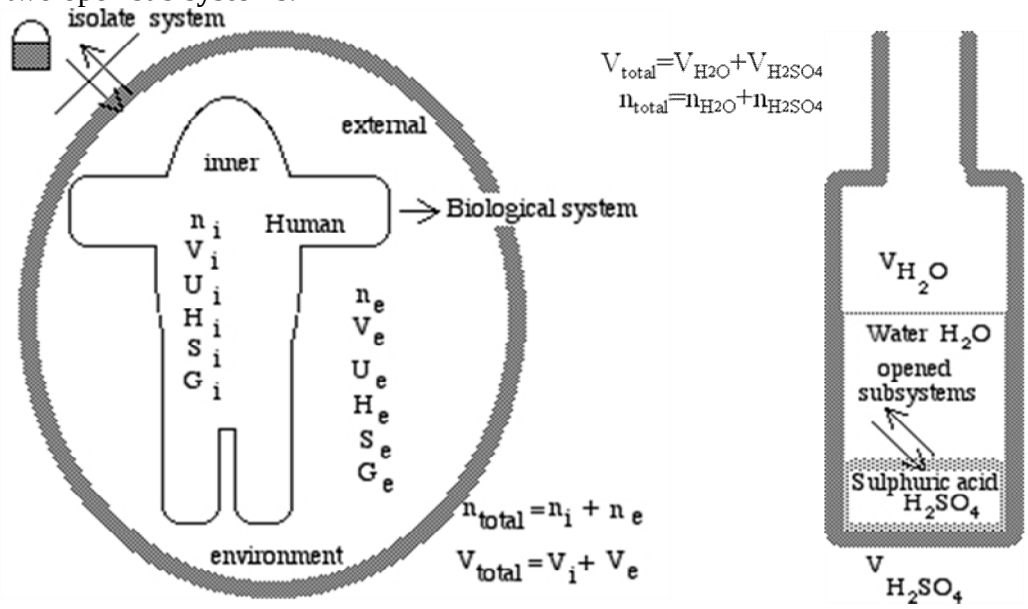
Thermodynamics –Equilibrium-Homeostasis

Method for studies of energy and mass exchange in Nature, Human and Cells **.**

Meanings of: **Thermodynamics** – Heat motion: *Greek, Latin -English languages*
Equilibrium – **equi-equi**valent: *Greek-English,*
librare*-balance*: *Latin-English languages*
Homeostasis – equal staying: *Greek-English language*

Isolate **System** n=const, V=const, U=const, H=const, S=const, G=const.
contains at least two open sub **systems**.

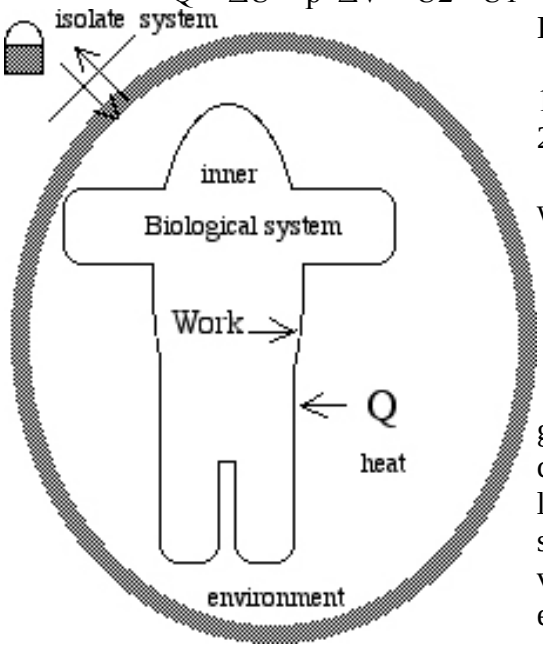


Are two shapes of sub **systems**: homogeneous and heterogeneous
Biological sub **systems** (Human) are to environment organic regulated opened sub **systems** for mass and energy exchange (metabolism) of O_2, H_2O, food (carbohydrates, proteins, fats) and out of organism of CO_2, H_2O, metabolic wastes.

Enthalpy H = U +p*V heat content of system

Heat Q of environment supplied is growth the heat content ΔH of biological sub system:

$$Q = \Delta U + p*\Delta V = U2 - U1 + p(V2 - V1) = U2 + pV2 - (U1 + pV1) = H2 - H1 = \Delta H$$



If environment sub system adds heat Q to the biological sub system, heat Q is used:
1.) for increasing of the ΔU internal energy and
2.) for a work W, that does against environment thus:

$$Q = \Delta U + W$$

where Q is heat amount of environment and
W=p*Δ V is the work of biological sub system and
ΔU is a internal energy change of biological sub system.

Biochemistry Thermodynamics

Living cells and organisms must perform **work W** to stay alive, to grow, and to reproduce. The ability to harness energy **G** and to channel => it into biological work **W** is a fundamental property of all living organisms; it must have been acquired at **start** in molecular and so to cellular evolution. Modern organisms carry out a remarkable variety of energy **G** transductions =>, conversions of one **1** form of energy $\mathbf{G_1}$ to (an-) other $\mathbf{G_o}$. They use the chemical energy **G** in fuels to bring about the synthesis of complex, highly ordered macromolecules from **simple precursors**. They also convert the chemical energy **G** of fuels into concentration **C** gradients and electrical **E** gradients, into ***motion*** work **W** and ***heat*** **H**, and, in a few organisms such as fireflies and deep-sea fish, into ***light*** **~hv**. Photosynthetic organisms transduce light energy **~hv** into all these other forms of **energy**.

Hess Law calculation of reaction heat content change

Heat of reaction depends only on the initial and final compounds,but
it does not depend on the way of reaction.

Combustion heat of compound is the enthalpy change in a reaction,
in which 1 mole of the compound is completely combusted to CO_2 and H_2O.

$$\Delta H_{reaction} = \Sigma\Delta H^{combustions}_{initial\_compounds} - \Sigma\Delta H^{combustions}_{products}$$

Standard enthalpies H° (or **ΔH°**) and **standard entropies S°** (or **ΔS°**) for compound**.**

Standard enthalpy and standard entropy of compound molecule are change in a reaction,
in which 1 mole of the compound is formed from free elements
at standard conditions T=298 K, p=101.3 kPa

Standard enthalpy change for reaction products and initial compounds:

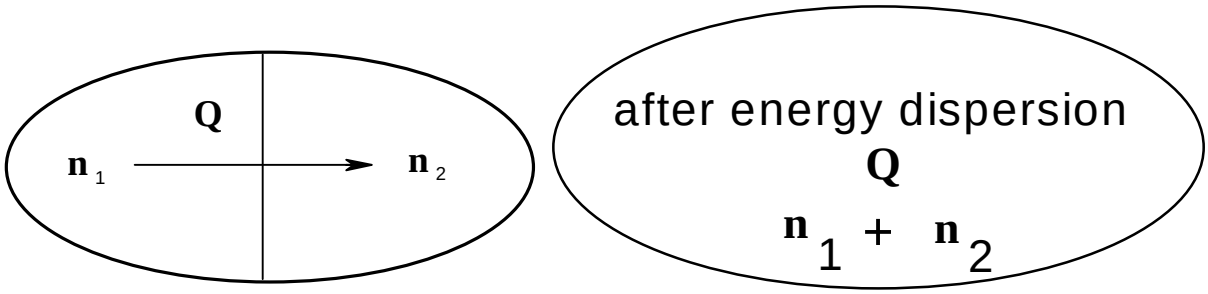
$$\mathbf{\Delta H_{reaction}} = \Sigma\Delta\mathbf{H}^{\circ}_{products} - \Sigma\Delta\mathbf{H}^{\circ}_{initial};$$

Standard entropy change for reaction products and initial compounds:

$$\mathbf{\Delta S_{reaction}} = \Sigma\Delta\mathbf{S}^{\circ}_{products} - \Sigma\Delta\mathbf{S}^{\circ}_{initial};$$

Thermodynamics II Law. Measure of **energy dispersion** per one unit on temperature **T** degree is
1. **entropy amount S** value and 2. for reaction products is **entropy change**

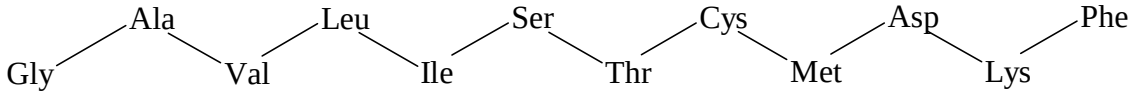
1. The amount of heat dispersed from warmer body $\mathbf{n_1}$ to cooler surroundings body.
Energy of system is dispersed on more great count of particles sum $\mathbf{n_1} + \mathbf{n_2}$.



$\mathbf{T_1} > \mathbf{T_2}$ =>Energy dispersion=> $\mathbf{T_1} > \mathbf{T} > \mathbf{T_2}$

Heat of reaction dispersion $-\mathbf{\Delta H_{reaction}}$ per temperature **T** unit is **entropy growth positive**
into environment as surrounding $\mathbf{\Delta S_{dispersed}} = -\mathbf{\Delta H_{reaction}} / \mathbf{T}$

2. Polypeptide chain protein molecule own united system of 12 amino acids:
Glycine, Alanine, Valine, Leucine, Isoleucine. Serine,
Threonine, Cysteine, Methionine, Aspartate, Lysine and Phenylalanine.



After hydrolysis (decomposition) reaction => to separate in to 12 small molecules :
H1 H2 H3 H4 H5 H6 H7 H8 H9 H10 H11 H12:
Gly + Ala + Val + Leu + Ile + Ser + Thr + Cys + Met + Asp + Lys + Phe

Decomposition reaction (hydrolysis) Energy dispersion on temperature **T** unit as system disorder chaos increase $\mathbf{\Delta S_{reaction}}$ for the decomposition reaction is entropy growth positive: $\Delta\mathbf{s_{reaction}} = \Sigma\Delta\mathbf{S}_{product} - \Sigma\Delta\mathbf{S}_{initial} > 0$.

Total entropy $\mathbf{\Delta S_{total}}$ is energy dispersion sum of heat plus disorder chaos for hydrolysis decomposition reaction: $\mathbf{\Delta S_{total}} = \mathbf{\Delta S_{reaction}} + \mathbf{\Delta S_{dispersed}} > 0$ growth positive

Note: Synthesis reaction alone is impossible $\mathbf{\Delta S_{total}} < 0$ as negative because chaos decreases in high ordered polymer and energy accumulates from near surrounding of environment.

II Law of thermodynamics spontaneous Energy dispersion Law

Internal energy U or enthalpy H of system has two summing parts:

$U = F + S \bullet T$; at constant volume V=const
$H = G + S \bullet T$; at constant pressure p=101,3 kPa on see level.

1. free energy F (Helmholtz's energy) or G (Gibbs's free energy) and 2. lost energy S•T ,
where S entropy of lost in surrounding energy per temperature T unit degree multiplied by T temperature in Kelvin grades is "bound" dispersed as lost energy in environment:

1. G free Gibbs's energy at constant pressure is more appropriate, because most processes on Earth occur at constant pressure p=101,3 kPa.

For isolate system, where U and H are constant, unchanged. It means enthalpy change $\Delta H=0$ is zero as H is constant: $\Delta H = \Delta G + \Delta S \bullet T = 0$.

Spontaneous process always take a place and free energy $\Delta G<0$ growth smaller that compensates with a growth of entropy $\Delta S>0$, so that sum of the free Energy and bound energies changes compensate each other. In other word's growth of entropy $\Delta S>0$ in bound energy $\Delta S \bullet T>0$ is compensated with free Energy $\Delta G<0$ decrease as sum is zero:$0=\Delta G+\Delta S \bullet T$.

So free energy decrease in spontaneous process converts to free energy loss "bound" to environment:

$$G \downarrow => \uparrow S \bullet T$$

and dispersion in surrounding as well as "lost free energy ΔG" change is negative value and converts equal increased to bound energy $\Delta S \bullet T$, at constant pressure p = const. the change of value ΔH determine character of reaction: exothermic $\Delta H <0$ or endothermic $\Delta H >0$

$$\Delta G = \Delta H - \Delta S \bullet T$$

At this can conclude :
1. is process exoergic spontaneous as $\Delta G = \Delta H - \Delta S \bullet T<0$ negative or
2. is process endoergic non–spontaneous, forbidden as $\Delta G = \Delta H - \Delta S \bullet T>0$ positive.

The chemical mechanisms that underlie energy **G** transductions => have fascinated and challenged scientist for centuries. **Antoine Lavoisier** (1743-1794), before he lost his head in the French Revolution, recognized that animals somehow transform chemical fuels (foods) into heat **H** and that this process of respiration is **essential** to **life**. He observed that …in general, respiration O_2 is nothing but a slow **combustion** of carbon **C** and hydrogen **H**, which is entirely similar to that which occurs in a lighted lamp or candle, and that, from this point of view, animals that respire are true **combustible** bodies that **burn** and consume themselves.

…One may say that this analogy between **combustion** and **respiration** has not escaped the notice of the poets, or rather the philosophers of antiquity, and which they had expounded and interpreted. This fire stolen from heaven, this torch of Prometheus, does not only represent an ingenious and poetic idea, it is a faithful picture of the operations of **nature**, at least for animals that breathe O_2; one may therefore say, with the ancients, that the torch of life lights itself at the moment the infant breathes for the first time, and it does not extinguish itself except at death.

Biochemical studies have revealed much of the chemistry underlying that "torch of life". **Biological energy G** transductions => obey the same **physical laws** that govern all other natural processes. It is therefore essential for a student of bio-medical-sciences to understand these biochemistry laws and how they apply to the flow => of **energy G** in the biosphere. In this chapter we first review the laws of thermodynamics and the quantitative relationships among free **energy G**, **enthalpy H** (**internal heat content** of substance), and **bound energy T•S** (**temperature** and **entropy** factorial). We then describe the special role of **ATP** in **biochemical energy G** exchanges. Finally, we consider the importance of *oxidation-reduction reactions* in living cells, the thermodynamics of **electron e^- transfer** reactions, and the **electron e^- carriers** commonly employed as cofactors of the enzymes that catalyze these **reactions**.

*From a memoir by Armand Seguin and Antoine Lavoisier, dated 1789, quoted in Lavoisier, A. (1862) Oeuvres de Lavoisier, Imprimerie Imperiale, Paris.

Biochemistry synthesis and decomposition reaction four types

1. EXOTHERMIC, EXOERGIC DECOMPOSITION REACTION of hydrolysis and bio oxidation

Oxidoreductases E.1 classes enzymes, as oxidative phosphorylation summary: exoergic exothermic

$$C_6H_{12}O_6 + 6O_{2aqua} + 6H_2O \Rightarrow 6HCO_3^- + 6H_3O^+ + \Delta G_{react} + Q;\ \Delta G_{react} = -2570{,}4\ ^{kJ}/_{mol};\ \Delta H_{react} = -2805.27\ ^{kJ}/_{mol}$$

E.2 class degrading enzymes Hydrolases-digestive peptidases exoergic exothermic::

$$Gly\text{-}Gly_{aqua} + H_2O \xrightarrow{peptidase} Gly_{aqua} + Gly_{aqua} + Q + \Delta G\ ;\ \Delta G_{react} = -80.99\ ^{kJ}/_{mol}\ ;\ \Delta H_{react} = -60.58\ ^{kJ}/_{mol}$$

This type of reaction can be written in a general way as:

$$AB \Rightarrow A + B, \quad \Delta H<0 \text{ and } \Delta S>0\ ;\ \Delta G = \Delta H - T\bullet\Delta S < 0,$$

one can see, that the first component of it (Δ**H**) is negative. Δ**S** itself is positive, but as there is a minus sign before it, the second component of it (**- T•ΔS**) is also negative. This means, that Δ**G** is always negative for this type of reactions..

Conclusion: an exothermic decomposition reaction is spontaneous at all conditions.

2. EXOTHERMIC REACTIONS OF SYNTHESIS

An **EXOTHERMIC REACTION OF SYNTHESIS** in a general way can be written as:

$$A + B \Rightarrow AB, \quad \Delta H<0 \text{ and } \Delta S<0\ ;\ \Delta G = \Delta H - T\bullet\Delta S$$

the first component Δ**H** of the equation is negative, but the second one - positive (Δ**S** is itself negative, but there is a minus sign before it). As one of the components is positive, but the other negative, the result Δ**G** can be negative, if the negative component Δ**H** by its absolute value is greater, than the positive component **(-TΔS)**:

$$|\Delta H| > |T\bullet\Delta S|$$

This is possible, if the temperature is low enough human body temperature 310.15 K

Conclusion: A synthesis reaction, that is exothermic, is spontaneous at low enough temperatures.

3. ENDOTHERMIC , EXOERGIC REACTION OF DECOMPOSITION

An example of an endothermic reaction of decomposition in a general form can be written as:

$$AB \Rightarrow A + B \quad \Delta H>0 \text{ and } \Delta S>0\ ;\ \Delta G = \Delta H - T\bullet\Delta S$$

Thus, the first component (Δ**H**) in the equation is positive, but the second one (-**T•**Δ**S**) - negative as entropy change itself is a positive value, but the minus sign in the equation turns the second component of equation negative.

In such a way, the change of Gibbs's Energy Δ**G** can be negative (and the reaction can be spontaneous), if the negative component is greater, than the positive one: $|T\bullet\Delta S| > |\Delta H|$

An endothermic reaction of decomposition occurs spontaneously at high enough temperatures.

4. ENDOTHERMIC, ENDOERGIC REACTION OF SYNTHESIS.

Oxidoreductase class E.1 enzymes, as for photosynthesis: endoergic endothermic:

$$6HCO_3^- + 6H_3O^+ + \Delta G_{react} + Q \Rightarrow C_6H_{12}O_6 + 6O_{2aqua} + 6H_2O;\ \Delta G_{react} = +2570{,}4\ ^{kJ}/_{mol};\ \Delta H_{react} = +2805.27\ ^{kJ}/_{mol}$$

Protein peptide bond synthesis hydrolase class E.2 enzymes, as for Ribosomes: endoergic endothermic:

$$Gly_{aqua} + Gly_{aqua} + Q + \Delta G \xrightarrow{ribosome} Gly\text{-}Gly_{aqua} + H_2O\ ;\ \Delta G_{react} = +80.99\ ^{kJ}/_{mol}\ ;\ \Delta H_{react} = +60.58\ ^{kJ}/_{mol}$$

This kind of reactions can be generally expressed as: **A + B => AB** **ΔH>0 and ΔS<0**

Thus, both components of Δ**G** are positive and therefore Δ**G** is positive at any temperature. It means, that this type of reaction can never be spontaneous - in other words,

*an endothermic reaction of synthesis is **thermodynamically forbidden**.*

We can easily notice, that cases 1 and 4 and cases 2 and 3 are reverse reactions to each other. Two more **conclusions** can be done:

1) If the direct reaction is always spontaneous, the reverse one is forbidden.(cases 1 and 4).

2) If the direct reaction is spontaneous at high temperatures, the reverse one must be carried out at low temperatures.

Biochemical Thermodynamics

Thermodynamics is the quantitative study of the energy **G** transductions => that occur in living cells and of the nature and function of the **chemical** processes underlying these transductions =>. Although many of the principles of **thermodynamics** have been introduced in earlier studies and may be familiar to you, a review of the quantitative aspects of these principles is useful here.

Biochemical Energy Transformations Thermodynamics explanation

Many quantitative observations made by physicists and chemists on the inter-conversion of different forms of energy led, in the nineteenth **19th** century, to the formulation of two **2** fundamental **laws** of thermodynamics. The first **1st law** is the principle of the conservation of energy and mass:
for any physical or chemical change, the total amount of energy **U = const** (**internal** energy)
in the **isolate system** *remains constant; energy may change form or it may be transported between regions* (**open subsystems** constituting the total **isolate system**), *but it cannot be created or destroyed*
(because of **isolate system**).
The second **2nd law** of thermodynamics, which can be stated in several forms, says that the **isolate system** always tends to use own **free** energy **G** content toward increasing **bound** energy **T•S**:
in all natural processes, the entropy **S** *of the* **isolate system** *increases* .

