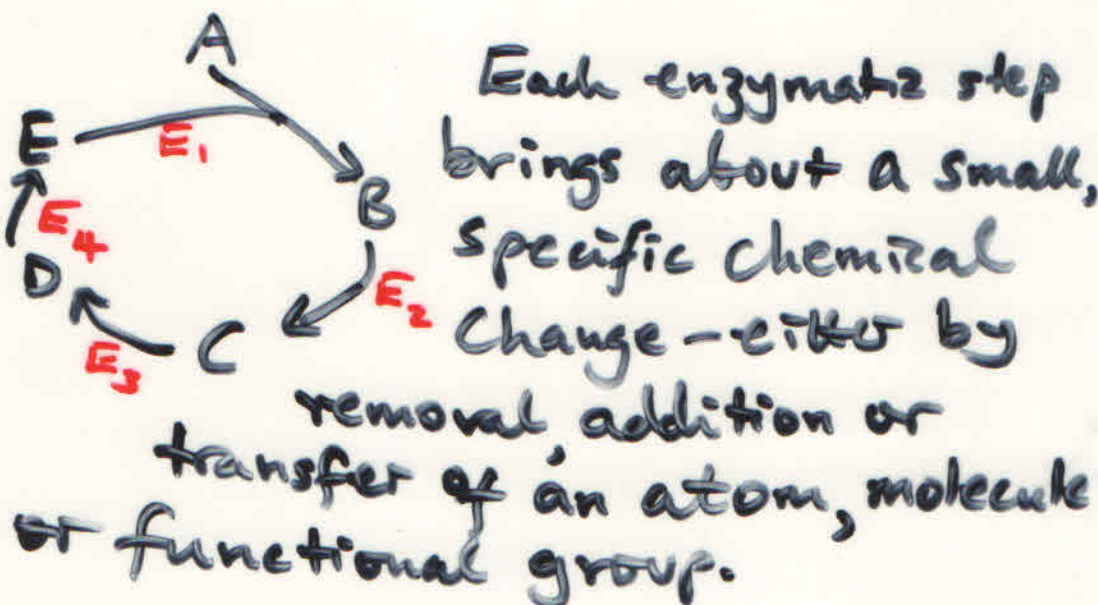
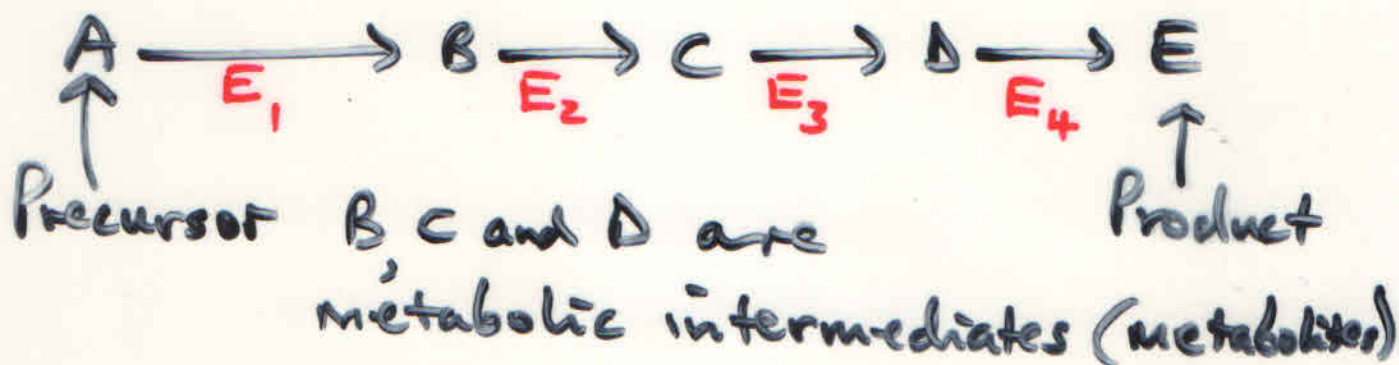


A SURVEY OF METABOLISM

①

1. Basically, metabolism is the synthesis and degradation of cell components. It involves pathways that are promoted by a sequence of enzyme systems. Enzymes participate sequentially in a consecutive, linked fashion so that the product of the 1st enzyme becomes the substrate of the 2nd enzyme and so on.

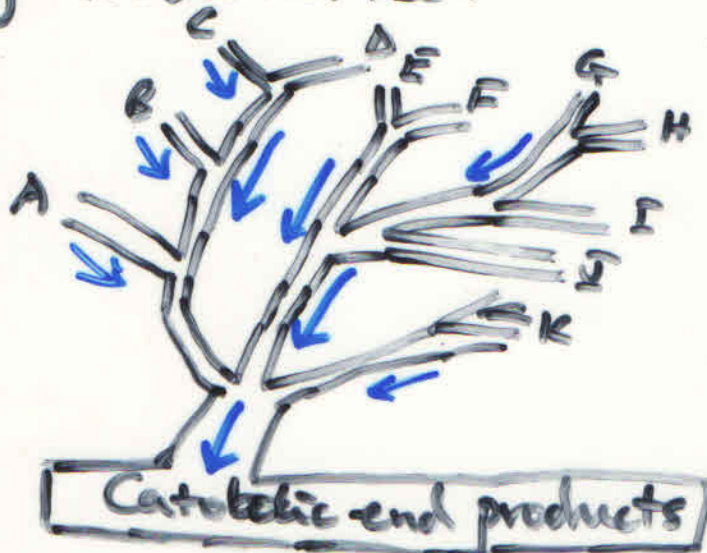
The pathway may be linear or circular or cyclic.



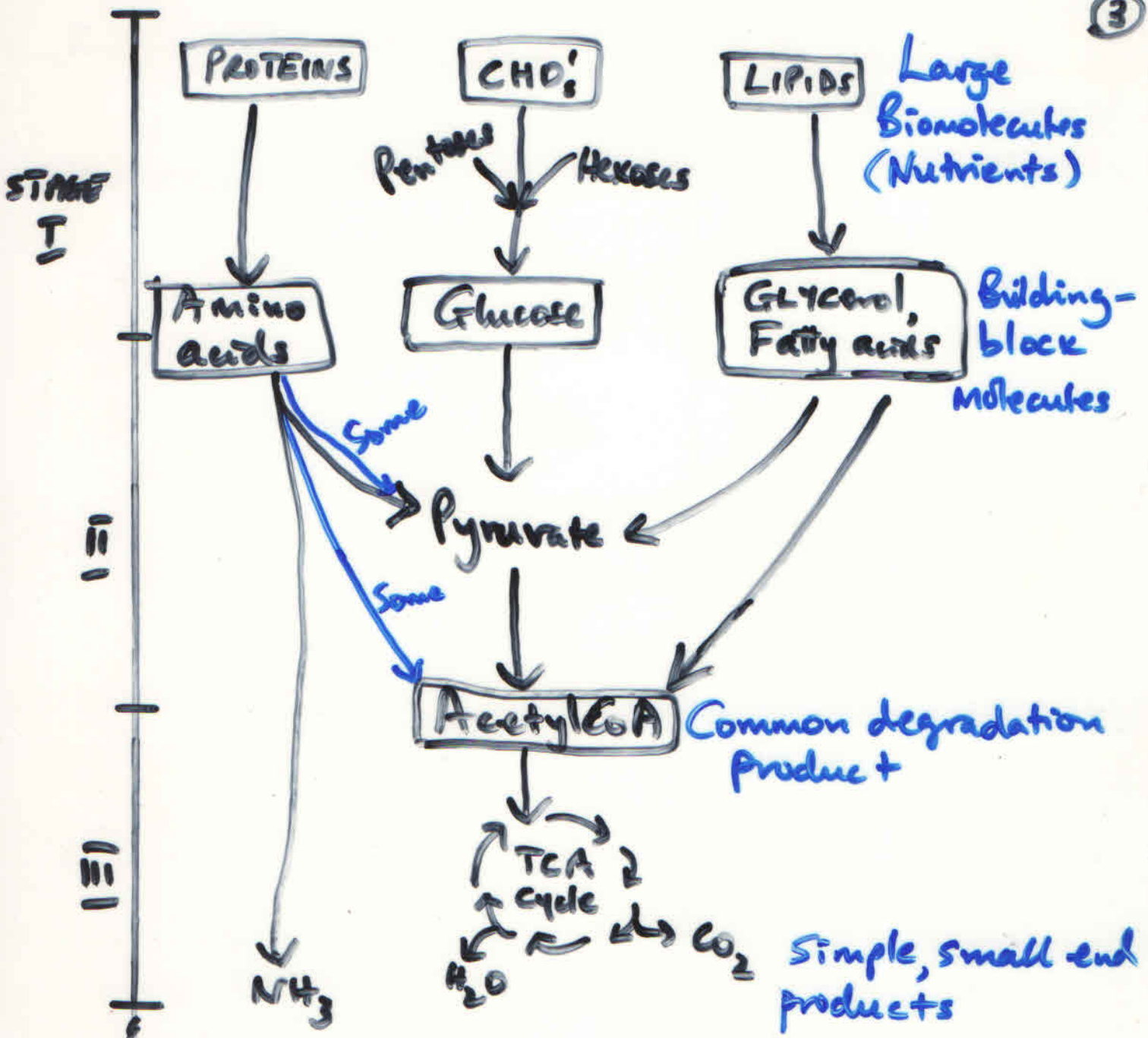
2. Metabolism consists of catabolic and anabolic pathways. (2)

(a) Catabolism

It is the degradative phase in which organic nutrients e.g. CHO , lipids and proteins are broken down into smaller, simpler end products e.g. CO_2 , NH_3 , H_2O . Nutrients come from the environment or from the cell's storage. Catabolism is accompanied by release of free energy arising from the organic molecule. Catabolic pathways converge to a few end products. The final pathway resembles a widening river, fed by many tributaries.



The major energy-yielding nutrients are catabolized via 3 stages.



