

The Glycolysis Metabolic Pathway and Biochemistry

Erich R. Kuechler
Student Lecture Seminar
E-mail
Office Hours

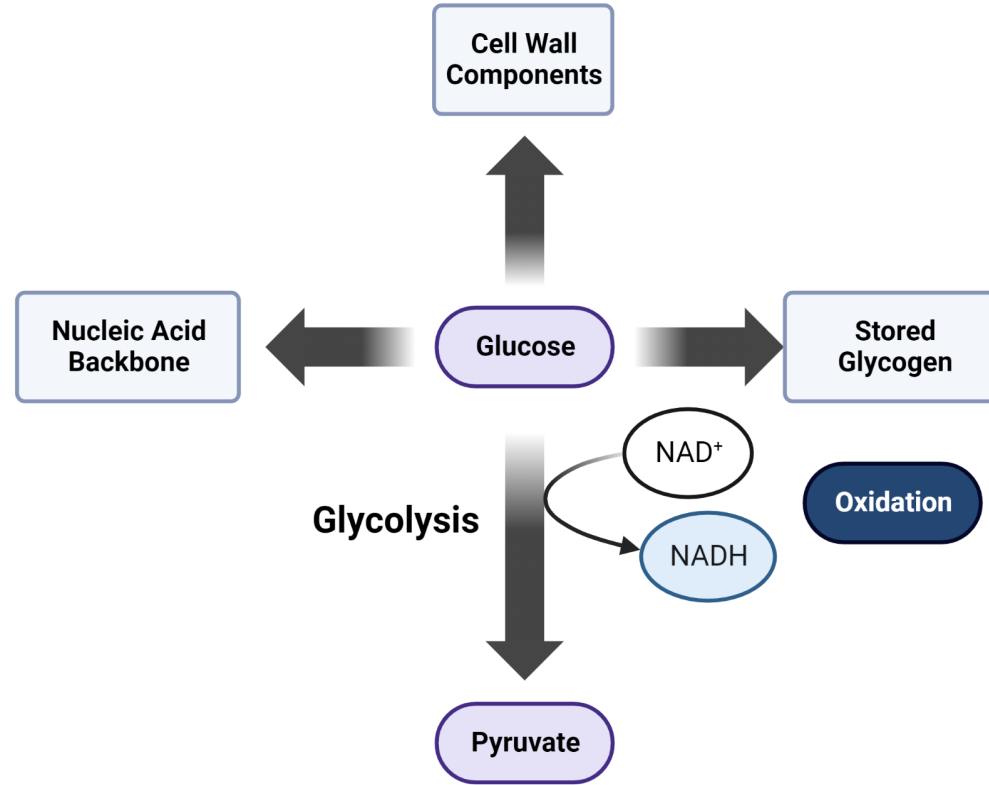
Lecture Slides can be found @
https://github.com/ekuechler/2022_truman

Learning Objectives:

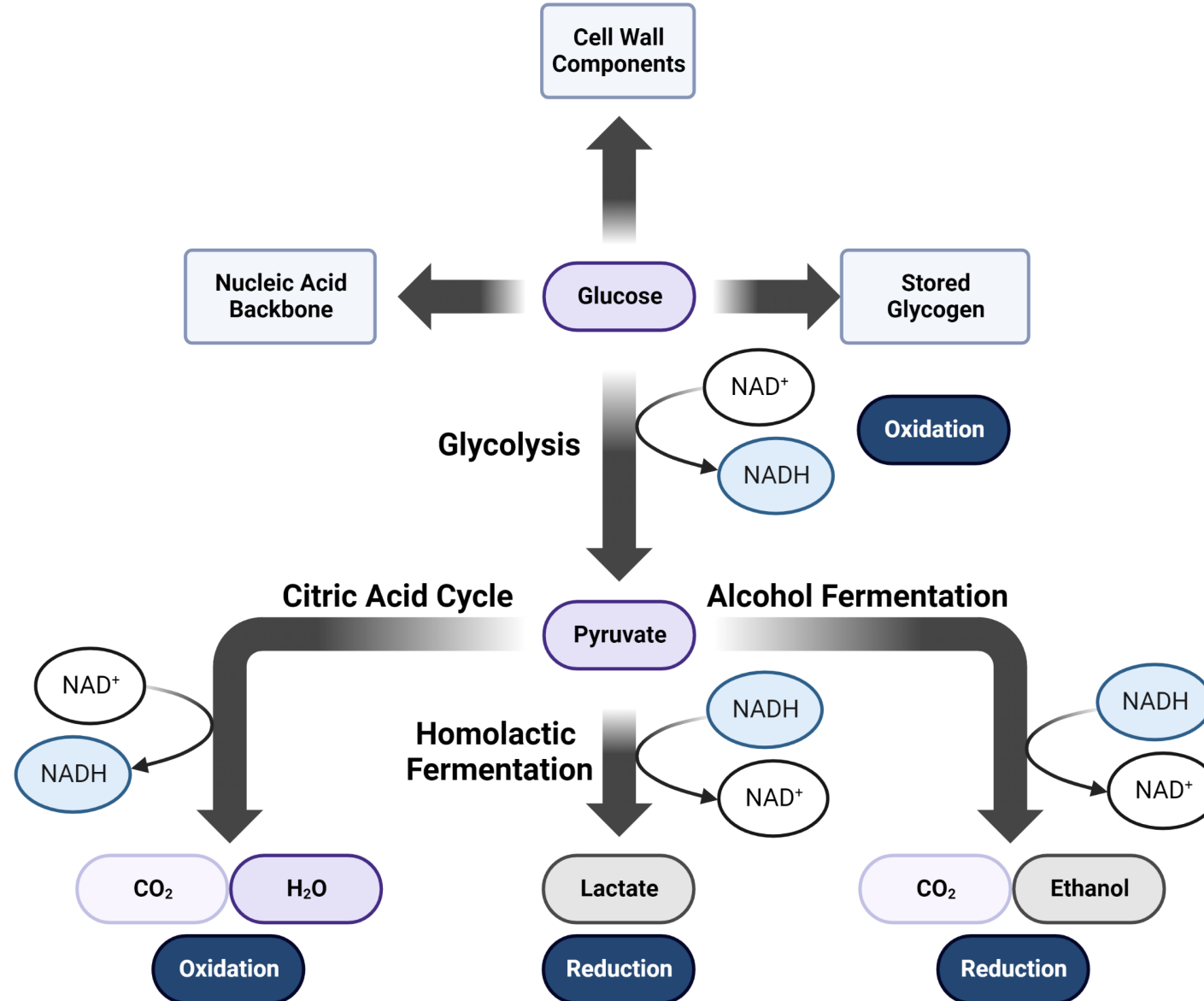
Today We Will Learn How to:

- Summarize the key steps in the glycolysis metabolic pathway
- Recall the structural features, function, and general biochemical reaction of kinases
- Recognize enzymes associated to this pathway
- Articulate the mechanism of action of several enzymes in the glycolysis metabolic pathway

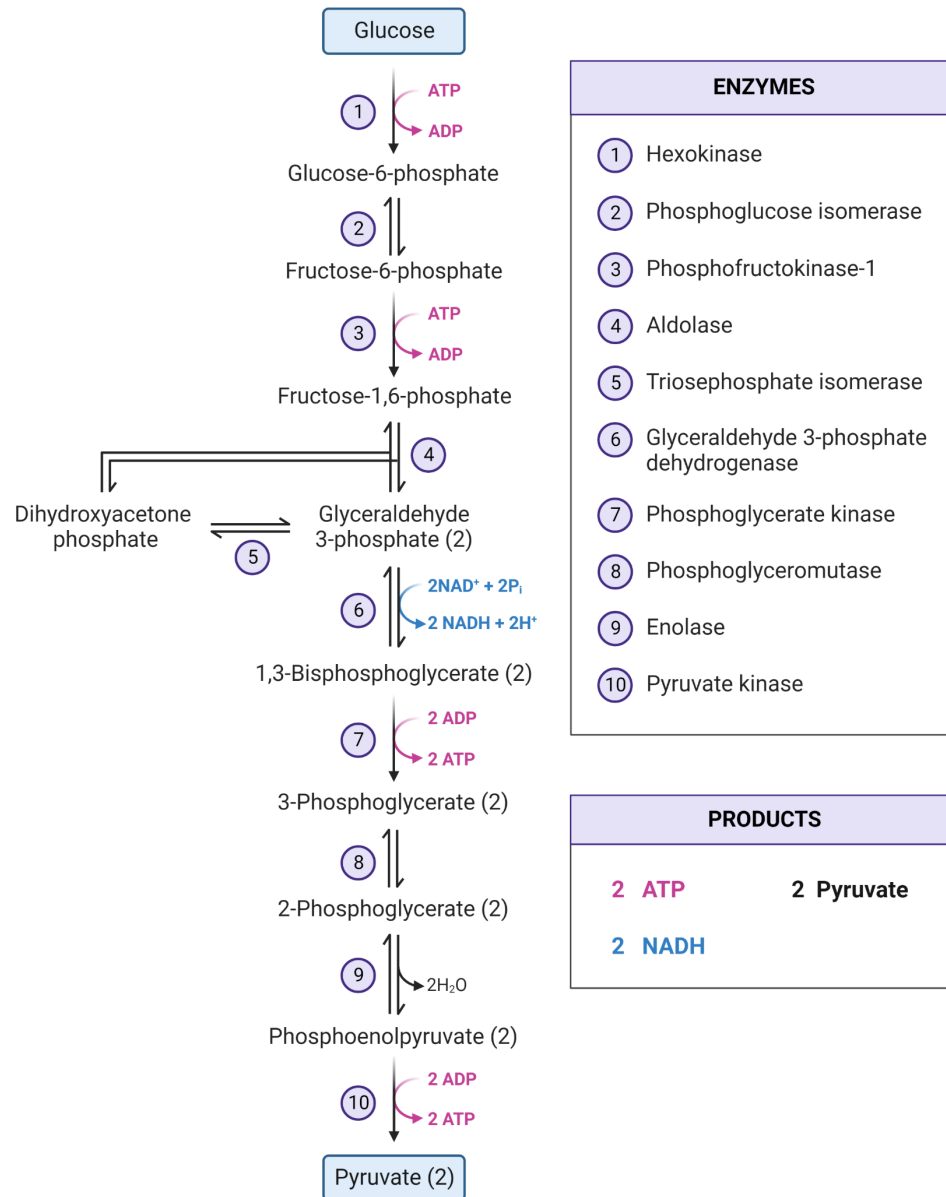
Glucose in the Body



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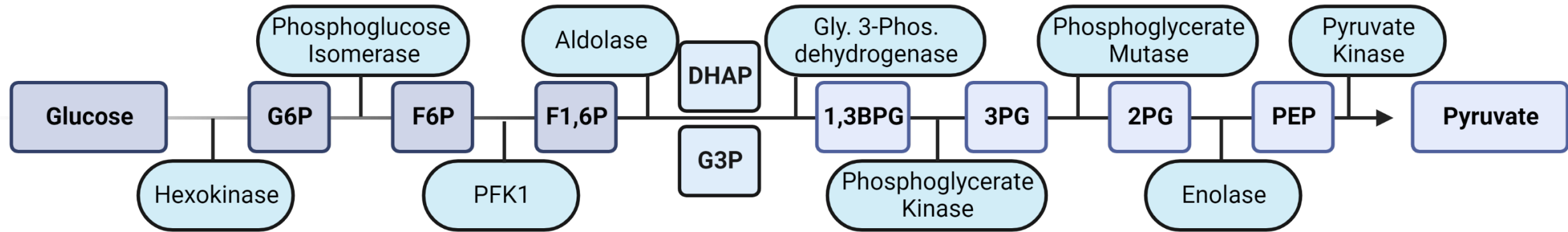


Glucose Metabolism: Overview



- Nearly universal.
- Conserves energy as ATP (adenosine triphosphate) and NADH (nicotinamide adenine dinucleotide)
- All ten steps involve phosphorylated compounds of six or three carbons.
- Is highly regulated.

