Chemical potential μ and Homeostasis

Professor Ilya Prigogine **chemical potential μ** of compound **A** shows, how much change of **free energy** ΔG_A brings into system of our interest when adding the **1 mol** amount of compound **A** in the mixture.

In a fact: how great amount of free energy belongs to one **1 mol** of compound in mixture.

Free energy $\Delta G°_A$ has the pure compound **A** itself per **1 mol** amount,

the **chemical potential** μ_A of compound **A** if amount with in mixture others for molar number is $\Delta n_A = 1$ **mol**

$$\mu_A = \frac{\Delta G_A}{\Delta n_A}\ ;\ \mu_A = \Delta G°_A + R \bullet T \bullet \ln(X_A)\text{ , where } X_A \text{ is concentration of A unit less mol fraction } X_A = \frac{n_A}{n_{total}} \quad (5)$$

For pure compound **A** when $n_A = n_{total}$ **mol fraction** is $X_A = 1$ so $\ln(1) = 0$ and

$\mu = \Delta G°_A$ that present **standard free energy** of formation the **1 mol** pure compound **A** from elements.

Conflict in consideration pure compound $\Delta G°_A$ greater as mixture amount for one mole $|\mu_A| < |\Delta G°_A|$.

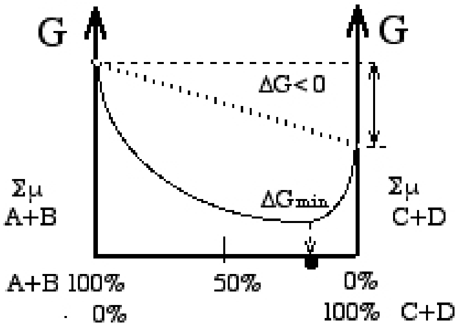
Minimisation in mixture I. Prigogine, R. Defey. "Chemical Thermodynamics".1954, Longmans Green & co ©.

Chemical equilibrium and Thermodynamics of energy minimum

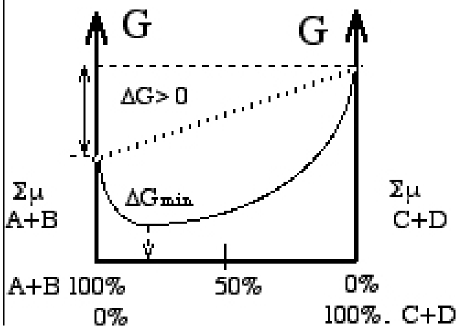
Free energy change-difference of pure products and reactants $\Delta G_{reaction}$ is criteria of process direction spontaneous for pure products 100% (negative $\Delta G_{reaction} < 0$) or thermodynamic forbidden, as products are absent 0%, but reactants are pure 100% (positive $\Delta G_{reaction} > 0$).

In state of equilibrium sum of chemical potentials for reactant compounds is equal to sum of chemical potentials for products – according chemical reaction equation reactants aA + bB and products cC + dD:

$aA + bB \underset{revers}{\overset{direct}{\rightleftarrows}} cC + dD$; **chemical potential** sum at equilibrium are equal $a\mu_A + b\mu_B = c\mu_C + d\mu_D$,



Strong electrolytes



weak acids and electrolytes

The concentrations **X** of **reactants** and **products** at **equilibrium** mixture define the **equilibrium constant**, K_{eq}. **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 zero: $0 = \Delta G = \Sigma\mu_{product} - \Sigma\mu_{reactant}$ as minimum energy in mixture. Than energy minimum ΔG_{eq} is calculated of mixture **chemical potential** sum equivalence $a\mu_A + b\mu_B = c\mu_C + d\mu_D$;

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

In contrast non equilibrium are Biochemistry conditions :

$$\Delta G_{Homeostasis} = \Delta G_{eq} + R \bullet T \bullet \ln\left(\frac{X_C^c \bullet X_D^d}{X_A^a \bullet X_B^b}\right) \neq 0 \qquad (1\text{-}4)$$

Reaching equilibrium becomes zero: $\Delta G_{Homeostasis} = \Delta G_{eq} + R \bullet T \bullet \ln\left(\frac{X_C^c \bullet X_D^d}{X_A^a \bullet X_B^b}\right) = 0$ and calculates ΔG_{eq}

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

In each sum a, b, c, and d are the number of molecules of A, B, C, and D participating in active mass law, 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 (reactants and products) at the minimum point of **equilibrium** mixture.

When the **equilibrium** is shifted out then start to work Le Chatelier's principal toward reaching **equilibrium** as Prigogine attractor the **free**-energy change minimum point ΔG_{min}. Under **standard conditions** (**298.15 K** or **25 °C**), when reactants and products are present in **molar fraction** concentrations, at partial pressures for total pressure as sum $p_{total} = 101.3$ **kilo-Pascals** (**kPa**), the force driving the system toward equilibrium is defined as Prigogine attractor **free**-energy change minimum point ΔG_{eq}. By this definition the **standard state** for reactions maintains 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 involve hydrogen ions and water $X_{H_3O^+}$ as **pH** and [H_2O]=**55.346 M** and in well-buffered aqueous solutions with Prigogine attractors **pH=7.36**. Both the **pH** and the concentration of water [H_2O] are biochemical **constants**.

