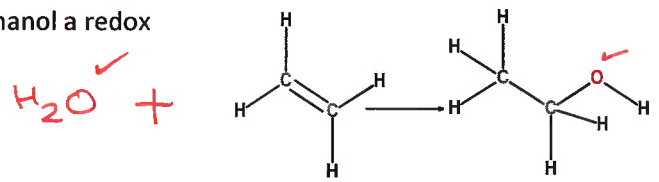


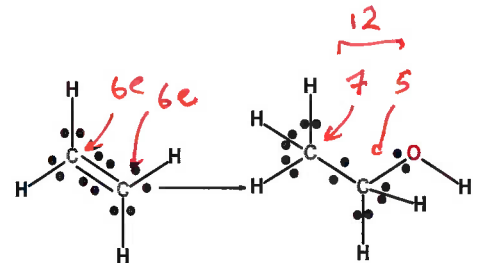
## Lecture 28: Organic Redox Reactions, Non-Equilibrium Thermodynamics & Pathway Flux

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

Method A:

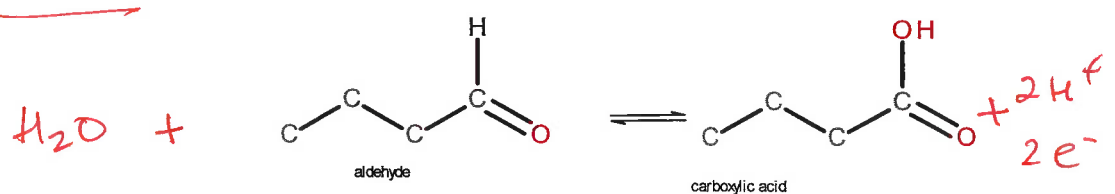


Method B:

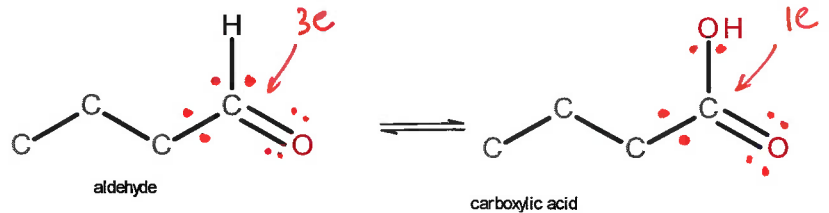


**Example:** Is the conversion of an aldehyde to a carboxylic acid a redox reaction?

Method A:



Method B:



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

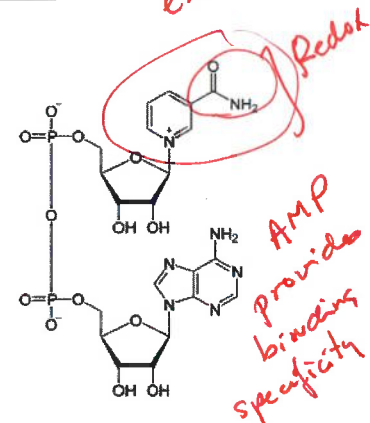
Compound	$\Delta H^\circ$ Combustion (kJ/mol)	$\Delta\Delta H^\circ$ Combustion
Ethane (CH <sub>3</sub> -CH <sub>3</sub> )	-1550	
Ethene (CH <sub>2</sub> =CH <sub>2</sub> )	-1410	140 (FAD)
Ethanol (H <sub>3</sub> C-CH <sub>2</sub> -OH)	-1360	50 (not redox)
Acetaldehyde (CH <sub>3</sub> -CH=O)	-1160	200 (NAD <sup>+</sup> )
Acetic acid (CH <sub>3</sub> -COOH)	-870	290 (NAD <sup>+</sup> )

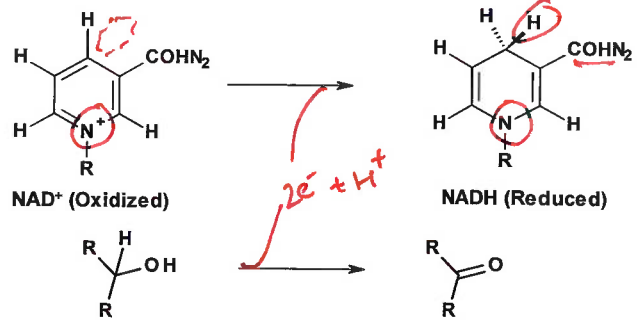
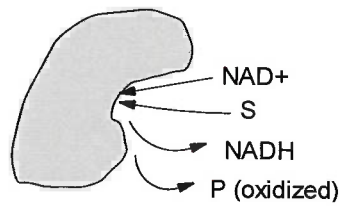
Mo oxidation

