Ch17

Glycolysis

جهاد السابر هنكاي سد

First path involved in Glucose metabolism

- Glucose is the most preferred type of organic molecule for energy extraction inside our cells

- There are multiple path that are used to completly convert Glucose into other molecules or completly oxidized Glucose to extract the chemical pothential energy stored in cov. bond of Glucose molecule

* our cells capable of extracting energy from other monosa. / Biological molecule fats, a.a

First path → Glycolysis
↓
- Glucose splitting to pyruvate
- consist of 10 reactions catalized with 10 different enzymes

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Glucose → 2 pyruvate +2ATP+ 2NADH
(6 carbon) (each 3 carbon)

- Glycolysis → serve many functions:

(1) ATP production
بس مش بنسبة عالية
but some cells rely only on
Glycolysis like Red blood cells

(2) provide cells with metabolite
ex ethanol
carbon in Glucose could be used for the syn. of the molecules ribose, sugar, fattyacids, a.a

Glycolysis → 2 phases

energy invesment phase - cell loss 2ATP -

energy payoff - cell produce 4 ATP -

* Different type of chemical reaction happening during Glycolysis

1 → phosphorylation: reaction where an enzyme has a phosphate Group

2 → Isomerization: sugars converted to steriosomers

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3 → Cleavage: 6 carbon sugar will be splcat into 2 molecules - 3carbon -

* Energy invesment phase

1 → phosphorylation reaction, mediated by enzyme called hexokinase (Glucokinase) cells loss ATP in this step

so → Glucose molecule reseve the phosphate in the 6 carbon
وهاي الخطوة مهمة لأنو
It allows the cells to convert Glucose to G6P & now it has a negative charge, so the Glucose will remain inside the cell & it can't leave the cell easily because of the presence of phosphate

2 → G6P → F6P (steriosomer to each other)
Aldose → ketose

The enzyme used is called Glucose phosphate isomerase → mediate isomeration reaction

- Carbonyl Group is moving to the middle of molecule & that's important to allow the spleating of molecule into 2

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3 F6P → will reseve another phosphate, so another ATP molecule will be lost

& now we have a molecule have 6 carbons & both end have a phosphate & the enzyme catalize this reaction is called phosphofructokinase

↳ involve in phosphorylation

Cofactor Mg^{+2} تعطي Reaction وتعدل which is important in the function of these enzyme because it will neutrilize negative charge on ATP

4 FBP → is ready now for the cleavage by the enzyme aldolase

↓

require that the carbonyl Group to be closer to the middle where the middle C. bond will be broken & now this molecule is split into 2 sugars, each sugar consist of 3 carbon

G3P , DHAP
(ketose)

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* 2ATP molecule was speant de there is an enzyme that can convert the G3P to DHAP

أو إنزيم واسمو

Triose phosphate isomerase

- بس G3P ح تكمل مع Glycolysis وهاي الحالة بتضعف إنو Glucose ما بتفادر الـ cell , بتنحليها صعب إنها تفادر

* G 6P → Could be used by another path. called pentose phosphate path - PPP -

→ imp. for the synthesis of Ribose → imp. component for nucleotid

اذا الـ cell بدها تضاعف DNA يعني بالاعتماد على اصطناع الـ cell بتأكل Glycolysis أو لا

Also could be used for Glycogen synthesis, If there is alot of sugar in blood G6P could be stored as Glycogen

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Note → Adding a phosphate Group decreases the permeability of this molecule through the membrane, so it remain inside the cell

- The isomeration reaction activates F6p for a sub sequence reaction that is mediated by aldolase

* Adding a second Group of phosphate insures that when this molecule is spleating into 2, the 2 moleculey are generated have a phosphate Group (negative charge hard to leave the cell)

PFK → • under control, tetramer, consist of 2 type of subunit (L) & (M), & there are different M & L compination of these subunits in different types of cell & these different compination are called isozymes

carry the same function but these different types allows to control the activity of this enzyme in different ways

• Muscley have PFK that consist of M sub. all of them are M-My-, liver all L-Ly-

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PFK: inhibited by ATP &
Fructose-1,6 biphosphate

Contor by allosteric effectors

↑ATP inhibit
↓ATP enhance activity

* In the second phase the Glyceraldehyde-3-phosphate will be oxidized & this reaction require Co-enzyme NAD^+ & catalized by Glyceraldehyde-3-phosphate dehydrogenase

Catalize oxidation/reduction reaction &
it will reserve a phosphate Group (ATP من ثم)

It's inorganic phosphate & now we have 2 phosphate Group connected to Glyceraldehyde backbone & now the molecule is called 1,3-biphosphoglycerate

* Now some electrons / 2electrons will be removed from Glyceraldehyde-3-phosphate & will be given to NAD^+ to produce NADH

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- This addition of phosphate allows the cell to activate bisphosphogl.., so now 2 phosphate Group with negative charges very close together which mean this molecule is unstable & then it will be easier for the next step to take 1 of phosphate & Give it to ADP to produce ATP

نهاية سلايد ٢

* dehydrogenase enzyme catalising this reaction rely on a cystene resedio in it's active site for catalysis

* The pyruvate could be also converted to alcohol ethanol through alcoholic fermentation or into lactic acid fermentation

* In alcohol fermintation the pyruvate first loses one of the carboxylic acid as CO_2 & now we have 2 carbons instead of 3 (acetaldehyde)

& then the enzyme alcohol dehydrogenase will reduce acetaldehyde to ethanol

Involves oxidization reduction reaction

NADH → loss $\bar{e}$

acetaldehyde → gain $\bar{e}$

Five Apple
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* سبب تحويل ال pyruvate ال cell لـ ethanol
عشان يطلع منها NAD+
because in order for Glycolysis to
happen it require NAD+

* In lactic acid fermentation

Pyruvate → lactate
by enzyme lactate dehydrogenase

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produce
2 ATP, 2NADH
2 pyruvate

take place
in cytoplasm
(cytosol)

Glycolysis

Glycos.
↓
2 pyru.
in all
living
cells

can
occur with
or without
oxygen

Chapter 17

connected to path. that
are impor. for production of
nucleotide, synth. of Glycogen [a.a]
lipids, imp. source for ATP &
sometimes the only source of ATP
for certain type of cells - In certain type
of condition

mainly
produce ATP
by Glycolysis

The Overall Pathway of Glycolysis

- Glycolysis is the first stage of glucose metabolism
- One molecule of glucose is converted to pyruvate which gives rise to 2 molecules of ATP via substrate level phosphorylation.
- Note that all of the steps of glycolysis are enzymatically catalyzed.

t plays a key role in the way organisms extract energy
om nutrients

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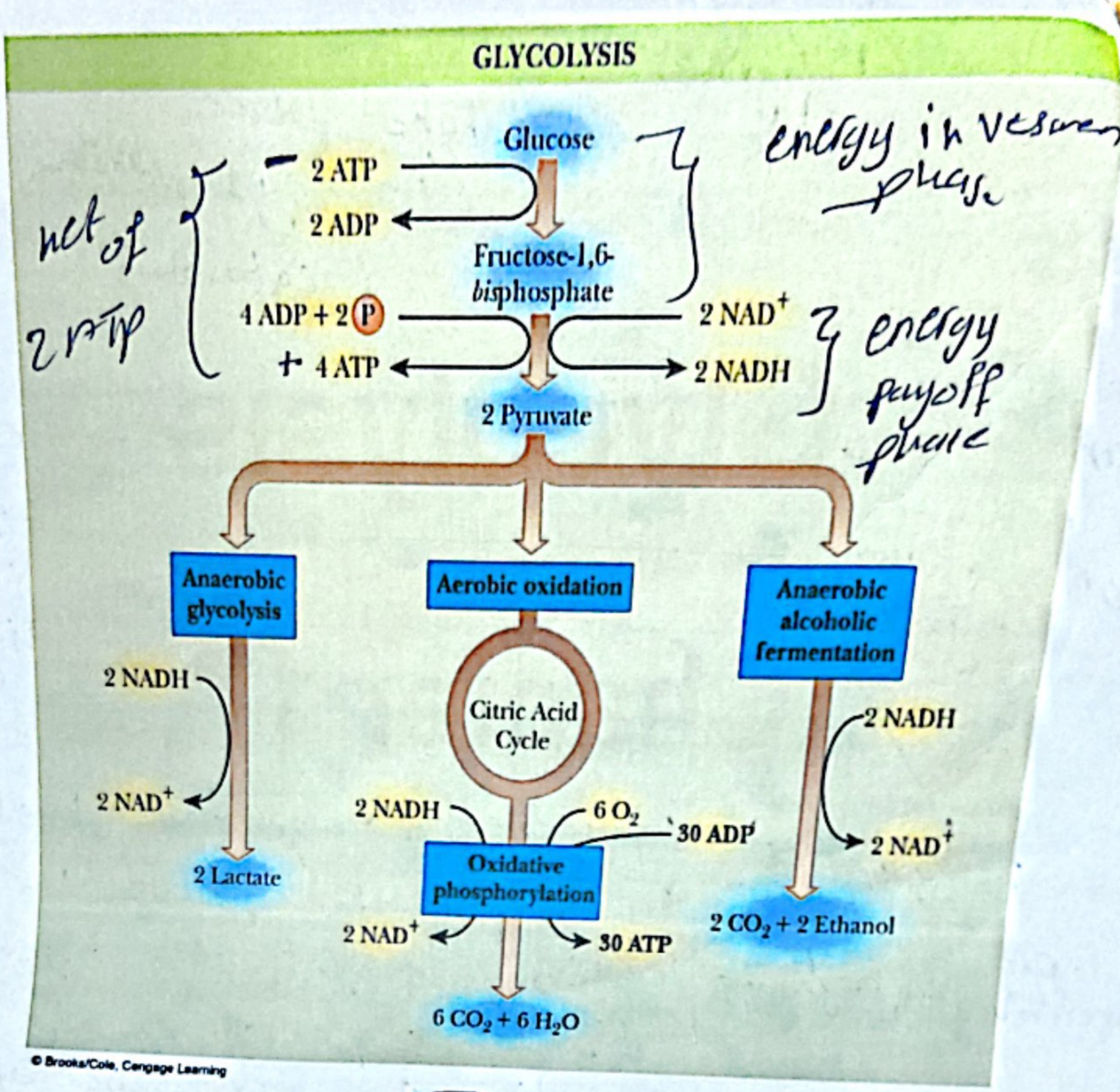
Fates of Pyruvate From Glycolysis



