METABOLISM

1- Biochemistry (3rd Edition) 3rd Edition

by Christopher K. Mathews , Kensal E. van Holde, Kevin G. Ahern

2- Lehninger Principles of Biochemistry 4th Edition

by David L. Nelson , Michael M. Cox

3- **Biochemistry: International Edition**

by Lubert Stryer , Jeremy M. Berg , John L. Tymoczko

4- Textbook of Biochemistry With Clinical Correlations, Fourth Edition

by Thomas M. Devlin

INTRODUCTION TO METABOLISM AND SOME BIOENERGETIC CONSIDRATION

Concepts

- **Intermediary metabolism**:

all reactions concerned with storing and generating metabolic energy and with using that energy in biosynthesis of low molecular weight compound and energy storage compounds(de novo protein and nucleic acid Not included)

- **Energy metabolism**:

  is that part of intermediary metabolism consisting of pathways that store or generate metabolic energy.

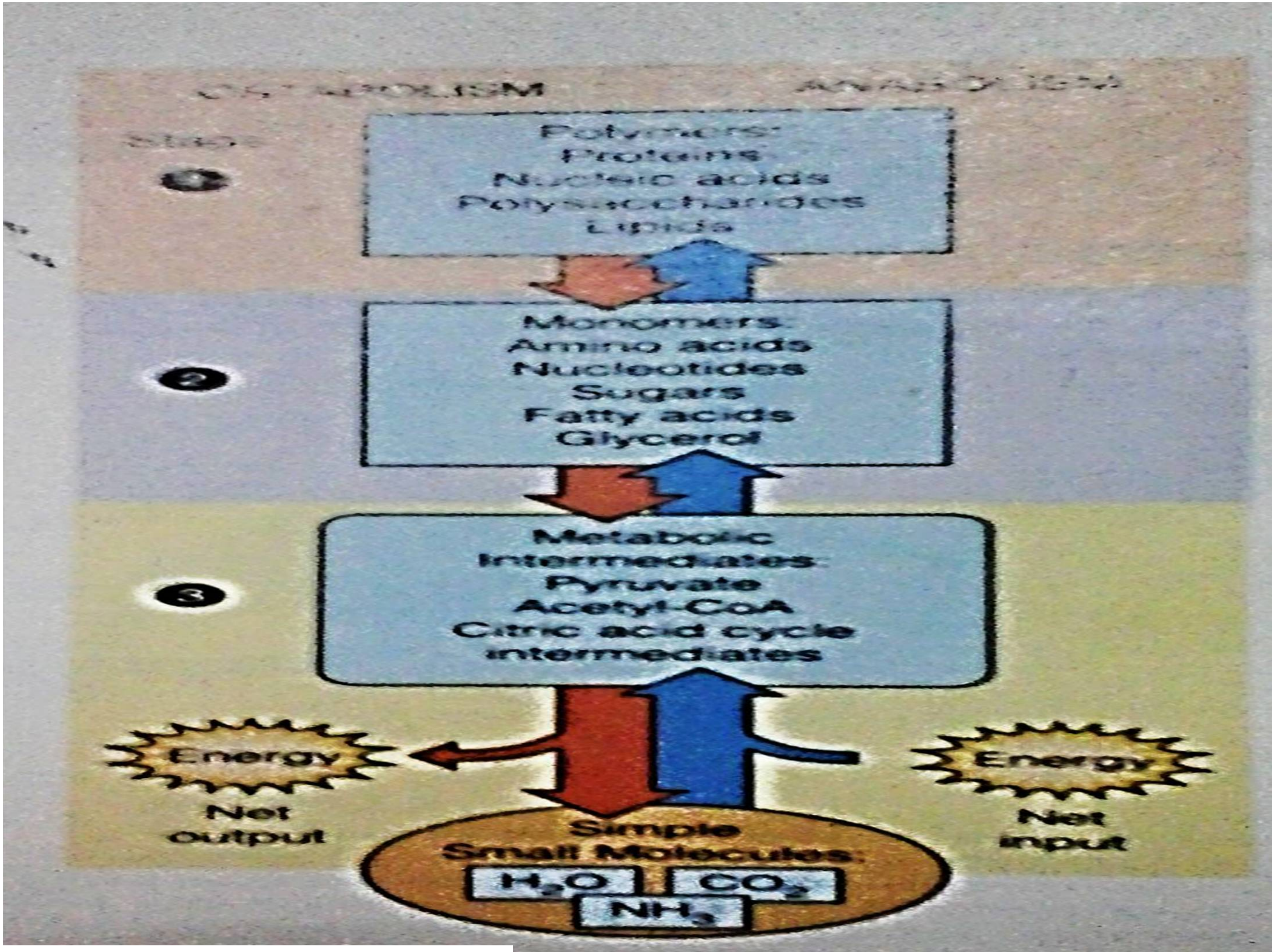
- **Central pathways (of metabolism):**

  are substantially the same pathways in many different organisms, and they account for relatively large amounts of mass transfer and energy generation within a cell; they are the quantitatively major pathways.

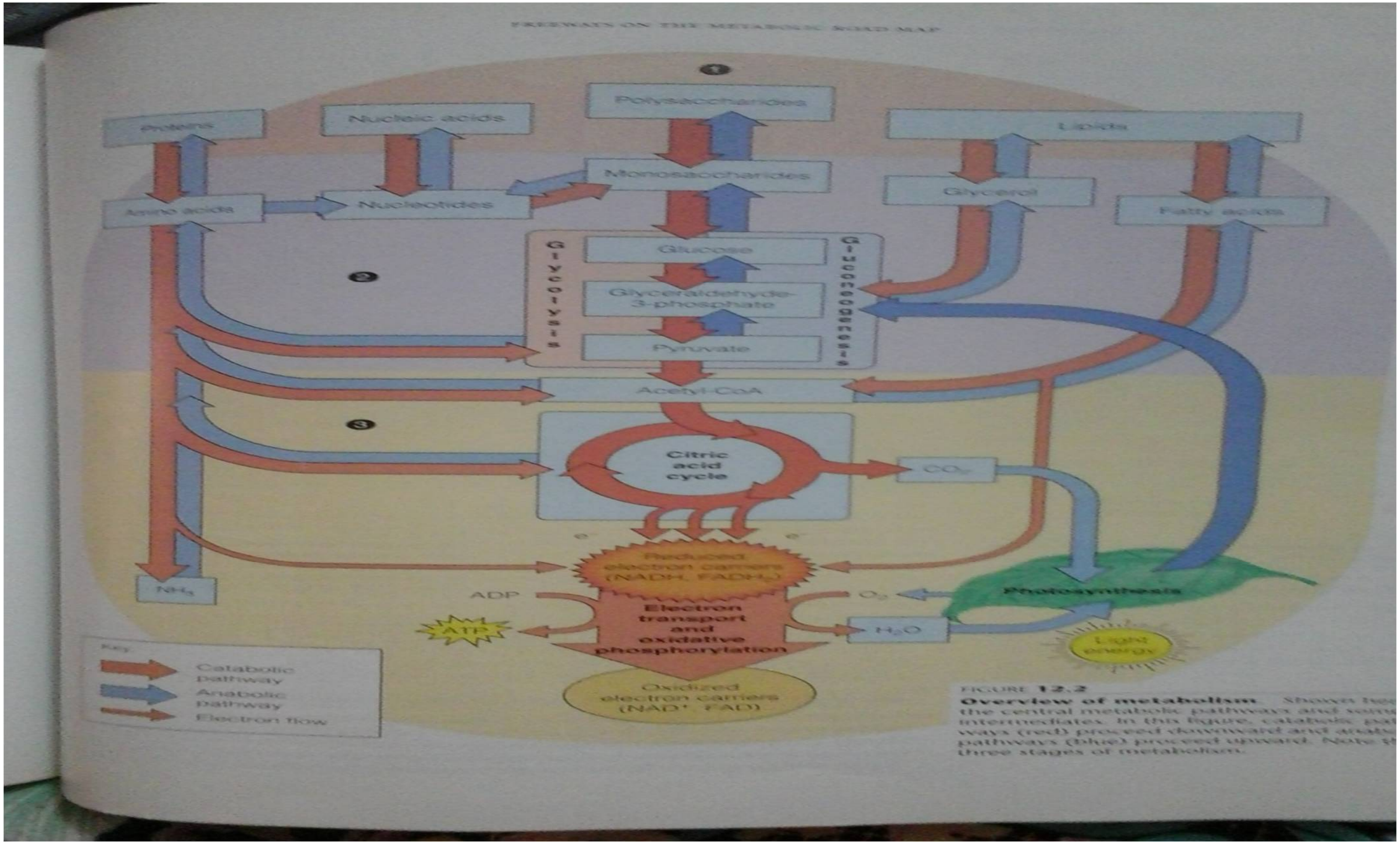
- All multicellular organisms and many bacteria are **aerobic organisms**; they depend absolutely upon **respiration**, the coupling of energy generation to the oxidation of nutrients by **oxygen.**
- **metabolite** (noun) : substance undergoing change during metabolism, are the intermediates and products of metabolism

- **Oxidation and Reduction in Organic Chemistry**
  - A **reduction** will result in a net **increase in the number of C-H bonds, or a net decrease in the number of C-O bonds** (or equivalent, such as C-Cl, C-Br, etc).
  - An oxidation will result in a net decrease in the number of C-H bonds, or a net increase in the number of C-O bonds (or equivalent).

- PYRUVATE → ETHANOL


CATABOLISM
ANABOLISM
Stage
1
Polymers:
Proteins
Nucleic acids
Polysaccharides
Lipids
2
Monomers:
Amino acids
Nucleotides
Sugars
Fatty acids
Glycerol
3
Metabolic
Intermediates:
Pyruvate
Acetyl-CoA
Citric acid cycle
intermediates
Energy
Net
output
Energy
Net
input
Simple
Small Molecules:
H_2O
CO_2
NH_3

FREE WAYS ON THE METABOLIC ROAD MAP



over view of metabolism.jpg - Shortcut.lnk

CENTRAL PATHWAYS OF ENERGY METABOLISM

- Glycolysis (glucose) → pyruvate
- Fermentation (anaerobic) pyruvate → ethanol
- Oxidative metabolism-respiration- (aerobic)

pyruvate → **acetyl-coenzyme A** ← β−oxidation of fatty acid

some amino acids

anabolic direction

CITRIC ACID CYCLE (CAC)

- In aerobic all catabolic pathways converge on the **CAC**
  - oxidative reactions of CAC generate reduced electron carriers whose re-oxidation derives ATP biosynthesis.(through e-transport& oxidative phosphorylation)

DISTINCT PATHWAY FOR BIOSYNTHESIS AND DEGRDATION

- i.e. fatty acid synthesis takes place in cytosol, by distinct mechanisms and different enzymes than fatty acid oxidation which occur in mitochonderia

❖Reasons :

1. Exergonicity & endergonicity (of each pathway)
2. Need to control the flow of metabolites in relation to the bio-energetic status a cell

Ex: futile cycle → regulation → substrate cycle

Bio-energetic considerations

- **Oxidation as metabolic energy**
- **BIOLOGICAL OXIDATIONS** are **oxidation** reactions occur without a large increase in temperature and with capture of some of the free energy as chemical energy.

- Metabolic energy capture occurs largely through the synthesis of ATP, a molecule designed to provide energy for biological work. The capture of energy is quite efficient.

- i.e : catabolism of glucose, for example, about 40% of the 2870 kJ/mol of energy released is used to drive the synthesis of ATP from ADP and Pi.

- More highly reduced a substrate , the higher its potential for generating biological energy
- Biological energy is used for

  1- countless reaction

  2- transport materials across membranes

  3- transmit nerve impulses

  4- contract muscles

Important Points about ΔG

1. **Three important terms relating to the free energy change of a process are:**

a- **ΔG** - the total free energy change for a reaction under any conditions

b- $\Delta G°$- free energy under standard conditions (all concentrations of 1M)

