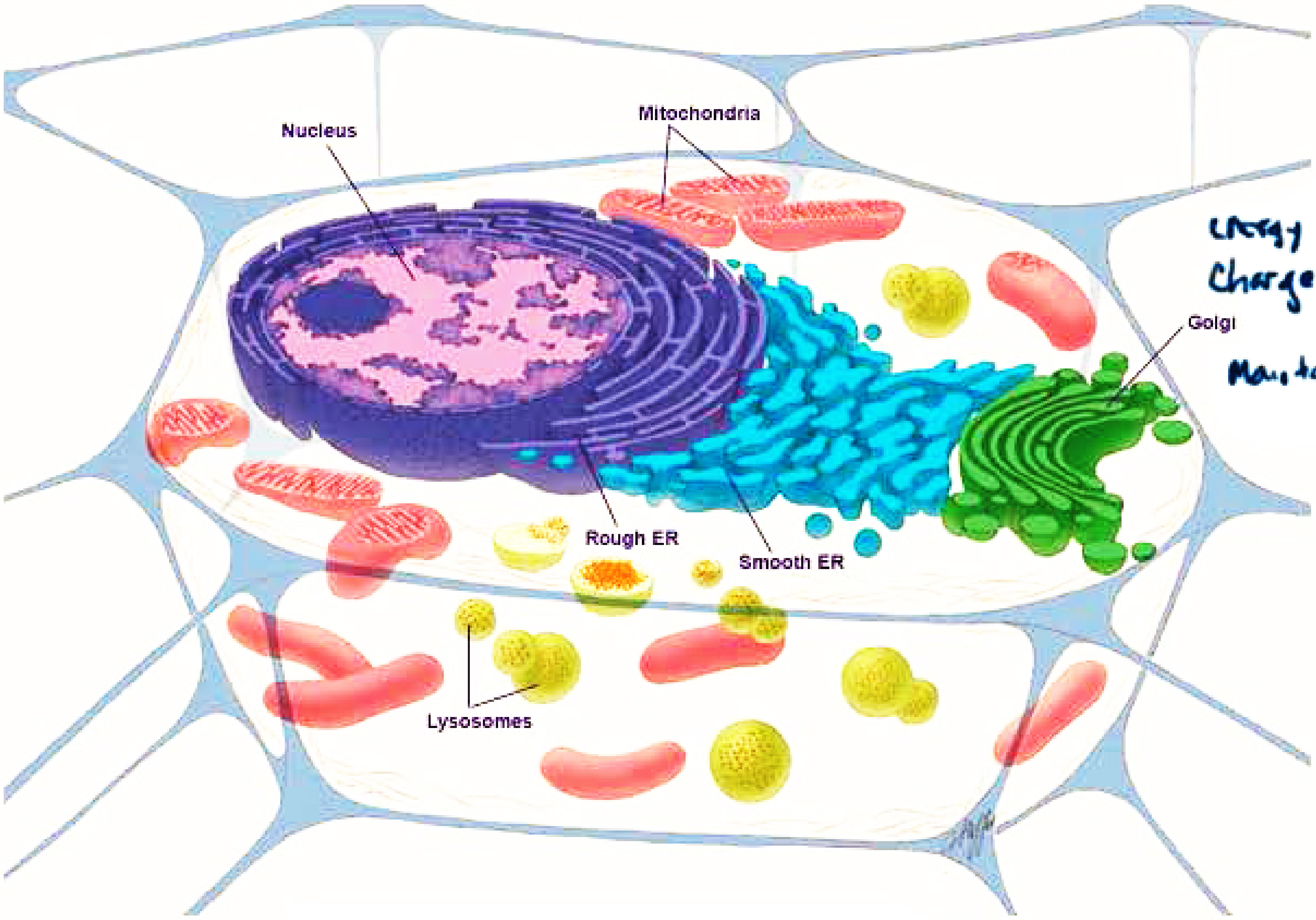
Module 10

Glycolysis and Pyruvate Dehydrogenase

Session Slides with Notes

Energy Metabolism



Energy Charge : $\dfrac{[ATP] + \frac{1}{2}[ADP]}{[ATP] + [ADP] + [AMP]}$

Maintained

0.85 - 0.90

- substrate level phosphorylation
- oxidative phosphorylation

$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O \qquad \Delta G^\circ \sim -3000kJ$$

$$36\,ADP + 36\,P_i \longrightarrow 36\,ATP \qquad \Delta G^\circ \sim +1100kJ$$

$$ATP \xrightarrow[H_2O]{} ADP + P_i \qquad \Delta G^\circ \sim -30kJ$$

$$A \rightleftharpoons B$$

$$K = \frac{[B]}{[A]}$$

$$K = e^{-\Delta G^\circ/RT}$$

$$\Delta G^\circ = -RT\ln K$$

nonspontaneous $K_x = e^{-\Delta G^\circ_x/RT}$

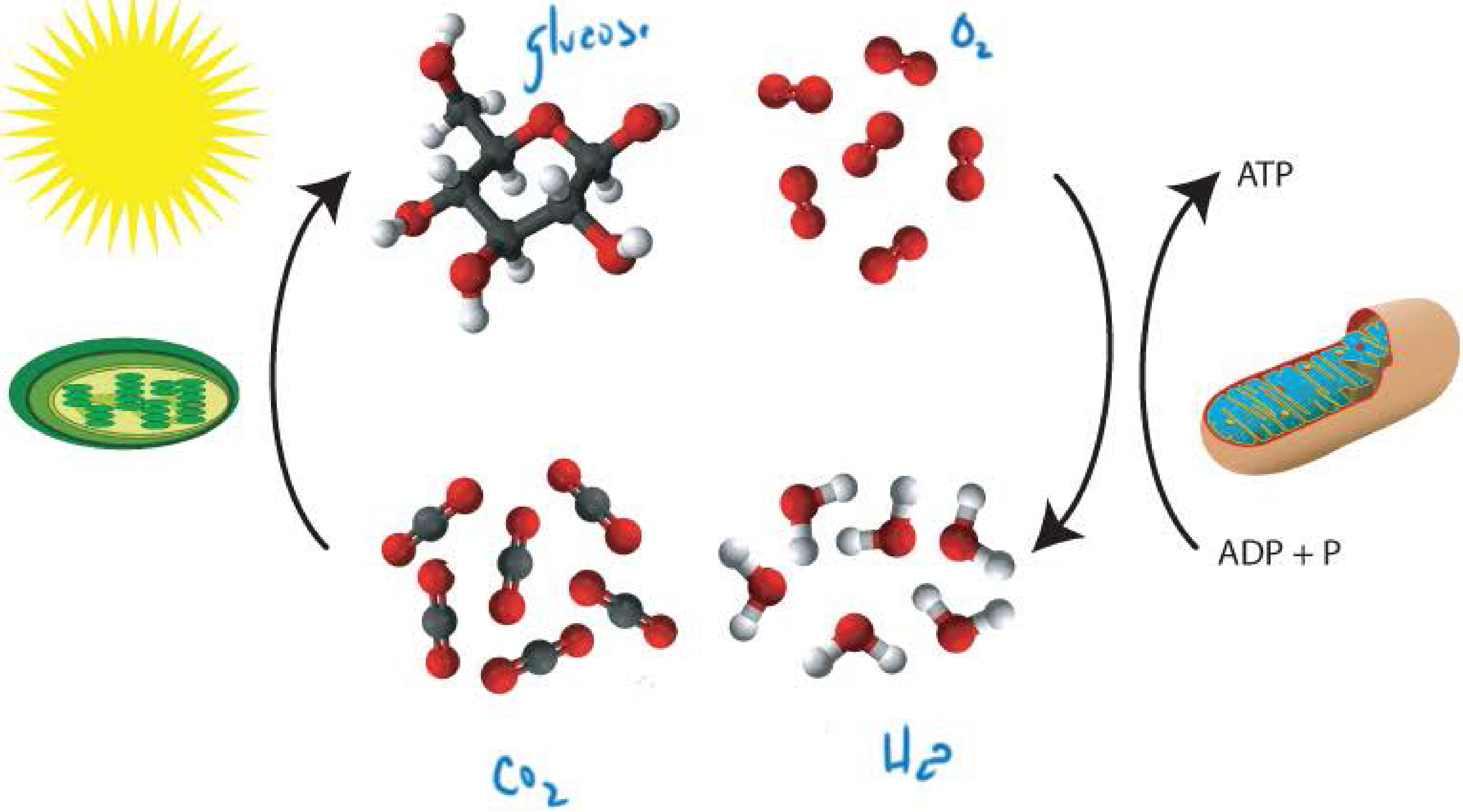
couple with ATP cleavage

coupled process

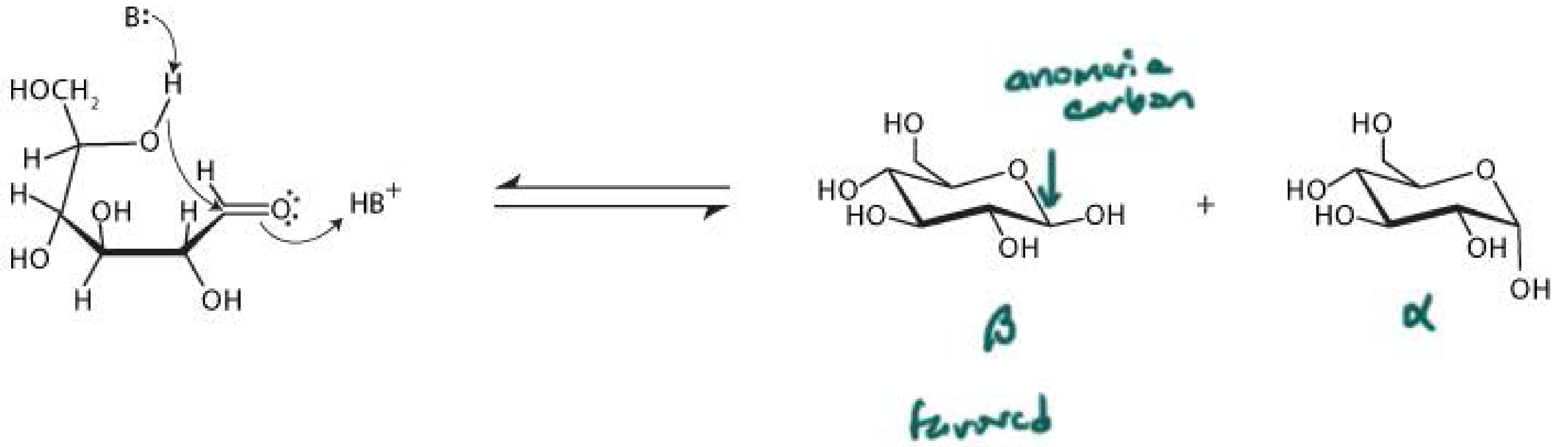
$$K_y = e^{-(\Delta G^\circ_x + \Delta G^\circ_{ATP})/RT}$$