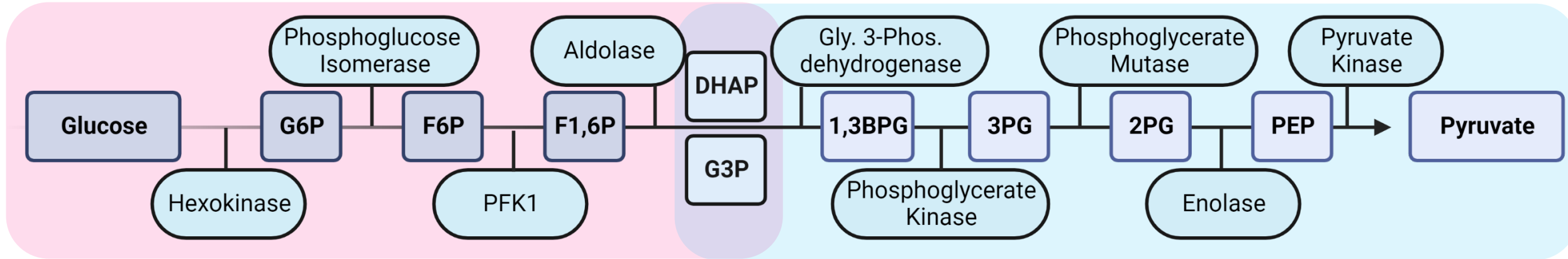
Glycolysis: Setup and Payoff



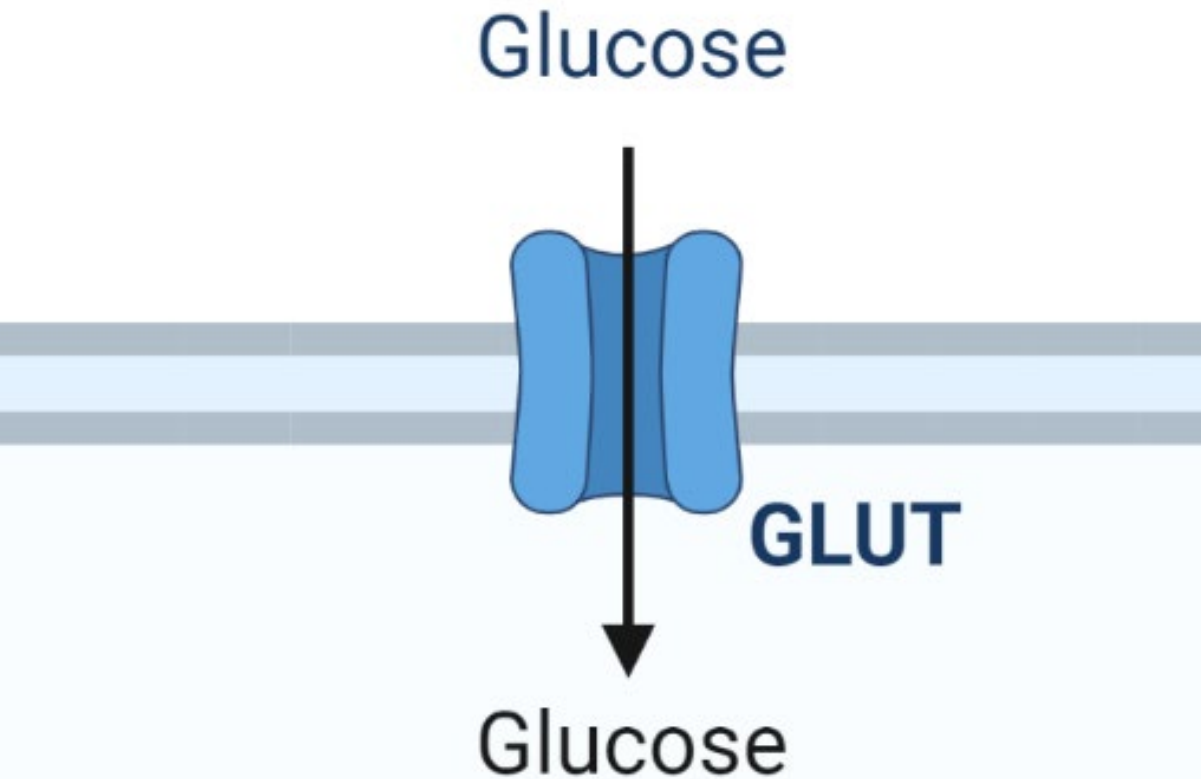
Glycolysis: Setup and Payoff

Preparatory Phase of Glycolysis

Payoff Phase of Glycolysis

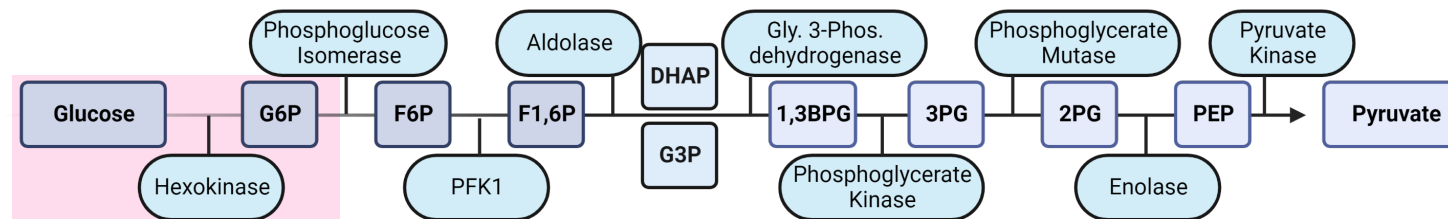
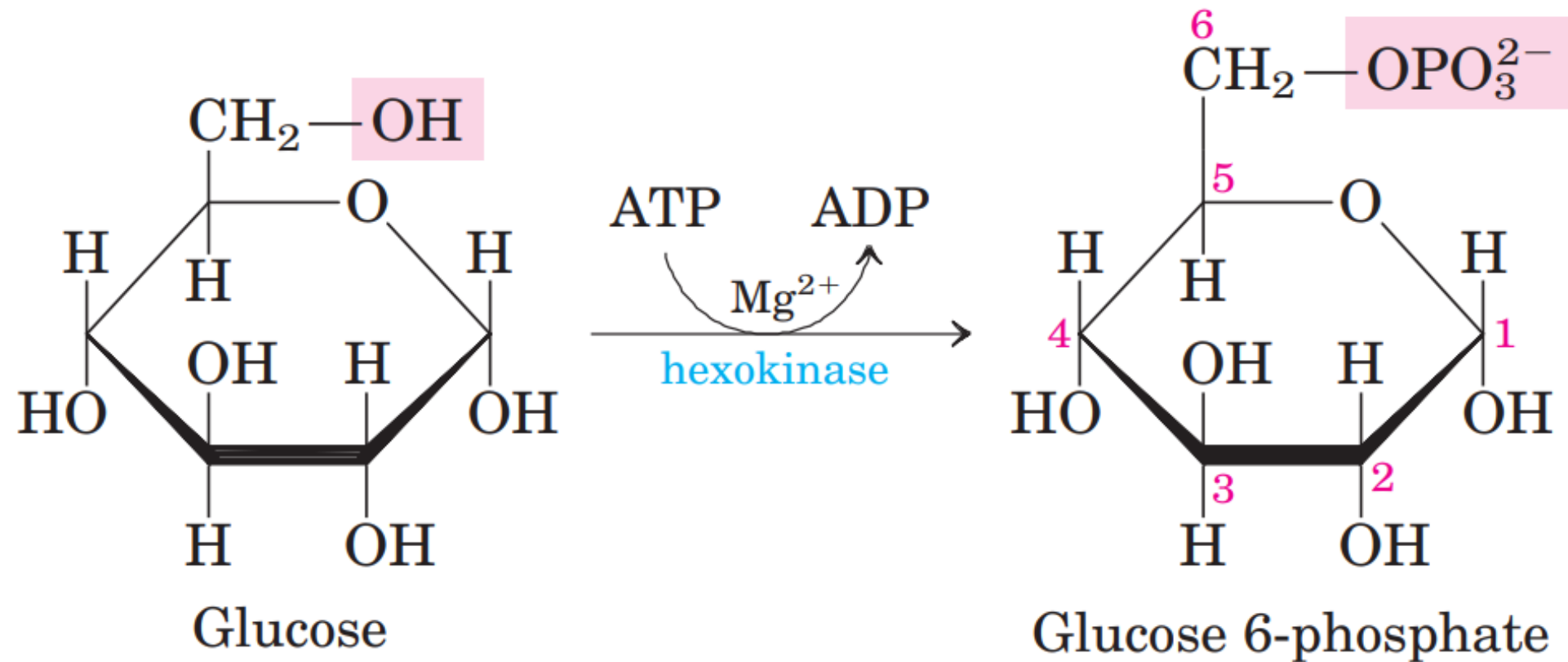


Glucose Cellular Import:

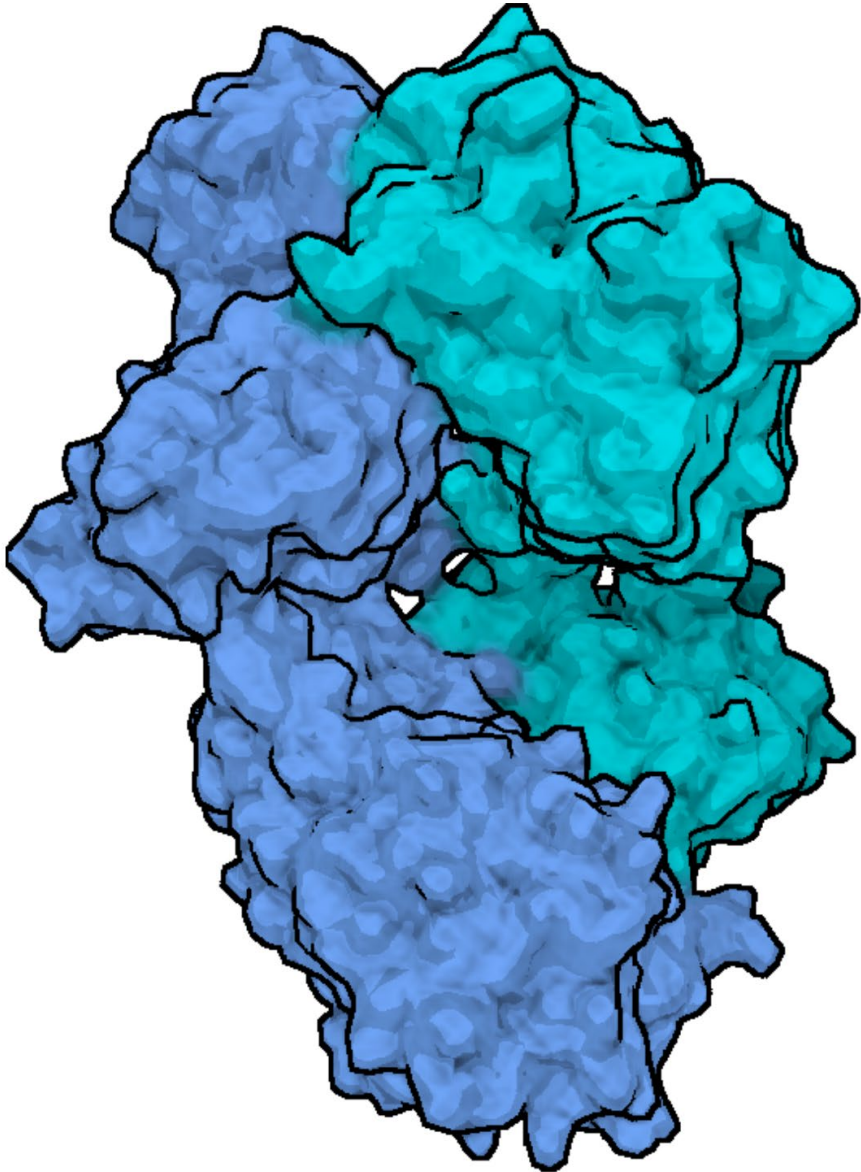


Transporter	Tissues Expressed	Notes
GLUT1	All, Red Blood Cells	Basal uptake of glucose
GLUT2	Liver, Pancreas, Intestine	Highest K_M
GLUT3	Brain	High affinity basal uptake
GLUT4	Muscle, Fat, Heart	Insulin regulated

