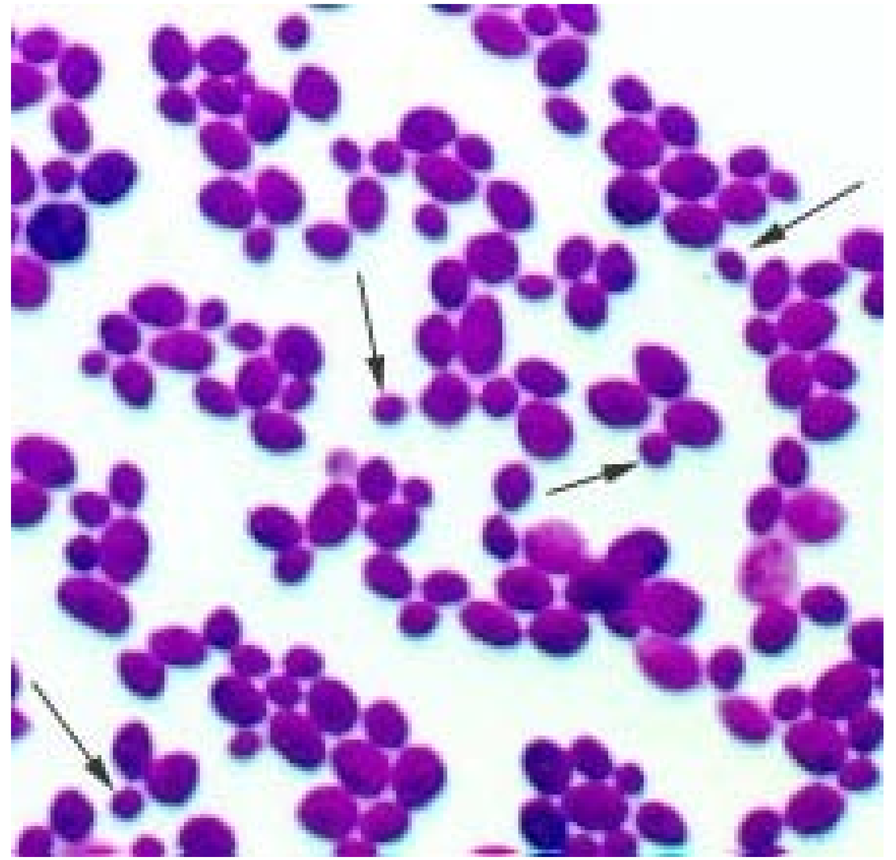
The "father of microbiology"

Paster (1822-1895)



Saccharomyces cerevisiae is a species of ***budding yeast***





Eduard Buchner (May 20, 1860 – August 13, 1917) was a German chemist and zymologist, the winner of the 1907 Nobel Prize in Chemistry “for his *biochemical researches and discovery of cell-free fermentation”* .

Buchner

The Nobel Prize in Chemistry 1929
Arthur Harden, Hans von Euler-Chelpin

Arthur Harden

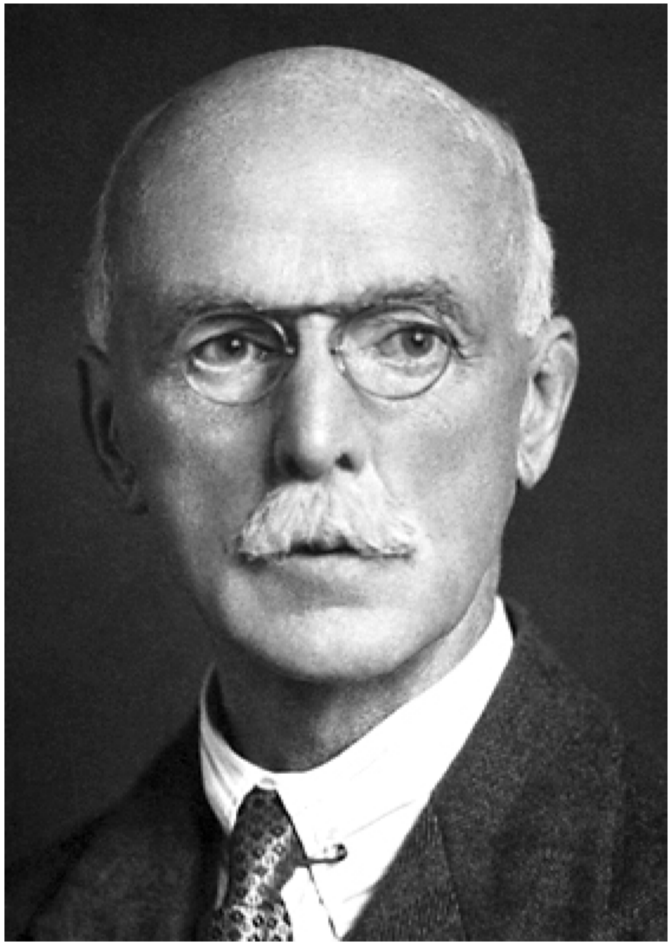
Born: 12 October 1865, Manchester, United Kingdom

Died: 17 June 1940, Bourne, United Kingdom

Affiliation at the time of the award: London University, London, United Kingdom

Prize motivation: "for their investigations on the fermentation of sugar and fermentative enzymes"

Field: Biochemistry



Hans von Euler-Chelpin 1873–1964

Unnumbered 14 p528
Lehninger Principles of Biochemistry, Fifth Edition

The Nobel Prize in Physiology or Medicine 1922
Archibald V. Hill, Otto Meyerhof

Otto Fritz Meyerhof

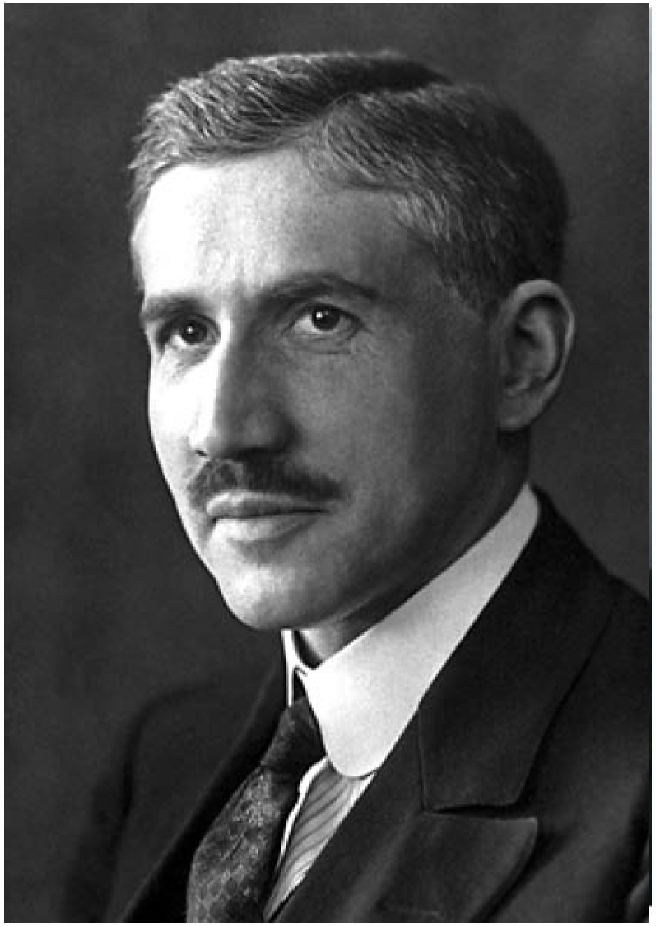
Born: 12 April 1884, Hanover, Germany

Died: 6 October 1951, Philadelphia, PA, USA

Affiliation at the time of the award: Kiel University, Kiel, Germany

Prize motivation: "for his discovery of the fixed relationship between the consumption of oxygen and the metabolism of lactic acid in the muscle"

Otto Meyerhof received his Nobel Prize one year later, in 1923.



Gustav Embden
1874–1933

Definition

glykys-, sweet or sugar； lysis,spliting

The pathway by which glucose is converted to lactate in muscle

The anaerobic catabolic pathway by which a molecule of glucose is broken down into two molecules of pyruvate.

Embden-Meyerhof-Pathway, EMP

(埃姆登-迈耶霍夫途径) Germany

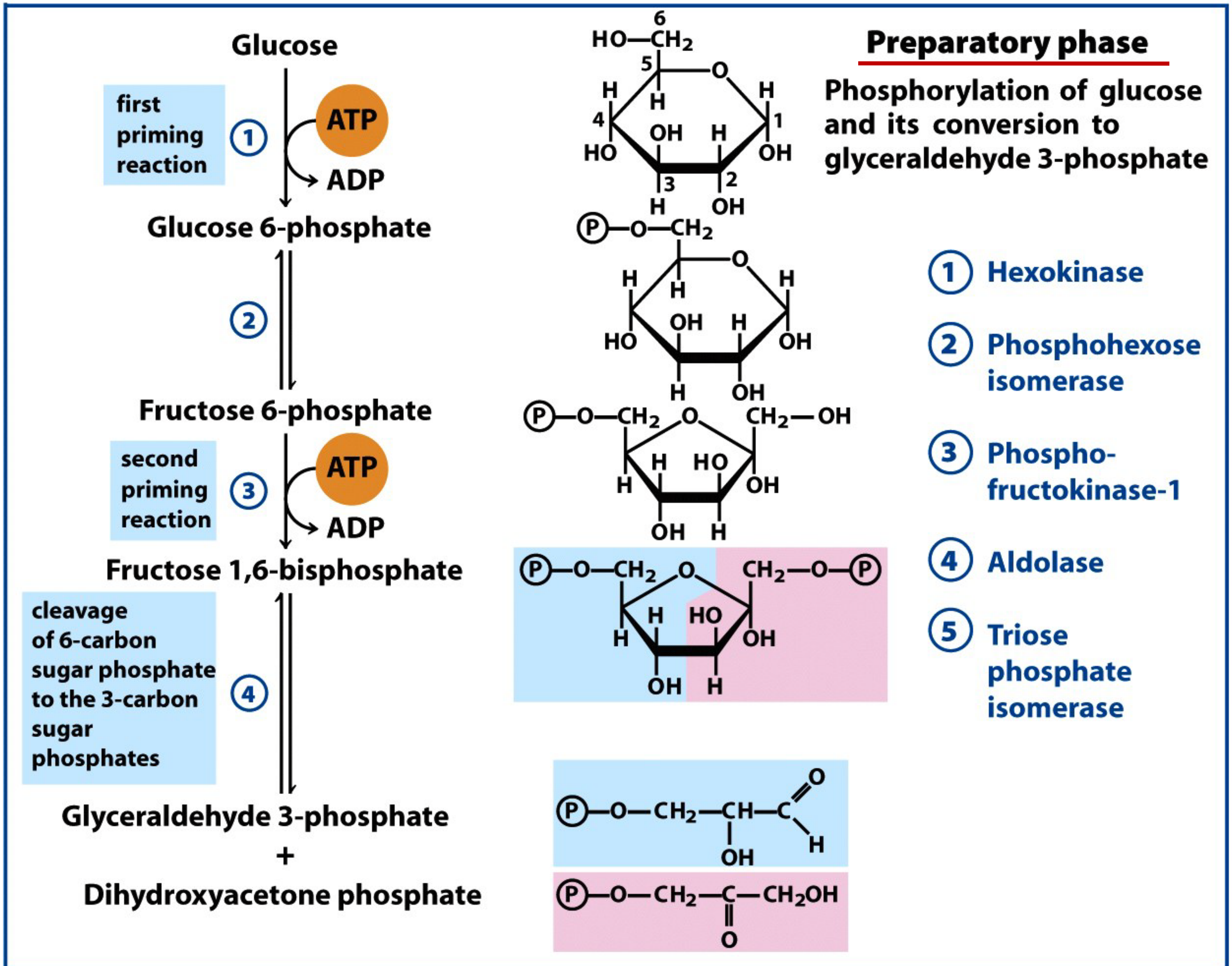


Figure 14-2a
Lehninger Principles of Biochemistry, Fifth Edition

The two phases of glycolysis

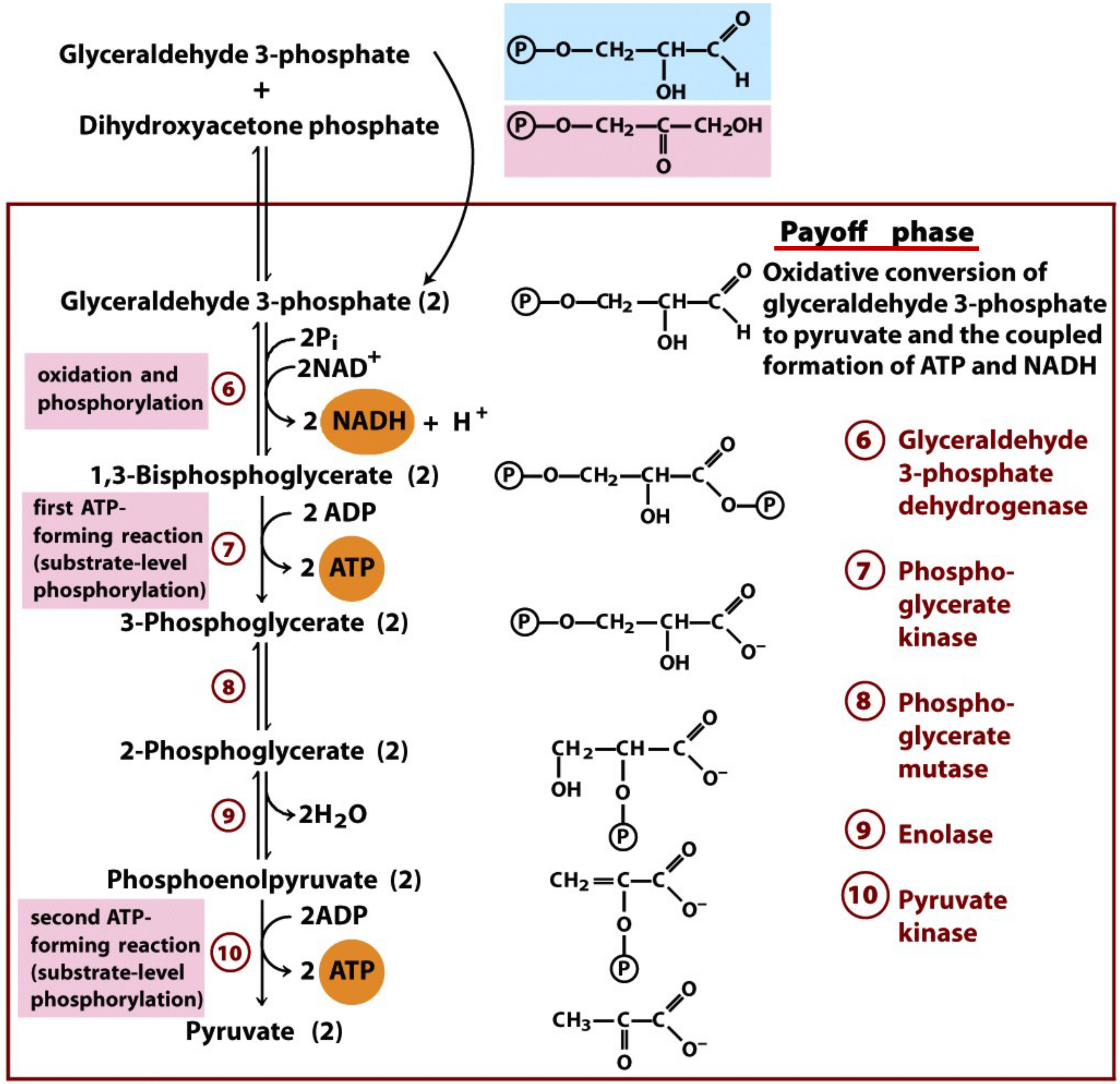


Figure 14-2b

Lehninger Principles of Biochemistry, Fifth Edition

ATP and NADP formation Coupled to Glycolysis

$$C_6H_{12}O_6 + 2NAD^+ \longrightarrow 2H_3C\text{-}CO\text{-}COO^- + 2NADH + 2H^+$$

$$\Delta G'^{o} = -146 \text{ KJ/mol}$$

$$2ADP + 2Pi \longrightarrow 2ATP + 2H_2O$$

$$\Delta G'^{o} = 2 \times 30.5 = 61.0 \text{ KJ/mol}$$

$$C_6H_{12}O_6 + 2ADP + 2Pi + 2NAD^+ \longrightarrow 2 \text{ pyruvate} + 2ATP + 2NADH + 2H^+$$

$$\Delta G'^{o} = -146 + 61 = -85 \text{ KJ/mol}$$

under standard-state conditions: (61/146) $\times$100% = **41.7%**

大部分汽油机仅仅在**30%**左右

The efficiency of energy conservation for glucose degradation through glycolysis, TCA cycle and oxidative phosphorylation is close to 65%

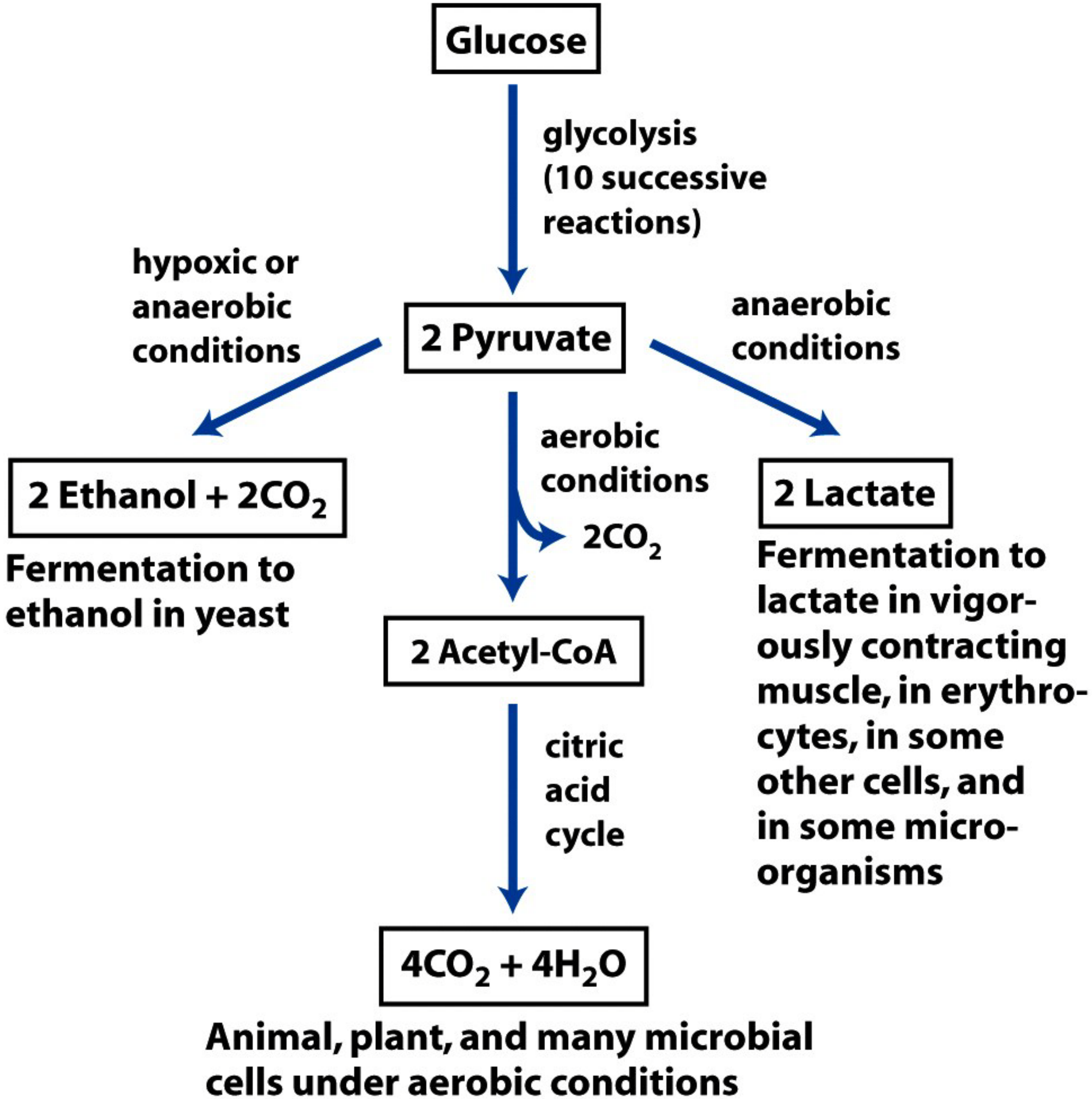
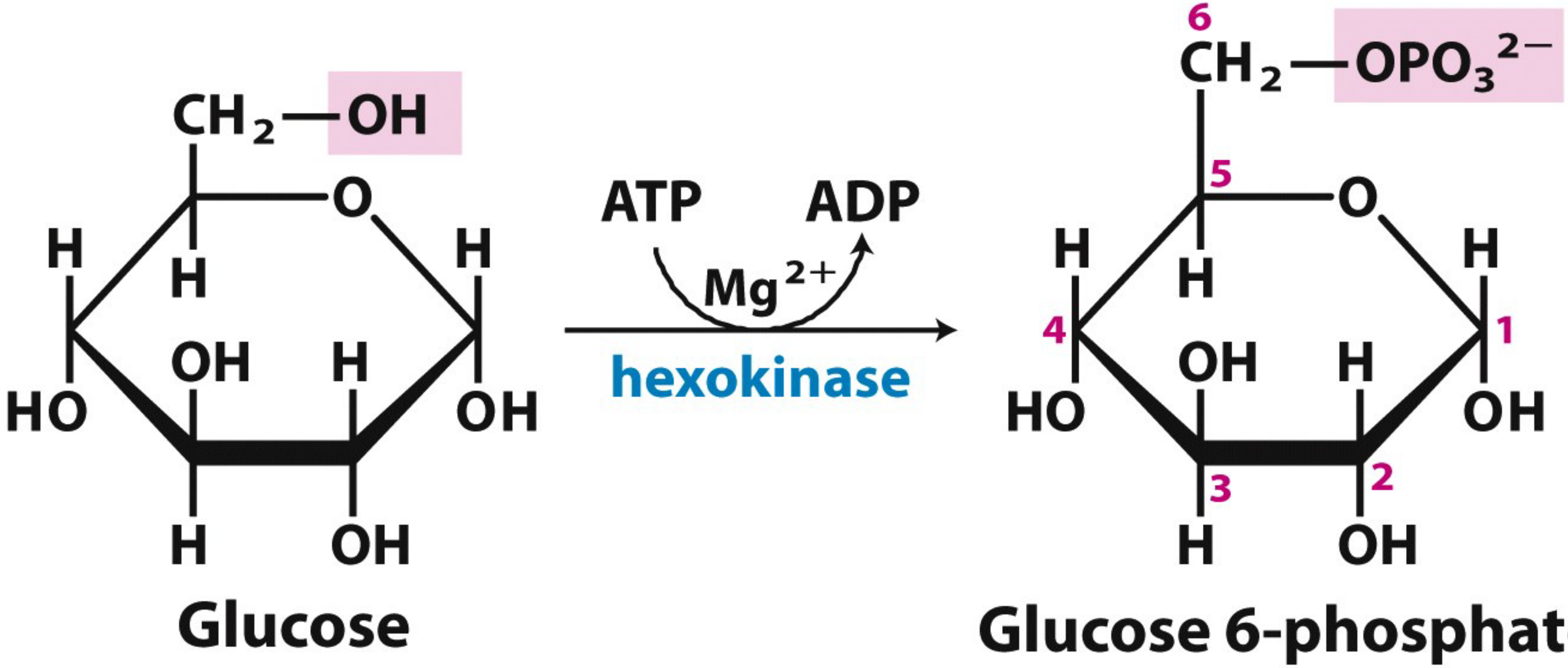


