

Energy and human life

PRINCIPLES OF BIOENERGETICS

1- Bioenergetics and Thermodynamics

Chemical energy

- Carbohydrates
- Fats
- Others

Chemical waste

- Carbon dioxide
- Water

Heat

ATP

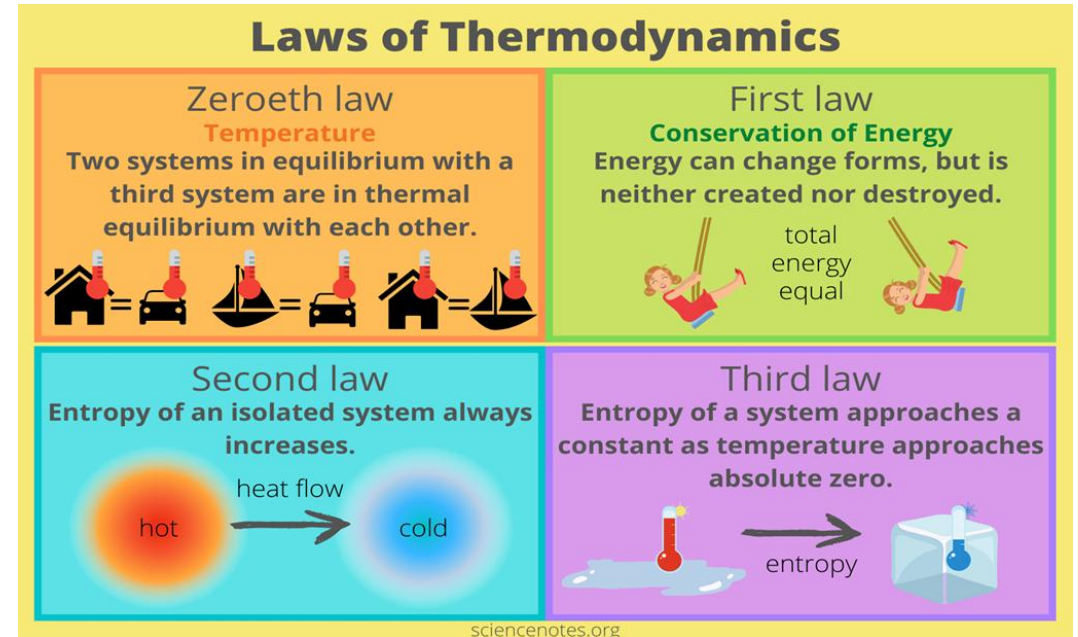
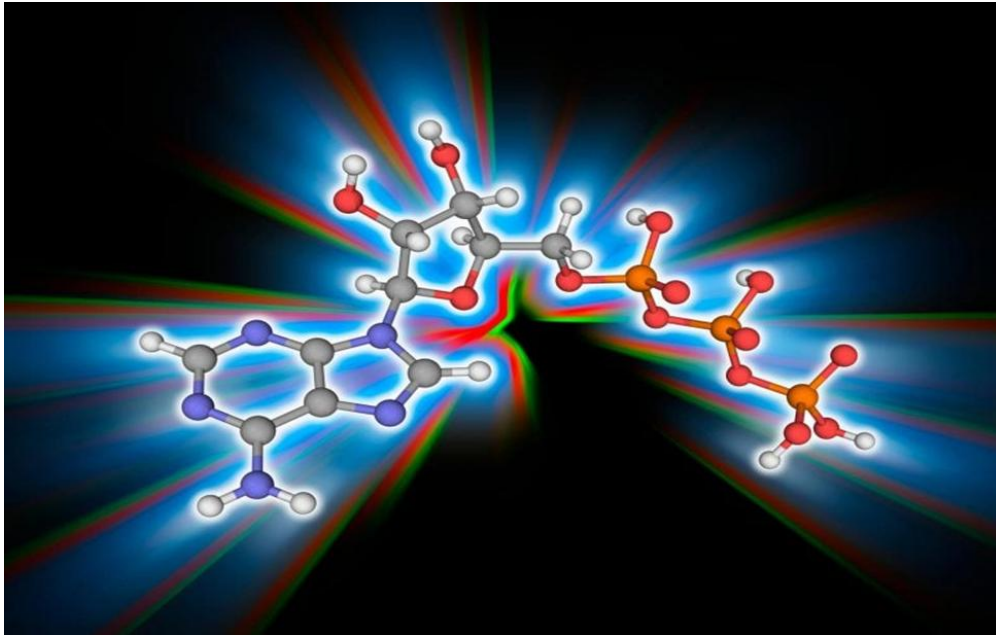
- body's "energy currency"

DEFINITION

- The quantitative study of the energy transductions that occur in living cells and of the nature and function of the chemical processes underlying these transductions.



LECTURE 1: THE LAWS OF ENERGY AND CELLULAR CURRENCY



THE CLINICAL STAGE: A CASE OF LETHARGY

- **Clinical Presentation**
 - A 2-month-old infant presents with lethargy, poor feeding, and hypoglycemia indicating a metabolic crisis.
- **Laboratory Findings**
 - Initial labs reveal low blood glucose and mild metabolic acidosis, signaling disrupted metabolism.
- **Biochemical Diagnostic Question**
 - The clinical challenge is differentiating fuel deficiency from impaired energy utilization in the patient.
- **Importance of Bioenergetics**
 - Understanding bioenergetics is critical for diagnosing and managing metabolic crises in pediatric patients.



BIOLOGICAL ENERGY TRANSFORMATIONS OBEY THE LAWS OF THERMODYNAMICS



The **1st** law
(**conservation of energy**): for any change, the total amount of energy in the universe remains constant;



The **2nd** law of thermodynamics: the universe always tends toward increasing disorder (or); in all natural processes, the **entropy of the universe increases**.



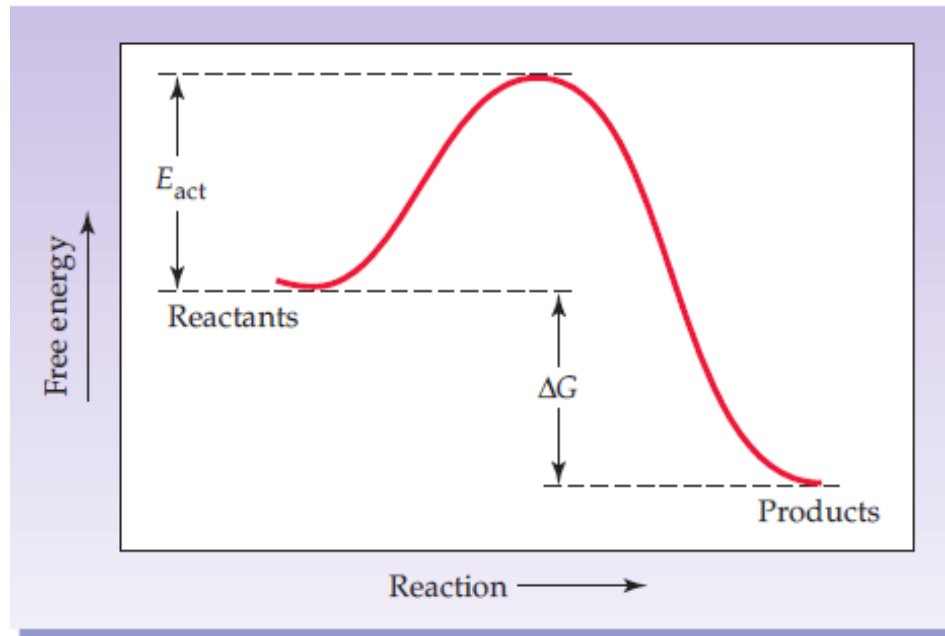
Signs for spontaneous systems...

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

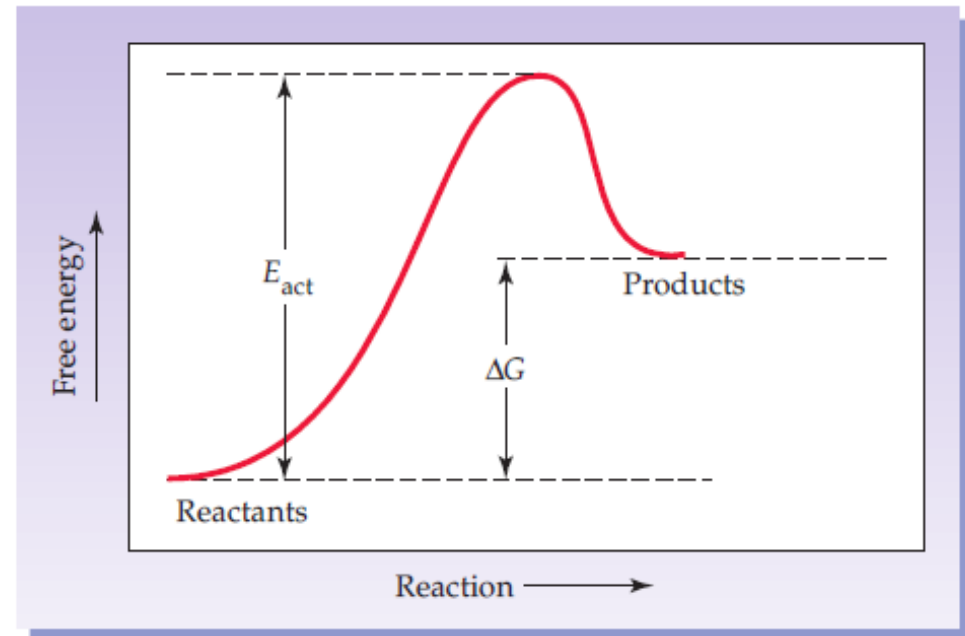


WHY DO CHEMICAL REACTIONS OCCUR?