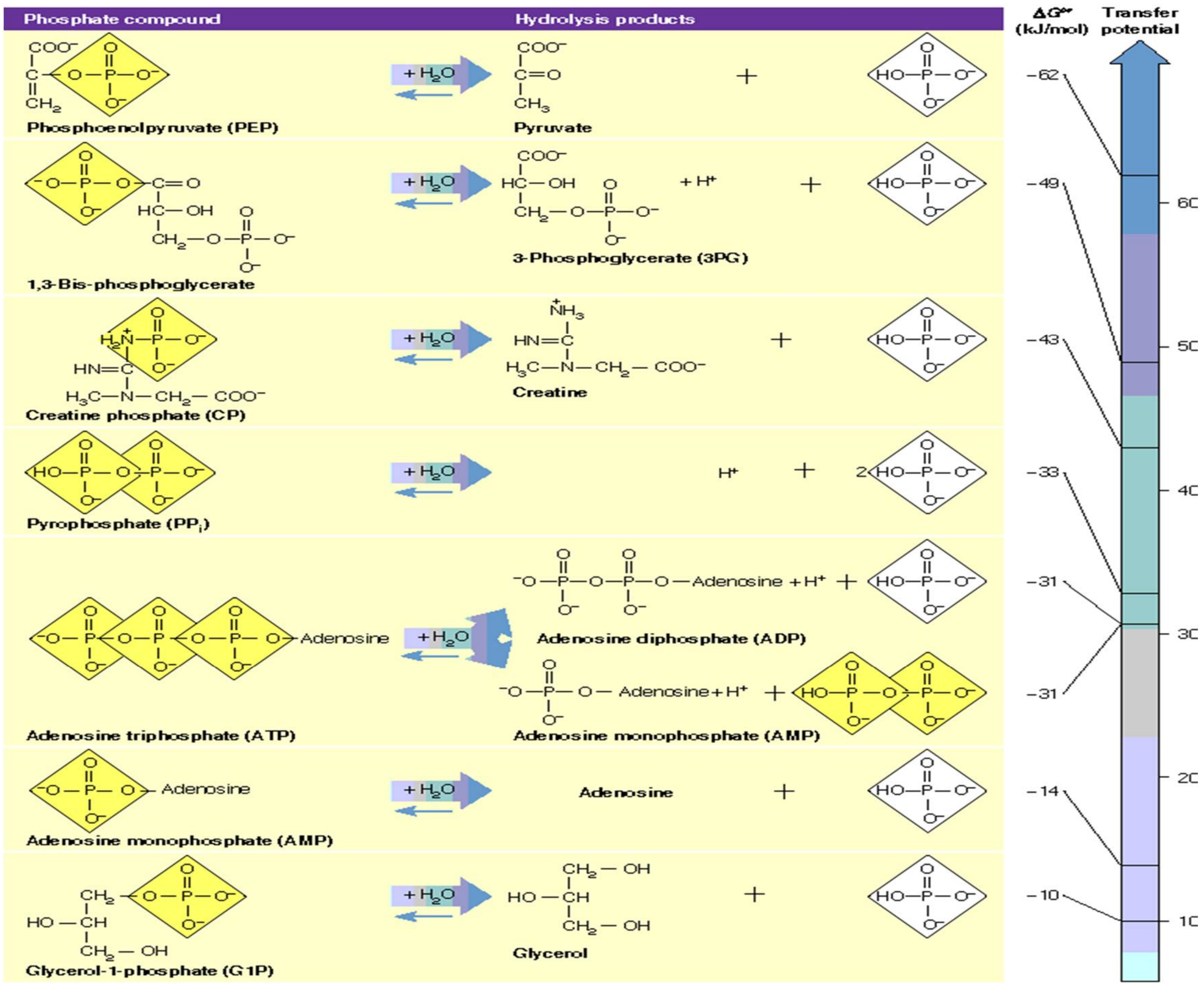
c- $\Delta G°'$ - the free energy change under standard biological conditions (all concentrations 1M, [H2O] = constant, and pH = 7.0)

Thus, a positive may influence a reaction, but cellular conditions may make the overall for the reaction negative.

2. ΔG and only ΔG determines whether a reaction is favorable as written.. Only when is negative is a reaction favored. **The sign of $\Delta G°$ or $\Delta G°'$ does not determine the direction a reaction will proceed.**

3. ΔG depends on temperature ($\Delta G = \Delta H - T\Delta S$). This can be a factor for a given reaction occurring in different organisms living under very different conditions of temperature.

Energetic Biomolecules



HYDROLYSIS REACTIONS FOR SOME BIOCHEMICALLY IMPORTANT PHOSPHATE COMPOUNDS

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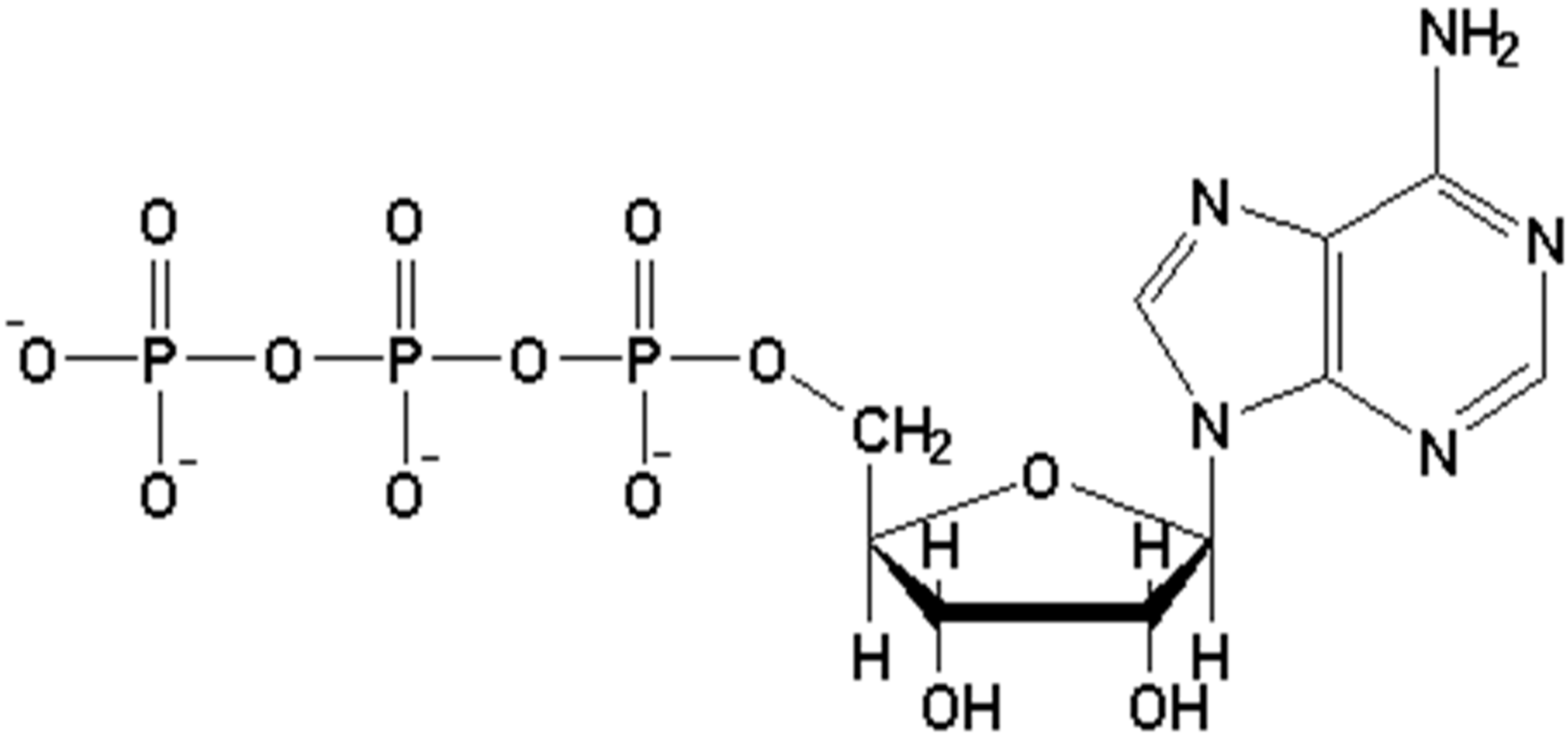
(ATP) Adenosine Tri Phosphate:



Adenosine triphosphate (ATP)

ATP as Free Energy Currency

- thermodynamically unstable compound
- used to provide energy in a wide variety of metabolic reactions
- Hydrolysis of either phosphoanhydride bond in **ATP** has a $\Delta G^{\circ\prime}$ of about -31 kJ/mol.
- **ATP** breakdown is usually coupled with thermodynamically unfavorable reaction.
- **ATP** has a high "phosphoryl group transfer potential" rather than calling it a high energy compound.
- **ATP** hydrolysis under cellular conditions yields **ADP** + Pi or **AMP** + PPi.
- Effective $\Delta G'$ values in cells may be close to -50 kJ/mol

Energy Yields, respiratory Quotients, and Reducing Equivalents

- More highly reduced a substrate , the higher its potential for generating biological energy

Fat has higher caloric content than carbohydrate

$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$ $\Delta G°' = -3.74$ kcal/g

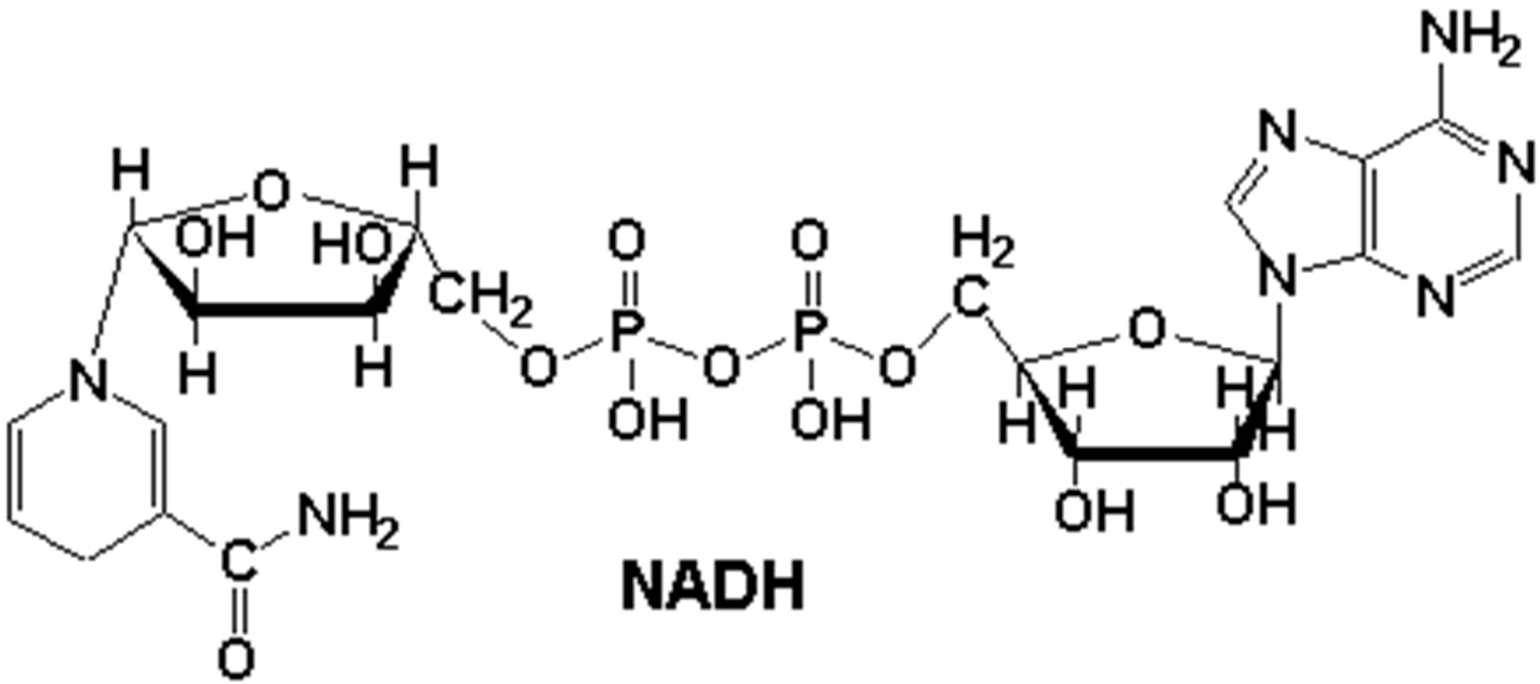
- RQ =1 (mol CO2/mol of O2)

$C_{16}H_{32}O_2 + 23O_2 \longrightarrow 16CO_2 + 6H_2O$ $\Delta G°' = -9.30$kcal/g

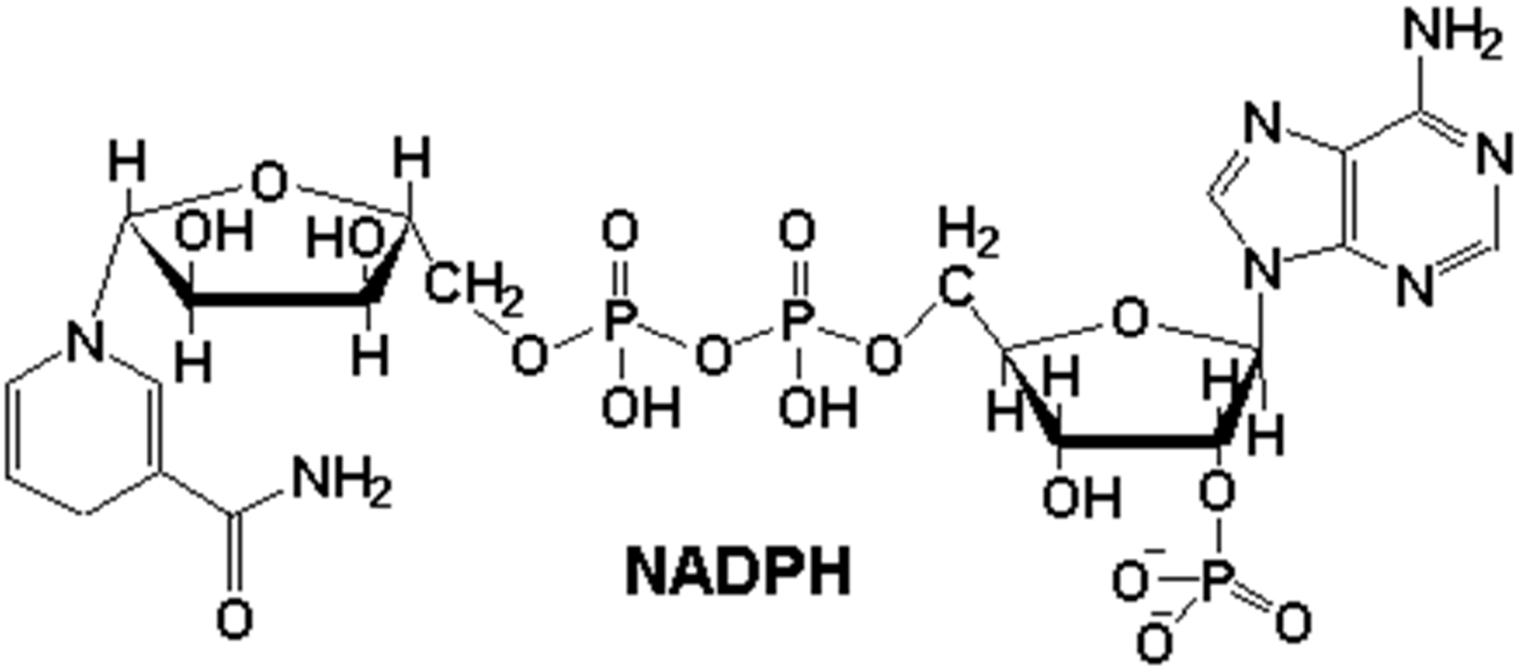
RQ = 0.7 (why?)

