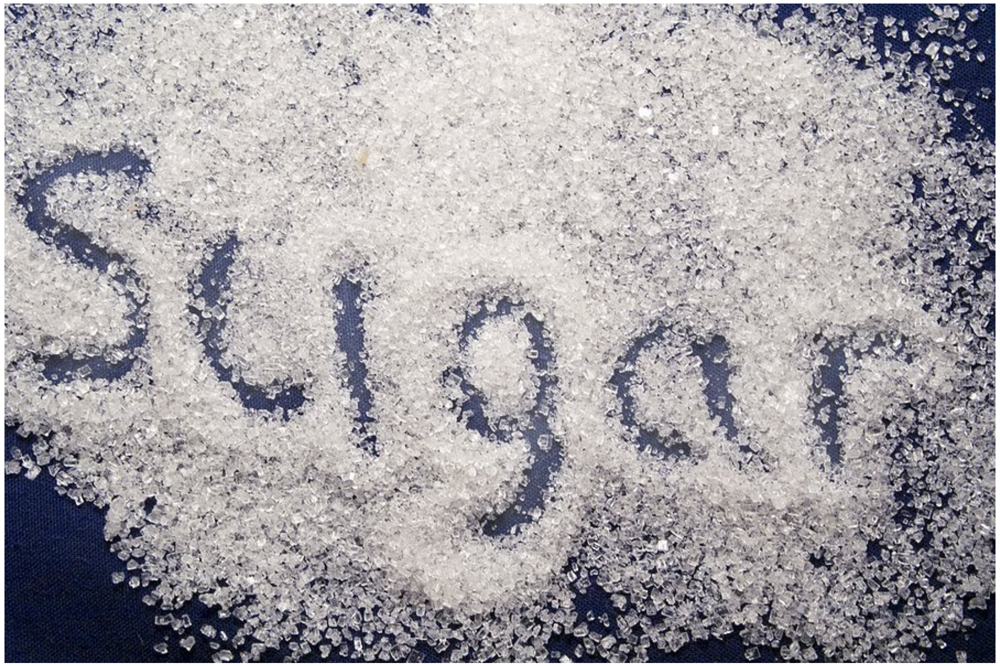
Glycolysis Chapter 18

Stepwise degradation of glucose



Essential Features of Glycolysis

- **1 Glucose → 2 pyruvates**

Via 10 enzyme catalysed steps

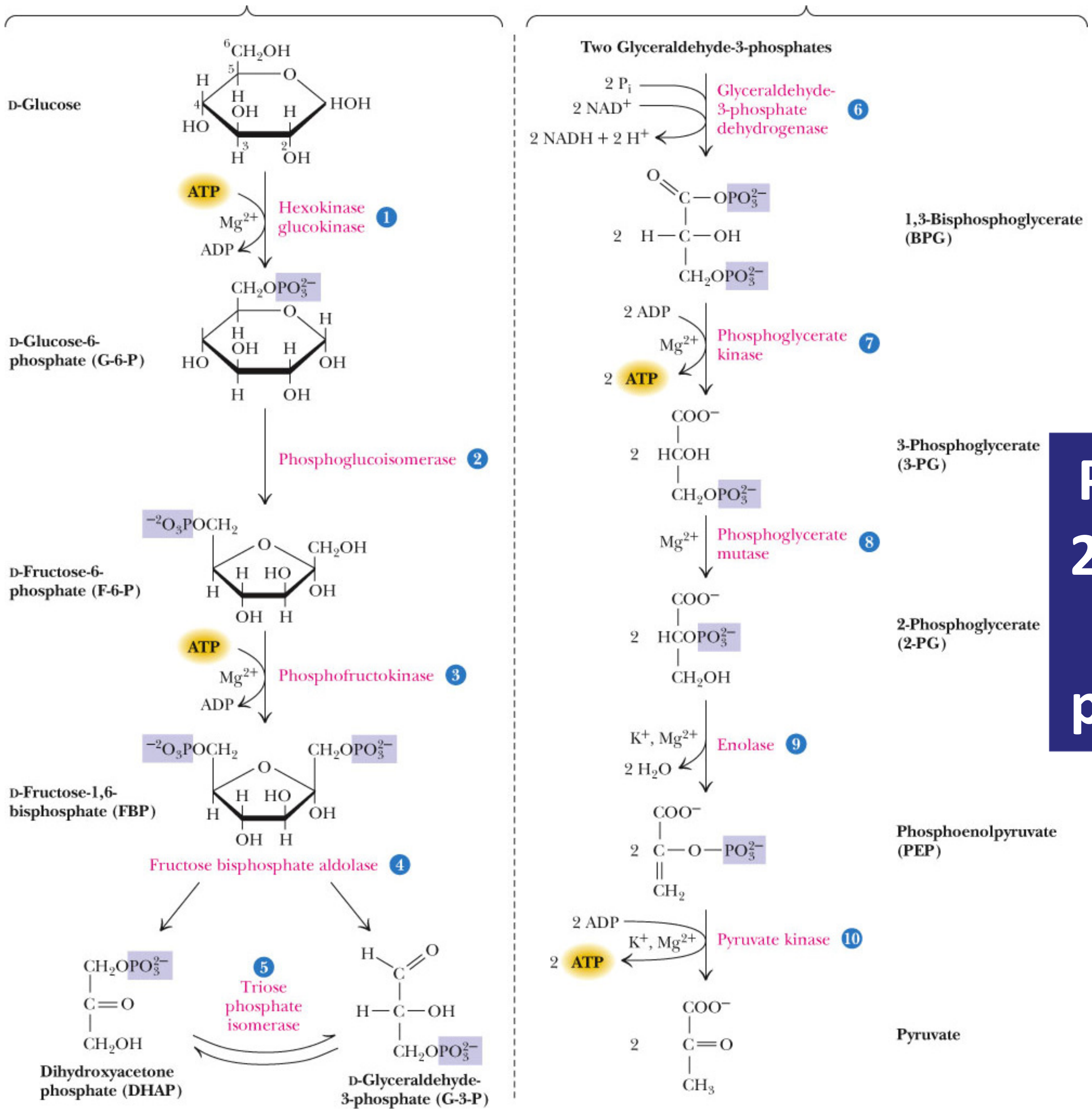
- Only source of metabolic energy

Brain, kidney contracting skeletal muscle, erythrocytes, sperm cells

- Pyruvate is a versatile metabolite

Depending on availability of oxygen

Phase 1: 1 Glucose → 2 GAP



Phase 2: 2 GAP → 2 pyruvate

Glycolysis – a Snap Shot

- **Reaction 1**: Glucose is phosphorylated by **Hexokinase (Glucokinase**) – the first priming reaction (ATP required)
- **Reaction 2**: **Phosphoglucoisomerase** catalyses the isomerisation of glucose-6-phosphate
- **Reaction 3**: ATP drives a second phosphorylation reaction using **Phosphofructokinase** – the second priming reaction
- **Reaction 4**: Cleavage using **Fructose Bisphosphate Aldolase** produces two 3-carbon intermediates
- **Reaction 5**: **Triose Phosphate Isomerase** completes the first phase of glycolysis