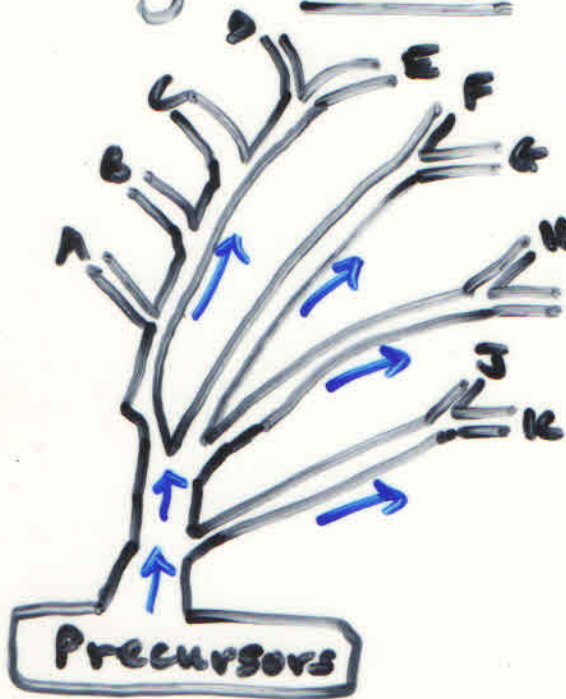
At certain steps in a catabolic pathway, some of the free energy is conserved by means of coupled enzymatic reactions in the form of ATP or NADPH.

Catabolism - It is a "downhill" process that is accompanied by loss of "free" energy - energy that can do work at constant temp. and pressure.

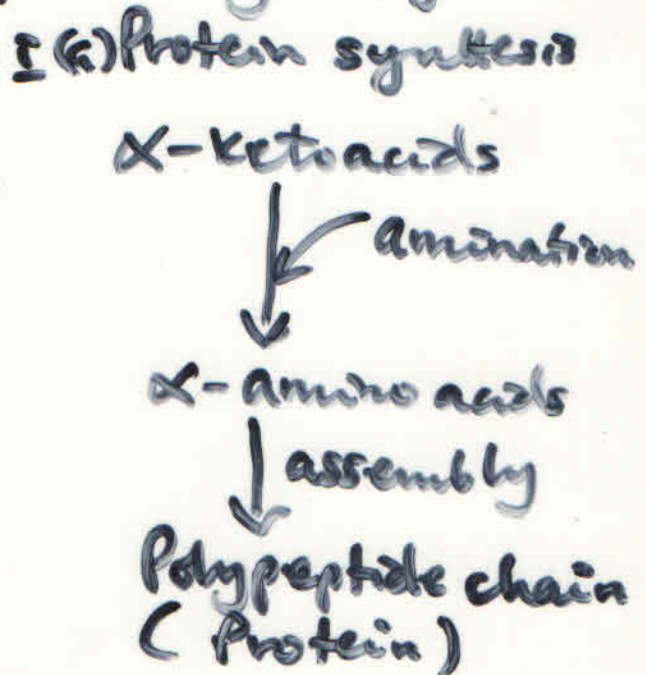
(b) Anabolism

It is the biosynthetic phase of metabolism. Small precursors or building-block molecules are built up into large macromolecules e.g. proteins, Nucleic acids. Anabolism usually results in increased size and complexity of structure. It involves input of free energy furnished by ATP and/or NADPH.

Pathways diverge to yield many products.



Anabolism also occurs in stages e.g.

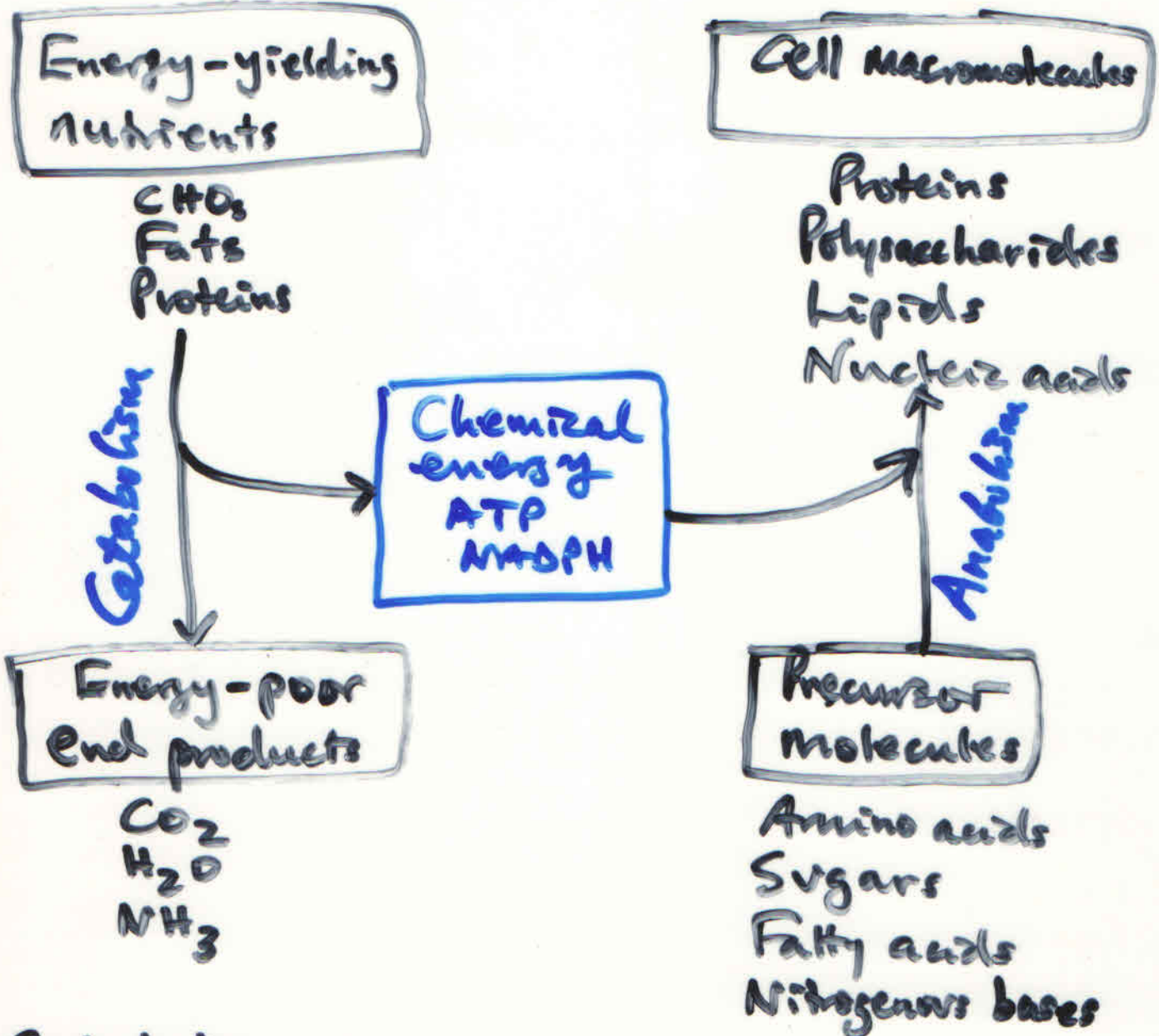


b) Lipid synthesis

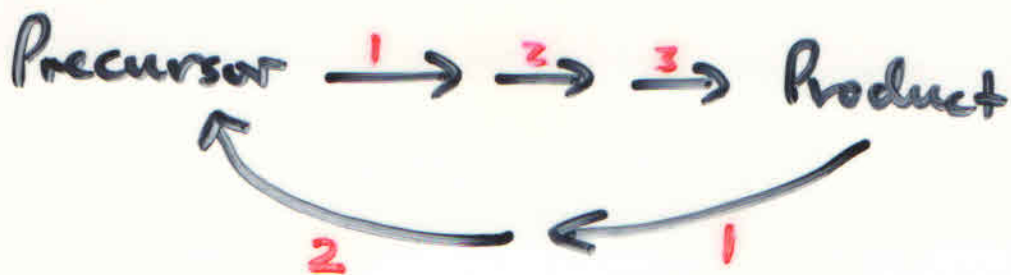


Anabolism - It is a ~~downhill~~ Uphill process requiring input of free energy or gain of free energy.

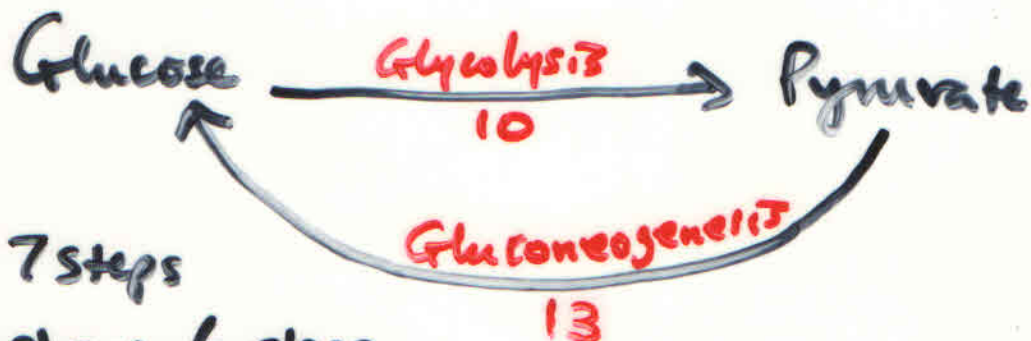
There is an energy-relationship between cataboliz and anaboliz pathways. It is linked by chemical energy in form of ATP and NADPH.



- Catabolism and Anabolism take place simultaneously in cells and their rates are regulated independently.
- * There are important differences between corresponding catabolic and anabolic pathways;



e.g.



Share 7 steps

Do not share 6 steps

\therefore Oppositely directed catabolic and anabolic pathways are not identical. Why?

a) Pathway taken in catabolism may be energetically impossible in anabolism.

