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Sugars and Glycolysis: glucose breakdown or catabolism

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Objectives

- Sugars for energy pathways
  - 6C sugars or hexoses are the main sources of energy

  Textbook Chap. 9

- Breaking down glucose: glycolysis
  - 2 phases: starting up and then producing high energy molecules for the cell
  - 10 reactions
  - Input = 2 ATPs
  - Output = 4 ATPs and 2 NADHs (+ 2 3C pyruvate ions)

  Textbook Chap. 12

Diverse Functions of Carbohydrates

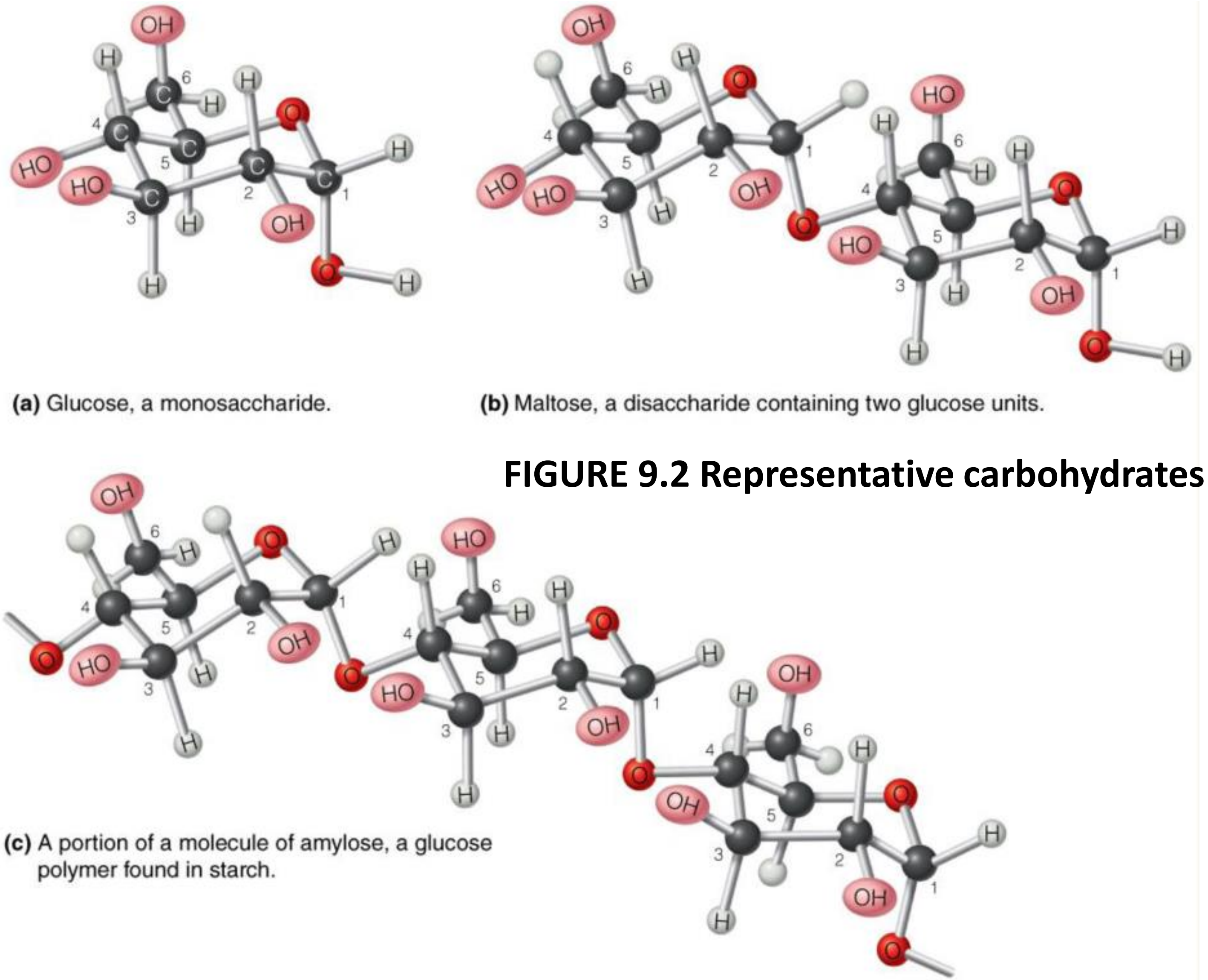
- Carbohydrates have diverse functions:

  1) Storage and generation of energy (e.g., glucose, glycogen, starch)
  2) Molecular recognition (e.g., immune system)
  3) Cellular protection (e.g., bacterial and plant cell walls)
  4) Cell adhesion (e.g., glycoproteins)
  5) Biological lubrication (e.g., glycosaminoglycans)
  6) Building and maintaining biological structure (e.g., cellulose, chitin)

Carbohydrate Terminology

- **Monosaccharide**: Simple sugars and derivatives with 3 to 9 carbon atoms
- **Oligosaccharide**: Compound formed by linking several monosaccharides together (e.g., disaccharide, with 2)
- **Polysaccharide**: Polymer formed from multiple saccharide units; may be homopolysaccharide or heteropolysaccharide
- **Glycan**: Generic term for oligosaccharides and polysaccharides

Example mono-, di- and polysaccharides



(a) Glucose, a monosaccharide.

(b) Maltose, a disaccharide containing two glucose units.

FIGURE 9.2 Representative carbohydrates

(c) A portion of a molecule of amylose, a glucose polymer found in starch.

Carbs for powering the cell

- Simple sugars and polysaccharides store energy
- The structure of carbohydrates is important in understanding how they are metabolized
  - Carbohydrates have the general formula $[\mathbf{C.H_2O}]_n$
    - *usually contain an **aldehyde** or **ketone** group as well as **many hydroxyl groups***
  - We need to understand the structures of the simplest sugars to very complex carbohydrates
  - The simplest carbohydrates contain only **three carbon (3C) atoms** and are derived from glycerol.

The 3-carbon sugars (trioses): $\{CH_2O\} \times 3$ – brief overview

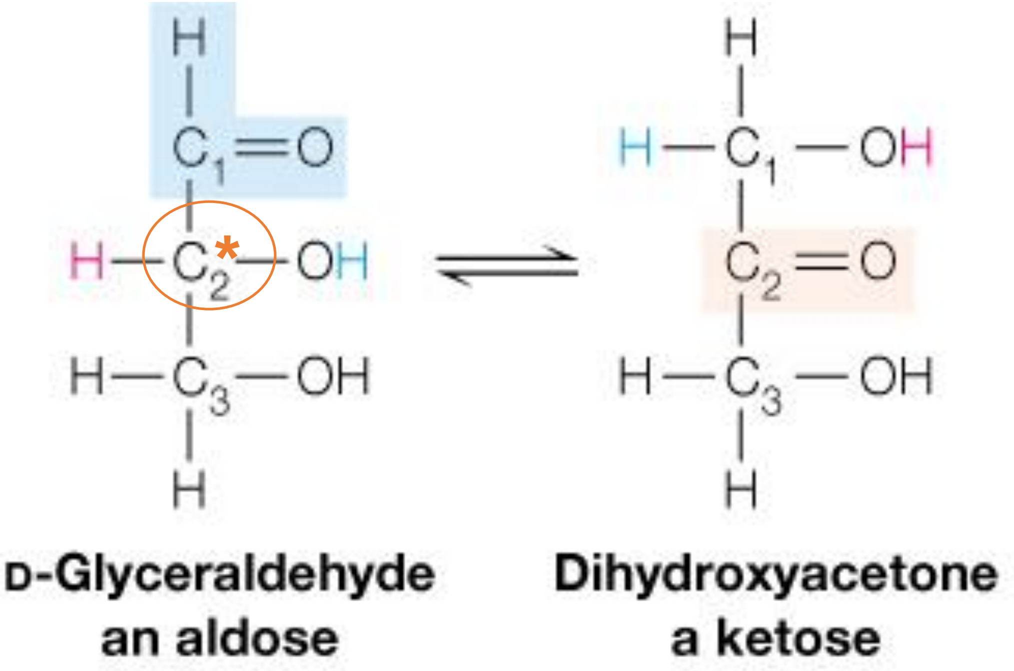
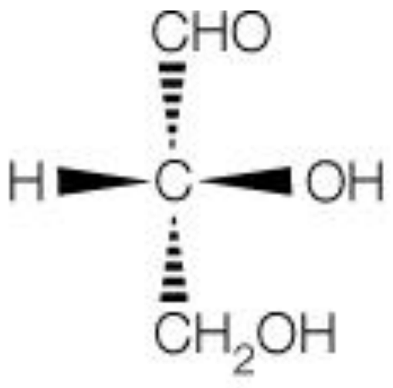


FIGURE 9.3 Trioses, the simplest monosaccharides.

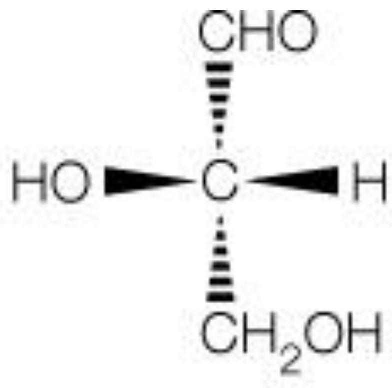
- **Aldose**: glceraldehyde and **ketose**: dihydroxyacetone
- D and L (or R and S) forms are determined by the configuration of the optically active C, linked to four different groups (usually marked C*)
- D is important for the sweet taste of sugar

Enantiomers

- Fischer projections (see top) are the most compact way to represent stereochemistry
- The wedge-dash representations of the D- and L-forms glyceraldehyde are also shown (bottom)



D-Glyceraldehyde



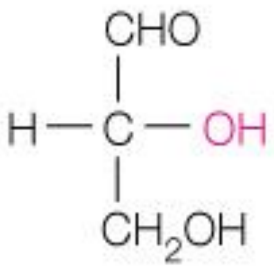
L-Glyceraldehyde

Carbon number:

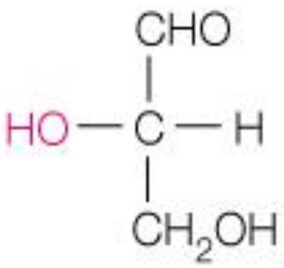
1

2

3

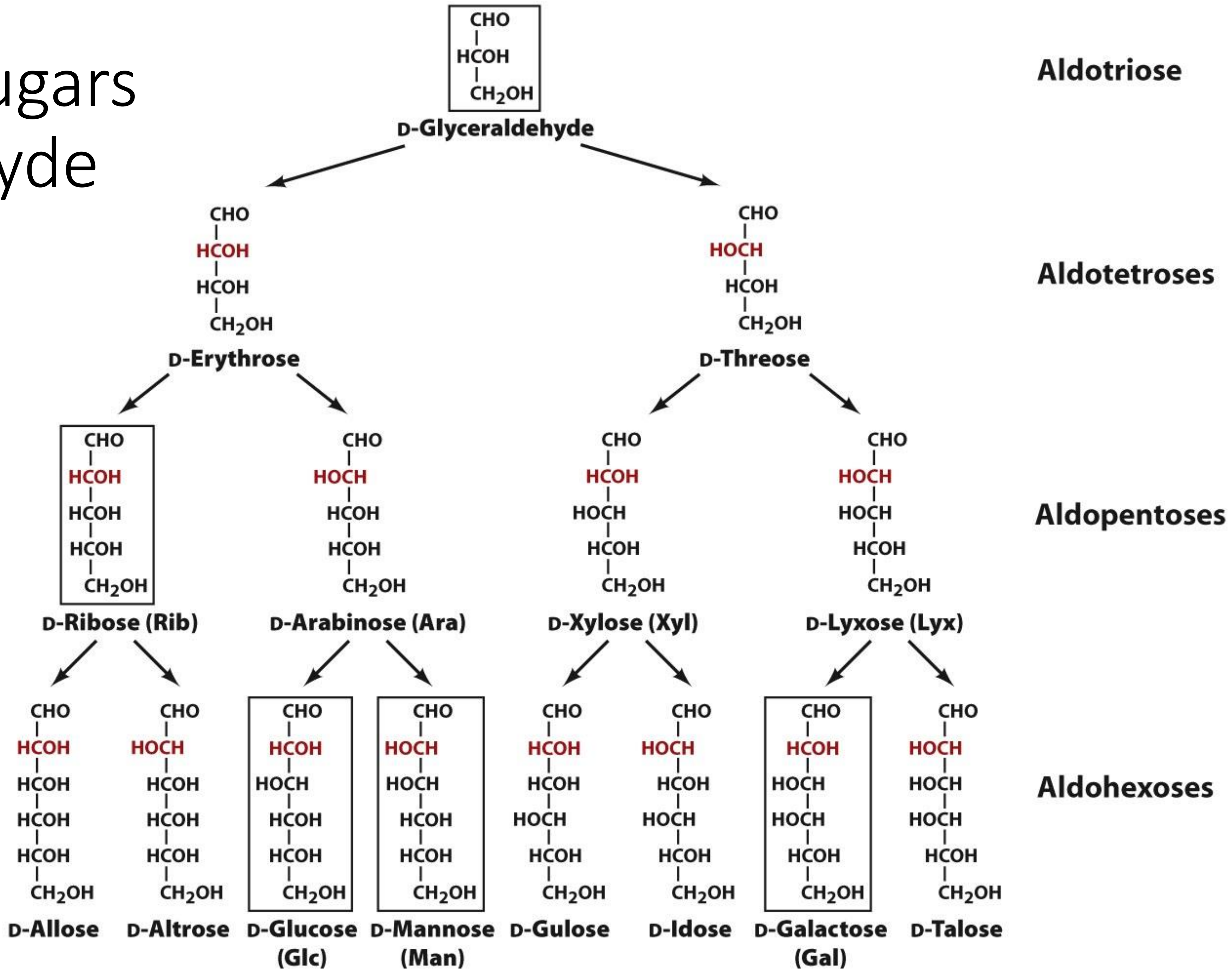


D-Glyceraldehyde



L-Glyceraldehyde

Aldoses are sugars with an aldehyde group



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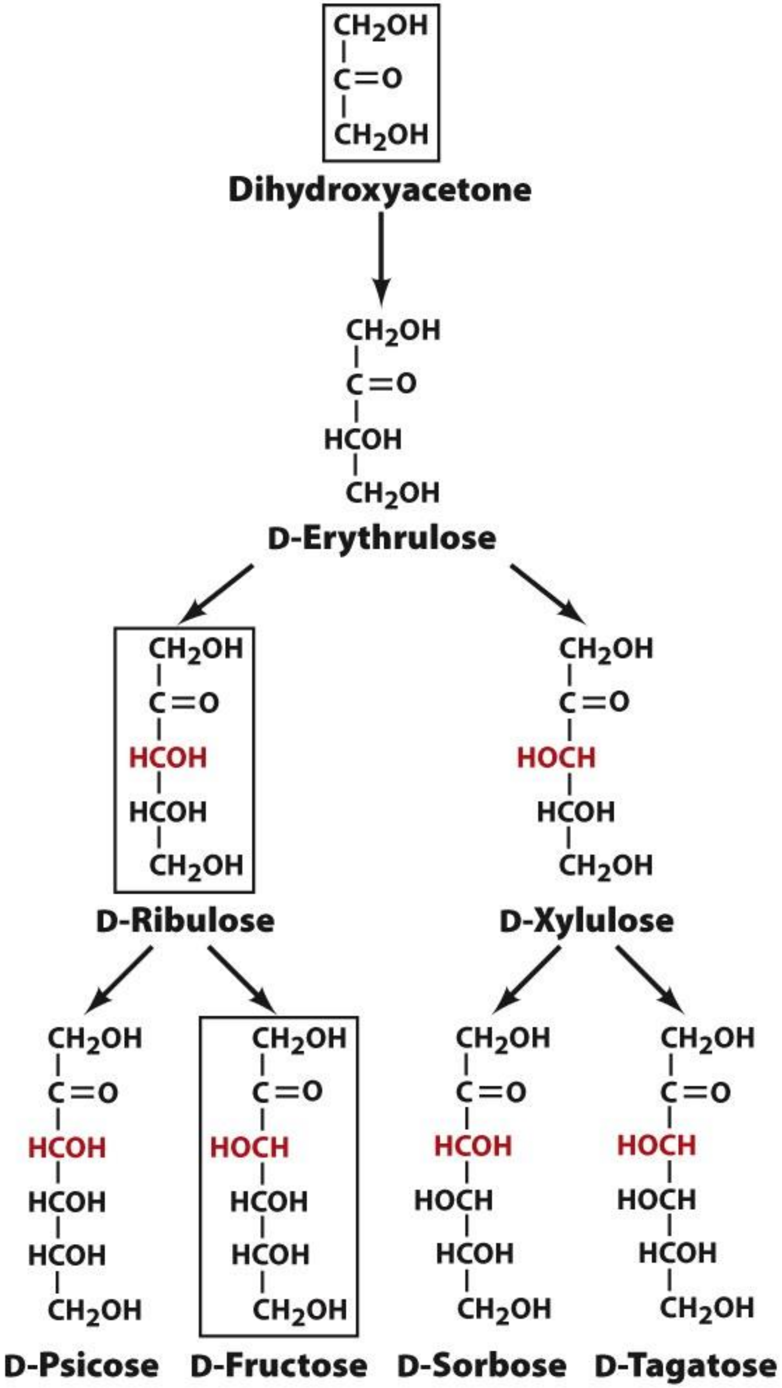
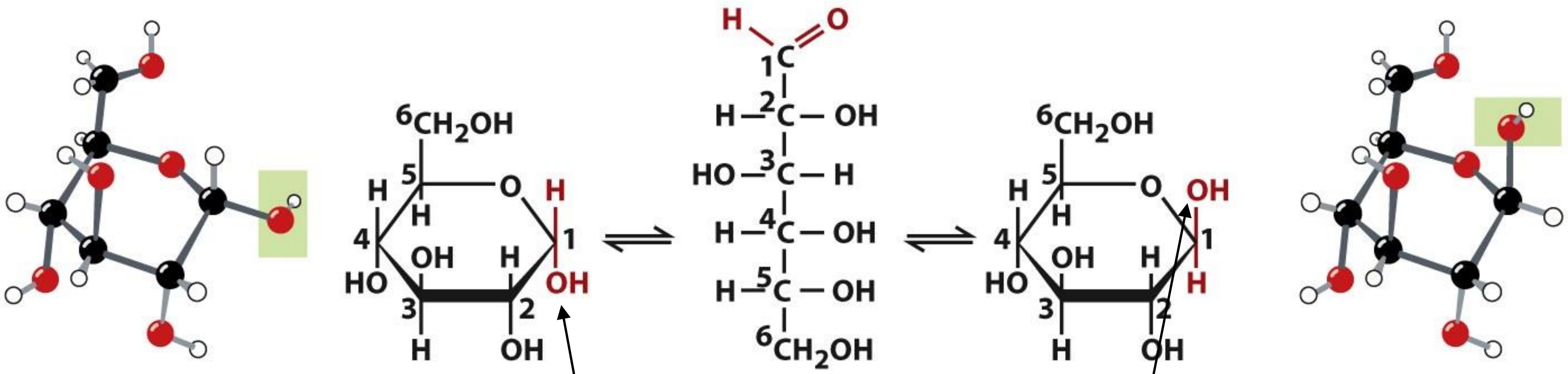
Ketoses are sugars with a ketone group



Monosaccharides

- **Hexose** (6C) and **pentose** (5C) sugars are also called just monosaccharides: these are very important biologically.
- They can ***cyclise*** by forming rings called *hemiacetals*, forming a chiral centre:
    - The ring formed has two distinct conformations around the chiral carbon, α and β (alpha and beta).

α & β stereoisomers of Glucose



α-D-Glucopyranose

D-Glucose (linear form)

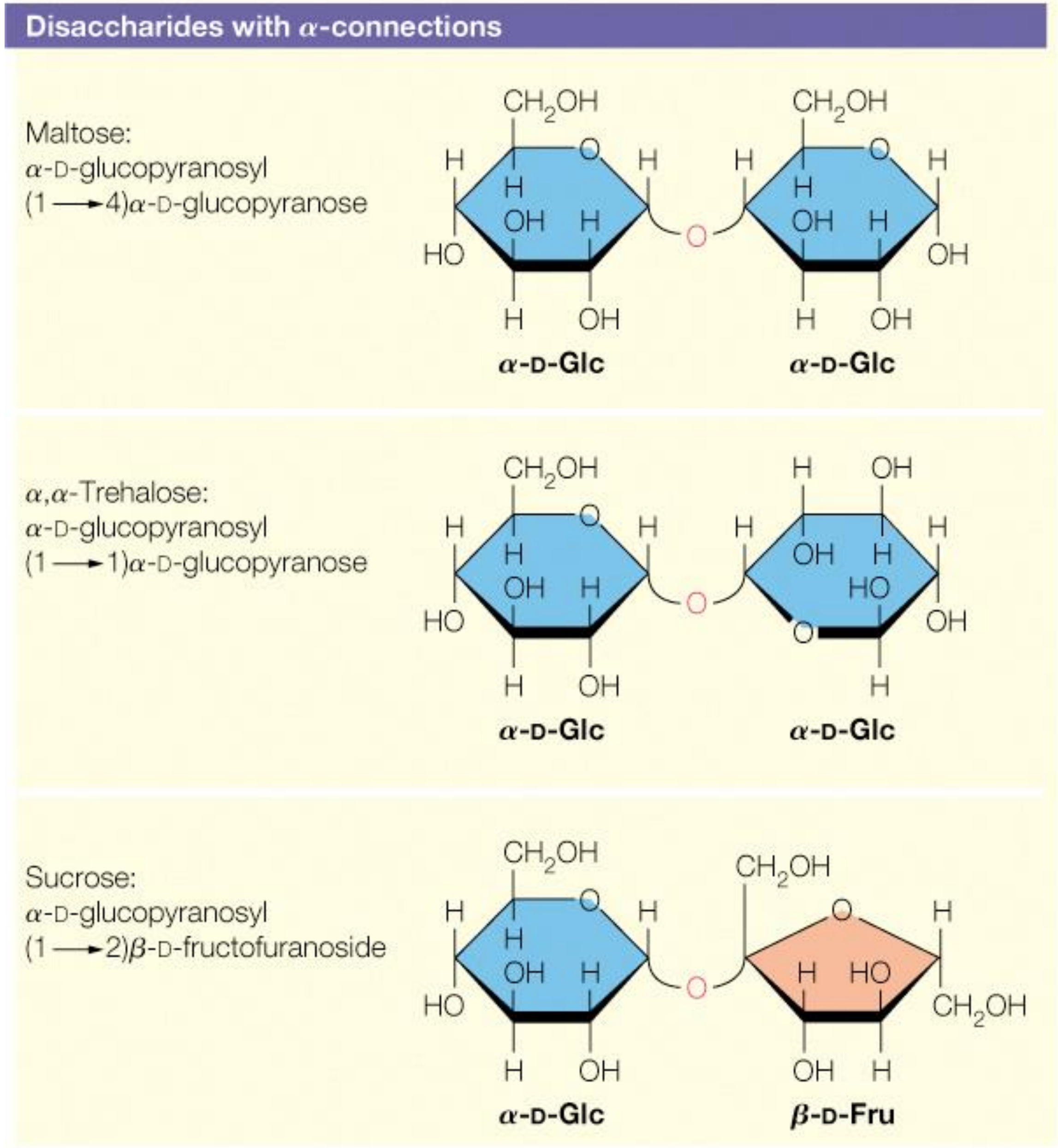
β-D-Glucopyranose

α – below the ring

β – above the ring

Polymerization of simple sugars

- Dimers of monosaccharides: α- and β-glycosidic bonds (similar to peptide bonds)
- Formed by condensation
- Glc: glucose; Fru: fructose;
- Gal: galactose (next slide)



(a) Disaccharides linked through the C-1 of the α anomer: maltose, trehalose, and sucrose.

FIGURE 9.14 Structures of some important disaccharides.

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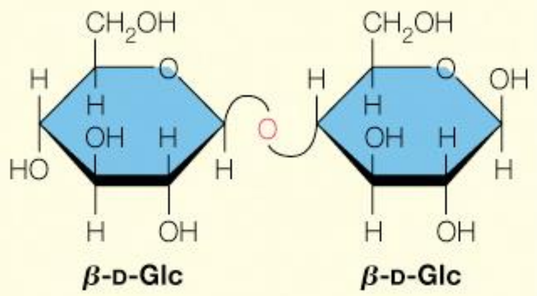
Representative Disaccharides and Their Biochemical Roles

TABLE 9.2 Occurrence and biochemical roles of some representative disaccharides

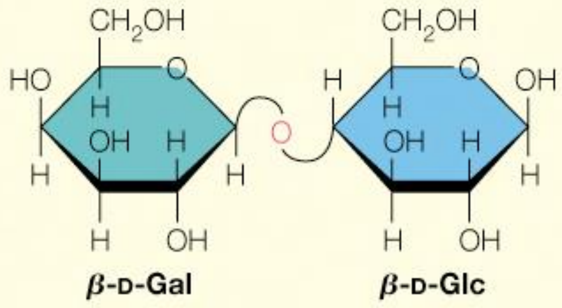
Disaccharide	Structure	Natural Occurrence	Physiological Role
Sucrose	Glcα(1 $\longrightarrow$ 2)Fruβ	Many fruits, seeds, roots, honey	A final product of photosynthesis, used as a primary energy source in many organisms
Lactose	Galβ(1 $\longrightarrow$ 4)Glc	Milk, some plant sources	A major animal energy source
α,α-Trehalose	Glcα(1 $\longrightarrow$ 1)Glcα	Yeast, other fungi, insect blood	A major circulatory sugar in insects; used for energy
Maltose	Glcα(1 $\longrightarrow$ 4)Glc	Plants (starch) and animals (glycogen)	The dimer derived from the starch and glycogen polymers
Cellobiose	Glcβ(1 $\longrightarrow$ 4)Glc	Plants (cellulose)	The dimer of the cellulose polymer
Gentiobiose	Glcβ(1 $\longrightarrow$ 6)Glc	Some plants (e.g., gentians)	Constituent of plant glycosides and some polysaccharides