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 $X_{Mg^{2+}}$. Physical constants based on this <u>biochemical</u> **equilibrium state** are called **standard equilibrium condition** and are written ΔG_{eq} with a zero index (as $\Delta G_{Mg^{2+}}=0$ and $X_{Mg^{2+}}=1$) to distinguish them from the **standard condition** used by chemists and physicists. (Notice that the symbol ΔG_{eq} is a change from the symbol $\Delta G_{reaction}$ 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 **equilibrium free** energy ΔG_{eq} change 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 as constants are included in new constant of equations 1-3, so are integrated, incorporated into new constants: ΔG_{eq} 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_{eq} 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_{eq} show the energy and mass relation of compounds. The **standard free**-energy $\Delta G_{reaction}$ change of a chemical reaction is greater by absolute value mathematical as ΔG_{eq} minimized at equilibrium with constant K_{eq}. If **equilibrium** constant for reaction is K_{eq} = **1.0**, than Prigogine attractor minimised energy equal to $0= \Delta G_{eq}=\Delta G_{reaction}$ **standard free**-energy change of that reaction. If K_{eq} of a reaction is greater than **>1.0**, its $\Delta G_{reaction} < \Delta G_{eq} < 0$ is negative. If K_{eq} is less than **<1.0**, $0 < \Delta G_{eq} < \Delta G_{reaction}$ is positive. Because Prigogine attractor of equilibrium point has minimized energy change by absolute value in mixture of compounds.

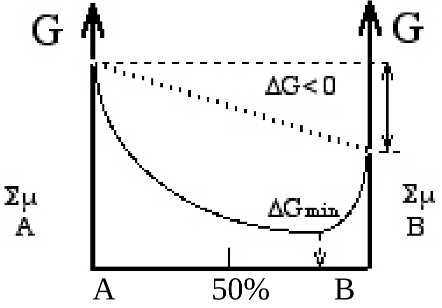
The **standard free**-energy change $\Delta G_{reaction}$ have to calculate as the difference between the pure 100% **products**, and the pure 100% **reactants** under **standard conditions** for pure compounds:

$$\Delta G_{reaction} = \Sigma\ \Delta G°_{product} - \Sigma\ \Delta G°_{reactant} \qquad . (1\text{-}3a)$$

When $\Delta G_{reaction}$ **<0** is negative, but at equilibrium point in mixture of chemical potential expressions logarithmic value shows smaller by absolute number but so ever negative value $\Delta G_{Hess} < \Delta G_{eq} < 0$. All chemical reactions tend to go in the conversion direction that results in a decrease in the f**ree** energy of the **system**. A positive value of $0<\Delta G_{eq}<\Delta G_{reaction}$ means that the **products** of the reaction contain more **free** energy than the **reactants** and this reaction will tend to go in the conversion reverse $\xleftarrow{\text{reverse}}$ direction.

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

Glc 1-P^{2-}=>Glc6-P^{2-};$\Delta G_{reaction}=\Delta G°_{Glc\_6P}-\Delta G°_{Glc\_61}$ = -1296,262-(-1289,221)=-7,042 $^{kJ}/_{mol}$ exoergic.



Chemical reaction start with **18 mM glucose 1-phosphate** and the final mixture will contain **1 mM glucose 1-phosphate** and **17 mM glucose 6-phosphate** at 25°C. **Enzymes** do not affect the point position of **equilibrium**; they merely fasten its attainment time. From these data we can calculate the **equilibrium** constant and **free**-energy change on Prigogine attractor energy minimum:, **equilibrium** shifts to right side:

K_{eq} = [**Glc 6-phosphate**]/[**Glc 1-phosphate**] = **17** mM/**1** mM = 17

$\Delta G_{eq} = -R•T•\ln(K_{eq}) = -R•T•\ln(17) = - -7.02\ ^{kJ}/_{mo}$

Spontaneous exoergic reaction, as **free**-energy change **ΔG<0** is negative, when the reaction starts with **Glc 1-phosphate** and **Glc 6-phosphate**, the conversion of **glucose 1-phosphate** to **glucose 6-phosphate** proceeds with a loss (release) of free energy.

Pure reagents change in table 1-1 $\Delta G_{reaction}$ =-7,03 $^{kJ}/_{mo}$ is greater as attractor minimum ΔG_{eq}= -7.02 $^{kJ}/_{mol}$.

For the reverse reaction (the conversion to **glucose 1-phosphate** $\xleftarrow{\text{reverse}}$ from **glucose 6-phosphate**), **+7.02** $^{kJ}/_{mol}$ is the same number but the opposite sign. Reverse reaction is thermodynamic forbidden.

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

Table 1-1 gives the **standard free**-energy changes $\Delta G_{reaction}$ for some representative chemical reactions in Hess law thermodynamic calculations. $\Delta G_{reaction} = \Delta H_{reaction} - T\ \Delta S_{reaction}$. (1-3b)

Note that **hydrolysis** of simple **esters**, **amides**, **peptides**, and **glycosides**, as well as **rearrangements** and **eliminations**, proceed with relatively small **free**-energy changes $\Delta G_{reaction}$, whereas **hydrolysis** of **acid**

anhydrides occurs with relatively large decreases in **free**-energy ΔG_{Hess}. The complete **oxidation** of organic compounds such as **glucose** or **palmitate** to CO_2 and H_2O, which in cells occurs in many complex enzyme reaction step wises, results in very large decreases in **standard free** energy ΔG_{Hess}. However, **free**-energy changes ΔG_{Hess} 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 pure compound. To describe the energy released under the **homeostasis** mixture **conditions** for cells one has to use chemical potential 1-4. The expression for the **actual homeostasis free**-energy change ΔG_{eq} calculation at equilibrium position as Prigogine attractor minimum is essential.