"Hill and Boulder Analogy"

b) The two pathways must be independently regulated otherwise slowing one would also slow the other.

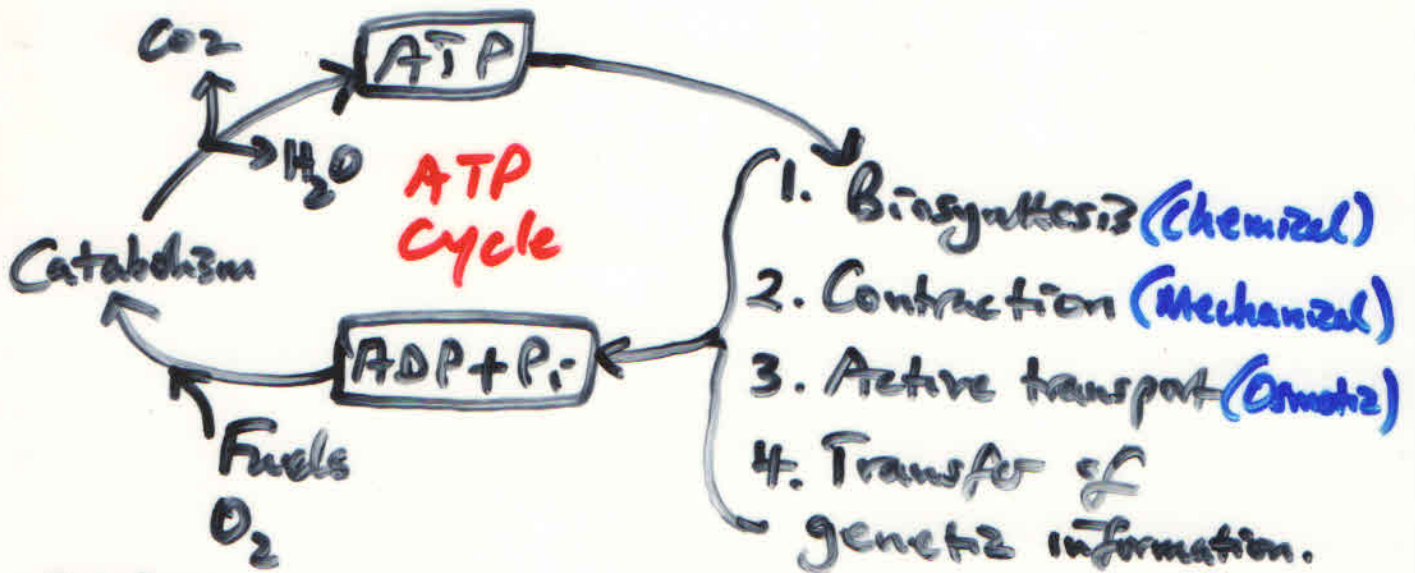


$A \rightarrow B$ and $B \rightarrow A$ are regulated steps — Regulatory enzymes.

c) Opposite catabolic and anabolic routes take place in different parts of the cell. e.g. FA metabolism in liver.

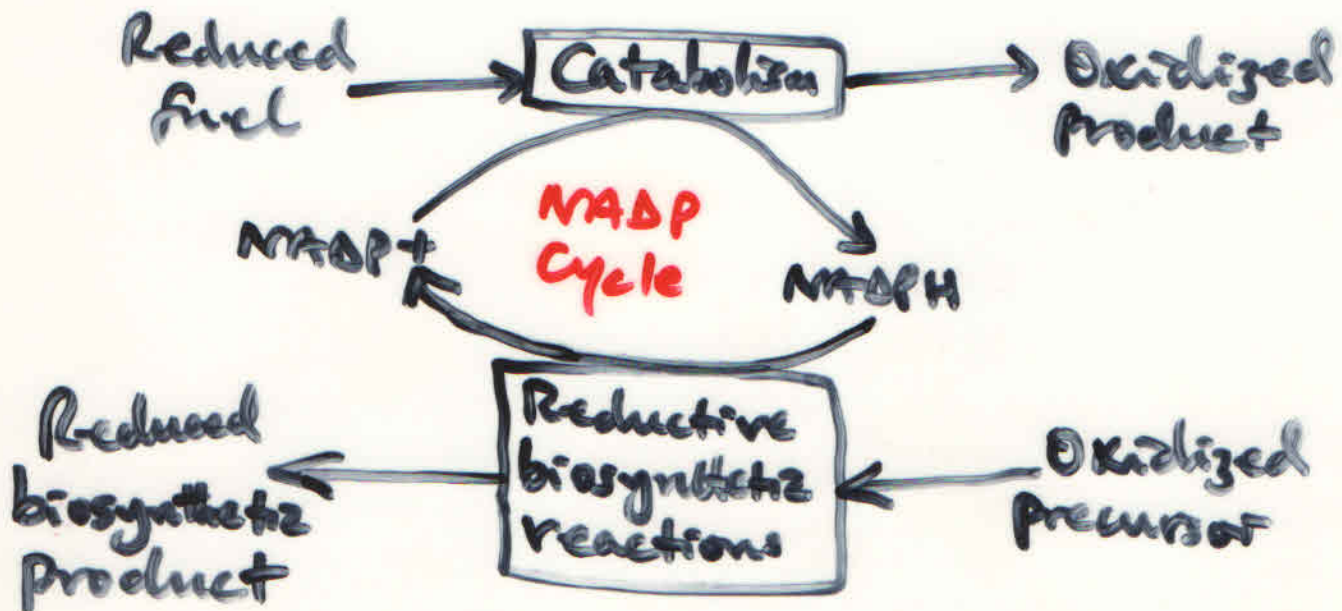
Q. What is the role of ATP and NADPH? ⑦

1. ATP carries energy from catabolism to anabolic reactions.



ATP serves as the energy-carrying link between energy-yielding and energy-requiring cellular processes.

2. NADPH carries energy in form of reducing power. In form of hydrogen atoms or electrons.



Remember:

8

Cell metabolism is an economical, tightly regulated process. Energy is produced as per cell requirements and not by availability or concentration of fuels.

Regulation is at 3 Levels;

1) ~~Allosteric~~ Regulatory enzymes - Catalyse irreversible steps.

e.g. Cataboliz - ATP acts as a regulator or inhibitor of an early step.

Anaboliz - end product acts as an inhibitor of an earlier step.

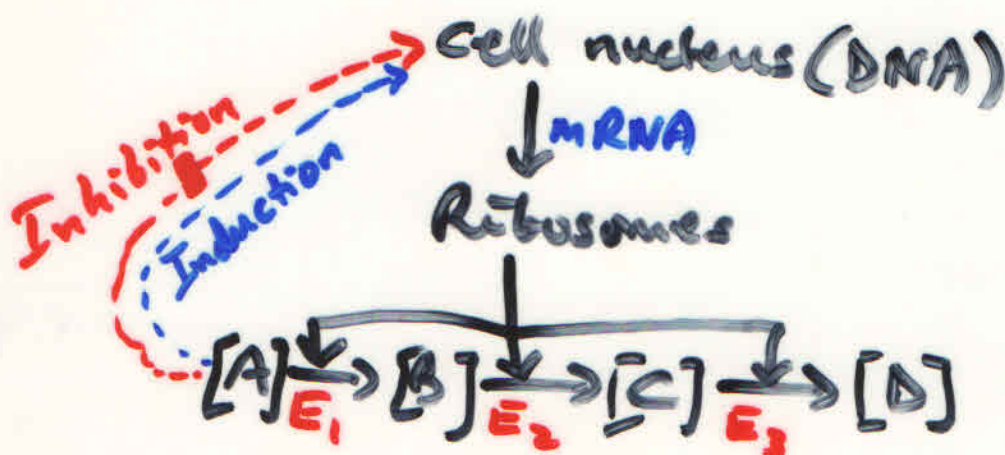
2) Hormonal

e.g. Epinephrine \rightarrow Liver \rightarrow Stimulation of glycogen to glucose raising blood glucose level.

3) [E] in the cell - Induction

e.g. Low protein diet \rightarrow \downarrow [Enzymes]

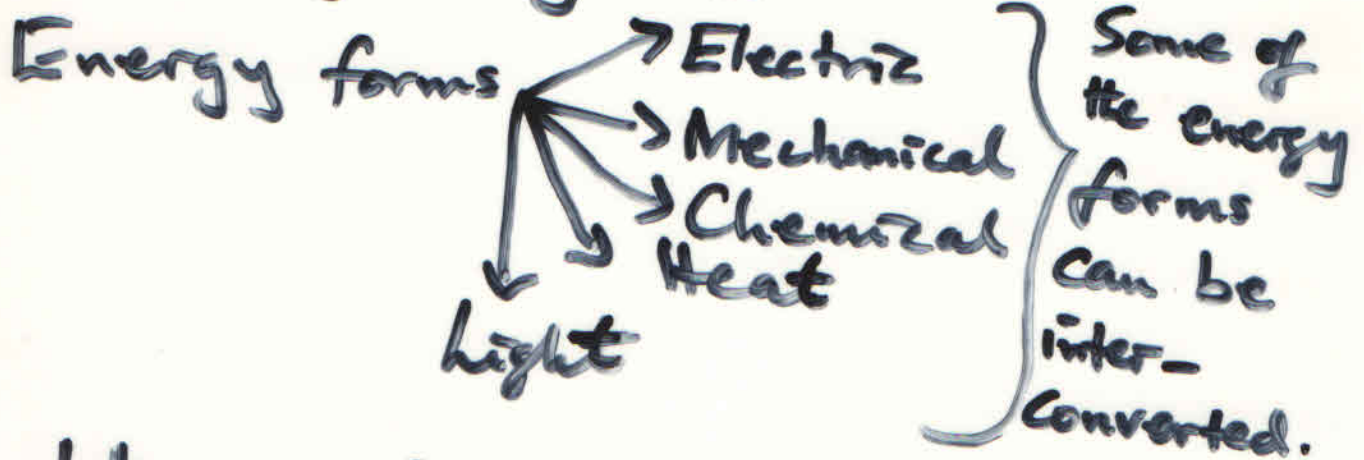
High " " \rightarrow \uparrow [E]



CELL BIOENERGETICS

①

Is the field of Biochemistry concerned with the transformation and use of energy by living cells.



