

CHEM 539

Molecular Metabolism: Pathways and Regulation
Spring 2015

PPT Set 2a

Glucose transport; glycolysis; degradation of
other monosaccharides; alternatives to glycolysis

Plasma membrane-bound glucose transporters

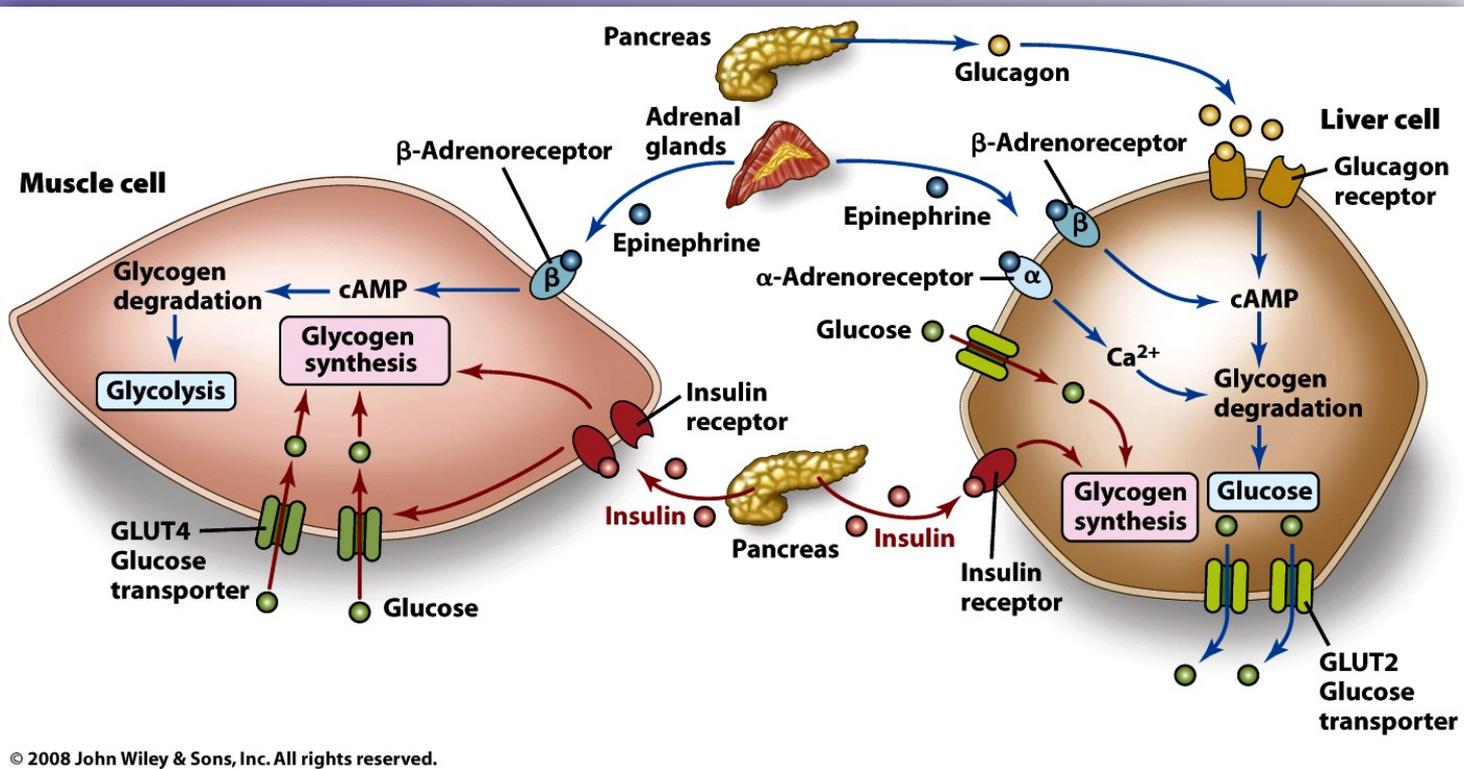


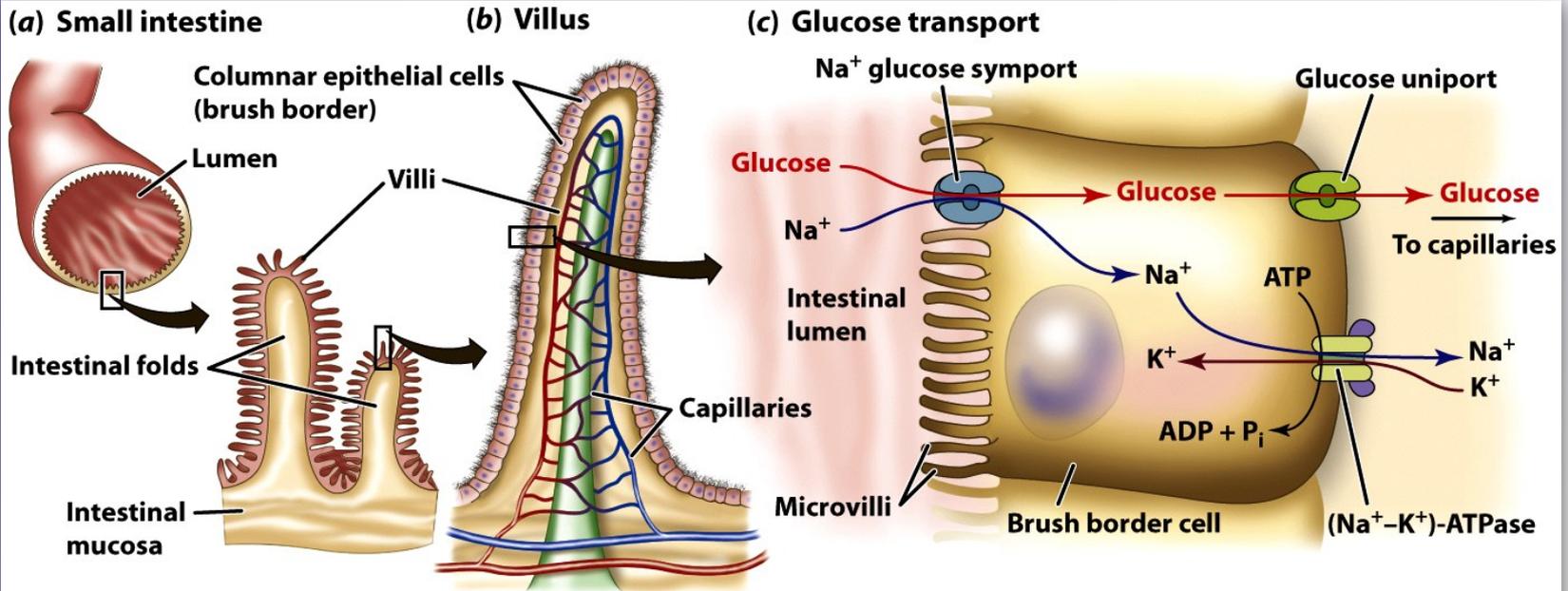
TABLE 12-1 Properties of Selected Members of Human Glucose Transporters (GLUT)