- Reducing equivalent: express degree of substrate oxidation (1 mole of H atom)

NAD^+, $NADP^+$ $\longrightarrow$ NADH, NADPH (major source for reductive biosynthesis)



NADH



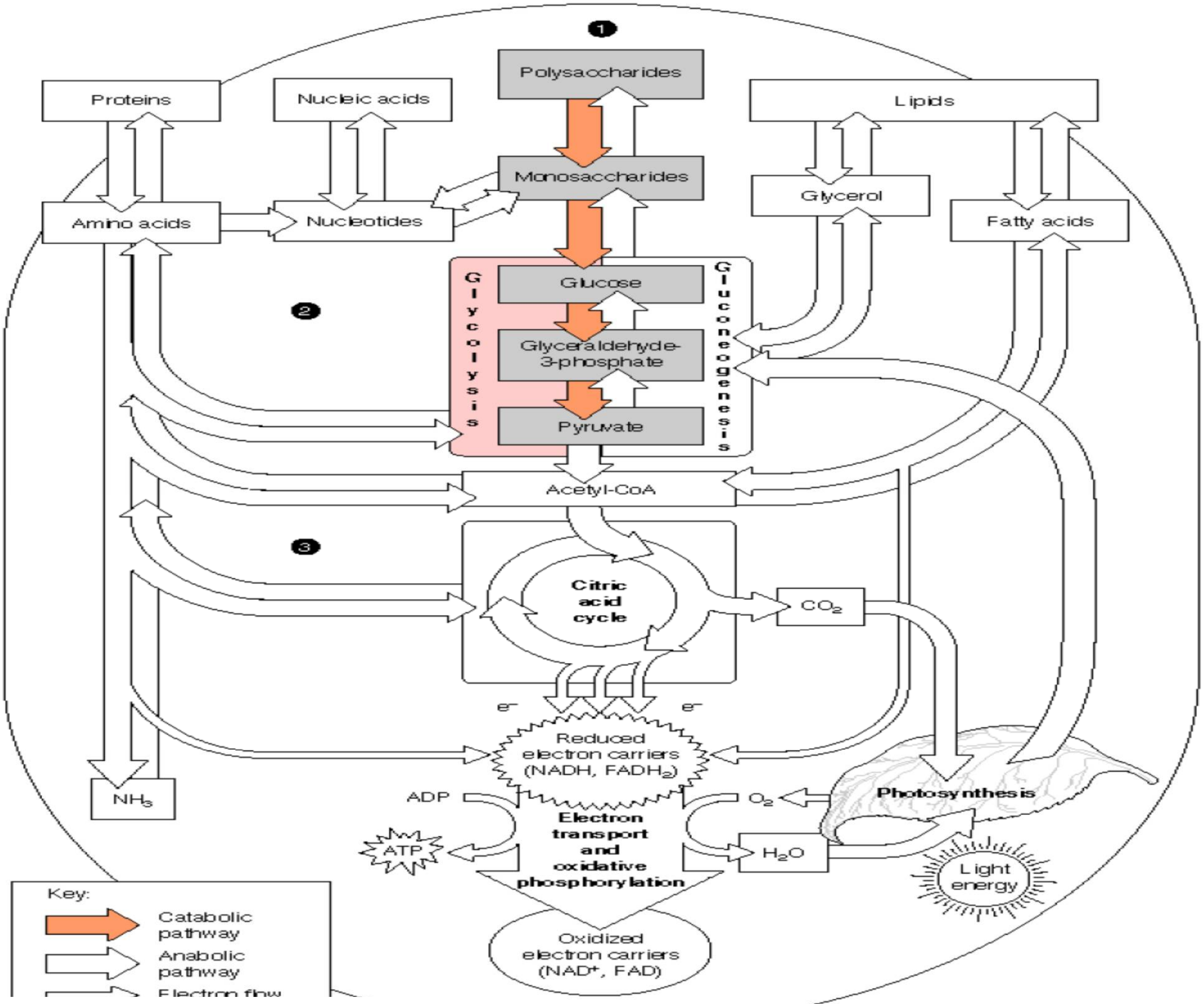
NADPH

CARBOHYDRATE METABOLISM

ANAEROBIC PROCESSES

• Glycolysis

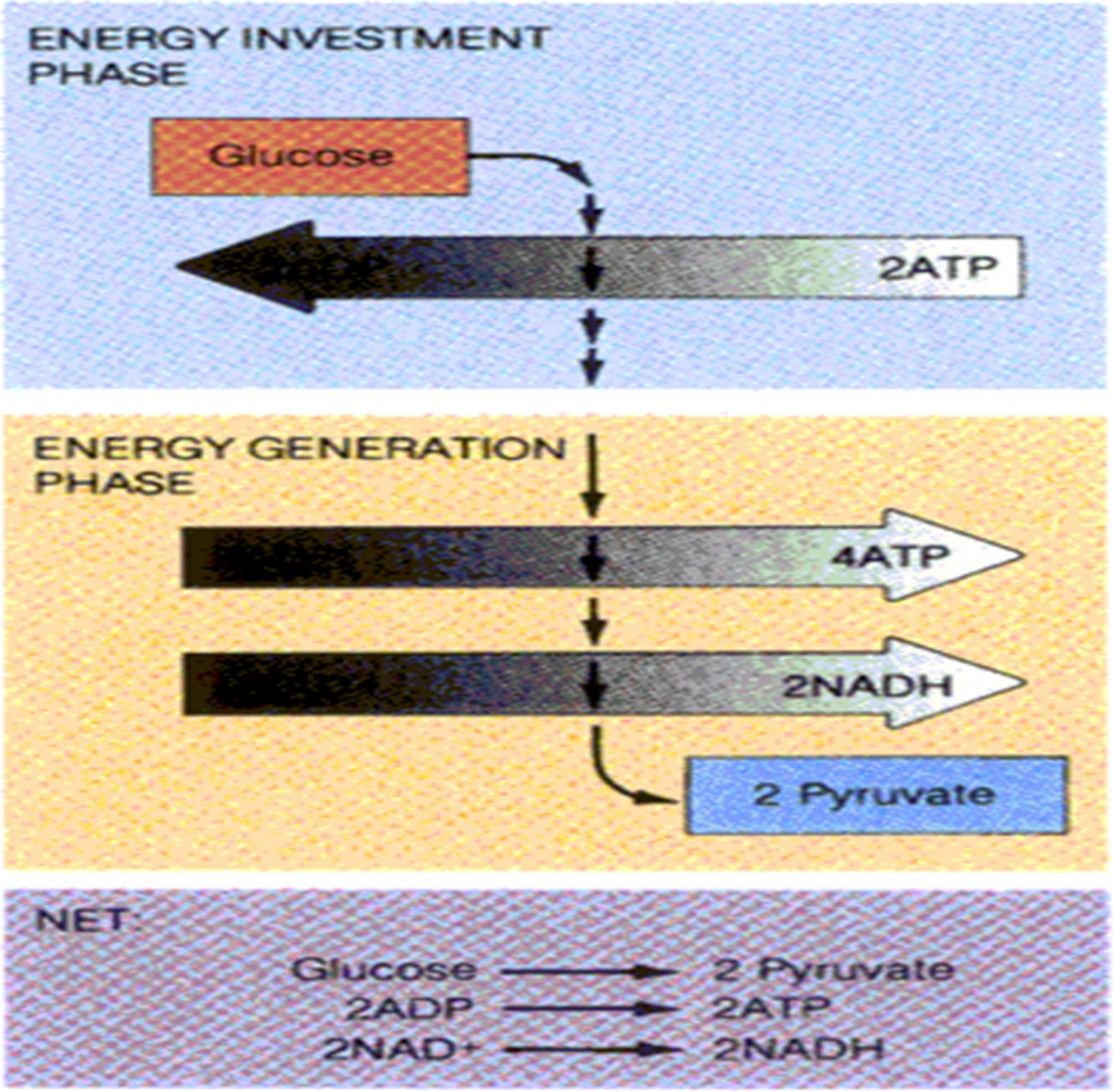
- Earliast metabolic pathway
- Universal in living cells
- Regulation of glycolysis is well understood
- The central metabolic role this pathway plays in generating both energy and metabolic intermediates for other pathways

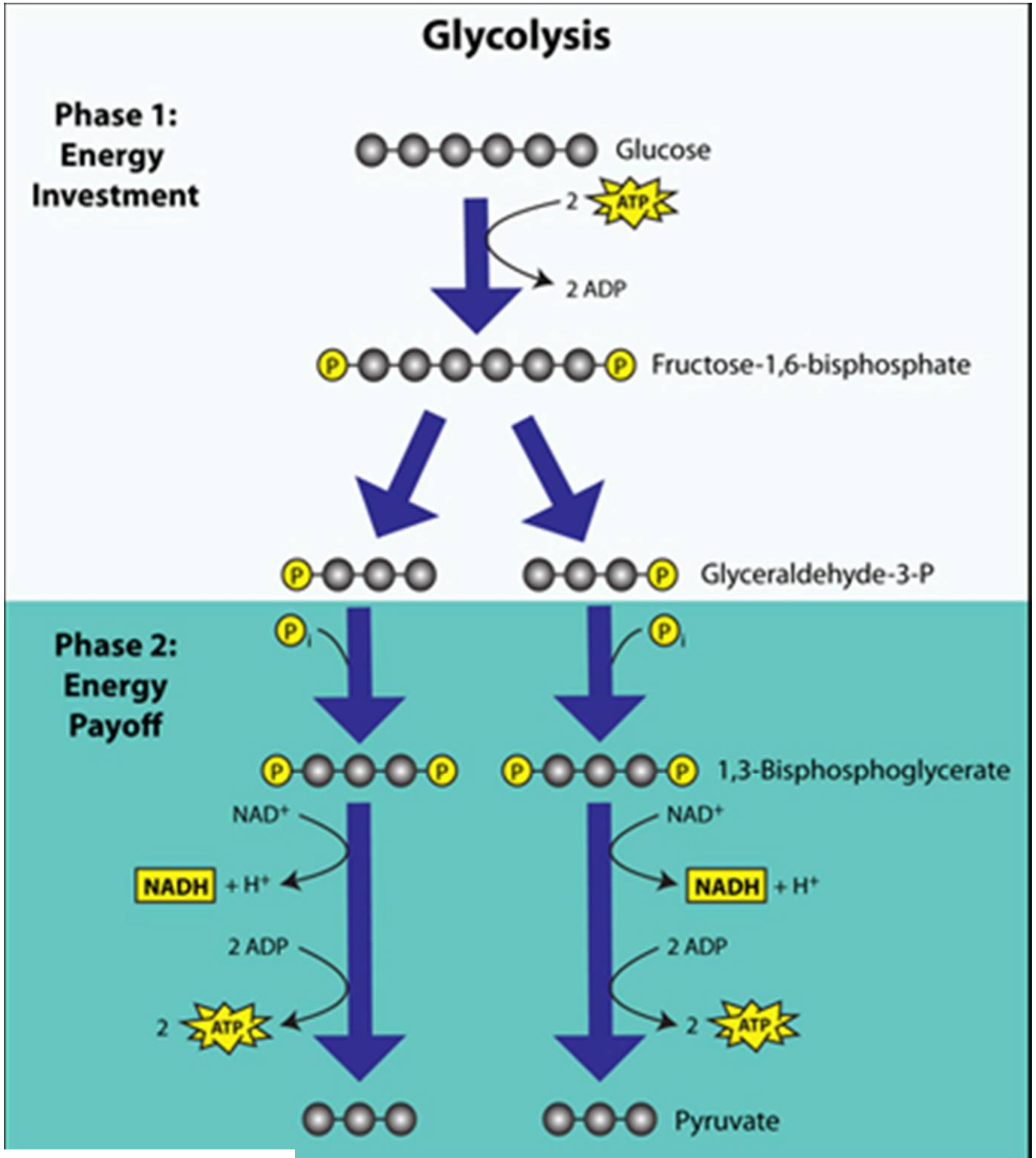

1
Polysaccharides
Proteins
Nucleic acids
Lipids
Monosaccharides
Glycerol
Amino acids
Nucleotides
Fatty acids
2
Glycolysis
Glucose
Gluconeogenesis
Glyceraldehyde-3-phosphate
Pyruvate
Acetyl-CoA
3
Citric acid cycle
CO_2
e⁻
e⁻
Reduced electron carriers (NADH, $FADH_2$)
NH_3
ADP
O_2
Photosynthesis
Electron transport and oxidative phosphorylation
ATP
H_2O
Light energy
Key:
Catabolic pathway
Anabolic pathway
Electron flow
Oxidized electron carriers (NAD^+, FAD)