$$\Delta G = \Delta G_{eq} + \mathbf{R\bullet T\bullet \ln}(XD^{d}\bullet XC^{c})/(XA^{a}\bullet XB^{b}) \neq 0;\ 0 = \Delta G_{eq} + \mathbf{R\bullet T\bullet \ln}(K_{eq}) \qquad \text{at equilibrium zero (1-4)}$$

There have to distinguish two **2** quantities: shifted equilibrium **free**-energy change ΔG, and the **equilibrium free**-energy change ΔG_{eq}. Chemical reaction has **equilibrium** point position **free**-energy change per one **1 mol** of **reagents** which maybe positive $\Delta G_{eq}>0$, negative $\Delta G_{eq}<0$, or zero $\Delta G_{eq}=0$, depending on the equilibrium mixture constant K_{eq} logarithm. The **equilibrium** point position **free**-energy change ΔG_{eq} tells us in which direction and how much work reaction must attempt for reaching **equilibrium** at temperature **25 °C** or T_o**=298.15 K**, and the pressure **p** = **101.3 kPa** (**1 atm**) and at **equilibrium** mixture concentrations K_{eq}. Thus ΔG_{eq} is a constant: as Prigogine attractor free energy change minimum for equilibrium. Actual **free**-energy change, ΔG, is a function of **reactant** and **product** concentrations **X** and of the temperature **T=310.15 K** stationary dominating in human body reaction, which is shifted out of **equilibrium** point position. Moreover, the ΔG of any reaction proceeding => spontaneously toward its **equilibrium** state is always negative $\Delta G<0$, and minimum value reaches ΔG_{eq} , if the reverse ← reaction shift to point position of **equilibrium**, and is zero $\Delta G=0$. Expression $(XD^{d}\bullet XC^{c})/(XA^{a}\bullet XB^{b}) = K_{eq}$, indicating that no more work $W= -\Delta G=0$ can be done by the reaction: $aA + bB = cC + dD$ according expression (1-3)

Table 1-1. Standard Free-Energy Changes for pure compounds hydrolise ΔG_{Hess} at I=0,25 M (298.15 K)