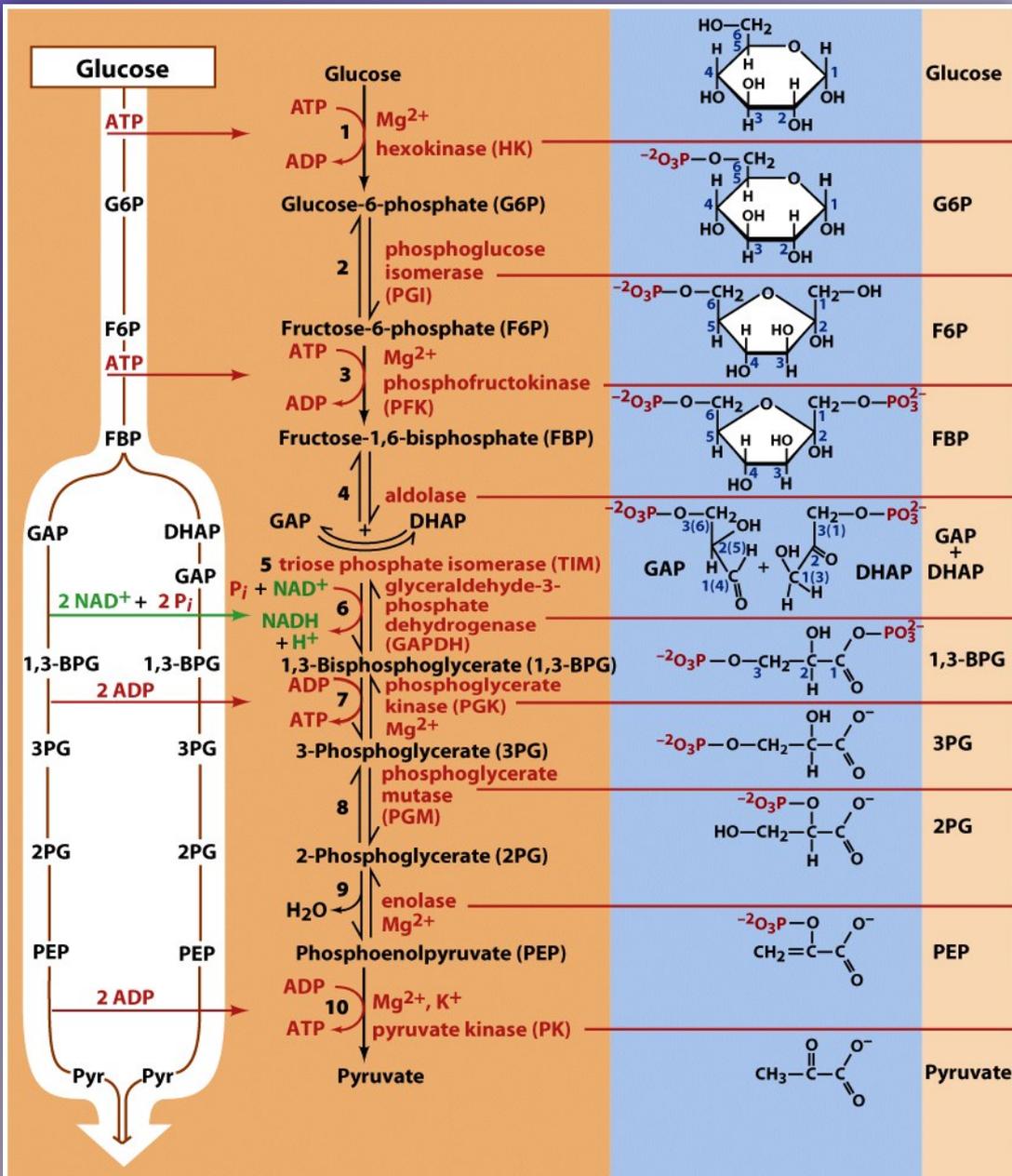
Transporters	Major Tissue Distribution	Properties
GLUT 1	Brain, microvessels, red blood cells, placenta, kidney, and many other cells	Low K_m (about 1 mM), ubiquitous basal transporter
GLUT 2	Liver, pancreatic β -cell, small intestine	High K_m (15–20 mM)
GLUT 3	Brain, placenta, fetal muscle	Low K_m , 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

Active transport of glucose driven by an ion gradient





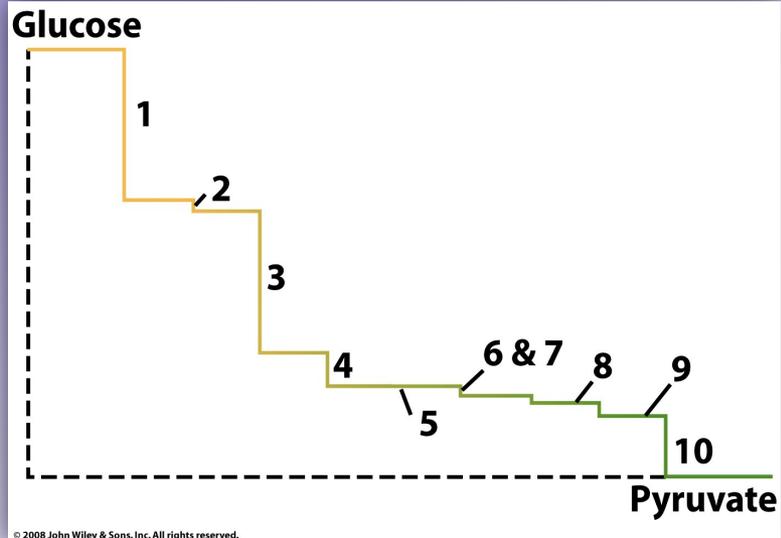
Overview of the ten reactions of glycolysis

Table 15-1 **$\Delta G^{\circ'}$ and ΔG for the Reactions of Glycolysis in Heart Muscle^a**

Reaction	Enzyme	$\Delta G^{\circ'}$ (kJ · mol ⁻¹)	ΔG (kJ · 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

^aCalculated from data in Newsholme, E.A. and Start, C., *Regulation in Metabolism*, p. 97, Wiley (1973).

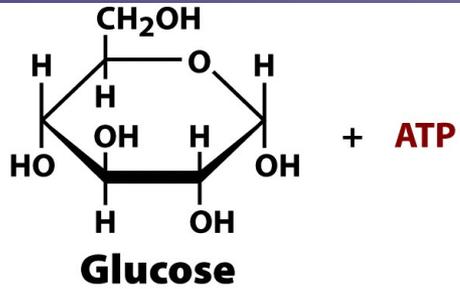
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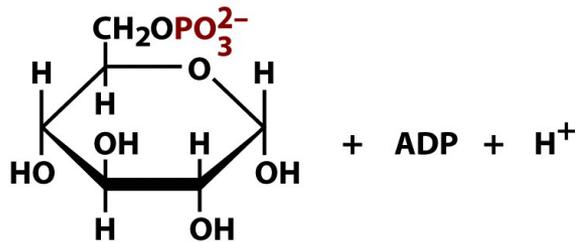
Free energy changes
in glycolysis

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Hexokinase (muscle)