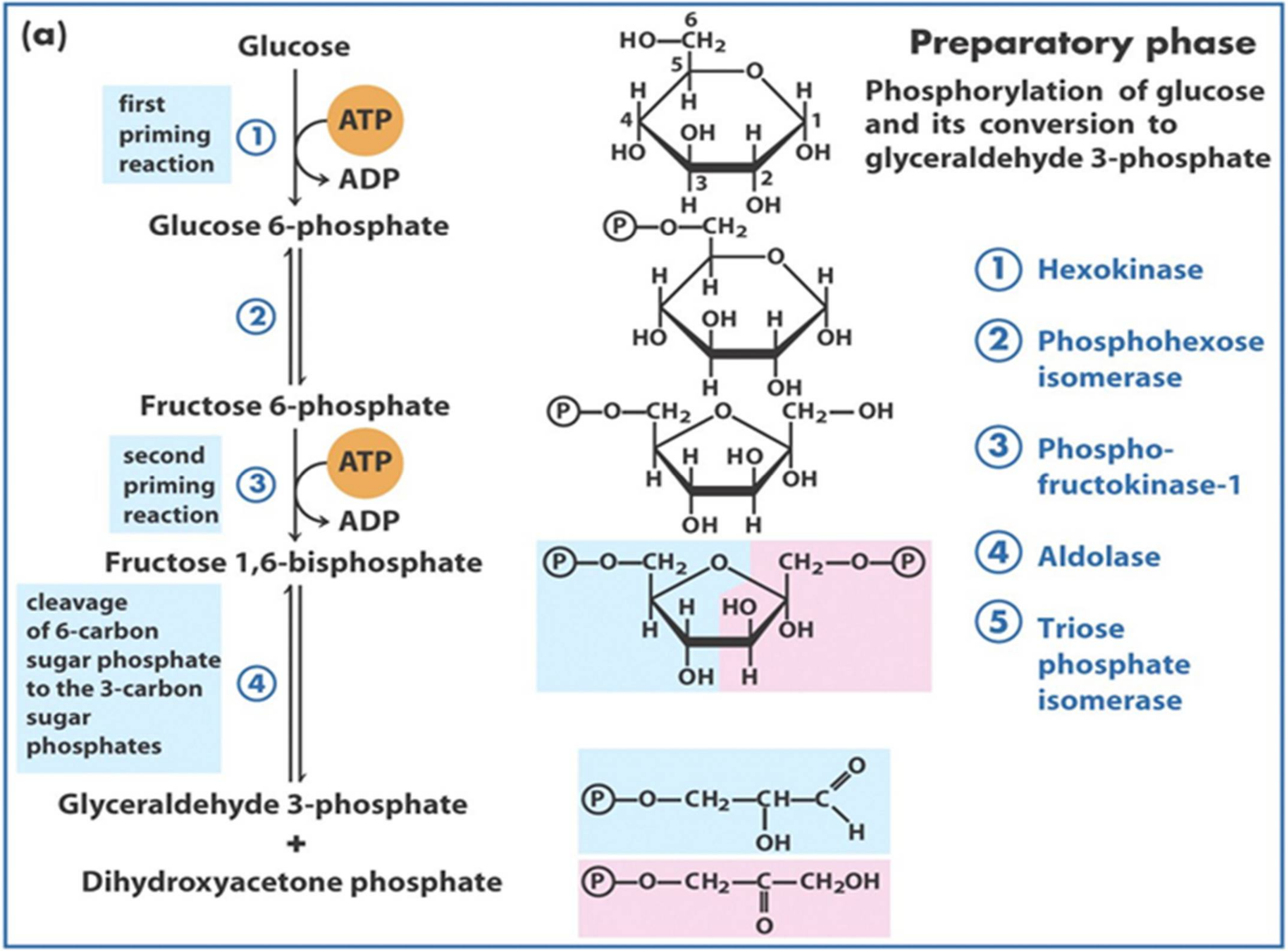
Summary of Glycolysis

- **Glycolysis** is a central metabolic pathway involving metabolism of the sugar **glucose**
- Divided into a phase in which **ATP** energy is invested and a phase in which ATP energy is generated
- The starting point for glycolysis is the molecule **glucose** and the process ends with formation of two **pyruvate** molecules
- Additional products of glycolysis include two **ATPs** and two **NADHs.**

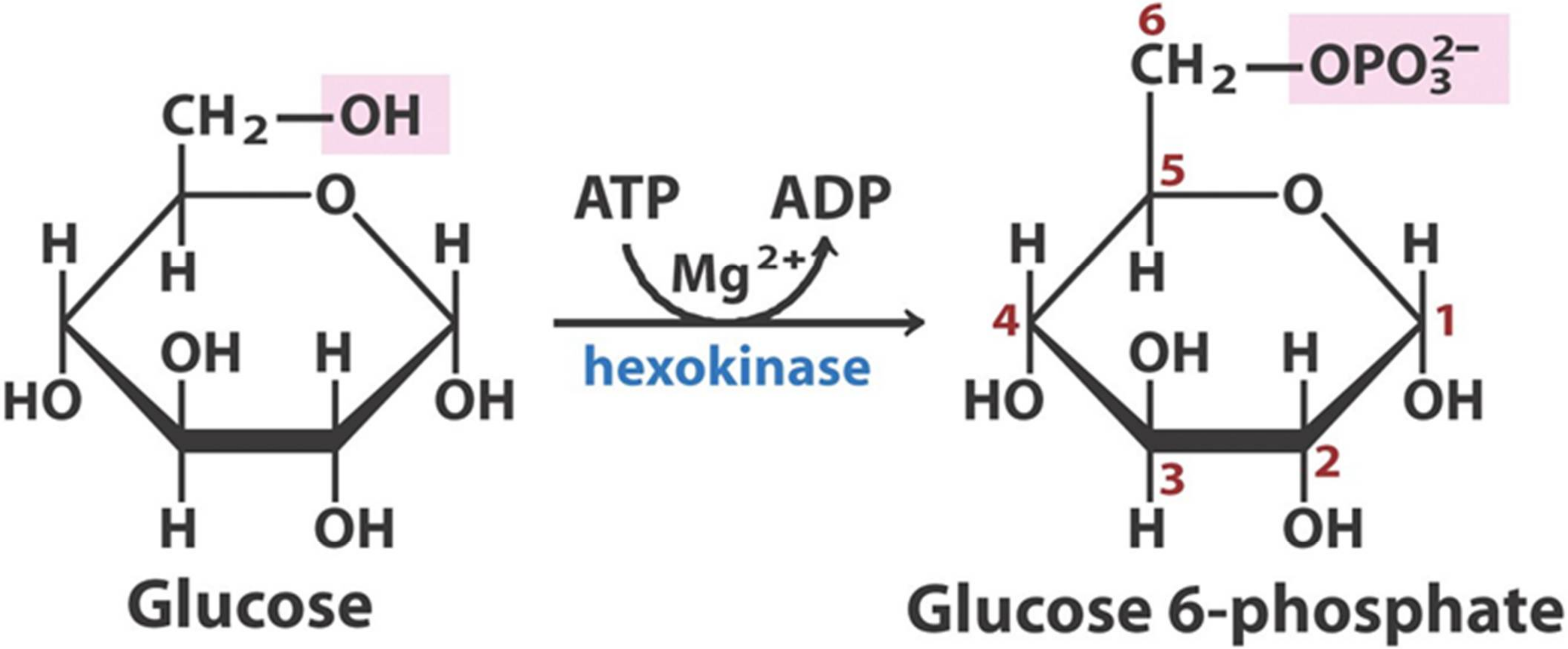
The two phases of glycolysis and the products of glycolysis.




Glycolysis
Phase 1: Energy Investment
Glucose
2 ATP
2 ADP
Fructose-1,6-bisphosphate
Glyceraldehyde-3-P
Phase 2: Energy Payoff
P i
P i
1,3-Bisphosphoglycerate
NAD+
NADH + H+
NAD+
NADH + H+
2 ADP
2 ATP
2 ADP
2 ATP
Pyruvate

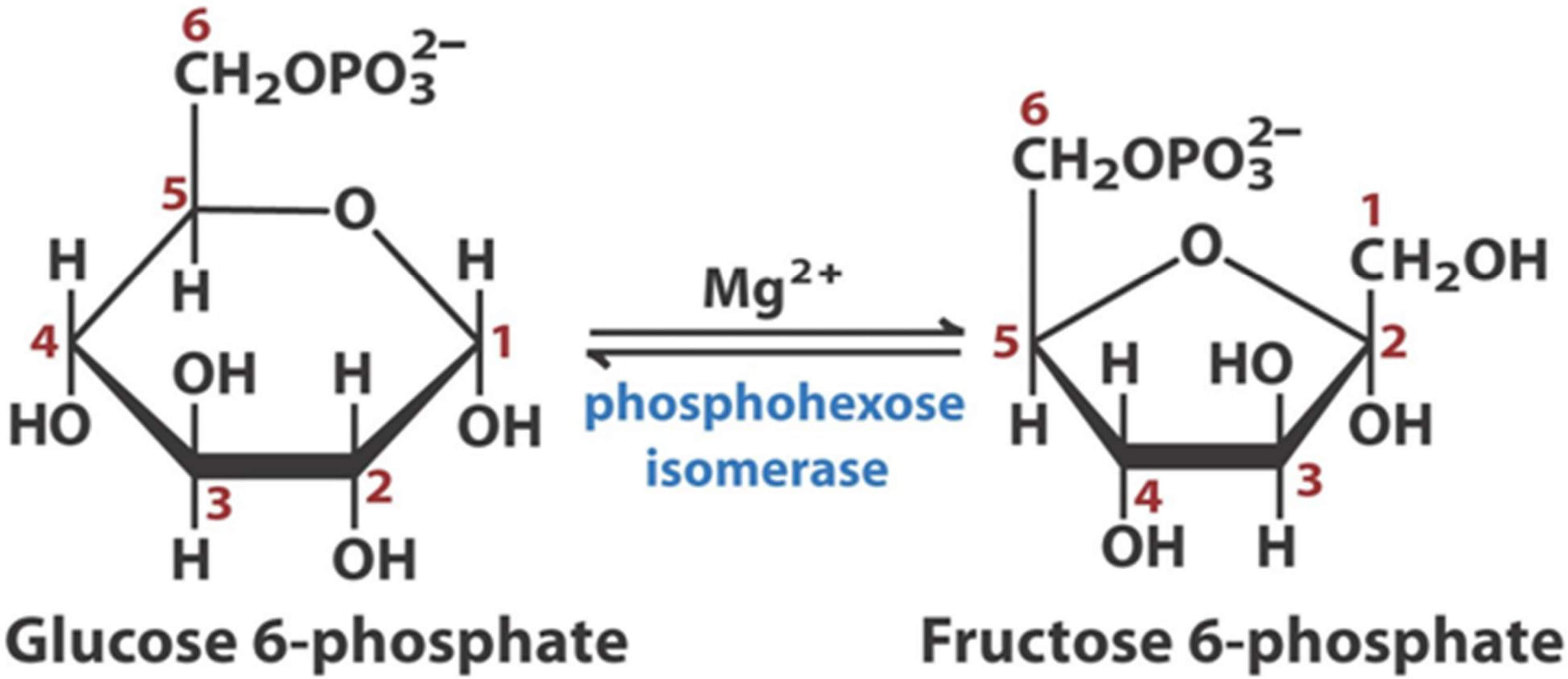

(a)
Preparatory phase
Phosphorylation of glucose and its conversion to glyceraldehyde 3-phosphate
Glucose
first priming reaction
1
ATP
ADP
Glucose 6-phosphate
2
Fructose 6-phosphate
second priming reaction
3
ATP
ADP
Fructose 1,6-bisphosphate
cleavage of 6-carbon sugar phosphate to the 3-carbon sugar phosphates
4
Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
1 Hexokinase
2 Phosphohexose isomerase
3 Phospho-fructokinase-1
4 Aldolase
5 Triose phosphate isomerase