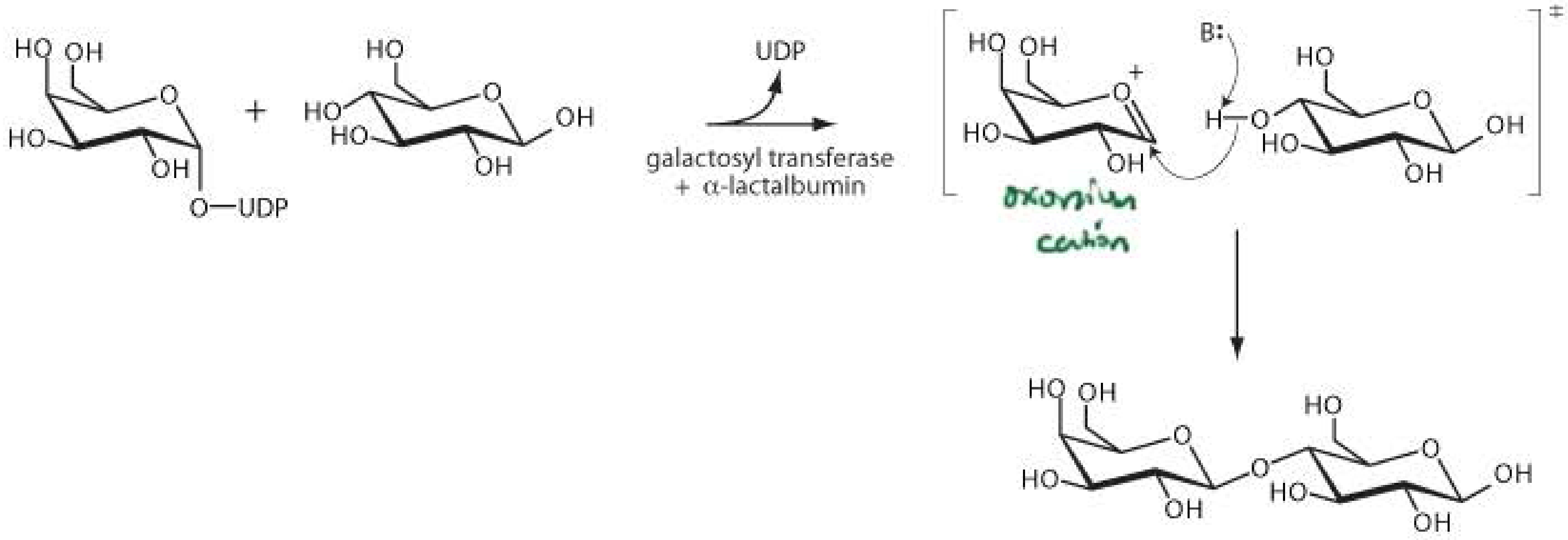
$$K_y = K_x K_{ATP}$$

Coupling with ATP cleavage shifted K about 10^8 in favor of products

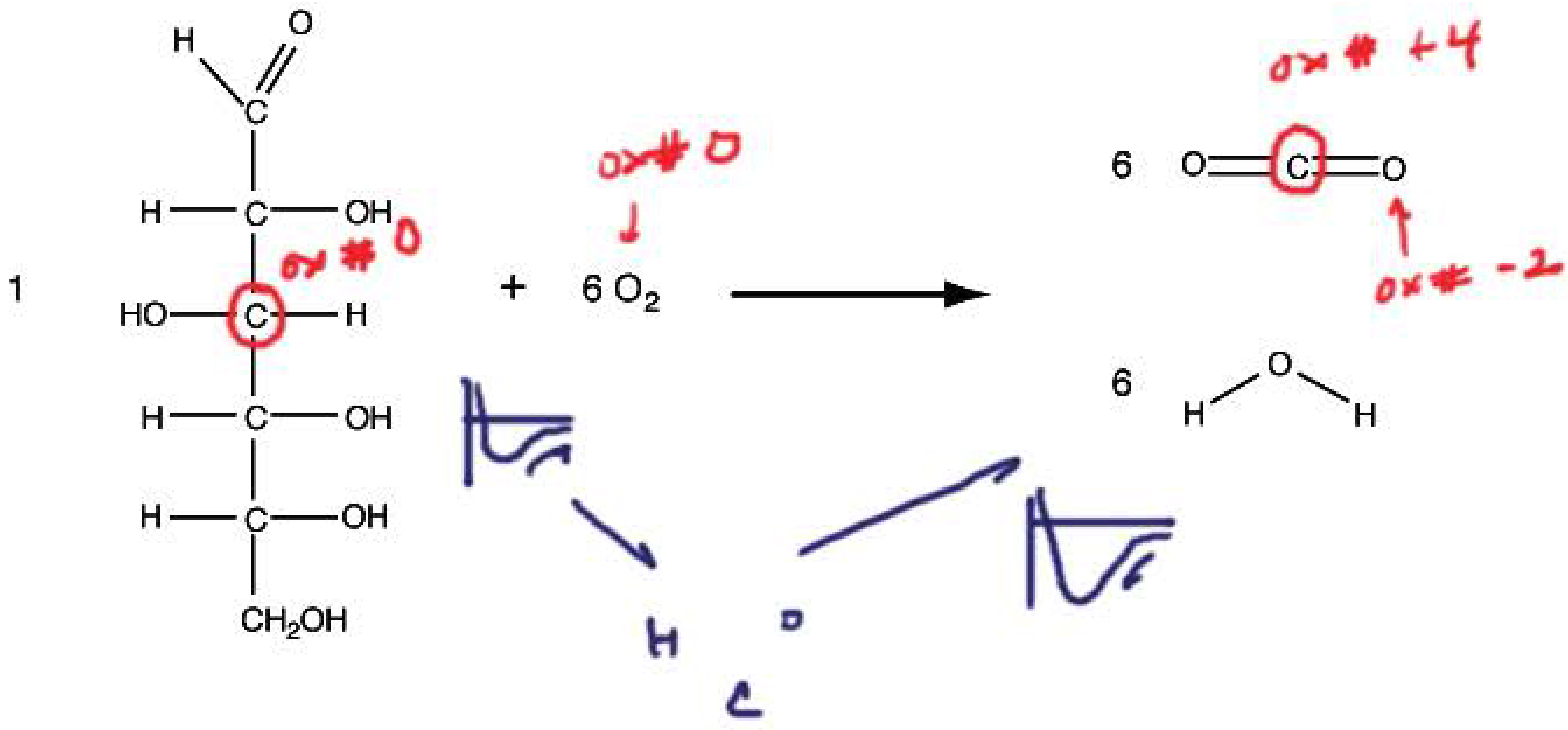

glucose
O_2
ATP
ADP + P
Co_2
H2

Glucose Ring Formation (hemiacetal formation)

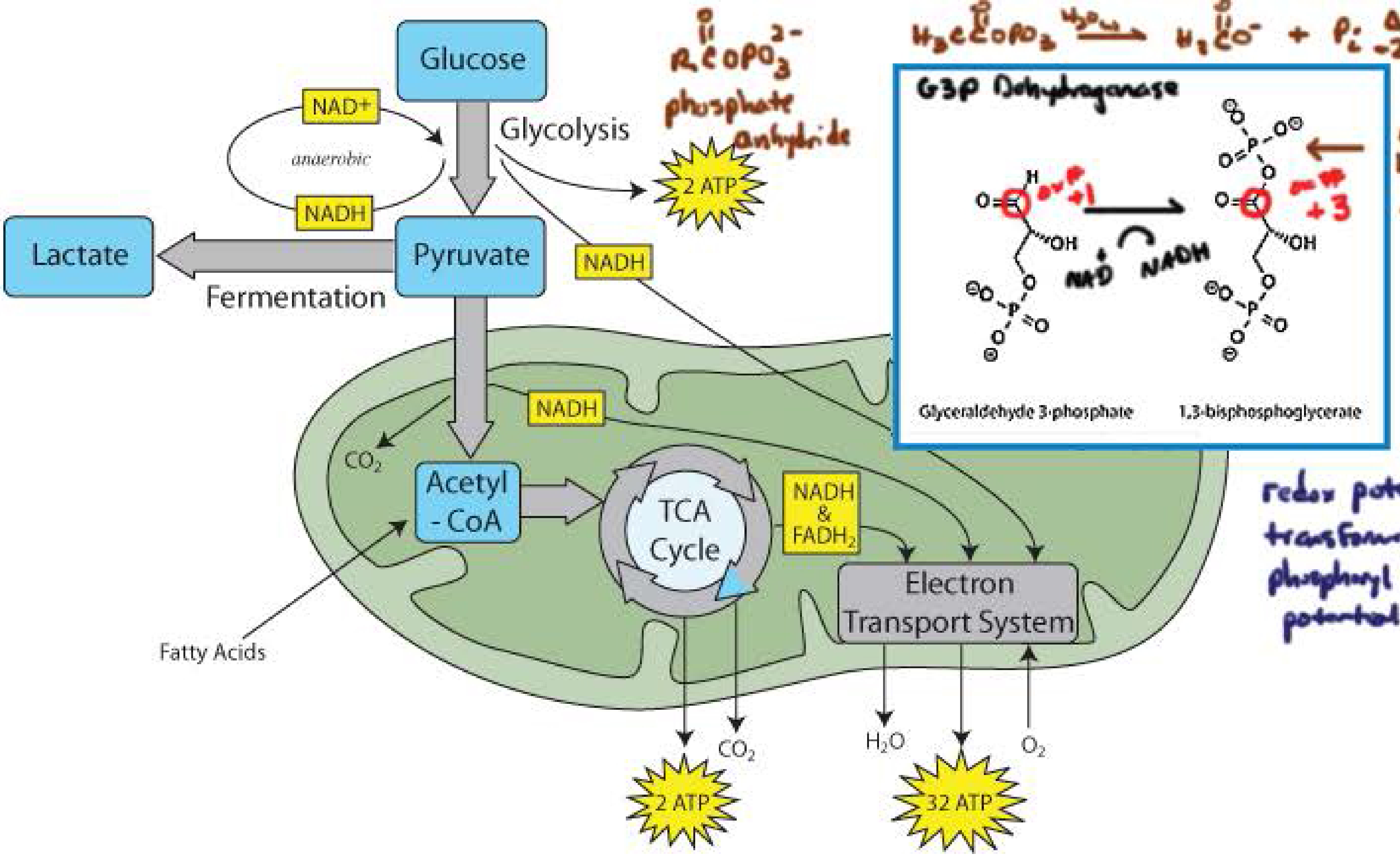




O—UDP
+
UDP
galactosyl transferase
+ α-lactalbumin
B:
H
‡
oxonium cation


1
+ 6 O₂
6
6
ox # 0
ox # 0
ox # +4
ox # -2
H
O
C

$H_3C\overset{O}{\overset{\|}{C}}OPO_3 \xrightarrow{H_2O} H_3\overset{O}{\overset{\|}{C}}O^- + P_i$ $\frac{\Delta G^o}{-20kJ}$

