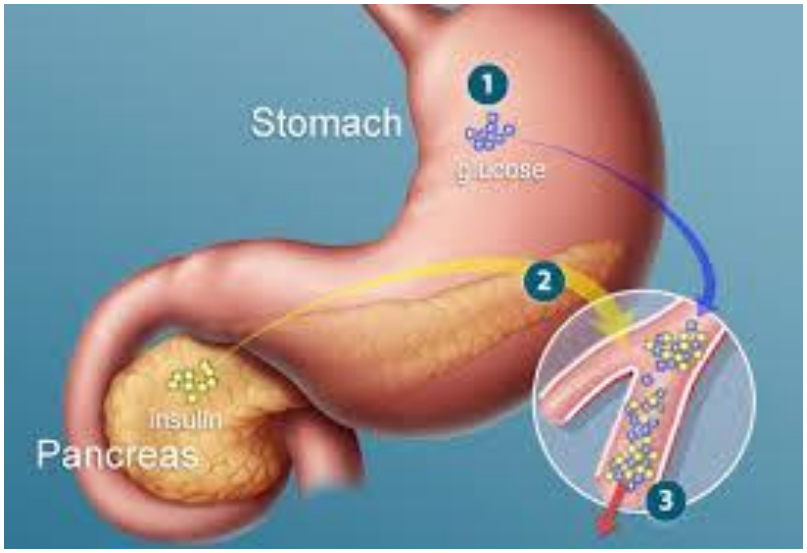
Glycolysis I



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Glucose as Energy Substrate

- To function properly, our cells are in need for energy which can be generated from the metabolism of various biomolecules such as carbohydrates, proteins and lipids
- Actually CHO particularly glucose is a major energy substrate in certain tissues like brain
- What are the metabolic pathways of glucose inside our cells?

sweet spliting

Glycolysis

- Glycolysis is the metabolic pathway which converts glucose (6C) into 2 pyruvate molecules (3C)
- It occurs in the cell cytosol

* بس فيه جزء منها بصير في Mitochondria لأنه إنزيمات بعض الخطوات موجودة في Mitochondria

- Glycolysis takes place in nearly all organisms both aerobic and anaerobic (i.e. microorganisms live in O_2 free environments)

فيها glycolysis is initial metabolic pathway which is followed by kreb cycle , electron transporting chain then complete oxidation of glucose into CO_2 H_2O ATP

بتوفر كمية كبيرة من الطاقة لأنه بصير فيها كل العمليات

مصدر الطاقة الوحيد الها هو glycolysis

بصير حرق كامل للـ glucose في خلايانا

بتوفر كمية قليلة من الطاقة لأنه بصير فيها بس glycolysis

* لا يحتاج لـ O_2 عشان يصير

- Glycolysis is a sequence of ten oxygen-independent and enzyme-catalyzed steps

كل خطوة الها إنزيم معين

* The importance of intermediate

1 كويدنا نحرق سكريات تانية غير glucose لازم يتحول هذا السكر إلى أحد intermediate و بعدين يدخل لـ glycolysis pathway

- The intermediates either provide entry points to the cycle or themselves directly useful (biosynthetic intermediates)

احنا بنشوف بـ (cycle) أول مادة اللي هي glucose وآخر مادة اللي هي (pyruwate)

باقي المواد اللي بالوسط بنسميها intermediates

2 2 different أساسي بين (Link) metabolic pathway

3 has anabolic role

Glycolysis

End result 2 ATP

- The entire pathway is divided into two distinct phases:

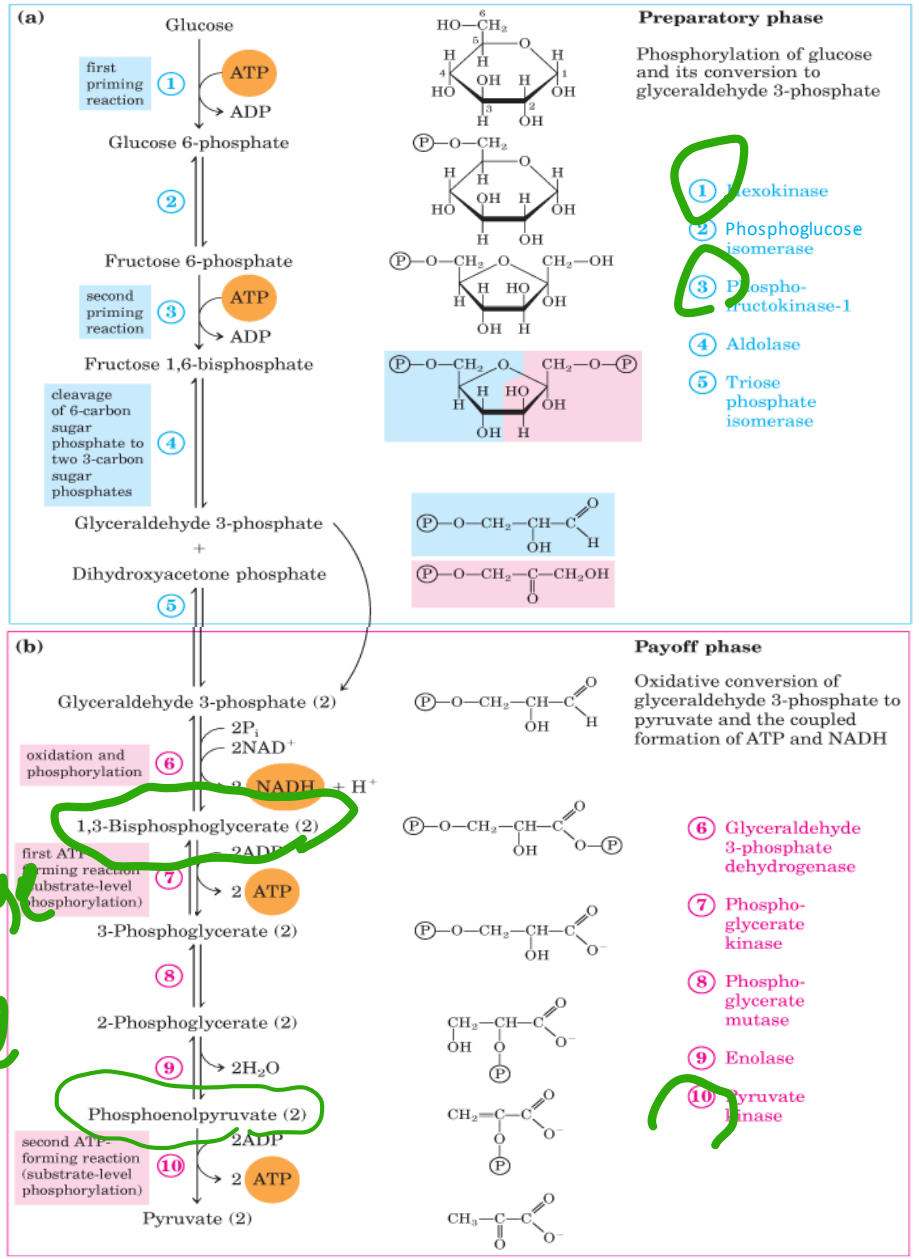
A. Energy Investment Phase
تحضيري
(Preparatory Phase) نستهلك طاقة

