

Carbohydrate metabolism

Utilization of glucose

- **Oxidation**
 - For energy
 - HMP shunt
 - Uronic acid pathway
- **Storage**
- **Conversion to fat**
- **Conversion to other carbohydrate**
 - ❖ Pentose sugar
 - ❖ Fructose
 - ❖ galactose
- **Conversion to amino acid**

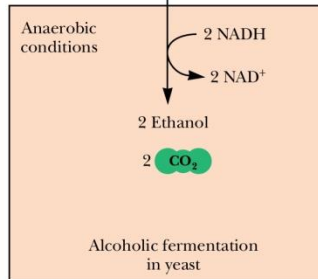
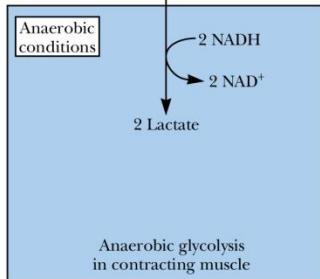
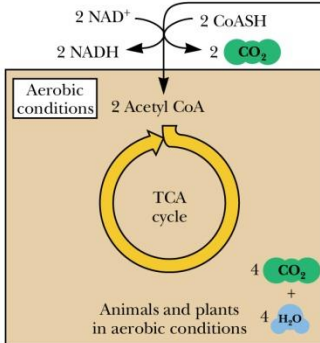
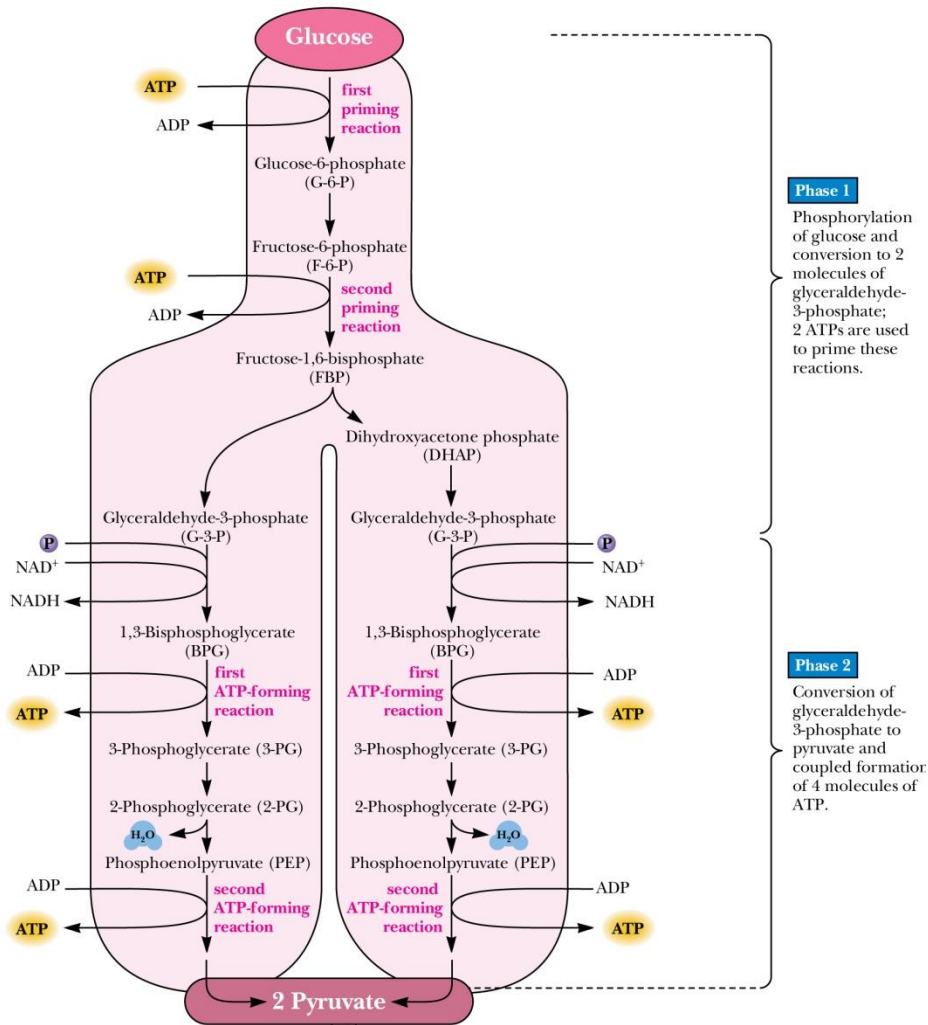
Glycolysis

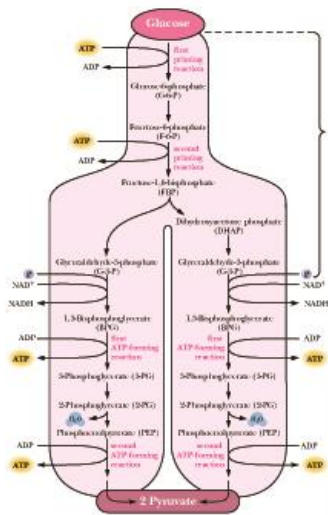
- Glykys---- sweet
- Lysis ----- splitting
- Aerobic glycolysis- pyruvate
- Anaerobic glycolysis (EMP)- Lactate

Biomedical importance

- Major pathway for glucose metabolism
- Provides ATP in absence of O₂
- Heart muscles are adapted for aerobic performances so relatively low glycolysis
- Inherited enzyme deficiency like hexokinase/ pyruvate kinase deficiency can produce hemolytic anemia
- In cancerous cell glycolysis is very high so level of pyruvate and lactate is also high
- Lactate is used for gluconeogenesis in liver which is energy expensive process responsible for cancer cachexia

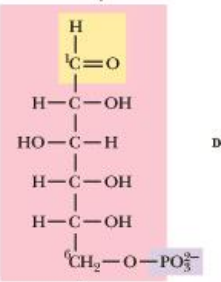
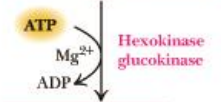
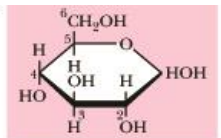
- **Site of Glycolysis**
cytosol of most of the cells
- **Source of Glucose**
- **Entry of the Glucose in to the Cells**
by facilitated transport
- **Liver:** insulin-independent transport mechanism
- **Extra hepatic tissues:** carrier is dependent on insulin



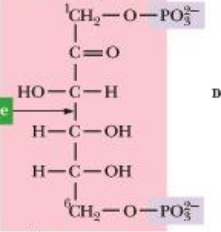
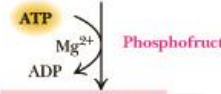
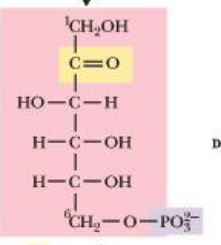


In the first five steps of glycolysis, one 6-carbon molecule of glucose is split into two 3-carbon compounds.

2 molecules of ATP are required to prime these reactions.

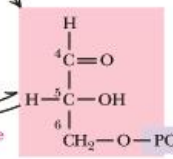
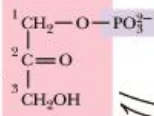


