№ 10. RELATIONSHIP BETWEEN FREE ENERGY AND EQUILIBIUM CONSTANT. EXERGONIC, ENDERGONIC, ANERGONIC REACTIONS. COUPLED PROCESSES. COMPOUNDS WITH ENERGY–RICH BONDS.

I. The standard Gibbs free energy

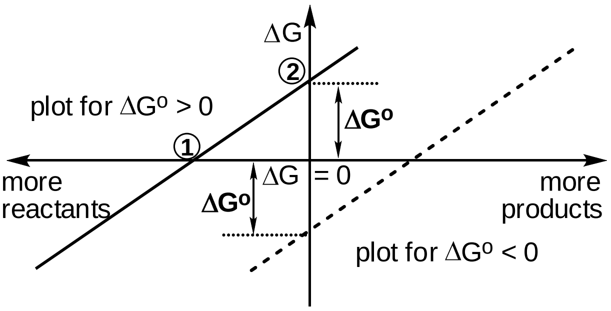
The superscript ^{o} sign indicates that all components in a system (reactants and products) are in their ***standard states*** which concept is especially important in the case of the free energy. Standard state conditions are:

- one atmosphere pressure (1.10^5 Pa); gases – partial pressure 1 atm, pure liquids – under a total (hydrostatic) pressure of 1 atm, solids – the pure solid under 1 atm pressure;
- temperature T = 298 K (*t* = 25^oC);
- all solutes have effective concentration of 1 $mol.L^{-1}$ (1 $mol.dm^{-3}$). ("Effective" concentrations approach real concentrations as the latter approach zero, at about 10^{-4} molar.);
- pH = 7

These same definitions apply to standard enthalpies (ΔH°) and internal energies (ΔU°). The equation for standard free energy change is: $\mathbf{\Delta G^o = \Delta H^o - T\Delta S^o}$

The Gibbs free energy change **ΔG and ΔG^o are plain different!** The most important thing to remember is that the term ΔG^o refers to a **single, specific chemical changes in which all components (reactants and products) are in their standard states.** The graphs clearly illustrate this difference:

The solid line on the left plots the values of **ΔG** for a reaction with $\mathbf{\Delta G^o > 0}$. Notice that there are an infinite number of these values, depending on the progress of the reaction. In contrast, there is only a single value of $\mathbf{\Delta G^o}$, (at intercept point 2) corresponding to the composition at which free energy does not change, **ΔG = 0** (at point 1). Similarly, the dashed line is for $\mathbf{\Delta G^o < 0}$ reaction, showing single value of negative $\mathbf{\Delta G^o}$.



II. Relationship between free energy changes and equilibrium constant

A very general statement tells: **The road to equilibrium is down the free energy hill !** In summary: Under conditions of constant temperature and pressure, chemical change will tend to occur in whatever direction **that leads to a decrease in the value of the Gibbs free energy**. When **G** falls as far as it can, all net change comes to a stop. **The *equilibrium composition* of the mixture is determined by $\mathbf{\Delta G^o}$ which also defines the *equilibrium constant* K.** For an ideal gas has been proven:

$$G_2 = G_1 + RT\ln\frac{P_2}{P_1}$$

and when the initial state is at standard pressure P_1= 1 atm,

$$G = G^o + RT\ln\left(\frac{P}{1\ \text{atm}}\right)$$

It follows, for a gas: $\mathbf{G = G^o + R\,T\ln P}$, and for a solution: $\mathbf{G = G^o + R\,T\ln C}$.

$$aA + bB \rightleftharpoons cC + dD$$

The Gibbs free energy change for any chemical reaction is the difference between sum of energies of products and sum of energies of reactants: $\mathbf{\Delta G = G_C + G_D - G_A - G_B}$. The equation for standard free energy change $\mathbf{\Delta G^o = \Delta H^o - T\Delta S^o}$ **cannot be used in non-standard conditions.** Therefore, **ΔG** is expressed for solutions by $\mathbf{\Delta G = \Delta G^o + R\,T\ln C}$ (or using pressure **P** for gases):

$$\mathbf{\Delta G = \Delta G^o + RT\ln\frac{[C]^c\,[D]^d}{[A]^a\,[B]^b}} \qquad \mathbf{\Delta G = \Delta G^o + RT\ln Q}$$