5 steps

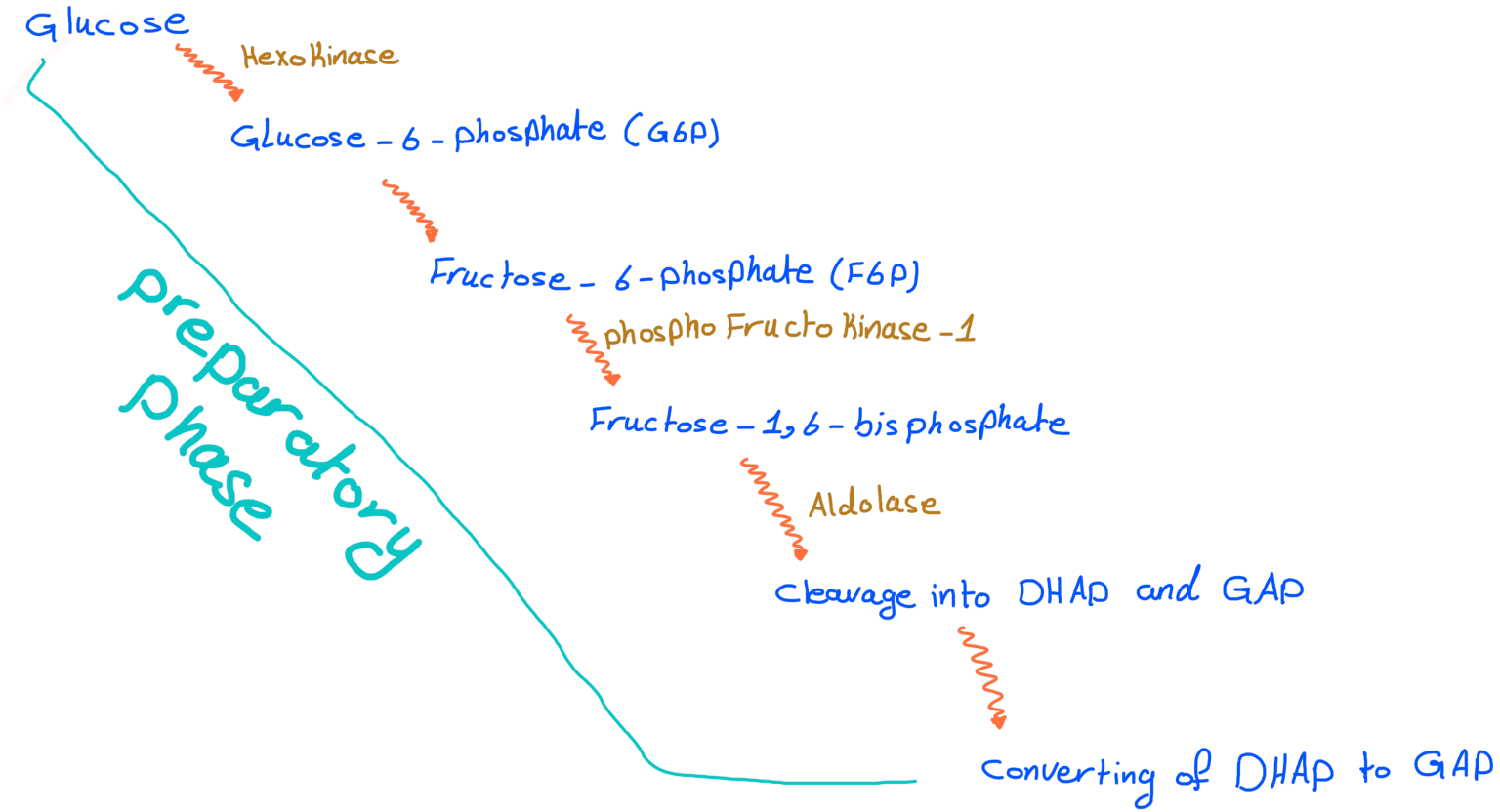
B. Energy Generation Phase

(Pay Off Phase) بنتج طاقة

سداد 5 steps



Substrate high energy molecule



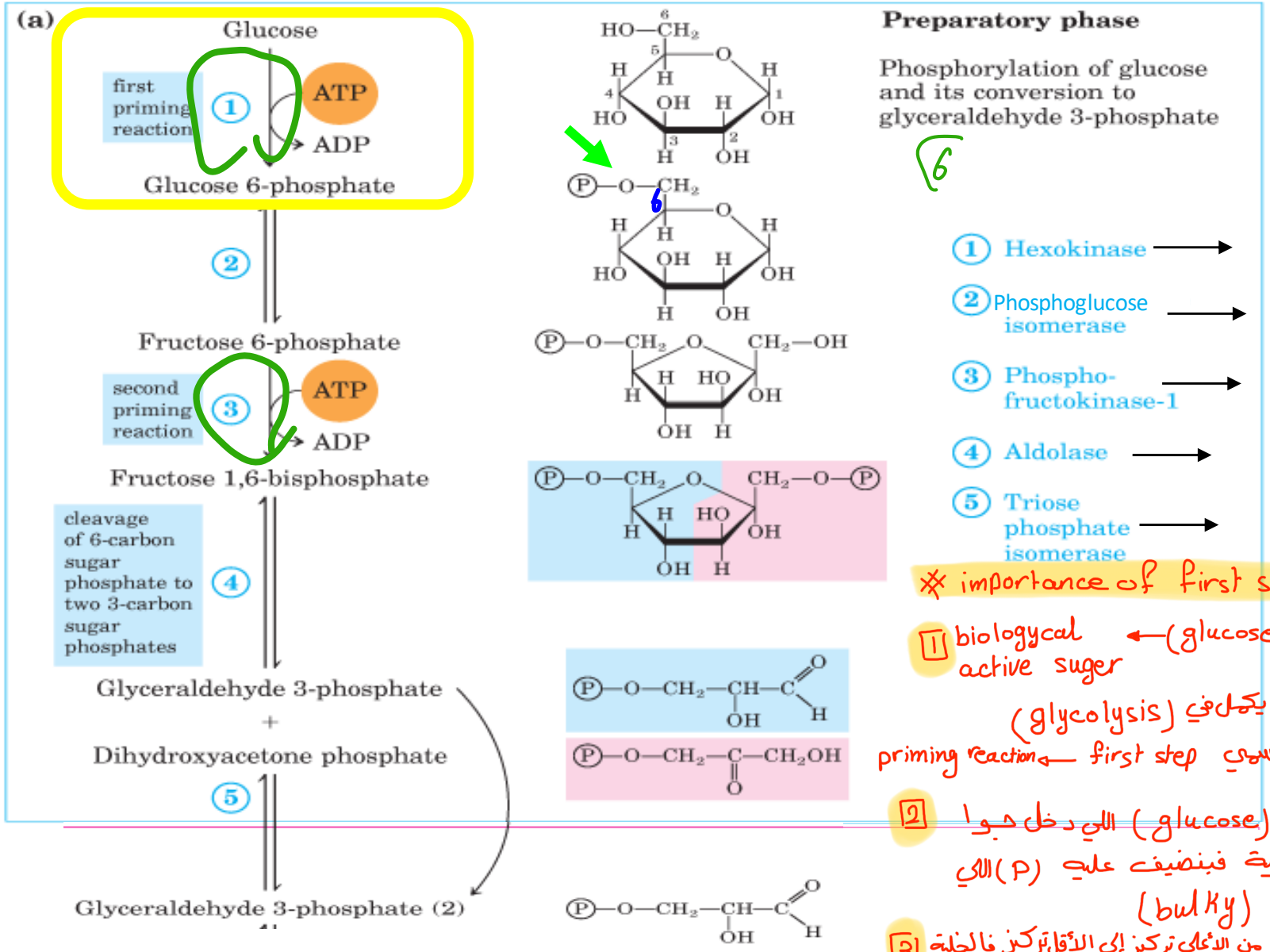
- Kinase : اي تفاعل فيه فوسفات p سواء اضفنا او خذفنا

- Isomerase: اي تفاعل يغير المادة إلى نظيرها mutase: احد انواع isomerase ال

- Aldolase:

- Dehydrogenase : عند ازالة H

A. Preparatory Phase



※ importance of first step

1. biologycal active suger ← (glucose) أخلي الخلية
فيقدر يكمل في (glycolysis)
priming reaction ← first step ليه بنسمي *

2. نحبس (glucose) اللي دخل جوا الخلية فنضيف عليه (P) اللي يخلي (bulky)

3. الانتقال بالعادة يكون من الأعلى تركيز إلى الأقل تركيز فالخلية عند لحظة معينة رح يكون فيها تركيز glucose عالي فيبطل glucose يدخل للخلية ← ليه احنا بنربطه ب (P) عشان نضمن على الخلية ونحكيلها ما فيه (glucose) دخل كليك فيستمر دخول (glucose)

A. Preparatory Phase

- **Step 1:** Hexokinases catalyze the ATP- dependent phosphorylation of glucose to produce glucose-6-phosphate (G6P)
- Hexokinase is a transferase enzyme which phosphorylates hexoses by transferring an inorganic phosphate from ATP usually to hydroxyl O at C6
- Irreversible reaction (another enzyme catalyzes the dephosphorylation, only found in specific tissues). Therefore, it is a target site for cycle regulation
- This first priming reaction is important to maintain the influx of glucose through glucose transporters (GLUTs) and at the same time to trap the transported glucose molecules inside the cell

Hexokinases

- 4 isoforms (isozymes) of hexokinase (I, II, III & IV) which differ in their **location**, **catalysis** and **regulation** thereby, contributing to different pattern of glucose metabolism in different tissues
- Hexokinase I, II & III are nonspecific and can phosphorylate a variety of hexoses (e.g. glucose, fructose, mannose) but type I is involved in **catabolic pathways** like glycolysis whereas type II & III are involved in **anabolic pathways** like glycogenesis
- Hexokinase IV is called glucokinase expressed in liver and pancreatic β-cells. It is specific for D-glucose

Hexokinases

النوع الـ 4

*Km value: the concentration of substrate which permits the enzyme to achive half v-max

العلاقة عكسية

- Glucokinase has low affinity for glucose (high Km value) compared to others (low Km value)
- Therefore, glucokinase in liver is active only at high blood glucose level to accumulate G6P for glycogen synthesis but in the pancreas it acts as glucose sensor to control insulin release from beta cells

