For internal circulation only

Bioenergetics:

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

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Redox Potential:

Capacity of a molecule to accept or donate electrons.

Redox potentials provide a quantitative measure of the oxidizing or reducing power of a molecule.

The effective redox potential depends on the proportion of the oxidized and reduced forms.

NADPH/NADP couple (maintained by cells at almost 100% in the reduced form) is much better biological reducing agent than NADH/NAD (no more than 30% reduced under normal conditions) despite the fact that the standard redox potentials are identical.

Free energy of a reaction

The **free energy change** (**ΔG**) of a reaction determines its spontaneity. A reaction is spontaneous if ΔG is negative (if the free energy of products is less than that of reactants).

For a reaction **A + B ⇌ C + D**

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

- **$G^{o'}$** = standard free energy change (at pH 7, 1M reactants & products); **R** = gas constant; **T** = temp.

For a reaction **A + B ⇌ C + D**

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

$\Delta G^{0'}$ of a reaction may be positive, & ΔG negative, depending on cellular concentrations of reactants and products.

Many reactions for which $\Delta G^{0'}$ is positive are spontaneous because other reactions cause depletion of products or maintenance of high substrate concentration.

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

K'_{eq}, the ratio [C][D]/[A][B] at equilibrium, is the **equilibrium constant**.

An equilibrium constant (**K'_{eq}**) **greater than one** indicates a **spontaneous** reaction (negative $\Delta G^{\circ\prime}$).

$$\Delta G = \Delta G^{o\prime} + RT \ln \frac{[C][D]}{[A][B]}$$

$$0 = \Delta G^{o\prime} + RT \ln \frac{[C][D]}{[A][B]}$$

$$\Delta G^{o\prime} = -RT \ln \frac{[C][D]}{[A][B]}$$

defining $K'_{eq} = \frac{[C][D]}{[A][B]}$

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

Electron Transfer

An electron transfer reaction:

$$A_{ox} + B_{red} \rightleftharpoons A_{red} + B_{ox}$$

A_{ox} is the oxidized form of **A** (the oxidant)

B_{red} is the reduced form of **B** (the reductant).

For such an electron transfer, one may consider two half-cell reactions:

$$A_{ox} + n\,e^- \rightleftharpoons A_{red} \qquad \text{e.g.,} \quad Fe^{+++} + e^- \rightleftharpoons Fe^{++}$$

$$B_{ox} + n\,e^- \rightleftharpoons B_{red}$$

$A_{ox} + n\,e^- \rightleftharpoons A_{red}$

$B_{ox} + n\,e^- \rightleftharpoons B_{red}$

For each half reaction:

$$E = E^{\circ\prime} - RT/nF\ (\ln [reduced]/[oxidized])$$

e.g., for the first half reaction:

$$E = E^{\circ\prime} - RT/nF\ (\ln [A_{red}]/[A_{ox}])$$

E = voltage, R = gas const., F = Faraday, n = # of e^-.

When $[A_{red}] = [A_{ox}]$, $E = E^{\circ\prime}$.

$E^{\circ\prime}$ is the **mid-point potential**, or standard redox potential, the potential at which **[oxidant] = [reductant]** for the half reaction.

For an electron transfer:

$$\Delta E^{\circ\prime} = E^{\circ\prime}_{(oxidant)} - E^{\circ\prime}_{(reductant)} = E^{\circ\prime}_{(acceptor)} - E^{\circ\prime}_{(donor)}$$

$$\Delta G^{0\prime} = -nF\Delta E^{\circ\prime}$$

($E^{\circ\prime}$ is the mid-point potential)

An electron transfer reaction is **spontaneous** (negative ΔG) if **E°'** of the donor is more negative than **E°'** of the acceptor, i.e., when there is a **positive $\Delta E^{\circ\prime}$**.

Consider transfer of 2 electrons from NADH to oxygen:

a. $\frac{1}{2}\ O_2 + 2H^+ + 2e^- \rightarrow H_2O$

$E°' = +0.815\ V$

b. $NAD^+ + 2H^+ + 2e^- \rightarrow NADH + H^+$

$E°' = -0.315\ V$

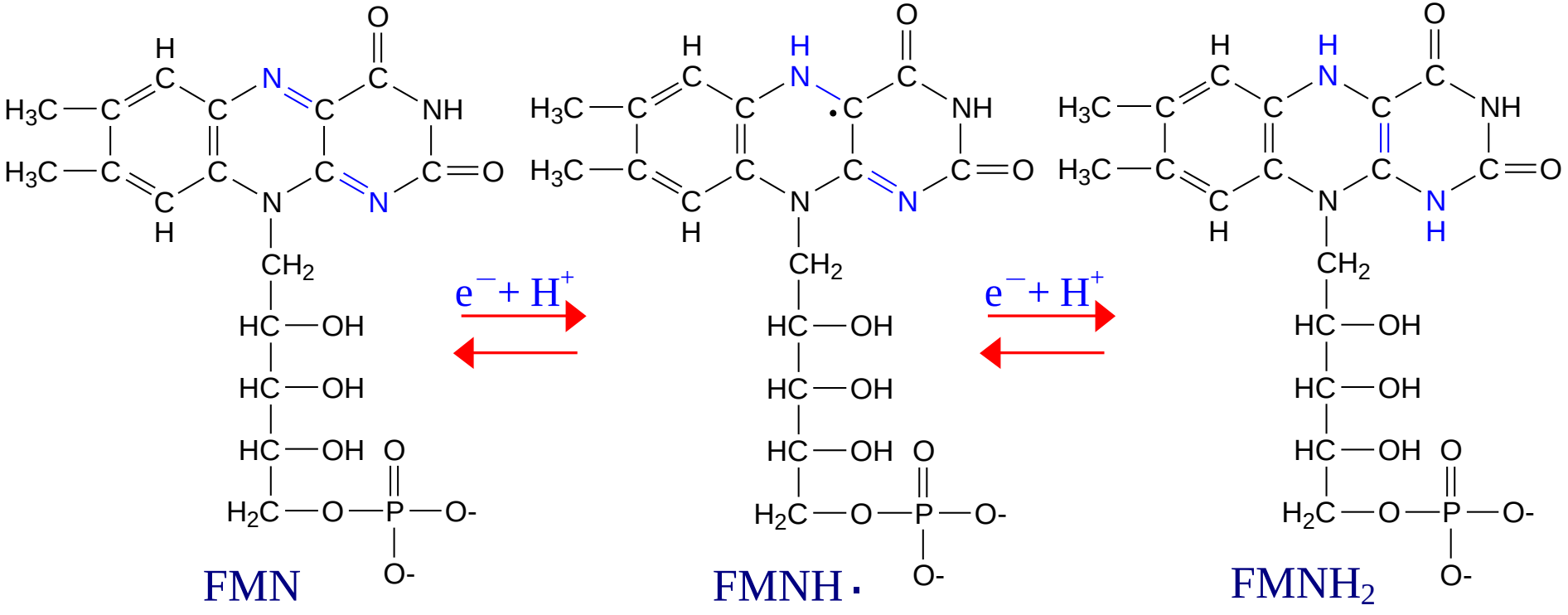
Subtracting reaction b from a:

c. $\frac{1}{2}\ O_2 + NADH + H^+ \rightarrow H_2O + NAD^+$

$E°' = +1.13\ V$

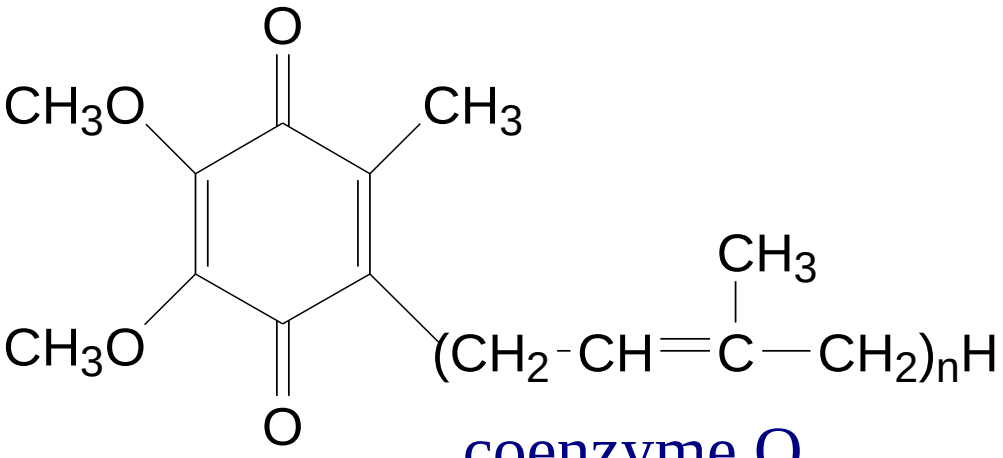
$\Delta G = -nF\Delta E^{0'} = -2(96494)(1.13) = -218\ kJ/mol$

Electron Carriers

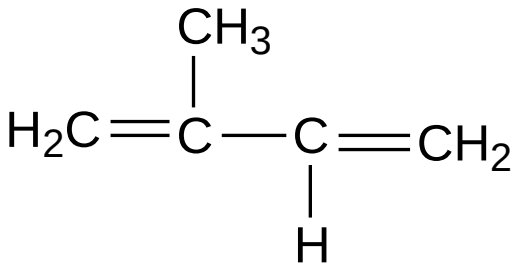


FMN, when bound at the active site of some enzymes, can accept **1 e⁻** to form the half-reduced **semiquinone radical**. The semiquinone can accept a 2nd e⁻ to yield $FMNH_2$.

Since it can accept/donate **1 or 2 e⁻**, FMN has an important **role** mediating e⁻ transfer between carriers that transfer 2e⁻ (e.g., NADH) & those that can accept only 1e⁻ (e.g., Fe^{+++}).



coenzyme Q

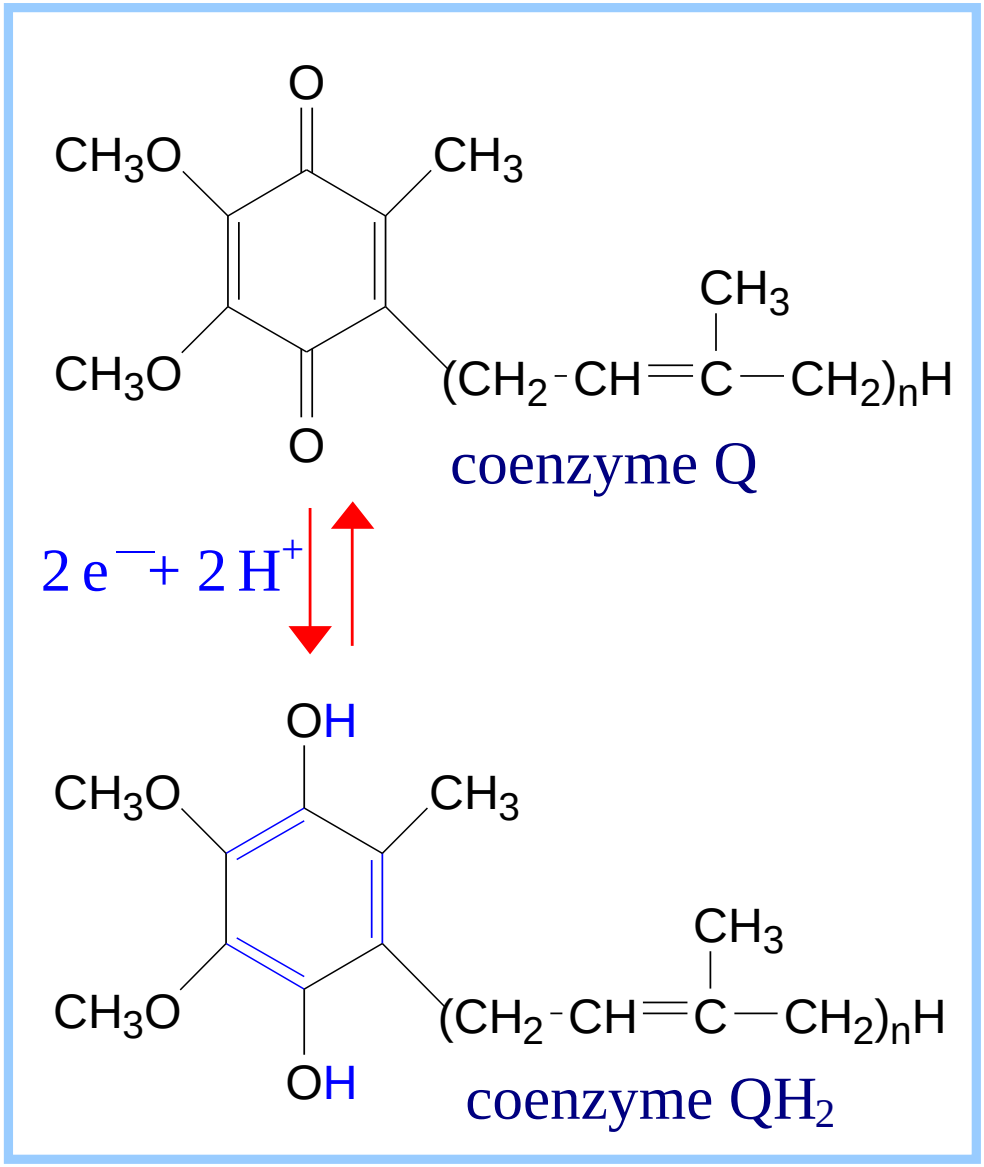


isoprene

Coenzyme Q (CoQ, Q, ubiquinone) is very **hydrophobic**. It dissolves in the hydrocarbon core of a membrane.