Disaccharides with β-connections

Cellobiose:
β-D-glucopyranosyl
(1 $\longrightarrow$ 4)β-D-glucopyranose

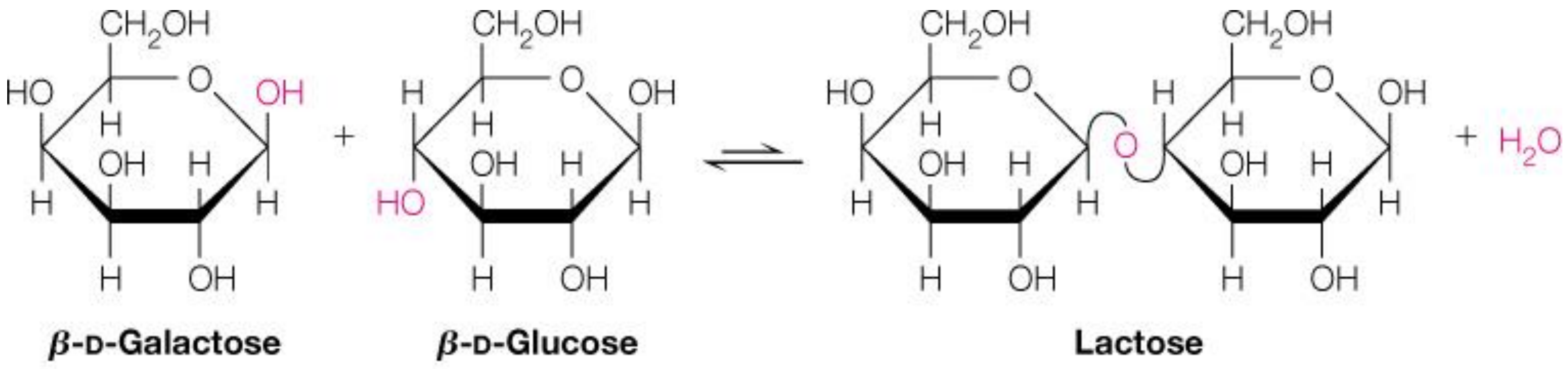


Lactose:
β-D-galactopyranosyl
(1 $\longrightarrow$ 4)β-D-glucopyranose



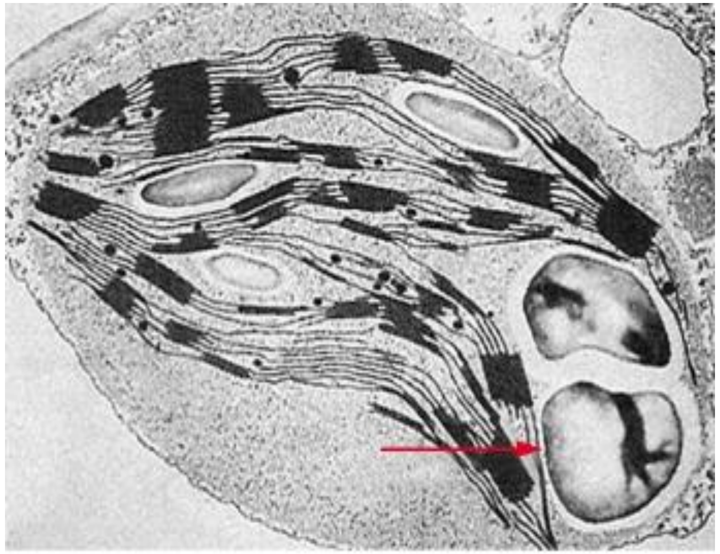
Stability and Formation of Glycosidic Bonds

- Glycosidic bonds are formed between monomeric saccharides by condensation reaction1



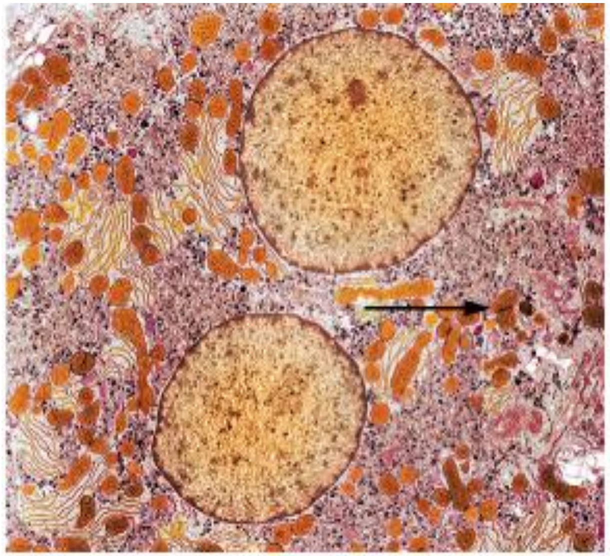
- However, the reaction (as written) is thermodynamically unfavourable

Energy Storage Polysaccharides: Starch (Amylose and Amylopectin) and Glycogen



(a) Starch granules in a plant leaf chloroplast.

(b) Starch granules in potato tuber cells.



(c) Glycogen granules in liver.

FIGURE 9.16 Storage of starch and glycogen in granules.

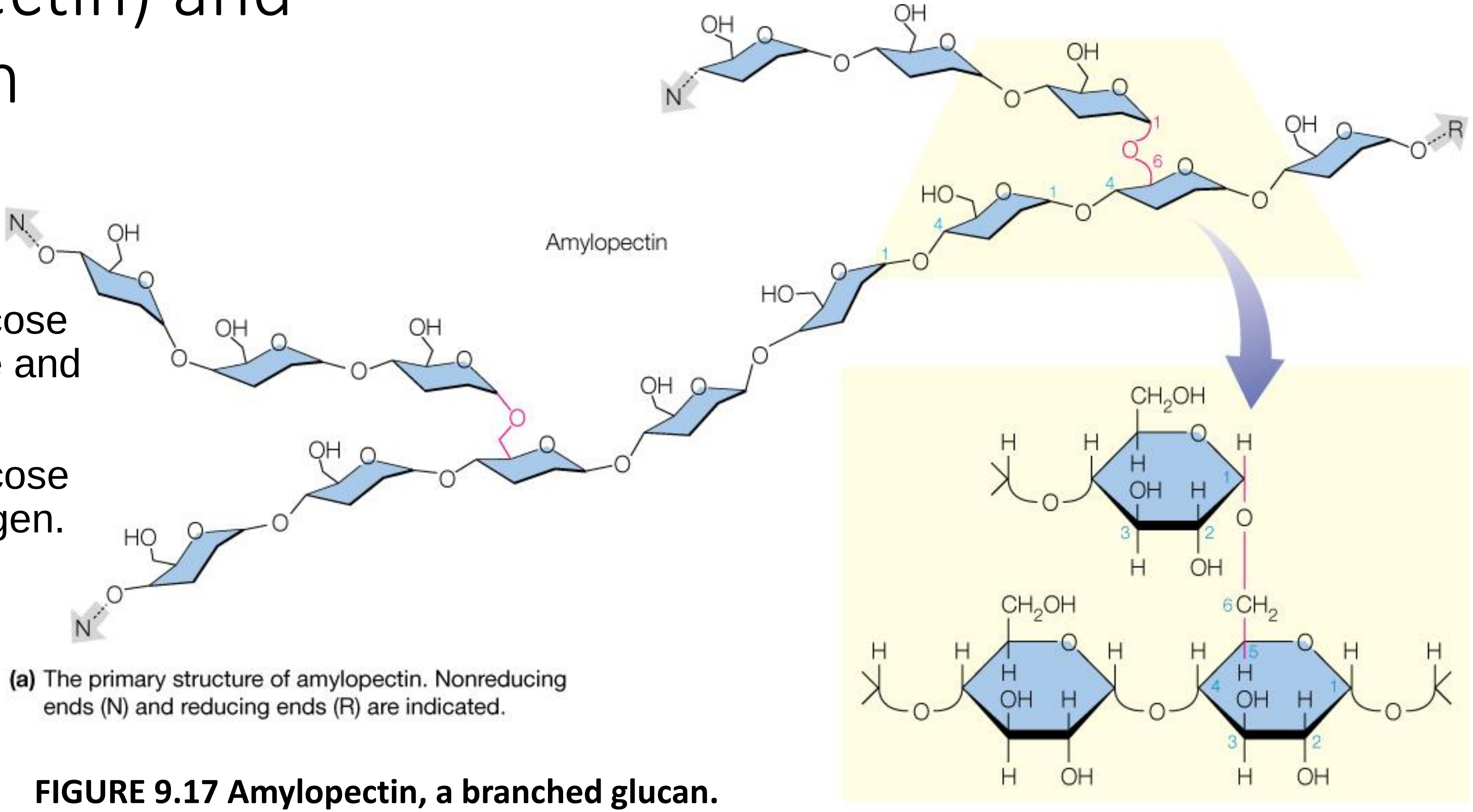
- Starch (plants) contains both amylopectin, α(1→4) glucose polymer with α(1→6) branches, and amylose, α(1→4) unbranched polymer
- Glycogen (animals/microbes) is like amylopectin, but higher MW with shorter and more frequent branch points

Starch (Amylose and Amylopectin) and Glycogen

- **Starch** and **glycogen** are <u>**both**</u> ***polymers of*** ***<u>glucose</u>*** residues linked by **α (alpha) linkages**

➢ β(1,4)-linked D-glucose is found in cellulose and chitin

➢ α(1,4)-linked D-glucose in starch and glycogen.



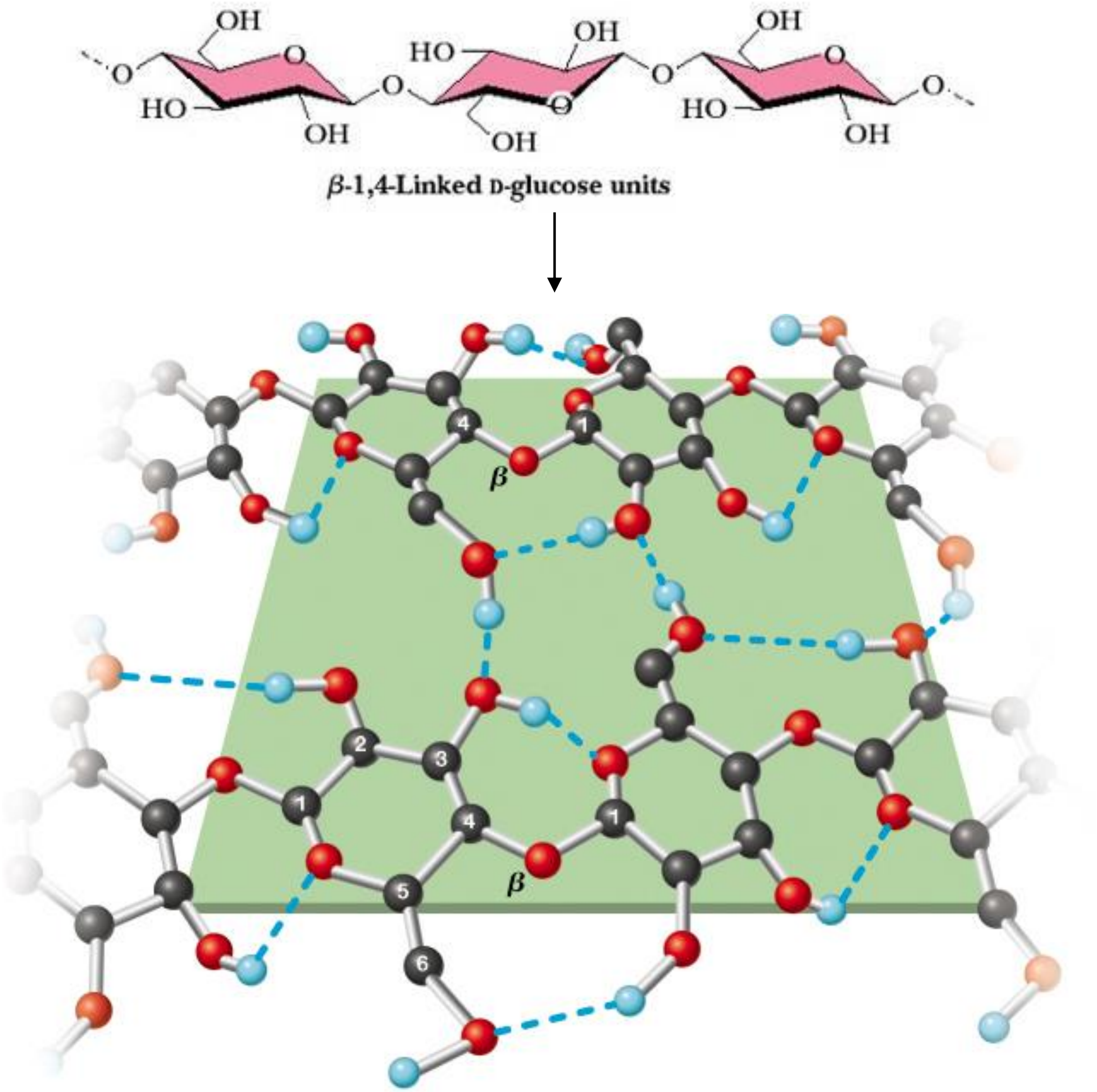
(a) The primary structure of amylopectin. Nonreducing ends (N) and reducing ends (R) are indicated.

(b) Detailed structure of a branch point.

FIGURE 9.17 Amylopectin, a branched glucan.

Cellulose

- In plant cell walls
- We cannot use this in sugar metabolism as we do not have the enzymes that can break these β(1,4)-glycosidic bonds
- Termites can!