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- **Reaction 6**: **Glyceraldehyde-3-Phosphate Dehydrogenase** produces a high energy intermediate
- **Reaction 7**: **Phosphoglycerate Kinase**: regenerates ATP used
- **Reaction 8**: **Phosphoglycerate Mutase** catalyses a phosphoryl transfer reaction
- **Reaction 9**: **Enolase** produces PEP via a dehydration reaction
- **Reaction 10**: **Pyruvate Kinase** produces pyruvate & more ATP

All the glycolytic reactions and their thermodynamics

TABLE 18.1 Reactions and Thermodynamics of Glycolysis

Reaction	Enzyme	$\Delta G°'$ (kJ/mol)	K_{eq} at 25°C	ΔG (kJ/mol)
α-D-Glucose + ATP^{4-} ⇌ glucose-6-phosphate^{2-} + ADP^{3-} + H^+	Hexokinase Glucokinase	−16.7	850	−33.9*
Glucose-6-phosphate^{2-} ⇌ fructose-6-phosphate^{2-}	Phosphoglucoisomerase	+1.67	0.51	−2.92
Fructose-6-phosphate^{2-} + ATP^{4-} ⇌ fructose-1,6-bisphosphate^{4-} + ADP^{3-} + H^+	Phosphofructokinase	−14.2	310	−18.8
Fructose-1,6-bisphosphate^{4-} ⇌ dihydroxyacetone-P^{2-} + glyceraldehyde-3-P^{2-}	Fructose bisphosphate aldolase	+23.9	6.43×10^{-5}	−0.23
Dihydroxyacetone-P^{2-} ⇌ glyceraldehyde-3-P^{2-}	Triose phosphate isomerase	+7.56	0.0472	+2.41
Glyceraldehyde-3-P^{2-} + P_i^{2-} + NAD^+ ⇌ 1,3-bisphosphoglycerate^{4-} + NADH + H^+	Glyceraldehyde-3-P dehydrogenase	+6.30	0.0786	−1.29
1,3-Bisphosphoglycerate^{4-} + ADP^{3-} ⇌ 3-P-glycerate^{3-} + ATP^{4-}	Phosphoglycerate kinase	−18.9	2060	+0.1
3-Phosphoglycerate^{3-} ⇌ 2-phosphoglycerate^{3-}	Phosphoglycerate mutase	+4.4	0.169	+0.83
2-Phosphoglycerate^{3-} ⇌ phosphoenolpyruvate^{3-} + H_2O	Enolase	+1.8	0.483	+1.1
Phosphoenolpyruvate^{3-} + ADP^{3-} + H^+ ⇌ pyruvate$^-$ + ATP^{4-}	Pyruvate kinase	−31.7	3.63×10^5	−23.0
Pyruvate$^-$ + NADH + H^+ ⇌ lactate$^-$ + NAD^+	Lactate dehydrogenase	−25.2	2.63×10^4	−14.8

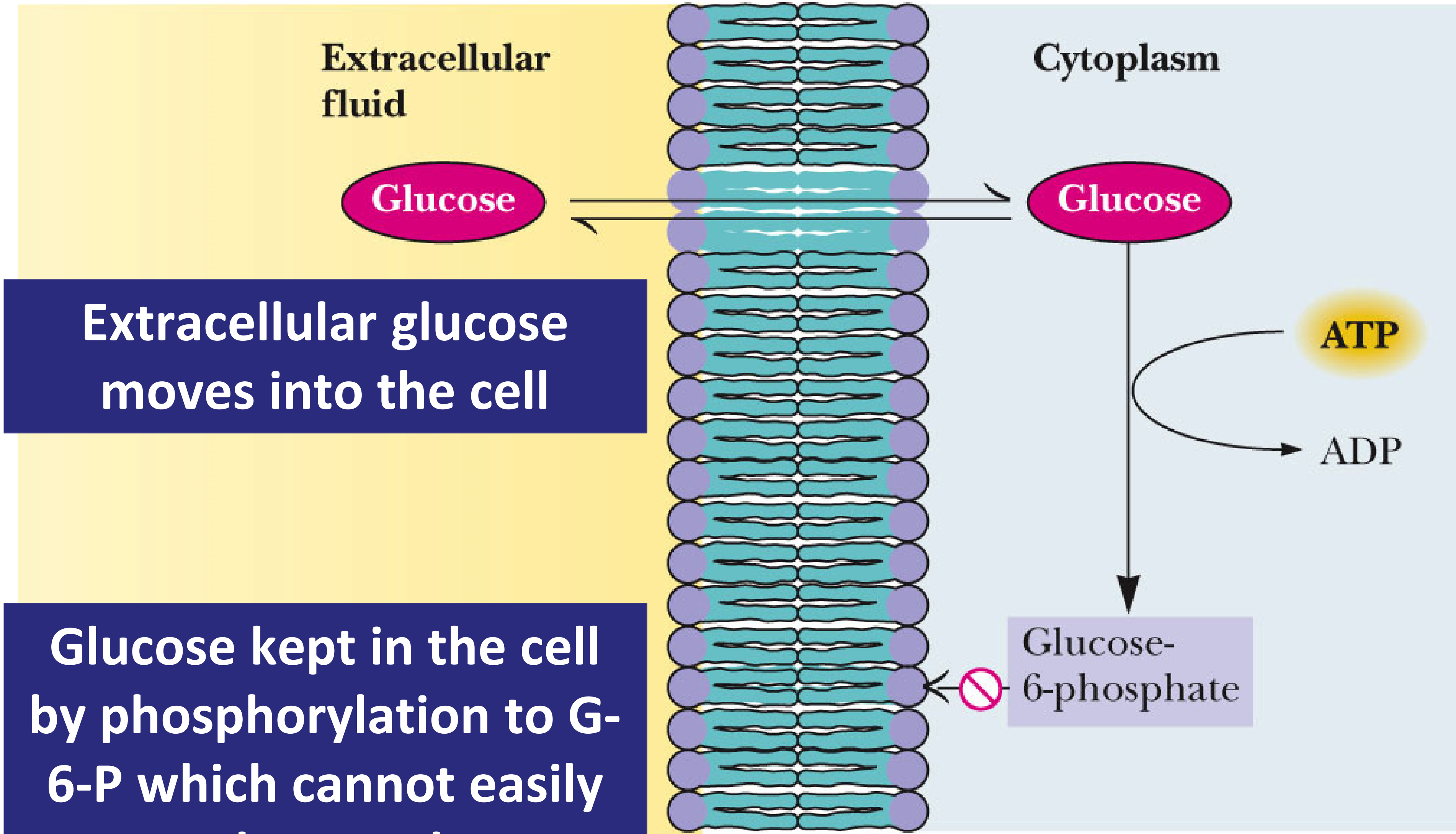
Reaction 1

- Phosphorylation of glucose at C6
- Thermodynamically unfavourable ?