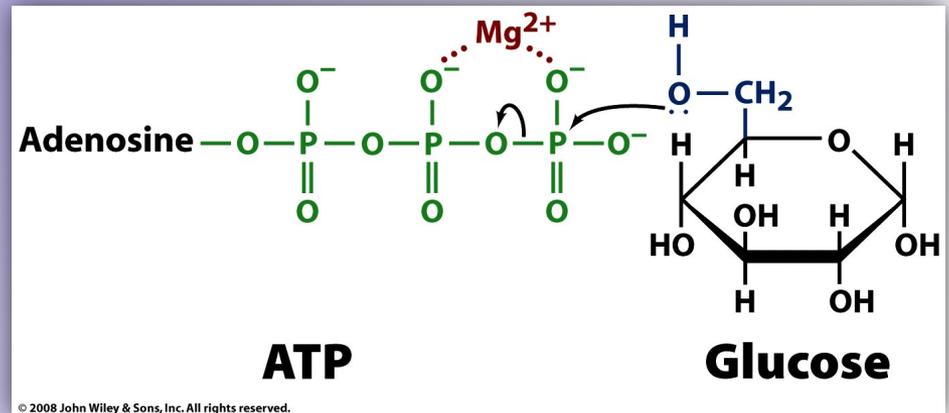


hexokinase
Mg²⁺

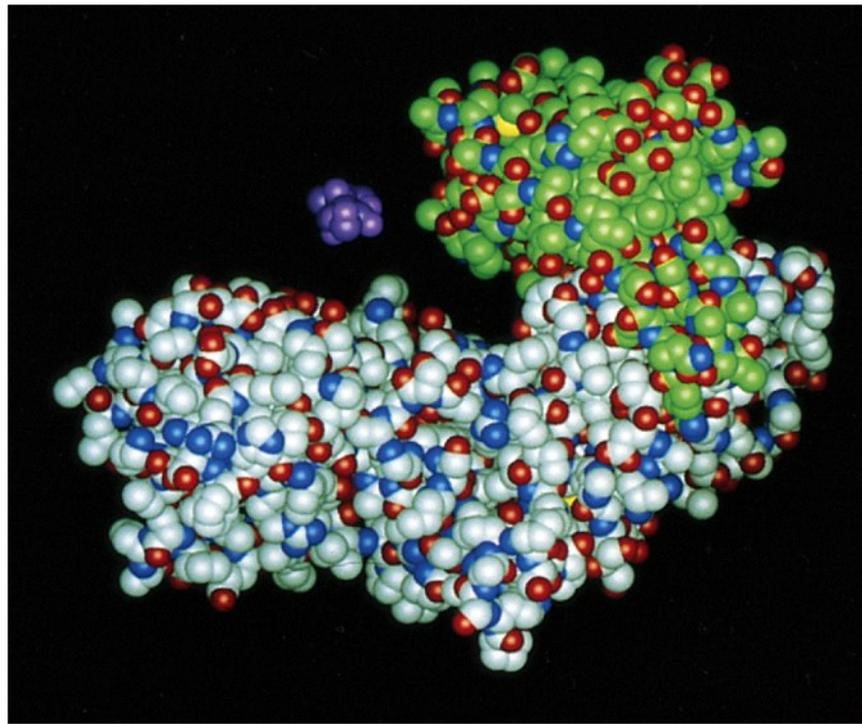


Glucose-6-phosphate (G6P)

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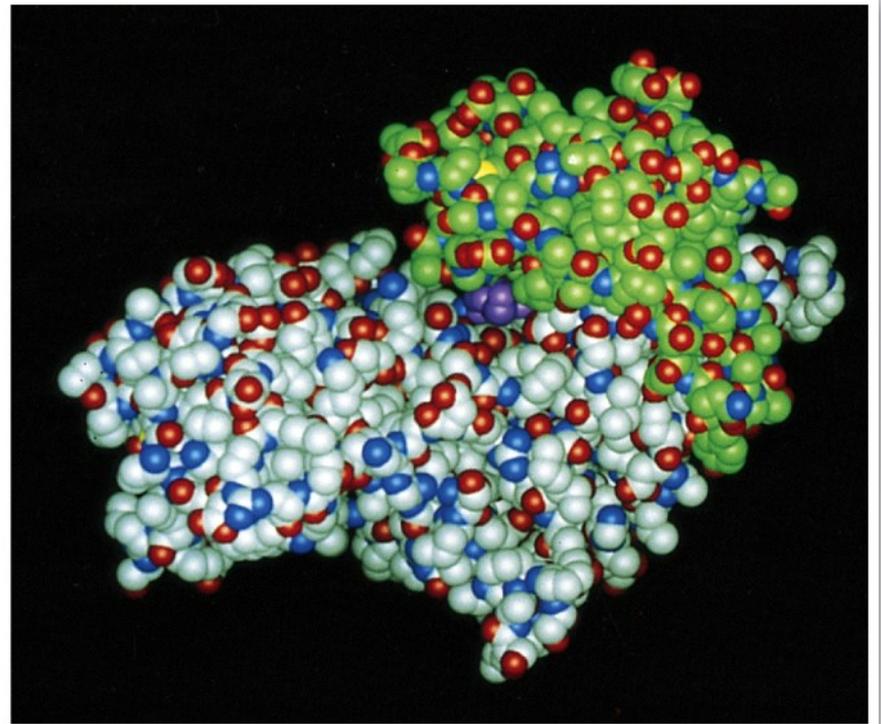


Conformational change in hexokinase upon substrate binding



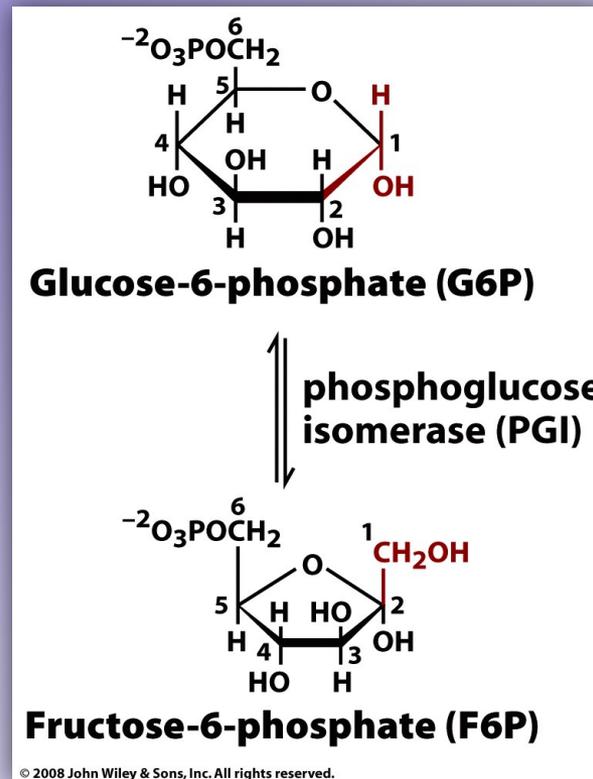
(a)