- The concept of activation energy
- ΔG and ΔG^0



(a) An exergonic reaction



(b) An endergonic reaction



ΔG IS A STATE FUNCTION?!

- ΔG is not affected by the mechanism of the reaction



$$\Delta G_{A \rightarrow B} = \cancel{GB} - GA$$

$$\Delta G_{B \rightarrow C} = \cancel{GC} - \cancel{GB}$$

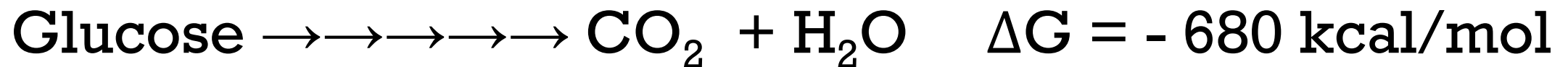
$$GC - GA = \Delta G_{A \rightarrow C}$$



- Combustion of glucose in calorimeter



In the cell



ΔG IS AFFECTED BY CONCENTRATION



HOW ΔG AND ΔG^0 RELATE?

- Concentrations of reactants and products = 1 mole/L

- $\Delta G = \Delta G^0 + RT \ln \frac{[\text{Products}]}{[\text{Reactants}]}$

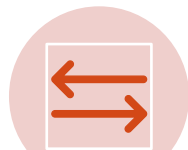
- $\Delta G = \Delta G^0 + RT \ 2.3 \log \frac{[\text{Products}]}{[\text{Reactants}]}$



THE STANDARD FREE-ENERGY CHANGE IS DIRECTLY RELATED TO THE EQUILIBRIUM CONSTANT (K_{eq})



Equilibrium is reached at the end!



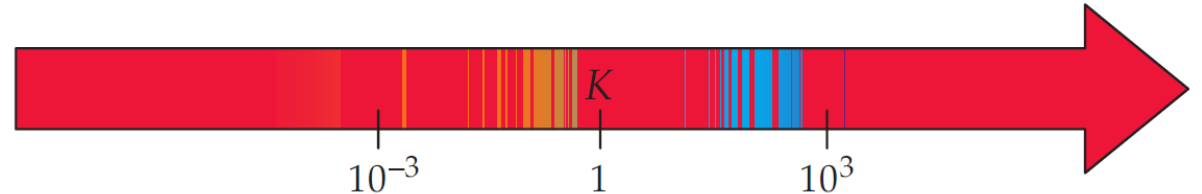
At equilibrium: concentrations are fixed; rates are exactly equal



The concentrations define the equilibrium constant



K very small



K very large

Reaction goes hardly at all

More reactants than products present

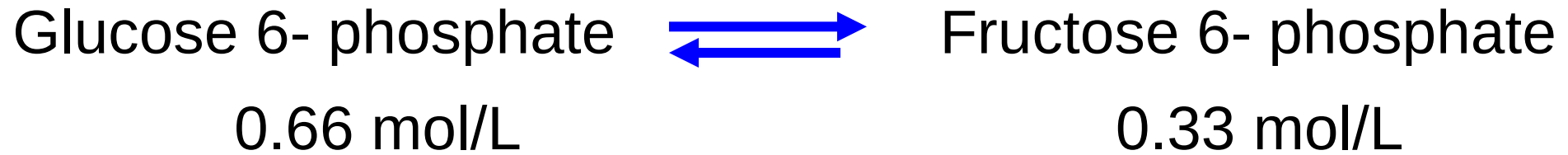
More products than reactants present

Reaction goes to completion

$$K_{eq} = \frac{[C]^c [D]^d}{[A]^a [B]^b}$$

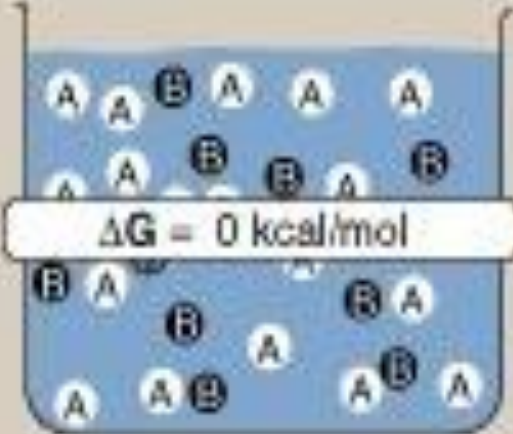
$$\Delta G = \Delta G^\circ + RT \ln \frac{[\text{Products}]}{[\text{Reactants}]}$$





C Equilibrium conditions

(A) = 0.66 mol/L (B) = 0.33 mol/L



$\Delta G = 0 \text{ kcal/mol}$

$(A) \rightleftharpoons (B)$

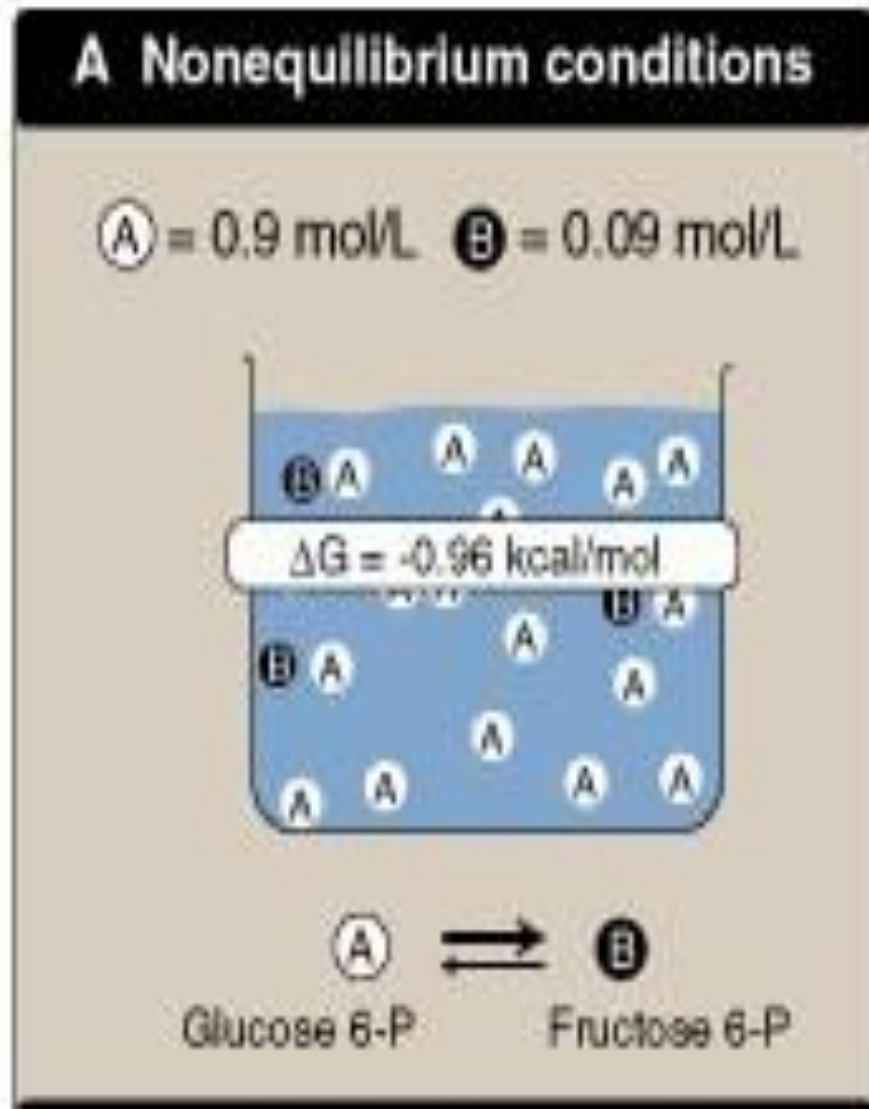
$K_{eq} = \frac{[\text{Fructose 6-phosphate}]}{[\text{Glucose 6-phosphate}]} = 0.504$