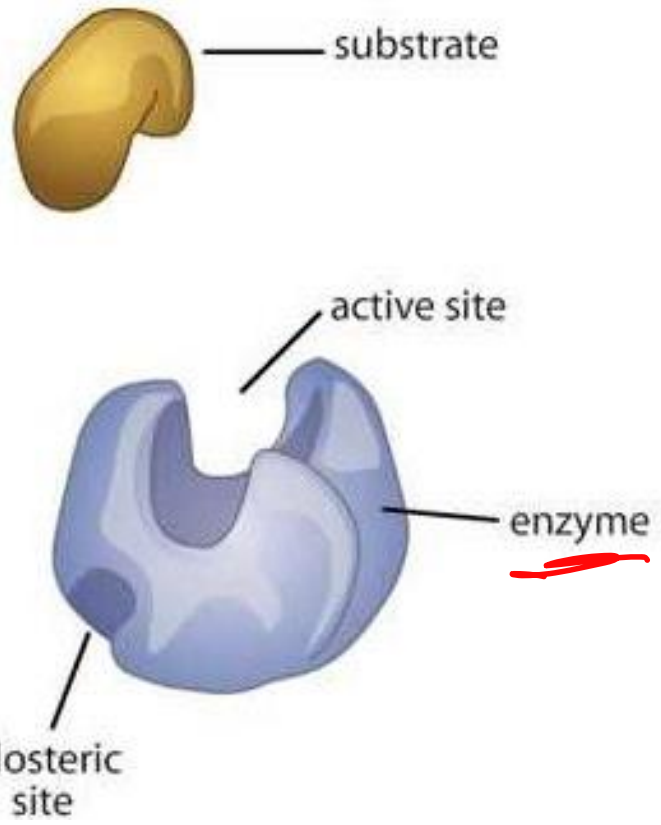
→ glucose in blood عالي بنفرز لما يكون

- Hexokinase isoforms (except isoform IV) are allosterically inhibited by G6P only at high level

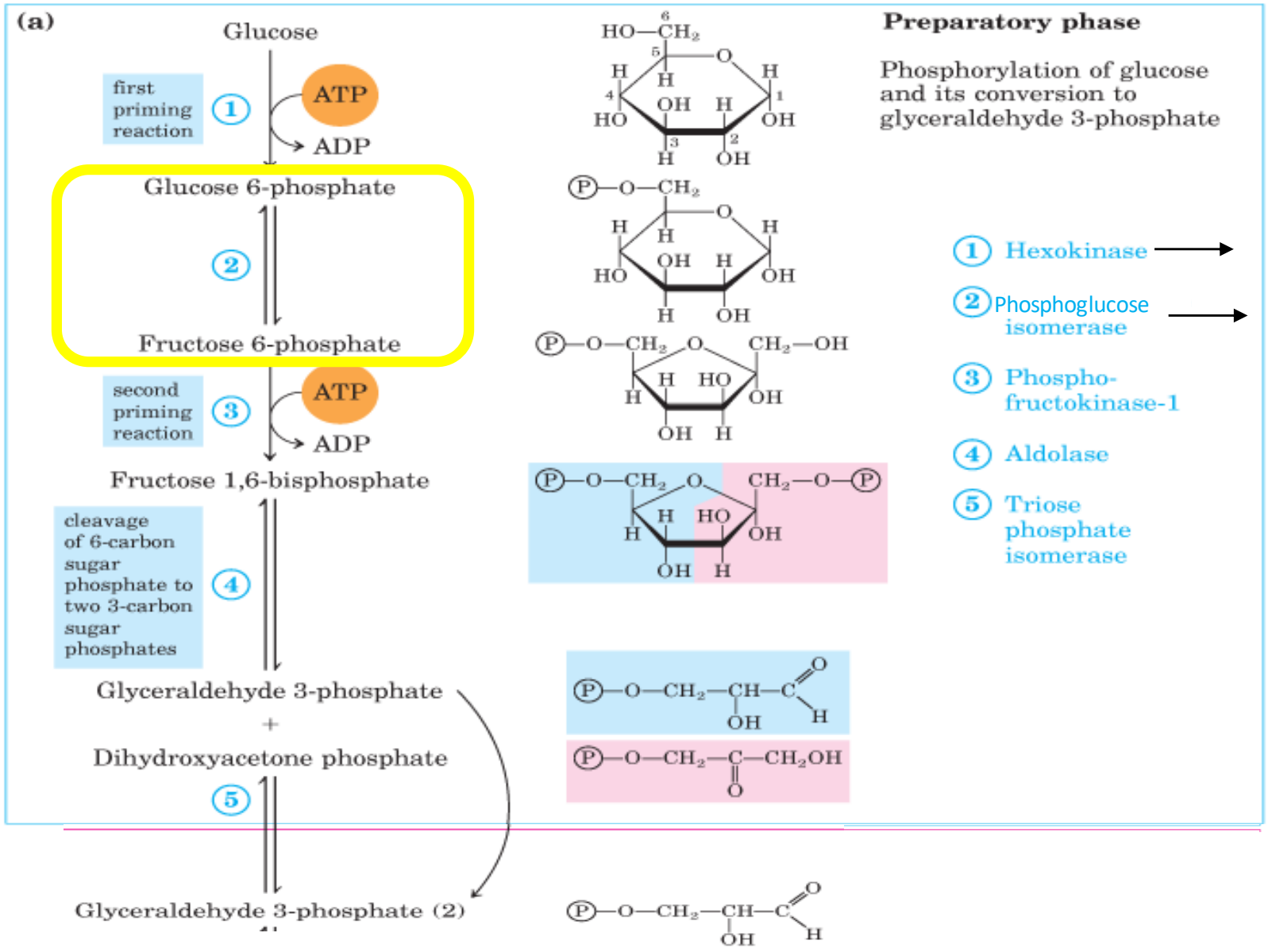
→ inhibitor

Hexokinases

- Hexokinase is an allosteric enzyme with two binding sites: catalytic site (binds substrate) and regulatory site (allosteric site binds effectors)