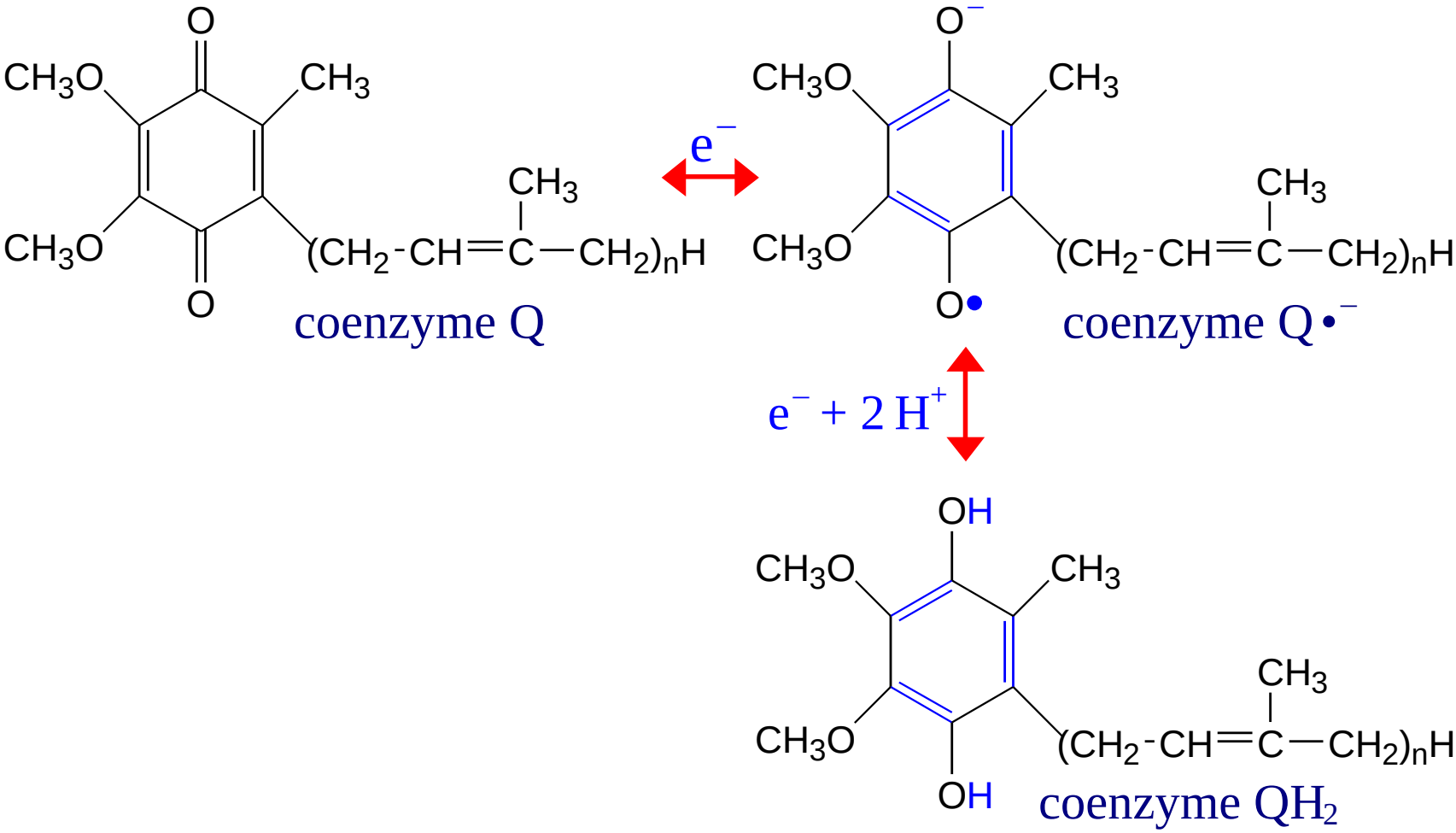
It includes a long **isoprenoid tail**, with multiple units having a carbon skeleton comparable to that of isoprene. In human cells, most often n = 10.

Q_{10}'s isoprenoid tail is longer than the width of a bilayer. It may be folded to yield a more compact structure, & is postulated to reside in the central domain of a membrane, **between the 2 lipid monolayers**.

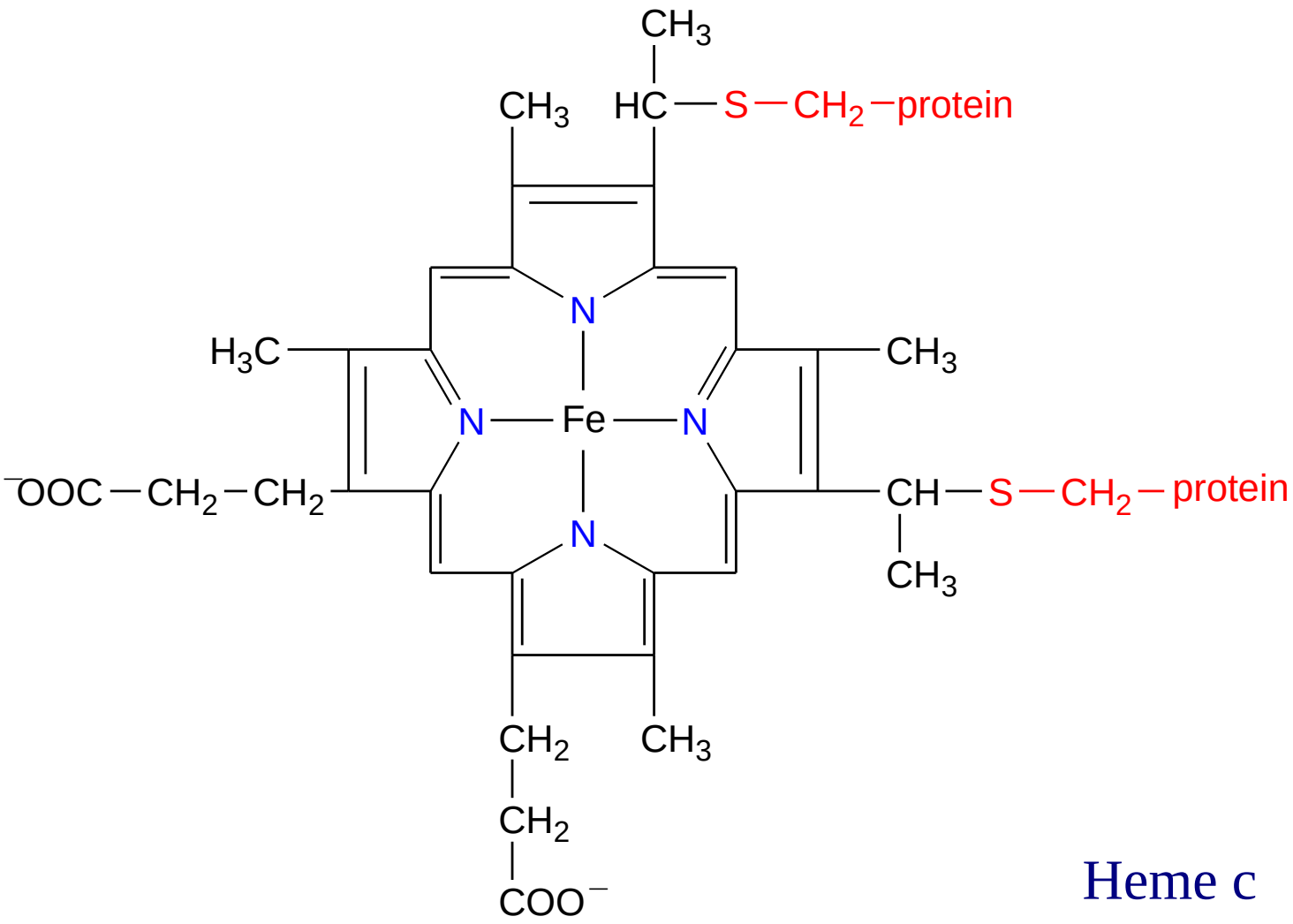


The **quinone** ring of coenzyme Q can be reduced to the **quinol** in a $2e^-$ reaction:

$Q + 2\ e^- + 2\ H^+ \rightleftharpoons QH_2$.



When bound to special sites in respiratory complexes, **CoQ** can accept **1 e⁻** to form a **semiquinone radical (Q·⁻)**. Thus CoQ, like FMN, can mediate between 1 e⁻ & 2 e⁻ donors/acceptors.