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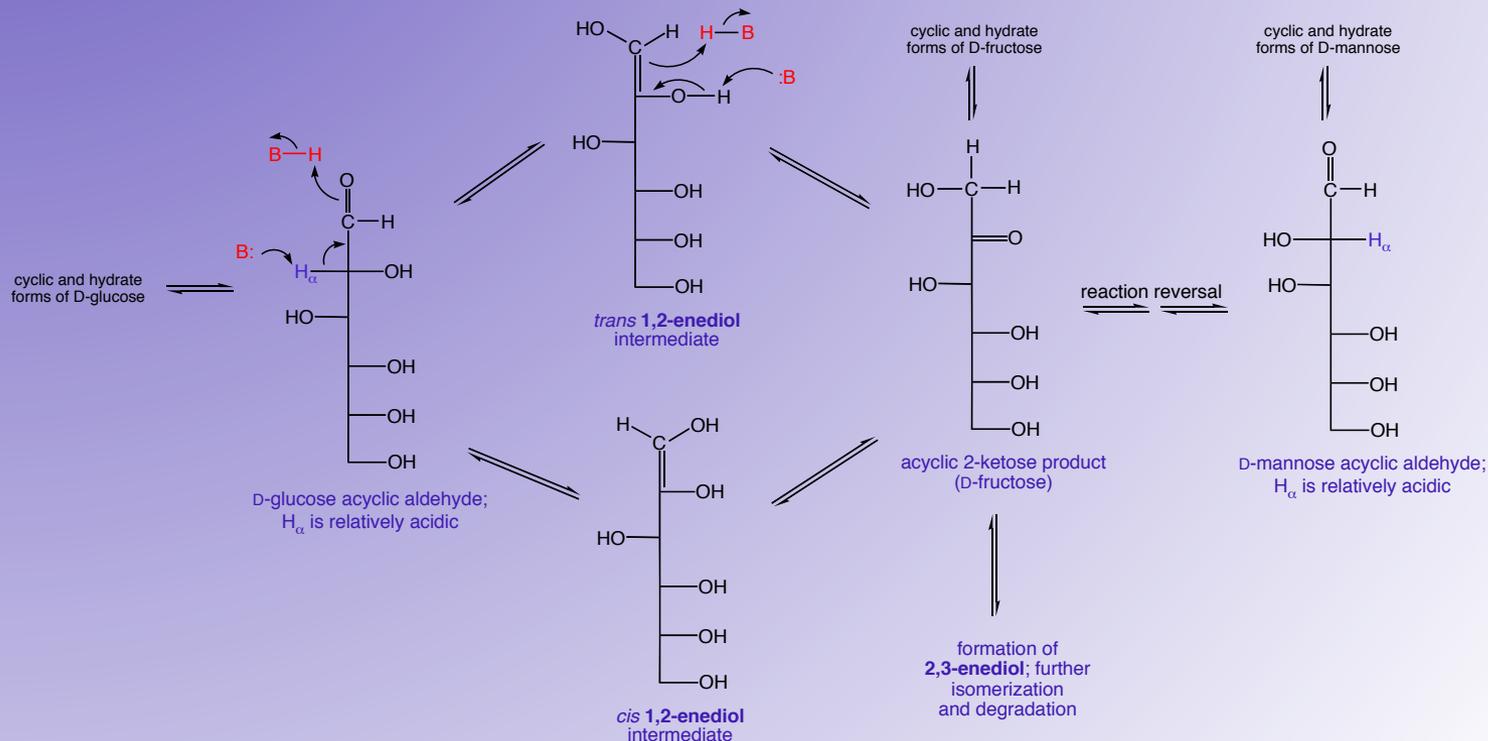
(b)

Phosphoglucoisomerase (PGI)



Aldose - 2-ketose isomerization in solution: A base-catalyzed reaction (Lobry deBruyn- Alberta van Ekenstein reaction)

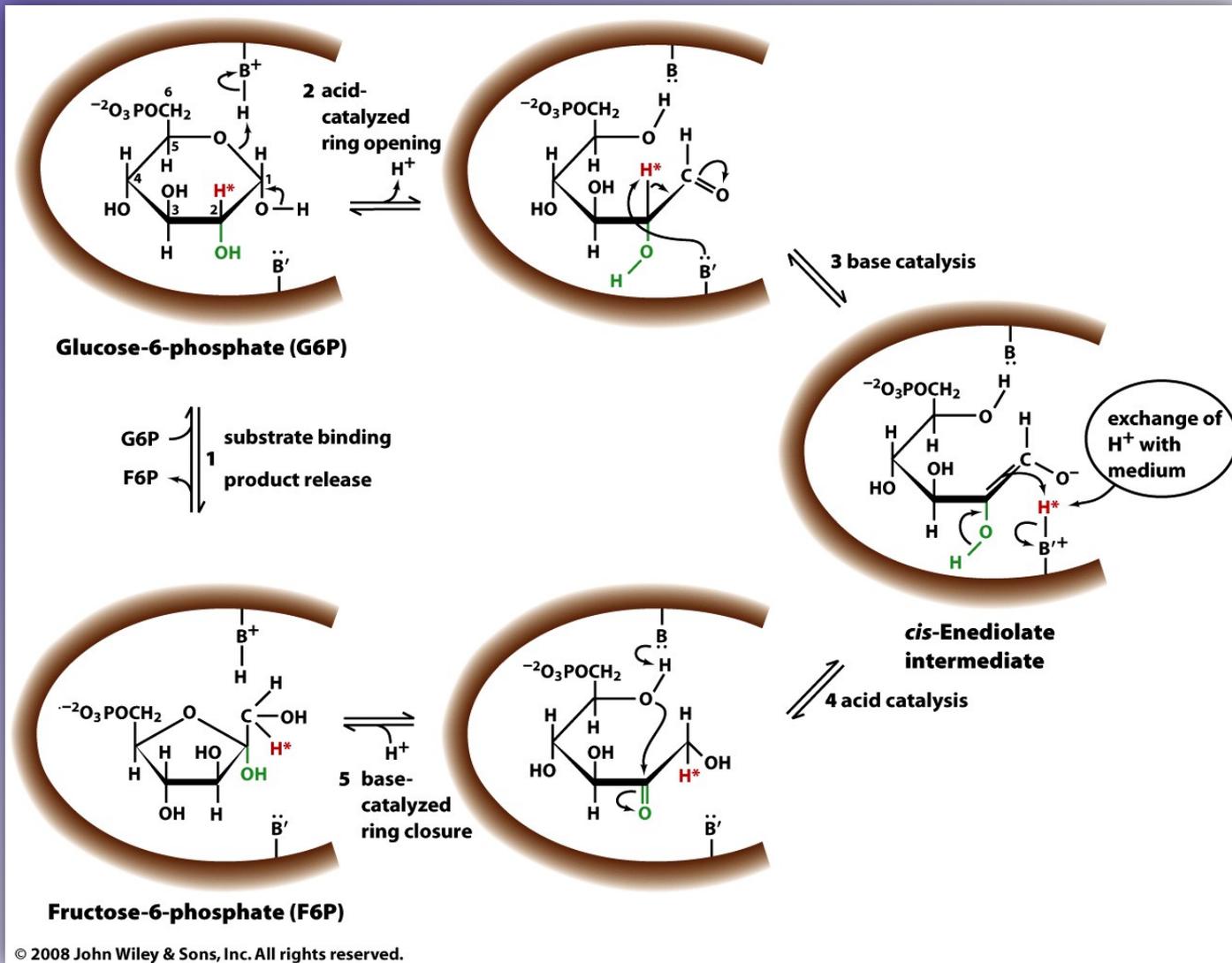
A chemical pathway for the interconversion of an aldose with its 2-ketose



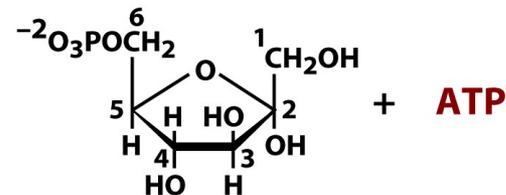
Since chirality at C2 is lost in transit through the enediol intermediates, both C2-epimeric D-aldoses are observed at equilibrium. The formation of both *cis* and *trans* enediols is possible during non-enzyme catalyzed aldose-ketose isomerization.