$$\Delta G = \Delta G^{\circ} + RT \ln \frac{0.33}{0.66}$$

$$\Delta G^{\circ} = + 0.4 \text{ kcal/mol}$$



Glucose 6- phosphate $\rightleftharpoons$ Fructose 6- phosphate



$$\Delta G^{\circ} = + 0.4 \text{ kcal/mol}$$

$$\Delta G = \Delta G^{\circ} + RT \ln 0.09/0.9$$

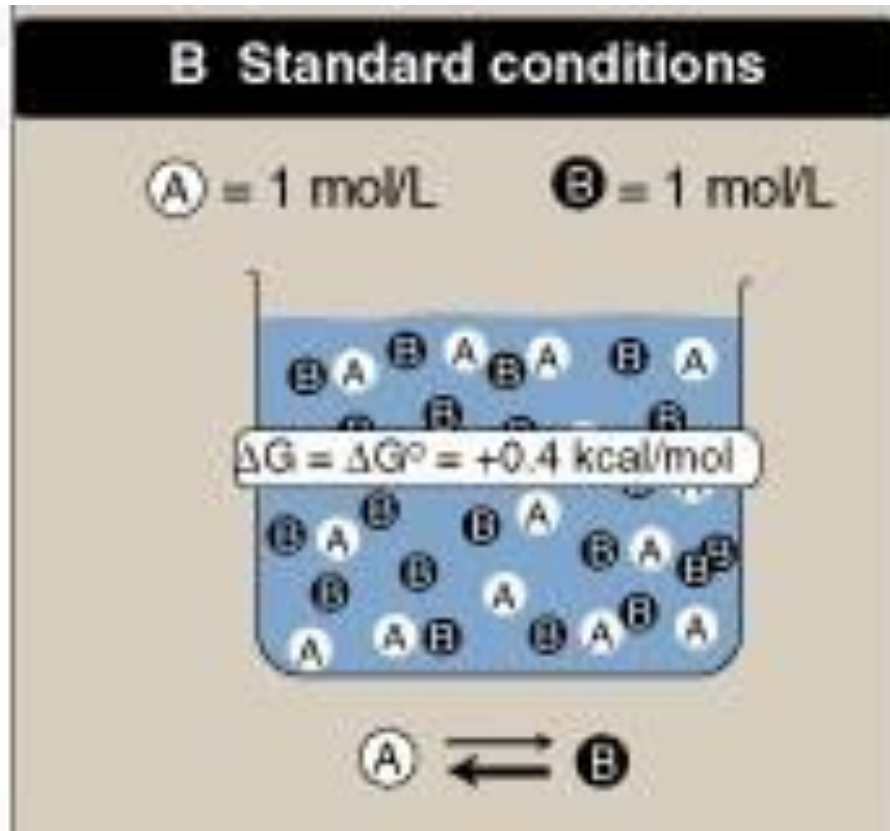
$$\Delta G = - 0.96$$



Glucose 6- phosphate
1 mol/L



Fructose 6- phosphate
1 mol/L



$$\Delta G = \Delta G^\circ + RT \, 2.3 \log 1/1$$

$$\Delta G = \Delta G^\circ$$



ΔG & K_{eq}

For a reaction $A + B \leftrightarrow C + D$

$$\Delta G = \Delta G^{\circ'} + RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

- At equilibrium, $\Delta G=0$
- Can a reaction has a +ve ΔG° & still be favorable?

K'_{eq}	$\Delta G^{\circ'}$ kJ/mol	Starting with 1 M reactants & products, the reaction:
10^4	- 23	proceeds forward (spontaneous)
10^2	- 11	proceeds forward (spontaneous)
$10^0 = 1$	0	is at equilibrium
10^{-2}	+ 11	reverses to form “reactants”
10^{-4}	+ 23	reverses to form “reactants”

$$\Delta G = \Delta G^{\circ'} + RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

$$0 = \Delta G^{\circ'} + RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

$$\Delta G^{\circ'} = - RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

$$\text{defining } K'_{eq} = \left(\frac{[C][D]}{[A][B]} \right)$$

$$\Delta G^{\circ'} = - RT \ln K'_{eq}$$

ΔG° AND K_{eq}

1	0

How much change in ΔG compared to changes in K_{eq}

If $K_{eq} = 1$, then $\Delta G^\circ = 0$

If $K_{eq} > 1$, then $\Delta G^\circ < 0$

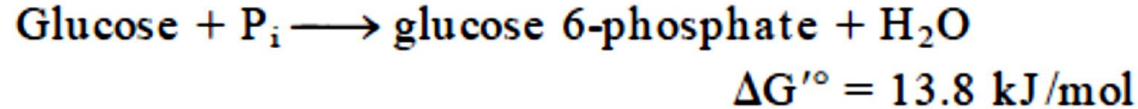
If $K_{eq} < 1$, then $\Delta G^\circ > 0$

$$\Delta G = \Delta G^\circ + RT \ln \frac{[\text{Products}]}{[\text{Reactants}]}$$

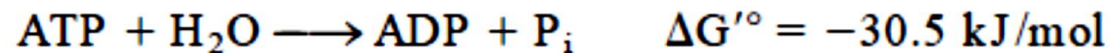


ΔG & K_{eq}

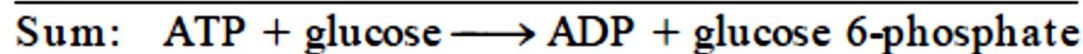
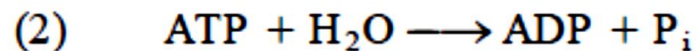
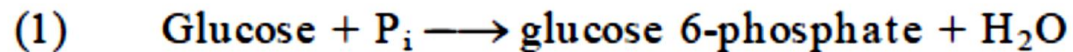
- ΔG is additive for multiple subsequent reactions
- K_{eq} is multiplicative for subsequent reactions



$$K'_{eq_1} = \frac{[\text{glucose 6-phosphate}]}{[\text{glucose}][P_i]} = 3.9 \times 10^{-3} \text{ M}^{-1}$$



$$K'_{eq_2} = \frac{[\text{ADP}][P_i]}{[\text{ATP}]} = 2.0 \times 10^5 \text{ M}$$



$$\Delta G'^{\circ} = 13.8 \text{ kJ/mol} + (-30.5 \text{ kJ/mol}) = -16.7 \text{ kJ/mol}$$

$$K'_{eq_3} = \frac{[\text{glucose 6-phosphate}][\text{ADP}][P_i]}{[\text{glucose}][P_i][\text{ATP}]}$$
$$= (K'_{eq_1})(K'_{eq_2}) = (3.9 \times 10^{-3} \text{ M}^{-1})(2.0 \times 10^5 \text{ M})$$
$$= 7.8 \times 10^2$$



THE EFFECT OF CHANGING CONDITIONS ON EQUILIBRIA

- When a stress is applied to a system at equilibrium, the equilibrium shifts to relieve the stress
- Effect of Changes in Concentration
 - What happens if a reactant/product is continuously supplied/ removed?
 - Metabolic reactions sometimes take advantage of this effect
- Effect of Changes in Temperature
 - Endothermic/exothermic are favored by increase/decrease in temperature, respectively.
- Effect of a catalyst on equilibrium

Le Chatelier's Principle

Disturbing a system at dynamic equilibrium shifts the equilibrium in the direction that counteracts the change.

$A + B \rightleftharpoons C + D$

Concentration	Temperature	Pressure
 reactant concentration  favors product formation	 ↑ temperature favors endothermic reaction	 ↑ pressure favors side with fewer molecules
 product concentration  favors reactant formation	 ↓ temperature favors exothermic reaction	 ↓ pressure favors side with more molecules

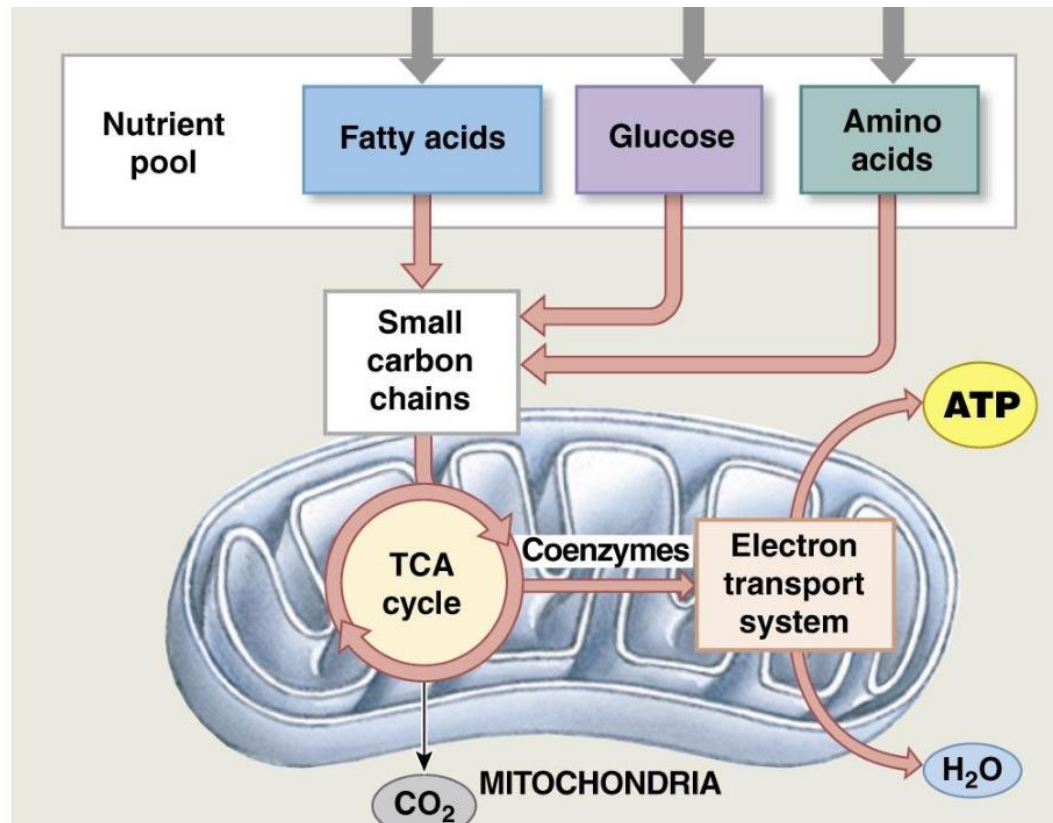
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PRINCIPLES OF BIOENERGETICS