Hydrolysis reactions free energy change ΔG_{eq} at equilibrium and in Hess calculation law	ΔG_{Hess}	${}^{kJ}/_{mol}$
$CH_3COOOCCH_3+H_2O=2CH_3COOH;\Delta G_{Leninger}=-91,1\ {}^{kJ}/_{mol};K_{Leninger}=49,07;\Delta G_{eq}=-9,65\ {}^{kJ}/_{mol}$	**-19,745**	pH<4,5
$CH_3COOOCCH_3+3H_2O=>2CH_3COO^{-}+2H_3O^{+};\ K_{eq}=3,871*10^{-8};\ \Delta G_{eq}=42,31\ {}^{kJ}/_{mol}$	87,757	pH=7,36
$H_2PO_4^{-}+H_2O=>HPO_4^{2-}+H_3O^{+};\Delta G_{Lehninger}=64,96\ {}^{kJ}/_{mol};\ K_{eq2}=\mathbf{1.143\bullet 10^{-9}};\Delta G_{eq}=51,04\ {}^{kJ}/_{mol};\Delta G_{Hess}=$	70	pK=7,199
$ATP^{3-}+H_2O=>ADP^{2-}+H_2PO_4^{-};\ \Delta G_{Leninger}=-30,5\ {}^{kJ}/_{mol};\ K_{eqL}=3984,946;\ \Delta G_{eqL}=-20,55\ {}^{kJ}/_{mol};$	-32,309	pH<7,199
$ATP^{4-}+2H_2O=>ADP^{3-}+HPO_4^{2-}+H_3O^{+};K_b=3,14296*10^{-6};\Delta G_b=31,409\ {}^{kJ}/_{mo};$	71,408	pH=7,36
$ATP^{4-}+2H_2O=>AMP^{3-}+2HPO_4^{2-}+2H_3O^{+};\ \Delta G_{Leninger}=-64,8\ {}^{kJ}/_{mol};$	-	pH=7,36
$ATP^{4-}+H_2O=>AMP^{2-}+\mathbf{H_2P_2O_7^{2-}};1761359=K_{Leni}=97454074;\Delta G_{Leh}=-45.6;\ \Delta G_{eq}=-35,65\ {}^{kJ}/_{mol}$	**-49.727**	pH<6,72
$ATP^{4-}+2H_2O=>AMP^{2-}+\mathbf{HP_2O_7^{3-}+H_3O^{+}};\mathbf{K_a=K_{eq}[H_3O^{+}]/[H_2O]}=0,00139024;\Delta G_a=16,31\ {}^{kJ}/_{mol}$	58,83	pH=7,36
$\mathbf{HP_2O_7^{3-}+H_2O=>H_2PO_4^{-}+HPO_4^{2-}};K_{Lehninger}=2310,57;\ \Delta G_{eqL}=-9,251\ {}^{kJ}/_{mol};\Delta G_{Lehninge}=-19.2\ {}^{kJ}/_{mol}$	-48,73	pH<7,199
$\mathbf{HP_2O_7^{3-}}+2H_2O=>2HPO_4^{2-}+\mathbf{H_3O^{+}};\mathbf{K_a}=K_{eqL}[H_3O^{+}]/[H_2O]=10^{-7,48244849};\ \Delta G_a=42,71\ {}^{kJ}/_{mol};K_{eqL}=41,76$	**87,48**	pH=7,36
$UDPGlc^{2-}+H_2O=>UMP^{1-}+Glc1P^{1-};\ K_{Leninger}=10^{7,75333};\ \Delta G_{Leninger}=-43;\Delta G_{aLeninger}=-33,05\ {}^{kJ}/_{mol};$	-128,64	pH<7,199
Esters ↓; $UDPGlc^{2-}+3H_2O=>UMP^{2-}+Glc1P^{2-}+2H_3O^{+};K_{eq}=10^{-12,4};\ \Delta G_{eq}=70,868\ {}^{kJ}/_{mol}$; 424 or	**113**	pH=7,36
$CH_3CH_2\text{-}O\text{-}OCCH_3+H_2O=>CH_3CH_2OH+HOOCCH_3;K_L=2715;\ \Delta G_L=-19.6;\ \Delta G_{eL}=-9,65\ {}^{kJ}/_{mol};$	**-19,745**	pH<4,76
$CH_3CH_2OOCCH_3+H_2O=>CH_3CH_2OH+{}^{-}OOCCH_3;\ K_{eL}=49,07;\ K_{ee}=10^{-7,41};\ \Delta G_{eL}=42,3\ {}^{kJ}/_{mol};$	87,757	pH=7,36
$Glc6P^{2--}+H_2O=>Glc+HPO_4^{2-};\Delta G_L=-13.8\ {}^{kJ}/_{mol};K_{aL}=K_L/[H_2O]=4,728;\ \Delta G_{aL}=-3,851\ {}^{kJ}/_{mol}$	-38,55	I=0,25 M
$\mathbf{Glc+ATP^{4-}+H_2O=>Glc6P^{2-}+ADP^{3-}+H_3O^{+}};K_{eq}=5,83\bullet 10^{2};\ \mathbf{\Delta G_{eq}=-R\bullet T\bullet ln(K_{eq})}=-15,78\ {}^{kJ}/_{mol}$	-50,285	pH=7,36
Amidi and peptides $\Delta G_{Leninger}=-13,8\ {}^{kJ}/_{mol};\ K_{Lehmiger}=261,62$		
$Gln+\mathbf{H_2O}=>Glu^{-}+NH_4^{+};\ \Delta G_{Lehninger}=-14,2\ {}^{kJ}/_{mol};\ \mathbf{K_{aL}=K_{Leninger}/[H_2O]}=307,4;$	**-48**	7,36≥pH
$Glu^{-}+NH_4^{+}+ATP^{4-}+H_2O=>Gln+ADP^{3-}+HPO_4^{2-}+\mathbf{H_3O^{+}};\ \mathbf{\Delta G_{ab}=35,7}\ {}^{kJ}/_{mol};\ \mathbf{K_{ab}}=10^{-6,24738937};$	**68,78**	pH=7,36
$GlyGly+H_2O=>2Gly;\ K_{Leninger}=40,906;\Delta G_{Leninger}=-9.2;K_{eqL}=40,906/55,3=0,7392655;$	-57,3	pH=7,36
Glycosides; $\Delta G_{eqL}=\mathbf{-R\bullet T\bullet ln}(K_{eqL})=-8,3144\bullet 298,15\bullet \mathbf{ln}(0,7392655)=0,7489\ {}^{kJ}/_{mol};$	I=? M	-
$Maltose+H_2O=>2Glc;\ K_{eq}=K_{Leninger}=519,4;\ \Delta G_{Leninger}=-15.5\ {}^{kJ}/_{mol};$	**-155**	pH=7,36
$Lactose+H_2O=>Glc+Gal;\ K_{eq}=610.35=K_{Lehninger};\ \Delta G_{Leninger}=-15.9\ {}^{kJ}/_{mol};$	**-20,334**	pH=7,36
Group transfer (transferases)		
$Glc1P^{2-}=>Glc6P^{2-};K_{eq}=[Glc6P]/[Glc1P]=17;\Delta G_{eq}=-RTln(K_{eq})=-7,02\ {}^{kJ}/_{mol}$;BioThermodyn06	**-7.041**	I=0,25 M
$Fruc6P^{2-}=>Glc6P^{2-};\ K_{Leninger}=1,98531=10^{0,29783};;\Delta G_{Leninger}=-1,7\ {}^{kJ}/_{mol}$	**-3,173**	pH=7,36
Water H_2O elimination		I=0,25M
$Malate=>Fumarate+H_2O;\ \Delta G_{Leninger}=\Delta G_{eq}=3,1\ {}^{kJ}/_{mol};\ K_{eq}=K_{Leninger}=0,28635$	**3,6165**	pH=7,36
Oxidation with molecular oxygen O_2 ; $Glucose+6O_2=>6CO_2+6H_2O;\ \Delta G_{Leninger}=-2840\ {}^{kJ}/_{mol};$	-	-
$\mathbf{C_6H_{12}O_6+6O_{2aqua}+6H_2O=>6HCO_3^{-}+6H_3O^{+}}=>6CO_{2aqua}+12H_2O;\ K_{Lehninger}=10^{497,55};$	**-2921,5**	aqua
$Palmitic\ acid+23O_{2aqua}=>16CO_{2aqua}+16H_2O;\Delta G_{Leninger}=-9770\ {}^{kJ}/_{mo};\ K_{Lehninger}=10^{1711,6428};$		
$\mathbf{C_{16}H_{32}O_{2s}}+16H_2O+23O_{2aqua}=16HCO_3^{-}\ \vert+16H_3O^{+}=16CO_{2aqua}+32H_2O=16CO_{2gas}\uparrow+32H_2O$	**-12020**	aqua

