

Glycolysis

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Imports

Glycolysis

Glycolysis is a metabolic pathway involving the stepwise degradation of glucose

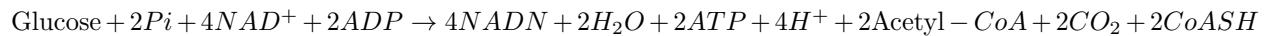
NOTE: All ATP formation which occurs in glycolysis is produced via substrate level phosphorylation.

Background

Glycolysis is a very ancient process, which arose relatively early on in evolutionary history. As a result of its age, today almost all living organisms undergo some form of glycolysis. Glycolysis is an anaerobic process, as it arose before oxygen formed a large substituent of the earth's atmosphere. Even in aerobic organisms glycolysis still remains anaerobic, although the products of glycolysis are then fed into other aerobic pathways.

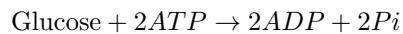
Process

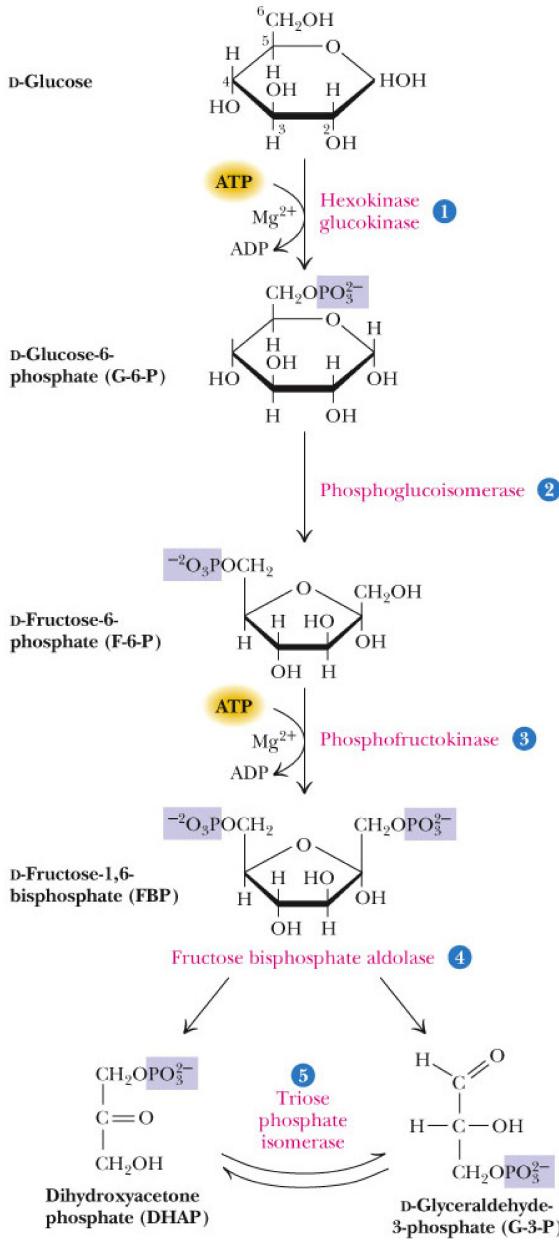
Glycolysis involves the break down of glucose molecule into pyruvate through ten enzyme catalysed steps. These ten steps can be generally grouped into two phases, the initially priming phase in which glucose is transformed into a less stable form, a process which requires energy provided by coupling with ATP hydrolysis, and the second energy release phase in which new ATP is generated. For each one molecule of glucose metabolised, two molecules of pyruvate are produced. The balanced equation for the overall reaction is as follows:



Phase #1 (Priming)

Phase one includes the first 5 reactions of glycolysis, in which, overall, Glyceraldehyde-3-phosphate is produced by the splitting of glucose. The balanced equation for this phase is as follows:



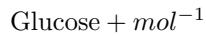


Energy requirements

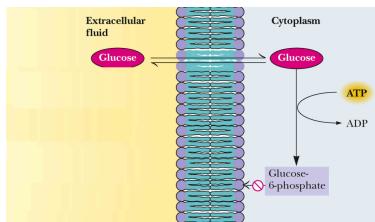
2 ATP molecules are used up in this phase.