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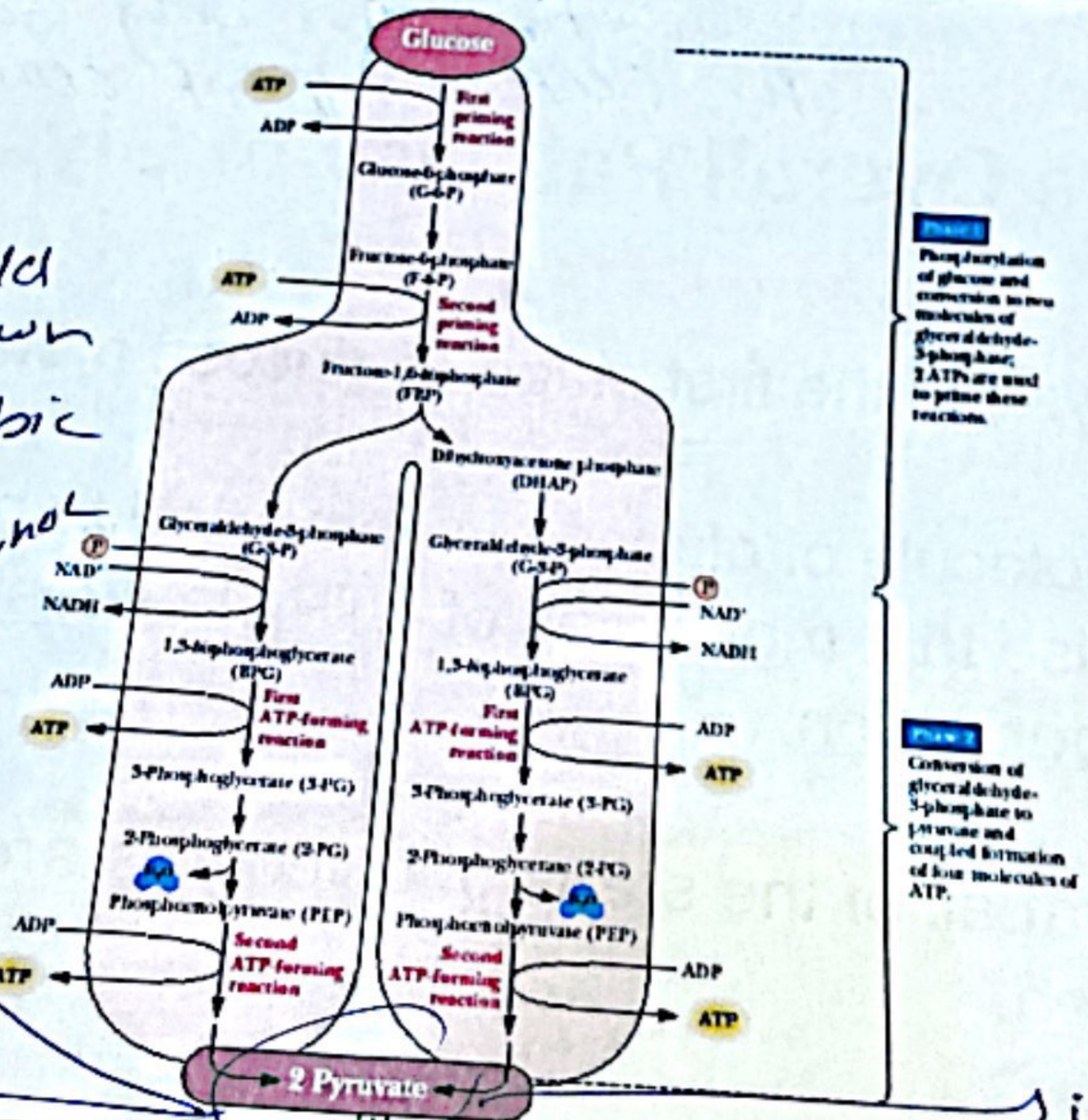
pyruvate could be broken down under anaerobic conditi to lactate or ethanol

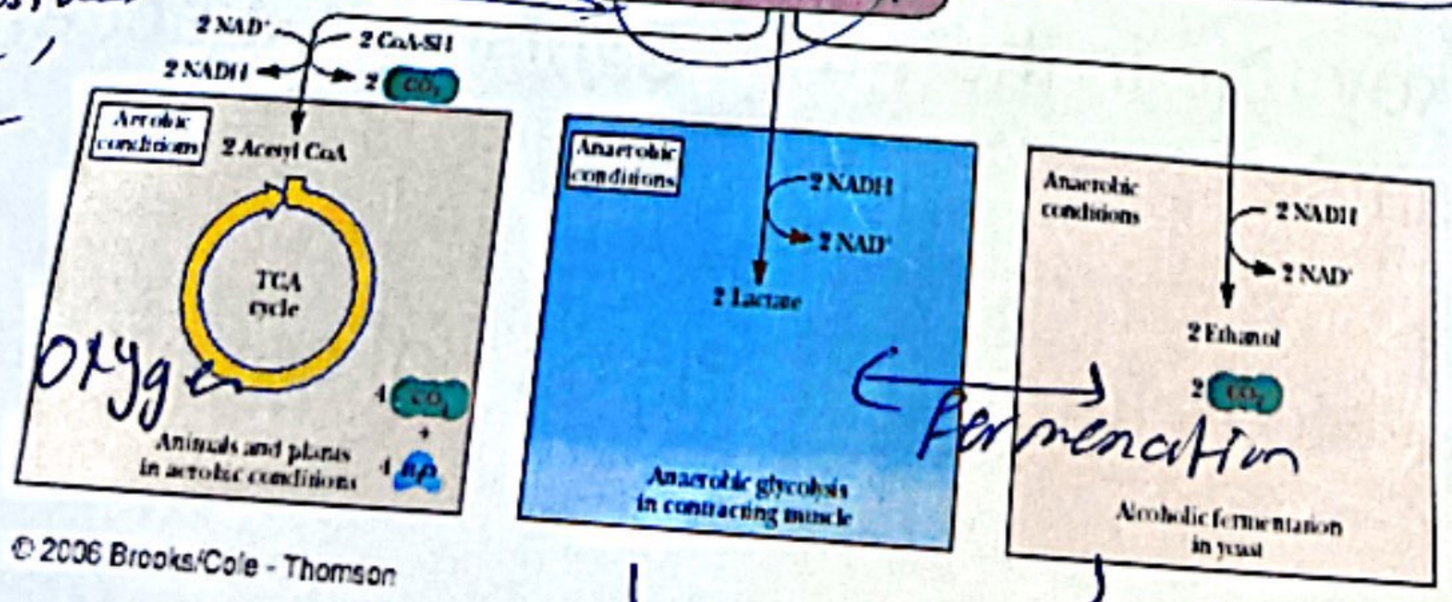


Phase 1: Phosphorylation of glucose and conversion to two molecules of glyceraldehyde-3-phosphate; 2 ATPs are used to prime these reactions.

