Glucose Transport, Glycolysis and Hexose Metabolism

CHEM 420 – Principles of Biochemistry
Instructor – Anthony S. Serianni

Chapter 17: Voet/Voet, *Biochemistry*, 2011
Fall 2015

November 6 & 9

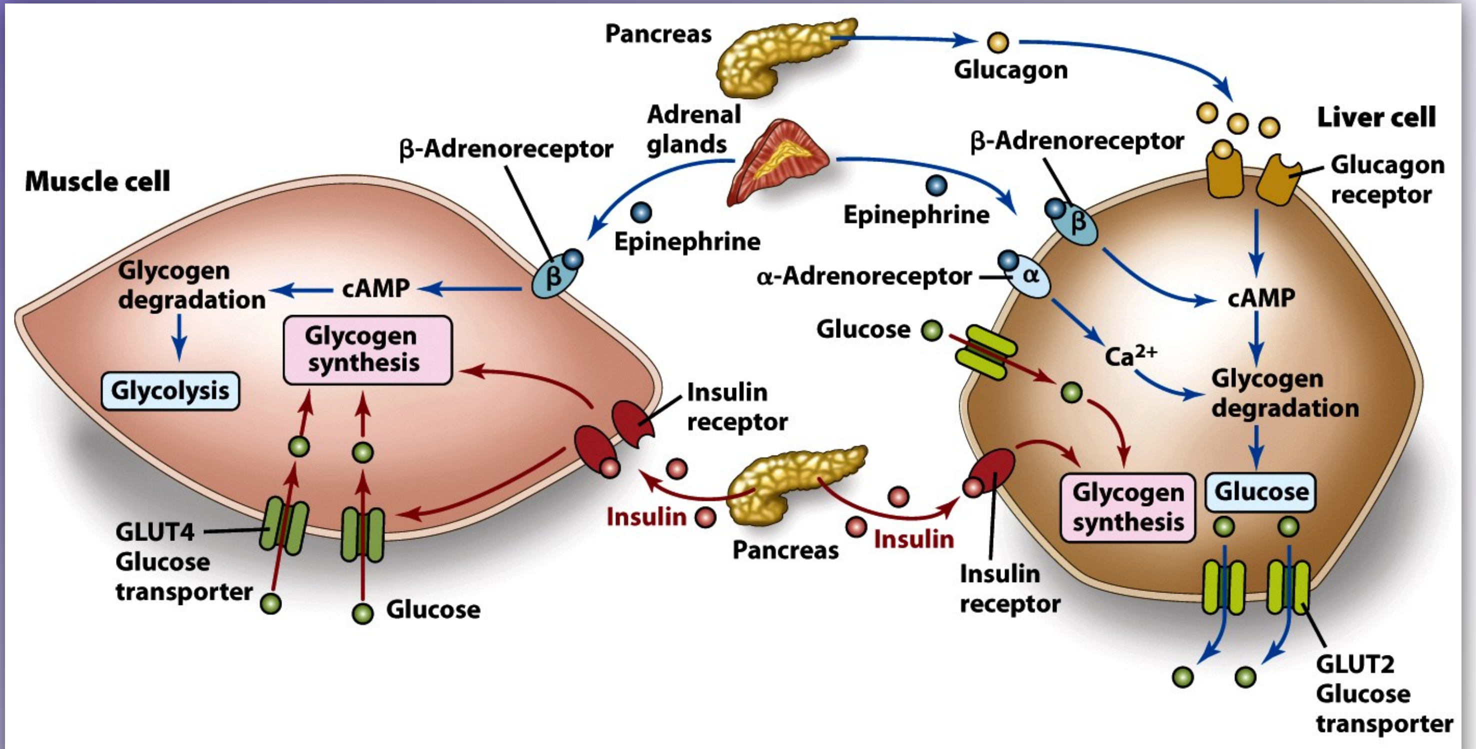
TABLE 12-1 Properties of Selected Members of Human Glucose Transporters (GLUT)

Transporters	Major Tissue Distribution	Properties
GLUT 1	Brain, microvessels, red blood cells, placenta, kidney, and many other cells	Low K_m (about 1 mM), ubiquitous basal transporter
GLUT 2	Liver, pancreatic β-cell, small intestine	High K_m (15–20 mM)
GLUT 3	Brain, placenta, fetal muscle	Low K_m, provide glucose for tissue cells metabolically dependent on glucose
GLUT 4	Skeletal and heart muscle, fat tissue (adipocytes)	K_m (5 mM), insulin responsive transporter
GLUT 5	Small intestine, testes	Exhibits high affinity for fructose
SGLT 1	Small intestine and renal tubules	Low K_m (0.1–1.0 mM)
SGLT 2	Renal tubules	Low K_m (1.6 mM)

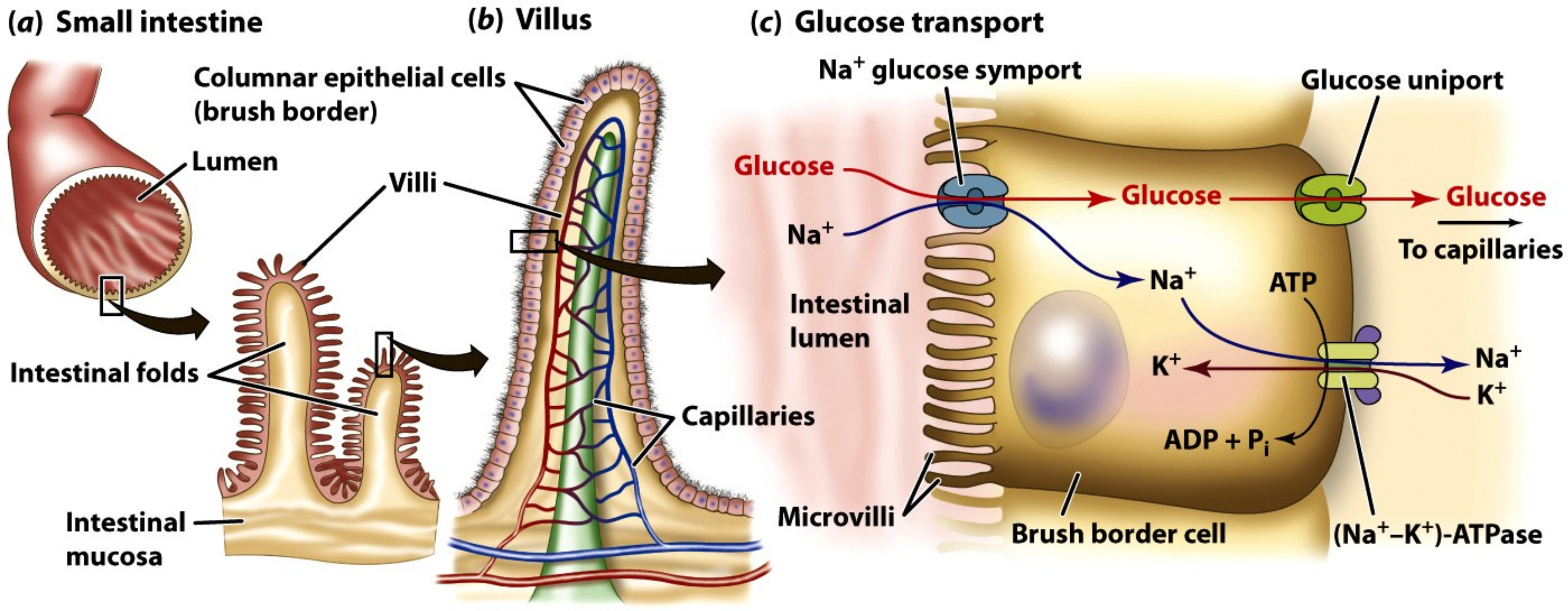
GLUT: concentration gradient-dependent facilitated transport with specific carrier; either insulin dependent or insulin independent

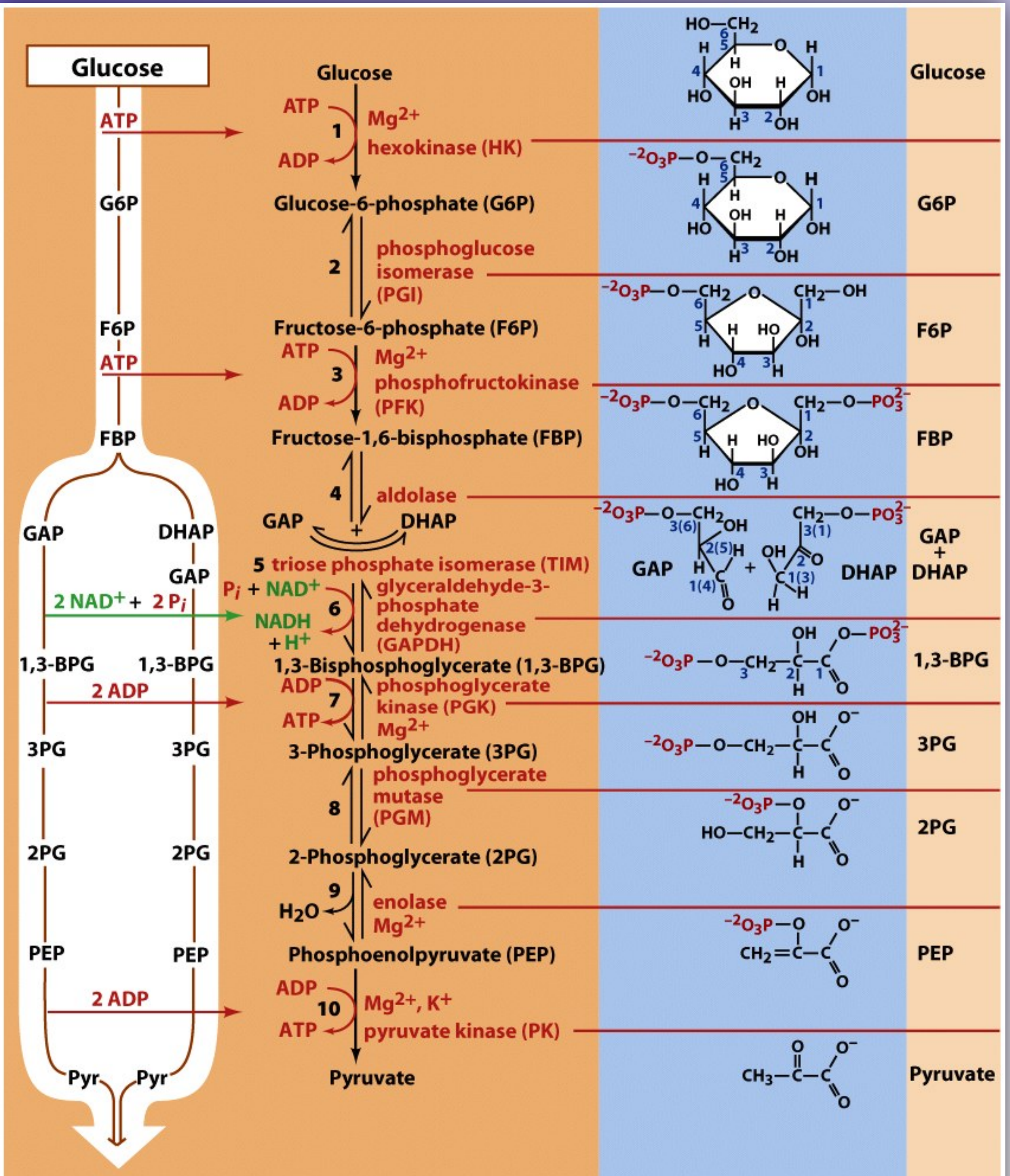
SGLT: active transport

Plasma membrane-bound glucose transporters



Active transport of glucose driven by an ion gradient

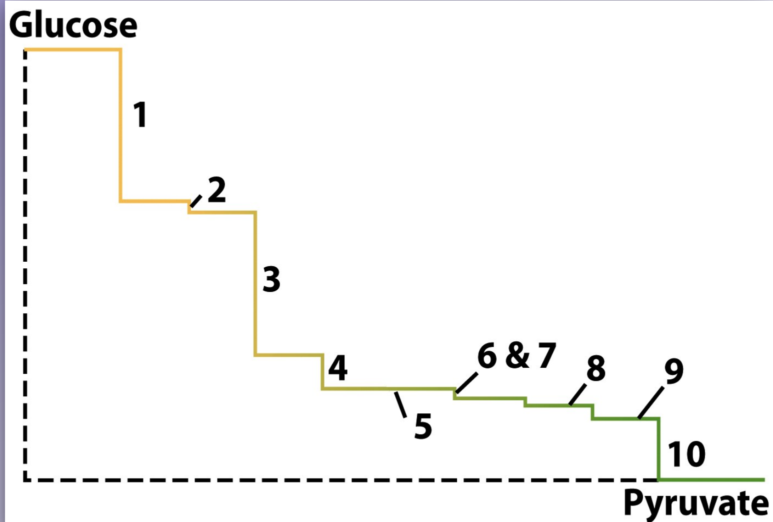




Overview of the ten reactions of glycolysis

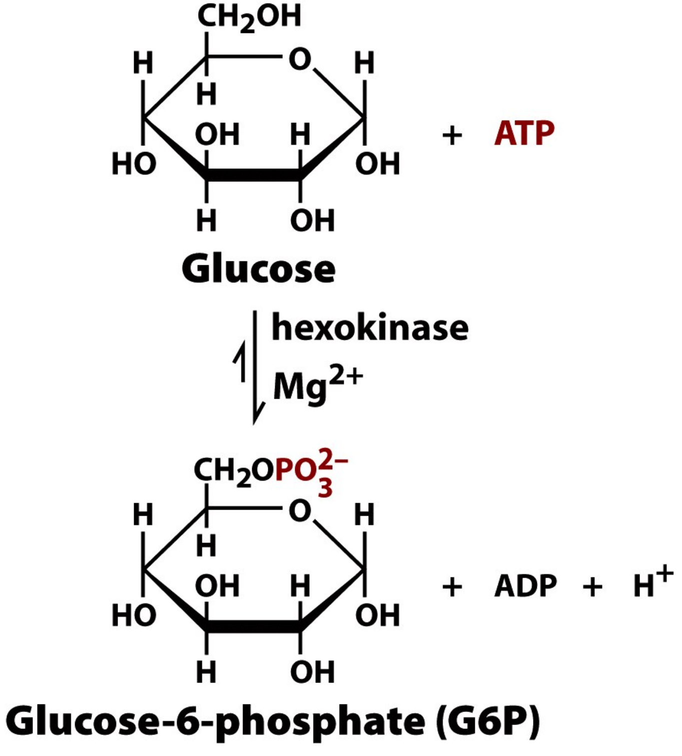
Table 15-1	$\Delta G^{\circ\prime}$ and ΔG for the Reactions of Glycolysis in Heart Muscle[a]		
Reaction	**Enzyme**	**$\Delta G^{\circ\prime}$ ($kJ \cdot mol^{-1}$)**	**ΔG ($kJ \cdot mol^{-1}$)**
1	Hexokinase	−20.9	−27.2
2	PGI	+2.2	−1.4
3	PFK	−17.2	−25.9
4	Aldolase	+22.8	−5.9
5	TIM	+7.9	~0
6 + 7	GAPDH + PGK	−16.7	−1.1
8	PGM	+4.7	−0.6
9	Enolase	−3.2	−2.4
10	PK	−23.0	−13.9