2- Phosphoryl Group Transfers and ATP

THE ENERGY FLOW

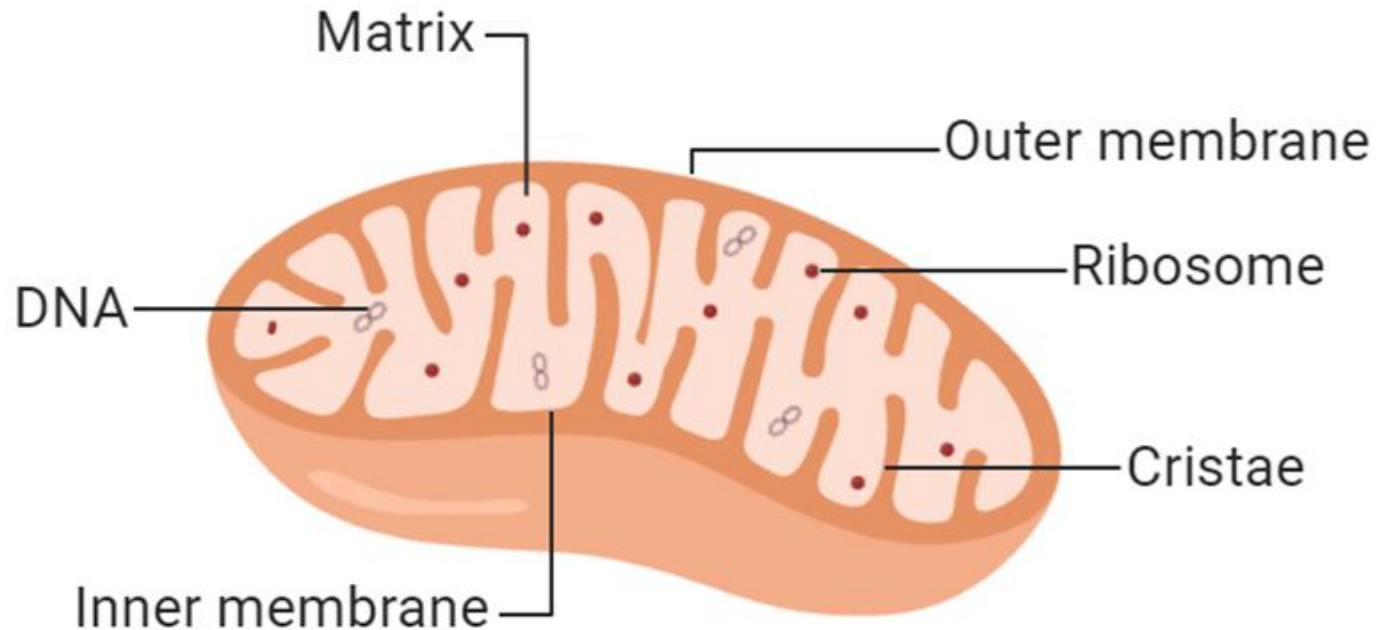


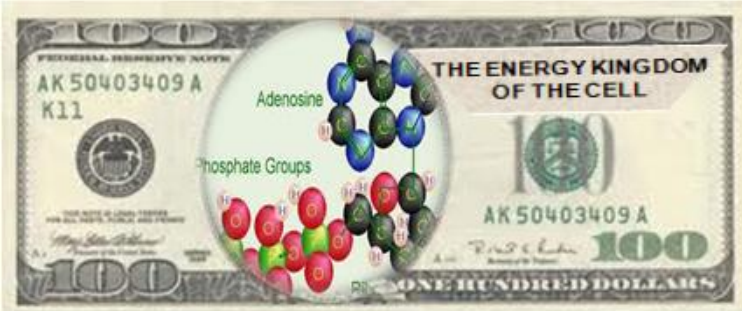
- Ingestion, digestion, & absorption
- Metabolism (Acetyl CoA)
- TCA
- Oxidative phosphorylation



THE ENERGY MACHINERY OF THE CELL

- Prokaryotic cells vs. eukaryotic cells
- The mitochondria (singular, mitochondrion) (90% of the body's energy ATP)
- The number of mitochondria is greatest in eye, brain, heart, & muscle, where the need for energy is greatest
- The ability of mitochondria to reproduce (athletes)
- Maternal inheritance





ATP

- **ATP is the energy currency of the cell**
- **What is a high energy molecule?**
- **Why ATP?**
 - **Has an intermediate energy value, so can be coupled**

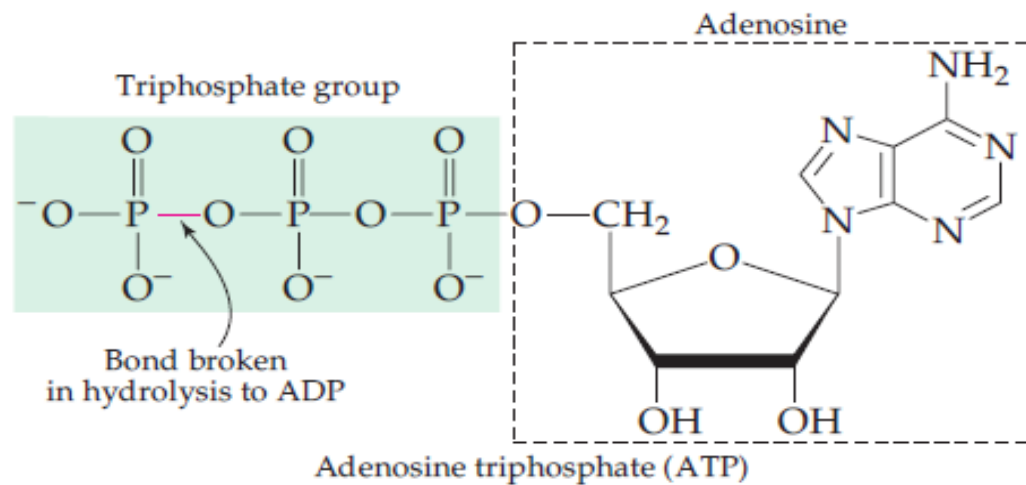
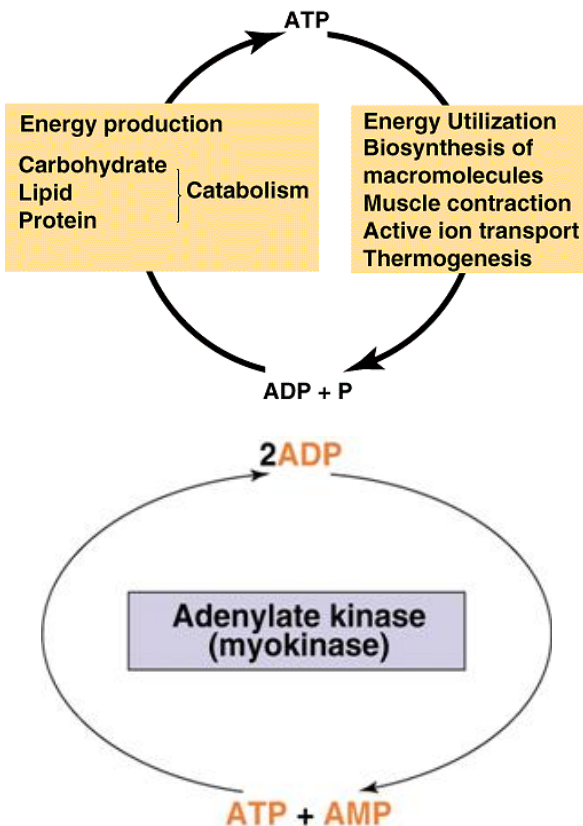


TABLE 13–6 Standard Free Energies of Hydrolysis of Some Phosphorylated Compounds and Acetyl-CoA (a Thioester)

	ΔG°	
	(kJ/mol)	(kcal/mol)
Phosphoenolpyruvate	−61.9	−14.8
1,3-bisphosphoglycerate ($\rightarrow$ 3-phosphoglycerate + P_i)	−49.3	−11.8
Phosphocreatine	−43.0	−10.3
ADP ($\rightarrow$ AMP + P_i)	−32.8	−7.8
ATP ($\rightarrow$ ADP + P_i)	−30.5	−7.3
ATP ($\rightarrow$ AMP + PP_i)	−45.6	−10.9
AMP ($\rightarrow$ adenosine + P_i)	−14.2	−3.4
PP_i ($\rightarrow$ 2 P_i)	−19.2	−4.0
Glucose 1-phosphate	−20.9	−5.0
Fructose 6-phosphate	−15.9	−3.8
Glucose 6-phosphate	−13.8	−3.3
Glycerol 1-phosphate	−9.2	−2.2
Acetyl-CoA	−31.4	−7.5

IS ATP A GOOD LONG-TERM ENERGY STORAGE MOLECULE?

- As food in the cells is gradually oxidized, the released energy is used to re-form the ATP so that the cell always maintains a supply of this essential molecule



Tissue	ATP turnover (mole/day)
Brain	20.4
Heart	11.4
Kidney	17.4
Liver	21.6
Muscle	19.8
Total	90.6



$$90.6 * 551 \text{ (g/mole)} = 49,920 \text{ g ATP}$$

BIOCHEMICAL REACTIONS OR PATHWAYS!