Phosphoglucoisomerase

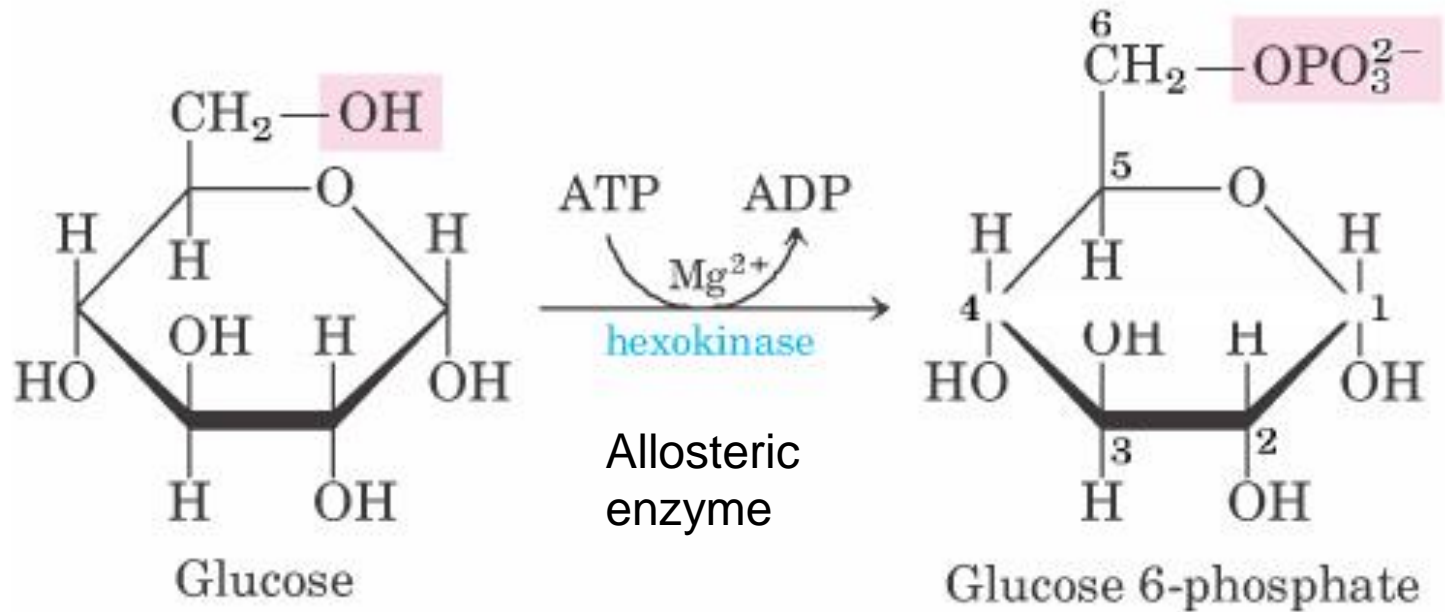


Aldol cleavage

Fructose biphosphate aldolase



Triose phosphate isomerase



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

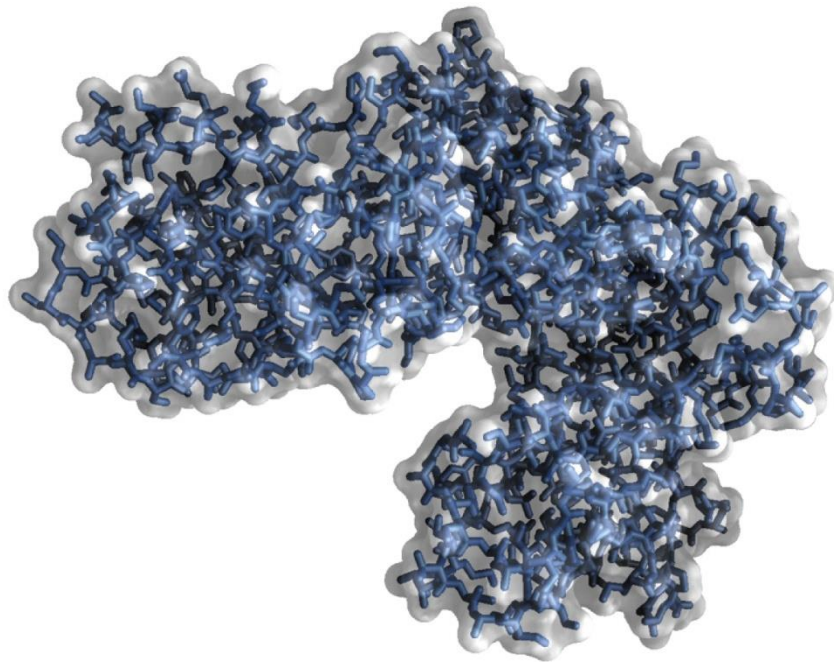
Glucokinase

Hexokinase

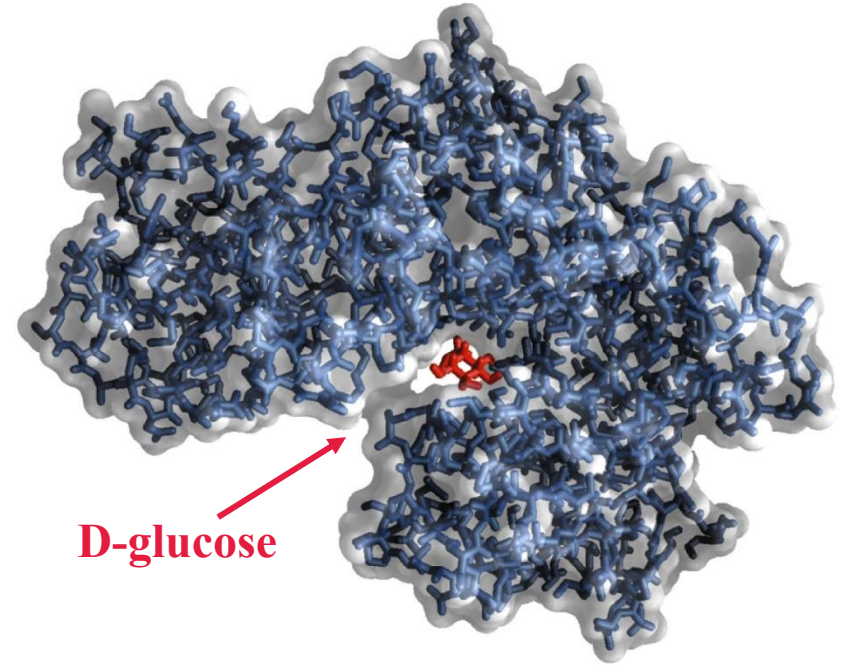
1
ε
i
C
V
ε
+

Induced Fit in Hexokinase

Closing of the 2 lobes places ATP in close proximity to the C6 -OH group & excludes water from the active site



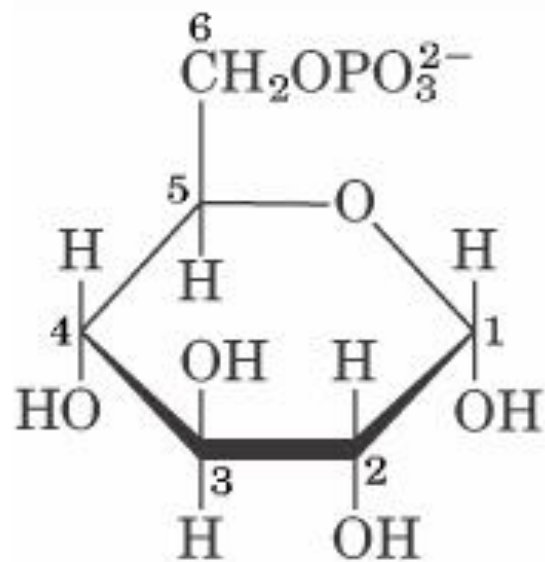
(a)



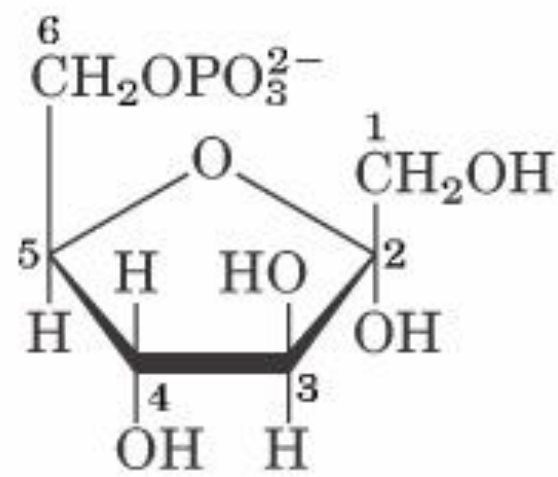
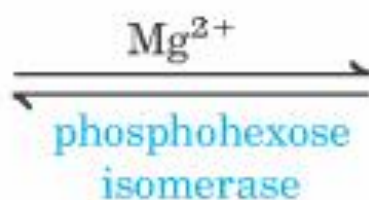
(b)

Glucose induces a large conformational change in hexokinase

Substrate induced conformational change is responsible for the enzyme's specificity