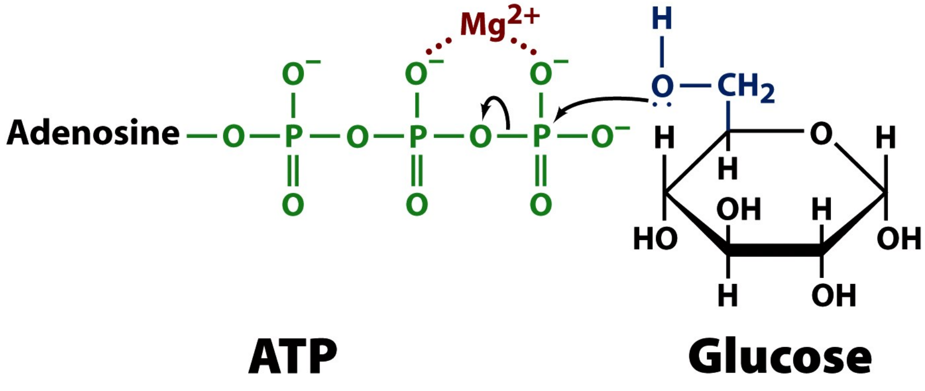
[a]Calculated from data in Newsholme, E.A. and Start, C., *Regulation in Metabolism*, p. 97, Wiley (1973).



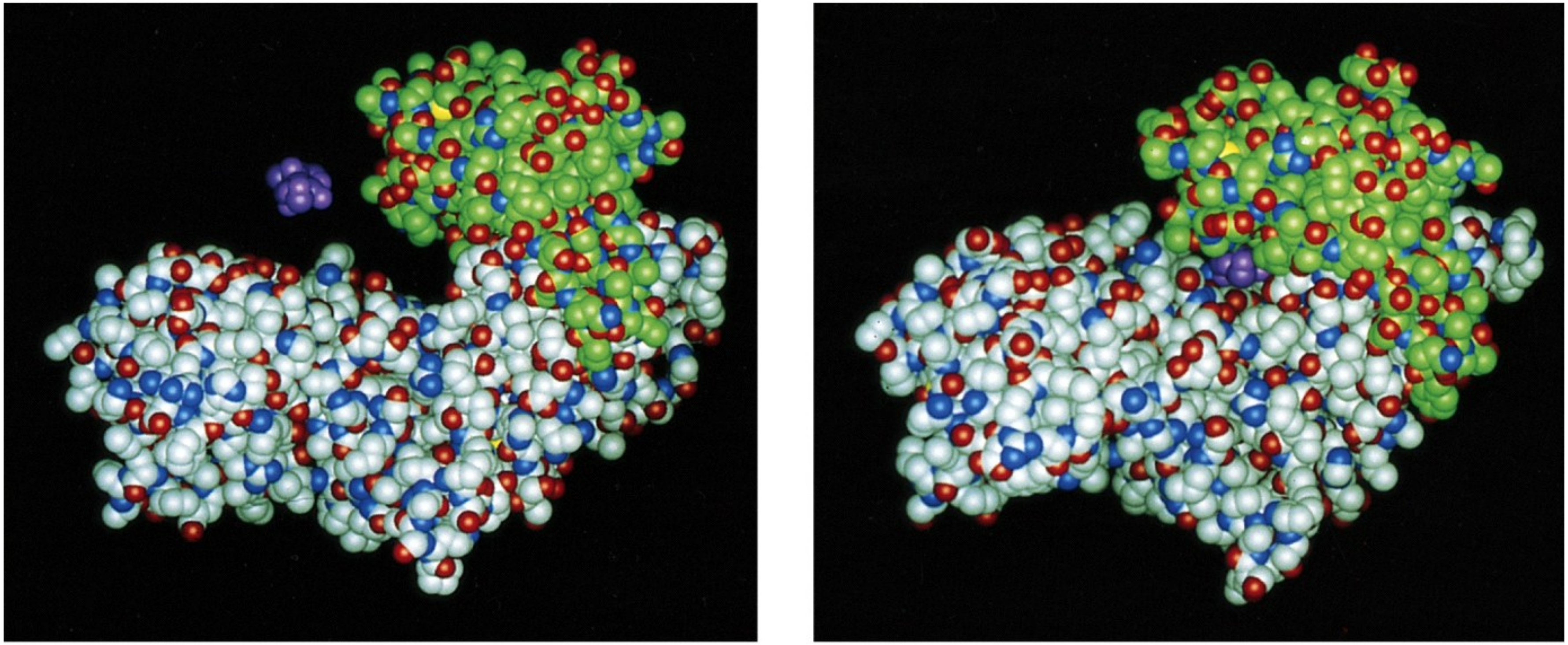
Free energy changes in glycolysis

Hexokinase (muscle)



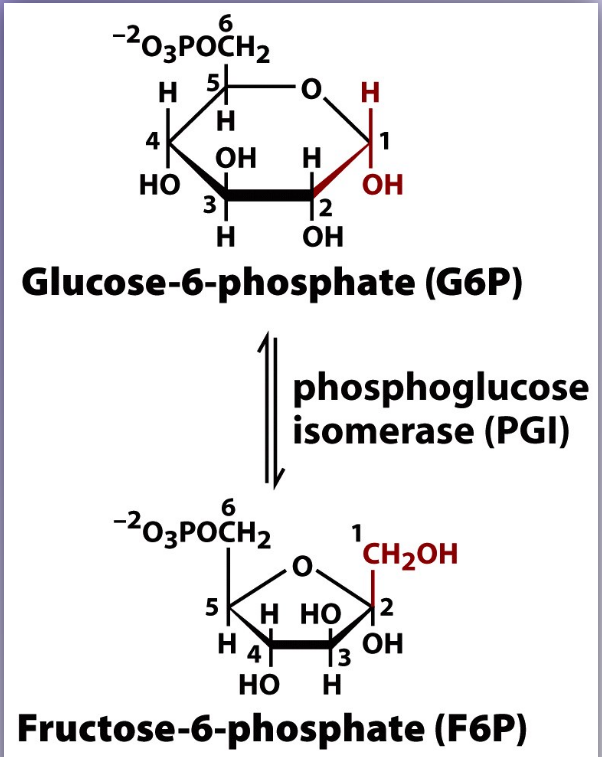


Conformational change in hexokinase upon substrate binding

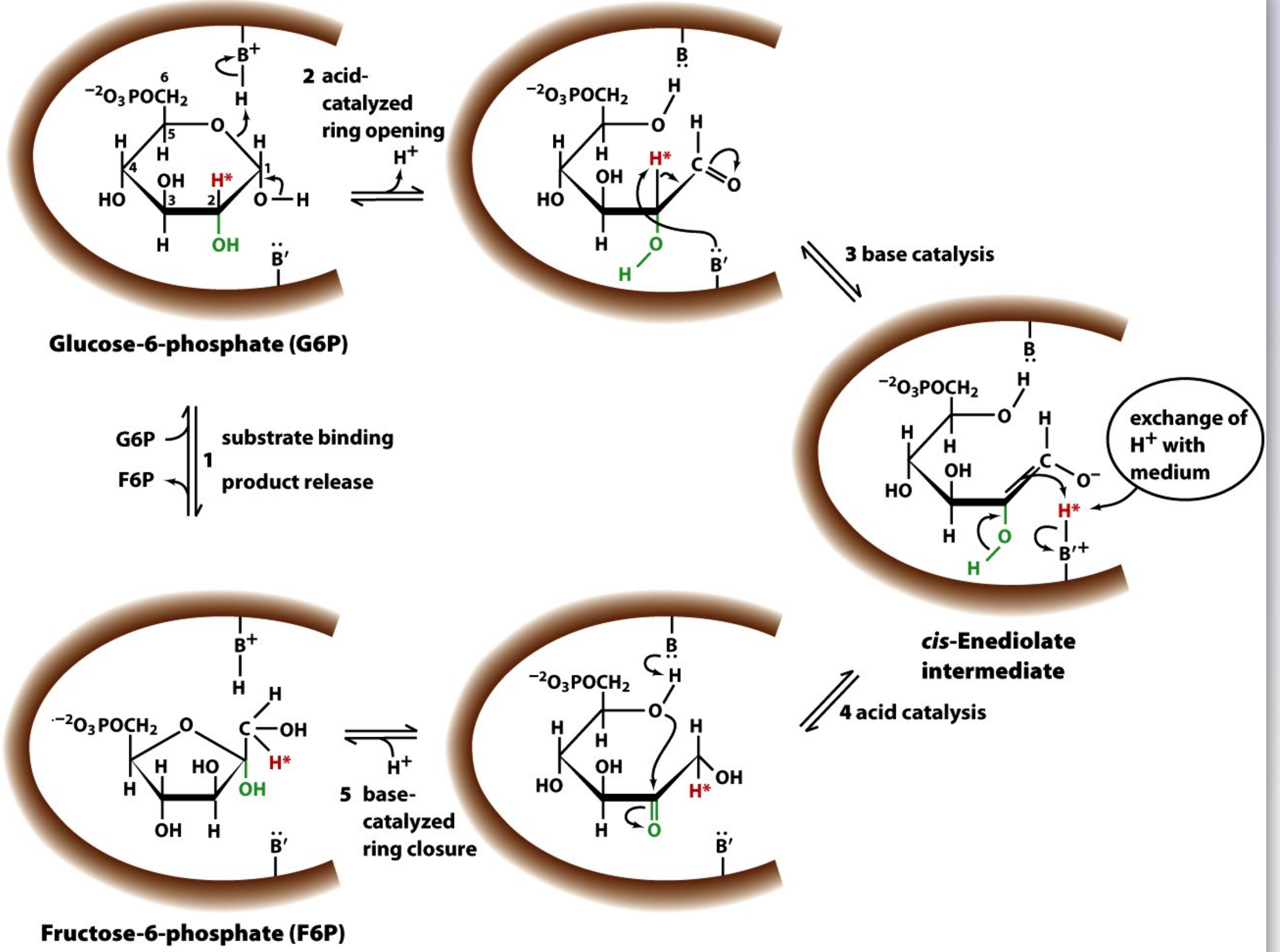


(a) (b)

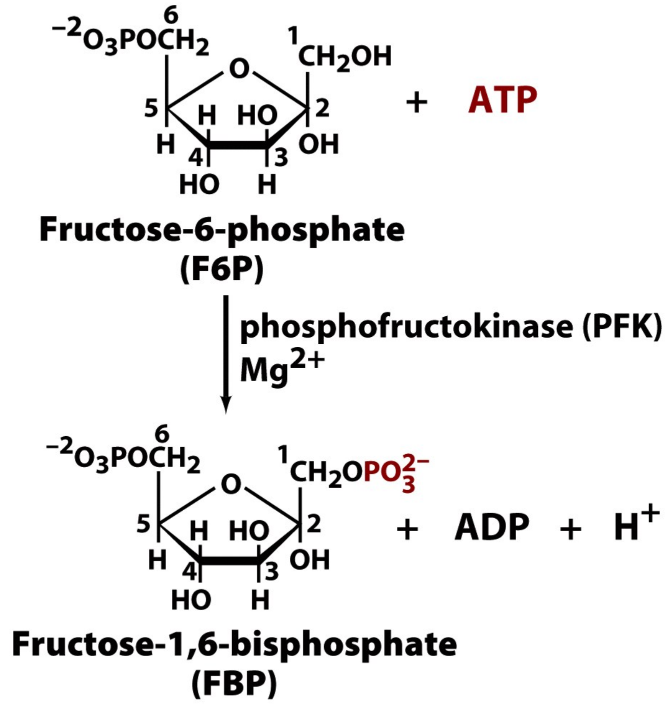
Phosphoglucoisomerase (PGI)