- **Are interdependent**
- **Are subjected to thermodynamics laws**
- **Coordinated by sensitive means of communication**
- **Allosteric enzymes are the predominant regulators**
- **Pathways are linear, cyclic or spiral**

A linear sequence

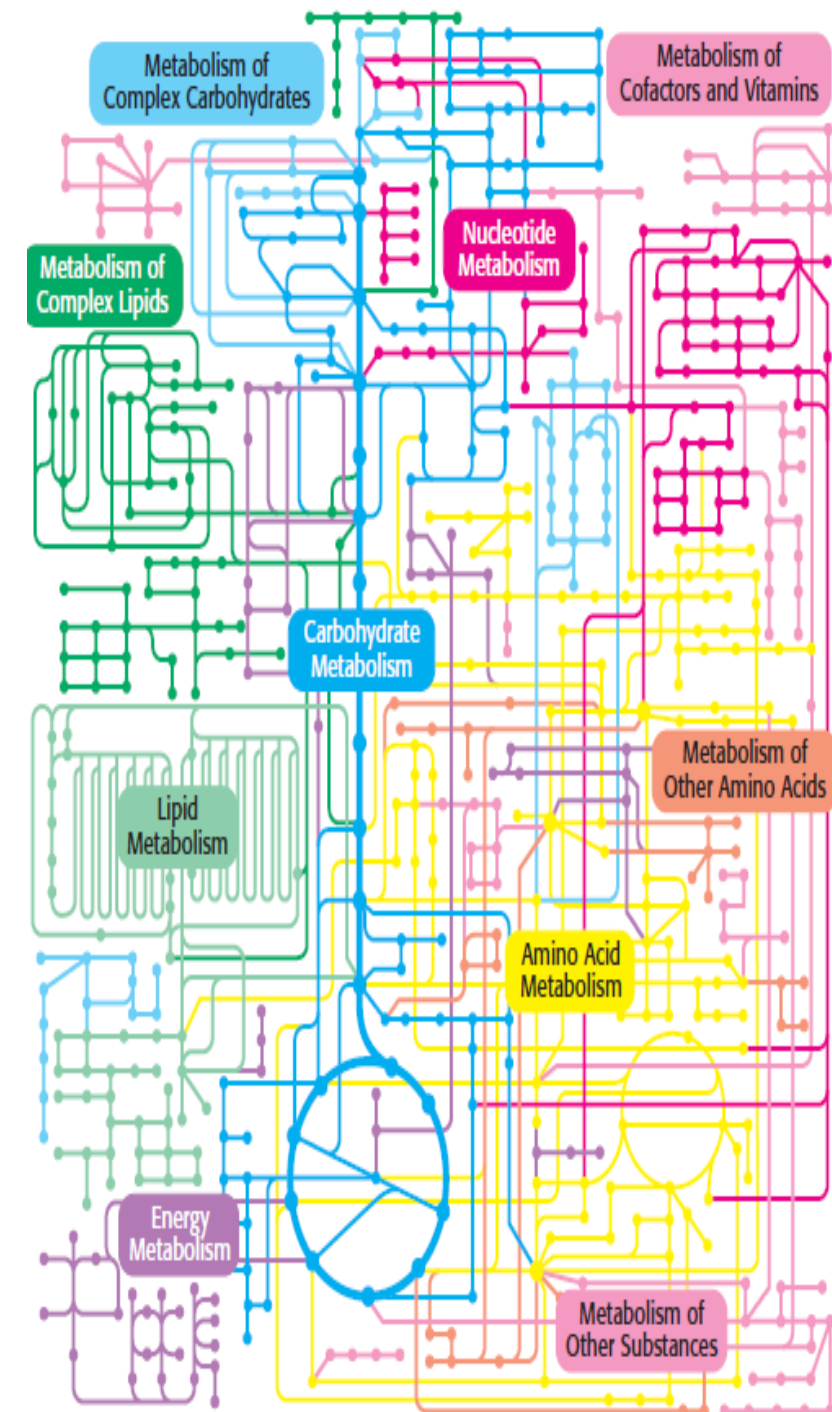
A $\xrightarrow{\text{Enzyme 1}}$ B $\xrightarrow{\text{Enzyme 2}}$ C $\xrightarrow{\text{Enzyme 3}}$...

A cyclic sequence

Enzyme 4 $\rightarrow$ A $\xrightarrow{\text{Enzyme 1}}$ B $\xrightarrow{\text{Enzyme 2}}$ C $\xrightarrow{\text{Enzyme 3}}$ D $\xrightarrow{\text{Enzyme 4}}$ A

A spiral sequence

A $\xrightarrow{\text{Enzymes 1} \rightarrow 4}$ B $\xrightarrow{\text{Enzymes 1} \rightarrow 4}$ C $\xrightarrow{\text{Enzymes 1} \rightarrow 4}$...
Final product



EXERGONIC REACTIONS AND PATHWAYS IN BIOCHEMISTRY

- Complex structures → simple structures

Proteins → amino acids

Starch → n glucose

glucose + O_2 → CO_2 + H_2O

- More specifically

- Hydrolysis reactions

- Decarboxylation reactions (release of CO_2)

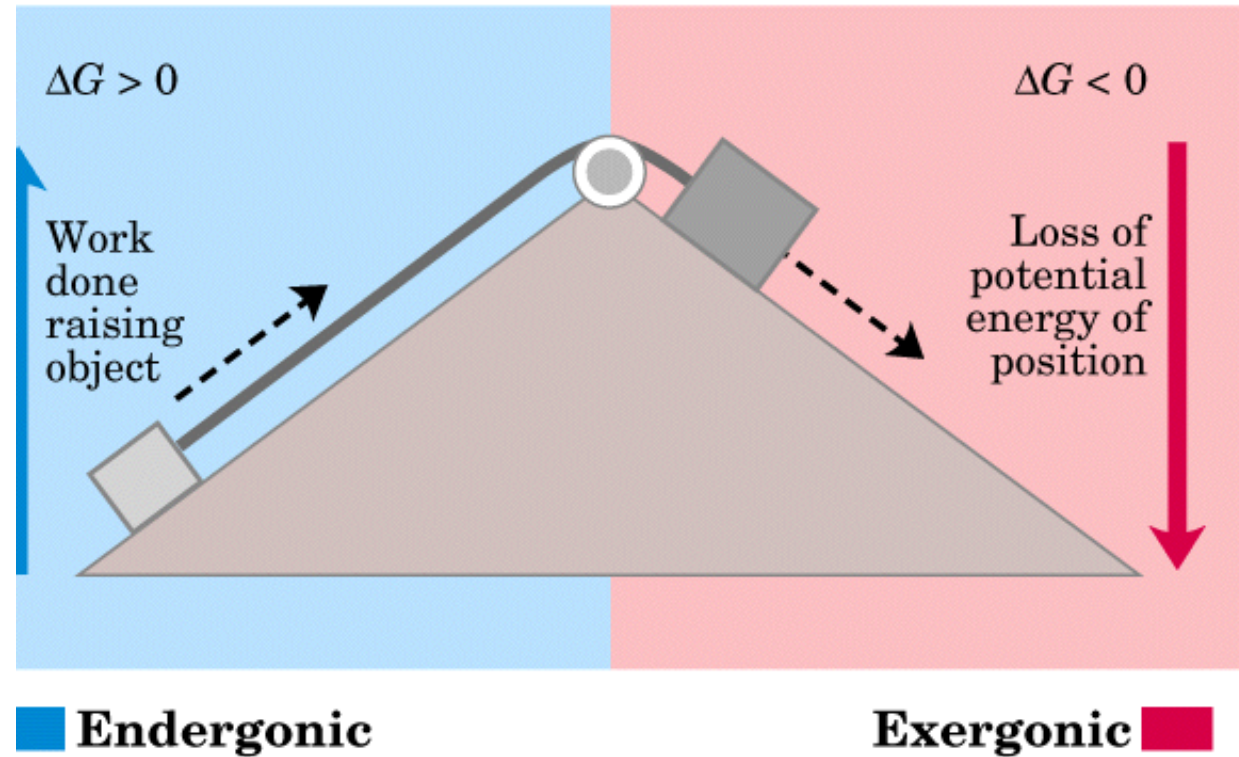
pyruvate (C3) → acetyl-CoA(C2) + CO_2

- Oxidation with O_2





(a) Mechanical example



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK? MAKING THE IMPOSSIBLE POSSIBLE



The coupling concept - **phosphoryl transfer reactions**

CLINICAL CASE: PYRUVATE KINASE DEFICIENCY

- **Role of Pyruvate Kinase**

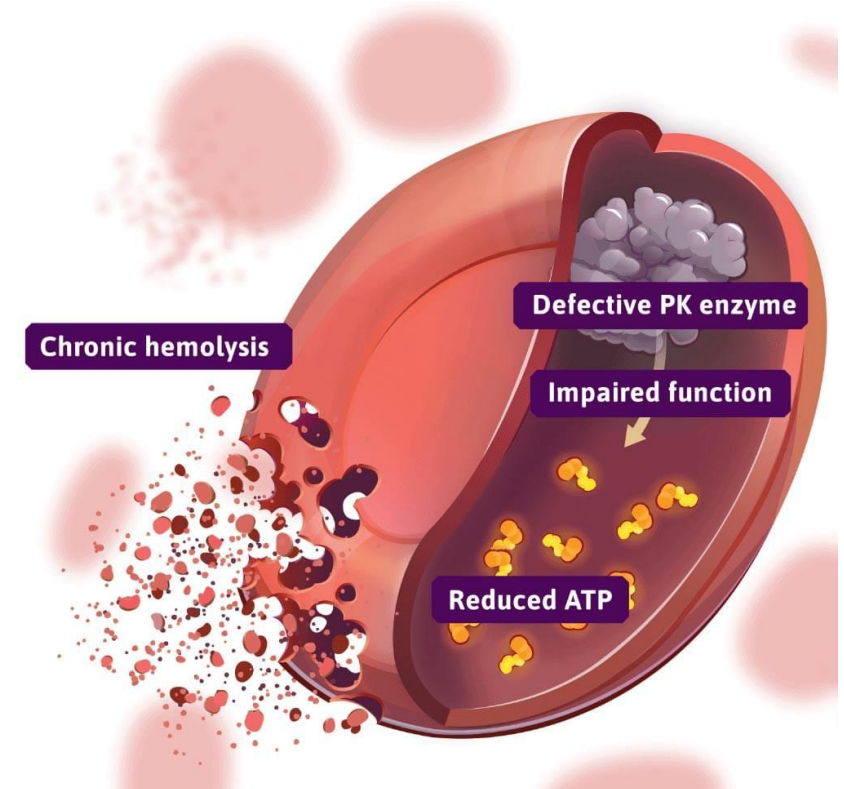
- Pyruvate kinase catalyzes a crucial step in glycolysis important for ATP generation in red blood cells.

- **Impact of Deficiency**

- Deficiency in pyruvate kinase reduces ATP production, causing red blood cell rigidity and hemolytic anemia.