Reaction #1

Glucose is phosphorylated by hexokinase or glucokinase to form glucose-6-phosphate. The reaction is coupled with the hydrolysis of one ATP molecule. The balanced equation for this reaction is as follows:



The phosphorylation of glucose also assist in glucose take up by the cell, as glucose in the extracellular fluid diffused in to replace the glucose used up in the cytoplasm. Once the glucose has been phosphorylated it cannot easily cross the membrane and so little is lost.



NOTE: Extracellular glucose will move into the cell as glucose is converted from glucose to glucose 6 phosphate, by the law of mass action.

NOTE: Reaction one is often referred to as the first priming reaction.

Enzymes

The reaction can be catalysed by glucokinase, or hexokinase. Both glucokinase and hexokinase require magnesium ions to function. Glucokinase only functions at high glucose levels whereas hexokinase binds glucose at low glucose concentrations, hence glucokinase is only active after consumption of a high glucose meal.

Regulation.

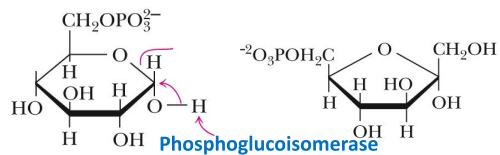
Hexokinase is one of the regulated enzymes in glycolysis, the reaction is targeted as a regulation point due to its large negative free energy change.

Energetics

The reaction itself is not thermodynamically favorable, and hence must be coupled with ATP hydrolysis to achieve spontaneity.

Reaction #2

Glucose-6 Phosphate is converted into fructose 6 phosphate by phosphoglucoisomerase. The balanced equation for the reaction is as follows.

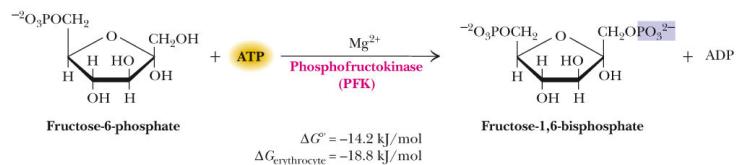


Enzyme

Phosphoglucoisomerase catalyses the reaction. This enzyme requires magnesium ions to function.

Reaction #3

Fructose-6-phosphate is phosphorylated into fructose-1,6-bisphosphate by phosphofructokinase. The reaction is natively endothermic so must be coupled with ATP Hydrolysis to occur. The balanced reaction is given as:



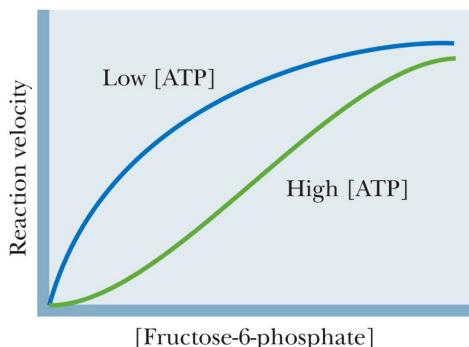
NOTE: Reaction 3 is often referred to as the second primary reaction.

Enzyme

The reaction is catalysed by phosphofructokinase.

Regulation

The phosphofructokinase reaction controls the rate of glycolysis. Intermediates of the citric acid cycle form allosteric inhibitor's which act on phosphofructokinase. More specifically phosphofructokinase is inhibited by Phosphoenolpyruvate ,citrate and ATP. Additionally low PH also has an inhibitory effect.