Phase 2: Conversion of glyceraldehyde-3-phosphate to pyruvate and coupled formation of four molecules of ATP.

could be used to make alanine, lysine, isoleucine, valine

once it's produced it could be further oxidized through TCA cycle & the conversion of pyruvate to acetyl CoA through enzyme pyruvate dehydrog



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absence of oxygen

Fig. 17-2, p.465

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lation of glucose to give glucose

n of glucose-6-phosphate to give **fructose-**

on of fructose-6-phosphate to yield
hosphate

se-1,6,-bisphosphate to give DHAP
phosphate and dihydrooxyacetone

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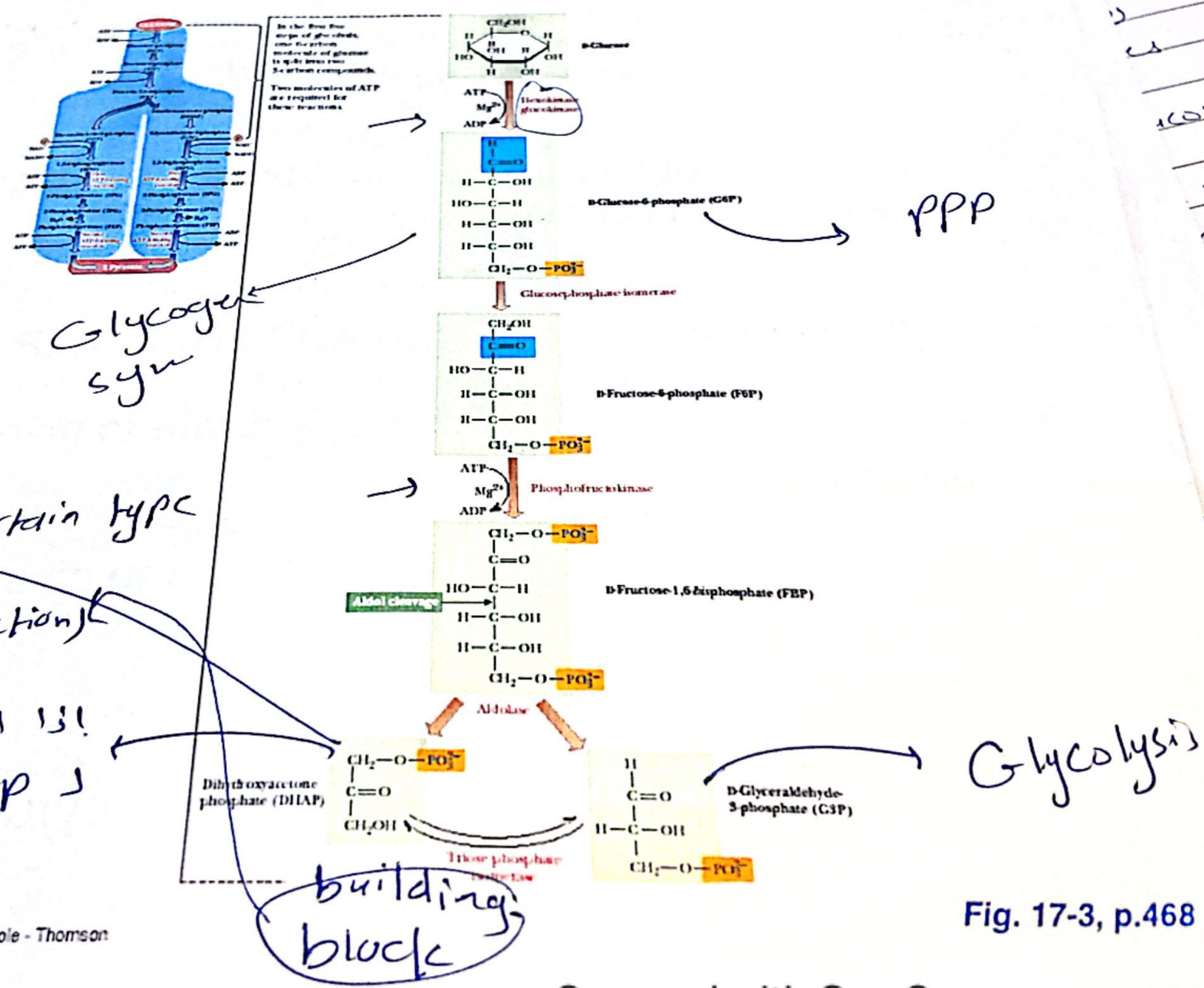

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Fig. 17-3, p.468

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* If the cell need to stop Glycolysis because there is a lot of energy, the cell will stop enzymes catalize 1, 3, 10

Table 17.1

The Reactions of Glycolysis and Their Standard Free-Energy Changes

Step	Reaction	Enzyme	$\Delta G^{\circ\prime}$ kJ mol^{-1}	$\Delta G^{\circ\prime}$ kcal mol^{-1}	ΔG^{**} kJ/mol
1	Glucose + ATP → Glucose-6-phosphate + ADP	Hexokinase/Glucokinase	−16.7	−4.0	−33.9
2	Glucose-6-phosphate → Fructose-6-phosphate	Glucose phosphate isomerase	+1.67	+0.4	−2.92
3	Fructose-6-phosphate + ATP → Fructose-1,6-*bis*phosphate + ADP	Phosphofructokinase	−14.2	−3.4	−18.8
4	Fructose-1,6-*bis*phosphate → Dihydroxyacetone phosphate + Glyceraldehyde-3-phosphate	Aldolase	+23.9	+5.7	−0.23
5	Dihydroxyacetone phosphate → Glyceraldehyde-3-phosphate	Triose phosphate isomerase	+7.56	+1.8	+2.41
6	2(Glyceraldehyde-3-phosphate + NAD^+ + P_i → 1,3-*bis*phosphoglycerate + NADH + H^+)	Glyceraldehyde-3-P dehydrogenase	2(+6.20)	2(+1.5)	2(−1.29)
7	2(1,3-*bis*phosphoglycerate + ADP → 3-Phosphoglycerate + ATP)	Phosphoglycerate kinase	2(−18.8)	2(−4.5)	2(+0.1)
8	2(3-Phosphoglycerate → 2-Phosphoglycerate)	Phosphoglyceromutase	2(+4.4)	2(+1.1)	2(+0.83)
9	2(2-Phosphoglycerate → Phosphoenolpyruvate + H_2O)	Enolase	2(+1.8)	2(+0.4)	2(+1.1)
10	2(Phosphoenolpyruvate + ADP → Pyruvate + ATP)	Pyruvate kinase	2(−31.4)	2(−7.5)	2(−23.0)
Overall	Glucose + 2 ADP + 2 P_i + NAD^+ → 2 Pyruvate → 2 ATP + NADH + H^+		−73.3	−17.5	−98.0
	2 Pyruvate + NADH + H^+ → Lactate + NAD^+	Lactate dehydrogenase	2(−25.1)	2(−6.0)	2(−14.8)
	Glucose + 2 ADP + 2 P_i → 2 Lactate + 2 ATP		−123.5	−29.5	−127.6

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are control points of this pathway

1, 3, 10 → these reactions have large negative ΔG, other reactions they have small ±ΔG (around zero), these 3 reactions are far from equili. & irreversible & can be only rever. by different enzymes