Reaction One: Hexokinase, the First Investment

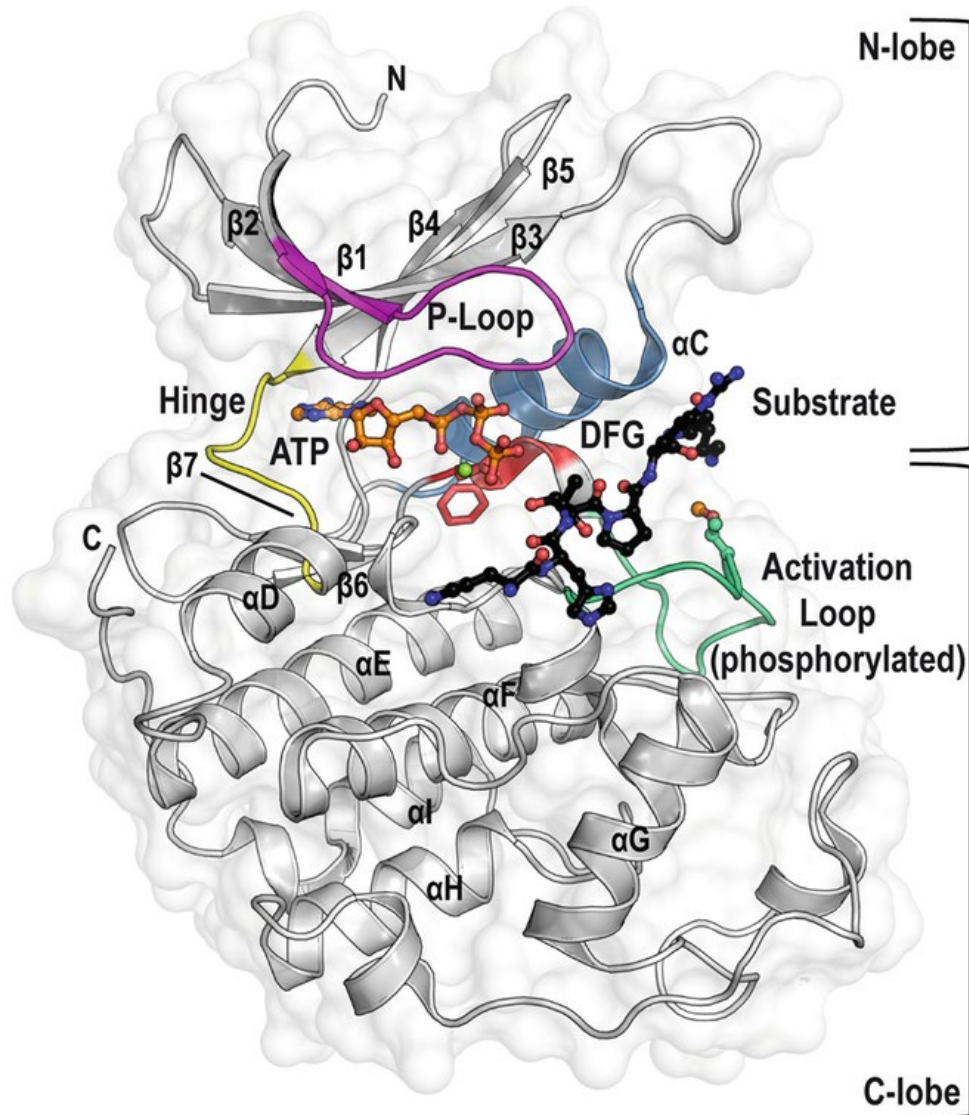


Kinase Catalytic Domains: Hexokinase



- Like the other nine enzymes of glycolysis, hexokinase is a soluble, cytosolic protein.
- Required Mg^{2+} for activity.
- Undergoes a profound change in shape, an induced fit, when it binds glucose.
- The two domains of the protein move around 8Å closer during ATP binding
- This movement aligns ATP closer to bound glucose and blocks solvent access to the active site, which could hydrolyze the activated bonds of ATP

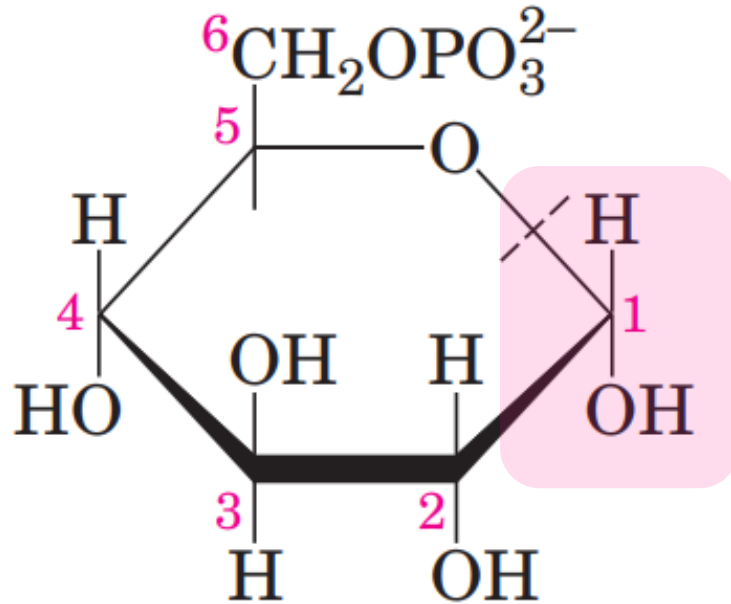
Kinase Catalytic Domains: Molecular Detail



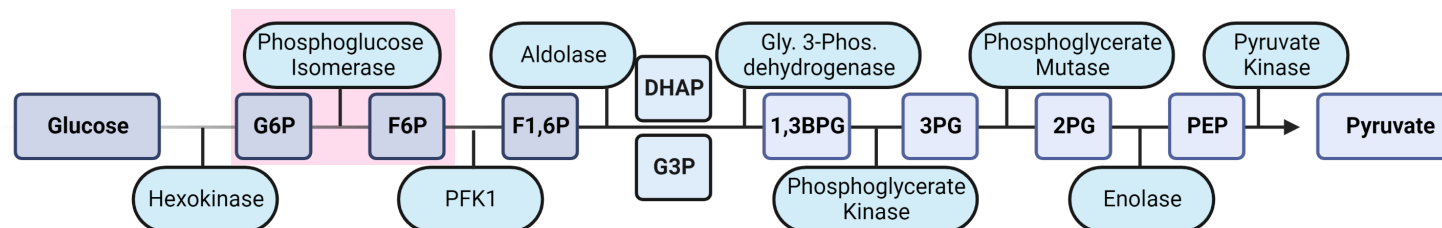
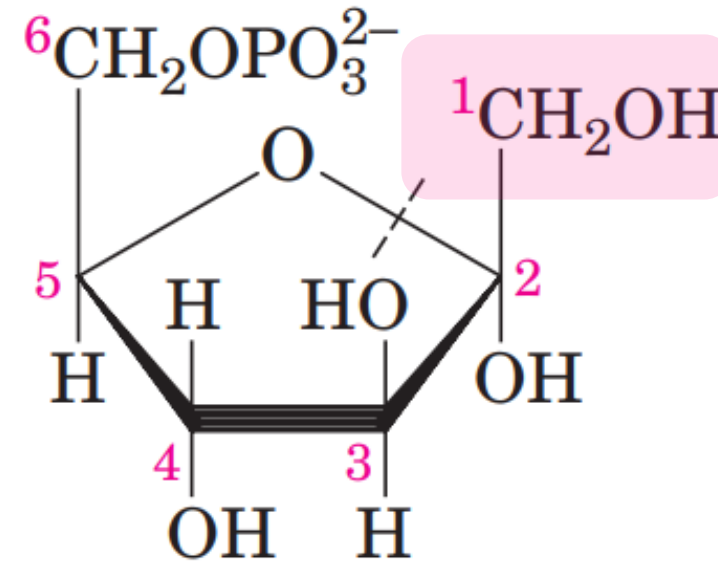
- ATP forms hydrogen bonds with hinge region
- P-Loop region has a GXGX ϕ G motif which coordinates the ATP phosphates
- The β 3-sheet contains a conserved VIAK motif that forms a salt bridge with ATP phosphate groups and the α C helix.
- A DFG (Asp-Phe-Gly) motif marks the beginning of the activation loop. The conserved Asp interacts with Mg^{2+} itself coordinating to the ATP phosphates