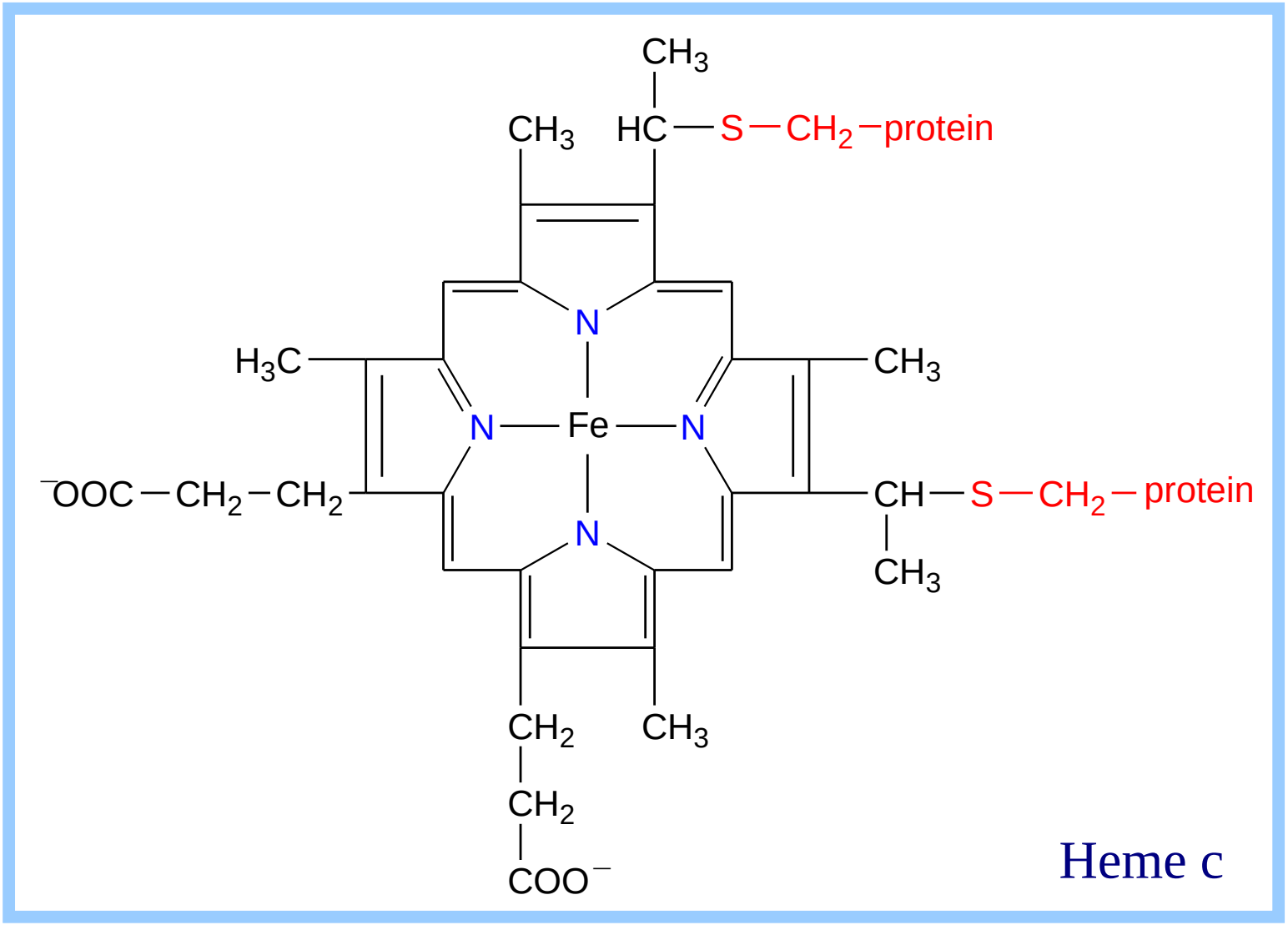


Heme c

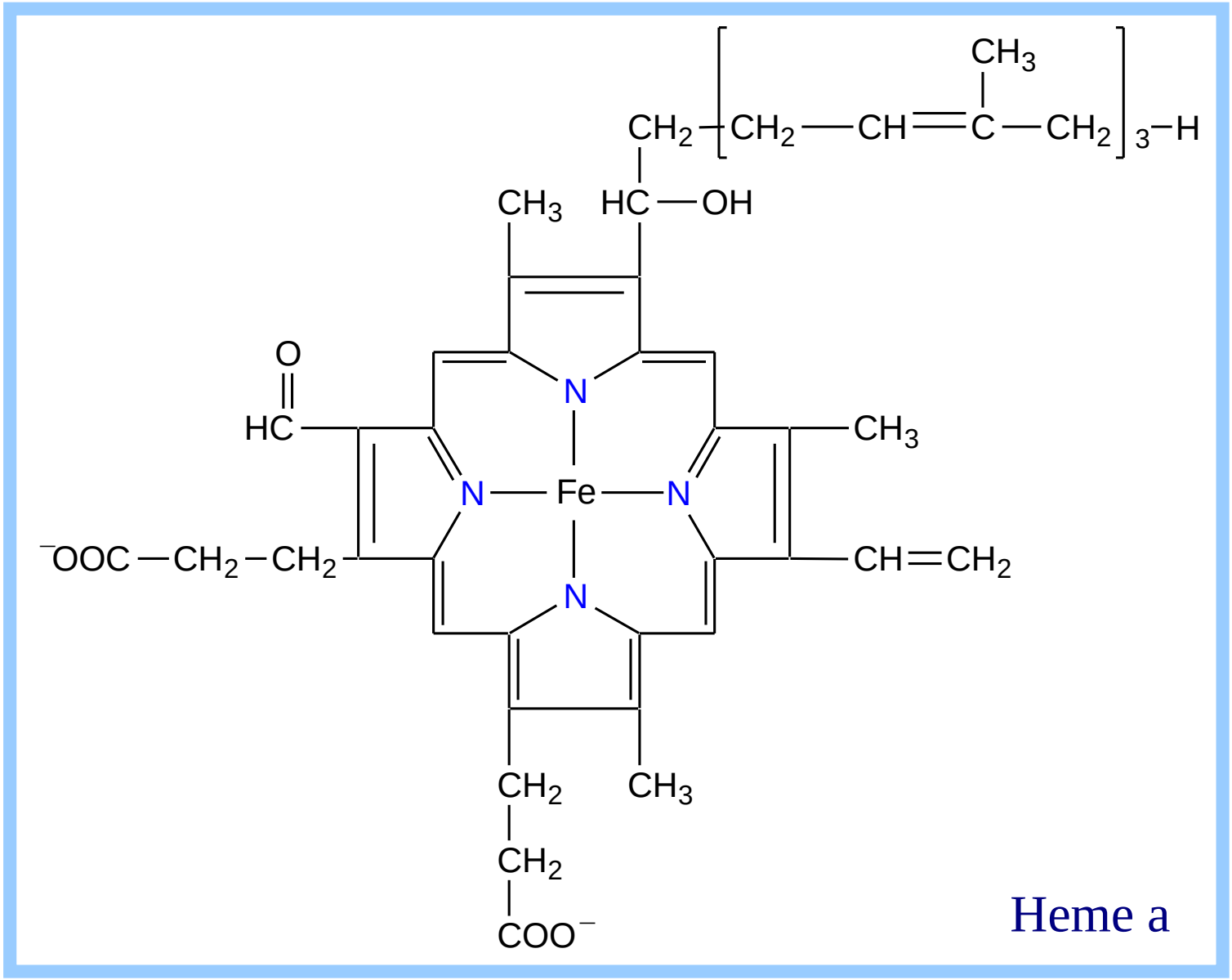
Heme is a prosthetic group of **cytochromes**.

Heme contains an iron atom in a porphyrin ring system.

The **Fe** is bonded to 4 **N** atoms of the porphyrin ring.

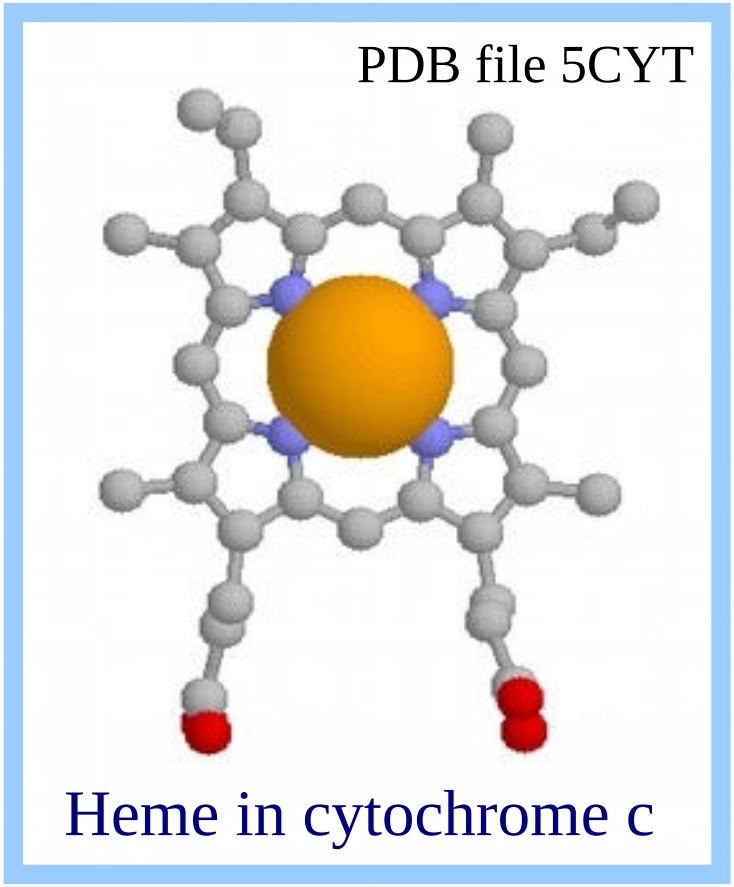


Hemes in the 3 classes of cytochrome (**a**, **b**, **c**) differ slightly in substituents on the porphyrin ring system. A common feature is 2 propionate side-chains. Only **heme c** is covalently linked to the protein via thioether bonds to **cysteine** residues.



Heme a is unique in having a long farnesyl side-chain that includes 3 isoprenoid units.

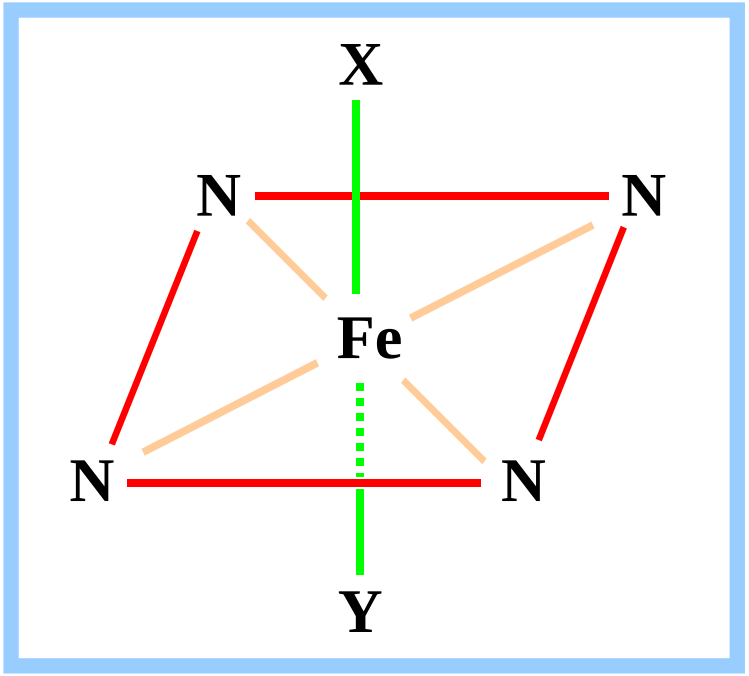
In the RasMol display of heme c at right, the porphyrin ring system is displayed as ball & sticks, while **Fe** is displayed as spacefill.

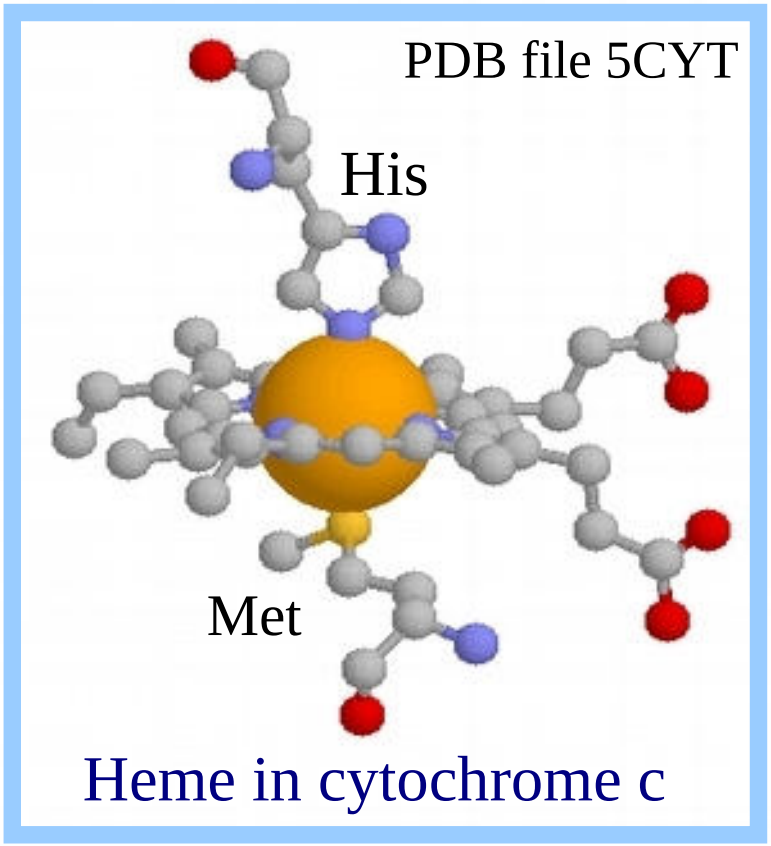


The heme iron can undergo a **1 e⁻** transition between ferric and ferrous states: **$Fe^{+++} + e^- \triangle\triangle Fe^{++}$**

The porphyrin ring is planar.

The heme **Fe** is usually bonded to **2 axial ligands**, above & below the heme plane (X,Y) in addition to **4 N** of porphyrin.





Heme in cytochrome c

Axial ligands may be **S** or **N** atoms of amino acid side-chains.

Axial ligands in cyt c are Met **S** (yellow) and His **N** (blue).

A heme that binds O_2 may have an open (empty) axial ligand position.

Cytochromes are proteins with heme prosthetic groups. They absorb light at characteristic wavelengths.

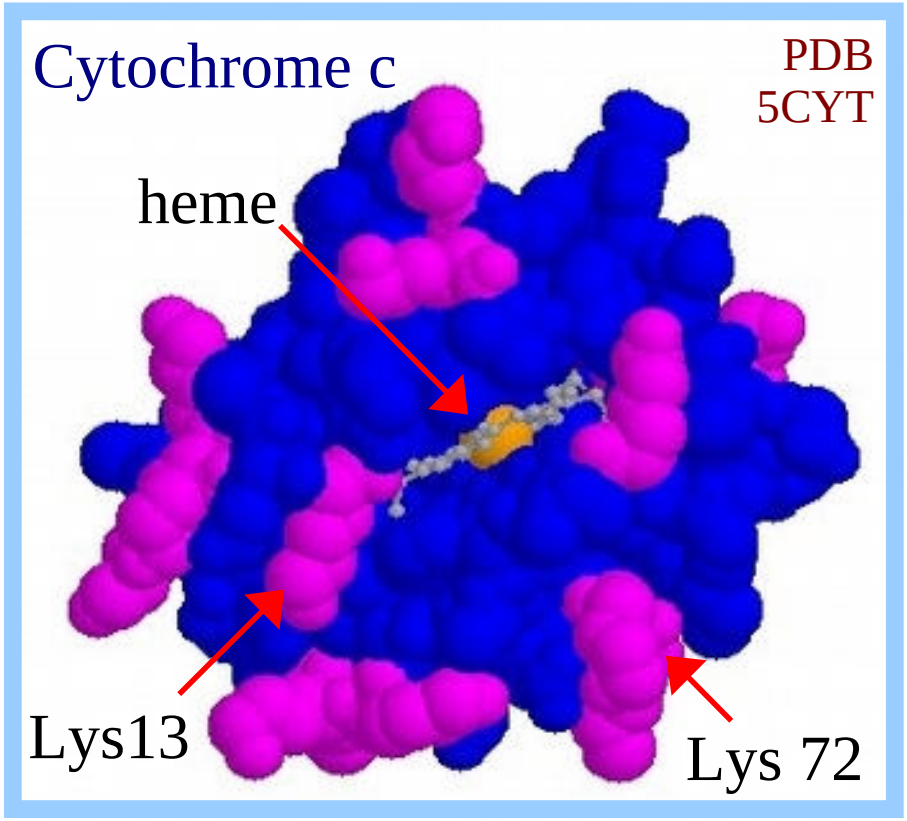
Absorbance changes upon oxidation/reduction of the heme iron provide a basis for monitoring heme redox state.

- Some cytochromes are part of large integral **membrane complexes**, each consisting of several polypeptides & including multiple electron carriers.

  Individual **heme prosthetic groups** may be separately designated as **cytochromes**, even if in the same protein.

  E.g., hemes a & a_3 that are part of the respiratory chain complex IV are often referred to as cytochromes a & a_3.

- **Cytochrome c** is instead a small, water-soluble protein with a single heme group.

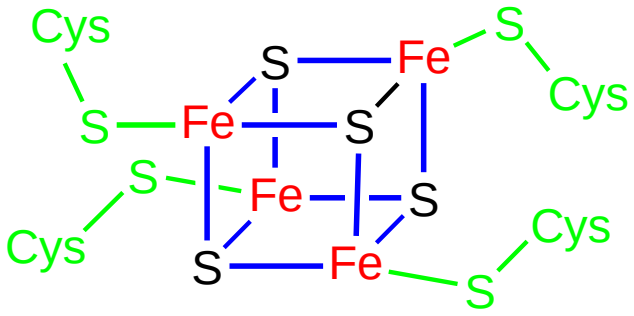


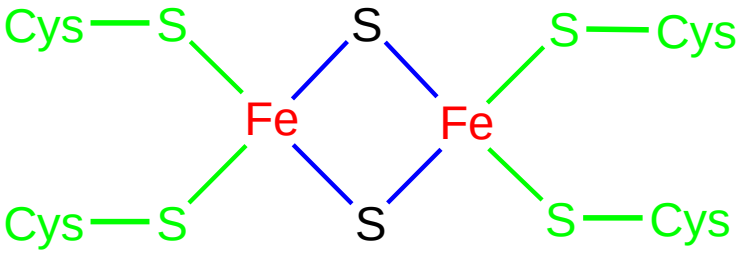
complex IV

cyt. c

Positively charged lysine residues (in magenta) surround the heme crevice on the surface of **cytochrome c**.