- **Energy Coupling in Cells**

- This case highlights how energy coupling via ATP is vital for maintaining cellular health and function.



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

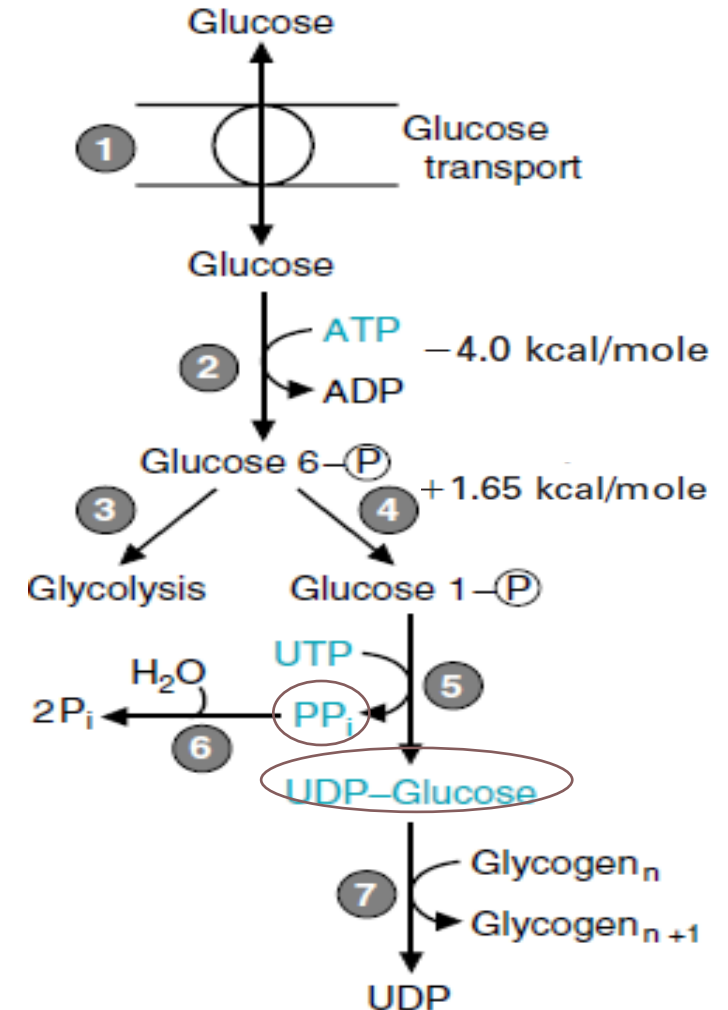
I. ΔG^0 Values are additive

i. Through phosphoryl transfer reactions:

- Step 2 (+3.3 vs. -4 kcal/mole)
- Step 2 + 4 = -2.35 kcal/mole
- The net value for synthesis is irrelevant to the presence or absence of enzymes

ii. Activated intermediates (step 4 is facilitated by steps 5&6)

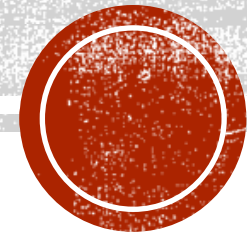
II. ΔG Depends on Substrate and Product Concentration (step 4 has a ratio of 6/94; +1.65 kcal/mol, if 3/94; -0.4kcal/mol)

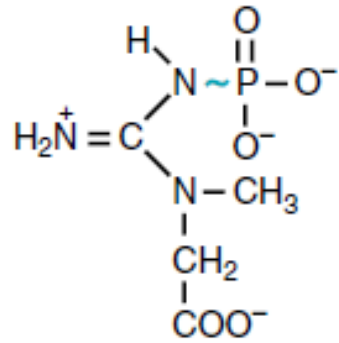


	Concentration (mM)*			
	ATP	ADP ⁱ	AMP	P _i
Rat hepatocyte	3.38	1.32	0.29	4.8
Rat myocyte	8.05	0.93	0.04	8.05
Rat neuron	2.59	0.73	0.06	2.72
Human erythrocyte	2.25	0.25	0.02	1.65
E coli cell	7.90	1.04	0.82	7.9

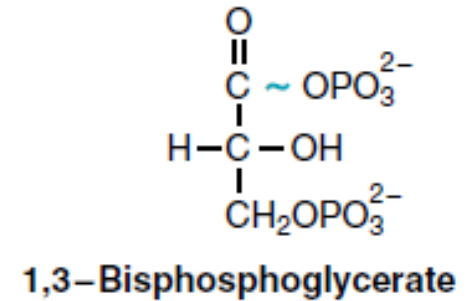
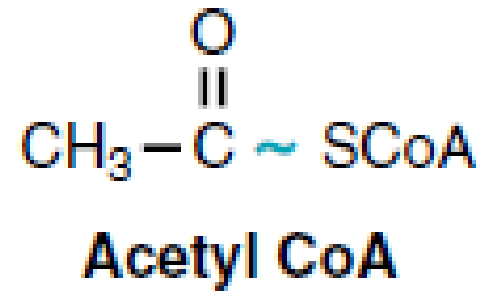
THE FREE-ENERGY CHANGE FOR ATP HYDROLYSIS IS LARGE AND NEGATIVE

Not fixed and depends on concentrations





Creatine phosphate



HOW DO OUR CELLS GET ENERGY FOR UNFAVORABLE BIOCHEMICAL WORK?

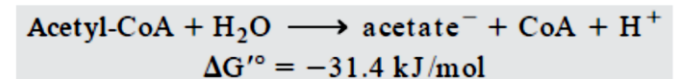
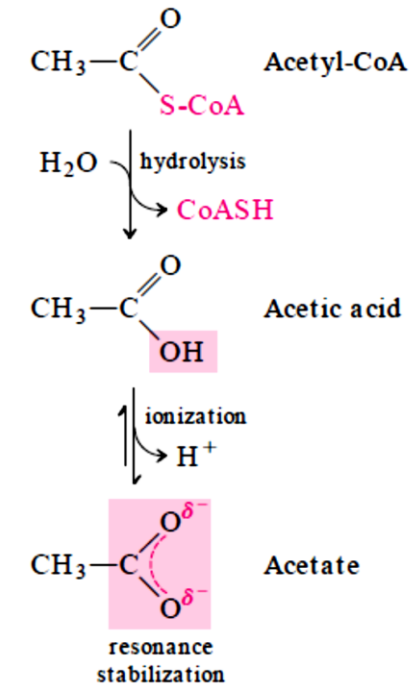
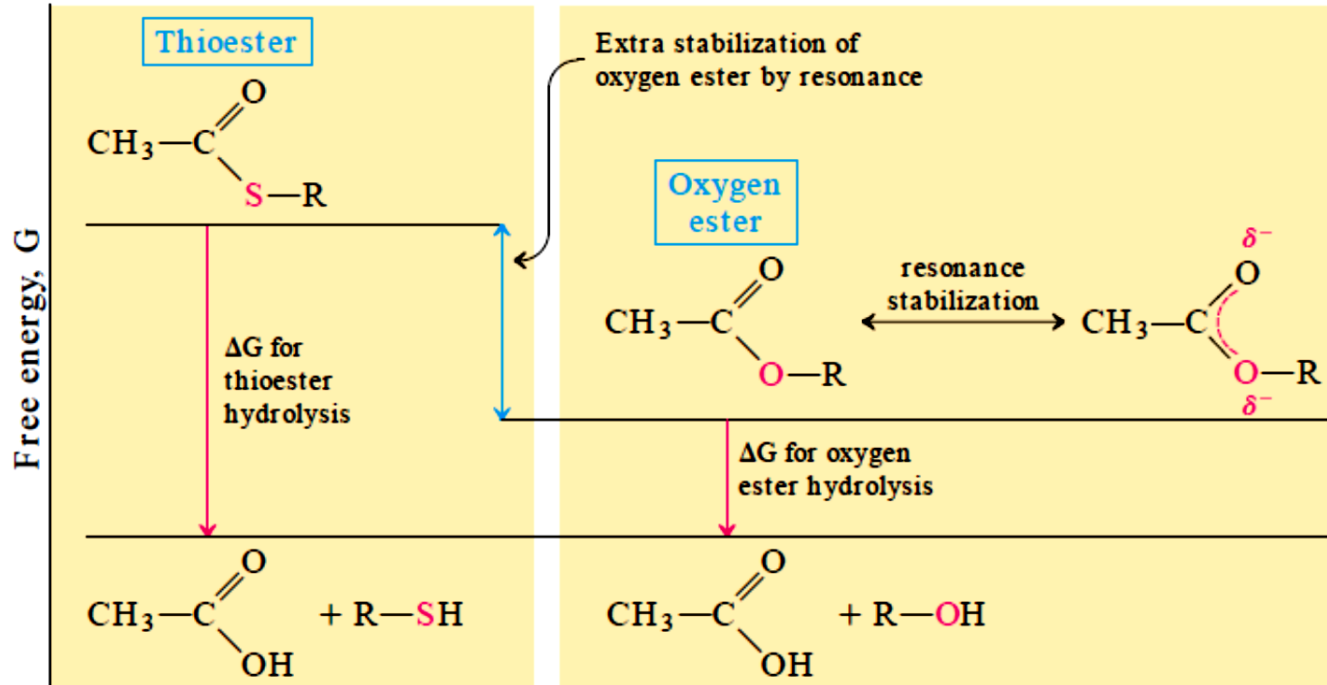
III. Activated Intermediates other than ATP; UTP is used for combining sugars, CTP in lipid synthesis, and GTP in protein synthesis