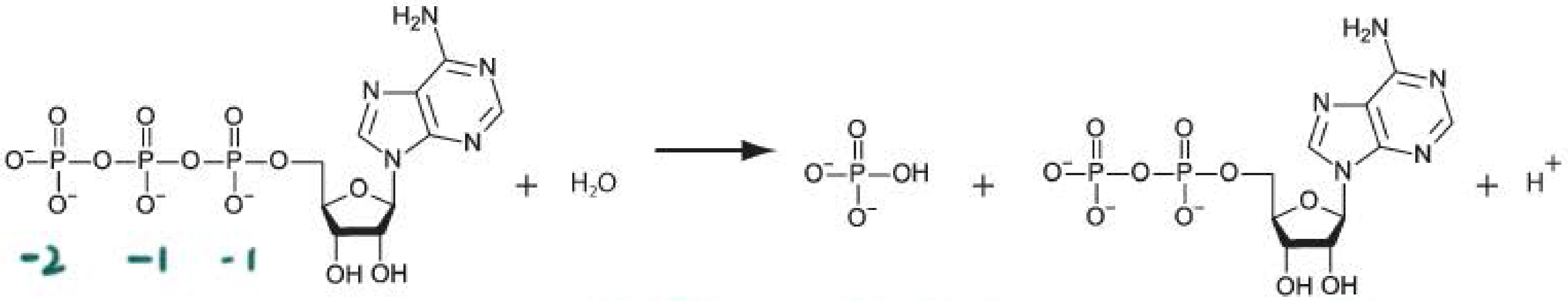


ΔG^o hydrolysis

-45kJ

redox potential transformed into phosphoryl transfer potential

Hydrolysis of ATP

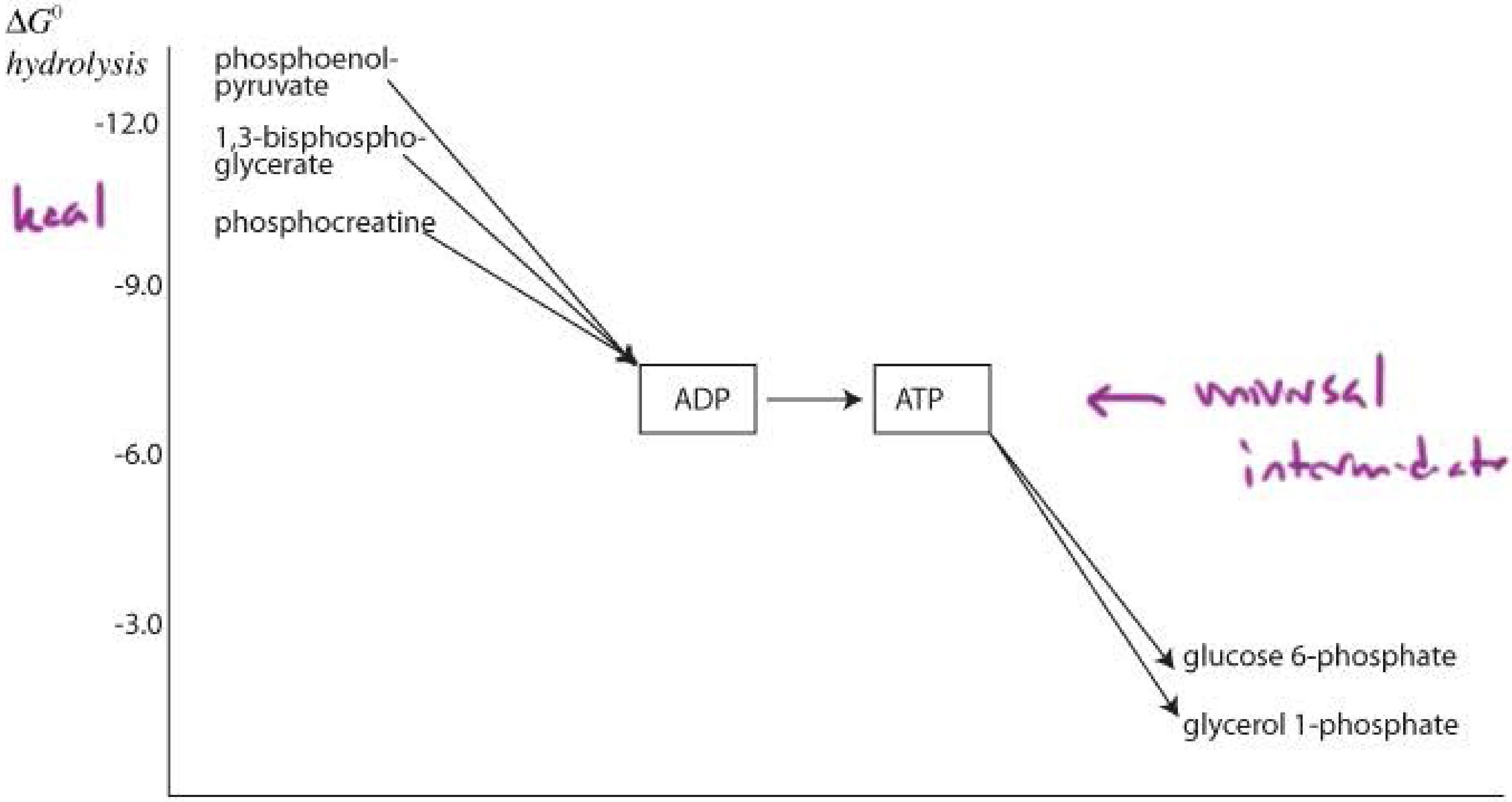


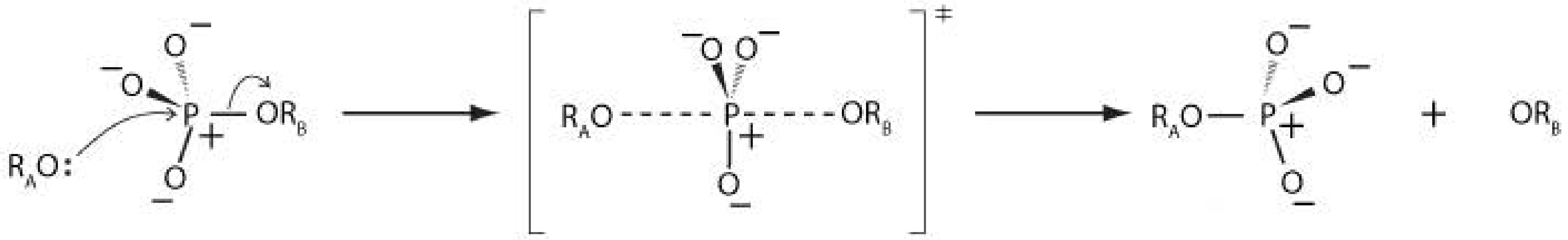
$\Delta G° \sim -30\,kJ$

$\overset{\ominus}{\Delta U} \Rightarrow \overset{\ominus}{\Delta H} \Rightarrow \overset{\ominus}{\Delta G}$

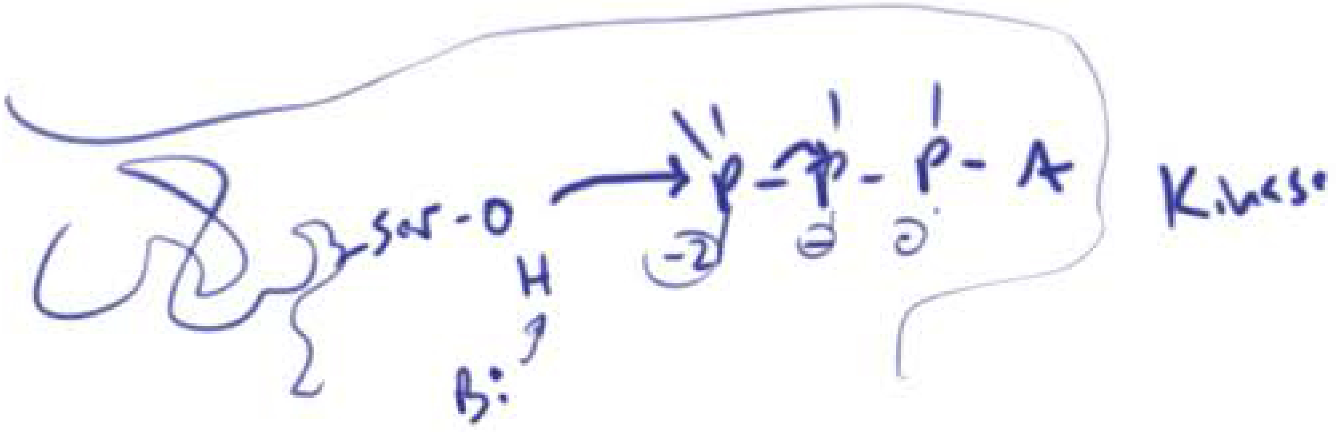
- electrostatic repulsion ★
- resonance
- hydration

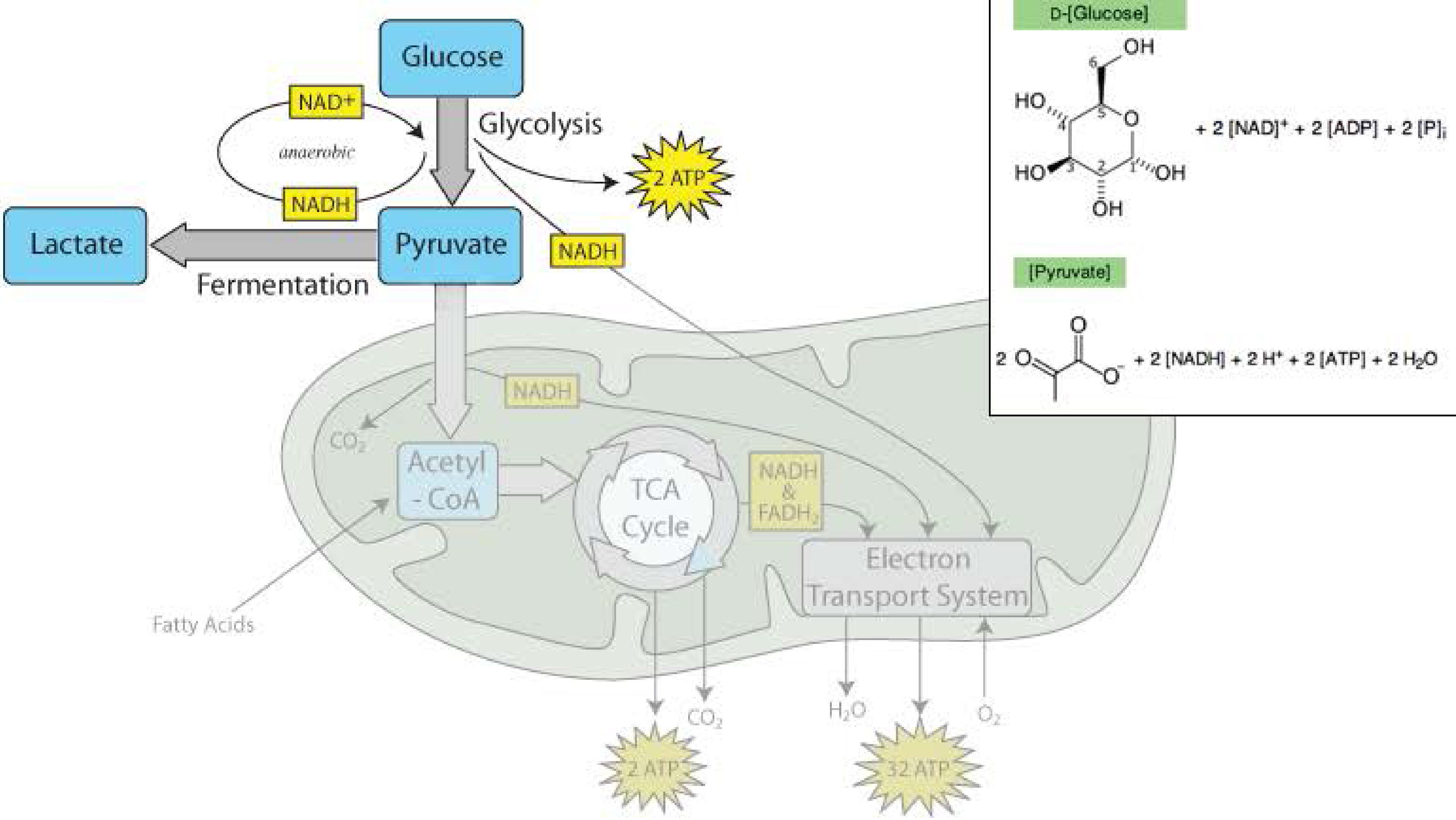
$$U = \frac{k q_1 q_2}{r}$$


ΔG^0 hydrolysis
-12.0
-9.0
-6.0
-3.0
kcal
phosphoenol-pyruvate
1,3-bisphospho-glycerate
phosphocreatine
ADP
ATP
← universal intermediate
glucose 6-phosphate
glycerol 1-phosphate



like SN2
across the
phosphate



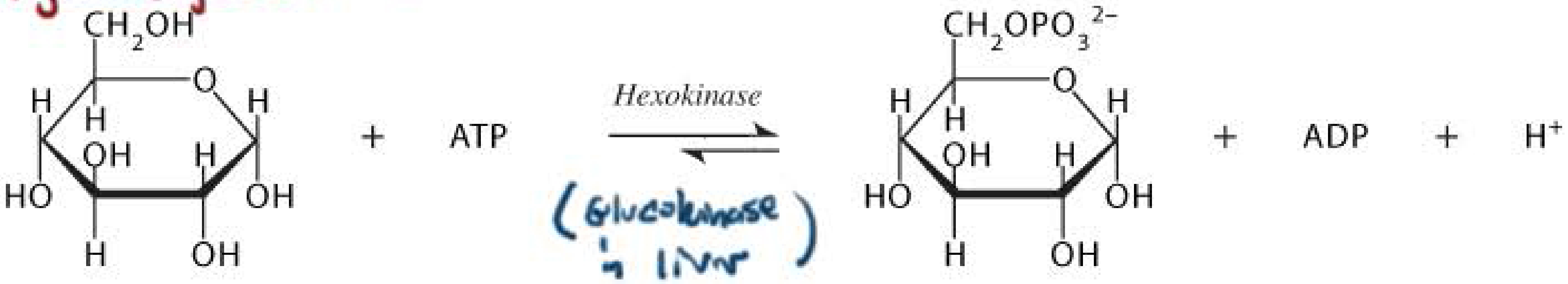

Glucose
Glycolysis
NAD+
anaerobic
NADH
2 ATP
Lactate
Pyruvate
NADH
Fermentation
NADH
CO2
Acetyl - CoA
TCA Cycle
NADH & FADH2
Electron Transport System
Fatty Acids
2 ATP
CO2
H2O
32 ATP
O2
D-[Glucose]
OH
HO
O
HO
OH
OH
+ 2 [NAD]+ + 2 [ADP] + 2 [P]i
[Pyruvate]
2
+ 2 [NADH] + 2 H+ + 2 [ATP] + 2 H2O