These may interact with anionic residues on membrane complexes to which cyt c binds, when receiving or donating an e^-.





Iron-Sulfur Centers

4-iron Fe-S

2-iron Fe-S

Fe-S spacefill; cysteine ball & stick.

Fe orange; S yellow.

PDB 2FUG

Two iron-sulfur centers from complex I

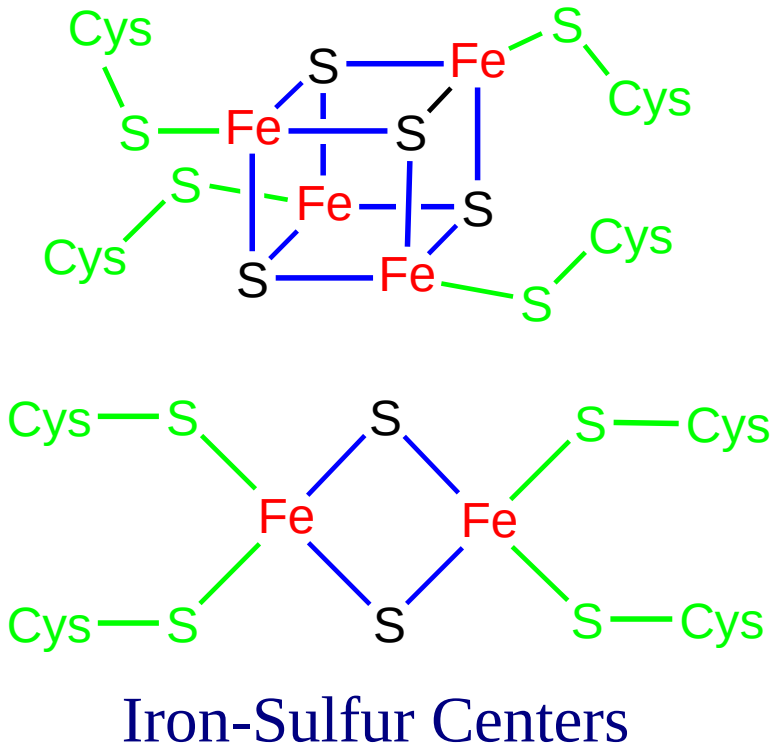
Iron-sulfur centers (**Fe-S**) are prosthetic groups containing **2, 3, 4 or 8 iron atoms** complexed to elemental & cysteine **S**.

4-Fe centers have a tetrahedral structure, with **Fe** & **S** atoms alternating as vertices of a cube.

Cysteine residues provide **S** ligands to the iron, while also holding these prosthetic groups in place within the protein.

Electron transfer proteins may contain multiple Fe-S centers.

Iron-sulfur centers transfer only **one electron**, even if they contain two or more iron atoms, because of the close proximity of the iron atoms.



Iron-Sulfur Centers

E.g., a 4-Fe center might cycle between redox states:

Fe^{+++}_{3}, Fe^{++}_{1} (oxidized) **+ 1 e^{-}** ΔΔ **Fe^{+++}_{2}, Fe^{++}_{2}** (reduced)

Energy coupling

- A spontaneous reaction may drive a non-spontaneous reaction.
- **Free energy changes** of coupled reactions are **additive**.

A. Some enzyme-catalyzed reactions are interpretable as **two coupled half-reactions**, one spontaneous and the other non-spontaneous.

- At the enzyme active site, the coupled reaction is kinetically facilitated, while individual half-reactions are prevented.
- Free energy changes of half reactions may be summed, to yield the free energy of the coupled reaction.

For example, in the reaction catalyzed by the Glycolysis enzyme **Hexokinase**, the half-reactions are:

$ATP + H_2O \Leftrightarrow ADP + P_i \qquad \Delta G^{0\prime} = -31$ kJ/mol

$P_i + glucose \Leftrightarrow glucose\text{-}6\text{-}P + H_2O \qquad \Delta G^{0\prime} = +14$ kJ/mol

Coupled reaction:

$ATP + glucose \Leftrightarrow ADP + glucose\text{-}6\text{-}P \qquad \Delta G^{0\prime} = -17$ kJ/mol

The structure of the enzyme active site, from which H_2O is excluded, prevents the individual hydrolytic reactions, while favoring the coupled reaction.

B. Two separate reactions, occurring in the same cellular compartment, one spontaneous and the other not, may be coupled by a **common intermediate** (reactant or product).

A hypothetical, but typical, example involving PP_i:

Enzyme 1:

$A + ATP \Leftrightarrow B + AMP + PP_i$ $\Delta G^{0\prime} = +15$ kJ/mol

Enzyme 2:

$PP_i + H_2O \Leftrightarrow 2\,P_i$ $\Delta G^{0\prime} = -33$ kJ/mol

Overall spontaneous reaction:

$A + ATP + H_2O \Leftrightarrow B + AMP + 2\,P_i$ $\Delta G^{0\prime} = -18$ kJ/mol

Pyrophosphate (PP_i) is often the product of a reaction that needs a driving force.

Its spontaneous hydrolysis, catalyzed by Pyrophosphatase enzyme, drives the reaction for which PP_i is a product.

Nernst Equation:

This equation relates the membrane potential to the concentration of a diffusible ion in equilibrium with the potential on each side of the membrane.

$\Delta\phi = 2.303\ RT \log([Cin]/[Cout])/zF$

Where: $\Delta\phi$ **is the membrane potential in volts**

R is the gas constant [8.31 joules/ degree/ mole]

T is the absolute temperature

Cin and Cout are the two ionic concentrations

Z is the electric charge on the ion

F is the faraday constant [96,500 coulombs/ mol].

The factor 2.303 arises from the use of $\log_{10}$ instead of $\log_n$

When the system reaches equilibrium, the tendency for the diffusible ion to escape through the membrane, down its concentration gradient, is exactly balanced by the electrical force attracting it in the opposite direction.

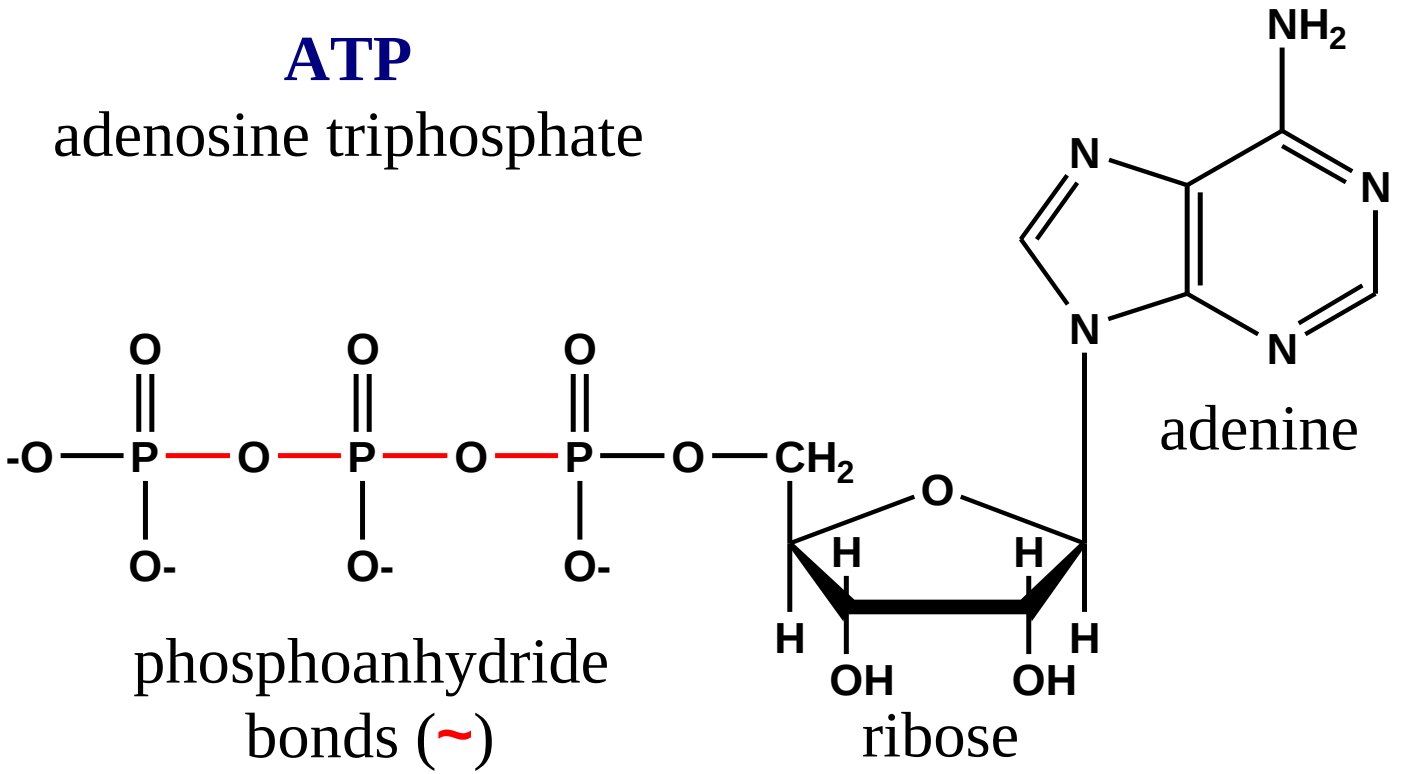
This implies that free energy can be available in the form of an ion gradient across a membrane.

No useful work can be obtained from ions subject to the Nernst equation (unless the electrical gradient is altered) because these ions have already reached equilibrium with the membrane potential. Energy can be obtained by dissipation of a gradient for non diffusible ions across the membrane.

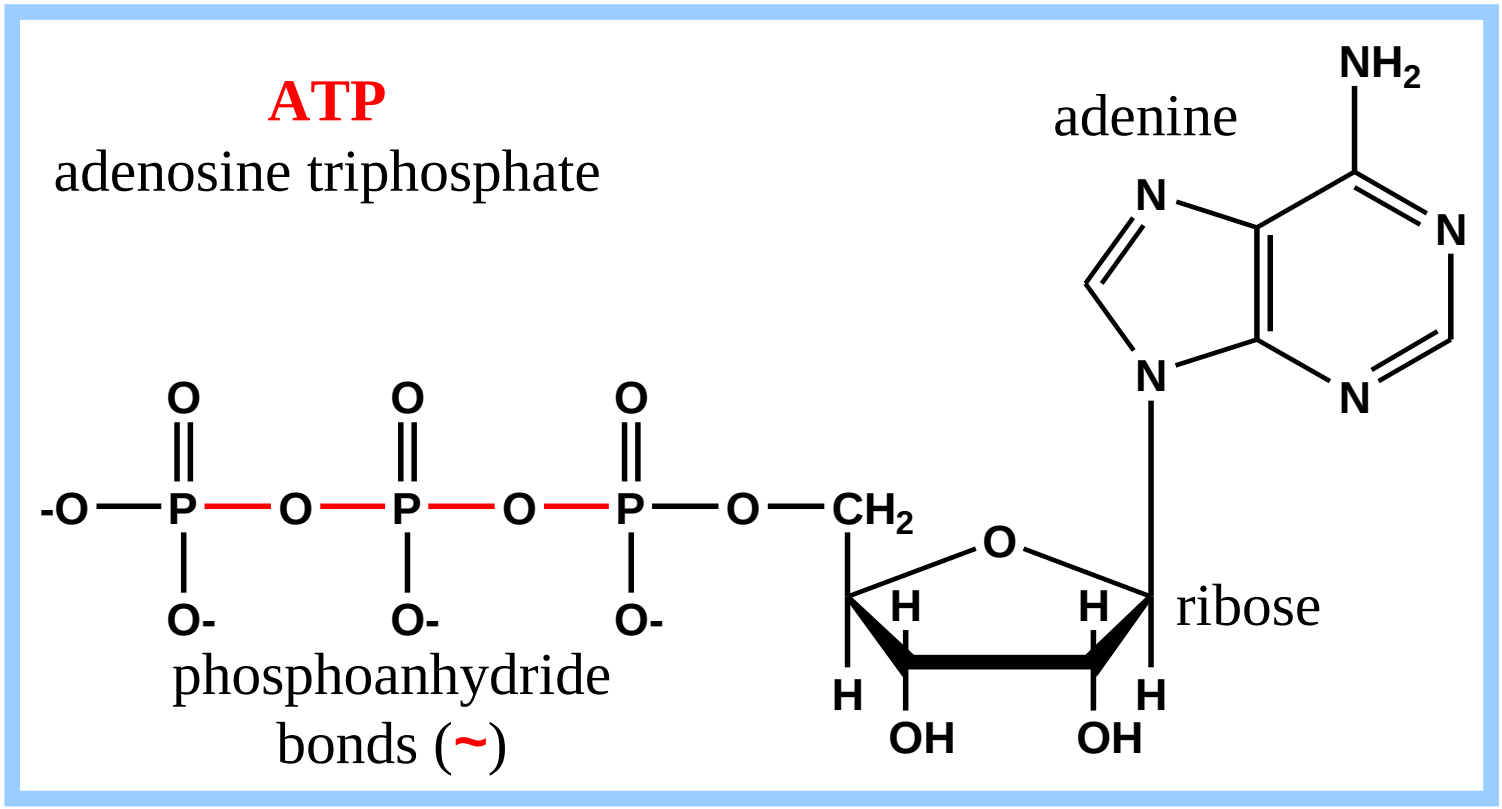
“High energy” bonds

ATP

adenosine triphosphate



Phosphoanhydride bonds (formed by splitting out H_2O between 2 phosphoric acids or between carboxylic & phosphoric acids) have a **large negative △G of hydrolysis**.