Living organisms consist of collections of molecules much more highly organized as well as synthesized into polymers or assembled into compartments of water soluble and water insoluble mediums than the surrounding materials from which they are constructed, and organisms maintain and produce order, seemingly oblivious to the second **2nd law** of thermodynamics. But living organisms are **open systems** and do not violate the second **2nd law**; they operate strictly within it collaborating with **surroundings** (**environment**). To discuss the application of the second **2nd law** to biological systems, we must first **1st** define those **systems** and their **surroundings**. The **reacting system** is the **opened** collection of matter that is undergoing a particular chemical or physical process; it may be an organism, a cell, or two **2** reacting compounds. The **reacting system** and its **surroundings** together constitute the **isolate system**. In the laboratory, some chemical or physical processes can be carried out in **isolate** or **closed systems**, in which no material **mass** or energy **U** is exchanged with the **surroundings**. Living cells and organisms, however, are **open systems**, exchanging both material **mass** and energy **U** with their **surroundings**; living systems are never at **equilibrium** with their **surroundings**, and the constant transactions between **system** and **surroundings** explain how organisms can create order within themselves while operating within the second **2nd law** of thermodynamics.

Earlier in this text we defined three **3** thermodynamic quantities that describe the energy changes Δ**G**, Δ**H**, and Δ**S•T** occurring in a chemical reaction. **Gibbs free** energy (**G**) expresses the amount of energy capable of doing work **W** during a reaction at constant temperature **T** and pressure **p** (studied earlier). When a reaction from **1** => to **2** proceeds with the release of **free** energy Δ**G** (i.e., when the system changes so as to possess less **free** energy $\mathbf{G_2}$ difference of change will be negative $\Delta\mathbf{G=C_2-G_1}$), the **free**-energy change, $\Delta\mathbf{G<0}$, has a negative value and the reaction is said to be **exoergonic**. In **endoergonic** reactions, the system gains **free** energy and $\Delta\mathbf{G>0}$ is positive. **Enthalpy**, **H**, is the **heat content** of the reacting **system**. It reflects the number **n** and kinds of chemical bonds in the **reactants** to => **products**. When a chemical reaction releases **heat** $\Delta\mathbf{H<0}$, it is said to be **exothermic**; the **heat content** of the **products** is less than that of the **reactants** and $\Delta\mathbf{H=H_2-H_1}$ has, by convention, a negative value. **Reacting systems** that take up heat $\Delta\mathbf{H>0}$ from their **surroundings** are **endothermic** and have positive values of $\Delta\mathbf{H=H_2-H_1}$ (studied earlier). Entropy, **S**, is a quantitative expression for the dispersion of **free energy** $\Delta\mathbf{G<0}$ in a system (Box 14-1). When the **products** of a reaction are decomposed more complex **reactants** and has more dispersed or dissipated **free energy** than the **reactants**, the reaction is said to proceed with a gain in **bound** energy **T•**Δ**S** and rise entropy $\Delta\mathbf{S>0}$ (studied earlier). The units of Δ**G** and Δ**H** are **joules**/**mole** or **calories**/**mole** (recall that **1 cal** equals **4.184 J** units of **entropy** are **joules**/**mole**/**Kelvin** (**J**/**mol**/**K**) (Table 1-1).

Under the conditions existing in biological systems (including constant temperature **T** and pressure **p**), changes in **free** energy Δ**G**, **enthalpy** Δ**H**, and **entropy** Δ**S** are related to each other quantitatively by the equation (1-1)

$$\Delta\mathbf{G} = \Delta\mathbf{H} - \mathbf{T}\bullet\Delta\mathbf{S} \qquad (1\text{-}1)$$

in which $\Delta\mathbf{G} = \mathbf{G_2} - \mathbf{G_1}$ is the change in **Gibbs free** energy of the reacting **system**, $\Delta\mathbf{H} = \mathbf{H_2} - \mathbf{H_1}$ is the change in **enthalpy** of the **system**, **T** is the absolute temperature, and $\Delta\mathbf{S} = \mathbf{S_2} - \mathbf{S_1}$ is the change in **entropy** of the **system**. By convention, $\Delta\mathbf{S>0}$ has a positive (+) sign when **entropy S** increases and $\Delta\mathbf{H<0}$, as noted above, has a negative (-) sign when **heat** is released by the **system** to its **surroundings** as well **system** has lost the **heat content H.** Either of these conditions, which are typical of **favorable** processes, tend to make $\Delta\mathbf{G<0}$ negative. In fact, Δ**G** of a spontaneously reacting system is always negative $\Delta\mathbf{G<0}$.

Table 1-1. Some Physical Constants and Units Used in Thermodynamics

Boltzmann constant, **k = 1.381 • 10^{-23} J/K**
Avogadro's number, **N_A = 6.022 • 10^{23} mol^{-1}**
Faraday constant, **F = 96 485 J/V/mol**
Gas constant, **R = 8.3144 J/mol/K (= 1.987 cal/mol/K)**
Units of **∆G** and **∆H** are **kJ/mol** (or **kcal/mol**)
Units of **∆S** are **J/mol/K** (or **cal/mol/K**); **1 cal = 4.184 J**
Units of absolute temperature, **T**, are Kelvin, **K**; **25 °C = 298,15 K** ; **37 °C** = **310,15** K;
At **25 °C**, **RT = 2.479 kJ/mol** (= **0.592 kcal/mol)**

The second **2nd law** of thermodynamics states that the **bound** energy **T•∆S** and **entropy** to the **isolate system** increases during all chemical and physical processes behalf of free energy **G** decrease, but it does not require that the **entropy** increase take place in the **reacting system** itself as member of **sub-systems** included into **isolate system**. The **synthesized** products within cells as they grow and divide **free** energy **∆G>0** increase is more than compensated for by the decomposition they create **free** energy losing **∆G<0** in their **surroundings** in the course of growth and division (Box 1-1, case 2). In living organisms preserve their internal **free** energy **∆G>0** increase by taking from the **surroundings free** energy **∆G<0** which is lost in the form of high nutrients **free** energy $\mathbf{G_n}$ or sunlight **free** energy **~hv□= G_s**, and returning to their **surroundings** an equal amount of energy as **heat H** and **entropy S**.

Entropy: The Entity of Energy dispersion measure per one Kelvine degree

The term **entropy S**, which literally means a " **change within**"(*Greek* **en** - in, **tropos** - turning), was first used in 1851 by Rudolf Clausius, one of the formulators of the second **2nd law** of thermodynamics. A rigorous quantitative definition of **entropy S** involves statistical and probability considerations. However, its nature can be illustrated qualitatively by three **3** simple examples using **bound** energy **T•S** terms, each demonstrating one aspect of **entropy S**. The key descriptors of **entropy S** are ***randomness*** and *dissipation* of energy in **system**, manifested in different ways over one unit of Kelvine degree temperature.

Case I - The Teakettle and the Dispersion of Heat Entropy growth as **enthaplpy** decreases**.** We know that steam generated from boiling water can do useful work **W**. But suppose we turn off the burner under a teakettle full of water at **100 'C** (the "**system**") in the kitchen (the "**surroundings**") and allow the teakettle to cool. As it cools, no work is done, but heat passes from the teakettle to the surroundings, raising the temperature **T** of the **surroundings** (the kitchen) by an infinitesimally small amount until complete equilibrium is attained. At this point all parts of the teakettle and the kitchen are at precisely the same temperature **T**. The **heat** energy dispersion **-∆H_{tea}** that was once concentrated in the teakettle of hot water at **100 °C** for number of moles only **n_{tea}**, *potentially* capable of doing work **W**, has lost as dispersed among total number of moles **n_{tea}+n_{kitch}** including surroundings. Its equivalent in **heat** energy is still present commonly in the teakettle + kitchen (i.e., the '**isolate system**') but has become completely randomized throughout. This energy is no longer available to do work =×=>**W** because there is no temperature differential within the kitchen and teakettle. Moreover, the increase in **entropy** **∆$S_{dispersion}$** and **bound** energy **T•∆$S_{dispersion}$** of the teakettle + kitchen (the **isolate system**) is irreversible because the **heat -∆H_{tea}** dissipation to all members among total number of moles **n_{tes}+n_{kitch}.** We know from everyday experience that **heat -∆H_{tea}=T•∆$S_{dispersion}$** never spontaneously passes back from the kitchen into the teakettle to raise the temperature **T** of the water to **100 °C** again because **bound** energy **T•∆S_{total}** is lost energy within dissipation of **heat** and loose of heat content – enthalpy negative change **-∆H_{tea}.**
Case 2: The decomposition of Glucose by the Oxidation of Glucose. Entropy **∆S_{total}** has a sum of condition not only for **bound heat** energy **T•∆$S_{dispersion}$** but of **matter chemical disorder** change in chemical reaction to **T•S_{react}.** Aerobic (hetero-trophic) organisms extract **free** energy **∆G_{react}** from **glucose** obtained from their **surroundings** by **oxidizing** the **glucose** with molecular oxygen **O_{2aqua}** in water solutions also obtained from the **surroundings**. The end products of this oxidative metabolism, **CO_{2aqua}** and **H_2O**, are released and returned to the surroundings. In this process the **surroundings** undergo an increase in **bound** energy **T•∆S_{total}** and entropy **∆S_{total},** whereas the organism itself remains in a steady state and undergoes to homeostasys (no change) in its internal state **G_{in}, H_{in},** and **T•S_{in}**. The **exoergonic** and **exothermic oxidative decomposition reaction**, illustrated by the equation for the oxidation of **glucose** T=310.15 K (37°**C**):

$C_6H_{12}O_6$+ $6O_{2aqua}$+$6H_2O$=>$6HCO_3^-$+$6H_3O^+$+∆G_{react} +Q; ∆G_{react}= -3049,55 $^{kJ}/_{mol}$ **;** ∆H_{react}= -2805,27 $^{kJ}/_{mol}$
Glucose ∆S_{react}= 787,625 $^{J}/_{mol/K}$ **exoergonic** **exothermic**
-∆H_{react}/T=∆$S_{dispersion}$ = 9044,8815 $^{J}/_{mol/K}$; **∆G_{bound}=T•∆S_{total}**= 310.15 *9.832507 =3049.55 kJ/mol;
∆S_{total} =∆$S_{dispersion}$ +∆S_{react} = 9044,8815 $^{J}/_{mol/K}$ + 787,625 $^{J}/_{mol/K}$ = 9832,507 $^{J}/_{mol/K}$

We can represent this schematically as

7 molecules and 12 ionic molecules of products in water medium □(aqua)

O_{2aqua} O_{2aqua} | **HCO_3^- HCO_3^-** | **6 HCO_3^-** | The atoms contained in **1** molecule of **glucose**

$(_{aqua})O_{2aqua}$ O_{2aqua} | **HCO_3^- HCO_3^-** | plus **6** molecules of oxygen O_{2aqua},a total of **7** molecules,

O_{2aqua} O_{2aqua} => **HCO_3^- HCO_3^-** | | $(_{aqua})$ are more randomly dispersed by the **oxidation**

Glucose ◊ | **H_3O^+ H_3O^+ H_3O^+** | reaction and are now present in a total of

$C_6H_{12}O_6$ $(_{aqua})$ | **H_3O^+ H_3O^+ H_3O^+** | $(_{aqua})$ | **12** ionic molecules (**$6HCO_3^-$+$6H_3O^+$**).

Whenever a chemical reaction results in an increase in the number **n** of molecules-of moles or when a solid substance is converted into **liquid** or **gaseous** products, which allow more freedom of molecular movement and take up more volume than solids in decomposition reaction ,and thus **bound** energy **T•ΔS$_{total}$** as well entropy of reaction **ΔS**$_{react}$= 787,625 $^{J}/_{mol/K}$ and heat dispersion **ΔS$_{dispersion}$** = 9044,8815 $^{J}/_{mol/K}$ increases.

Case 3- Information and Entropy The following short passage from Julius Caesar, Act IV, Scene 3, is spoken by Brutus, when he realizes that he must face Mark Antony's army. It is an information-rich non random arrangement of **129** letters or **163** characters including space **28** and punctuation **6** marks of the English alphabet: **163-28-6**

There is a tide in the affairs of men, voy inThie tide irs affof meoes.dlin, lem
Which, taken at the flood, leads on to fortune; bou aWis ch, takat t ahe fl ono,isads
Omitted, all the voyage of their life ted, all t shalhe theenage ofir d infe tone;
Is bound in shallows and in miseries. Is nherd inlowOmi thets a fortun eri

In addition to what this passage says overtly, it has many hidden meanings. It not only reflects a complex sequence of events m the play, it also echoes the play's ideas on conflict, ambition, and the demands of leadership. Permeated with Shakespeare's understanding of human nature, it is very rich in information.

However, if the **129** letters making up this quotation were allowed to fall into a completely random, chaotic pattern, as shown in the following box, they would have no meaning whatsoever. In this form the **129** letters contain little or no **information**, but they are very rich m entropy **S** because of random dispersion. Such considerations have led to the conclusion that **information** carrying **letters** or **molecules** are a form of **free** energy **G** accumulation; **information carriers** have bring "small **bound** energy **T•S** or entropy **S**." In fact, the branch of mathematics called information theory, which is basic to the programming logic of computers, is closely related to thermodynamic theory **T•ΔS + ΔG = ΔH ≈ 0**. Living organisms are highly **synthesized products**, non-random and very large **polymer** structures, immensely rich in **information** and **free** energy **ΔG** and thus **bound** energy **T•ΔS** or entropy-poor.

Cells Require Sources of Free Energy

Cells are **isothermal** systems-they function at essentially constant temperature **T = const** (and constant pressure **p = 101.3 kPa**). **Heat ΔH** flow => is not a source of energy for cells because heat can do work **W** only as it passes to a zone or object at a lower **T** temperature. The energy that cells can and must use is **free** energy change **ΔG**, described by the **Gibbs free**-energy function **G**, which allows prediction of the direction of chemical reactions, their exact **equilibrium** position, and the amount of work **W** they can in theory perform at constant temperature **T** and pressure **p**. Hetero-trophic cells acquire **free** energy **ΔG** from nutrient molecules, and photosynthetic cells acquire it from absorbed solar radiation **~hν = ΔG**. Both kinds of cells transform this **free** energy into **ATP** and other **energy-rich** compounds capable of providing energy **ΔG** for biological work **W = -ΔG** at constant temperature **T**.

The Standard Free-Energy Change Is Directly Related to the Equilibrium Constant

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 **X** of **reactants** and **products**, the rates **v** of the forward => and reverse <= reactions are exactly equal **v=> <=v** and no further net change occurs in the system.

Equilibrium is the question about at first **1st chemical potential** and at second **2nd** about **balance** of reaction Rates.

Chemical potential μ

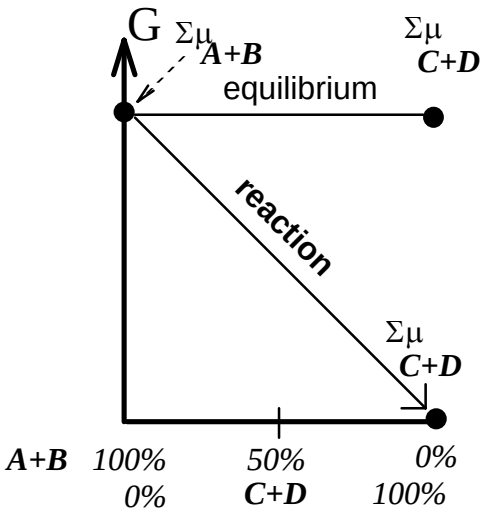
Chemical potential show, how much change of **free** energy ΔG_A brings into system-reaction adding of 1 mole amount of compound **A**. In a fact: how great amount of **free** energy belongs to one **1 mol** in mixture. It means how much free energy ΔG_A has itself per **1 mole** compound **A** , if amount of compound in molar numbers is Δn_A **= 1 mole :** $\mu_A = \frac{\Delta G_A}{\Delta n_A} = \Delta G°_A + R \bullet T \bullet \ln(X_A)$ (1-2)

chemical potential of compound **A**, where: $\Delta G°_A$, **kJ/mol - standard chemical potential** at standard conditions **T = 298.16 K ,** pressure **p = 101.3 kPa**; **R = 8.3144 J/mol/K** - universal gas constant; $\ln(X_A)$ - natural logarithmic function from argument X_A and X_A, unless - **molar fraction** concentration of compound **A**, expressed as $X_A = n_A/n_{total}$ and laying between $0<X_A\leq 1$ (absence and pure) compound **A** concentrations, where n_A, **mol - number** of **moles** for compound **A** and n_{total} , **mol** - total **number** of **moles** all present compounds **total** including water. Logarithmic function properties $\ln(1) = 0$ yield that **standard chemical potential** $\Delta G°_A = \mu_A$ at $X_A = 1$ is pure **A** compound **1 mol free** energy content $\Delta G°_A$, assuming **standard free** energy of **formation** $G°_A$ from elements for compound **A** per one **1 mole.**
Reaction proceeds completely forward until end only when **products** of reaction have hardly little disposition to reverse change back into **reactants**. In other words these **products** of reaction have trifling remarkable or zero value of chemical potential $\mu_{products} = 0$, affinity turns back to **reactants**: **A ←x— products.**

Thermo dynamical conditions of chemical equilibrium

Provided chemical potential of reaction products is taking into consideration (it has anything remarkable level of value) , then reaction proceeds not completely until end, go not on completely 100% to reactants conversion to products, but one can observe the setting in equilibrium.
In state of equilibrium sum of chemical potentials for initial compounds is equal to sum of chemical potentials for products – according chemical reaction equation reactants aA + bB and products cC + dD:

aA + bB $\underset{\text{revers}}{\overset{\text{direct}}{\rightleftarrows}}$ cC + dD



reactants - initial compounds products because compound factor-coefficients a, b, c, and d means

$a\mu_A + b\mu_B = c\mu_C + d\mu_D$

A+A+A a times molecule A and so on B, C, and D takes a part in reaction as is seen in expression of equilibrium.
The concentrations **X** of **reactants** and **products** at **equilibrium** define the **equilibrium constant**, **Keq** (see the Chemical Equilibrium). In the general reaction **chemical potential** sum for **reactants** $\Sigma\mu_{reactant}$ and **products** $\Sigma\mu_{product}$ at equilibrium are equal:
$\Sigma\mu_{reactant} = \Sigma\mu_{product}$ **;**
and free energy change for reaction is
$\Delta G_{reaction} = \Sigma\mu_{product} - \Sigma\mu_{reactant}$.

As the chemical potential sum at equilibrium are equal $a\mu_A + b\mu_B = c\mu_C + d\mu_D$ **;**

$a\bullet(\Delta G°_A + R\bullet T\bullet\ln(X_A)+b\bullet(\Delta G°_B + R\bullet T\bullet\ln(X_B)=c\bullet(\Delta G°_C + R\bullet T\bullet\ln(X_C)+d\bullet(\Delta G°_D + R\bullet T\bullet\ln(X_D)$

$(a\bullet\Delta G°_A + b\bullet\Delta G°_B) - (d\bullet\Delta G°_D + c\bullet\Delta G°_C) = R\bullet T\bullet\{[c\bullet\ln(X_C) + d\bullet\ln(X_D)] - [a\bullet\ln(X_A) + b\bullet\ln(X_B)]\}$

$-\Delta G°_{reaction} = -[(d\bullet\Delta G°_D + c\bullet\Delta G°_C) - (a\bullet\Delta G°_A + b\bullet\Delta G°_B)] = R\bullet T\bullet\{[\ln(X_D^d) + \ln(X_C^c)] - [\ln(X_A^a) + \ln(X_B^b)]\}$

$-\Delta G°_{reaction} = - [\Sigma\Delta G°_{product} - \Sigma\Delta G°_{reactant}] = R\bullet T\bullet\{\ln(X_D^d \bullet X_C^c) - \ln(X_A^a \bullet X_B^b)\}$

$$-\Delta G°_{reaction} = - [\Sigma\Delta G°_{product} - \Sigma\Delta G°_{reactant}] = R\bullet T\bullet\ln\left(\frac{X_C^c \bullet X_D^d}{X_A^a \bullet X_B^b}\right)$$

$$-\Delta G°_{reaction} = R\bullet T\bullet\ln\left(\frac{X_C^c \bullet X_D^d}{X_A^a \bullet X_B^b}\right) = R\bullet T\bullet\ln(K_{eq}) \; ; \; K_{eq} = \frac{X_C^c \bullet X_D^d}{X_A^a \bullet X_B^b} \quad (1\text{-}3)$$

In each sum a, b, c, and d are the number of molecules of A, B, C, and D participating, the **equilibrium constant** is expressed by (1-3) where X_A, X_B, X_C, and X_D are the **molar fraction** concentrations of the reaction components at the point of **equilibrium**.