Figure 14-3

Three possible catabolic fates of the pyruvate formed in glycolysis

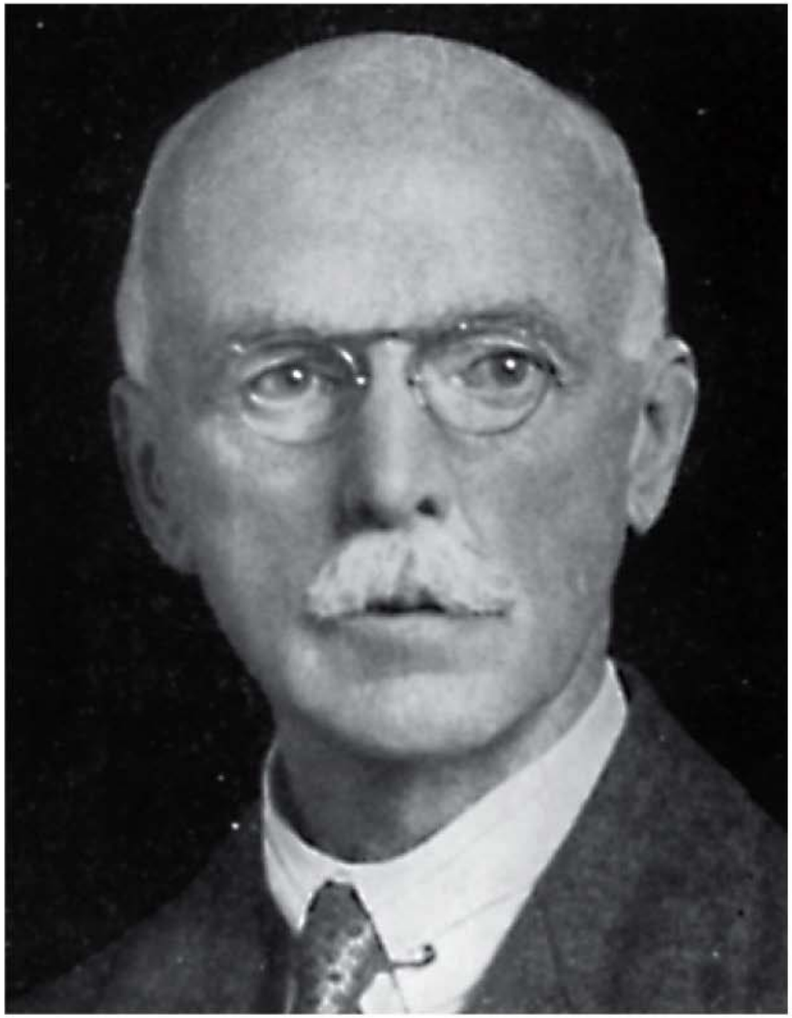
Step 1



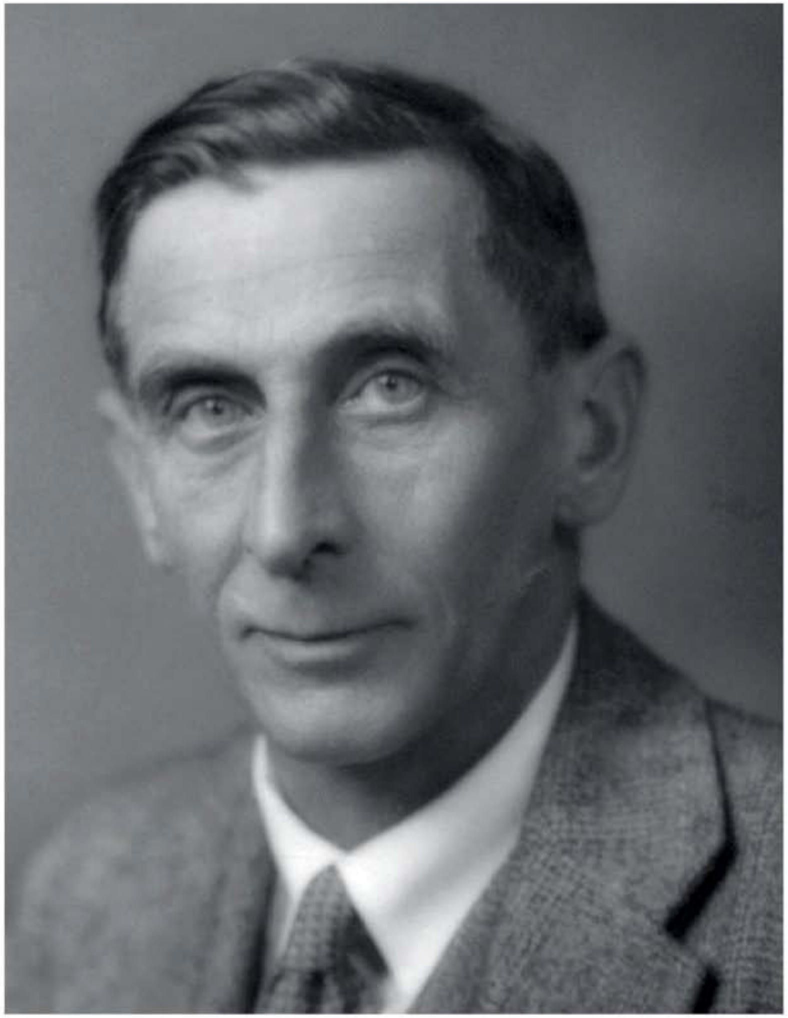
$$\Delta G'^{\circ} = -16.7\ \text{kJ/mol}$$

Unnumbered 14 p532a

Lehninger Principles of Biochemistry, Fifth Edition



Arthur Harden
1865–1940



William Young
1878–1942

Unnumbered 14 p531

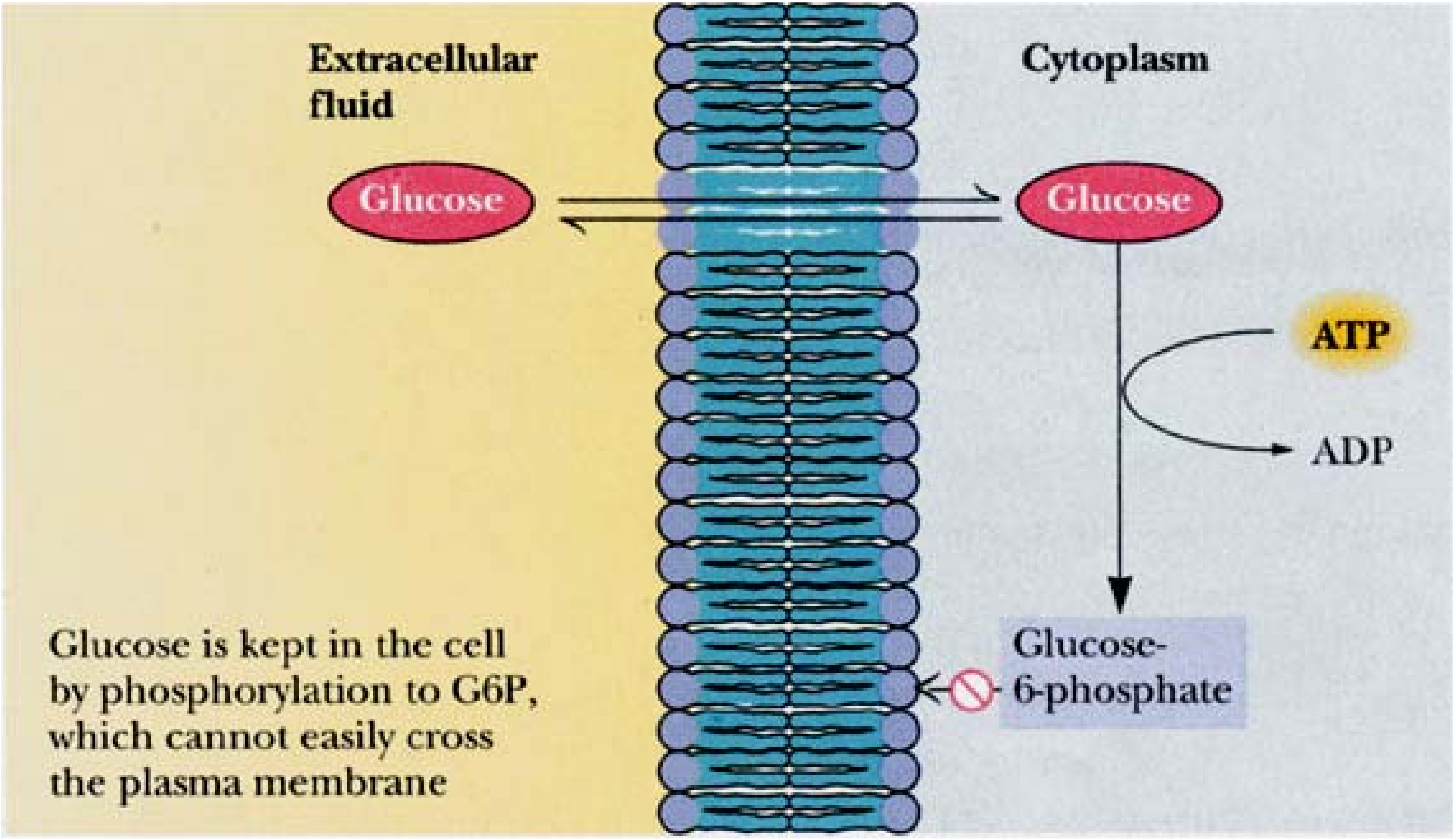
Lehninger Principles of Biochemistry, Fifth Edition

Importance of phosphorylated intermediates

1. Because the plasma membrane generally lacks transporters for phosphorylated sugar， the phosphorylated glycolytic intermediates cannot leave the cell.

2. Phosphoryl groups are essential components in the enzymatic conservation of metobolic energy.

3. Binding energy resulting from the binding of phosphate groups to the active sites of enzymes lowers the activation energy and increases the specificity of the enzymatic reactions



Phosphorylation of glucose by ATP creates a charged molecule that cannot easily cross the plasma membrane.

Hexokinase:

K_m = 0.1mM   blood glucose 4-5mM

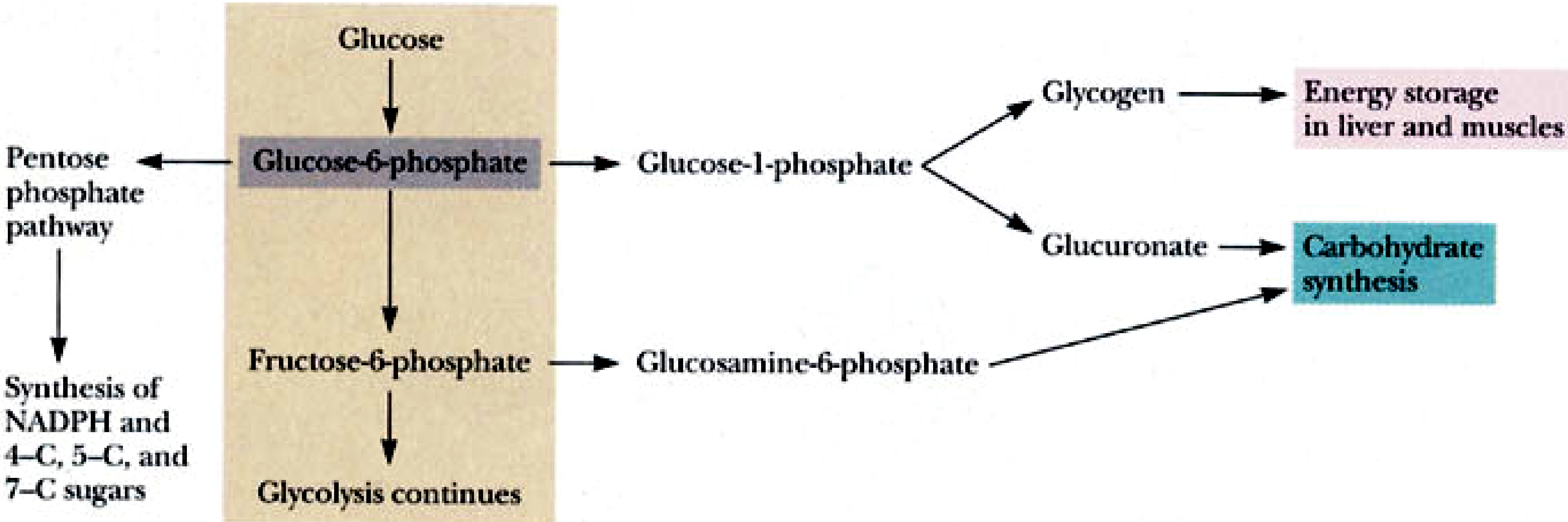
allosterical inhibitor : G-6-P

isozymes: HK1,2,3,4

Glucokinase (HK4):

K_m = 10.0 mM

not product- inhibited



Glucose-6-phosphate is the branch point for several carbohydrate metabolic pathways.

When glucose levels are low, hexokinase is responsible for phosphorylating glucose for glycolysis;

When glucose levels are high, glucokinase phosphorylates glucose for storage as glycogen.

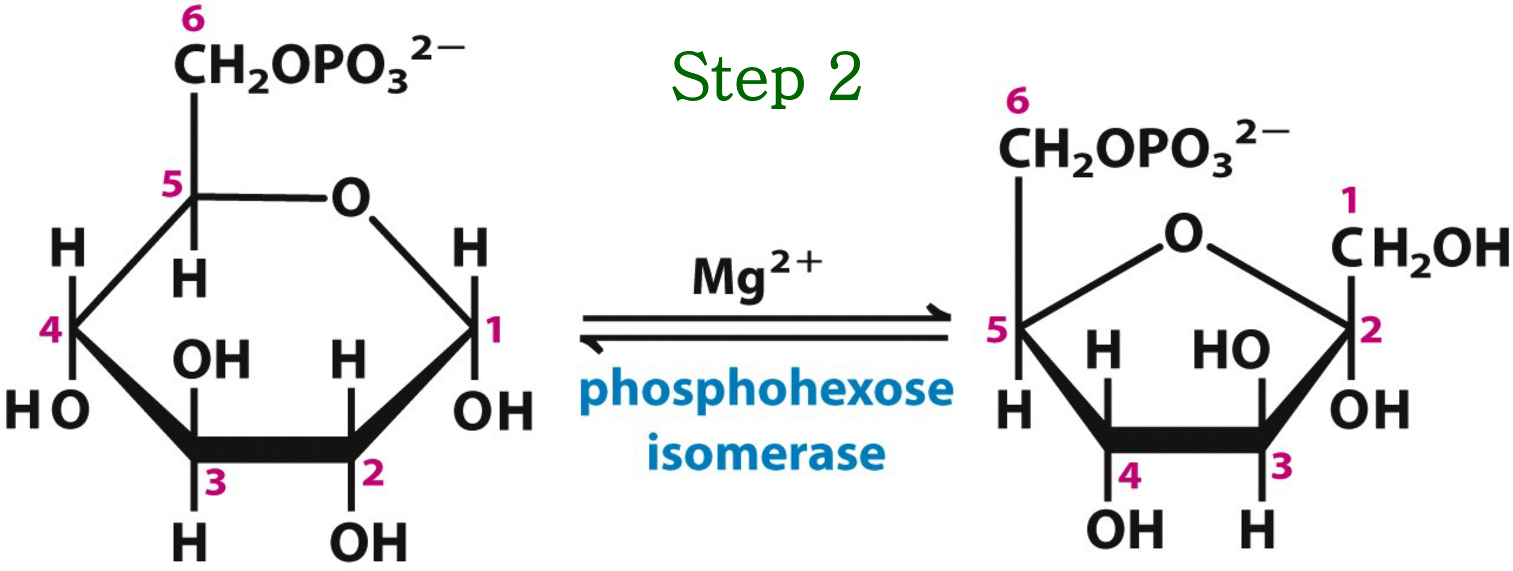
Insulin ——→ glucokinase ——⊣ diabetes mellitus

