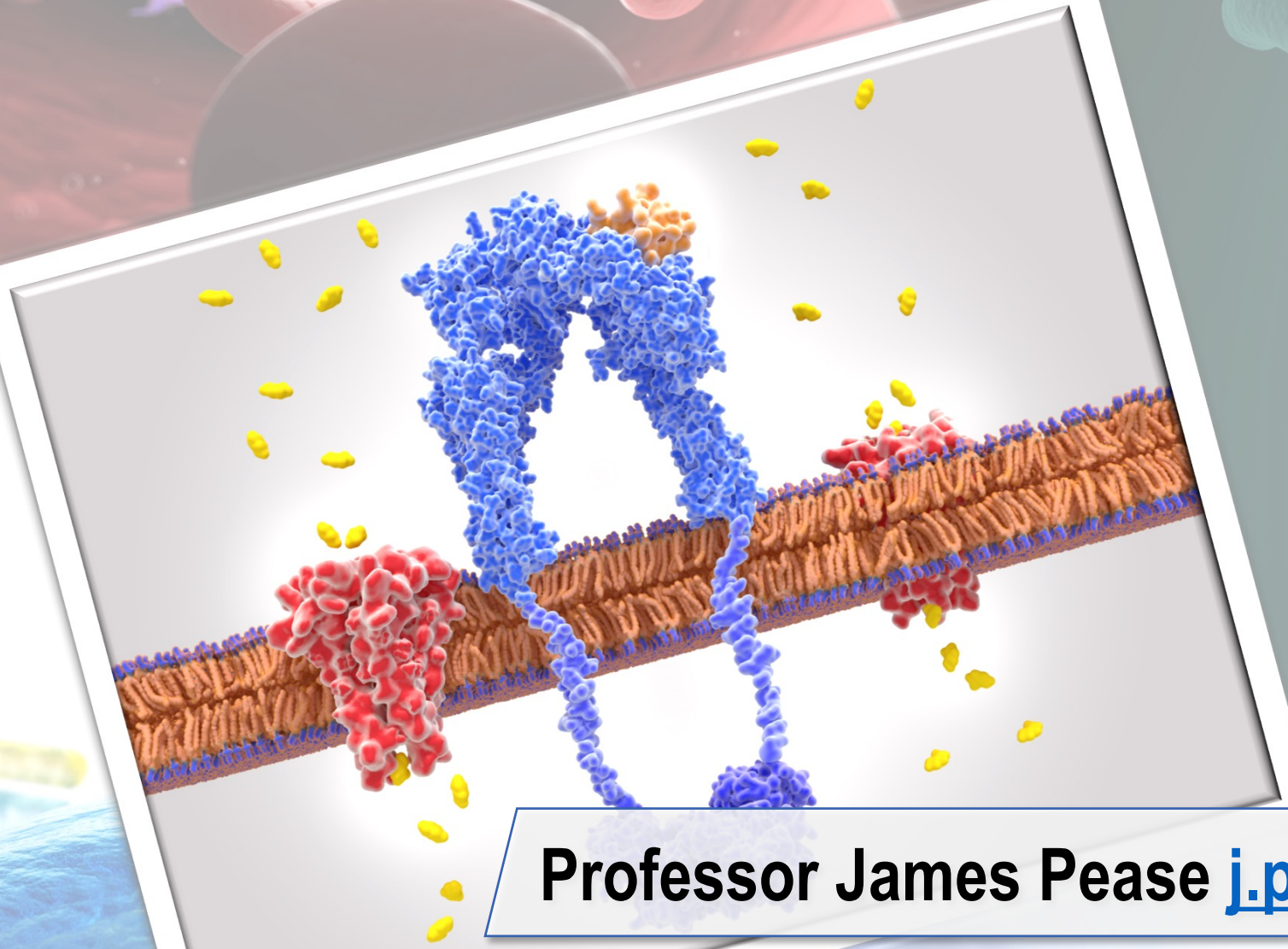
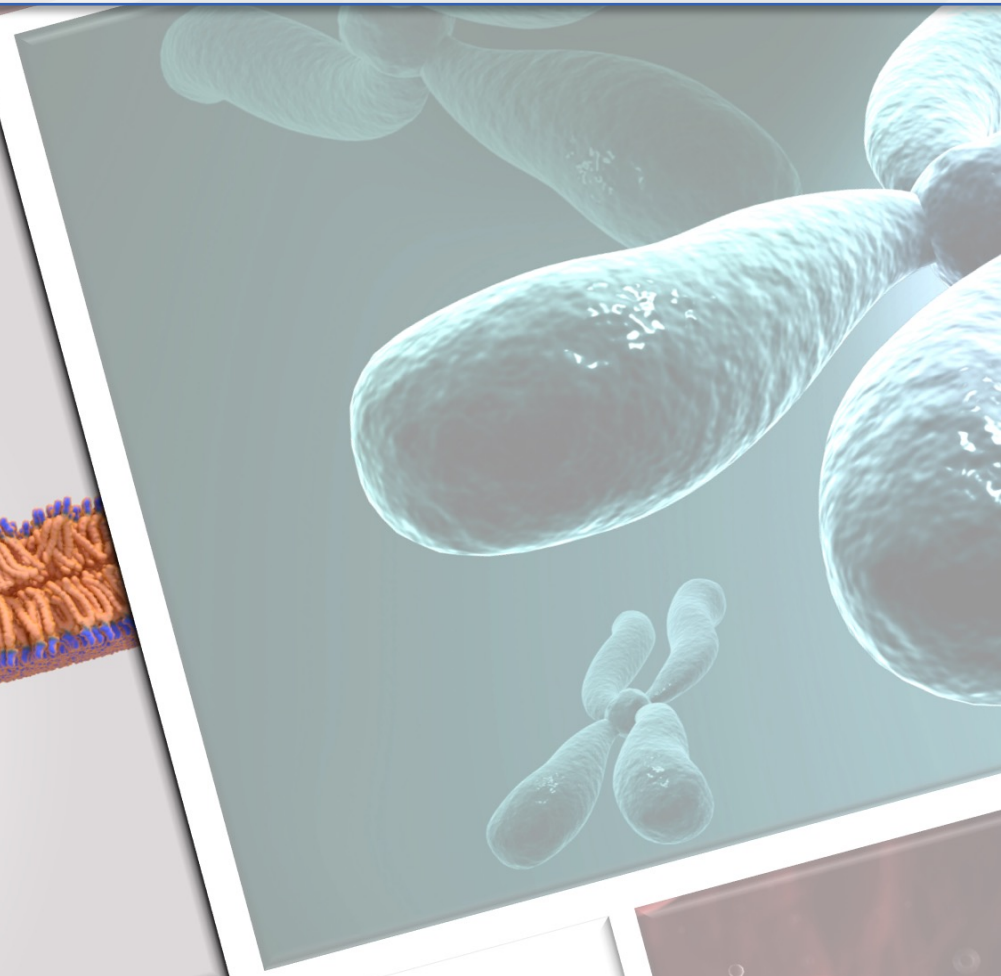
IMPERIAL

Cell metabolism 1





Professor James Pease j.pease@imperial .ac.uk

Session Plan

Part 1

An overview of metabolism

- The 6 reaction types
- The 10 reactions of glycolysis
- The pentose phosphate pathway

Part 2

The three fates of pyruvate

- Alcoholic fermentation
- Lactate production
- Acetyl CoA production

1-POM-1-1: Cell metabolism: Summarise the metabolism of carbohydrates, fats and proteins in health, exercise, illness and disease.