irreversible far from equili

Table 17-1, p.469

Conversion of Glucose to Glyceraldehyde-3-Phosphate

- In step 1 of glycolysis, glucose is phosphorylated to give glucose-6-phosphate

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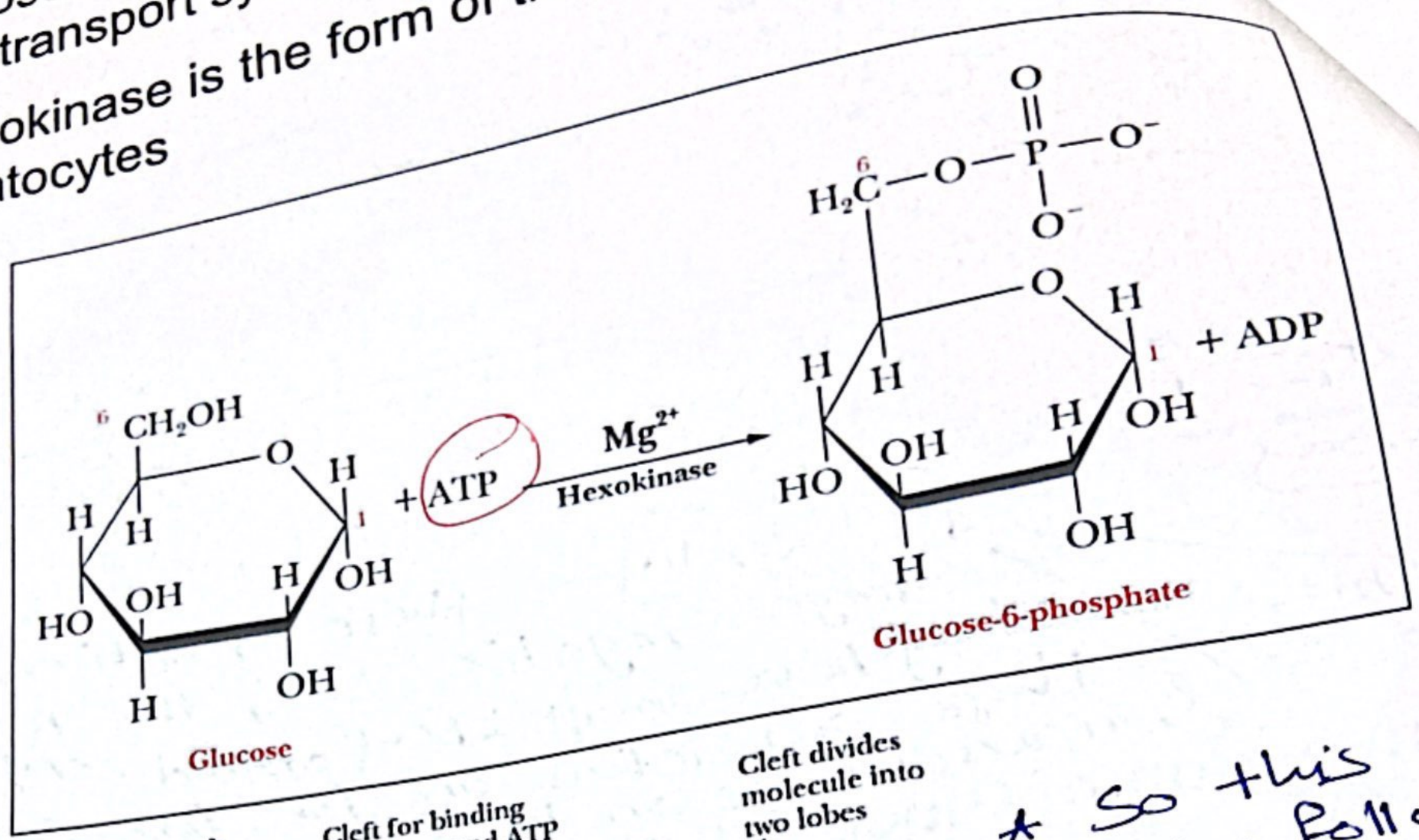
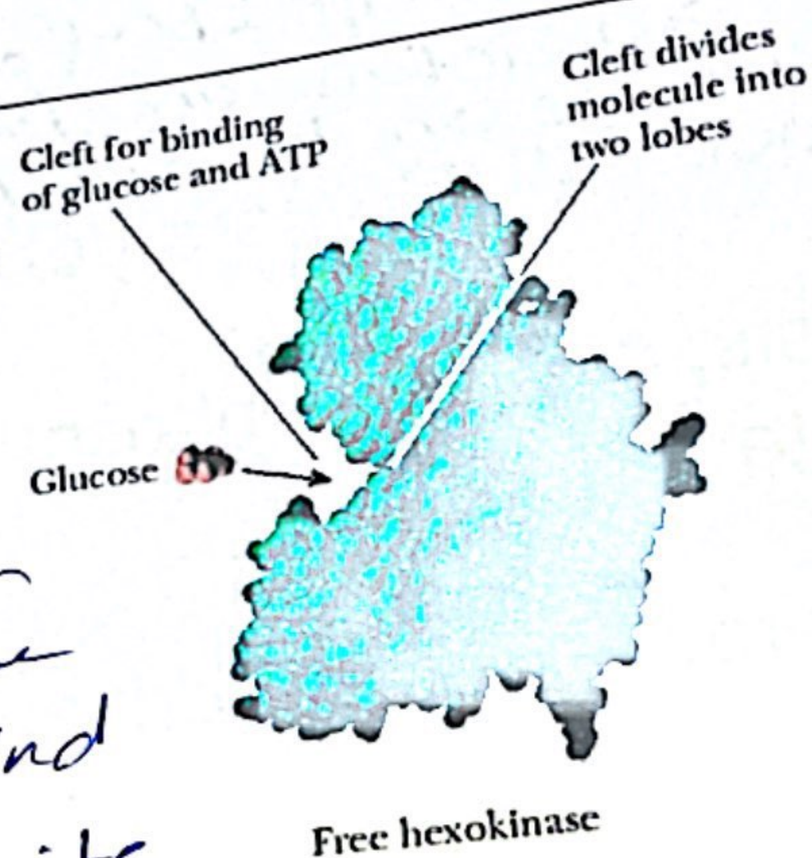
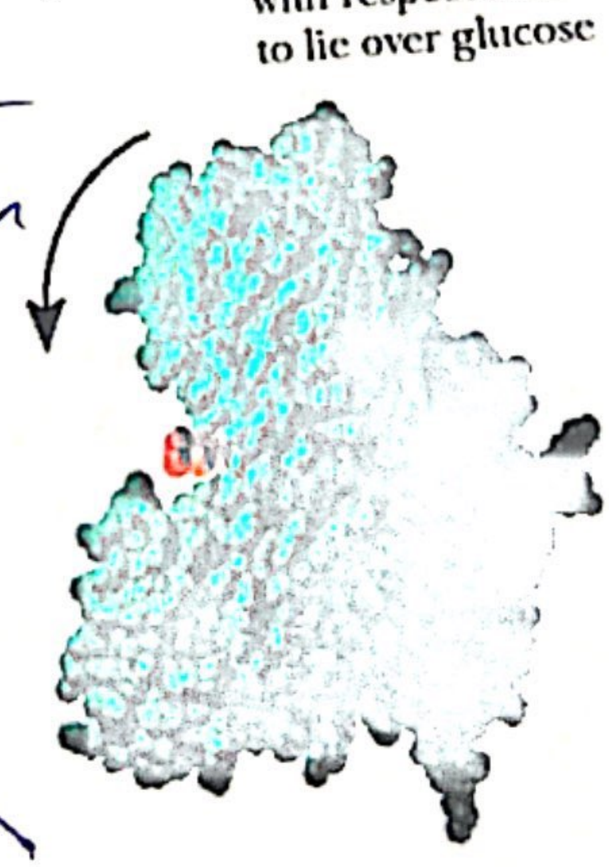
- The phosp
glucose into an an
lack transport systems for p
- Glucokinase is the form of the enzyme
hepatocytes



*This enzyme is made of 2 major lobes & the active site in middle between lobes, so the Glucose go & bind in the active site that is between the 2 lobes, once the Glucose bind the 2 lobes close on each other, & now we have "



* So this enzyme follows the induced-fit model of enzyme catalysis



Hexokinase–glucose complex

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Phosphofructokinase is a key regulatory enzy

- **Phosphofructokinase (PFK):** one of the key enzyme of Glycolysis
- Exists as a tetramer and subject to allosteric feedback regulation
- The tetramer is composed of L and M subunits
  - M_4, M_3L, M_2L_2, ML_3, and L_4 all exist. Combinations of these subunits are called Isozyme
  - Muscles are rich in M_4; the liver is rich in L_4
- ATP is an allosteric effector;
  - high levels inhibit the enzyme
  - low levels activate it
- Fructose-1,6-bisphosphate is also an allosteric effector

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Summary

- In the first stages of glycolysis, glucose is con
to two molecules of glyceraldehyde-3-phosphat
2 ATP molecule are lost
- The key intermediate in this series of reactions is fructose-1,6-bisphosphate.
- The enzyme that catalyzes this reaction, phosphofructokinase, is subject to allosteric control

Phase II starts (payoff phase)
Glyceraldehyde-3-Phosphate is converted to Pyruvate

- The first reaction that begins the conversion to pyruvate involves the oxidation of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate
- This reaction involves addition of a phosphate group, as well as an electron transfer reaction from glyceraldehyde-3-phosphate to NAD^+
- The **oxidizing** agent, NAD^+, is **reduced** to NADH
- Mixed anhydride of two acid by loss of W

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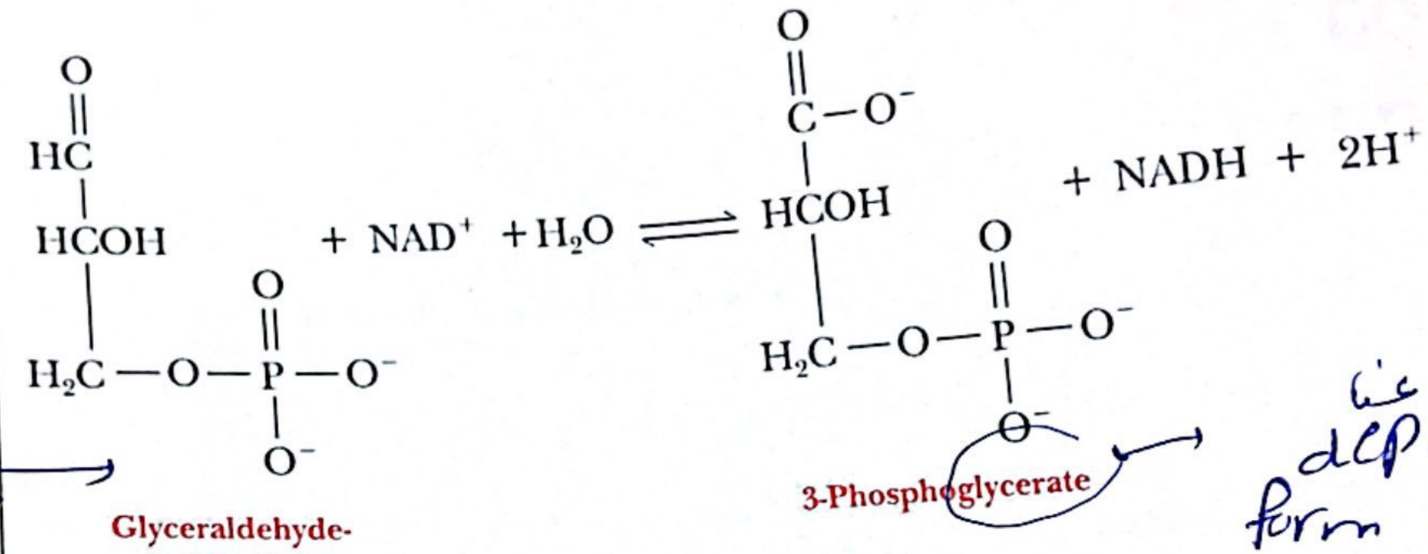
Oxidation and Phosphorylation Reactions