A. Preparatory Phase

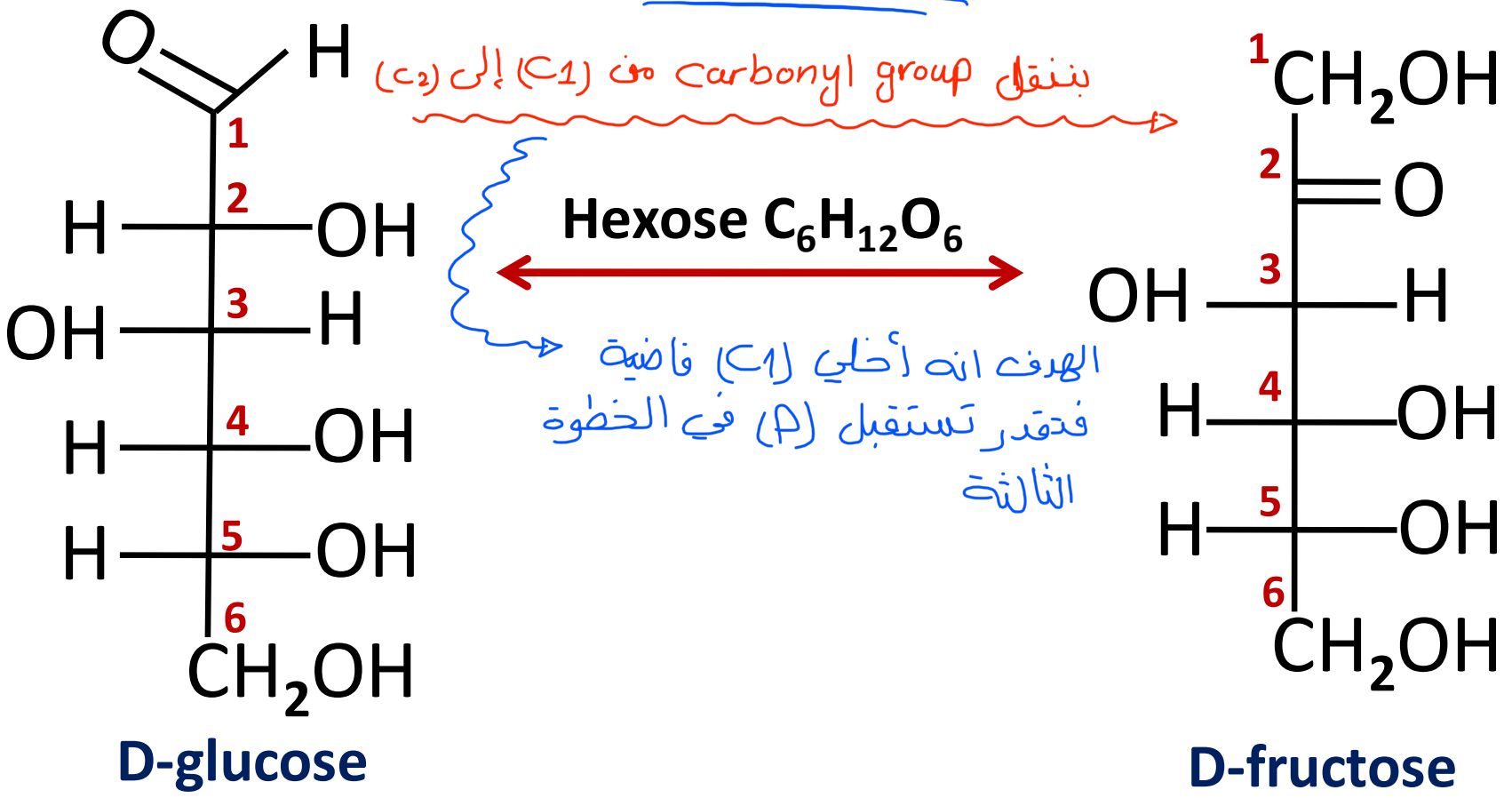


phosphorylation

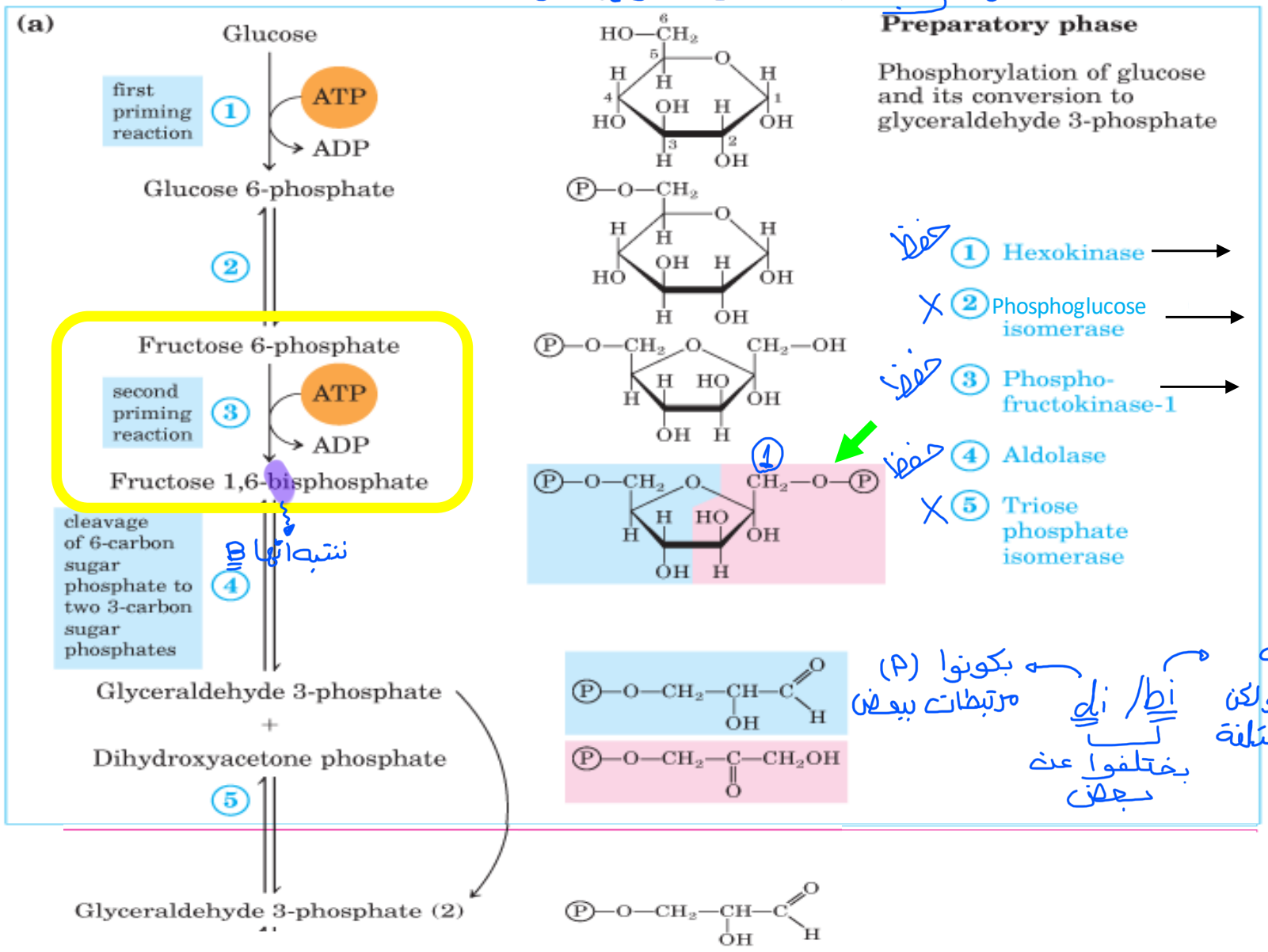
isomerization

A. Preparatory Phase

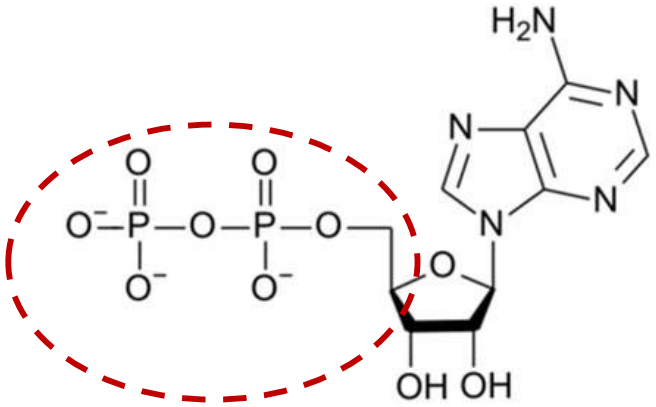
- **Step 2:** Phosphoglucose isomerase (PGI) interconverts G6P and F6P (reversible reaction).
- Indeed, **Mannose and Fructose** can enter the glycolysis pathway at this point



