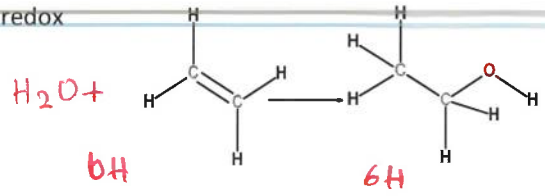
Lecture 28: Organic Redox Reactions, Non-Equilibrium Thermodynamics & Pathway Flux

Example: Is the conversion of ethene to ethanol a redox reaction?

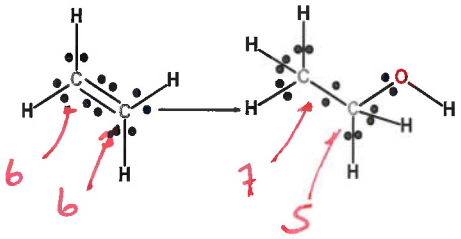
Method A:



Not a redox reaction

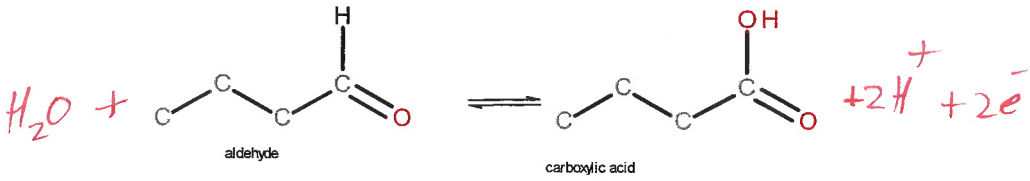
Method B:

No change over the entire molecule



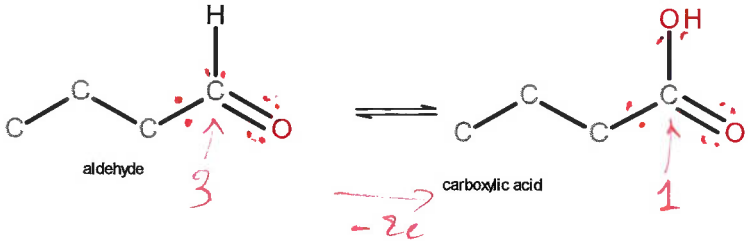
Example: Is the conversion of an aldehyde to a carboxylic acid a redox reaction?

Method A:



Method B:

oxidation

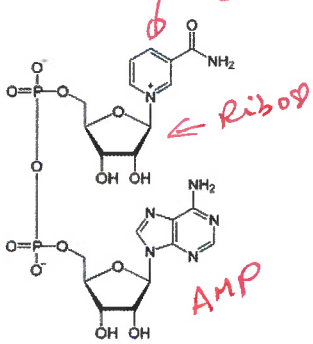


Not all 2e redox reactions release the same amount of energy:

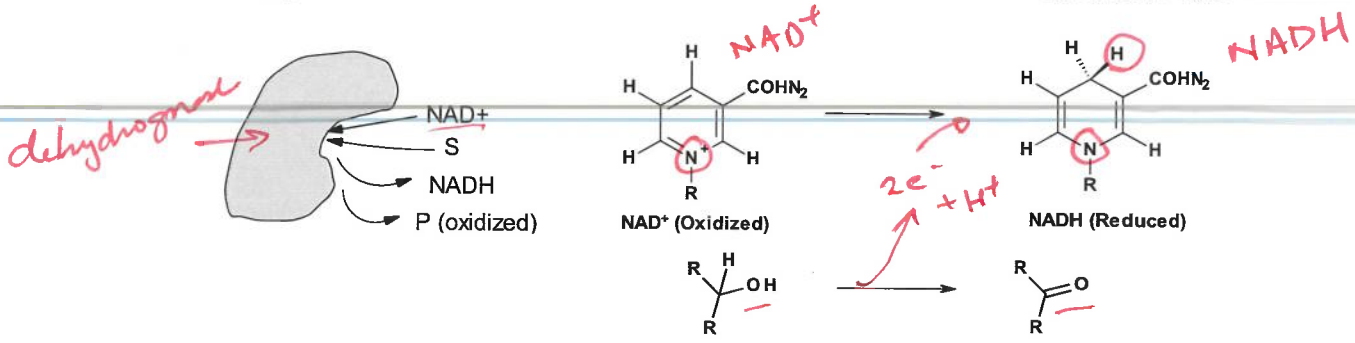
Compound	$\Delta H^\circ_{Combustion}$ (kJ/mol)	$\Delta\Delta H^\circ_{Combustion}$
Ethane (CH_3-CH_3)	-1550	
Ethene (CH_2=CH_2)	-1410	140 (FAD)
Ethanol (H_3C-CH_2-OH)	-1360	50 (not redox)
Acetaldehyde (CH_3-CH=O)	-1160	200 (NAD^+)
Acetic acid (CH_3-COOH)	-870	290 (NAD^+)