Glucose levels low **Glucose levels high**

Hexokinase/glucokinase

Glucose + ATP → glucose-6-phosphate + ADP + H^+
$\Delta G^{o\prime}$ = -16.7 kJ/mol

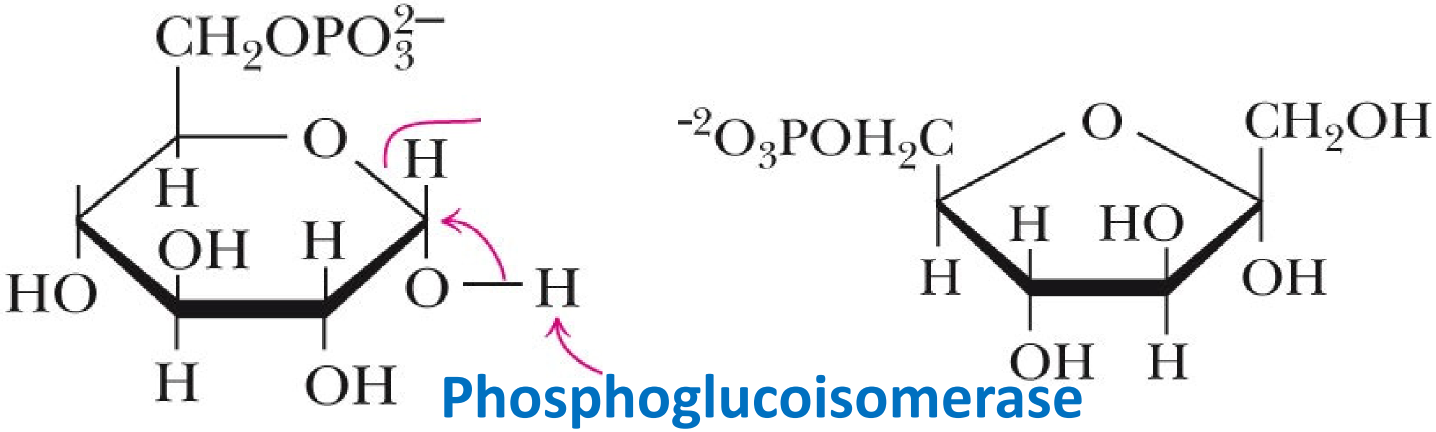


Extracellular glucose moves into the cell

Glucose kept in the cell by phosphorylation to G-6-P which cannot easily cross the membrane

Reaction 2

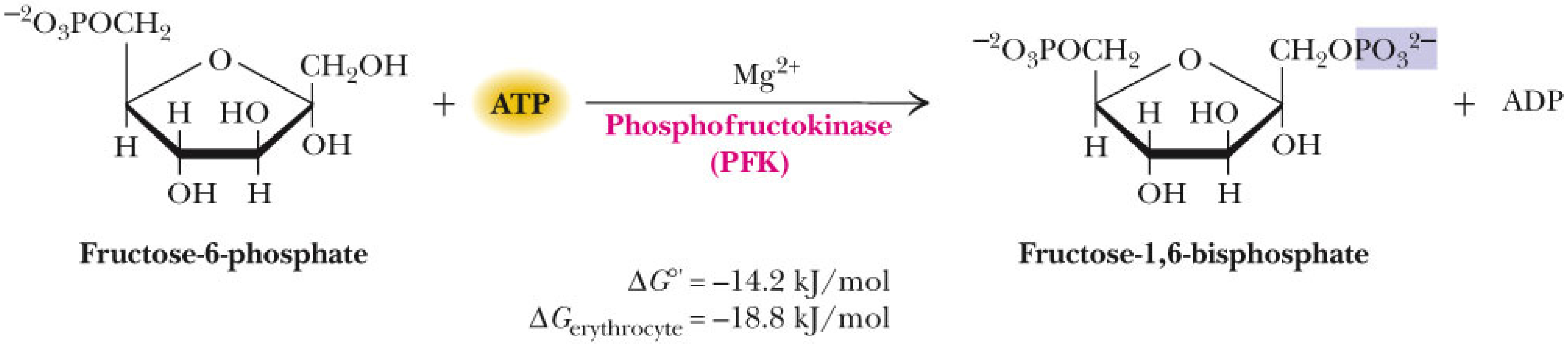
- Isomerisation of glucose 6 phosphate to fructose 6 phosphate



glucose-6-phosphate → Fructose-6-phosphate
ΔGº' = 1.67 kJ/mol

Reaction 3

- Fructose-6-phosphate phosphorylated at C1 to form fructose 1,6-bisphosphate



phosphofructokinase

F6P + ATP → fructose-1,6-bisphosphate + ADP
$\Delta G°' = -14.2$ kJ/mol

Regulation of phosphofructokinase

- PFK reaction controls the **rate of glycolysis**
- ATP → **Substrate**

  ↓ ?

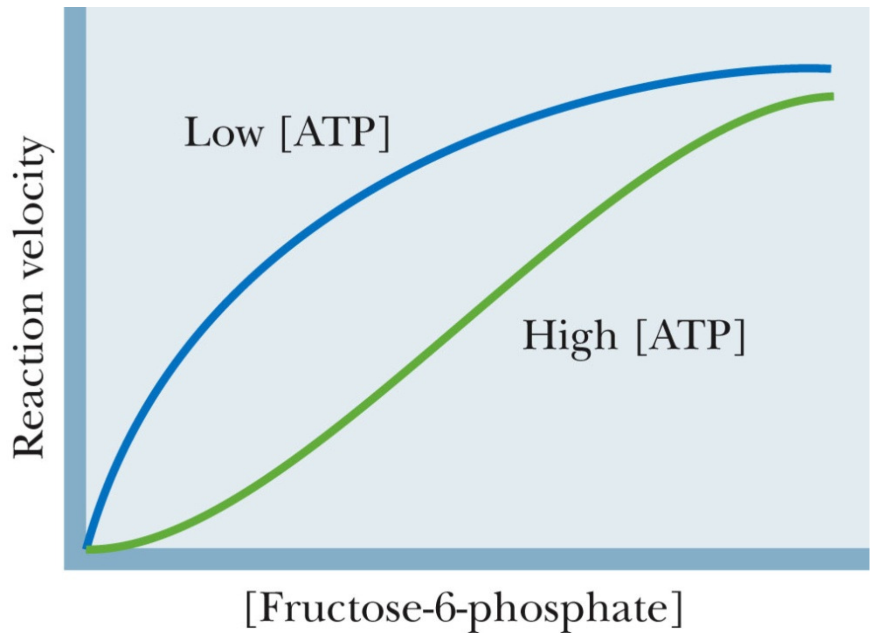
  Allosteric inhibitor

Regulation of phosphofructokinase

- PFK reaction controls the rate of glycolysis
- ATP → **Substrate**

↓ **?**

Allosteric inhibitor



Regulation of phosphofructokinase

- Glycolysis and citric acid (TCA) cycle are coupled via PFK
- Citrate → **Intermediate of citric acid cycle**