When a reacting system is not at **equilibrium,** the tendency to move toward equilibrium represents a driving force, the magnitude of which can be expressed as the **free**-energy change for the reaction, $\Delta G_{reaction}$. Under **standard conditions** (**298.15 K** or **25 °C**), when reactants and products are present in **molar fraction** concentrations or, for gases, at partial pressures for total pressure as sum p_{total} **= 101.3 kilo-pascals** (**kPa**) or **1 atm**, the force driving the system toward equilibrium is defined as the **standard free**-energy change, $\Delta G°_{reaction}$. By this definition, the **standard state** for reactions that involve hydrogen ions is $X_{H3O}+$ is **pH** maintaining equilibrium constant value in ratio $\frac{X_C^c \bullet X_D^d}{X_A^a \bullet X_B^b}$ = K_{eq}. Most biochemical reactions occur in well-buffered aqueous solutions near **pH = 7.36** (for blood plasma); both the **pH** and the concentration of water [H_2O] (**55.346 M**) is essentially **constant**. For convenience of calculations, biochemists therefore define a different **standard state**, in which the concentration of H_3O^+ is $10^{-7.36}$ **M** (**pH = 7.36**) and that of water is [H_2O] = **55.346 M**; for reactions that involve Mg^{2+} (including most reactions for which **ATP** is a substrate), its concentration in solution is commonly taken to be constant at **1 mM**, but Mg^{2+} has not sense as matter for equilibrium because magnesium Mg^{2+} ion usually is a catalysts and therefore dose not affecting **equilibrium** constant K_{eq} by its concentration as X_{Mg2+}. Physical constants based on this biochemical **standard state** are called **standard transformed constants** and are written ΔG_o with a zero index (as ΔG_{Mg2+}=0 and X_{Mg2+}**=1**) to distinguish them from the **normal constants** used by chemists and physicists. (Notice that the symbol ΔG_o is a change from the symbol $\Delta G°$ used in earlier editions of thermodynamics and in most other textbooks. The change, recommended by an international committee of chemists and biochemists, is intended to emphasize that the **transformed free** energy ΔG_o is the criterion for e**quilibrium**.) By convention, when H_2O, H_3O^+ (Mg^{2+} excepting as catalyst) are r**eactants** or **products**, their concentrations could not be included in equations such as equation 1-3 but are instead incorporated into the constants ΔG_o and K_{oeq}= K_{eq}/[H_2O] or K_{oeq}= K_{eq}*[H_2O].

Just as K_{oeq} is a physical constant characteristic for each reaction, so too is ΔG_o a constant. As is noted in General Chemistry course (equilibrium and Second Law of Thermodynamics), there is a simple relationship between K_{oeq} and ΔG_o show the energy and mass relation of compounds. The **standard free**-energy $\Delta G°$ change of a chemical reaction is simply an alternative mathematical way of expressing its equilibrium constant K_{eq}. The **equilibrium** constant for a given chemical reaction is K_{eq} = **1.0**, the **standard free**-energy change of that reaction is $\Delta G°$ = **0. 0** (the natural logarithm of **1 ln(1) = 0** is zero). If K_{eq} of a reaction is greater than **>1.0**, its $\Delta G°$ **< 0** is negative. If K_{eq} is less than **<1.0**, $\Delta G°$ **> 0** is positive. Because the relationship between $\Delta G°$ and K_{eq} is exponential, relatively small changes in $\Delta G°$ correspond to large changes in K_{eq}.

It may be helpful to think of the **standard free**-energy change $\Delta G°$ in another way. $\Delta G°$ is the difference between the **free**-energy content of the **products**, and the **free**-energy content of the **reactants** under **standard conditions** (1-3). When $\Delta G° = G_2 - G_1 < 0$ is negative, the **products** G_2 contain less **free** energy than the **reactants** and the reaction will proceed **spontaneously** under **standard conditions** G_1; all chemical reactions tend to go in the conversion direction that results in a decrease in the f**ree** energy to G_2 of the **system**. A positive value of $\Delta G° = G_2 - G_1 > 0$ means that the **products** G_2 of the reaction contain more **free** energy than the **reactants** G_1 and this reaction will tend to go in the conversion reverse $\xleftarrow{\text{reverse}}$ direction to G_1.

As an example, let us make a simple calculation of the **standard free**-energy change $\Delta G°$ of the reaction catalyzed by the enzyme **phospho-gluco-mutase** (**glucose** symbol is **Glc** of three letters):

Glc 1-phosphate —=> **Glc 6-phosphate**

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 will contain **1 mM glucose 1-phosphate** and **19 mm glucose 6-phosphate** at **25°C**. (Remember that **enzymes** do not affect the point of **equilibrium** of a reaction; they merely hasten its attainment.) From these data we can calculate the **equilibrium** constant and **standard free**-energy change:
K_{eq} = [**Glc 6-phosphate**]/[**Glc 1-phosphate**] = **19 mM/1 mM = 19** shifted to right side
$\Delta G°$ = **-R•T•ln(**K_{eq} **)** = **-R•T•ln(19**) = **-7.296 kJ/mol** spontaneous

Because the **standard free**-energy change $\Delta G° < 0$ is negative, when the reaction starts with **glucose 1-phosphate** and **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 to **glucose 1-phosphate** $\xleftarrow{\text{reverse}}$ from **glucose 6-phosphate**), $\Delta G°$ = **7.296 kJ/mol** has the same magnitude but the opposite sign, reverse reaction no spontaneous.

Actual Free-Energy Changes Depend on Reactant and Product Concentrations in **Homeostasis**

Table 1-1 gives the **standard free**-energy changes $\Delta G°$ for some representative chemical reactions. Note that **hydrolysis** of simple **esters**, **amides**, **peptides**, and **glycosides**, as well as **rearrangements** and **eliminations**, proceed with relatively small **standard free**-energy changes $\Delta G°$, whereas **hydrolysis** of **acid anhydrides** occurs with relatively large decreases in **standard free**-energy $\Delta G°$. The complete **oxidation** of organic compounds such as **glucose** or **palmitate** to CO_2 and H_2O, which in cells requires many steps, results in very large decreases in **standard free** energy $\Delta G°$. However, **standard free**-energy changes $\Delta G°$ such as those in Table 1-1 indicate how much **free** energy is available from a reaction under **standard conditions** for one **1 mol** of compound. To describe the energy released under the **homeostasis conditions** existing in real cells, an expression for the **actual Homeostasis free**-energy change $\Delta G_{reaction}$ calculation is essential.

$$\Delta G_{reaction} = \Delta G°_{reaction} + R \cdot T \cdot \ln\left(\frac{X_C^c \cdot X_D^d}{X_A^a \cdot X_B^b}\right) \neq 0;\ 0 = \Delta G°_{reaction} + R \cdot T \cdot \ln(K_{eq}) \text{ at equilibrium zero (1-4)}$$

We must be careful to distinguish between two **2** different quantities: the **free**-energy change, ΔG, and the **standard free**-energy change, $\Delta G°$. Each chemical reaction has a characteristic **standard free**-energy change per one **1 mol** of **reactant**, which maybe positive $\Delta G°>0$, negative $\Delta G°<0$, or sometimes zero $\Delta G°=0$, depending on the equilibrium constant K_{eq} of the reaction. The **standard free**-energy change $\Delta G°$ tells us in which direction and how far a given reaction must go to reach **equilibrium** when the temperature is **25 °C** or T_o **= 298.15 K**, and the pressure **p** is **101.3 kPa** (**1 atm**) and component concentrations at **equilibrium** are **X**. Thus $\Delta G°$ 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 **X** and of the temperature **T = 310.15 K** prevailing during the reaction in human body, which will not necessarily match the **standard conditions** as defined above. Moreover, the ΔG of any reaction proceeding => spontaneously toward its **equilibrium** state is always negative $\Delta G<0$, becomes less negative as the reverse ← reaction proceeds, and is zero $\Delta G = 0$ at the point of **equilibrium** $(X_D^d \cdot X_C^c)/(X_A^a \cdot X_B^b) = K_{eq}$, indicating that no more work $W = -\Delta G = 0$ can be done by the reaction: a**A** + b**B** = c**C** + d**D** according expression (1-4)

ΔG and $\Delta G°$ for any reaction are related by the equation (1-4). in which the terms in red are those actually prevailing in the system under observation. The concentration **X** terms in this equation express the effects commonly called **mass action**. As an example, let us suppose that the reaction a**A** + b**B** = c**C** + d**D** is taking place at the **standard conditions** of temperature T_o **= 298.15 K** (**25 °C**) and pressure (**101.3 kPa**) but that the concentrations of X_A, X_B, X_C, and X_D into reaction mixture are not equal and that none of the components is present at the standard concentration **X** of **1.0** like pure compounds. To determine the actual **free**-energy change, ΔG , under these **nonstandard conditions** of concentration **X** as the reaction proceeds from left => to right, we simply enter the actual concentrations of X_A, X_B, X_C, and X_D in Equation 1-4; the values of **R**, T_o, and $\Delta G°$ are the standard values. ΔG is negative $\Delta G<0$ and approaches zero $\Delta G=>0$ as the reaction proceeds because the actual reactants concentrations of X_A and X_B decrease and products concentrations of X_C, and X_D increase. Notice that when a reaction is at **equilibrium**-when there is no **force** driving the reaction in either direction and ΔG is zero-Equation 1-4 reduces to $\Delta G° = - R \cdot T \cdot \ln(K_{eq})$ and $0 = \Delta G° + R \cdot T \cdot \ln(K_{eq})$ the equation relating the **standard free**-energy change and **equilibrium** constant K_{eq} as noted above (1-4).

Biological mediums usually have some certain hydrogen ion $[H_3O^+]$ concentrations expressed as $pH = -\log([H_3O^+])$ for: blood plasma and cytosol **pH = 7.36**; mitochondria matrix **pH = 8.37**; mitochondria inter membrane space **pH = 5.0**; saliva juice **pH = 6.8**; stomach juice **pH = 1.2** (before meals). Extracting from **equilibrium** mixture constant K_{eq} as expression $R \cdot T \cdot \ln(X_{H3O}{}^{+n})$ by mathematical separation of logarithm ratio in (1-4) may correct **standard free**-energy $\Delta G°$ value to non-**standard conditions** for **pH** of medium of $[H_3O^+] = 10^{-pH}$ **M** solution where **n** is the number of hydrogen ions H_3O^+ involved in reaction **equilibrium** mixture according given reaction equation. Addition or subtraction to **standard free**-energy $\Delta G°$ value yield $\Delta G_o = \Delta G° \pm R \cdot T \cdot \ln(X_{H3O}{}^{+n})$ non-**standard free**-energy at given medium **pH conditions** ($-R \cdot T \cdot \ln(X_{H3O}{}^{+n})$ agree for **reactant** and $+R \cdot T \cdot \ln(X_{H3O}{}^{+n})$ for **product**).

Table 1-1. Standard Free-Energy Changes of Some Chemical Reactions at 25 °C (298.15 K)

Hydrolysis reactions type and its standard free energy change ΔG° in units of	(kJ/mol)	(kcal/mol)
Acetic acid and phosphoric acid anhydrides		
$CH_3CO\text{-}O\text{-}OCCH_3 + H_2O$ => $2\ CH_3COO^-H^+$	-91.100	-21.80
$CH_3CO\text{-}O\text{-}OCCH_3 + 3\ H_2O$ => $2\ CH_3COO^- + 2\ H_3O^+$ 3.317/4.184=0.793	-3.317	-0.793
$ATP^{4-} + H_2O$ => $ADP^{3-} + H_2PO_4^-$	-30.500	-7.30
$ATP^{4-} + 2\ H_2O$ => $ADP^{3-} + HPO_4^{2-} + H_3O^+$ 34.46048/4.184=8.23625	34.4605	8.24
$ATP^{4-} + H_2O$ => $AMP^{2-} + {}^-HOPO_2\text{-}O\text{-}O_2POH^-$	-45.600	-10.90
${}^-HOPO_2\text{-}O\text{-}O_2POH^- + H_2O$ => $2\ H_2PO_4^-$	-19.200	-4.60
${}^-HOPO_2\text{-}O\text{-}O_2POH^- + H_2O$ => $2\ HPO_4^{2-} + 2\ H_3O^+$ 110.72096/4.184=26.46294	110.721	26.46
$UDP\text{-}Glu^{2-} + H_2O$ => $UMP^- +$ Glc 1-phosphate$^-$	-43.000	-10.30
Esters		
$CH_3CH_2\text{-}O\text{-}OCCH_3 + H_2O$ => $CH_3CH_2\text{-}OH + HO\text{-}OCCH_3$	-19.600	-4.70
$CH_3CH_2\text{-}O\text{-}OCCH_3 + 2\ H_2O$ => $CH_3CH_2\text{-}OH + {}^-O\text{-}OCCH_3 + H_3O^+$ acetate+ H^+	24.2905	5.806
Glc 6-phosphate$^-$ + H_2O => Glc + $H_2PO_4^-$ 24.29048/4.184=5.80556	-13.800	-3.30
Glc 6-phosphate$^-$ + $2\ H_2O$ => Glc + $HPO_4^{2-} + H_3O^+$ 51.16048/4.184=12.22765	51.1605	12.23
Amides and peptides		
Glutamine + H_2O => glutamate$^-$ + NH_4^+ 67.09/4.184=16,03	-14.200	-3.40
Glycylglycine + H_2O => 2 glycine $\Delta G_r=\Delta H_r-T*\Delta S$=67.09 kJ/mol	-9.200	-2.20
Glycosides $\Delta G_r=\Delta H_r-T*\Delta S$ =-25.9-298.15*-0.3118965= -25.9+92.9919=67.09 kJ/mol	+67.09	+16.03
Maltose + H_2O => 2 glucose	-15.500	-3.70
Lactose + H_2O => glucose + galactose	-15.900	-3.80
Rearrangements		
Glucose 1-phosphate$^-$ => glucose 6-phosphate$^-$	-7.300	-1.70
Fructose 6-phosphate$^-$ => glucose 6-phosphate$^-$	-1.700	-0.40
Elimination of water H_2O		
Malate => Fumarate + H_2O	3.1	0.8
Oxidations with molecular oxygen O_2		
Glucose + $6\ O_{2aqua}$ => $6\ CO_{2aqua} + 6\ H_2O$	-2 840	-686
Palmitatic Acid + $23\ O_{2aqua}$ => $16\ CO_{2aqua} + 16\ H_2O$	-9 770	-2 338

The criterion for spontaneity of a reaction is the value of **ΔG**, not **ΔG°**. A reaction with a positive **ΔG°>0** can go in the forward direction if **ΔG<0** is negative. This is possible if the term **R•T•ln**([**products**]/[**reactants**]) in equation 1-4 is negative (-) and has a larger absolute value greater > than **ΔG°**. For example, the immediate removal of the **products** of a reaction can keep the ratio [**products**]/[**reactants**] well below **<1**, such that the term **R•T•ln**([**products**]/[**reactants**]) has a large, negative (-) value.

ΔG° and **ΔG** are expressions of the maximum amount of **free** energy per one **1 mol** of compound that a given reaction can theoretically deliver an amount of energy that could be realized only if a perfectly efficient device were available to trap or harness it. Given that no such device is possible (some **free** energy **ΔG** is always lost to **bound** energy **T•ΔS** or entropy **S** during any process), the amount of work **W ≤ -ΔG** done by the reaction at constant temperature **T = const** and pressure is always less than the theoretical amount **ΔG**.

Another important point is that some thermodynamically favorable reactions (that is, reactions for which **ΔG°<0** is large and negative) do not occur at measurable rates. For example, **combustion** of firewood to **CO_{2aqua}** and **H_2O** is very favorable thermodynamically, but firewood remains stable for years because the activation energy **E_a** (see Reaction Rate (Velocity) and Kinetics) for the **combustion** reaction is higher than the energy **E_r** available at room temperature. If the necessary activation energy **E_a** is provided (with a lighted match, for example), combustion will begin, converting the wood to the more stable products **CO_{2aqua}** and **H_2O** and releasing energy as **heat -ΔH** and light **~hv**. The **heat -ΔH** released by this **exothermic** reaction provides the activation energy **E_a** for **combustion** of neighboring regions of the firewood; the process is self-perpetuating.