Summary of simple sugars

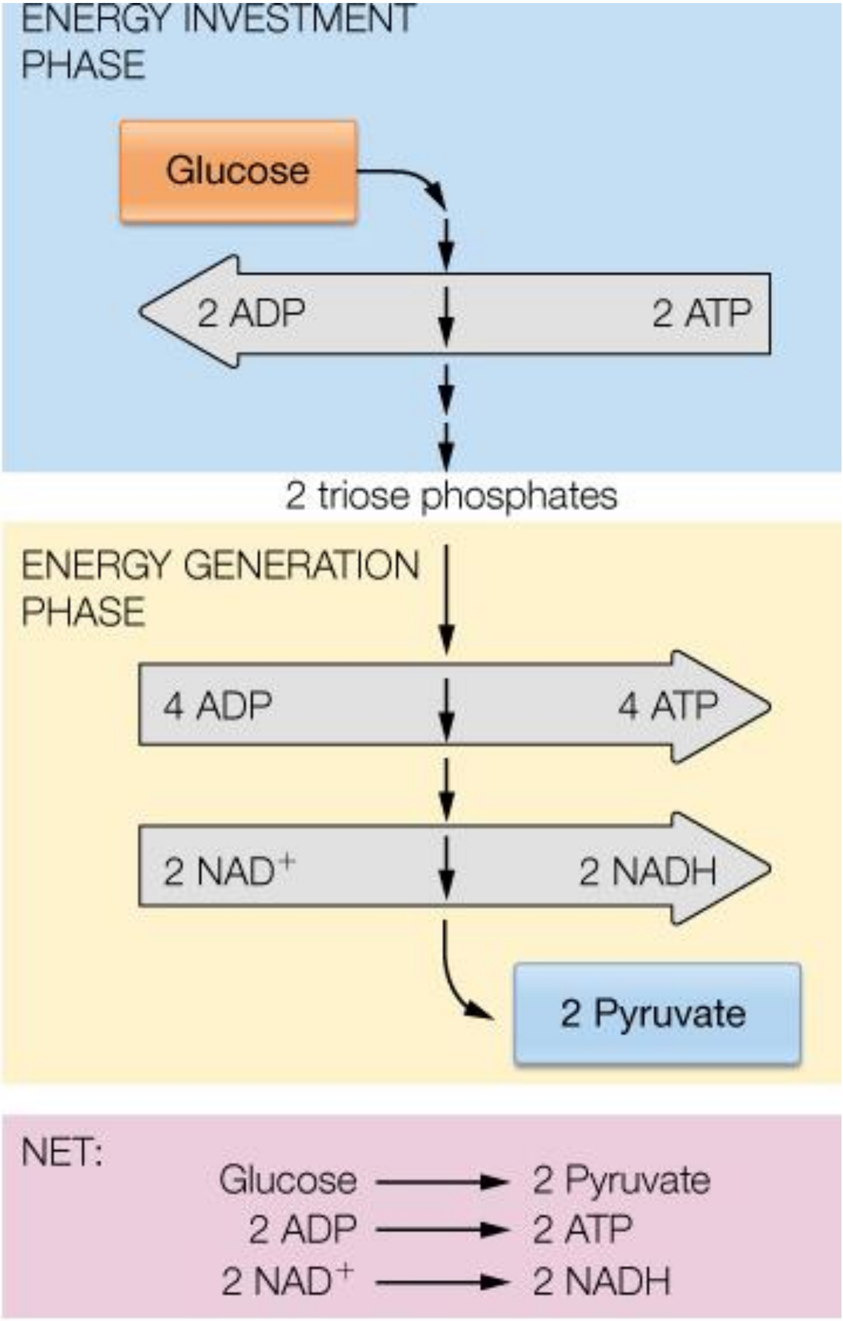
- 6C sugars (hexoses) are most important for energy metabolism
  - Most important are **D-glucose** and **D-fructose**
- 5C sugars (pentoses) make nucleotides: D-ribose
- Polymers of glucose are called complex carbohydrates or polysaccharides
  - We make glycogen from glucose
  - Plants make starch
  - Both these polymers have α (alpha) bonds
  - There are other polymers such as cellulose and chitin, which we cannot digest.

Glycolysis

- Glycolysis is the *catabolic* process by which **glucose** (6C) and other hexoses are converted to **pyruvate** (2x 3C)
- Glycolysis occurs in almost every living cell
- Glycolysis **does not require oxygen** (i.e. anaerobic)
- The glycolytic pathway was the first major metabolic pathway to be elucidated
  - ***Embden-Meyerhof-Parnas*** pathway

Phases of Glycolysis

- Glycolysis has 10 reactions, which can be divided into two distinct phases:
  - ➢one to invest energy and
  - ➢one to generate energy
- In the energy-investment phase, two ATPs are consumed to break down glucose into two triose phosphates
- In the energy-generation phase, the triose phosphates are oxidized to two pyruvic acids, thereby producing four ATP and two NADH
- Overall: Glucose + 2 ADP + 2 PO_4^- + 2 NAD^+ are converted to 2 pyruvic acid + 2 ATP + 2 NADH + $2H^+$



The Energy-Investment Phase of Glycolysis

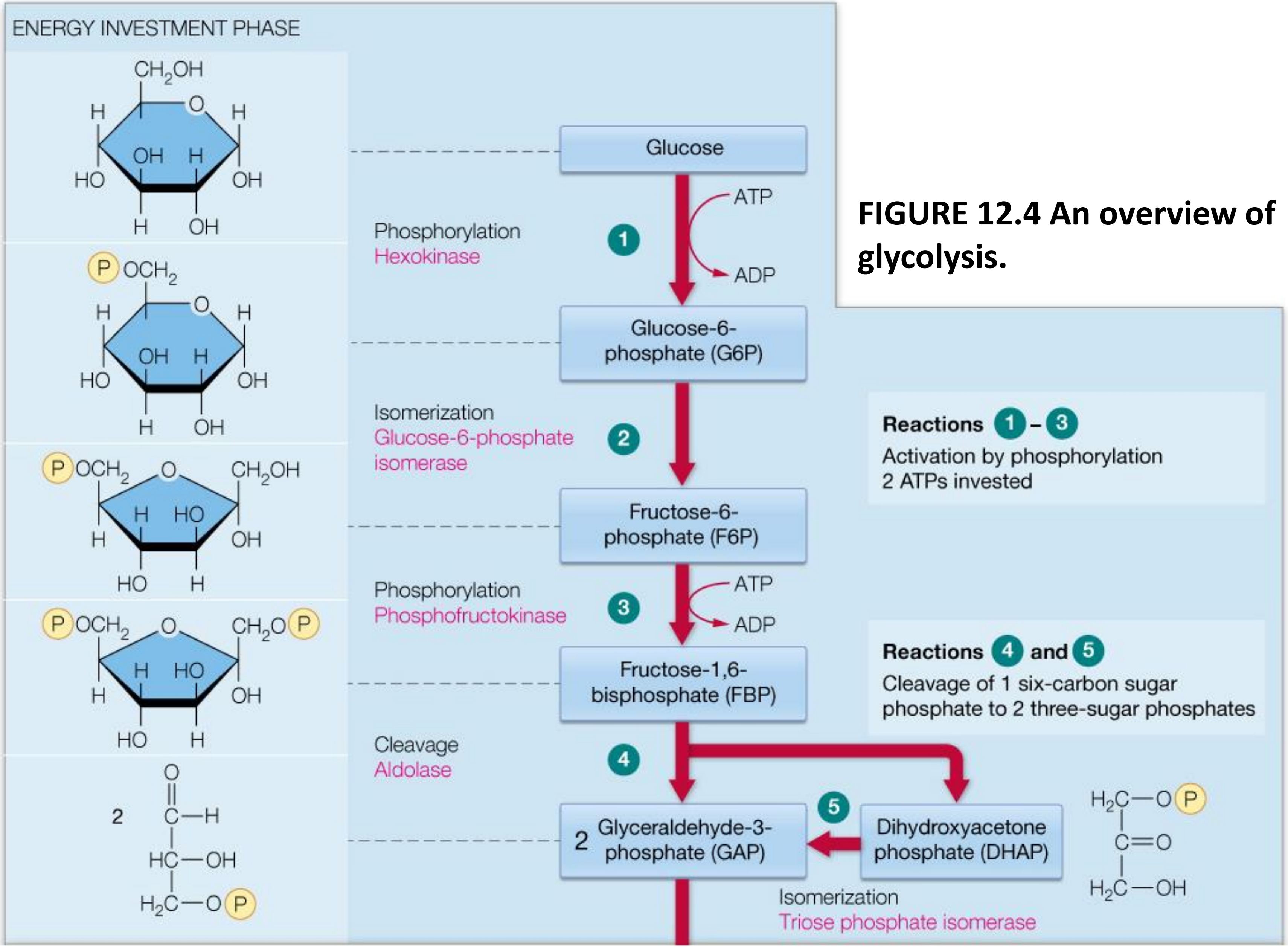


FIGURE 12.4 An overview of glycolysis.

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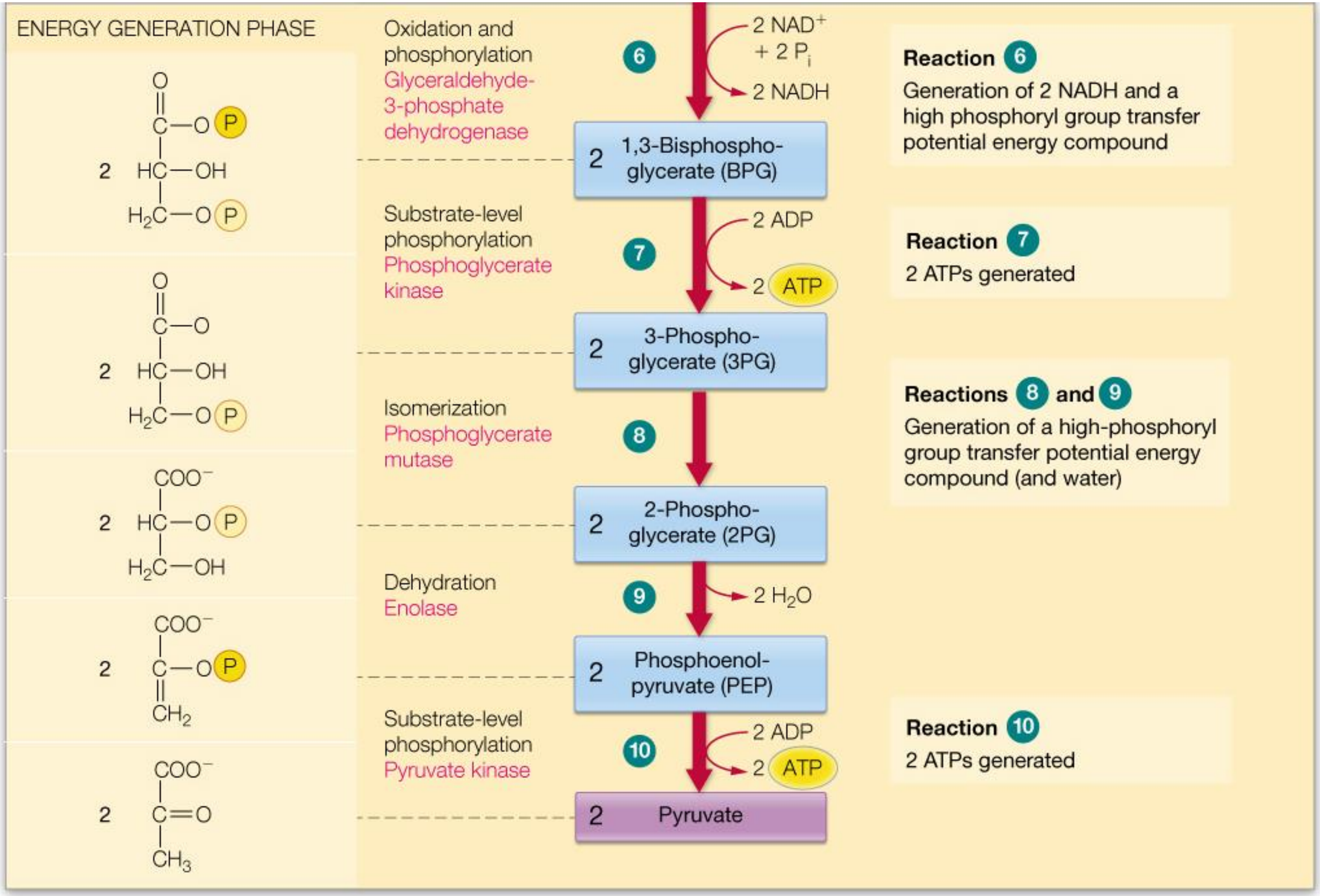
The Energy-Generation Phase of Glycolysis



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The Reactions of Glycolysis

Summary

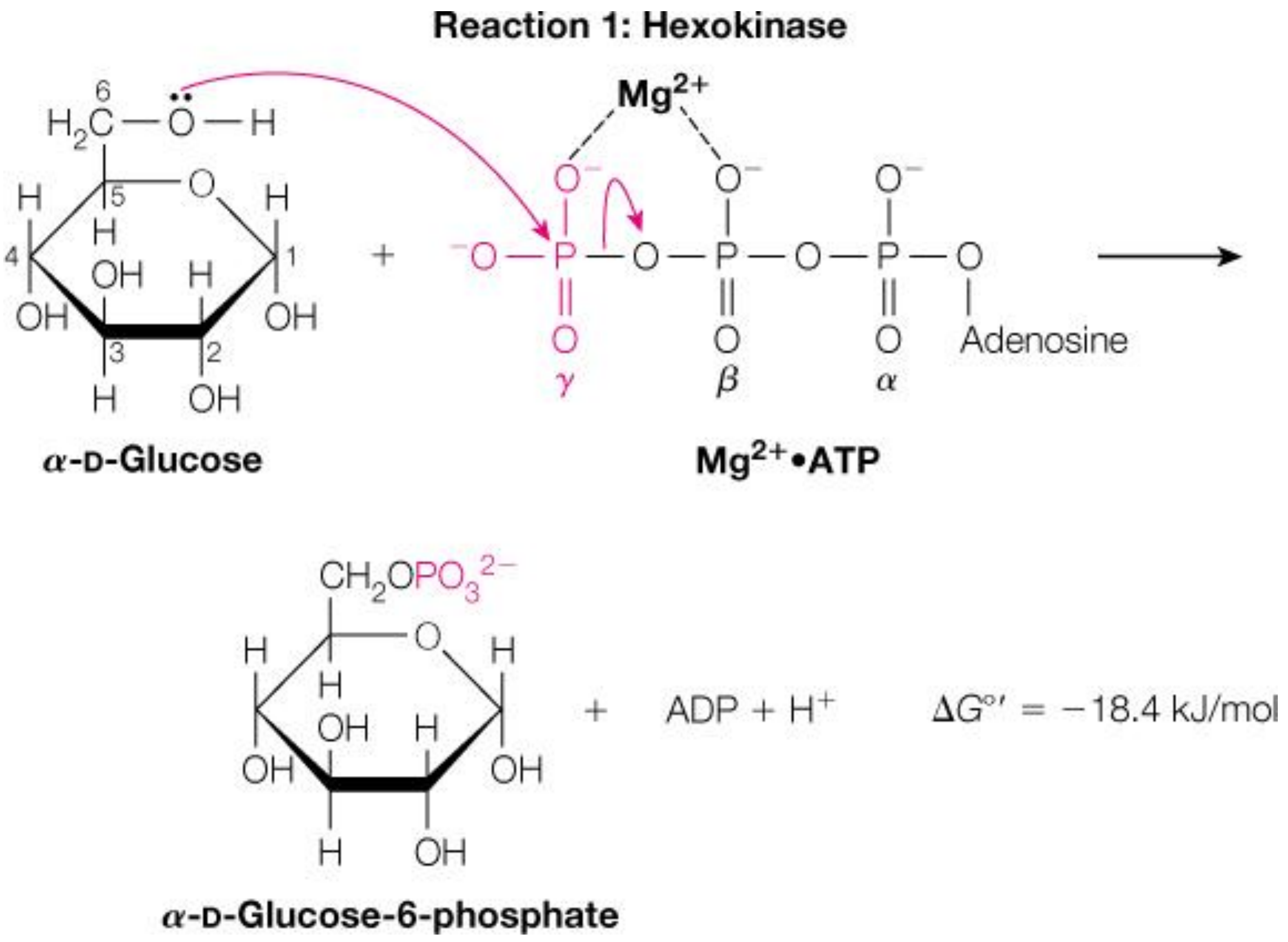
- 10 steps in glycolysis.
- Enzymes in this pathway catalyze phosphorylation reactions, isomerizations, carbon–carbon bond cleavage, and dehydration.
- ATP is consumed in Steps 1 and 3 but regenerated in Steps 7 and 10, with a net yield of 2 ATP per glucose molecule.
- For each glucose, 2 NADH are produced in Step 6.
- *Note*: metabolism requires ATP and reducing molecules such as NADH – so both these are important products from glycolysis.