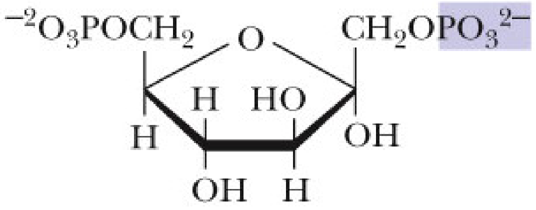
↓

Allosteric inhibitor of PFK

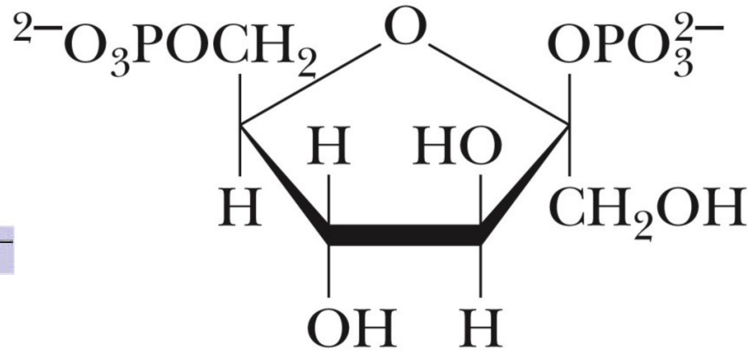
Regulation of phosphofructokinase

- Fructose 2,6 bisphosphate

Allosteric activator of PFK



Fructose-1,6-bisphosphate



Fructose-2,6-bisphosphate

1. **Decreases inhibitory effect** of ATP
2. **Inhibits** fructose 1,6 bisphosphatase

Reaction 4

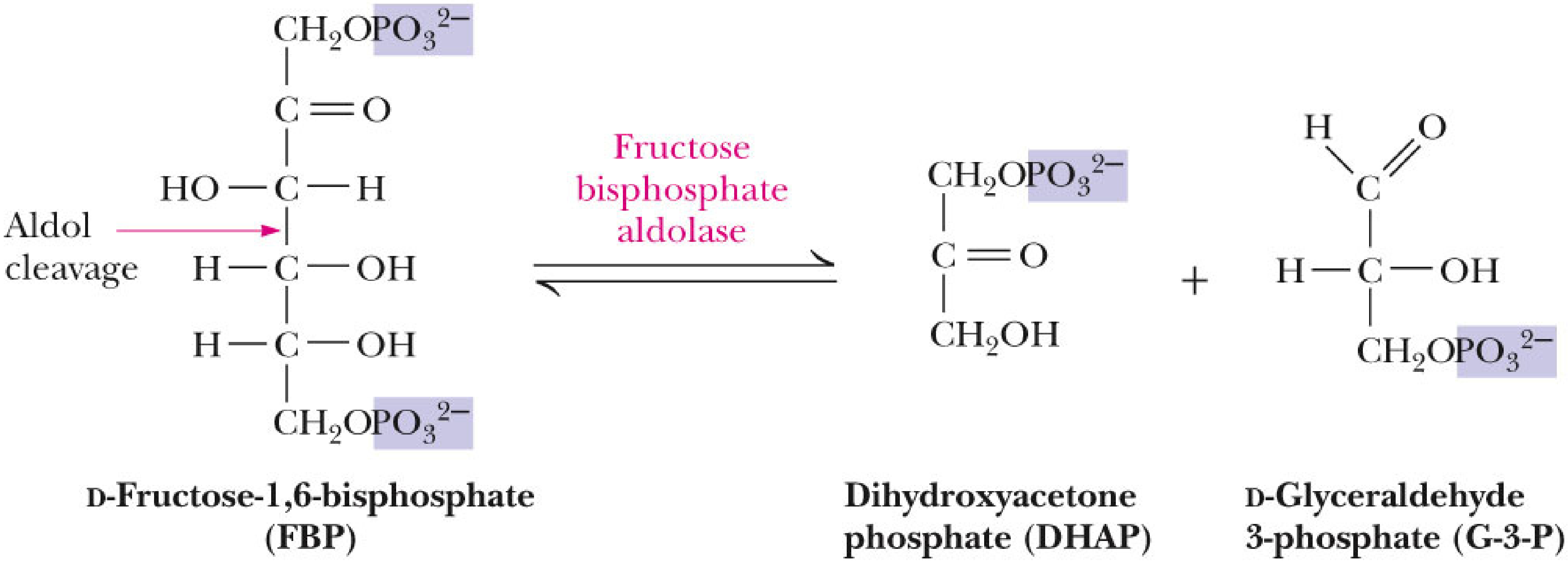
- Fructose 1,6 bisphosphate cleaved between C3 and C4 → 2 triose phosphates

Dihydroxyacetone phosphate (DHAP)

Glyceraldehyde-3-phosphate (GAP)

Fructose bisphosphate aldolase

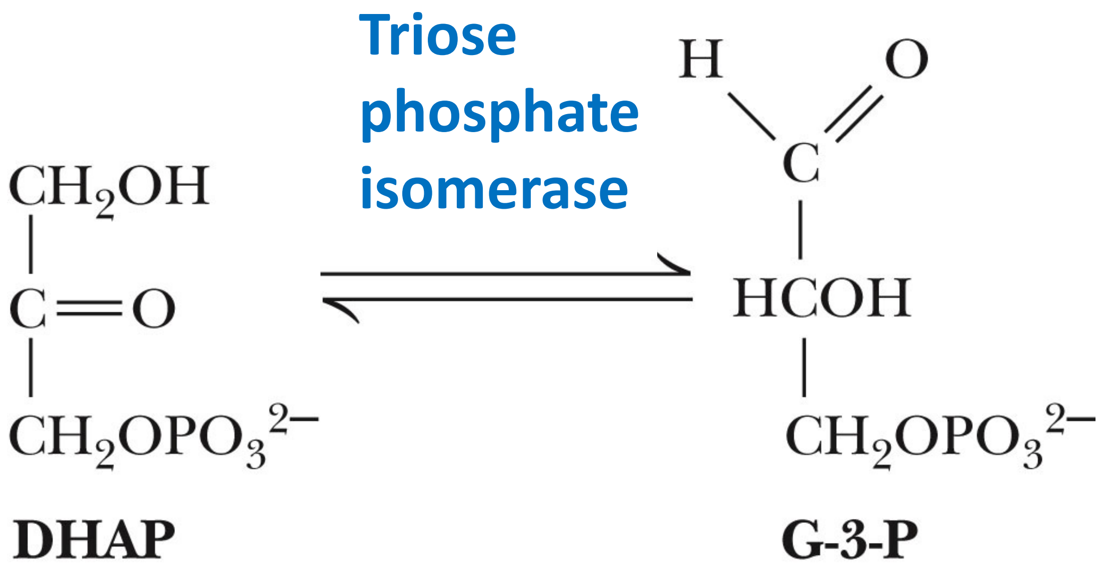
F1,6bP → DHAP + GAP
$\Delta G^{o'}$ = +23.9 kJ/mol