In living cells, reactions that would be extremely slow and long time if uncatalyzed are caused to occur, not by supplying additional **heat -ΔH**, but by lowering the activation energy **E_a** with an **enzyme**. An **enzyme** provides an **alternative reaction pathway** with a lower activation energy **E_a** than the uncatalyzed reaction, so that at room temperature a large fraction of the **substrate** molecules have enough thermal energy **-ΔH** to overcome the **activation barrier**, and the reaction rate increases dramatically **10^6**. The **free**-energy change **ΔG** for a reaction is independent of the **pathway** by which the reaction occurs; it depends only on the nature **ΔG°**

and concentration **X** of **reactants** and the final **products**. **Enzymes** cannot, therefore, change equilibrium constants $\mathbf{K_{eq}}$; but they can and do increase the rate at which a reaction proceeds in the direction dictated by **thermodynamics homeostasis (stationary) conditions**. **Free-Energy Changes ΔG Are Additive**

In the case of two **2** sequential chemical reactions, **A** ⇔ **B** and **B** ⇔ **C**, each reaction has its own **equilibrium** constant $\mathbf{K_{eq1}}$, $\mathbf{K_{eq2}}$ and each has its characteristic **standard free**-energy change, $\Delta\mathbf{G°_1}$ and $\Delta\mathbf{G°_2}$. As the two reactions are sequential, **B** cancels out to give the overall reaction **A** ⇔ **C**, which has its own **equilibrium** constant $\mathbf{K_{eq}}$ and thus its own **standard free**-energy change, $\Delta\mathbf{G°}_{total}$ The ΔG° values of sequential chemical reactions are additive. For the overall reaction **A** ⇔ **C**, $\Delta\mathbf{G°}_{total} = \Delta\mathbf{G°_1} + \Delta\mathbf{G°_2}$ is the algebraic sum of the individual **standard free**-energy changes, $\Delta\mathbf{G°_1}$ and $\Delta\mathbf{G°_2}$, and the overall **equilibrium** constant $\mathbf{K_{eq}} = \mathbf{K_{eq1}}\bullet\mathbf{K_{eq2}}$ is the factorial of the individual **equilibrium** constant $\mathbf{K_{eq1}}$ and $\mathbf{K_{eq2}}$ of the two **2** separate sequential reactions. The principle of biochemical thermodynamics explains how unfavorable (**endoergic**) reaction can be driven in the forward => direction by coupling it to a highly **exoergic** reaction through a **common intermediate**. For example, the synthesis of **glucose 6-phosphate** is the first **1st** step in the utilization of **glucose** by many organisms $\Delta\mathbf{G°}_{1total}$ = **-16.70 kJ/mol**:

a1 Glucose + $\mathbf{H_2PO_4^-}$ => **glucose 6-phosphate**$^-$ + $\mathbf{H_2O}$; $\Delta\mathbf{G°_{a1}}$ = **13.80 kJ/mol** not **pH** dependent reaction **1**

a2 Glucose + $\mathbf{HPO_4^{2-}}$ + $\mathbf{H_3O^+}$ => **glucose 6-phosphate**$^-$ + 2 $\mathbf{H_2O}$; $\Delta\mathbf{G°_{a2}}$ = **-51.16 kJ/mol**

The positive value of ΔG°>0 predicts that under **standard conditions** the reaction **a1** will tend not to proceed spontaneously in the direction => written. In accounting reaction **a2** with $\mathbf{HPO_4^{2-}}$ + $\mathbf{H_3O^+}$ is affecting by **pH** of medium and can be derived by hydrogen ion concentration $\mathbf{[H_3O^+]=10^{-pH}}$ **M** (**pH = 7.36**) as with appropriate **pH** value. Cellular **hydrolysis** of **ATP**$^{4-}$ to **ADP**$^{3-}$ producing $\mathbf{H_2PO_4^-}$ is **exoergic b1** $\Delta\mathbf{G°_{b1}}$= **-30.500 kJ/mol** or producing $\mathbf{HPO_4^{2-}}$ +$\mathbf{H_3O^+}$ in **endoergic b2** $\Delta\mathbf{G°_{b2}}$ = **34.4605 kJ/mol** driven by hydrogen ion concentration $[\mathbf{H3O^+}]=\mathbf{10^{-7.36}}$ **M** in blood **pH = 7.36**:

b1 $ATP^{4-} + H_2O$ => $ADP^{3-} + H_2PO_4^-$; $\Delta\mathbf{G°_{b1}}$ = **-30.500 kJ/mol** (1-5)

b2 ATP^{4-}+2 H_2O => ADP^{3-}+HPO_4^{2-}+H_3O^+ ; $\Delta\mathbf{G°_{b2}}$ = **34.4605 kJ/mol** (**pH = 7.36**)

These two **2** reactions share the common intermediates $\mathbf{H_2PO_4^-}$ or $\mathbf{HPO_4^{2-}}$ + $\mathbf{H_3O^+}$ and $\mathbf{H_2O}$ or 2 $\mathbf{H_2O}$ and may be expressed as sequential reactions **1** and **2**: **-51.16+34.4605= -16.6995 kJ/mol**

a1 Glucose + $\mathbf{H_2PO_4^-}$	=> **glucose 6-phosphate**$^-$ + $\mathbf{H_2O}$	; $\Delta\mathbf{G°_{a1}}$	= **13.80 kJ/mol**
b1 $ATP^{4-} + H_2O$	=> $ADP^{3-} + H_2PO_4^-$;	; $\Delta\mathbf{G°_{b1}}$	= **-30.500 kJ/mol**
Sum **1**: **Glucose** + ATP^{4-}	=> **glucose 6-phosphate**$^-$ + ADP^{3-}	; $\Delta\mathbf{G°}_{1total}$	= **-16.70 kJ/mol**
a2 Glucose + $\mathbf{HPO_4^{2-}}$ + $\mathbf{H_3O^+}$	=> **glucose 6-phosphate**$^-$ + 2 $\mathbf{H_2O}$	; $\Delta\mathbf{G°_{a2}}$	= **-51.16 kJ/mol**
b2 ATP^{4-}+2 H_2O	=> ADP^{3-}+HPO_4^{2-} + H_3O^+	; $\Delta\mathbf{G°_{b2}}$	= **34.4605 kJ/mol**
Sum **2**: **Glucose** + ATP^{4-}	=> **glucose 6-phosphate**$^-$ + ADP^{3-}	; $\Delta\mathbf{G°}_{2total}$	= **-16.6995 kJ/mol**

The overall **standard free**-energy change $\Delta\mathbf{G°}_{total}$= **-16.7 kJ/mol** is obtained by adding the ΔG° values for individual reactions.

The overall reaction is **exoergic**. In this case, energy stored in the bonds of ATP^{4-} is used to drive the synthesis of **glucose 6-phosphate**$^-$, even though its formation from **glucose** and **phosphate a1** is **endoergic** or **pH** affected **hydrolyze b2** is **endoergic**. Any way the **pathway** of **glucose 6-phosphate** formation by **phosphoryl transfer** from ATP^{4-} is different from reactions (**a**) and (**b**) above in both cases **1** and **2**, but the net result is the same as the sum of the two **2** reactions. In thermodynamic calculations, all that matters is the **state** of the **system** at the **beginning** (**reactants**) of the process, and its **state** at the **end** (**products**), the route between the **initial** and **final states** is immaterial.

We have said that ΔG° is a way of expressing the **equilibrium** constants $\mathbf{K_{a1eq}}$ and $\mathbf{K_{a2eq}}$ for a reaction. For reaction (**a**) **1** and **2** above at standard **T=298.15K and T=310.15K**,

$$\mathbf{K_{a1eq298}} = \frac{[Glc6P^-]\bullet[H_2O]}{[Glc]\bullet[H_2PO_4^-]} = \mathbf{3.823\bullet10^{-3}} \;\&\; \mathbf{K_{a1eq310}} = \frac{[Glc6P^-]\bullet[H_2O]}{[Glc]\bullet[H_2PO_4^-]} = \mathbf{4.7418\bullet10^{-3}};$$

$$\mathbf{K_{a2eq298}} = \frac{[Glc6P^-]\bullet[H_2O]^2}{[Glc]\bullet[HPO_4^{2-}]\bullet[H_3O^+]} = \mathbf{9.177\bullet10^{8}} \;\&\; \mathbf{K_{a2eq310}} = \frac{[Glc6P^-]\bullet[H_2O]^2}{[Glc]\bullet[HPO_4^{2-}]\bullet[H_3O^+]} = \mathbf{4.1299\bullet10^{8}}$$

Notice if $\mathbf{H_2O}$ is not included in this expression one should divide the **standard equilibrium** constants by water concentration $[\mathbf{H_2O}]$ = **55.1398 M** at cell temperature **T = 310.15 K** to get non-**standard equilibrium** constant. The **equilibrium** constants $\mathbf{K_{b1}}$ and $\mathbf{K_{b2}}$ for the **hydrolysis** of ATP^{4-} are

$$\mathbf{K_{b1298}} = \frac{[ADP^{3-}]\bullet[H_2PO_4^-]}{[ATP^{4-}]\bullet[H_2O]} = \mathbf{2.2041\bullet10^{5}} \;\&\; \mathbf{K_{b1310}} = \frac{[ADP^{3-}]\bullet[H_2PO_4^-]}{[ATP^{4-}]\bullet[H_2O]} = \mathbf{1.3693\bullet10^{5}};$$

$\mathbf{K_{b2298}}=\frac{[ADP^{3-}]\bullet[HPO_4^{2-}]\bullet[H_3O^+]}{[ATP^{4-}]\bullet[H_2O]^2}=\mathbf{9.1821\bullet10^{-7}}$ or $\mathbf{K_{b2310}}=\frac{[ADP^{3-}]\bullet[HPO_4^{2-}]\bullet[H_3O^+]}{[ATP^{4-}]\bullet[H_2O]^2}=\mathbf{1.5722\bullet10^{-6}}$

The equilibrium constant for the two coupled reactions is
0.0047418*136930=649.2946740=412990000*0.0000015722=649.3028780000
649.3028780000/0.0047418=136931.73014467

$\mathbf{K_{eq1}}=\frac{[Glc6P^-]\bullet[H_2O]}{[Glc]\bullet[H_2PO_4^-]}\bullet\frac{[ADP^{3-}]\bullet[H_2PO_4^-]}{[ATP^{4-}]\bullet[H_2O]}=\frac{[ADP^{3-}]\bullet[Glc6P^-]}{[Glc]\bullet[ATP^{4-}]}=\mathbf{K_{a1eq}\bullet K_{b1}}=\mathbf{842.63}$ or $\mathbf{649.3}$

$\mathbf{K_{eq2}}=\frac{[Glc6P^-]\bullet[H_2O]^2}{[Glc]\bullet[HPO_4^{2-}]\bullet[H_3O^+]}\bullet\frac{[ADP^{3-}]\bullet[HPO_4^{2-}]\bullet[H_3O^+]}{[ATP^{4-}]\bullet[H_2O]^2}=\frac{[ADP^{3-}]\bullet[Glc6P^-]}{[Glc]\bullet[ATP^{4-}]}=\mathbf{842.64}$ or $\mathbf{649.3}$

This calculation illustrates an important point about **equilibrium** constants $\mathbf{K_{eq}}$:, although the $\Delta\mathbf{G°}$ values for two **2** reactions that sum to a third **3rd** are additive, the $\mathbf{K_{eq}}$ for a reaction that is the sum of two **2** reactions is the product of their individual $\mathbf{K_{a1eq}\bullet K_{b1}}$ or $\mathbf{K_{a2eq}\bullet K_{b2}}$ values yielding $\mathbf{K_{eq1}}$ **= 649.3** or $\mathbf{K_{eq2}}$ **= 649.3** at human body temperature **T=310.15K** (**37°C**) respectively. **Equilibrium** constants are multiplicative. By coupling ATP^{4-} **hydrolysis** to glucose 6-phosphate$^-$ synthesis, the $\mathbf{K_{eq}}$ for formation of glucose 6-phosphate$^-$ has been raised by a factor of about ~ $\mathbf{10^5 = 136931.7}$ **factor** ($\mathbf{K_{a1eq}\bullet K_{b1}}$ **= 649.3 /** $\mathbf{K_{a1eq310}}$ **=** $\mathbf{4.7418\bullet10^{-3}}$ **)**. This **common - intermediate** strategy is employed by all living cells in the synthesis of metabolic **intermediates** and cellular **components**. Obviously, the strategy works only if compounds such as ATP^{4-} are continuously available. In the following chapters we consider several of the most important cellular **pathways** for producing ATP^{4-}.

Phosphoryl Group Transfers and ATP

Having developed some fundamental principles of energy changes in chemical **systems**, we can now examine the **energy cycle** in cells and the special role of ATP^{4-} as the **energy currency** that links catabolism and anabolism (see Fig. 1-1a). Heterotrophic cells obtain **free** energy in a chemical form by the catabolism of **nutrient** molecules, and they use that energy to make ATP^{4-} from ADP^{3-} and $H_2PO_4^-$. ATP^{4-} then donates some of its chemical energy to **endoergonic** processes such as the **synthesis** of metabolic **intermediates** and **macromolecules** from **smaller precursors**, the **transport** of substances across membranes against concentration **C** gradients, and mechanical motion. This donation of energy from ATP^{4-} generally involves the covalent participation of **ATP** in the reaction that is to be driven, with the eventual result that ATP^{4-} is converted to ADP^{3-} and $H_2PO_4^-$ or, in some reactions, to AMP^{2-} and 2 $H_2PO_4^-$. We discuss here the chemical basis for the large **free**-energy changes $\Delta\mathbf{G}$ that accompany **hydrolysis** of ATP^{4-} and other **high-energy phosphate** compounds, and we show that most cases of energy donation by ATP^{4-} involve group transfer, not simple **hydrolysis** of ATP^{4-}. To illustrate the range of **energy transductions** in which ATP^{4-} provides the energy, we consider the **synthesis** of information-rich **macromolecules**, the transport of solutes across membranes, and motion produced by muscle contraction.

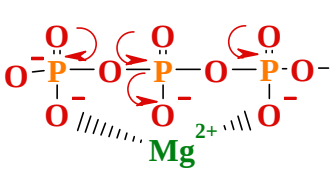
The Free-Energy Change for ATP Hydrolysis Is Large and Negative

Figure 1-1b summarizes the chemical basis for the relatively large, negative, **standard free** energy $\Delta\mathbf{G°<0}$ of **hydrolysis** of ATP^{4-}. The **hydrolytic** cleavage of the terminal **phosphoric acid anhydride** (**phospho-anhydride**) bond in ATP^{4-} separates one of the three **3** negatively charged **phosphates** and thus relieves some of the electrostatic repulsion in ATP^{4-}; the $H_2PO_4^-$ released is stabilized by the formation of several resonance forms not possible in ATP^{4-}; and ADP^{3-}, the other direct product of **hydrolysis** ADP^{2-}, immediately ionizes to ADP^{3-}, releasing $\mathbf{H^+}$ into a medium $\mathbf{H_2O}$ of very low [$\mathbf{H_3O^+}$] ($\mathbf{10^{-7.36}}$ **M**). Because the concentrations of the direct products of ATP^{4-} **hydrolysis** are far below the concentrations at **equilibrium**, mass action favors the hydrolysis reaction due to high water influence **2** $\mathbf{H_2O}$ on **equilibrium** 1-5.

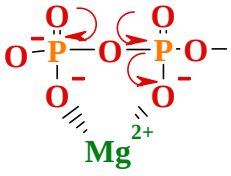
Although the **hydrolysis** of ATP^{4-} is highly **exoergonic** ($\Delta\mathbf{G°}$ **34.4605 kJ/mol** at cellular **conditions**), the molecule is kinetically stable at **pH = 7.36** because the activation energy $\mathbf{E_a}$ for ATP^{4-} **hydrolysis** is relatively high. Rapid cleavage rate **v** of the **phospho-anhydride** bonds occurs only when **catalyzed** by an **enzyme** which decrease activation energy $\mathbf{E_a}$ dramatically.

The **free**-energy change $\Delta\mathbf{G°}$ for ATP^{4-} hydrolysis is **34.4605 kJ/mol** under **standard conditions**, but the actual **free** energy of hydrolysis ($\Delta\mathbf{G}$) of ATP^{4-} in living cells is very different: the cellular concentrations of ATP^{4-}, ADP^{3-}, and $H_2PO_4^-$+HPO_4^{2-} are not identical and are much lower than the **1.0 M** (Table 1-2). Furthermore, $\mathbf{Mg^{2+}}$ in the cytosol binds to ATP^{4-} and ADP^{3-} (Fig. 1-1b), and for most **enzymatic** reactions that involve ATP^{4-} as **phosphoryl** group **donor**, the true substrate is $\mathbf{MgATP^{2-}}$. The relevant $\Delta\mathbf{G°}$ is therefore that for $\mathbf{MgATP^{2-}}$**- hydrolysis**. Box 1-1 shows how $\Delta\mathbf{G}$ for ATP^{4-} **hydrolysis** in the intact erythrocyte can be calculated from the data in Table 1-2. In intact cells, $\Delta\mathbf{G}$ for ATP^{4-} **hydrolysis**, usually designated $\Delta\mathbf{G}_p$ is much

more negative than ΔG°, ranging from **- 50** to **- 65 kJ/mol**. ΔG_p is often called the **phosphorylation potential.** In the following discussions we use the **standard free**-energy change for ATP^{4-} **hydrolysis**, because this allows comparison, on the same basis, with the energetics of other cellular reactions. Remember, however, that in living cells **ΔG** is the relevant quantity-for ATP^{4-} **hydrolysis** and all other reactions-and may be quite different form **ΔG°**.



-Ribose-Adenine MgATP^{2-}

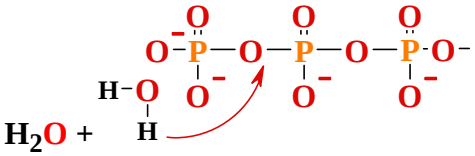


-Ribose-Adenine MgADP^{-}

Figure 1-2. Mg^{2+} and **ATP^{4-}**. Formation of **Mg^{2+}** complexes partially shields the negative charges **2-** and influences the **conformation** of the **phosphate** groups in **nucleotides** such as **ATP^{4-}** and **ADP^{3-}**.

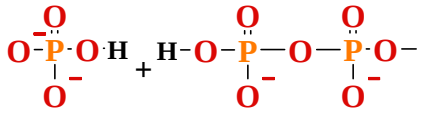
Stored nutrients ← Ingested foods ♦ Solar photons ♦ catabolic reactions **pathways exoergonic** ←
=>**ATP^{4-}** =>**ATP^{4-}** =>**ATP^{4-}** =>**ATP^{4-}** =>**ATP^{4-}** =>**ADP^{3-}** =>**AMP^{2-}**=>**$^{-}HO_3POPO_3H^{-}$** **HPO_4^{2-}**
=> Osmotic work => Mechanical work => Complex biomolecules => anabolic reaction **pathway endoergonic**

Figure 1-1a. ATP^{4-} is the shared chemical intermediate linking energy releasing anabolism to energy requiring catabolism cell processes. Its role in the cell is analogous to that of money in an economy it is "earned/produced" in **exoergonic** reactions and "spent/consumed" in **endoergonic** ones.



H_2O +

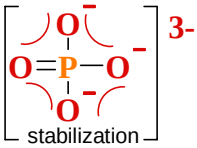
-Ribose-Adenine ATP^{4-} hydrolysis, with relief of charge repulsion



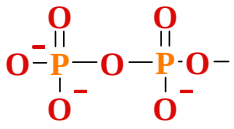
H_2O +

-Ribose-Adenine ADP^{2-}

resonance ionization



+ H^+ **H_3O^+ +**



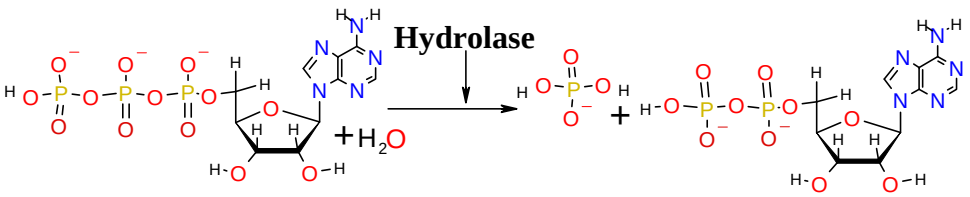
-Ribose-Adenine + ADP^{3-}

Figure 1-1b. Chemical basis for the **large free-energy change** associated with **ATP hydrolysis**. First **1st**, **hydrolysis**, by causing charge separation, relieves **electrostatic repulsion** among the four **4** negative (**-**) charges on **ATP^{4-}**. Second **2nd**, inorganic **phosphate** (**HPO_4^{2-}**) released by **hydrolysis** is stabilized by formation of a resonance hybrid, in which each of the four **4 P=O** bonds has the same degree of double-bond character and the **proton H^+** (hydrogen ion **H_3O^+**) is not permanently associated with any one of the oxygens **=O-H**. Some degree of resonance stabilization also occurs in phosphates involved in **ester** or **anhydride** linkages, but fewer resonance forms are possible than for **PO_4^{3-}**. Third **3rd**, ADP^{2-} produced by the **hydrolysis** immediately ionizes, releasing a **proton H^+** => into a **+ H_2O** medium of very low [**H_3O^+**] (**pH = 7.36**) forming ADP^{3-} and **H_3O^+**. A fourth **4th** factor (not shown) that favors ATP^{4-} **hydrolysis** is the greater degree of **solvation** (**hydration**) of the products **HPO_4^{2-}** and **ADP^{3-}** relative to **ATP^{4-}** which further stabilizes the **products** relative to the **reactants**.

ATP^{4-} + 2 H_2O => ADP^{3-} + HPO_4^{2-}+ H_3O^+; ΔG° = 34.4605 kJ/mol

ATP driven FORBIDDEN REACTIONS IN LIVING CELLS

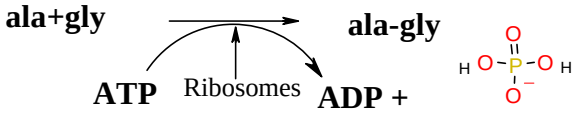
Synthesis for **ala + gly => ala-gly + H_2O;** is thermodynamically forbidden non-spontaneous. In hydrolysis of **ATP** molecules with water is formed adenosine diphosphate **ADP** and phosphate:



ATP hydrolyse with water release free energy. In the biochemical mechanisms the forbidden processes are combined together with hydrolysis of **ATP**. Liberated water in the synthesis of peptide **ala-gly** is used for hydrolysis of **ATP**. Ribosome join two reactions together in tandem process, the summary reaction becomes spontaneous:

ala + gly => ala-gly +H_2O ΔG=+17.2 kJ/mol

ATP^{4-} + H_2O => ADP^{3-} + $H_2PO_4^-$ + H_3O^+ ; ΔG= -30.5 kJ/mol



COMPLEX and ENZYME governed REACTIONS in human organism number 3 is Enzymatic joint tandem complex reactions drive thermodynamically forbidden REACTIONS.