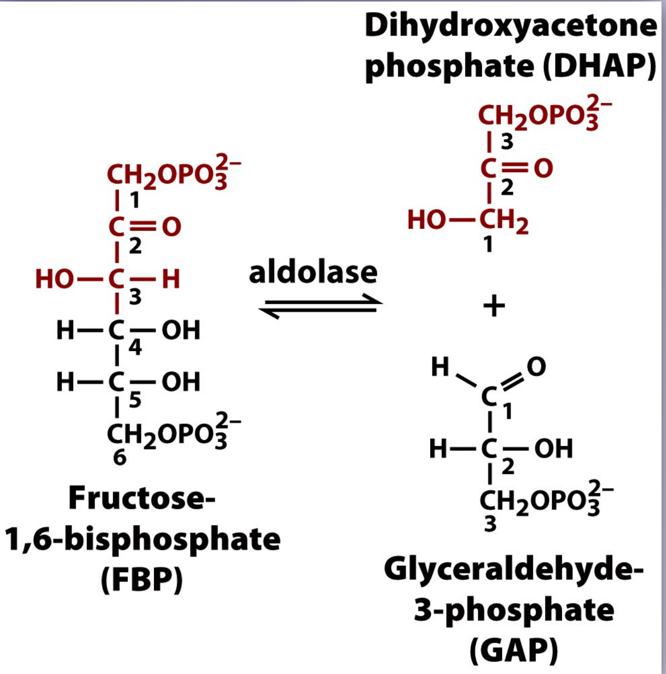
PGI mechanism



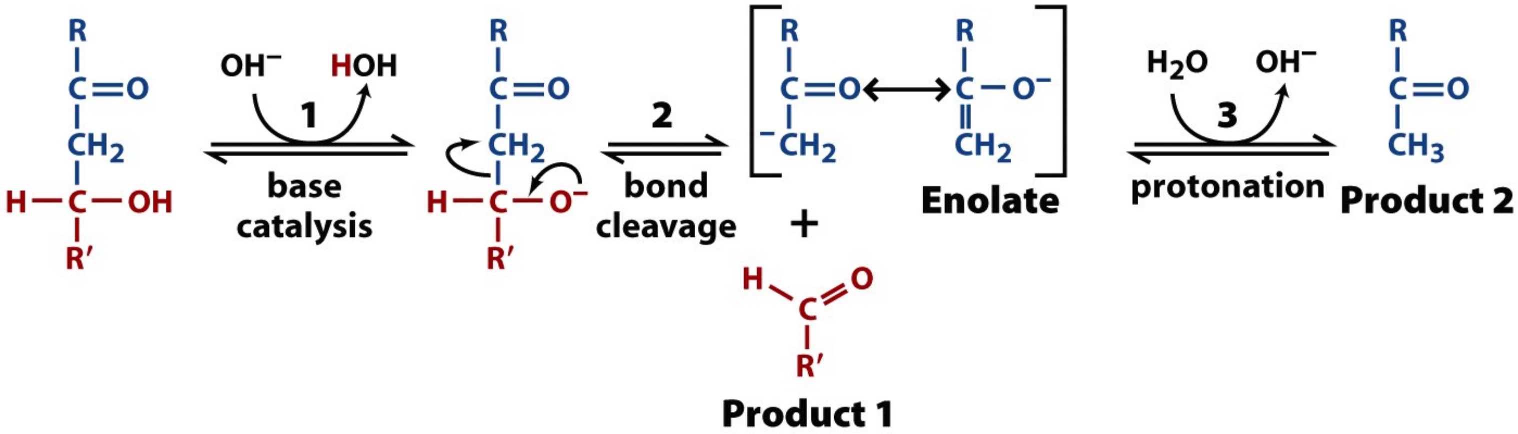
Phosphofructokinase (PFK)



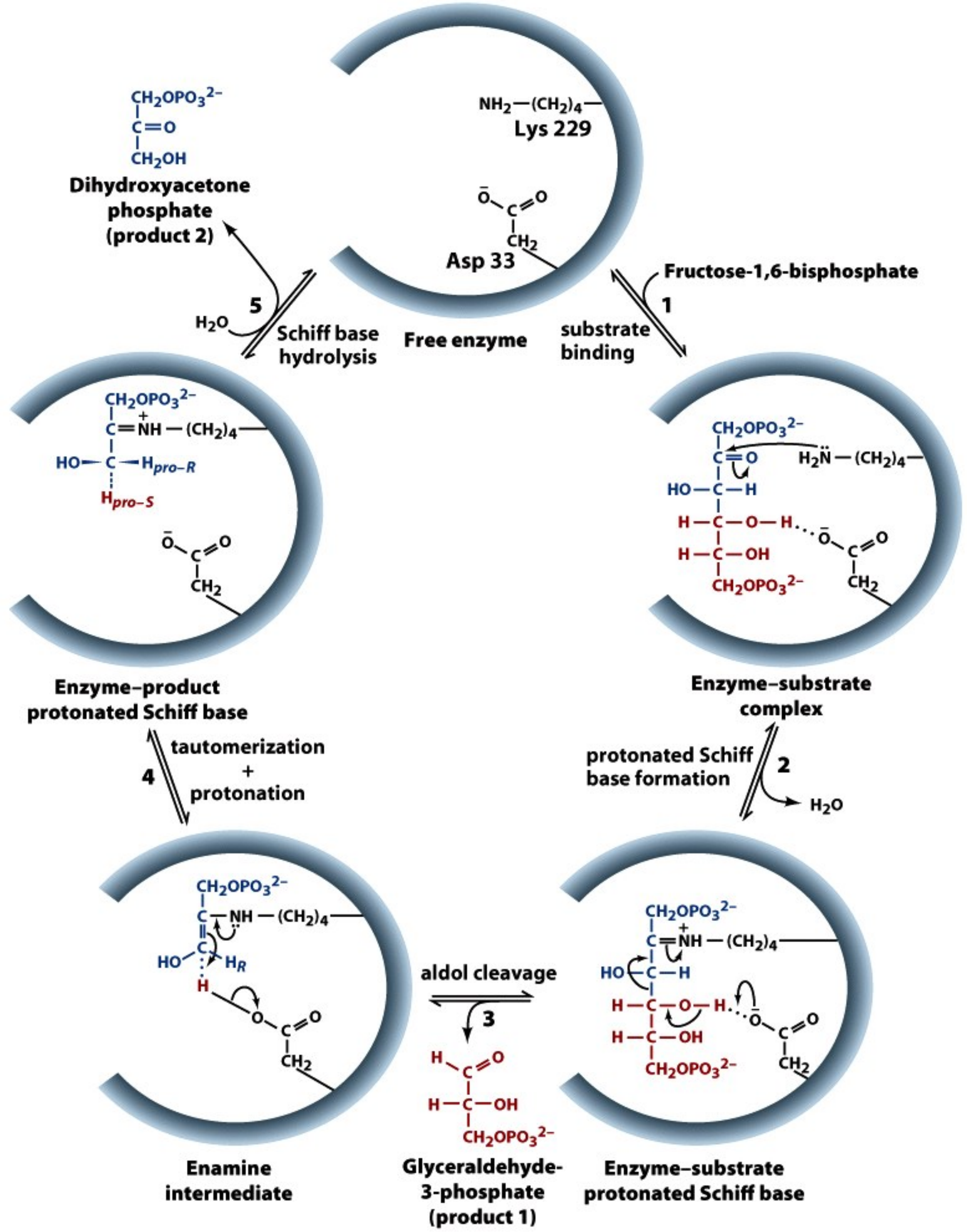
Aldolase


Dihydroxyacetone phosphate (DHAP)
$CH_2OPO_3^{2-}$
C=O
HO—CH_2
aldolase
+
Fructose-1,6-bisphosphate (FBP)
$CH_2OPO_3^{2-}$
C=O
HO—C—H
H—C—OH
H—C—OH
$CH_2OPO_3^{2-}$
Glyceraldehyde-3-phosphate (GAP)
H
O
C
H—C—OH
$CH_2OPO_3^{2-}$

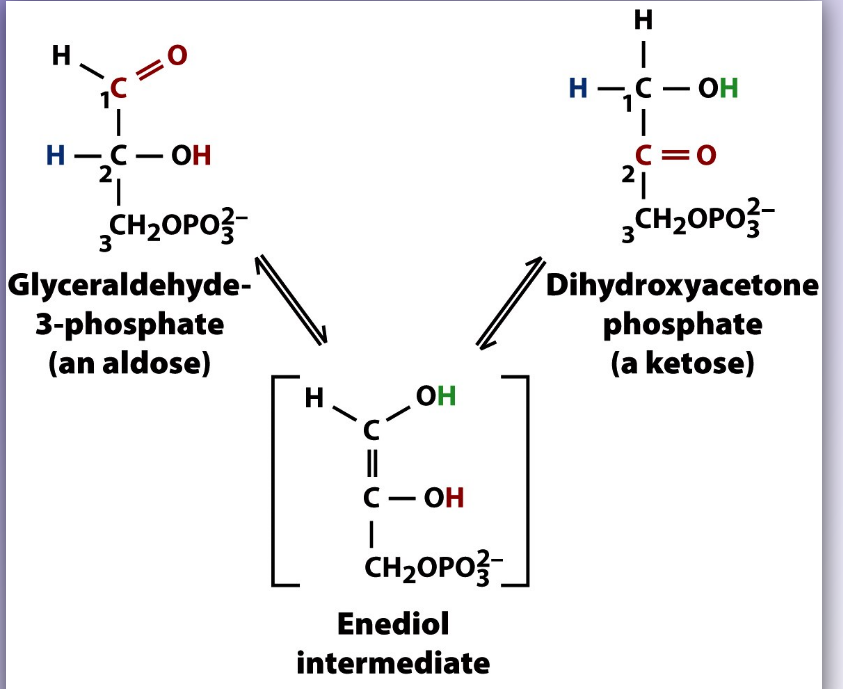
General mechanism of base-catalyzed aldol cleavage



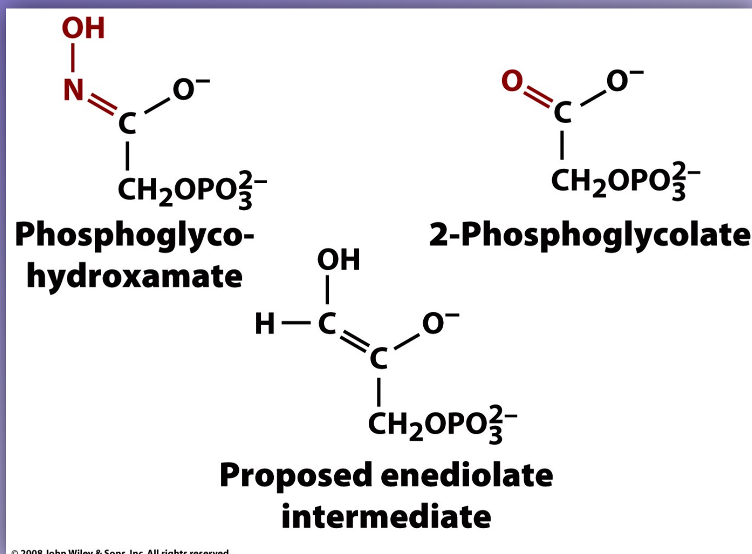
Proposed aldolase mechanism

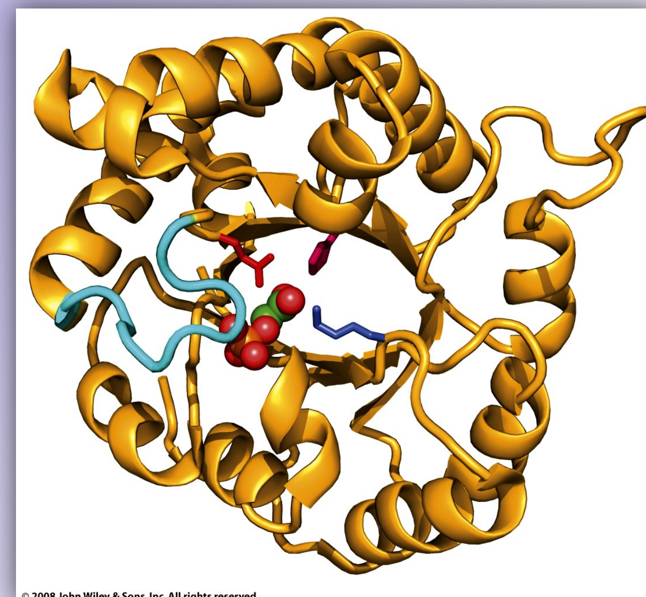


Triose-phosphate isomerase (TPI)