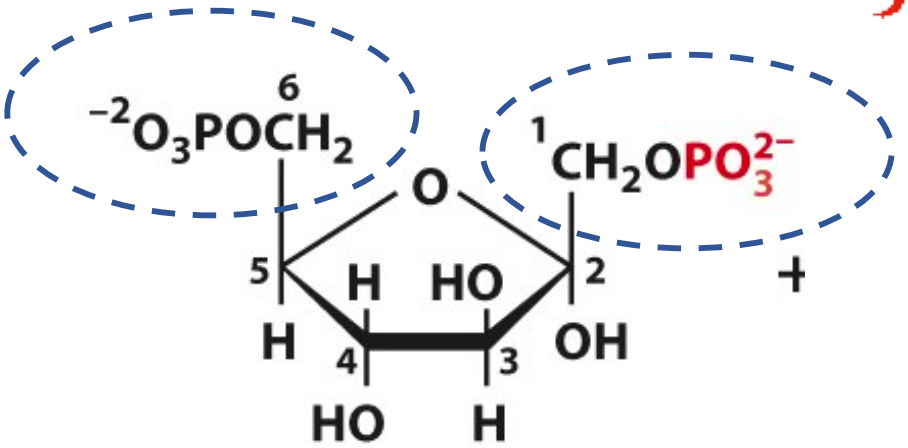
A. Preparatory Phase



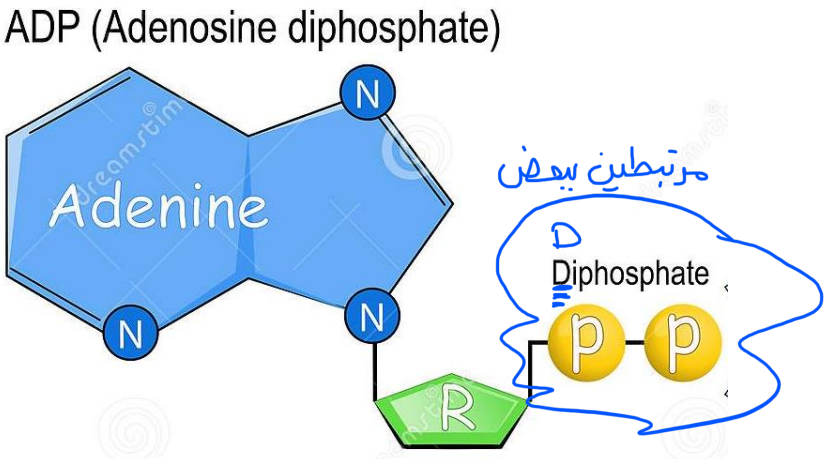
A. Preparatory Phase

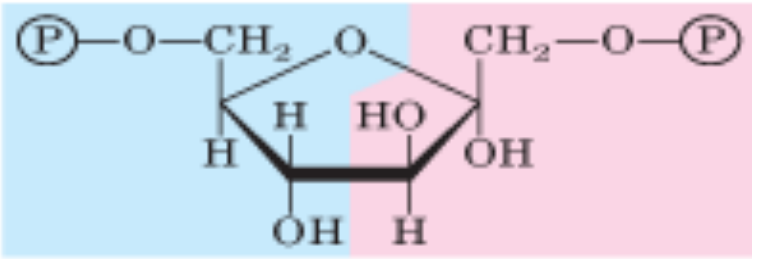


ADP



Fructose 1,6 bisphosphate

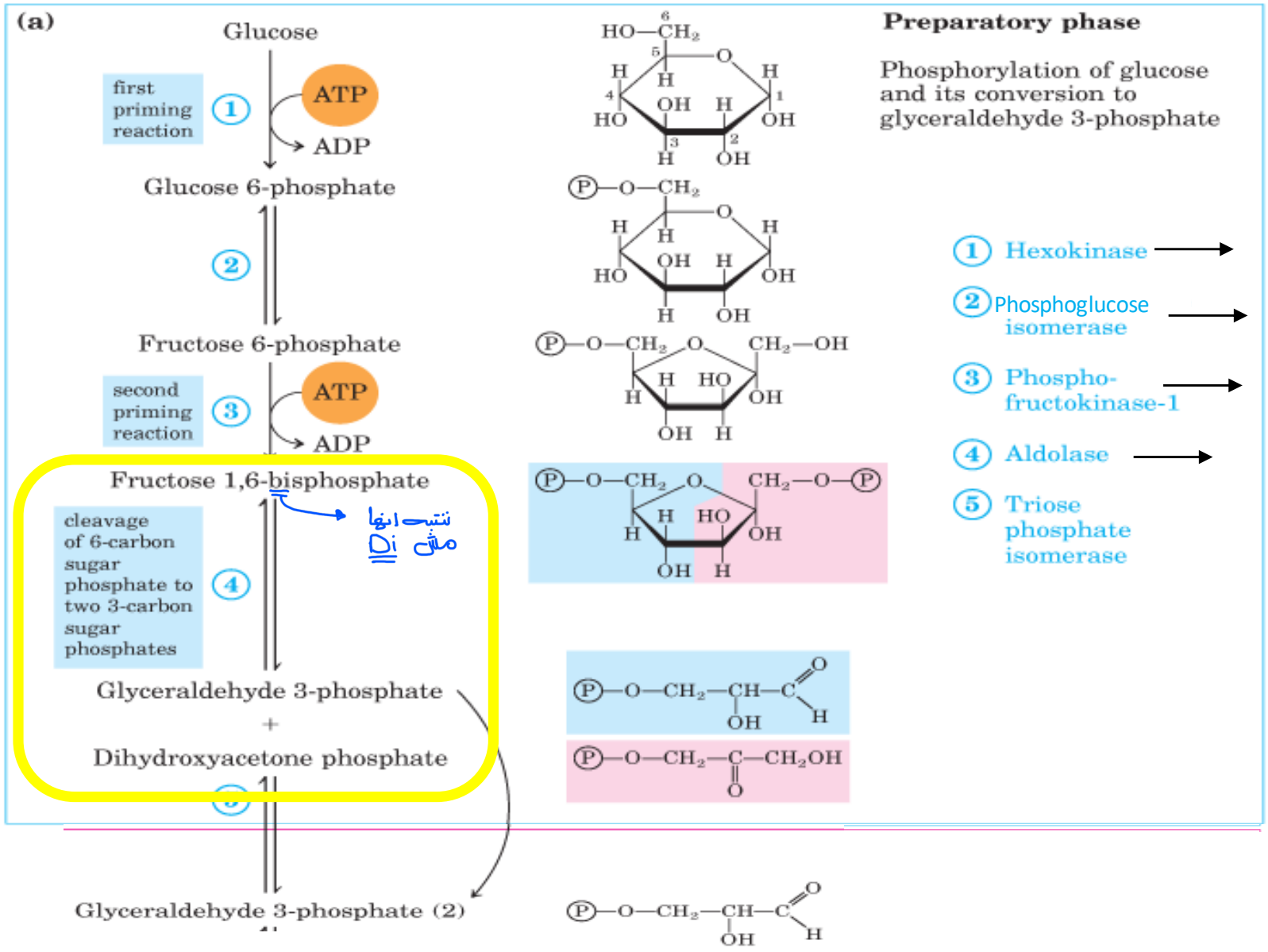




A. Preparatory Phase

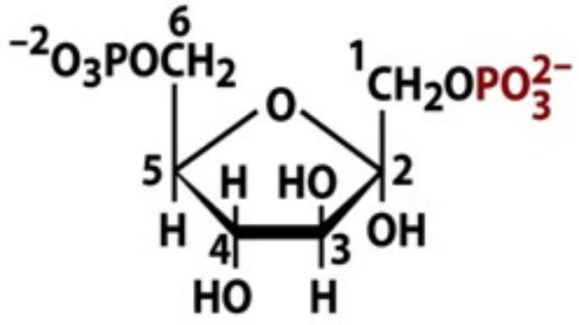
- **Step 3:** This is the rate limiting or key regulatory step. The activity of phosphofructokinase-1 (PFK-1) enzyme can be controlled. PFK-1 catalyzes the phosphorylation of hydroxyl oxygen at C1 to produce **fructose-1,6-bisphosphate**
- **Step 4:** Aldolase enzyme catalyzes the cleavage to two triose phosphates: DHAP (dihydroxyacetone phosphate) and GAP (glyceraldehyde-3-phosphate)
- The addition of the second phosphate group on C1 from the previous step destabilizes the hexose ring and facilitates the cleavage reaction

A. Preparatory Phase



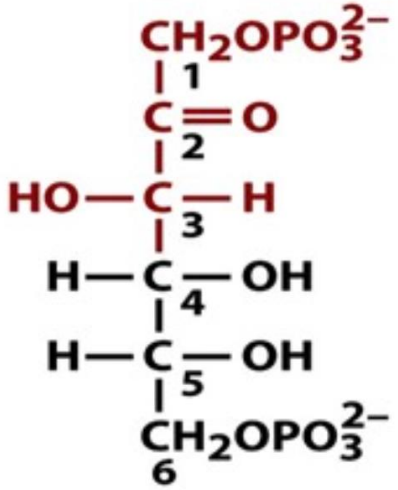
Aldolase Mechanism of Action

Haworth and Fischer Projections Equivalency



Fructose-1,6-bisphosphate (FBP)

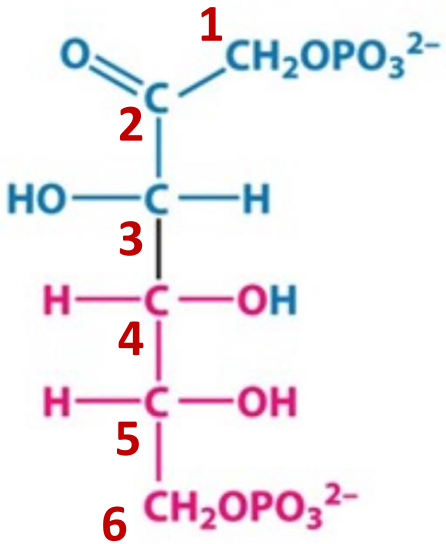
≡



Fructose-1,6-bisphosphate (FBP)

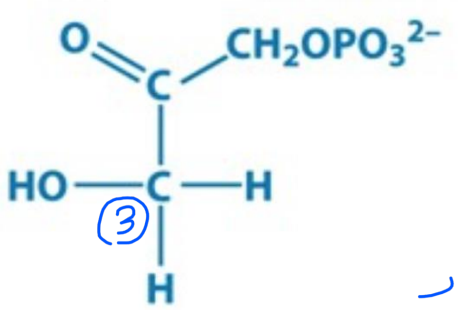
Aldolase Mechanism of Action

Six Carbon Sugar Cleaved to Two Three Carbon Units



Fructose 1,6-bisphosphate (F-1, 6-BP)

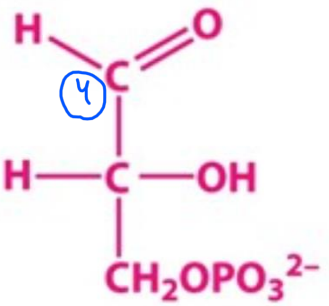
Aldolase



Dihydroxyacetone phosphate (DHAP)

حفظ الاختصار

+



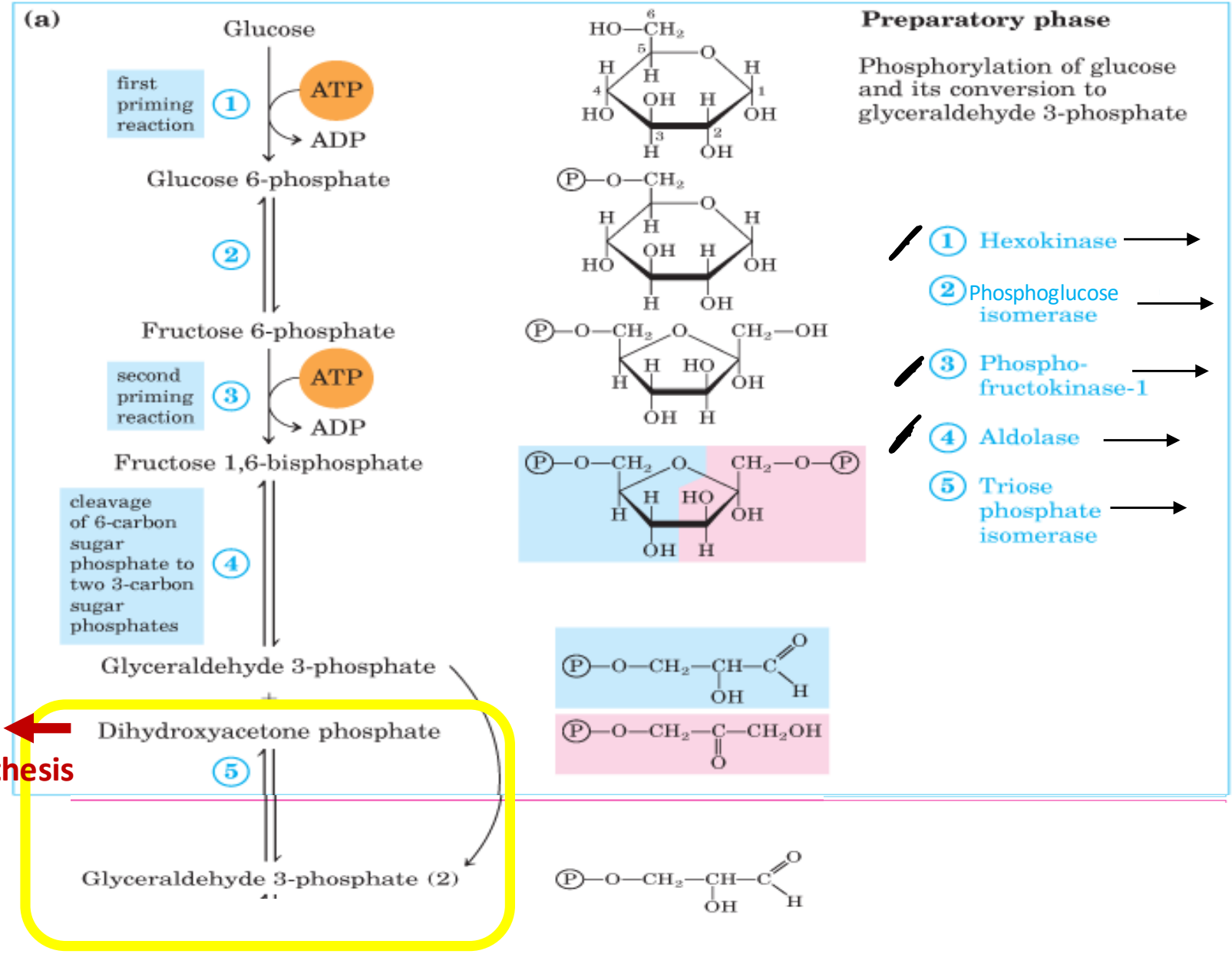
Glyceraldehyde 3-phosphate (GAP)

