Chapter 11
Catabolism of Hexoses

Glucose is the focal point of carbohydrate breakdown.

Glycolysis: A pathway made up of 10 steps in which **glucose** ($C_6H_{12}O_6$) is transformed into 2 molecules of **pyruvate** ($C_3H_3O_3$).

It is an ancient **anerobic** process: *i.e.* does **not** require O_2.

The pathway, enzymes and reactions are nearly identical in all eukaryotic cells!

Most of the differences are in **regulation** of the pathway.

Phase I - Preparatory:

5 steps - Glucose is phosphorylated and split into 2 triose phosphates.

This phase costs 2 ATP.

Phase II – Payoff:

5 steps - oxidation and phosphorylation yield 2 NADH + 4 ATP

Net yield of ATP = 2.

Net yield of NADH = 2

Mass Balance

$C_6H_{12}O_6 + 2ATP + 2NAD^+ + 4ADP + 2P_i \rightarrow 2C_3H_3O_3 + 2ADP + 2NADH + 2H^+ + 4ATP + 2H_2O$

After Cancellation:

$C_6H_{12}O_6 + 2NAD^+ + 2ADP + 2P_i \rightarrow 2C_3H_3O_3 + 2NADH + 2H^+ + 2ATP + 2H_2O +$

Energy Balance

The pathway is "***exergonic***" under **standard conditions** (25°C, 1atm, 1M); 146 kJ/mol are released.

Complete oxidation of glucose yields 2,840 kJ/mol so only 146/2840 = 5.2% of the *G* of glucose is released during glycolysis.

42% of this is used to make 2 ATP.

$2ADP + 2P_i \rightarrow 2ATP$

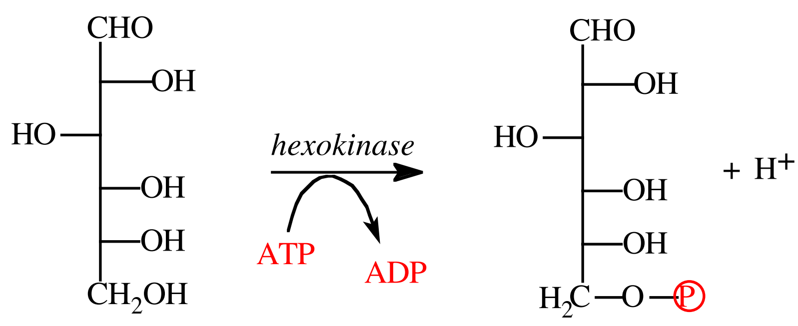
$\Delta G'^o = 2(30.5) = 61$ kJ/mol

61/146 = 42 % conserved

85/146 = 58% "lost" – but ensures the process is down the free energy hill.

Notes on Individual Reactions:

1\.



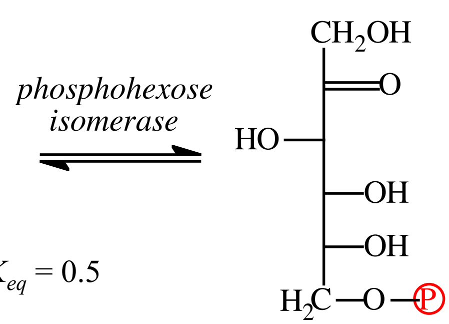
Glc → Glc-6-P

$\Delta G'^{o} = -16.7$ kJ/mol $K_{eq} = 845$ "*irreversible*" reaction

A **kinase** transfers the terminal phosphate of ATP to an acceptor.

MgATP is the substrate.

2\.

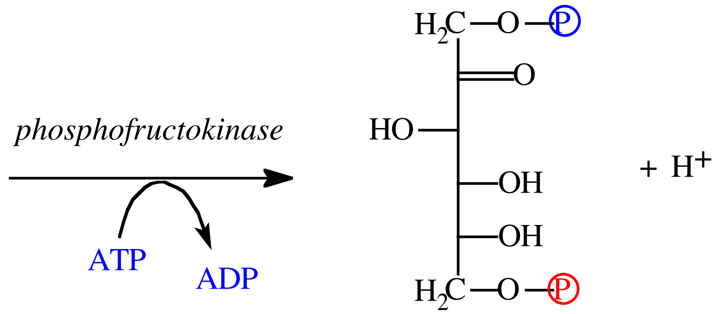


$\Delta G'^{o} = +1.7$ kJ/mol $K_{eq} = 0.5$

Fru-6-P

aldose $\rightleftharpoons$ enediol $\rightleftharpoons$ ketose

3.