Reaction 1: Hexokinase Uses 1st ATP: activation of glucose by phosphorylation

- Mg^{2+}-controlled reaction
- Mg^{2+} ensures only the third phosphate is available for cleavage

Hexokinase isoforms:

- different substrate specificities (many hexoses, not only glucose) and binding affinities
- low K_M for isoforms I, II, III
- **high K_M for hexokinase IV,** liver enzyme also called **glucokinase**
- hexokinase IV is a “glucostat,” allowing the liver to adjust its rate to varying blood glucose levels



This is energetically unfavorable work:

overcoming unfavourable conditions….

- By coupling an energetically favourable reaction with an unfavourable one:

$$\text{Glucose} + P_i \rightleftharpoons \text{glucose-6-phosphate} \quad \Delta G^{o\prime} = +13.8 \text{ kJ/mole}$$

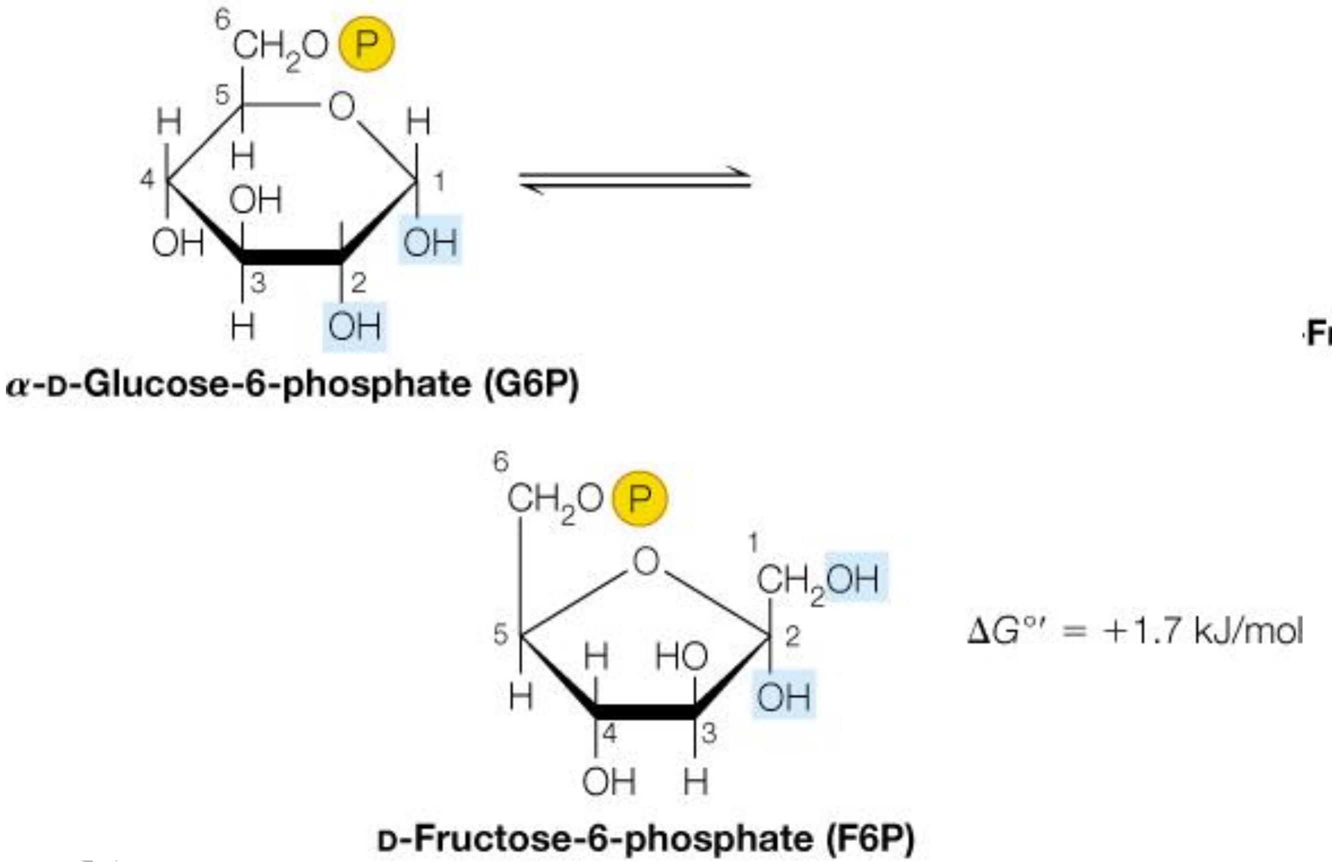
$$\text{ATP} + H_2O \rightleftharpoons \text{ADP} + P_i + H^+ \quad \Delta G^{o\prime} = -32.2 \text{ kJ/mole}$$

$$\text{ATP} + \text{Glucose} \rightleftharpoons \text{ADP} + \text{Glu-6-phosphate} \quad \Delta G^{o\prime} = -18.4 \text{ kJ/mole}$$

Reaction 2: Phosophoglucose Isomerase

(from glucose to fructose, a ketone sugar)

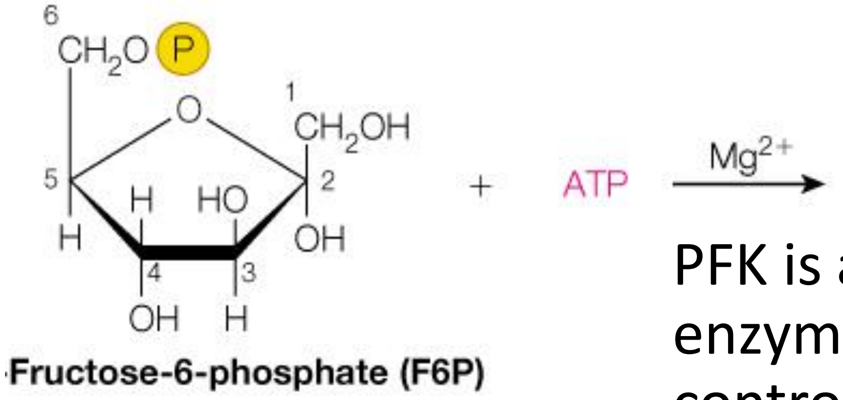
Reaction 2: Glucose-6-phosphate isomerase



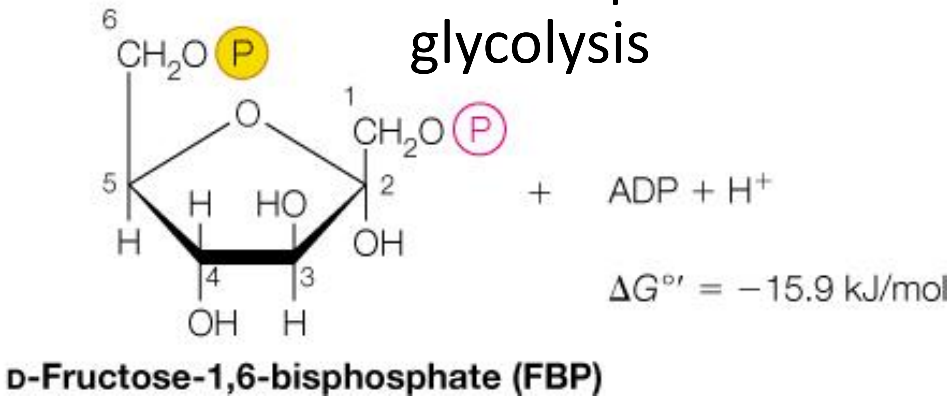
Reaction 3: Phosphofructokinase adds 2nd ATP to F6P:

second phosphate added to make sugar ready for breakdown

Reaction 3: Phosphofructokinase



PFK is an allosteric enzyme and a major control point for glycolysis

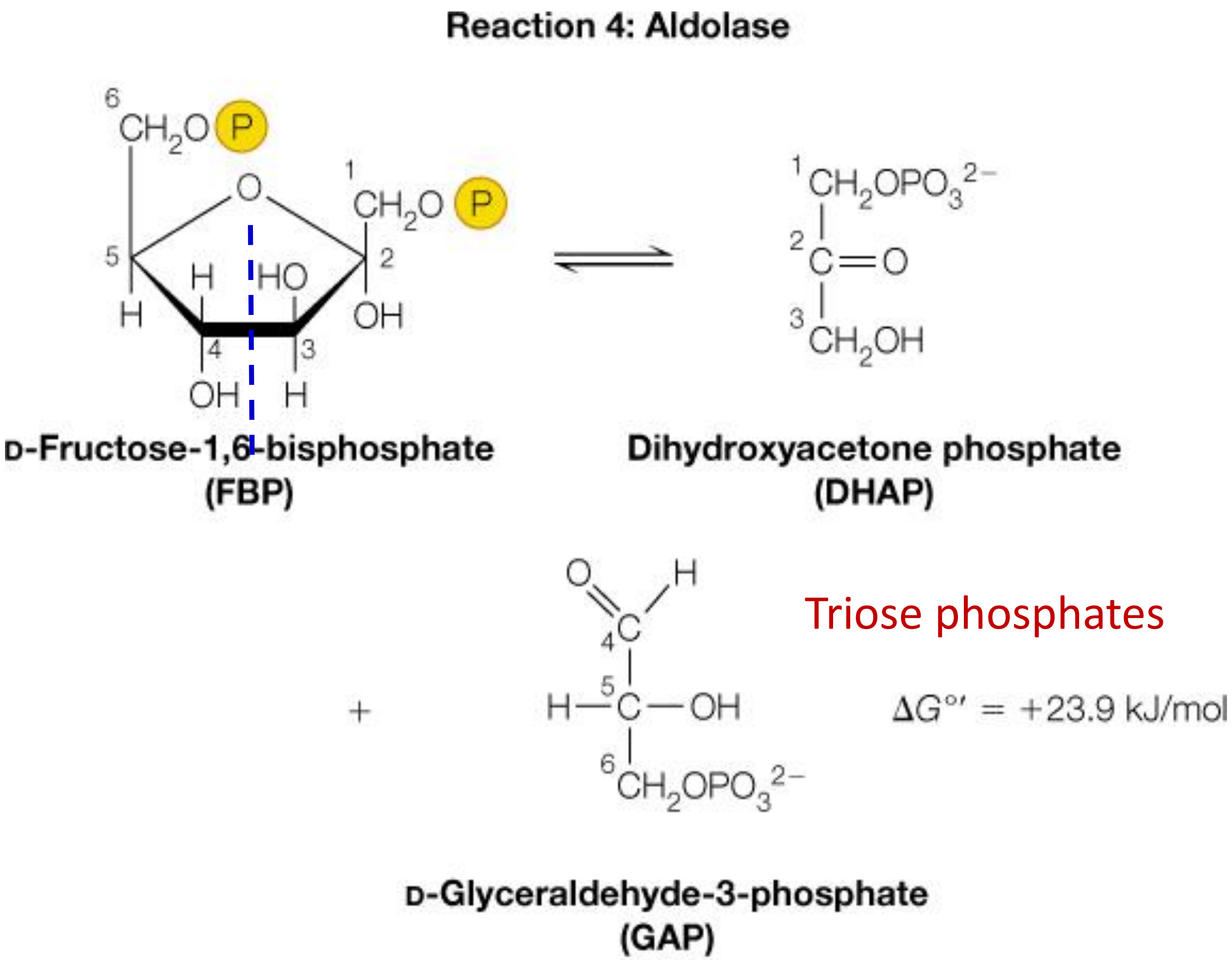


Reaction 4: Aldolase can break FBP:

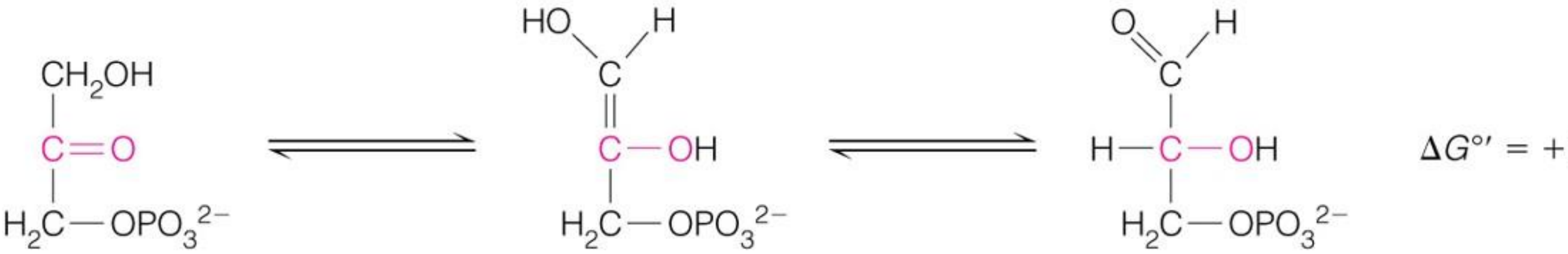
6-Carbon FBP to 3-Carbon GAP & DHAP

Aldolase cleaves fructose 1,6-bisphosphate (F1,6BP) into two triose phosphates in a reversible reaction.