When one form is converted into another, there is always some loss of energy e.g. Electric motor - due to friction, the motor generates heat which is lost.

⇒ Thermodynamics - a branch of physical science that deals with energy changes.

1st Law - In any physical or chemical change, the total amount of energy in the Universe remains constant.

"Conservation of energy" - Energy can not be created or destroyed but can only be changed from one form to another.

2nd Law - All physical or chemical

Changes tend to proceed in such a direction that useful energy undergoes irreversible degradation into a random, disordered form called entropy. The changes come to a stop at an equilibrium point at which the entropy formed is the maximum possible under existing conditions.

Q. What is useful energy?

- 1) Free energy
- 2) Heat energy - can do work only thru' a change in/of temp or pressure.

Q. What is 'useless' energy?

Entropy - energy in state of randomness or disorder.

e.g.

1. Analogy of the Teakettle and the randomization of heat.

2. Oxidation of Glucose



7 molecules

12 molecules

Increase in molecular disorder. ↑ Entropy.

System = An animal / a cell or
2 reacting compounds



Surroundings = with which the system
can exchange energy.

In biological systems, chemical reactions
take place at constant Temp. and
Pressure. Changes in free energy and
entropy are related quantitatively
by the equation;

$$\Delta G = \Delta H - T \Delta S \text{ where}$$

ΔG = Change in free energy of the
reacting system.

ΔH = Change in its heat content or
enthalpy.

T = Absolute temp. at which the
process is taking place.

ΔS = Change in entropy of the Universe.

NB When any chemical reaction proceeds
to its equilibrium point, entropy
of the Universe always increases.

$\therefore \Delta S$ has a + sign.

Q. What energy changes take place in aerobic cells?



STD Conditions { Temp. = 25°C (298K)
Pressure = 1.0 atm (760 mm Hg)

$$\Delta G = -686,000 \text{ cal/mol}$$

$$\Delta H = -673,000 \text{ "}$$

$$\therefore \Delta S = \frac{\Delta H - \Delta G}{T}$$

$$= \frac{-673,000 - (-686,000)}{298}$$

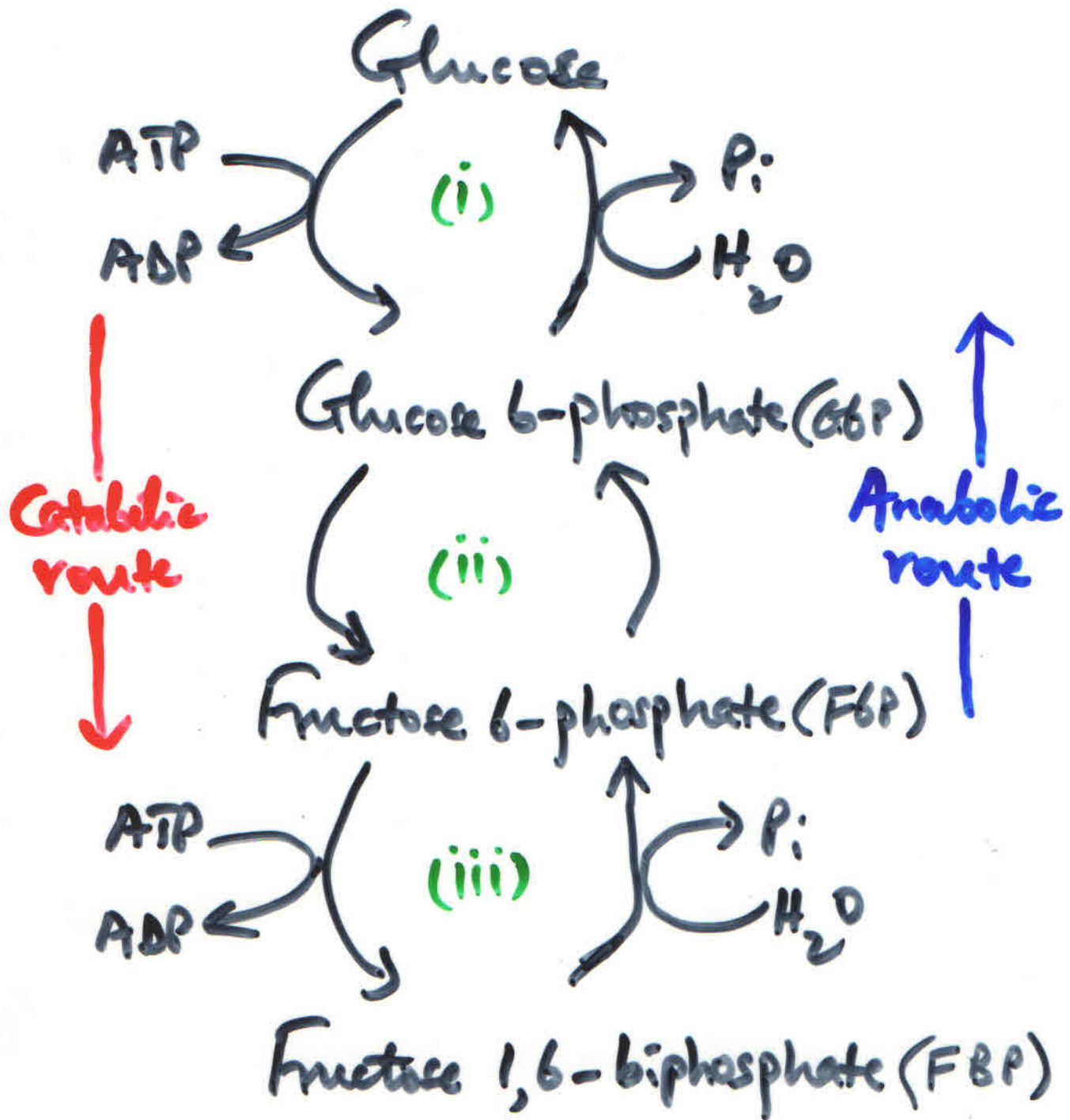
≈ +44 cal/mol = The entropy of the Universe has increased.

Q. How is the free energy of chemical reactions measured and expressed in quantitative terms?

Every reaction has a characteristic Standard free energy change (ΔG°) which can be calculated. It is a constant for any given reaction.

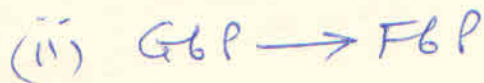
25°C / 1.0 atm

HOMEWORK

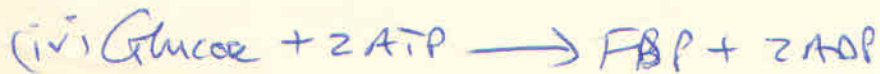


Homework

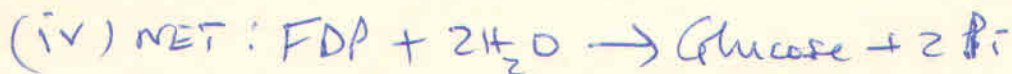
(a) Write a balanced equation for ~~the~~ each step in the catabolic route.



(b) NET Write the net equation that results when the individual steps are added,



(c) Repeat parts (a) and (b) for the anabolic route.



(d) What are the distinguishing differences, based on the net reactions between the catabolic and anabolic routes?

Are the 2 pathways simply the reverse of each other?

1. Catabolic 2 ATPs used
- Anabolic 2 H₂O used

↓
No!

(e) Could the Glucose-G6P interconversions in the catabolic and ~~the~~ anabolic routes be catalysed by the same enzyme?

- No. There are 2 different ~~enzyme~~ reactions requiring different inputs.

(f) Could the G6P-F6P interconversion in the catabolic and anabolic ~~net~~ routes be catalysed by the same enzyme?

YES; Why? No inputs differences.

Phosphoglucose isomerase.

ΔG° can be calculated from the equilibrium constant (K'_{eq}).



$K'_{eq} = \frac{[C][D]}{[A][B]}$ where all are in Molar concentrations at the point of equilibrium under STD conditions.

When,



$K'_{eq} = \frac{[C]^c [D]^d}{[A]^a [B]^b}$

When K'_{eq} is calculated, ΔG° is ~~calculated~~ using the equation;

$\Delta G^\circ = -2.303 RT \log K'_{eq}$ where

$R = 1.987 \text{ cal/mol/K}$ (Gas Constant)

$\Delta G^\circ =$ Units of calories per mole of reactant.

Calorie = Amount of energy which in the form of heat can raise the temp. of 1 gram of H_2O at $15^\circ C$ by $1^\circ C$.

| When K'_{eq} is; | ΔG° is; | Starting with 1M components, the reaction; |
|--------------------|----------------------|--|
| > 1.0 | Negative | Proceeds forward |
| 1.0 | Zero | Is at equilibrium |
| < 1.0 | Positive | Proceeds in reverse |

| When K'_{eq} is; | ΔG° (Cal/mol) is; |
|--------------------|--------------------------------|
| 0.001 | +4089 |
| 0.01 | +2726 |
| 0.1 | +1363 |
| 1.0 | 0 |
| 10.0 | -1363 |
| 100.0 | -2726 |
| 1000.0 | -4089 |

In biochemical reactions, ΔG° is written as $\Delta G^{\circ'}$ because reactions take place near pH 7.0 = ~~is~~ pH.

1.0 cal = 4.184 J

In Biology and Medicine, the Cal is usually used.

$\Delta G^{\circ'}$ = Characteristic values for different chemical reactions.