Session Plan

Part 1

An overview of metabolism

- The 6 reaction types
- The 10 reactions of glycolysis
- The pentose phosphate pathway

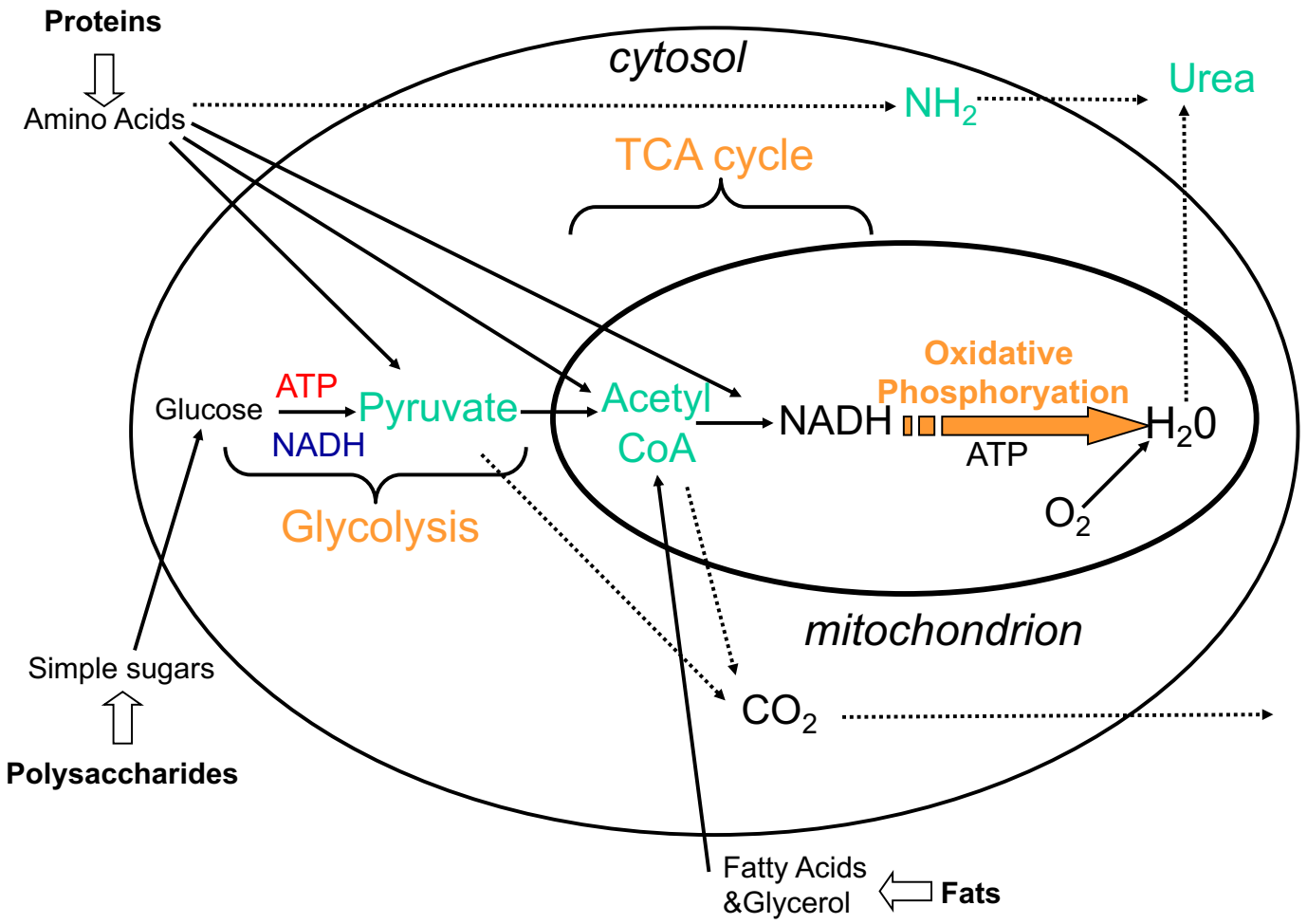
Part 2

The three fates of pyruvate

- Alcoholic fermentation
- Lactate production
- Acetyl CoA production

1-POM-1-1: Cell metabolism: Summarise the metabolism of carbohydrates, fats and proteins in health, exercise, illness and disease.

An overview of cellular metabolism

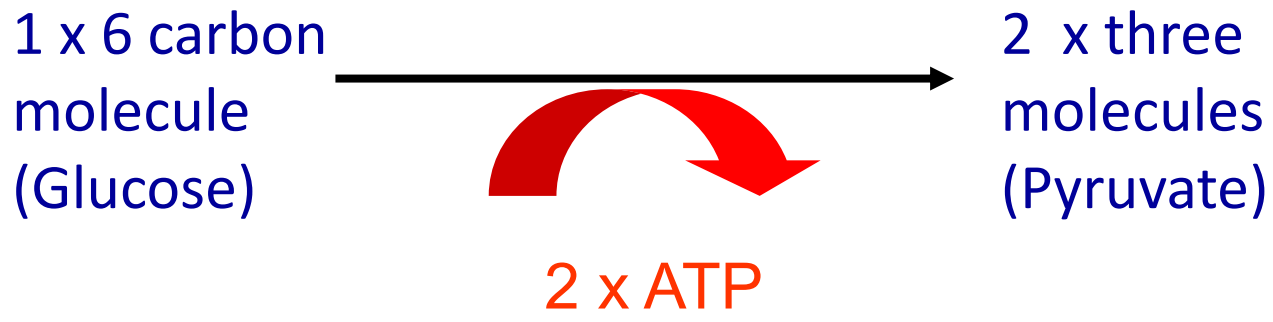


Over the next few sessions, we will cover the biochemical pathways which make up this slide

Just 6 types of reactions define metabolism

Type of Reaction	Description
Oxidation-reduction	Electron transfer
Ligation requiring ATP cleavage	Formation of covalent bonds (i.e., carbon-carbon bonds)
Isomerization	Rearrangement of atoms to form isomers
Group transfer	Transfer of a functional group from one molecule to another
Hydrolytic	Cleavage of bonds by the addition of water
Addition or removal of functional groups	Addition of functional groups to double bonds or their removal to form double bonds

Glycolysis is Central to Metabolism



Glycolysis

- From the Greek glycos (sugar) and lysis (breaking)
- Glycolysis is essentially an anaerobic process, occurring in the cytoplasm of cells and is probably a throwback to the pathways used by prehistoric anaerobic bacteria.

Glycolysis – main concepts

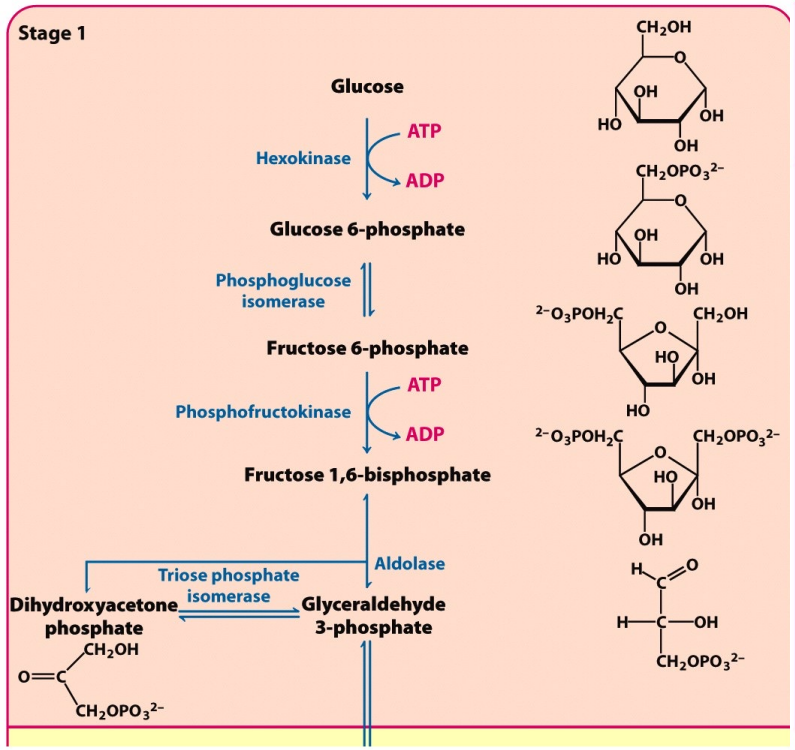


Figure 16.2 part 1
Biochemistry, Seventh Edition

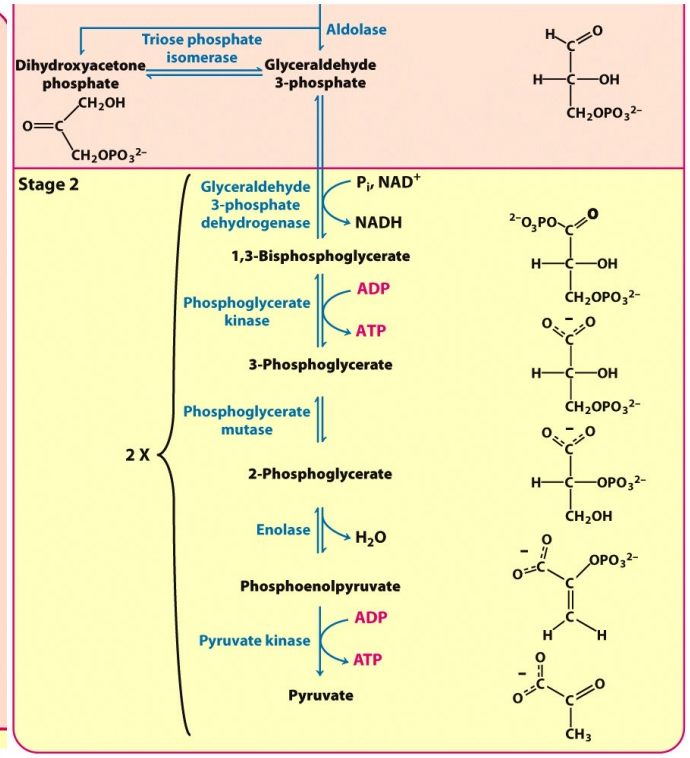


Figure 16.2 part 2
Biochemistry, Seventh Edition

- Within the ten reactions that make up the glycolysis pathway, there are two main concepts:

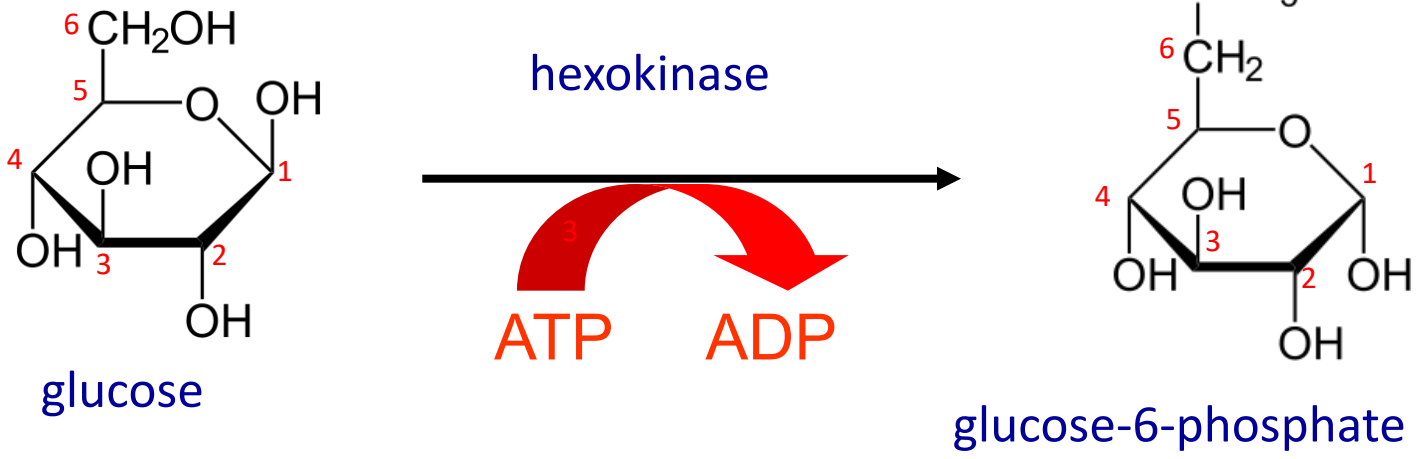
  (i) Formation of a High Energy Compound
  (ii) Splitting of a High Energy Compound

- Step (i) involves the investment of energy in the form of **ATP**.

- Step (ii) produces useful energy in the form of **ATP** generation.

1-POM-1-1: Cell metabolism: Summarise the metabolism of carbohydrates, fats and proteins in health, exercise, illness and disease.

Glycolysis – A game of two halves – Step 1



glucose

glucose-6-phosphate

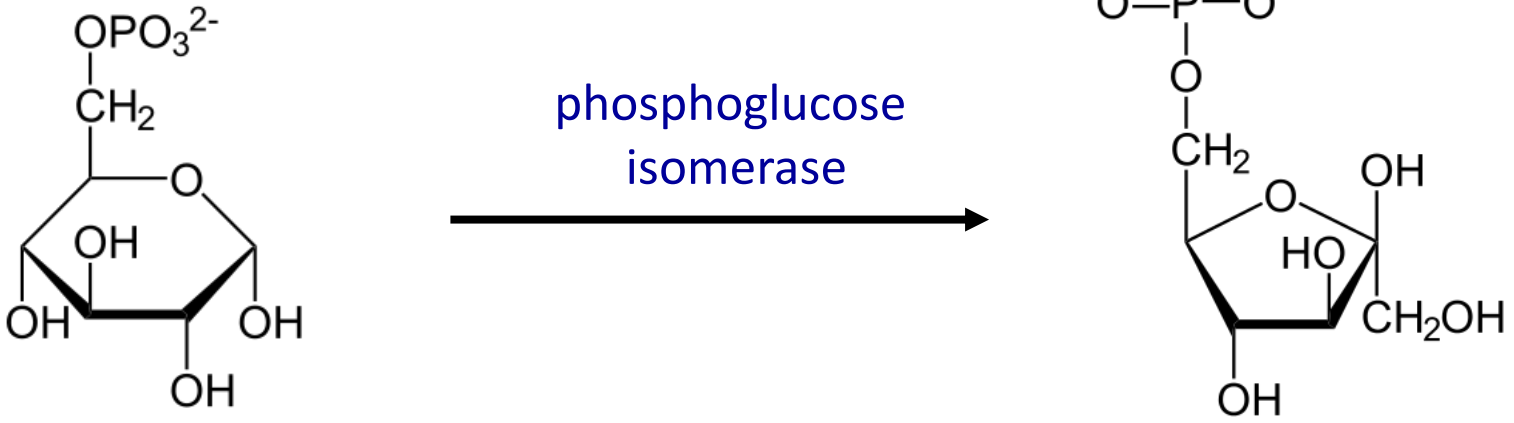
+ H^+

Q. What type of reaction is this?

GROUP TRANSFER

- This reaction is essentially irreversible - commits the cell to the subsequent reactions.
- Also traps glucose inside the cell by means of the negative charge.
- Glucose-6-phosphate also the starting point for pentose phosphate pathway a.k.a. hexose monophosphate shunt. Haem – Red blood cells.

Glycolysis – A game of two halves – Step 2



glucose-6-phosphate

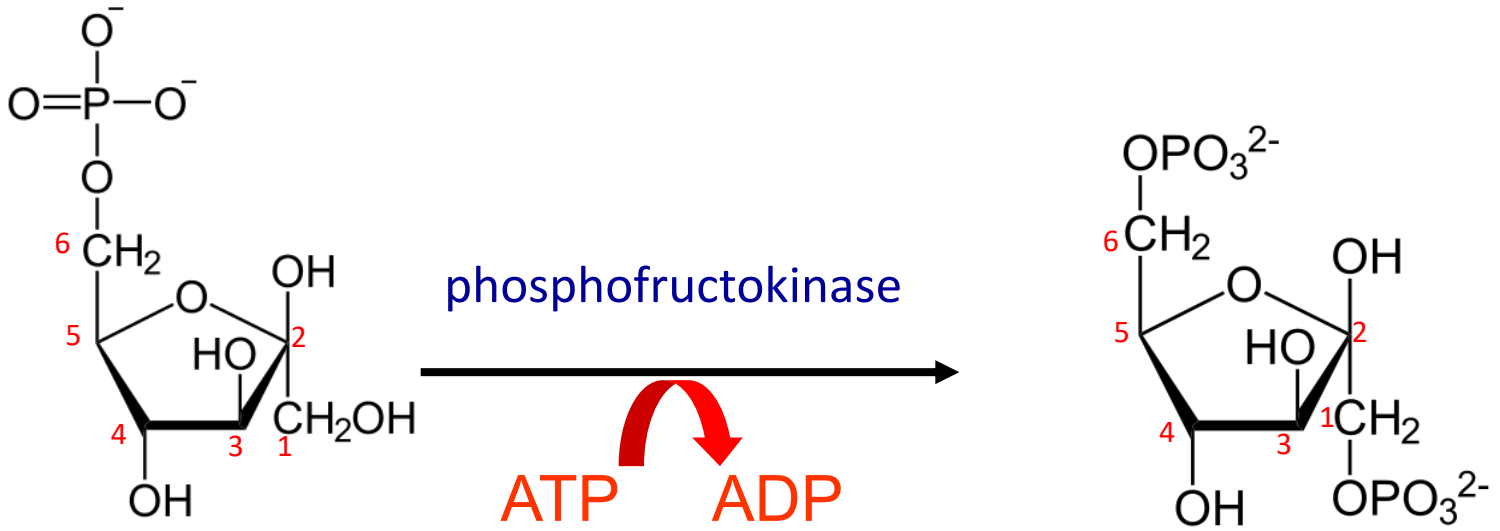
fructose-6-phosphate

- The logic behind this reaction is that fructose can be split into equal halves when subsequently cleaved.