The **standard free energy** ΔG° of **hydrolysis** of **ATP** is **-30.5 kJ/mol**. In the cell, however, the concentrations **C** of **ATP**, **ADP**, and P_i= [$H_2PO_4^-$]+[HPO_4^{2-}] are not only unequal but much lower than the standard **1 M** concentrations **C** (see Table 14-5). Moreover, the cellular **pH** may differ somewhat from the standard **pH** of **7.0**. Thus the *actual* **free energy** ΔG° of **hydrolysis** of **ATP** under intracellular conditions (ΔG_p) differs from the standard **free energy** change, ΔG°. We can easily calculate ΔG° For example, in human **erythrocytes** the concentrations **C** of **ATP**, **ADP**, and P_i= [$H_2PO_4^-$]+[HPO_4^{2-}] are **2.25**, **0.25**, and **1.65 mM**, respectively. Let us assume for simplicity that the **pH** is **7.36** and the temperature **T** is **310.15 K** (**37 °C**), the standard **pH** and temperature **T**. The actual **free energy** ΔG° of **hydrolysis** of **ATP** in the **erythrocyte** under these conditions is given by the relationship:

$$ATP^{4-} + 2\ H_2O \Rightarrow ADP^{3-} + HPO_4^{2-} + H_3O^+ ;\ \Delta G^\circ + R\cdot T\cdot \ln\left(\frac{[ADP^{3-}]\bullet[HPO_4^{2-}]\bullet[H_3O^+]}{[ATP^{4-}]\bullet[H_2O]^2}\right)$$

$$K^\circ_{H2PO4}=\frac{[HPO_4^{2-}]\bullet[H_3O^+]}{[H_2PO_4^-]\bullet[H_2O]};\ P_i = 1.65\ mM=[H_2PO_4^-]+[HPO_4^{2-}];\ [H_2PO_4^-]=\frac{[HPO_4^{2-}]\bullet[H_3O^+]}{K_{H2PO4}\bullet[H_2O]};$$

$$[HPO_4^{2-}]+[HPO_4^{2-}]\frac{[H_3O^+]}{K_{H2PO4}\bullet[H_2O]} = 1.65\cdot10^{-3}\ M = [HPO_4^{2-}]\bullet\left(1+\frac{[H_3O^+]}{K_{H2PO4}\bullet[H_2O]}\right);$$

$$[HPO_4^{2-}]=\frac{1.65/1000}{\left(1+\frac{[H_3O^+]}{K_{H2PO4}\bullet[H_2O]}\right)}=9.8\cdot10^{-4};\ \Delta G^\circ+R\cdot T\cdot\ln\left(\frac{1.65/1000\bullet[ADP^{3-}]\bullet[H_3O^+]}{\left(1+\frac{[H_3O^+]}{K_{H2PO4}\bullet[H_2O]}\right)\bullet[ATP^{4-}]\bullet[H\ O]^2}\right)=\Delta G$$

Substituting the appropriate values we obtain: $9.7619\cdot10^{-4}$; $7.54131702976667\cdot10^{-3}$

$$\Delta G = 34.4606\ J/mol + (8.3144\ J/mol/K\cdot310.16\ K)\cdot\ln\frac{2.50\bullet10^{-4}\bullet1.65\bullet10^{-3}\bullet10^{-7.36}]}{2.25\bullet10^{-3}\bullet55.1398^2} = 8.3144*310.16...$$

= 34.4605 J/mol + (2 579 J/mol) •ln($1.557\cdot10^{-15}$) =2.50000*16.5/1000*0.00100/0.00225/55.5/55.5

= 34.4605 J/mol - 87 926 J/mol = -87926 = -14.334704*2578.79 = **0.00595**

-87.926+34.4605 = -53470; 1.22237350416395E-15;1.55726588989979E-15

9.18209607918563E-07;0.00000157222194454 ; 2.63215279227133E-15

= -53.47 kJ/mol at **T = 273.15 + 37 K ; $1.57\cdot10^{-6}$ = K_{eq}** instead **$9.18\cdot10^{-7}$ = K_{eq}** at **T = 273.15 + 25 K**

Thus ΔG, the **free energy** change required to **synthesize** **ATP** from **ADP** and HPO_4^{2-}+$H_2PO_4^-$ = P_i under the conditions prevailing in the **erythrocyte** would be **-53.47 kJ/mol**.

Because the concentrations **C** of **ATP**, **ADP**, and [HPO_4^{2-} + $H_2PO_4^-$] differ from one cell type to another (see Table 1-2), ΔG for **ATP hydrolysis** likewise differs among cells. Moreover, in any given cell, ΔG can vary from time to time, depending on the **metabolic conditions** in the cell and how they influence the concentrations **C** of **ATP**, **ADP**, [HPO_4^{2-} + $H_2PO_4^-$], and H_3O^+ (**pH**). We can calculate the actual **free energy** change ΔG for any given metabolic reaction as it occurs in the cell, providing we know the concentrations **C** of all the reactants

and products of the reaction and other factors (such as **pH**, temperature **T** [, and concentration **C** of Mg^{2+}]) that may affect the **ΔG°** and thus the calculated **free energy ΔG°** change, **free energy ΔG**.

Adenine Nucleotide, **Inorganic Phosphate**, and **Phospho-creatine Concentrations** in Some **Cells***

Table 1-2.

	Concentration C (mM)				or -log(C)=pH		ATP	PCr
		ATP	ADP	°AMP	P_i	PCr	pH	ΔG, kJ/mol	ΔG, kJ/mol
	Rat hepatocyte	3.38	1.32	0.29	4.80	0.0	7.36	**-47.47**	**-60.065**
pH = 7.36	Rat myocyte mitochondria	8.05	0.93	0.04	8.05	28.0	8.37	**-54.09**	**-72.995**
pH = 7.36	Rat myocyte	8.05	0.93	0.04	8.05	28.0	7.36	**-49.28**	**-68.18**
	Rat neuron	2.59	0.73	0.06	2.72	4.7	7.36	**-49.78**	**-67.41**
	Human erythrocyte	2.25	0.25	0.02	1.65	0.0	7.36	**-53.47**	**-66.06**
	E. coli cell	7.90	1.04	0.82	7.90	0.0	7.36	**-51.74**	**-64.33**

* For **erythrocytes** the concentrations **C** are those of the cytosol (human **erythrocytes** lack a nucleus and mitochondria). In the other types of cells the data are for the entire cell contents, although **the cytosol** and the mitochondria have very different concentrations **C** of **ADP**. **PCr** is **phospho-creatine**, discussed on above. **This value** reflects total concentration; the true value for **free ADP** may be much lower (see above).

To further complicate the issue, the total concentrations **C** of **ATP**, **ADP**, HPO_4^{2-} **+** $H_2PO_4^-$, and H_3O^+ may be substantially higher than the free concentrations **C**, which are the thermodynamically relevant values. The difference is due to **tight binding** of **ATP**, **ADP**, and HPO_4^{2-} **+** $H_2PO_4^-$ to cellular proteins. For example, the concentration **C** of **free ADP** in resting muscle has been variously estimated at between **1** and **37 μM**. Using the value **25 μM** in the calculation outlined above, we get a **ΔG** of **-53.47 kJ/mol**. The exact value of **ΔG** is perhaps less instructive than the generalization we can make about actual **free energy ΔG** changes: in vivo, the energy released by **ATP hydrolysis** is greater than the standard **free energy** change, **ΔG°**.

Other Phosphorylated Compounds, Thio-esters also have Large Free Energies of Hydrolysis

Phospho-enol-pyruvate (Fig. 1-3) contains a **phosphate ester** bond that can undergo **hydrolysis** to yield the **enol** form of **pyruvate**, and this direct product is stabilized relative to the **reactant**. This is the greatest contributing factor to the high standard **free** energy of **hydrolysis** of **phospho-enol-pyruvate**:

Phospho-enol-pyruvate^{2-} + H_2O => pyruvate$^-$ + $H_2PO_4^-$ **; ΔG° = -61.9 kJ/mol**

Phospho-enol-pyruvate^{2-} + 2 H_2O => pyruvate$^-$ + HPO_4^{2-} + H_3O^+ **; ΔG° = 3.06 kJ/mol**

Another three-carbon C_3 compound, **1,3-bis-phospho-glycerate** (Fig. 1-4), contains an **anhydride** bond between the carboxyl group **-CO-O-**PO_3^- at C_1 and **phosphoric acid**. **Hydrolysis** of this **acyl phosphate** is accompanied by a large, negative (-), standard free-energy change **ΔG°** or positive (+) under influence of medium **pH**, which can, again, be explained in terms of the structure of **reactant** and **products**:

a1 1,3-bis-phospho-glycerate^{4-} + H_2O => 3-phospho-glycerate^{3-} + $H_2PO_4^-$; $\Delta G°_{a1}$ **= - 49.30 kJ/mol**

b1 ADP^{3-} + $H_2PO_4^-$ => ATP^{4-} + H_2O **;** $\Delta G°_{b1}$ **= 30.500 kJ/mol**

Sum **1**: 1,3-P-glycerate^{4-}+ ADP^{3-} => 3-P-glycerate^{3-} **+** ATP^{4-}+ H_2O ; $\Delta G°_{1total}$ **= -18.800 kJ/mol**

a2 1,3-bis-phospho-glycerate^{4-}+ 2 H_2O => 3-phospho-glycerate^{3-} + HPO_4^{2-}+ H_3O^+ ; $\Delta G°_{a2}$ **= 15.660 kJ/mol**

b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **;** $\Delta G°_{b2}$ **= - 34.4605 kJ/mol**

Sum **2**: 1,3-P-glycerate^{4-} + ADP^{3-} => 3-P-glycerate^{3-} **+** ATP^{4-}+ H_2O ; $\Delta G°_{2total}$ **= -18.800 kJ/mol**

30.500-49.30= -18.800 kJ/mol

When H_2O is added across the anhydride bond of **1,3-bis-phospho-glycerate**, one **1** of the direct products, **3-phospho-glyceric acid**, can immediately lose a proton H^+ to give the **carboxylate ion**, **3-phospho-glycerate**, which has two **2** equally probable resonance forms (Fig. 1-4). Removal of the direct **product** (**3-phospho-glyceric acid**) and formation of the resonance-stabilized ion favors the forward reaction.

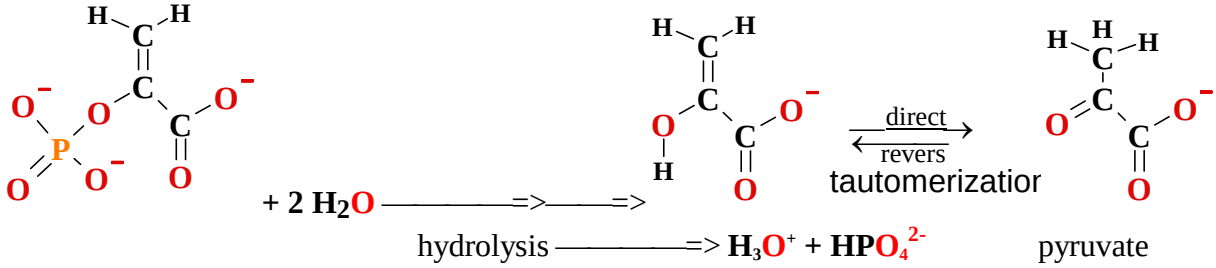


Figure 1-3. Hydrolysis of phospho-enol-pyruvate (PEP).
Catalyzed by **pyruvate kinase**, this reaction is followed by spontaneous **tautomerization** of the **product**, **pyruvate**. **Tautomerization** is not possible in **PEP**, and thus the products of **hydrolysis** are stabilized relative to the **reactants**. Resonance stabilization of **Pi = HPO_4^{2-} + $H_2PO_4^-$** also occurs, as shown in Figure 1-1b.

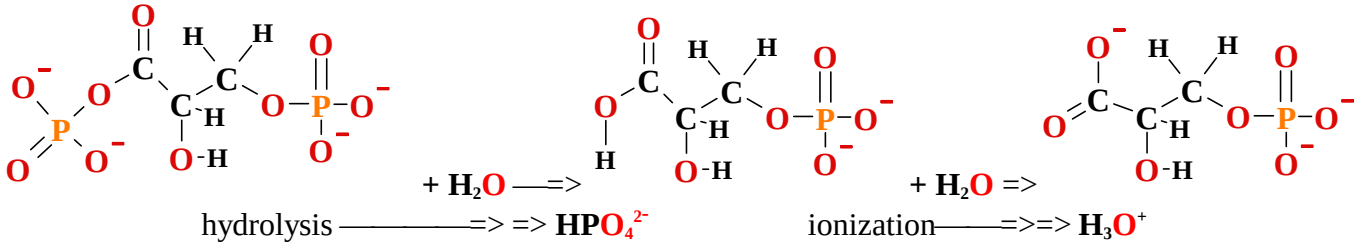


Figure 1-4. Hydrolysis of **1,3-bis-phospho-glycerate.** The direct product of **hydrolysis** is **3-phospho-glyceric acid**, which has an undissociated **carboxylic acid** group, but **dissociation** occurs immediately. This **ionization** and the resonance structures it makes possible stabilize the **product** relative to the **reactants**. Resonance stabilization of **Pi = HPO_4^{2-} + $H_2PO_4^-$** further contributes to the negative **free**-energy change **ΔG< 0**.

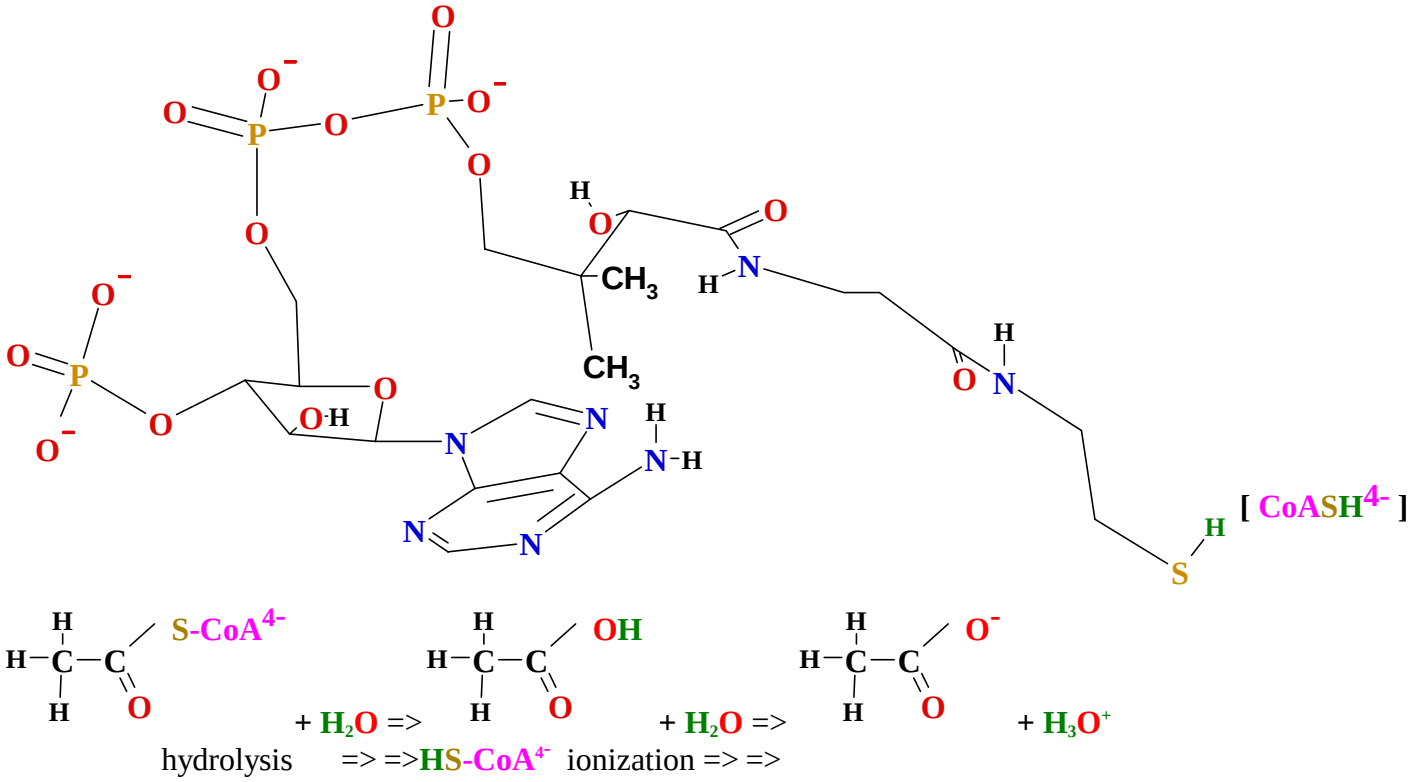


Figure 1-5. Hydrolysis of **acetyl-coenzyme A**. **Acetyl-CoA** is a **thio-ester** with a large, negative (-), **standard free** energy **ΔG< 0** of **hydrolysis**. **Thio-esters** contain a sulfur **S** atom in the position occupied by an oxygen **O** atom in oxygen **-O- esters**.