Reaction 1



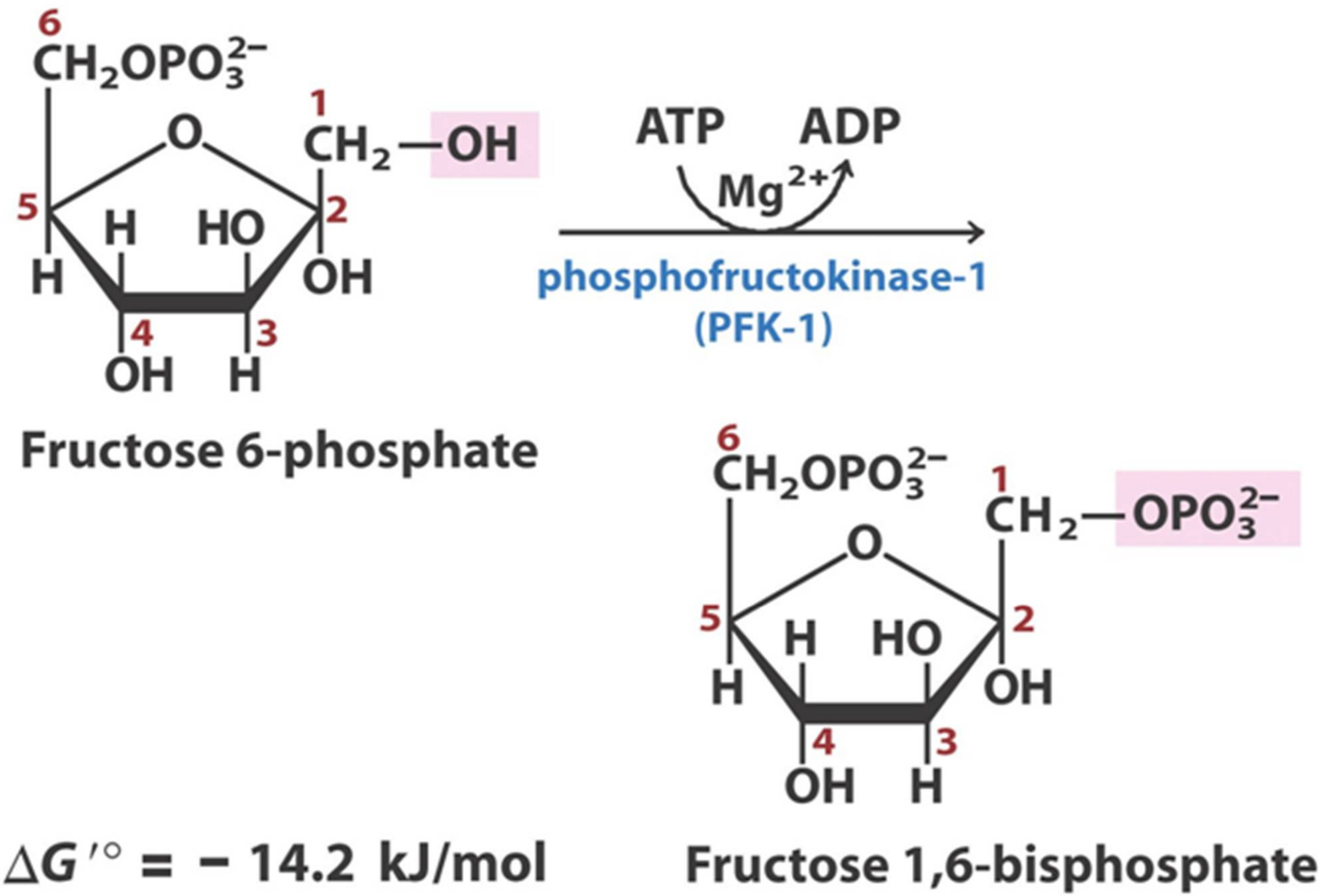
$$\Delta G'^{\circ} = -16.7 \text{ kJ/mol}$$