PGI mechanism

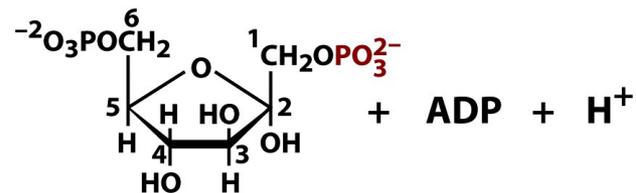


Phosphofructokinase (PFK)



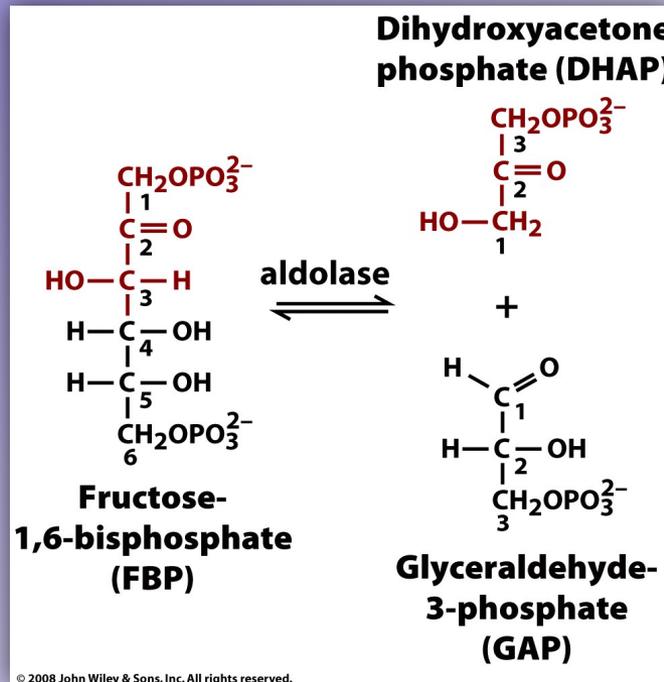
**Fructose-6-phosphate
(F6P)**

phosphofructokinase (PFK)
 Mg^{2+}

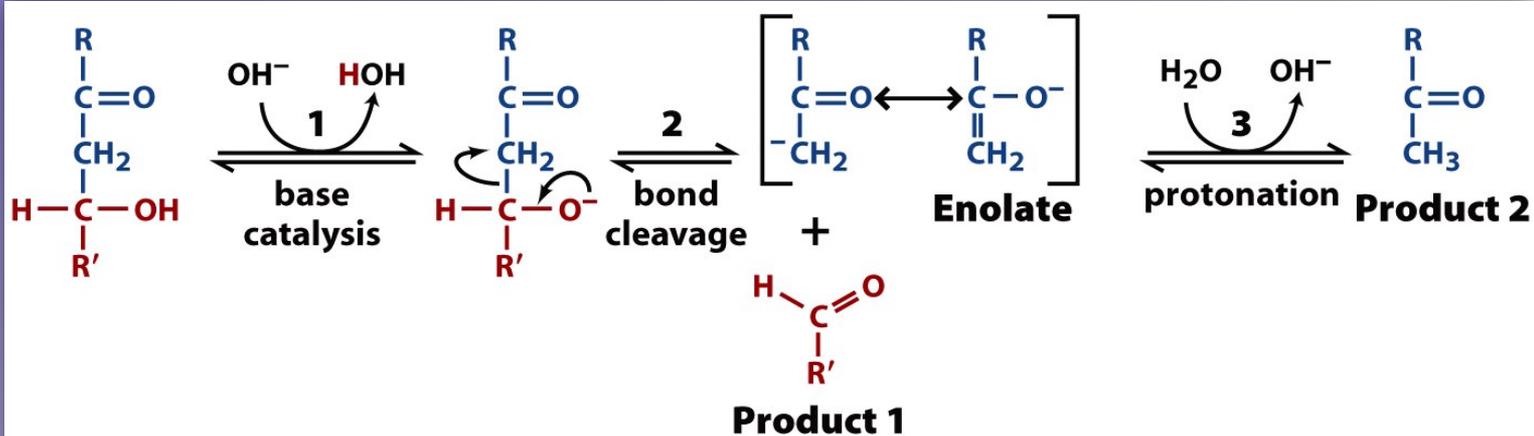


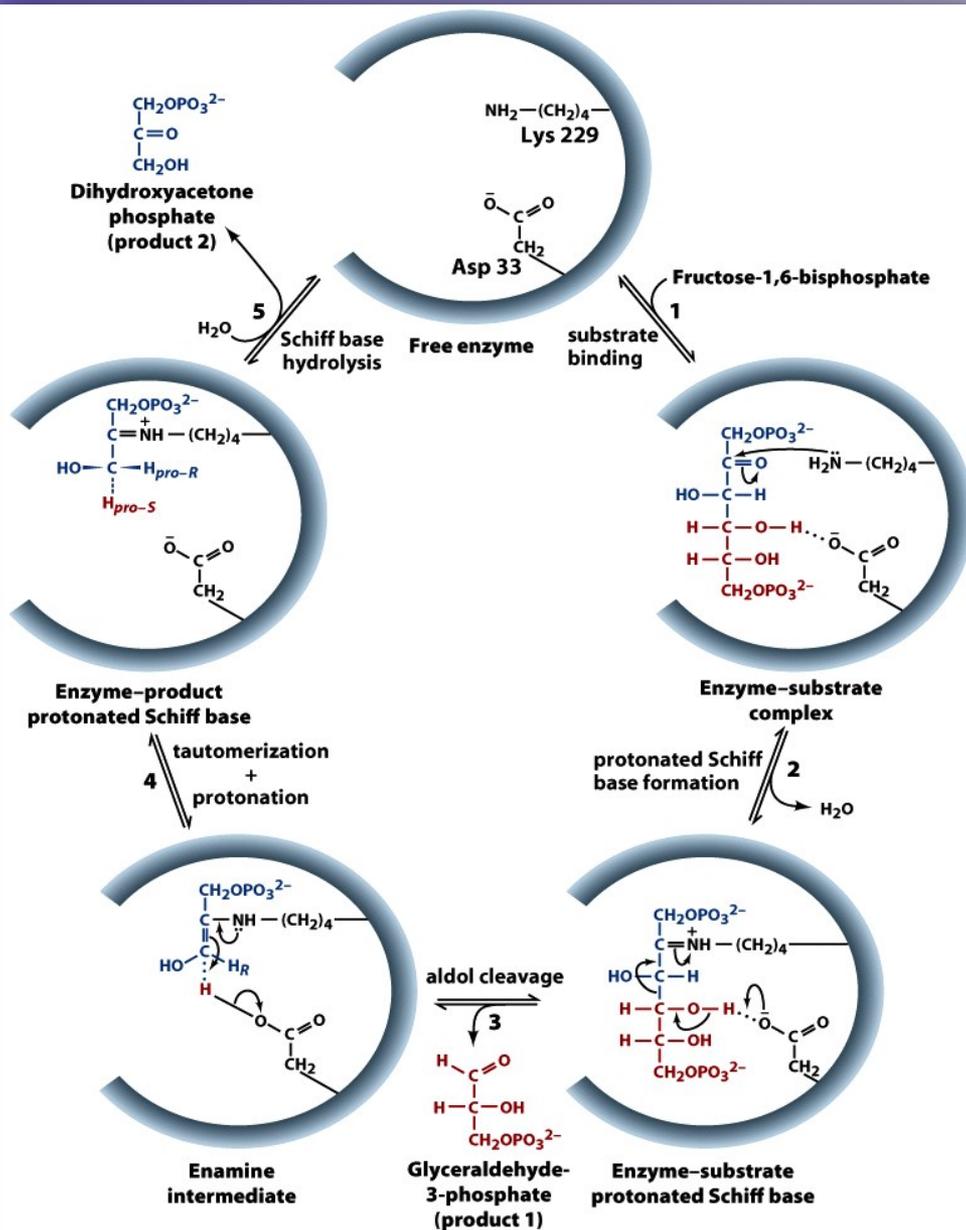