Thio-esters, in which a sulfur atom **S** replaces the usual oxygen **O** in the **ester** bond, also have large, negative (-), **standard free** energies **ΔG°** of **hydrolysis**. **Acetyl-coenzyme A**, or **acetyl-CoA** (Fig. 1-5), is one **1** of many **thio-esters** important in metabolism. The **acyl** group in these compounds is activated for **trans-acylation**, **condensation**, or **oxidation-reduction** reactions. **Thio-esters** undergo much less resonance stabilization than do oxygen **-O- esters** (Fig. 1-6); consequently, the difference in free energy **ΔG°** between the **reactant** and its **hydrolysis products**, which are resonance- stabilized, is greater for **thio-esters** than for

comparable oxygen **O esters**. In both cases, **hydrolysis** of the **ester** generates a **carboxylic acid**, which can ionize and assume several resonance forms (Fig. 1-6). Together, these factors result in the large, negative (-) Δ**G°** for **acetyl-CoA hydrolysis:**

a1 Acetyl-CoA^{4-} + H_2O => CH_3COOH + CoA^{4-} ; $\Delta G°_{a1}$ = **- 31.400 kJ/mol**

b1 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O ; $\Delta G°_{b1}$ = **- 34.4605 kJ/mol**

Sum **1**:Acetyl-CoA^{4-}+ADP^{3-}+HPO_4^{2-}+H_3O^+=>CH_3COOH+CoA^{4-}+ATP^{4-}+H_2O;$\Delta G°_{1total}$=**-65.8605 kJ/mol**

a2 Acetyl-CoA^{4-} + 2 H_2O =>CH_3COO^- + CoA^{4-} + H_3O^+ ; $\Delta G°_{a2}$ = **-7.500 kJ/mol**

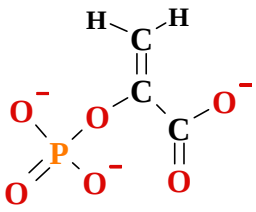
b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O ; $\Delta G°_{b2}$ = **- 34.4605 kJ/mol**

Sum **2**: Acetyl-CoA^{4-} + HPO_4^{2-} + ADP^{3-}=> CH_3COO^- + CoA^{4-} + ATP^{4-} ; $\Delta G°_{2total}$ = **-41.9605 kJ/mol**

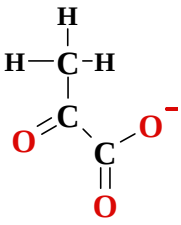
-31.4-34.4605= -65.8605 kJ/mol

To summarize, for **hydrolysis** reactions with large, negative (-), **standard free**-energy changes Δ**G°**, the **products** are more stable than the **reactants** for one **1** or more of the following reasons: (**1**) the bond strain in **reactants** due to **electrostatic repulsion** is relieved by **charge separation**, as for **ATP**$^{4-}$ (described earlier); (**2**) the **products** are stabilized by ionization, as for **ATP**$^{4-}$, **acyl phosphates**, and **thio-esters**; (**3**) the products are stabilized by **isomerization** (**tautomerization**), as for **phospho-enol-pyruvate**; and/or (**4**) the **products** are stabilized by resonance, as for **creatine** released from **phospho-creatine**, **carboxylate** ion released from

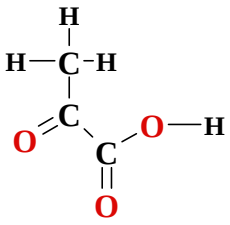
acyl phosphates and **thio-esters**, and phosphate (**P_i = [HPO_4^{2-} + $H_2PO_4^-$]**) released from **anhydride** or **ester** linkages.**PEP**



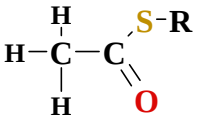
Pyruvate enol form



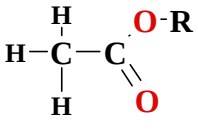
Pyruvate keto form



Thio-S-ester



Oxygen -O- ester=>=>=>=>=>=>

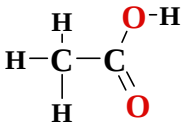


+ **H_2O**

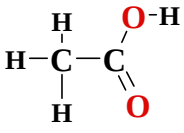
=> Extra stabilization by resonance

ΔG_t for thio-ester hydrolysis

ΔG_o for **Oxygen -O- ester** hydrolysis



+ **R— S H**



+ **R—OH**

Figure 1-6. Free energy **ΔG** of **hydrolysis** for **thio-esters** and oxygen **O esters**. The **products** of both types of **hydrolysis** reaction have about the same **free**-energy content (**G**), but the **thio-ester** has a higher free-energy **G_t** content than the oxygen **O ester**. Orbital overlap between the **O** and **C** atoms allows resonance stabilization in oxygen **O esters**, but orbital overlap between **S** and **C** atoms is poorer and little resonance stabilization occurs. **Thio-ester** yield **free energy change** is much more negative as **$-\Delta G_t > -\Delta G_O$** oxygen **O ester.**

Creatine Biosynthesis

Phospho-creatine, derived from **creatine**, is an important energy **E** buffer in skeletal muscle (Hydrolyses of Phosphorylated Compounds). **Creatine** is synthesized from glycine **Gly** and arginine **Arg** (Fig. 1-7), with methionine **Met**, in form of **S**-adenosyl-methionine **SAM**, as methyl group **-CH_3** donor.

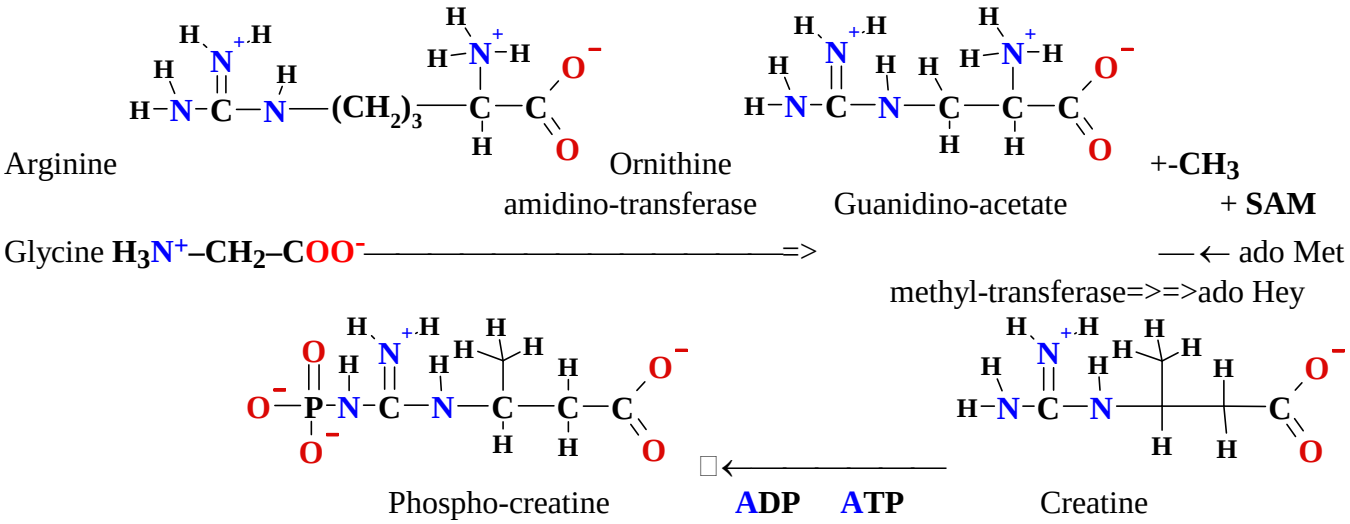


Figure 1-7. Biosynthesis of creatine and **phospho-creatine**. **Creatine** is made from three amino acids **AA** glycine **Gly**, arginine **Arg** and methionine **Met**. Thus pathway shows the versatility of amino acids **AA** as precursor of other nitrogenous biomolecules.

Phospho-creatine (Fig. 1-7), also called **creatine phosphate**, serves as a ready source of **phosphoryl** groups for the quick synthesis of **ATP** from **ADP**. The **phospho-creatine** (**PCr**) concentration **C** in skeletal muscle is approximately **30 mM**, nearly ten **10•** times the concentration **C** of **ATP**, and in other tissues such as smooth muscle, brain, and kidney is **5** to **10 mM**. The **enzyme creatine kinase** catalyzes the reversible reaction

ADP + PCr ←—**Mg** creatine kinase—=> **ATP + Cr** ; **ΔG° = -12.5955 kJ/mol**

When a sudden demand for energy **E** depletes **ATP**, the **PCr** reservoir is used to replenish **ATP** at the rate considerably faster than **ATP** can be synthesized by **catabolism** is used to replenish the **PCr** reservoir by reversal of the **creatine kinase** reaction. Organisms in the lower phyla employ other **PCr**-like molecules (collectively called **phospho-genes**) as **phosphoryl** reservoirs.

Inorganic **poly-phosphate** (**polyP**) is a linear polymer composed of hundreds **100** of P_i residues linked through **phospho-anhydride** bonds. This polymer, present in cells of all organisms, has about the same **phosphoryl** group transfer potential **PP_i**, but its biological roles remain uncertain. In *Escherichia coli*, **polyP** accumulation confers a survival advantage during periods of nutritional or oxidative stress. The enzyme **poly-phosphate kinase** catalyzes the reaction

ATP + $polyP_n$ ←—**Mg**—=> **ADP + $polyP_{n+1}$** ; **ΔG° = -20.0 kJ/mol**

by a mechanism involving an enzyme-bound **phospho-histidine** intermediate (recall the mechanism of **nucleoside di-phosphate kinase**, described above). Because the reaction is reversible, **polyP** (like **PCr**) could serve as a reservoir of **phosphoryl** group donor analogous to **ATP** for **kinase**-catalyzed transfers. The shortest **poly-phosphate**, **PP_i** (**n = 2**) can serve as the energy **E** source for active transport of **H^+** in plant vacuoles. **PP_i** is also the usual **phosphoryl** group donor for at least one **1** form of the enzyme **phospho-fructo-kinase** in plants, a role normally played by **ATP** in animals and microbes. The finding of high concentration C of **polyP** in volcanic condensates and steam vents suggests that it could have served as an energy **E** source in pre-biotic and early cellular evolution.

The corresponding equilibrium depends on the **pH** (and the concentration of free **H_2O**). Writing of a chemical equation when **ATP hydrolyzed** at a **pH** above **7.36** or **8.37** (in mitochondria). The absence of catalyst **Mg^{2+}** doesn't affect equilibrium constant **K_{eq}**, represented by : 1.57222194453997E-06

ATP^{4-} + $2H_2O$←=>**ADP^{3-} + HPO_4^{2-} + H_3O^+ ; $1.57•10^{-6}$ = K_{eq}=[ADP^{3-}]•[HPO_4^{2-}]•[H_3O^+]/[ATP^{4-}]/[H_2O]^2**

Constant **K_{eq}** depends only on temperature **T**, pressure, and **ionic strength**.

ATP Provides Energy by Group Transfers, Not by Simple Hydrolysis

Throughout this subject of **General Chemistry** you will encounter reactions or processes for which **ATP** supplies energy, and the contribution of **ATP** to these reactions is commonly indicated as in Figure 1-8a, with a single arrow showing the conversion of **ATP** to **ADP** and P_i, or of **ATP** to **AMP** and PP_i (**pyro-phosphate**).

Table 3. Standard Free Energies of Hydrolysis of Some Phosphorylated Compounds and Acetyl-CoA

Hydronium ions absent and H_3O^+ present hydrolyze reactions	ΔG° =>	kJ/mol	kcal/mol
Phospho-enol-pyruvate^{2-} + H_2O => pyruvate$^-$ + $H_2PO_4^-$ 3.06000/4.184=0.73136		-61.90	-14.80
1,3-bis-phospho-glycerate^{4-} + H_2O =>3-phospho-glycerate^{3-} + $H_2PO_4^{2-}$ -25.399518		-49.30	-11.80
Pcreatine$^-$ + H_2O => creatine + $H_2PO_4^-$ -25.399518/4.184=-6.070630		-43.00	-10.30
ADP^{3-} + H_2O => AMP^{2-} + $H_2PO_4^-$ 21.865/4.184=5.226		-32.80	-7.80
ATP^{4-} + H_2O => ADP^{3-} + $H_2PO_4^-$		-30.50	-7.30
ATP^{4-} + H_2O => AMP^{2-} + $^-HOPO_2OPO_2OH^-$		-45.60	-10.90
AMP$^-$ + H_2O => adenosine + $H_2PO_4^-$		-14.20	-3.40
$HOPO_2OPO_2OH^-$ + H_2O => + $H_2PO_4^-$ + $H_2PO_4^-$ -19.20/4.184=-4.589		-19.22	-4.60
Glucose-1-phosphate$^-$ + H_2O => Glucose + $H_2PO_4^-$ 44.06048/4.184=10.53071		-20.90	-5.00
Fructose-6-phosphate$^-$ + H_2O => Fructose + $H_2PO_4^-$ 49.06148/4.184=11.72598		-15.90	-3.80
Glucose-6-phosphate$^-$ + H_2O => Glucose + $H_2PO_4^-$ 51.1604816/4.184=12.2276486		-13.80	-3.30
Glycerol-1-phosphate$^-$ + H_2O => Glycerol + $H_2PO_4^-$ 55.7604816/4.184=13.3270750		-9.20	-2.20
Palmitate-CoA^{4-} + H_2O => $CH_3(CH_2)_{14}COOH$ + HSCoA^{4-} -32.3/4.184= -7.720		-32.30	-7.72
Acetyl-CoA^{4-} + H_2O => CH_3COOH + CoA^{4-} -7.5000/4.184=-1.7925		-31.40	-7.50
Phospho-enol-pyruvate^{2-} + 2 H_2O => pyruvate$^-$ + HPO_4^{2-} + H_3O^+		3.06	0.73
1,3-bis-phospho-glycerate^{4-} + 2 H_2O =>3-phospho-glycerate^{3-} + HPO_4^{2-} + H_3O^+		15.66	3.74
Pcreatine$^-$ + 2 H_2O => creatine + HPO_4^{2-} + H_3O^+ 15.66048/4.184=3.74294		21.865	5.23
ADP^{3-} + 2 H_2O => AMP^{2-} + HPO_4^{2-} + H_3O^+ 32.16048/4.184=7.68654		32.16	7.69
ATP^{4-} + 2 H_2O => ADP^{3-} + HPO_4^{2-} + H_3O^+ 34.4605/4.184=8.2363		34.46	8.24
AMP$^-$ + 2 H_2O => adenosine + HPO_4^{2-} + H_3O^+ 50.76048/4.184=12.13205		50.76	12.13
$HOPO_2OPO_2OH^-$ + 3 H_2O => HPO_4^{2-} + H_3O^+ + HPO_4^{2-} + H_3O^+		110.72	26.46
H_3PO_4 + H_2O => $H_2PO_4^-$ + H_3O^+ 22.20168/4.184=5.30633 **; K_{eq1}= 1.29•10^{-4}**		12.66	5.31
$H_2PO_4^-$ + H_2O => HPO_4^{2-} + H_3O^+ 51.03359/4.184=12.19732**; K_{eq2}= 1.15•10^{-9}**		64.96	12.20
HPO_4^{2-} + H_2O => PO_4^{3-} + H_3O^+ 80.39058/4.184=19.21381 **; K_{eq3}= 8.25•10^{-15}**		94.48	19.21
Glucose-1-phosphate$^-$ + 2 H_2O => Glucose + HPO_4^{2-} + H_3O^+		44.06	10.53
Fructose-6-phosphate$^-$ + 2 H_2O => Fructose + HPO_4^{2-} + H_3O^+		49.06	11.73
Glucose-6-phosphate$^-$ + 2 H_2O => Glucose + HPO_4^{2-} + H_3O^+		51.16	12.23
Glycerol-1-phosphate$^-$ + 2 H_2O => Glycerol + HPO_4^{2-} + H_3O^+ 55.76/4.184= 13.327		55.76	13.33
Palmitate-CoA^{4-}+ 2H_2O => $CH_3(CH_2)_{14}COO^-$+H_3O^+ + HSCoA^{4-} -8.40/4.184=-2.008		-8.40	-2.01
Acetyl-CoA^{4-} + 2 H_2O => CH_3COO^- + CoA^{4-} + H_3O^+		-7.50	-1.79

When written this **way,** these reactions of **ATP** appear to be simple **hydrolysis** reactions in which water **H_2O** displaces either P_i or PP_i, and one is tempted to say that an **ATP**-dependent reaction is "driven by the **hydrolysis** of **ATP**." This is not the case. **ATP hydrolysis** per se usually accomplishes nothing but the liberation of **heat** **ΔH**, which cannot drive a chemical process in an isothermal **T = const** system. Single reaction arrows such as those in Figure 1-8a almost invariably represent two-**2**-step processes (Fig. 1-8b) in which part of the **ATP** molecule, a **phosphoryl** or **pyro-phosphoryl** 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 **ΔG > 0** content. In the second **2nd** step, the **phosphate**-containing moiety that was transferred in the first **1st** step is dis placed, generating P_i, PP_i, or **AMP**. Thus **ATP** participates **covalently** in the **enzyme**- catalyzed reaction to which it contributes **free** energy **ΔG**.

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 **2** 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** (**DNA** Metabolism) also involve direct **hydrolysis** of **phospho-anhydride** 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** (Bio-Signaling).

The **phosphate** compounds found in living organisms can be divided somewhat arbitrarily into two **2** groups, according **pH** dependent and **pH** independent reactions Table 3. and 1-4. Another way based on their **standard free** energies **ΔG°** of **hydrolysis** (Fig. 1-9). "High-energy'' compounds have a **ΔG°** of **hydrolysis** more negative than **-25 kJ/mol**; "low-energy'' compounds have a less negative **ΔG°**. Based on this criterion, **ATP**, with a **ΔG°** of h**ydrolysis** of **-30.5 kJ/mol** (**-7.3 kcal/mol**), is a high-energy compound; **glucose 6-phosphate**, with a **ΔG°** of hydrolysis of **- 13.8 kJ/mol** (**- 3.3 kcal/mol)**, is a low--energy compound.

a1 Phospho-**creatine**$^-$ + **H_2O** => **Creatine + $H_2PO_4^-$**; ; **$\Delta G°_{a1}$ = -43.000 kJ/mol**
b1 ADP^{3-} + $H_2O_4^-$ =>; ATP^{4-} + H_2O **; $\Delta G°_{b1}$ = 30.500 kJ/mol**

Sum **1**: **Phospho-creatine**$^-$ + ADP^{3-} => **Creatine +** ATP^{4-} ; **$\Delta G°_{1total}$ = -12.500 kJ/mol**
a2 **Phospho-creatine**$^-$ + **2 H_2O** => **Creatine + HPO_4^{2-} + H_3O^+**; ; **$\Delta G°_{a2}$ = 21.865 kJ/mol**
b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **; $\Delta G°_{b2}$ = - 34.4605 kJ/mol**

Sum **2**: **Phospho-creatine**$^-$ + ADP^{3-} => **Creatine +** ATP^{4-} ; **$\Delta G°_{2total}$ = -12.5955 kJ/mol**
-34.4605+21.865= -12.500 kJ/mol

Creatine kinase mb □fraction appears in blood after damage of myocyte or neuron cell wall.

The term "high--energy **phosphate** bond," long used by biochemists to describe the **P-O** bond broken in **hydrolysis** reactions, is incorrect and misleading as it wrongly suggests that the bond itself contains the energy and **enthalpy** of dissociation **$\Delta H_{P-O}°$= 370 kJ/mol** is positive In fact, the breaking of all chemical bonds requires an input of energy **ΔH° > 0**. The **free** energy released **ΔG°** by **hydrolysis** of **phosphate** compounds does not come from the specific bond that is broken; it results from the **products** of the reaction having smaller free-energy G ° content than the **reactants**. For simplicity, we will sometimes use the term "high-energy **phosphate** compound" when referring to **ATP** or other **phosphate** compounds with a large, negative (-), **standard free** energy change **ΔG°< 0** of **hydrolysis**.

As is evident from the **additive free**-energy changes **$\Delta G°=G°_{prod}-G°_{react}$** of sequential **$\Delta G°=\Delta G°_1+\Delta G°_2$** reactions **a** and sequential **b**, 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 **phospho-enol-pyruvate** (**PEP**) releases more energy **ΔG°< 0** 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**: coupled reactions **a** and **b** both type **1** and **2 :**

a1 Phospho-enol-pyruvate^{2-} + H_2O => pyruvate$^-$ + $H_2PO_4^-$; **$\Delta G°_{a1}$ = - 61.90 kJ/mol**
b1 ADP^{3-} + $H_2PO_4^-$ =>; ATP^{4-} + H_2O **; $\Delta G°_{b1}$ = 30.500 kJ/mol**

Sum **1**: Phospho-enol-pyruvate^{2-} + ADP^{3-} => pyruvate$^-$ + ATP^{4-} ; **$\Delta G°_{1total}$ = -31.400 kJ/mol**

a2 Phospho-enol-pyruvate^{2-} + 2 H_2O => pyruvate$^-$ + HPO_4^{2-} + H_3O^+ ; **$\Delta G°_{a2}$ = 3.06 kJ/mol**
b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **; $\Delta G°_{b2}$ = - 34.4605 kJ/mol**

Sum **2**: Phospho-enol-pyruvate^{2-} + ADP^{3-} => pyruvate$^-$ + ATP^{4-} ; **$\Delta G°_{2total}$ = -31.4005 kJ/mol**
-34.4605+3.06= -31.4005 kJ/mol

We can therefore describe **phosphorylated** compounds as having a high or low **phosphoryl** group transfer **potential ΔG°.** The **phosphoryl** group transfer **potential ΔG°** of **phospho-enol-pyruvate** is very high, that of **ATP** is high, and that of **glucose 6-phosphate** is low.

a1 $^-HOPO_2OPO_2OH^-$ + H_2O => + $H_2PO_4^-$ + $H_2PO_4^-$; **$\Delta G°_{a1}$ = -19.00 kJ/mol**
b1 ADP^{3-} + $H_2PO_4^-$ =>; ATP^{4-} + H_2O **; $\Delta G°_{b1}$ = 30.500 kJ/mol**

Sum **1**: $^-HOPO_2OPO_2OH^-$ + ADP^{3-} => $H_2PO_4^-$ + ATP^{4-} ; **$\Delta G°_{1total}$ = 11.500 kJ/mol**

a2 $^-HOPO_2OPO_2OH^-$ + 3 H_2O => HPO_4^{2-} + H_3O^+ + HPO_4^{2-} + H_3O^+ ; **$\Delta G°_{a2}$ = 110.72 kJ/mol**
b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **; $\Delta G°_{b2}$ = - 34.4605 kJ/mol**

Sum **2**: $^-HOPO_2OPO_2OH^-$+ ADP^{3-} + H_2O => HPO_4^{2-} + H_3O^+ + ATP^{4-} ; **$\Delta G°_{2total}$ = 76.2595 kJ/mol**
-34.4605+110.72= 76.2595 kJ/mol

a1 $^-HOPO_2OPO_2OH^-$ + H_2O => + $H_2PO_4^-$ + $H_2PO_4^-$; **$\Delta G°_{a1}$ = -19.00 kJ/mol**
b1 ADP^{3-} + $H_2PO_4^-$ =>; ATP^{4-} + H_2O **; $\Delta G°_{b1}$ = 30.500 kJ/mol**

Sum **1**: $^-HOPO_2OPO_2OH^-$ + ADP^{3-} => $H_2PO_4^-$ + ATP^{4-} ; **$\Delta G°_{1total}$ = 11.500 kJ/mol**

a2 $^-HOPO_2OPO_2OH^-$ + 3 H_2O => HPO_4^{2-} + H_3O^+ + HPO_4^{2-} + H_3O^+ ; **$\Delta G°_{a2}$ = 110.72 kJ/mol**
b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **; $\Delta G°_{b2}$ = - 34.4605 kJ/mol**

Sum **2**: $^-HOPO_2OPO_2OH^-$+ ADP^{3-} + H_2O => HPO_4^{2-} + H_3O^+ + ATP^{4-} ; **$\Delta G°_{2total}$ = 76.2595 kJ/mol**
-34.4605+110.72= 76.2595 kJ/mol

Table 1-4. ATP coupling reactions for group **transfer** at **standard conditions**.