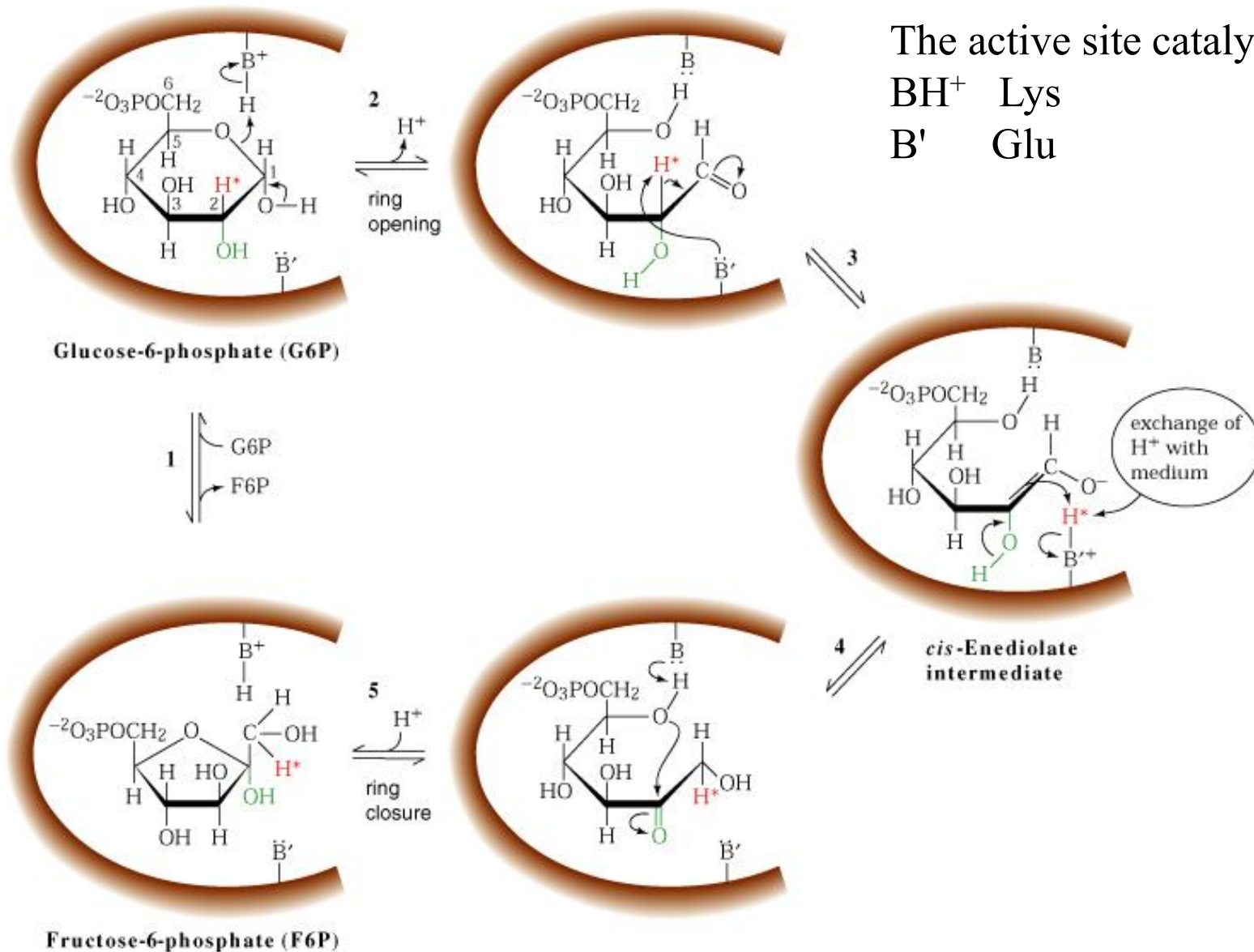
Glucose 6-phosphate

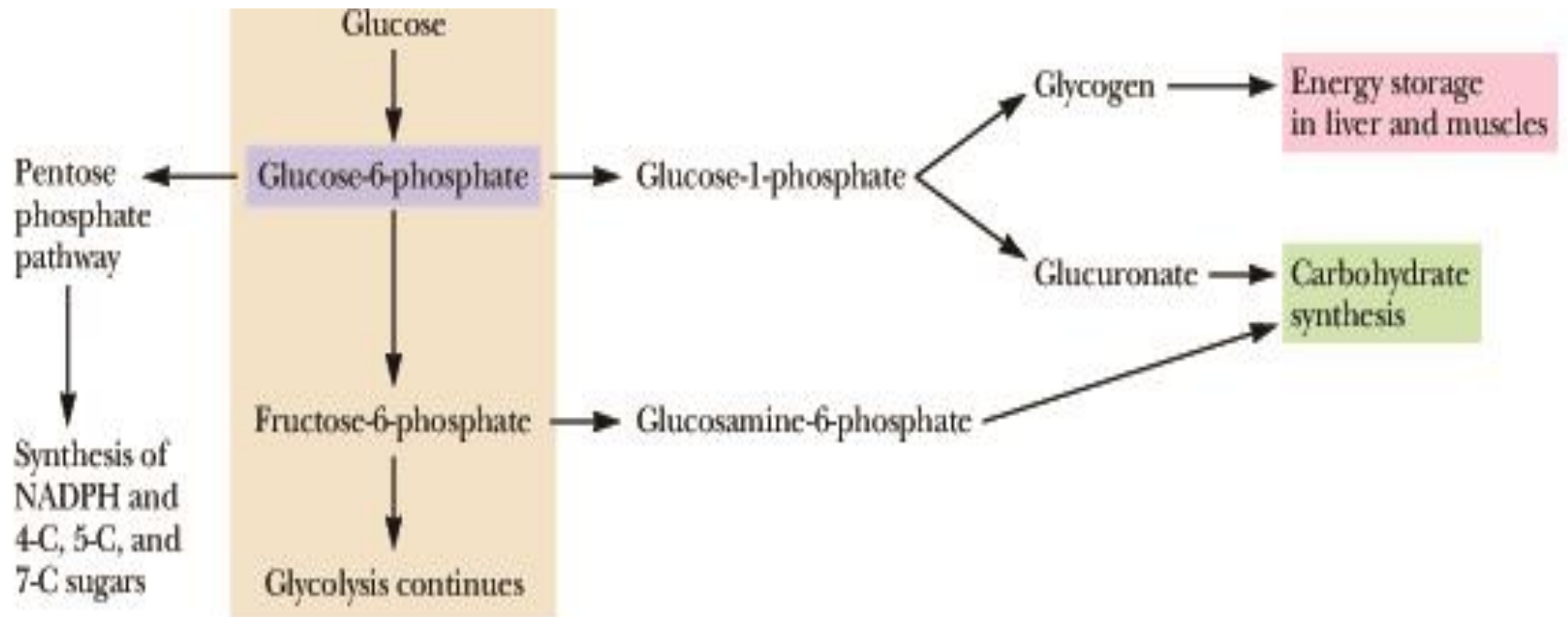


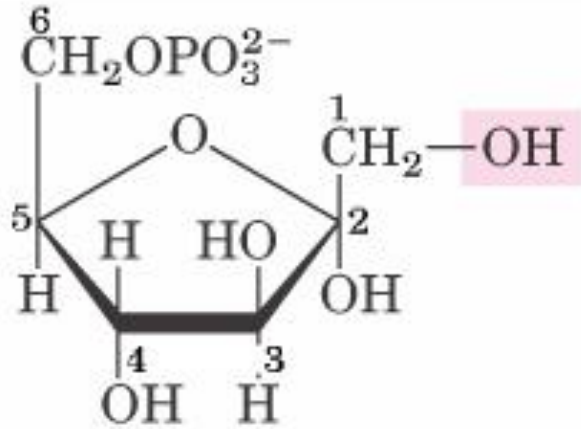
Fructose 6-phosphate

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

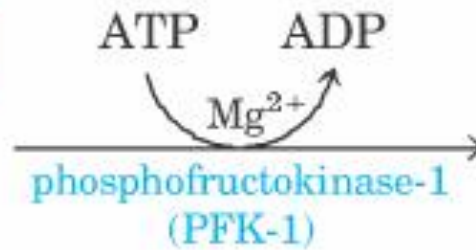
Reaction mechanism of phosphohexose isomerase