Reaction 2: *isomerization*



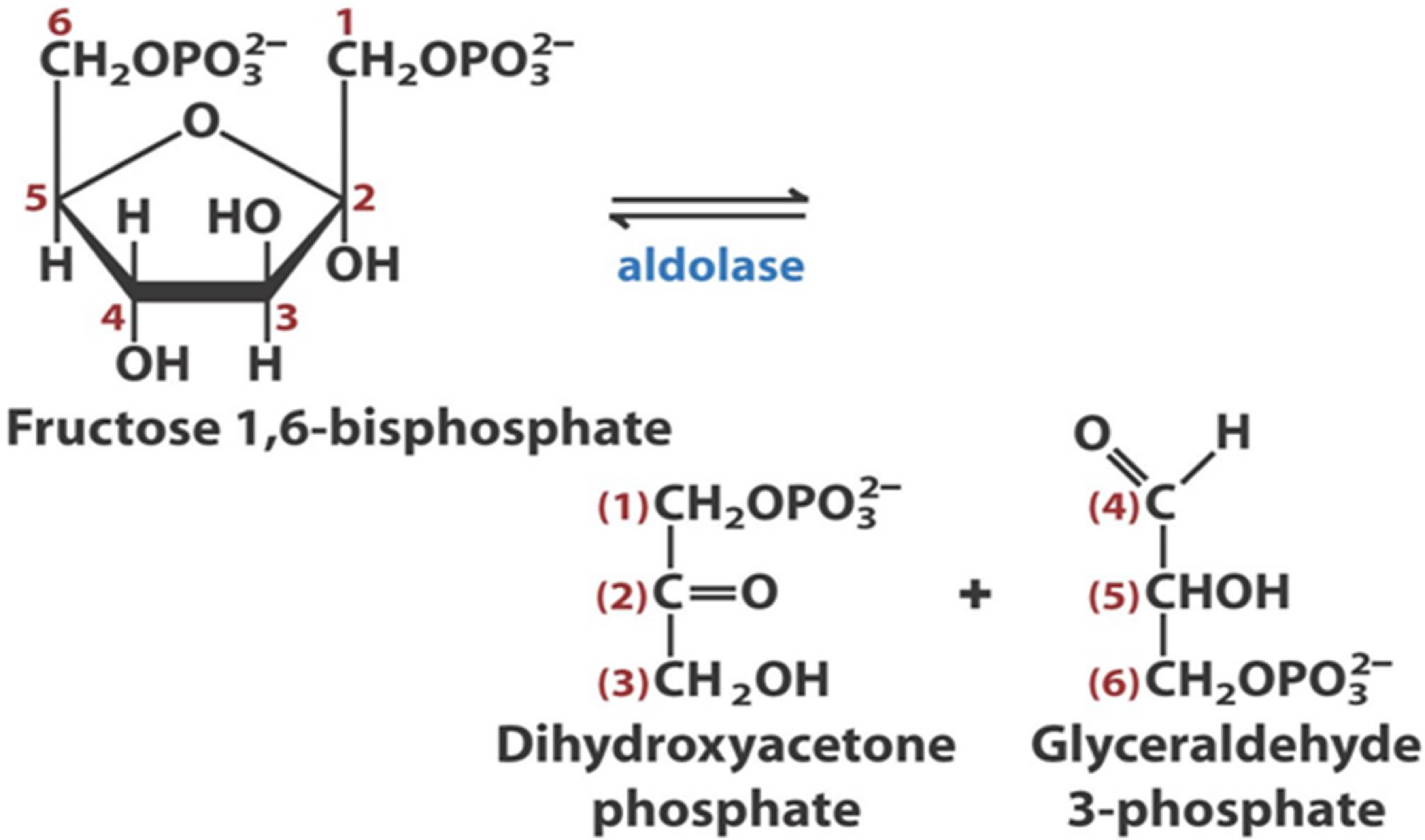
$\Delta G'^{\circ} = 1.7$ kJ/mol

Reaction 3: *phosphorylation*



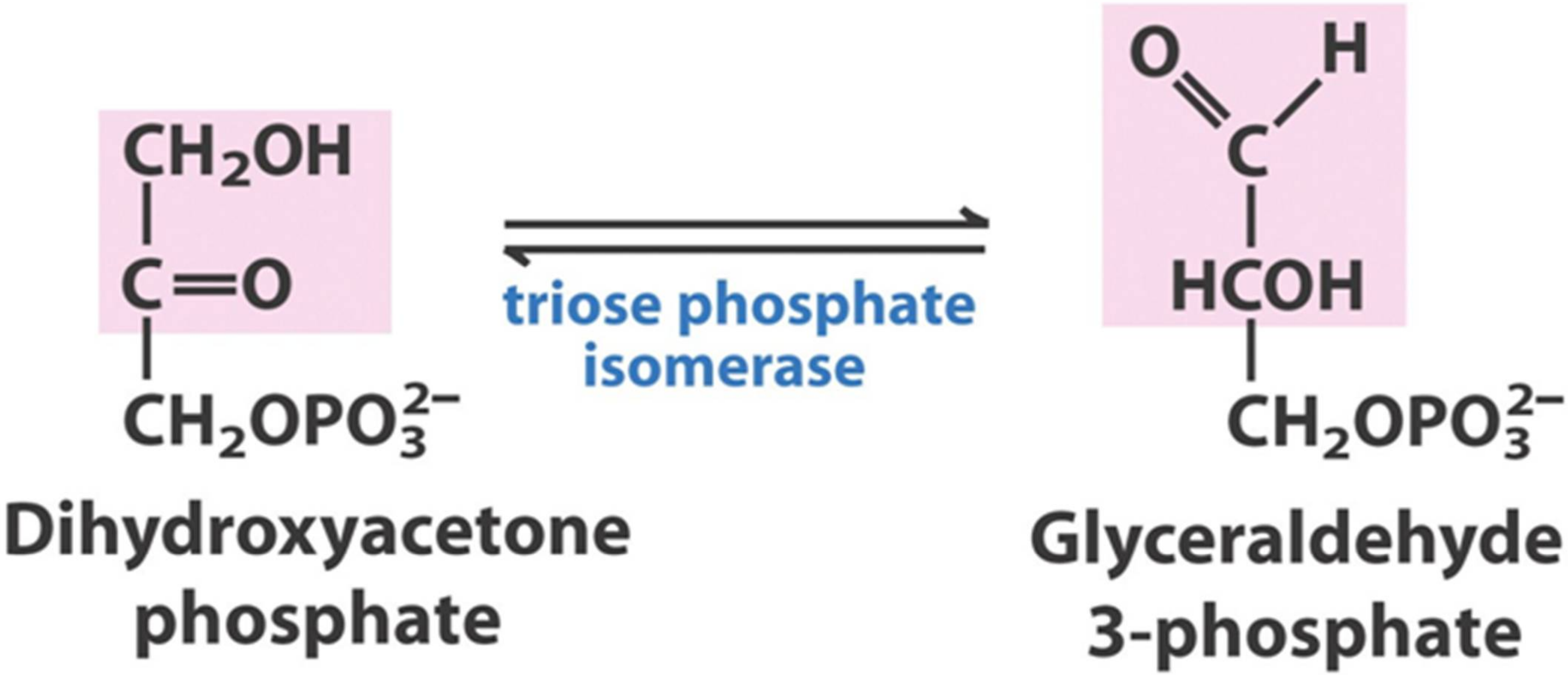
$\Delta G'^{\circ} = -14.2$ kJ/mol

Reaction 4: *cleavage*



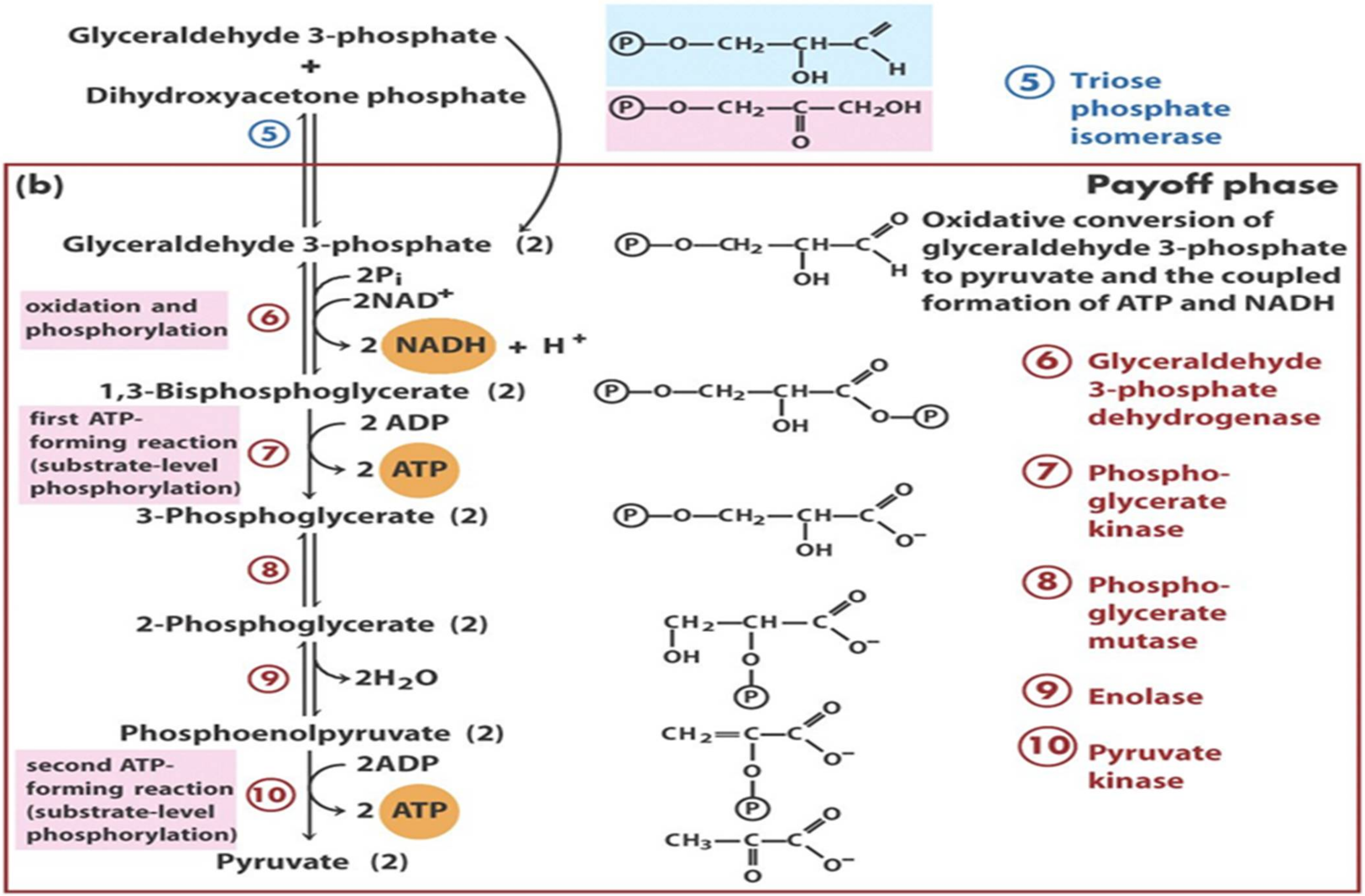
$\Delta G'^{\circ} = 23.8$ kJ/mol

Reaction 5: *isomerization*

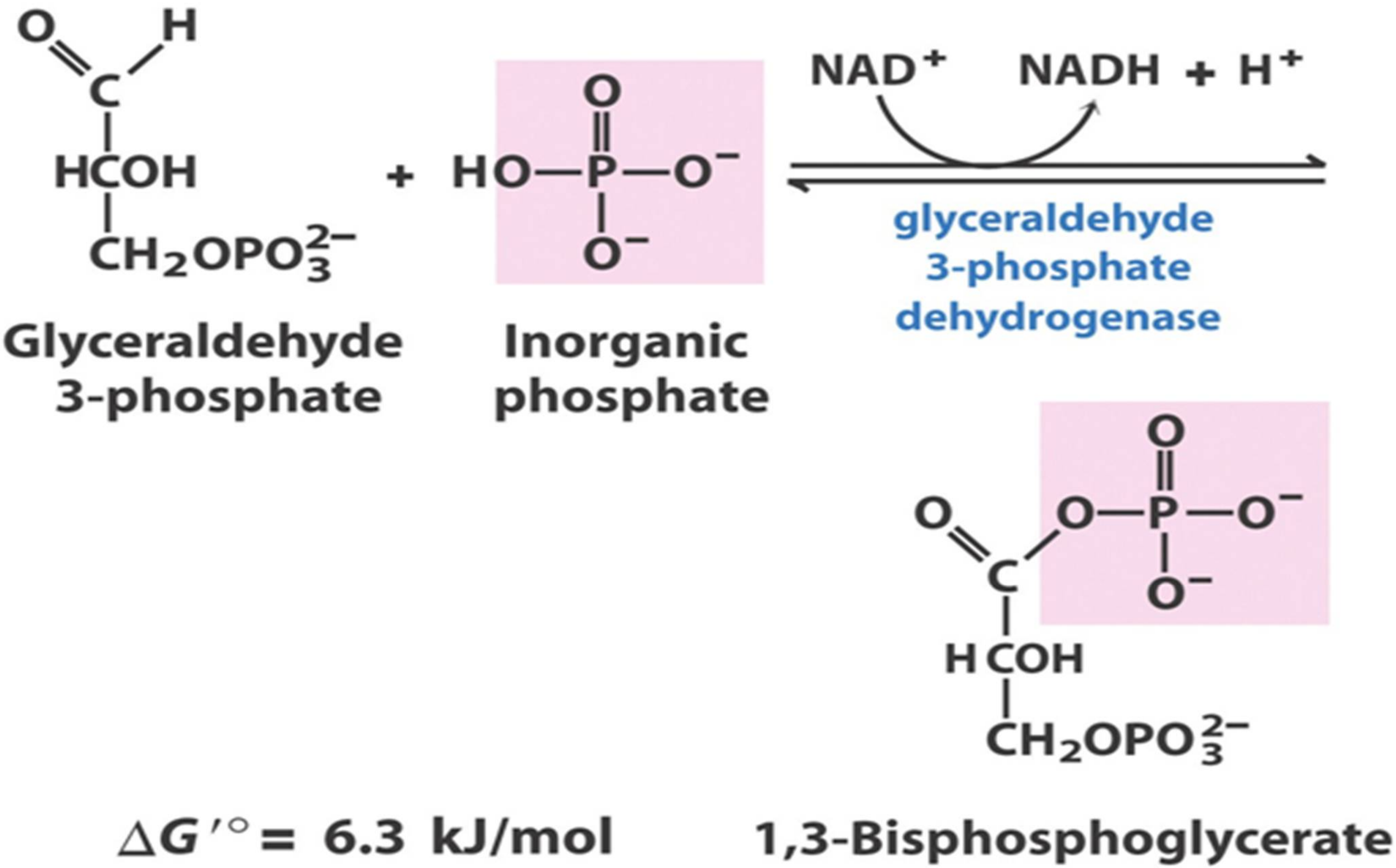


$\Delta G'^{\circ} = 7.5$ kJ/mol

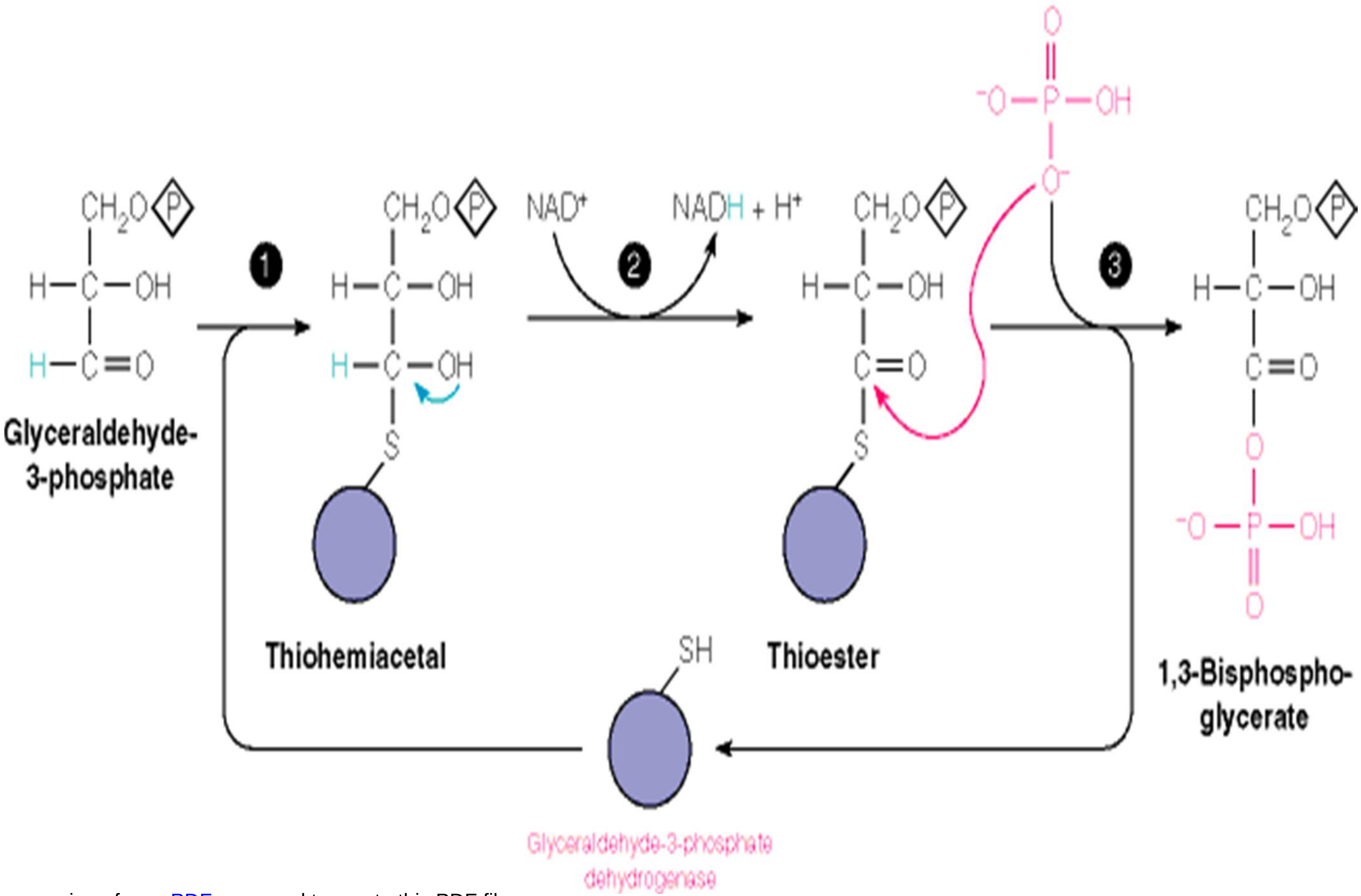
2nd phase


Glyceraldehyde 3-phosphate
+
Dihydroxyacetone phosphate
5
5 Triose phosphate isomerase
(b)
Payoff phase
Glyceraldehyde 3-phosphate (2)
Oxidative conversion of glyceraldehyde 3-phosphate to pyruvate and the coupled formation of ATP and NADH
2Pi
2NAD+
oxidation and phosphorylation
6
2 NADH + H+
1,3-Bisphosphoglycerate (2)
6 Glyceraldehyde 3-phosphate dehydrogenase
first ATP-forming reaction (substrate-level phosphorylation)
7
2 ADP
2 ATP
3-Phosphoglycerate (2)
7 Phospho-glycerate kinase
8
8 Phospho-glycerate mutase
2-Phosphoglycerate (2)
9
2H2O
9 Enolase
Phosphoenolpyruvate (2)
10 Pyruvate kinase
second ATP-forming reaction (substrate-level phosphorylation)
10
2ADP
2 ATP
Pyruvate (2)