at same time

1. Oxidation of glyceraldehyde-3-phosphate ($\Delta G^{\circ\prime} = -43.1$ kJ mol^{-1} = -10.3 kcal mol^{-1})



enzyme Dehydrogenase

i.e deprotonated form of carboxylic acid of Glycerol

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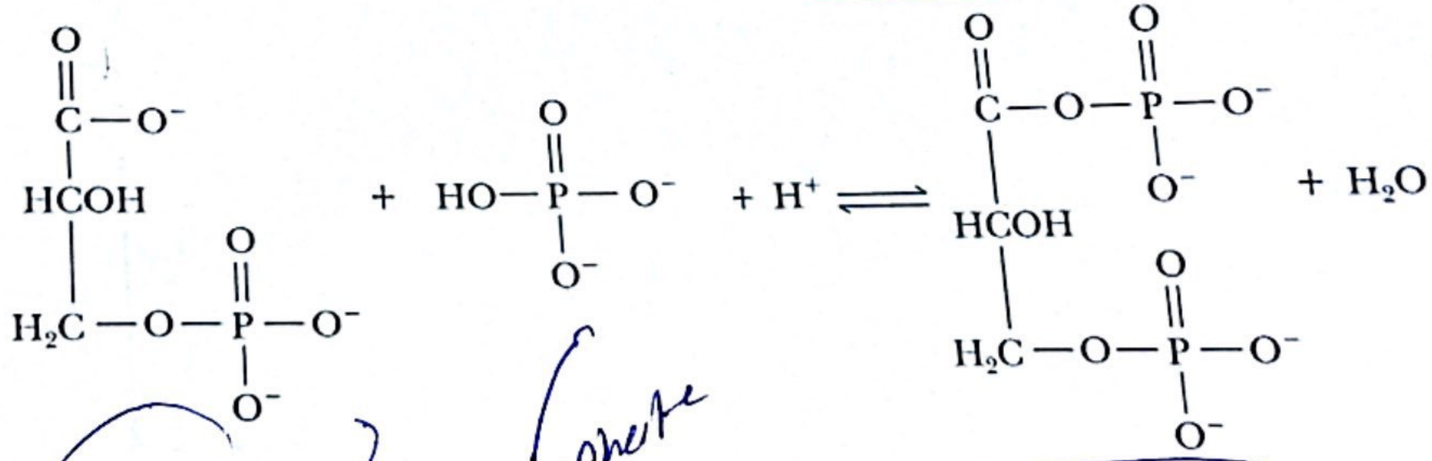
2. Phosphorylation of 3-phosphoglycerate ($\Delta G^{\circ\prime} = 49.3$ kJ mol^{-1} = 11.8 kcal mol^{-1})



phosphate group

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هذا هاد molecule جاهز لكسر واحد من P

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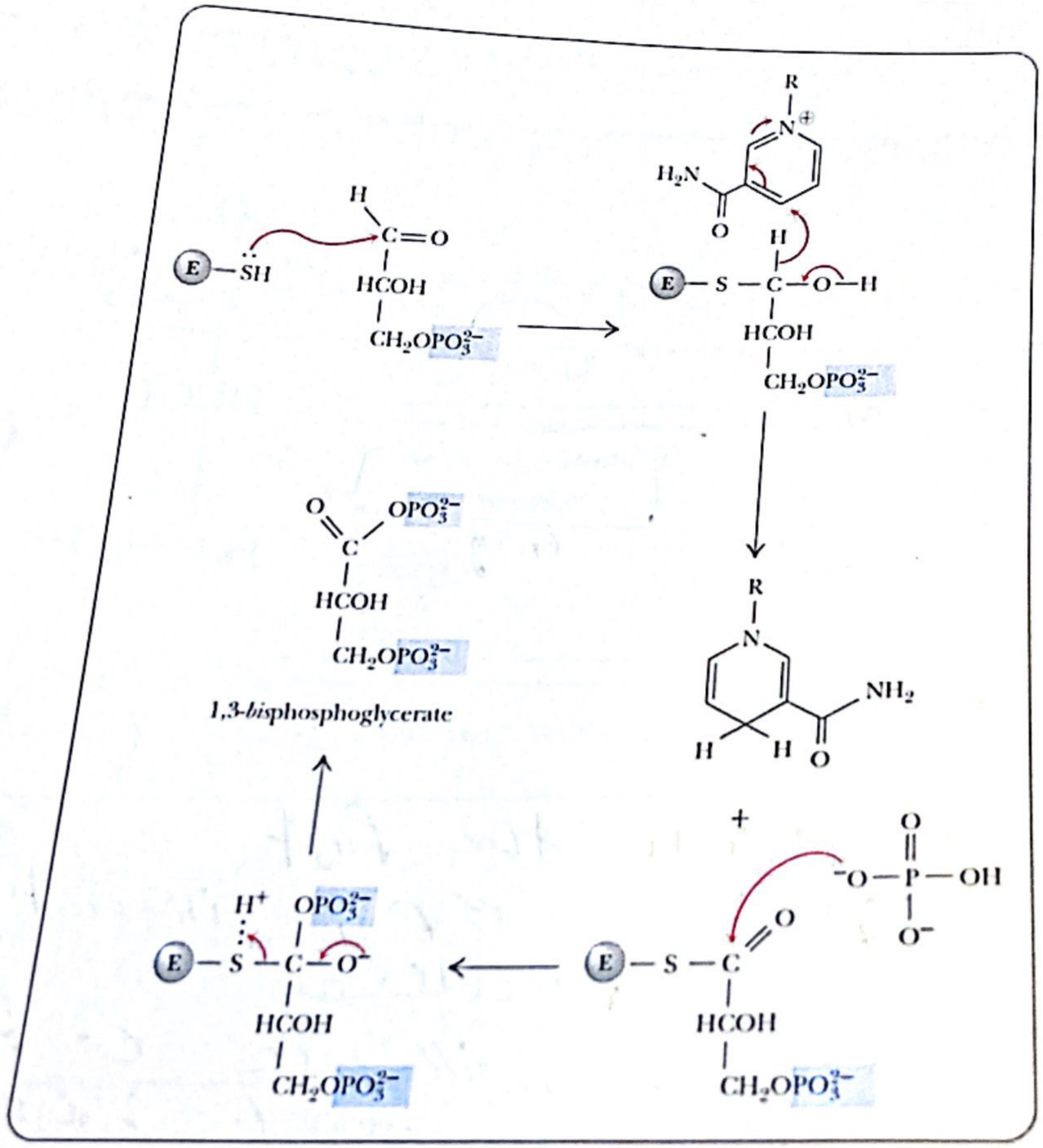
Cysteine's Role in Glyceraldehyde-3-phosphate Dehydrogenase

CO



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هنو
thiol
Group in
active site
وهاد بتايود وهاد
oxidation of
Glyceraldehyde
3-phosphate
into 3phospho-
Glycerate