	ΔG°=> kJ/mol	kcal/mol
1,3-P-glycerate^{4-} + ADP^{3-} => 3-P-glycerate^{3-} + ATP^{4-}+ H_2O -18.8/4.184= -4.493	**-18.800**	-4.49
Palmitate-CoA^{4-}+AMP^{2-}+ 2$H_2PO_4^-$=>$CH_3(CH_2)_{14}COOH$+HSCoA^{4-}+ATP^{4-}+H_2O 32.5/4.184= 7.768	**32.500**	7.77
Acetyl-CoA^{4-}+ HPO_4^{2-}+ ADP^{3-}=> CH_3COO^-+ CoA^{4-}+ ATP^{4-}-41.96/4.184= -10.028	**-41.9605**	-10.03
Phospho-enol-pyruvate^{2-} + ADP^{3-} => pyruvate$^-$ + ATP^{4-} -31.4005/4.184=-7.5049	**-31.4005**	-7.05
Phospho-creatine$^-$ + ADP^{3-} => **Creatine** + ATP^{4-} -12.5/4.184=-2.988	**-12.500**	-2.99
Glu 6-phosphate$^-$ + ADP^{3-} => **Glucose** + ATP^{4-} -16.7/4.184=-3.991	**-16.70**	-3.99
$^-HOPO_2OPO_2OH^-$ + ADP^{3-} => $H_2PO_4^-$ + ATP^{4-} 11.5/4.184=2.749	**11.500**	2.75
Glu-1-phosphate$^-$ + ADP^{3-} => Glucose + ATP^{4-} 9.600/4.184=2.294	**9.600**	2.29
Fructose-6-phosphate$^-$ + ADP^{3-} => Fructose + ATP^{4-} 14.6/4.184=3.489	**14.600**	3.49
Glutamine + ADP^{3-} + $H_2PO_4^-$ => Glutamate$^-$ + NH_4^+ + ATP^{4-}-16.3/4.184=-3.896	**16.300**	3.90
Glycerol-1-phosphate$^-$ + ADP^{3-} => Glycerol + ATP^{4-} 21.300/4.184=5.091	**21.300**	5.09
PalmCoA^{4-}+AMP^{2-}+2HPO_4^{2-}+H_3O^+=>$CH_3(CH_2)_{14}COO^-$+HSCoA^{4-}+ATP^{4-}+2H_2O	**-73.5200**	-17.57
Acetyl-CoA^{4-}+ADP^{3-}+HPO_4^{2-}+H_3O^+=>CH_3COOH+CoA^{4-}+ATP^{4-}+H_2O -73.52/4.184= -17.57	**-65.8605**	-15.74
Gln + ADP^{3-}+ HPO_4^{2-}+ H_3O^+ => Glu$^-$+ NH_4^++ ATP^{4-}+ H_2O48.6605/4.184=11.6301	**-48.6605**	-11.63
$^-HOPO_2OPO_2OH^-$+ ADP^{3-}+ H_2O => HPO_4^{2-}+ H_3O^++ ATP^{4-}76.2595/4.184=18.2265	**76.2595**	18.23

a1 Glycerol-1-phosphate$^-$ + H_2O => Glycerol + $H_2PO_4^-$; **ΔG°$_{a1}$ = - -9.20 kJ/mol**

b1 ADP^{3-} + $H_2PO_4^-$ =>; ATP^{4-} + H_2O **; ΔG°$_{b1}$ = 30.500 kJ/mol**

Sum **1**: Glycerol-1-phosphate$^-$ + ADP^{3-} => Glycerol + ATP^{4-} ; **ΔG°$_{1total}$ = 21.300 kJ/mol**

a2 Glycerol-1-phosphate$^-$ + 2 H_2O => Glycerol + HPO_4^{2-} + H_3O^+ ; **ΔG°$_{a2}$ = 55.76 kJ/mol**

b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **; ΔG°$_{b2}$ = - 34.4605 kJ/mol**

Sum **2**: Glycerol-1-phosphate$^-$ + ADP^{3-} => Glycerol + ATP^{4-} ; **ΔG°$_{2total}$ = 14.5995 kJ/mol**

-9.2+30.500= 21.300 kJ/mol

a1 Fructose-6-phosphate$^-$ + H_2O => Fructose + $H_2PO_4^-$; **ΔG°$_{a1}$ = - 15.90 kJ/mol**

b1 ADP^{3-} + $H_2PO_4^-$ =>; ATP^{4-} + H_2O **; ΔG°$_{b1}$ = 30.500 kJ/mol**

Sum **1**: Fructose-6-phosphate$^-$ + ADP^{3-} => Fructose + ATP^{4-} ; **ΔG°$_{1total}$ = 14.600 kJ/mol**

a2 Fructose-6-phosphate$^-$ + 2 H_2O => Fructose + HPO_4^{2-} + H_3O^+ ; **ΔG°$_{a2}$ = 49.06 kJ/mol**

b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **; ΔG°$_{b2}$ = - 34.4605 kJ/mol**

Sum **2**: Fructose-6-phosphate$^-$ + ADP^{3-} => Fructose + ATP^{4-} ; **ΔG°$_{2total}$ = 14.5995 kJ/mol**

-15.90+30.500= 14.600 kJ/mol

a1 Glucose-1-phosphate$^-$ + H_2O => Glucose + $H_2PO_4^-$; **ΔG°$_{a1}$ = - 20.90 kJ/mol**

b1 ADP^{3-} + $H_2PO_4^-$ □□; ATP^{4-} + H_2O **; ΔG°$_{b1}$ = 30.500 kJ/mol**

Sum **1**: Glucose-1-phosphate$^-$ + ADP^{3-} => Glucose + ATP^{4-} ; **ΔG°$_{1total}$ = 9.600 kJ/mol**

a2 Glucose-1-phosphate$^-$ + 2 H_2O => Glucose + HPO_4^{2-} + H_3O^+ ; **ΔG°$_{a2}$ = 44.06 kJ/mol**

b2 ADP^{3-}+ HPO_4^{2-} + H_3O^+ => ATP^{4-}+2 H_2O **; ΔG°$_{b2}$ = - 34.4605 kJ/mol**

Sum **2**: Glucose-1-phosphate$^-$ + ADP^{3-} => Glucose + ATP^{4-} ; **ΔG°$_{2total}$ = 9.5995 kJ/mol**

-34.4605+44.06= 9.5995 kJ/mol

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 $\Delta G°$ into that compound, so that it has more **free** energy $\Delta G°$ to give up during subsequent metabolic transformations. We described above how the **synthesis** of **glucose 6-phosphate** is accomplished by **phosphoryl** group transfer from **ATP**. In the Glycolysis Catabolism we see how this **phosphorylation** of

(**a**) Written as

one-step reaction $ATP^{4-} + H_2O \rightleftharpoons ADP^{3-} + HPO_4^{2-}$

Glutamate + NH_4^+ + HOH_2^+ Glutamate

←ATP^{4-}

=>ATP^{3-}

1 step

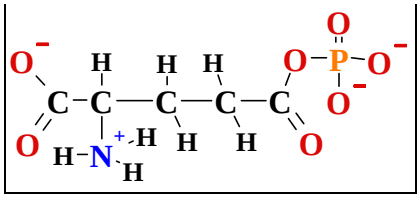
————————=>

=>=>=> **2** step

=>=>+H_2OH^+

=>=>+HPO_4^{2-}

=>=>+ NH_4^+



(**b**) Actual two-2-step reaction

Figure 1-8. Nucleophilic displacement reactions of **ATP** Any of the three **3 P** atoms (□, □, or ,□) may serve as the **electrophilic target** for **nucleophilic attack** by the labeled **nucleophile R—^{18}O:** in this case. The **nucleophile** may be an **alcohol** (**R-OH**), a **carboxyl** group (**RCOO$^-$**), or a **phospho-anhydride** (a **nucleoside mono-** or **diphosphate**, for example). (**a**) When the oxygen **O** of the **nucleophil attacks** the **7** position, the **bridge oxygen -O-** of the **product** is labeled, indicating that the group transferred from **ATP** is a **phosphoryl** (**-PO$_3^{2-}$**), not a **phosphate** (**-OPO$_3^{2-}$**). (**b**) **Attack** on the □ position displaces **AMP** and leads to the transfer of a **pyro-phosphoryl** (not **pyro-phosphate**) group to the **nucleophile**. (**c**) **Attack** on the position displaces **PP$_i$** and transfers the **adenylyl** group to the **nucleophile**.

a1 $Glutamate^{2-} + NH_4^+ \Rightarrow Glutamine^- + H_2O$; $\Delta G°_{a1}$ = **14.200 kJ/mol**

b1 $□ATP^{4-} + 2\ H_2O \Rightarrow ADP^{3-} + HPO_4^{2-} + H_3O^+$; $\Delta G°_{b1}$ = **34.4605 kJ/mol**

Sum **1**: $Glutamate^{2-} + NH_4^+ + ATP^{4-} + H_2O \Rightarrow Glutamine^- + ADP^{3-} + HPO_4^{2-} + H_3O^+$; $\Delta G°_{1total}$ **= 48.6605 kJ/mol**

a2 $Glutamate^{2-} + NH_4^+ \Rightarrow Glutamine^- + H_2O$; $\Delta G°_{a2}$ = **14.200 kJ/mol**

b2 $ATP^{4-} + H_2O \Rightarrow ADP^{3-} + H_2PO_4^-$; $\Delta G°_{b2}$ = **- 30.500 kJ/mol**

Sum **2**: $Glutamate^{2-} + NH_4^+ + ATP^{4-} \Rightarrow Glutamine^- + ADP^{3-} + H_2PO_4^-$; $\Delta G°_{2total}$ = **-16.300 kJ/mol**

14.2-30.5= -16.3 kJ/mol

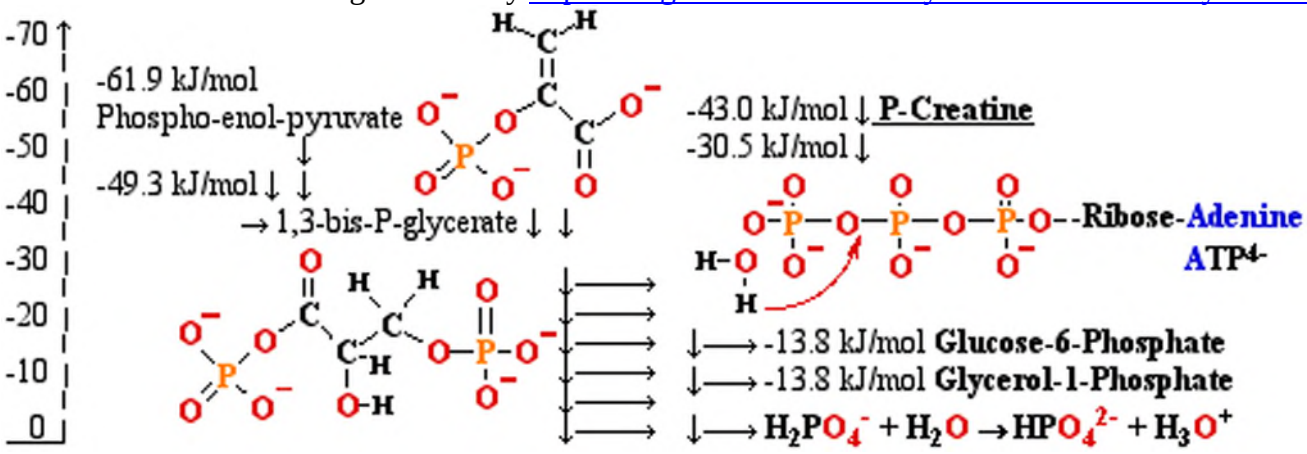


Figure 1-9. Ranking of **biological phosphate** compounds by **standard free** energies ∆**G°** of **hydrolysis**. This shows the flow of **phosphoryl** groups, represented by $\mathbf{P_i}$, from high-energy phosphoryl donors via **ATP** to **acceptor** molecules (such as **glucose** and **glycerol**) to form their low-energy **phosphate** derivatives. This flow of **phosphoryl** groups, catalyzed by **enzymes** called **kinases**, proceeds with an overall loss of **free** energy ∆**G°< 0** under **intracellular conditions**. **Hydrolysis** of low--energy **phosphate** compounds releases $\mathbf{P_i}$ which has an even lower **phosphoryl** group transfer potential ∆**G°** (as defined in the text).

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 ∆**G°** 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 ∆**G°** currency in all living cells.

One more chemical feature of **ATP** is crucial to its role in metabolism: although in aqueous $\mathbf{H_2O}$ solution **ATP** is **thermodynamically** unstable and is therefore a good **phosphoryl** group donor, it is ***kinetically*** stable. Because of the huge activation energies $\mathbf{E_a}$ (**200** to **400 kJ/mol**) required for **uncatalyzed** cleavage of its **phospho-anhydride** bonds, **ATP** does not spontaneously donate **phosphoryl** groups to water $\mathbf{H_2O}$ or to the hundreds **100÷200** of other potential **acceptors** in the cell. Only when specific **enzymes** are present to lower the energy of activation $\mathbf{E_a}$ does **phosphoryl** group transfer from **ATP** occur. The cell is therefore able to **regulate** the disposition of the energy ∆**G°** carried by **ATP** by regulating the various **enzymes** that act on it.

Three positions on ATP for attack by

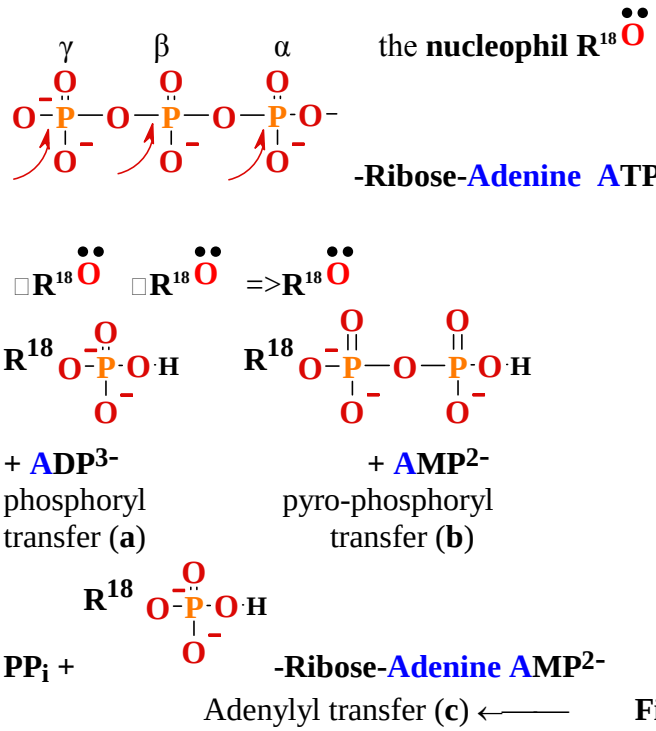


Figure 1-10. Nucleophil displacement reactions of **ATP**

Any of the three **3 P** atoms (α, β, or ,γ) may serve as the **electrophilic target** for **nucleophilic attack** by the labeled **nucleophil R—^{18}O:** in this case. The **nucleophil** may be an **alcohol** (**R-OH**), a **carboxyl** group (**RCOO$^-$**), or a **phospho-anhydride** (a **nucleoside mono**- or **diphosphate**, for example).

(**a**) When the oxygen **O** of the **nucleophil attacks** the **7** position, the **bridge oxygen -O-** of the **product** is labeled, indicating that the group transferred from **ATP** is a **phosphoryl** (**-PO$_3^{2-}$**), not a **phosphate** (**-OPO$_3^{2-}$**).

(**b**) **Attack** on the □ position displaces **AMP** and leads to the transfer of a **pyro-phosphoryl** (not **pyro-phosphate**) group to the **nucleophil**.

(**c**) **Attack** on the position displaces **PP$_i$** and transfers the **adenylyl** group to the **nucleophil**.

ATP Donates Phosphoryl, Pyro-phosphoryl, and Adenylyl Groups

The reactions of **ATP** are generally **SN2** (**substitution nucleophilic** bimolecular) **nucleophilic** displacements, in which the **nucleophil** may be, for example, the oxygen **O** of an **alcohol** or **carboxylate** or a **nitrogen** of **creatine** or of the side chain of **arginine** or **histidine**. Each of the three **3 phosphates** of **ATP** is susceptible to **nucleophilic attack** (Fig. 1-10), and each position of **attack** yields a different type of **product**.

Nucleophilic attack by an **alcohol** on the □ **phosphate** (Fig. 1- 10a) displaces **ADP** and **produces** a new **phosphate ester**. Studies with **^{18}O**-labeled **reactants** have shown that the bridge oxygen **O** in the new compound is derived from the **alcohol**, not from **ATP**; the group transferred from **ATP** is a **phosphoryl** (**-PO$_3^{2-}$**), not a **phosphate** (**-OPO$_3^{2-}$**). **Phosphoryl** group transfer from **ATP** to **glutamate** (Fig. 1-8) or to **glucose** (**hexokinase**) involves **attack** at the γ position of the **ATP** molecule.

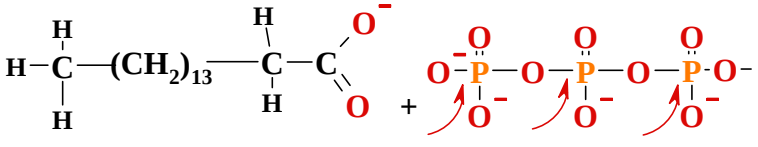
Attack at the □ **phosphate** of **ATP** displaces **AMP** and transfers a **pyro-phosphoryl** (not **pyrophosphate**) group to the **attacking nucleophil** (Fig. 1-10b). For example, the formation of **5'-phospho-ribose 1-pyro-phosphate**, a key intermediate in **nucleotide synthesis**, occurs as an **-OH** of the **ribose attacks** the □ **phosphate**.