Brief Report

NEONATAL DIABETES MELLITUS DUE TO COMPLETE GLUCOKINASE DEFICIENCY

1588 · N Engl J Med, Vol. 344, No. 21 · May 24, 2001

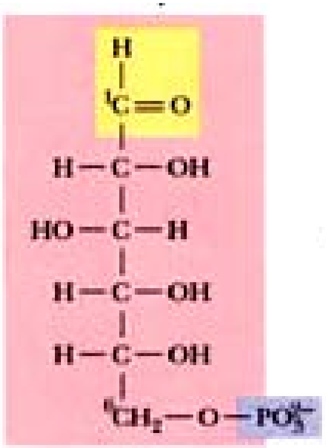
Step 2

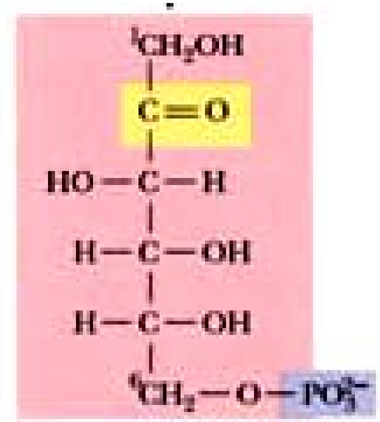


Glucose 6-phosphate

Fructose 6-phosphate

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





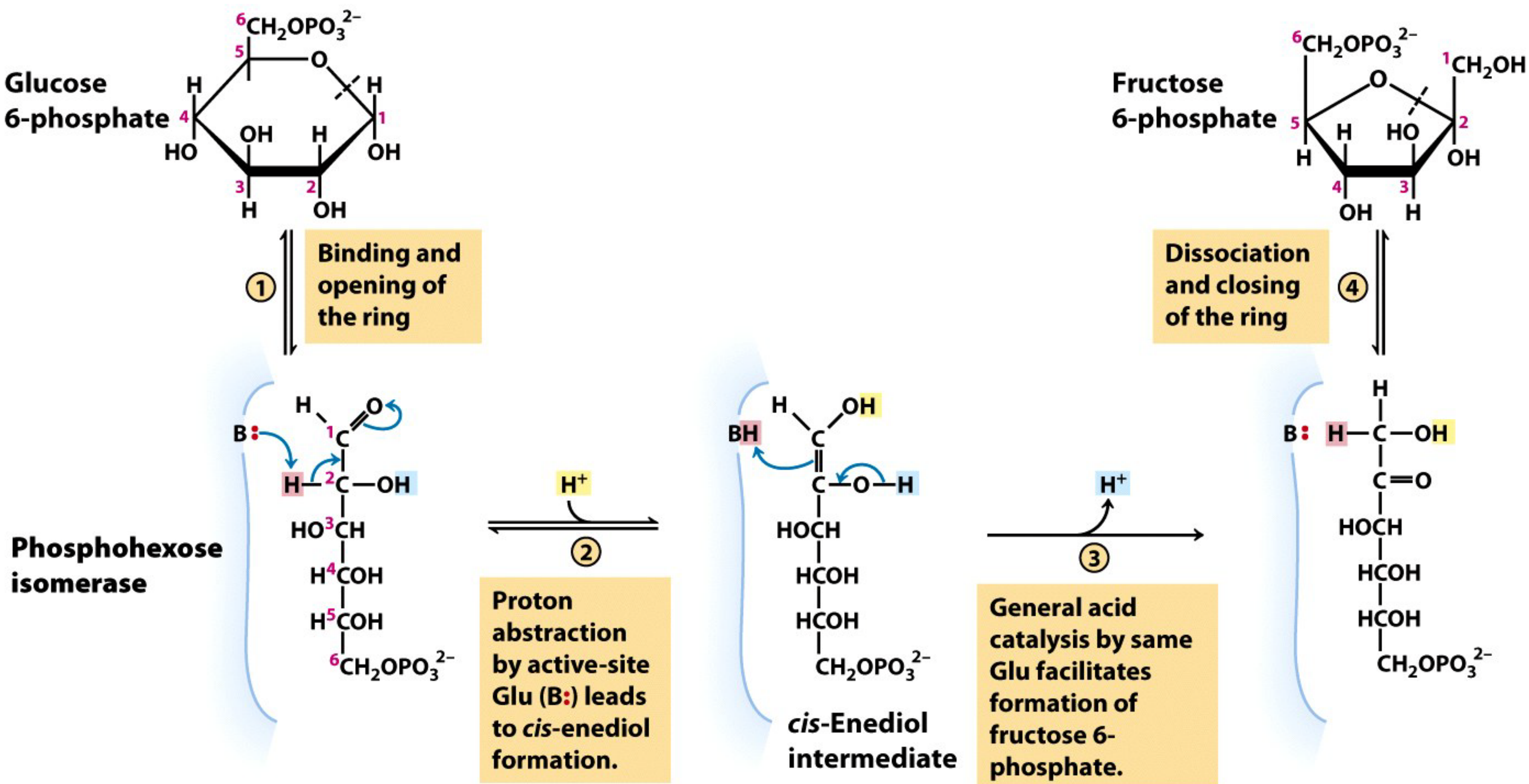


Figure 14-4

Lehninger Principles of Biochemistry, Fifth Edition

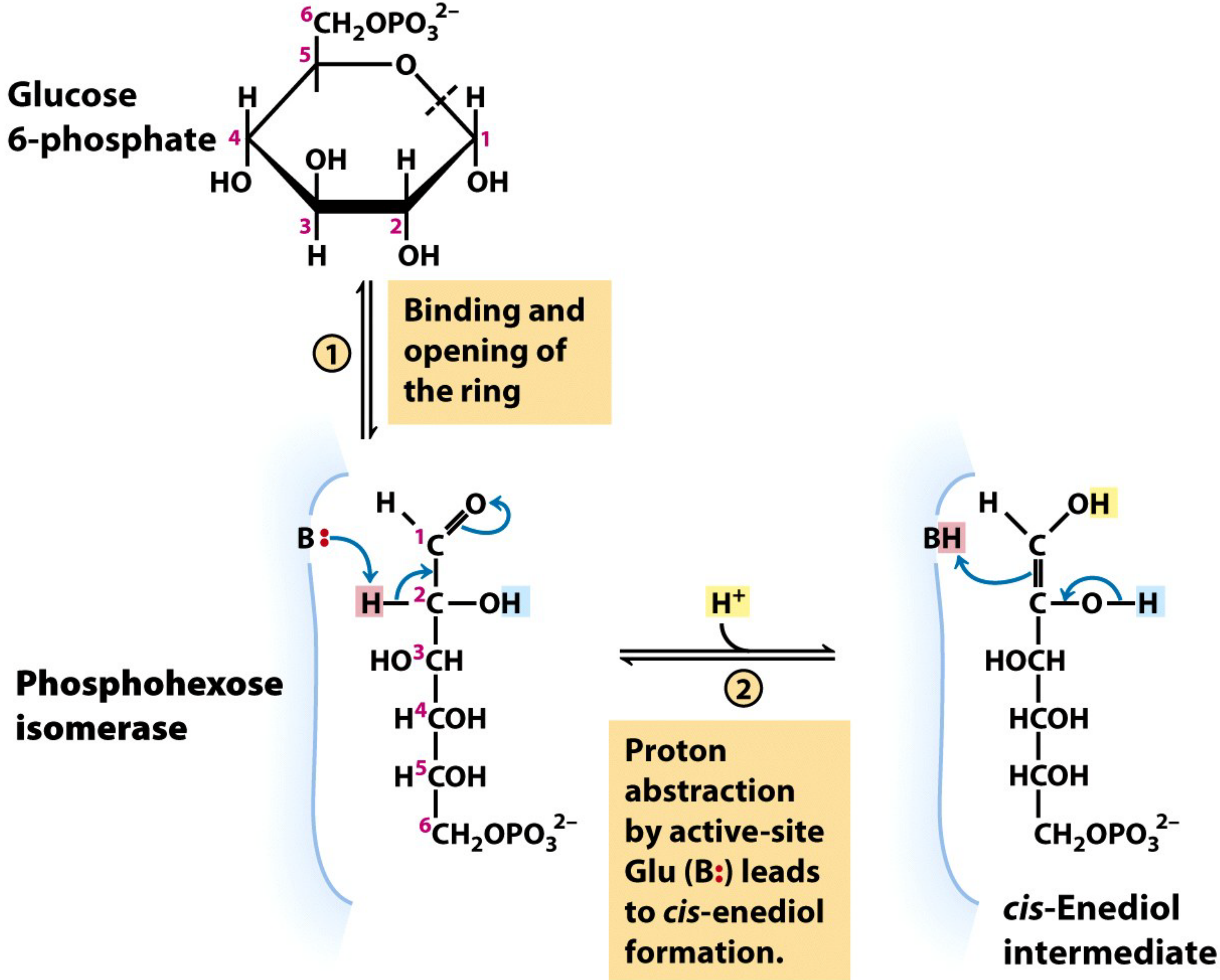


Figure 14-4 part 1

Lehninger Principles of Biochemistry, Fifth Edition

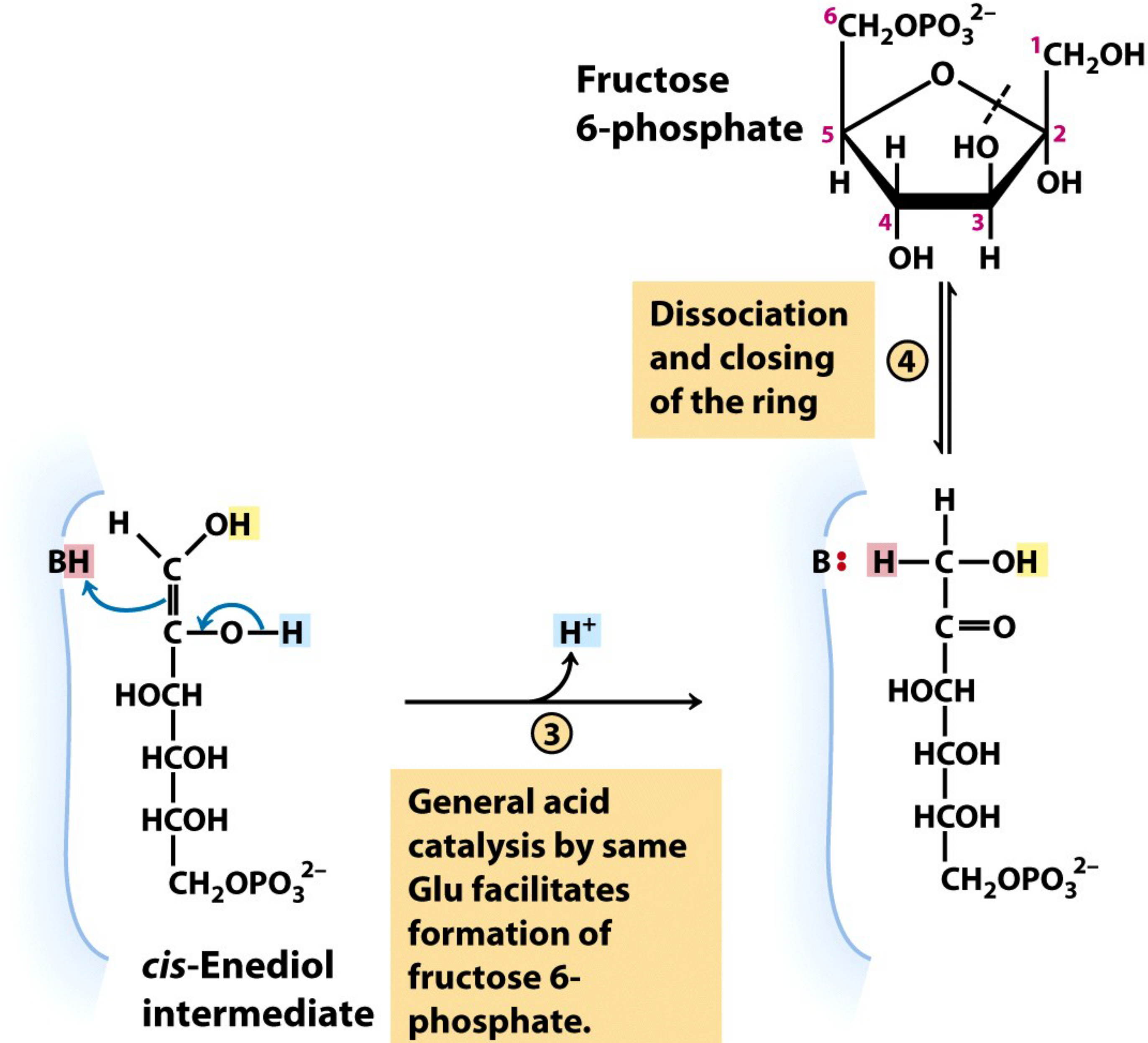
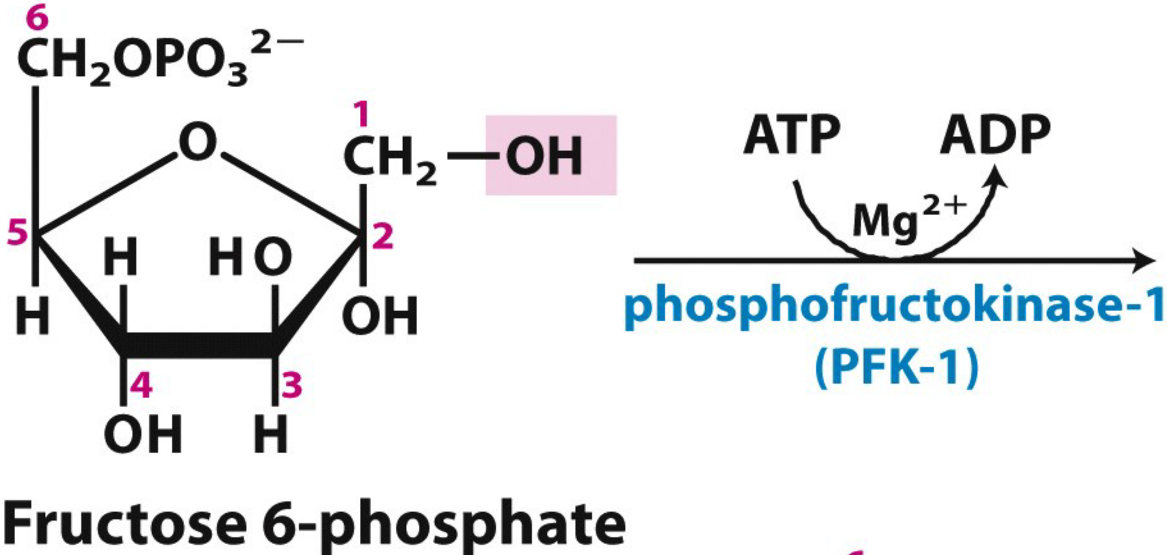
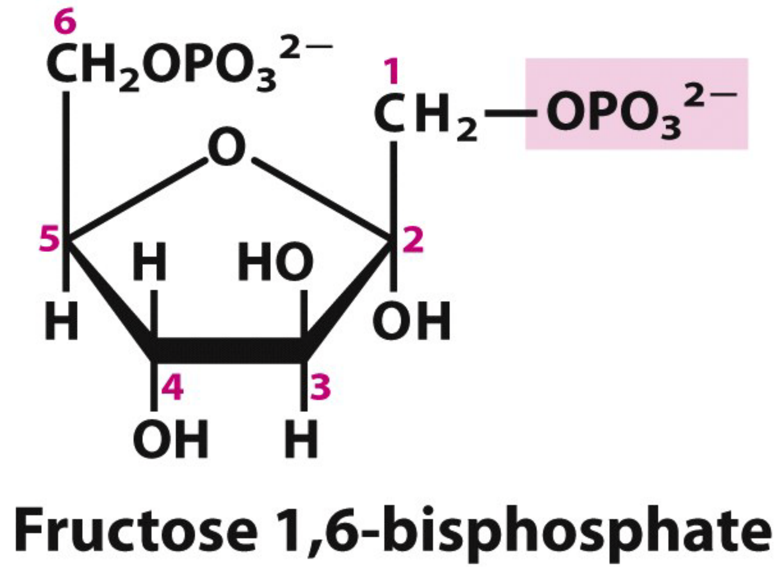


Figure 14-4 part 2
Lehninger Principles of Biochemistry, Fifth Edition

Step 3



The first committed step

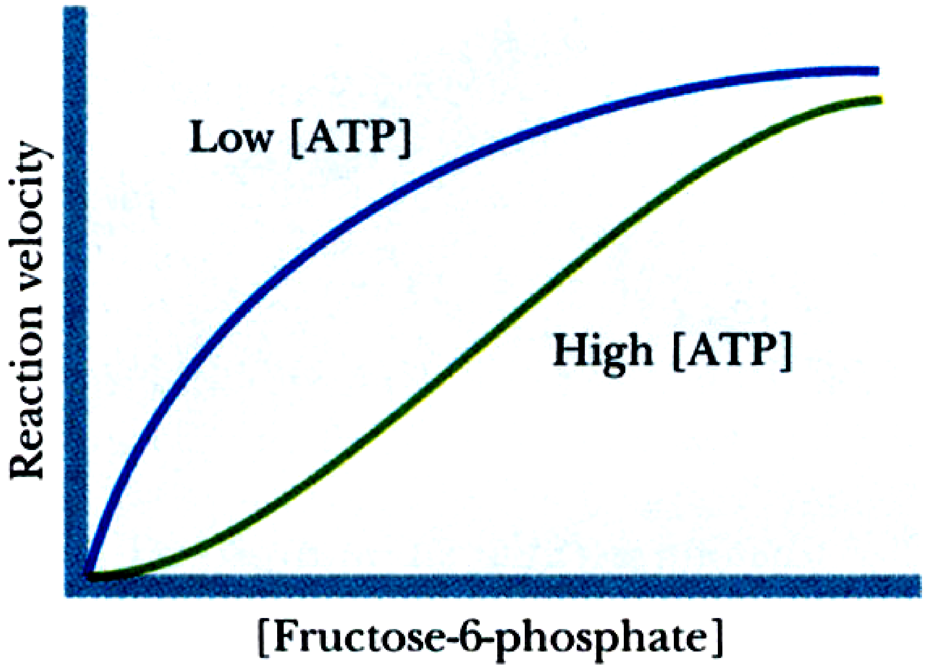


Harden–Young ester

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

Regulation of phosphofructokinase 1

A. ATP is an allosteric inhibitor

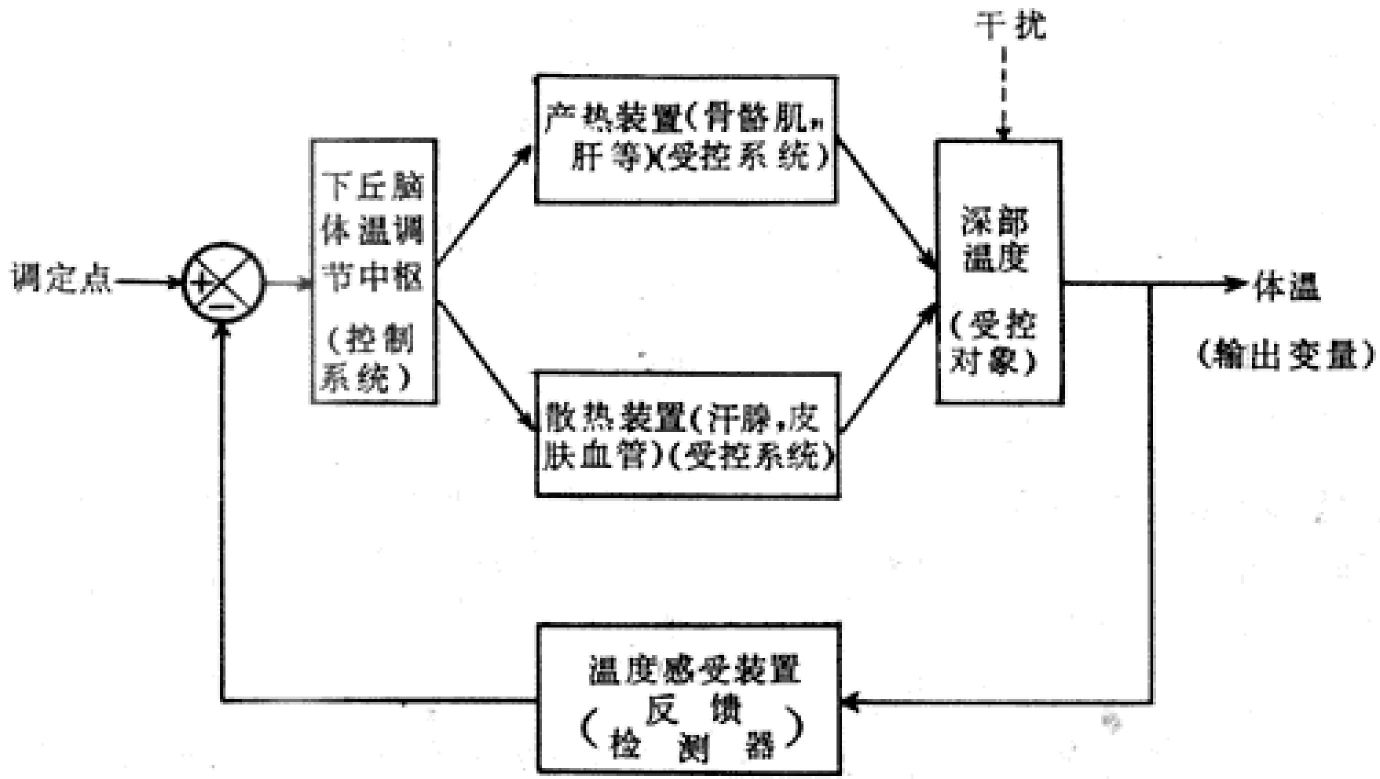


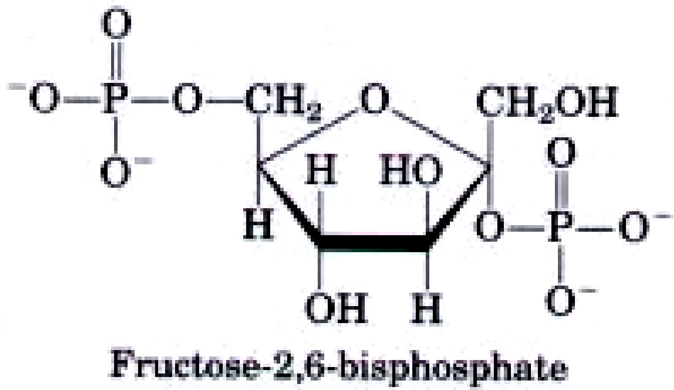
B. AMP reverses the inhibition induced by ATP. ATP concentration varies a little, while AMP concentration varies a lot, so the rate of glycolysis varies a lot.

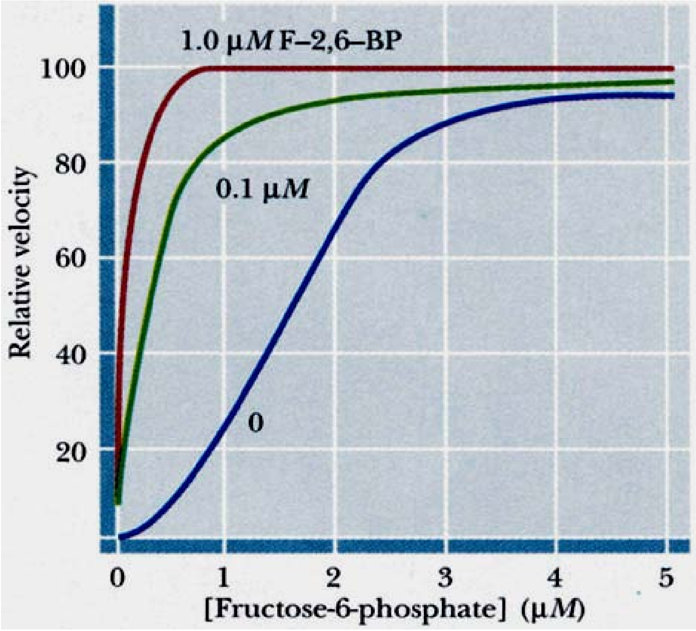
C. Citrate is another allosteric inhibitor of phosphofructokinase. Inhibition of glycolysis by citrate ensures that, if the citric acid cycle is already saturated, there is no need for glucose to “ feed ” the citric acid cycle.

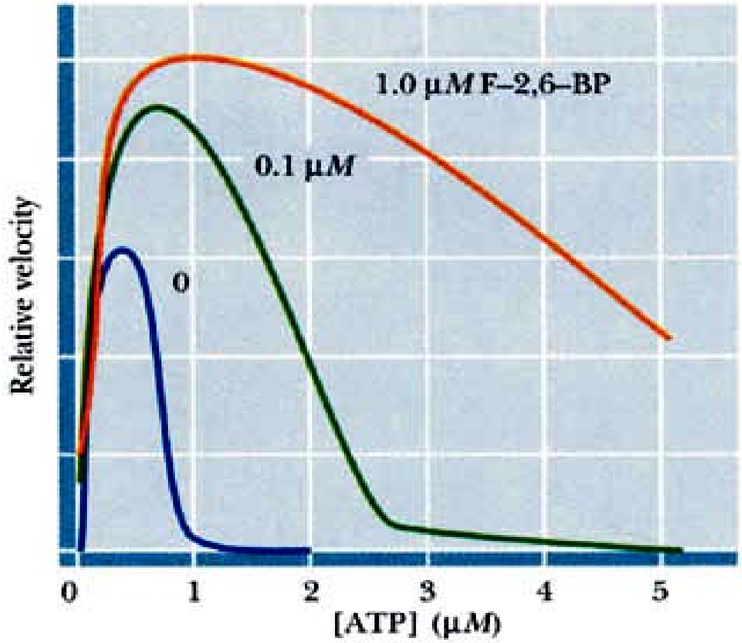
D. β- D- fructose-2,6-bisphosphate is an allosteric activator for phosphofructokinase-1.