Although $\Delta G^{\circ\prime}$ for the reaction is positive, ΔG under intracellular conditions is negative so that the reaction proceeds as written *in vivo*

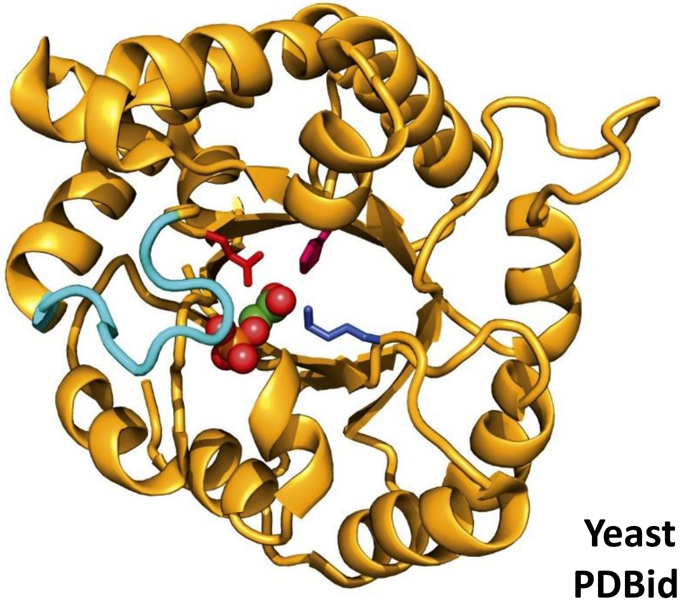


Reaction 5: Triose Phosphate Isomerase (TIM):
Making more GAP for Phase II



Dihydroxyacetone phosphate (DHAP) ⇌ Enediol intermediate ⇌ D-Glyceraldehyde-3-phosphate (GAP)

$\Delta G^{\circ\prime} = +7.6$ kJ/mol

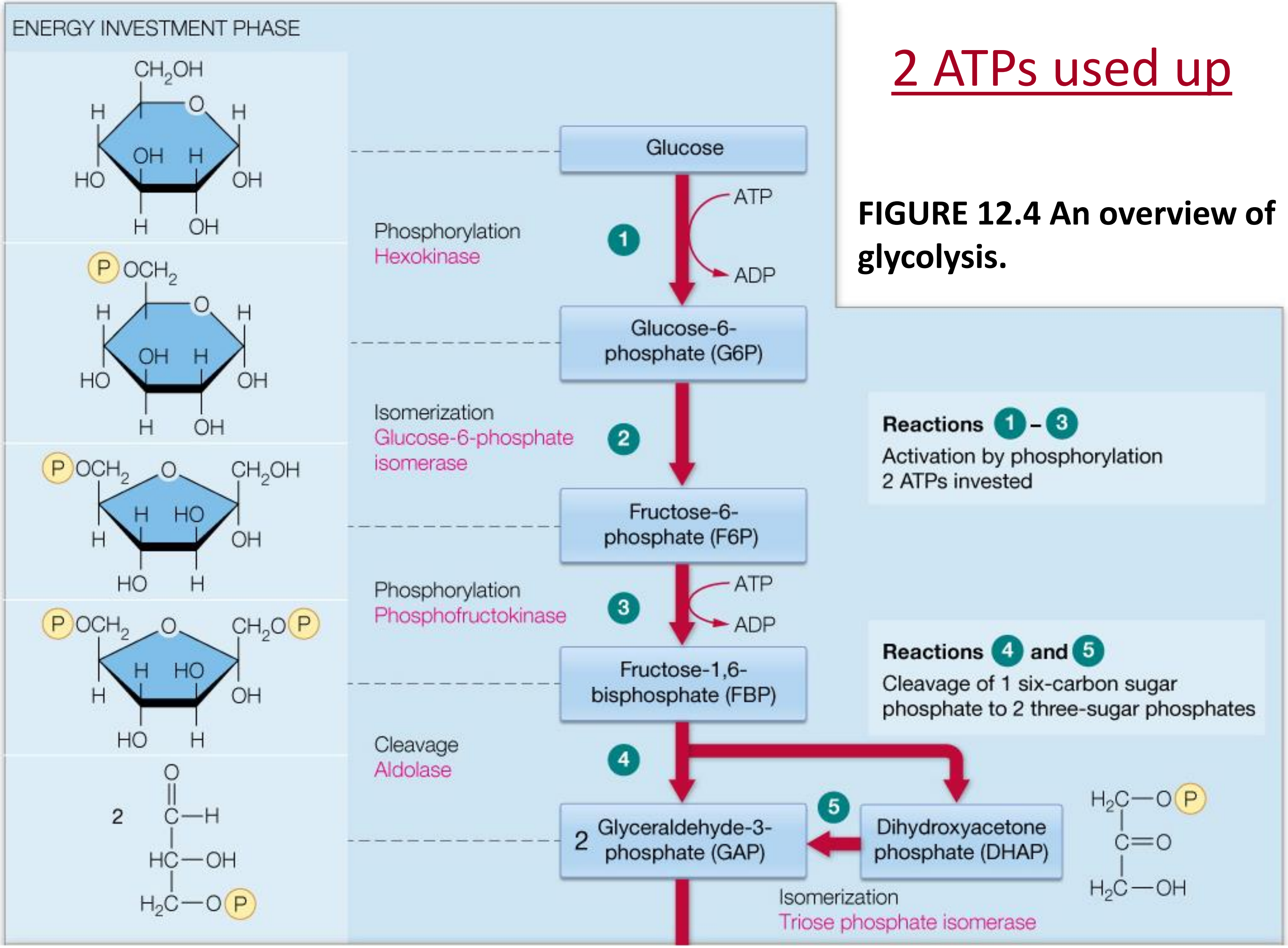


Yeast TIM
PDBid 2YPI

Figure 15-6

The TIM barrel is an example of the α/β repeating fold, which has a parallel β-sheet, connected by α-helices
A flexible loop closes over the active site, where the ligand is bound.

Glycolysis Investment Phase Recap



<u>2 ATPs used up</u>

FIGURE 12.4 An overview of glycolysis.

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First Stage of Glycolysis - Summary

- Three 6C sugar or hexose phosphates (from polysaccharides)
  - ➢ glucose-6-phosphate
  - ➢ fructose-6-phosphate
  - ➢ Fructose-1,6-bisphosphate
- Two ATPs consumed
- Mg^{2+} cofactor
- Two 3C sugar or triose phosphates generated
  - ➢ DHAP and GAP can change into each other