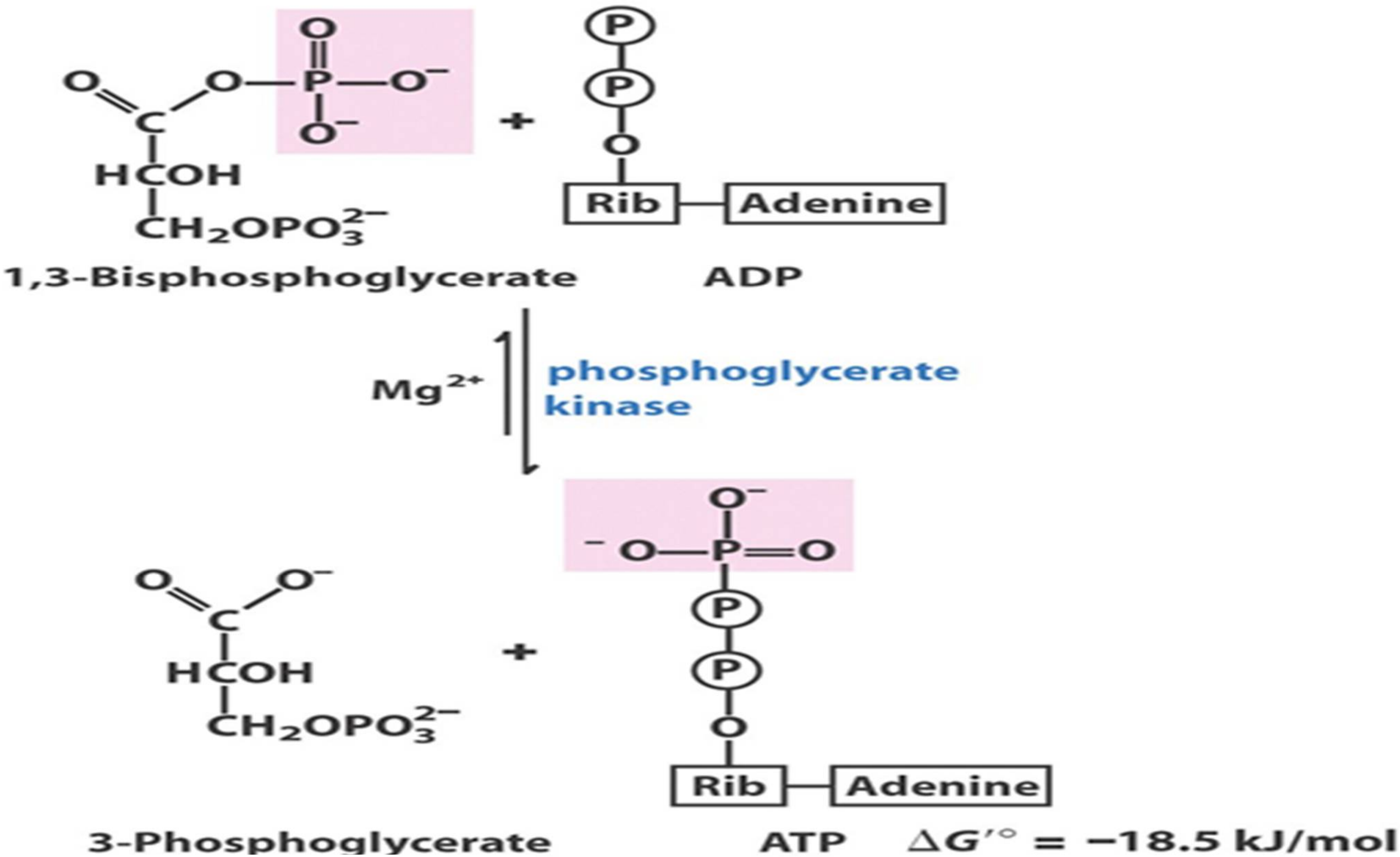
Reaction 6: *oxidation*



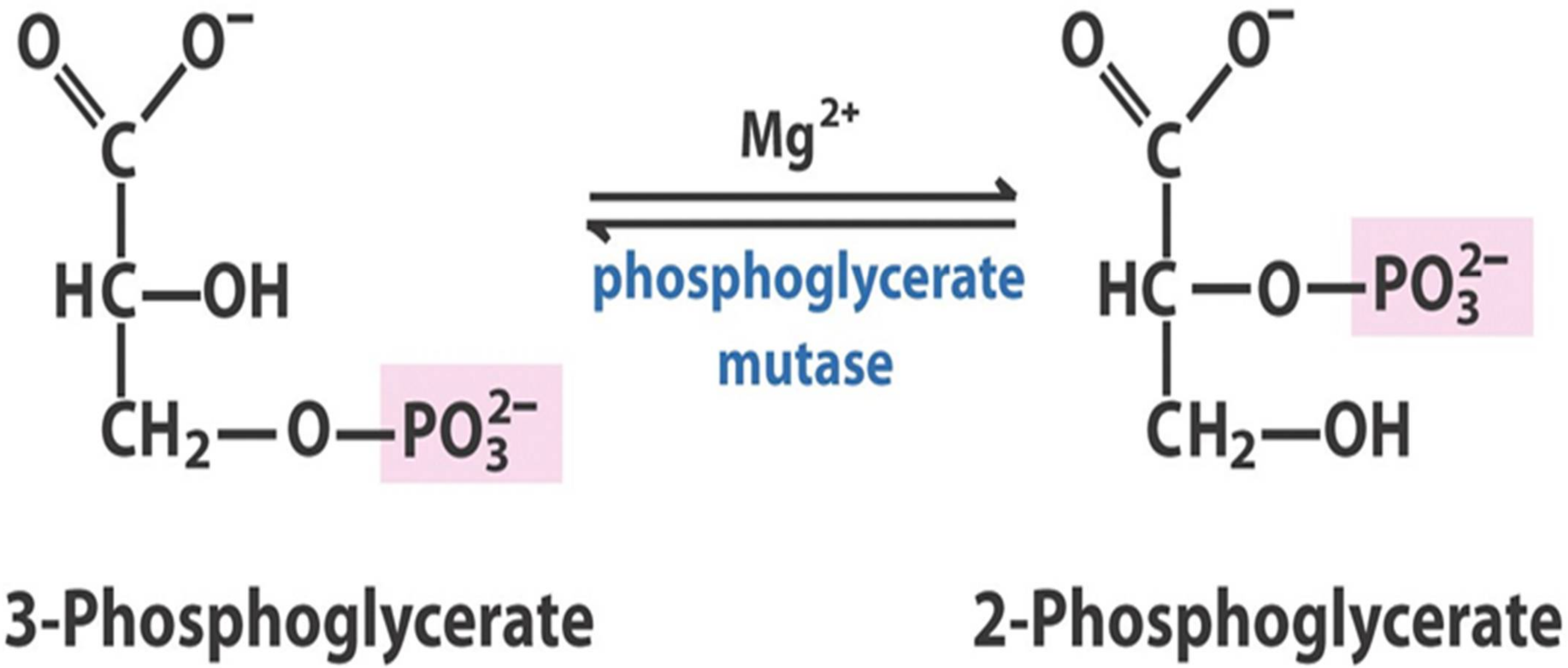
Reaction pathway for glyceraldehyde-3-phosphate dehydrogenase



Reaction 7: *substrate level phosphorylation*

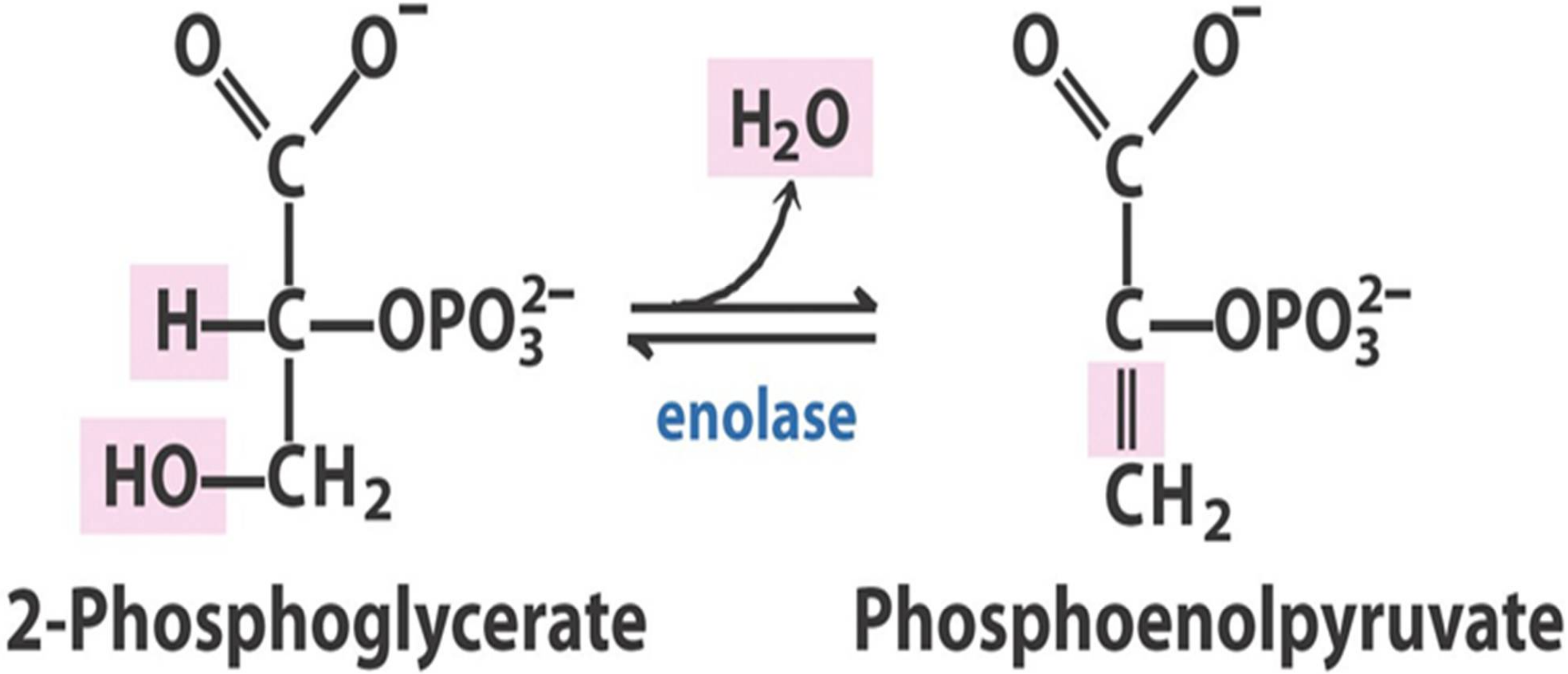


Reaction 8: *shift of phosphoryl group*



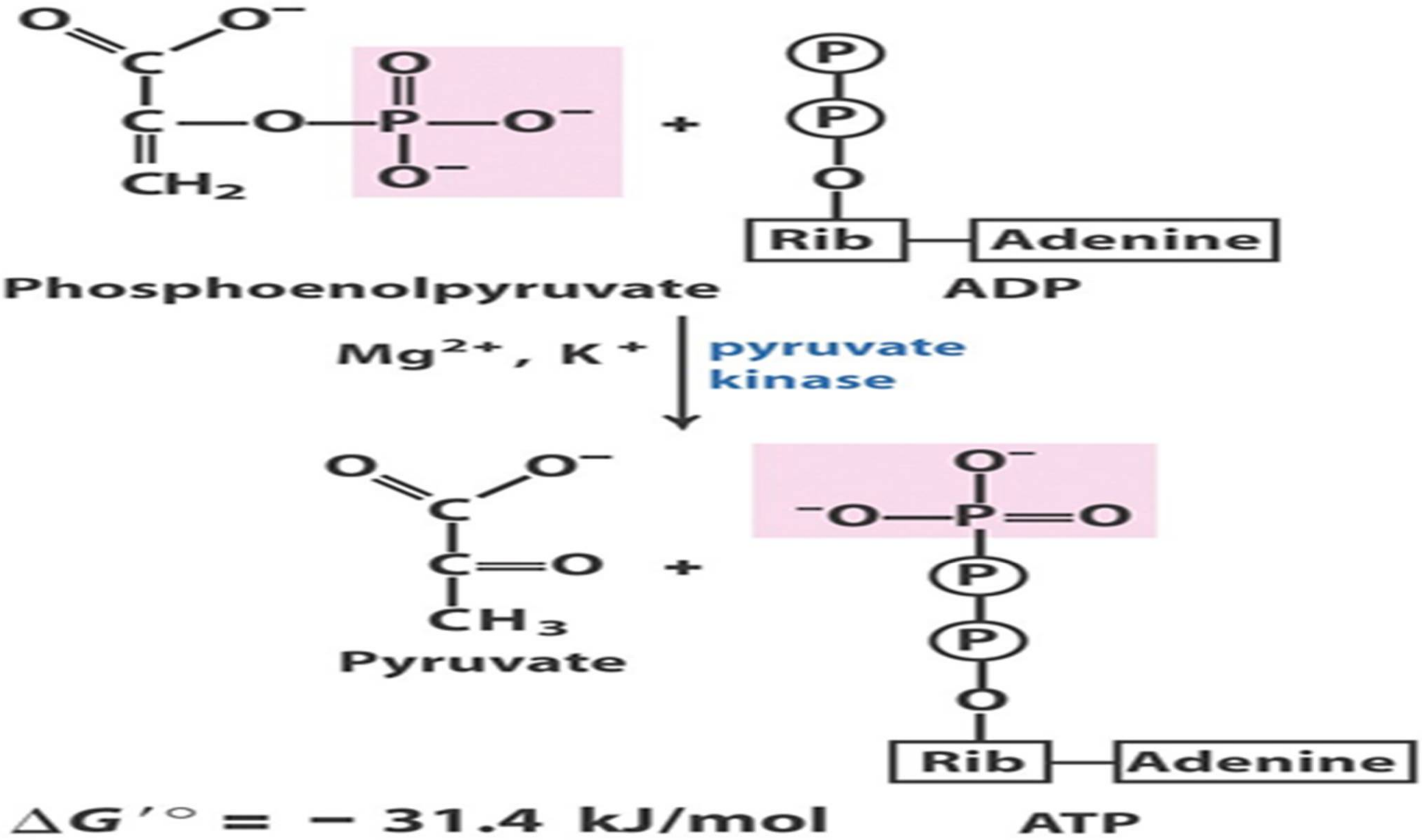
$\Delta G'^\circ = 4.4$ kJ/mol

Reaction 9: *dehydration*

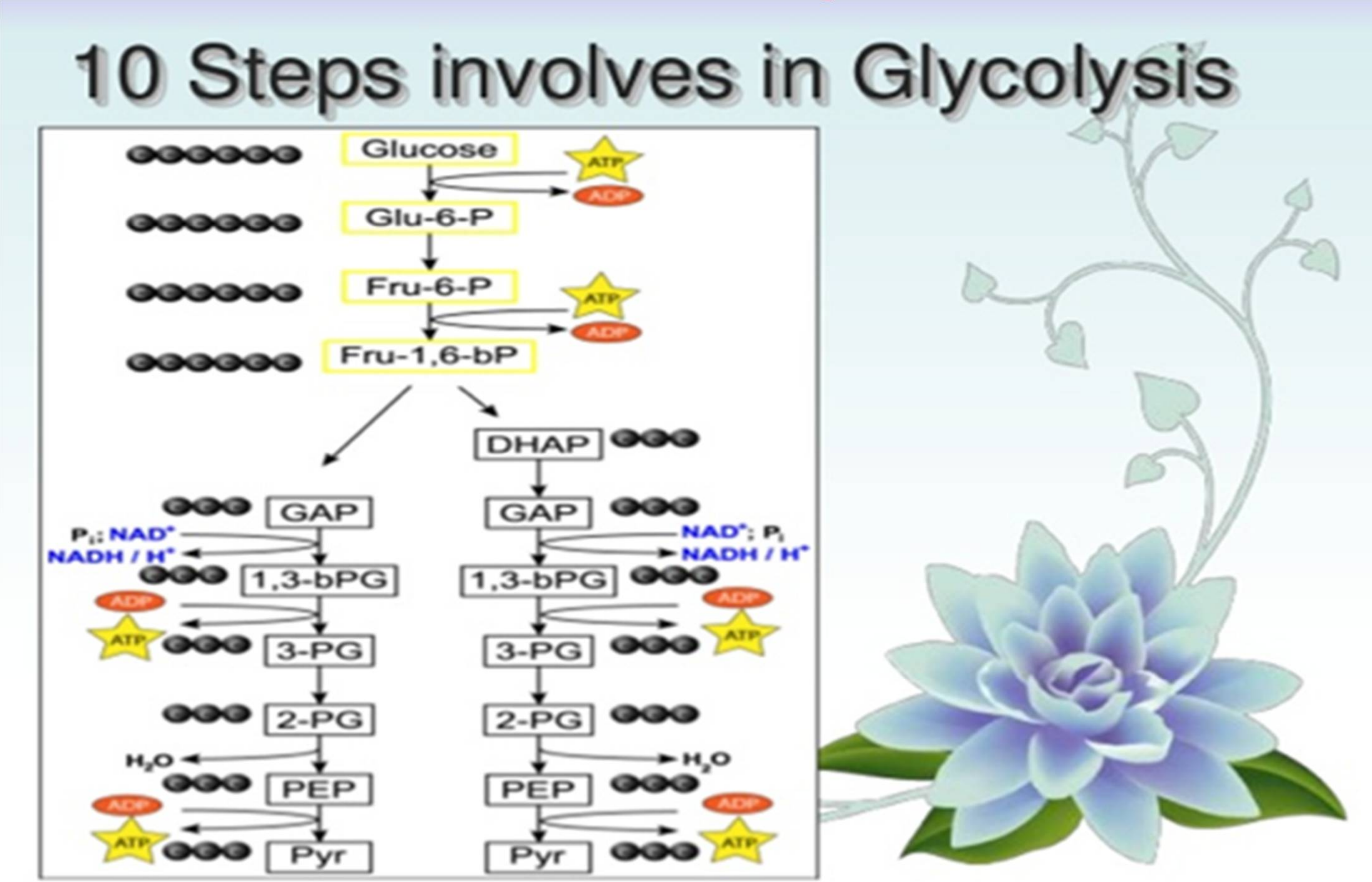


$\Delta G'^{\circ} = 7.5$ kJ/mol

Reaction 10: *substrate level phosphorylation*



Summary



10 Steps involves in Glycolysis
Glucose
ATP
ADP
Glu-6-P
Fru-6-P
ATP
ADP
Fru-1,6-bP
DHAP
GAP
GAP
Pi; NAD+
NADH / H+
NAD+; Pi
NADH / H+
1,3-bPG
1,3-bPG
ADP
ATP
ADP
ATP
3-PG
3-PG
2-PG
2-PG
H2O
H2O
PEP
PEP
ADP
ATP
ADP
ATP
Pyr
Pyr

Strategy of glycolysis

1. The process of **glycolysis** requires ATP energy input before ATP and NADH energy can be released. This breaks **glycolysis** into two phases - an energy input phase (reactions 1-5) and an energy release phase (reactions 6-10). The energy input phase includes two reactions (**hexokinase** and **phosphofructokinase**), each where ATP is used.