Negative feedback


干扰
调定点
+
−
下丘脑体温调节中枢
（控制系统）
产热装置（骨骼肌，肝等）（受控系统）
散热装置（汗腺，皮肤血管）（受控系统）
深部温度
（受控对象）
体温
（输出变量）
温度感受装置
（反馈检测器）

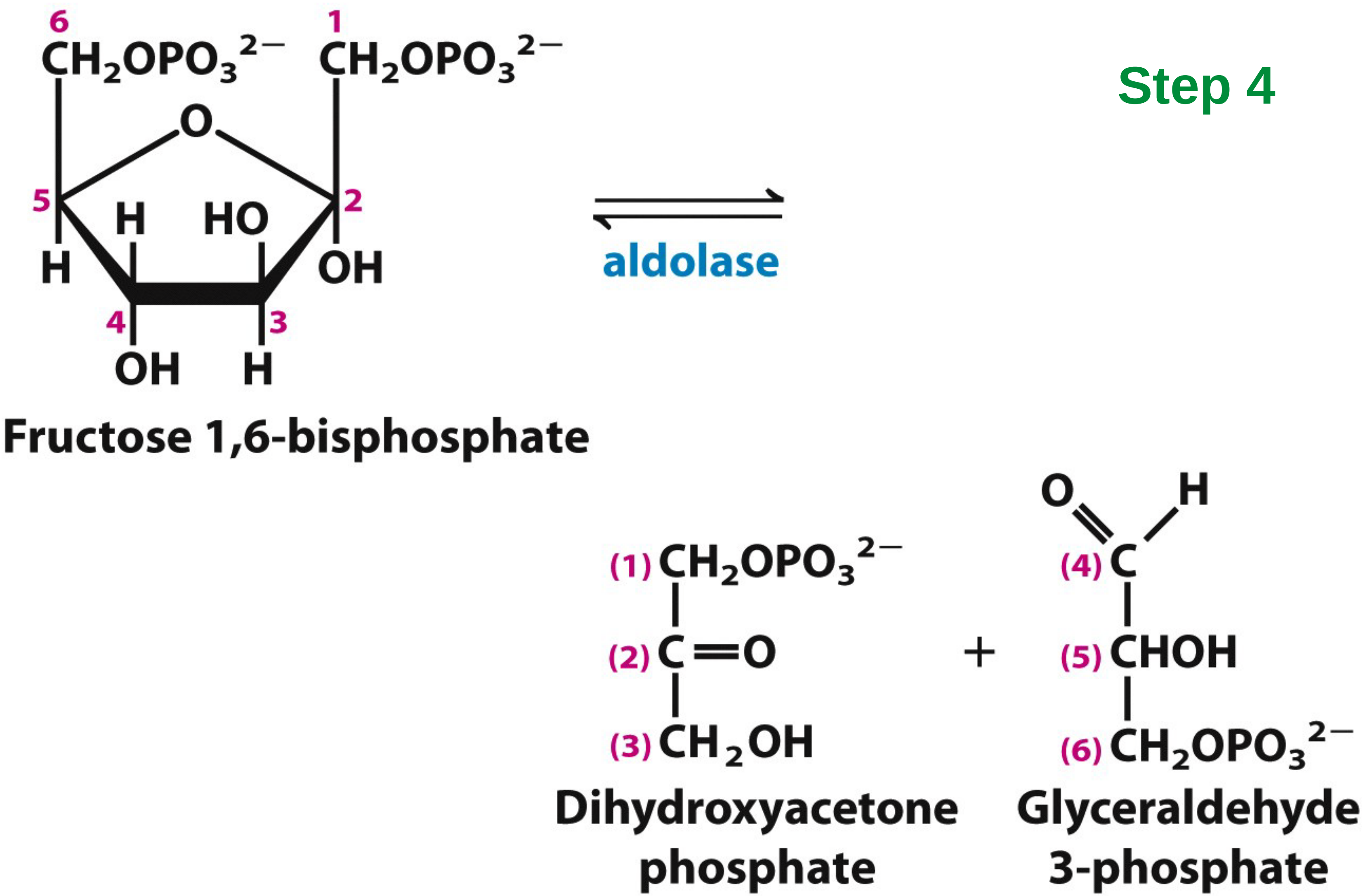






1. Increase the affinity of kinase for substrate
2. Decrease the inhibitory effects of ATP
3. Inhibit fructose-1, 6-bisphosphatase