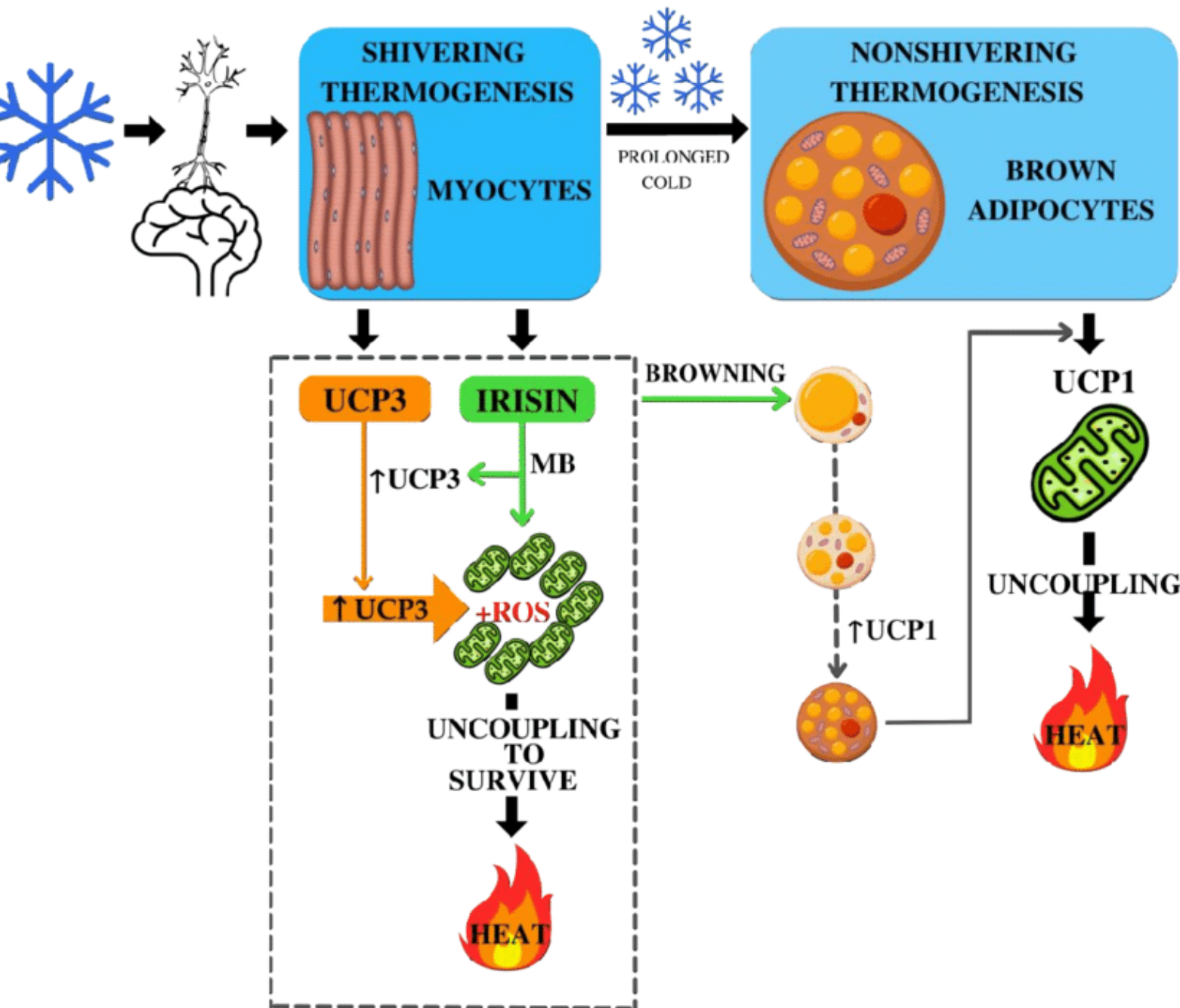


THE ACETYL COA AS AN EXAMPLE OF COUPLING

- CoA is a universal carrier (donor) of Acyl groups
- Forms a thio-ester bond with carboxyl group

- Acetyl CoA + H₂O → Acetate + CoA $\Delta G^\circ = -7.5 \text{ kcal}$
- Acetylcholine + H₂O → Acetate + Choline $\Delta G^\circ = -3 \text{ kcal}$





THERMOGENESIS

- The first law of thermodynamics
- Heat production is a natural consequence of “burning fuels”
- Thermogenesis refers to energy expended for generating heat
- Shivering thermogenesis
- Non-shivering thermogenesis



PRINCIPLES OF BIOENERGETICS

3- Biological Oxidation-Reduction Reactions
(Redox)

OXIDATION-REDUCTION REACTIONS (REDOX)

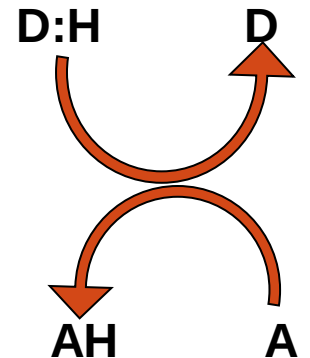
- **Oxidation:**

- Gain of Oxygen
- Loss of Hydrogen
- Loss of electrons

- **Reduction:**

- Gain of Hydrogen
- Gain of electron
- Loss of Oxygen

- **E (redox Potential):** it is a **POTENTIAL ENERGY** that measures the tendency of oxidant/reductant to gain/lose electrons, to become reduced/oxidized
- Electrons move from compounds with lower reduction potential (more negative) to compounds with higher reduction potential (more positive)
- Oxidation and reduction must occur simultaneously



REDUCTION POTENTIAL



Type of reaction?

What determine the direction of the reaction?



Type of reaction

What determine the direction of the reaction?

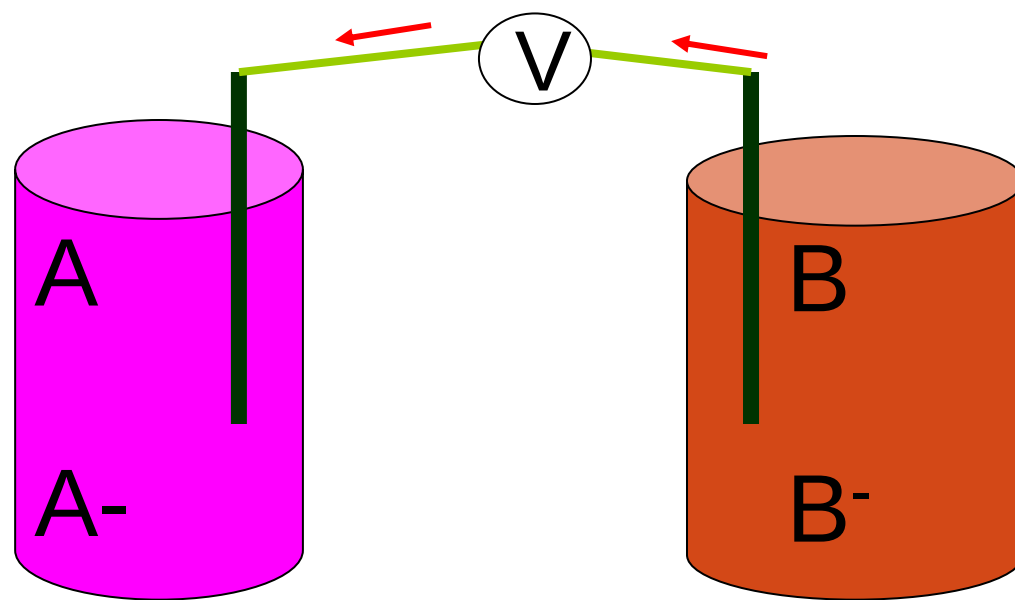


REDUCTION POTENTIAL AND DIRECTION OF THE REACTION



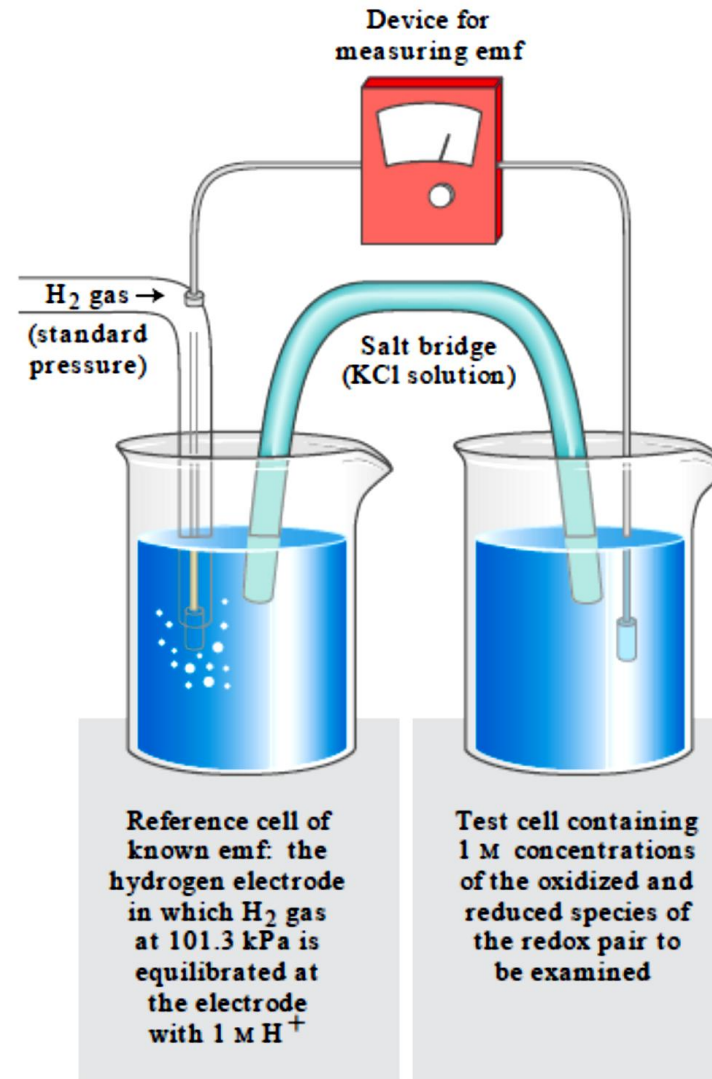
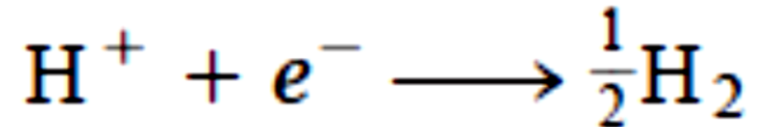
B oxidized form
B⁻ reduced form

Redox couple



WHAT IS THE STANDARD?