**Fructose-1,6-bisphosphate
(FBP)**

Aldolase



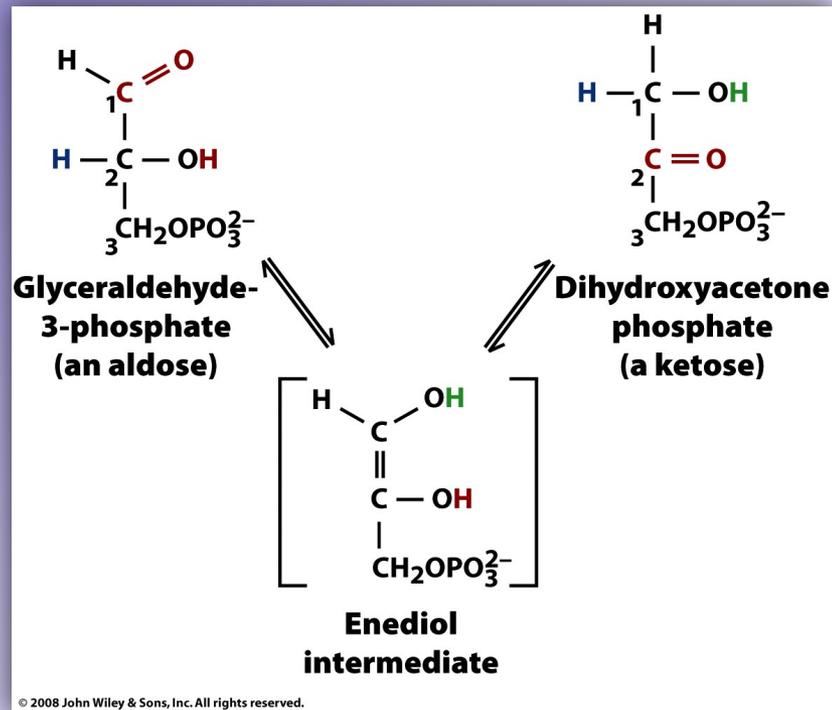
General mechanism of base-catalyzed aldol cleavage



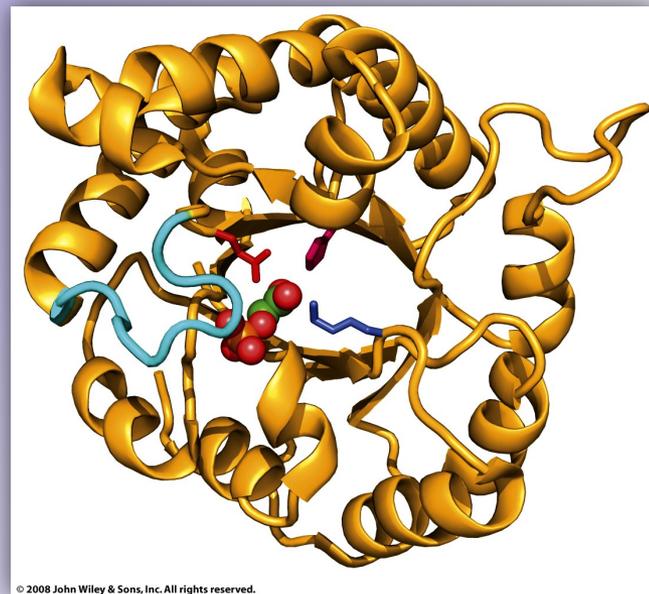
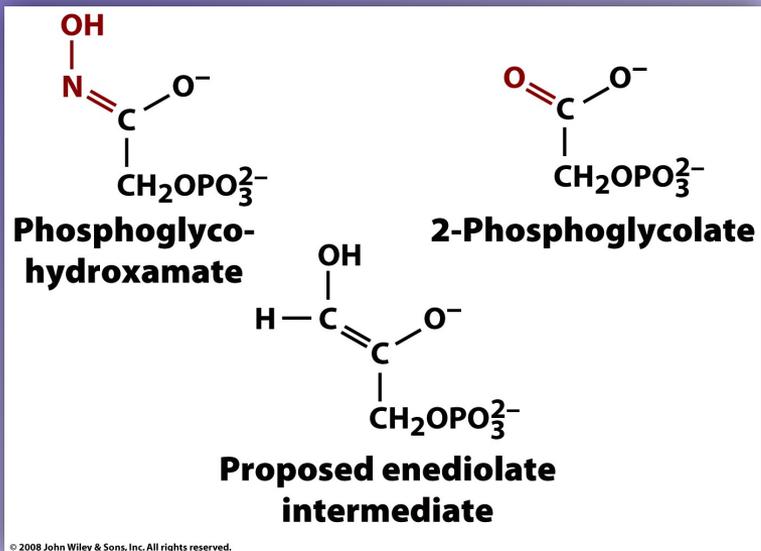


Proposed aldolase mechanism

Triose-phosphate isomerase (TPI)