Step 4



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

Unnumbered 14 p533
Lehninger Principles of Biochemistry, Fifth Edition

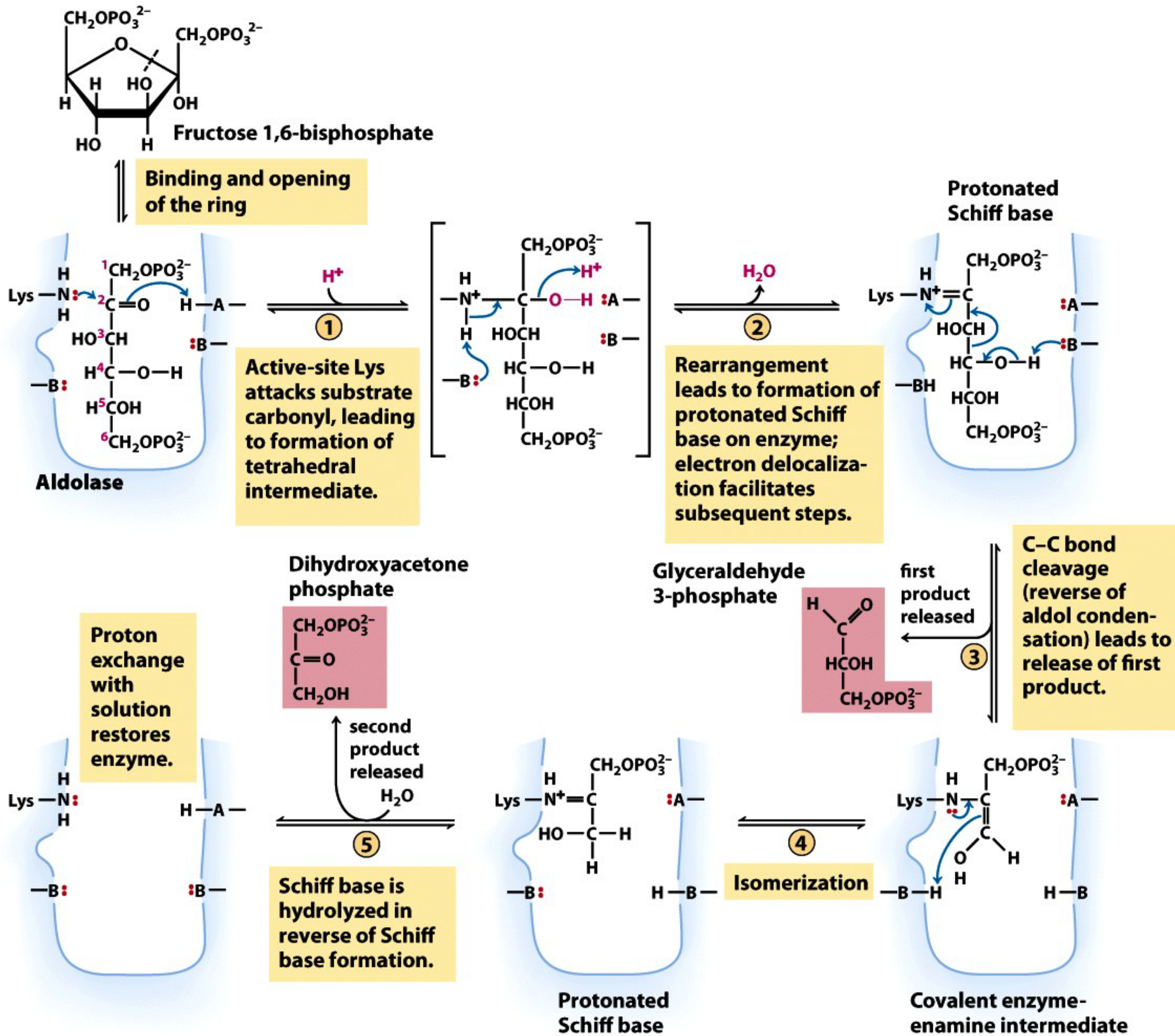


Figure 14-5

Lehninger Principles of Biochemistry, Fifth Edition

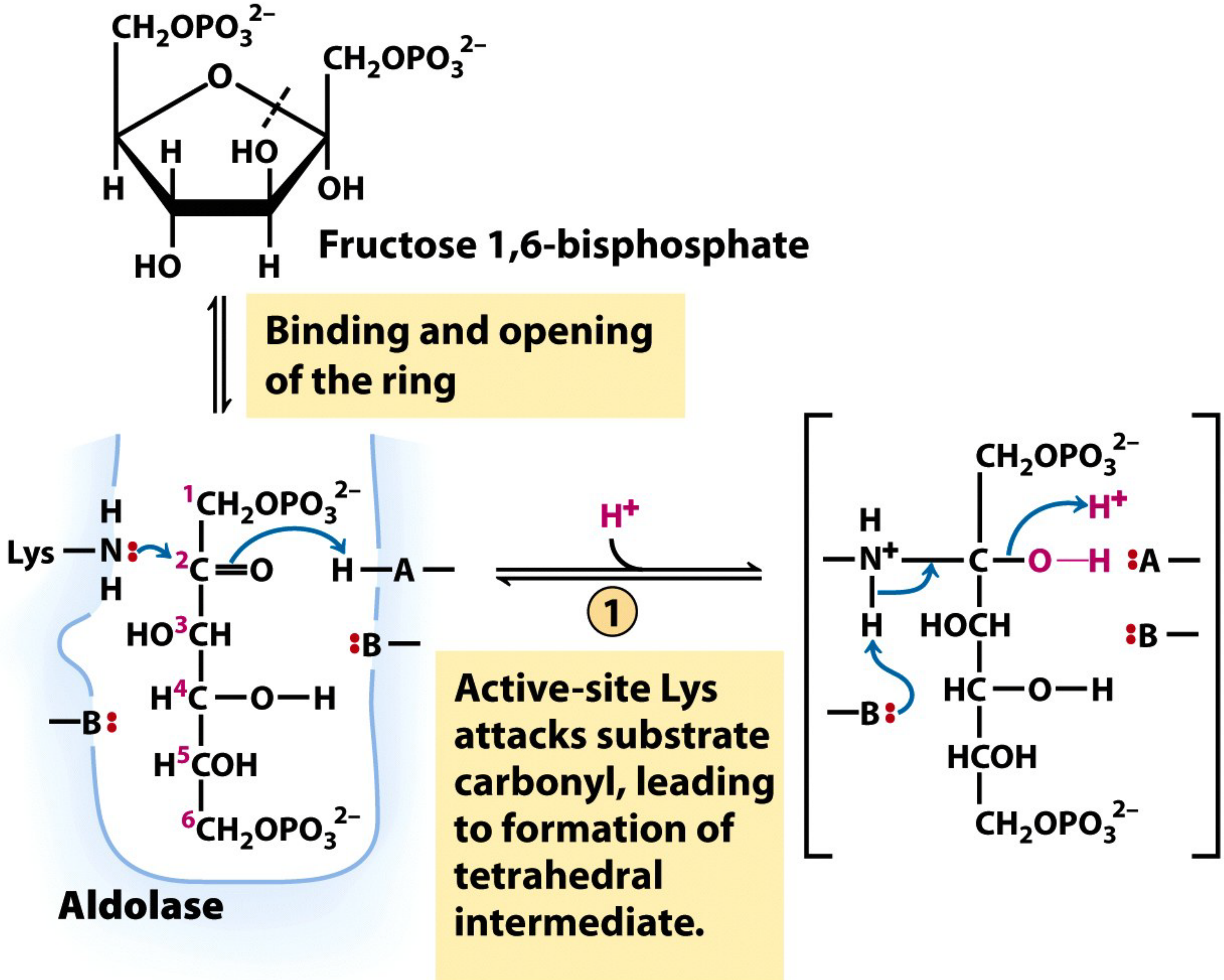


Figure 14-5 part 1
Lehninger Principles of Biochemistry, Fifth Edition

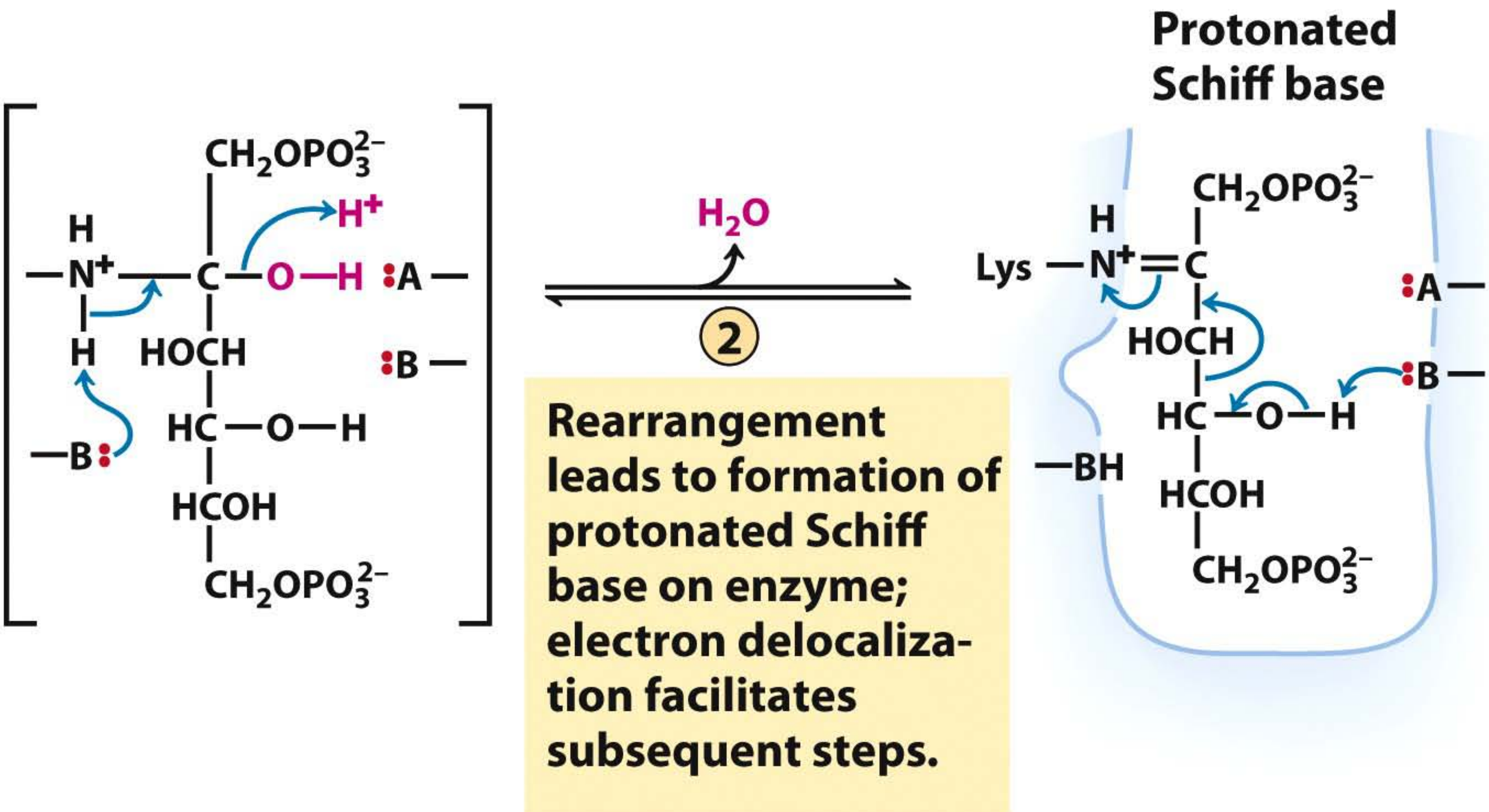


Figure 14-5 part 2
Lehninger Principles of Biochemistry, Fifth Edition

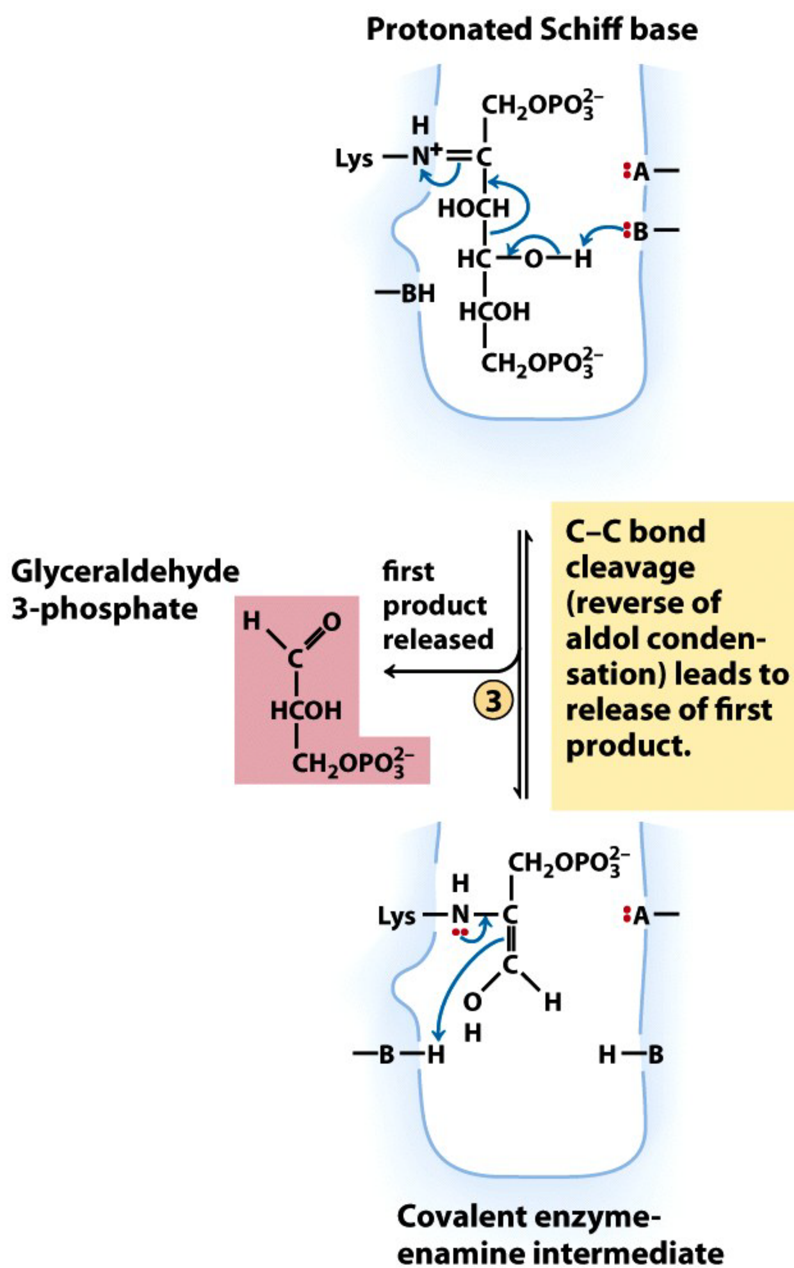


Figure 14-5 part 3

Lehninger Principles of Biochemistry, Fifth Edition

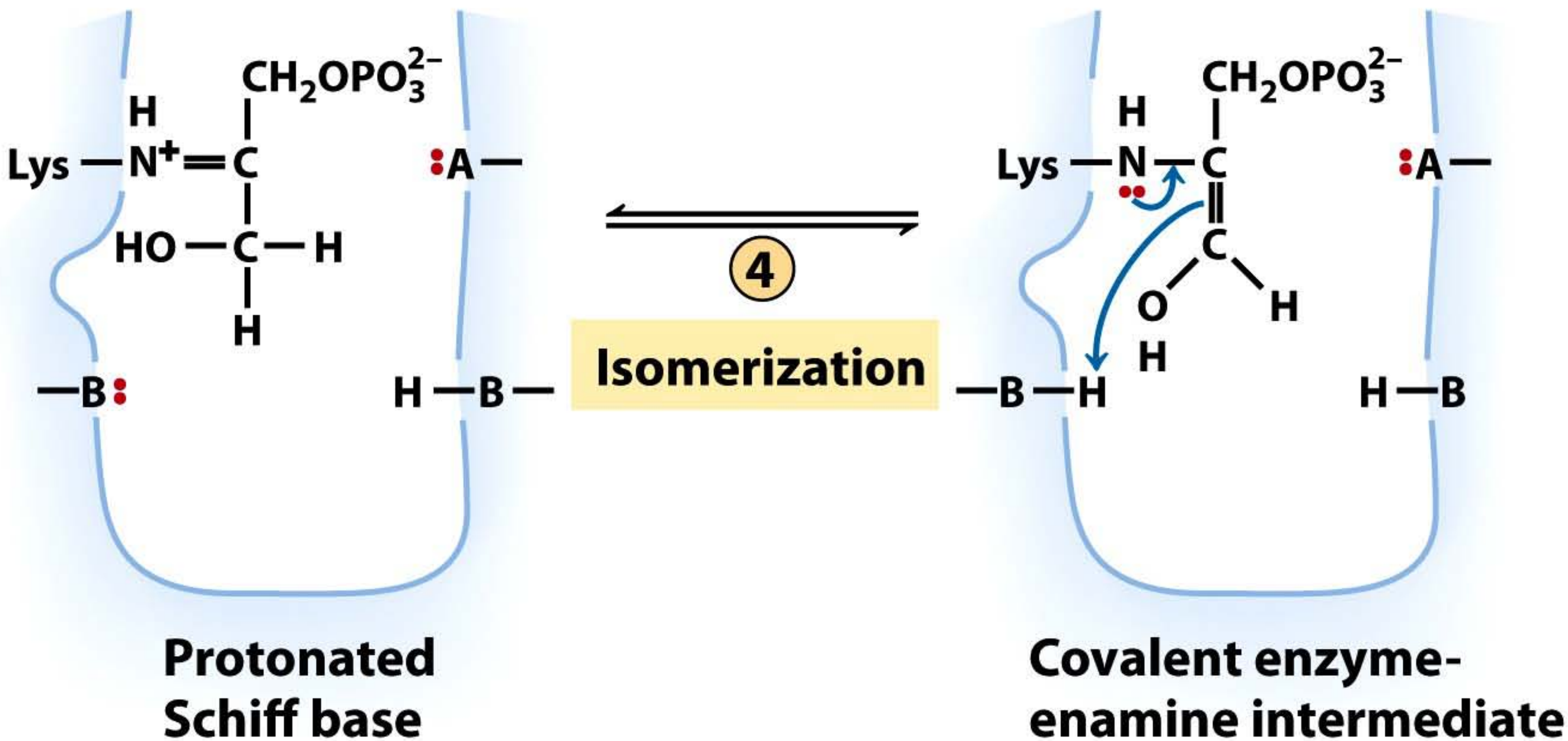


Figure 14-5 part 4

Lehninger Principles of Biochemistry, Fifth Edition

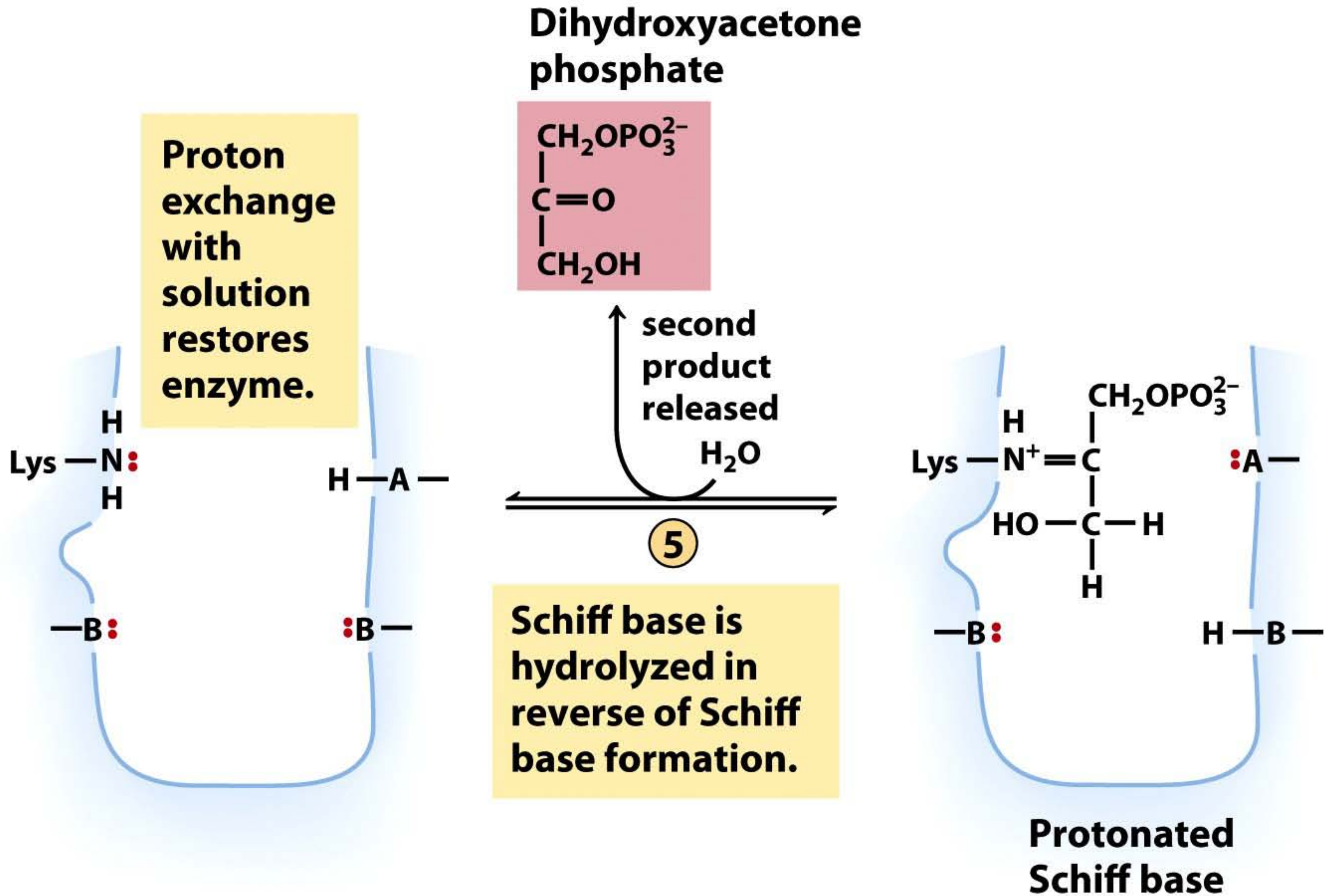
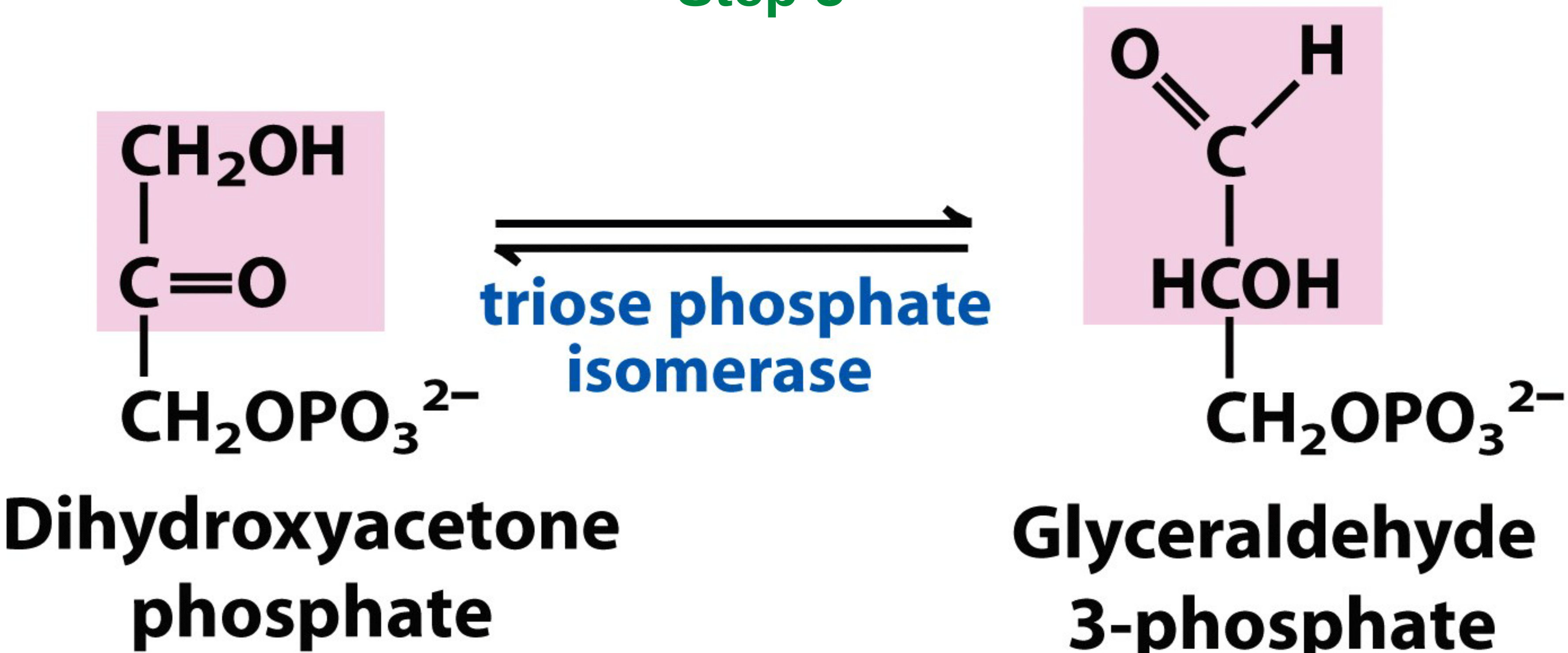


Figure 14-5 part 5

Lehninger Principles of Biochemistry, Fifth Edition

Step 5



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

Unnumbered 14 p534
Lehninger Principles of Biochemistry, Fifth Edition

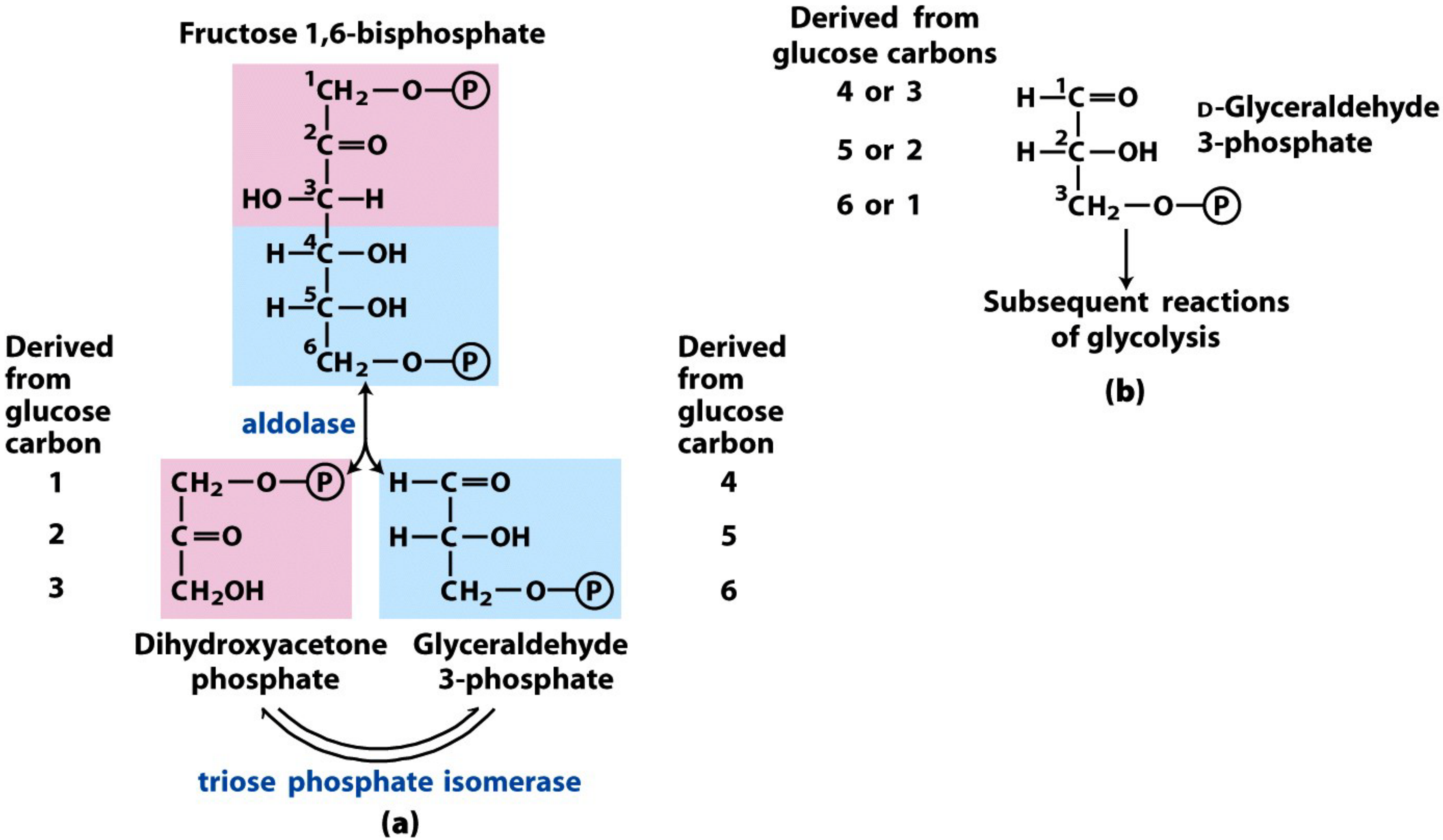


Figure 14-6

Fate of the glucose carbons in the formation of glyceraldehyde 3-phosphate

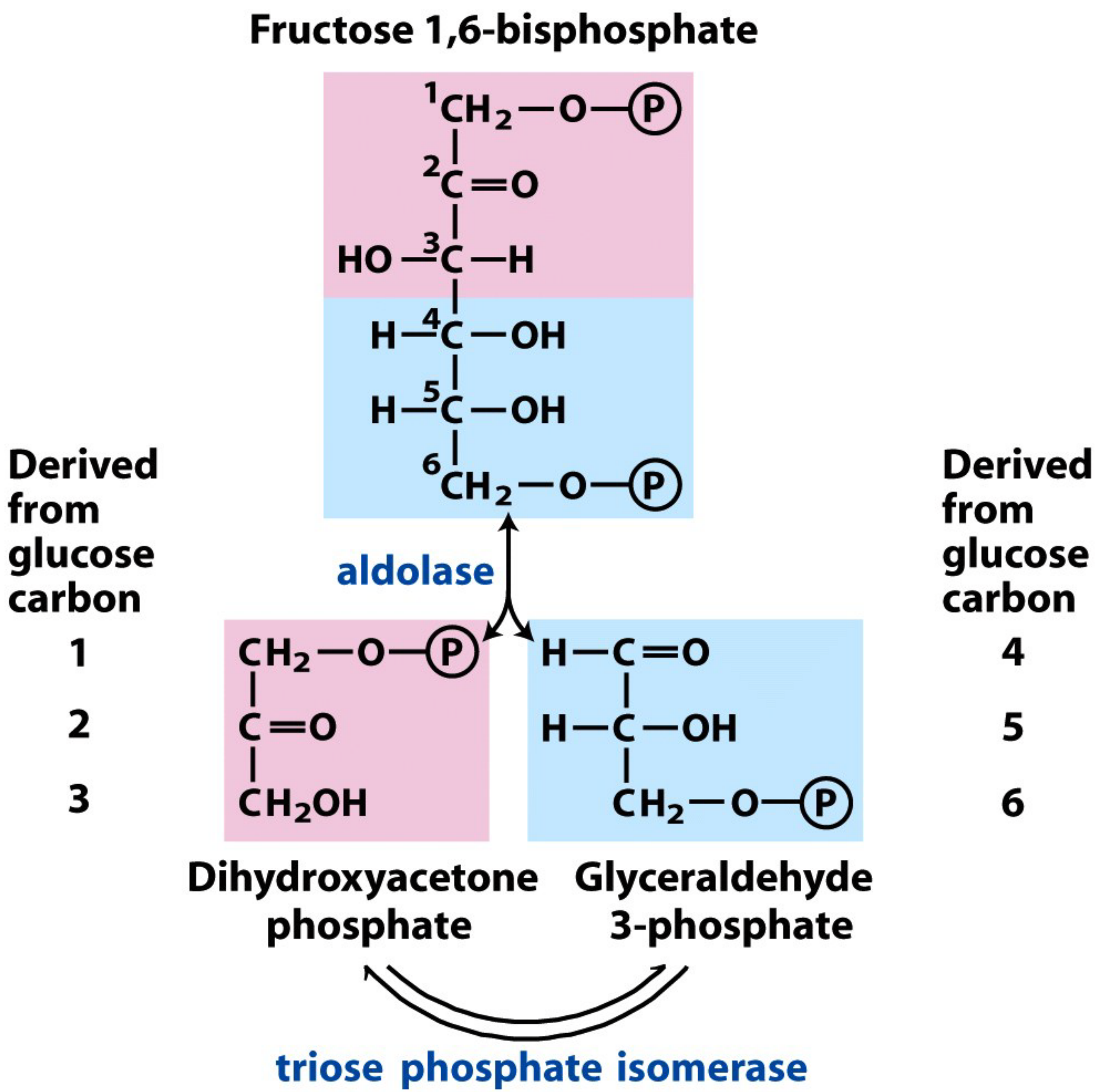


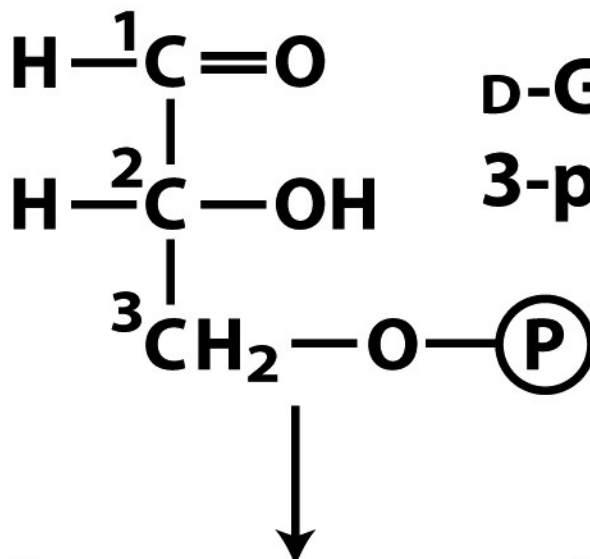
Figure 14-6a
Lehninger Principles of Biochemistry, Fifth Edition