Reaction Two: Glucose Isomerization to Fructose

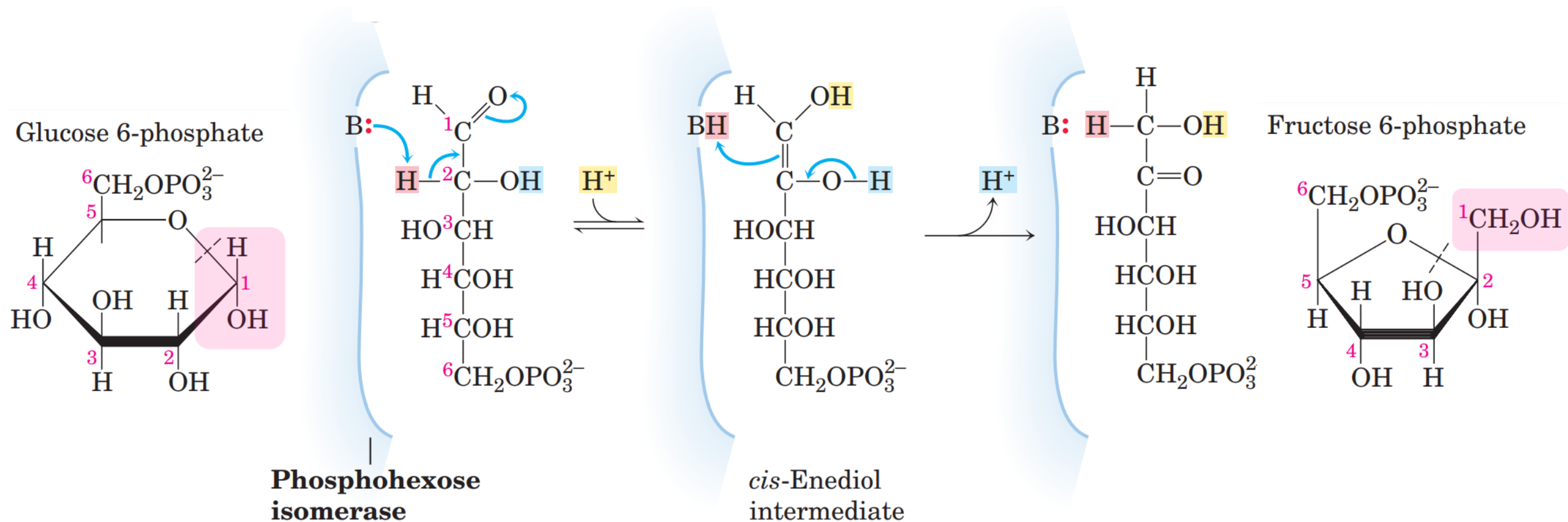
Glucose 6-phosphate



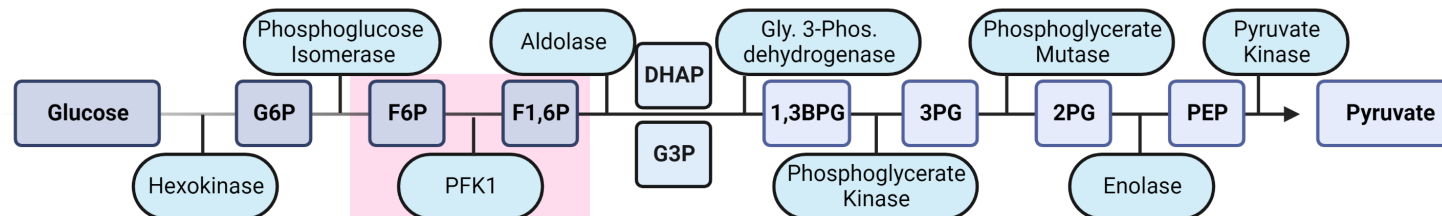
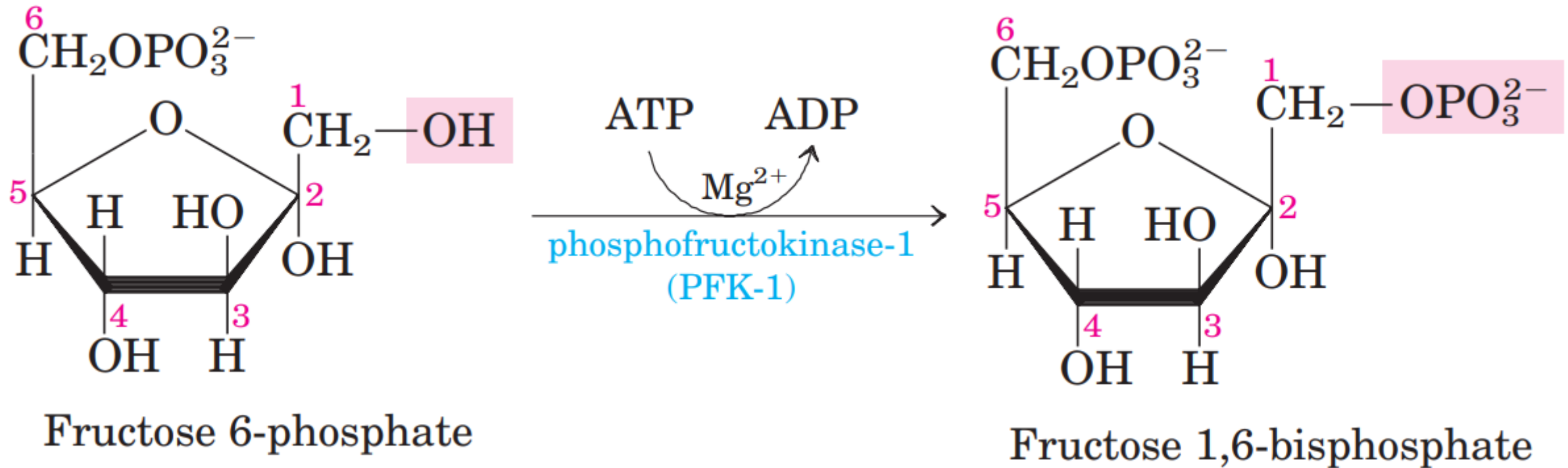
Fructose 6-phosphate



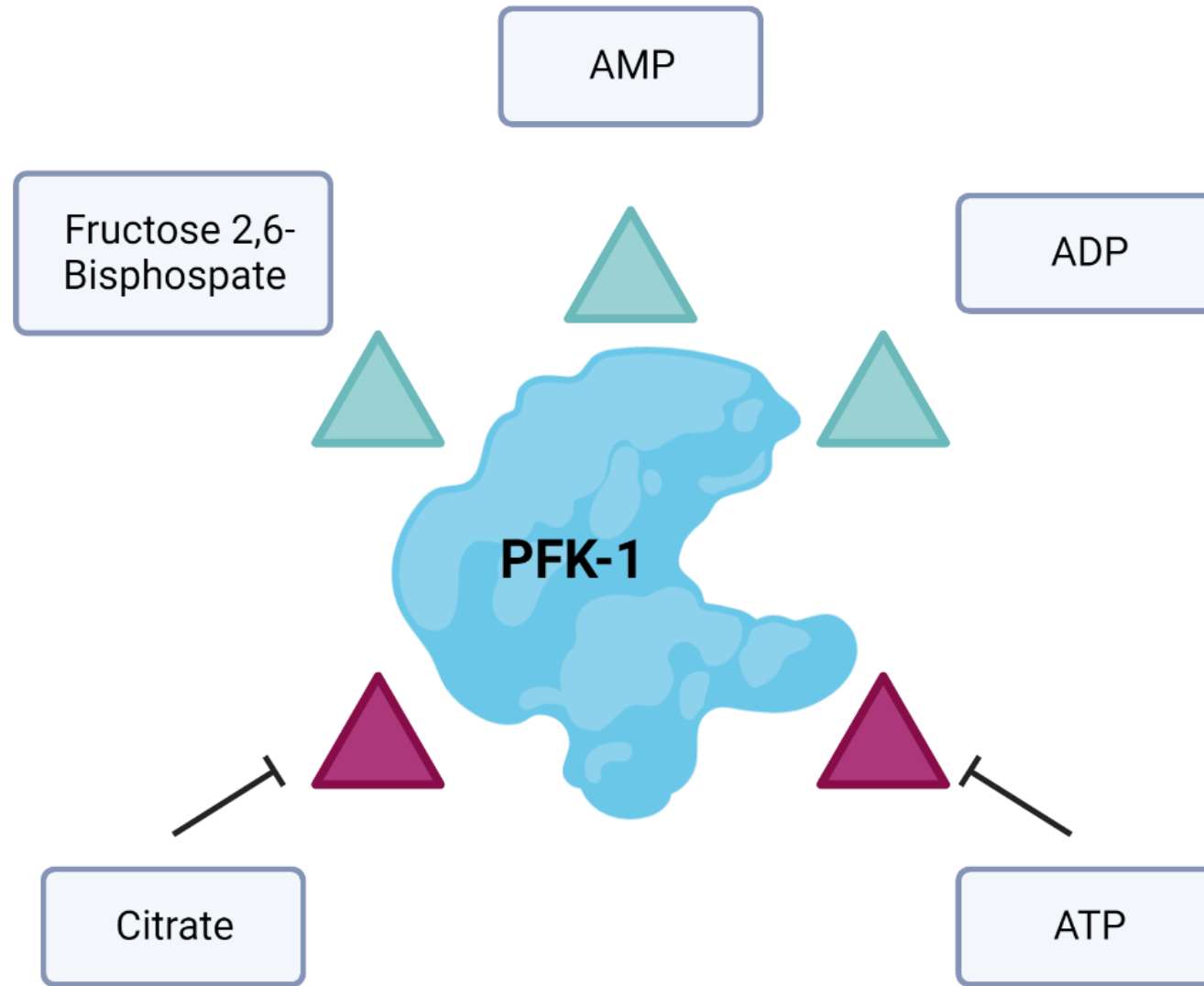
Reaction Two: Mechanism



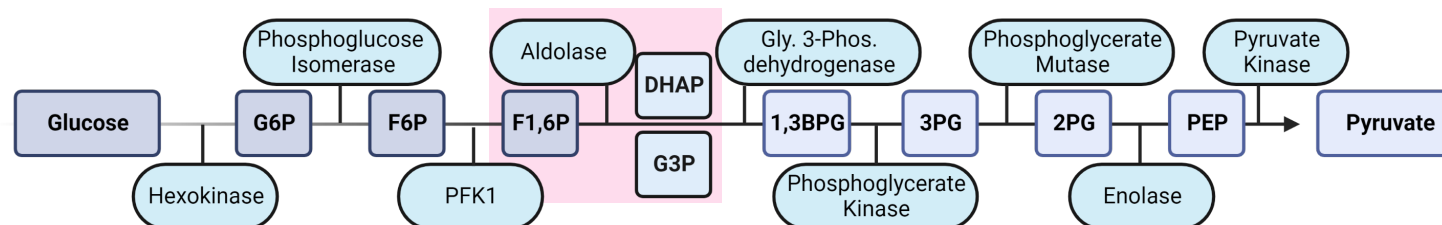
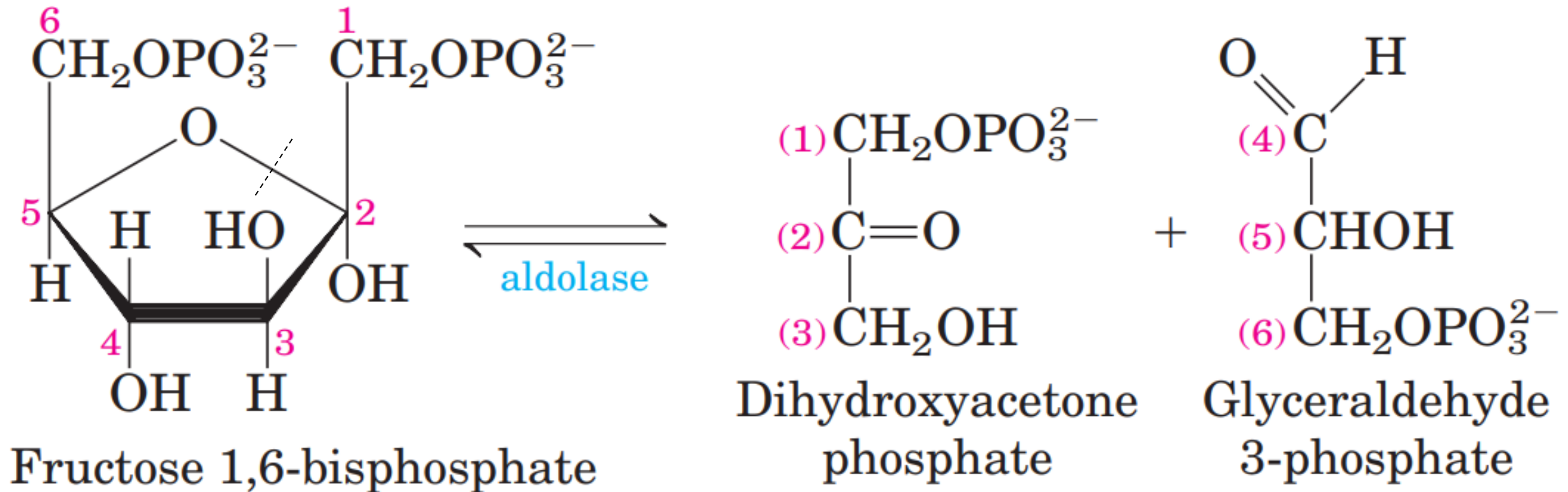
Reaction Three: PFK-1, the Second Investment



