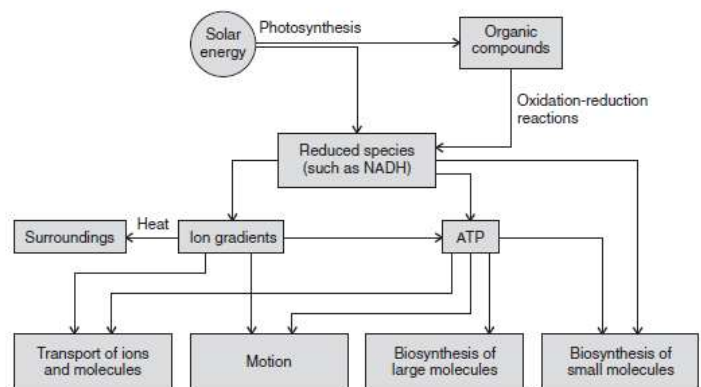


Bioenergetics

- Living cells and organisms must perform work to stay alive, to grow, and to reproduce.
- The ability to harness energy and to channel it into biological work is a fundamental property of all living organisms.
- Modern organisms carry out a remarkable variety of energy transductions, conversions of one form of energy to another.
- They use the chemical energy in fuels to bring about the synthesis of complex, highly ordered macromolecules from simple precursors.
- They also convert the chemical energy of fuels into: concentration gradients and electrical gradients, into motion and heat, and, in a few organisms such as fireflies and some deep-sea fish, into light.
- Photosynthetic organisms transduce light energy into all these other forms of energy.
- Biological energy transductions obey the laws of thermodynamics that govern all other natural processes.



Bioenergetics

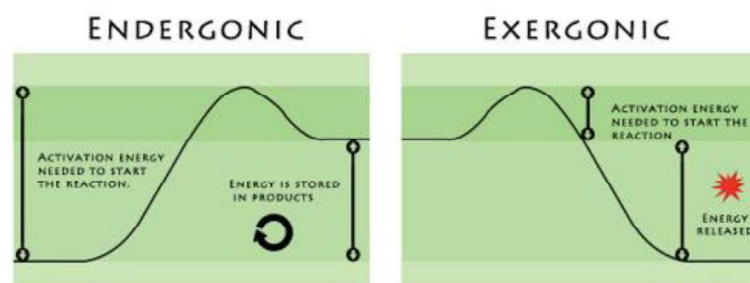
- Bioenergetics is the quantitative study of the energy transductions that occur in living cells and of the nature and function of the chemical processes underlying these transductions.
- Living organisms consist of collections of molecules much more highly organized than the surrounding materials from which they are constructed, and organisms maintain and produce order, seemingly contradictory to the second law of thermodynamics.

- But living organisms do not violate the second law; they operate strictly within it.
- The reacting system is the collection of matter that is undergoing a particular chemical or physical process; it may be an organism, a cell, or two reacting compounds.
- The reacting system and its surroundings together constitute the universe.
- The second law of thermodynamics states that the entropy *of the universe* increases during all chemical and physical processes, but it does not require that the entropy increase take place *in the reacting system* itself.
- The order produced within cells as they grow and divide is more than compensated for by the disorder they create in their surroundings in the course of growth and division.
- Living cells and organisms are open systems, exchanging both material and energy with their surroundings.
- Living systems are never at equilibrium with their surroundings.
- Living organisms preserve their internal order by taking from the surroundings free energy in the form of nutrients or sunlight, and returning to their surroundings an equal amount of energy as heat and entropy.

Gibbs energy drives life

- Cells are isothermal systems—they function at essentially constant temperature (they also function at constant pressure).
- Heat flow is not a source of energy for cells, because heat can do work only as it passes to a zone or object at a lower temperature.
- The energy that cells can and must use is free energy, described by the Gibbs energy function G , which allows prediction of the direction of chemical reactions, their exact equilibrium position, and the amount of work they can in theory perform at constant temperature and pressure.

- In closed systems, chemical reactions proceed spontaneously until **equilibrium** is reached. When a system is at equilibrium, the rate of product formation exactly equals the rate at which product is converted to reactant.
- Thus there is no net change in the concentration of reactants and products; a *steady state* is achieved. The energy change as the system moves from its initial state to equilibrium, with no changes in temperature or pressure, is given by the Gibbs free energy change, G .
- The magnitude of G depends on the particular chemical reaction and on how far from equilibrium the system is initially.
- Each compound involved in a chemical reaction contains a certain amount of potential energy, related to the kind and number of its bonds.
- In reactions that occur spontaneously, the products have less free energy than the reactants, thus the reaction releases free energy, which is then available to do work.
- Only part of the energy released in exergonic chemical reactions can be used to accomplish work. In living systems some energy is dissipated as heat or lost to increasing entropy.
- Such reactions are exergonic; the decline in free energy from reactants to products is expressed as a negative value.
- Endergonic reactions require an input of energy, and their G values are positive.



ATP as the energy currency

- Heterotrophic cells acquire free energy from nutrient molecules, and photosynthetic cells acquire it from absorbed solar radiation.
- Both kinds of cells transform this free energy into ATP and other energy-rich compounds capable of providing energy for biological work at constant temperature.

- The composition of a reacting system (a mixture of chemical reactants and products) tends to continue changing until equilibrium is reached.
- At the equilibrium concentration of reactants and products, the rates of the forward and reverse reactions are exactly equal and no further net change occurs in the system.
- The concentrations of reactants and products *at equilibrium* define the equilibrium constant, K_{eq} .
- In the general reaction $aA + bB \rightleftharpoons cC + dD$, where a , b , c , and d are the number of molecules of A, B, C, and D participating, the equilibrium constant is given by

$$K_{\text{eq}} = \frac{[C]^c [D]^d}{[A]^a [B]^b}$$

- where [A], [B], [C], and [D] are the molar concentrations of the reaction components at the point of equilibrium.

- Under standard conditions, the force driving the system toward equilibrium is defined as the standard free-energy change, ΔG° .
- By this definition, the standard state for reactions that involve hydrogen ions is $[H^+] = 1 \text{ M}$, or $\text{pH} = 0$.
- Most biochemical reactions, however, occur in well-buffered aqueous solutions near $\text{pH} 7$; both the pH and the concentration of water (55.5 M) are essentially constant.
- For convenience of calculations, biochemists therefore define a different standard state, the biological standard state, in which the concentration of $[H^+]$ is 10^{-7} M ($\text{pH} = 7$) and that of water is 55.5 M ; for reactions that involve Mg^{2+} (including most in which ATP is a reactant), its concentration in solution is commonly taken to be constant at 1 mM .
- Physical constants based on this biochemical standard state are called **biological standard state** or **transformed standard state constants** and are written as (such as $\Delta G'^\circ$ and K'_{eq}) to distinguish them.

$$\Delta G'^\circ = -RT \ln K'_{\text{eq}}$$

- If the equilibrium constant for a given chemical reaction is 1.0, the standard free-energy change of that reaction is 0.0 (the natural logarithm of 1.0 is zero).
- If K_{eq}' of a reaction is greater than 1.0, its $\Delta G'^{\circ}$ is negative.
- If K_{eq}' is less than 1.0, $\Delta G'^{\circ}$ is positive.
- Because the relationship between $\Delta G'^{\circ}$ and K_{eq}' is exponential, relatively small changes in $\Delta G'^{\circ}$ correspond to large changes in K_{eq}' .