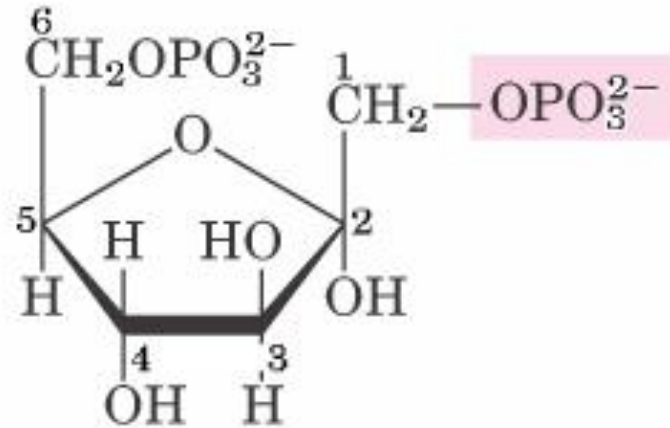




Fructose 6-phosphate



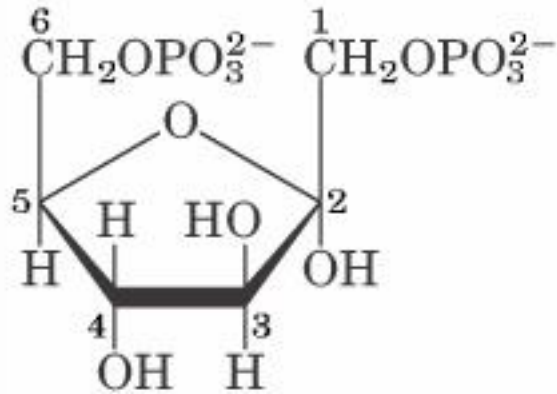
Allosteric
enzyme



Fructose 1,6-bisphosphate

Rate limiting step

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



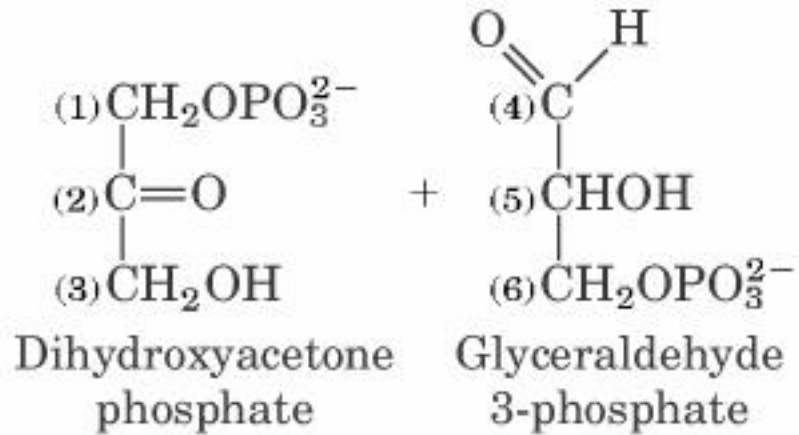
Fructose 1,6-bisphosphate



Aldolase-A: require carbonyl group at C-2

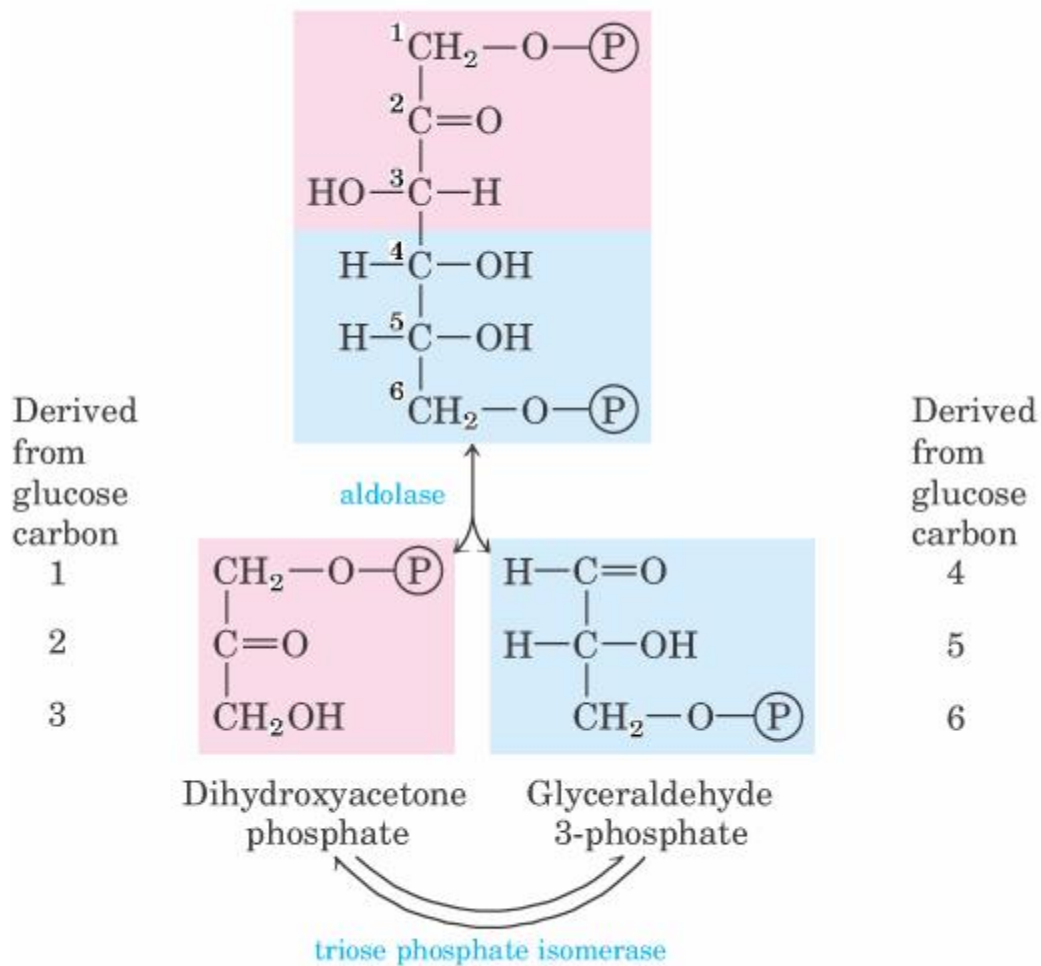
Aldolase B: convert Fru1P

↓
gluceraldehyde + DHAP

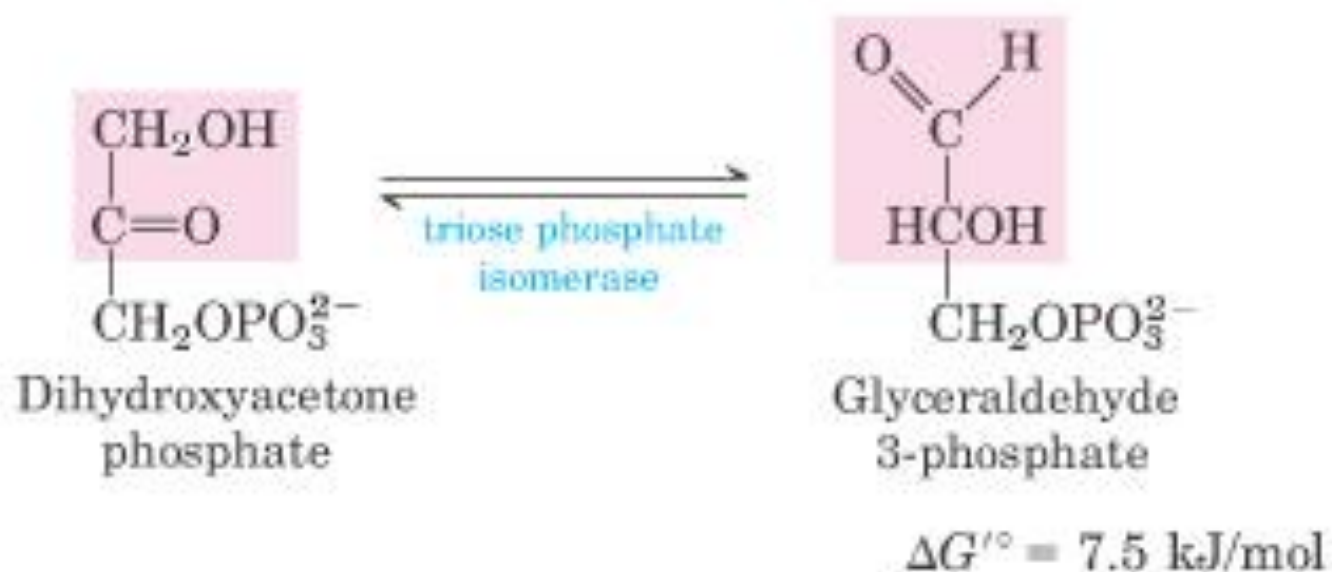


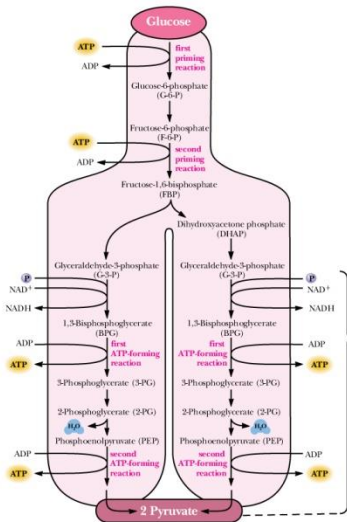
$$\Delta G'^{\circ} = 23.8 \text{ kJ/mol}$$

Fructose 1,6-bisphosphate



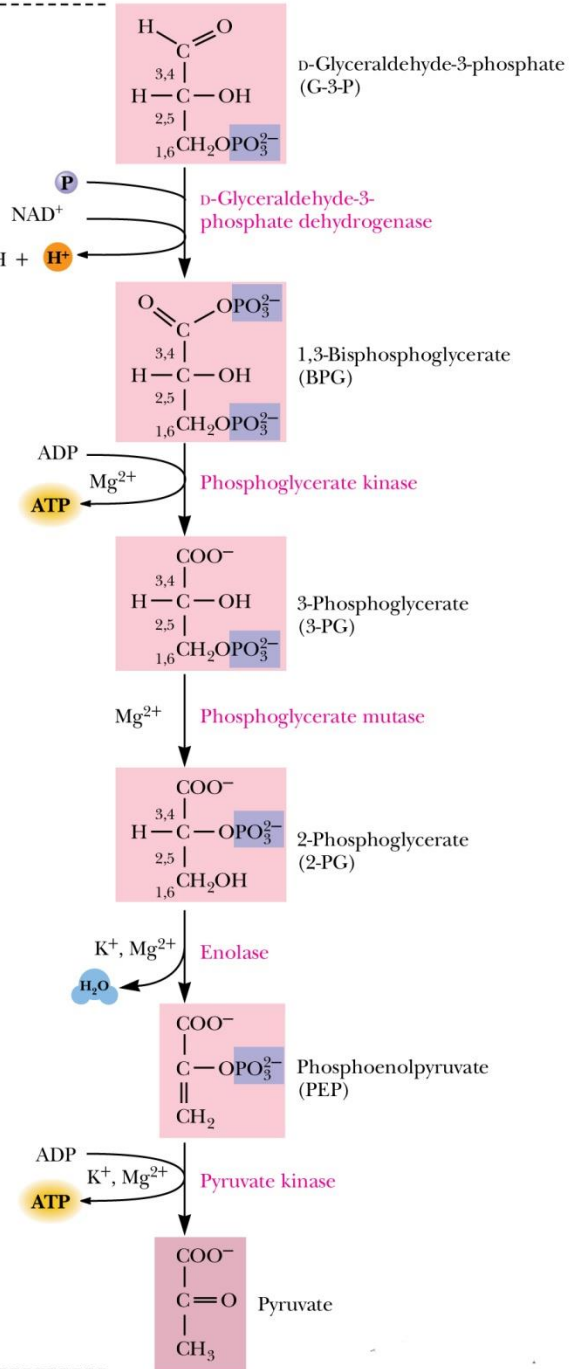
(a)

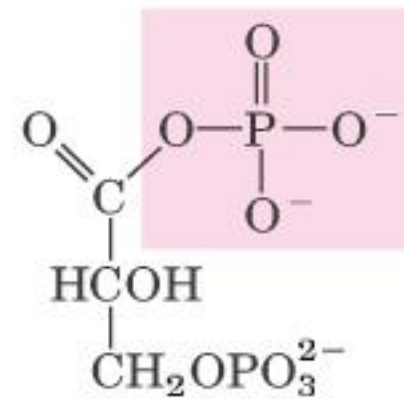
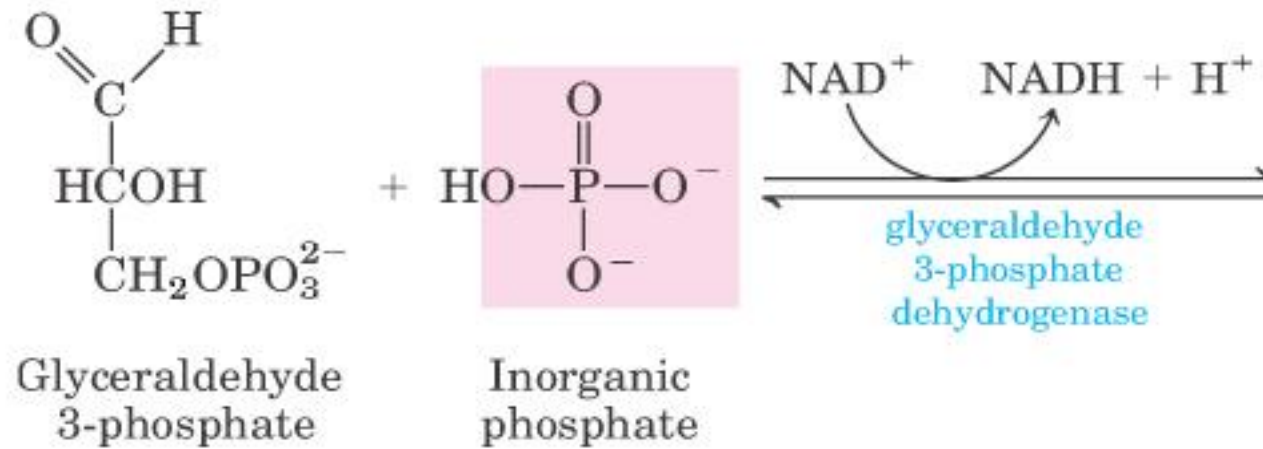




In the second phase of glycolysis, glyceraldehyde-3-phosphate is converted to pyruvate.