Organic Electron Carriers (Redox Couples): Two compounds are widely used in biological reductions and oxidations. These are *nicotinamide adenine dinucleotide* (**NAD**) and *flavin adenine dinucleotide* (**FAD**). If these compounds are involved it's a good bet that a 2-electron oxidation/reduction has occurred.

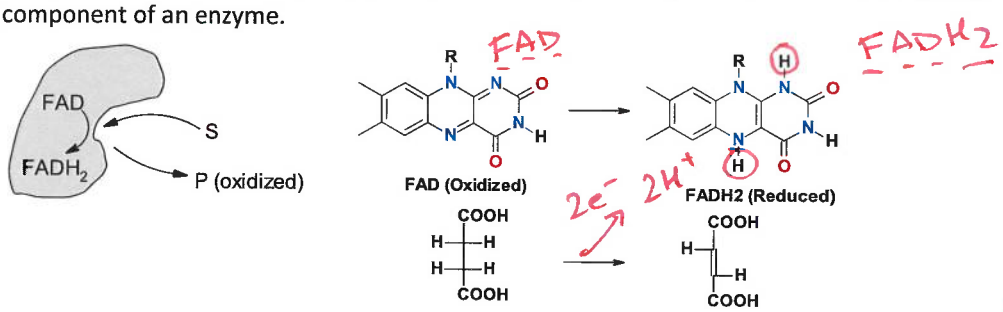
Nicotinamide (electron carrier)

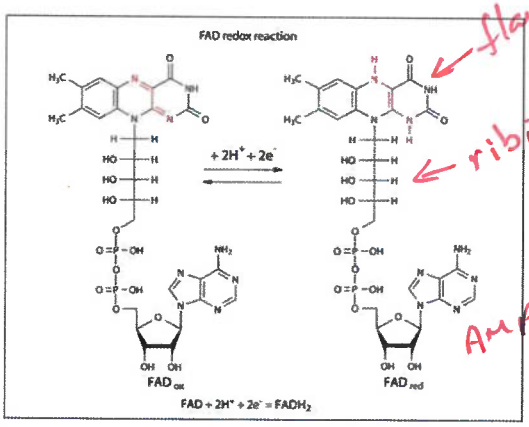


- NAD^+ is loosely bound to enzymes and can thus be considered a true substrate. Usually, two electrons are transferred and one proton.



- FAD is tightly bound to enzymes and is thus considered a **cofactor**, i.e. an essential non-amino acid component of an enzyme.





Standard and Gibbs Free Energy:

ΔG°, the standard energy, is the energy released when one mole of reactants are converted to one mole of products.

$$\mu_B^o - \mu_A^o = \Delta G^o = -RT \ln K_{EQ} = -RT \ln \frac{[B_{EQ}]}{[A_{EQ}]}.$$

It is defined by the **equilibrium position** of the reaction and it depends on the difference in the **intrinsic** energies of the two compounds:

μ_A° = chemical energy of pure compound A

μ_B° = chemical energy of pure compound B

The intrinsic energy is related to the change in the electronic configuration by the reaction. The electronic configuration is related to the standard chemical potential, μ°.