Derived from glucose carbons

4 or 3

5 or 2

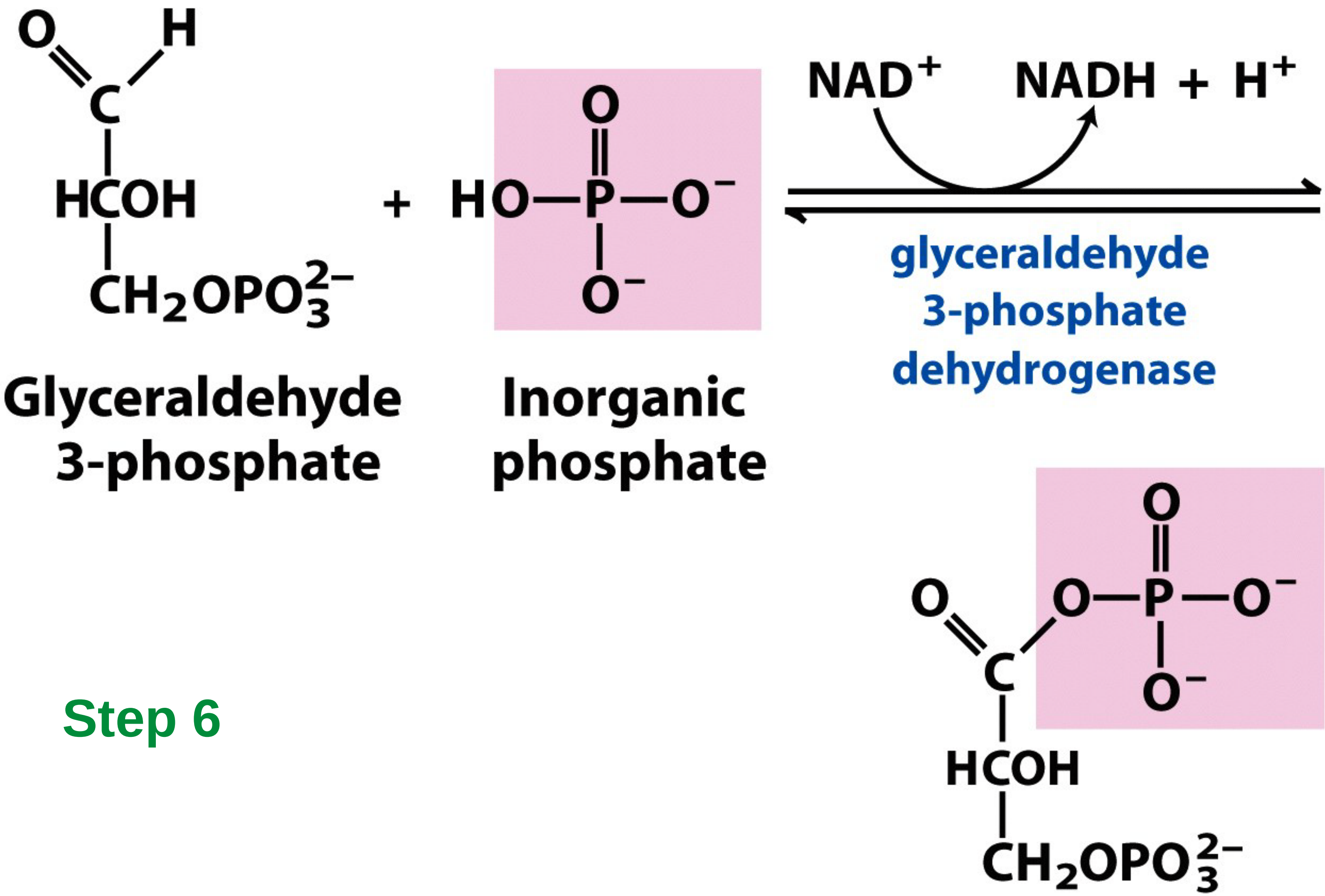
6 or 1



D-Glyceraldehyde 3-phosphate

Subsequent reactions of glycolysis

Figure 14-6b
Lehninger Principles of Biochemistry, Fifth Edition



Step 6

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

1,3-Bisphosphoglycerate

Unnumbered 14 p535
Lehninger Principles of Biochemistry, Fifth Edition

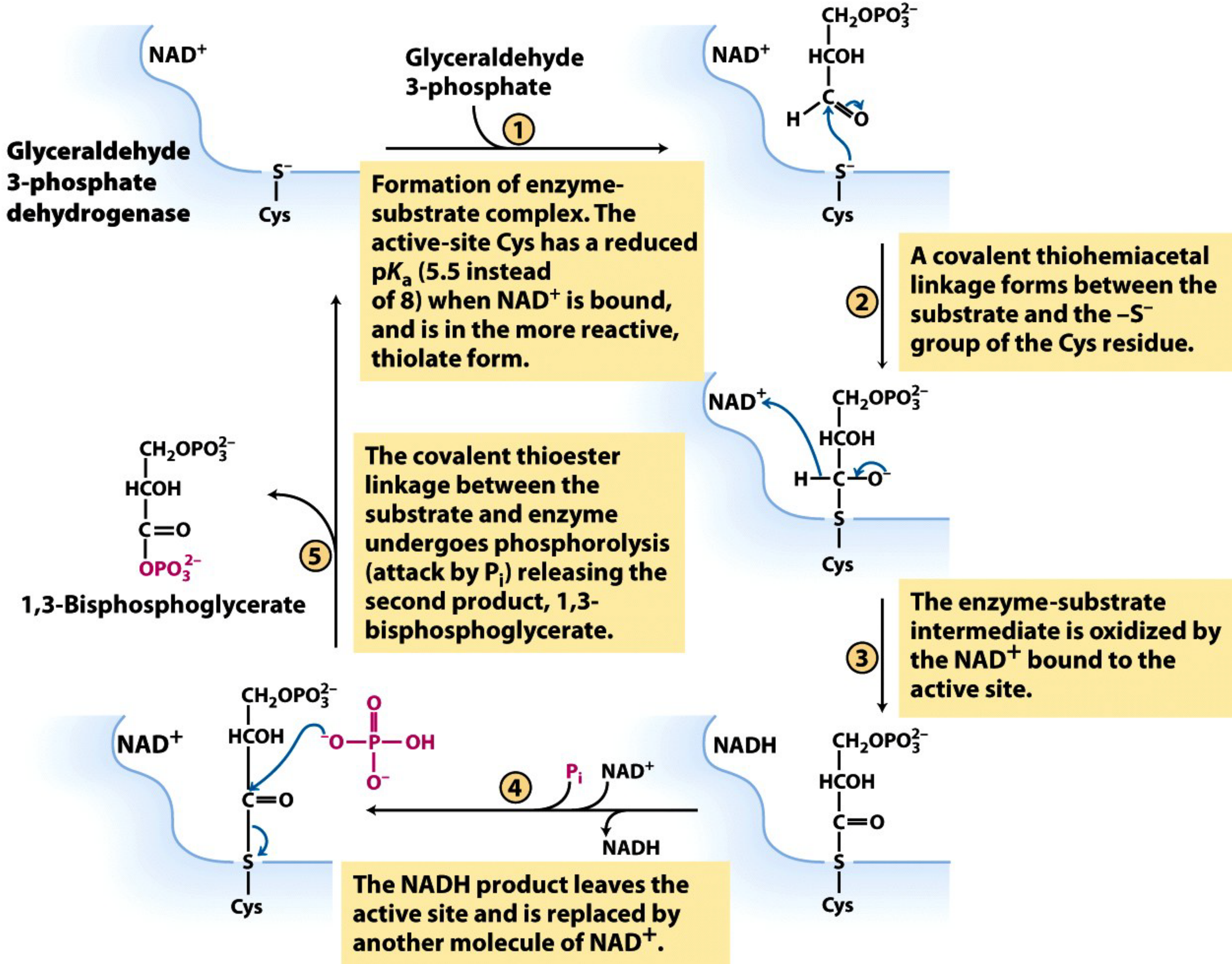


Figure 14-7

Lehninger Principles of Biochemistry, Fifth Edition

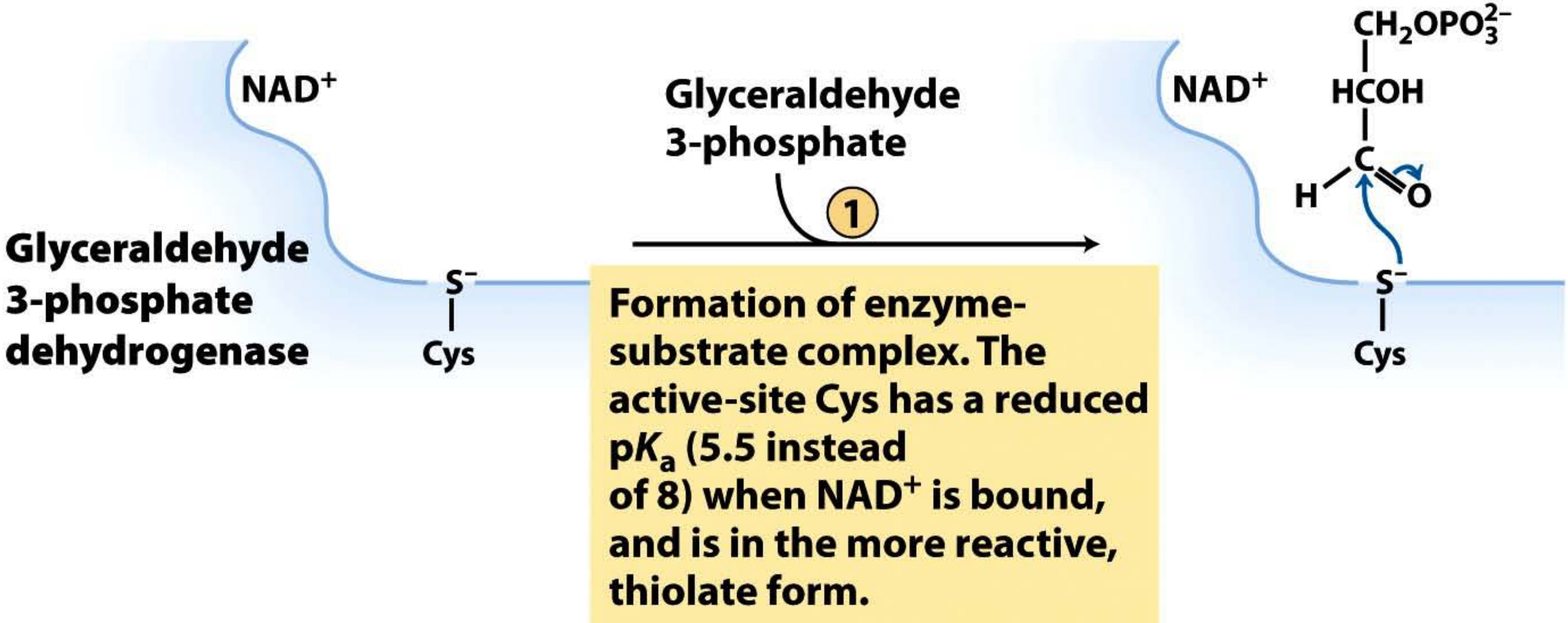


Figure 14-7 part 1

Lehninger Principles of Biochemistry, Fifth Edition

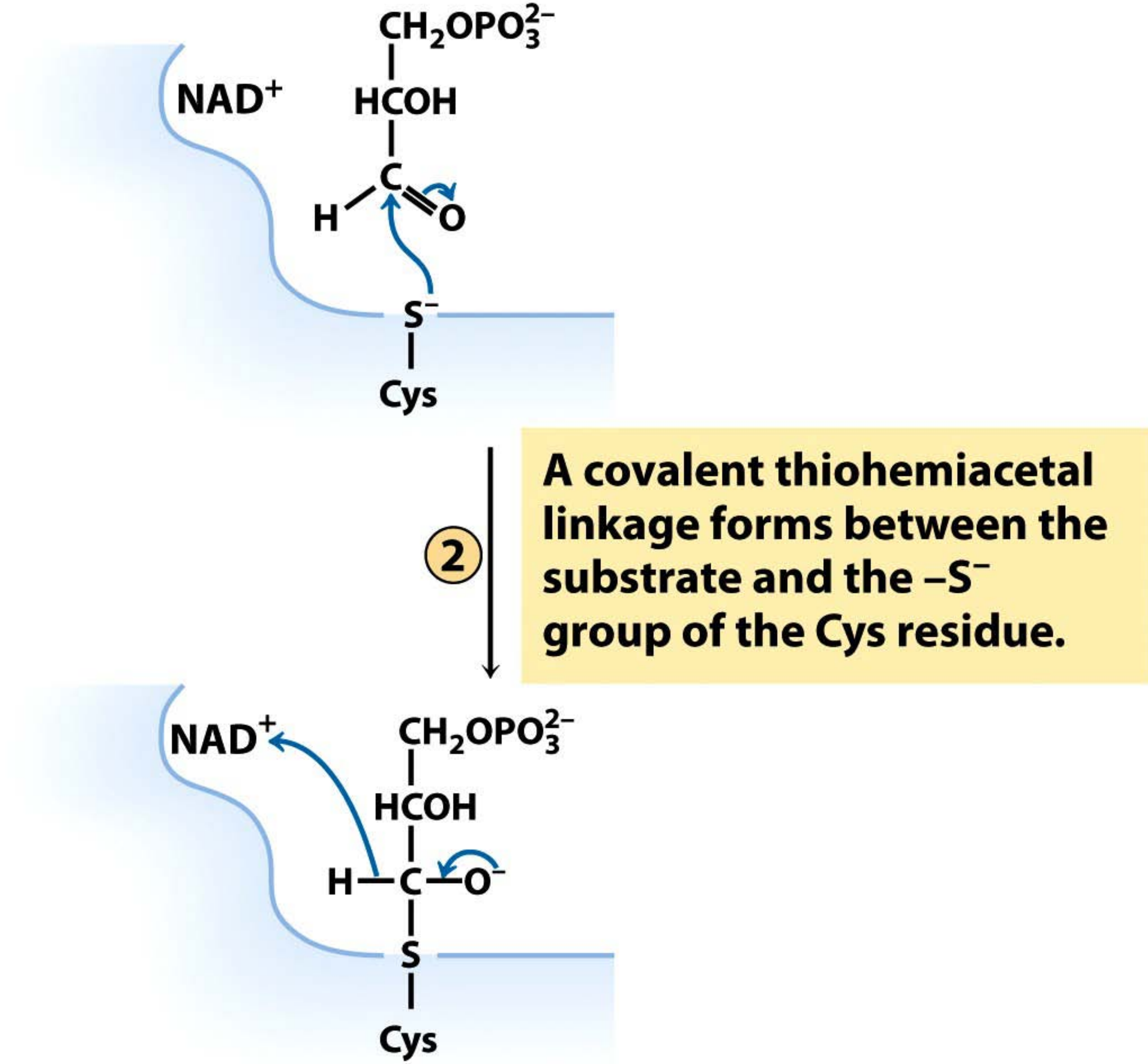


Figure 14-7 part 2
Lehninger Principles of Biochemistry, Fifth Edition

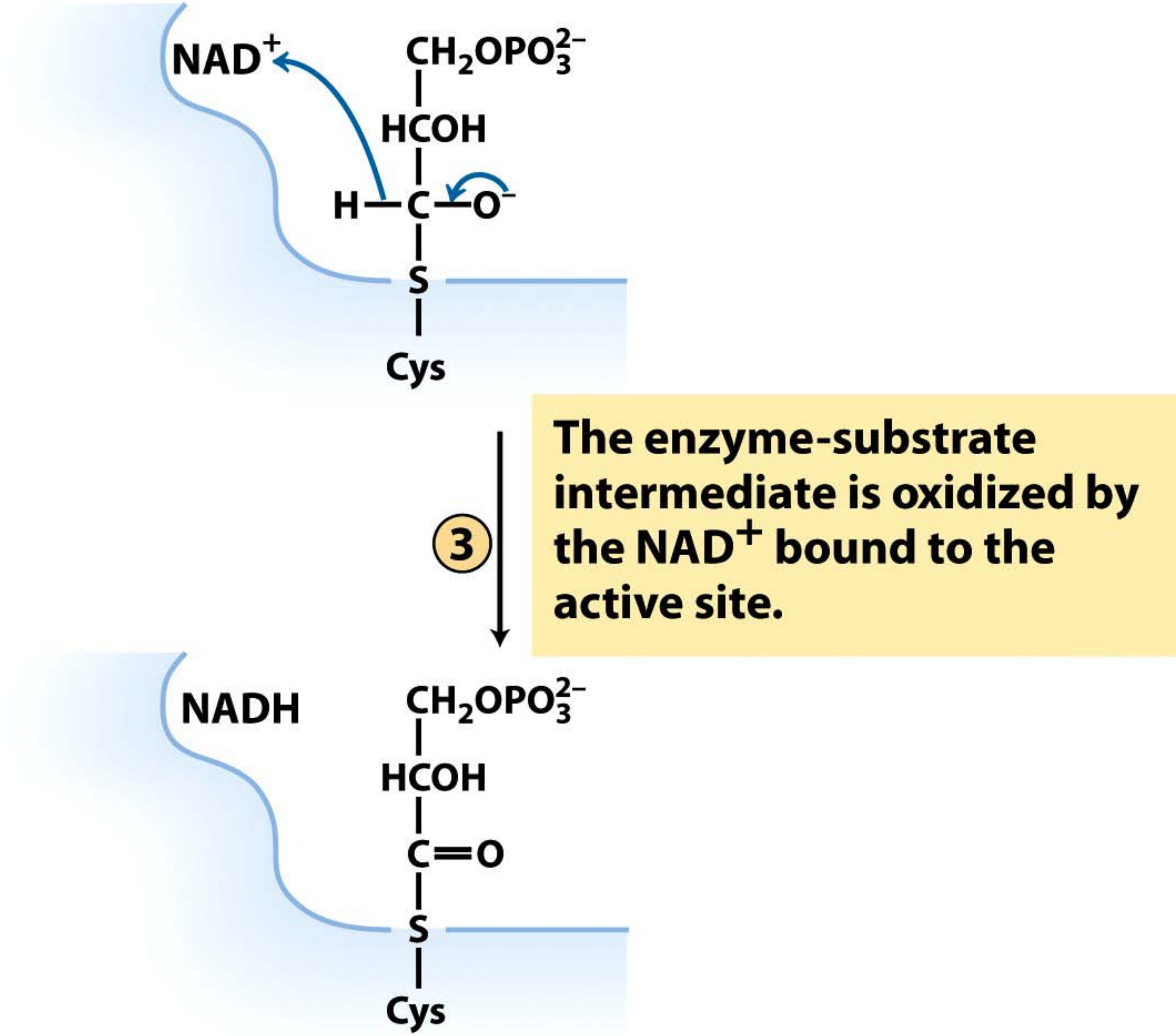


Figure 14-7 part 3
Lehninger Principles of Biochemistry, Fifth Edition

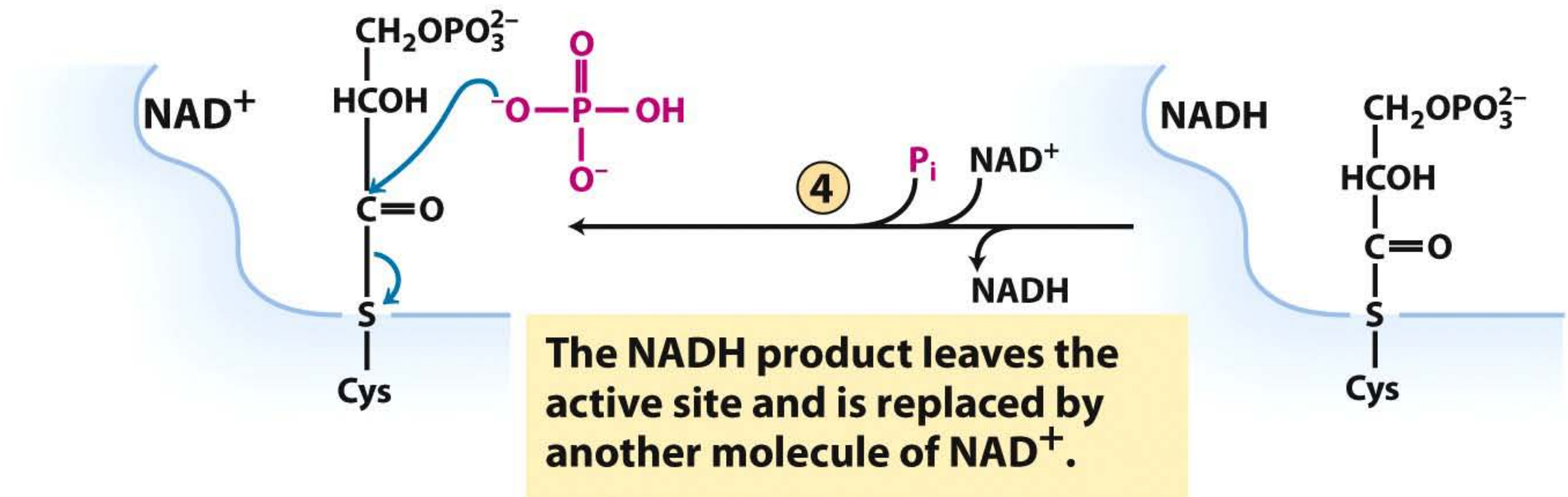


Figure 14-7 part 4
Lehninger Principles of Biochemistry, Fifth Edition

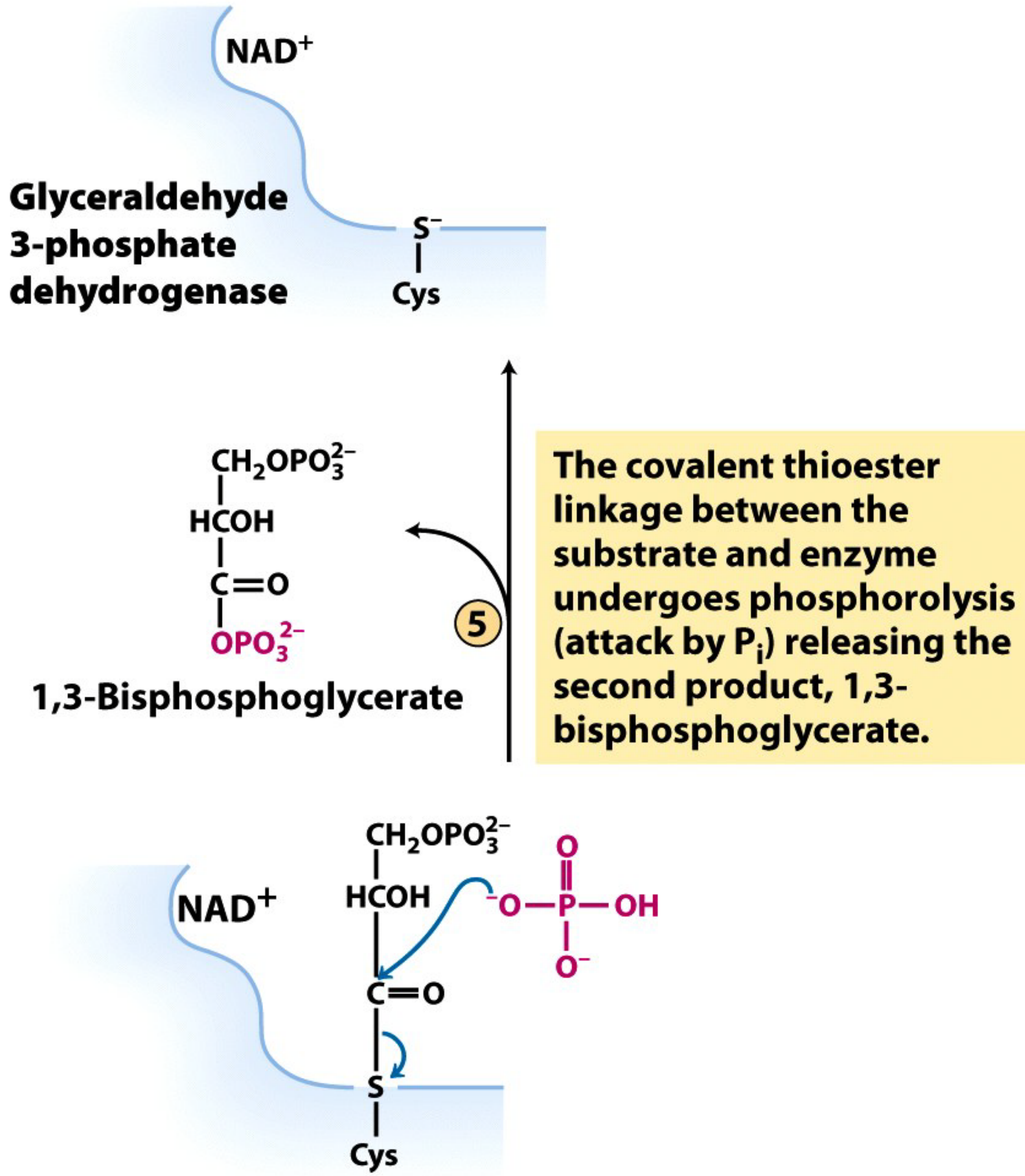
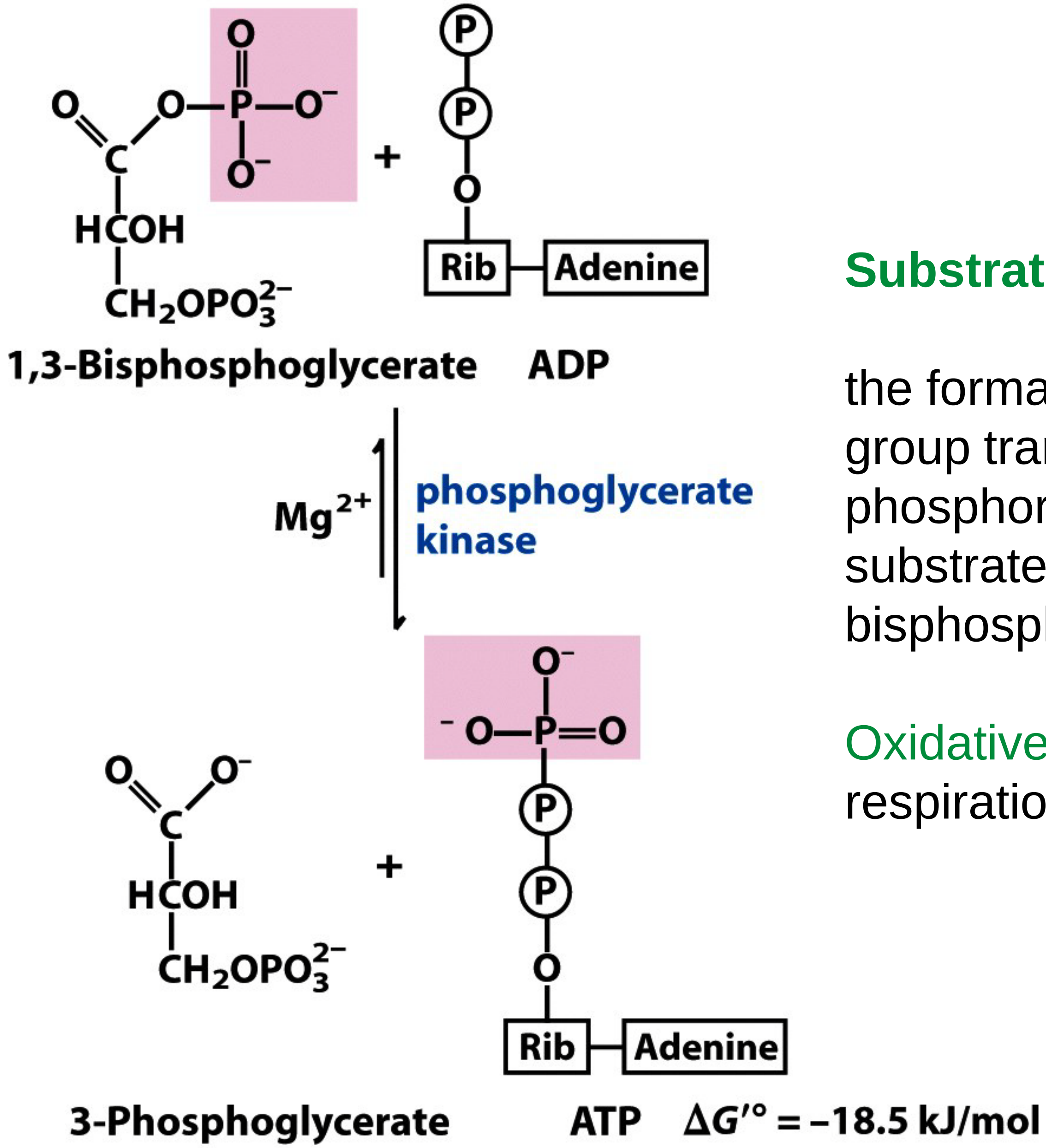


Figure 14-7 part 5

Lehninger Principles of Biochemistry, Fifth Edition



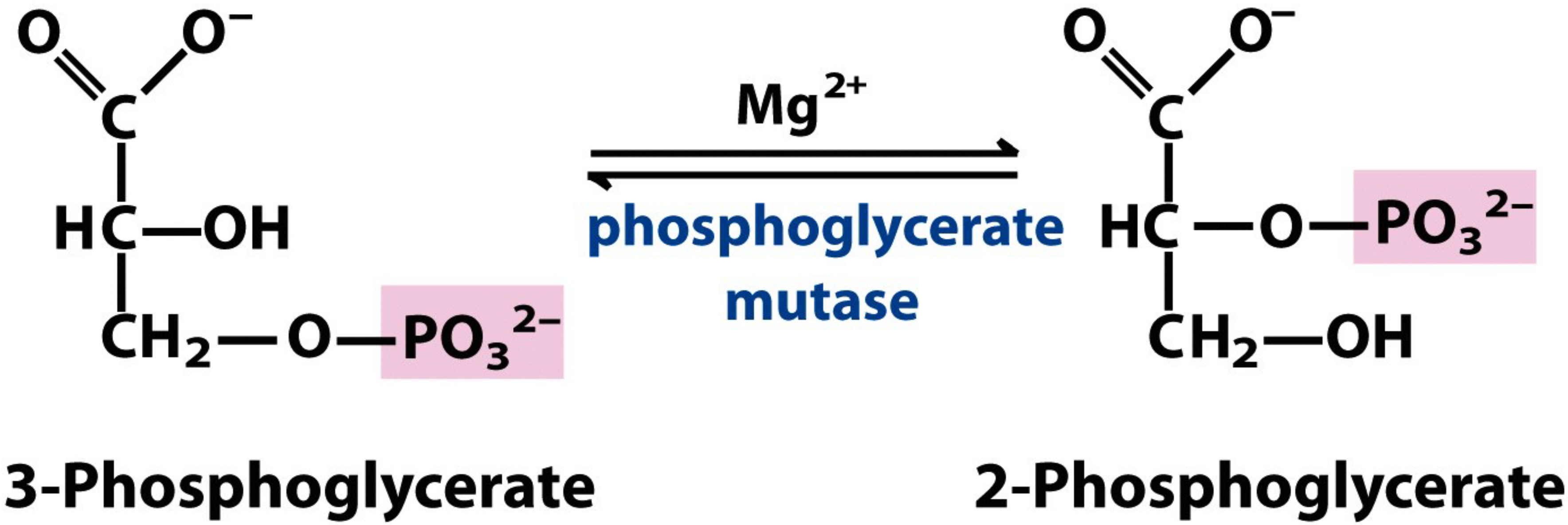
Step 7

Substrate-level phosphorylation:

the formation of ATP by phosphoryl group transfer from a high-energy phosphoryl group containing substrate such as 1,3-bisphosphoglycerate to ADP