These reactions yield 4 molecules of ATP, 2 for each molecule of pyruvate produced.

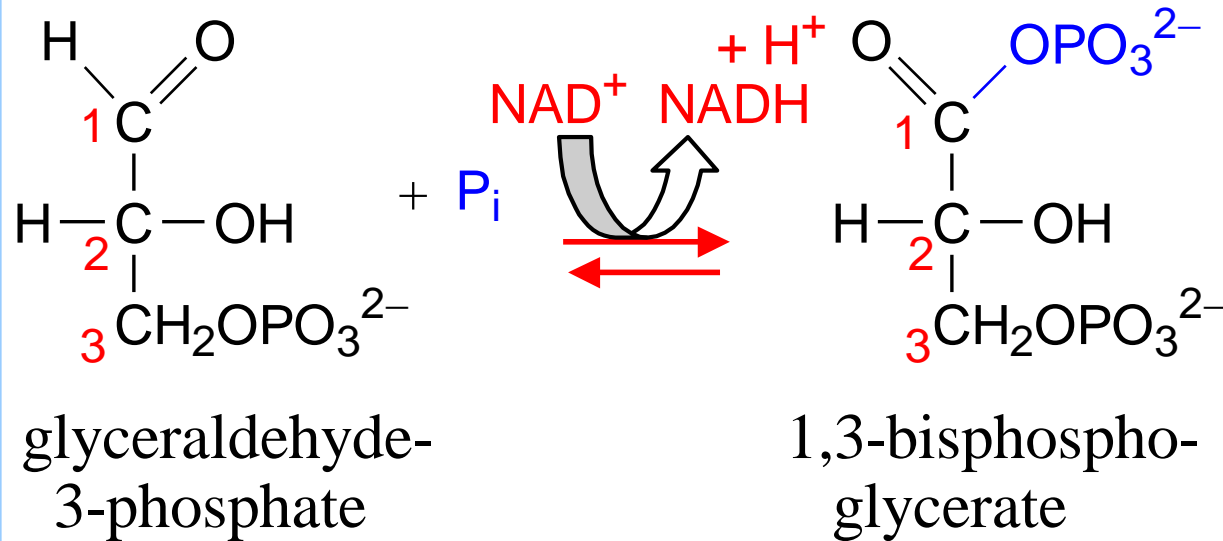




1,3-Bisphosphoglycerate

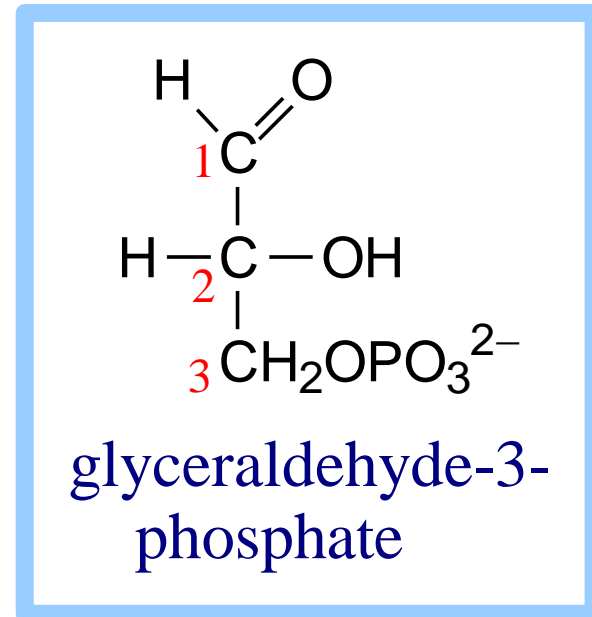
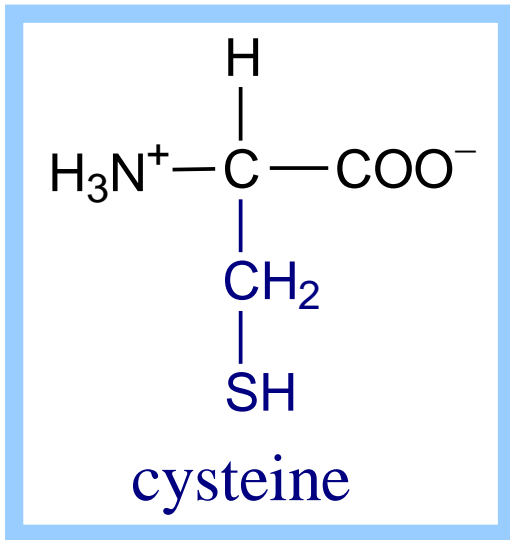
$$\Delta G'^{\circ} = 6.3 \text{ kJ/mol}$$

Glyceraldehyde-3-phosphate Dehydrogenase



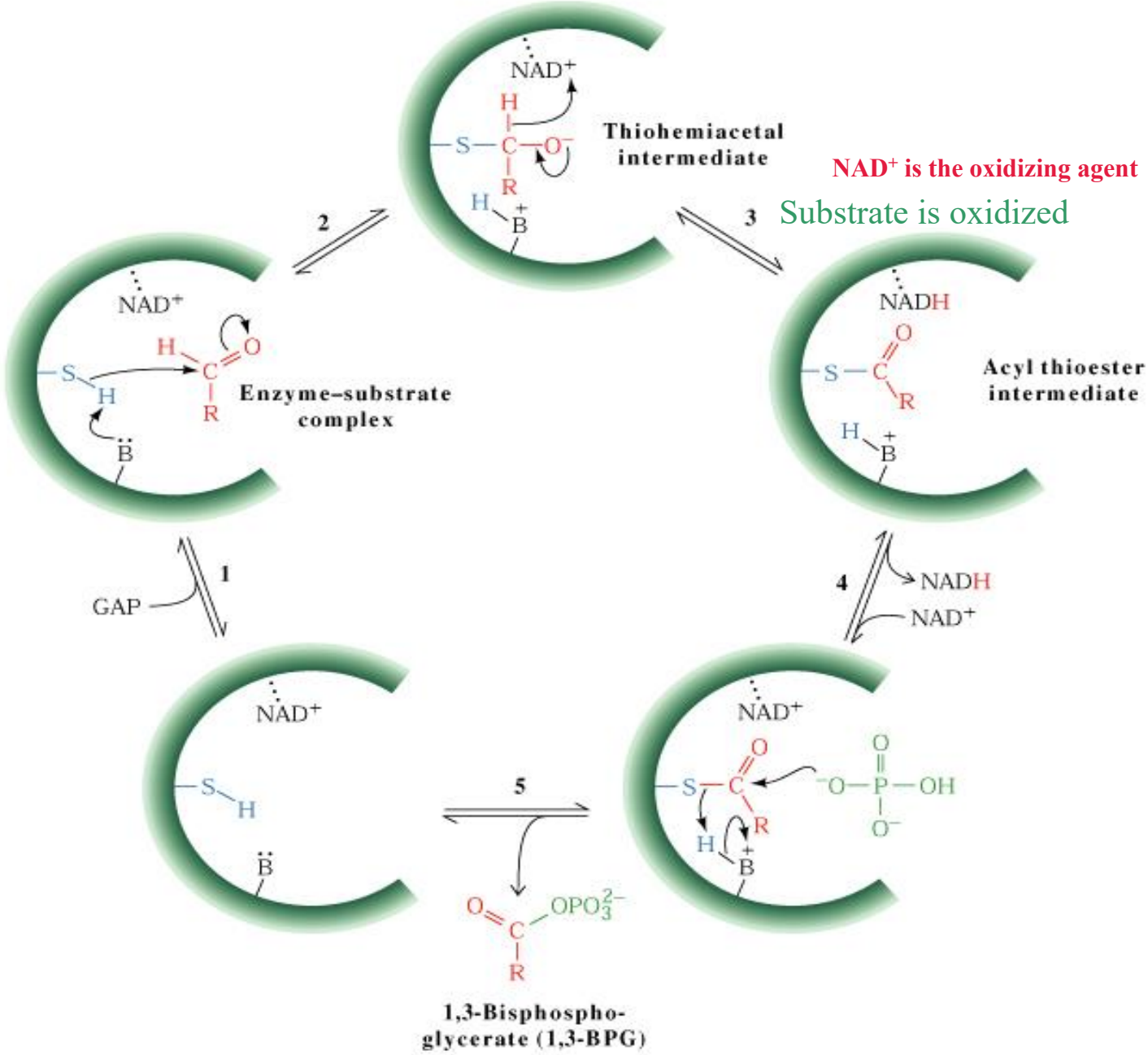
Exergonic oxidation of the aldehyde in glyceraldehyde-3-phosphate, to a carboxylic acid, drives formation of an **acyl phosphate**, a "high energy" bond ($\sim\text{P}$).