حفظ الاختصار

What is the bond to be cleaved?

glycosidic bond between $C_3 - C_4$

A. Preparatory Phase



phosphorylation

isomerization

phosphorylation

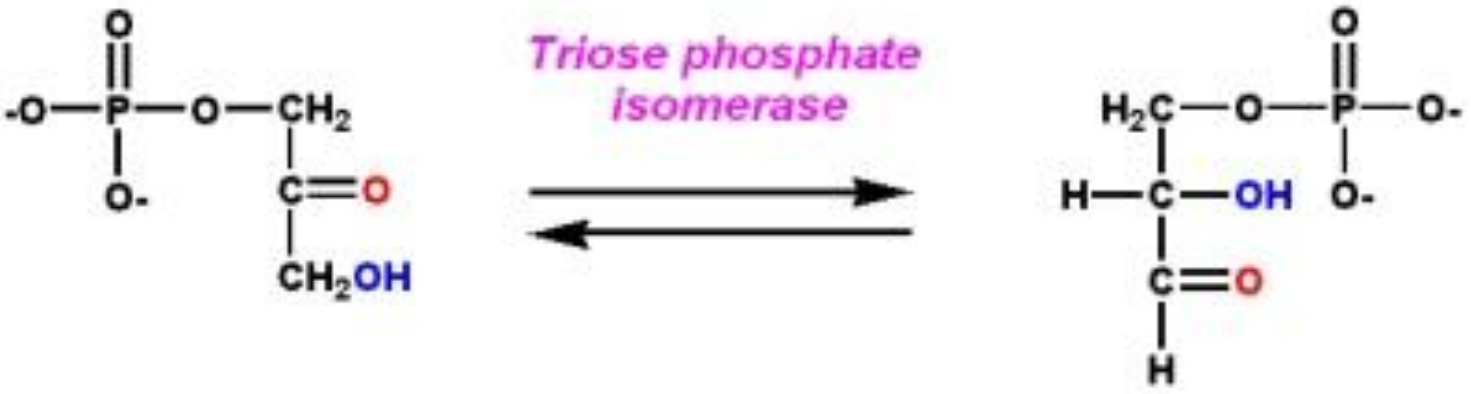
cleavage

isomerization

T.G synthesis

A. Preparatory Phase

- **Step 5:** Isomerization of **DHAP** by triose phosphate isomerase (TPI) to **GAP** to proceed further in glycolysis as GAP is the substrate for the next reaction. This reaction is reversible