-ΔG

[Glucose 6 phosphatase in gluconeogenesis]

Hexokinase

• inhibited by G6P



(Glucokinase in liver)

Glucose

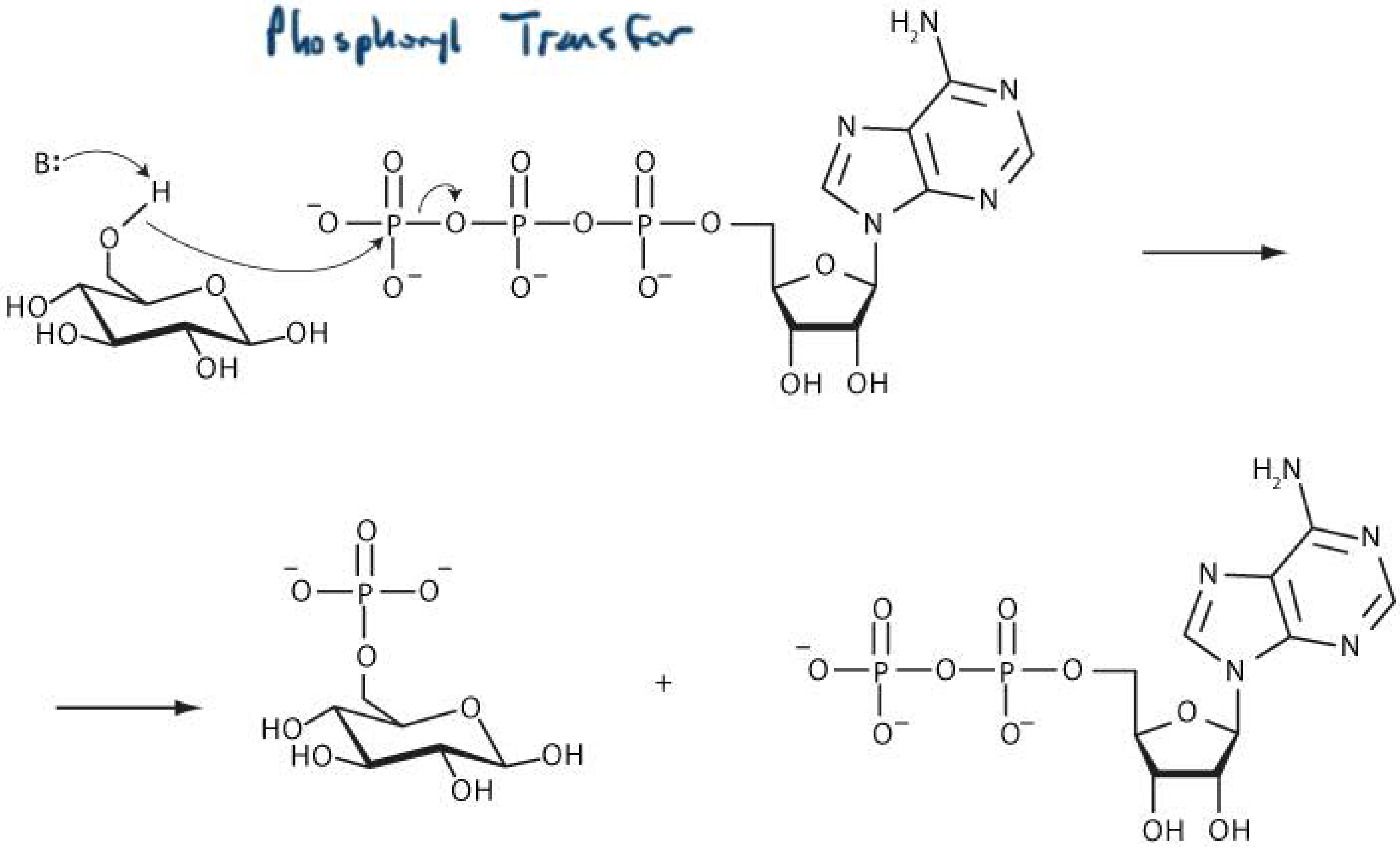
Glucose-6-Phosphate

Glucose-6-Phosphate → PPP

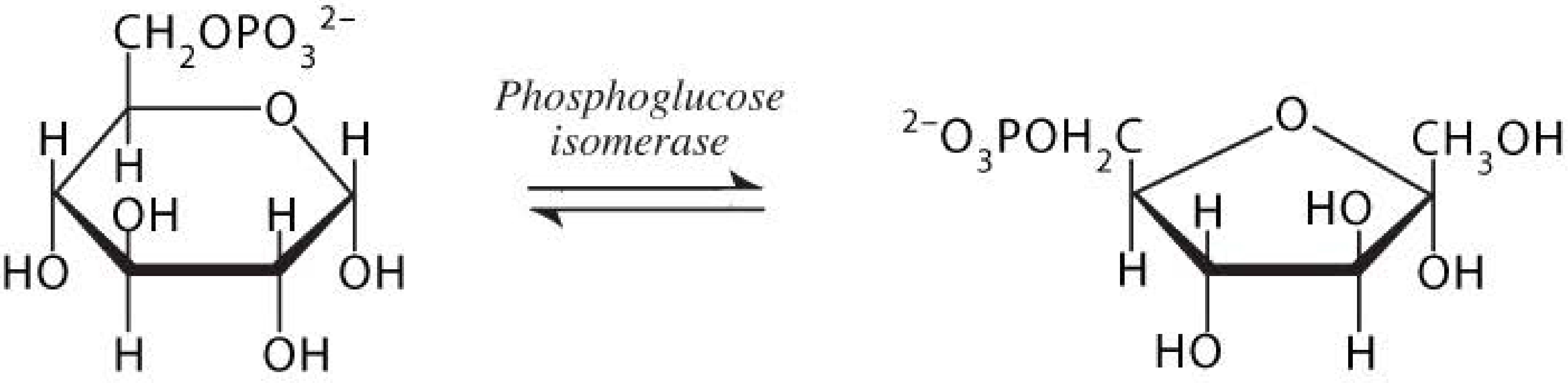
Glucose-6-Phosphate → glycolysis

Glucose-6-Phosphate → G1P → glycogen synthesis

Phosphoryl Transfer

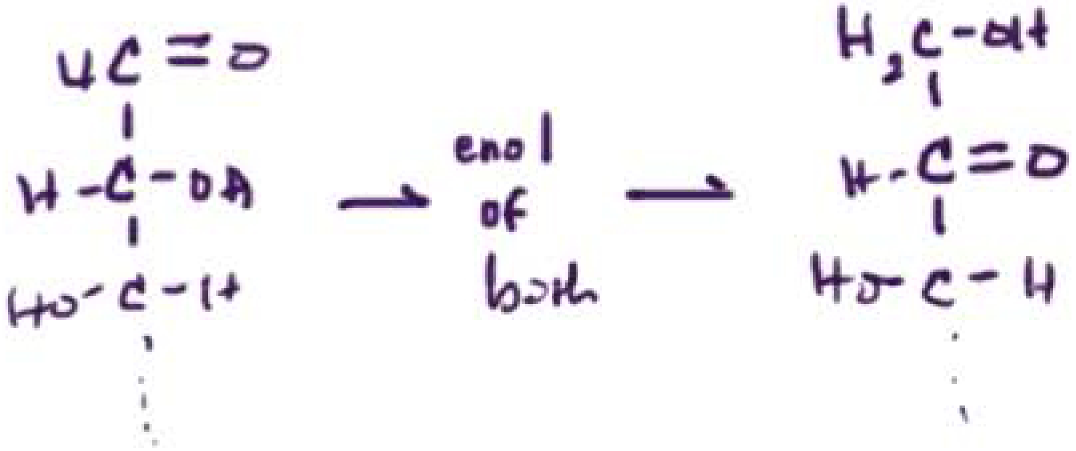


Phosphoglucose Isomerase



G6P

F6P



ΔG ⊖

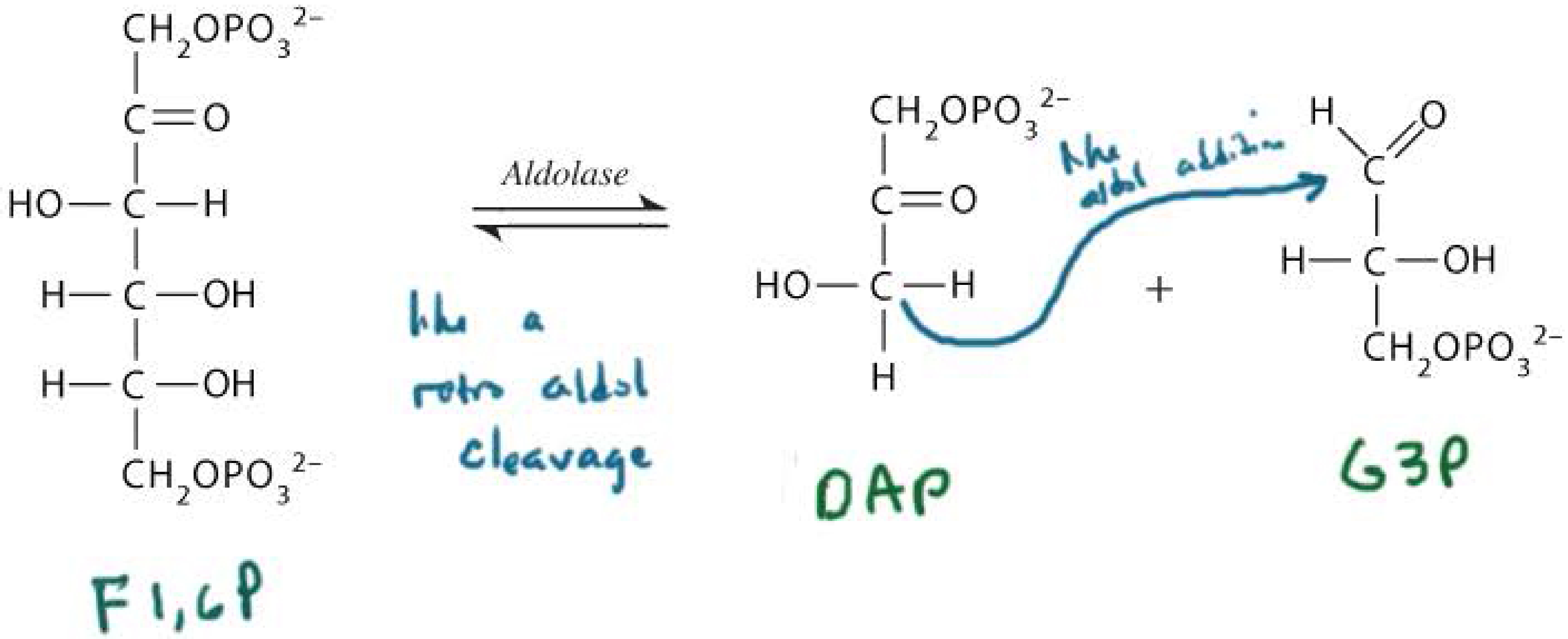
Fructose 1,6 Bisphosphatase

Phosphofructokinase PFK I

F6P

Fructose 1,6 Bisphosphate

- Committed step
- multisubunit allosteric enzyme
- cooperativity
- allosteric promoters and inhibitors
  - AMP ↑ • ATP ↓
  - Citrate ↓ ← signal of adequate precursors
  - Fructose 2,6 Bisphosphate ← strong activator of glycolysis. formed by PFK II
    - mechanism by which signaling can effect metabolic profile.