IMPORTANT!

where: **R** is the ideal gas constant, 8.314 J/K.mol; **T** is the absolute temperature in Kelvin; **ln** is natural logarithm with base e=2.7182 (the notation ln(x) is identical to $\log_e(x)$; as well as lg(x) is identical to $\log_{10}(x)$;

the conversion between natural and common, with base 10, logarithms is ln(x) = 2.303 *lg*(x)); **Q** is the reaction quotient, expressed with molar concentrations **[...]** or partial pressures, **P**:

$$Q = \frac{[C]^c\,[D]^d}{[A]^a\,[B]^b} \quad \text{or} \quad \frac{P_C^c\;P_D^d}{P_A^a\;P_B^b} \qquad \text{also:}\; Q = \frac{C_C^c\;C_D^d}{C_A^a\;C_B^b}$$

The reaction quotient is written:

Since the conversion from natural into logarithm to base 10 is ln(x)=2,303.*lg*(x), the free energy change often is presented as:

$\Delta G = \Delta G^o + 2.303\ R\ T\ lgQ$. It is very important to remember that the concentration (partial pressure) **terms in Q are "current" concentrations *at any time*** during the progress of the reaction. **The free energy G is a quantity that always decreases during the course of any natural process.** Thus as a chemical reaction takes place, **G only falls** and will never become more positive. Eventually a point is reached where any further transformation of reactants into products would cause **G** to increase. At this point **G** is at a minimum (compare with plots shown later), and no further net change can take place; then the reaction is at equilibrium.

In contrast to ΔG^o which **is a *constant* for a given reaction, ΔG varies continuously as the composition changes, finally reaching zero at equilibrium. The Gibbs free energy change, ΔG, is the "distance" from the equilibrium state of a given reaction.** At equilibrium **ΔG = 0** and the reaction quotient has the value of the equilibrium constant, **Q = K**, so we can write:

$$0 = \Delta G^o + RT\ln K \qquad \Delta G^o = -RT\ln K$$

IMPORTANT!

This equation is one of the most important in chemistry because it relates the equilibrium composition of a chemical reaction system to measurable, known, and accessible in handbook tables physical properties of the reactants and products. If we know the enthalpies and the entropies of a set of substances, **we can calculate the equilibrium constant of any reaction** involving these substances without the need to know anything about the mechanism of the reaction using:

$$\ln K = -\frac{\Delta G^o}{RT}$$

Mathematically identical forms of the above equation are: $K_{eq} = e^{\left(-\frac{\Delta G^o}{RT}\right)}$; $K_{eq} = \exp(-\Delta G^o/RT)$

III. Equilibrium and temperature

We have already discussed how changing the temperature will increase or decrease the tendency for a process to take place, depending on the sign of **ΔS^o**. How a change in the temperature will affect the value of an equilibrium constant whose value is known at some fixed temperature? Suppose that the equilibrium constant has the value **K_1** at temperature **T_1** and we wish to estimate what the equilibrium constant value **K_2** would be at temperature **T_2**. In order to do that we need to combine the expressions for standard Gibbs free energy $\Delta G^o = \Delta H^o - T\Delta G^o$ and $\Delta G^o = -R\ T\ \ln K$. We obtain for two temperatures:

$$\Delta H^o - T_1\Delta S^o = -RT_1\ln K_1$$

$$\Delta H^o - T_2\Delta S^o = -RT_2\ln K_2$$

Division of first equation by **T_1** and of the second by **T_2** gives:

$$\frac{\Delta H^o}{T_1} - \Delta S^o = -R\ln K_1$$

$$\frac{\Delta H^o}{T_2} - \Delta S^o = -R\ln K_2$$

The difference of these two equations is:

$$\begin{array}{rl} & \dfrac{\Delta H^o}{T_1} - \Delta S^o = -R\ln K_1 \\ - & \\ & \dfrac{\Delta H^o}{T_2} - \Delta S^o = -R\ln K_2 \\ \hline \end{array}$$