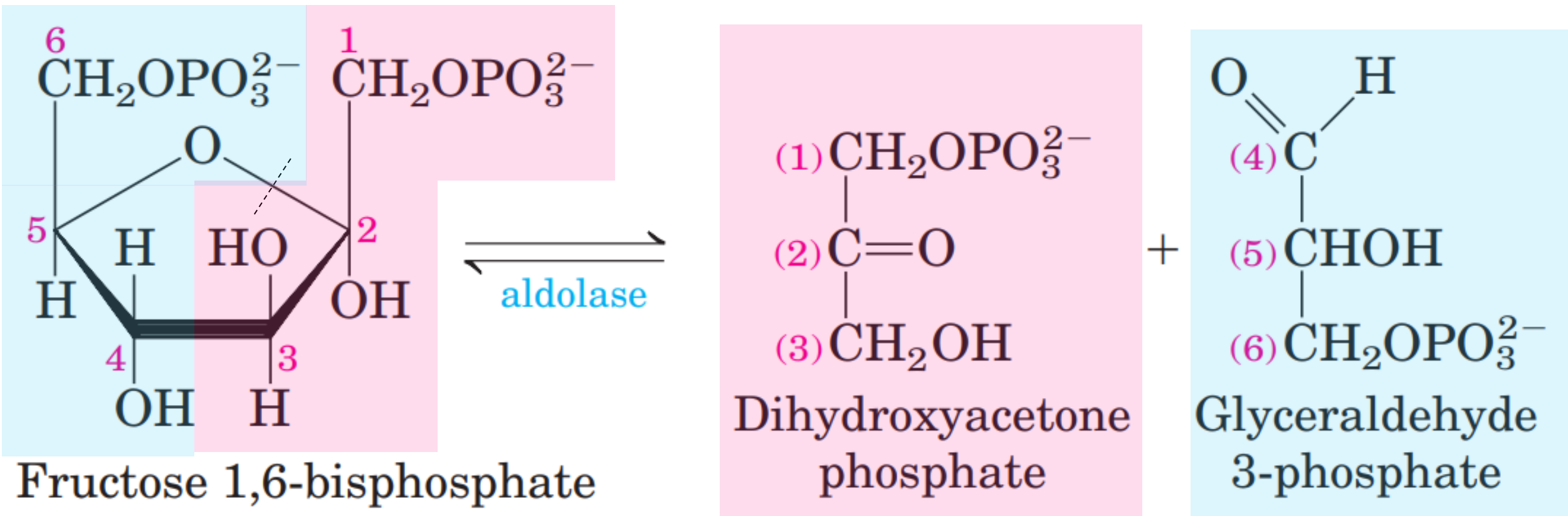
PFK-1 Regulation



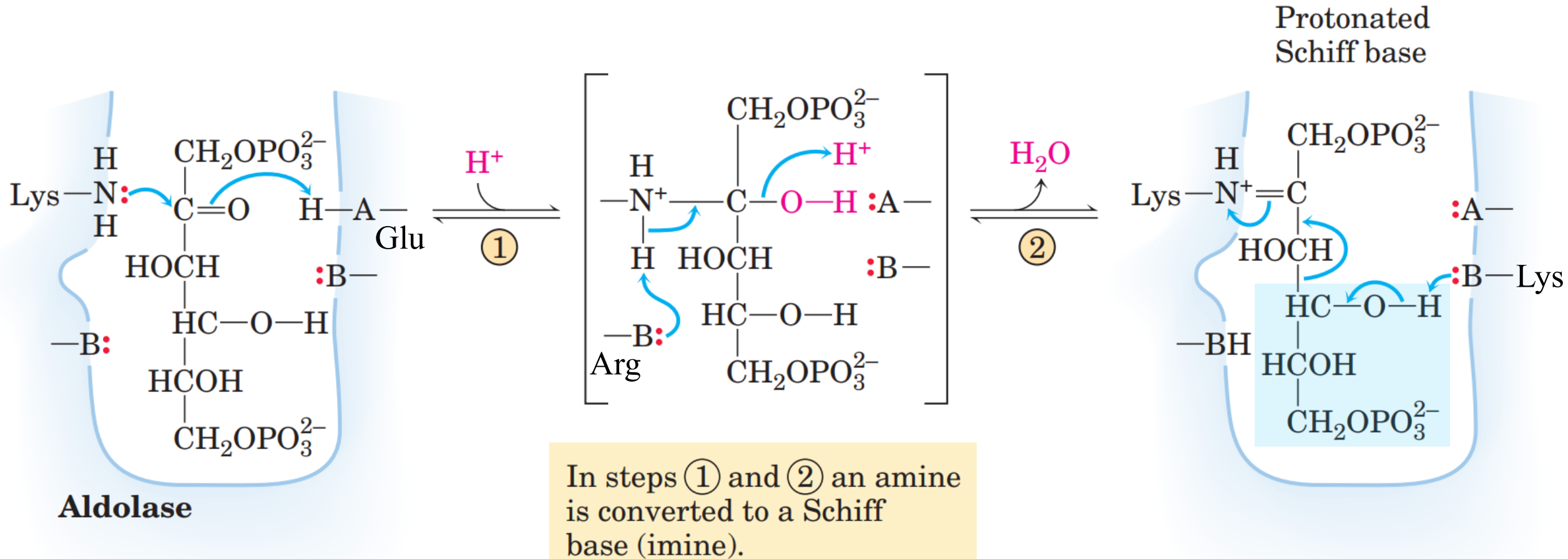
Reaction Four: The '*Lysis*' of Glycolysis



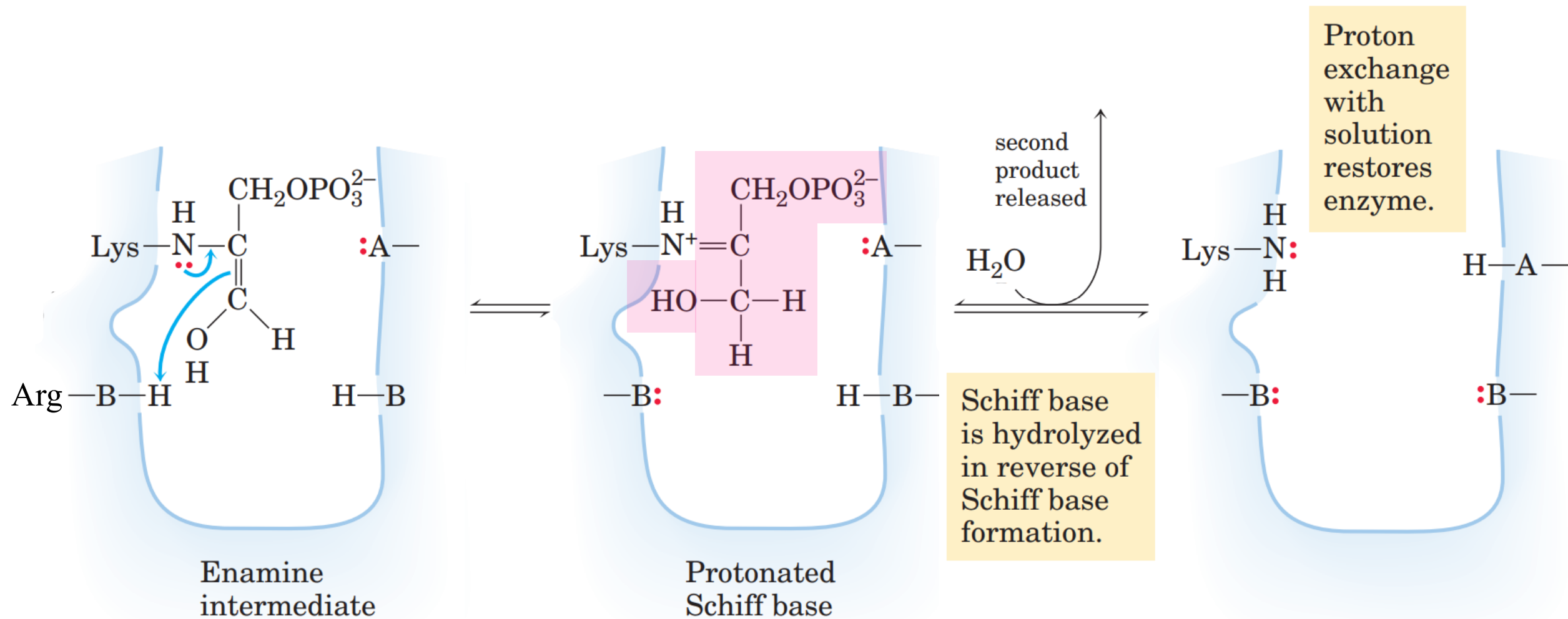
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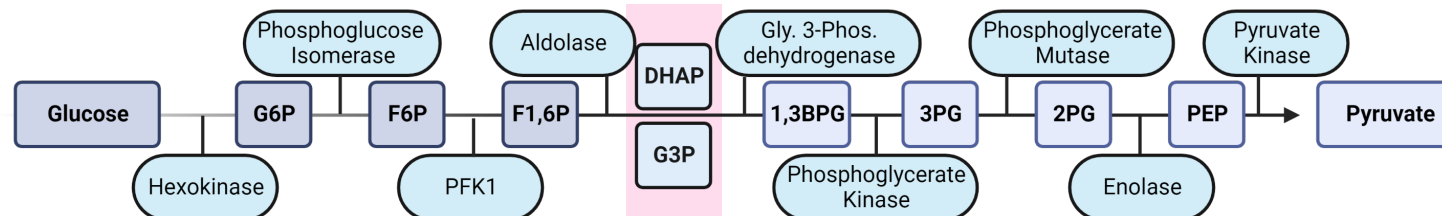
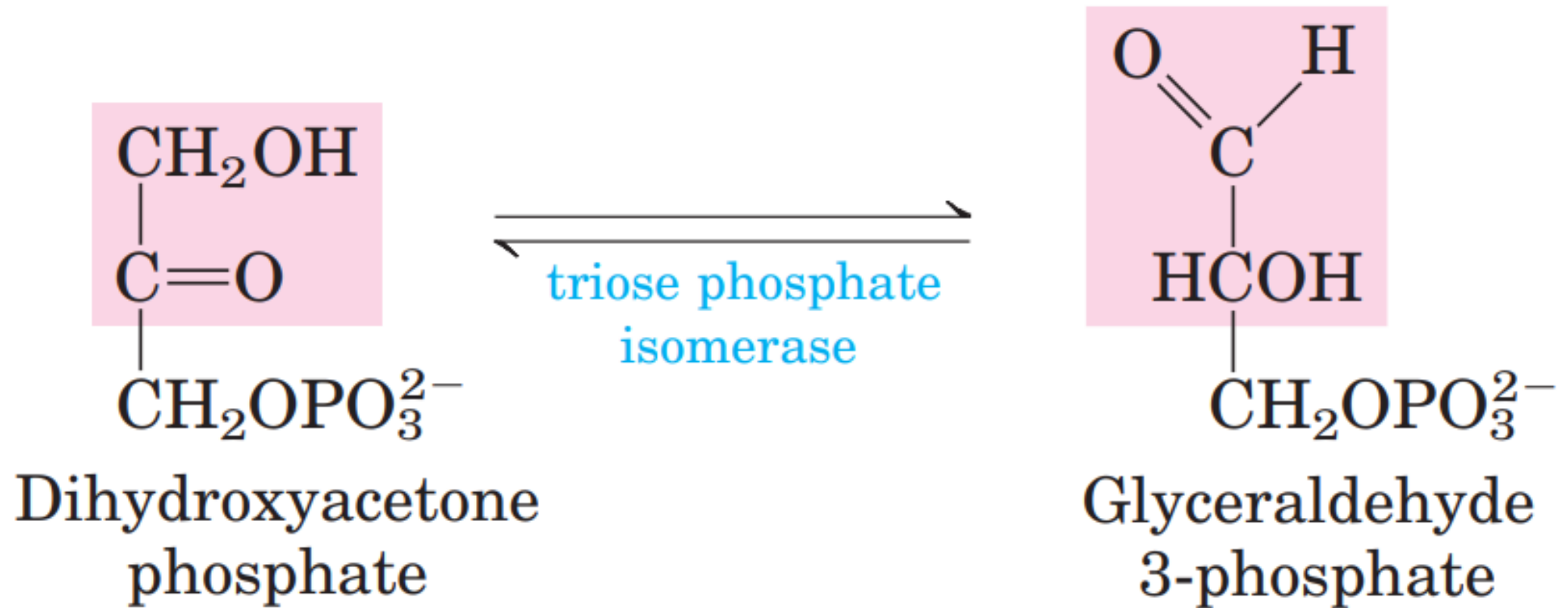
Reaction Four: The Mechanism