Aldol cleavage, involves removal of a proton from C4–hydroxyl group in a reaction catalysed by an aspartate and a lysine residue of fructose bisphosphate aldolase

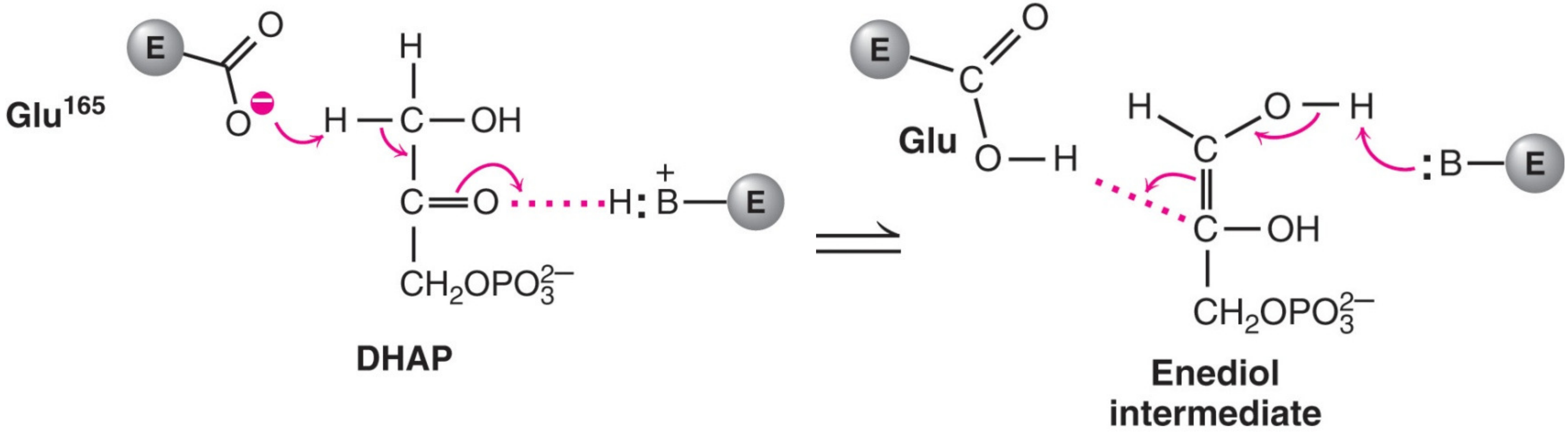
Reaction 5

- **Glyceraldehyde-3-phosphate** proceeds directly to phase 2
- **DHAP** must first also be converted to glyceraldehyde-3-phosphate

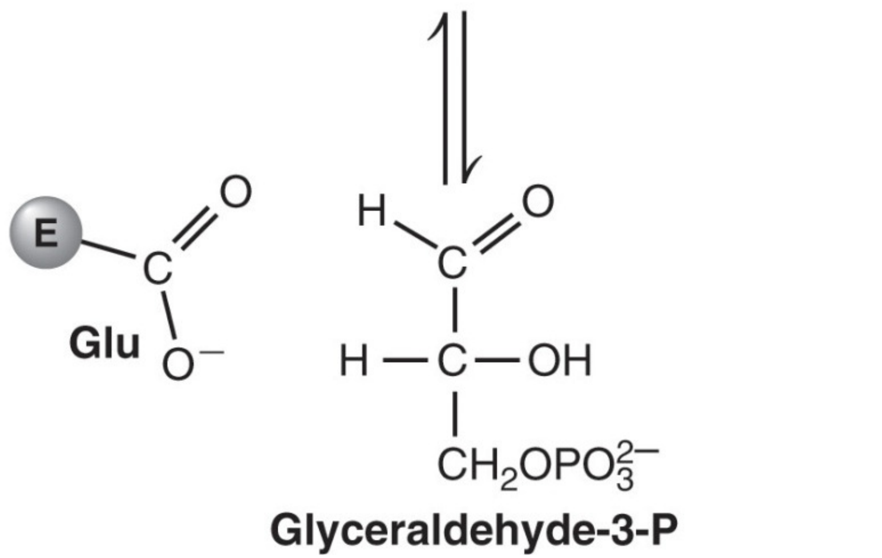


$$\Delta G°' = +7.56 \text{ kJ/mol}$$

Reaction mechanism of TIM



TIM with substrate analogue in active site



Second Phase of Glycolysis

- **Energy release** **4 - 2 = 2 ATPs generated**
- **Reaction 6:**

Glyceraldehyde 3 phosphate → 1,3-bisphosphoglycerate

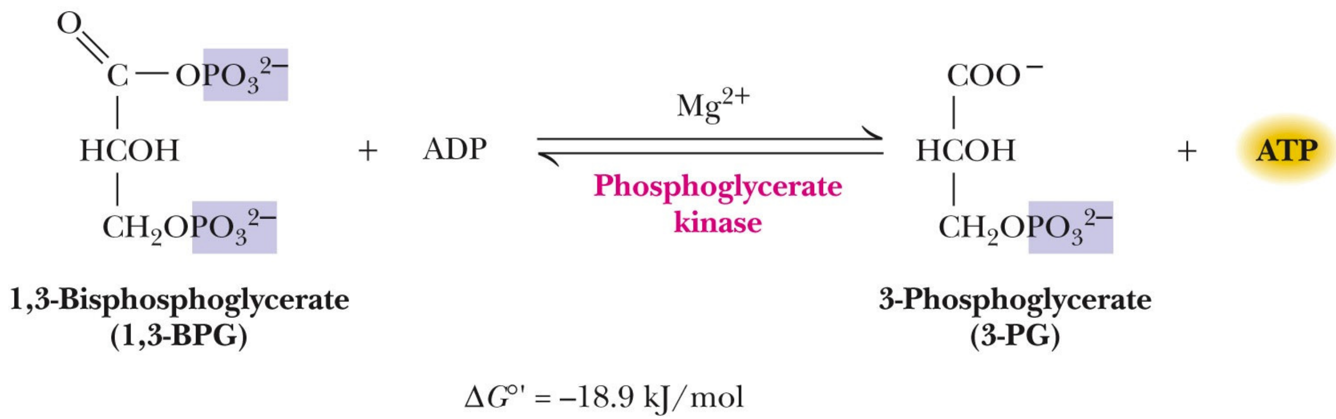
Glyceraldehyde 3 phosphate dehydrogenase

$\Delta G = +6.3$ kJ/mol

Reaction 7

- Glycolytic pathway breaks even:

Energy lost = Energy gained



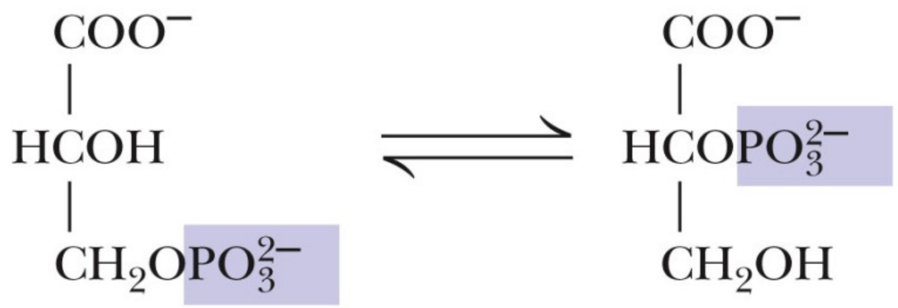
Phosphoglycerate kinase/ Mg^{++}

1,3 BPG + ADP → 3 phosphoglycerate + ATP
$\Delta G^{o\prime}$ = -18.9kJ/mol

Reaction 8

- 3 phosphoglycerate → 2 phosphoglycerate

Phosphoglycerate mutase



3-Phosphoglycerate (3-PG) **2-Phosphoglycerate (2-PG)**

Phosphoglycerate mutase

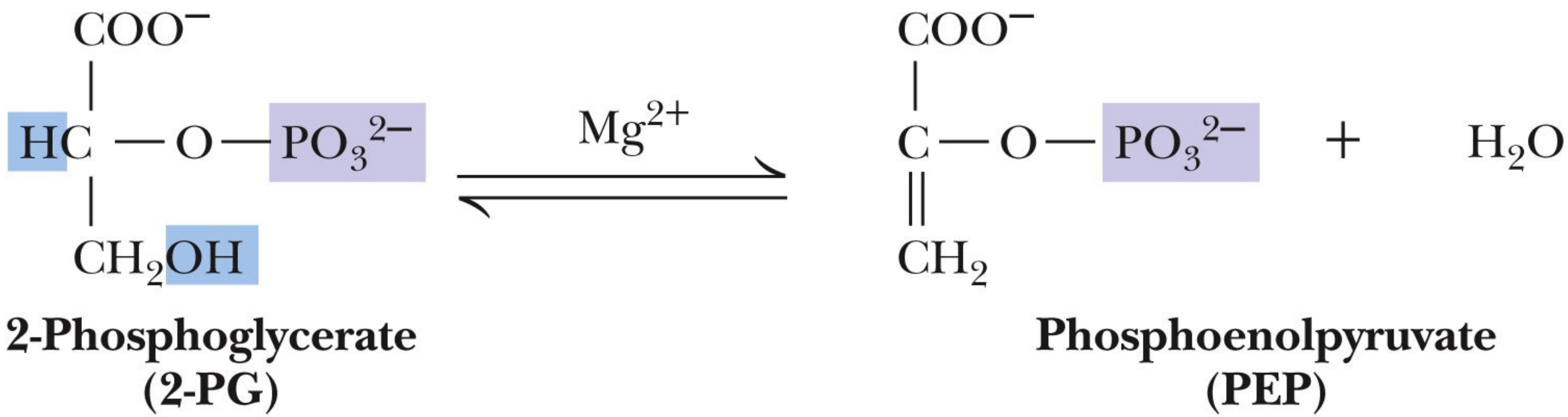
$\Delta G°' = +4.4$ kJ/mol

Reaction 9

- 2 phosphoglycerate → phosphoenolpyruvate

enolase

- Dehydration reaction



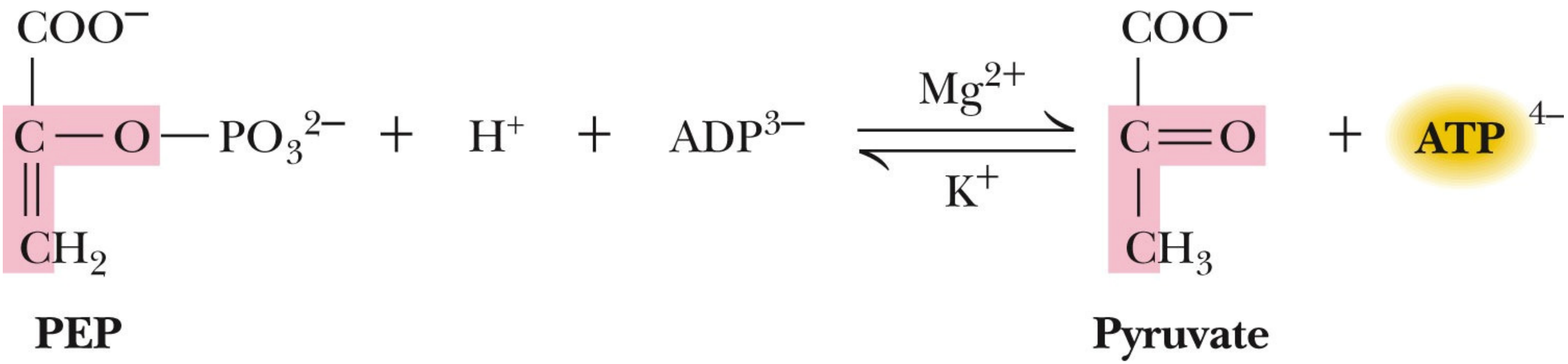
? $\Delta G°' = +1.8$ kJ/mol

Reaction 10

- Phosphoenolpyruvate → pyruvate

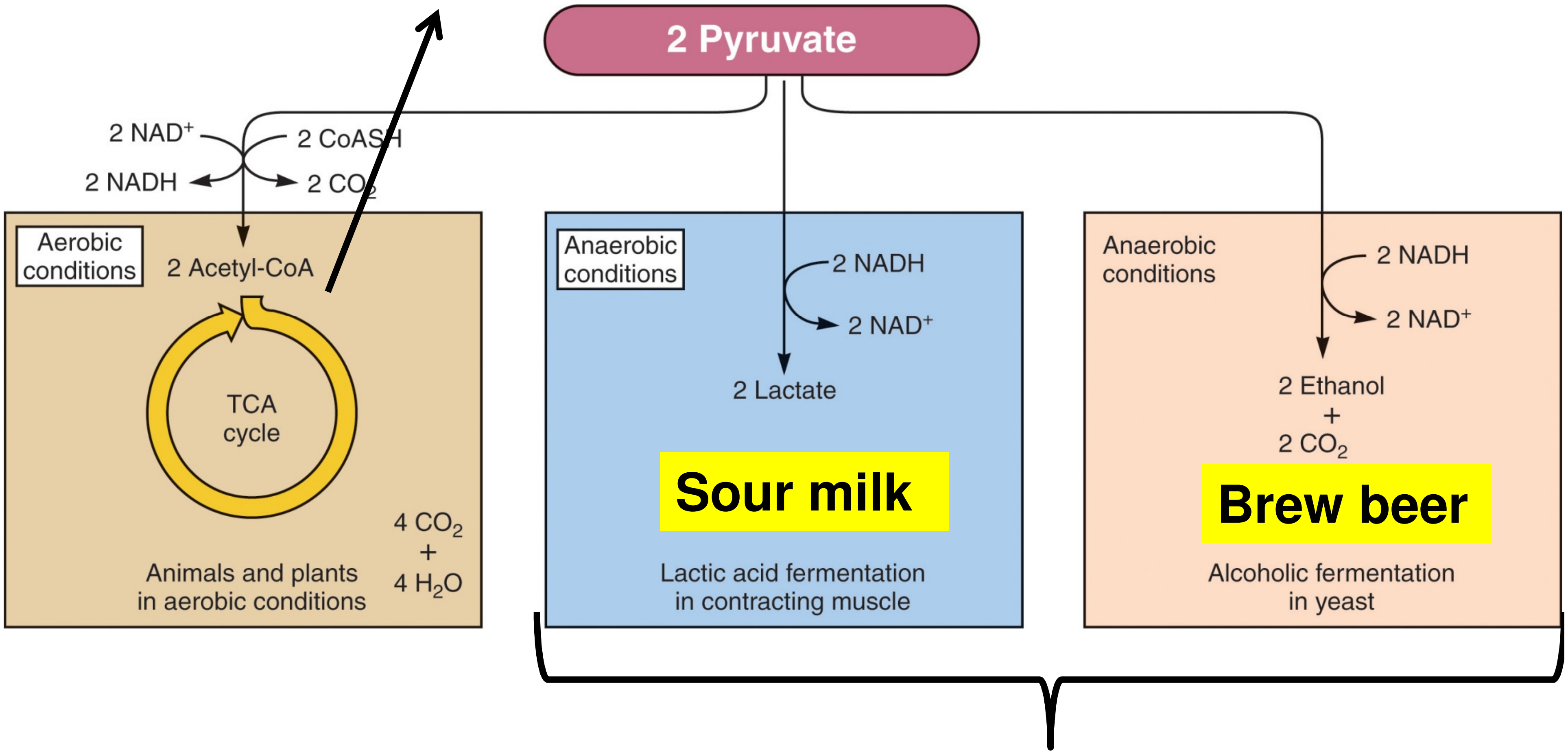
  Pyruvate kinase

- Transfer of a phosphoryl group from PEP to ADP to **generate ATP** and pyruvate