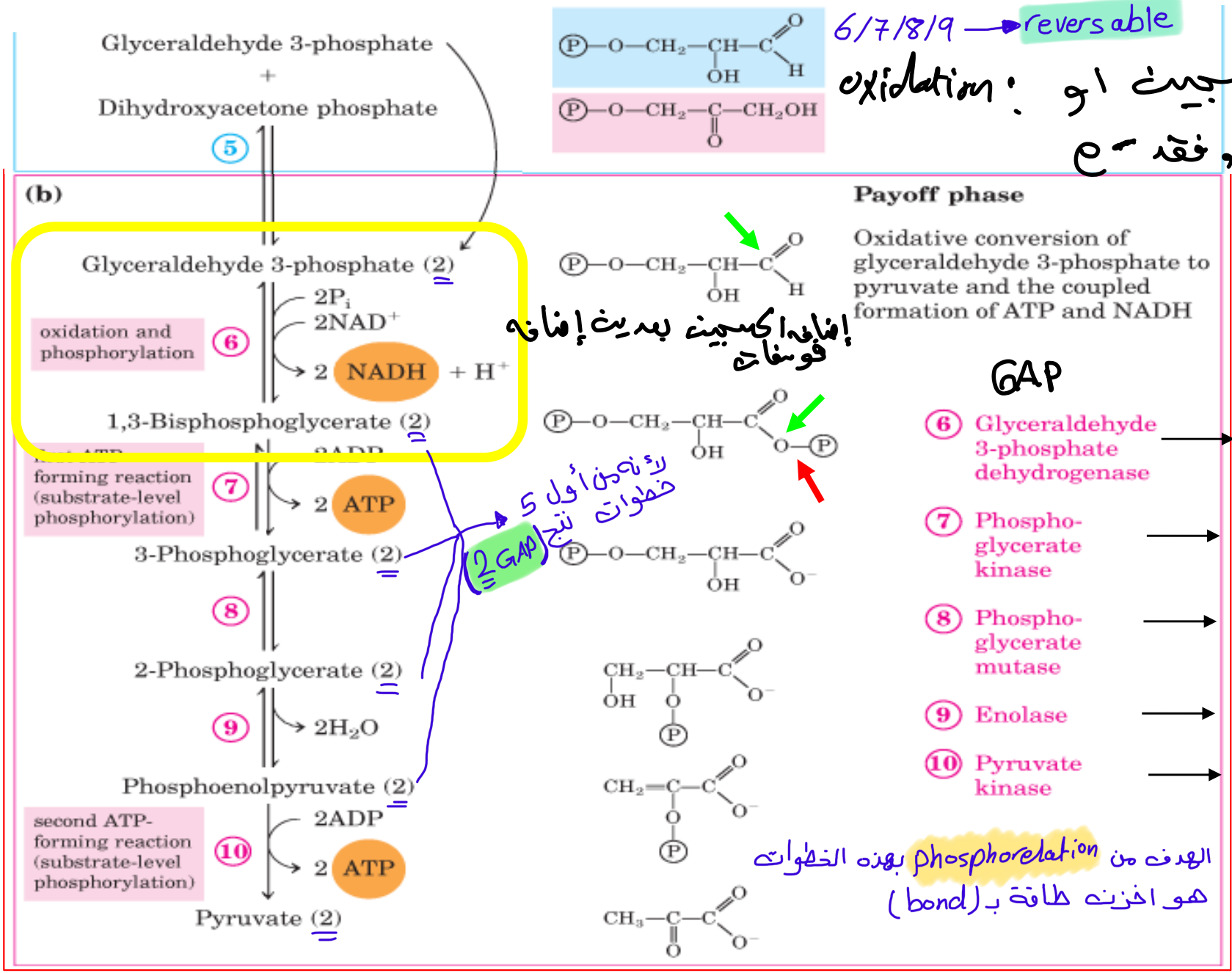
Triacylglycerol صنع

DHAP

Link أول glycolysis بين and Lipid metabolism

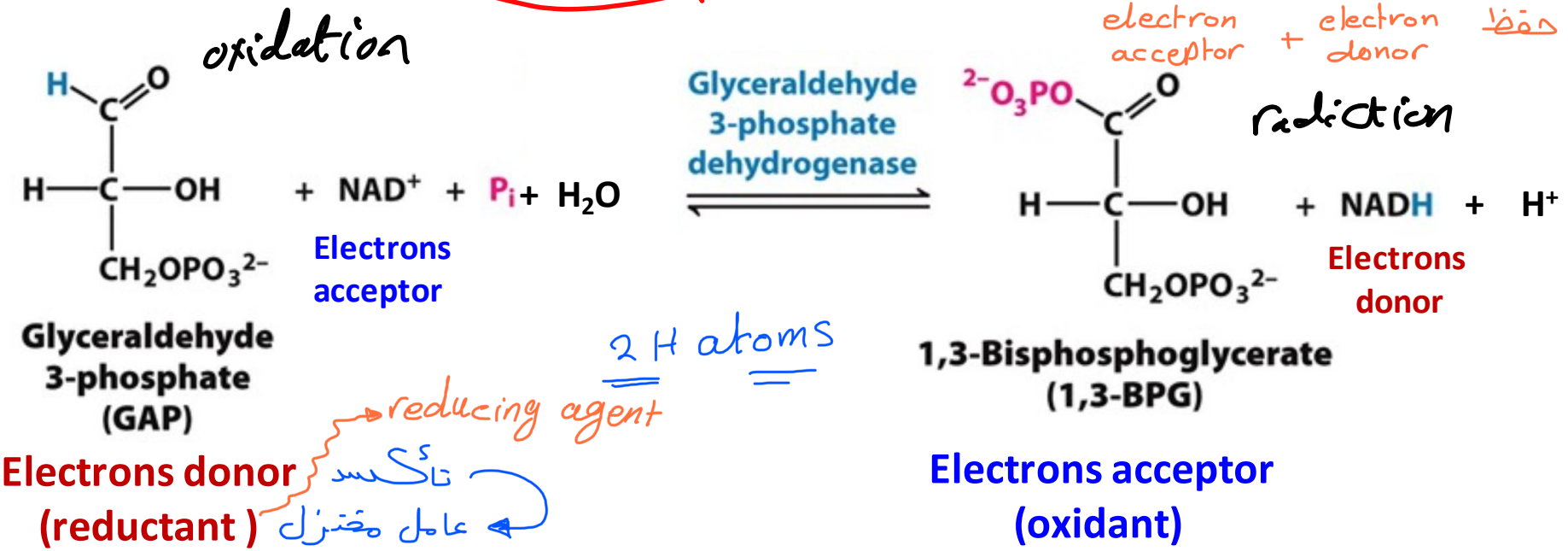
GAP

B. Pay Off Phase



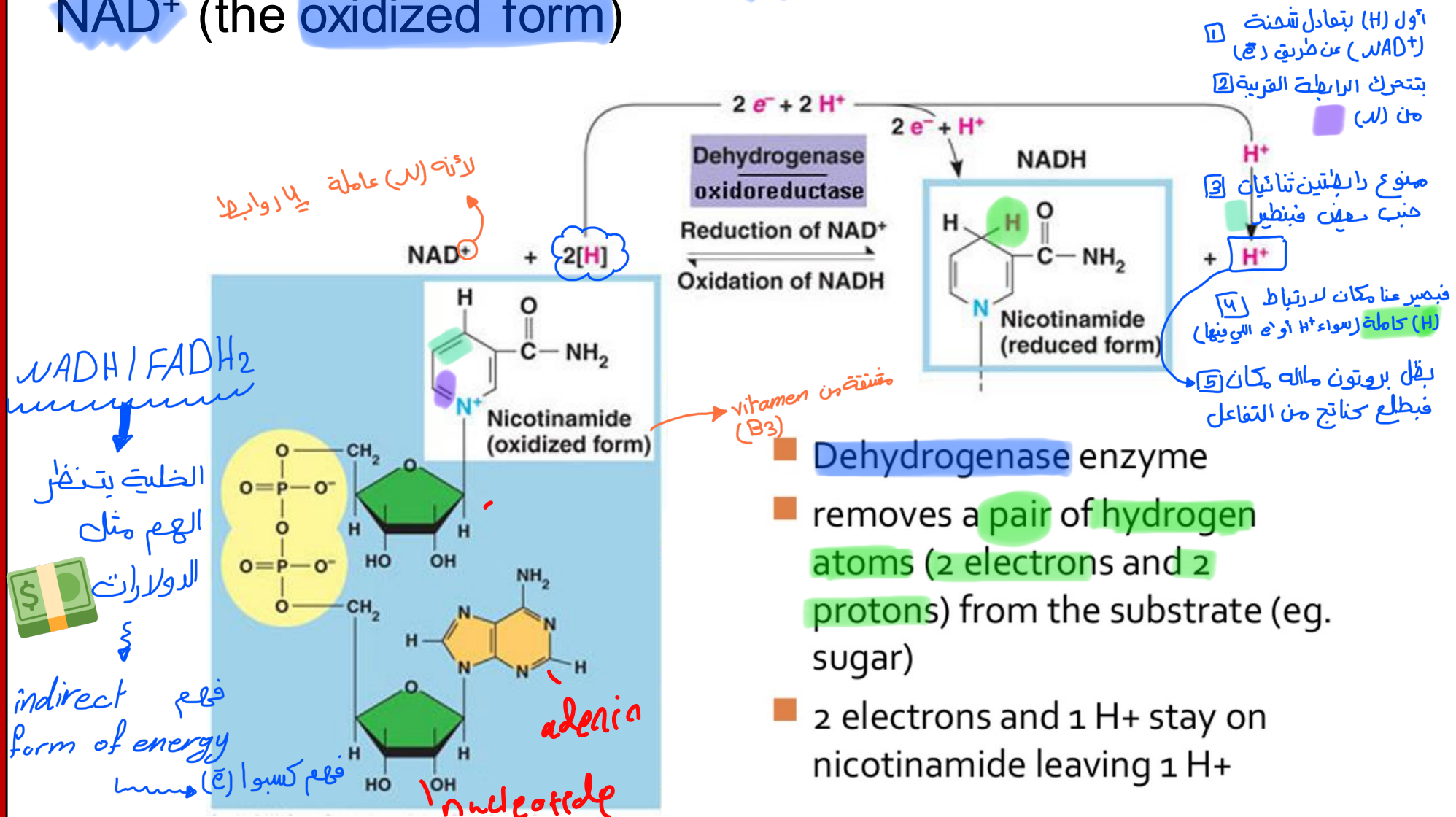
B. Pay Off Phase

- **Step 6**: GAP dehydrogenase enzyme catalyzes the oxidative phosphorylation of GAP (electron donor) into super-high-energy compound (**1,3-BPG**) and the transfer of electrons into the coenzyme NAD^+ (electron acceptor) forming **NADH**
- Dehydrogenases are named as electrons donor substrate -dehydrogenase



Nicotinamide Adenine Dinucleotide

- **NAD (Nicotinamide adenine dinucleotide)** is a coenzyme which exists in two forms: NADH (the reduced form) and NAD^+ (the oxidized form)



- Dehydrogenase enzyme
- removes a pair of hydrogen atoms (2 electrons and 2 protons) from the substrate (eg. sugar)
- 2 electrons and 1 H+ stay on nicotinamide leaving 1 H+

Nicotinamide Adenine Dinucleotide

- **NAD (Nicotinamide adenine dinucleotide)** is a coenzyme of dehydrogenases
- The reduced form NADH is electrons carrier and it is called **energy rich molecule**. It is an indirect form of energy

(أسماء أخرى لـ NADH)