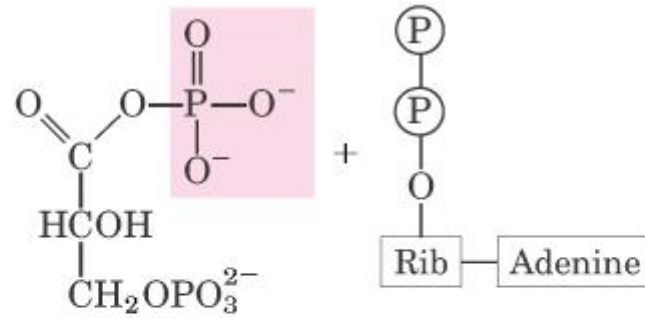
This is the only step in Glycolysis in which **NAD⁺** is reduced to NADH.



cysteine thiol present at the active site of
Glyceraldehyde-3-phosphate Dehydrogenase

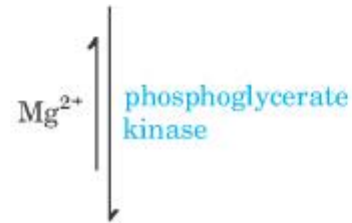
Sulphydryl group



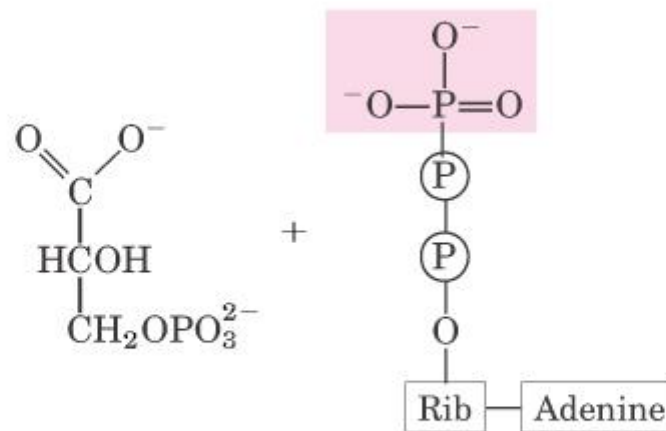


1,3-Bisphosphoglycerate

ADP



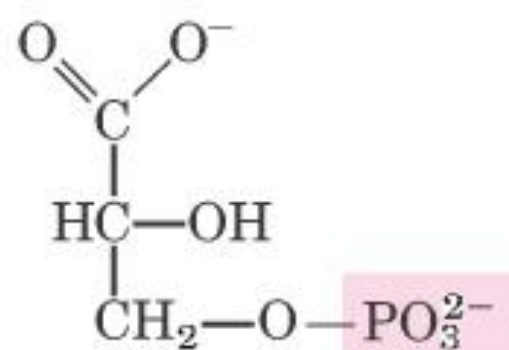
Substrate level phosphorylation



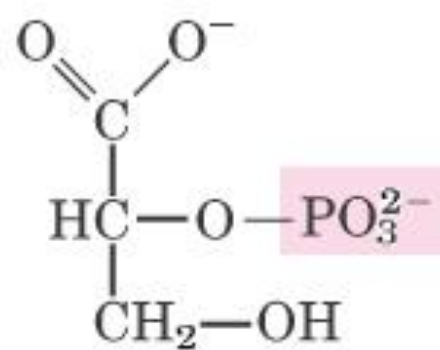
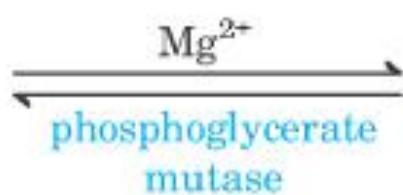
3-Phosphoglycerate

ATP

$\Delta G'^{\circ} = -18.5 \text{ kJ/mol}$



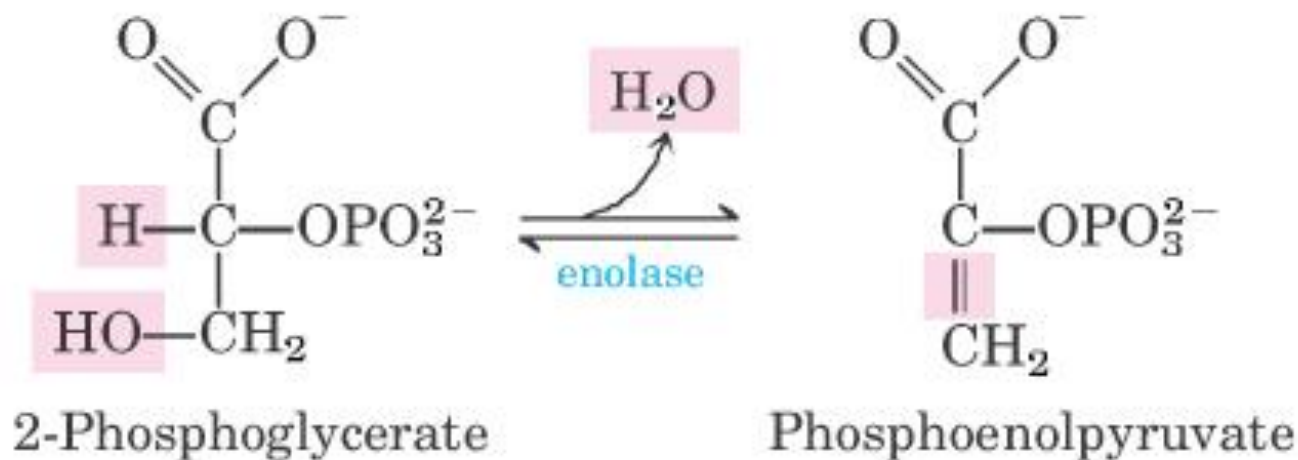
3-Phosphoglycerate



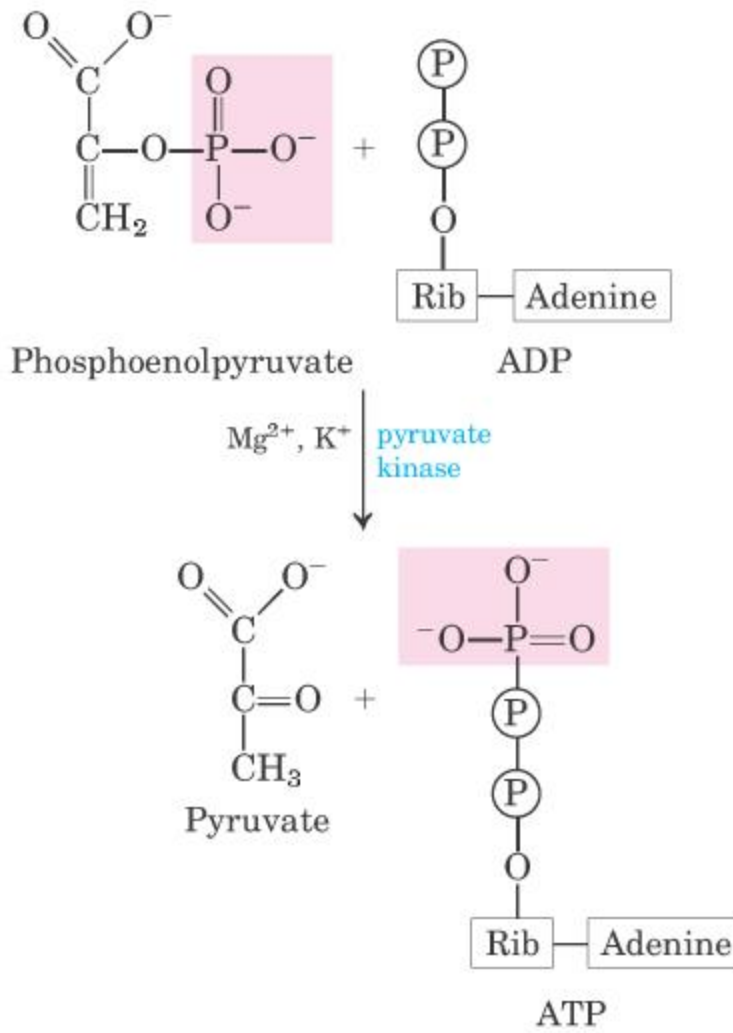
2-Phosphoglycerate

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

CHAPMAN (2011)