like a retro aldol cleavage

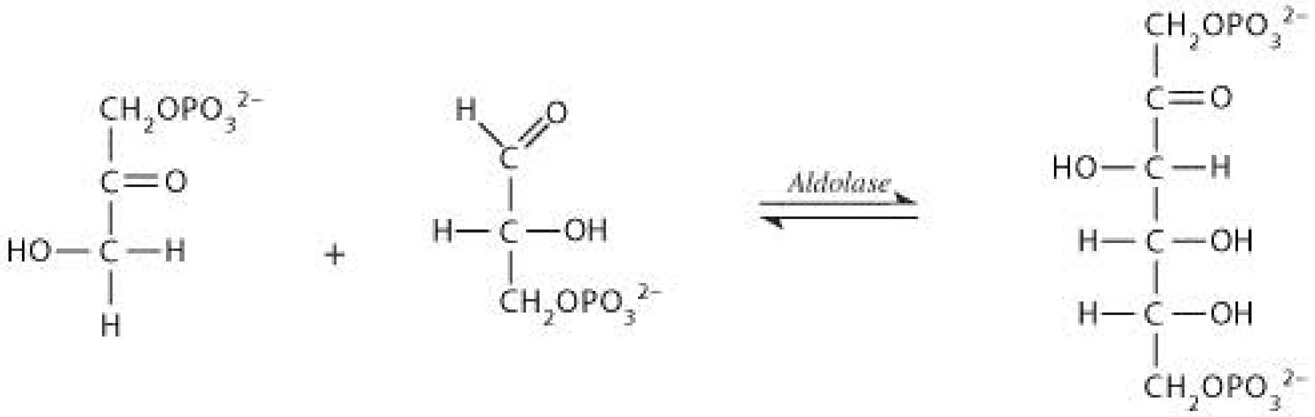
like aldol addition

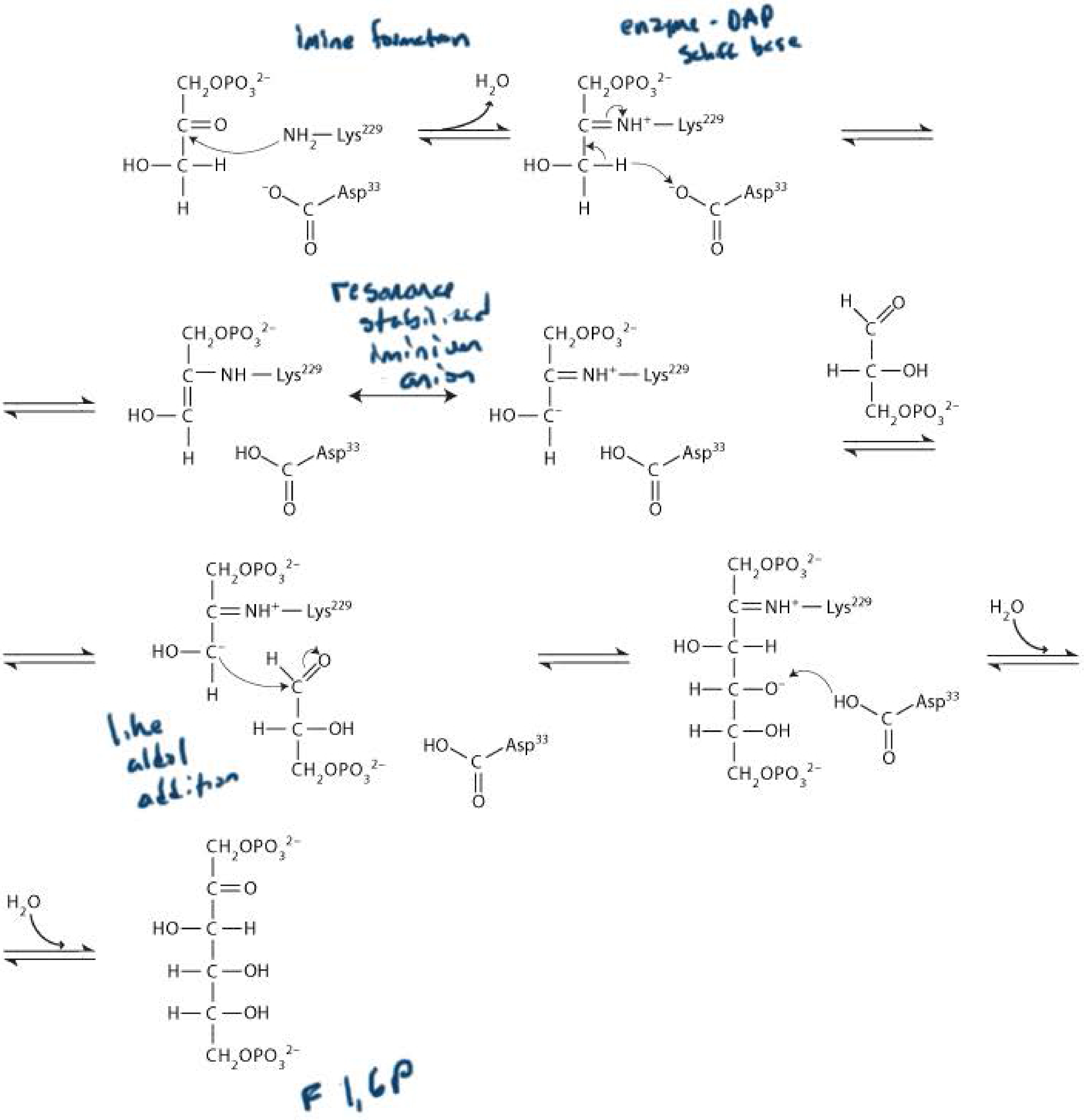
F1,6P

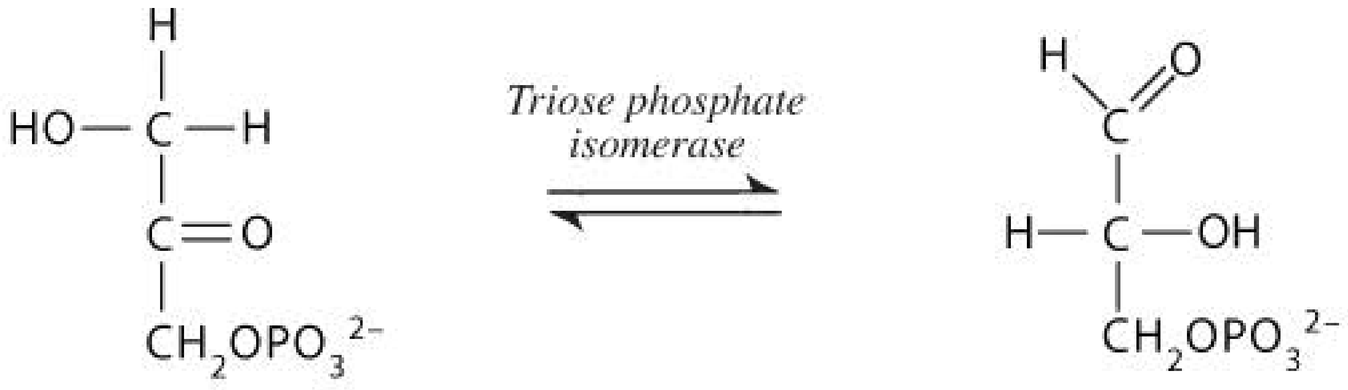
DAP

G3P

Gluconeogenesis Direction







DAP G3P

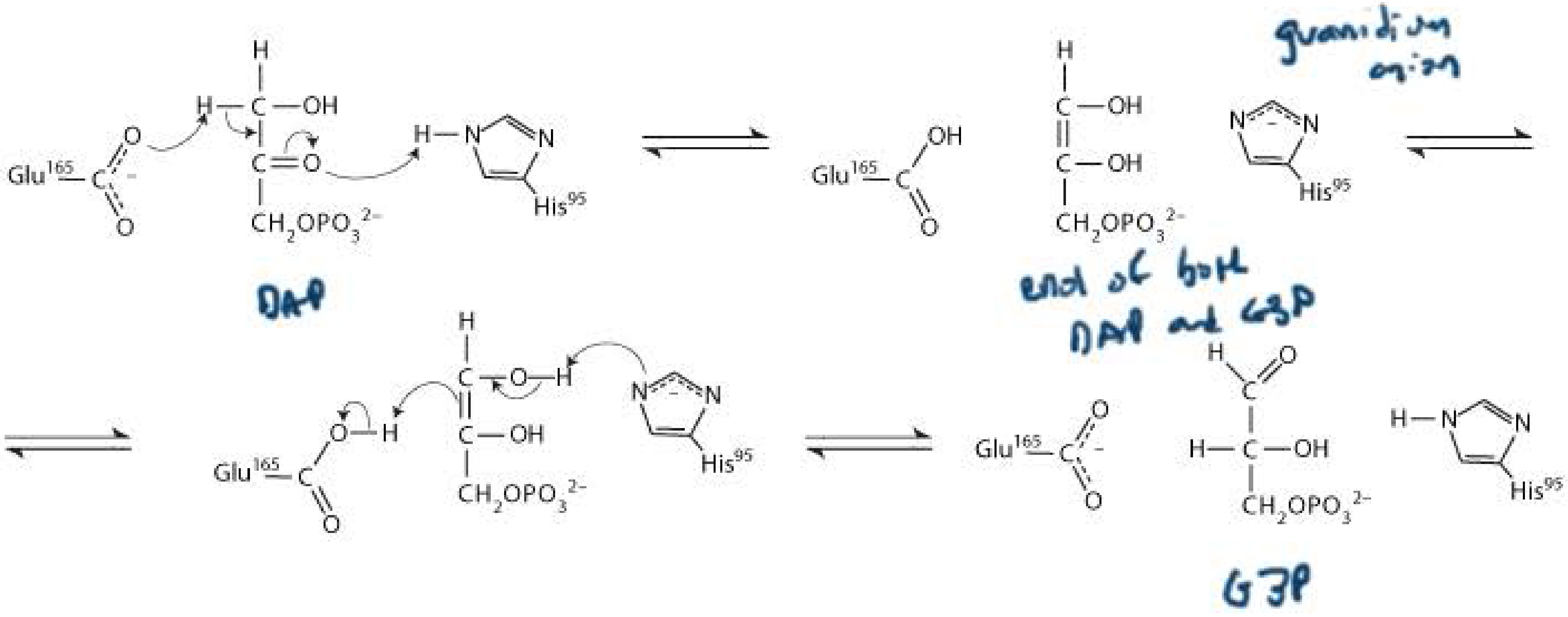
actually has $+\Delta G^\circ$

$$\overset{\ominus}{\Delta G} = \overset{\oplus}{\Delta G^\circ} + 2.3RT\,\log \overset{\ominus}{Q}$$