oxidations release large amounts of E. - diff levels of energy release

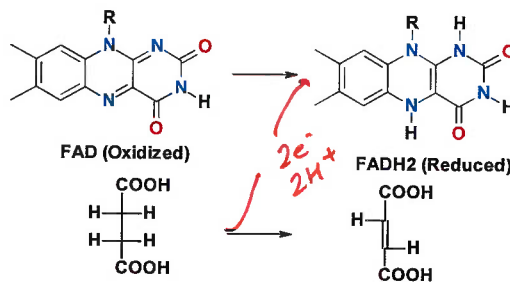
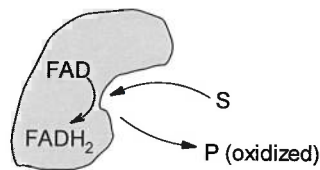
**Organic Electron Carriers (Redox Couples):** Two compounds are widely used in biological reductions and oxidations. These are *nicotinamide adenine dinucleotide (NAD)* and *flavin adenine dinucleotide (FAD)*. If these compounds are involved it's a good bet that a 2 electron oxidation/reduction has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

- NAD<sup>+</sup> 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:**

$\Delta G^\circ$ , the standard energy, is the energy released when one mole of reactants are converted to one mole of products.

$$\mu_B^\circ - \mu_A^\circ = \Delta G^\circ = -RT \ln K_{EQ} = -RT \ln \frac{[B]_{EQ}}{[A]_{EQ}}$$

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

$$\mu_A^\circ = \text{chemical energy of pure compound A}$$

$$\mu_B^\circ = \text{chemical energy of pure compound B}$$

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,  $\mu^\circ$ .

$\Delta G^\circ$  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, possibly non-equilibrium, position to its equilibrium position.

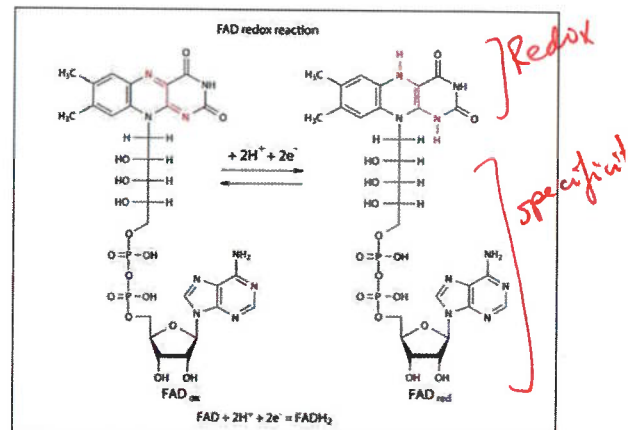
The Gibbs free energy,  $\Delta G$ , is used to describe non-equilibrium conditions. It is the difference between the **chemical potential** of each compound ( $\mu$ ). For the reaction  $A \leftrightarrow B$ :

$$\Delta G = \mu_B - \mu_A = (\mu_B^\circ + RT \ln[B]) - (\mu_A^\circ + RT \ln[A])$$

$$= (\mu_B^\circ - \mu_A^\circ) + RT \ln[B] - RT \ln[A]$$

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

Handwritten red notes: ← any conc of [A] & [B]



1 mole A → 1 mole B  
energy =  $\Delta G^\circ$

$$\mu_A = \mu_A^\circ + RT \ln[A]$$

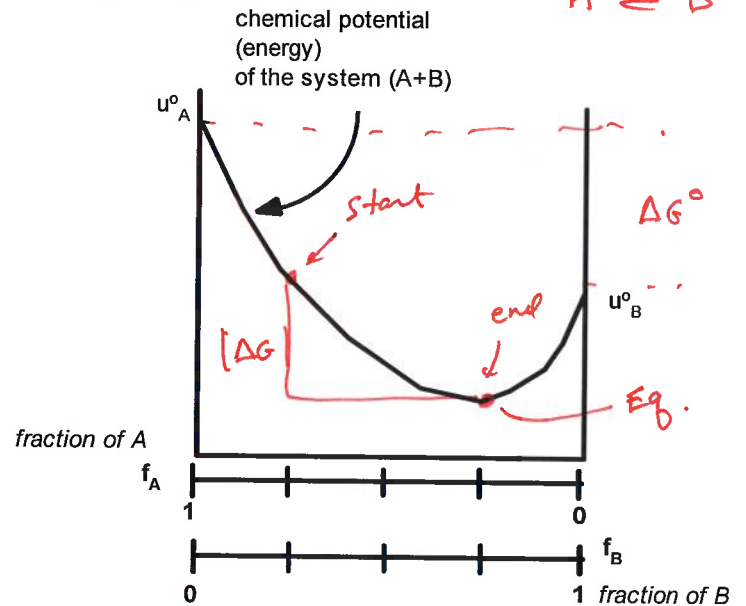
The  $RT \ln[X]$  term accounts for the entropy of mixing. At 1 M (standard state)  $\ln 1 = 0$ .