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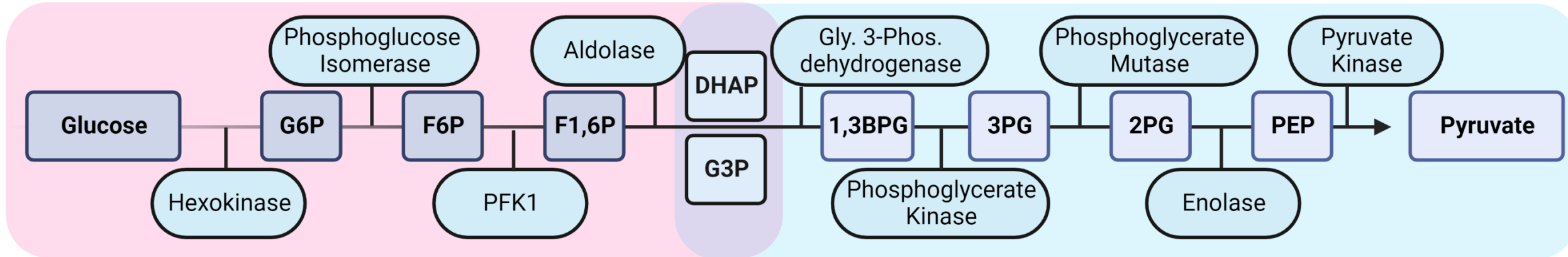
Reaction Five: Three Carbon Isomerization



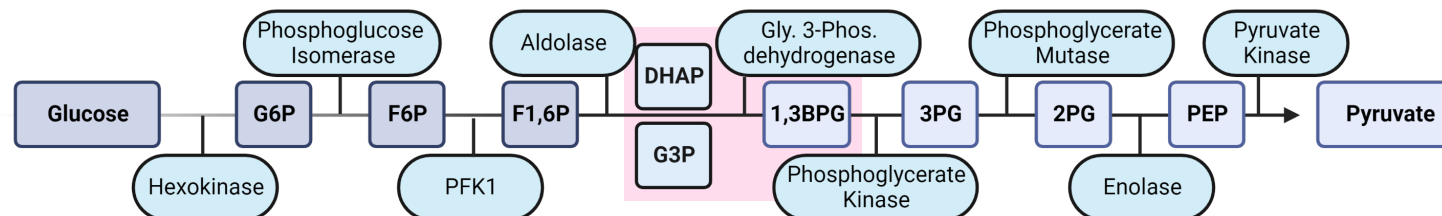
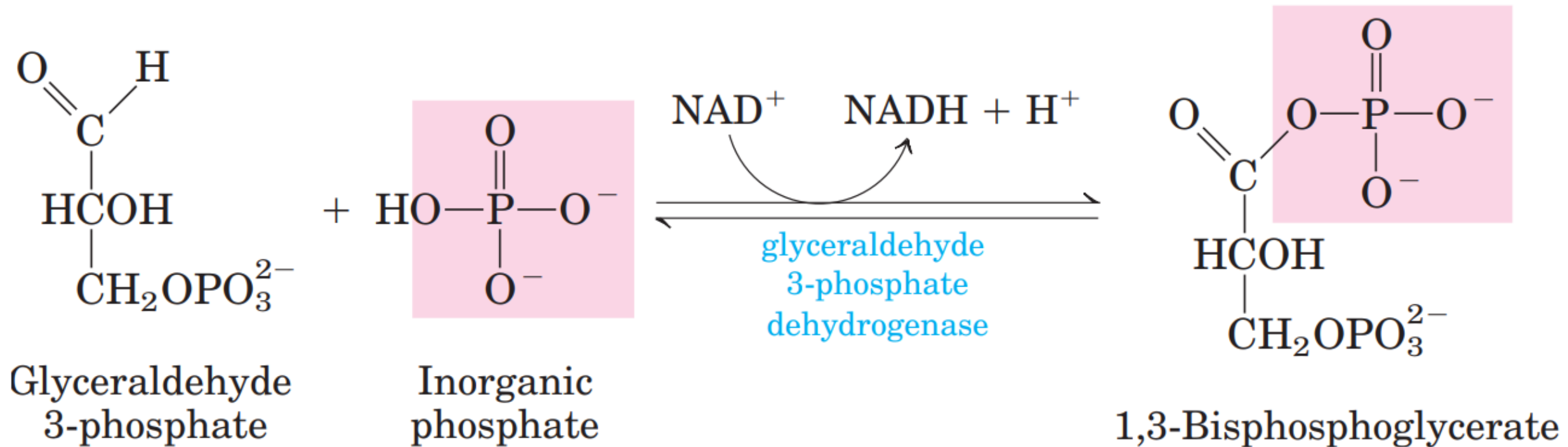
Glycolysis: Setup and Payoff

Preparatory Phase of Glycolysis

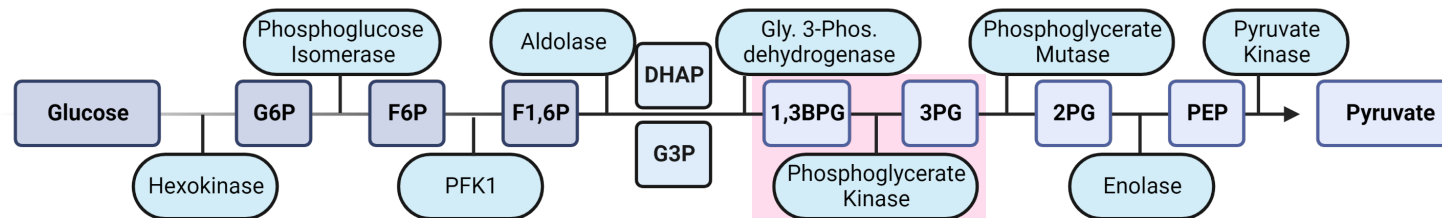
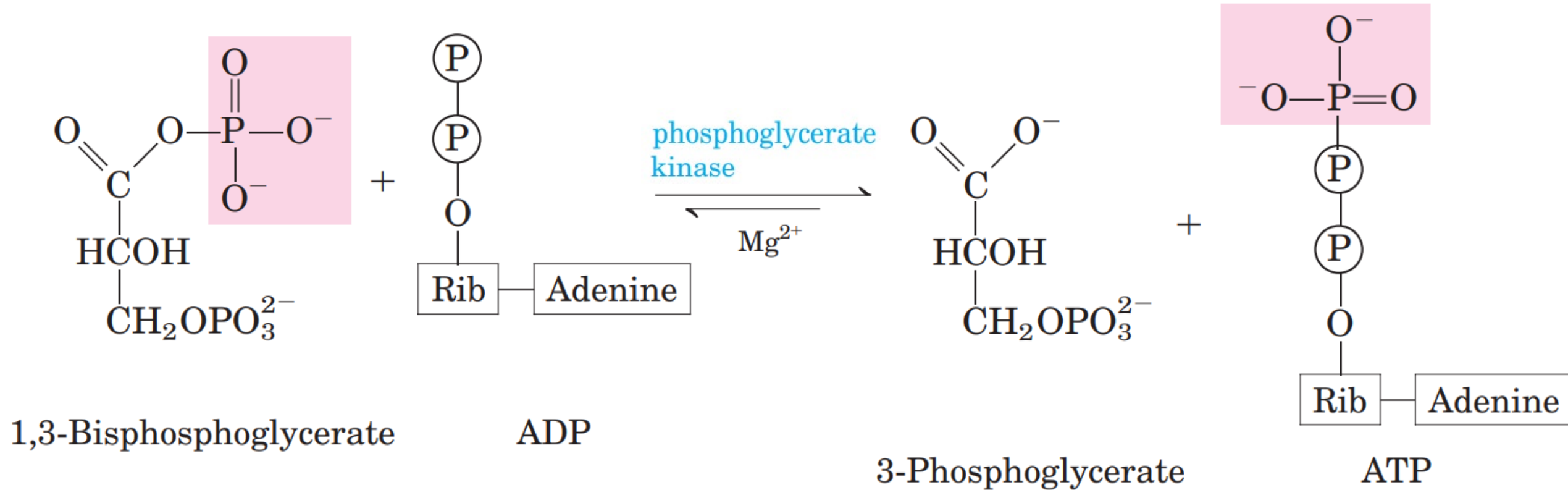
Payoff Phase of Glycolysis



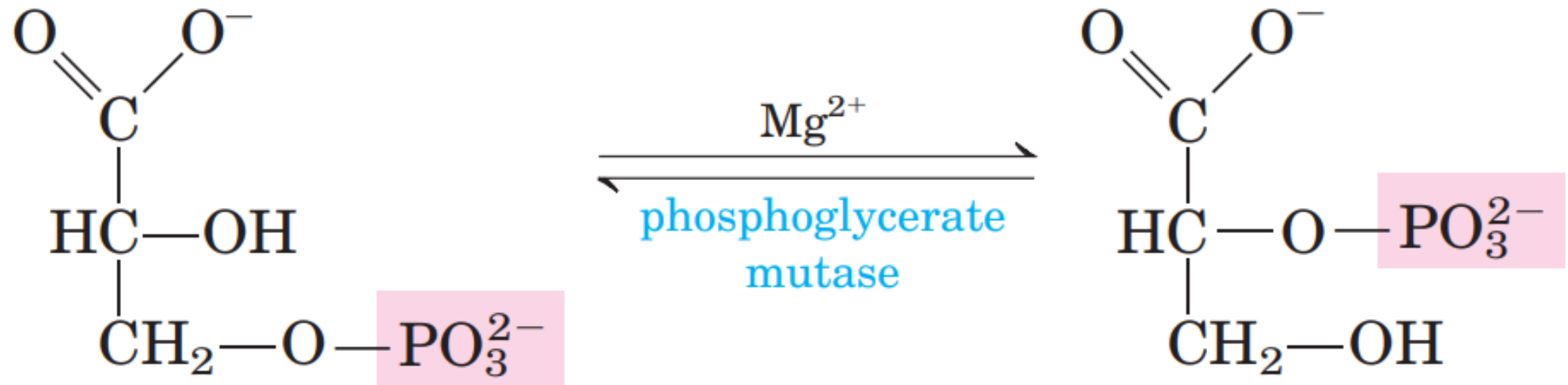
Reaction Six: Oxidation by Inorganic Phosphate