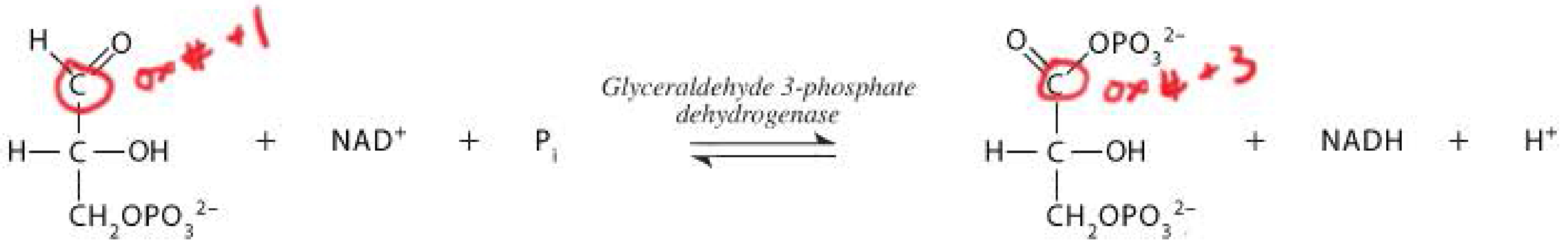
$$Q \sim \frac{1}{30}$$

$$Q = \frac{[G3P]}{[DAP]}$$


Triose phosphate isomerase


Glu165
His95
guanidium anion
DAP
end of both DAP and G3P
G3P

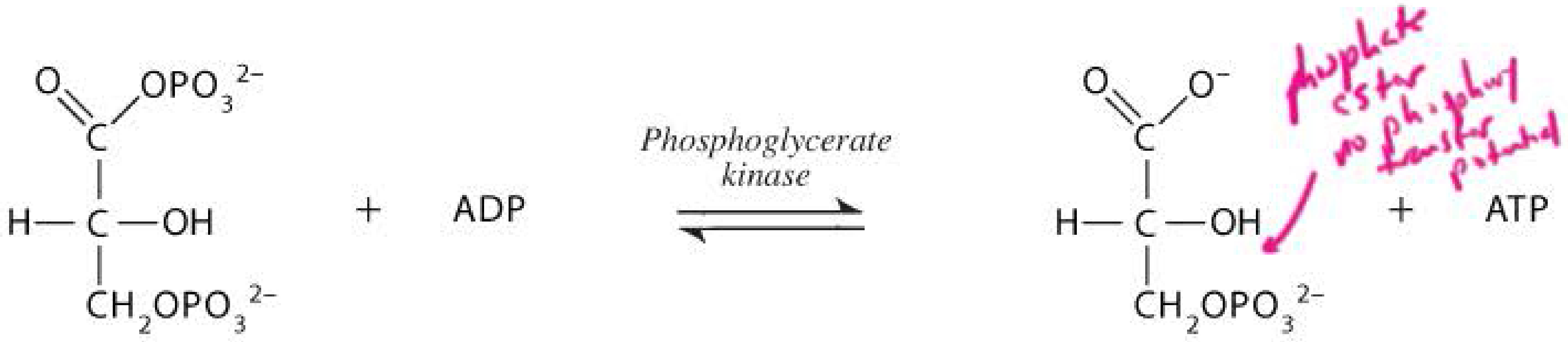
G3P Dehydrognase



G3P

1,3 BPG

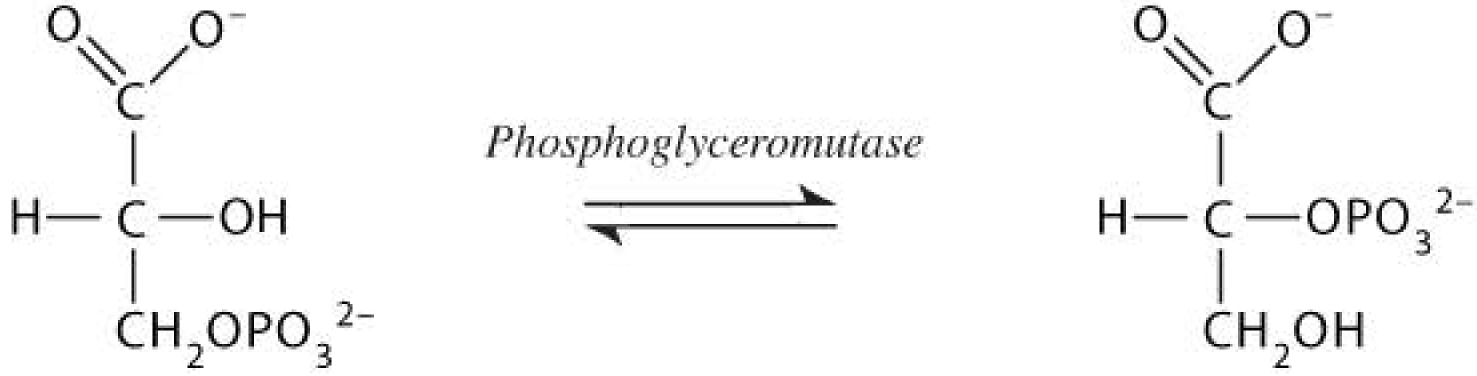
redox potential
transformed into
phosphoryl transfer
potential



phosphate ester no phosphoryl transfer potential

1,3 BPG

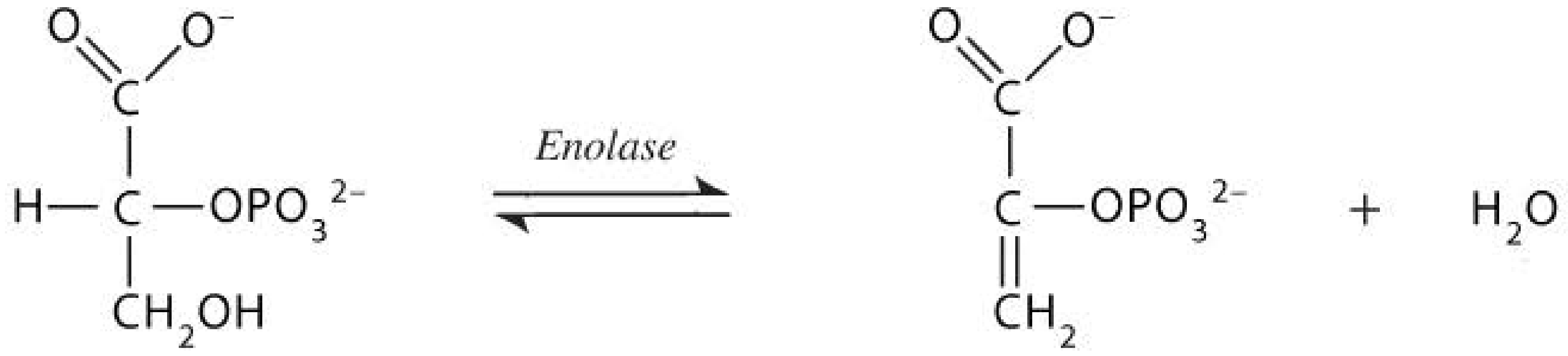
3 Phosphoglycerate



3 Phosphoglycerate

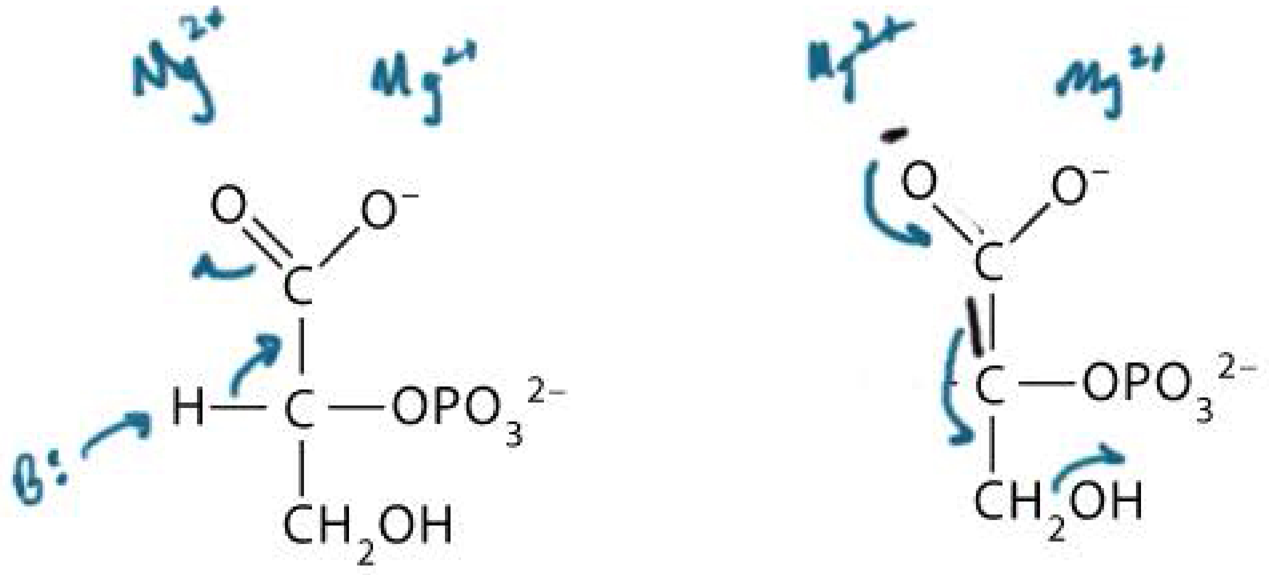
2-Phosphoglycerate

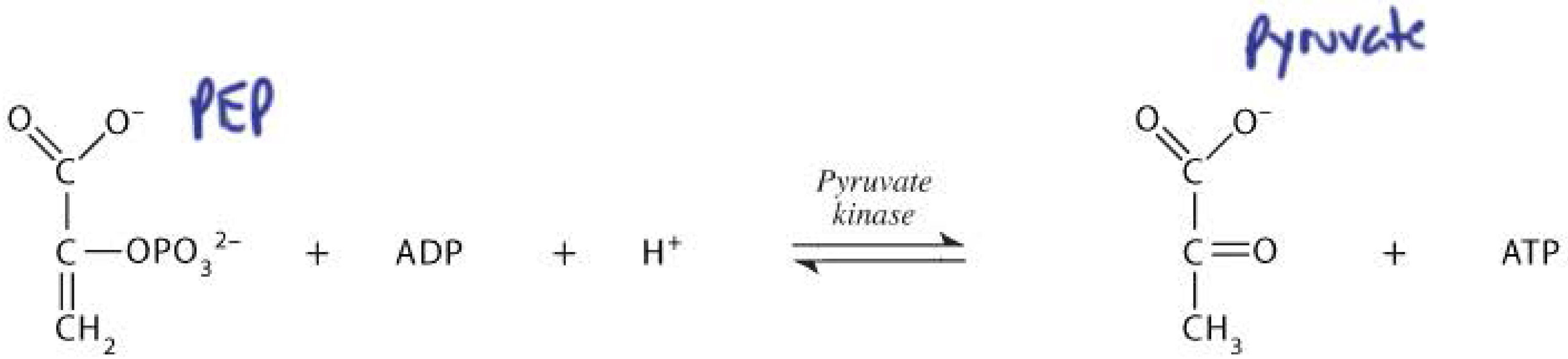
Enolase



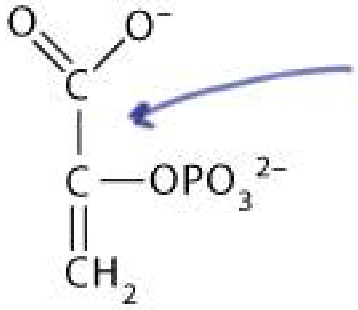
2-Phosphoglycerate

Phosphoenolpyruvate

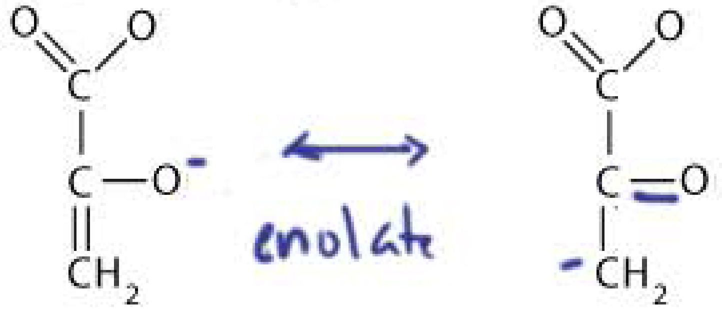


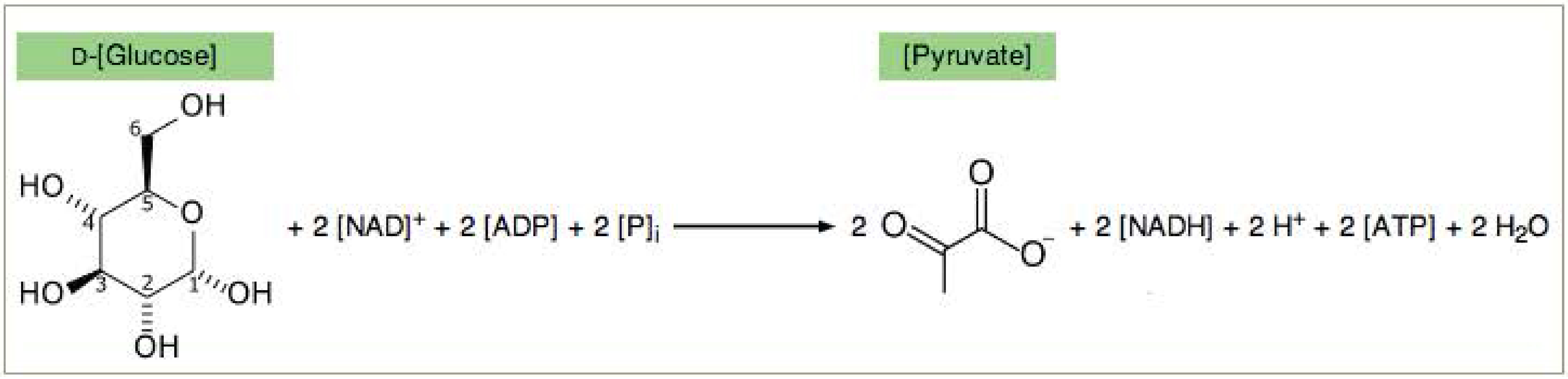


Why does PEP have so much phosphoryl transfer potential?