Oxidative phosphorylation, respiration-linked phosphorylation

Step 8



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

Unnumbered 14 p537
Lehninger Principles of Biochemistry, Fifth Edition

Phosphoglycerate mutase

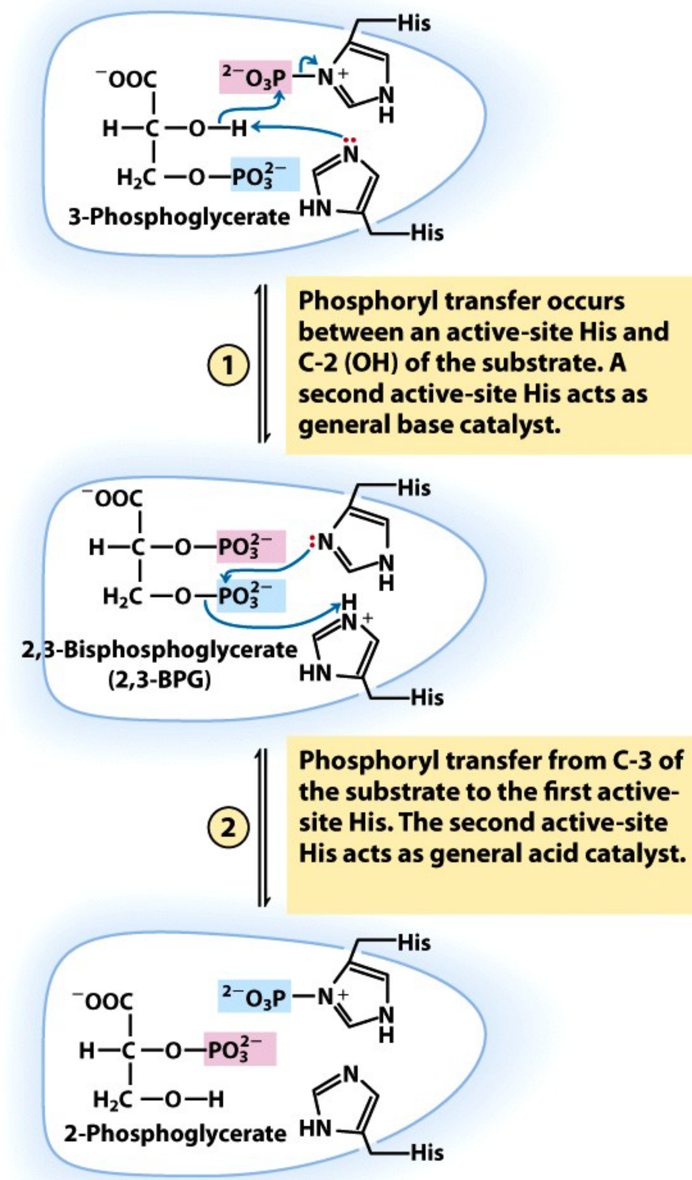
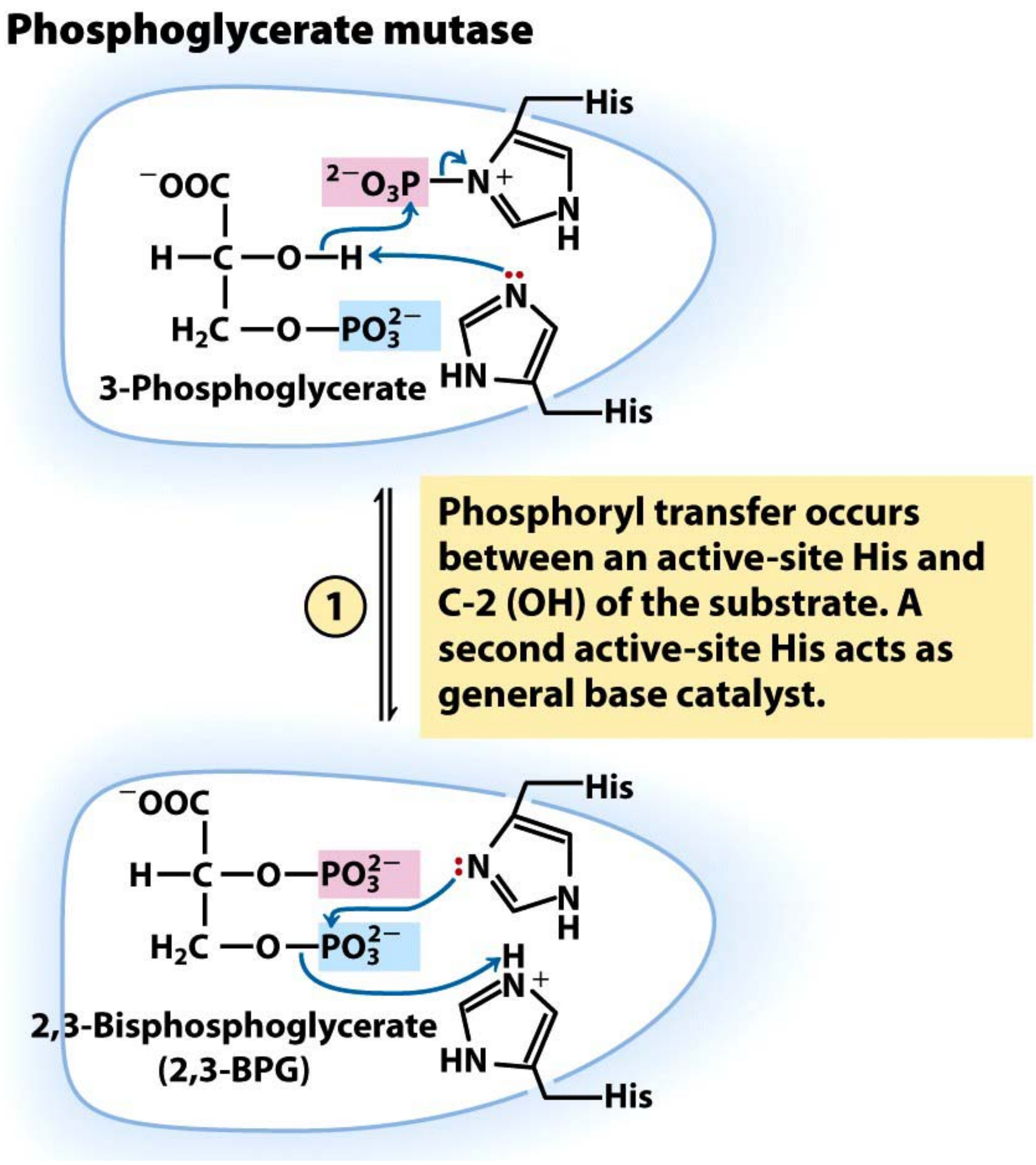


Figure 14-8

Small amount of 2,3-BPG is required to phosphorylate the enzyme and thus initiate this reaction



The phosphoglycerate mutase reaction

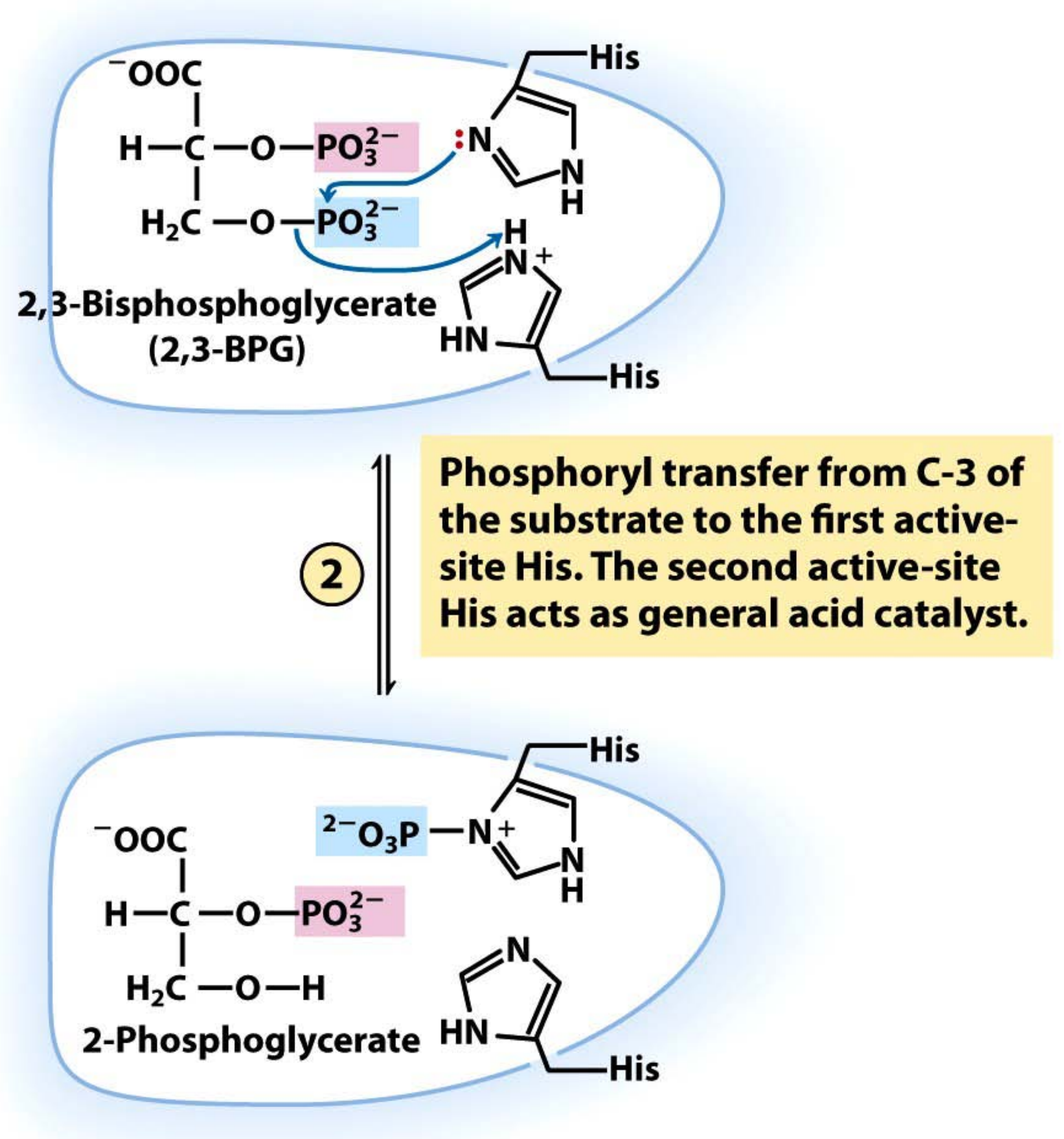
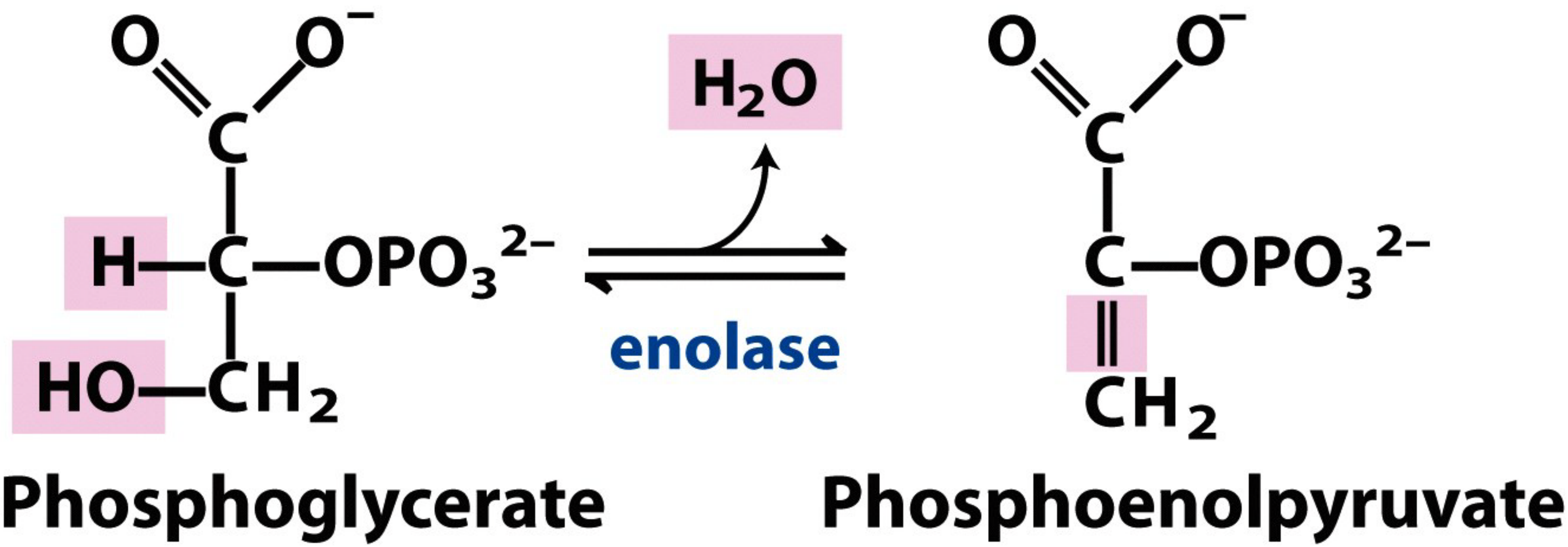