$$\Delta H^o\left(\frac{1}{T_1} - \frac{1}{T_2}\right) = -R(\ln K_1 - \ln K_2)$$

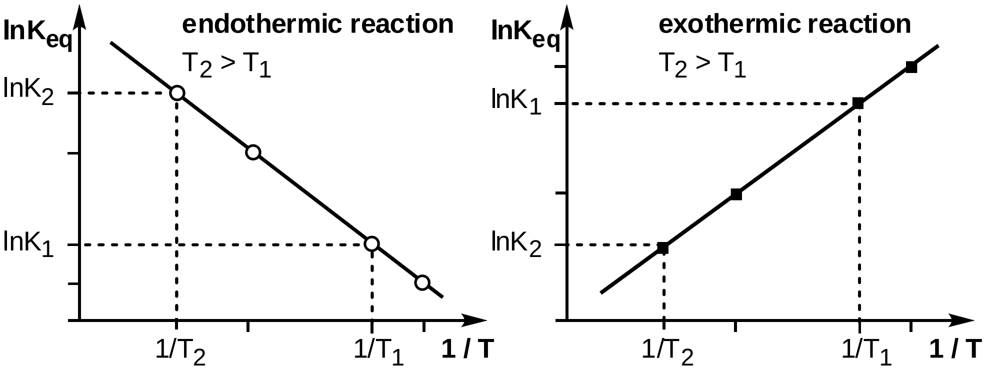
Since difference of logarithms (ln*a* – ln*b*) is a logarithm of ratio (ln(*a/b*)) and a negative logarithm is equal to the positive logarithm of reciprocal value (– ln*a*) = (ln1/*a*), we can write the last equation as:

$$\ln\frac{K_2}{K_1} = \frac{\Delta H^o}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

This important relationship allows calculating the equilibrium constant at any temperature if we know the value of equilibrium constant at some other temperature and the standard enthalpies difference.

Do you remember the Le Châtelier Principle? Just derived equation is the Le Châtelier Principle's theoretical foundation with respect to the effect of the temperature on equilibrium: if the reaction is **exothermic** ($\Delta H^o < 0$, negative), then **increasing temperature, $T_2 > T_1$**, will **cause decrease in K ($K_2 < K_1$)** – that is, the equilibrium will "shift to the left". In an **endothermic** reaction ($\Delta H^o > 0$) **increasing temperature will cause increase of K value** – the equilibrium will "shift to the right", $K_2 > K_1$.

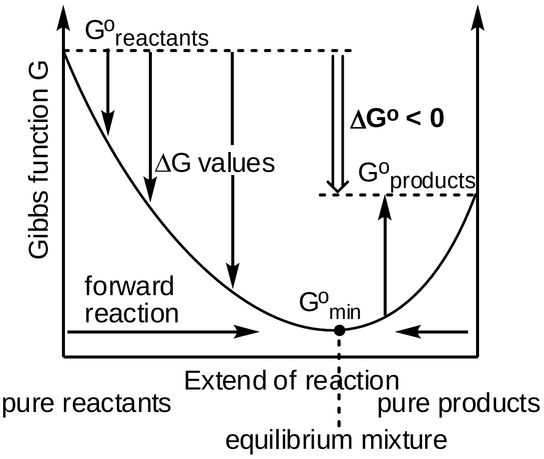
The next plots illustrate these relationships, and how having on hand numerical values of K_{eq} and temperatures is possible to calculate unknown equilibrium constant for the same reaction:



This is an extremely important relationship, but not just because of its use in calculating the temperature dependence of an equilibrium constant. Even **more important is its application in the "reverse" direction, *i.e.* to experimentally determine ΔH^o from two values of the equilibrium constant measured at different temperatures.** Equilibrium constants are determined experimentally easier than heats of a reaction.