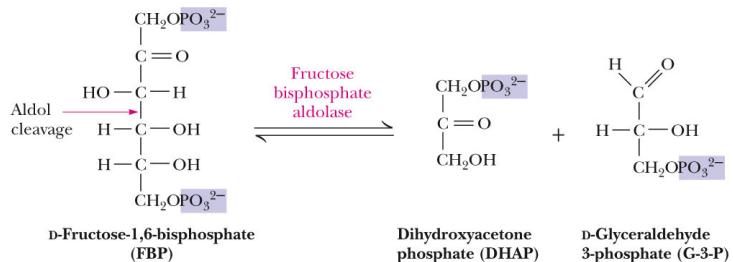


Phosphofructokinase is activated by Fructose 2-6 bisphosphate, which decreases the inhibitory effect of ATP and inhibits fructose 1,6 bisphosphatase. Fructose 2-6 bisphosphate is produced from fructose 6 phosphate so high levels of fructose 6 phosphate lead to faster fructose 6 phosphate metabolism

Reaction #4

Fructose 1,6 biphosphate is cleaved by Fructose disphosphate aldolase to form Dihydroxyacetone phosphate (DHAP), and Glyceraldehyde-3-phosphate (GAP).The ballanced equation for the reaction is:





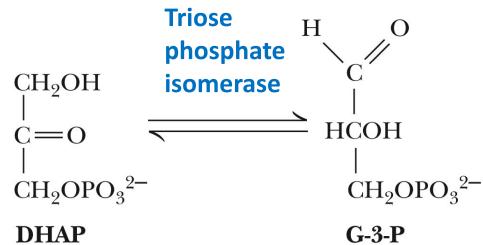
This Aldol cleavage involves the removal of a proton from the $C^{4\prime}$ -hydroxyl group in a reaction catalysed by an aspartate and a lysine residue of fructose bisphosphate aldolase.

Enzyme

The reaction is catalysed by Fructose bisphosphate aldolase.

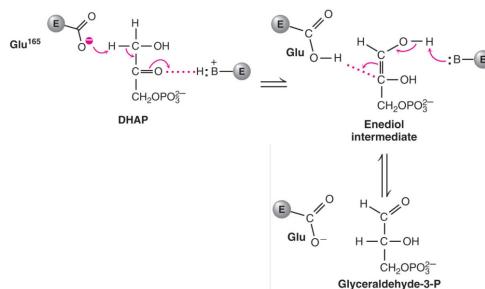
Reaction #5

Dihydroxyacetone phosphate is converted to glyceraldehyde-3-phosphate by triose phosphate isomerase. The balanced equation for the reaction is as follows:



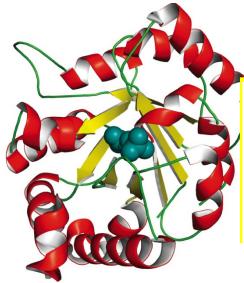
Reaction Mechanism

The DHAP is deprotonated by Glu^{165} leading to the formation of an enediol intermediate this intermediate is then reprotonated and converted to glyceraldehyde, with the Glu molecule leaving as an oxianion.



Enzyme

This reaction is catalysed by Triose phosphate isomerase.