- Hydrogen electrode
- H₂ Gas sensor



REDUCTION POTENTIAL AND DIRECTION OF THE REACTION



X oxidized form
X⁻ reduced form

Redox couple

X⁻ has higher tendency to lose electrons than H₂ does



Negative reduction potential



STANDARD REDUCTION POTENTIAL (E°)

$$E = E^{\circ} + \frac{RT}{nF} \ln \frac{[\text{electron acceptor}]}{[\text{electron donor}]}$$

$$E = E^{\circ} + \frac{0.026 \text{ V}}{n} \ln \frac{[\text{electron acceptor}]}{[\text{electron donor}]}$$



REDUCTION POTENTIAL

Oxidized + e ⁻	→ Reduced	$\Delta E^{\circ} (V)$
Succinate	α ketoglutarate	- 0.67
Acetate	Acetaldehyde	- 0.60
NAD⁺	NADH	- 0.32
Acetaldehyde	Ethanol	- 0.20
Pyruvate	Lactate	- 0.19
Fumarate	Succinate	+ 0.03
Cytochrome ⁺³	Cytochrome ⁺²	+ 0.22
oxygen	water	+ 0.82



TABLE 13–7 Standard Reduction Potentials of Some Biologically Important Half-Reactions, at pH 7.0 and 25 °C (298 K)

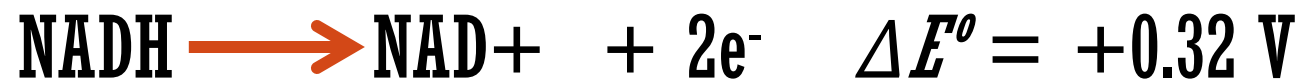
<i>Half-reaction</i>	<i>E° (V)</i>
$\frac{1}{2}\text{O}_2 + 2\text{H}^+ + 2e^- \longrightarrow \text{H}_2\text{O}$	0.816
$\text{Fe}^{3+} + e^- \longrightarrow \text{Fe}^{2+}$	0.771
$\text{NO}_3^- + 2\text{H}^+ + 2e^- \longrightarrow \text{NO}_2^- + \text{H}_2\text{O}$	0.421
Cytochrome <i>f</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>f</i> (Fe^{2+})	0.365
$\text{Fe}(\text{CN})_6^{3-}$ (ferricyanide) + $e^- \longrightarrow \text{Fe}(\text{CN})_6^{4-}$	0.36
Cytochrome <i>a</i> ₃ (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>a</i> ₃ (Fe^{2+})	0.35
$\text{O}_2 + 2\text{H}^+ + 2e^- \longrightarrow \text{H}_2\text{O}_2$	0.295
Cytochrome <i>a</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>a</i> (Fe^{2+})	0.29
Cytochrome <i>c</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>c</i> (Fe^{2+})	0.254
Cytochrome <i>c</i> ₁ (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>c</i> ₁ (Fe^{2+})	0.22
Cytochrome <i>b</i> (Fe^{3+}) + $e^- \longrightarrow$ cytochrome <i>b</i> (Fe^{2+})	0.077
Ubiquinone + $2\text{H}^+ + 2e^- \longrightarrow$ ubiquinol + H_2	0.045
Fumarate ²⁻ + $2\text{H}^+ + 2e^- \longrightarrow$ succinate ²⁻	0.031
$2\text{H}^+ + 2e^- \longrightarrow \text{H}_2$ (at standard conditions, pH 0)	0.000
Gotyl-CoA + $2\text{H}^+ + 2e^- \longrightarrow$ butyryl-CoA	−0.015
Oxaloacetate ²⁻ + $2\text{H}^+ + 2e^- \longrightarrow$ malate ²⁻	−0.166
Pyruvate ⁻ + $2\text{H}^+ + 2e^- \longrightarrow$ lactate ⁻	−0.185
Acetaldehyde + $2\text{H}^+ + 2e^- \longrightarrow$ ethanol	−0.197
FAD + $2\text{H}^+ + 2e^- \longrightarrow \text{FADH}_2$	−0.219*
Glutathione + $2\text{H}^+ + 2e^- \longrightarrow$ 2 reduced glutathione	−0.23
$\text{S} + 2\text{H}^+ + 2e^- \longrightarrow \text{H}_2\text{S}$	−0.243
Lipoic acid + $2\text{H}^+ + 2e^- \longrightarrow$ dihydrolipoic acid	−0.29
$\text{NAD}^+ + \text{H}^+ + 2e^- \longrightarrow \text{NADH}$	−0.320
$\text{NADP}^+ + \text{H}^+ + 2e^- \longrightarrow \text{NADPH}$	−0.324
Acetoacetate + $2\text{H}^+ + 2e^- \longrightarrow \beta$ -hydroxybutyrate	−0.346
α -Ketoglutarate + $\text{CO}_2 + 2\text{H}^+ + 2e^- \longrightarrow$ isocitrate	−0.38
$2\text{H}^+ + 2e^- \longrightarrow \text{H}_2$ (at pH 7)	−0.414
Ferredoxin (Fe^{3+}) + $e^- \longrightarrow$ ferredoxin (Fe^{2+})	−0.432



CALCULATION OF ΔG° FROM ΔE°

- $\Delta G^\circ = - n f \Delta E^\circ$ $\Delta G = -n \mathcal{F} \Delta E$ or $\Delta G'^\circ = -n \mathcal{F} \Delta E'^\circ$
 - $\mathcal{F}$ = Farady constant = 23.06 kcal/Volt

- Calculate ΔG° of the following reaction



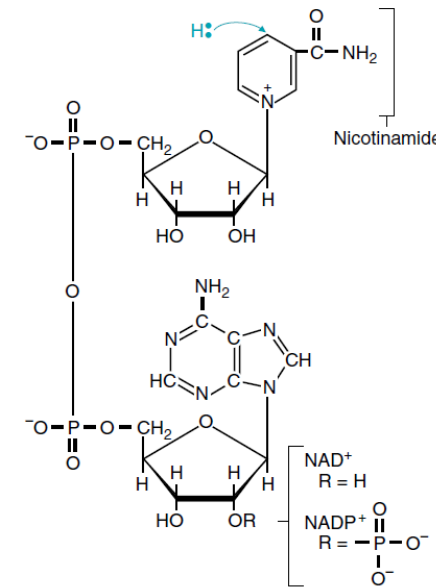
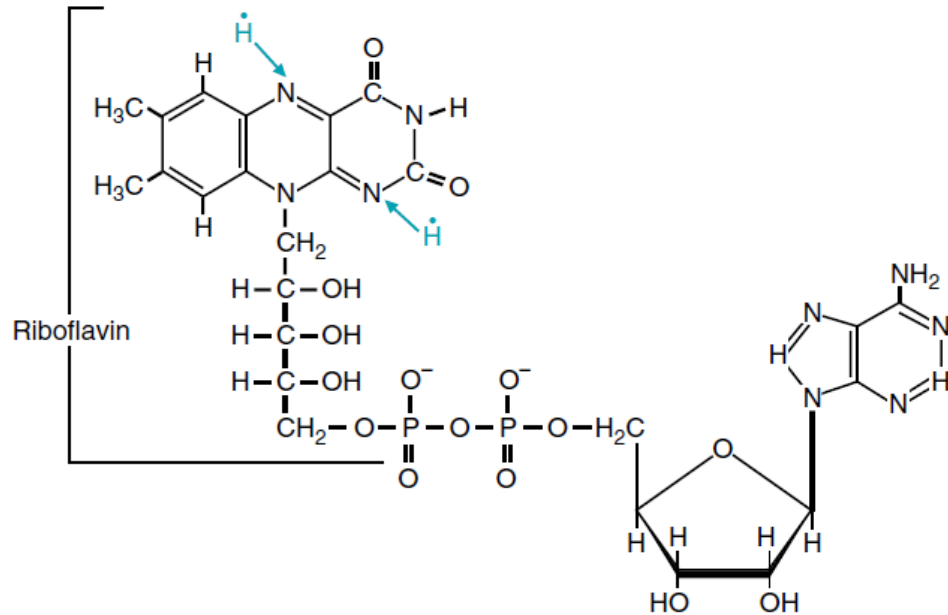
$$\Delta G^\circ = - 52.6 \text{ kcal/mol}$$



OXIDATION-REDUCTION REACTIONS (REDOX)

- $\Delta E = E_A - E_D$
- $\Delta E^0 =$ at standard condition
- Does ΔE determine the feasibility of a reaction?
 - $\Delta G^0 = -nf\Delta E^0$
- In other words; energy (work) can be derived from the transfer of electrons Or
- Oxidation of food can be used to synthesize ATP





OXIDATION-REDUCTION REACTIONS (REDOX)

- Always involve a pair of chemicals: an electron donor and an electron acceptor (Food vs. NAD^+)
- NAD^+ vs. FAD
- NAD^+ vs. NADP^+ (fatty acid synthesis and detoxification reactions)