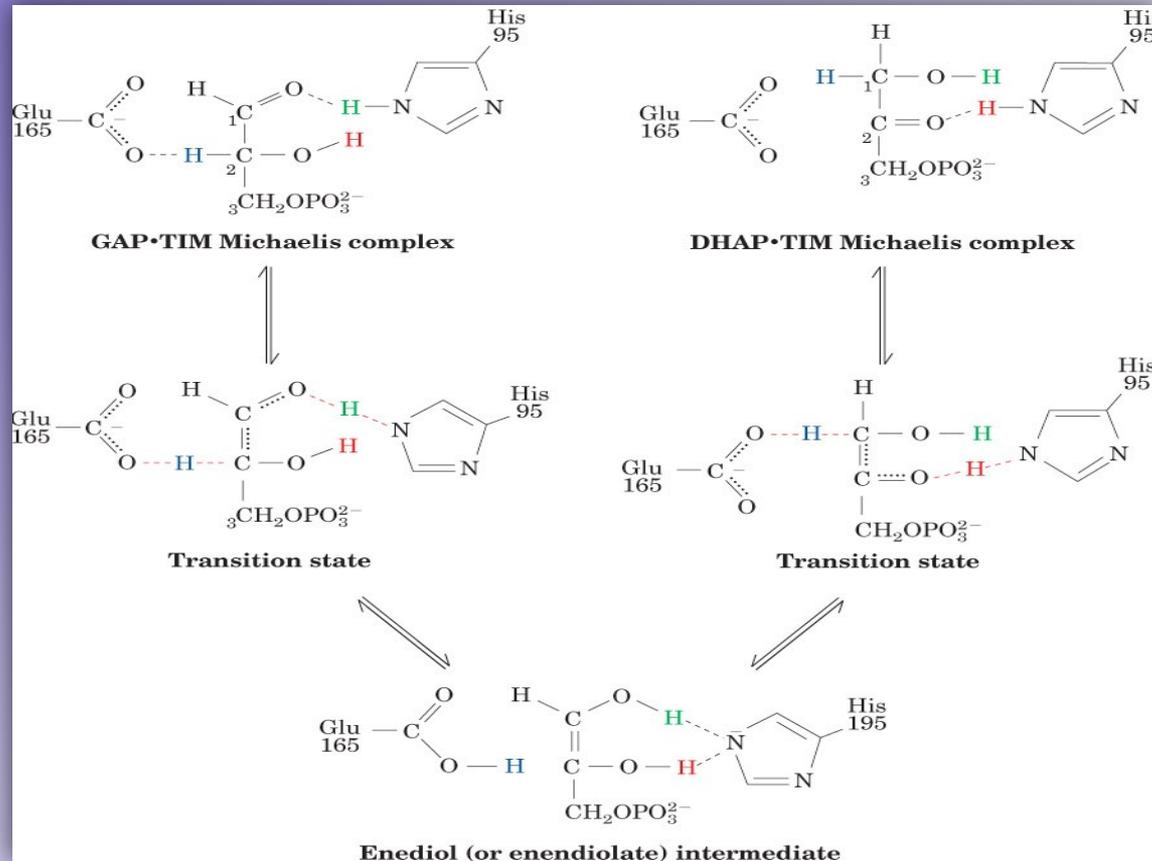


Transition-state analogs of TPI

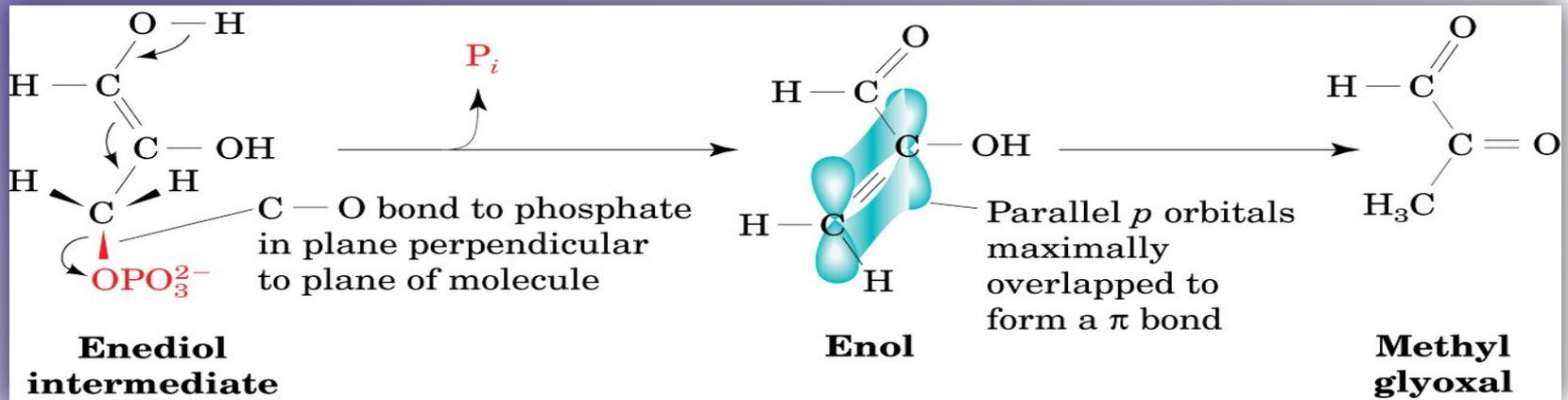


**TPI complexed
with 2-phosphoglycolate**

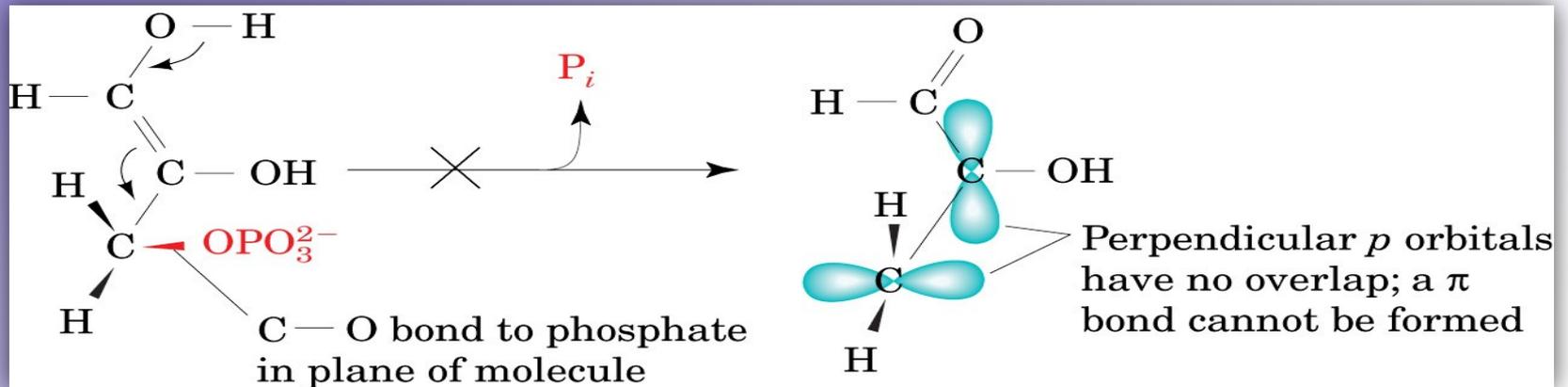
Proposed enzymatic mechanism of the TPI reaction

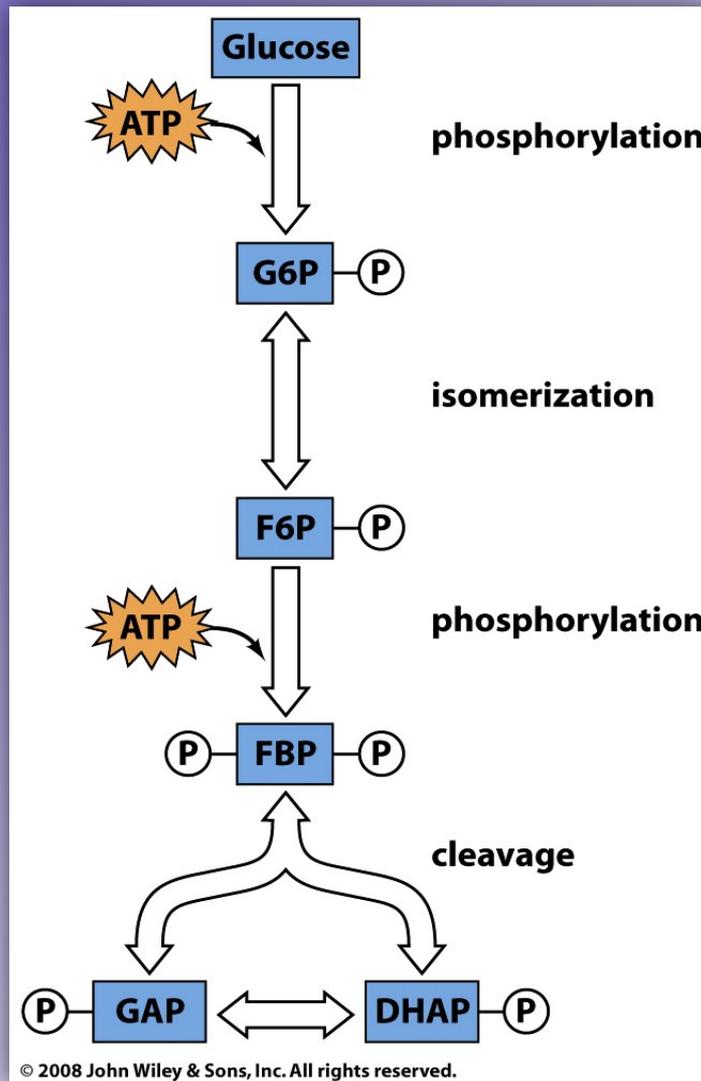


The spontaneous decomposition of the enediol intermediate in the TIM reaction to form methylglyoxal through the elimination of a phosphate group



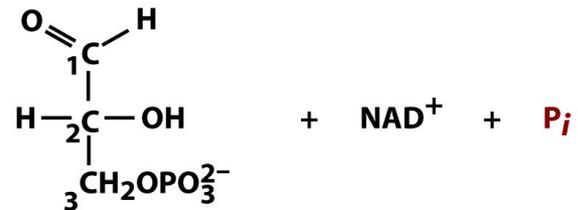
The spontaneous decomposition of the enediol intermediate in the TIM reaction to form methylglyoxal through the elimination of a phosphate group