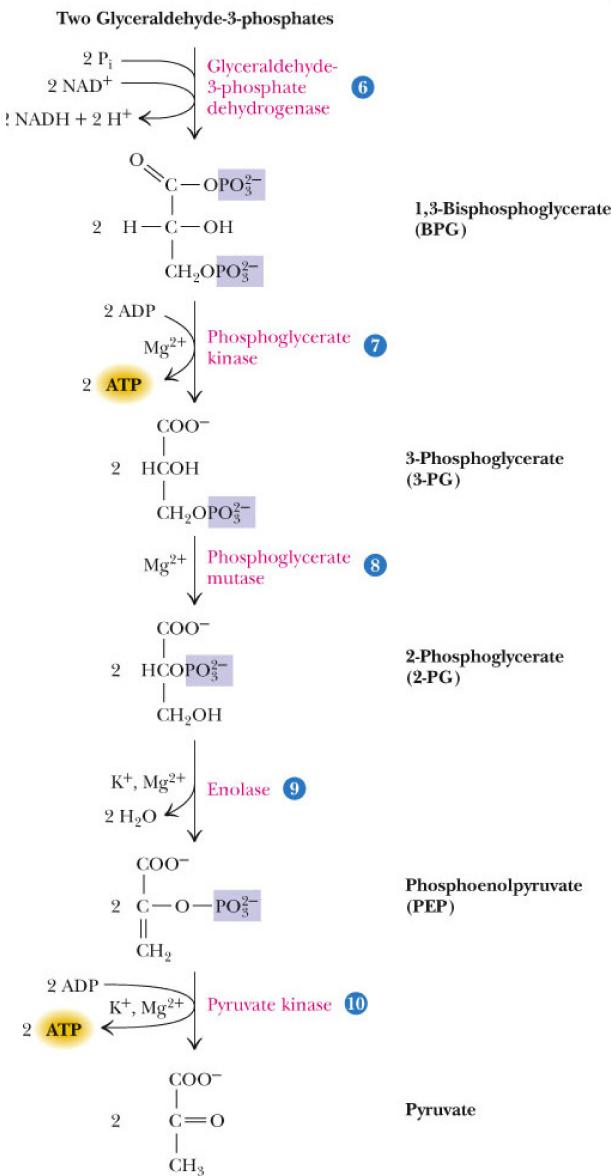


Phase #2

Phase two includes the last 5 reactions of glycolysis in which, overall, glyceraldehyde 3 phosphate is converted to pyruvate.

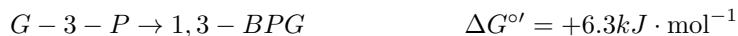
Energetics

Overall 2 ATP molecules are generated in this phase.



Reaction #6

Glyceraldehyde-3-phosphate is dehydrogenated to 1,3, bisphosphoglycerate by glyceraldehyde dehydrogenase (a high energy intermediate. The balanced equation for this reaction is as follows:



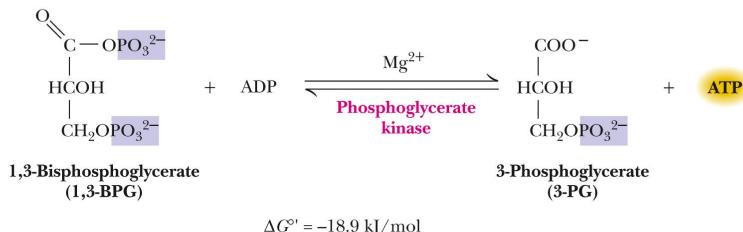
NOTE: In the absence of oxygen reaction 6 cannot occur if there is no NAD^+ the recycling of NAD^+ via the reduction of pyruvate.

Enzyme

The reaction is catalysed by glyceraldehyde dehydrogenase

reaction #7

1,3-Bisphosphoglycerate is dephosphorylated by phosphoglycerate kinase to form 3 phosphoglycerate. The reaction is coupled to ADP phosphorylation. The balanced equation for this reaction is as follows:



Enzyme

This reaction is catalysed by phosphoglycerate kinase, which is dependant on Mg²⁺ ions for its activity.

Regulation

This reaction has a large negative ΔG and hence is a site of regulation.

Cofactors

ATP Production

regenerates ATP used earlier in Glycolysis.

Energetics

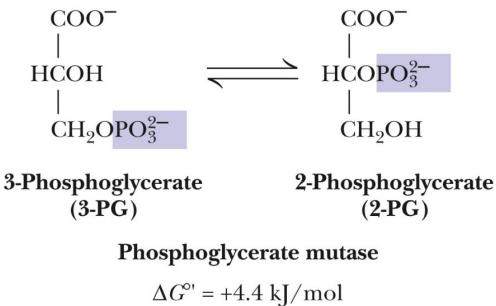
Reaction seven is highly exergonic, and so is capable of driving the endergonic reaction 6 when coupled to it. ATP is also generated making up for that used up earlier in glycolysis.