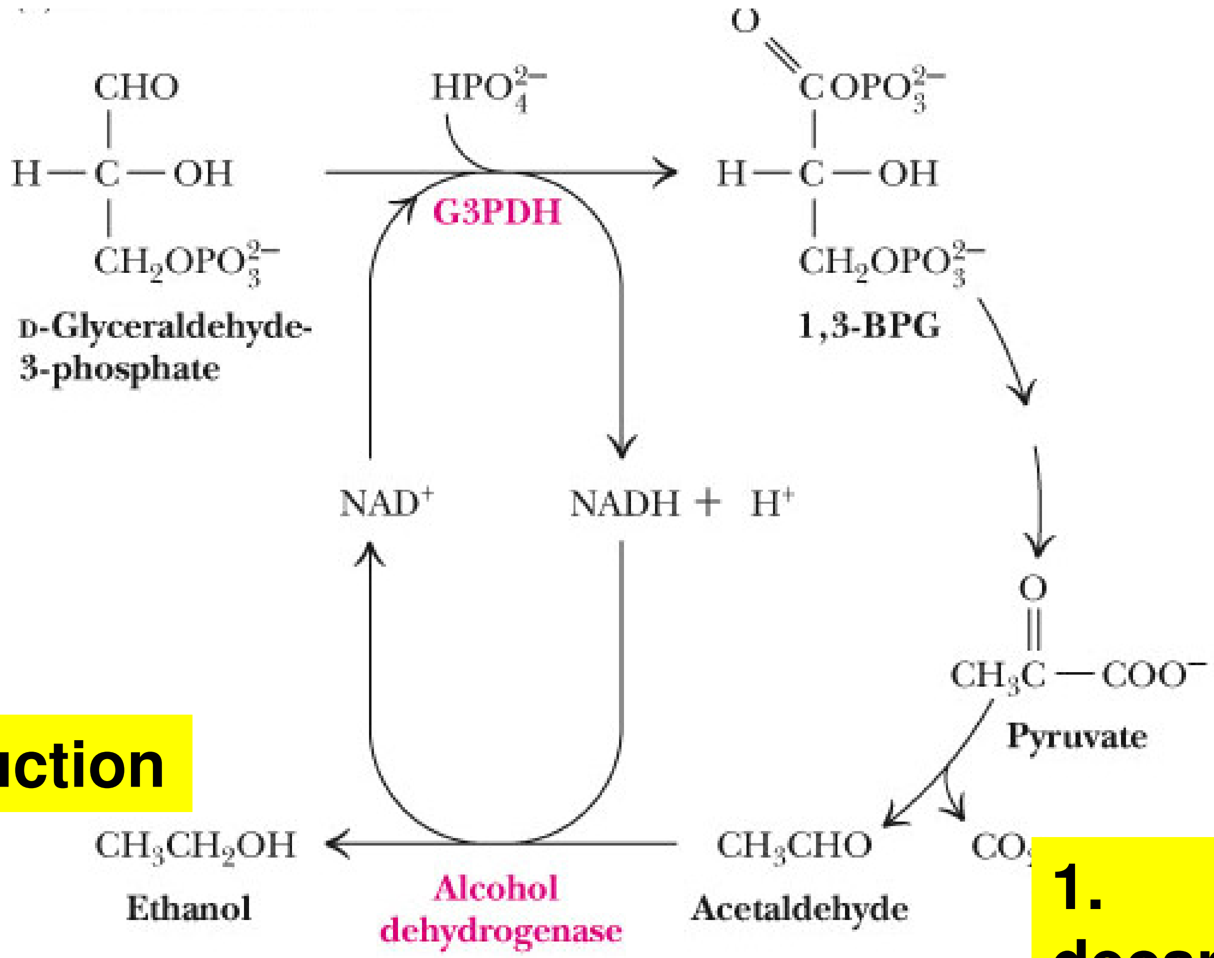
$\Delta G°' = -31.7$ kJ/mol

Metabolic fates of pyruvate



Alcoholic fermentation

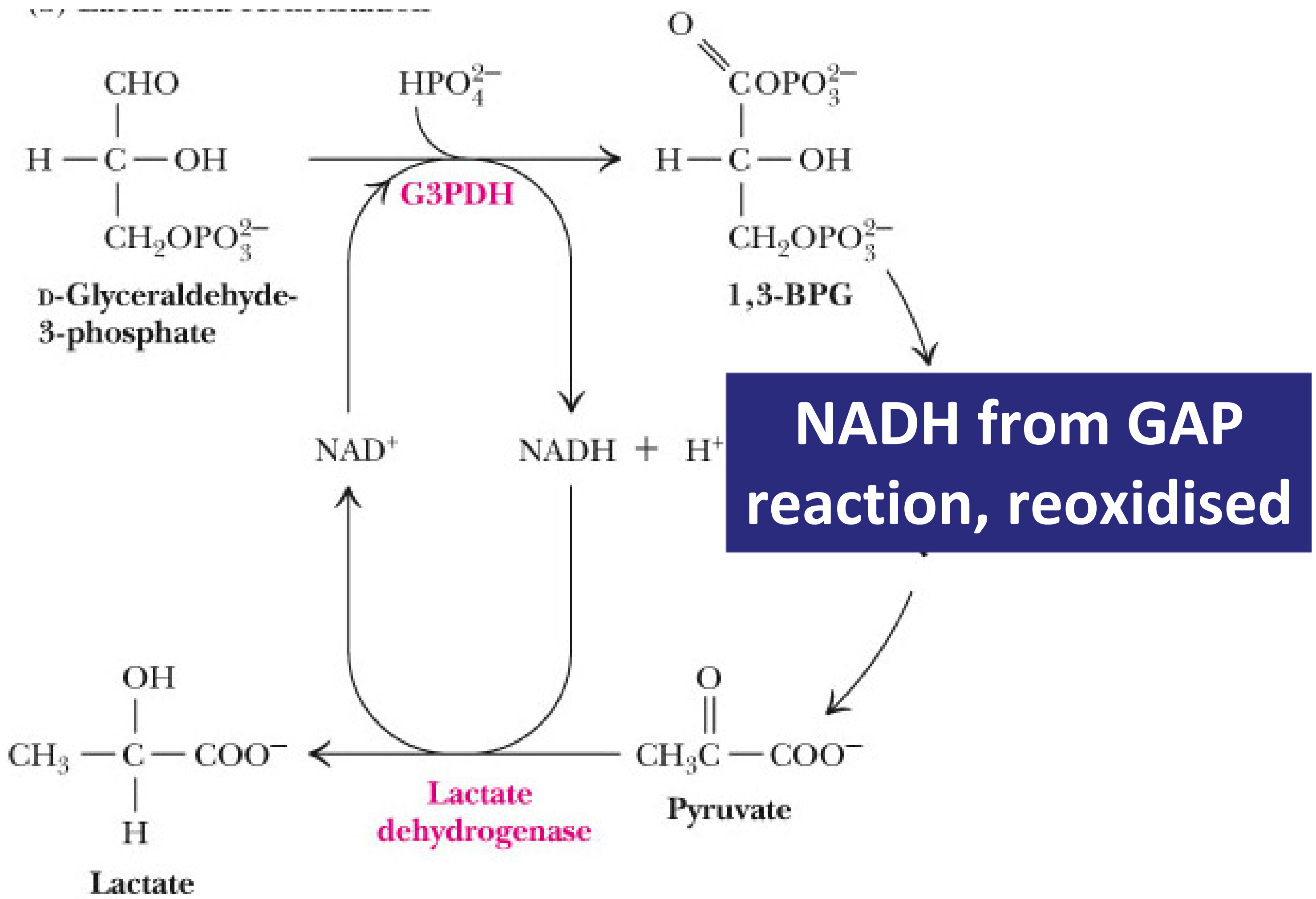
Fermentation: production of energy by reaction pathways involving redox where