$\Delta \mathbf{G}_{\text{Homeostasis}}$ and $\Delta \mathbf{G}_{\mathbf{eq}}$ connected in the equation (1-4). in which the terms are actually dominating at experimental observation. The concentration **X** terms in this equation express the reflects **mass action**. As an example, let us write general reaction a**A** + b**B** = c**C** + d**D** which works at the **standard conditions** of temperature $\mathbf{T}_o$ **= 298.15 K** (**25 °C**) and pressure (**101.3 kPa**) but we simply enter the equilibrium concentrations of $\mathbf{X}_A$, $\mathbf{X}_B$, $\mathbf{X}_C$, and $\mathbf{X}_D$ in Equation 1-4; the values of **R**, $\mathbf{T}_o$, and calculate the $\Delta \mathbf{G}_{\mathbf{eq}}$. Actual concentrations of $\mathbf{X}_A$, $\mathbf{X}_B$, $\mathbf{X}_C$, and $\mathbf{X}_D$ in Equation 1-4 with negative $\Delta \mathbf{G}_{\text{non\_equilibrium}}$ **<0** changes to reach zero =>**0** as direct reaction reactants concentrations of $\mathbf{X}_A$ and $\mathbf{X}_B$ decrease and products concentrations of $\mathbf{X}_C$, and $\mathbf{X}_D$ increase. Notice that when a reaction is at **equilibrium**-when there is no **force** driving the reaction in either direction and Δ**G** is zero-Equation 1-4 to calculate $\Delta \mathbf{G}_{\mathbf{eq}} = -\,\mathbf{R \cdot T \cdot ln}(\mathbf{K}_{\mathbf{eq}})$ as $\mathbf{0} = \Delta \mathbf{G}_{\mathbf{eq}} + \mathbf{R \cdot T \cdot ln}(\mathbf{K}_{\mathbf{eq}})$ the equation relating the **equilibrium free**-energy change with **equilibrium** constant $\mathbf{K}_{\mathbf{eq}}$ as noted above (1-4).

Biological mediums usually have some certain hydrogen ion $[\mathbf{H_3O^+}]$ concentrations expressed as logarithmic exponent $\mathbf{pH = -log([H_3O^+])}$ for: <u>blood</u> plasma and <u>cytosole</u> **pH = 7.36**; <u>mitochondria</u> matrix **pH = 7.36**;

<u>mitochondria</u> inter membrane space **pH = 5.0**; <u>saliva</u> juice **pH = 6.8**; <u>stomach</u> juice **pH = 1.2** (before meals). Extracting from **equilibrium** mixture constant $\mathbf{K}_{\mathbf{eq}}$ as expression $\mathbf{R \cdot T \cdot ln}(\mathbf{X}_{H_3O^+}^{\mathbf{n}})$ by mathematical separation of logarithm ratio in (1-4) may correct **equilibrium free**-energy $\Delta \mathbf{G}_{\mathbf{eq}}$ value to **conditions** for **pH** of medium of $[\mathbf{H_3O^+}] = \mathbf{10^{-pH}\ M}$ solution where **n** is the number of hydrogen ions $\mathbf{H_3O^+}$ involved in reaction **equilibrium** mixture according given reaction equation. Addition or subtraction to **standard free**-energy $\Delta \mathbf{G}_{\mathbf{eq}}$ value yield $\Delta \mathbf{G}_{\text{pH}} = \Delta \mathbf{G}_{\mathbf{eq}} \pm \mathbf{R \cdot T \cdot ln}(\mathbf{X}_{H_3O^+}^{\mathbf{n}})$ **pH conditions free**-energy at given medium ($-\mathbf{R \cdot T \cdot ln}(\mathbf{X}_{H_3O^+}^{\mathbf{n}})$ agree for **reactant** and $+\mathbf{R \cdot T \cdot ln}(\mathbf{X}_{H_3O^+}^{\mathbf{n}})$ for **product**).

The criterion for spontaneity of a reaction is the value of equilibrium $\Delta \mathbf{G}_{\mathbf{eq}}$. Equilibrium with a positive $\Delta \mathbf{G}_{\mathbf{eq}} \mathbf{>0}$ can go in the forward direction if $\Delta \mathbf{G}_{\text{Homeostasis}}$ **<0** is negative. This is possible if the expression in equation 1-4 is negative (-) $\mathbf{R \cdot T \cdot ln}$([**products**]/[**reactants**]) and has a larger absolute value greater > than $\Delta \mathbf{G}_{\mathbf{eq}}$. For example, the immediate removal of the **products** of a reaction can keep the ratio well below **<1**, so expression has a large, negative value, like CATALASE erase $\mathbf{H_2O_2}_{\text{aqua}}$ in products for succinate 100% of efficiency convertion to fumarate by dehydrogenase enzyme of Krebs cycle.

$\Delta \mathbf{G}_{\mathbf{eq}}$ and $\Delta \mathbf{G}_{\text{Homeostasis}}$ 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 Δ**G** is always lost to **bound** energy $\mathbf{T \cdot \Delta S}$ and entropy Δ**S** during any process), the amount of work $\mathbf{W \leq -\Delta G}$ done by the reaction at constant temperature **T=const** and pressure is always less than the theoretical amount Δ**G**.