Nucleophilic attack at the □ position of **ATP** displaces **PP$_i$** and transfers **adenylate** (**5'-AMP**) as an **adenylyl** group (Fig. 1-10c); the reaction is an **adenylylation** (a-den'-i-li-la'-shun, probably the most ungainly word in the biochemical language). Notice that **hydrolysis** of the α-β **phospho-anhydride** bond releases considerably more energy (**-45.6 kJ/mol**) than **hydrolysis** of the β-γ bond (**-30.5 kJ/mol**) (Table 3). Furthermore, the **PP$_i$** formed as a byproduct of the **adenylylation** is **hydrolyzed** to two **2 P$_i$** by the ubiquitous enzyme **inorganic pyro-phosphatase,** releasing **-19 kJ/mol** and "push" for the **adenylylation** reaction. In thereby providing a further energy effect, both **2 phospho-anhydride** bonds of **ATP** are split in the overall reaction. **Adenylylation** reactions are therefore thermodynamically very favorable. When the energy of **ATP** is used to drive a particularly unfavorable metabolic reaction, **adenylylation** is often the mechanism of **energy coupling**. **Fatty acid** activation is a good example of this **energy-coupling** strategy.

The first step in the activation of a **fatty acid**-either for **energy-yielding oxidation** (see **fatty acid** conversion to => **acyl-CoA**) or for use in the **synthesis** of more complex **lipids** (Lipid Biosynthesis)-is its attachment to the **carrier coenzyme A** (Fig. 1-11). The direct condensation of a **fatty acid** with **coenzyme A** is **endoergonic**, but the formation of **fatty acyl-CoA** is made **exoergonic** by stepwise removal of two **2 phosphoryl** groups from **ATP** First **1st**, **adenylylate** (**AMP**) is transferred from **ATP** to the **carboxyl** group of the **fatty acid**, forming a mixed **anhydride** (**fatty acyl adenylate**) and liberating **PP$_i$.** The **thiol** group of **coenzyme A** then displaces the **adenylate** group and forms a **thio-ester** with the **fatty acid**. The sum of these two **2** reactions is energetically equivalent to the **exoergonic hydrolysis** of **ATP** to **AMP** and **PP$_i$** (**$\Delta G° = -45.6$ kJ/mol**) and the **endoergonic**: formation of **fatty acyl-CoA** (**$\Delta G° = 31.4$ kJ/mol**). The formation of **fatty acyl-CoA** is made energetically favorable by **hydrolysis** of the **PP$_i$** by **inorganic pyro-phosphatase**. Thus, in the activation of a **fatty acid**, both of the **phospho-anhydride** bonds of **ATP** are broken. The resulting **$\Delta G°$** is the sum of the **$\Delta G°$** values for the breakage of these bonds, or **- 45.6 kJ/mol + (- 19.22) kJ/mol:**

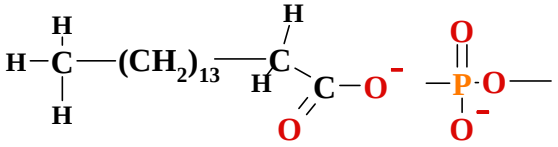
ATP^{4-} + 2 H$_2$O —=> AMP^{2-} + 2 H$_2$PO$_4^-$; $\Delta G° = -64.8$ kJ/mol

The activation of **amino acids** before their **polymerization** into proteins (see **Amino-acylation** of **tRNA)** is accomplished by an analogous set of reactions in which a **transfer RNA** molecule takes the place of **coenzyme A**. An unusual use of the cleavage of **ATP** to **AMP** and **PP_i** occurs in the firefly, which uses **ATP** as an energy source to produce light flashes (Box 1-3).



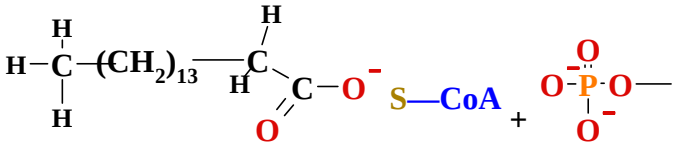
-Ribose-Adenine ATP^{4-}

Palmitate => **PP_i^{2-}—inorganic pyro-phosphatase=> 2 $H_2PO_4^-$**



-Ribose-Adenine Palmitate—**AMP^-**

Palmitoyl-**adenylate**← **CoASH** Coenzyme A



-Ribose-Adenine ATP^{4-}

which it forms a **thio-ester** bond that conserves some of the energy "**invested**" from **ATP**.

Figure 1-11. Adenylylation reaction in **activation** of a **fatty acid.** Both **phospho-anhydride** bonds of **ATP** are eventually broken in the formation of **palmitoyl-coenzyme A**. First **1st**, **ATP donates adenylate** (**AMP**), forming the **fatty acyl-adenylate** and releasing **PP_i**, which is **hydrolyzed** by **inorganic pyro-phosphatase**. The "**energized**" **fatty acyl** group is then transferred to **coenzyme A** (**CoASH**), with

a1 $CH_3(CH_2)_{14}COOH + HSCoA^{4-} => Palmitate\text{-}CoA^{4-} + H_2O$; **$\Delta G°_{a1}$ = 32.3 kJ/mol**

b1 $ATP^{4-} + H_2O => AMP^{2-} + {}^-HOPO_2OPO_2OH^-$; **$\Delta G°_{b1}$ = - 45.60 kJ/mol**

c1 $HOPO_2OPO_2OH^- + H_2O => + H_2PO_4^- + H_2PO_4^-$; **$\Delta G°_{c1}$ = - 19.2 kJ/mol**

Sum **1**: $CH_3(CH_2)_{14}COOH + HSCoA^{4-} + ATP^{4-} + H_2O$ □□□ $Palmitate\text{-}CoA^{4-} + AMP^{2-} + 2\ H_2PO_4^-$

;**$\Delta G°_{1total}$= -32.5 kJ/mol**

a2 $CH_3(CH_2)_{14}COO^- + H_3O^+ + HSCoA^{4-} => Palmitate\text{-}CoA^{4-} + 2\ H_2O$; **$\Delta G°_{a2}$ = 8.400 kJ/mol**

b2 $ATP^{4-} + H_2O => AMP^{2-} + {}^-HOPO_2OPO_2OH^-$; **$\Delta G°_{b2}$ = - 45.60 kJ/mol**

c2 $HOPO_2OPO_2OH^- + 3\ H_2O => 2\ HPO_4^{2-} + 2\ H_3O^+$; **$\Delta G°_{c2}$ = 110.72 kJ/mol**

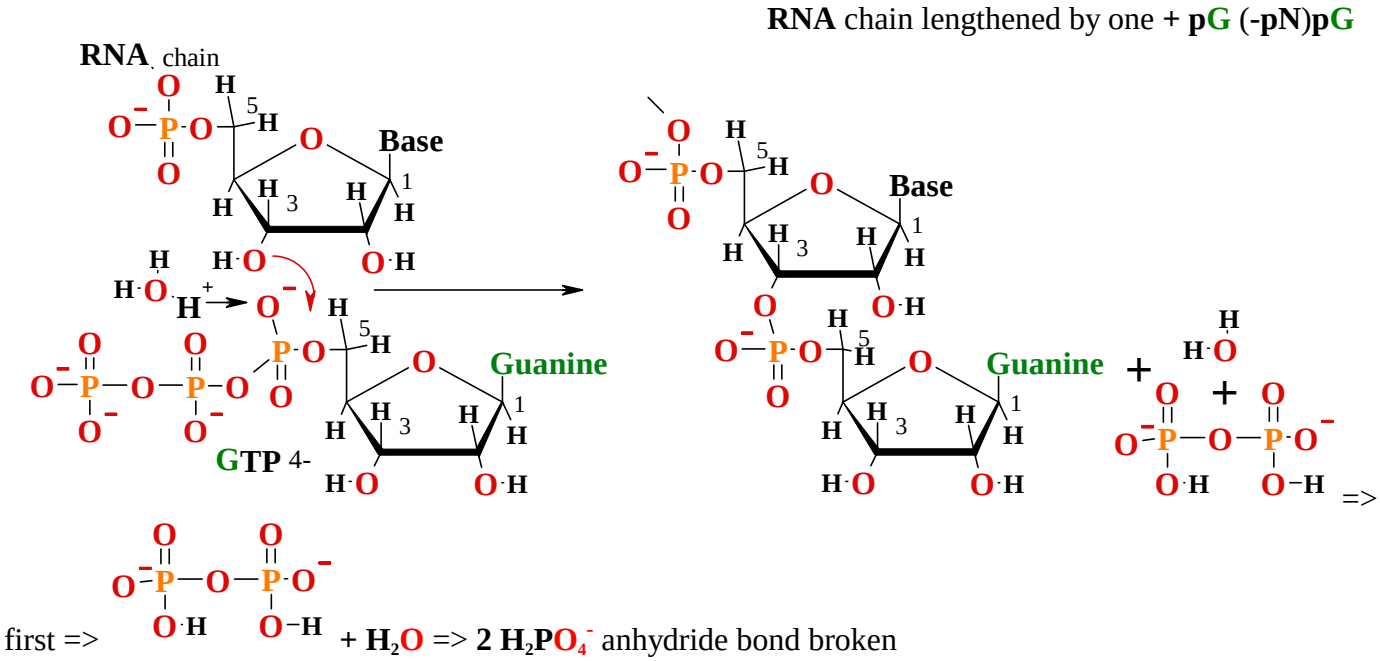
Sum **2**: $CH_3(CH_2)_{14}COO^- + HSCoA^{4-} + ATP^{4-} + 2\ H_2O$ =>□ $Palmitate\text{-}CoA^{4-} + AMP^{2-} + 2\ HPO_4^{2-} + H_3O^+$

; **$\Delta G°_{2total}$ = 73.52 kJ/mol**

8.4+110.72-45.6= 73.52 kJ/mol

Assembly of Informational Macromolecules Requires Energy

When **simple precursors** are assembled into **high molecular weight compounds** (**HMC**) **polymers** with **defined sequences** (**DNA**, **RNA**, proteins), as described in detail in Information Pathways of this studies, **free** energy ∆**G°** is required both **2** for the **condensation** of **monomeric units** and for the creation of **ordered sequences**. The **precursors** for **DNA** and **RNA synthesis** are **nucleoside triphosphates**, and **polymerization** is accompanied by cleavage of the **phospho-anhydride** linkage between the □ and □ **phosphates**, with the release of $\mathbf{PP_i}$ (Fig. 1-12). The moieties transferred to the growing **polymer** in these reactions are **adenylate** (**AMP**), **guanylate** (**GMP**), **cytidylate** (**CMP**), or **uridylate** (**UMP**) for **RNA synthesis**, and their **deoxy** analogs (with **TMP** in place of **UMP**) for **DNA synthesis**. As noted above, the activation of **amino acids** for protein **synthesis** involves the donation of **adenylate** groups from **ATP**, and we shall see in Protein Metabolism that several **steps** of protein **synthesis** on the **ribosome** are also accompanied by **GTP hydrolysis**. In all of these cases, the **exoergonic** breakdown of a **nucleoside triphosphate** is coupled to the **endoergonic** process of **synthesizing** a **polymer** of a **specific sequence**.



first => + $\mathbf{H_2O}$ => **2** $\mathbf{H_2PO_4^-}$ anhydride bond broken

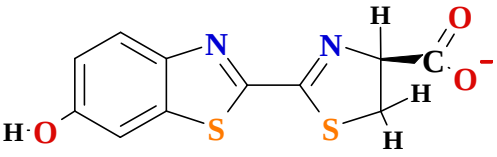
Figure 1-12. Nucleoside triphosphates GTP^{4-} in RNA synthesis. With each **nucleoside mono-phosphate** added to the growing chain, one $\mathbf{PP_i^{2-}}$ is released and **hydrolyzed** to two **2** of two **2 phospho-anhydride** bonds for each **nucleotide** added provides the energy ∆**G°** for forming the bonds in the **RNA polymer** and for assembling a **specific sequence nucleotides**.

N ribose 3 OH + GTP^{4-} + H_3O^+=> **N** ribose Phospho Guanine$^-$ + 2 $H_2PO_4^-$; ∆**G° = ? kJ/mol**

Box 1-3 Firefly Flashes: Glowing Reports of ATP

Bioluminescence requires considerable amounts of energy ΔG°. In the firefly, **ATP** is used in a set of reactions that converts chemical energy ΔG° into light energy ~hν. From many thousands of fireflies collected by children in and around Baltimore, William McElroy and his colleagues at The Johns Hopkins University isolated the principal biochemical components: **luciferin**, a **complex carboxylic acid**, and **luciferase**, an enzyme. The generation of a light flash ~hν requires activation of **luciferin** by an enzymatic reaction involving **pyro-phosphate** cleavage of **ATP** to form **luciferyl-adenylate**. In the presence of molecular oxygen O_2 and **luciferase**, the **luciferin** undergoes a multi-step **oxidative decarboxylation** to **oxy-luciferin**. This process is accompanied by emission of light ~hν. The color of the light flash ~hν differs with the firefly species and appears to be determined by differences in the structure of the **luciferase**. **Luciferin** is regenerated from **oxy-luciferin** in a subsequent series of reactions.

In the laboratory, pure firefly **luciferin** and **luciferase** are used to measure minute quantities of **ATP** by the intensity **I = k•[ATP]** of the light flash **Ψ** produced ~hν . As little as a few **pico-moles** (10^{-12} **Mol**) of **ATP** can be measured in this way. An enlightening extension of the studies in **luciferase** is the cloning of the **luciferase gene** into **tobacco** plants. When rinsing with a solution containing **luciferin**, the plants glowed ~hν in the dark **Ψ** (see a tobacco plant in which the **gene** for firefly **luciferase** is **expressed**).



Firefly **luciferin**

=> **Luciferin**=>=>=>=>=>=>=>=>=>=>=>=>=>

regeneration reactions

ATP^{4-} **PPi**$^{2-}$

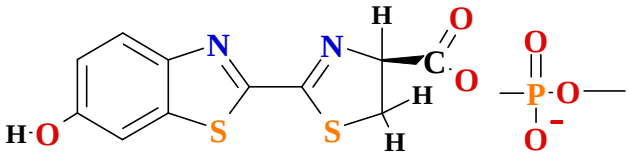
Oxy-luciferin

=> ~hν light flash Y +**C**O_2 + **AMP**$^{2-}$

← luciferase enzyme

← O_2

← **Luciferyl adenylate** ←←←←←←←←←←



-**Ribose-Adenine** Luciferyl—**AMP**$^{-}$

Important components in firefly bioluminescence, and the firefly bioluminescence cycle

ATP Energizes Active Transport and Muscle Contraction

ATP can supply the energy ΔG° for transporting an **ion** or a **molecule** across a membrane into another **aqueous** compartment where its concentration **C** is higher (see Biological Membranes and Transport - **active transport**). Transport processes are major consumers of energy ΔG°; in human **kidney** and **brain**, for example, as much as two-thirds **2/3** of the energy consumed at **rest** is used to pump Na^+ and K^+ across **plasma** membranes via the Na^+K^+**ATPase**. The **transport** of Na^+ and K^+ is driven by **cyclic phosphorylation** and **de-phosphorylation** of the **transporter** protein, with **ATP** as the **phosphoryl** group **donor** (see Na^+K^+**ATPase**). Na^+-dependent **phosphorylation** of the Na^+K^+**ATPase** forces a change in the protein's **conformation**, and K^+-dependent **de-phosphorylation** favors return to the **original conformation**. Each **cycle** in the **transport** process results in the conversion of **ATP** to **ADP** and P_i, and it is the free-energy change ΔG° of **ATP hydrolysis** that drives the **cyclic** changes in protein **conformation** that result in the **electro-genic pumping** of Na^+ and K^+. Note that, in this case, **ATP** interacts covalently by **phosphoryl** group transfer to the **enzyme**, not the **substrate**.

In the **contractile system** of skeletal muscle cells, **myosin** and **actin** are specialized to transduce the chemical energy ΔG° of **ATP** into **motion** (see **ATP** hydrolytic cycle of **myosin** subsequent reactions causing **contractile** motion). **ATP** binds tightly but non covalently to one **conformation** of **myosin**, holding the protein in that **conformation**. When **myosin catalyzes** the **hydrolysis** of its bound **ATP**, the **ADP** and P_i dissociate from the protein, allowing it to relax into a second **2nd conformation** until another molecule of **ATP** binds. The binding and subsequent **hydrolysis** of **ATP** (by **myosin ATPase**) provide the energy ΔG° that **forces cyclic** changes in the **conformation** of the **myosin head**. The change in **conformation** of many individual **myosin** molecules results in the sliding of **myosin fibrils** along **actin filaments** (see Muscle Contraction), which translates into macroscopic **contraction** of the **muscle fiber**. This production of mechanical motion at the

expense of **ATP** is, as noted earlier, one of the few cases in which **ATP hydrolysis** per se, rather than group transfer from **ATP**, is the source of the chemical energy ∆**G°** in a coupled process.

Trans-phosphorylations between Nucleotides Occur in All Cell Types

Although we have focused on **ATP** as the cell's energy currency ∆**G°** and **donor** of **phosphoryl** groups, all other **nucleoside triphosphates** (**GTP**, **UTP**, and **CTP**) and all the **de-oxy-nucleoside tri-phosphates** (**dATP**, **dGTP**, **dTTP**, and **dCTP**) are energetically equivalent to **ATP**. The **free**-energy changes ∆**G°** associated with **hydrolysis** of their **phospho-anhydride** linkages are very nearly identical with those shown in Table 1-4 for **ATP**. In preparation for their various biological roles, these other **nucleotides** are generated and maintained as the **nucleoside tri-phosphate** (**NTP**) forms by **phosphoryl** group transfer to the corresponding **nucleoside diphosphates** (**NDPs**) and **mono-phosphates** (**NMPs**).

ATP is the primary high--energy **phosphate** compound produced by catabolism, in the processes of **glycolysis**, **oxidative phosphorylation**, and, in **photo-synthetic** cells, **photo-phosphorylation**. Several enzymes then carry **phosphoryl** groups from **ATP** to the other **nucleotides**. **Nucleoside diphosphate kinase,** found in all cells, under action **Mg^{2+}** catalyzes the reaction:

ATP + **NDP** (or **dNDP**) —=> ADP + **NTP** (or **dNTP**); ∆**G° = 0 kJ/mol**

Although this reaction is fully reversible, the relatively high [**ATP**]/[**ADP**] ratio in cells normally drives the reaction to the right =>, with the net formation of **NTPs** and **dNTPs**. The enzyme actually catalyzes a two-**2**-step **phosphoryl transfer**. First **1st**, **phosphoryl** group transfer from **ATP** to an **active-site** His residue produces a **phospho-enzyme** intermediate; then the **phosphoryl** group is transferred from the **P-His** residue to an **NDP acceptor**. Because the enzyme is **non specific** for the **base** in the **NDP** and works equally well on **dNDPs** and **NDPs**, it can **synthesize** all **NTPs** and **dNTPs**, given the corresponding **NDPs** and a supply of **ATP**.

When **ADP** accumulates as a result of **phosphoryl** group transfers from **ATP**, such as when **muscle** is **contracting** vigorously, the **ADP** interferes with **ATP**-dependent **contraction**. **Adenylate kinase** under action **Mg^{2+}** catalyzes and removes **ADP** by the reaction

2 ADP —=> ATP + AMP ; ∆**G° = 0 kJ/mol**

This reaction is fully reversible, so the enzyme can also convert **AMP** (produced by **pyro-phosphoryl** or **adenylyl** group transfer from **ATP**) into **ADP**, which can then be **phosphorylated** to **ATP** through one of the catabolic **pathways**. A similar enzyme, **guanylate kinase**, converts **GMP** to **GDP** at the expense of **ATP**. By **pathways** such as these, energy ∆**G°** conserved in the catabolic production of **ATP** is used to supply the cell with all required **NTPs** and **dNTPs**.