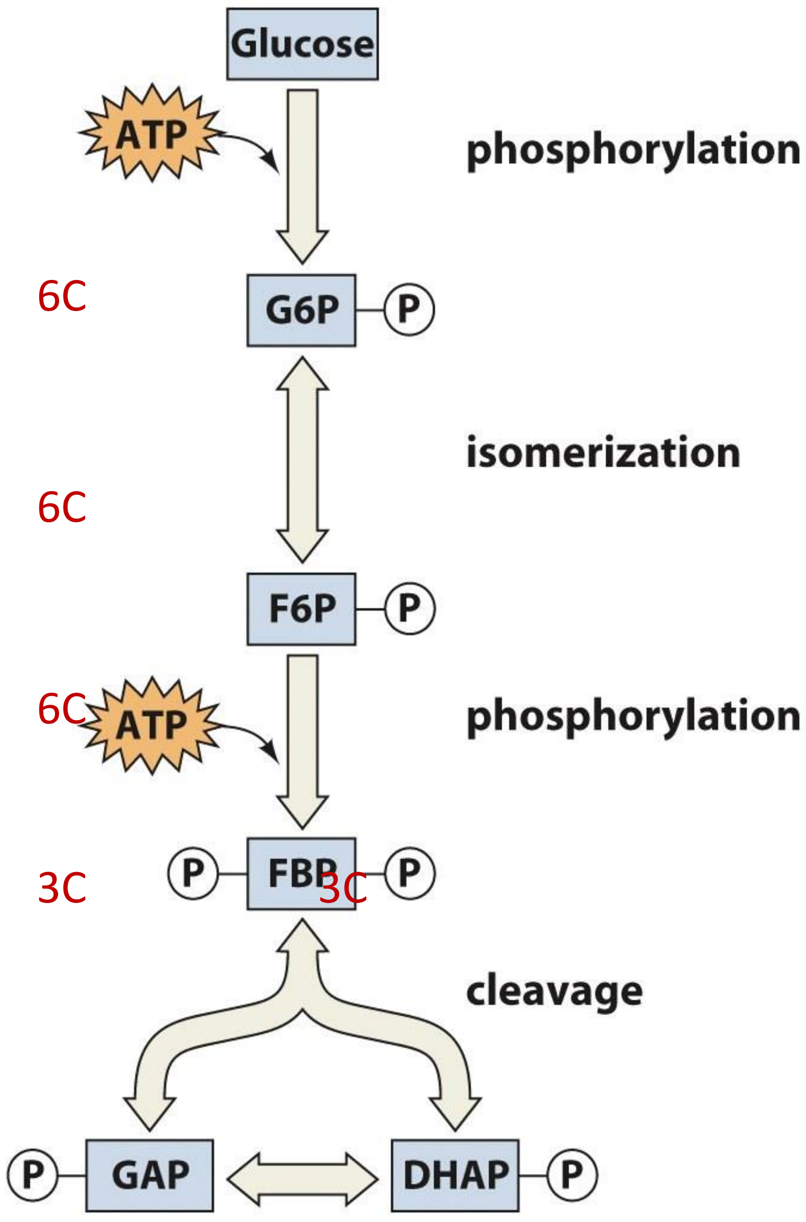


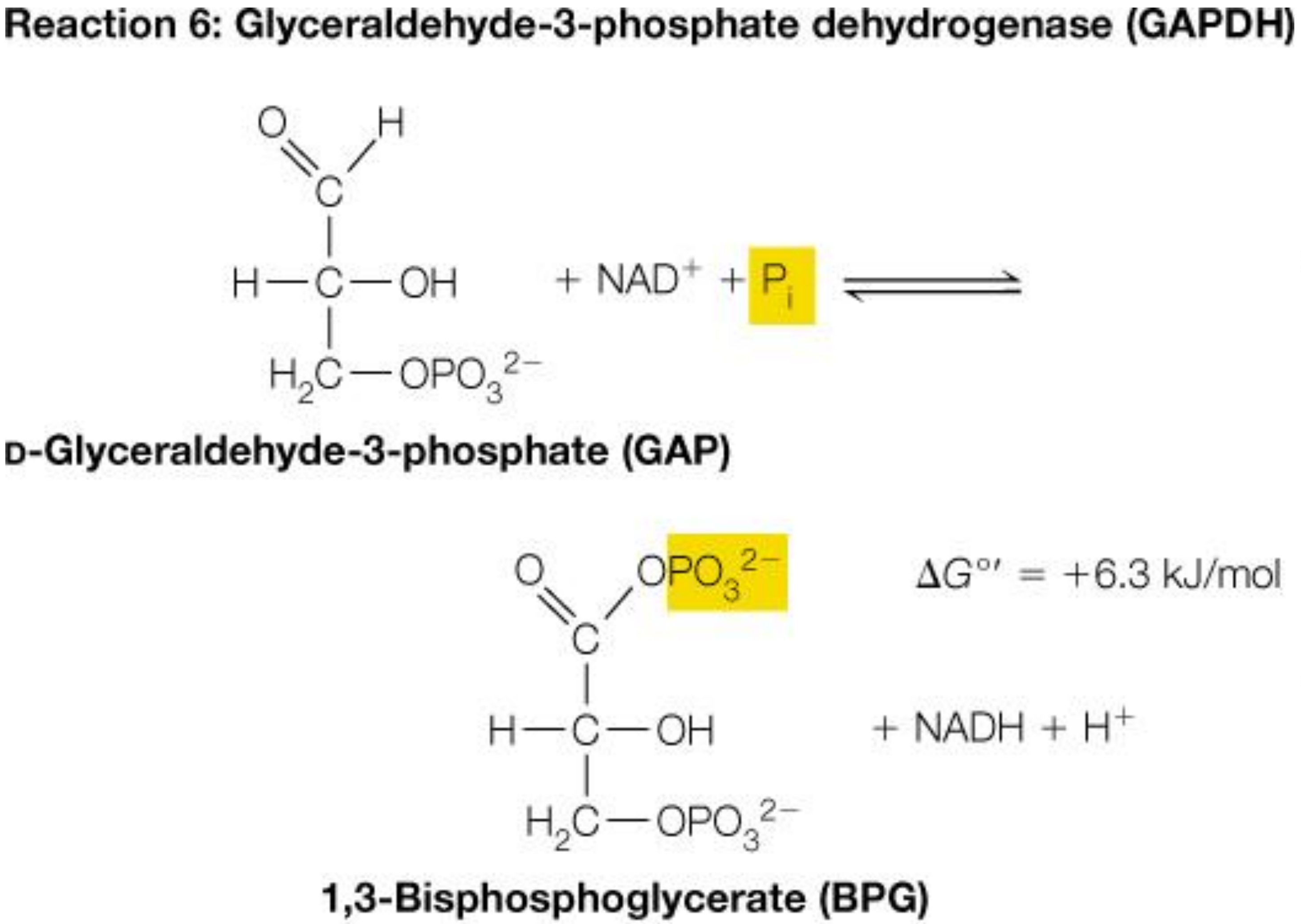
Figure 15-7

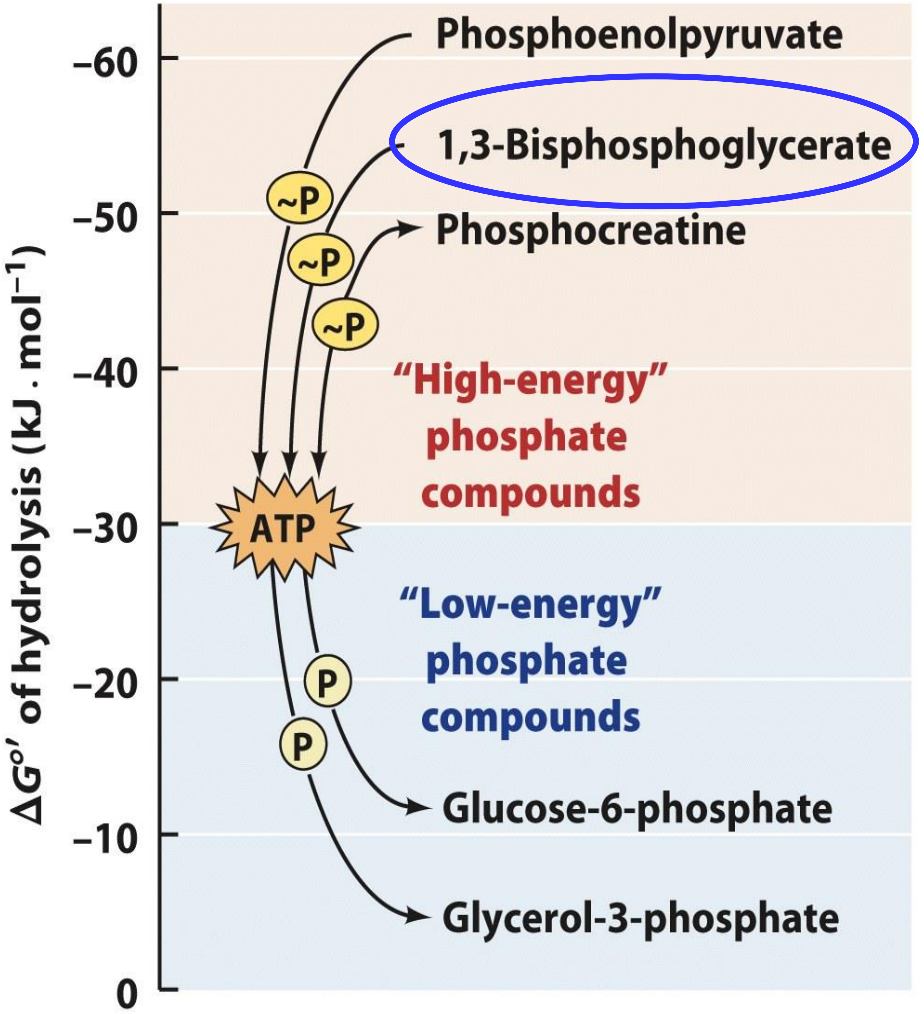
Reaction 6: Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH)

Forms 1st "High-Energy" Intermediate:

GAP required and NADH made

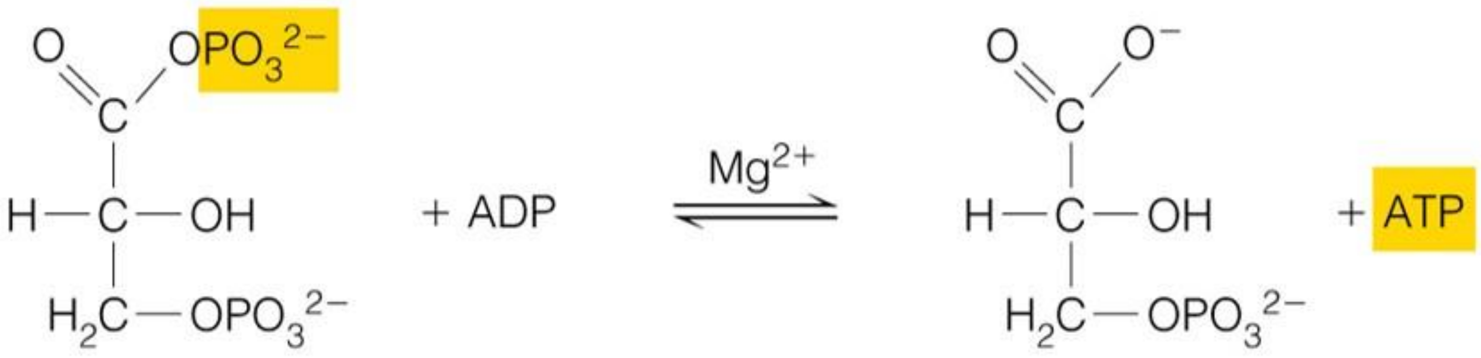
1,3-BPG: 2nd highest!





Reaction 7 – Phosphoglycerate Kinase (PGK)

*This is a **substrate-level phosphorylation**: drives Reaction 6.*

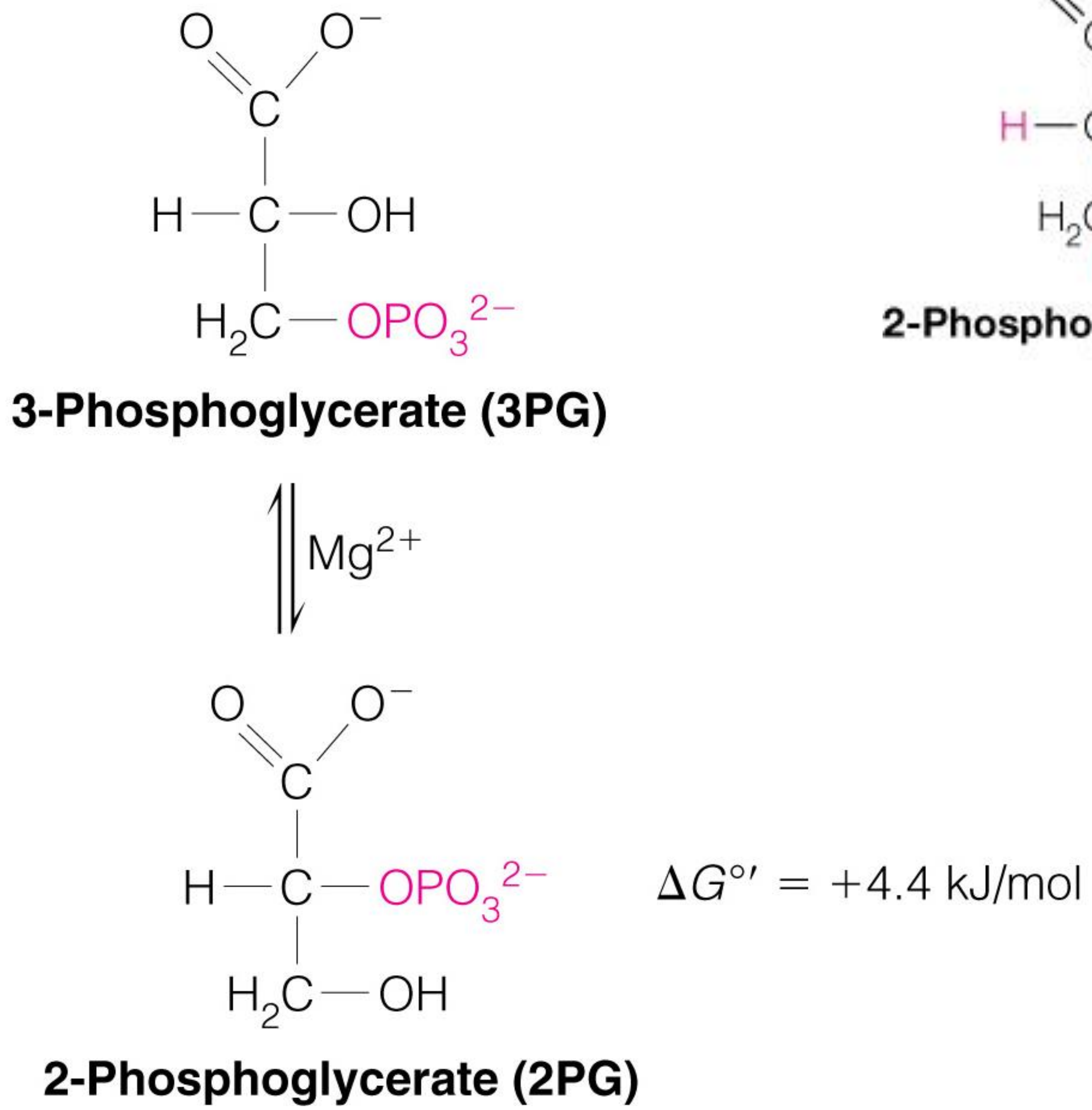


$\Delta G°' = -17.2$ kJ/mol

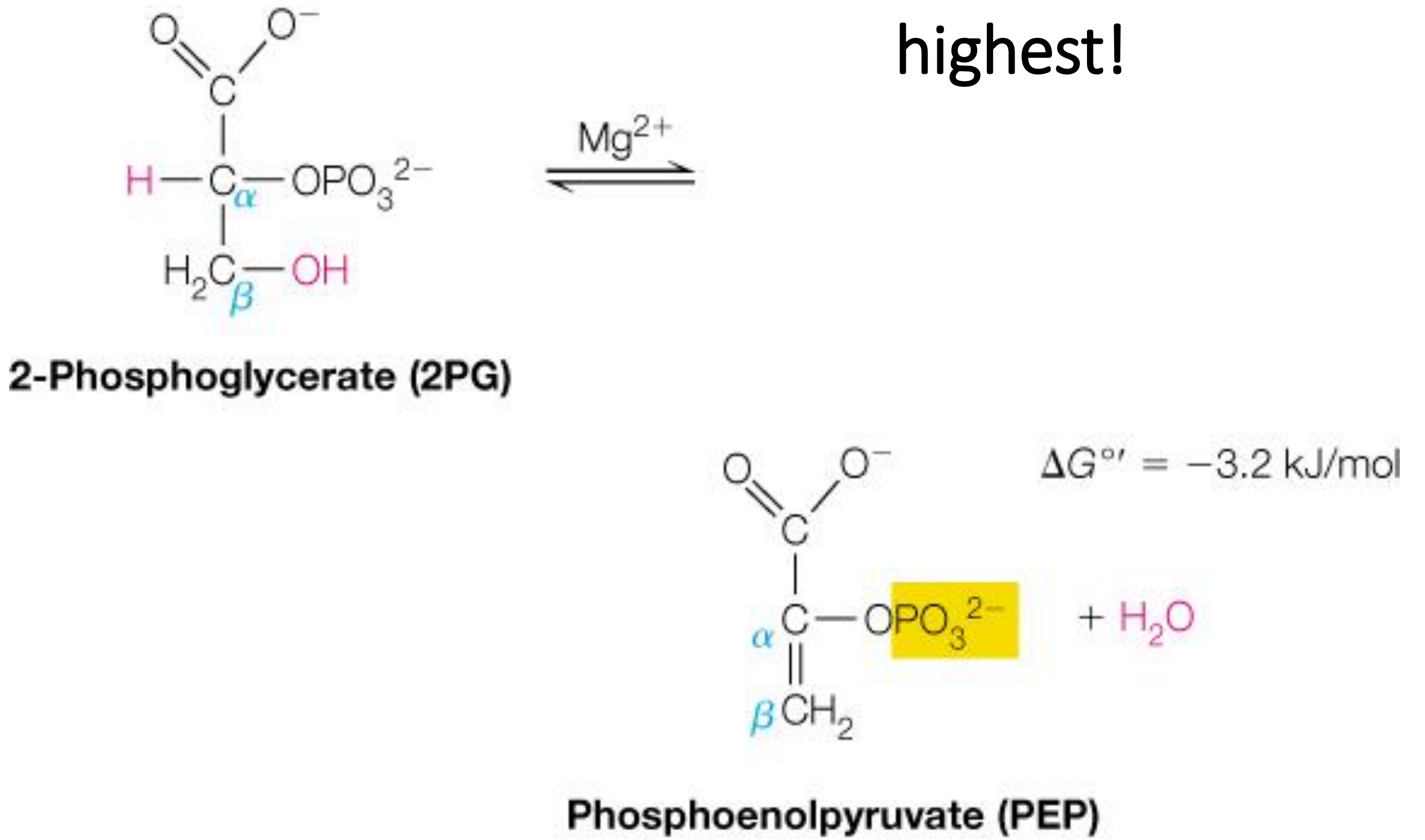
	$\Delta G°'$ (kJ/mol)
glyceraldehyde-3-P + P_i + NAD^+ $\rightarrow$ 1,3-bisphosphoglycerate + NADH + H^+	+ 6.3
1,3-bisphosphoglycerate + ADP $\rightarrow$ 3-phosphoglycerate + ATP	−17.2
glyceraldehyde-3-P + P_i + ADP + NAD^+ $\rightarrow$ 3-phosphoglycerate + ATP + NADH + H^+	$\Delta G°'_{Sum} = -10.9$

The energy of oxidation of an aldehyde to a carboxylic acid is conserved in the form of ATP through these two reactions

Reaction 8: Phosphoglycerate Mutase (PGM): Interconverts 3PG & 2PG



Reaction 9: Enolase Forms 2^{nd} "High-Energy" Intermediate: highest!



This is an α,β-elimination.

The elimination product is H_2O

Reaction 10: Pyruvate Kinase (PK) Generates 2nd ATP!