**1.  $|\Delta G|$  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  $|\Delta G|$ .

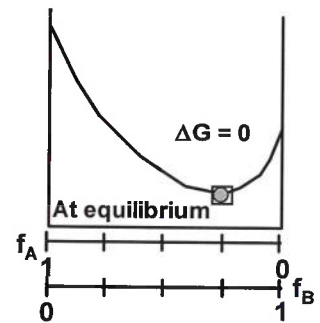
**Reflection:** Is energy released if the system starts at equilibrium and ends at equilibrium?



**2. The sign of  $\Delta G$  tells you the spontaneous direction of the reaction.**

**At equilibrium  $\Delta G = 0$ .** 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.

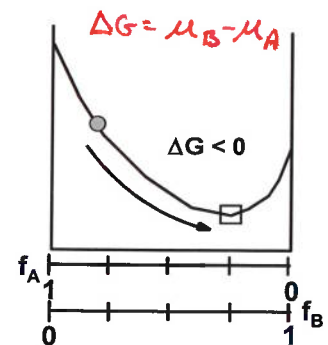
$$\begin{aligned} \Delta G &= (\mu_o^B + RT \ln[B]_{EQ}) - (\mu_o^A + RT \ln[A]_{EQ}) \\ &= (\mu_o^B - \mu_o^A) + RT \ln[B]_{EQ} - RT \ln[A]_{EQ} \\ &= \Delta G^0 + RT \ln \frac{[B]_{EQ}}{[A]_{EQ}} \\ &= -RT \ln \frac{[B]_{EQ}}{[A]_{EQ}} + RT \ln \frac{[B]_{EQ}}{[A]_{EQ}} = 0 \end{aligned}$$



**When  $[A] > [A_{eq}]$  then  $\Delta G < 0$  and  $A \rightarrow B$  is spontaneous.** Since A is flowing to B, the chemical potential of A must be higher than B, so  $\Delta G = \mu_B - \mu_A < 0$ .

$$\begin{aligned} \Delta G &= (\mu_o^B + RT \ln\{[B]_{EQ} - \delta\}) - (\mu_o^A + RT \ln\{[A]_{EQ} + \delta\}) \\ &= (\mu_o^B - \mu_o^A) + RT \ln\{[B]_{EQ} - \delta\} - RT \ln\{[A]_{EQ} + \delta\} \\ &= \Delta G^0 + RT \ln \frac{[B]_{EQ} - \delta}{[A]_{EQ} + \delta} = -RT \ln \frac{[B]_{EQ}}{[A]_{EQ}} + RT \ln \frac{[B]_{EQ} - \delta}{[A]_{EQ} + \delta} \\ &= RT \ln \frac{[B]_{EQ} - \delta}{[B]_{EQ}} + RT \ln \frac{[A]_{EQ}}{[A]_{EQ} + \delta} \end{aligned}$$

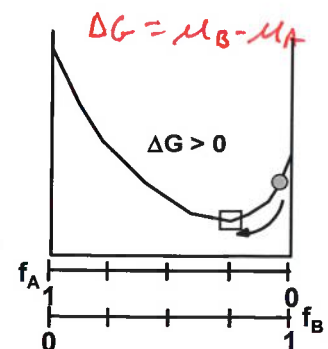
Both  $\ln$  terms are  $< 1$ , therefore  $\Delta G$  is  $< 0$ .