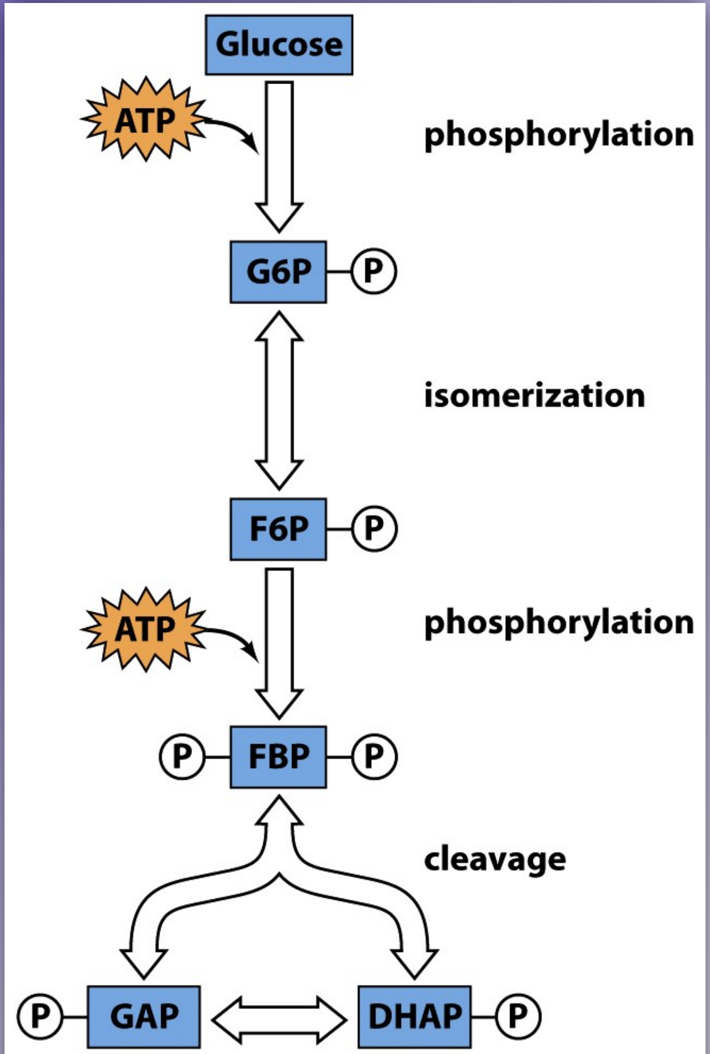


Transition-state analogs of TPI



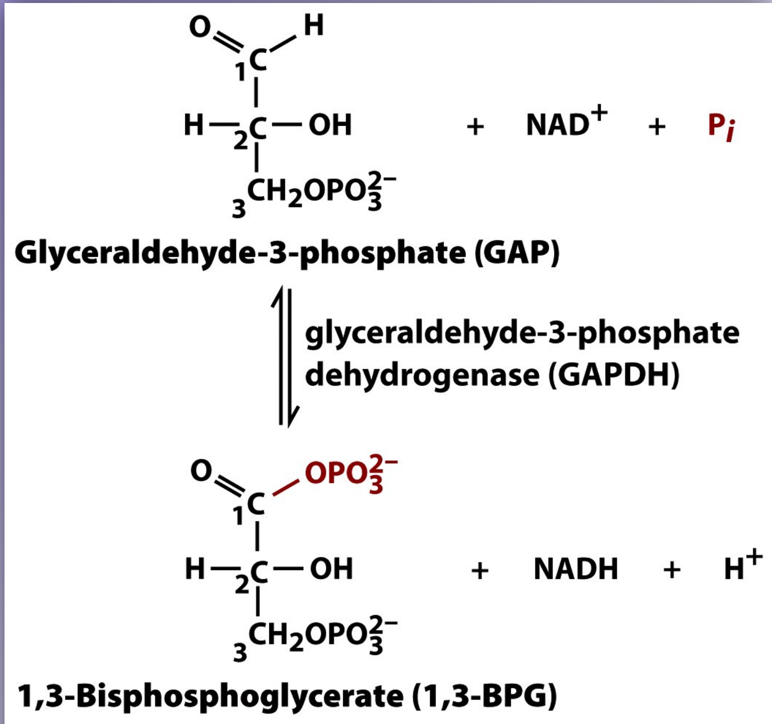


TPI complexed
with 2-phosphoglycolate

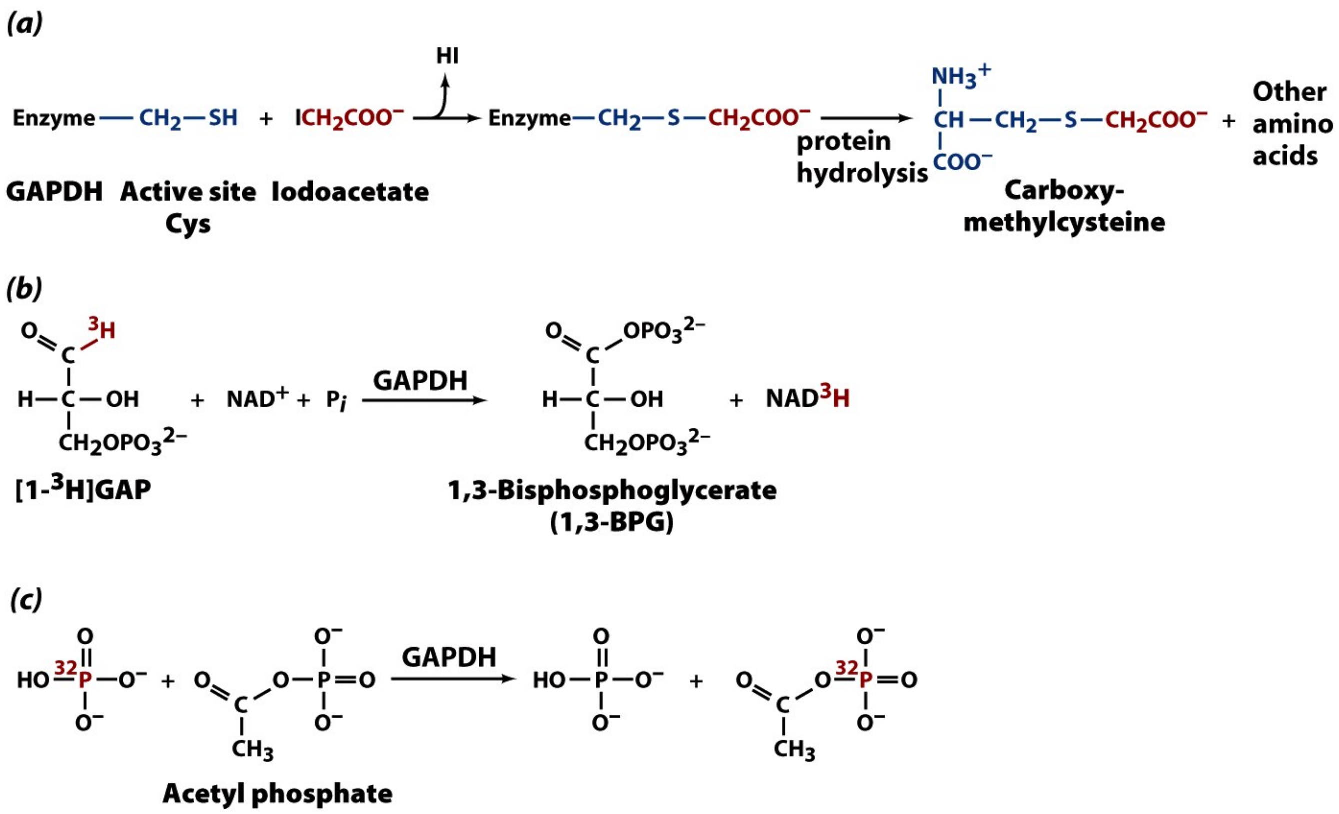


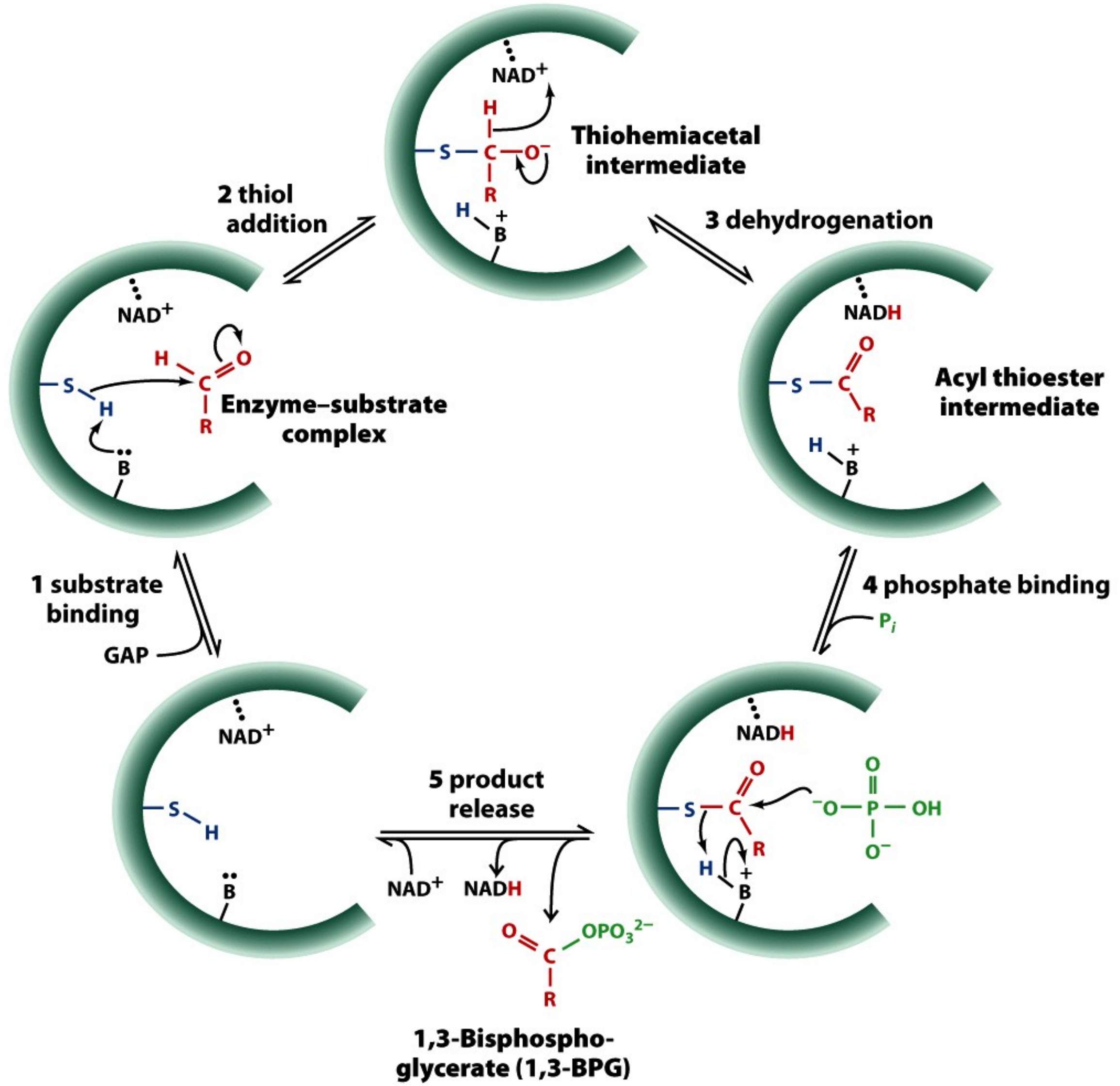
First half of glycolysis: ATP investment phase

Glyceraldehyde 3-P dehydrogenase



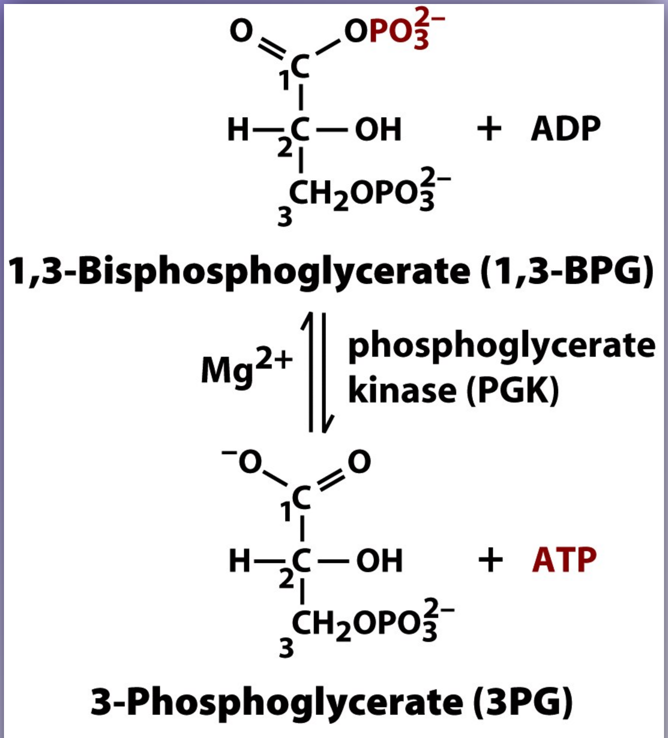
Characterizing the G3P dehydrogenase reaction





Proposed mechanism of G3P dehydrogenase

3-Phosphoglycerate kinase



First substrate-level phosphorylation reaction of glycolysis

Mechanism of the PGK reaction

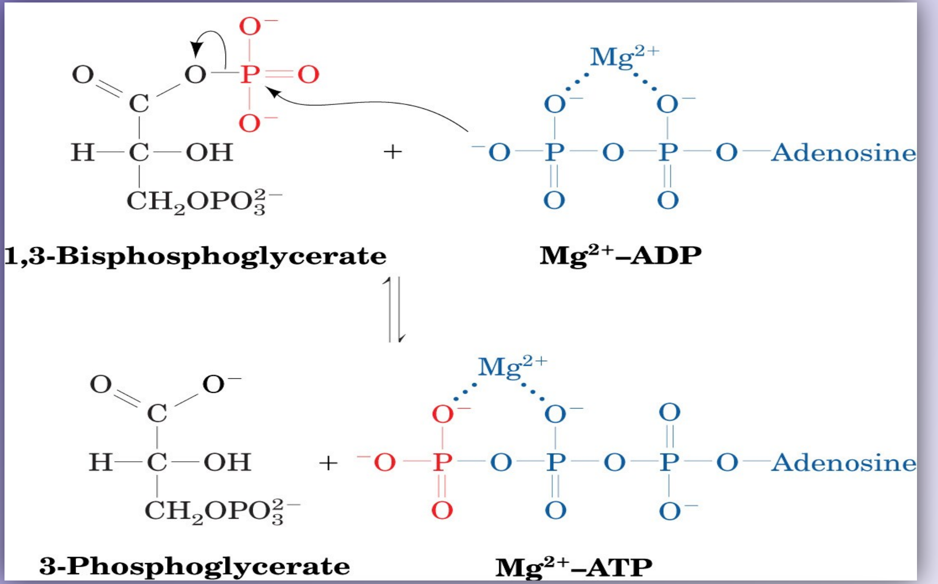


Table 15-1 $\Delta G°'$ and ΔG for the Reactions of Glycolysis in Heart Muscle[a]