TABLE 13-2 Relationship between the Equilibrium Constants and Standard Free-Energy Changes of Chemical Reactions

K'_{eq}	$\Delta G'^{\circ}$	
	(kJ/mol)	(kcal/mol)*
10^3	-17.1	-4.1
10^2	-11.4	-2.7
10^1	-5.7	-1.4
1	0.0	0.0
10^{-1}	5.7	1.4
10^{-2}	11.4	2.7
10^{-3}	17.1	4.1
10^{-4}	22.8	5.5
10^{-5}	28.5	6.8
10^{-6}	34.2	8.2

- It may be helpful to think of the standard free energy change in another way: $\Delta G'^{\circ}$ is the difference between the free-energy content of the products and the free-energy content of the reactants, under standard conditions.
- When $\Delta G'^{\circ}$ is negative, the products contain less free energy than the reactants and the reaction will proceed spontaneously under standard conditions; all chemical reactions tend to go in the direction that results in a decrease in the free energy of the system.
- A positive value of $\Delta G'^{\circ}$ means that the products of the reaction contain more free energy than the reactants, and this reaction will tend to go in the reverse direction.

TABLE 13–3 Relationships among K'_{eq} , $\Delta G'^{\circ}$, and the Direction of Chemical Reactions under Standard Conditions

When K'_{eq} is . . .	$\Delta G'^{\circ}$ is . . .	Starting with all components at 1 M, the reaction . . .
>1.0	negative	proceeds forward
1.0	zero	is at equilibrium
<1.0	positive	proceeds in reverse

- Calculate the standard free-energy change of the reaction catalyzed by the enzyme phosphoglucomutase given below information:



- Chemical analysis shows that whether we start with, say, 20 mM glucose 1-phosphate (but no glucose 6-phosphate) or with 20 mM glucose 6-phosphate (but no glucose 1-phosphate), the final equilibrium mixture at 25°C and pH = 7.0 will be the same: 1 mM glucose 1-phosphate and 19 mM glucose 6-phosphate.

$$K'_{\text{eq}} = \frac{[\text{glucose 6-phosphate}]}{[\text{glucose 1-phosphate}]} = \frac{19 \text{ mM}}{1 \text{ mM}} = 19$$

$$\begin{aligned} \Delta G'^{\circ} &= -RT \ln K'_{\text{eq}} \\ &= -(8.315 \text{ J/mol} \cdot \text{K})(298 \text{ K})(\ln 19) \\ &= -7.3 \text{ kJ/mol} \end{aligned}$$

- Because the standard free-energy change is negative, when the reaction starts with 1.0 M glucose 1-phosphate and 1.0 M glucose 6-phosphate, the conversion of glucose 1-phosphate to glucose 6-phosphate proceeds with a loss (release) of free energy.
- For the reverse reaction (the conversion of glucose 6-phosphate to glucose 1-phosphate), $\Delta G'^{\circ}$ has the same magnitude but the opposite sign.

- We must be careful to distinguish between two different quantities: the free-energy change, ΔG , and the standard free-energy change, $\Delta G'^{\circ}$.
- Each chemical reaction has a characteristic standard free-energy change, which may be positive, negative, or zero, depending on the equilibrium constant of the reaction.
- The standard free energy change tells us in which direction and how far a given reaction must go to reach equilibrium *when the initial concentration of each component is 1.0 M*, the pH is 7.0, the temperature is 25°C, and the pressure is 101.3 kPa.
- Thus $\Delta G'^{\circ}$ is a constant: it has a characteristic, unchanging value for a given reaction. But the *actual* free-energy change, ΔG , is a function of reactant and product concentrations and of the temperature prevailing during the reaction, which will not necessarily match the standard conditions as defined above.
- Moreover, the ΔG of any reaction proceeding spontaneously toward its equilibrium is always negative, becomes less negative as the reaction proceeds, and is zero at the point of equilibrium, indicating that no more work can be done by the reaction.

- ΔG and $\Delta G'^{\circ}$ for any reaction $A + B \rightleftharpoons C + D$ are related by the equation:

$$\Delta G = \Delta G'^{\circ} + RT \ln \frac{[C][D]}{[A][B]}$$

- When the reaction is in equilibrium $\Delta G = 0$

$$0 = \Delta G = \Delta G'^{\circ} + RT \ln \frac{[C]_{\text{eq}}[D]_{\text{eq}}}{[A]_{\text{eq}}[B]_{\text{eq}}}$$

$$\Delta G'^{\circ} = -RT \ln K'_{\text{eq}}$$

- However, the criterion for spontaneity of a reaction is the value of ΔG , not $\Delta G'^{\circ}$.

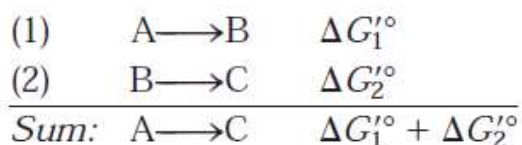
Enzymes lower the activation energy barrier

- Another important point is that some thermodynamically favorable reactions (that is, reactions for which ΔG° is large and negative) do not occur at measurable rates.
- For example, combustion of firewood to CO_2 and H_2O is very favorable thermodynamically, but firewood remains stable for years because the activation energy for the combustion reaction is higher than the energy available at room temperature.
- If the necessary activation energy is provided (with a lighted match, for example), combustion will begin, converting the wood to the more stable products CO_2 and H_2O and releasing energy as heat and light.
- The heat released by this exothermic reaction provides the activation energy for combustion of neighboring regions of the firewood; the process is self-perpetuating.
- In living cells, reactions that would be extremely slow *if uncatalyzed* are caused to proceed, not by supplying additional heat but by lowering the activation energy with an enzyme.
- An enzyme provides an alternative reaction pathway with a lower activation energy than the uncatalyzed reaction, so that at room temperature a large fraction of the substrate molecules have enough thermal energy to overcome the activation barrier, and the reaction rate increases dramatically.

Enzymes increase the rate of the reactions

- *The free-energy change for a reaction is independent of the pathway by which the reaction occurs;* it depends only on the nature and concentration of the initial reactants and the final products.
- Enzymes cannot, therefore, change equilibrium constants; but they can and do increase the *rate* at which a reaction proceeds in the direction dictated by thermodynamics.