Phosphoanhydride linkages are said to be **"high energy" bonds**. Bond energy is not high, just Δ G of hydrolysis.

"High energy" bonds are represented by the "~" symbol.

~P represents a phosphate group with a large negative Δ G of hydrolysis.

“High energy” bonds

Compounds with “high energy bonds” are said to have **high group transfer potential.**

For example, P_i may be spontaneously cleaved from ATP for transfer to another compound (e.g., to a hydroxyl group on glucose).

Potentially, **2 ~P bonds** can be cleaved, as 2 phosphates are released by hydrolysis from **ATP**.

$AMP\sim P\sim P \rightarrow AMP\sim P + P_i$ (ATP → ADP + P_i)

$AMP\sim P \rightarrow AMP + P_i$ (ADP → AMP + P_i)

Alternatively:

$AMP\sim P\sim P \rightarrow AMP + P\sim P$ (ATP → AMP + PP_i)

$P\sim P \rightarrow 2\ P_i$ (PP_i → $2P_i$)

- **ATP** often serves as an **energy source**.

  Hydrolytic **cleavage** of one or both of the "high energy" bonds of ATP is **coupled** to an energy-requiring (non-spontaneous) reaction. (Examples presented earlier.)

- **AMP** functions as an **energy sensor** & **regulator** of metabolism.

  When ATP production does not keep up with needs, a higher portion of a cell's adenine nucleotide pool is AMP.

  AMP stimulates metabolic **pathways** that **produce ATP**.

  - Some examples of this role involve direct allosteric **activation of pathway enzymes by AMP**.
  - Some regulatory effects of AMP are mediated by the enzyme **AMP-Activated Protein Kinase**.

A reaction important for equilibrating ~P among adenine nucleotides within a cell is that catalyzed by **Adenylate Kinase**:

ATP + AMP ⇔ 2 ADP

The Adenylate Kinase reaction is also important because the substrate for ATP synthesis, e.g., by mitochondrial ATP Synthase, is **ADP**, while some cellular reactions dephosphorylate ATP all the way to **AMP**.

The enzyme **Nucleoside Diphosphate Kinase** (**NuDiKi**) equilibrates **~P** among the various nucleotides that are needed, e.g., for synthesis of DNA & RNA.

NuDiKi catalyzes reversible reactions such as:

ATP + GDP ⇔ ADP + GTP,

ATP + UDP ⇔ ADP + UTP, etc.

Inorganic polyphosphate

Many organisms store energy as **inorganic polyphosphate**, a chain of many phosphate residues linked by phosphoanhydride bonds:

P~P~P~P~P...

Hydrolysis of P_i residues from polyphosphate may be coupled to energy-dependent reactions.

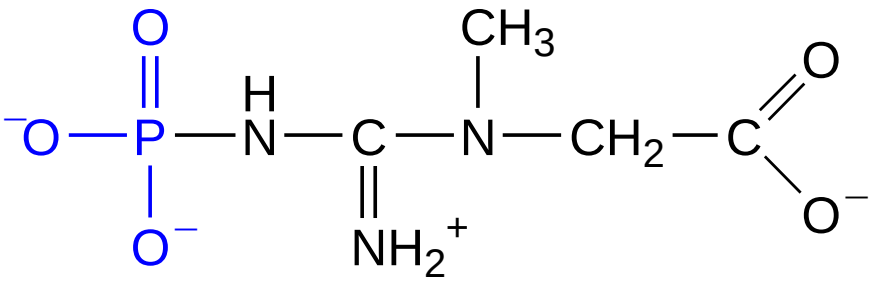
Depending on the organism or cell type, inorganic polyphosphate may have additional functions.

E.g., it may serve as a reservoir for P_i, a chelator of metal ions, a buffer, or a regulator.

Why do phosphoanhydride linkages have a high G of hydrolysis? Contributing factors for ATP & PP_i include:

- **Resonance stabilization** of products of hydrolysis exceeds resonance stabilization of the compound itself.
- **Electrostatic repulsion** between negatively charged phosphate oxygen atoms favors separation of the phosphates.

Phosphocreatine (creatine phosphate), another compound with a "high energy" phosphate linkage, is used in nerve & muscle for **storage of ~P bonds**.



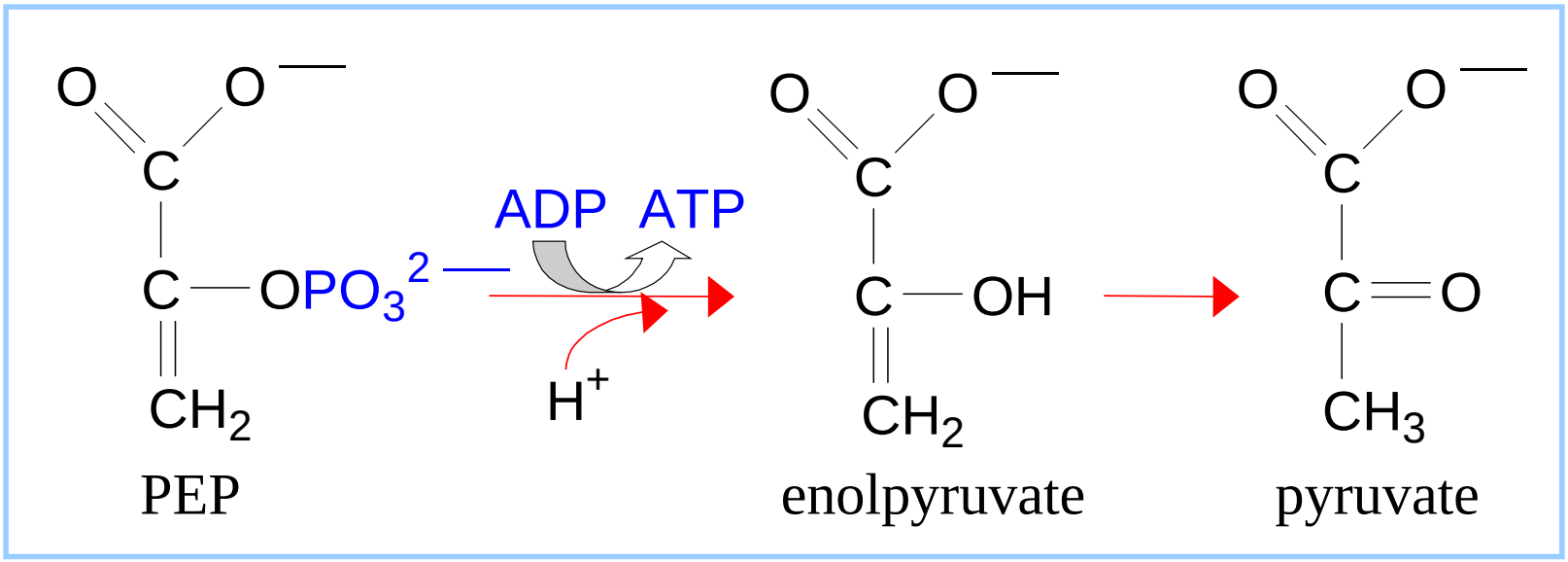
phosphocreatine

Creatine Kinase catalyzes:

Phosphocreatine + ADP ⇔ ATP + creatine

This is a **reversible** reaction, though the equilibrium constant slightly favors phosphocreatine formation.

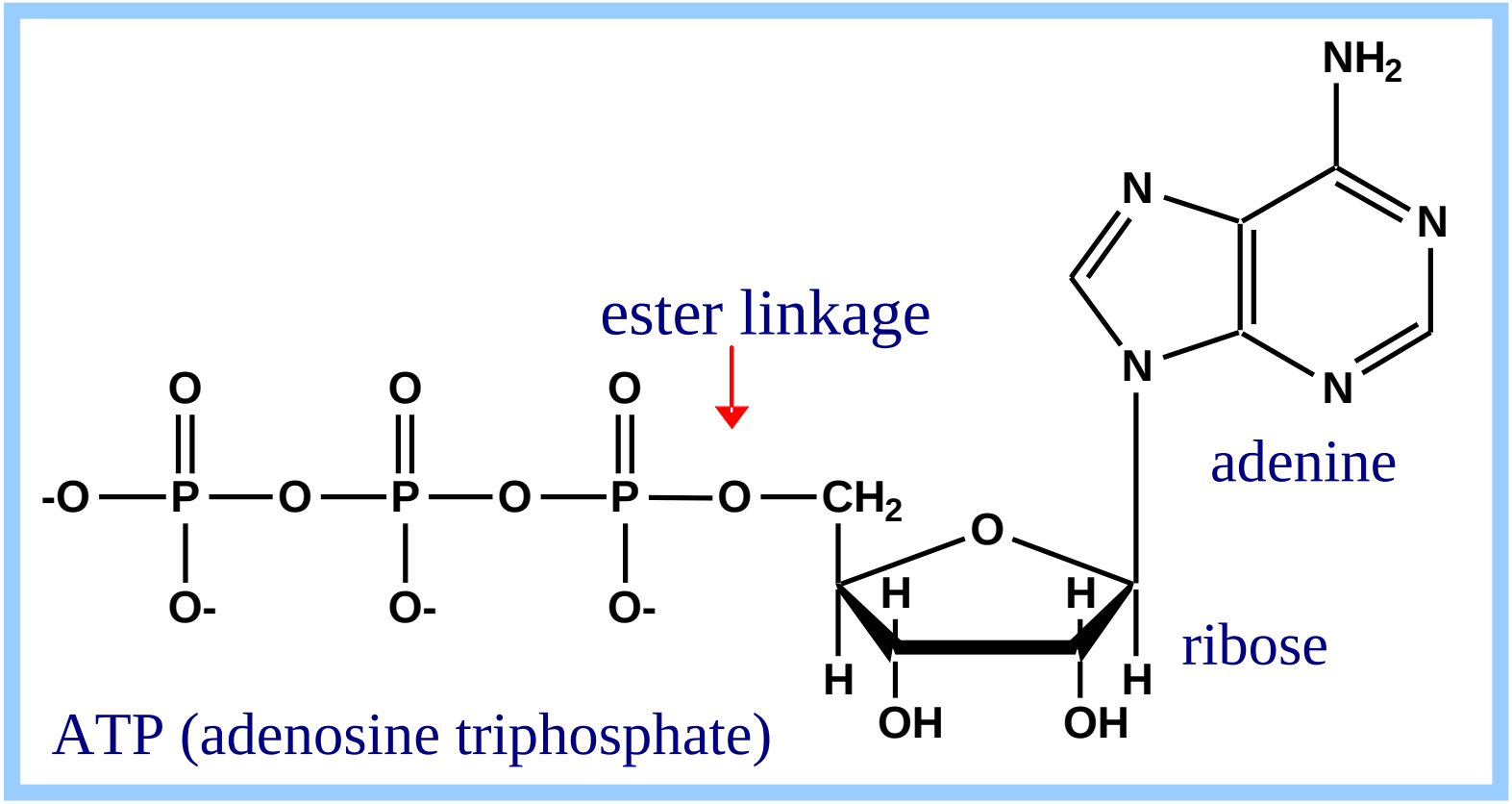
- Phosphocreatine is produced when ATP levels are high.
- When ATP is depleted during **exercise** in muscle, phosphate is transferred from phosphocreatine to ADP, to **replenish ATP**.



Phosphoenolpyruvate (PEP), involved in ATP synthesis in Glycolysis, has a very high ΔG of P_i hydrolysis.

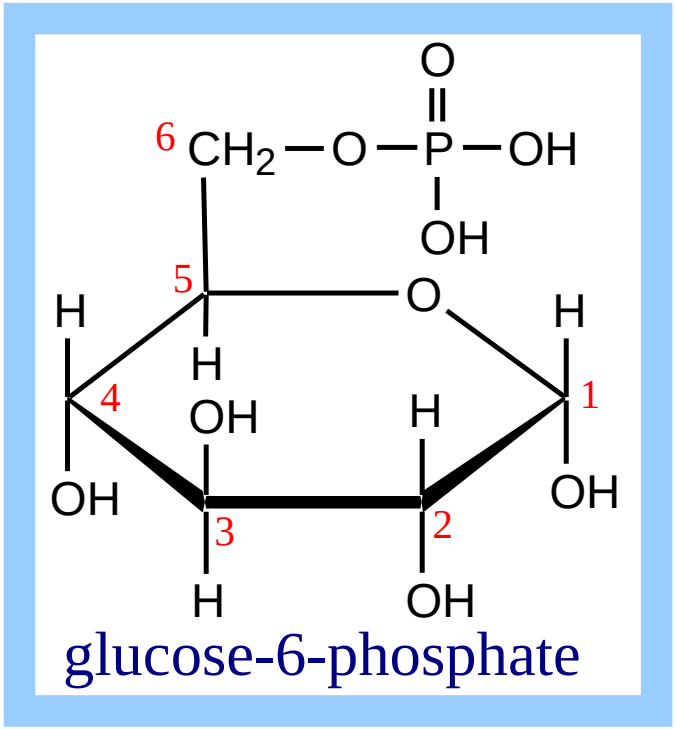
Removal of P_i from ester linkage in PEP is spontaneous because the enol spontaneously converts to a ketone.

The ester linkage in PEP is an exception.