Q. What type of reaction is this?

ISOMERISATION

Glycolysis – A game of two halves – Step 3



fructose-6-phosphate

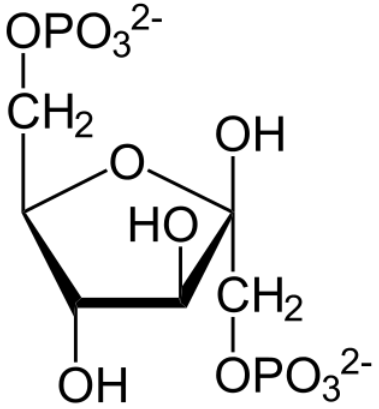
fructose-1,6-bisphosphate

- Regulation of phosphofructokinase is a key control step for the entry of sugars into the glycolysis pathway.

Q. What type of reaction is this?

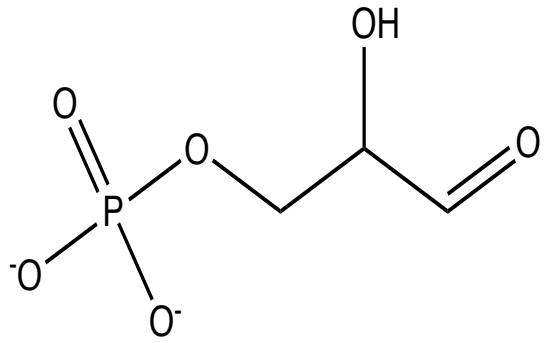
GROUP TRANSFER

Glycolysis – A game of two halves – Step 4



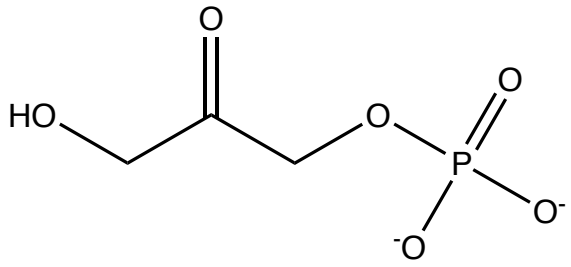
fructose-1,6-bisphosphate

aldolase



glyceraldehyde 3-phosphate

+



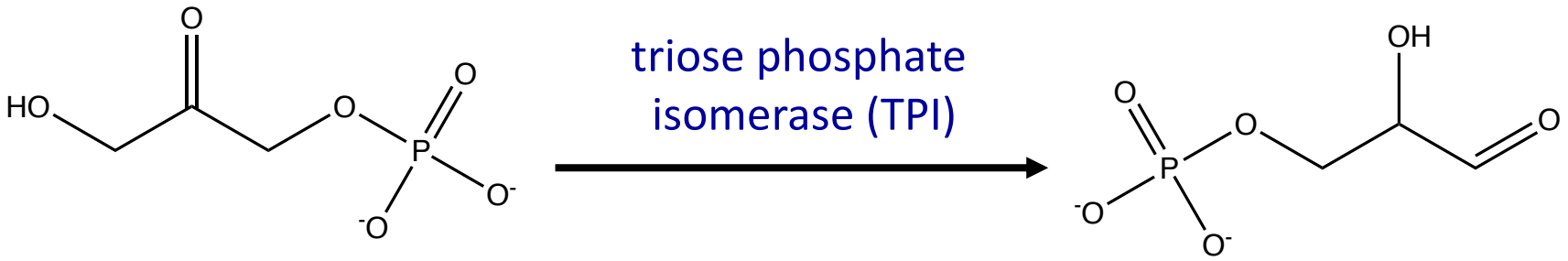
dihydroxyacetone phosphate

- Two high energy compounds have been generated.

Q. What type of reaction is this?

HYDROLYTIC

Glycolysis – a game of two halves – Step 5



dihydroxyacetone phosphate

glyceraldehyde 3-phosphate

Q. What type of reaction is this?

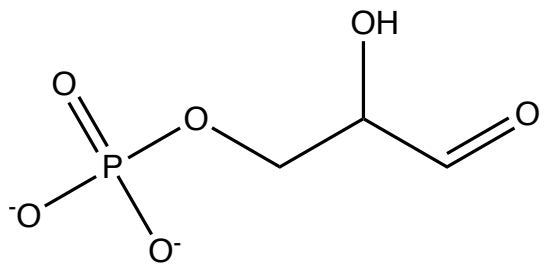
ISOMERISATION

Metabolic Diseases

- Deficiency in TPI is the only glycolytic enzymopathy that is fatal, with most sufferers dying within the first 6 years of their lives.

Glycolysis – The second half – Step 6

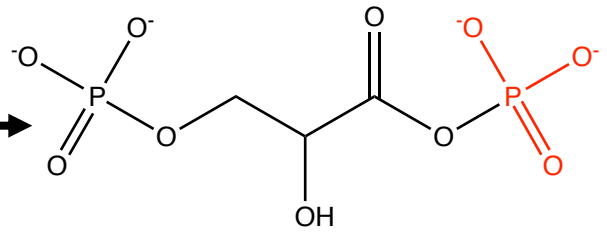
2X



glyceraldehyde 3-phosphate

glyceraldehyde 3-phosphate dehydrogenase

NAD^+ + Pi → NADH



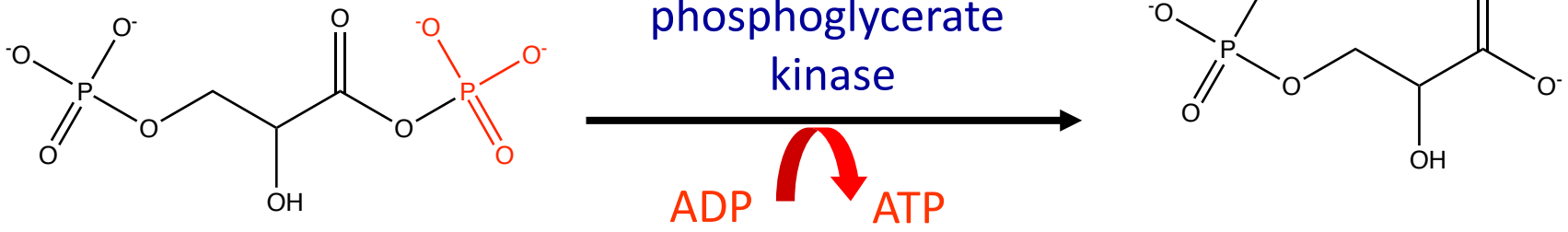
1,3-bisphosphoglycerate

- NADH is generated here which can be later used to generate yet more ATP within the mitochondria in a process known as **oxidative phosphorylation**

Q. What type of reaction is this?

REDOX and GROUP TRANSFER

Glycolysis – The second half – Step 7



1,3-bisphosphoglycerate

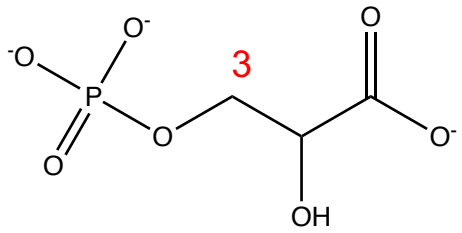
3-phosphoglycerate

- You may recall from the PoM primer that kinases transfer phosphate groups to molecules.
- Transfer of the high energy phosphate group to ADP, generating one ATP molecule in the process