- In the case of two sequential chemical reactions, $A \leftrightarrow B$ and $B \leftrightarrow C$, each reaction has its own equilibrium constant and each has its characteristic standard free energy change, $\Delta G'_1{}^\circ$ and $\Delta G'_2{}^\circ$.
- As the two reactions are sequential, B cancels out to give the overall reaction $A \leftrightarrow C$, which has its own equilibrium constant and thus its own standard free-energy change, $\Delta G'_{\text{total}}{}^\circ$.
- *Since the G values of sequential chemical reactions are additive, for the overall reaction $A \leftrightarrow C$, $\Delta G'_{\text{total}}{}^\circ$ is the sum of the individual standard free-energy changes, $\Delta G'_1{}^\circ$ and $\Delta G'_2{}^\circ$, of the two reactions: $\Delta G'_{\text{total}}{}^\circ = \Delta G'_1{}^\circ + \Delta G'_2{}^\circ$.*

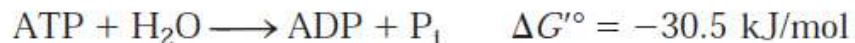


Coupled Reactions in Bioenergetics

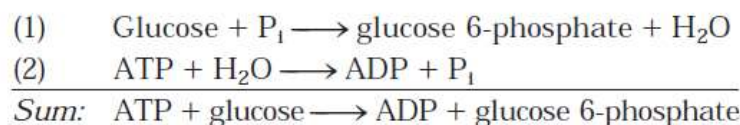
- This principle of bioenergetics explains how a thermodynamically unfavorable (endergonic) reaction can be driven in the forward direction by coupling it to a highly exergonic reaction through a common intermediate.
- For example, the synthesis of glucose 6-phosphate is the first step in the utilization of glucose by many organisms:



- The positive value of G predicts that under standard conditions the reaction will tend not to proceed spontaneously in the direction written. Another cellular reaction, the hydrolysis of ATP to ADP and P_i , is very exergonic:



- These two reactions share the common intermediates P_i and H_2O and may be expressed as sequential reactions:



- The overall standard free-energy change is obtained by adding the $\Delta G'^{\circ}$ values for individual reactions:

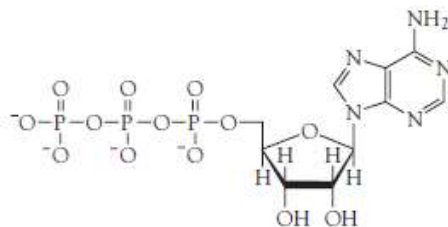
$$\Delta G'^{\circ} = 13.8 \text{ kJ/mol} + (-30.5 \text{ kJ/mol}) = -16.7 \text{ kJ/mol}$$

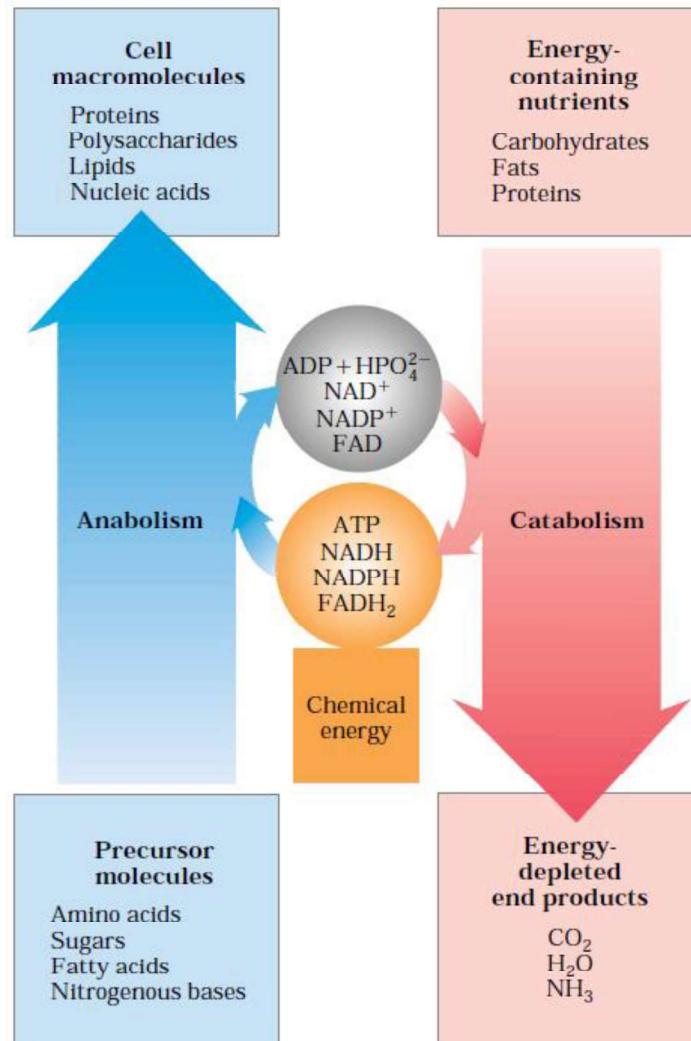
- The overall reaction is exergonic. In this case, energy stored in ATP is used to drive the synthesis of glucose 6-phosphate, even though its formation from glucose and inorganic phosphate (P_i) is endergonic.
- The *pathway* of glucose 6-phosphate formation by phosphoryl transfer from ATP is different from reactions (1) and (2) above, but the net result is the same as the sum of the two reactions (independent of the path).

- This common-intermediate strategy is employed by all living cells in the synthesis of metabolic intermediates and cellular components since most chemical reactions taking place in biological cells are either endothermic or exothermic, and cellular processes can continue only as long as there is a steady supply of energy to the cell.
- Obviously, the strategy works only if compounds such as ATP are continuously available.
- Furthermore, as we have seen previously, only the *conversion* of the supplied energy from one form to another or its transfer from place to place is possible.

ATP as the energy currency that links catabolism and anabolism

- Heterotrophic cells obtain free energy in a chemical form by the catabolism of nutrient molecules, and they use that energy to make ATP from ADP and Pi.
- ATP then donates some of its chemical energy to endergonic processes such as the synthesis of metabolic intermediates and macromolecules from smaller precursors, the transport of substances across membranes against concentration gradients, and mechanical motion.
- This donation of energy from ATP generally involves the covalent participation of ATP in the reaction that is to be driven, with the eventual result that ATP is converted to ADP and Pi or, in some reactions, to AMP and 2 Pi.