IV. Exergonic, endergonic and anergonic processes

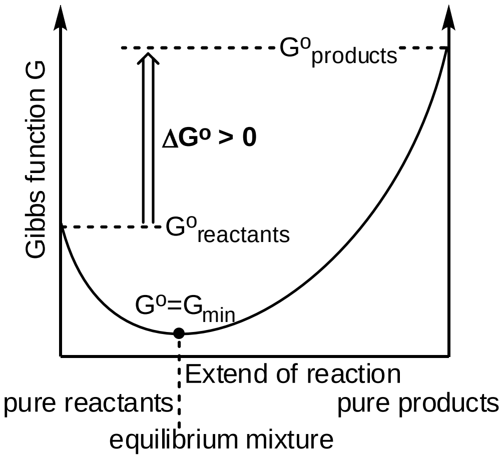
Exergonic (from Greek εξο – outside, εργον – work) means "releasing energy in the form of work". **Reactions are exergonic (at P = const, V = const) if and only when $\Delta G^o < 0$**, that is, decreasing standard Gibbs free energy in going from reactants into products: $\Delta G^o = G^o_{products} - G^o_{reactants} < 0$. When this is the case, we have a **spontaneous process** with large value of equilibrium constant, **K > 1** and **the equilibrium lies to the right**. **An example of exergonic reaction is cellular respiration.** The change of free energy during an exergonic reaction is illustrated in the graph, where the forward reaction is from pure reactants to products. Notice that there are many **ΔG** values during the reaction. The physical meaning of **ΔG** is that it tells us how far the free energy of the system has changed from **G°** of the pure reactants. As the reaction proceeds to the right, the composition changes, and **ΔG** begins to fall.



When the reaction reaches certain composition, **ΔG reaches its minimum value** and further reaction to the right (toward more products) would cause it to rise. But because free energy can only decrease but never increase, this does not happen. **The**

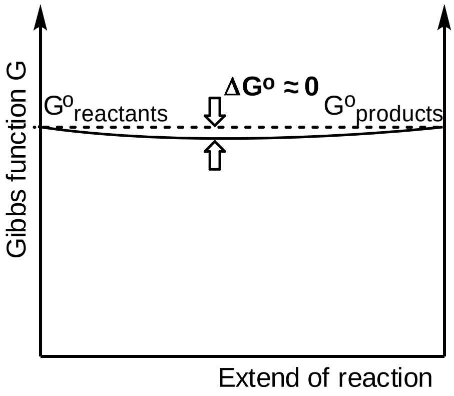
system remains permanently at its equilibrium composition corresponding to the K value. At this point ΔG = 0.

Endergonic reactions. If standard Gibbs free energy increases, **ΔG^o is positive (ΔG^o > 0), the reaction is *non-spontaneous*. Reactants are favored over products at equilibrium, and the equilibrium constant has small value, K < 1 – *i.e.* the equilibrium "lies at left"**. Such **energy requiring reactions** when converting reactants into products **are called endergonic**. The free energy change during an endergonic reaction is illustrated in the graph.



Despite the fact that endergonic reactions require energy to proceed, they **are quite common in nature, especially in biochemistry and physiology.** Examples of endergonic reactions in cells include protein synthesis, and the Na^+/K^+ pump which drives nerve conduction and muscle contraction. (Concentration of K^+ is high inside a cell, and concentration of Na^+ is low inside, relative to outside a cell.). How can endergonic reactions happen? **Endergonic reactions can be achieved if they are either *pulled* or *pushed* by an exergonic process. Such push is usually realized by coupling the reaction to another reaction which is strongly exergonic**, through a shared intermediate. **Catabolic reactions** (reactions that break down larger molecules into smaller molecules) in living organism **are usually exergonic** whereas **anabolic reactions** (reactions that synthesize more complex molecules) are almost **always endergonic**.

In **anergonic reactions $\Delta G^o \approx 0$**. The system is considered near the equilibrium state and the reaction may proceed as *exergonic* or *endergonic*, depending on the conditions.



In thermodynamic sense, **two reactions are said to be coupled when the product of one of them is the reactant in the other**:

$$\begin{array}{ccc} A \rightleftharpoons B & & B \rightleftharpoons C \\ \Delta G^o > 0 & & \Delta G^o < 0 \\ K_1 < 1 & & K_2 > 1 \end{array}$$

If the standard free energy change of the first reaction is positive but that of the second reaction is sufficiently negative, then for the **overall process ΔG^o will be negative** and we say that **the first reaction is "driven" by the second one**. This, of course, is just another way of describing an effect that you already know as the Le Châtelier principle: the removal of substance B by the second reaction causes the equilibrium of the first to "shift to the right". As a consequence of larger $K_{2\,eq}$ of the second step, the equilibrium constant of the overall reaction is the product of the equilibrium constants of the two steps, and favors product C (K_{total} > 1), as shown numerically here.