Q. What type of reaction is this?

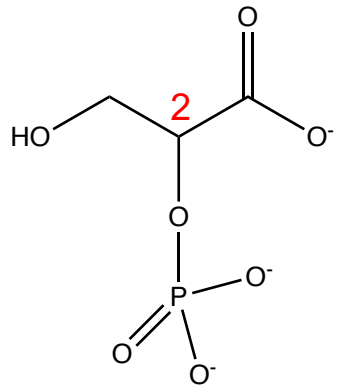
GROUP TRANSFER

Glycolysis – The second half – Step 8



3-phosphoglycerate

phosphoglycerate mutase



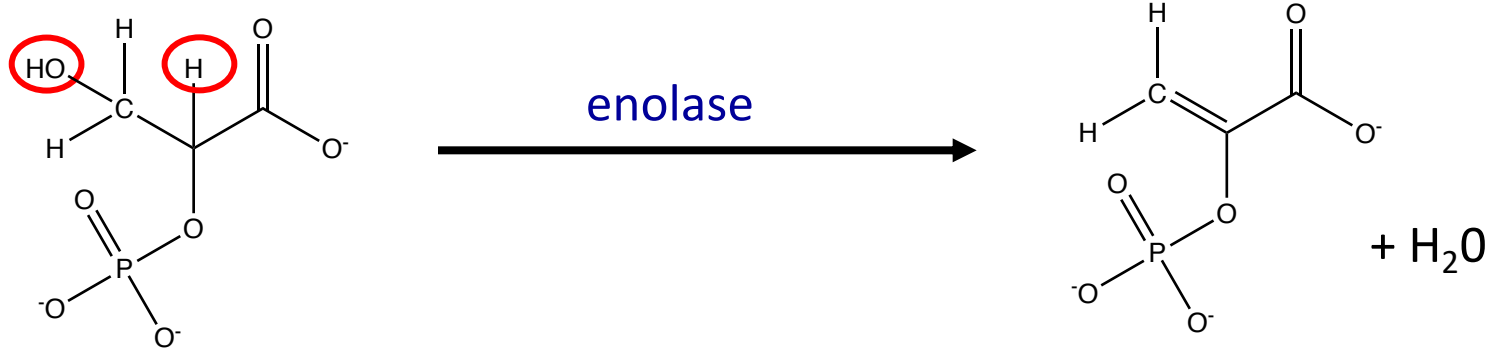
2-phosphoglycerate

- Effectively, a shuffling of the phosphate group from the 3 to the 2 position via removal and addition of phosphoryl groups.

Q. What type of reaction is this?

ISOMERISATION

Glycolysis – The second half – Step 9



2-phosphoglycerate

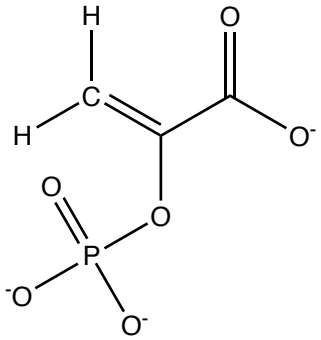
phosphoenolpyruvate

- Also known as a dehydration reaction for obvious reasons

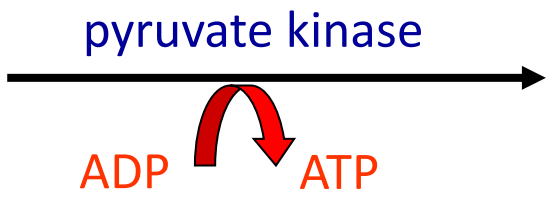
Q. What type of reaction is this?

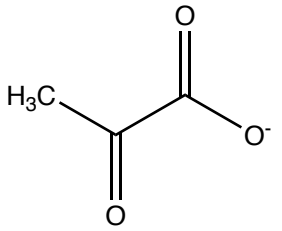
GROUP REMOVAL

Glycolysis – and finally……. Step 10



phosphoenolpyruvate





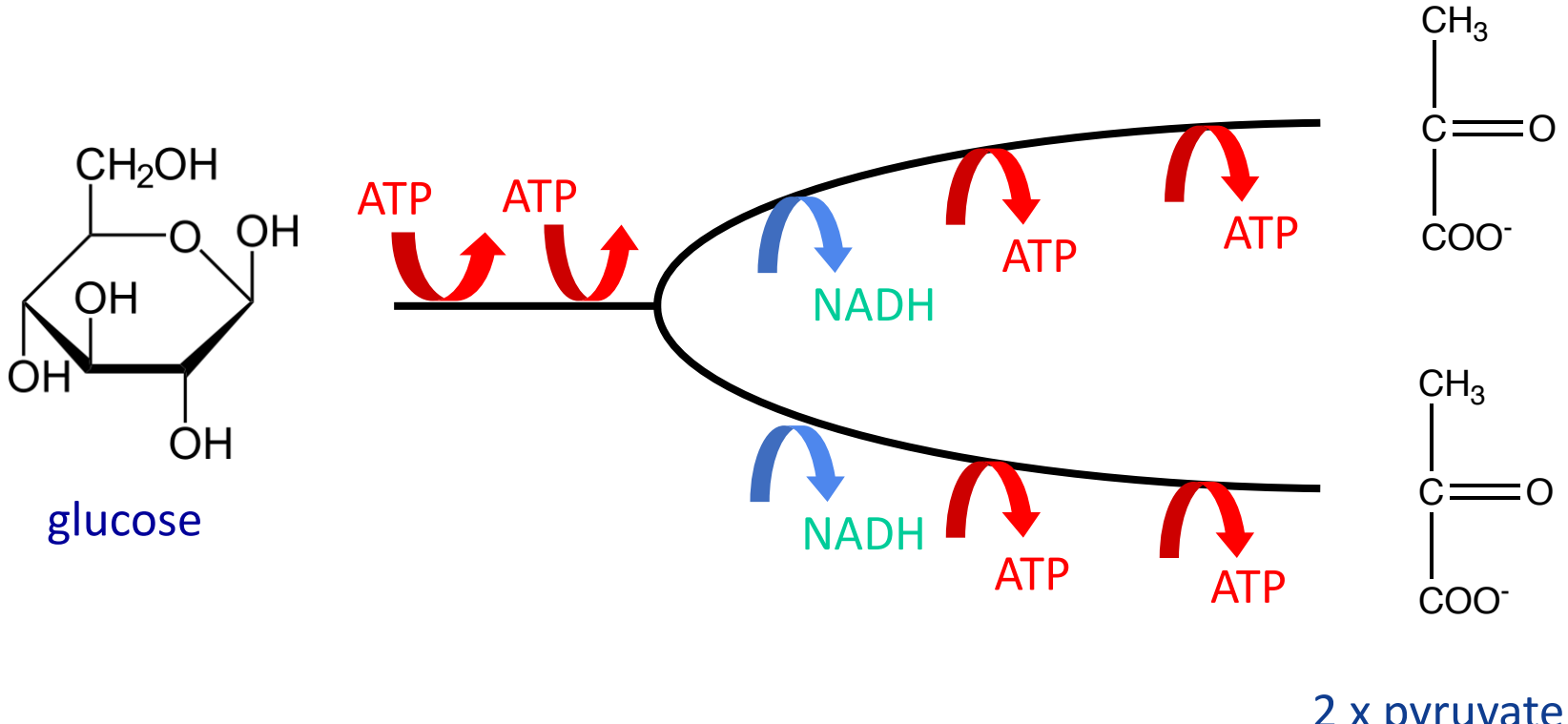
pyruvate

- Transfer of the high energy phosphate group to ADP, generating one ATP molecule in the process

Q. What type of reaction is this?

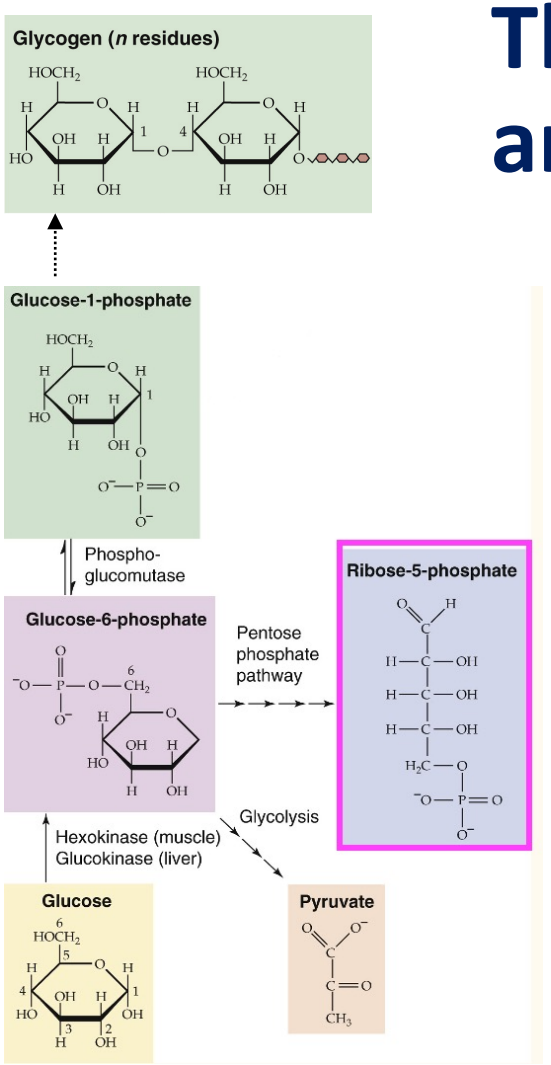
GROUP TRANSFER

The net result of glycolysis



- A net gain of 2 **ATP** molecules
- Also 2 **NADH** molecules which can be used to generate **ATP**.