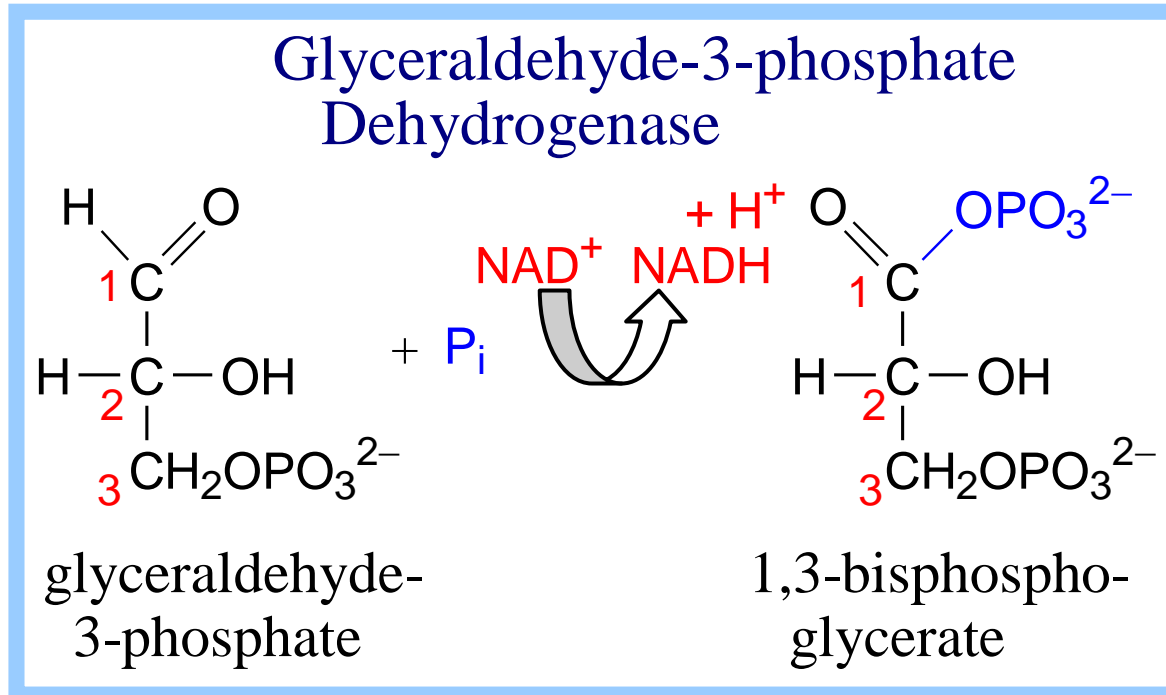
$$\Delta G'^{\circ} = 7.5 \text{ kJ/mol}$$



$$\Delta G'^{\circ} = -31.4 \text{ kJ/mol}$$

Fermentation:

Anaerobic organisms lack a respiratory chain.

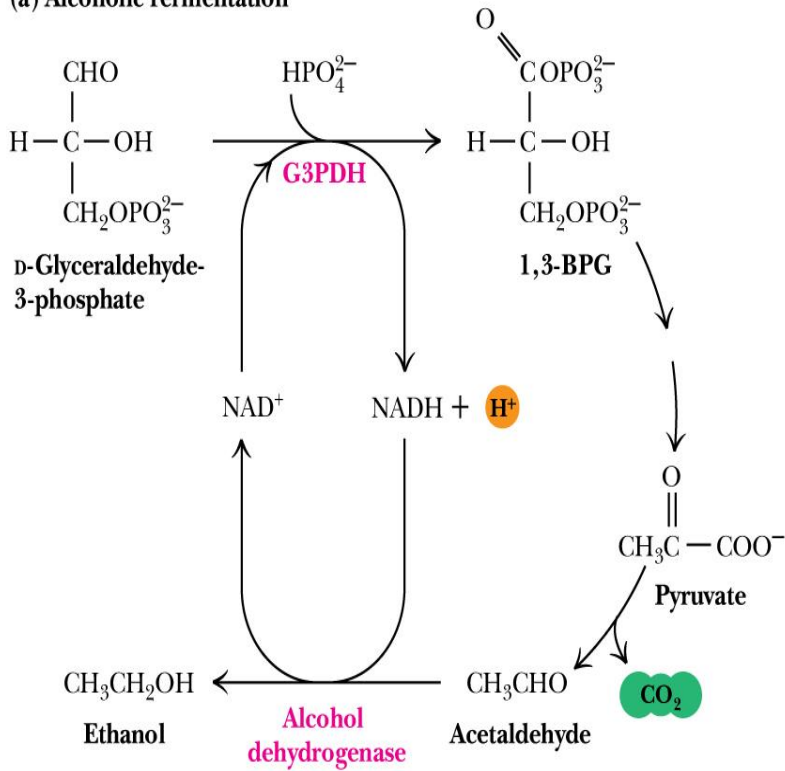


They **must reoxidize NADH** produced in Glycolysis through some other reaction, because **NAD⁺** is needed for the Glyceraldehyde-3-phosphate Dehydrogenase reaction.

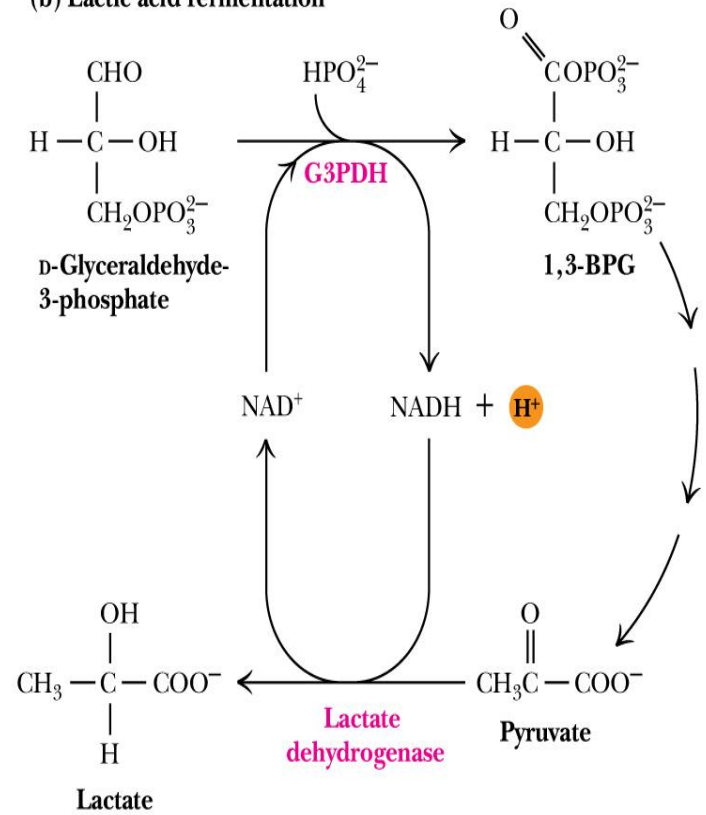
Usually NADH is reoxidized as **pyruvate** is converted to a **more reduced** compound.

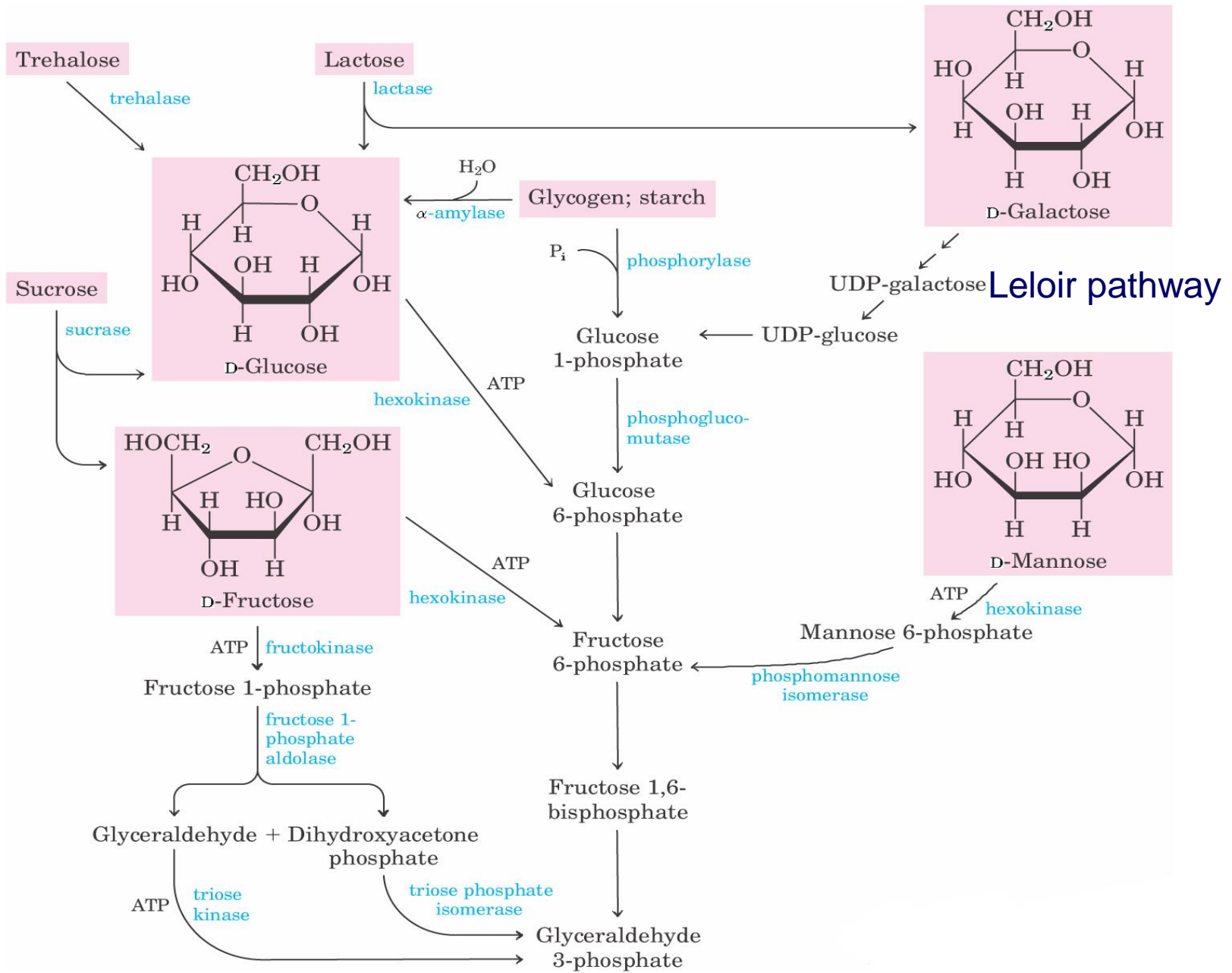
The complete pathway, including Glycolysis and the reoxidation of NADH, is called **fermentation**.