$$K_1 = \frac{[B]}{[A]} = 0.1 \qquad K_2 = \frac{[C]}{[B]} = 100$$

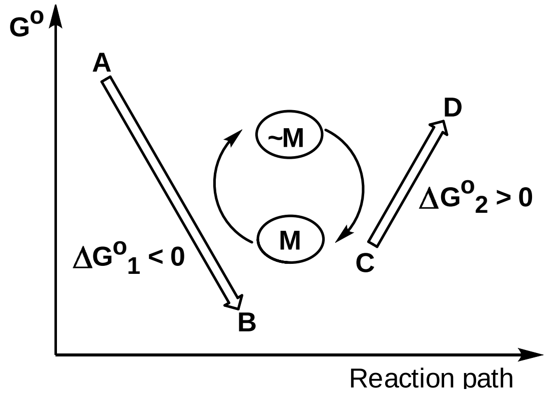
$$K = \frac{[C]}{[A]} = K_1.K_2 = 10$$

V. BIOENERGETICS

Although the previous type of coupling is common in biochemical sequences, more often they include parallel reactions occurring simultaneously. Such parallel reactions can be described in general form as:

$$A \rightleftharpoons B \quad (\Delta G^o < 0)$$
$$C \rightleftharpoons D \quad (\Delta G^o > 0)$$

If a living cell needs product from a non-spontaneous reaction (D from C, **+ ΔG_2^o**), it is coupled to another favorable reaction (A to B with **– ΔG_1^o**). **The coupling is realized via common intermediate, M, that changes forth and back and such reactions in biochemical sense are called coupled reactions**. It is important to specify that biochemical reaction coupling makes sense only when energy gained in the first step is larger than the energy needed for the second step, *i.e.* **$| -\Delta G_1^o | > \Delta G_2^o$**. Such reaction coupling is schematically presented in the Figure:



The transformations in this Figure expressed with chemical equations are:

$$\begin{array}{lcll} A + \cancel{M} & \rightleftharpoons & \cancel{\sim M} + B & -\Delta G^o_1 \\ C + \cancel{\sim M} & \rightleftharpoons & \cancel{M} + D & +\Delta G^o_2 \\ \hline A + C & \rightleftharpoons & B + D & -\Delta G^o_3 \text{ overall reaction} \end{array}$$

After summing the equations for individual transformations **A → B** and **C → D**, the intermediate compounds **M** and **~M** cancel out, and the total transformation **A → D** is accompanied by decrease of standard Gibbs free energy. **The purpose of coupling an exergonic reaction with an endergonic reaction is to use the energy of the former to drive the latter without losing all the energy as heat.** The designated with **~M** compound **is an intermediate compound with "high-energy bond"!**

Many of the reactions that take place in living organisms require a source of free energy to drive them. The immediate source of this energy in animals, fungi, and most bacteria, is the sugar glucose. Oxidation of glucose to carbon dioxide and water is accompanied by a large negative free energy change:

$$C_6H_{12}O_6 + 6\,O_2 \longrightarrow 6\,CO_2 + 6\,H_2O \quad (\Delta G^o = -2880 \text{ kJ/mol})$$

Of course it would not do to simply "burn" the glucose in the normal way; the energy change would be wasted as heat, and rather too quickly for the well-being of the organism! Effective utilization of this free energy requires a means of capturing it from the glucose and then releasing it in small amounts when and where it is needed. This is accomplished by breaking down the glucose in a series of a dozen or more steps in which the energy liberated in each stage is captured by "energy carrier" molecules, of which the most important are adenosine diphosphate, known as ADP (**P_i** means inorganic phosphate), and adenosine triphosphate (ATP).