If we start reaction with either 0.02M G1P or 0.02M G6P, the final equilibrium mixture will contain 0.001M G1P and 0.019M G6P at 25°C and pH 7.0.

$$K'_{eq} = \frac{[G6P]}{[G1P]} = \frac{0.019}{0.001} = 19.0$$

$$\begin{aligned} \Delta G^{\circ'} &= -2.303 RT \log K'_{eq} \\ &= -2.303 (1.987)(298) \log 19.0 \\ &= -1364 (1.28) \\ &\approx -1745 \text{ cal/mol} \\ &\approx -1.74 \text{ kcal/mol} \end{aligned}$$

∴ G1P → G6P is favored as it proceeds with loss of free energy. It has a - sign!

If + sign, = input of free energy

Others



Q. What is the difference between $\Delta G^{\circ'}$ and ΔG ?

$\Delta G^{\circ'}$ = Under STD conditions $\left\{ \begin{array}{l} \text{pH } 7.0 \\ 25^{\circ}\text{C} \\ 1 \text{ atm} \\ \text{IM concs.} \end{array} \right.$

ΔG = a function of the actual conditions of pH, Conc, temp. prevailing during the reaction - which are not necessarily the STD conditions.

ΔG of any reaction proceeding towards its equilibrium is always negative and becomes less negative as reaction proceeds and is zero at point of equilibrium.

Relationship between ΔG and $\Delta G^{\circ'}$;

$$\Delta G = \Delta G^{\circ'} + \underbrace{2.303 RT \log K'_{eq}}_{\text{Terms actually prevailing}}$$

→ $\Delta G^{\circ'}$ = constant for every reaction / Unchanging

→ $\Delta G^{\circ'}$ values of chemical reactions are additive e.g.



Overall is $A \rightarrow C$

$$\Delta G_3^{\circ'} = \Delta G_1^{\circ'} + \Delta G_2^{\circ'}$$

Homework

1) Calculation of ΔG° from K_{eq}

Calculate the ΔG° of the following metabolically important enzyme-catalyzed reactions at 25°C from the K_{eq} given (pH 7.0).

(a) $K_{eq} = 6.8 \quad -1.14 \text{ kcal/mol}$

(b) $K_{eq} = 0.0475 + 1.82 \text{ "}$

(c) $K_{eq} = 254 \quad -3.30 \text{ "}$

2) Calculation of K_{eq} from ΔG°

Calculate the K_{eq} for the following reactions at pH 7.0 and 25°C using the ~~ΔG°~~ given ΔG° values.

(a) $\Delta G^{\circ} = -3.3 \text{ kcal/mol} \approx 250$

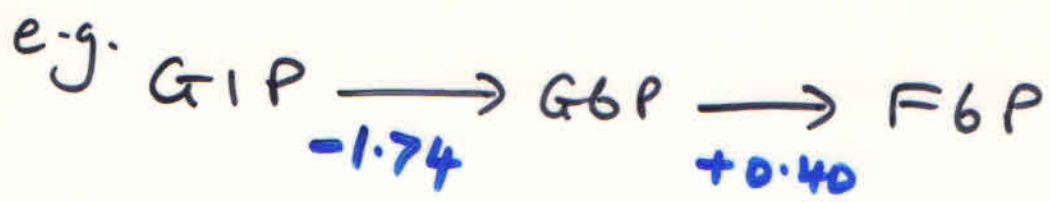
" = $-3.8 \text{ "} \approx 590$

" = $+0.75 \text{ "} \approx 0.28$

3) The ΔG° for coupled reactions.

Using the given ΔG° values, calculate the K_{eq} for the sum of the two reactions at 25°C .

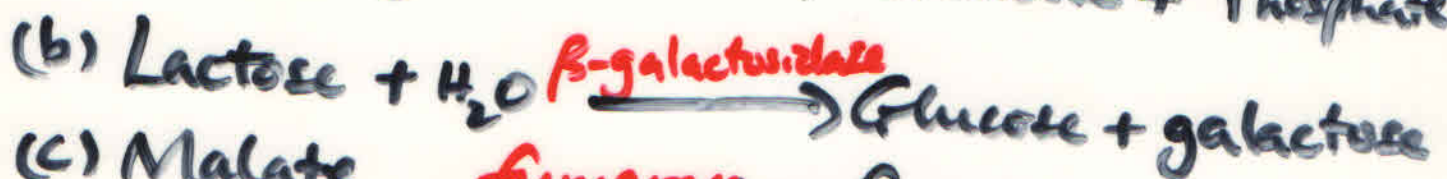
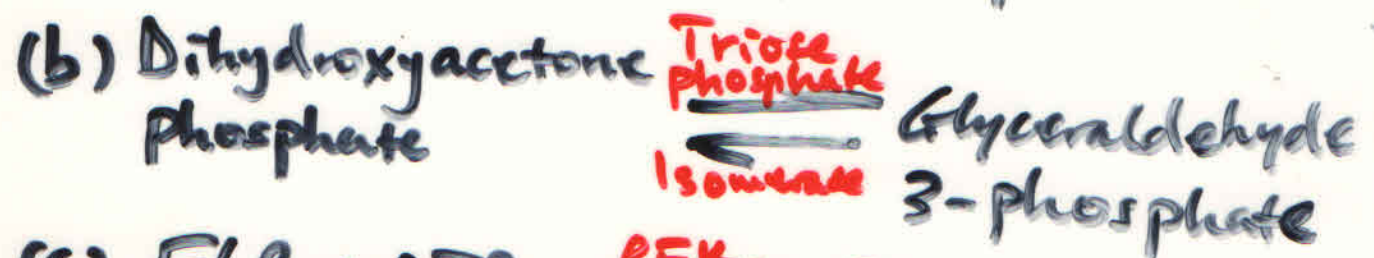




$\therefore G1P \longrightarrow F6P \quad \Delta G_s^{\circ} = -1.74 + (+0.40)$
 $= -1.34 \text{ kcal/mol}$

- A thermodynamically unfavorable reaction can be driven by a favorable one coupled to it.
- The overall free energy change for a chemically coupled series of reactions is equal to the sum of the free-energy changes of the individual steps.

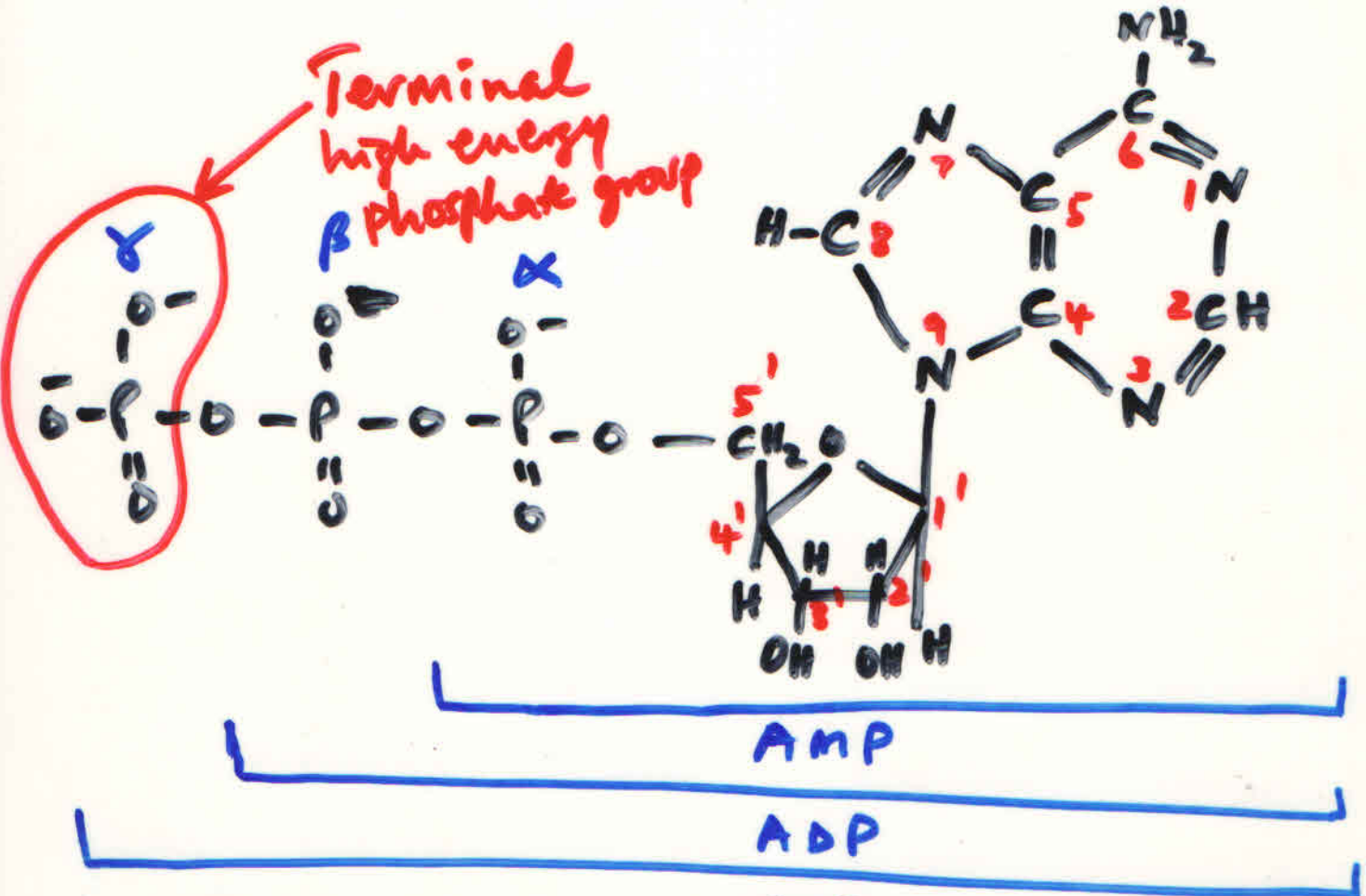
Problems



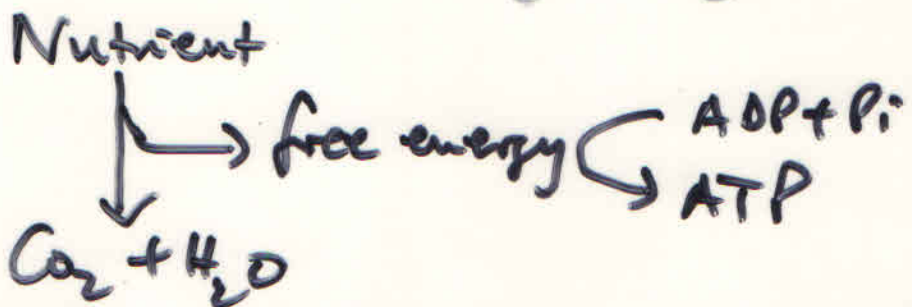
ATP = ADENOSINE TRIPHOSPHATE

It is a nucleotide consisting of an adenine base, a D-ribose and 3 phosphate groups.