Another important point is that some thermodynamically favorable reactions (that is, reactions for which $\Delta \mathbf{G}_{\mathbf{eq}}$ **<0** is large and negative) do not occur at measurable rates. For example, **combustion** of firewood to $\mathbf{CO_2}_{\text{aqua}}$ and $\mathbf{H_2O}$ is very favorable thermodynamically, but firewood remains stable for years because the activation energy $\mathbf{E_a}$ (see Reaction Rate (Velocity) and Kinetics) for the **combustion** reaction is higher than the energy $\mathbf{E_a}$ available at room temperature. If the necessary activation energy $\mathbf{E_a}$ is provided (with a lighted match, for example), combustion will begin, converting the wood to the more stable products $\mathbf{CO_2}_{\text{aqua}}$ and $\mathbf{H_2O}$ and releasing energy as **heat** $\mathbf{-\Delta H}$ and light **~hν**. The **heat** $\mathbf{-\Delta H}$ released by this **exothermic** reaction provides the activation energy $\mathbf{E_a}$ for **combustion** of neighboring regions of the firewood; the process is self-perpetuating.

All **enzymes** reactivity lowering the activation energy $\mathbf{E_a}$ and increase reactions velocity constant about million times $\mathbf{10^6}$. **Hess law** in living cells show **free**-energy change Δ**G** for a reaction is independent of the **pathway** by which the reaction occurs; it depends only on the reactants and products. **Enzymes** cannot change equilibria positions and constants $\mathbf{K}_{\mathbf{eq}}$; but remarkably increase the rate constant for velocity.

<u>**Free-Energy** changes ΔG are additive</u>

In the case of two **2** sequential chemical reactions, **A⇔B** and **B⇔C**, each reaction has its own **equilibrium** constant $\mathbf{K}_{\mathbf{eq1}}$, $\mathbf{K}_{\mathbf{eq2}}$ and each has its characteristic **equilibrium free**-energy change, $\Delta \mathbf{G}_{\mathbf{eq1}}$ and $\Delta \mathbf{G}_{\mathbf{eq2}}$. As the two reactions are sequential, **B** cancels out to give the overall reaction **A⇔C**, which has its own **equilibrium** constant $\mathbf{K}_{\mathbf{eq}}$ and thus its own **equilibrium free**-energy change, $\Delta \mathbf{G}_{\text{total}}$ The Δ**G** values of sequential chemical reactions are additive. For the overall reaction **A⇔C**, $\Delta \mathbf{G}_{\text{eq\_total}} = \Delta \mathbf{G}_{\mathbf{eq1}} + \Delta \mathbf{G}_{\mathbf{eq2}}$ is the algebraic sum of the individual **equilibrium free**-energy changes, $\Delta \mathbf{G}_{\mathbf{eq1}}$ and $\Delta \mathbf{G}_{\mathbf{eq2}}$, and the overall **equilibrium** constant

$\mathbf{K}_{\mathbf{eq}} = \mathbf{K}_{\mathbf{eq1}} \cdot \mathbf{K}_{\mathbf{eq2}}$ is the factorial of the individual **equilibrium** constant $\mathbf{K}_{\mathbf{eq1}}$ and $\mathbf{K}_{\mathbf{eq2}}$ of the two **2** sequential reactions.

Biochemical thermodynamics explains how unfavorable **endoergic** reaction can be driven in favorable by coupling it to a **exoergic** reaction in complex sequential order through a **common intermediate**. The **Glc 6-phosphate**$^-$ formation attractor intermediate concentration **pH = 7.36** make reaction **a** endoergic:

a Glucose + **HPO_4^{2-}** => **glucose 6-phosphate**$^-$ + **H_2O** ; ΔG_{aeq}==3,851 $^{kJ}/_{mol}$**;** $\Delta G_{aLehninger}$=13,8 $^{kJ}/_{mol}$

Cellular **hydrolysis** of **ATP^{4-}** to **ADP^{3-}** producing **HPO_4^{2-}** **+H_3O^+** in **endoergic b** ΔG_{beq} =31,41 $^{kJ}/_{mol}$ driven by hydrogen ion concentration [**$H3O^+$**]**=$10^{-7.36}$ M** in blood **pH = 7.36 exoergic b**:

b ATP^{4-}+2 H_2O => ADP^{3-}+HPO_4^{2-}+H_3O^+ **;** ΔG_{beq} =31,41 $^{kJ}/_{mol}$ (**pH = 7.36**) $\Delta G_{bLehninger}$=-30,5 $^{kJ}/_{mol}$ (1-5)

Homeostasis share Biochemistry constants for **H_3O^+** and **H_2O** concentrations and for Attractor pH=7,36.

$K_{bLeninger}$**=exp(-**$\Delta G_{bLehninger}$**/R/T**)=exp(30,5/8,3144/298,15)=220500;

$K_{bLeninger}$**=K_{beq}***$[H_2O]^2/[H_3O^+]$=220500,2= $\frac{[HPO_4^{2-}]\cdot[ADP^{3-}]\cdot[H_3O^+]}{[H_2O]^2[ATP^{4-}]}$

$\Delta G_{bLeninger}$**=-R•T•ln**($K_{bLeninger}$)=-8,3144•298,15•**ln**(220500,2)= -30,5 $^{kJ}/_{mol}$;

a **Glc** + **HPO_4^{2-}** => **$Clc6P^{2-}$** + **H_2O**; $\Delta G_{aLehninger}$=13,8 $^{kJ}/_{mol}$;

b ATP^{4-}+2 H_2O => ADP^{3-}+HPO_4^{2-} + H_3O^+; $\Delta G_{bLehninger}$=-30,5 $^{kJ}/_{mol}$**;**

Sum: **Glc** + ATP^{4-} ⁻+ H_2O => **$Glc6P^{2-}$** + ADP^{3-} + H_3O^+ ; $\Delta G_{totaleq}$ **=1**3,8 **+ -**30,5 $^{kJ}/_{mol}$= 16,8 $^{kJ}/_{mol}$;.