(a) Alcoholic fermentation



(b) Lactic acid fermentation





Inhibitors

Bromohydroxyacetone phosphate

- Structurally resemble to Dihydroxy acetone phosphate
- Bind with phosphotriose isomerase
- Accumulation of DHAP and FBP

Inhibitors

Arsenite

- Compete with inorganic phosphate for the conversion of glyceraldehyde 3 phosphate to 1,3 bis phosphoglycerate
- Produce 1 arseno 3 phosphoglycerate
- Hydrolyse to 3 phosphoglycerate
- In next step no ATP is produced

Inhibitors

Iodoacetate / iodoacetamide

- Bind (irreversibly) covalently to –SH group of Glyceraldehyde 3 PO₄ dehydrogenase
- Accumulation of glyceraldehyde 3 PO₄

Inhibitors

Fluoride

- Inhibit Enolase
- Important for blood glucose estimation

Regulation

Change in rate of enzyme synthesis
(induction/repression)

- Not rapid
- Through hormone

e.g. glucose metabolism

Regulation

Covalent modification (reversible phosphorylation)

- Hormones like epinephrine/ glucagone increase cAMP which activate Protein kinase results into phosphorylation of Pyruvate kinase and inactivate enzyme thus inhibit glycolysis
- Rapid process

Regulation

Allosteric modification

- PFK-1 is key reulator
- Inhibited by citrate, ATP, and H⁺
- Activated by Fructose 2,6 bisphosphate, AMP

Fructose 2,6 bisphosphate

- Regulate glycolysis and gluconeogenesis
- Allosteric activator for PFK-1 and stimulate glycolysis
- Inhibitor for Fructose bisphosphatase-1 so slowing gluconeogenesis

In RBC

- Do not have nucleus and cytoplasmic subcellular structures
- Entirely depend on glucose for energy by glycolysis
- Pyruvate dehydrogen complex is absent

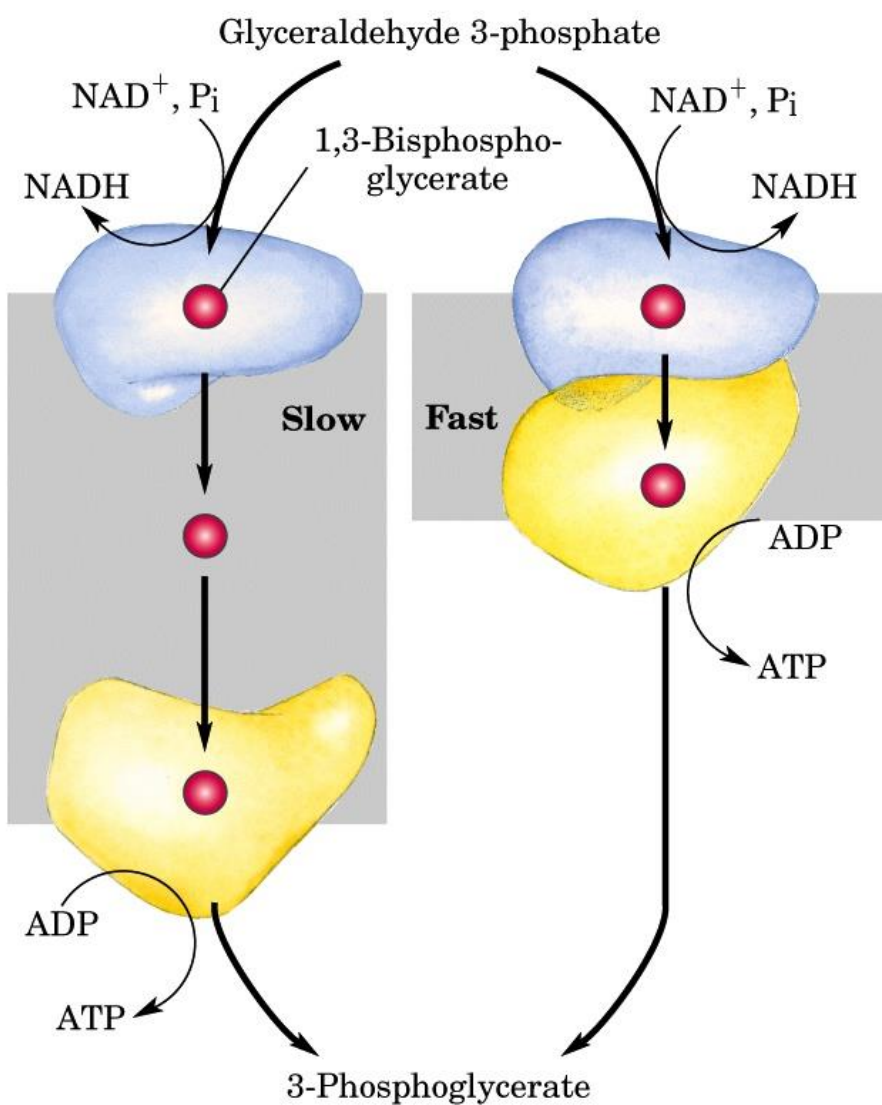
Rapaport leubering cycle

- In mammalian RBC
- Synthesis of 2,3 BPG
- Supplementary to glycolysis
- 1,3 BPG converted to 2,3 BPG by 2,3 BPG mutase
- Hydrolysed to 3 phosphoglycerate by 2,3 BPG phosphatase
- 2,3 BPG bind with Hb and reduces affinity for O₂

- **Pasteur effect** : inhibiting effect of oxygen on the fermentation process
- discovered in 1857 by [Louis Pasteur](#)

Practical utility

All the processes used in [alcohol](#) production are kept in anaerobic conditions, while breeding yeast for biomass is done in aerobic conditions, the broth being [aerated](#).

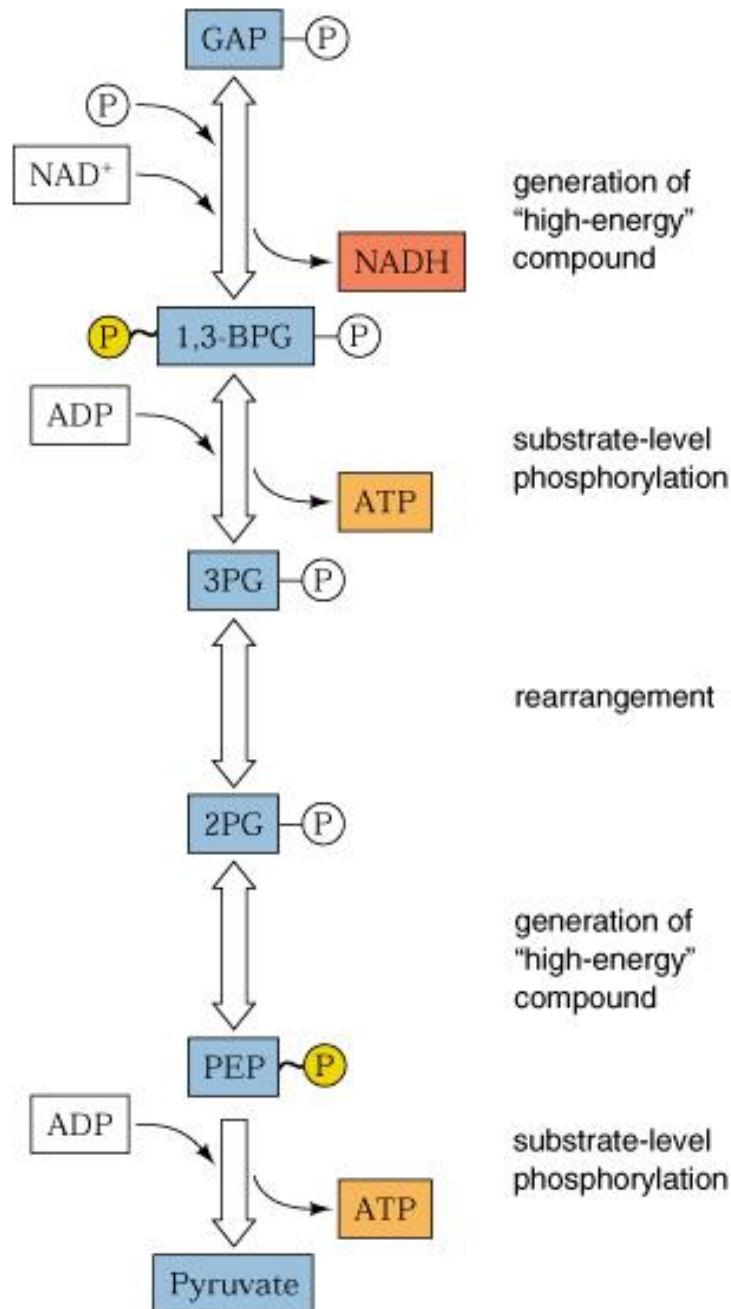


Substrate Channeling:

Intermediates may be handed off from one enzyme to another without ever becoming free in solution.

Sequential action of two separate enzymes: the product of the first enzyme (1,3-bisphosphoglycerate) diffuses to the second enzyme.

Substrate channeling through a functional complex of two enzymes: the intermediate (1,3-bisphosphoglycerate) is never released to the solvent.



Substrate-linked phosphorylation involves soluble enzymes and chemical intermediates.

Respiration-linked phosphorylation involves membrane-bound enzymes and transmembrane gradients of protons