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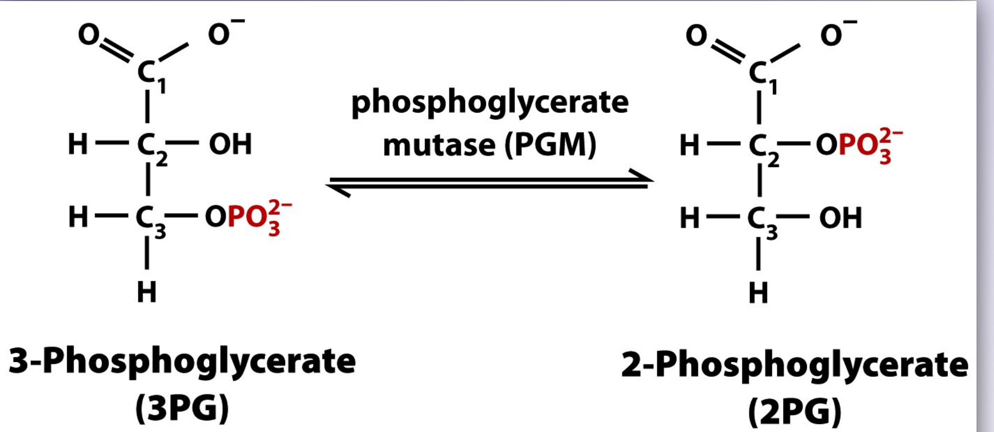
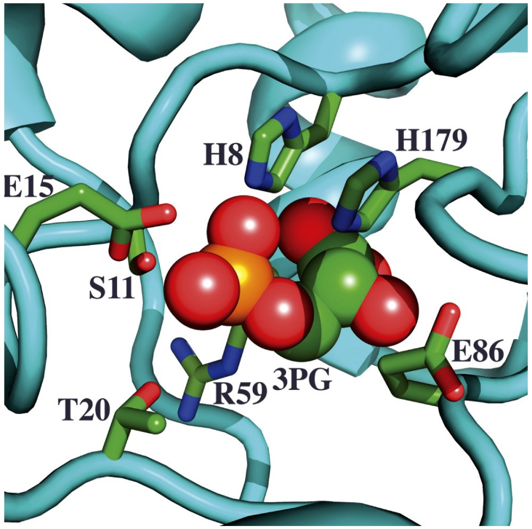
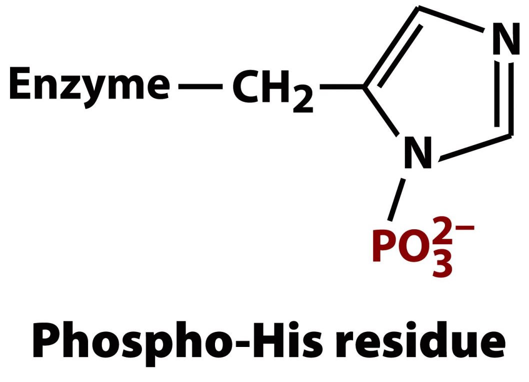
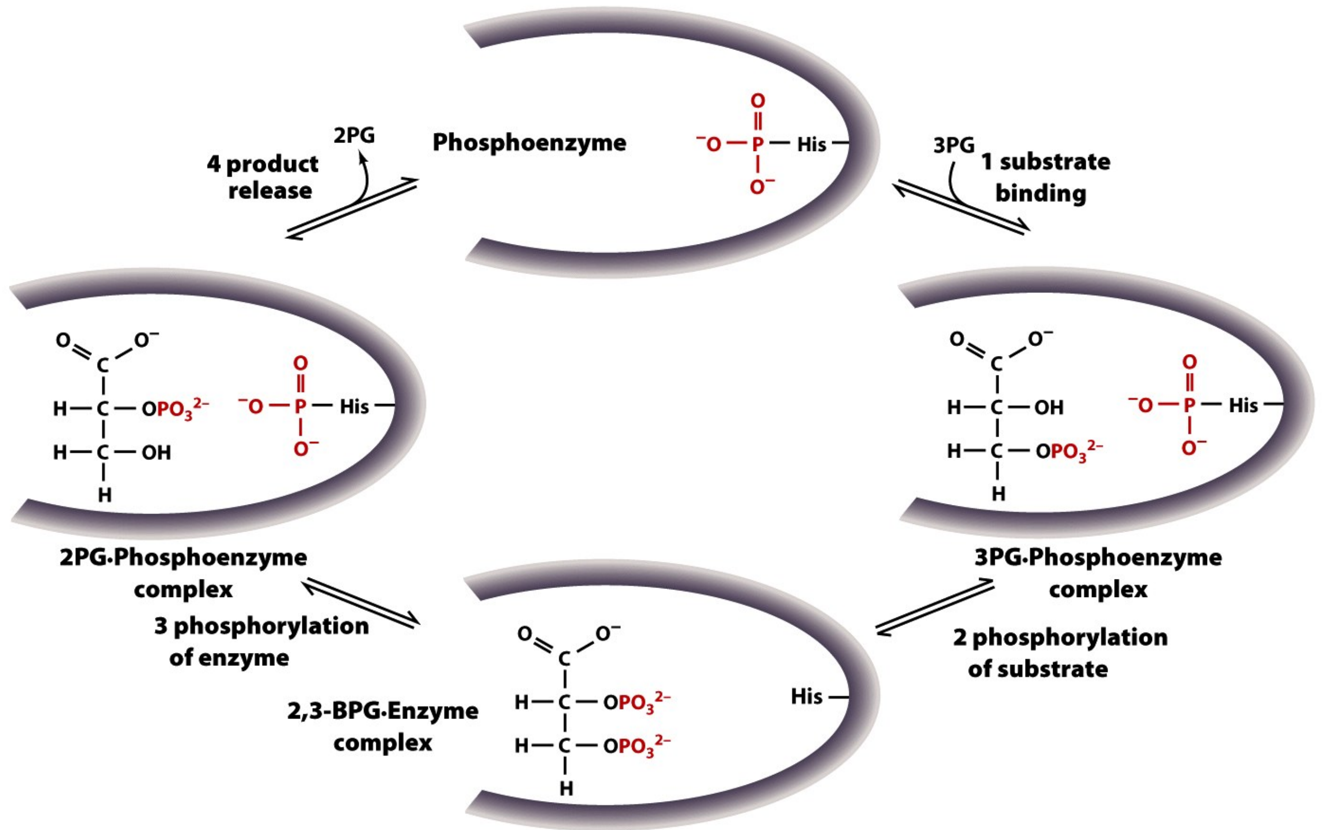
3-Phosphoglycerate mutase



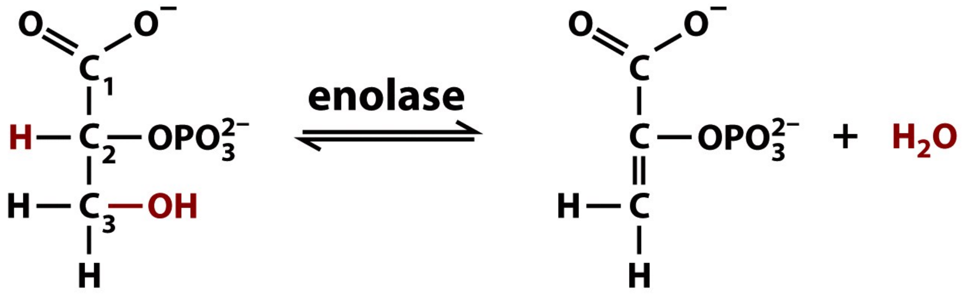

H8
H179
E15
S11
E86
3PG
R59
T20


Enzyme — CH2
N
N
PO3 2−
Phospho-His residue

Proposed mechanism of 3-phosphoglycerate mutase



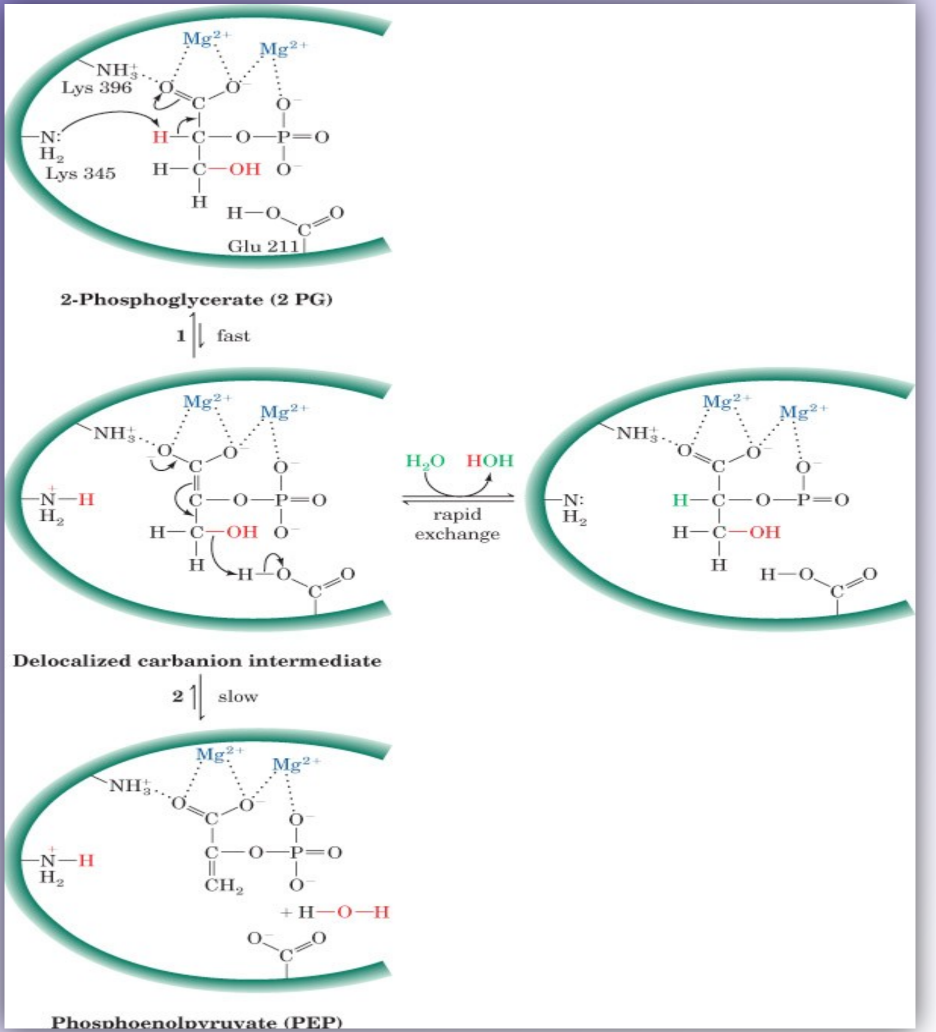
Enolase



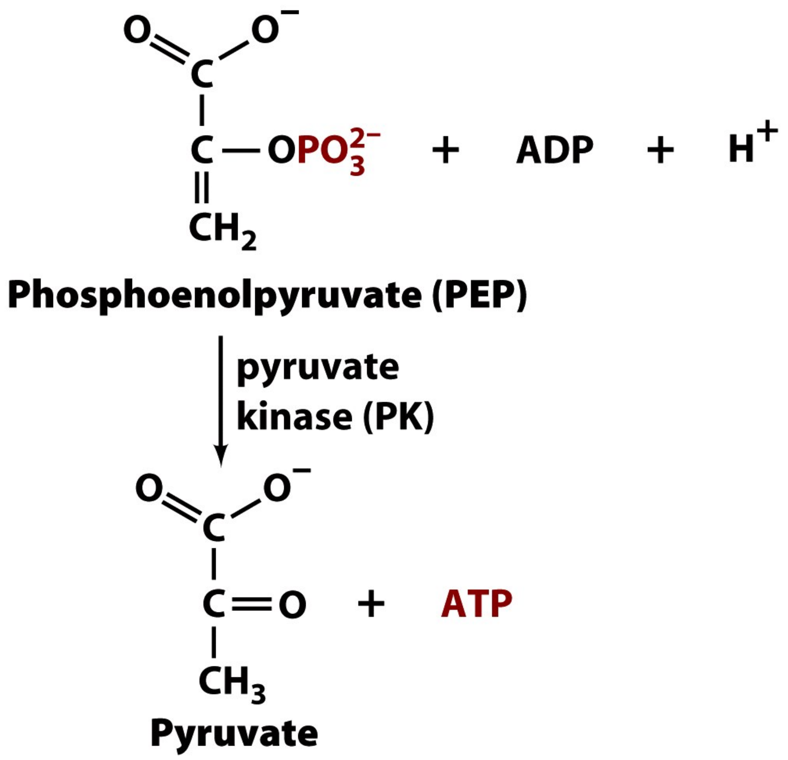
2-Phosphoglycerate (2PG)

Phosphoenolpyruvate (PEP)