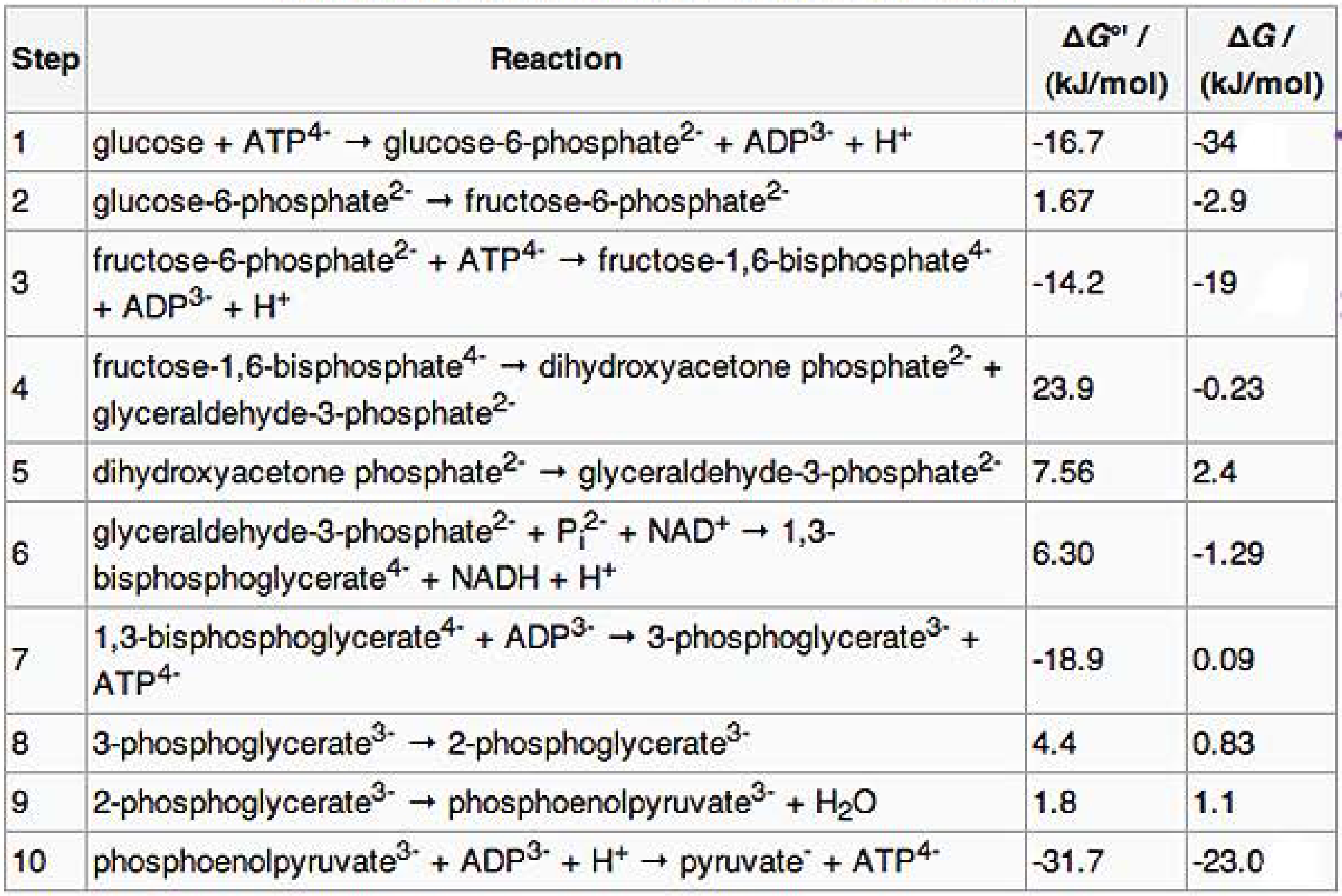


- partial double bond character
  shortened bond - compresses ⊖ charges
- phosphoryl transfer leaves behind an enolate



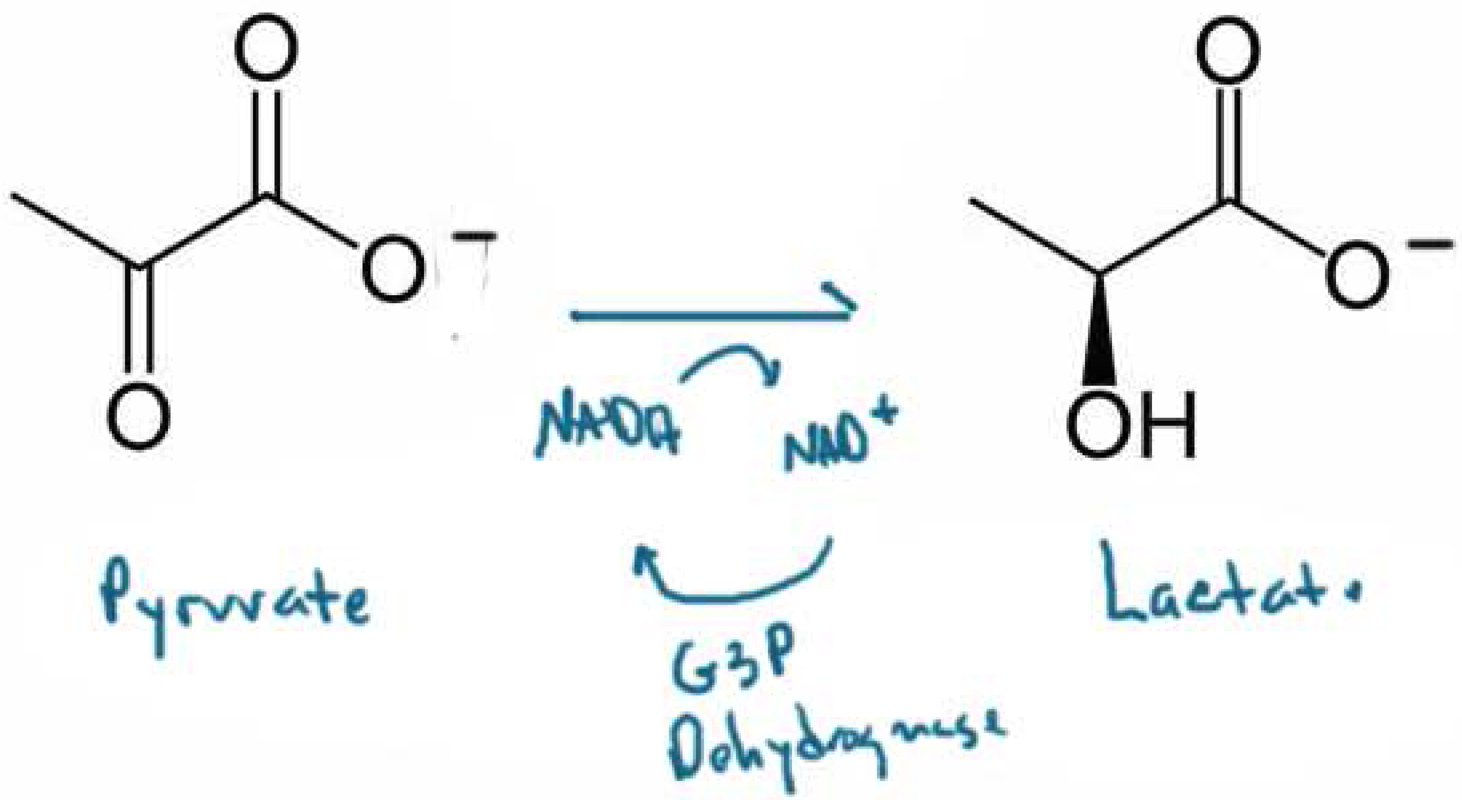

D-[Glucose]
[Pyruvate]
OH
6
HO
4
5
O
HO
3
2
1
OH
OH
+ 2 [NAD]$^+$ + 2 [ADP] + 2 [P]$_i$
2
O
O
O$^-$
+ 2 [NADH] + 2 H$^+$ + 2 [ATP] + 2 H_2O

Change in free energy for each step of glycolysis

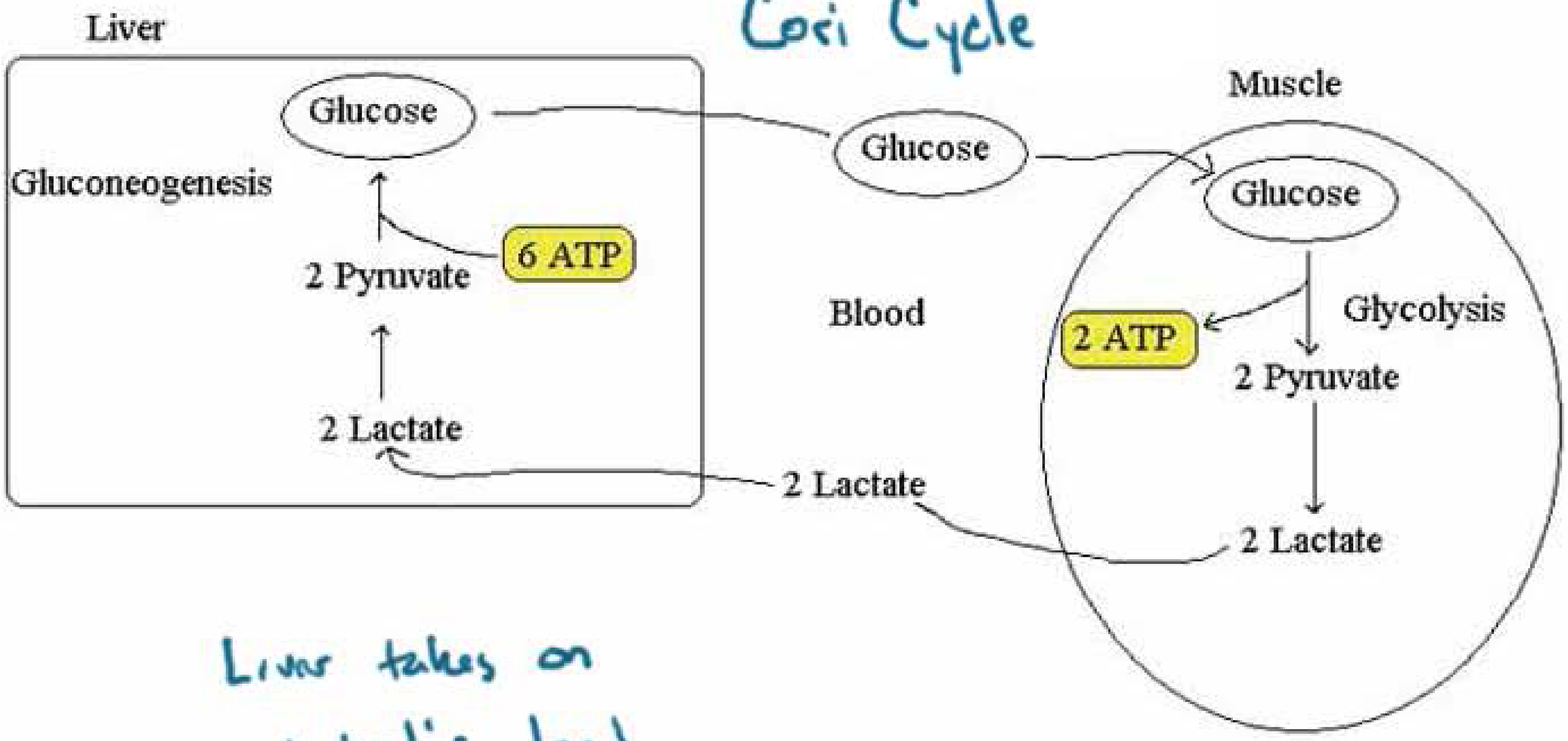


Step	Reaction	$\Delta G^{\circ\prime}$ / (kJ/mol)	ΔG / (kJ/mol)	
1	glucose + ATP^{4-} → glucose-6-phosphate^{2-} + ADP^{3-} + H^{+}	-16.7	-34	★
2	glucose-6-phosphate^{2-} → fructose-6-phosphate^{2-}	1.67	-2.9	
3	fructose-6-phosphate^{2-} + ATP^{4-} → fructose-1,6-bisphosphate^{4-} + ADP^{3-} + H^{+}	-14.2	-19	★
4	fructose-1,6-bisphosphate^{4-} → dihydroxyacetone phosphate^{2-} + glyceraldehyde-3-phosphate^{2-}	23.9	-0.23	
5	dihydroxyacetone phosphate^{2-} → glyceraldehyde-3-phosphate^{2-}	7.56	2.4	
6	glyceraldehyde-3-phosphate^{2-} + P$_i^{2-}$ + NAD^{+} → 1,3-bisphosphoglycerate^{4-} + NADH + H^{+}	6.30	-1.29	
7	1,3-bisphosphoglycerate^{4-} + ADP^{3-} → 3-phosphoglycerate^{3-} + ATP^{4-}	-18.9	0.09	
8	3-phosphoglycerate^{3-} → 2-phosphoglycerate^{3-}	4.4	0.83	
9	2-phosphoglycerate^{3-} → phosphoenolpyruvate^{3-} + H$_2$O	1.8	1.1	
10	phosphoenolpyruvate^{3-} + ADP^{3-} + H^{+} → pyruvate^{-} + ATP^{4-}	-31.7	-23.0	★