Reaction Seven: The First Payoff of ATP

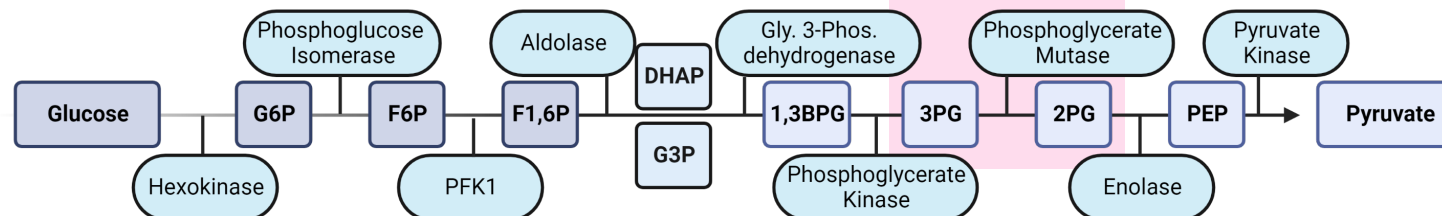


Reaction Eight: Mutase, 'moving' phosphates

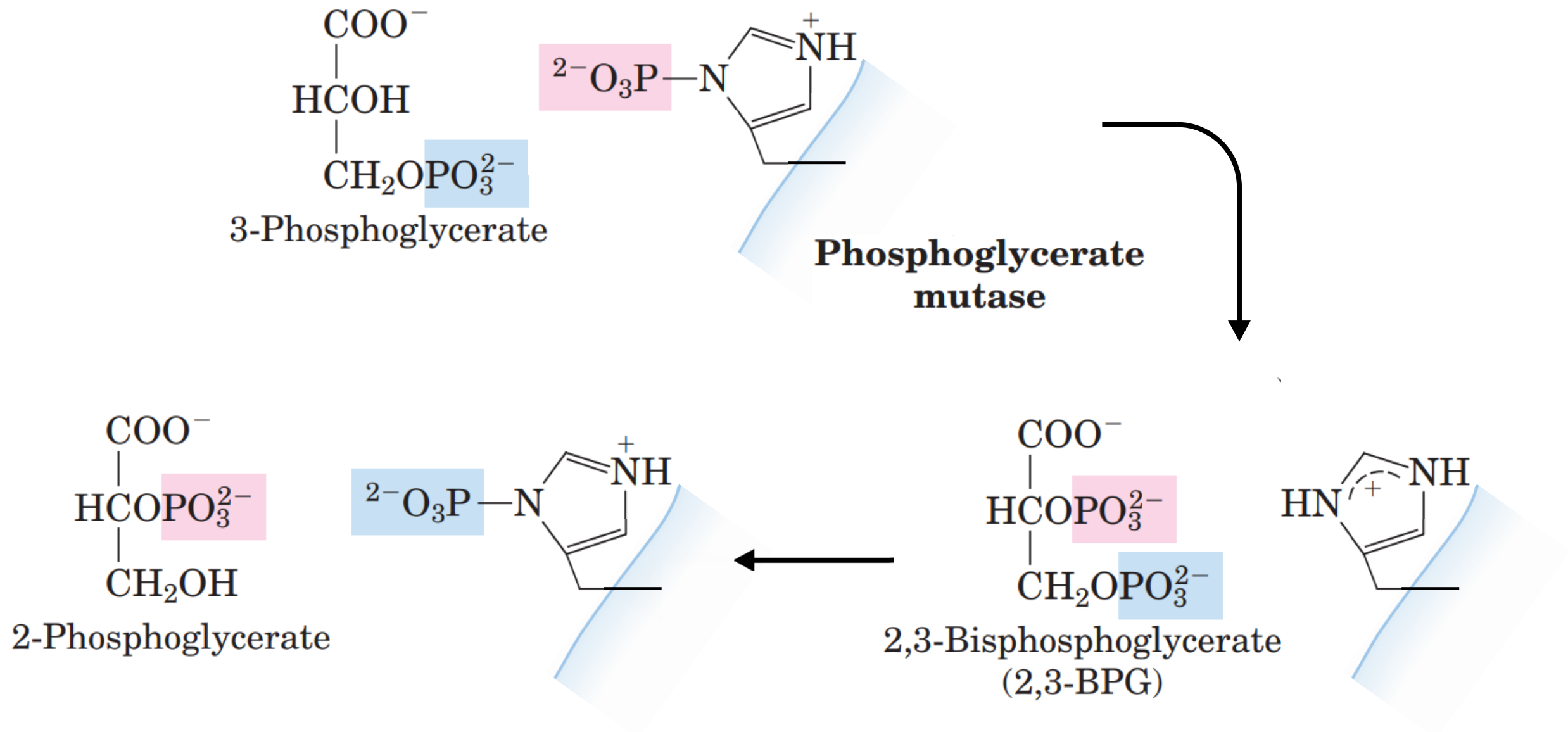


3-Phosphoglycerate

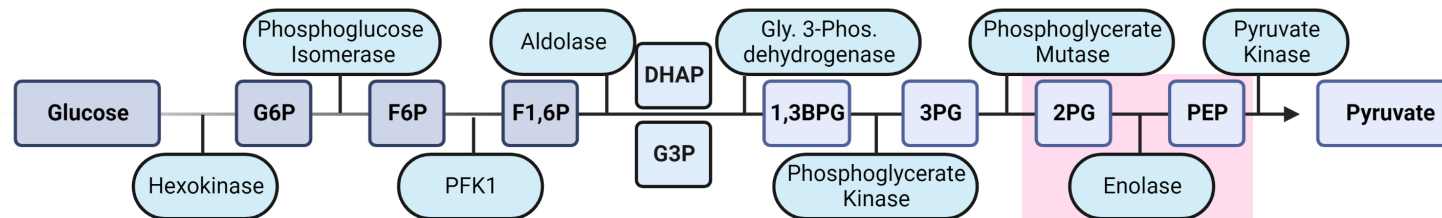
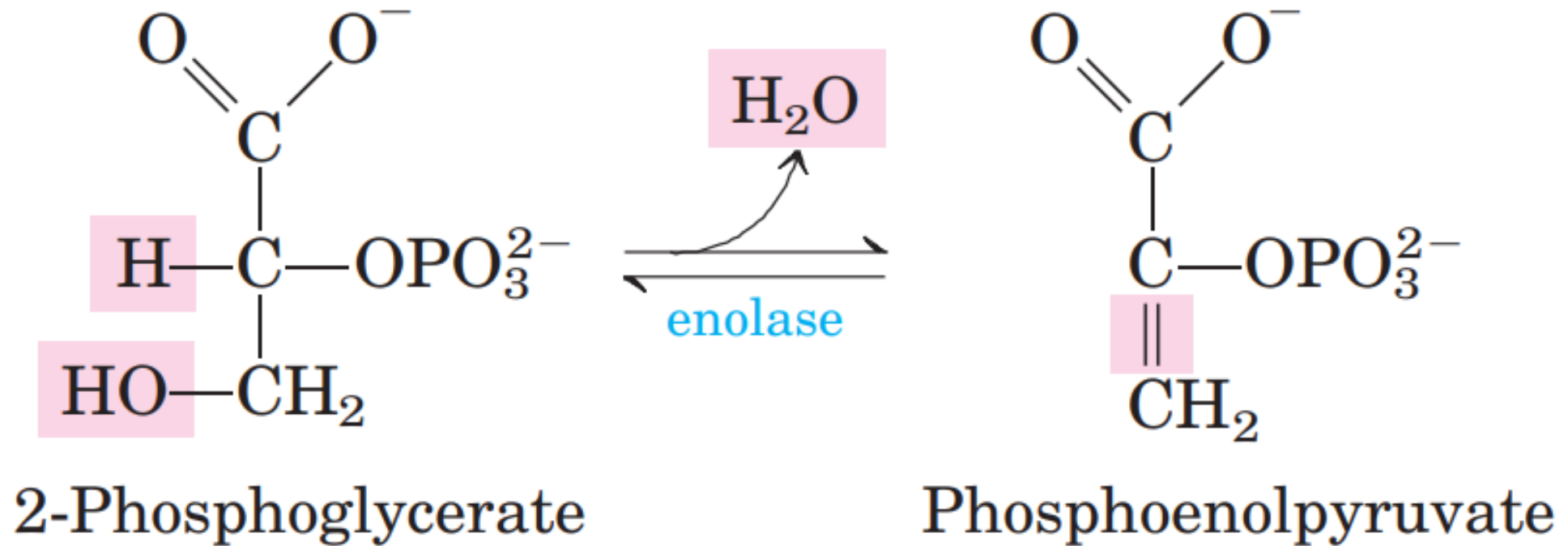
2-Phosphoglycerate



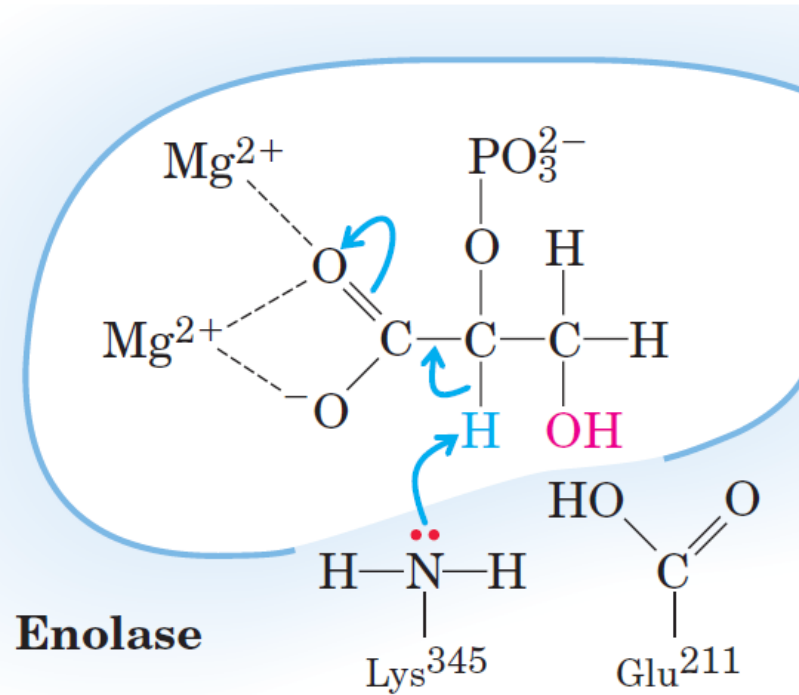
Reaction Eight: Phosphoglycerate Mutase Mechanism