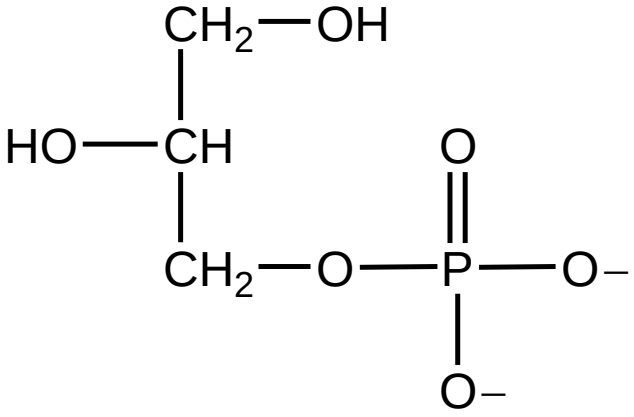


Generally **phosphate esters**, formed by splitting out water between a phosphoric acid and an OH group, have a **low but negative △G of hydrolysis**. Examples:

- the linkage between the first phosphate and the **ribose** hydroxyl of ATP.



glucose-6-phosphate



glycerol-3-phosphate

Other examples of **phosphate esters** with low but negative G of hydrolysis:

- the linkage between phosphate & a hydroxyl group in **glucose-6-phosphate** or **glycerol-3-phosphate**.

ATP has special roles in energy coupling & P_i transfer.

ΔG of phosphate hydrolysis from ATP is **intermediate** among examples below.

ATP can thus act as a P_i donor, & ATP can be synthesized by P_i transfer, e.g., from PEP.

Compound	$\Delta G^{o'}$ of phosphate hydrolysis, kJ/mol
Phosphoenolpyruvate (PEP)	− 61.9
Phosphocreatine	− 43.1
Pyrophosphate	− 33.5
ATP (to ADP)	− 30.5
Glucose-6-phosphate	− 13.8
Glycerol-3-phosphate	− 9.2

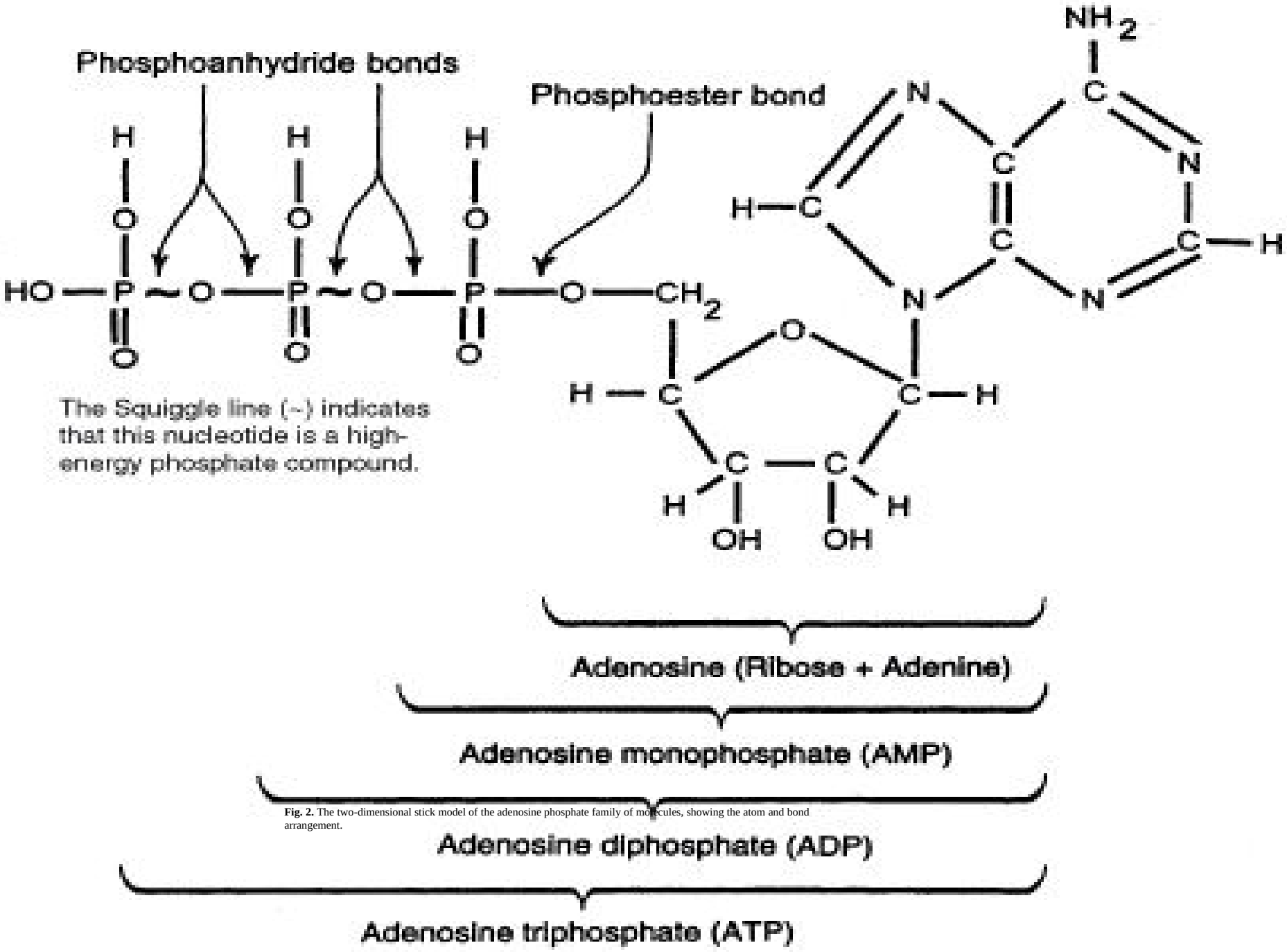
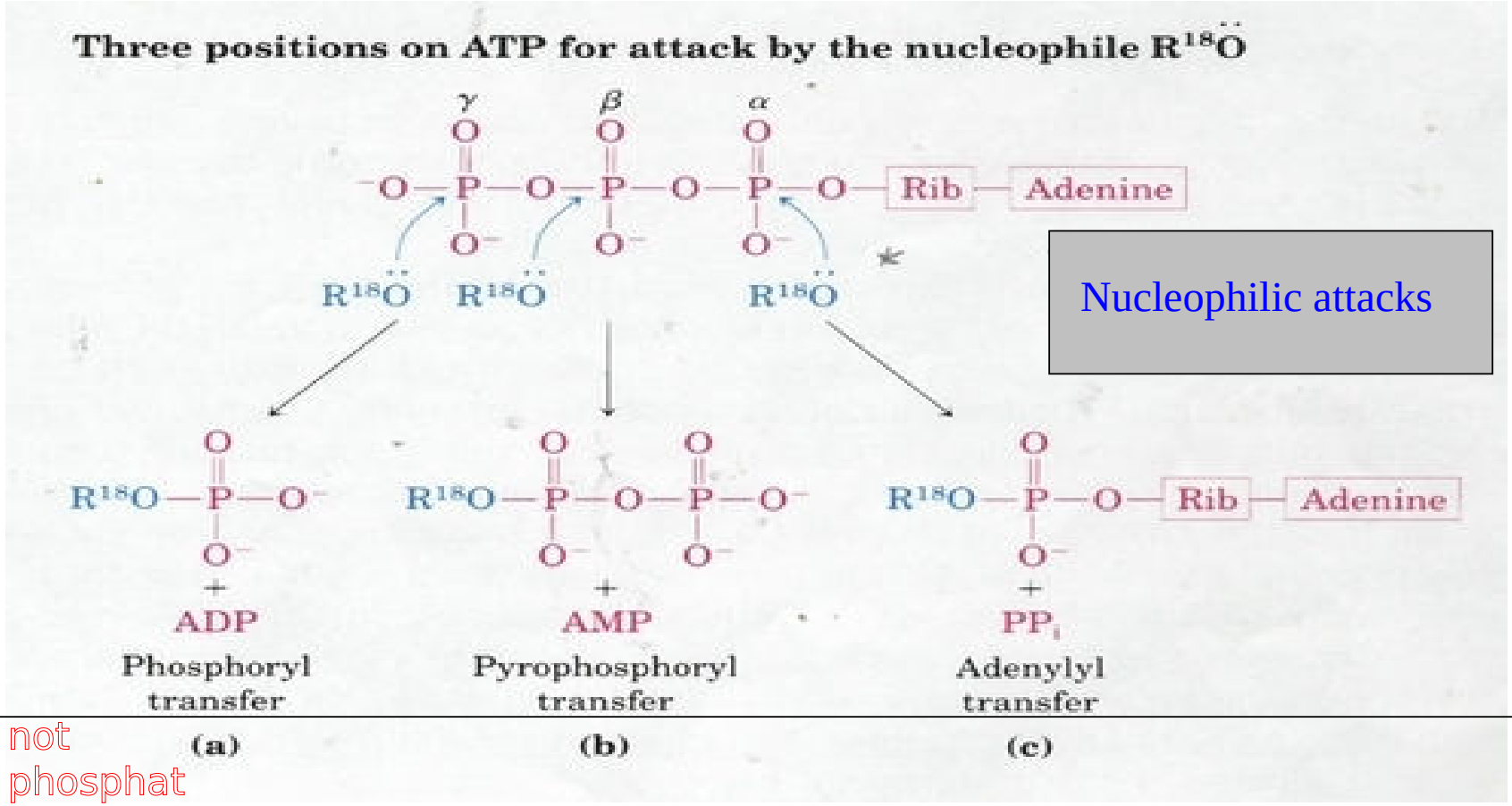


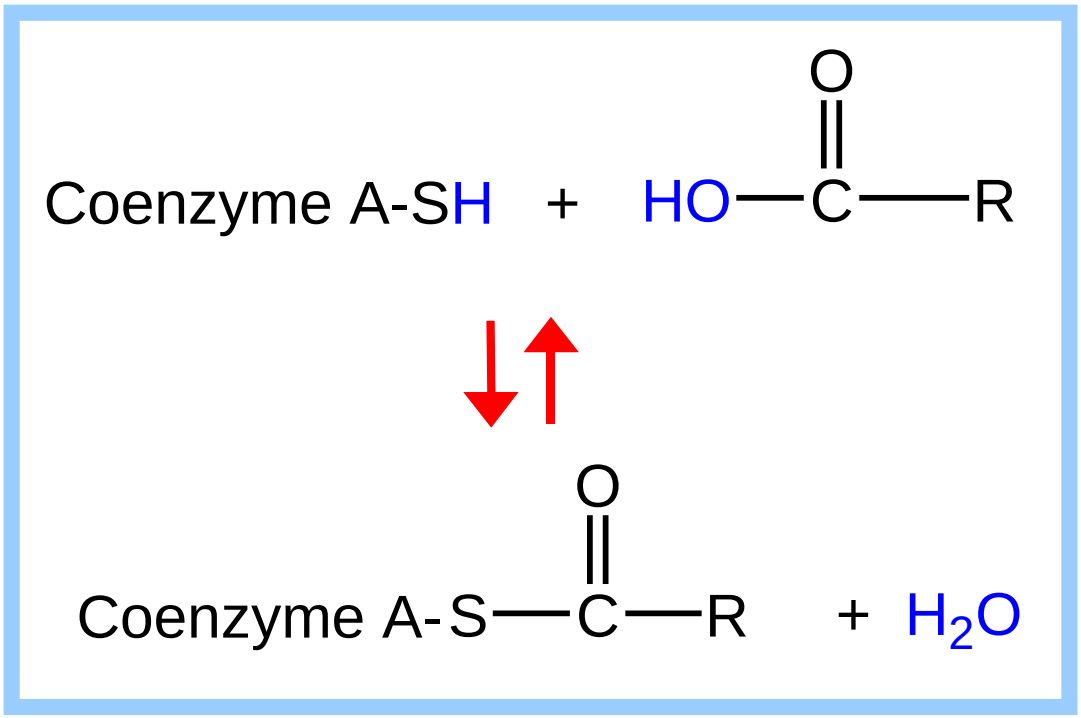
Fig. 2. The two-dimensional stick model of the adenosine phosphate family of molecules, showing the atom and bond arrangement.



not phosphate

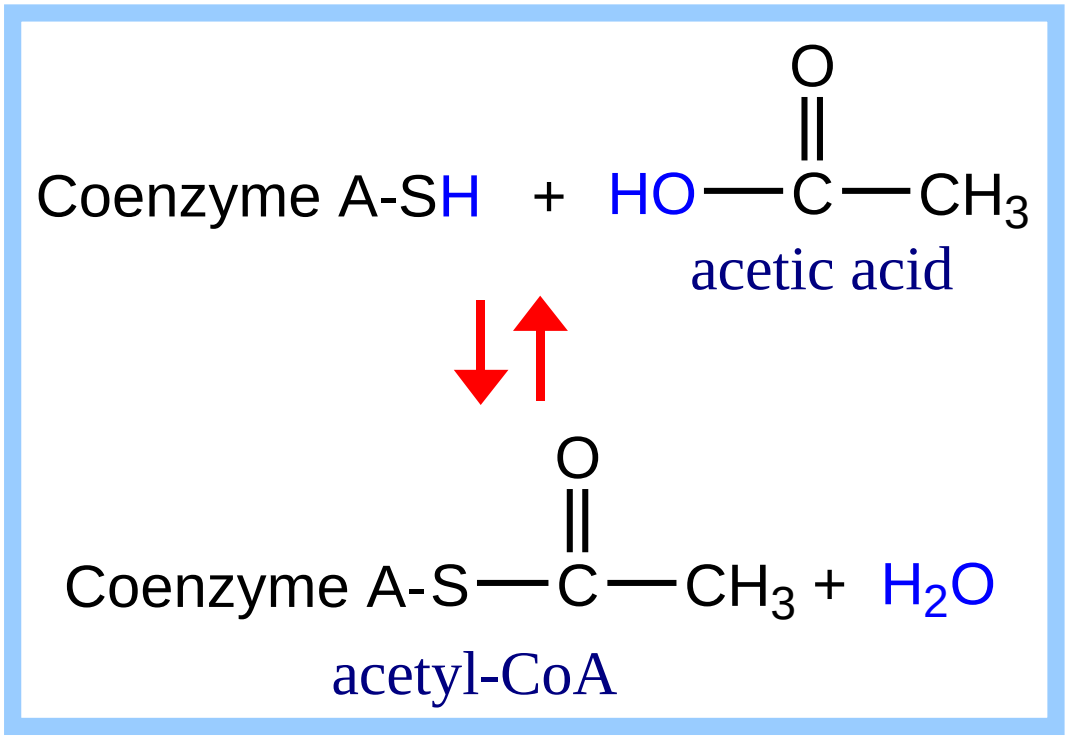
ATP usually provides energy by group transfer (forming covalent intermediates), not by simple hydrolysis.