ΔG° is also defined as the energy required to convert 1 mole of A to one mole of B.

In metabolism we are interested in determining how much energy can be released when the system goes from its current, usually non-equilibrium, position to its equilibrium position.

The Gibbs free energy, ΔG, is used to describe non-equilibrium conditions. It is the difference between the **chemical potential** of each compound (μ). For the reaction A ↔B:

$$\Delta G = \mu_B - \mu_A = (\mu_B^o + RT \ln[B]) - (\mu_A^o + RT \ln[A])$$
$$= (\mu_B^o - \mu_A^o) + RT \ln[B] - RT \ln[A]$$
$$= \Delta G^o + RT \ln \frac{[B]}{[A]}$$

STANDARD : ΔG°

$A \rightleftharpoons B$, ΔG°

$\Delta G^\circ = \mu^\circ_B - \mu^\circ_A$ diff in electronic structure.

mole A → mole B ΔG°

$\Delta G^\circ = -RT \ln K_{eq}$ energy required or released

$\mu_A = \mu_A^o + RT \ln[A]$ chem pot, entropy, standard energy

The *RT ln[X]* term accounts for the entropy of mixing. At 1 M (standard state) ln1=0.

Gibbs free energy

entropy change

electronic change

2. Electrons (Redox Chemistry)

An example of a redox reaction involving metals: $Fe^{3+} + Cu^{+} \leftrightarrow Fe^{2+} + Cu^{2+}$

This reaction can be broken down into two balanced half reactions:

$Fe^{3+} + e^{-} \leftrightarrow Fe^{2+}$ $\quad$ $Cu^{+} \leftrightarrow Cu^{2+} + e^{-}$

The iron is reduced from the 3^+ state to the 2^+ state while the copper is oxidized from the 1^+ state to the 2^+ state.

In biological oxidations and reductions the electrons are often carried by protons (i.e. hydrogen atom). A general rule for oxidation-reduction are:

Loss of electrons or hydrogen atom ($H^+ + e^-$) = oxidation

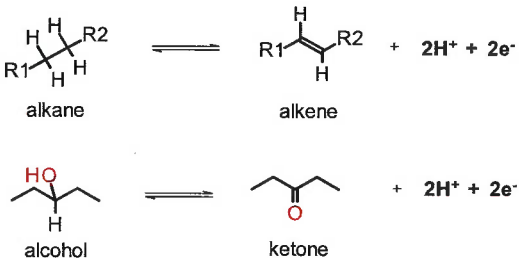
Gain of electrons or hydrogen atom = reduction

There are several common acronyms to help you remember the above, here are two:

LEO GER - lose electrons oxidation, gain electron reduction.

OIL RIG - oxidation involves loss, reduction involves gain.

In the case of biological systems, the redox state of an organic molecule may be difficult to discern. The following shows the oxidation (loss of hydrogen atoms) of two functional groups. Both of these reactions are oxidations since electrons were removed from the reactant, and both are 2 electron oxidations.



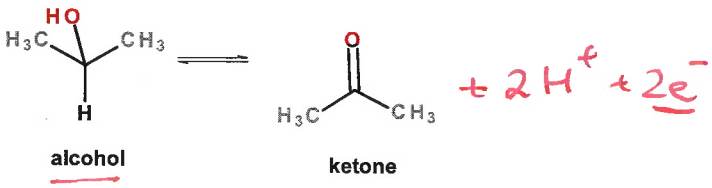
Balancing organic redox reactions.

Method A – Reaction/Product Balancing:

i) If oxygen is needed to balance the reaction, use H_2O.