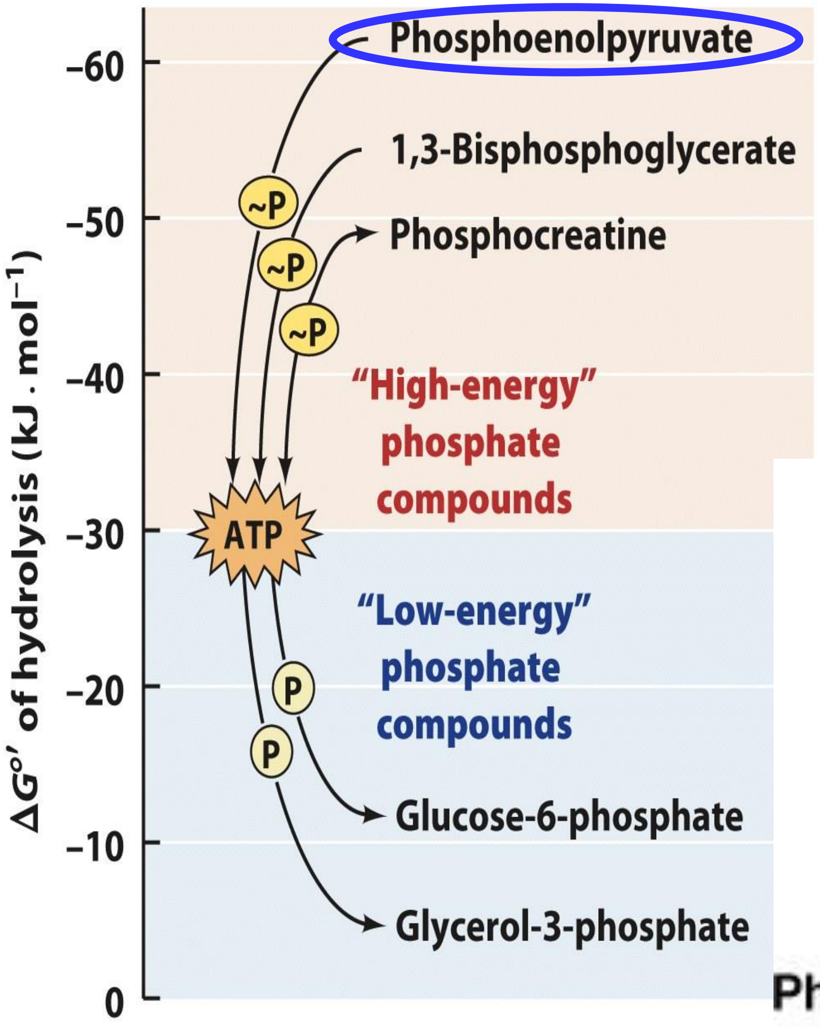
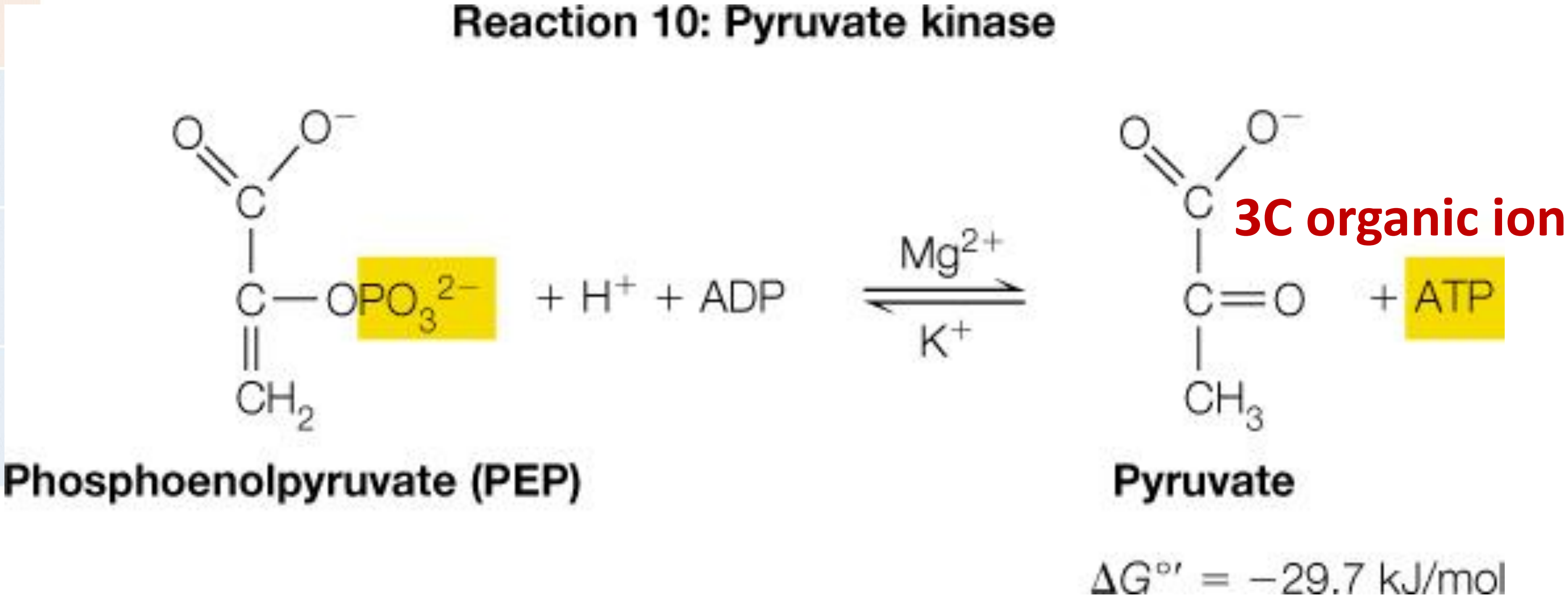


Figure 14-9

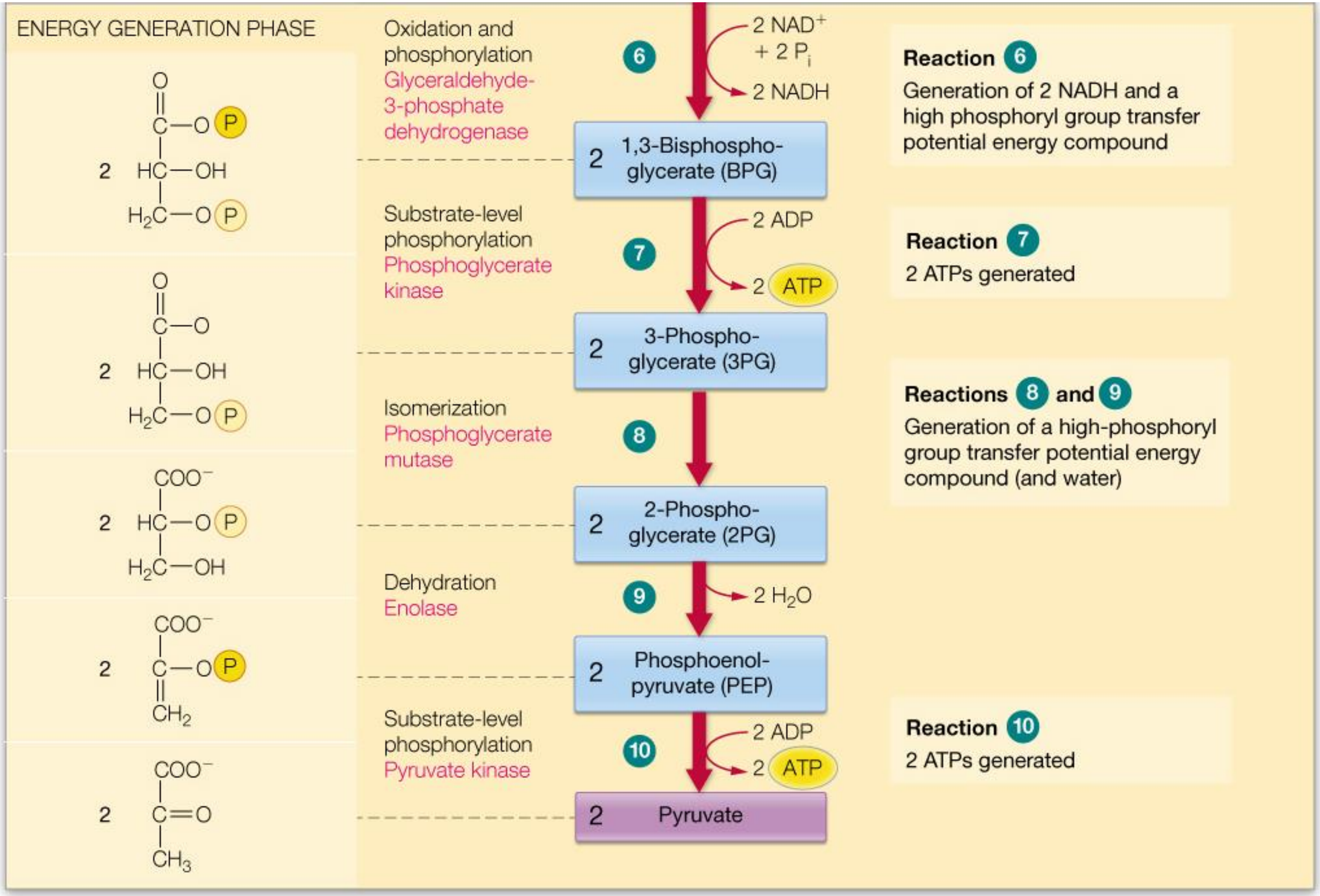
- 2nd glycolytic substrate-level phosphorylation
- Synthesis of ATP is endergonic



- Powered by the spontaneous tautomerization of the enolpyruvate to the more stable keto form (pyruvate)

The Energy-Generation Phase of Glycolysis

4 ATPs and 2 NADHs produced from 2 GAPs



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Second phase and Net result of Glycolysis

From one molecule of glucose (=2 GAPs), we get:

- **2 NADH**
- **2 pyruvates**
- **4 ATPs**

- **Less 2 ATPs used up**
- <u>Overall, **2 ATPs generated**</u>

- NADH produced must be reconverted (by oxidation) to NAD^+ for glycolysis to continue
  - Fermentation or
  - *Electron transport chain (aerobic)*

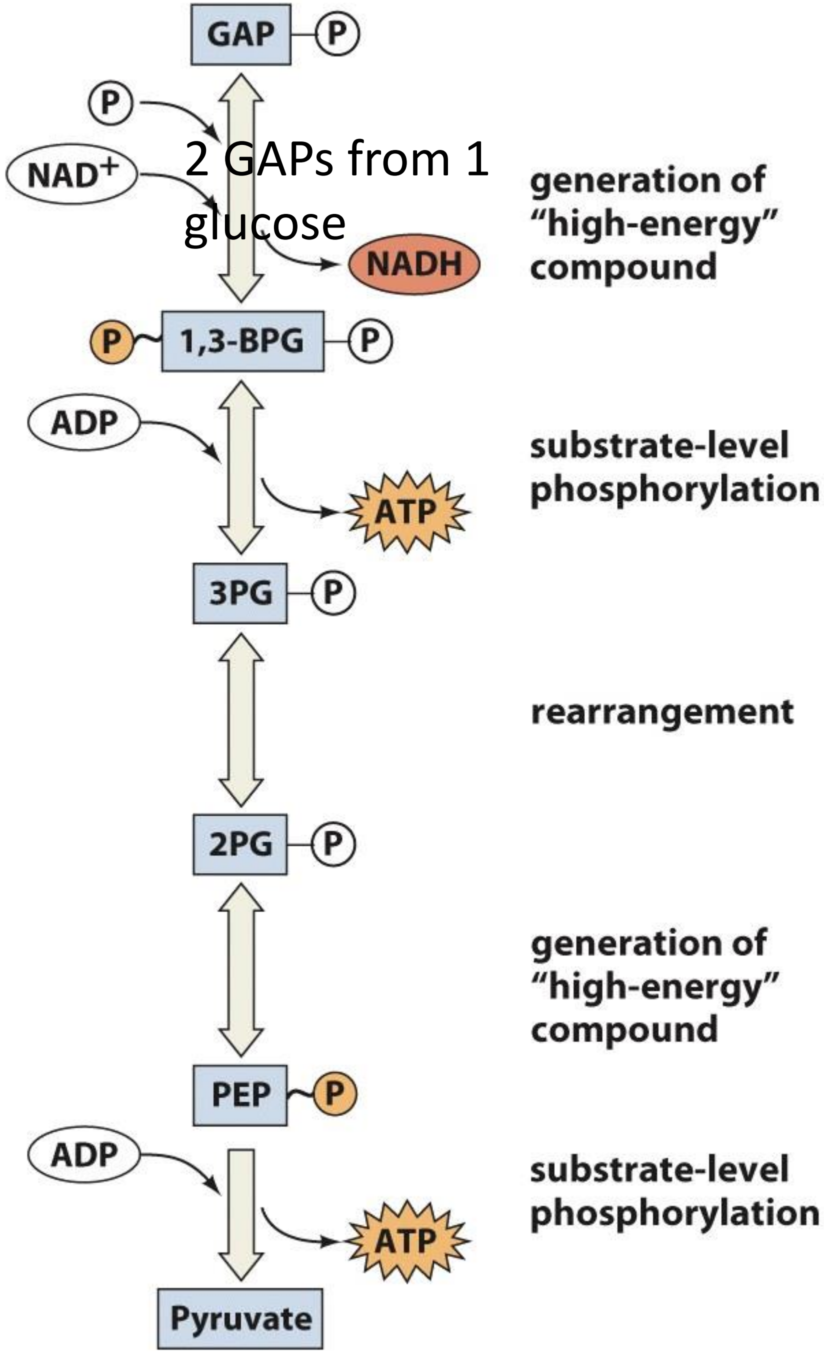

Figure 15-15

Glycolysis summary

- **Glycolysis** involves the breakdown of the 6C sugar, glucose to two 3C organic molecules, pyruvate while using the free energy released in the process to synthesize ATP from ADP and P*i*.
  - Anaerobic
  - Occurs in every cell
  - No CO_2 produced.
- The **10-reaction sequence** of glycolysis is divided into two stages: energy investment and energy generation.
  - Investment phase: 2 ATPs required for pathway activation
  - Generation phase: 4 ATPs and 2 NADHs produced.