Proposed reaction mechanism of enolase

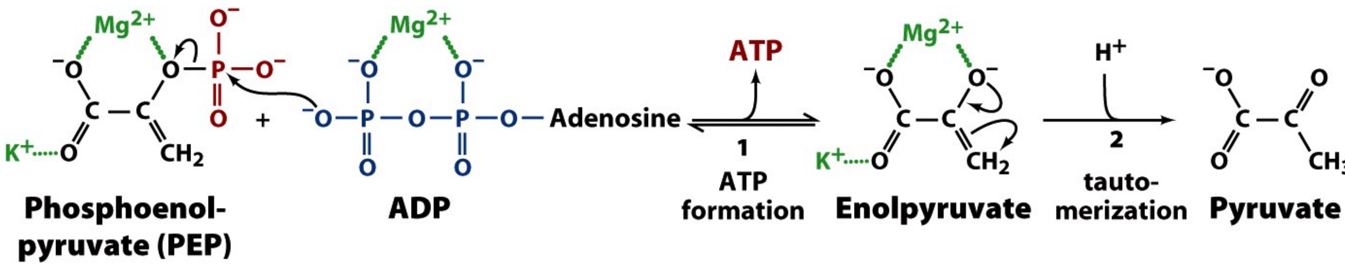


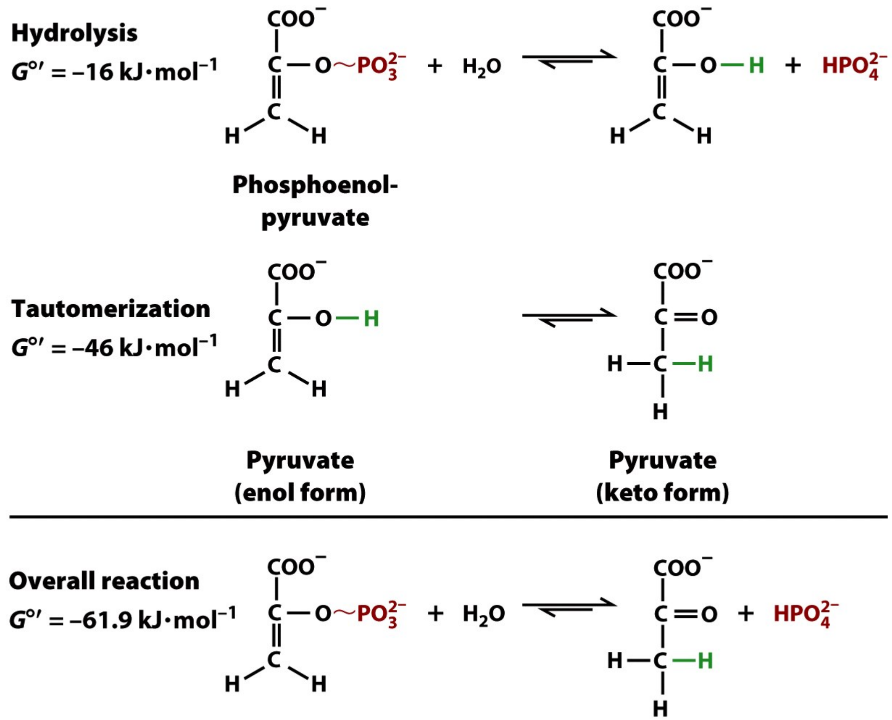
Pyruvate kinase

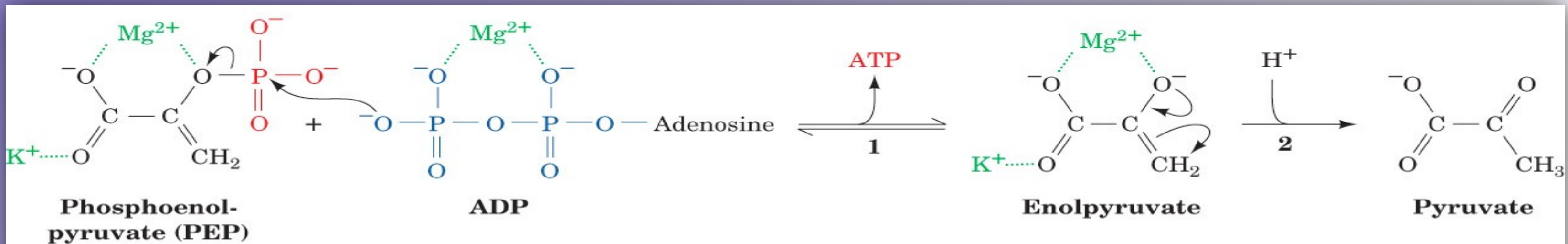


Second substrate-level phosphorylation reaction of glycolysis

Explanation of the very (-) change in free energy associated with the PK reaction



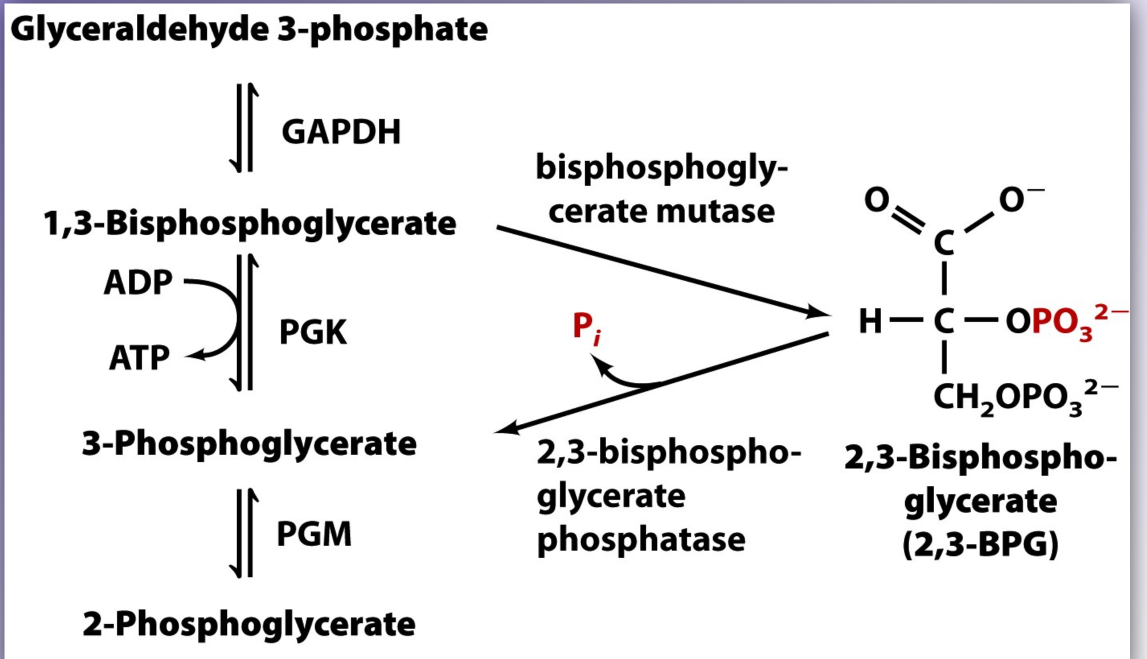




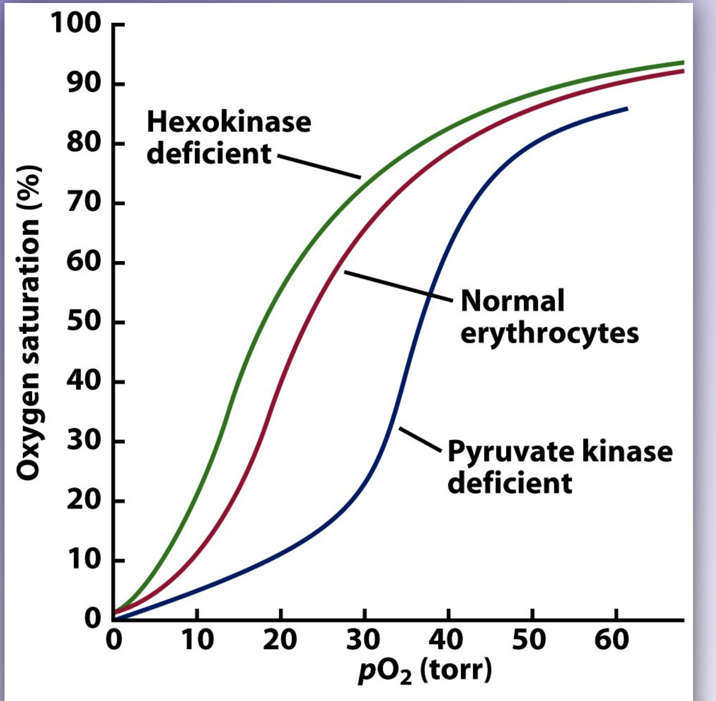
$\Delta G^{\circ\prime} = +14.4\ \mathrm{kJ{\cdot}mol^{-1}}$ $\Delta G^{\circ\prime} = -46\ \mathrm{kJ{\cdot}mol^{-1}}$

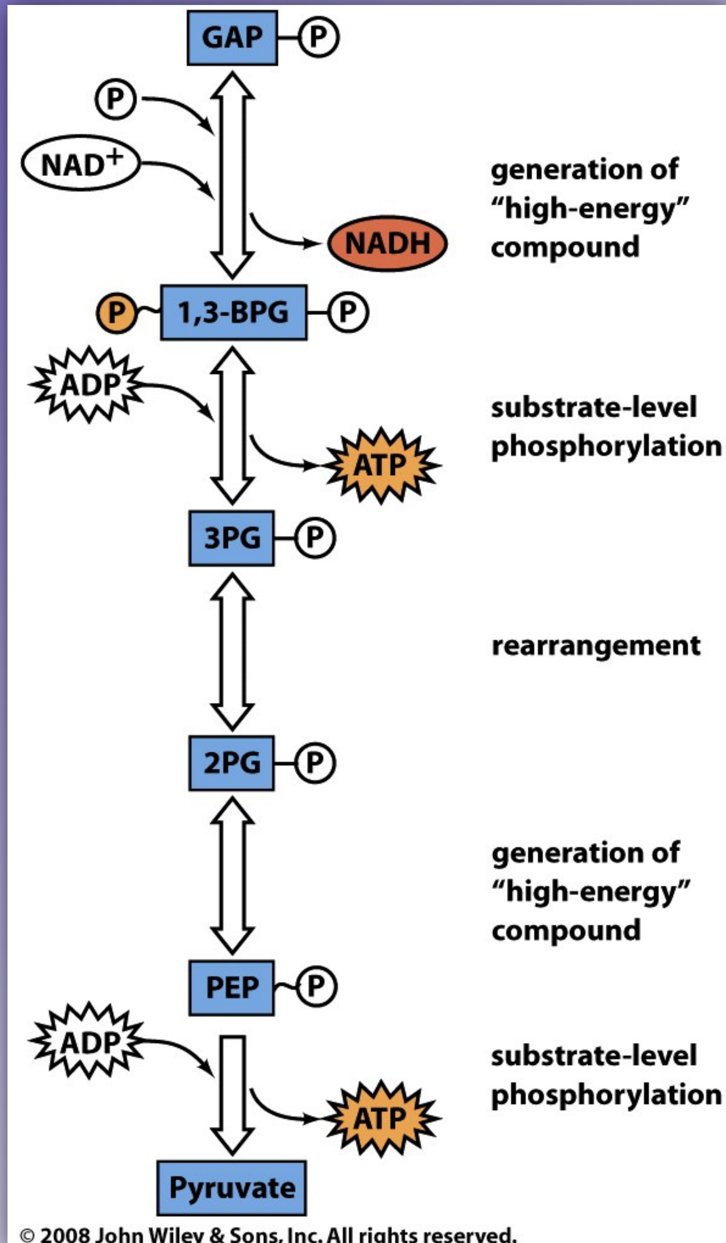
Overall $\Delta G^{\circ\prime} = -31.4\ \mathrm{kJ{\cdot}mol^{-1}}$

Glycolytic detour: 2,3-BPG biosynthesis in erythrocytes



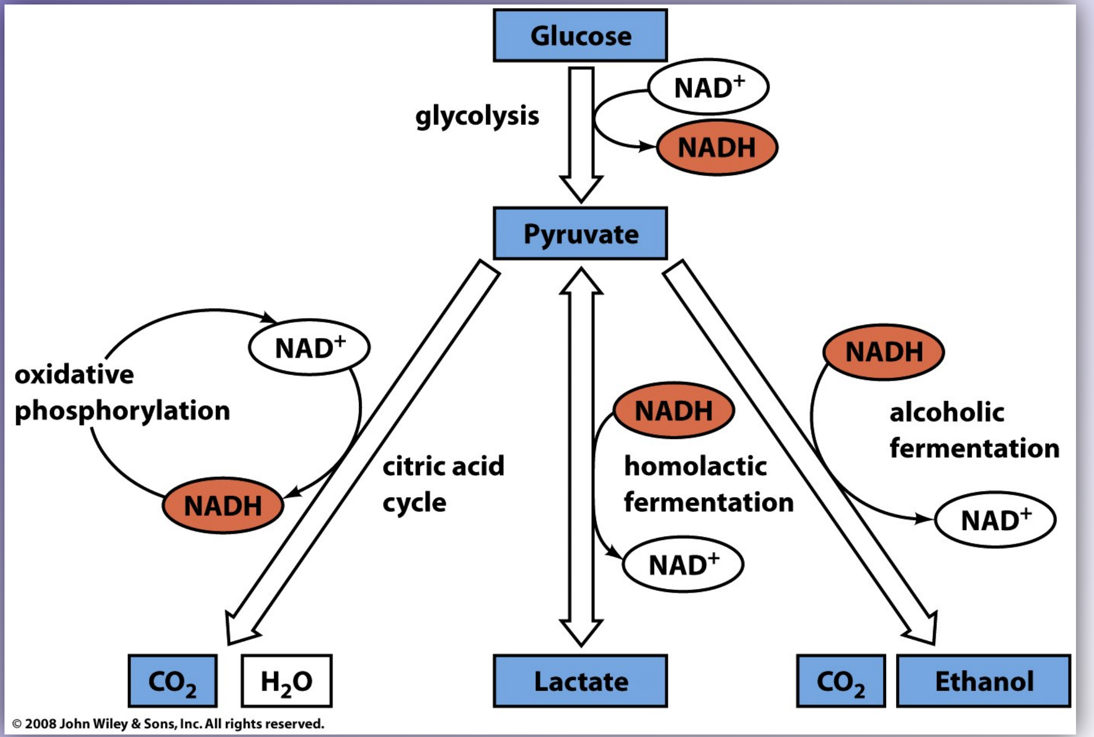
Impact of 2,3-BPG on O_2-hemoglobin binding affinity: hexokinase and PK deficiencies