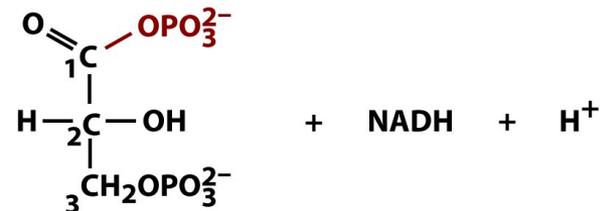


First half of
glycolysis:
ATP investment
phase

Glyceraldehyde 3-P dehydrogenase



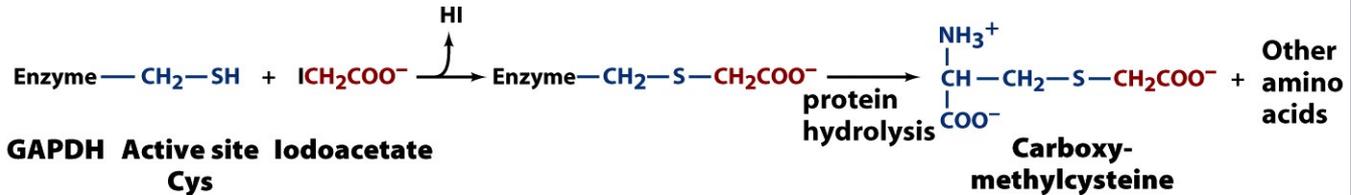
Glyceraldehyde-3-phosphate (GAP)



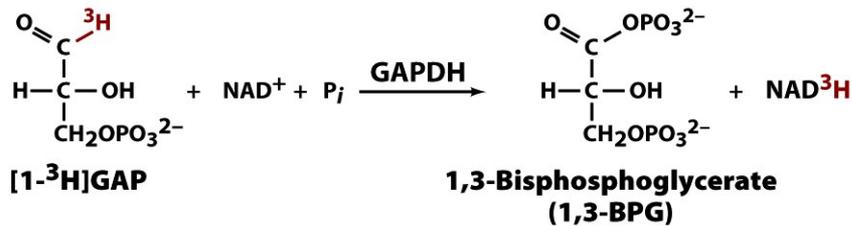
1,3-Bisphosphoglycerate (1,3-BPG)

Characterizing the G3P dehydrogenase reaction

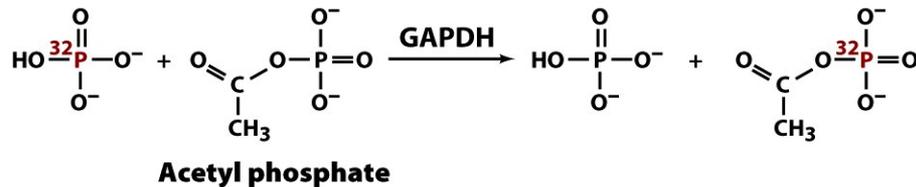
(a)

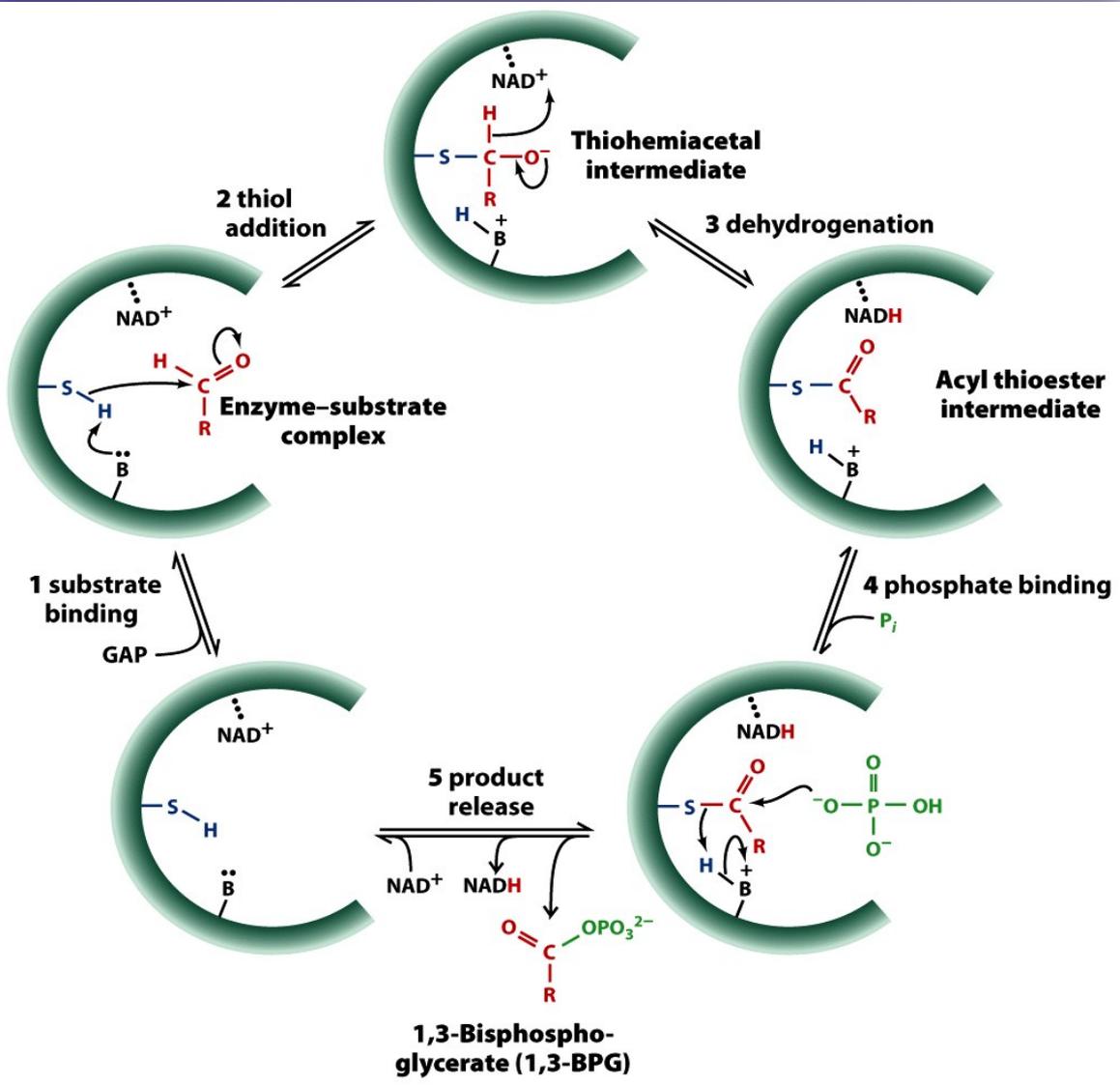


(b)



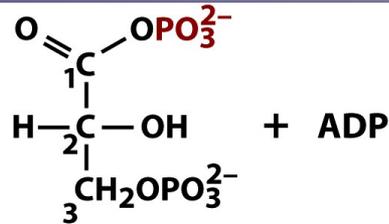
(c)



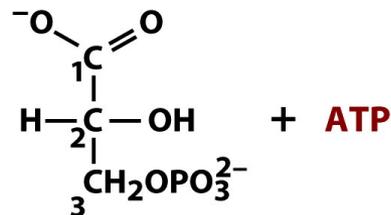


Proposed mechanism of GAP dehydrogenase

3-Phosphoglycerate kinase



1,3-Bisphosphoglycerate (1,3-BPG)



3-Phosphoglycerate (3PG)

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**First substrate-level
phosphorylation
reaction of glycolysis**