Reactions iis **exoergic**. Such a way ATP^{4-} molecules are used for **glucose 6-phosphate** synthesis driving, even formed from **glucose** and **phosphate** at attractor **pH=7,36** affected **a exoergic**. Any way the **pathway** of **glucose 6-phosphate** formation by **phosphoryl transfer** from ATP^{4-} through paths (**a**) and (**b**)**.** Both pathways sum give the free energy changes according Hess law calculation order products minus reactants.

Equilibrium ΔG_{eq} is a way of expressing the **equilibrium** constants K_{a1eq} for a reaction. For reaction (**a**) above at standard **T=298.15K** or human body temperature **T=310.15K** unfavored:

$$K_{a298}=\frac{[Glc6P^{2-}]\cdot[H_2O]}{[Glc]\cdot[HPO_4^{2-}]} = EXP(-13,8/8,3144/298,15)=0,00382 \; ; \; K_{a310}=0,004741$$

Notice concentration [**H_2O**]**=55.333 M** constant is included in its value, To calculate **standard equilibrium** constants in tables is to devide by, but at cell temperature **T = 310.15 K** by [**H_2O**] **= 55.1398 M**.

The **equilibrium** constants **K_b** for the **hydrolysis** of ATP^{4-} are at attractor pH=7,36 favored :

$$K_{b298}=\frac{[HPO_4^{2-}]\cdot[ADP^{3-}]\cdot[H_3O^+]}{[H_2O]^2\cdot[ATP^{4-}]}= 2747,96 \text{ or } K_{b310} = 1713,12 \text{ ; favored .}$$

The equilibrium constant for the two coupled reactions **T=298.15K** or human body temperature **T=310.15K** is

$$K_{eq298}=\frac{[Glc6P^{2-}]\cdot[H_2O]}{[Glc]\cdot[HPO_4^{2-}]} \bullet \frac{[HPO_4^{2-}]\cdot[ADP^{3-}]\cdot[H_3O^+]}{[H_2O]^2\cdot[ATP^{4-}]} = \frac{[Glc6P^{2-}]\cdot[ADP^{3-}]\cdot[H_3O^+]}{[Glc]\cdot[H_2O]\cdot[ATP^{4-}]} = 581,2,\ 447,84 = K_{eq310};$$

Equilibrium ΔG_{eq} value are additive for two **2** reactions that sum to a third **3rd**, Constant **K_{total}** for a reaction of two **2** reactions is the commutative **K_a•K_b** of values favored largest yielding with medium attractor value pH=7,36 **K_{eq298}=581,2** , **K_{eq310}=447,83** at human body temperature **T=310.15K** (**37°C**) respectively.

Equilibrium constants are commutative in joined (tandem) reactions as ATP^{4-} **hydrolysis** to glucose 6-phosphate$^-$ synthesis.. In coupling (tandem) reactions **common intermediate** employed is living cells strategy in metabolic synthesis as **photosynthesis**, polycondensation reactions (proteins, nucleic acids, polysaccharides, muscle contractions. This strategy works only if reactant ATP^{4-} is continuously available. In have to study this important cellular **pathways** for producing ATP^{4-}.

The **equilibrium free energy** chamge ΔG_{eq} of **hydrolysis** of **ATP^{4-}** is 31,41 $^{kJ}/_{mol}$. In the cell, however, the concentrations **C** of **ATP^{4-}**, **ADP^{3-}** and **$[H_2PO_4^-]+[HPO_4^{2-}]$** are not only unequal but much lower than the **1 M** concentrations **C** (see Table 1-2). Moreover, the cellular **pH** tends to attractor **pH** of **7.36**. Thus the *actual* **free energy** of **hydrolysis** of **ATP^{4-}** under intracellular conditions (1-5) differs from the equilibrium **free energy** change, ΔG_{eq}. We can easily calculate (1-5). For example, in human **erythrocytes** the concentrations **C** of **ATP^{4-}**, **ADP^{4-}** and **$[H_2PO_4^-]+[HPO_4^{2-}]$** are **2.25**, **0.25**, and **1.65 mM**, respectively. At known attractor values **pH=7.36** and the temperature **T 310.15 K** (**37 °C**) the standard are **pH** and temperature **T**. The actual **free energy** $\Delta G_{Homeostasis}$ of **hydrolysis** of **ATP** in the **erythrocyte** is in expressions:

$$ATP^{4-}+2\,H_2O \Rightarrow ADP^{3-}+HPO_4^{2-}+H_3O^+\ ;\ \Delta G_{Homeostasis}=\Delta G_{eq}+R\bullet T\bullet \ln\frac{[HPO_4^{2-}]\cdot[ADP^{3-}]\cdot[H_3O^+]}{[H_2O]^2\cdot[ATP^{4-}]} \quad (1\text{-}5)$$

$$K_{H2PO4}=\frac{[HPO_4^{2-}]_{aqua}\cdot[H_3O^+]}{[H_2PO_4^-]_{aqua}\cdot[H_2O]}\ ;\ P_i = 1.65\ mM=[H_2PO_4^-]+[HPO_4^{2-}];\ [H_2PO_4^-]=\frac{[HPO_4^{2-}]_{aqua}\cdot[H_3O^+]}{1{,}144*10^{-9}\cdot[H_2O]}\ ;$$