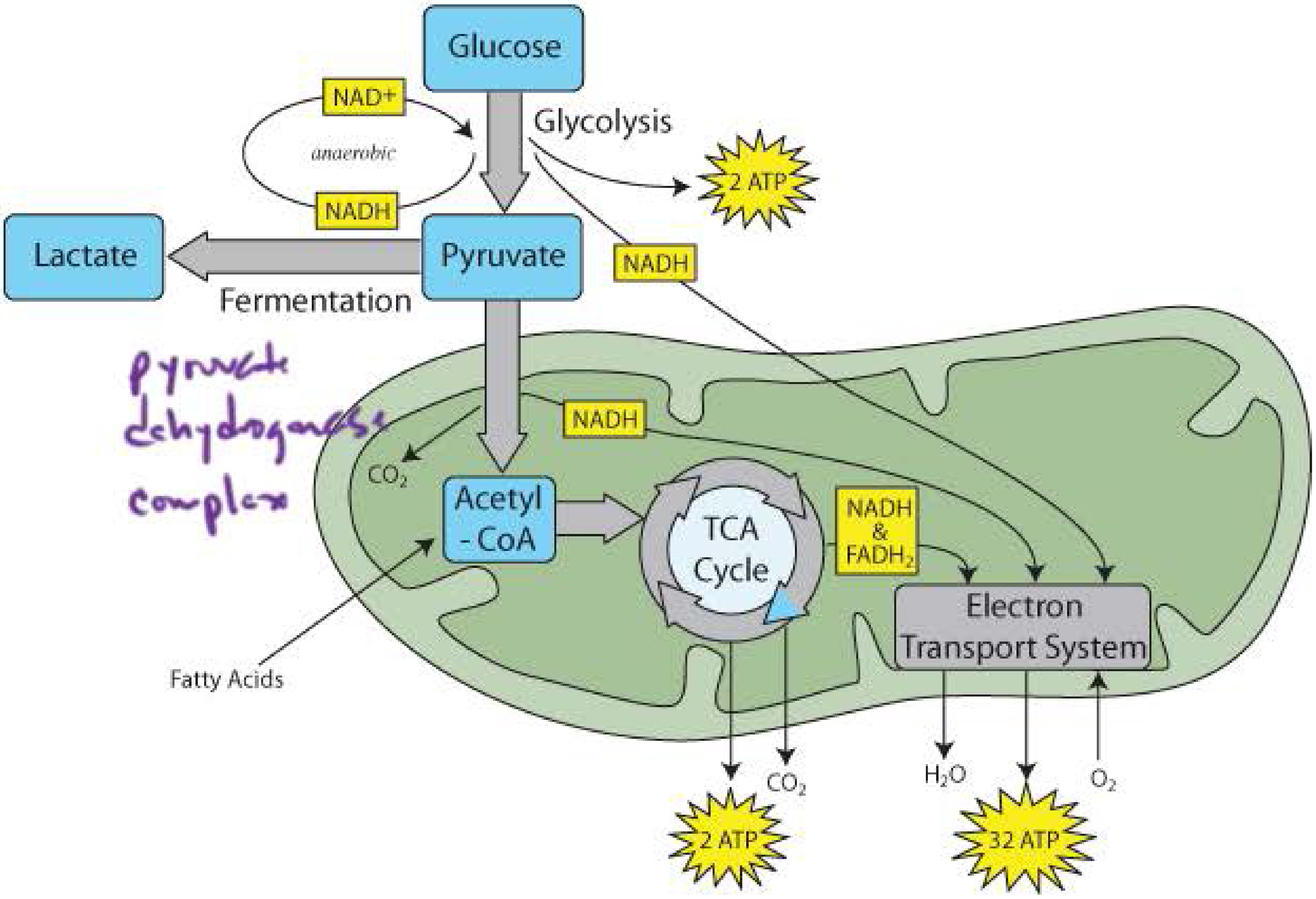
$$\Delta G = \Delta G^{\circ} + RT \ln Q$$


NADH
NAD$^+$
Pyruvate
Lactate
G3P
Dehydrogenase

Cori Cycle



Liver takes on metabolic load



pyruvate
dehydrogenase
complex

pyruvate

acetyl CoA

<u>Coenzymes</u>

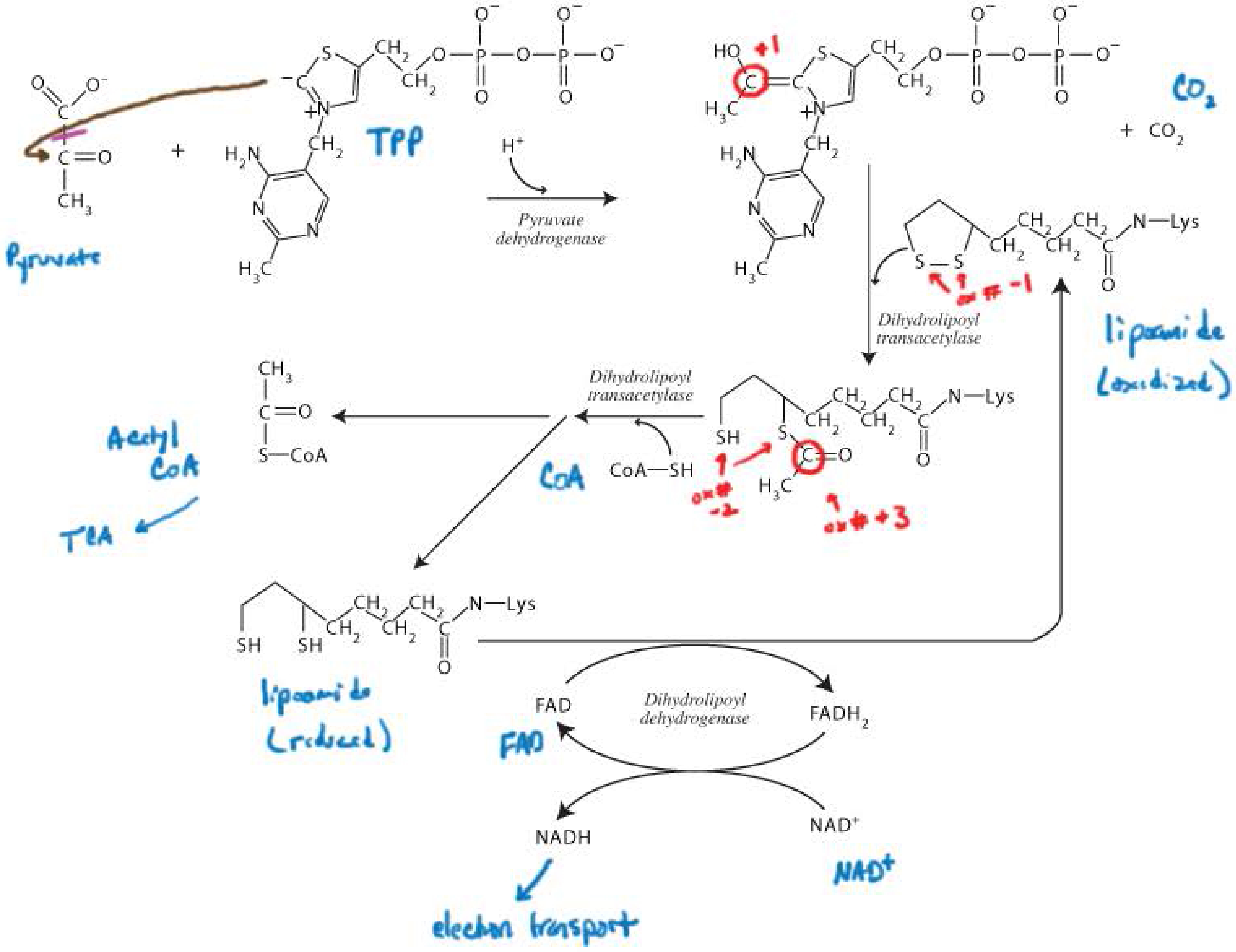
TPP

lipoamide

CoA

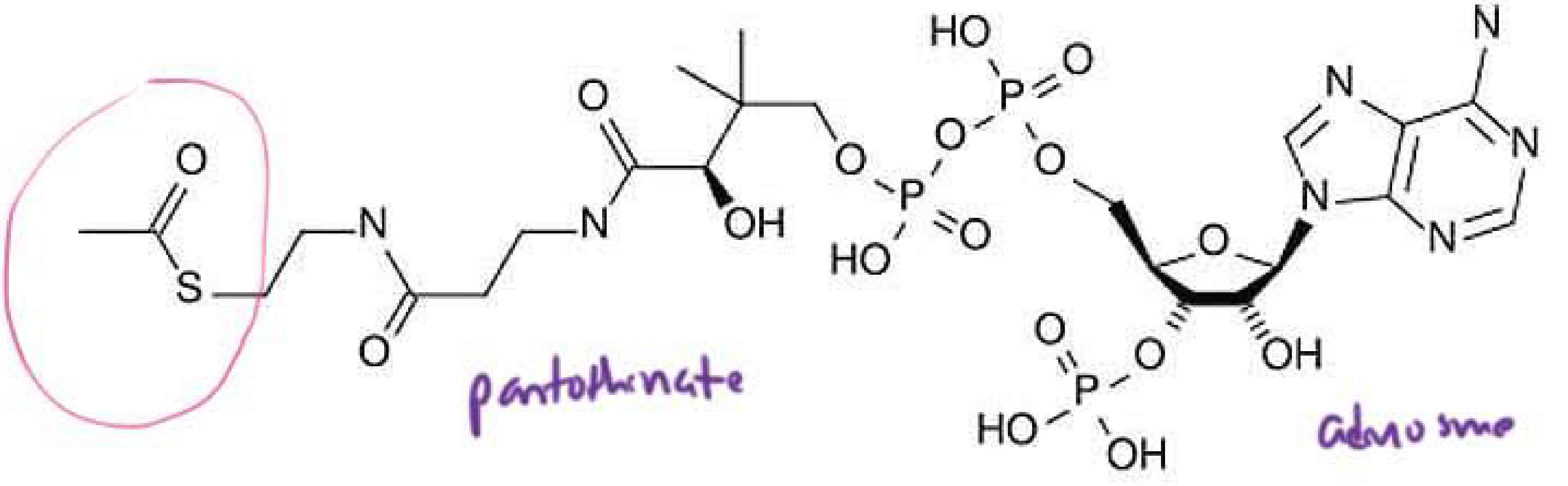
FAD

NAD$^+$



Pyruvate
TPP
H⁺
Pyruvate dehydrogenase
+1
+ CO₂
CO₂
Dihydrolipoyl transacetylase
ox# -1
lipoamide (oxidized)
N—Lys
Dihydrolipoyl transacetylase
CoA—SH
CoA
ox# -2
ox# +3
Acetyl CoA
S—CoA
TCA
lipoamide (reduced)
FAD
FAD
Dihydrolipoyl dehydrogenase
FADH₂
NADH
NAD⁺
NAD⁺
electron transport

acetyl CoA



$R\overset{O}{\overset{\|}{C}}SCoA$

← carrier of activated acyl groups