store the energy in electrons

electron transporting على بروح
pathway → 2.5 ATP إلى (ع) بحول

1 NADH = 2.5 ATP

١٤

B. Pay Off Phase

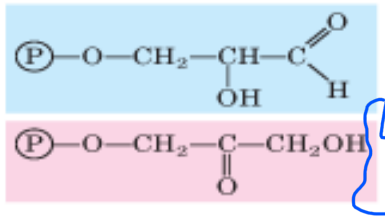
مهم جدًا

*super high energy

① 1,3-bisphosphoglycerate

② phosphoenol pyruvate

بخزنوا الطاقة في Bond



Payoff phase

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

* بأول 2 خطوات استهلكنا 2ATP

* بخطوة (7) أنتجنا 2ATP

فكأنه الخلية ما انتجت طاقة

⑥ Glyceraldehyde 3-phosphate dehydrogenase → Oxidative phosphorylation

⑦ Phospho-glycerate kinase → Substrate-level Phosphorylation

⑧ Phospho-glycerate mutase

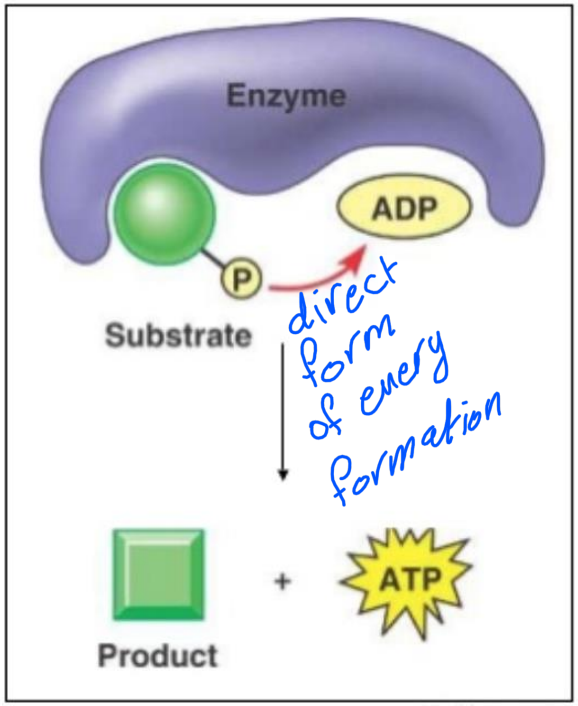
⑨ Enolase

⑩ Pyruvate kinase

B. Pay Off Phase

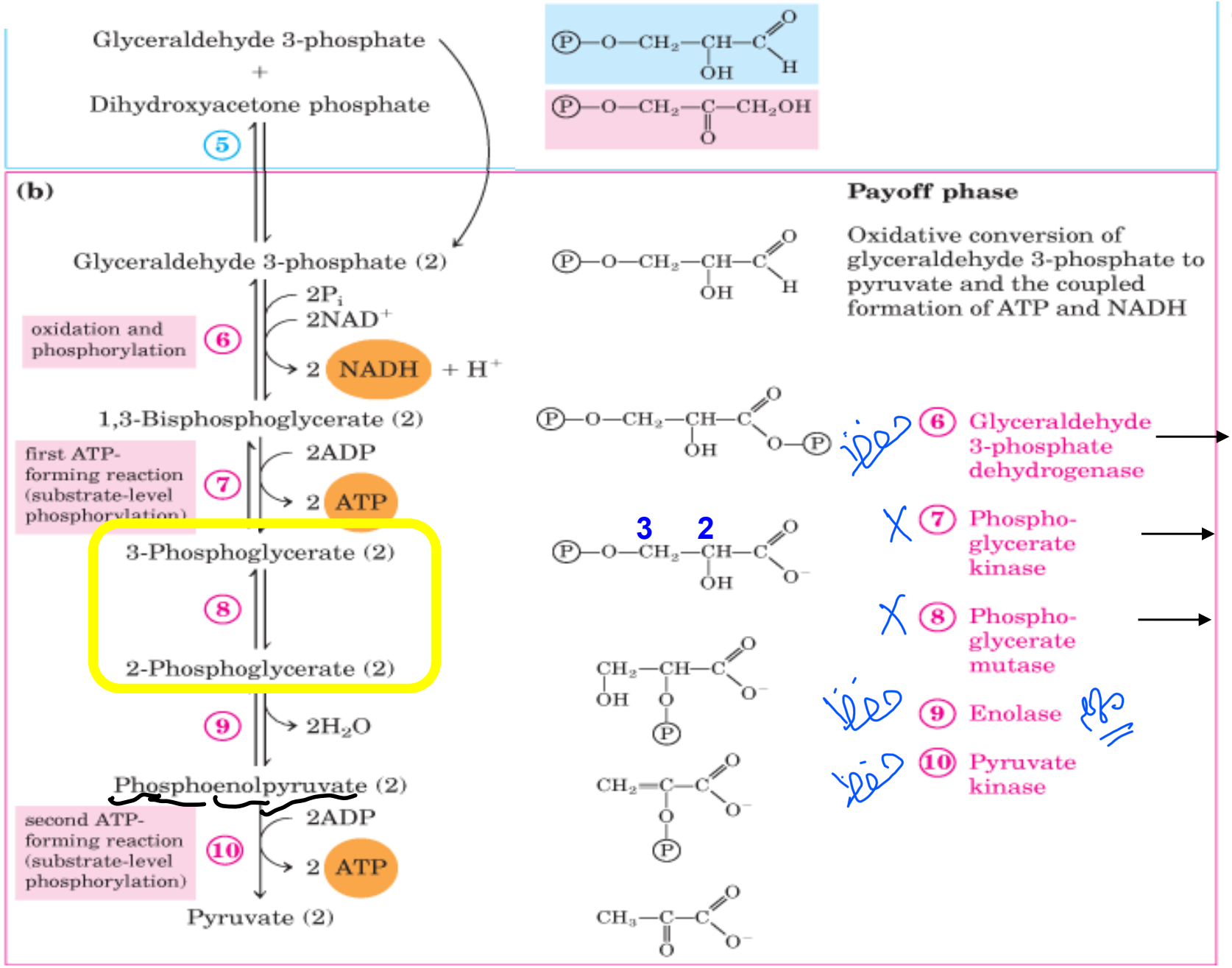
- **Step 7:** The **first ATP** molecule is generated by the substrate-level phosphorylation process catalyzed by phosphoglycerate kinase (PGK)
- 2 ATP molecules will be generated in this step
- Methods of ATP synthesis:

1. Substrate-level phosphorylation: it is a direct method of ATP synthesis by an enzyme which catalyzes the transfer of phosphate group from substrate to ADP
2. Oxidative phosphorylation: indirect method of ATP synthesis in which the oxidation of NADH/FADH2 and the subsequently transferred electrons indirectly drive ATP synthesis from ADP



An enzyme transfers phosphate from substrate to ADP

B. Pay Off Phase

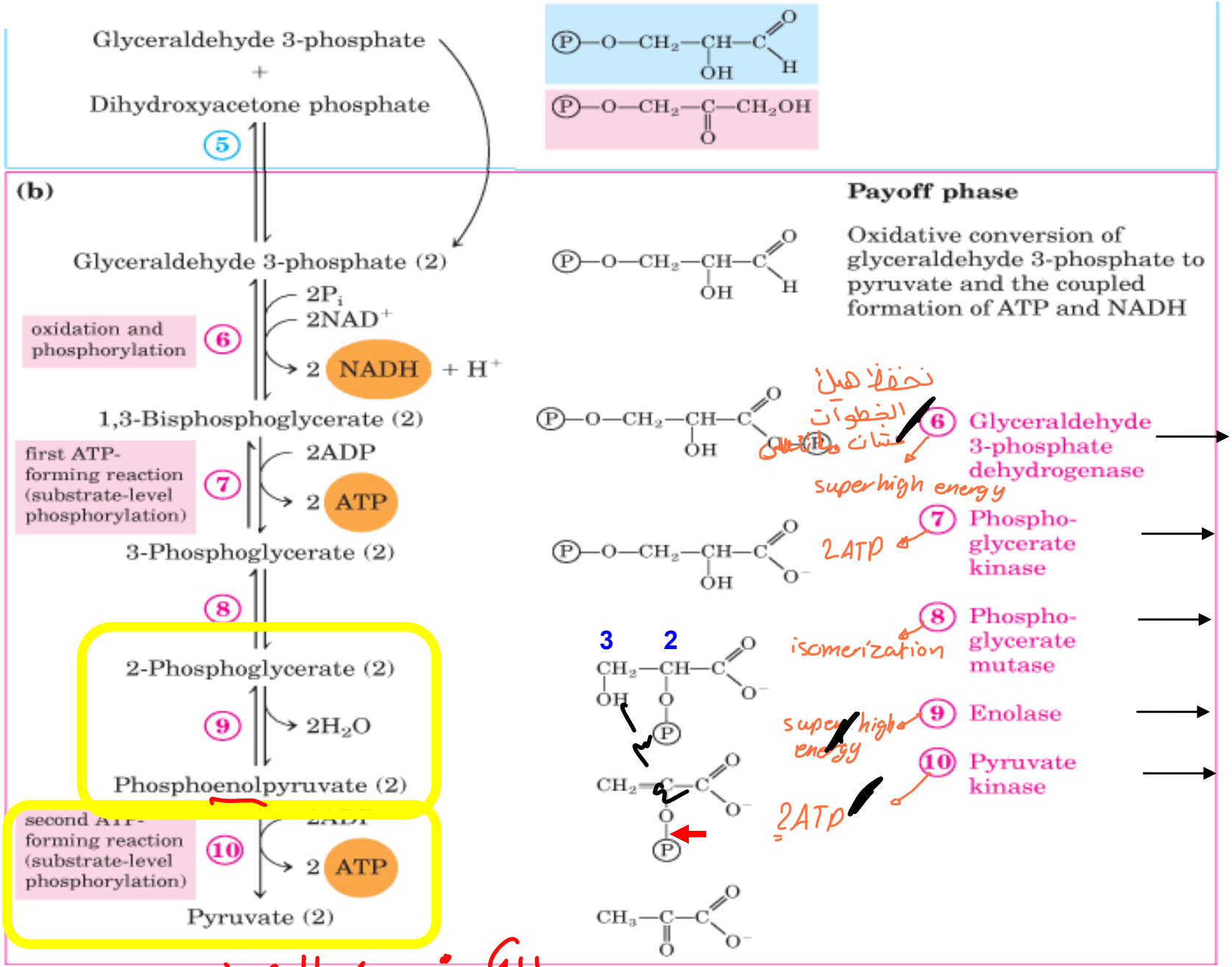


B. Pay Off Phase

- **Step 8:** Phosphoglycerate mutase (PGM) is an isomerase which catalyzes the isomerization of 3-phosphoglycerate to 2-phosphoglycerate
- It is actually an **internal shifting of P** group from C3 to C2 within the same molecule
- The main purpose of this step is the activation of the phosphate group to prepare for the generation of the second ATP in the next reactions
- **Step 9:** The synthesis of the second super-high-energy compound **phosphoenolpyruvate (PEP)** in a simple dehydration reaction catalyzed by enolase enzyme
- Enolase acts by catalyzing the cleavage of bond between C3 and oxygen of OH group thus enhancing the formation of double bond between C3 & C2 and subsequently H atom elimination from C2

بنزيد الطاقة في ضعاف

B. Pay Off Phase



B. Pay Off Phase

- The aim of this step is to increase the energy stored in the phosphate bond
- **Step 10:** The **second ATP** molecule is generated by the substrate-level phosphorylation process catalyzed by pyruvate kinase (PK). Pyruvate is the final product of glycolysis
- The activity of pyruvate kinase can be controlled (irreversible reaction) so this reaction is regulatory step
- The net result of glycolysis is the formation of:

  2 pyruvate

  2 ATP] Net — direct form

  2 NADH — indirect form of energy