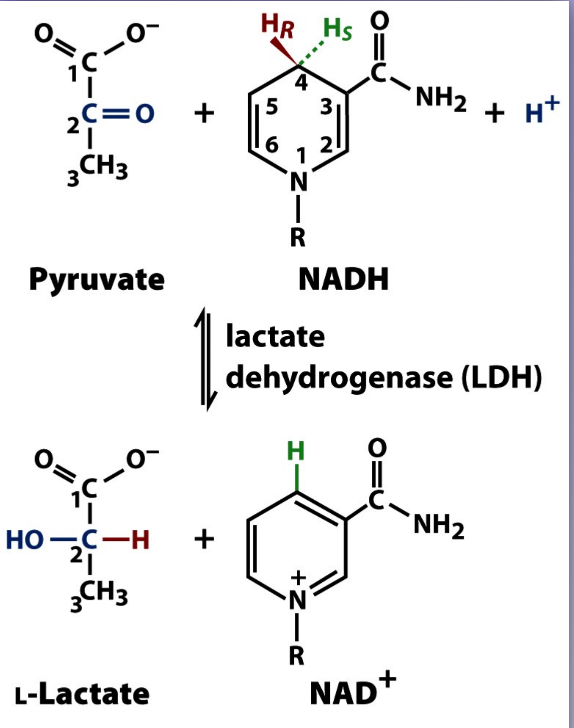


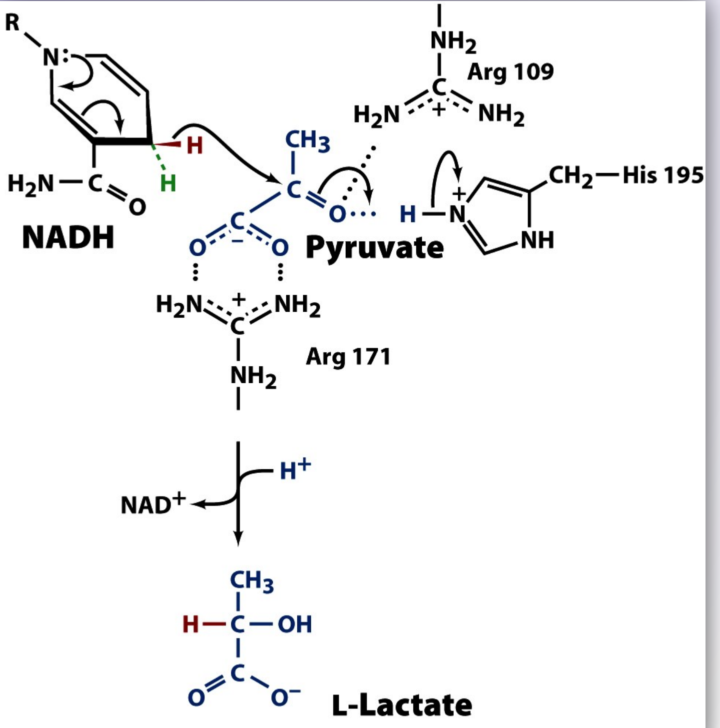
Second half of glycolysis: ATP-yielding phase

Metabolic fates of pyruvate

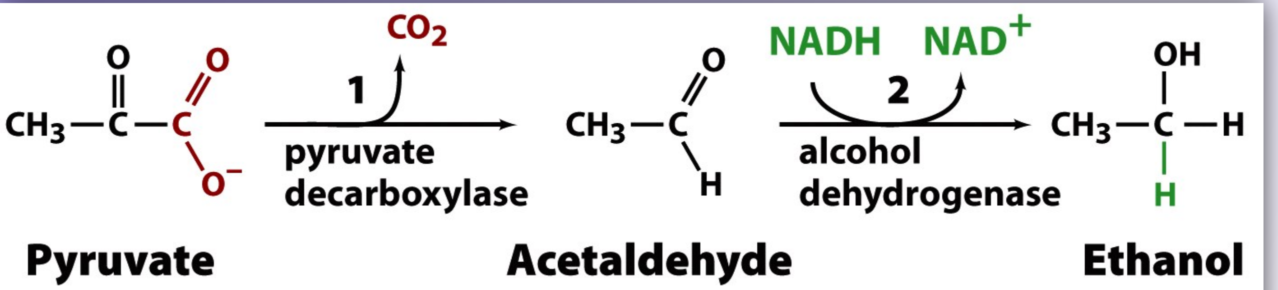


Conversion of pyruvate to lactate: LDH reaction

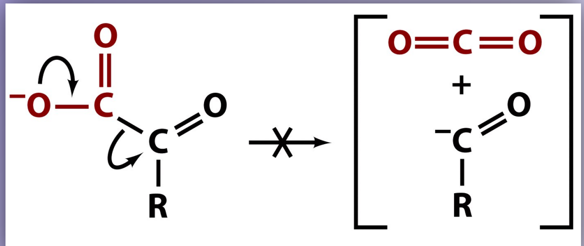


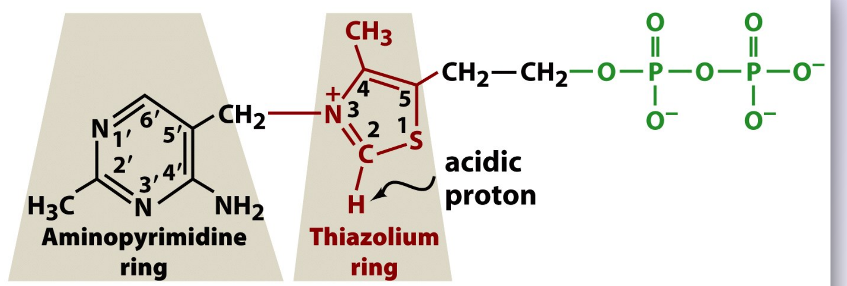


Conversion of pyruvate to ethanol via acetaldehyde

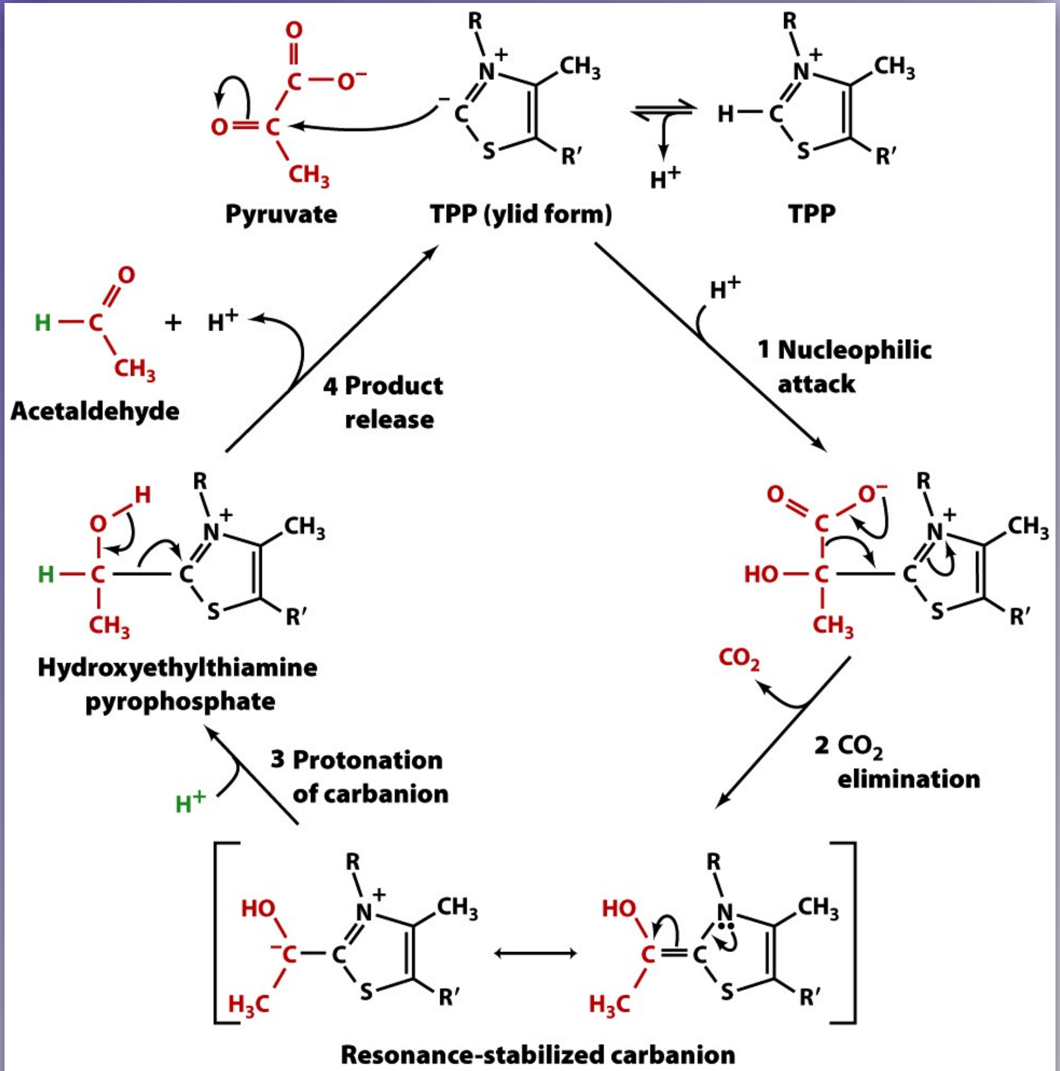


Enzyme-catalyzed decarboxylation of an α-ketoacid (pyruvate): TPP coenzyme is required for charge delocalization



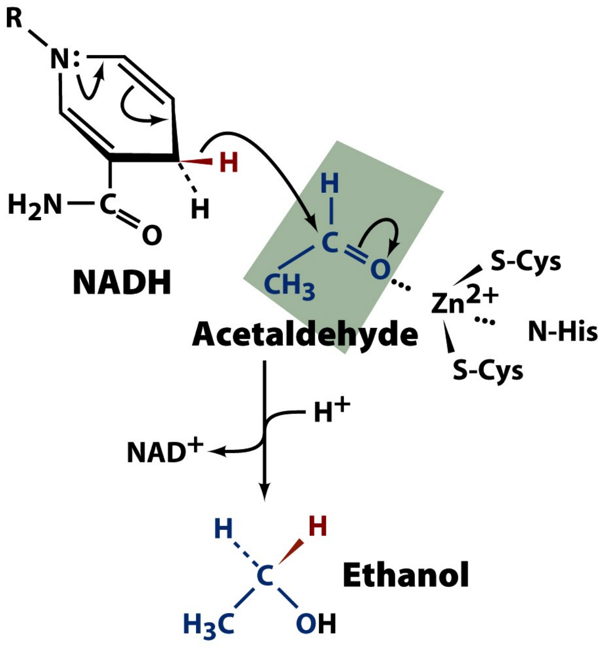


Thiamine pyrophosphate (TPP)



Proposed mechanism of pyruvate decarboxylase

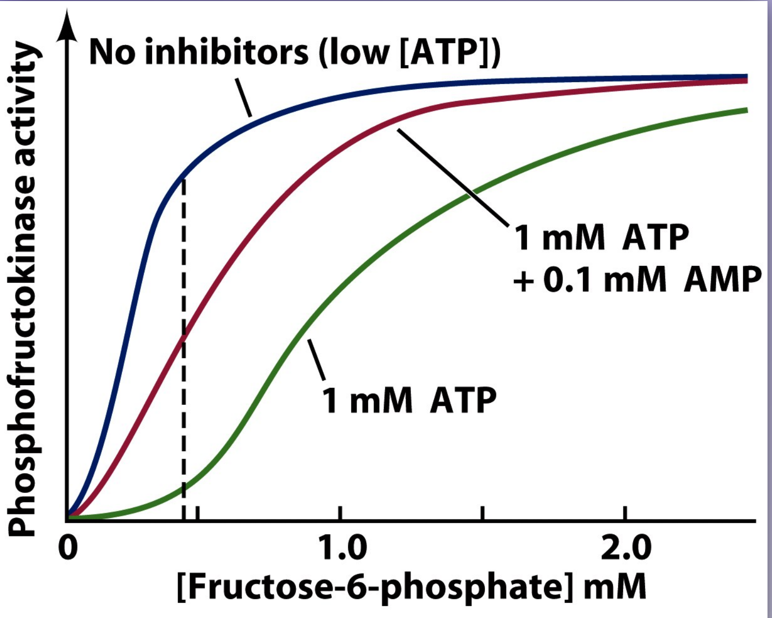
Alcohol dehydrogenase: Stereospecfic transfer of hydride from NADH to acetaldehyde