NOTE: Reaction 7 is the point at which the glycolytic pathway breaks even, that is, the magnitude of energy gained until that point equates to the magnitude of energy lost.

Reaction #8

phosphoglycerate is converted into 2 phosphoglycerate by phosphoglycerate mutase. (mutases move only one functional group). The Ballanced equation for this reaction is as follows:





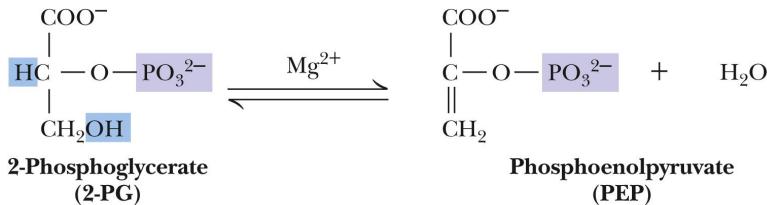
NOTE: This reaction prepares the substrate for the following reaction involving the synthesis of ATP, i.e. it helps prime the phosphate group for removal.

Reaction #9

2 phosphoglyverate is dehydrated to phosphoenolpyruvate by enolase.

Enzyme

This reaction is catalysed by Enolase, which requires Mg^{2+} ions to facilitate its activity. The balanced equation for the reaction is as follows:



The molecule is much less stable in its enol form so although it has gained only a small amount of energy, it still constitutes the much higher energy molecule.

NOTE: Enols tautomerise naturally to ketones.

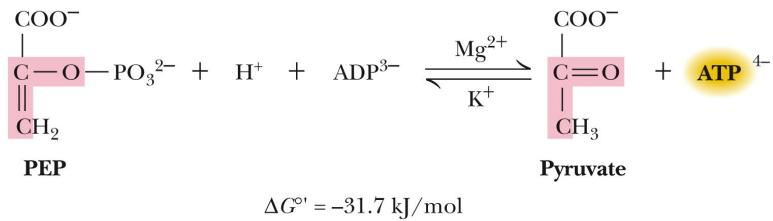
Reaction #10

Phosphoenolpyruvate is dephosphorylated by Pyruvate kinase to form Pyruvate. The reaction is coupled with ATP synthesis with the phosphoryl group removed from the PEP added directly to an ADP molecule. The pyruvate enol tautomer is rapidly converted into the more favourable keto tautomer. The balanced equation for the reaction is as follows:



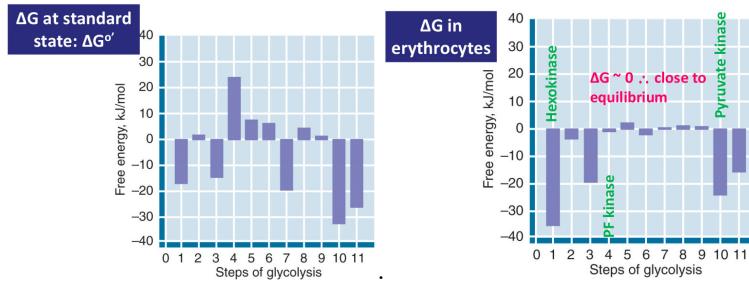
Enzyme

This reaction is catalysed by pyruvate kinase (phosphoenolpyruvate phosphatase), which requires Mg^{2+} and K^+ to function.



Energetics

An analysis of the biological standard free energy change for each reaction reveals no overall trends. However, under full physiological conditions the free energies are all very close to zero with ATP/ADP coupled reactions being highly exergonic.



Location

Glycolysis takes place within the cytoplasm.

Biological significance

Glycolysis is a particularly important process as in many cases glucose is the only source of metabolic energy. Cells of the brain kidney contractual skeletal muscles, erythrocytes, and sperm cell, are all solely reliant on glycolysis for energy.

Products

Pyruvate is a versatile metabolite, which can be fed into a number of different additional catabolic pathways.