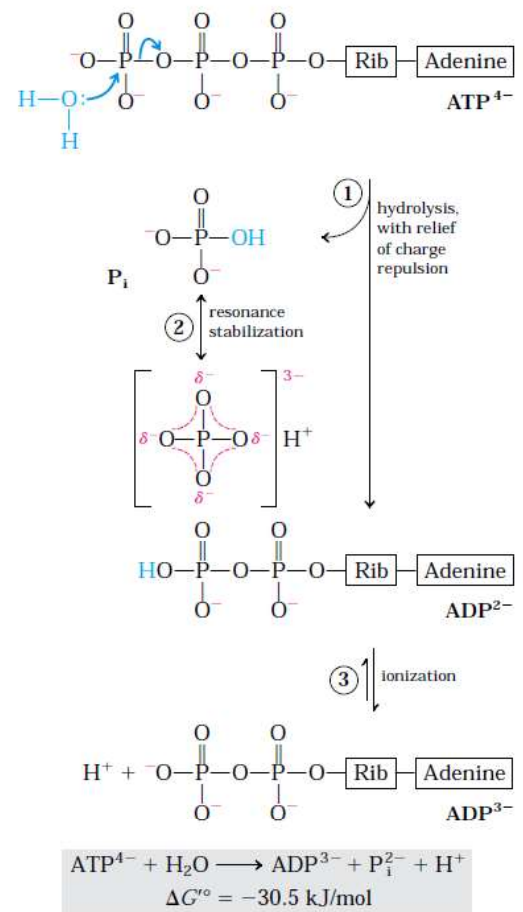


- We discuss here the chemical basis for the large free-energy changes that accompany hydrolysis of ATP and other high-energy phosphate compounds, and we show that most cases of energy donation by ATP involve group transfer, not simple hydrolysis of ATP.
- To illustrate the range of energy transductions in which ATP provides the energy, we consider the synthesis of information-rich macromolecules, the transport of solutes across membranes, and motion produced by muscle contraction.

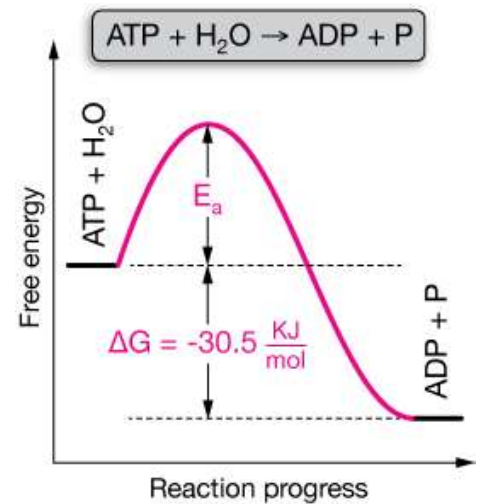
The chemical basis for the relatively large, negative, standard free energy of hydrolysis of ATP.

- The hydrolytic cleavage of the terminal phosphoric acid anhydride (phosphoanhydride) bond in ATP separates one of the three negatively charged phosphates and thus relieves some of the electrostatic repulsion in ATP; the P_i (HPO_4^{2-}) released is stabilized by the formation of several resonance forms not possible in ATP; and ADP^{2-} , the other direct product of hydrolysis, immediately ionizes, releasing H into a medium of very low $[H] = (\sim 10^{-7} \text{ M})$.
- Because the concentrations of the direct products of ATP hydrolysis are, in the cell, far below the concentrations at equilibrium, mass action favors the hydrolysis reaction in the cell.

	Concentration (mM)*			
	ATP	ADP ⁺	AMP	P _i
Rat hepatocyte	3.38	1.32	0.29	4.8
Rat myocyte	8.05	0.93	0.04	8.05
Rat neuron	2.59	0.73	0.06	2.72
Human erythrocyte	2.25	0.25	0.02	1.65
<i>E. coli</i> cell	7.90	1.04	0.82	7.9



- Although the hydrolysis of ATP is highly exergonic ($\Delta G'^{\circ} = -30.5$ kJ/mol), the molecule is kinetically stable at pH = 7 because the activation energy for ATP hydrolysis is relatively high.
- Rapid cleavage of the phosphoanhydride bonds occurs only when catalyzed by an enzyme.



- The standard free energy of hydrolysis of ATP is - 30.5 kJ/mol.
- In the cell, however, the concentrations of ATP, ADP, and Pi are not only unequal but much lower than the standard 1 M concentrations.
- Moreover, the cellular pH may differ somewhat from the standard pH of 7.0.
- Thus the *actual* free energy of hydrolysis of ATP under intracellular conditions (ΔG_p) differs from the standard free-energy change, $\Delta G'^{\circ}$.

- In human erythrocytes, the concentrations of ATP, ADP, and Pi are 2.25, 0.25, and 1.65 mM, respectively. Assume that the pH is 7.0 and the temperature is 25 C. Calculate the actual free energy of hydrolysis of ATP in the erythrocyte.

$$\Delta G_p = \Delta G'^{\circ} + RT \ln \frac{[\text{ADP}][\text{P}_i]}{[\text{ATP}]}$$

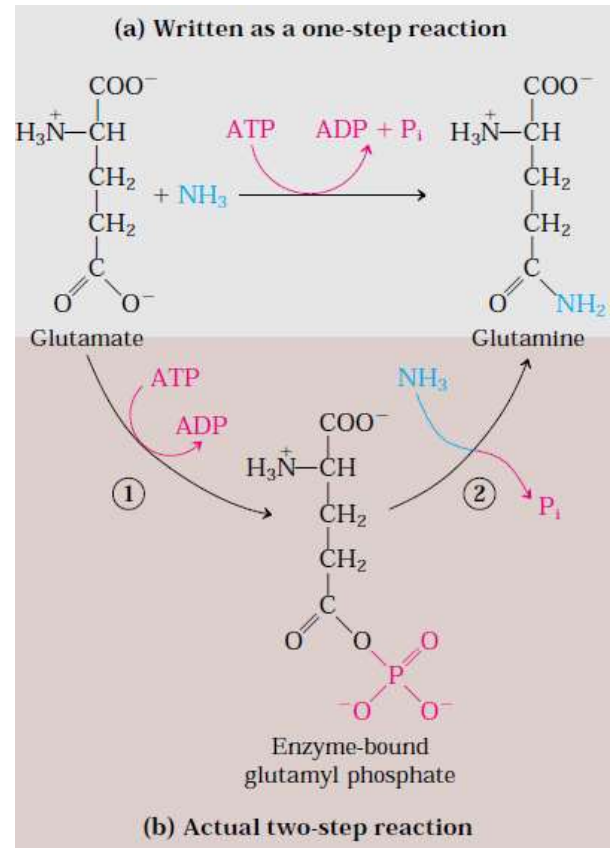
$$\Delta G_p = -30.5 \text{ kJ/mol} + \left[(8.315 \text{ J/mol} \cdot \text{K})(298 \text{ K}) \ln \frac{(0.25 \times 10^{-3})(1.65 \times 10^{-3})}{2.25 \times 10^{-3}} \right]$$

$$\begin{aligned} &= -30.5 \text{ kJ/mol} + (2.48 \text{ kJ/mol}) \ln 1.8 \times 10^{-4} \\ &= -30.5 \text{ kJ/mol} - 21 \text{ kJ/mol} \\ &= -52 \text{ kJ/mol} \end{aligned}$$

Thus ΔG_p , the actual free-energy change for ATP hydrolysis in the intact erythrocyte (-52 kJ/mol), is much larger than the standard free-energy change (-30.5 kJ/mol). By the same token, the free energy required to *synthesize* ATP from ADP and Pi under the conditions prevailing in the erythrocyte would be 52 kJ/mol.