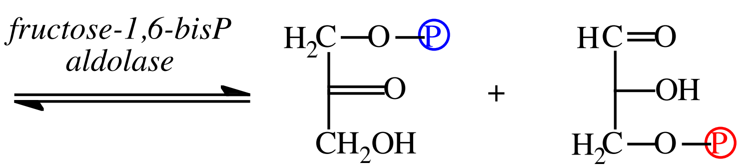
$\Delta G'^{o} = -14.2$ kJ/mol $\quad K_{eq} = 308$

Fru-1,6-bisP

PFK is an **allosteric** enzyme and the key control point in glycolysis.

It is **activated** by **AMP**, and **inhibited** by **ATP** and **citrate** at allosteric binding sites ≠ active site. In cancer cells, adding GlcNAc to Ser-529 inhibits it, slowing glycolysis.

4.



Dihydroxyacetone-P

D-Glyceraldehyde-3-P

$\Delta G'^{o} = +23.8$ kJ/mol $\quad K_{eq} = 7\text{x}10^{-5}$

Although the reaction appears irreversible, it is pulled forward by removal of products in the following steps and the overall free energy release by the entire pathway.

5.

triose-P-isomerase

DHAP ⇌ G-3-P

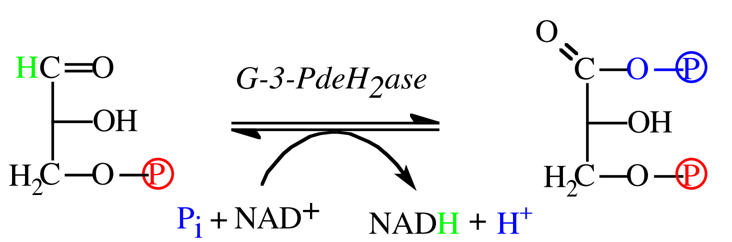
$\Delta G'^{o}$ = +7.5 kJ/mol K_{eq} = 0.05

This is just like reaction 2 in reverse:

ketose ⇌ enediol ⇌ aldose

There are now **two** G-3-P and from now on there are **two** reactants and **two** products for each step.

6.



Glyceraldehyde-3-P

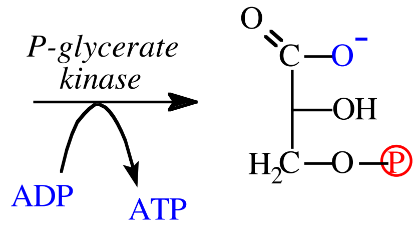
1,3-bisP-glycerate

$\Delta G'^{o}$ = +6.3 kJ/mol K_{eq} = 0.08

An aldehyde is oxidized to an acid and the G released is used to reduce NAD^+ and to form a high G phosphate (acyl phosphate) that conserves 49.3 kJ / mole.

Note that NAD^+ has been consumed and will have to be regenerated if glycolysis is to continue.

7.



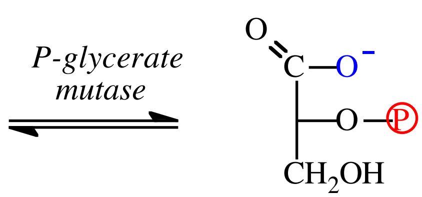
3-P-glycerate

$\Delta G'^{o} = -18.5$ kJ/mol $K_{eq} = 2000$

Substrate Level Phosphorylation

ATP is formed by the transfer of P_i from a very high free energy compound to ADP.

8.

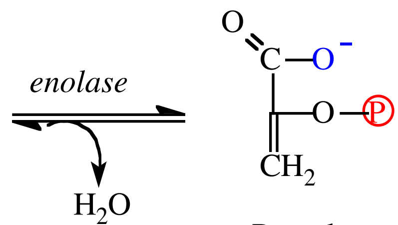


2-P-glycerate

$\Delta G'^{o} = +4.4$ kJ/mol $K_{eq} = 0.2$

A mutase is an enzyme that transfers a functional group.

9.

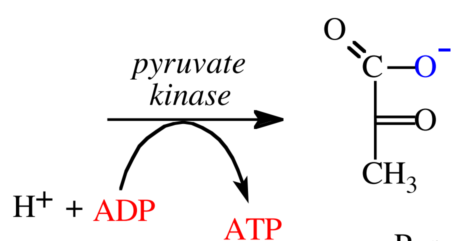


P-enolpyruvate

A dehydration.