CHEMISTRY



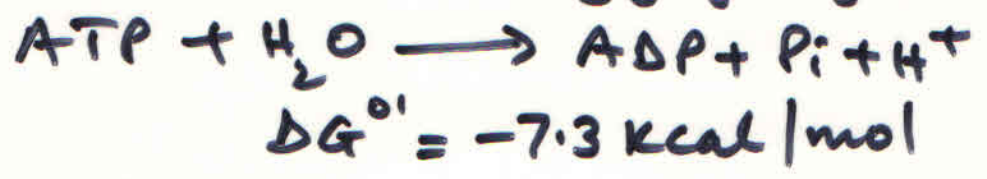
At pH 7.0 = ATP^{4-} Fully ionized



In cells, ATP and ADP exist as MgATP^{2-} and MgADP^- respectively. This is their active forms.

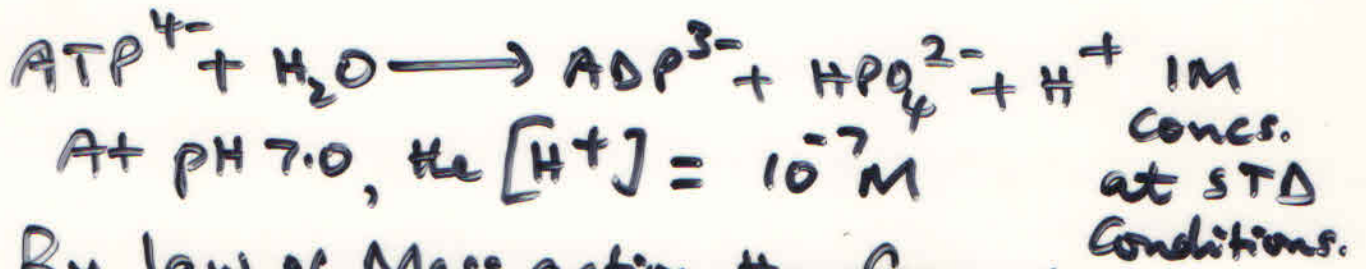
Q. How is ATP able to function as a link between energy-yielding reactions and energy-requiring reactions?

1. ATP has a high and characteristic standard free energy of hydrolysis.



Others:

| <u>Compound</u> | <u>$\Delta G^{\circ'}$ (Kcal/mol)</u> |
|-----------------------------|--|
| Phosphoenolpyruvate (PEP) | -14.8 |
| 3-Phosphoglycerol phosphate | -11.8 |
| Phosphocreatine | -10.3 |
| * ATP | -7.3 |
| GTP | -5.0 |
| G6P | -3.3 |



By law of Mass action, the forward reaction is favored i.e. compare $[\text{H}^+]$ and the Concs. of others.

10^{-7} M Vs 1.0 M Concs. of ATP, ADP and P_i at STD conditions.

But;



No extra H^+ is formed.

2. At pH 7.0, ATP molecules have 4 closely spaced negative charges which repel each other.

$G6P \rightarrow$ Glucose (no charge) so can "easily" recombine.

3. ADP^{3-} and HPO_4^{2-} are more stable with less free energy. The products have a smaller free energy content than the reactants ($ATP + H_2O$).

In cells, $\Delta G^{\circ'}$ is about -12 to -16 kcal/mol because the actual concs. of ATP, ADP and P_i are different (not 1M) and are much lower than in STD conditions.

$\Delta G_p = \Delta G$ in intact cells
↙ phosphorylation potential

e.g. Human RBCs

$$[ATP] = 2.25 \text{ mM}, [ADP] = 0.25 \mu\text{M}$$

$$[P_i] = 1.65 \text{ mM} \quad \text{Assume pH 7.0 / } 25^\circ\text{C}$$

$$\Delta G = \Delta G^{\circ'} + 2.303 RT \log \frac{[ADP][P_i]}{[ATP]}$$

$$\Delta G / \Delta G_p = -12.4 \text{ kcal/mol}$$

2 reactions ;



reactions. It can serve as the means of energy transfer from the first to the second reaction.



Super high energy compound

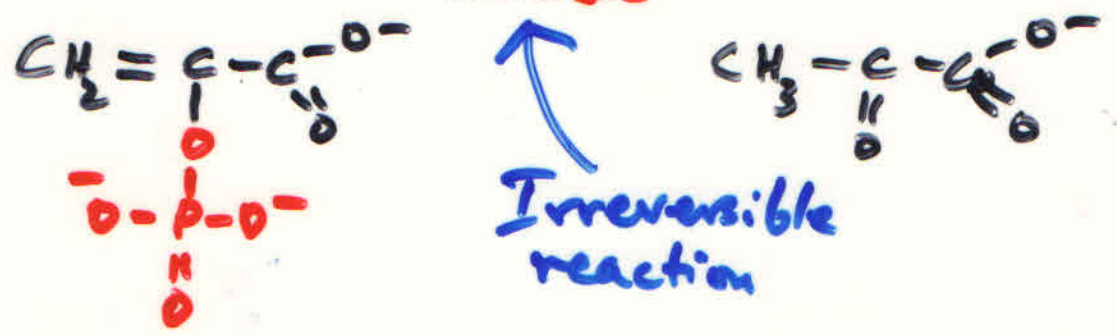
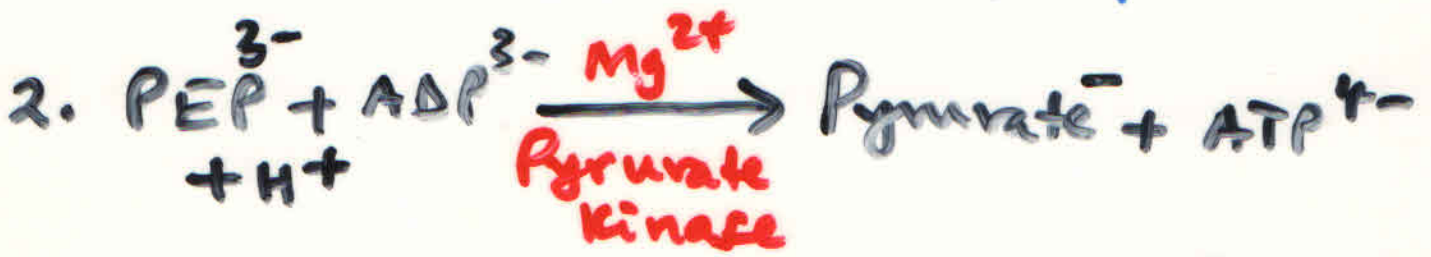
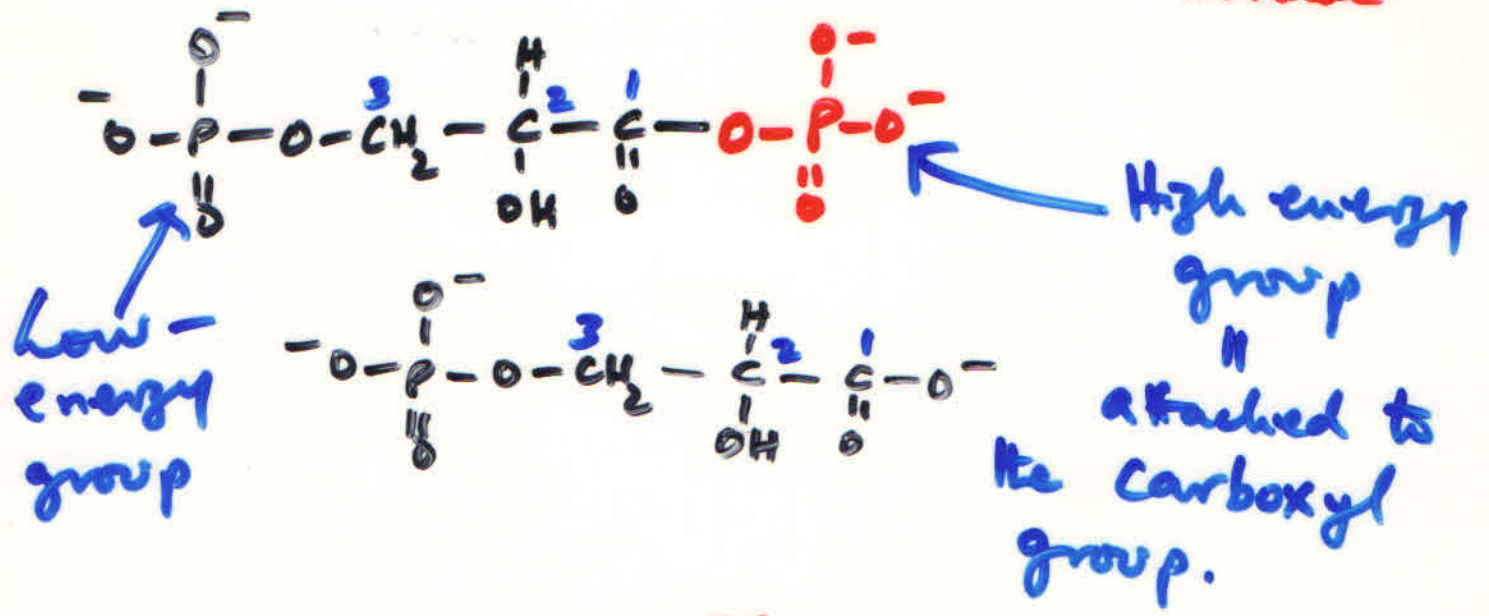
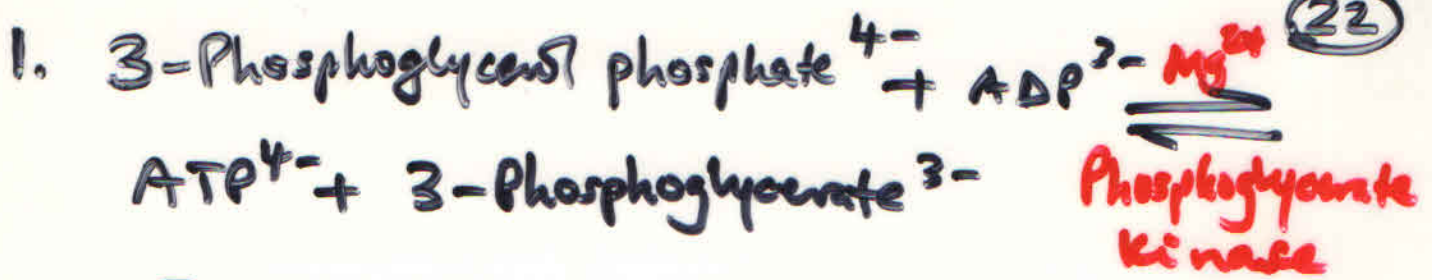