$$ADP + P_i \longrightarrow ATP \quad (\Delta G^o = +30.5 \text{ kJ/mol})$$

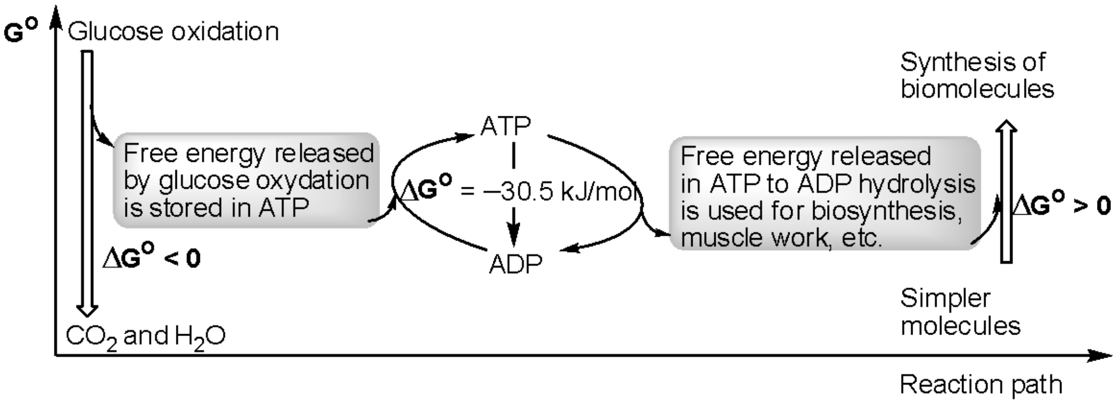
Consequently, the hydrolysis of ATP to ADP is accompanied by **large free energy change of $\Delta G^o = -30.5$ kJ/mol.** The 30.5 kJ/mol of free energy stored in each ATP molecule is released when the molecule travels to a site where it is needed and loses one of its phosphate groups, yielding inorganic phosphate and ADP, which eventually finds its way back the site of glucose metabolism for recycling back into ATP. Thus, ATP/ADP pair represents the most important example of an intermediate (**M / ~M**) in coupled biochemical reactions. **The complete breakdown of one molecule of glucose is coupled with the production of 38 molecules of ATP according to the overall reaction:**

$$C_6H_{12}O_6 + 6\,O_2 + 38\,P_i + 38\,ADP \longrightarrow 6\,CO_2 + 44\,H_2O + 38\,ATP$$

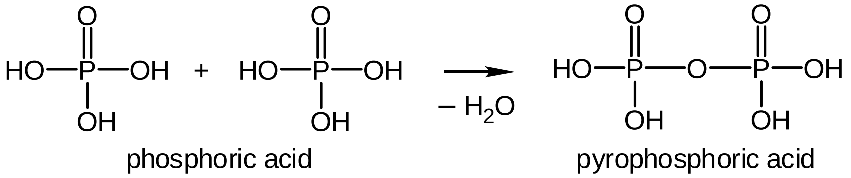
For each mole of glucose metabolized, 38 × (30 kJ) = 1140 kJ of free energy is captured as ATP, representing an energy efficiency of 1140/2880 = 0.4. **That is, 40% of the free energy obtainable from the oxidation of glucose is made available to drive other metabolic processes.** The rest is liberated as heat. (Just for comparison: the energy conversion efficiency of net electricity generation in various power plants is about 33%; of muscle – 14-27%; of photosynthesis – up to 6%. It turns out that Nature is very efficient in mammals with respect to energy conversions). The three main ways of ATP synthesis are substrate level phosphorylation, oxidative phosphorylation in cellular respiration (in the mitochondria), and photophosphorylation in photosynthesis. The total quantity of ATP in the human body is about 0.2 mole. Most of it is not synthesized *de novo*, but is generated from ADP. The energy used by human cells requires the hydrolysis of 100 to 150 moles of ATP daily, which is around 50 to 75 kg! This means that each ATP molecule is recycled 500 to 750 times during a single day. **ATP cannot be stored; hence its consumption closely follows its synthesis.** A suitable example is the first step of glycolysis where phosphorylation of glucose by ATP (adenosine triphosphate) gives ADP and glucose-6-phosphate:

$$\begin{array}{rlcll}
\textbf{Endergonic}: & \text{glucose} + HPO_4^{2-} & \longrightarrow & \text{glucose-6-phosphate} + H_2O & \Delta G^o = +13.8\ \text{kJ/mol} \\
\textbf{Exergonic}: & ATP + H_2O & \longrightarrow & ADP + HPO_4^{2-} + H^+ & \Delta G^o = -30.5\ \text{kJ/mol} \\
\hline
\textbf{Coupled}: & \text{glucose} + ATP & \longrightarrow & \text{glucose-6-phosphate} + ADP & \Delta G^o = -16.7\ \text{kJ/mol}
\end{array}$$