$\Delta G'^{o} = +7.5$ kJ/mol $K_{eq} = 0.05$

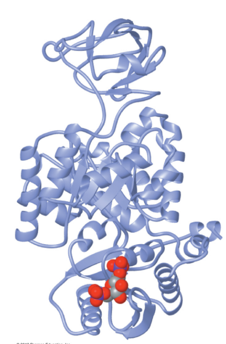
10.



Pyruvate

$\Delta G'^{o} = -31.4$ kJ/mol $K_{eq} = 3\text{x}10^5$

A second **substrate-level phosphorylation**.



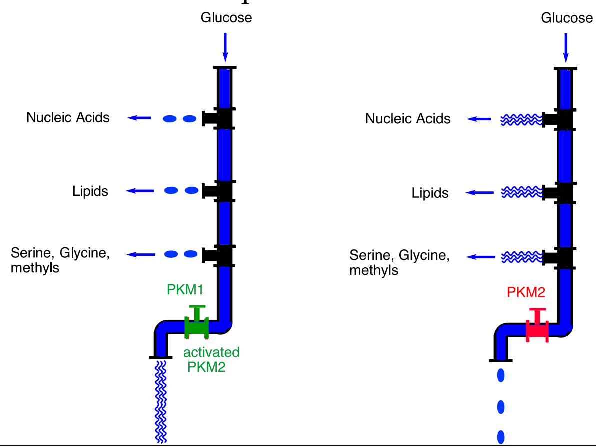
$\Delta G'^{o} = -61.9$ kJ/mol for PEP

30.5 kJ/mol is conserved as ATP and 31.4 kJ is used to drive glycolysis forward.

$-31.4 - 30.5 = -61.9$

PK is allosterically **inhibited** by **ATP**, **acetyl-CoA**, and **fatty acids**.

Cancer cells express an isoform of PK called PKM2 that is less active than the normal isoform PKM1. By slowing down glycolysis intermediates build up and are sent down pathways that generate molecules needed for cell replication.



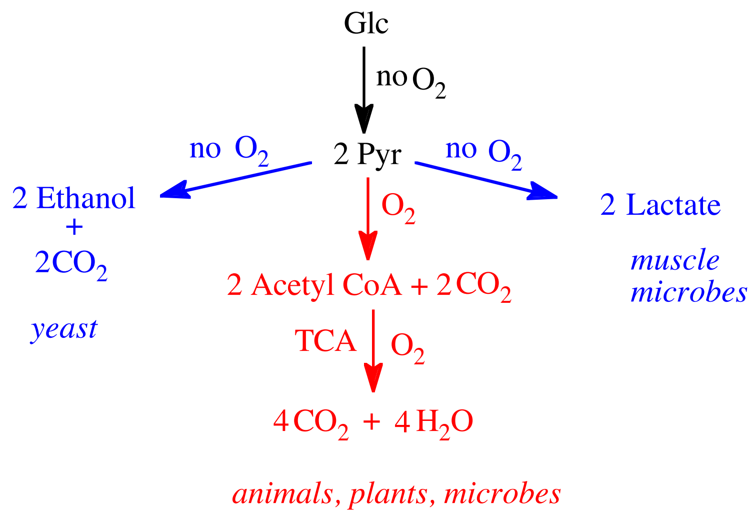
Some prokaryotes contain a more primitive pathway that converts glucose 6-phosphate into glyceraldehyde 3–phosphate and pyruvate.

They contain all the enzymes of the 2nd half of glycolysis.

This pathway is thought to be an ancient precursor of glycolysis.

Because only 1 glyceraldehyde 3-phosphate molecule is produced the ancient pathway yields only ½ the number of ATP molecules of glycolysis.

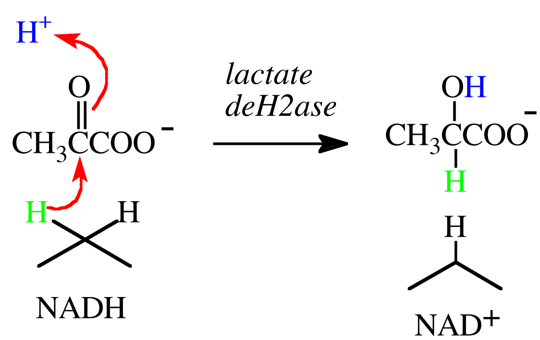
What happens to pyruvate? That depends on the cell and the conditions.