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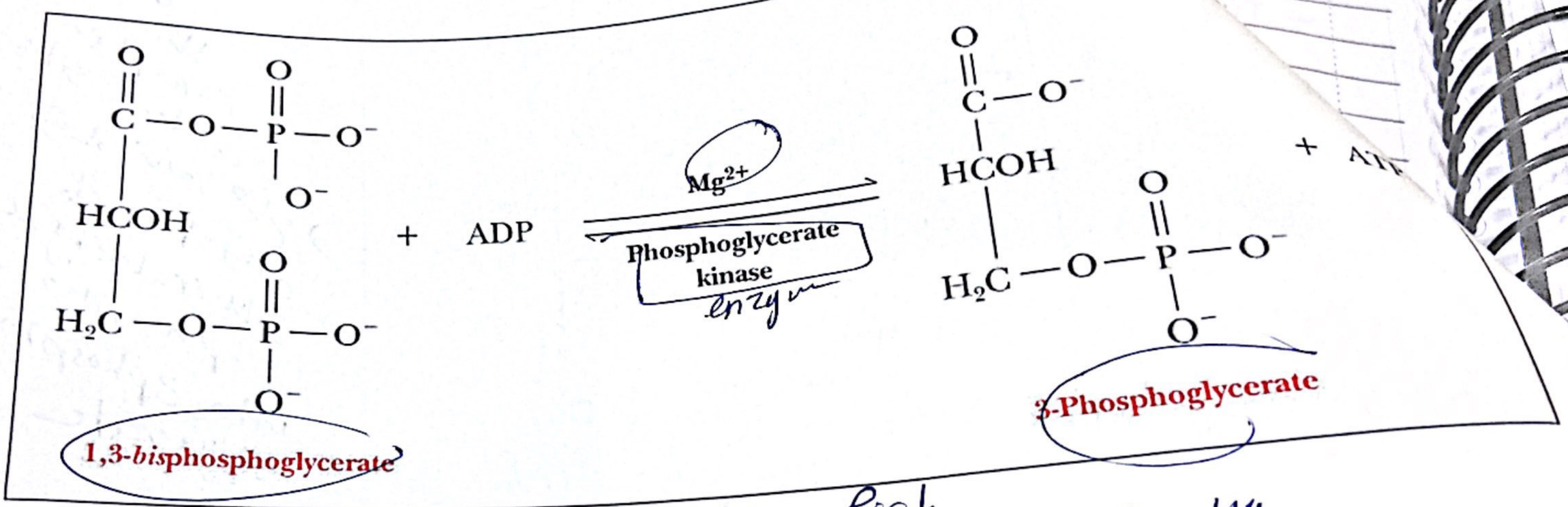
Glyceraldehyde-3-Phosphate to Py



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This is the first step where ATP is actually produced

enzyme will use Mg^{+2} (co factor كوفاكتور ATP, ADP)

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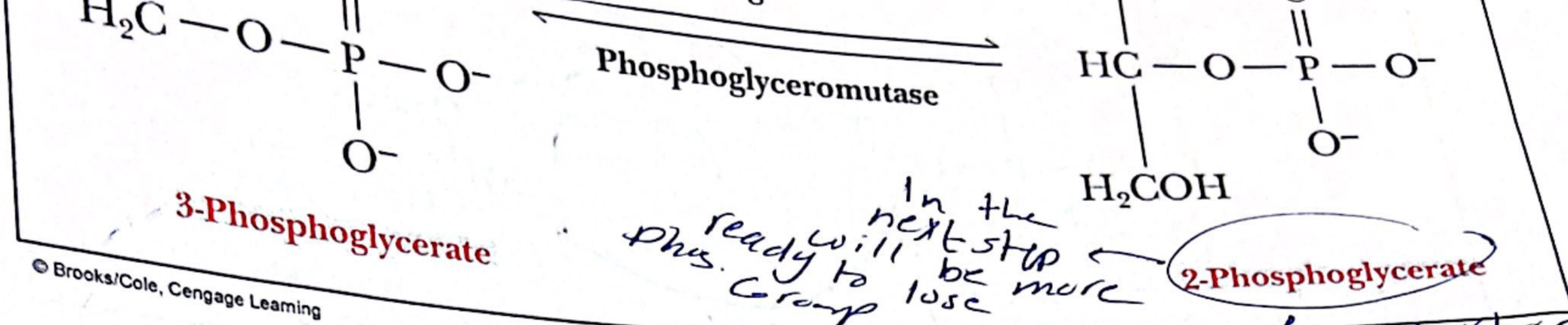


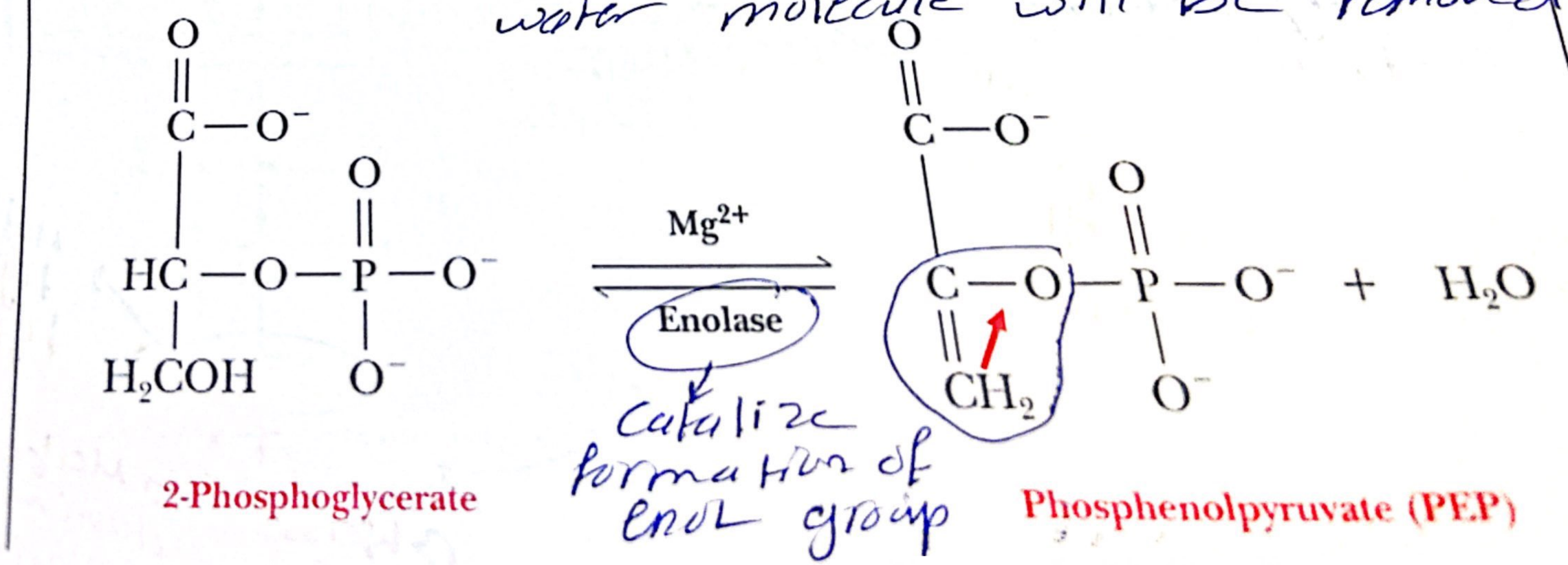
In the next step phos. Group will be more ready to lose

→ Moving phosphate group from carbon number 3 to 2, puts the negative charge of phosphate very close to carboxylic acid (not stable)

Glyceraldehyde-3-Phosphate to Pyruvate

- Next, 2-phosphoglycerate loses one molecule of water, producing **Phosphoenolpyruvate**
  - **It is just dehydration rxn**
- Enolase catalyzes the reaction and requires a Mg as cofactor
- Phosphoenolpyruvate contains a high energy bond