↑
acceptor molecule

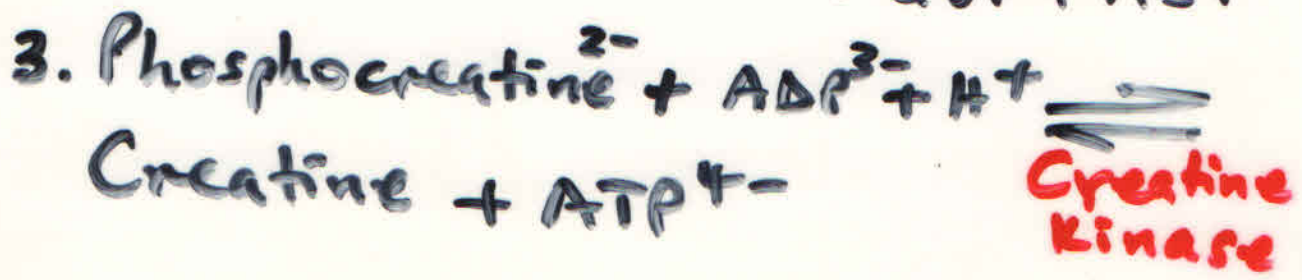
NB Transfer of phosphate group from $X-P$ to Y via ATP .

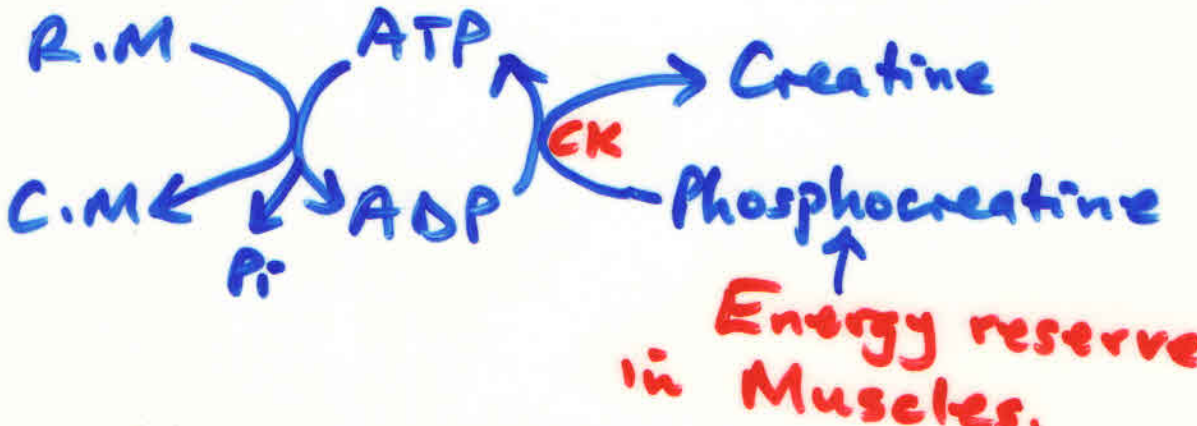
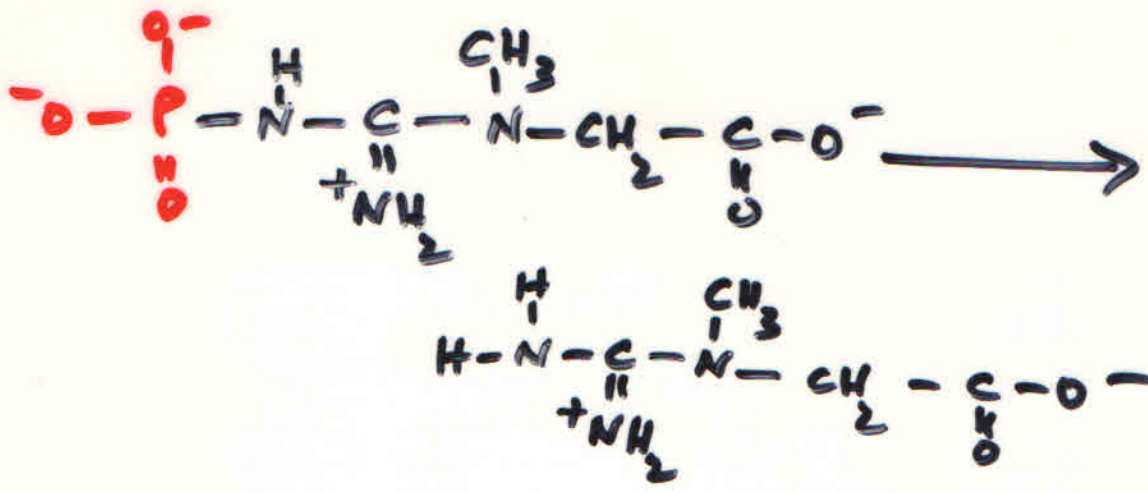
* Cells do not have kinases that directly transfer P from high energy phosphate compounds to an acceptor molecule e.g. Y .

Examples of super high energy phosphate compounds and their role in cells;

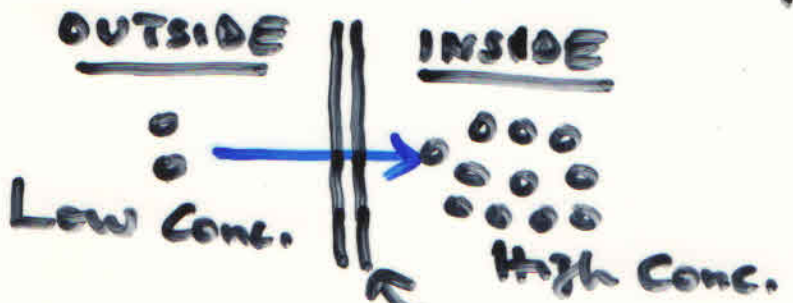


ATP⁴⁻ → Can be used to transfer a phosphate group to an acceptor molecule eg Glucose.





ATP is used to transport molecules, ions across membranes and against a conc. gradient = Active transport.