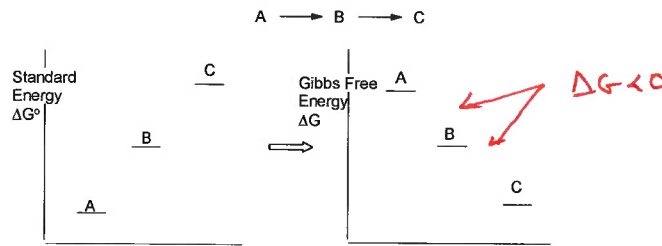
**When  $[B] > [B_{eq}]$  then  $\Delta G > 0$  and  $B \rightarrow A$  is spontaneous.** Since B is flowing to A, the chemical potential of B must be higher than A, so  $\Delta G = \mu_B - \mu_A > 0$ .

$$\begin{aligned} \Delta G &= (\mu_o^B + RT \ln\{[B]_{EQ} + \delta\}) - (\mu_o^A + RT \ln\{[A]_{EQ} - \delta\}) \\ &= (\mu_o^B - \mu_o^A) + RT \ln\{[B]_{EQ} + \delta\} - RT \ln\{[A]_{EQ} - \delta\} \\ &= \Delta G^0 + RT \ln \frac{[B]_{EQ} + \delta}{[A]_{EQ} - \delta} = -RT \ln \frac{[B]_{EQ}}{[A]_{EQ}} + RT \ln \frac{[B]_{EQ} + \delta}{[A]_{EQ} - \delta} \\ &= RT \ln \frac{[B]_{EQ} + \delta}{[B]_{EQ}} + RT \ln \frac{[A]_{EQ}}{[A]_{EQ} - \delta} \end{aligned}$$

Both  $\ln$  terms are  $> 1$ , therefore  $\Delta G$  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*.

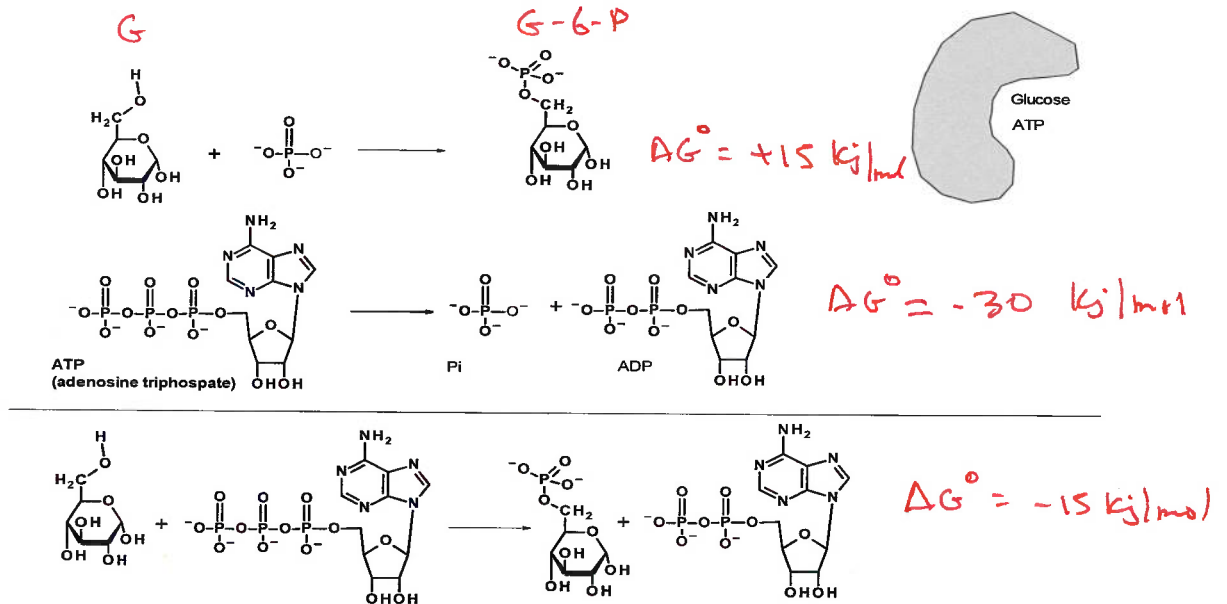


$$\Delta G = \Delta G^\circ + RT \ln \frac{[B]}{[A]}$$

direct coupling      indirect coupling

**Direct Coupling:** Many steps in biochemical pathways involve reactions that are extremely unfavorable, i.e. a large positive  $\Delta G^\circ$ . 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.*



**Indirect Coupling:** By lowering the concentration of the product below its equilibrium position, a reaction can be made spontaneous; the  $\Delta G$  becomes  $< 0$ . This generally implies that a reaction further down the pathway has a large negative  $\Delta G^\circ$ , such that the last compound in the pathway is kept below equilibrium concentration.

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

**Example of Indirect Coupling:** For the pathway  $A \rightarrow B$

- 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,  $\Delta G^\circ$ , of the first reaction ( $A \rightarrow B$ ) is  $+5.75$  kJ/mol.

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



Fav. convant  $B \rightarrow C$   
 $\therefore [B] \ll [B]_{eq}$