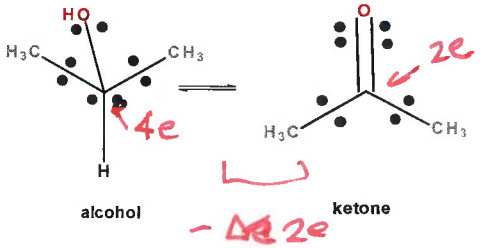
ii) Use H^+, or $H^+ + e^-$, or e^- to balance hydrogen atoms and/or charge.

A redox reaction has occurred if electrons appear on one side of the reaction. If they appear on the right side (products) then it is an oxidation – electrons were released from the reactants.



Method B – Determine Oxidation State of Individual Carbons: Count the number of electrons that are associated with carbon for each bond.

- If the other atom is less electronegative (e.g. H) carbon owns both electrons
- If the other atom is more electronegative (e.g. O) carbon owns none.
- If two carbons are involved, the electrons are equally shared.
- If the carbon has fewer electrons it has been oxidized.
- If the carbon gains electrons, it has been reduced,

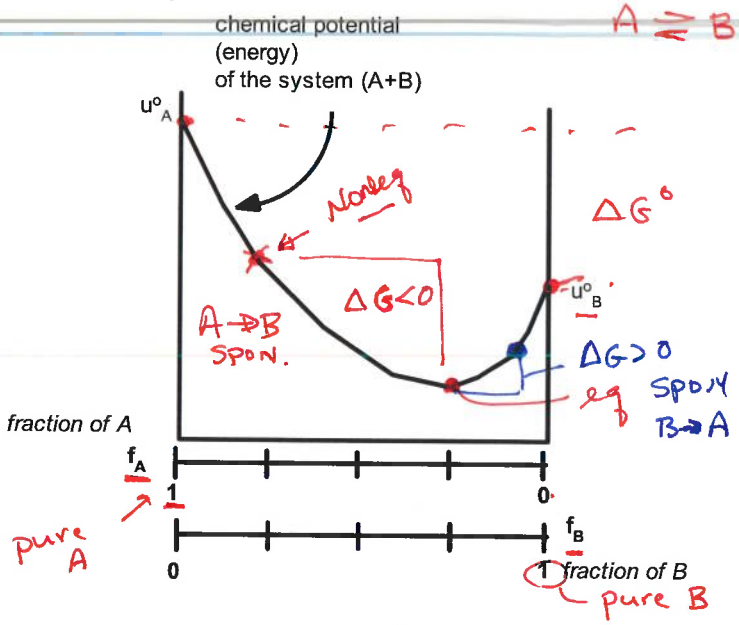


1. |ΔG| is the maximum energy released by the system as it approaches equilibrium. This energy can be captured to do work (or synthesize compounds).

The diagram on the right represents the chemical potential of a mixture of (A) and (B), as a function of their concentration. The lowest point is the equilibrium point (f_A=0.25, f_B=0.75).

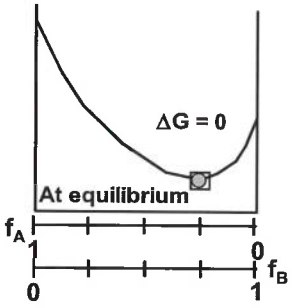
The difference in energy between the starting and ending position is |ΔG|.

Reflection: Is energy released if the system starts at equilibrium and ends at equilibrium?



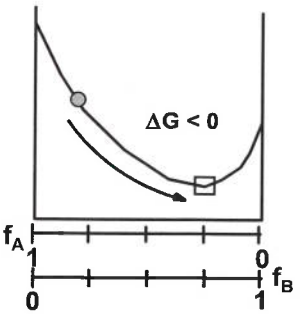
2. The sign of ΔG tells you the spontaneous direction of the reaction.