Lactic Acid Fermentation:

In hard-working muscle, sometimes we can't provide O_2 fast enough to replenish NAD^+ by the TCA cycle so pyruvate is quickly reduced to *L*-lactate to keep glycolysis going:

$\Delta G'^{o} = -25.1$ kJ/mol $\quad K_{eq} = 2.5 \times 10^4$

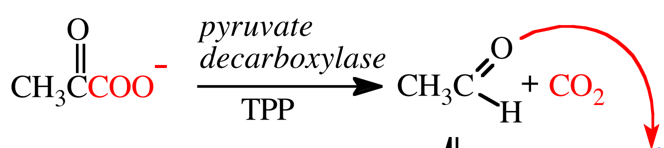


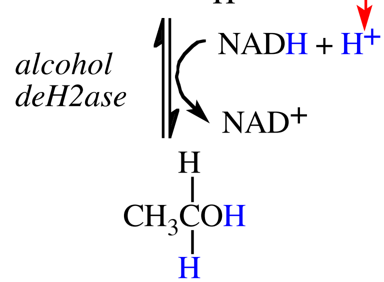
Note that the reaction is **stereospecific**, only the *L*-isomer of lactate is produced.

Lactate is in the same oxidation state as glucose: $C_6H_{12}O_6 = 2xC_3H_6O_3$

2 NAD^+ are produced from each of the 2 pyruvates from glycolysis which is exactly enough to keep glycolysis going.

Ethanol Fermentation:



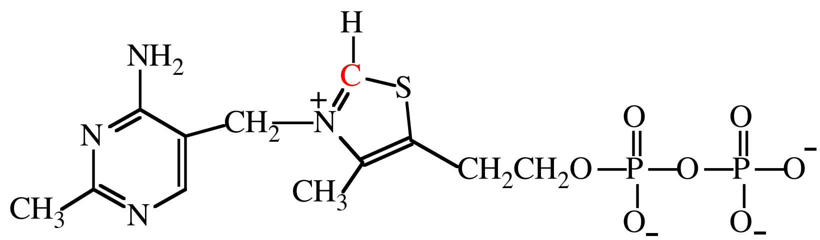


Again, just enough NAD^+ is made to replenish glycolysis.

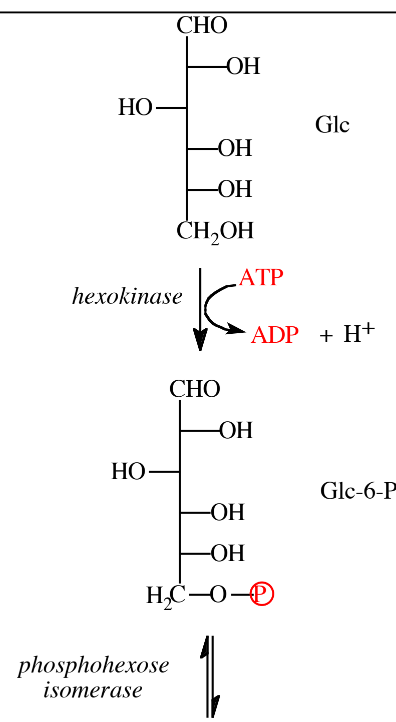
Yeast make ethanol from pyruvate;
the human liver enzyme oxidizes ethanol to acetaldehyde.

At 13-14% ethanol is poisonous.

Notice that a C—C bond has been broken. Often, enzymes require special co-factors to do this. There are many examples of enzymes for which **thiamine pyrophosphate (TPP)** is a co-factor. It is derived from Vitamin B1.



Summary



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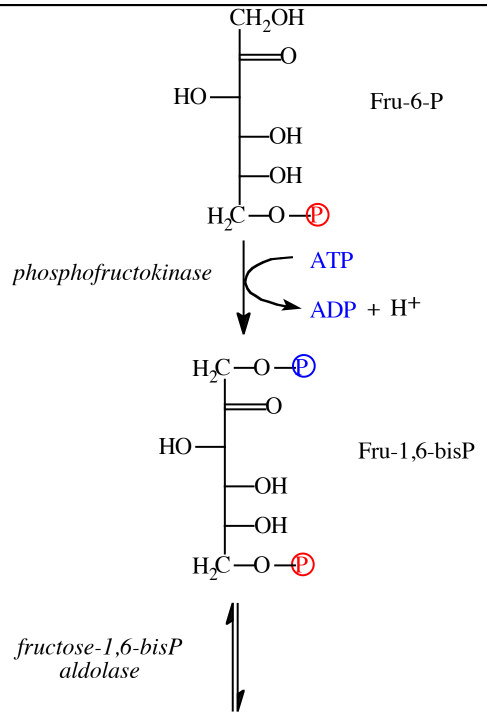
CH2OH
O
HO
OH
OH
H2C—O—P
Fru-6-P
phosphofructokinase
ATP
ADP + H+
H2C—O—P
Fru-1,6-bisP
fructose-1,6-bisP
aldolase