→ Dehydration reaction because water molecule will be removed



catalize formation of enol group

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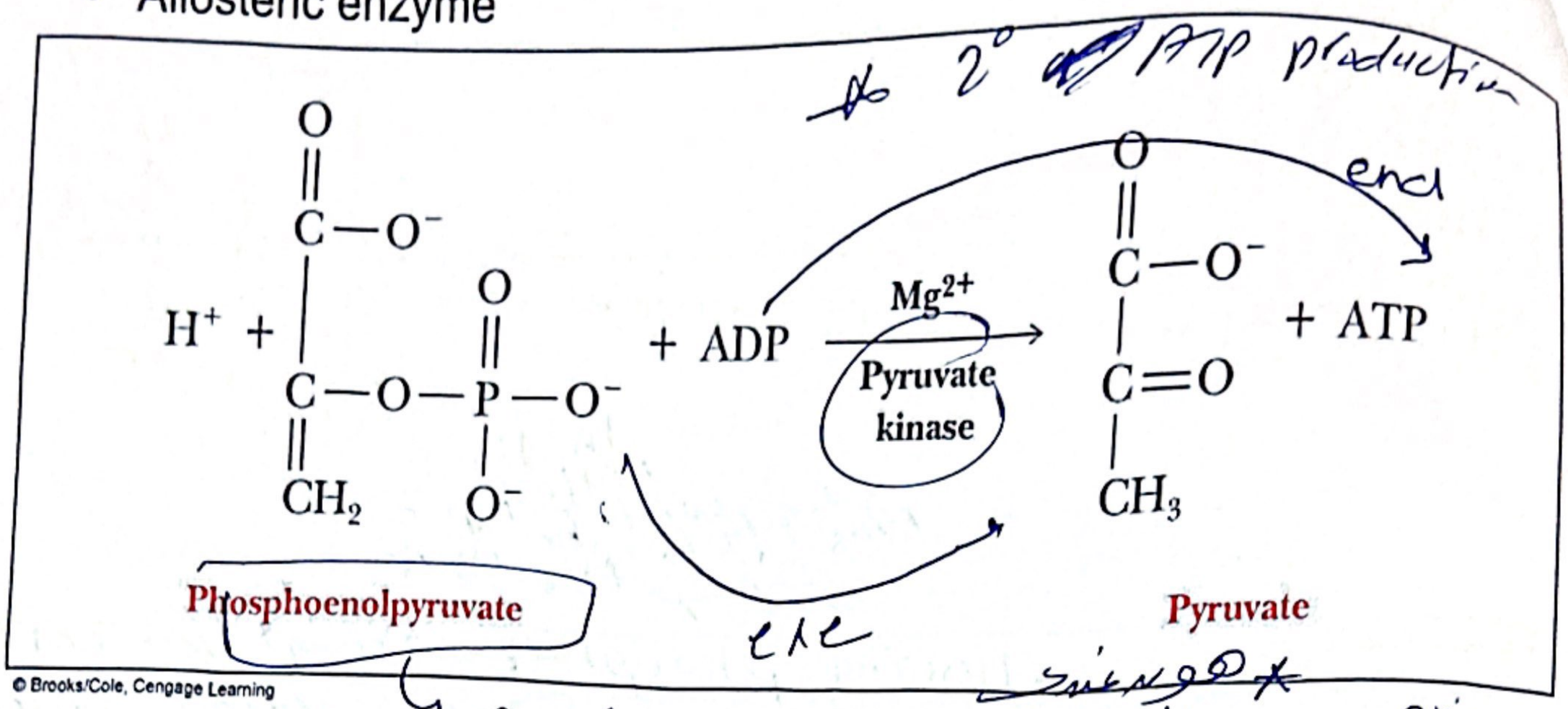
- Reaction is catalyzed by pyruvate kinase
  - Allosteric enzyme

to 2° ATP production



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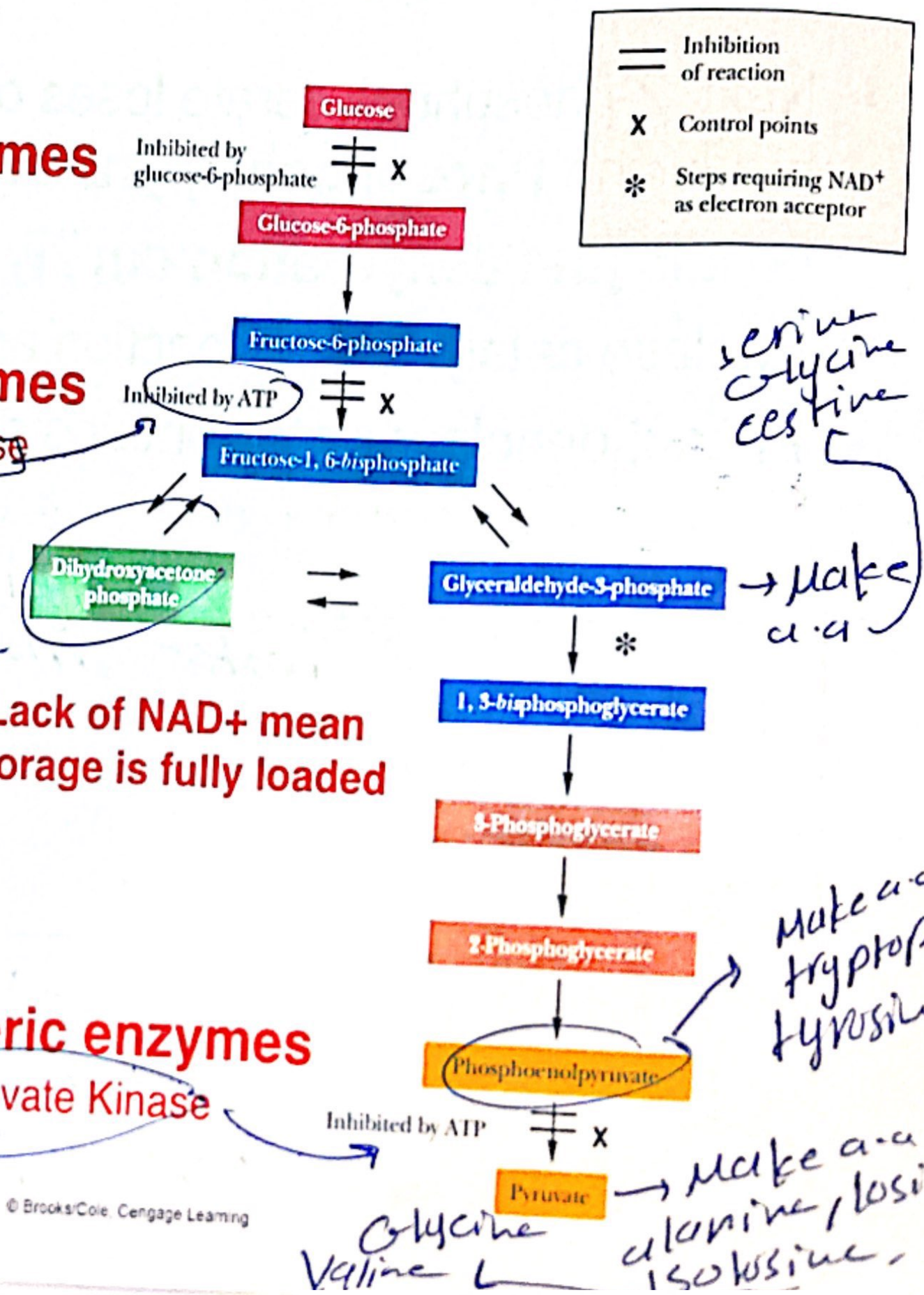
can loss phos.

energy reaction coupling

- exergonic reaction releases energy

Control Points in Glycolysis



Allosteric enzymes

Hexokinase

activity inhibited by Glucose-6-phosphate

Allosteric enzymes

Phosphofrectokinase

enzymes that catalize control points their activity could be controled

Lack of NAD+ mean storage is fully loaded

could be used to make certain type of lipids

serine glycine cestine

make a.a

Allosteric enzymes

Pyruvate Kinase

make a.a tryptophan tyrosine

make a.a alanine, lesine isolesine.

Glycine Valine

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...n of two ATP for each glucose

- There are three control points in the glycolytic pathway

Last the end of Glycolysis
what being made so far
is 2 ATP, 2 NADH
2 pyruvate (6 carbon
Glycolysis)

Phosphoenolpyruvate → Pyruvate + Pi $\Delta G^{\circ\prime}$ = - 61.9 kJ mol^{-1} = - 14.8 kcal mol^{-1}

ADP + Pi → ATP $\Delta G^{\circ\prime}$ = +30.5 kJ mol21 = + 7.3 kcal mol^{-1}

The net reaction is:

Phosphoenolpyruvate + ADP → Pyruvate + ATP

$\Delta G^{\circ\prime}$ = - 31.4 kJ mol^{-1} = - 7.5 kcal mol^{-1}

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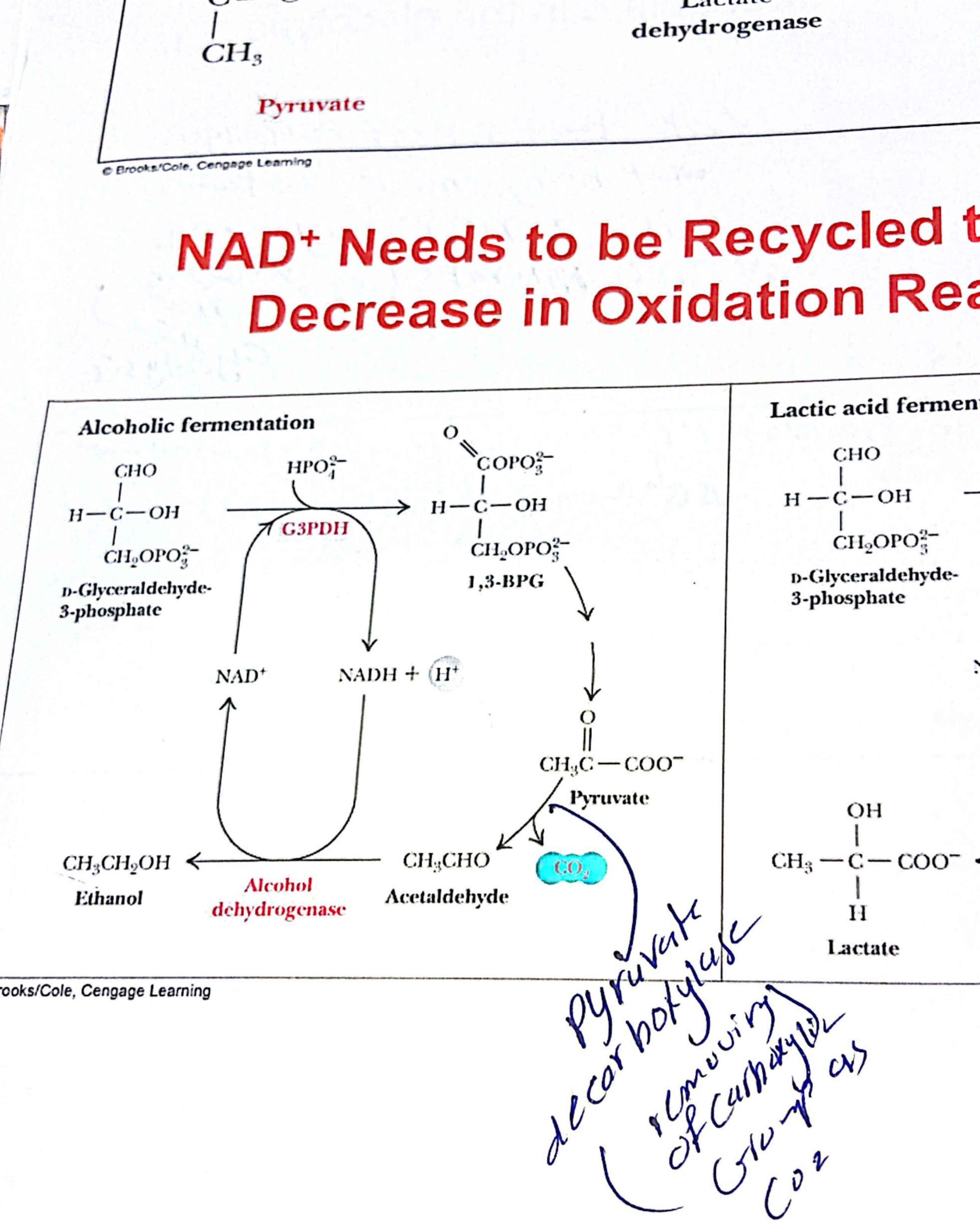

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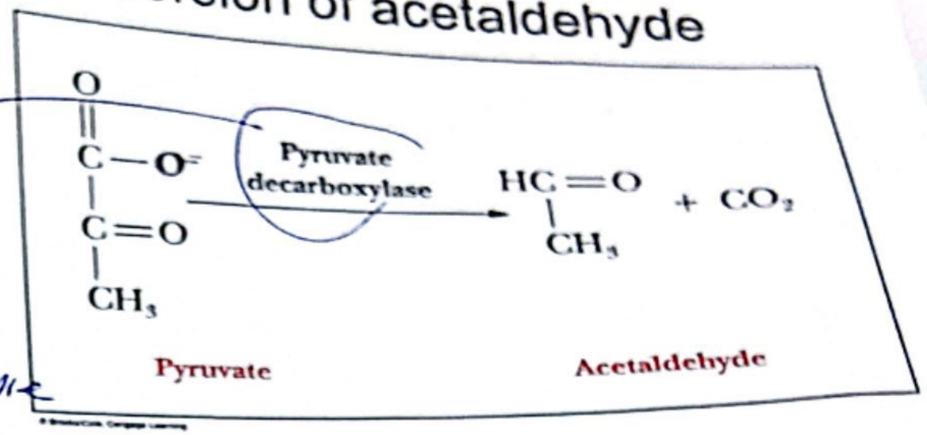
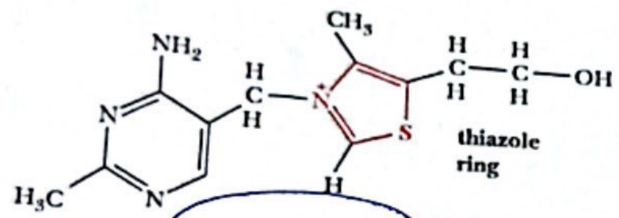
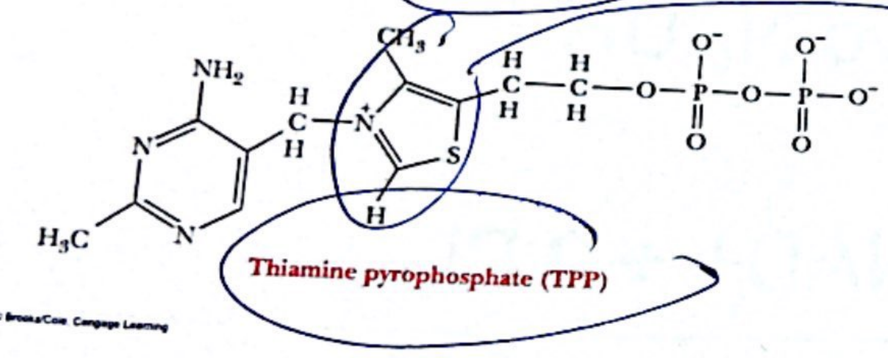
to ethanol ydrogenase catalyzes the conversion of acetaldehyde



the Require Co-factor Mg2+ & Co enzyme Thiamine pyrophosphate

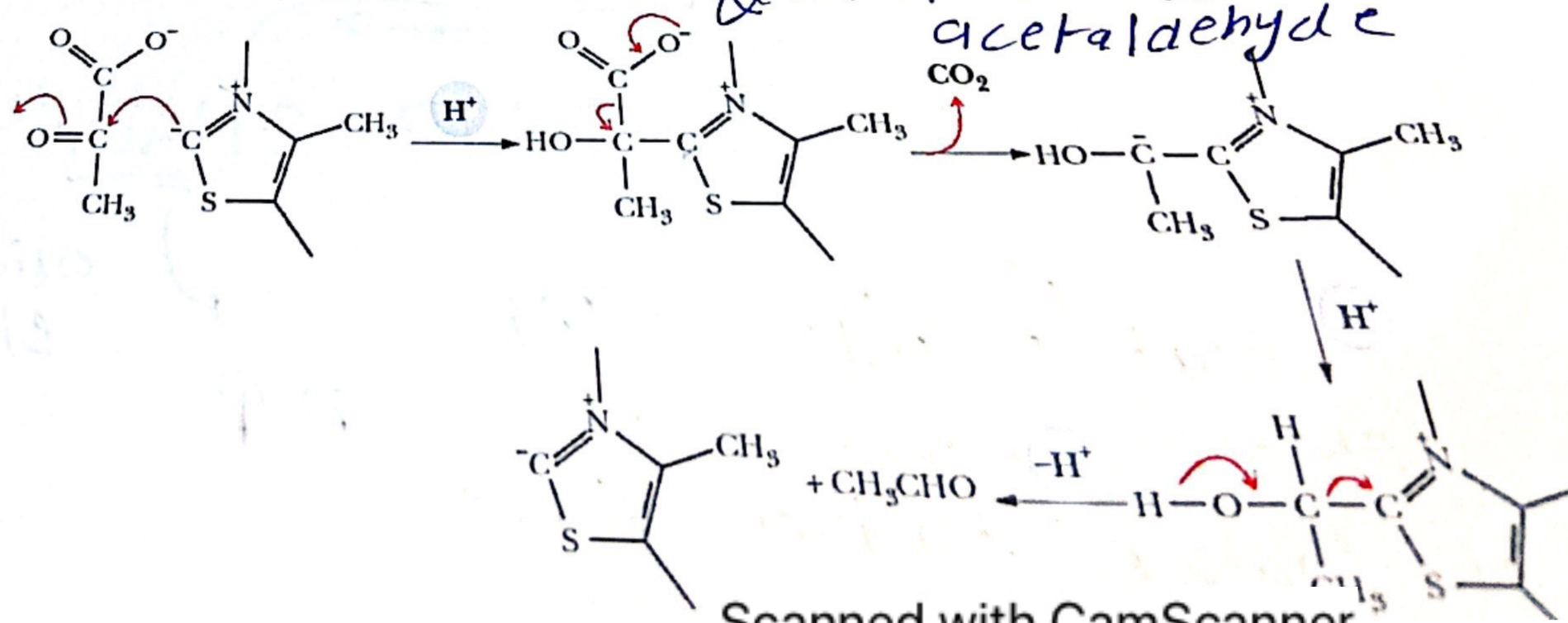
Structures of Thiamine and TPP





This ring allows the enzyme to attack the carbonyl Group in the middle of pyruvate & then the bond will be broke releasing the Carbon as co2 & what will remain is acetaldehyde

imp. عاقد يستعمل decarboxylase بدون



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The Energy Derived from Glucose Oxidation

- *Aerobic glycolysis* of glucose to pyruvate, *requires* two ATP to activate the process, with *production of four* ATP and two NADH.

Glucose + 2 ADP + 2 NAD+ + 2 Pi

4e

----->

2 Pyruvate + 2 ATP + 2 NADH + 2 H+

contain high energy electrons which mean it could be further oxidize to produce more ATP

ATP

oxidative Phospho. / electron transpo. chain

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