At equilibrium ΔG = 0. The difference in the chemical potentials of A and B is zero, no energy is released converting A to B, or B to A because there is no change in the concentration of A or B.



$$\Delta G = (\mu_o^B + RT\ln[B]_{EQ}) - (\mu_0^A + RT\ln[A]_{EQ})$$
$$= (\mu_o^B - \mu_0^A) + RT\ln[B]_{EQ} - RT\ln[A]_{EQ}$$
$$= \Delta G^0 + RT\ln\frac{[B_{EQ}]}{[A_{EQ}]}$$
$$= -RT\ln\frac{[B_{EQ}]}{[A_{EQ}]} + RT\ln\frac{[B_{EQ}]}{[A_{EQ}]} = 0$$

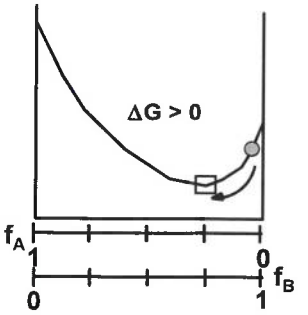
When [A] > [A_{EQ}] then ΔG < 0 and A→B is spontaneous. Since A is flowing to B, the chemical potential of A must be higher than B, so ΔG=μ_B-μ_A < 0.



$$\Delta G = (\mu_o^B + RT\ln\{[B]_{EQ} - \delta\}) - (\mu_0^A + RT\ln\{[A]_{EQ} + \delta\})$$
$$= (\mu_o^B - \mu_0^A) + RT\ln\{[B]_{EQ} - \delta\} - RT\ln\{[A]_{EQ} + \delta\}$$
$$= \Delta G^0 + RT\ln\frac{[B_{EQ}] - \delta}{[A_{EQ}] + \delta} = -RT\ln\frac{[B_{EQ}]}{[A_{EQ}]} + RT\ln\frac{[B_{EQ}] - \delta}{[A_{EQ}] + \delta}$$
$$= RT\ln\frac{[B]_{EQ} - \delta}{[B]_{EQ}} + RT\ln\frac{[A]_{EQ}}{[A]_{EQ} + \delta}$$

Both *ln* terms are <1, therefore ΔG is <0.

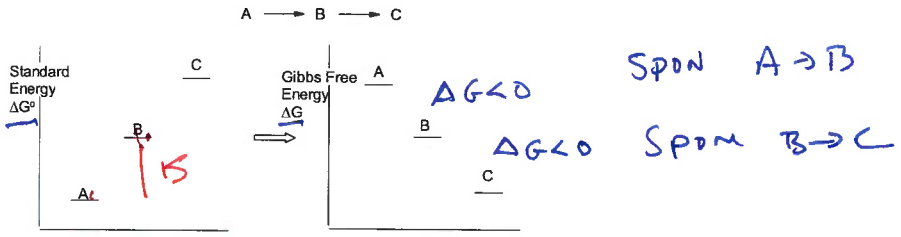
When [B] > [B_{EQ}] then ΔG > 0 and B→A is spontaneous. Since B is flowing to A, the chemical potential of B must be higher than A, so ΔG=μ_B-μ_A > 0.



$$\Delta G = (\mu_o^B + RT\ln\{[B]_{EQ} + \delta\}) - (\mu_0^A + RT\ln\{[A]_{EQ} - \delta\})$$
$$= (\mu_o^B - \mu_0^A) + RT\ln\{[B]_{EQ} + \delta\} - RT\ln\{[A]_{EQ} - \delta\}$$
$$= \Delta G^0 + RT\ln\frac{[B_{EQ}] + \delta}{[A_{EQ}] - \delta} = -RT\ln\frac{[B_{EQ}]}{[A_{EQ}]} + RT\ln\frac{[B_{EQ}] + \delta}{[A_{EQ}] - \delta}$$
$$= RT\ln\frac{[B]_{EQ} + \delta}{[B]_{EQ}} + RT\ln\frac{[A]_{EQ}}{[A]_{EQ} - \delta}$$