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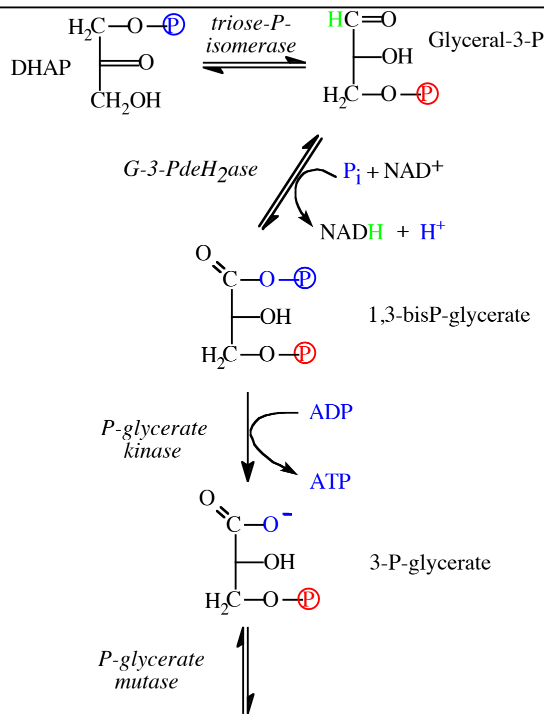
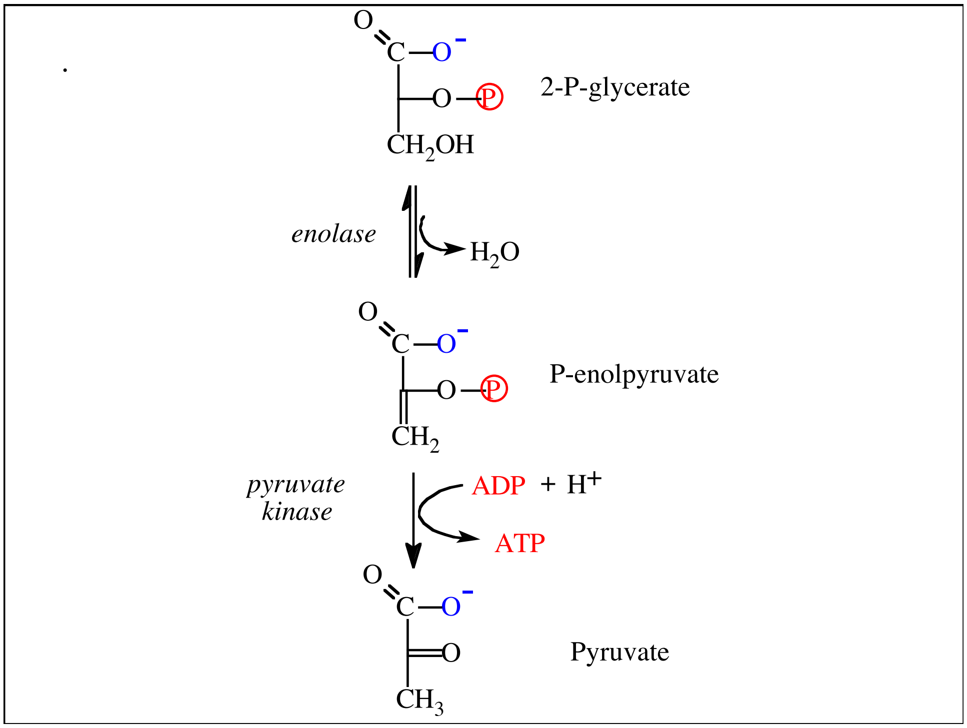

DHAP
H2C—O—P
CH2OH
triose-P-
isomerase
HC=O
OH
Glyceral-3-P
G-3-PdeH2ase
Pi + NAD+
NADH + H+
1,3-bisP-glycerate
P-glycerate
kinase
ADP
ATP
3-P-glycerate
P-glycerate
mutase


2-P-glycerate
enolase
H2O
P-enolpyruvate
pyruvate kinase
ADP + H+
ATP
Pyruvate