The pentose-phosphate pathway (PPP): another fate for glucose-6-phosphate



- A parallel pathway to glycolysis which is used in **anabolic** reactions to generate biosynthetic molecules e.g.

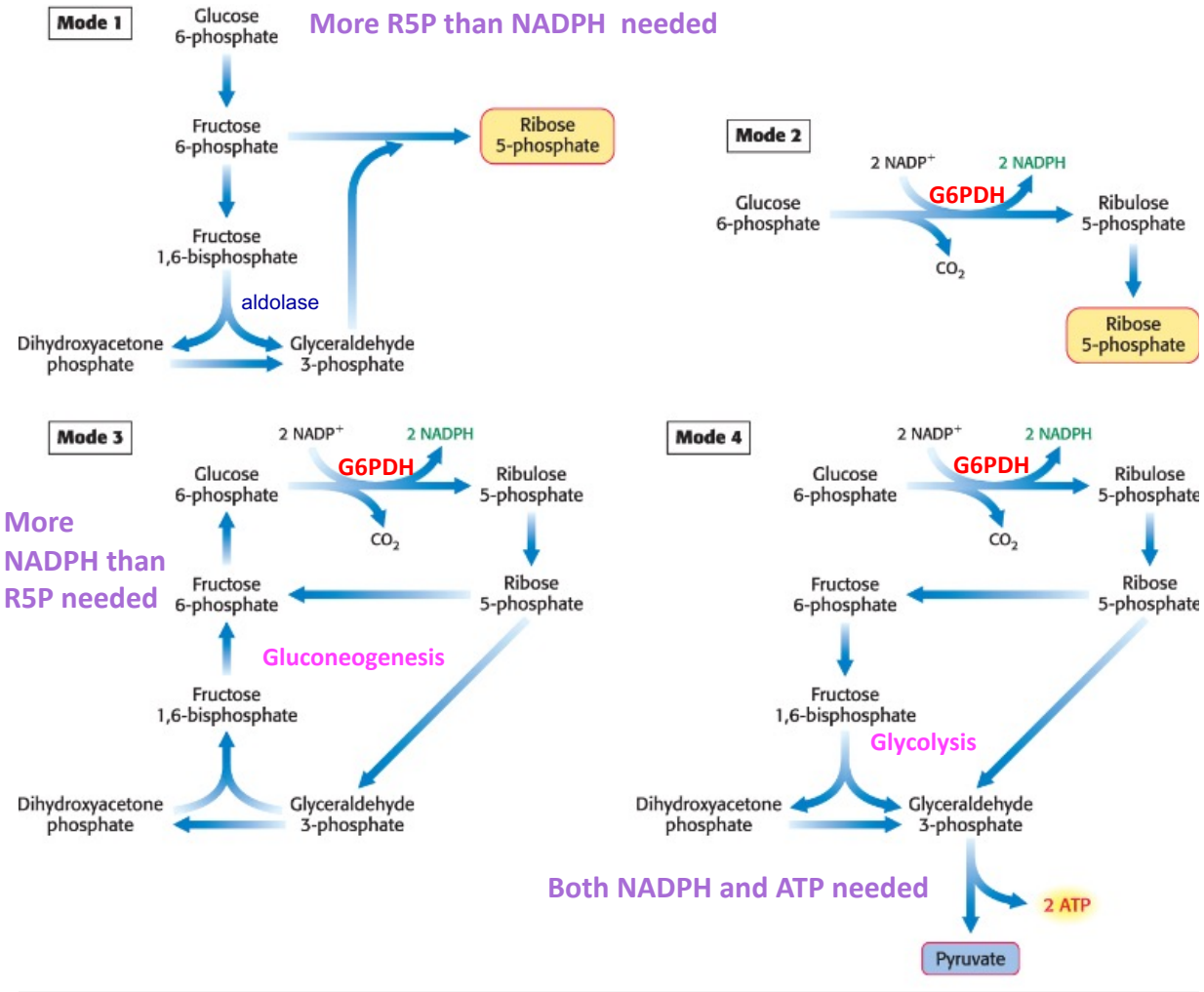
- NADPH relative of NADH (reducing power)
- Ribose 5-phosphate (DNA synthesis)

- An important pathway in tissues such as liver, adipose, adrenal cortex and red blood cells.

Medical Physiology, Chapter 58, 1170-1192.e1

1-POM-1-1: Cell metabolism: Summarise the metabolism of carbohydrates, fats and proteins in health, exercise, illness and disease.

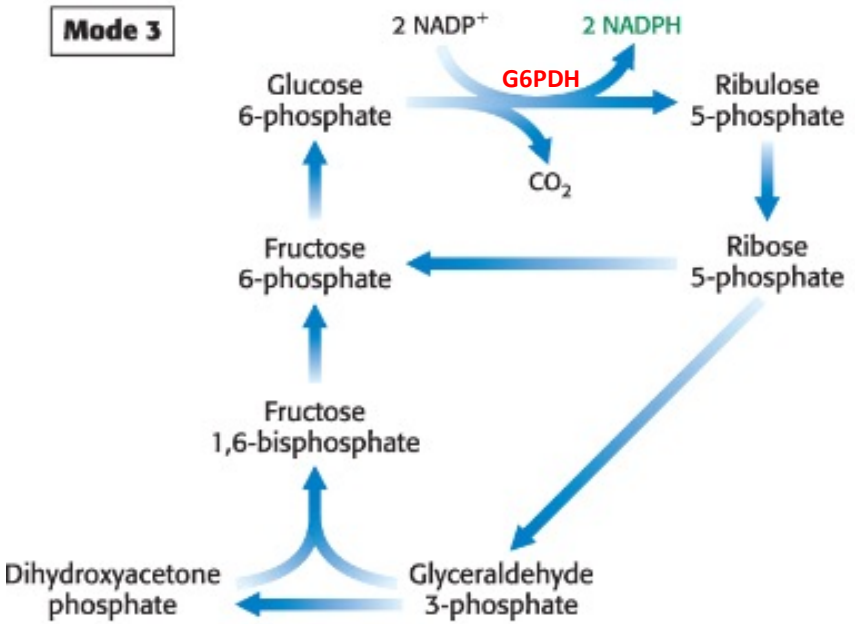
The pentose-phosphate pathway (PPP)



- Can run in various modes which are governed by cellular demands for molecules.
- Modes 1 & 2 – Ribose-5-phosphate produced for DNA synthesis (with/without NADPH)
- Mode 3 – Complete oxidation of G6P to give NADPH + CO_2
- Mode 4 – ATP and NADPH needed

G6PDH = Glucose-6-phosphate dehydrogenase

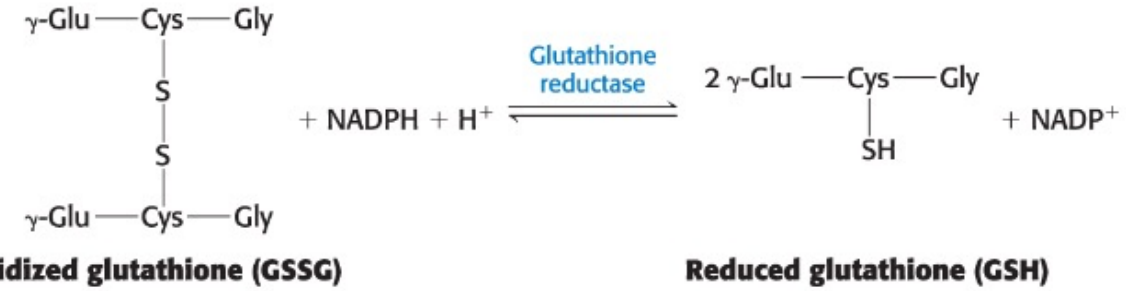
The PPP and red blood cells (RBCs)



- Glucose 6-phosphate is completely oxidised to CO_2 , producing NADPH.
- NADPH provides reducing power for maintaining reduced glutathione, a vital antioxidant in RBCs 1-POM-2-1

Glucose 6-phosphate + $12NADP^+$ + $7O_2$

→ $6CO_2$ + 12NADPH + $12H^+$ + Pi



Oxidized glutathione (GSSG) **Reduced glutathione (GSH)**

1-POM-1-1: Cell metabolism: Summarise the metabolism of carbohydrates, fats and proteins in health, exercise, illness and disease.