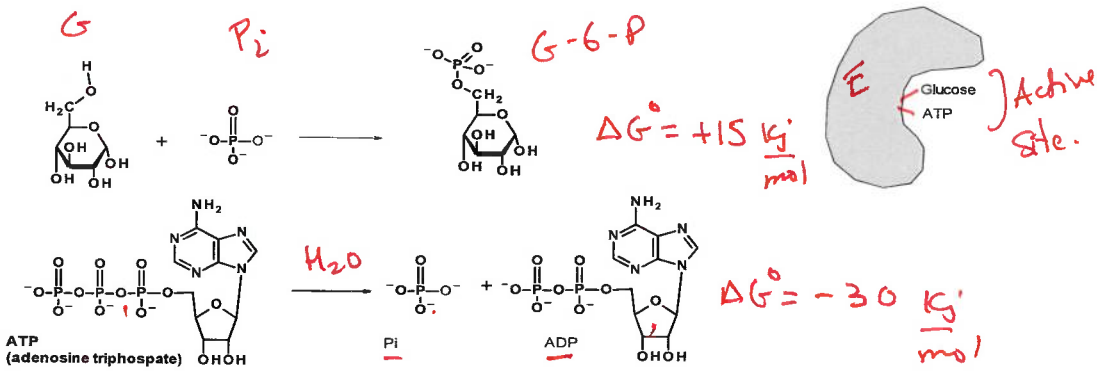
Both *ln* terms are >1, therefore ΔG is >0

4. Flux and Coupling of Reactions: A key feature of all biochemical pathways is that there is a constant flux of material through the pathway. To insure a constant flux through the pathway it is necessary to insure that the Gibbs energy of the products are lower in energy than the substrates, such that the natural flow is always from substrates to products *in each step of the pathway*.

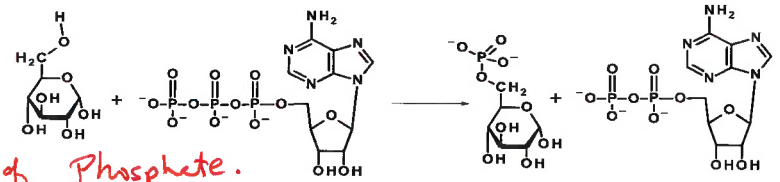


(1) **Direct Coupling:** Many steps in biochemical pathways involve reactions that are extremely unfavorable, i.e. a large positive ΔG°. This energy barrier reduced by the **direct coupling** of the unfavorable reaction to a favorable one, with both reactions occurring at the same time **in the active** site of one enzyme. The energetics of each reaction are most easily seen by considering the half-reactions. For example, the first reaction in glycolysis, catalyzed by the enzyme hexose kinase, converts glucose to glucose-6-phosphate.

The high energy of ATP is used to drive this unfavorable reaction by direct coupling. *The phosphate group is transferred directly from ATP to glucose. Hydrolysis of the phosphate would release the energy as heat which could not be productively used to phosphorylate glucose.*



Actual Reaction
direct transfer of Phosphate.



(2) **Indirect Coupling:** By lowering the concentration of the product below its equilibrium position, a reaction can be made spontaneous; the ΔG becomes < 0. This generally implies that a reaction further down the pathway has a large negative ΔG°, such that the last compound in the pathway is kept below equilibrium concentration.

$$\Delta G = \Delta G^0 + RT\ln\frac{[B]}{[A]}$$
$$= +5.75 + RT\ln\frac{10^{-5}}{10^{-3}}$$
$$= +5.75 + 2.5\ln 10^{-2}$$
$$= +5.75 - 11.51$$
$$= -5.76$$

$\Delta G = \Delta G^\circ + RT\ln\frac{B}{A}$ — ΔG°: direct coupling; $RT\ln\frac{B}{A}$: indirect coupling

Example of Indirect Coupling: For the pathway A→B

- Concentration of [A] is 10^{-3} M under normal metabolic conditions. This would give an *equilibrium* concentration of $[B]_{eq} = 10^{-4}$M (i.e. [A]>[B], at equilibrium).
- Standard free energy, ΔG°, of the first reaction (A→B) is +5.75 kJ/mol.

***Reflection**: What is the direction of the reaction if the concentration of [B] is 10^{-5} M? Why?*