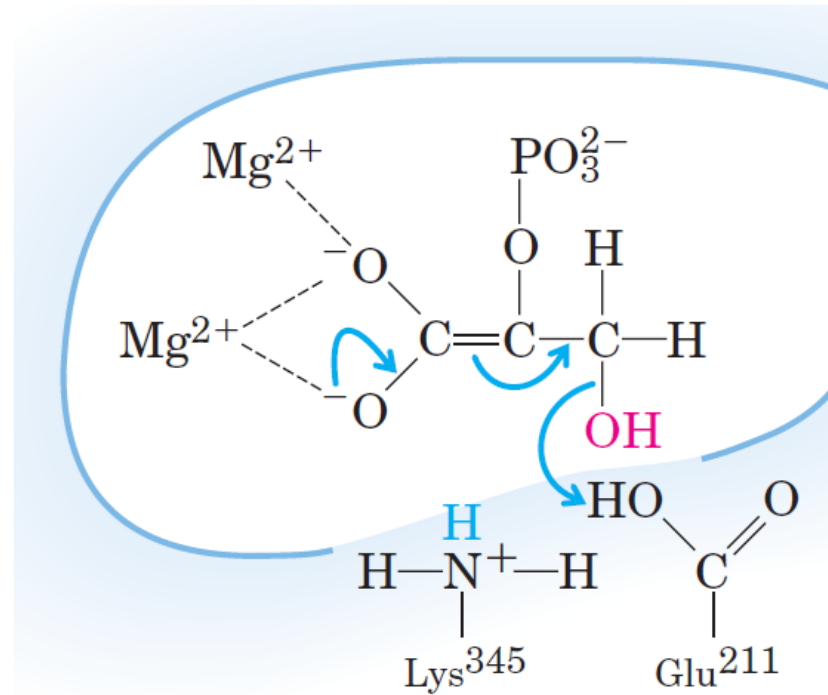
Reaction Nine: Enolase



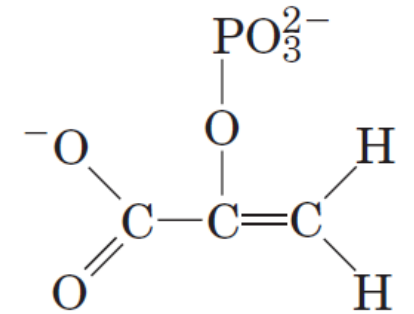
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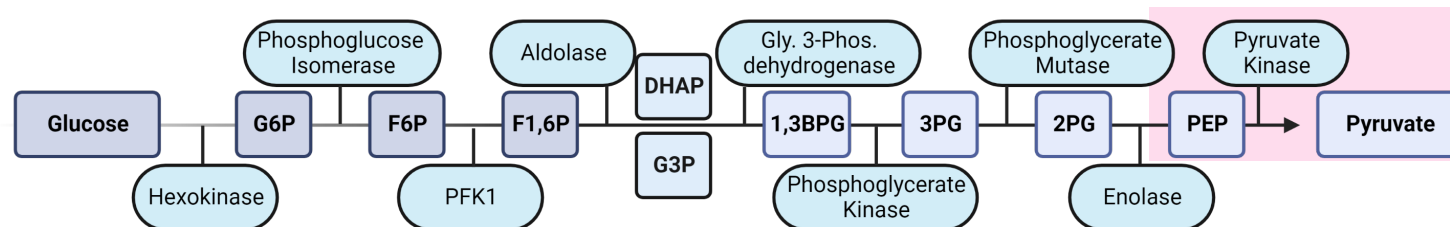
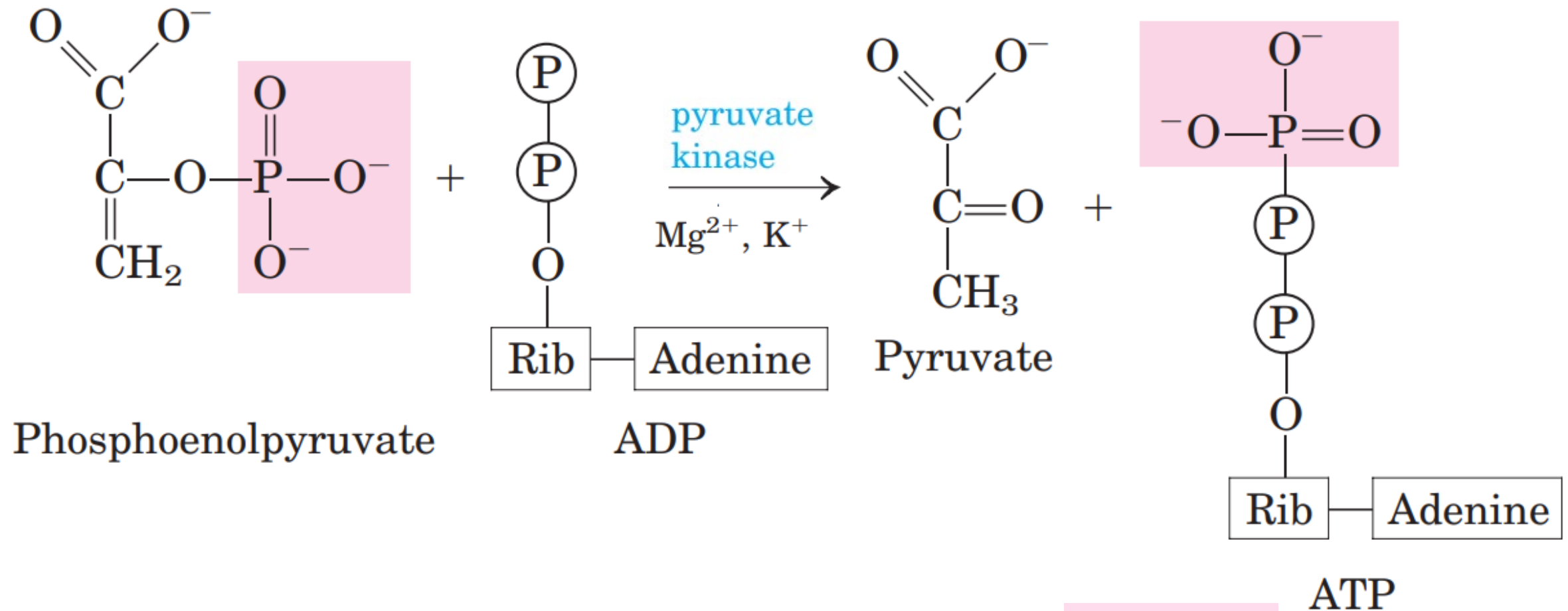
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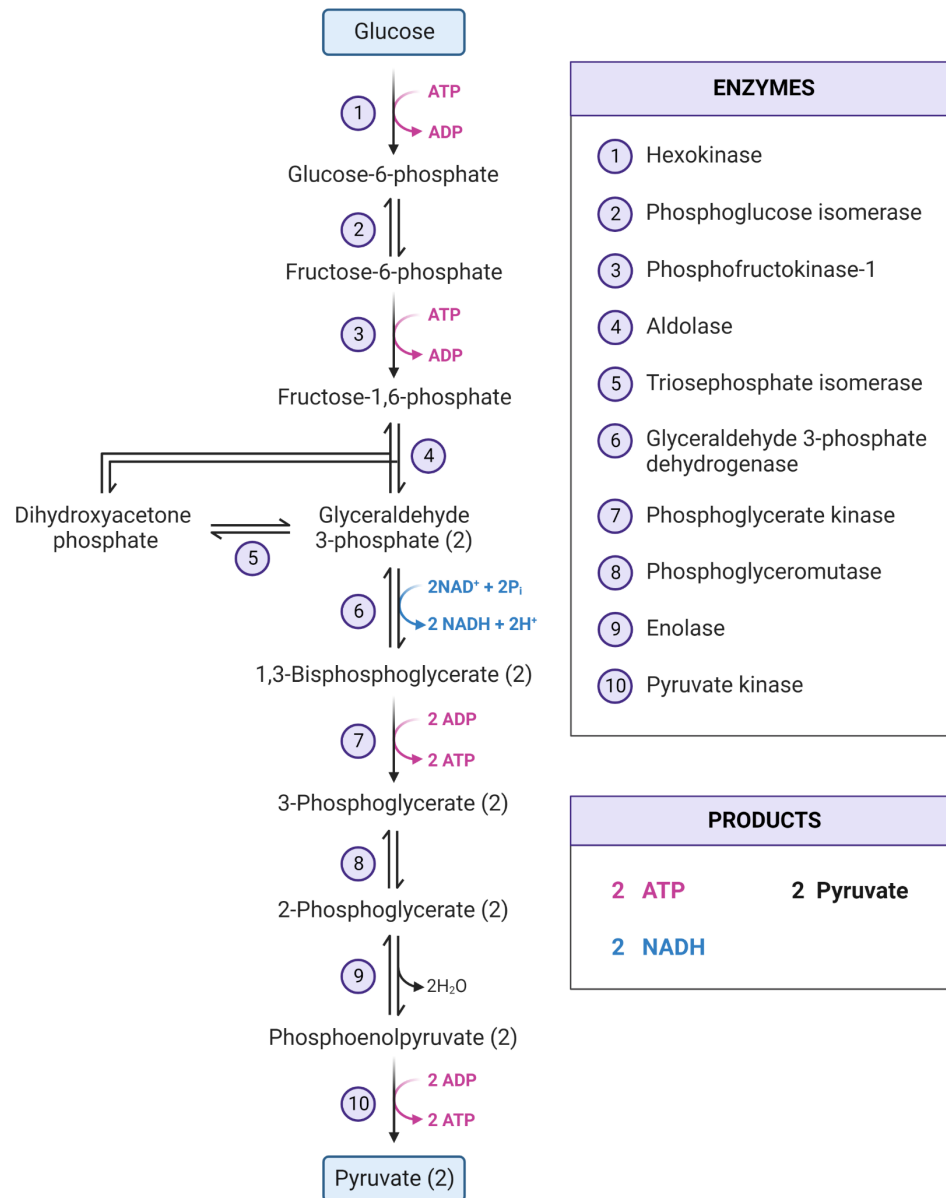
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Reaction Ten: Pyruvate Kinase, the Second Payoff



Glucose Metabolism: Overview



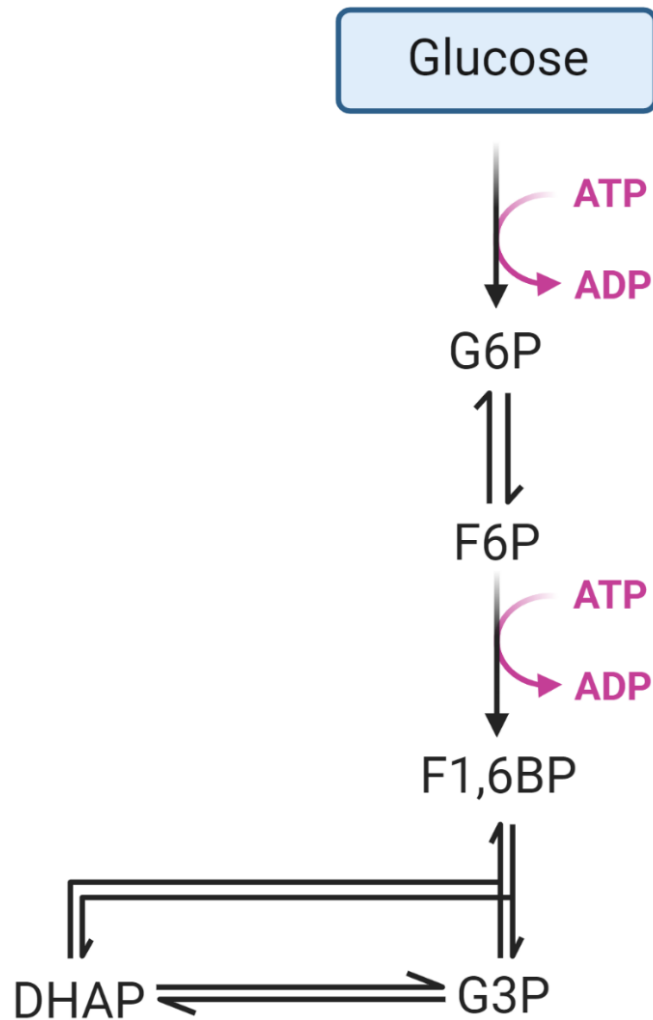
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Payoff Phase of Glycolysis