Because the concentrations of ATP, ADP, and Pi differ from one cell type to another, ΔG_p for ATP hydrolysis likewise differs among cells. Moreover, in any given cell, ΔG_p can vary from time to time, depending on the metabolic conditions in the cell and how they influence the concentrations of ATP, ADP, Pi, and H (pH).

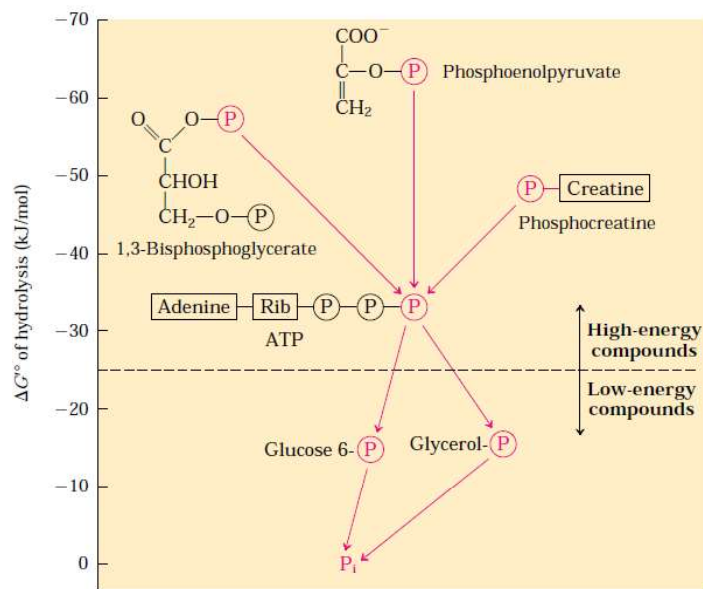
- The reactions or processes for which ATP supplies energy, and the contribution of ATP to these reactions is commonly indicated with a single arrow showing the conversion of ATP to ADP and Pi (or, in some cases, of ATP to AMP and pyrophosphate, PPi).
- When written this way, these reactions of ATP appear to be simple hydrolysis reactions in which water displaces Pi (or PPi), and one is tempted to say that an ATP-dependent reaction is “driven by the hydrolysis of ATP.”
- ATP hydrolysis per se usually accomplishes nothing but the liberation of heat, which cannot drive a chemical process in an isothermal system.
- A single reaction arrow almost invariably represents a two-step process in which part of the ATP molecule, a phosphoryl or pyrophosphoryl group or the adenylate moiety (AMP), is first transferred to a substrate molecule or to an amino acid residue in an enzyme, becoming covalently attached to the substrate or the enzyme and raising its free-energy content. Then, in a second step, the phosphate-containing moiety transferred in the first step is displaced, generating Pi, PPi, or AMP.
- Thus ATP participates *covalently* in the enzyme-catalyzed reaction to which it contributes free energy.



Free energy change accompanying ATP hydrolysis can only be used when this reaction is coupled to another by the contribution of an enzyme

- Some processes *do* involve direct hydrolysis of ATP (or GTP), however.
- For example, noncovalent binding of ATP (or of GTP), followed by its hydrolysis to ADP (or GDP) and P_i , can provide the energy to cycle some proteins between two conformations, producing mechanical motion.
- This occurs in muscle contraction and in the movement of enzymes along DNA or of ribosomes along messenger RNA.
- The energy-dependent reactions catalyzed by helicases, RecA protein, and some topoisomerases also involve direct hydrolysis of phosphoanhydride bonds.
- GTP-binding proteins that act in signaling pathways directly hydrolyze GTP to drive conformational changes that terminate signals triggered by hormones or by other extracellular factors.

- The phosphate compounds found in living organisms can be divided somewhat arbitrarily into two groups, based on their standard free energies of hydrolysis:
 - “High-energy” compounds have a $\Delta G'^{\circ}$ of hydrolysis more negative than -25 kJ/mol;
 - “Low-energy” compounds have a less negative $\Delta G'^{\circ}$ than -25 kJ/mol.
- Based on this criterion, ATP, with a $\Delta G'^{\circ}$ of hydrolysis of -30.5 kJ/mol (-7.3 kcal/mol), is a high-energy compound; glucose 6-phosphate, with a $\Delta G'^{\circ}$ of hydrolysis of -13.8 kJ/mol (-3.3 kcal/mol), is a low-energy compound.



- The term “high-energy phosphate bond,” long used by biochemists to describe the PO-O bond broken in hydrolysis reactions, is incorrect and misleading as it wrongly suggests that the bond itself contains the energy.
- In fact, the breaking of all chemical bonds requires an *input* of energy.
- The free energy released by hydrolysis of phosphate compounds does not come from the specific bond that is broken; it results from the products of the reaction having a lower free-energy content than the reactants.
- However, we will use “high-energy phosphate compound” when referring to ATP or other phosphate compounds with a large, negative, standard free energy of hydrolysis.

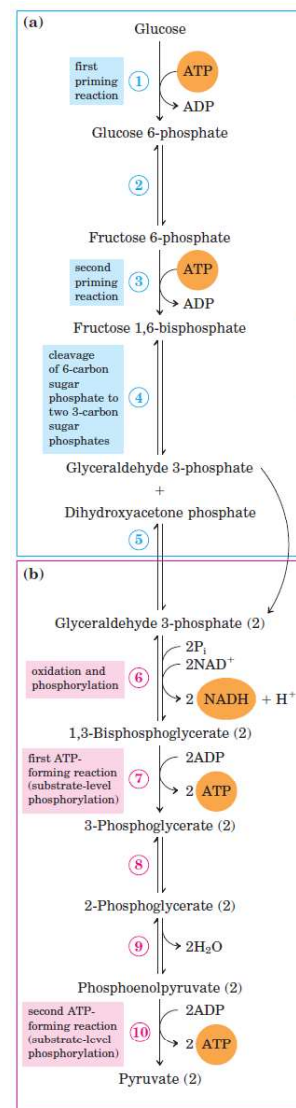
Average Bond Energies (kJ/mol)			
Bond	Energy	Bond	Energy
Single Bonds			
H—H	432	N—H	391
H—F	565	N—N	160
H—Cl	427	N—P	209
H—Br	363	N—O	201
H—I	295	N—F	272
		N—Cl	200
C—H	413	N—Br	243
C—C	347	N—I	159
C—Si	301		
C—N	305	O—H	467
C—O	358	O—P	351
C—P	264	O—O	204
C—S	259	O—S	265
C—F	453	O—F	190
C—Cl	339	O—Cl	203
C—Br	276	O—Br	234
C—I	216	O—I	234

- As is evident from the additivity of free-energy changes of sequential reactions, any phosphorylated compound can be synthesized by coupling the synthesis to the breakdown of another phosphorylated compound with a more negative free energy of hydrolysis.
- For example, because cleavage of P_i from phosphoenolpyruvate (PEP) releases more energy than is needed to drive the condensation of P_i with ADP, the direct donation of a phosphoryl group from PEP to ADP is thermodynamically feasible:

		$\Delta G'^{\circ}$ (kJ/mol)
(1)	$\text{PEP} + \text{H}_2\text{O} \longrightarrow \text{pyruvate} + P_i$	-61.9
(2)	$\text{ADP} + P_i \longrightarrow \text{ATP} + \text{H}_2\text{O}$	+30.5
<i>Sum:</i>	$\text{PEP} + \text{ADP} \longrightarrow \text{pyruvate} + \text{ATP}$	-31.4

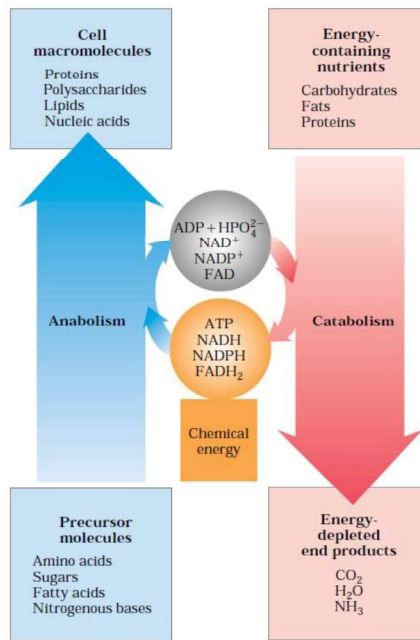
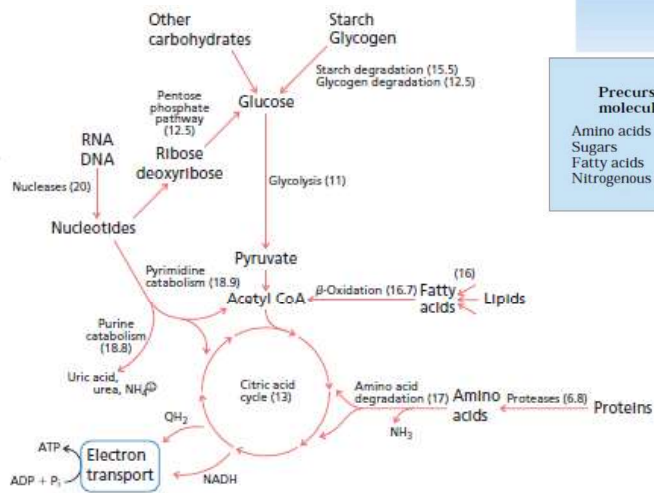
- Much of catabolism is directed toward the synthesis of high-energy phosphate compounds, but their formation is not an end in itself; they are the means of activating a very wide variety of compounds for further chemical transformation.
- The transfer of a phosphoryl group to a compound effectively puts free energy into that compound, so that it has more free energy to give up during subsequent metabolic transformations.

- We previously described how the synthesis of glucose 6-phosphate is accomplished by phosphoryl group transfer from ATP.
- This phosphorylation of glucose activates, or “primes,” the glucose for catabolic reactions that occur in nearly every living cell.
- Because of its intermediate position on the scale of group transfer potential, ATP can carry energy from high-energy phosphate compounds produced by catabolism to compounds such as glucose, converting them into more reactive species.
- ATP thus serves as the universal energy currency in all living cells.

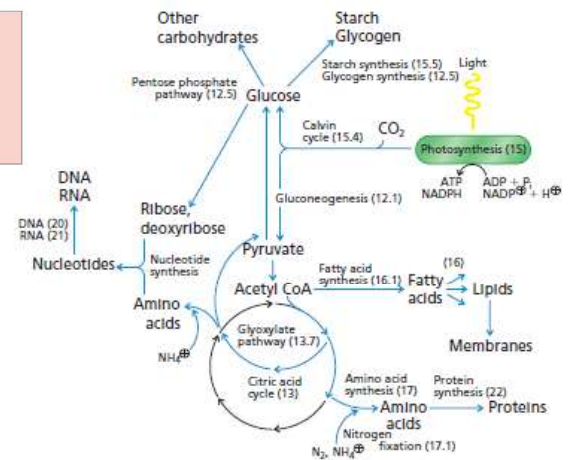


- One more chemical feature of ATP is crucial to its role in metabolism: although in aqueous solution ATP is thermodynamically unstable and is therefore a good phosphoryl group donor, it is *kinetically* stable.
- Because of the huge activation energies (200 to 400 kJ/mol) required for uncatalyzed cleavage of its phosphoanhydride bonds, ATP does not spontaneously donate phosphoryl groups to water or to the hundreds of other potential acceptors in the cell.
- Only when specific enzymes are present to lower the energy of activation does phosphoryl group transfer from ATP proceed.
- The cell is therefore able to regulate the disposition of the energy carried by ATP by regulating the various enzymes that act on it.