$$[HPO_4^{2-}]+[HPO_4^{2-}]\ \frac{[H_3O^+]}{1{,}144*10^{-9}\cdot[H_2O]}=1.65\bullet10^{-3}\ M=[HPO_4^{2-}]\bullet\left(1+\frac{[H_3O^+]}{1{,}144*10^{-9}\cdot[H_2O]}\right);$$

$$[HPO_4^{2-}]=\frac{1.65/1000}{\left(1+\dfrac{[H_3O^+]}{K_{H2PO4}\bullet[H_2O]}\right)}=9.8\bullet10^{-4};\ \Delta G_{eq}+R\bullet T\bullet \ln\left(\frac{1.65/1000\bullet[ADP^{3-}]\bullet[H_3O^+]}{\left(1+\dfrac{[H_3O^+]}{K_{H2PO4}\bullet[H_2O]}\right)\bullet[ATP^{4-}]\bullet[H_2O]^2}\right)=\Delta G$$

Substituting GIVEN values to obtain logarithmic argument: $9.192\bullet10^{-29}$; $10^{-28,04}$ and homeostasis energy change

$$\Delta G_{Homeostasis}=31{,}408\ ^{kJ}/_{mol}+(8.3144\ J/mol/K\bullet310.15\ K)\bullet \ln\frac{2.50\bullet10^{-4}\bullet1.65\bullet10^{-3}\bullet10^{-7.36}]}{2.25\bullet10^{-3}\bullet55.1398^2}=-55{,}16\ ^{kJ}/_{mol}$$

at **T = 273.15 + 37**=310,15 **K** ; in homeostasis **$2{,}6322\bullet10^{-15}$** $= K_{eritrocites}$ and equilibrium $3{,}1437*10^{-6}=K_{eq}$.

Thus the **free energy** change required to **synthesize** **ATP^{4-}** from **ADP^{3-}** and **$HPO_4^{2-}+H_2PO_4^-$** under the conditions prevailing in the **erythrocyte** would be accumulate **+55,16** $^{kJ}/_{mol}$ in **ATP^{4-}** one mole.

Table 1-2.Adenin Nucleotide, **phosphate** and **phospho-creatin concentrations** in **cells***

Concentration **C** (mM) or **-pH** **ATP^{4-}**31;408 $^{kJ}/_{mol}$ **PCr 64,46**;67,05 $^{kJ}/_{mol}$

298,15 K; 310,15 K

	ATP^{4-}	**ADP^{3-}**	**AMP^{2-}**	**P_i**	**PCr**	**pH**	**$\Delta G_{Homeostasis}$**	**$\Delta G_{Homeostasis}$**	$\Delta G_{Homeostasis}$
Rat hepatocyte	3.38	1.32	0.29	4.80	0.0	7.36	-49,17	**-112,025**	-114,615
Rat myocyte mitochondria	8.05	0.93	0.04	8.05	28.0	7.36	-50,97	**-124,955**	-127,545
Rat myocyte	8.05	0.93	0.04	8.05	28.0	7.36	-50,97	**-120,14**	-122,73
Rat neuron	2.59	0.73	0.06	2.72	4.7	7.36	-51,47	**-119,37**	-121,96
Human erythrocyte	2.25	0.25	0.02	1.65	0.0	7.36	**-55,16**	**-118,02**	-120,61
E. coli cell	7.90	1.04	0.82	7.90	0.0	7.36	-50,69	**-116,29**	-118,88

* For **erythrocytes** the concentrations **C** are those of the cytosole (human **erythrocytes** lack a nucleus and mitochondria). In the other types of cells the data are for the entire cell contents, although **the cytosole** and the mitochondria have very different concentrations **C** of **ADP**$^{3-}$. **PCr** is **phospho-creatine**, discussed on above.

This value reflects total concentration; the true value for **free ADP**$^{3-}$ may be much lower (see above).

Because the concentrations **C** of **ATP**$^{4-}$, **ADP**$^{3-}$, and [HPO_4^{2-} + $H_2PO_4^-$] differ from one cell type to another (see Table 1-2), Δ**G** for **ATP**$^{4-}$ **hydrolysis** likewise differs among cells. Moreover, in any given cell, Δ**G** can vary from time to time, depending on the **metabolic conditions** in the cell and how they influence the concentrations **C** of **ATP**$^{4-}$, **ADP**$^{3-}$, [HPO_4^{2-} + $H_2PO_4^-$], and H_3O^+ (**pH**). We can calculate the actual **free energy** change Δ**G** 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_{Hess} and thus the calculated **free energy** Δ**G** change.

To further complicate the issue, the total concentrations **C** of **ATP**$^{4-}$, **ADP**$^{3-}$, 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**$^{4-}$, **ADP**$^{3-}$, 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 **10** and **370 µM**. Using the value **250 µM** in the calculation outlined above, we get a $\Delta G_{Homeostasis}$ of **-55,16** $^{kJ}/_{mol}$. The exact value is perhaps less instructive than the generalization we can make about actual **free energy** changes: in vivo, the energy released by **ATP**$^{4-}$ **hydrolysis** is exoergic than the equilibrium or Hess **free energy** change

$$\Delta G_{eq}=31{,}41\ ^{kJ}/_{mol}\ \text{or}\ \Delta G_{Hess}=71{,}704\ ^{kJ}/_{mol}.$$

Note: Lehninger biochemistry conditions water concentration [H_2O]=**55.346 M** and Prigogine attractor vēalue **pH=7.36**. [H_3O^+] concentration $10^{-7.36}$ **M** as constants determine **homeostasis state** in living organism.