Progress Check

Part 1

- Glycolysis is a cytosolic process.
- 2 x ATP are made per mole of glucose
- ATP is first invested to generate a high energy compound then split to generate ATP.
- The pentose phosphate pathway runs in parallel, generating molecules for biosynthesis.

Part 2

- NAD^+ is regenerated by the production of alcohol (yeasts) or lactate (mammals).
- Acetyl CoA can be generated in the mitochondria
- Creatine phosphate buffers [ATP]

Session Plan

Part 1

An overview of metabolism

- The 6 reaction types
- The 10 reactions of glycolysis
- The pentose phosphate pathway

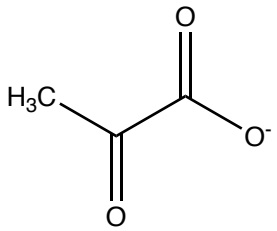
Part 2

The three fates of pyruvate

- Alcoholic fermentation
- Lactate production
- Acetyl CoA production

1-POM-1-1: Cell metabolism: Summarise the metabolism of carbohydrates, fats and proteins in health, exercise, illness and disease.

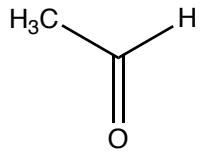
Pyruvate has three possible fates



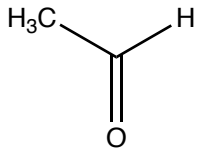
pyruvate

pyruvate decarboxylase

H^+ CO_2



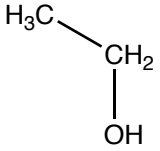
acetaldehyde



acetaldehyde

alcohol dehydrogenase

NADH + H^+ NAD^+

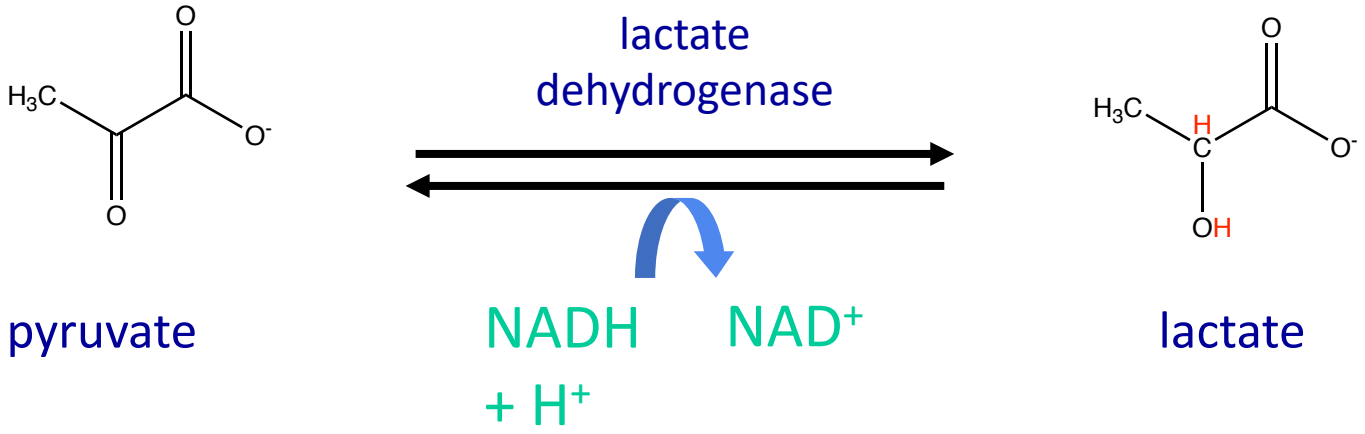


ethanol

(i) Alcoholic Fermentation

- This is characteristic of **yeasts** and can occur under **anaerobic** conditions.

Pyruvate has three possible fates



(ii) Generation of Lactate

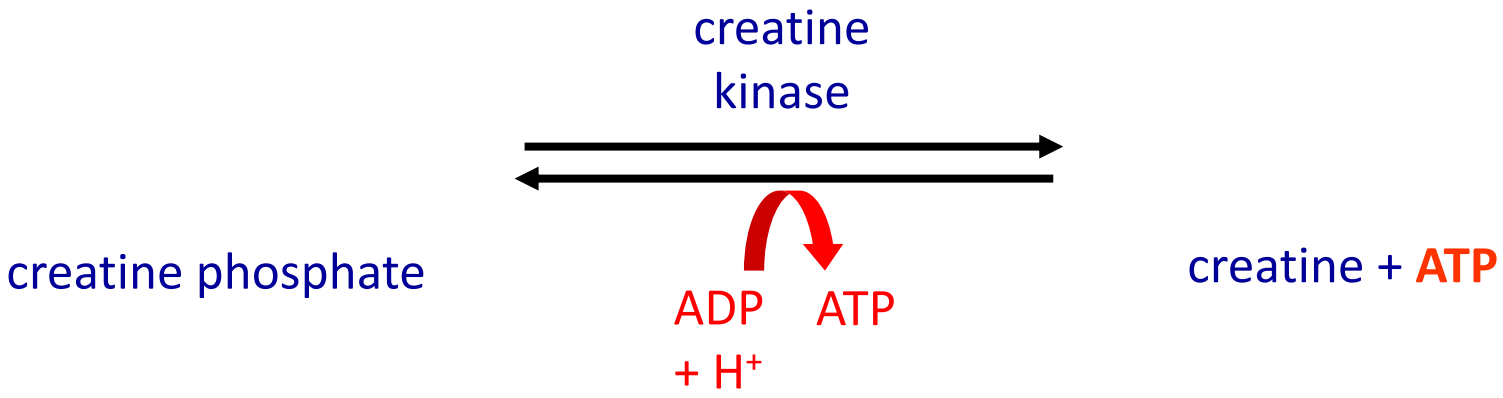
- This is also **anaerobic** and is characteristic of mammalian muscle during intense activity when oxygen is a **limiting factor**.

Regeneration of NAD^+ is essential

Both alcoholic fermentation and the generation of lactate serve one common purpose:

- They allow **NAD+** to be regenerated and thus glycolysis to continue, in conditions of oxygen deprivation.
- i.e. conditions in which the rate of **NADH** formation by glycolysis is greater than its rate of **NADH** oxidation by the respiratory chain (**MBC – Cell integrity**).
- **NAD^+** you recall, is needed for the dehydrogenation of glyceraldehyde 3-phosphate, which is the first step in generating **ATP** for the body.

Creatine phosphate as a buffer for [ATP]



- In muscle, the amount of ATP needed during exercise is only enough to sustain contraction for around one second.
- Thankfully, a large reservoir of creatine phosphate is on hand to buffer demands for phosphate (25mM creatine phosphate c.f. 4mM ATP in resting muscle).