Overview of Catabolic Pathways



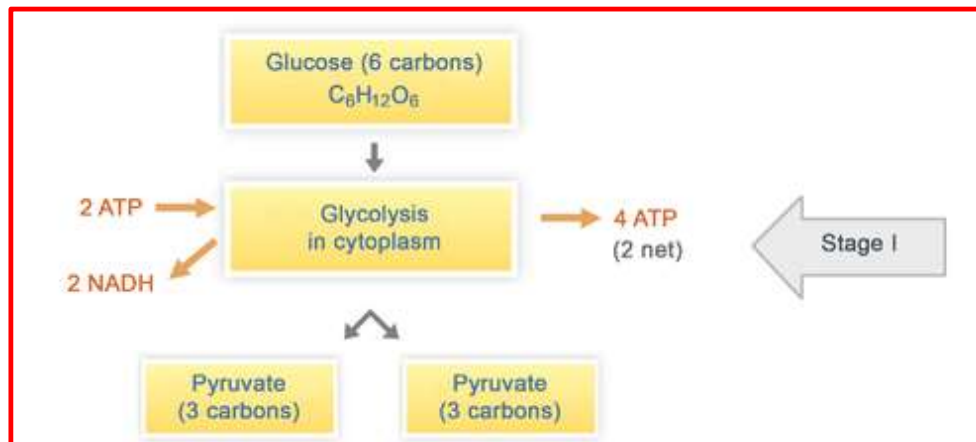
Overview of Anabolic Pathways



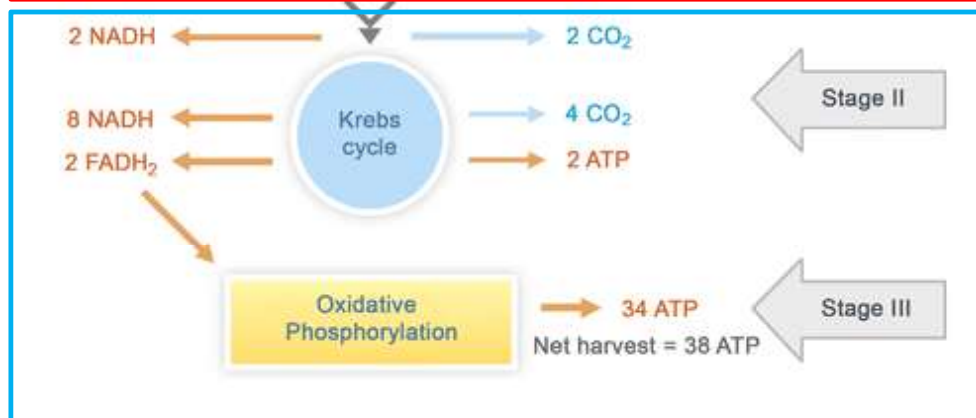
Cellular respiration

- The breakdown of glucose in the cell begins with **glycolysis**, a partial oxidation of glucose by nicotinamide adenine dinucleotide (NAD^+) to pyruvate ion, $\text{CH}_3\text{COCO}_2^-$.
- Metabolism continues in the form of the **citric acid cycle**, in which pyruvate ions are oxidized to CO_2 , and ends with **oxidative phosphorylation**, in which O_2 is reduced to H_2O .
- Glycolysis is the main source of energy during **anaerobic metabolism**, a form of metabolism in which inhaled O_2 does not play a role.
- The citric acid cycle and oxidative phosphorylation are the main mechanisms for the extraction of energy from carbohydrates during **aerobic metabolism**, a form of metabolism in which inhaled O_2 does play a role.

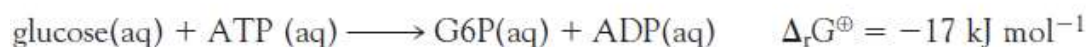
Cytoplasm



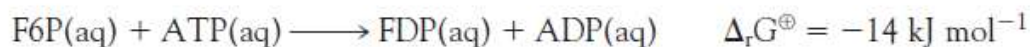
Mitochondria



- Glycolysis occurs in the *cytosol*, the aqueous material encapsulated by the cell membrane, and consists of 10 enzyme-catalyzed reactions.
- The process needs to be initiated by consumption of two molecules of ATP per molecule of glucose.
- The first ATP molecule is used to drive the phosphorylation of glucose to glucose-6-phosphate (G6P):

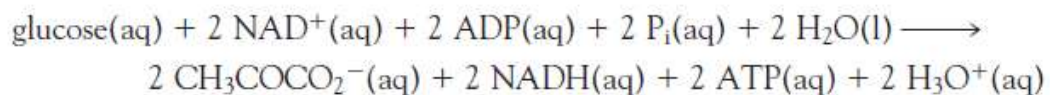


- The next step is the isomerization of G6P to fructose-6-phosphate (F6P).
- The second ATP molecule consumed during glycolysis drives the phosphorylation of F6P to fructose-1,6-diphosphate (FDP):

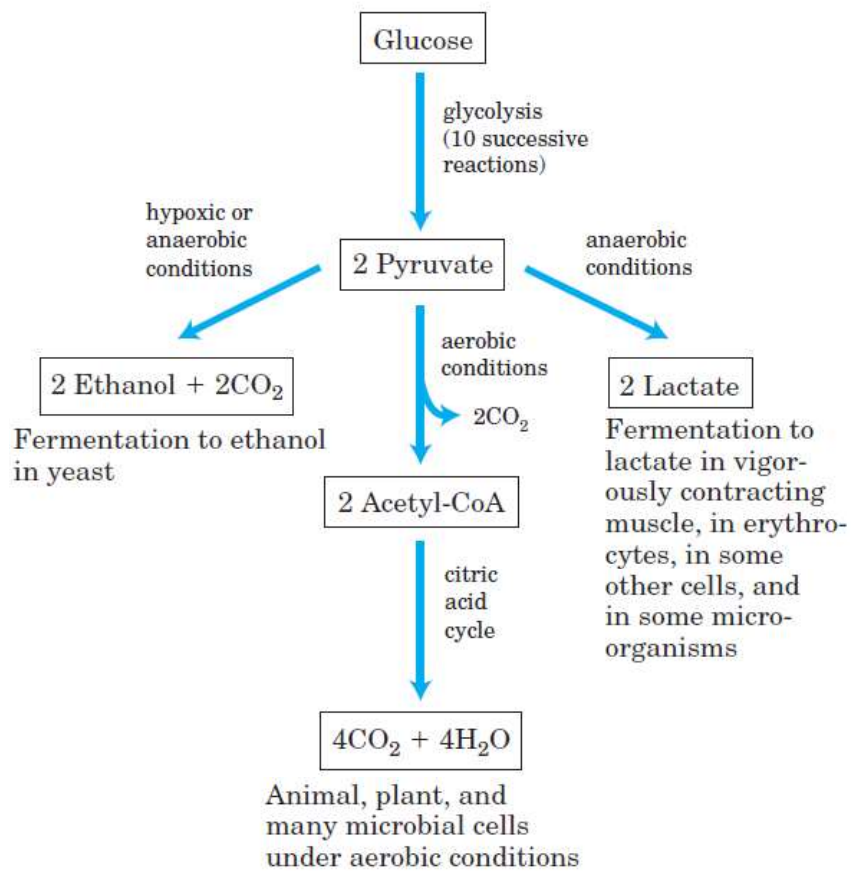


- In the next step, FDP is broken into two three-carbon units, dihydroxyacetone phosphate (1,3-dihydroxypropanone phosphate, $\text{CH}_2\text{OHCOCH}_2\text{OPO}_3^{2-}$) and glyceraldehyde-3-phosphate, which exist in mutual equilibrium.
- Only the glyceraldehyde- 3-phosphate is oxidized by NAD to pyruvate ion, with formation of two ATP molecules. As glycolysis proceeds, all the dihydroxyacetone phosphate is converted to glyceraldehyde-3-phosphate, so the result is the consumption of two NAD molecules and the formation of four ATP molecules per molecule of glucose.

- The oxidation of glucose by NAD to pyruvate ions has $\Delta_r G^\theta = -147 \text{ kJ mol}^{-1}$ at blood temperature.
- In glycolysis, the oxidation of one glucose molecule is coupled to the *net* conversion of two ADP molecules to two ATP molecules (two ATP molecules are consumed and four are formed), so the net reaction of glycolysis is

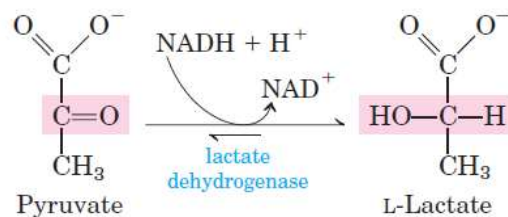


- The biological standard reaction Gibbs energy is $-(147) - 2(-31) \text{ kJ mol}^{-1} = 85 \text{ kJ mol}^{-1}$.
- The reaction is exergonic and therefore spontaneous under biological standard conditions: the oxidation of glucose is used to “recharge” the ATP.