$\Delta G = 2.303 RT \log \frac{C_2}{C_1}$ ← inside
 ← outside

e.g. Glucose transport

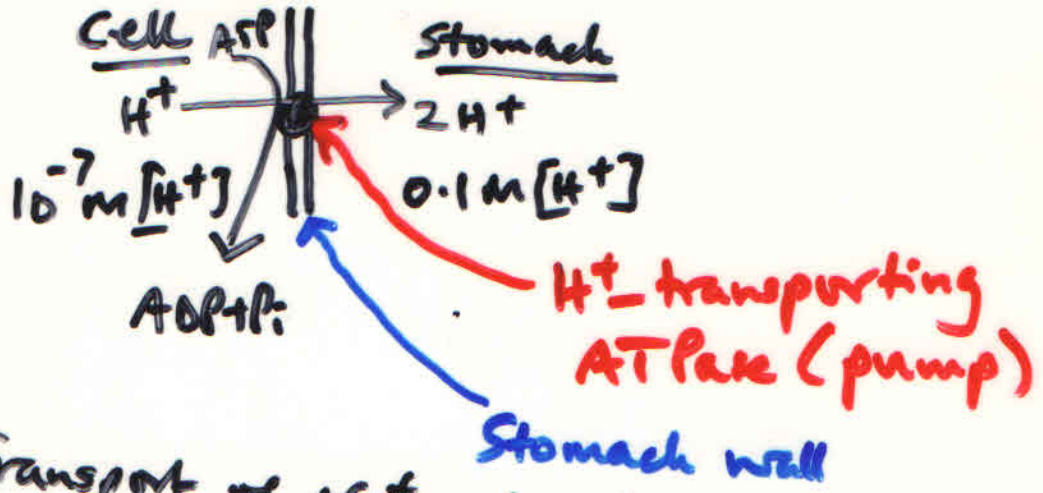
Outside 1mM Inside 100mM

$\Delta G = 2.303 \times (1.98) \times (298) \log 100$

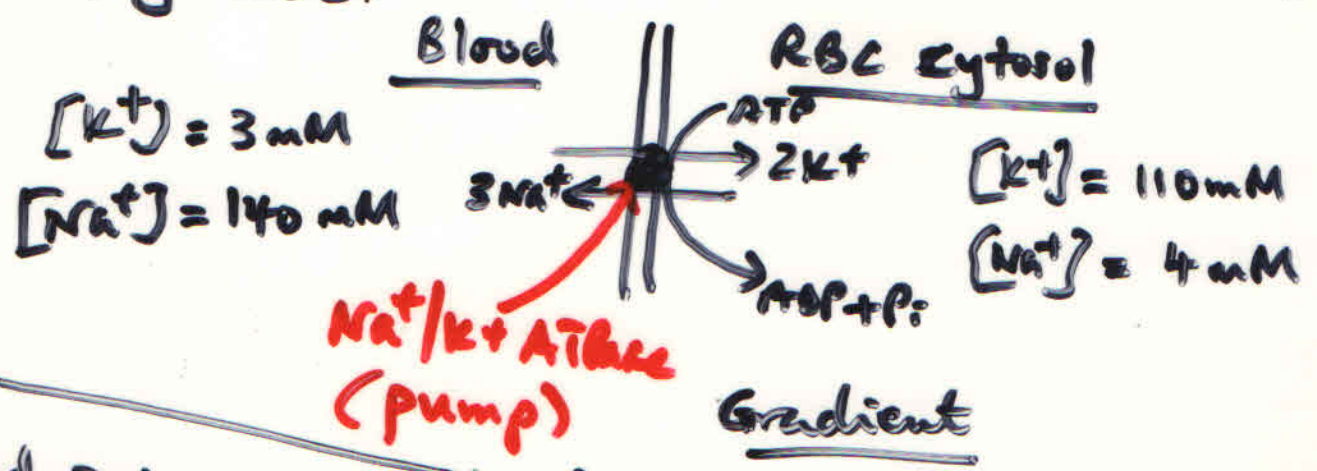
= + 2.7 kcal/mol = Energy required

to transport glucose against conc. gradient.

e.g. Parietal cells of stomach



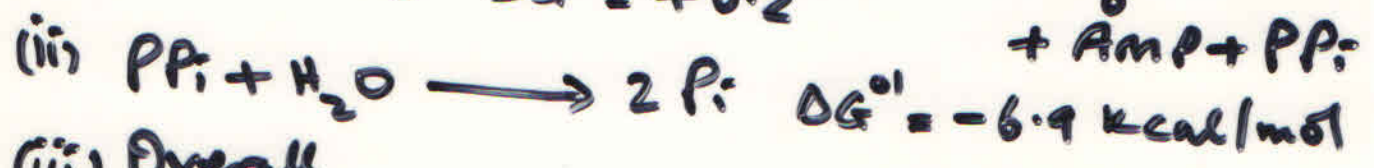
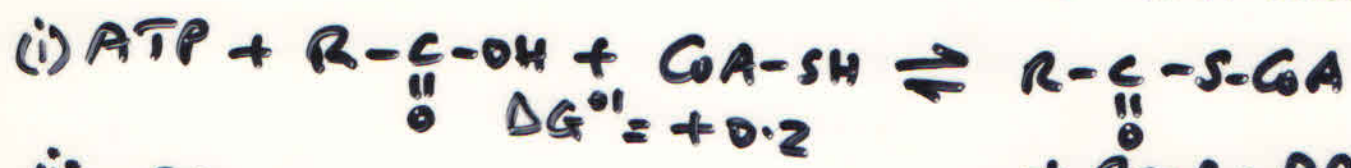
e.g. Transport of Na^+ and K^+ across the membrane by RBC.



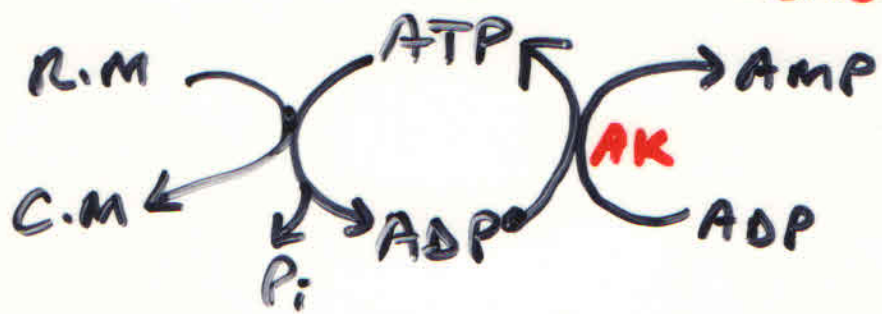
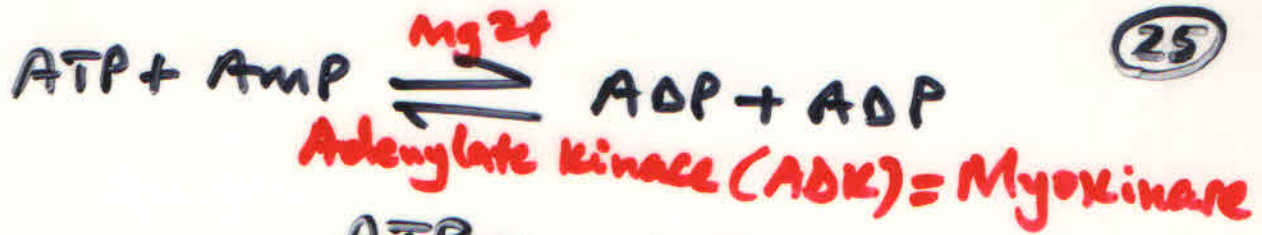
Read on;
The enzymatic cycle of the Na^+/K^+ ATPase

- 1) Controls cell volume
- 2) Nerve impulses
- 3) Drives the active transport of sugars and amino acids.

ATP can also be broken down to AMP and PP_i .

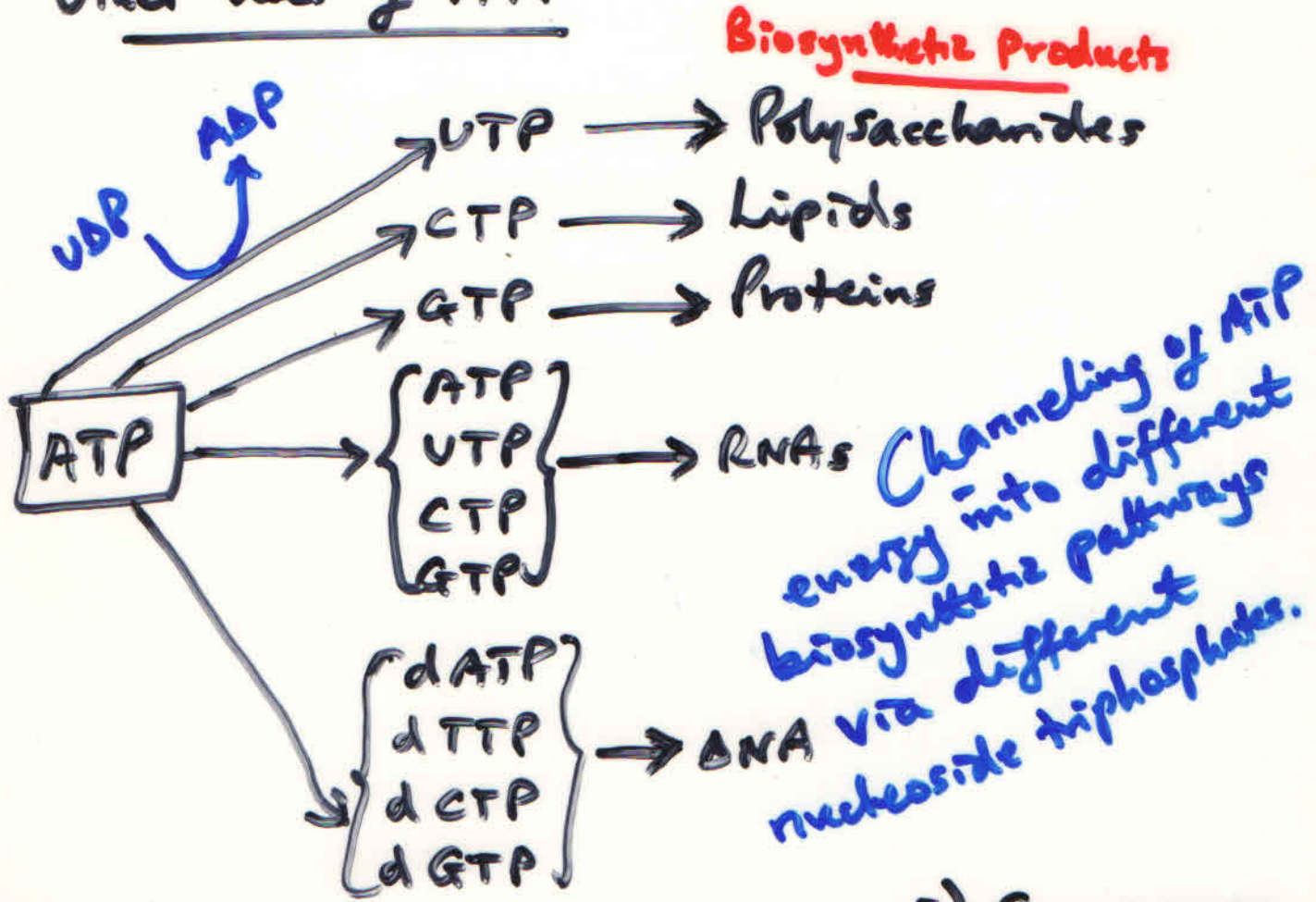


Q. What is the fate of AMP?



AK acting on ADP can supplement phosphocreatine as a source of ATP during muscle contraction.

Other uses of ATP



5) Coenzymes

Functions of Nucleotides:

- 1) Source of energy - ATP
- 2) Specific carriers of building-blocks
- 3) Precursors of Nucleic acids
- 4) Regulators e.g. cAMP, cGMP