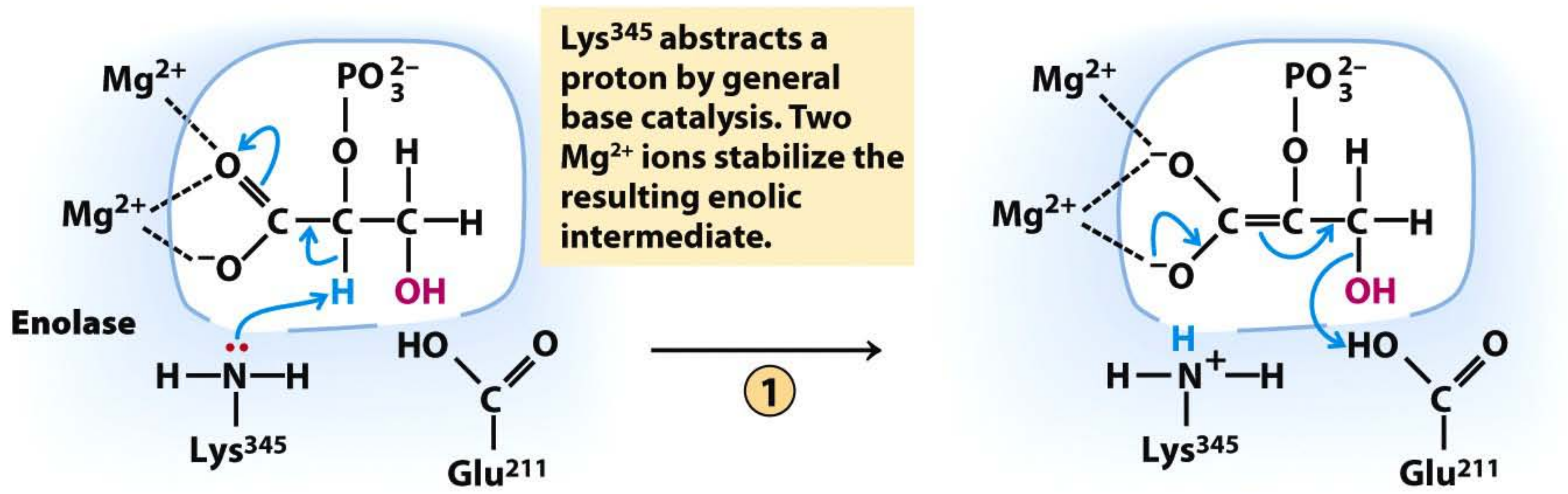
Figure 14-8 part 2

Step 9



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

Unnumbered 14 p538a
Lehninger Principles of Biochemistry, Fifth Edition

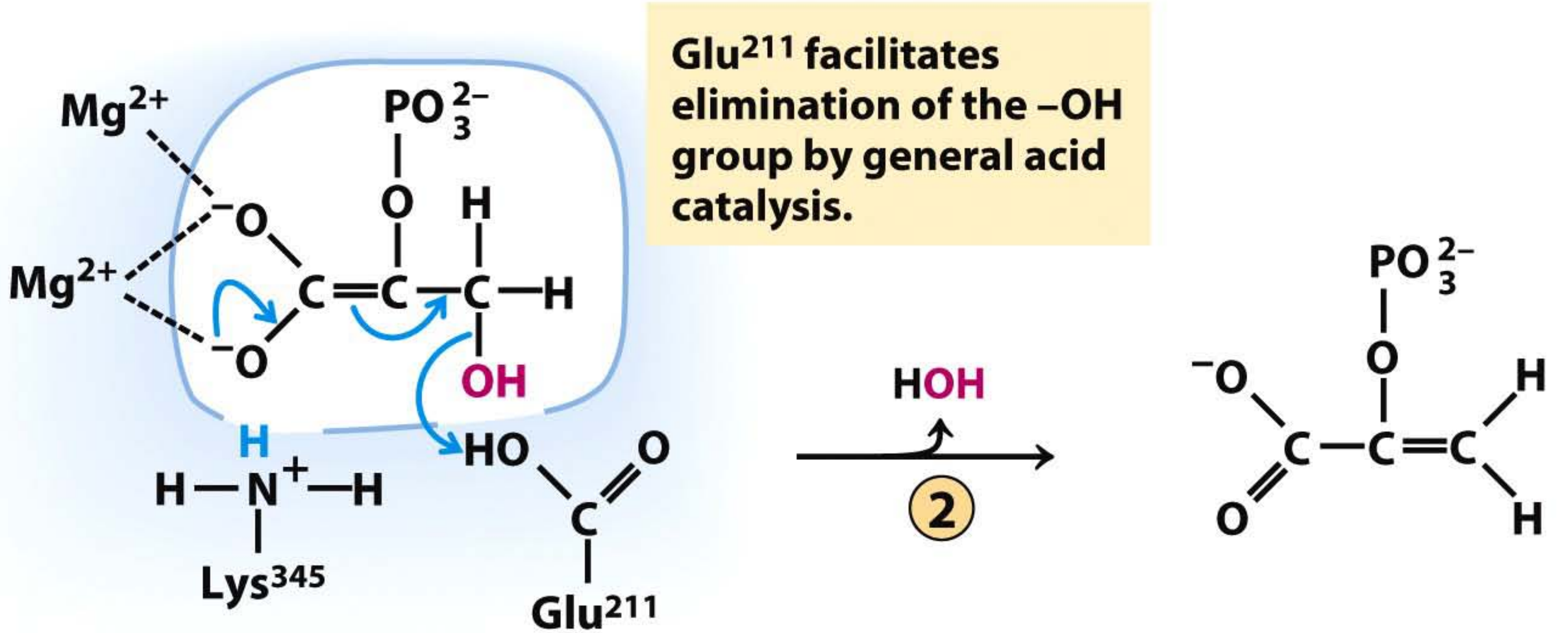


2-Phosphoglycerate bound to enzyme

Enolic intermediate

Figure 6-23a part 1
Lehninger Principles of Biochemistry, Fifth Edition

Two-step reaction catalyzed by enolase



Enolic intermediate

Phosphoenolpyruvate

Figure 6-23a part 2
Lehninger Principles of Biochemistry, Fifth Edition

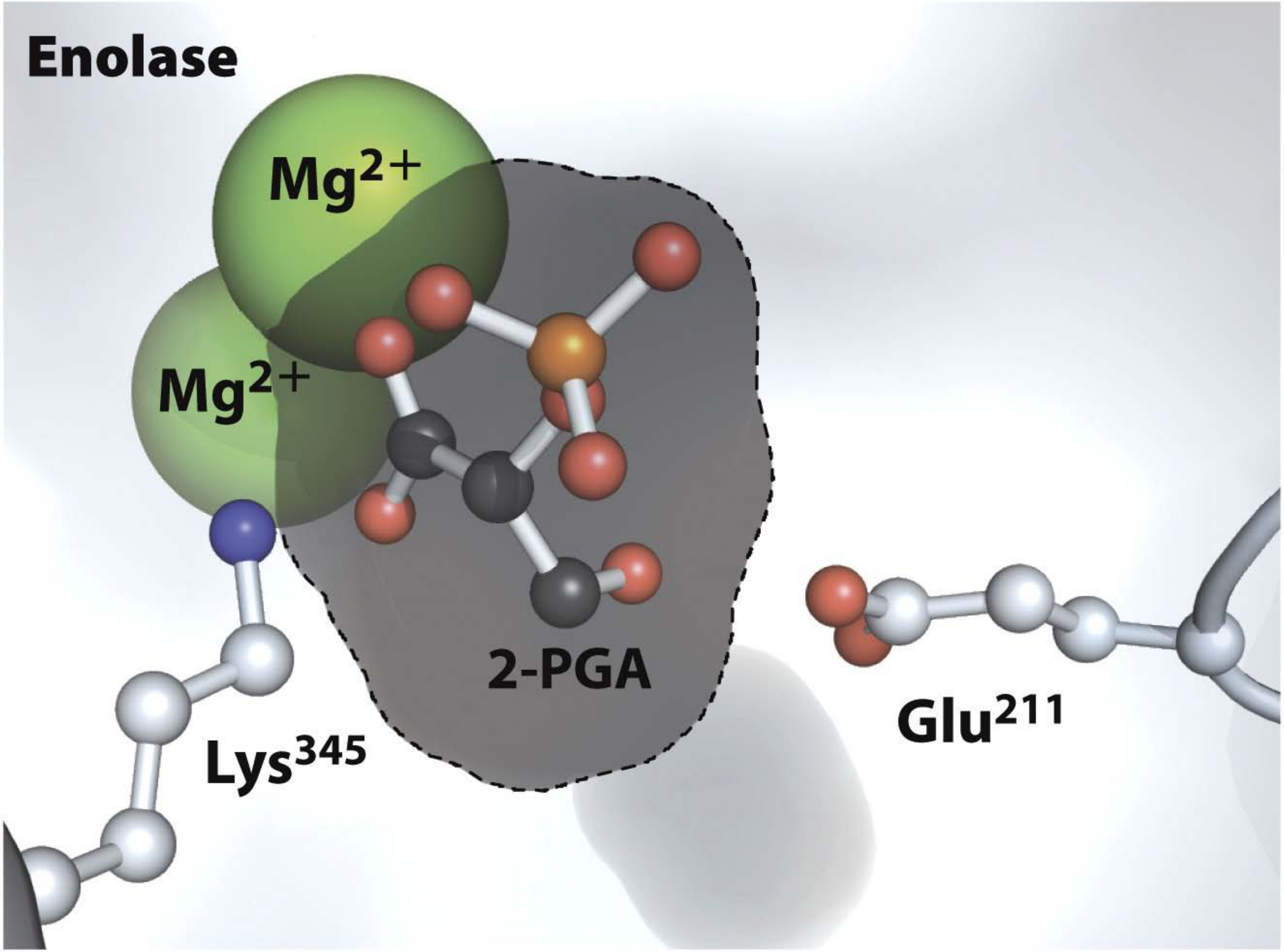
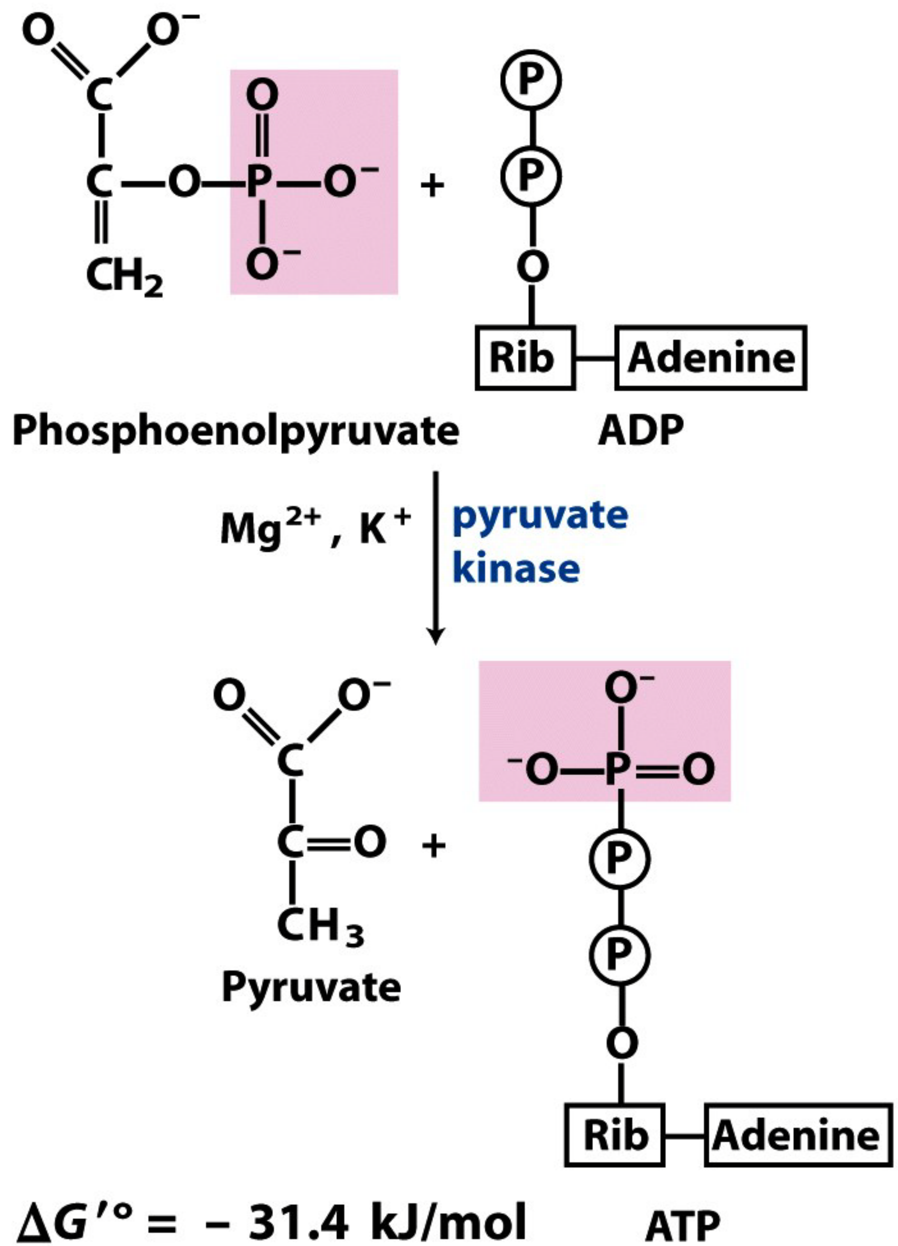
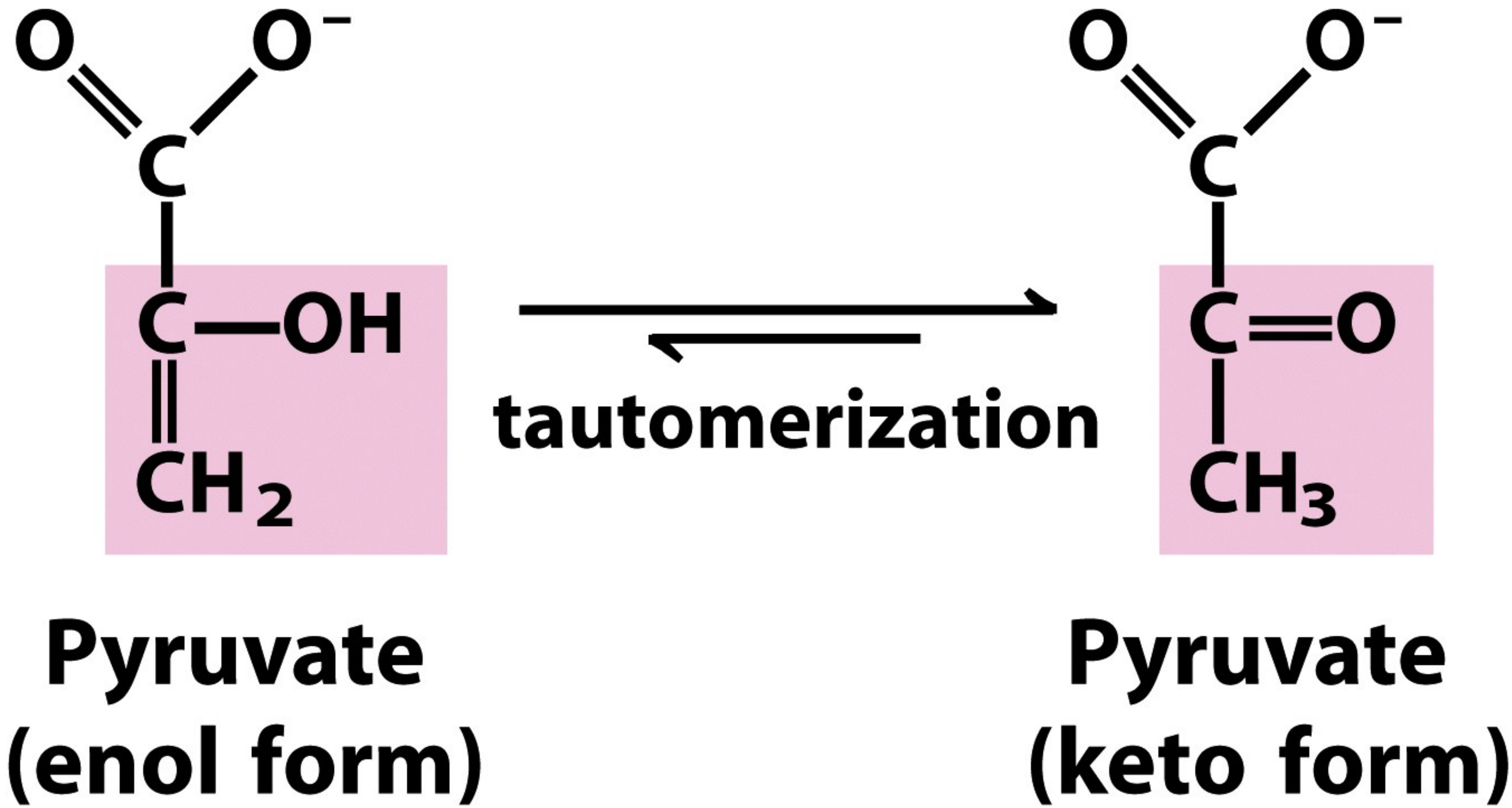


Figure 6-23b
Lehninger Principles of Biochemistry, Fifth Edition

Step 10



Unnumbered 14 p538b



Unnumbered 14 p538c
Lehninger Principles of Biochemistry, Fifth Edition

The overall reaction of glycolysis

$$Glu + 2NAD^+ + 2ADP + Pi \longrightarrow 2Pyr + 2NADH + 2H^+ + 2ATP$$

- The fate of carbon skeleton of glucose
- The yield of ATP
- The pathway of electron transfer

Glycolysis is under tight regulation

Hormones: insulin, glucagon, epinephrine

protein levels and activities of glycolytic enzymes

Energy status

Pasteur effect

The presence of oxygen inhibits glucose metabolism via glycolysis; The absence of oxygen promotes glycolysis and increases lactate production.

Warburg effect

Tumors of nearly all types carry out glycolysis at a much higher rate than normal tissue, even when oxygen is available

The Nobel Prize in Physiology or Medicine 1931
Otto Warburg

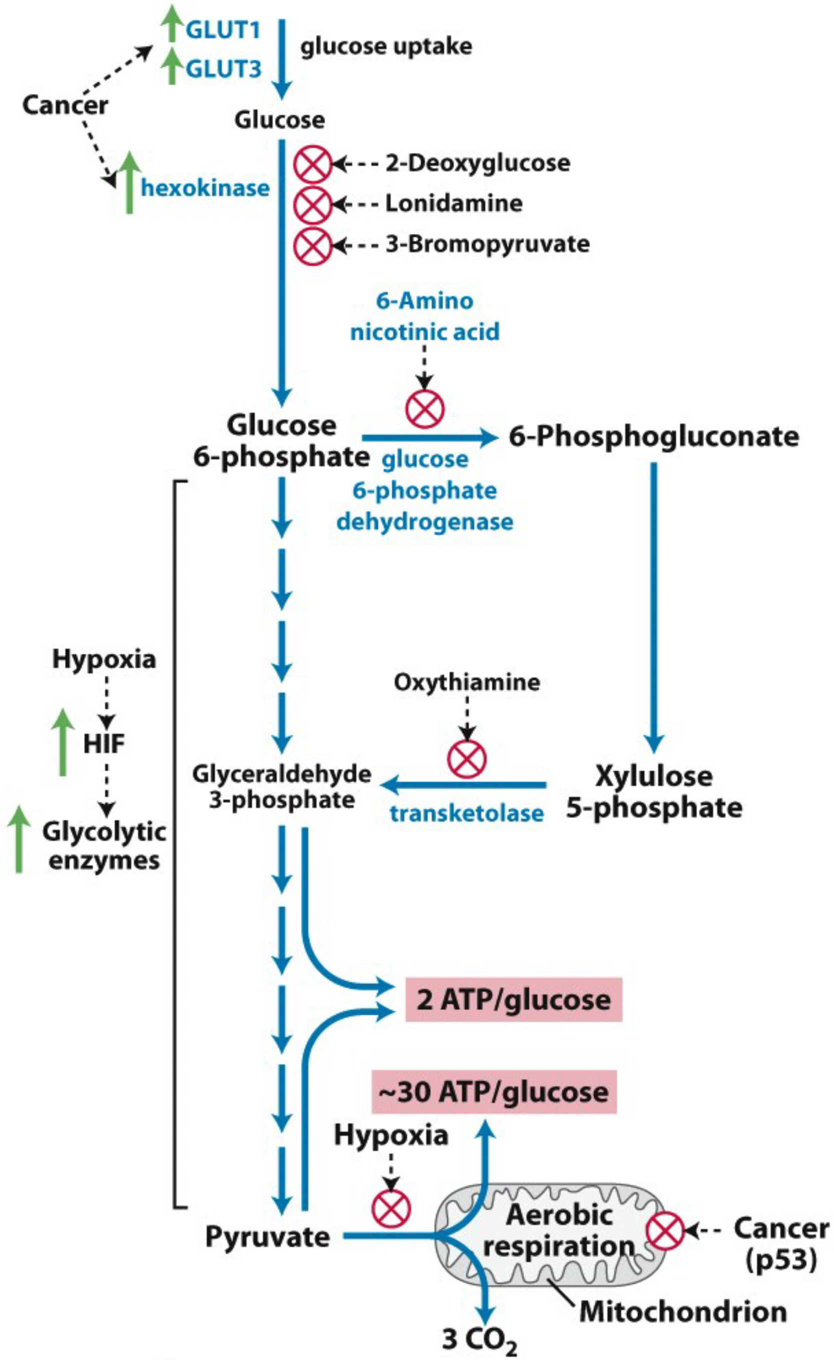
Otto Warburg, 1883–1970

He was awarded the Nobel Prize in Physiology for his "discovery of the nature and mode of action of the respiratory enzyme.“

respiratory enzyme containing Fe activates oxygen

In total, he was nominated an unprecedented three times for the Nobel prize for three separate achievements.

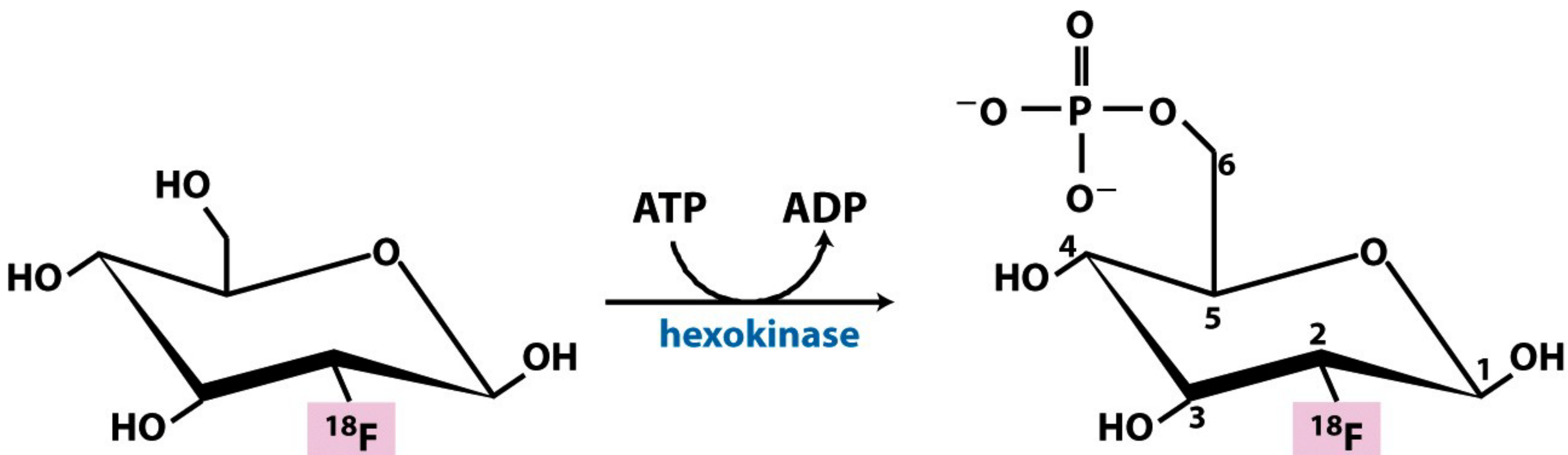
Discovery of flavine (FAD)



Box 14-1 figure 1

The following two steps may be essential for the transformation of a normal cell into a tumor cell in early stage:

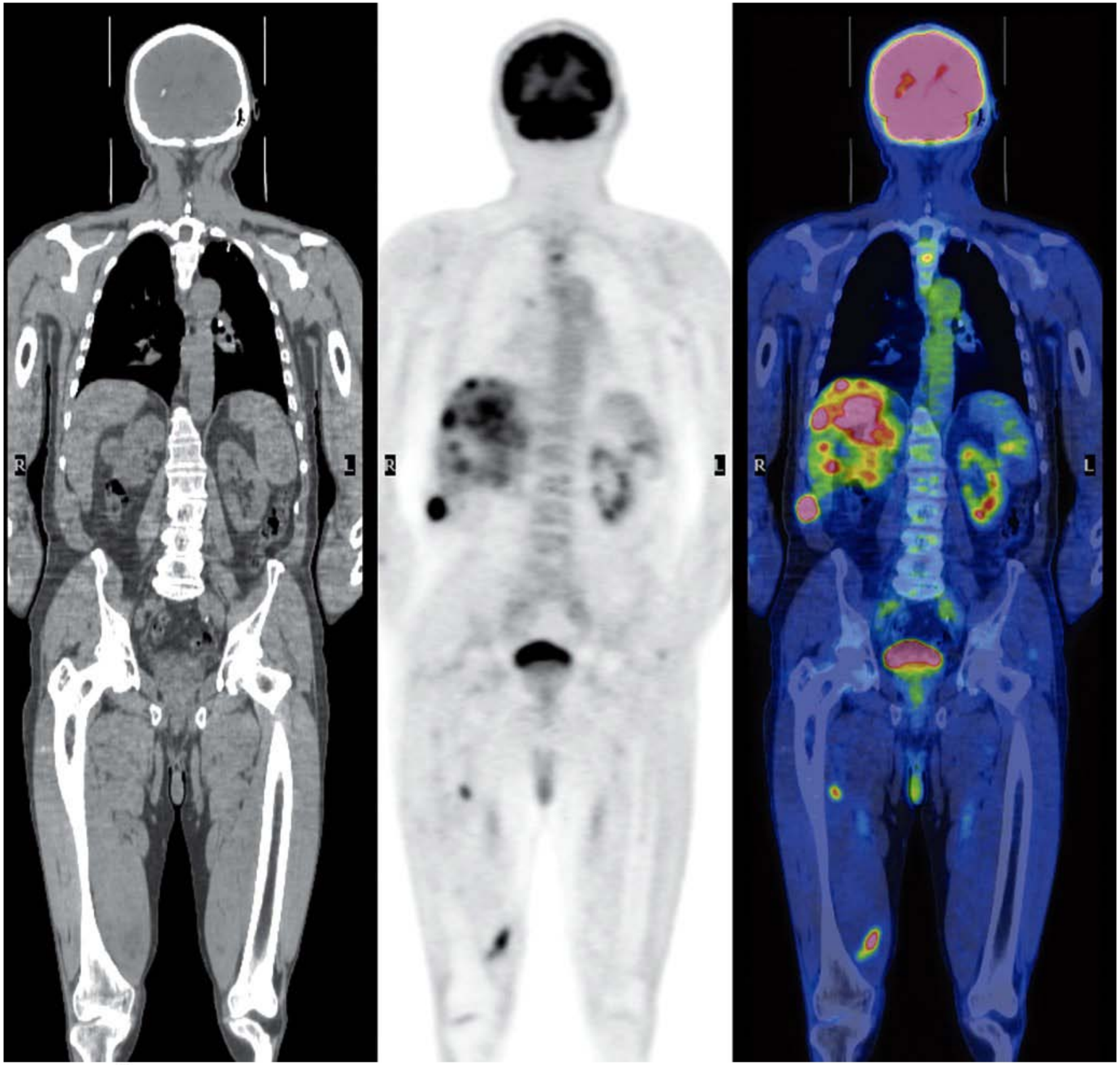
1) The change to dependence on glycolysis for ATP production
2) The development of tolerance to a low pH in the extracellular fluid.



[^{18}F]2-Fluoro-2-deoxyglucose (FdG)

[^{18}F]6-Phospho-2-fluoro-2-deoxyglucose (6-Phospho-FdG)

Box 14-1 figure 2
Lehninger Principles of Biochemistry, Fifth Edition



Box 14-1 figure 3

Lehninger Principles of Biochemistry, Fifth Edition

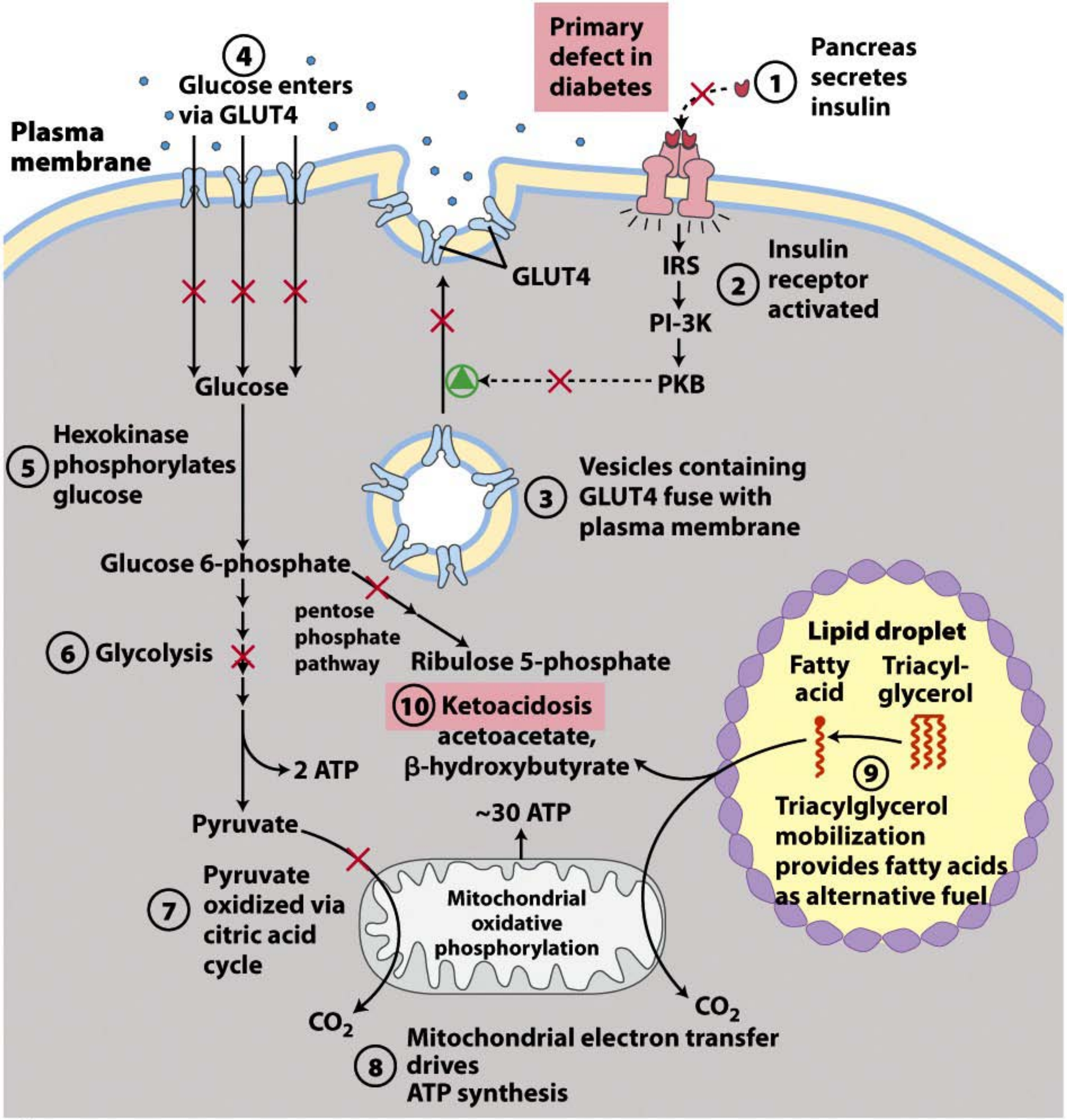


Figure 14-9

Effect of type 1 diabetes on carbohydrate and fat metabolism in an adipocyte