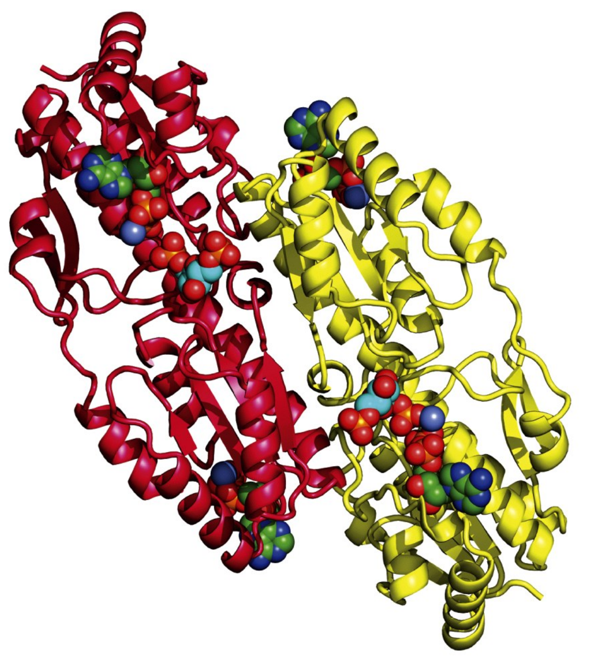


Some effectors of the non-equilibrium enzymes of glycolysis

Enzyme	Inhibitors	Activators[a]
HK	G6P	–
PFK	ATP, citrate, PEP	ADP, AMP, cAMP, FBP, F2,6P, F6P, NH_4^+, P_i
PK (muscle)	ATP	AMP, PEP, FBP

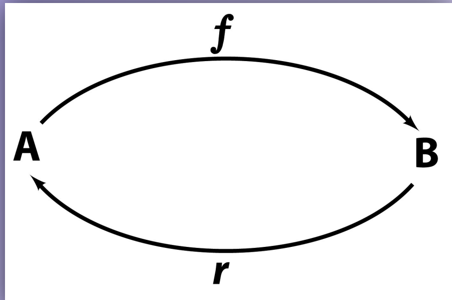
[a]The activators for PFK are better described as deinhibitors of ATP because they reverse the effect of inhibitory concentrations of ATP.

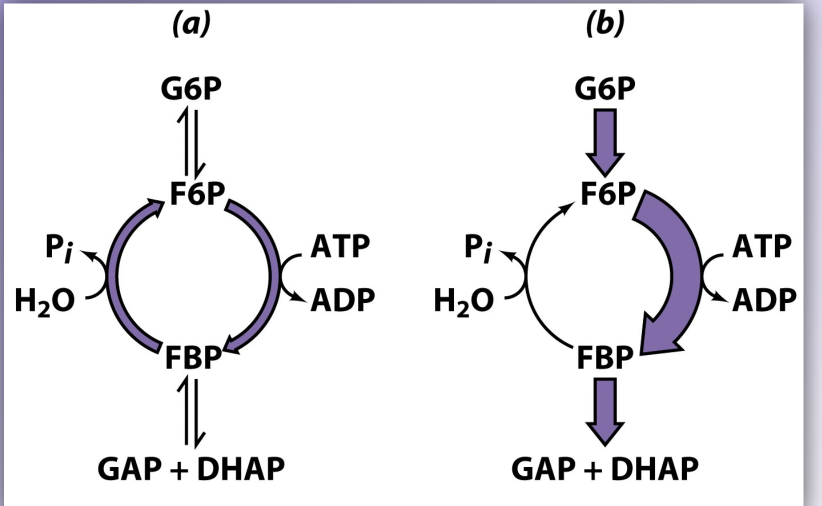




PFK is an allosteric enzyme (tetramer)

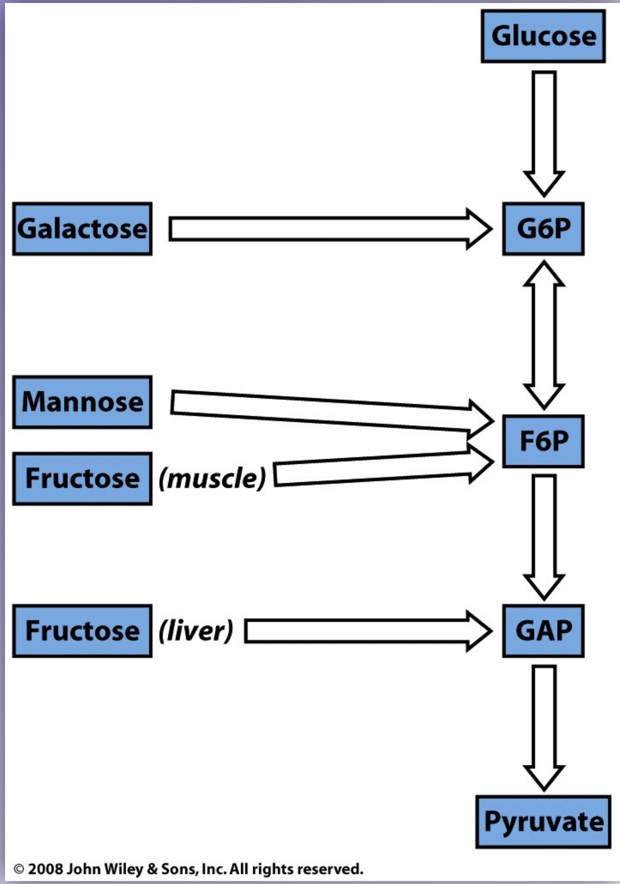
Control of glycolytic flux via substrate cycling



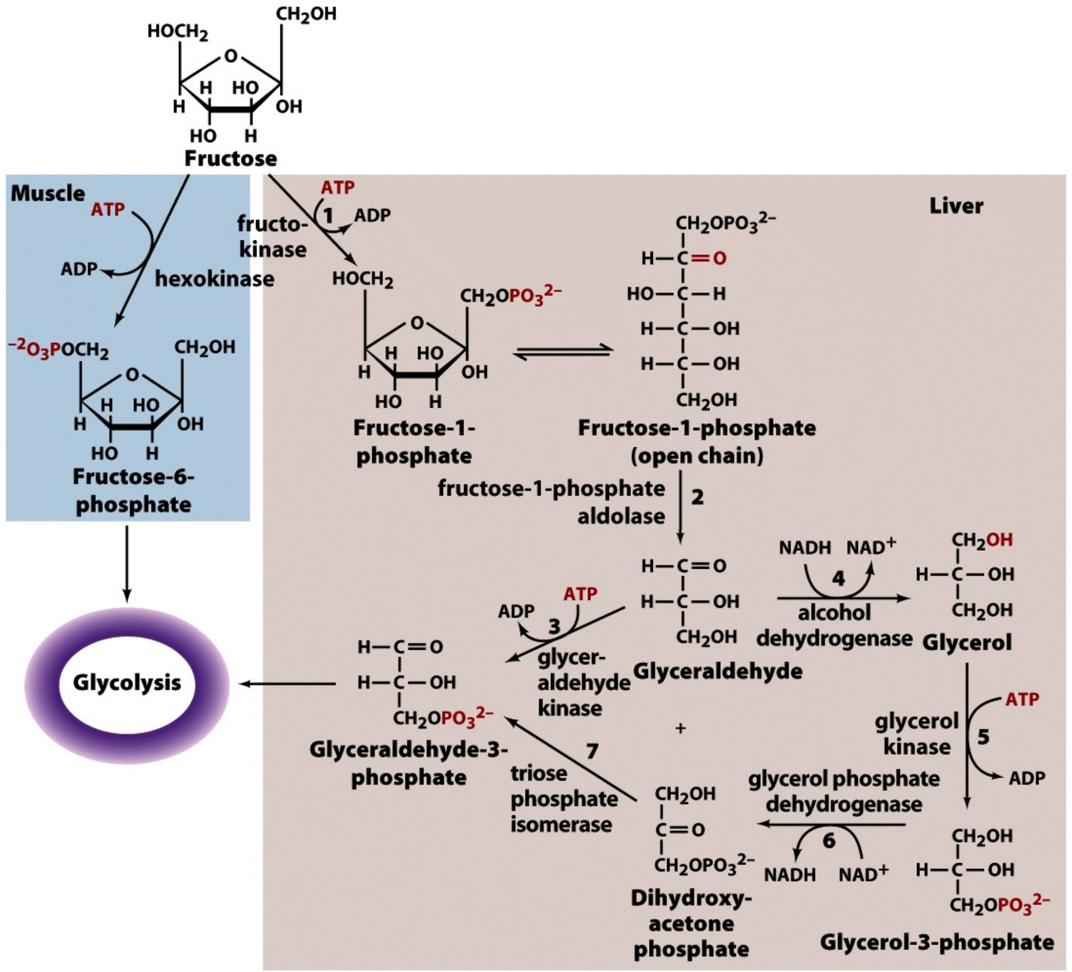


resting muscle   active muscle

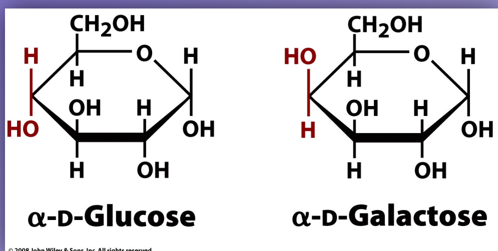
Entry routes of other monosaccharides into glycolysis

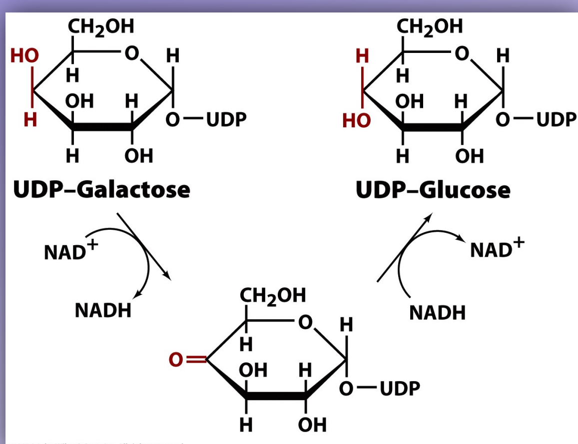


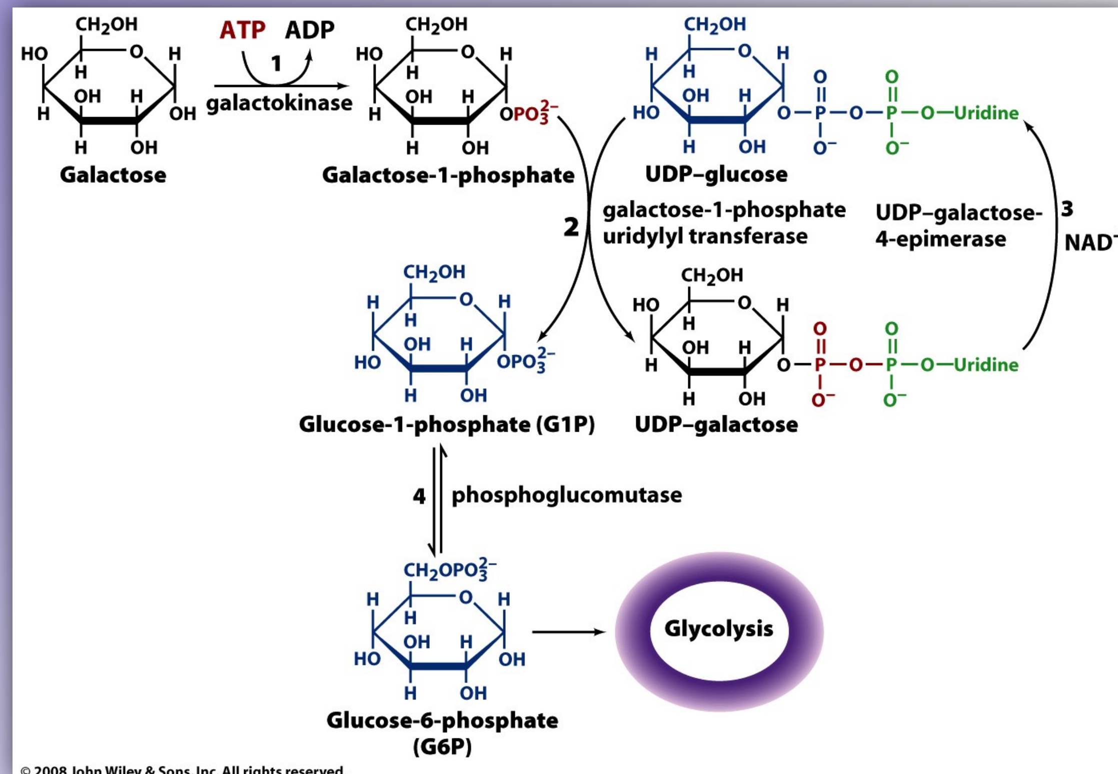
Metabolism of D-fructose is organ-dependent



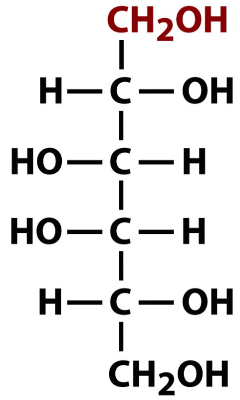
Metabolism of D-galactose (human)







By-product of galactosemia (step 2 deficient)
(buildup in lens of the eye - cataracts)



Galactitol

Metabolism of D-mannose (human)