2. **Glycolysis**, through the formation of **pyruvate**, includes a single oxidation step:

D-Glyceraldehyde-3-Phosphate + **NAD**+ + Pi **<=> 1,3 Bisphosphoglycerate** + **NADH** + H+

Because there are two molecules of G3P per molecule of **glucose**, there is a total of two molecules of NADH formed per molecule of **glucose**.

3. **1,3BPG** and **PEP** are phosphorylated compounds, each with a phosphoryl group that has a free energy higher than that of the phosphate on ADP. Thus 1,3BPG and PEP can transfer a phosphoryl group to **ADP** to form **ATP**. This is called **substrate level phosphorylation** and it yields four molecules of ATP per molecule of glucose in the energy releasing phase of glycolysis. Thus, the 10 reactions of **glycolysis** generate two net molecules of ATP per molecule of glucose.

METABOLIC FATES OF PYRUVATE

- **Under aerobic conditions**

pyruvate is transformed into **acetyl-CoA**, which then enters the **citric acid cycle**.

$$Glucose + 8ADP + 6H^{+} + 8P_{i} + O_{2} \longrightarrow 2\ pyruvate + 8ATP + 10H_{2}O$$

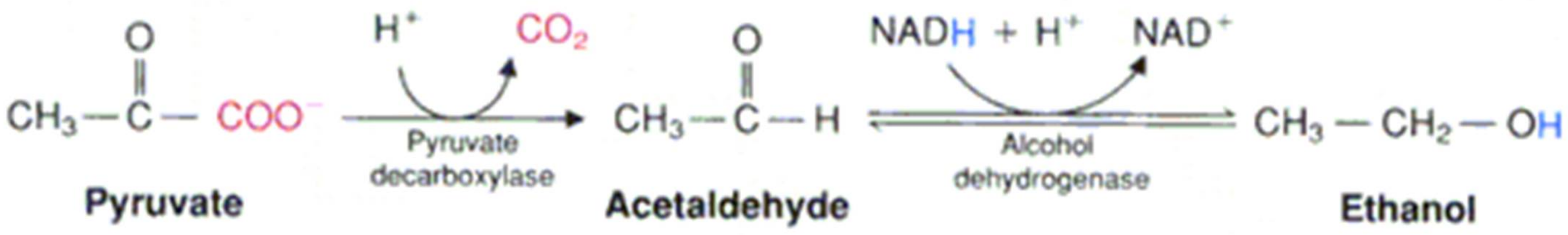
- **Under anaerobic conditions**

1. In *animal cells* and *lactic acid bacteria*, pyruvate is converted to lactate. In this case, NADH adds electrons to pyruvate, forming NAD+ and lactate.

Pyruvate + **NADH** + H^+ <=> **Lactate** + **NAD**$^+$

2. *Yeasts* recycle NADH to NAD+ by alcoholic fermentation:

Pyruvate -> acetaldehyde -> ethanol.


O
CH_3—C— COO⁻
Pyruvate
H⁺
CO₂
Pyruvate
decarboxylase
O
CH_3—C—H
Acetaldehyde
NADH + H⁺
NAD⁺
Alcohol
dehydrogenase
CH_3 — CH_2 — OH
Ethanol

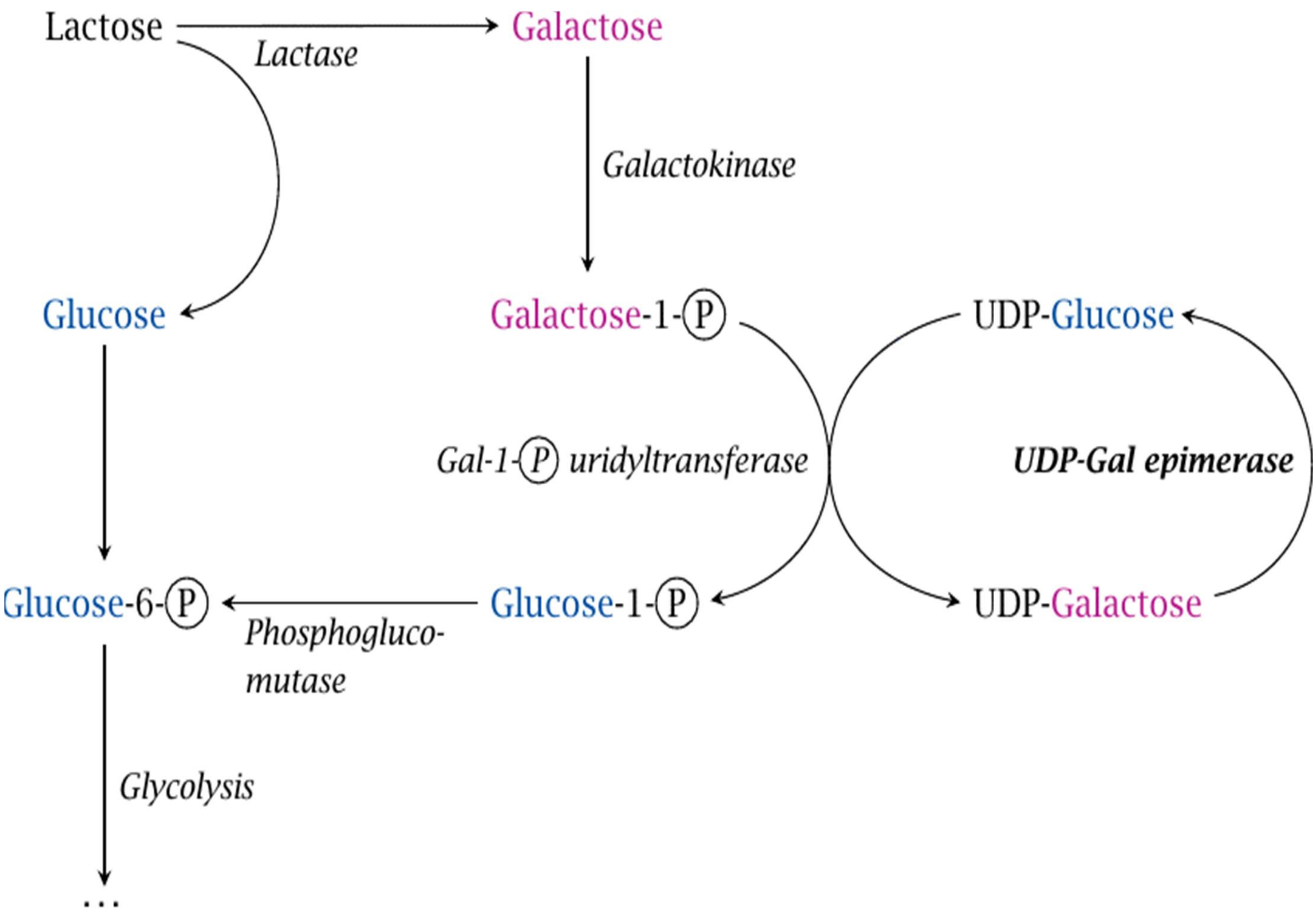
Entry of Other Sugars into the Glycolytic Pathway

1. Monosaccharide Sugars

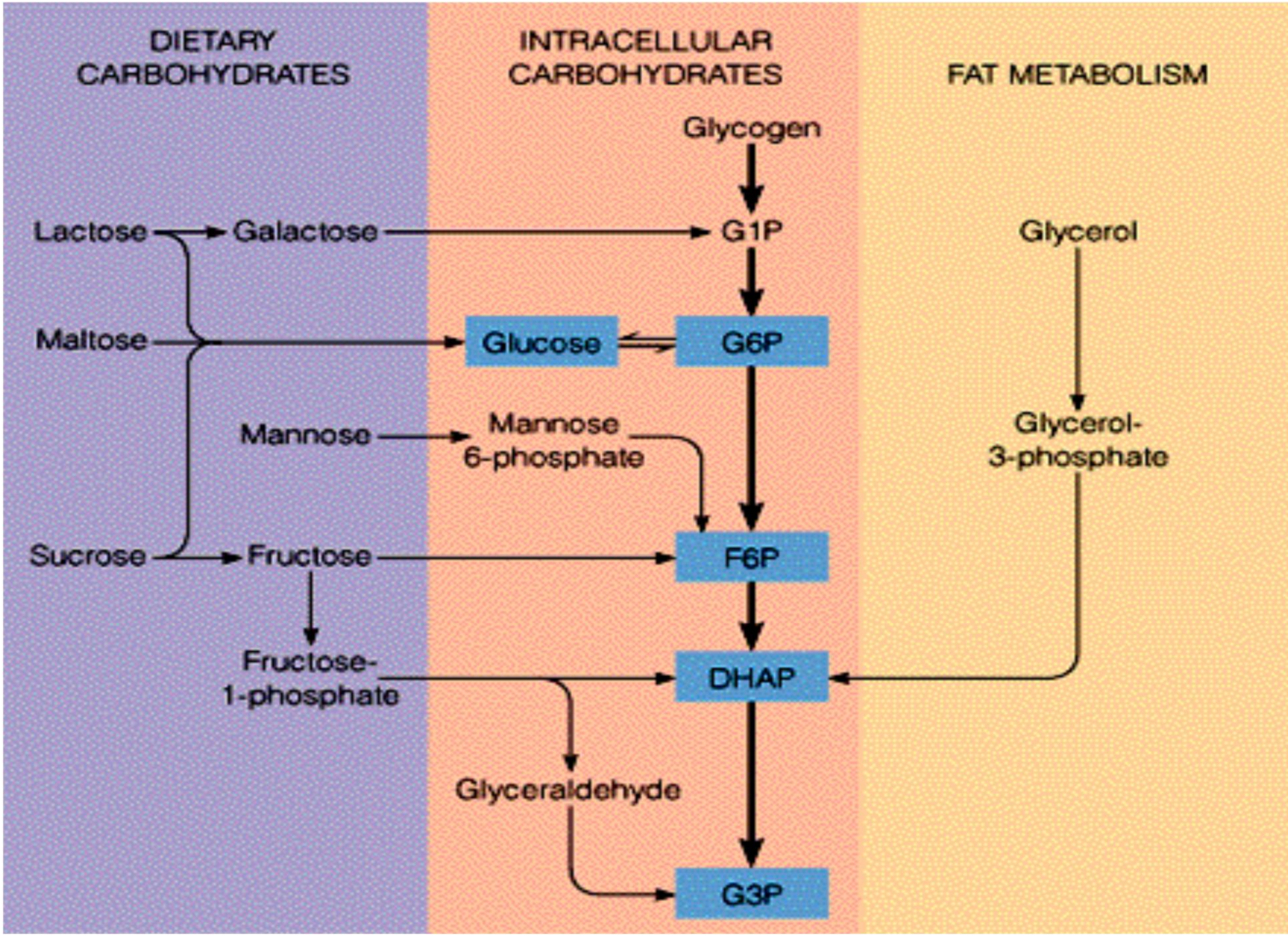
- **Galactose**, **mannose**, and **fructose** are the main sugars of interest. All can be phosphorylated at position six by **hexokinase** and **ATP (Note :**fructose can enter the the glycolytic pathway as fructose-1-phosphate.Galactose can also be converted to glucose via the**UDP-galactose-4-epimerase** catalyzed pathway)

2. Disaccharides

- The enzyme **lactase** breaks down the disaccharide **lactose** to yield the monosaccharides galactose and glucose. **Maltase** breaks down **maltose** to yield two molecules of glucose. **Sucrase** breaks down **sucrose** to yield fructose and glucose. All of these monosaccharidessubsequently enter glycolysis


Lactose
Galactose
Lactase
Galactokinase
Glucose
Galactose-1-(P)
UDP-Glucose
Gal-1-(P) uridyltransferase
UDP-Gal epimerase
Glucose-6-(P)
Glucose-1-(P)
UDP-Galactose
Phosphogluco-
mutase
Glycolysis
...

Routes for utilizing substrates other than glucose in glycolysis.



3. **Polysaccharides**

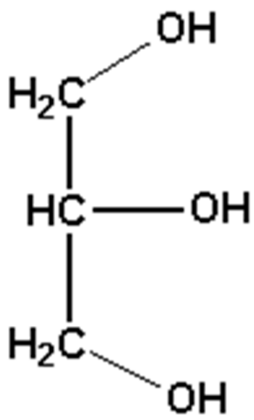
Glycogen (from animals), starch (e.g., **amylose** and **amylopectin** from plants), and **cellulose** (from plants)

- **Glycogen phosphorylase** catalyzes **phosphorolysis** of glycogen to **glucose-1-phosphate**

Glycerol

- Glycerol is a product of fat metabolism. It can be converted to **glycerol-3-phosphate** in the liver by **glycerol kinase**. This reaction consumes one molecule of ATP. Glycerol-3-phosphate is then oxidized by glycerol-3-phosphate dehydrogenase to

dihydroxyacetone phosphate (DHAP), reducing one molecule of NAD+ in the process. Once formed, **DHAP** can enter glycolysis



Glycerol