e$^-$ acceptors are organic molecules



2. reduction

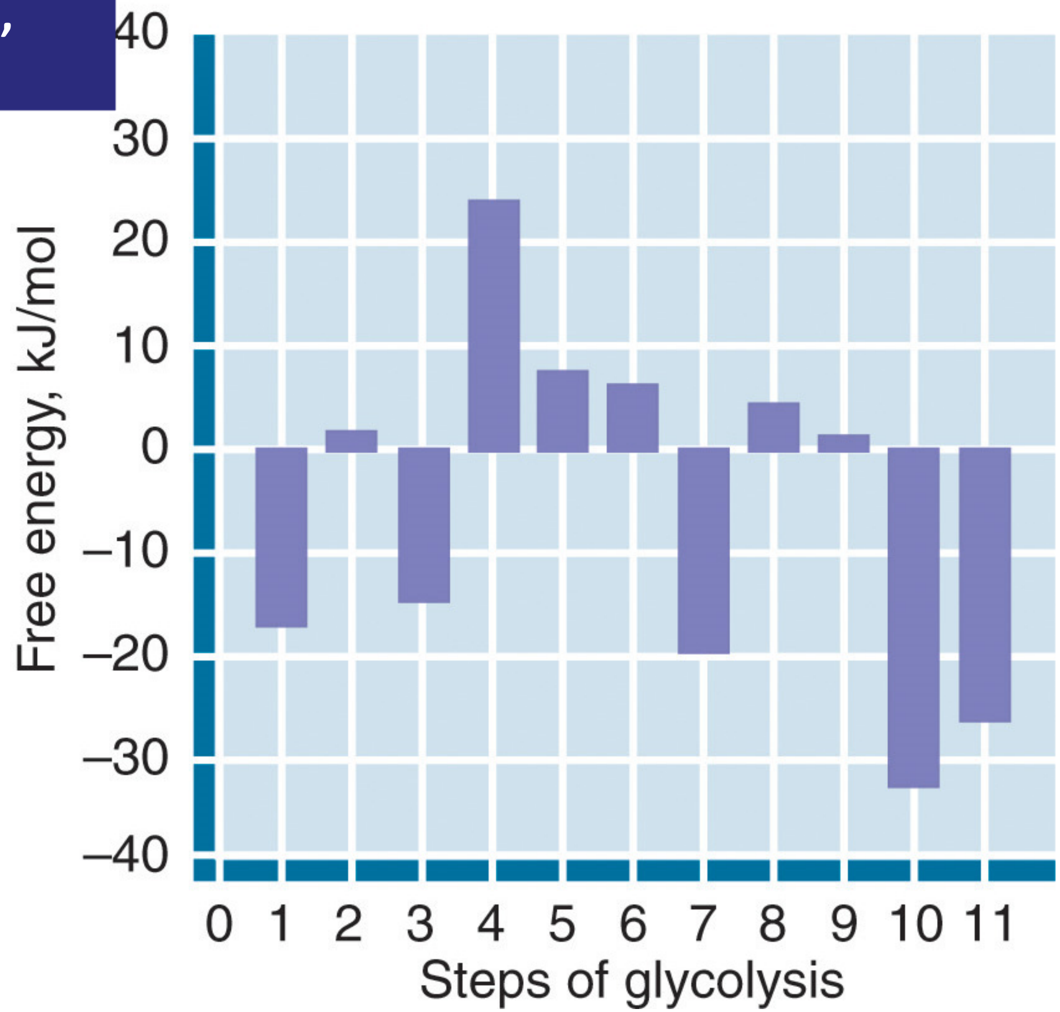
1. decarboxylation

Lactic acid fermentation



Regulation of Glycolysis

ΔG at standard state: ΔG°′



Regulation of Glycolysis

ΔG in erythrocytes