$\Delta G^{\circ\prime}$ (hydrolysis) = -31 kJ/mole (ATP) & -43.1 kJ/mole (CP)

MBC-Creatine kinase

ATP hydrolysis during exercise

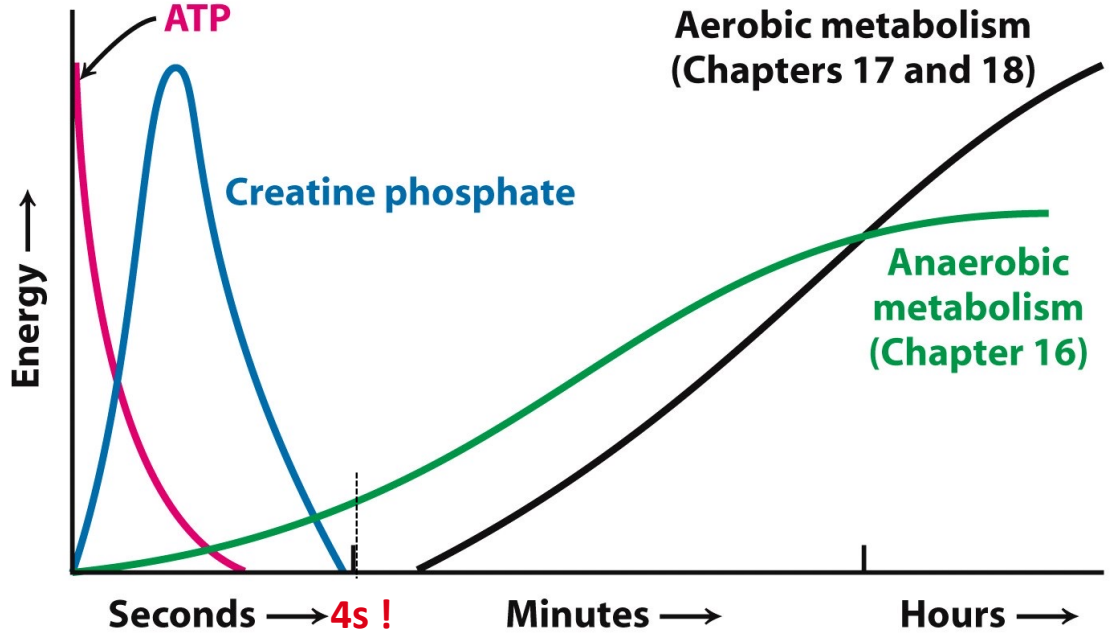
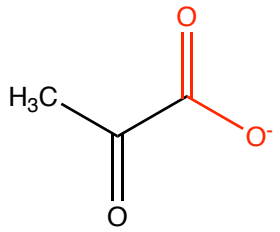


Figure 15.7
***Biochemistry*, Seventh Edition**

- Hence the use of creatine by athletes as a dietary supplement.

DOI: https://doi.org/10.1123/ijsnem.2019-0065

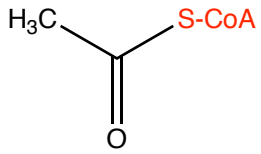
Pyruvate has three possible Fates



pyruvate + HS-CoA

pyruvate dehydrogenase complex

NAD+ NADH



acetyl CoA + CO_2

(iii) Acetyl CoA generation

This series of reactions occurs in the **mitochondria** of the cell.

The acetyl CoA thus formed is **committed** to entry into the **TCA cycle**.

Acetyl CoA

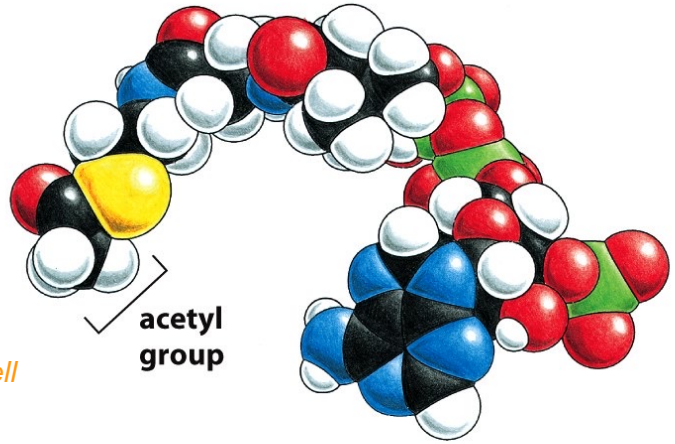
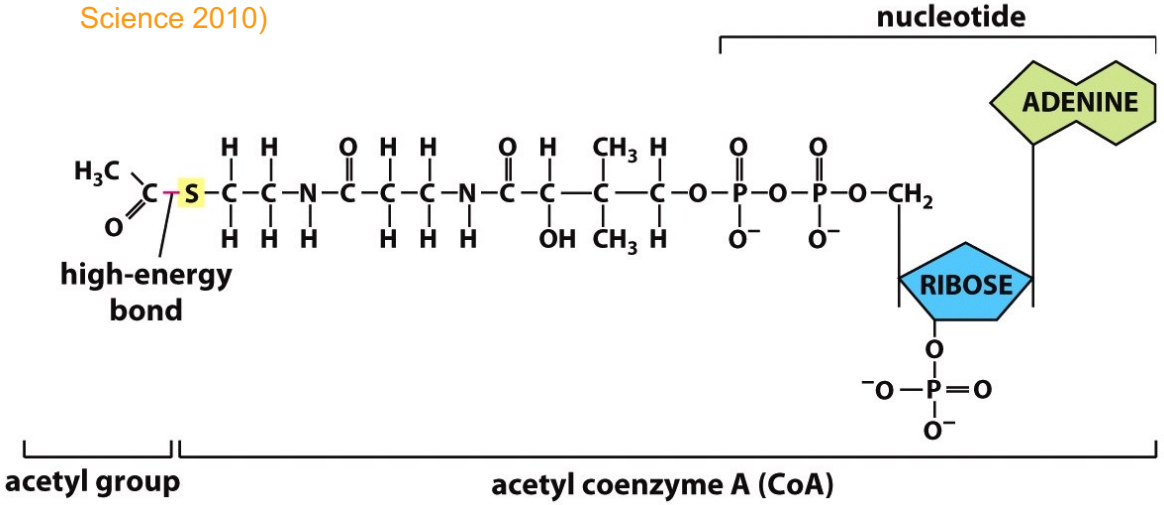


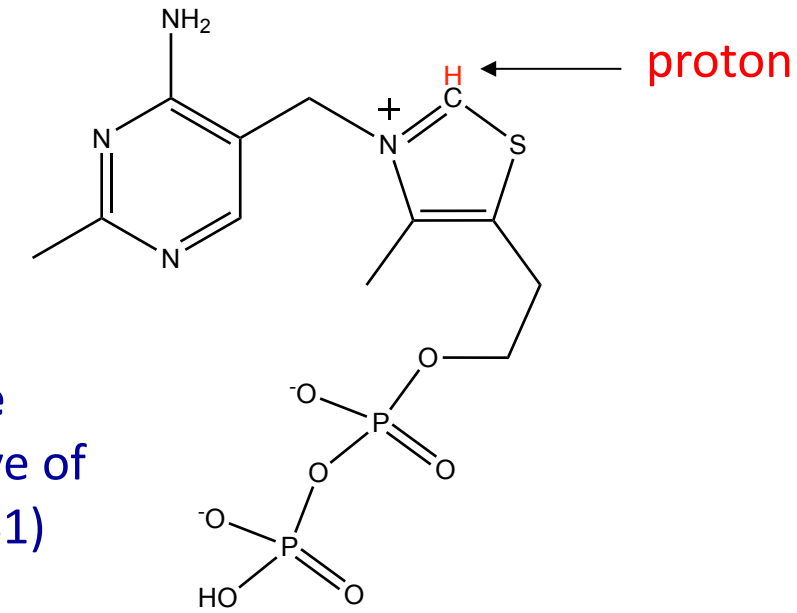
Figure 3-36 *Essential Cell Biology* (© Garland Science 2010)



- The thioester bond is a high-energy linkage, so it is readily hydrolysed, enabling acetyl CoA to donate the acetate (2C) to other molecules.
- RNA ancestry suggests it is of primeval origin.

1-POM-1-1: Cell metabolism: Summarise the metabolism of carbohydrates, fats and proteins in health, exercise, illness and disease.

Beri-Beri results from poor PDH function



proton

Thiamine
(derivative of vitamin B1)

Thiamine pyrophosphate is a cofactor of the PDH complex. It readily loses the highlighted proton and the resulting carbanion attacks pyruvate.

- A deficiency of thiamine is the cause of Beri-Beri, whose symptoms include damage to the peripheral nervous system, weakness of the musculature and decreased cardiac output.
- The brain is particularly vulnerable as it relies heavily on glucose metabolism (MBC-Integration of metabolism).

Christiaan Eijkman
1929 Nobel Prize

Progress Check

Part 1

- Glycolysis is a cytosolic process.
- 2 x ATP are made per mole of glucose
- ATP is first invested to generate a high energy compound then split to generate ATP.
- The pentose phosphate pathway runs in parallel, generating molecules for biosynthesis.

Part 2

- NAD^+ is regenerated by the production of alcohol (yeasts) or lactate (mammals).
- Acetyl CoA can be generated in the mitochondria
- Creatine phosphate buffers [ATP]