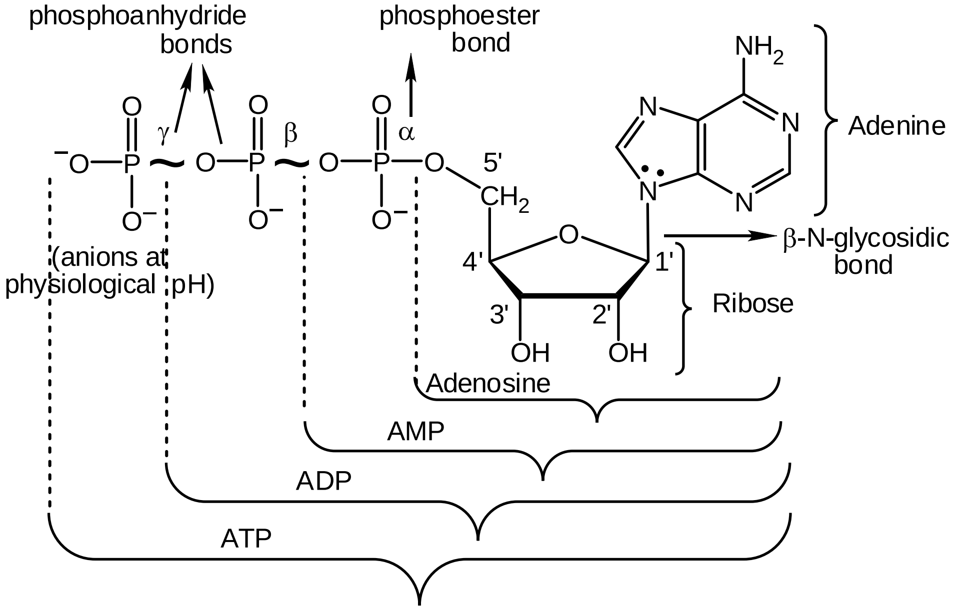
In principle, the syntheses of biomolecules requiring intake of energy with help from energy-rich compound, such as ATP, is presented schematically:



High-energy phosphate bonds **are pyrophosphate bonds** that are acid anhydride linkages, formed by taking phosphoric acid derivatives and dehydrating them. **The compounds that contain pyrophosphate bonds are called high-energy compounds. They include the nucleoside diphosphates and nucleoside triphosphates**. (“High-energy bonds” or “high-energy compounds” are somewhat misleading terms since the bond energies are normal! Only their hydrolysis energy balance is highly negative – releases a lot of free energy.)



The hydrolysis of phosphoanhydride bonds is exergonic under physiological conditions, releasing energy. The structure of ATP indicates with **~** the bonds that are hydrolyzed:



The term «high energy» with respect to these bonds can be misleading, because **the negative free energy change is not due directly to the breaking of the bonds themselves**. The breaking of these bonds, as with the breaking of most bonds, is an endergonic step (i.e., it absorbs energy, not releases it). The negative free energy change comes instead from the fact that **the bonds formed after hydrolysis** (including entropy change due to solvation) **are lower in energy than the bonds present before hydrolysis. ATP can be symbolized by**

$\overset{\gamma}{\text{P}}$ ~ P ~ P – R A, where the high-energy bonds are **~** (tilde).

The primary (first) phosphate group on the ATP molecule that is hydrolyzed when energy is needed to drive anabolic reactions is the γ-phosphate group. Located the farthest from the ribose sugar, it has a higher energy of hydrolysis than either the α- or β-phosphate.

$$\text{ATP} + \text{H}_2\text{O} \longrightarrow \text{ADP} + \text{P}_i \qquad \boldsymbol{\Delta G^o} = -30.5\ \text{kJ.mol}^{-1}$$

$$\text{ATP} + \text{H}_2\text{O} \longrightarrow \text{AMP} + \text{PP}_i \qquad \boldsymbol{\Delta G^o} = -45.6\ \text{kJ.mol}^{-1}$$

(The second chemical equation above gives total energy gain after hydrolysis of both γ- and β-phosphates, which energy is lower than twice that of γ-.)

Conclusion: The practical importance of the Gibbs energy is that it allows us to make predictions based on the properties (**ΔG^o** values) of the reactants and products themselves, eliminating the need to experiment. But bear in mind that **while thermodynamics always correctly predicts whether a given process *can* take place** (is spontaneous in the thermodynamic sense), **it is unable to tell us if it *will* take place at an observable rate.**