Some other "high energy" bonds:



A **thioester** forms between a carboxylic acid & a thiol (SH), e.g., the thiol of **coenzyme A** (abbreviated CoA-SH).

Thioesters are **~** linkages. In contrast to phosphate esters, thioesters have a large negative G of hydrolysis.



The thiol of coenzyme A can react with a carboxyl group of acetic acid (yielding **acetyl-CoA**) or a fatty acid (yielding fatty acyl-CoA).

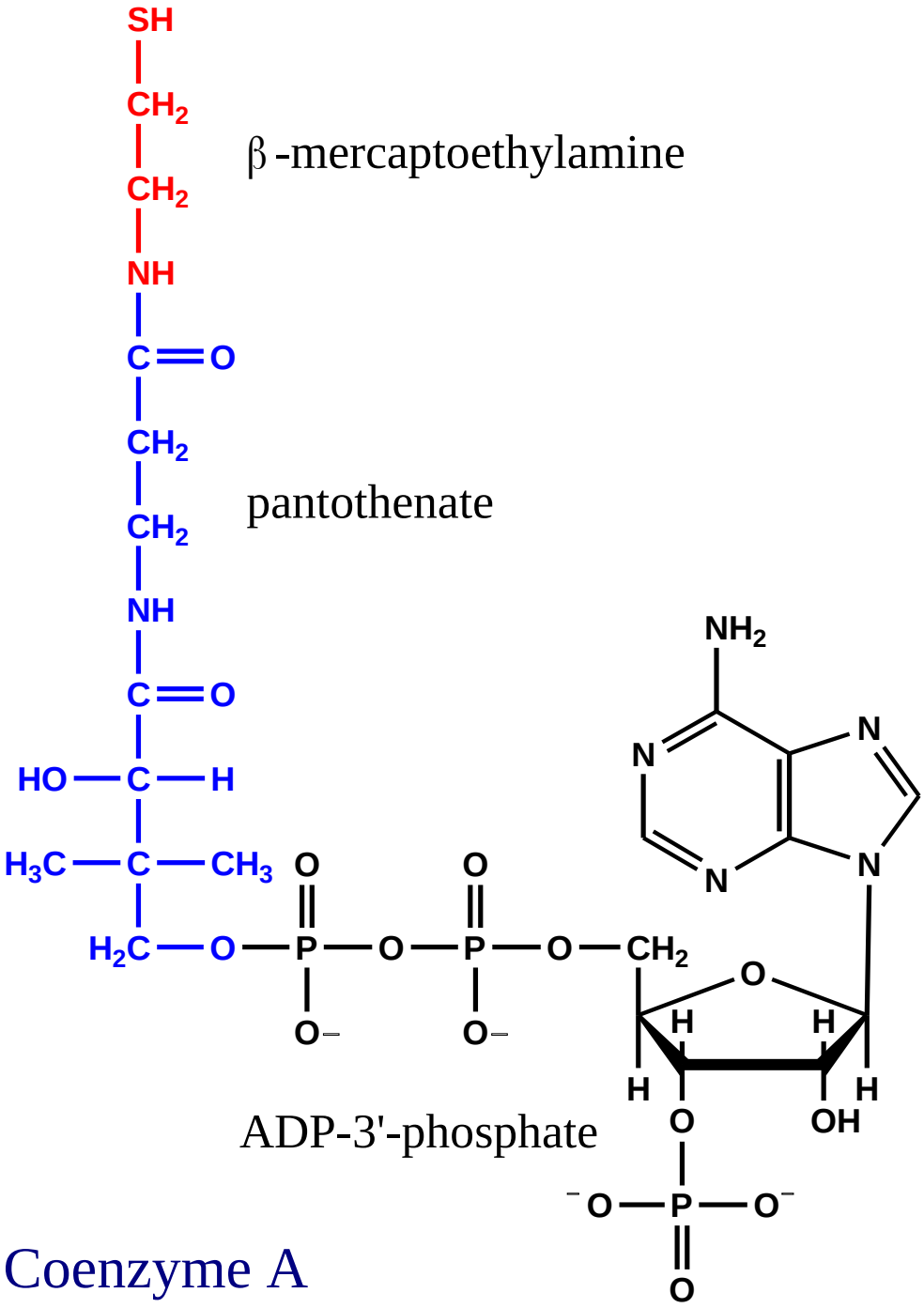
The spontaneity of thioester cleavage is essential to the role of coenzyme A as an **acyl group carrier**.

Like ATP, CoA has a high group transfer potential.

Coenzyme A includes **β-mercaptoethylamine**, in amide linkage to the carboxyl group of the B vitamin **pantothenate**.

The hydroxyl of pantothenate is in ester linkage to a phosphate of **ADP-3'-phosphate**.

The functional group is the **thiol** (SH) of β-mercaptoethylamine.

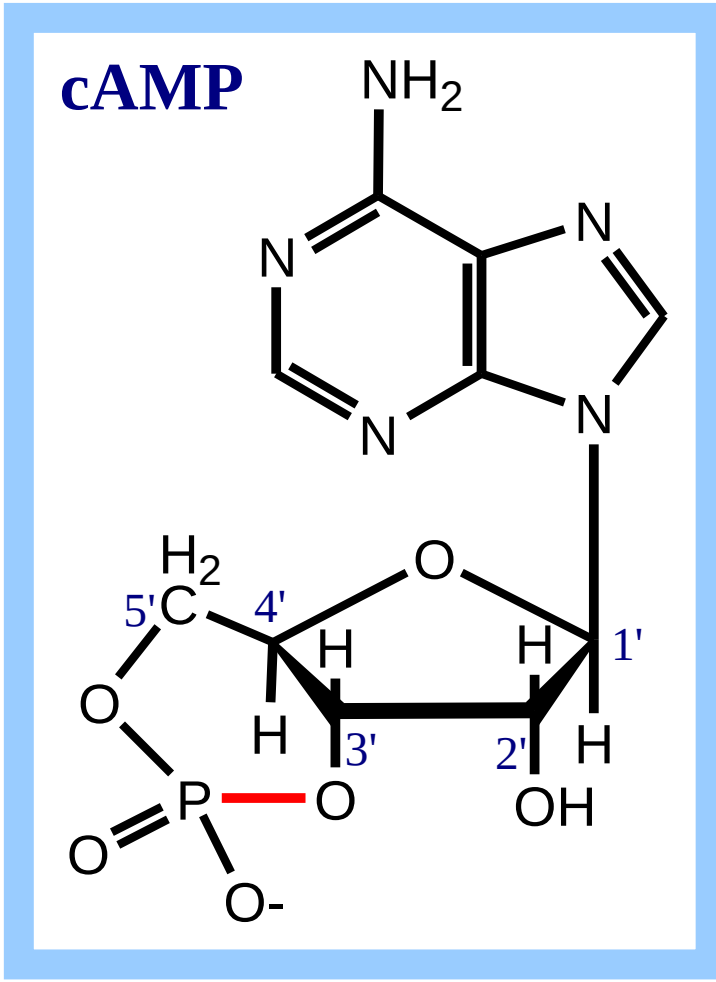


3',5'-Cyclic AMP (**cAMP**), is used by cells as a transient signal.

Adenylate Cyclase catalyzes cAMP synthesis: **ATP ⇒ cAMP + PP_i.**

The reaction is highly spontaneous due to the production of **PP_i**, which spontaneously hydrolyzes.

Phosphodiesterase catalyzes hydrolytic cleavage of one P_i ester (red), converting **cAMP ⇒ 5'-AMP**.



This is a highly spontaneous reaction, because cAMP is sterically constrained by having a phosphate with ester links to 2 hydroxyls of the same ribose. The lability of cAMP to hydrolysis makes it an excellent **transient signal**.

List compounds exemplifying the following **roles** of "high energy" bonds:

- **Energy transfer or storage**

  ATP, PP_i, polyphosphate, phosphocreatine

- **Group transfer**

  ATP, Coenzyme A

- **Transient signal**

  cyclic AMP

Kinetics vs Thermodynamics:

A **high activation energy barrier** usually causes hydrolysis of a “high energy” bond to be very **slow** in the absence of an enzyme catalyst.

This **kinetic stability** is **essential** to the role of ATP and other compounds with ~ bonds.

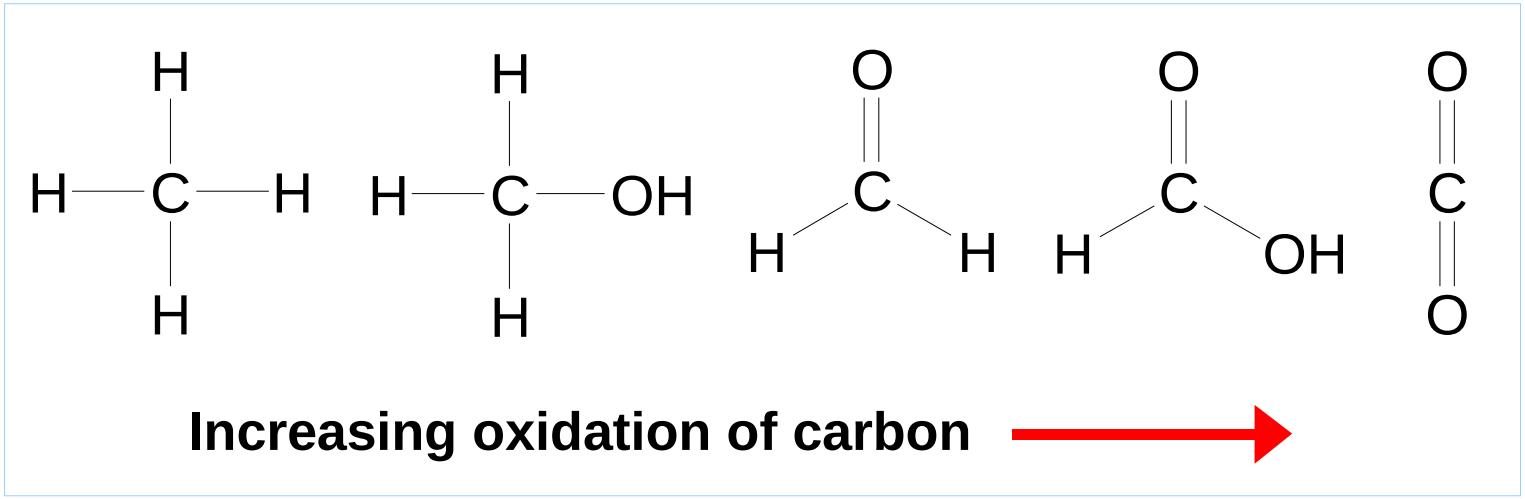
If ATP would rapidly hydrolyze in the absence of a catalyst, it could not serve its important roles in energy metabolism and phosphate transfer.

Phosphate is removed from ATP only when the reaction is coupled via enzyme catalysis to some other reaction useful to the cell, such as transport of an ion, phosphorylation of glucose, or regulation of an enzyme by phosphorylation of a serine residue.

Oxidation & reduction

Oxidation of an iron atom involves loss of an electron (to an acceptor): **Fe^{++}(reduced) Fe^{+++}(oxidized) + e^-**

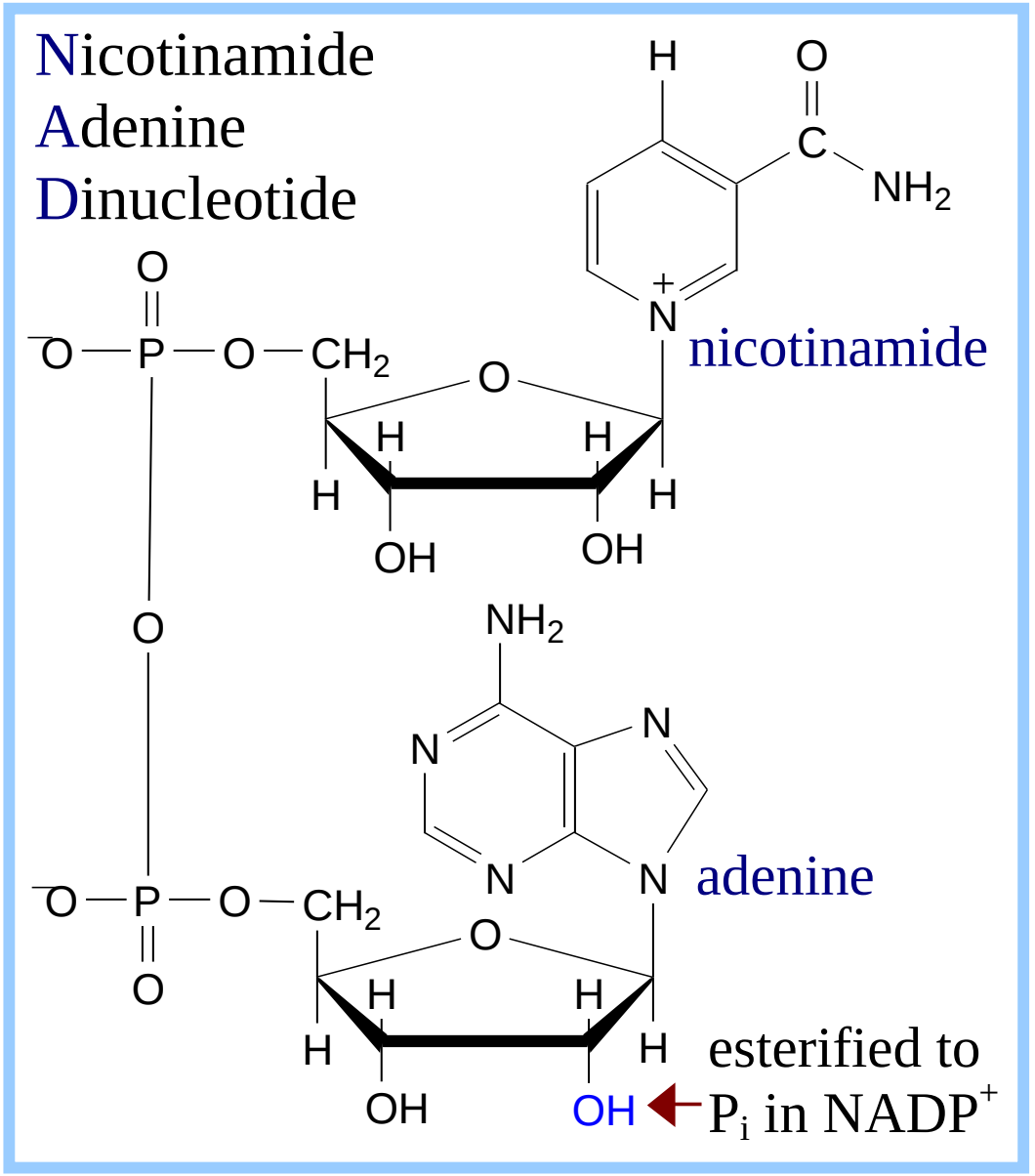
Since electrons in a C-O bond are associated more with O, increased oxidation of a C atom means increased number of C-O bonds. Oxidation of C is spontaneous.