Lactic Acid Fermentation

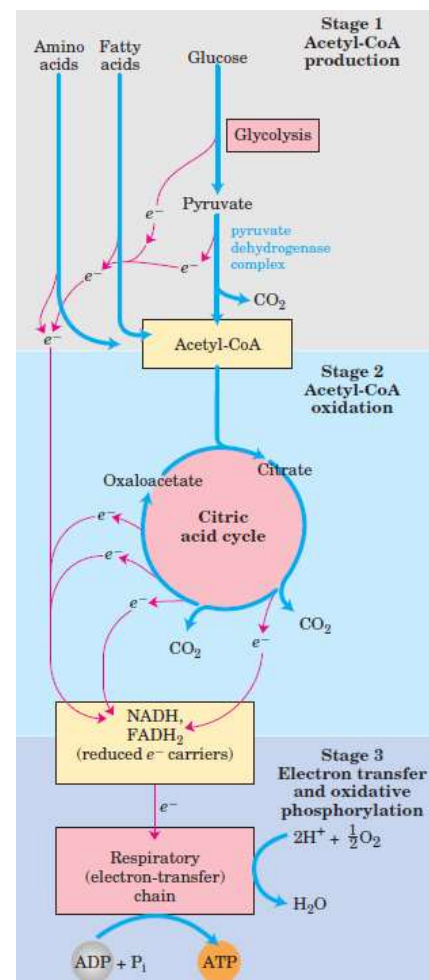
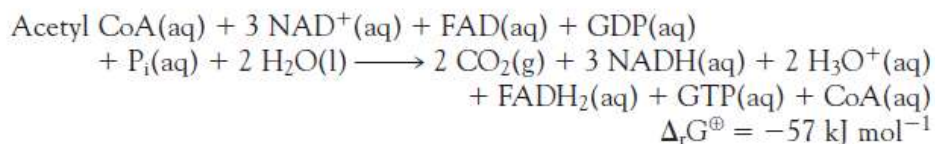
- In cells that are deprived of O₂, pyruvate ion is reduced to lactate ion, CH₃C(OH)CO₂⁻, by NADH.

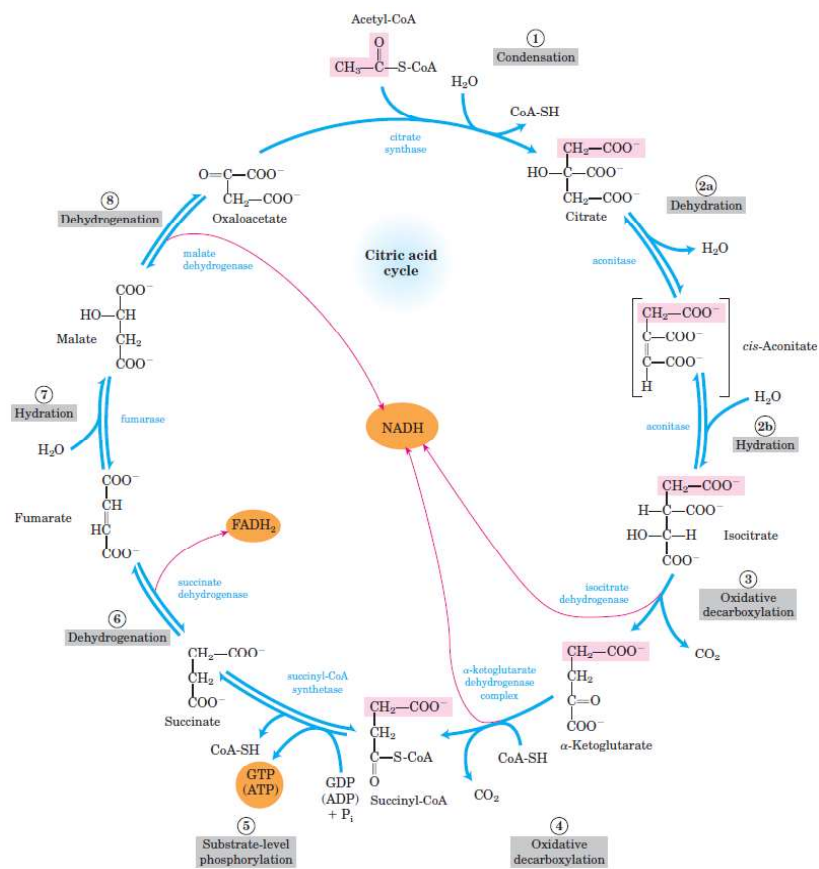


- Very vigorous exercise, such as bicycle racing, can decrease sharply the concentration of O₂ in muscle cells, and the condition known as muscle fatigue results from increased concentrations of lactate ion.

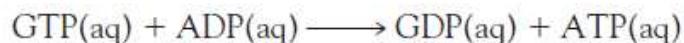
- The standard Gibbs energy of combustion of glucose is 2880 kJ mol^{-1} , so terminating its oxidation at pyruvate is a poor use of resources, similar to the partial combustion of hydrocarbon fuels in a badly tuned engine.
- In the presence of O_2 , pyruvate is oxidized further during the citric acid cycle and **oxidative phosphorylation**, which occur in the mitochondria of cells.

- The further oxidation of carbon derived from glucose begins with a reaction between pyruvate ion, NAD, and coenzyme A (CoA) to give acetyl CoA, NADH, and CO₂.
- Acetyl CoA is then oxidized by NAD and flavin adenine dinucleotide (FAD) in the citric acid cycle, which requires eight enzymes and results in the synthesis of GTP from GDP or ATP from ADP:

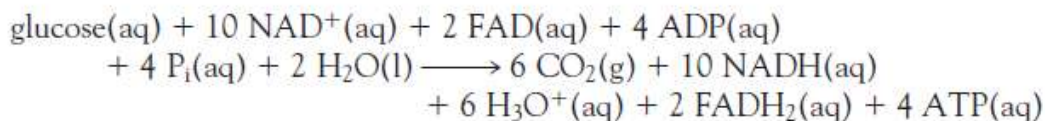




- In cells that produce GTP, the enzyme nucleoside diphosphate kinase catalyzes the transfer of a phosphate group to ADP to form ATP:



- For this reaction, $\Delta_r G^\theta = 0$ because the phosphate group transfer potentials for GTP and ATP are essentially identical. Overall, we write the oxidation of glucose as a result of glycolysis and the citric acid cycle as



- The NADH and FADH_2 go on to reduce O_2 during oxidative phosphorylation, which also produces ATP.
- The citric acid cycle and oxidative phosphorylation generate as many as 38 ATP molecules for each glucose molecule consumed.
- Each mole of ATP molecules extracts 31 kJ from the 2880 kJ supplied by 1 mol $\text{C}_6\text{H}_{12}\text{O}_6$ (180 g of glucose), so 1178 (31x38) kJ is stored for later use.
- Therefore, aerobic oxidation of glucose is much more efficient than glycolysis.