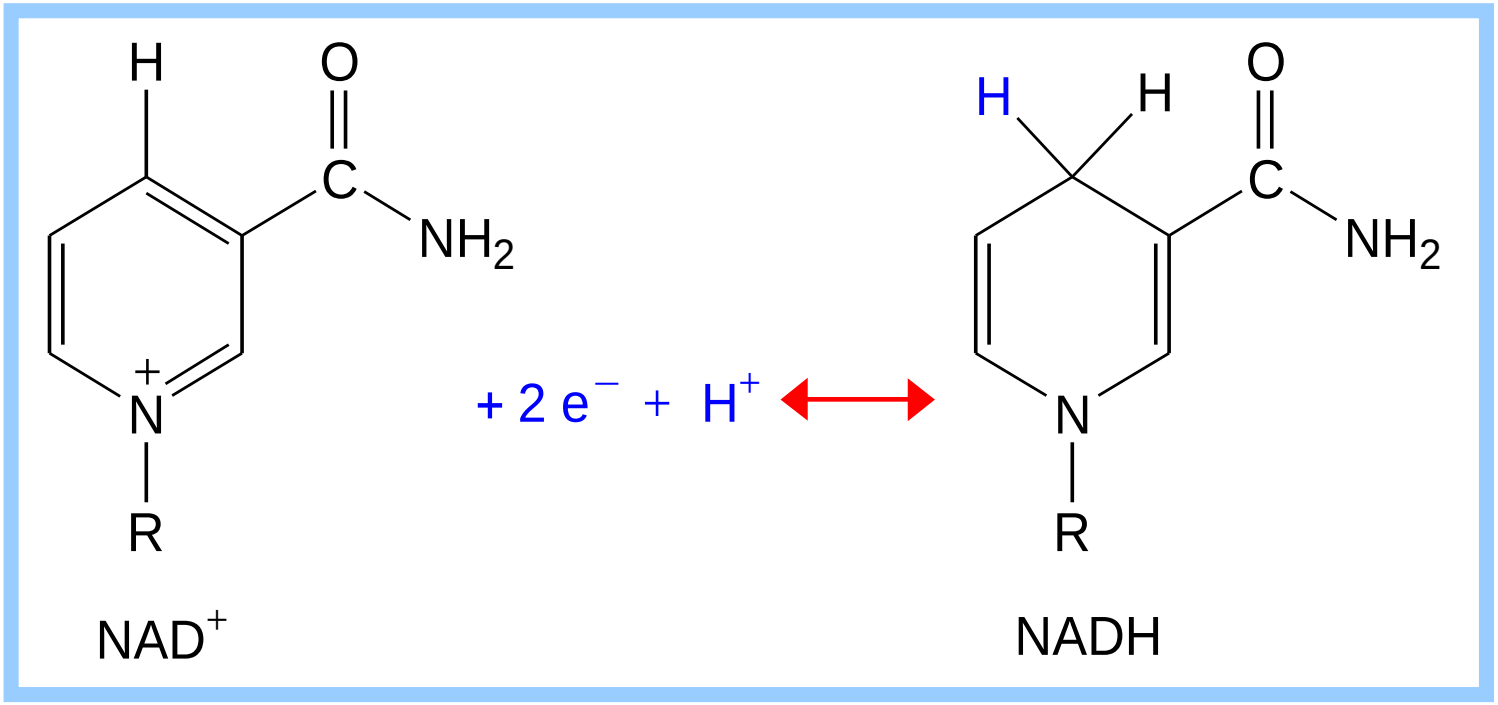
NAD$^+$, **N**icotinamide **A**denine **D**inucleotide, is an electron acceptor in catabolic pathways.

The nicotinamide ring, derived from the vitamin **niacin**, accepts 2 e^- & 1 H^+ (a hydride) in going to the reduced state, **NADH**.

NADP$^+$/NADPH is similar except for P_i. NADPH is e^- donor in synthetic pathways.



$NAD^+/NADH$

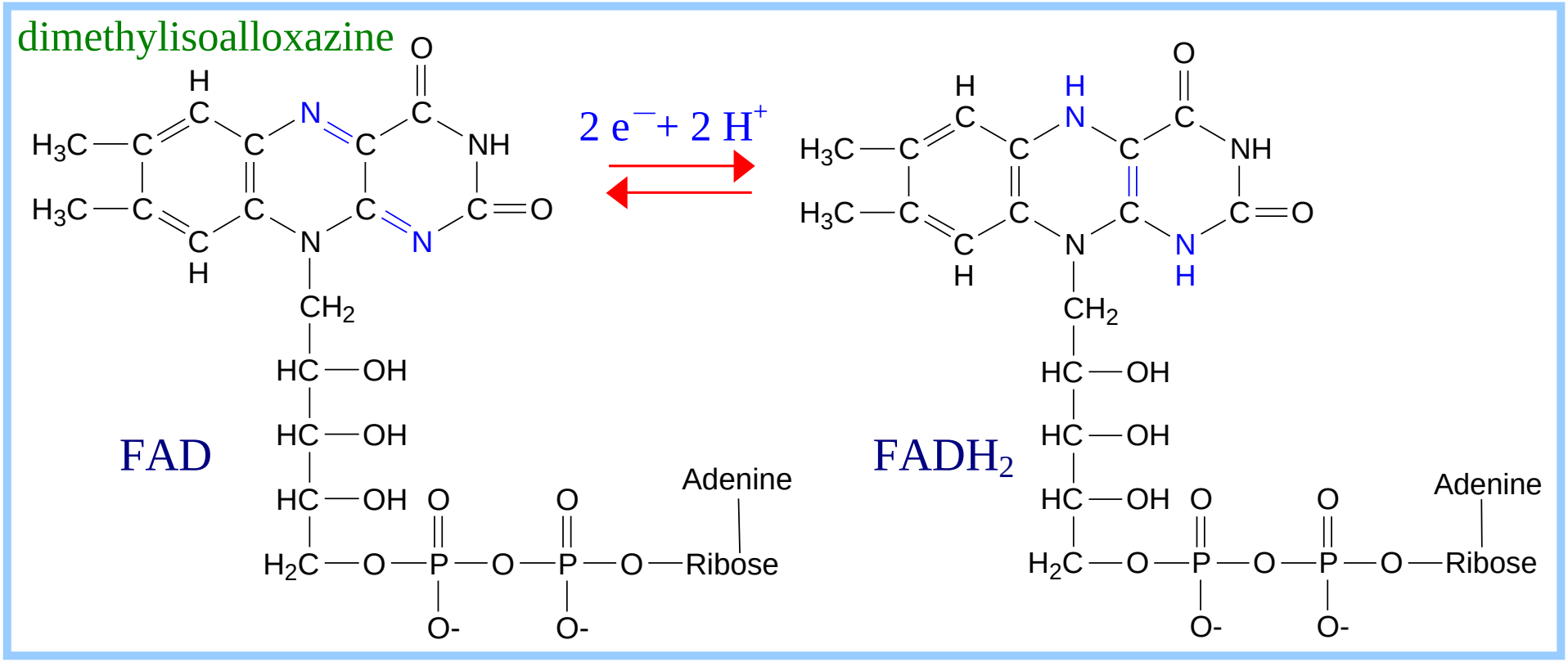


The electron transfer reaction may be summarized as :

$NAD^+ + 2e^- + H^+ \Leftrightarrow NADH.$

It may also be written as:

$NAD^+ + 2e^- + 2H^+ \Leftrightarrow NADH + H^+$



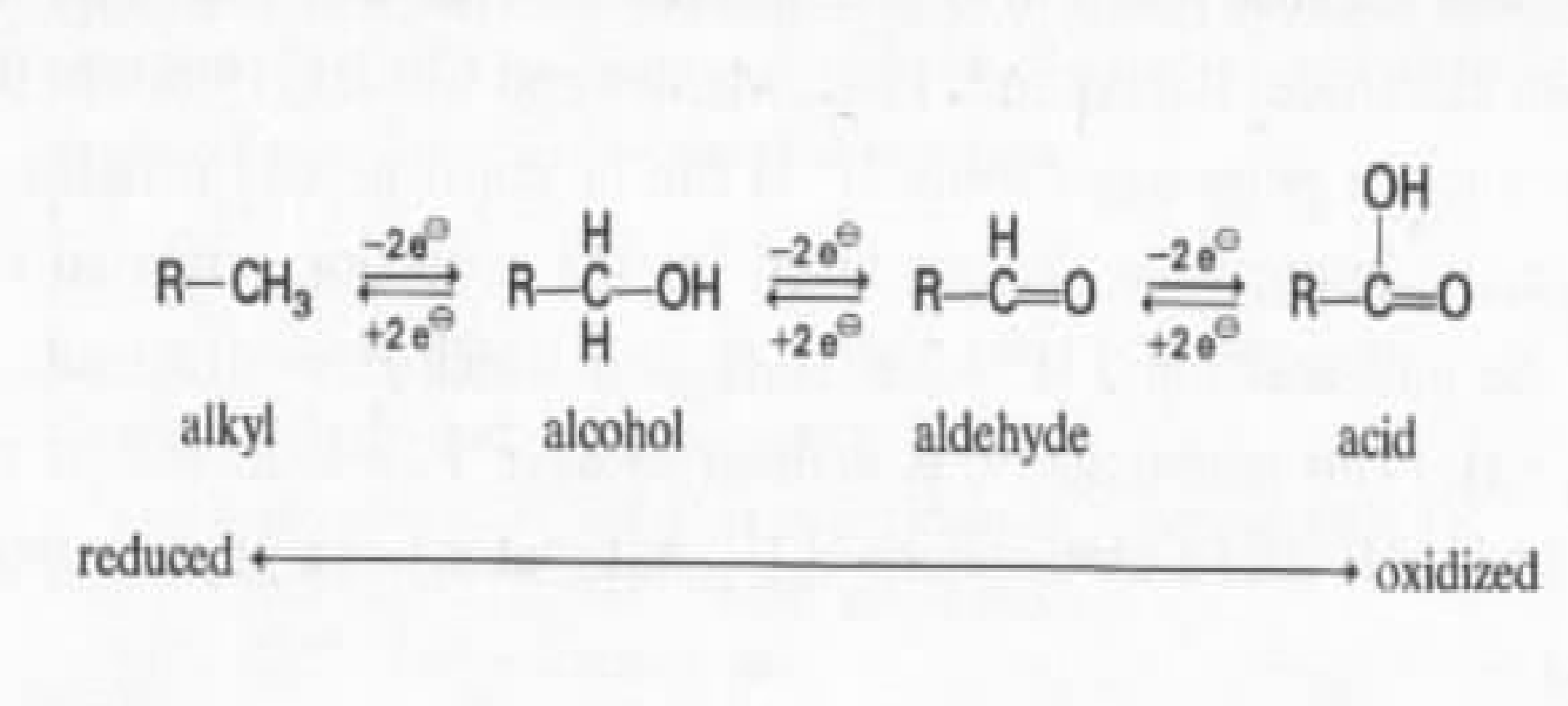
FAD (**F**lavin **A**denine **D**inucleotide), derived from the vitamin **riboflavin**, functions as an e^- acceptor. The dimethylisoalloxazine ring undergoes reduction/oxidation.

FAD accepts 2 e^- + 2 H^+ in going to its reduced state:

FAD + 2 e^- + 2 H^+ ⟺ $FADH_2$

Electron transfer via oxidation-reduction reactions generates biological energy

- When electrons flow from a low affinity carrier (e.g., glucose) to a high affinity carrier (e.g., O_2), an electromotive force (emf) will be generated (with energy released and work done).
- Oxidation of energy-rich biological fuels *often* means dehydrogenation (catalyzed by *dehydrogenases*) from carbons having various oxidation states.

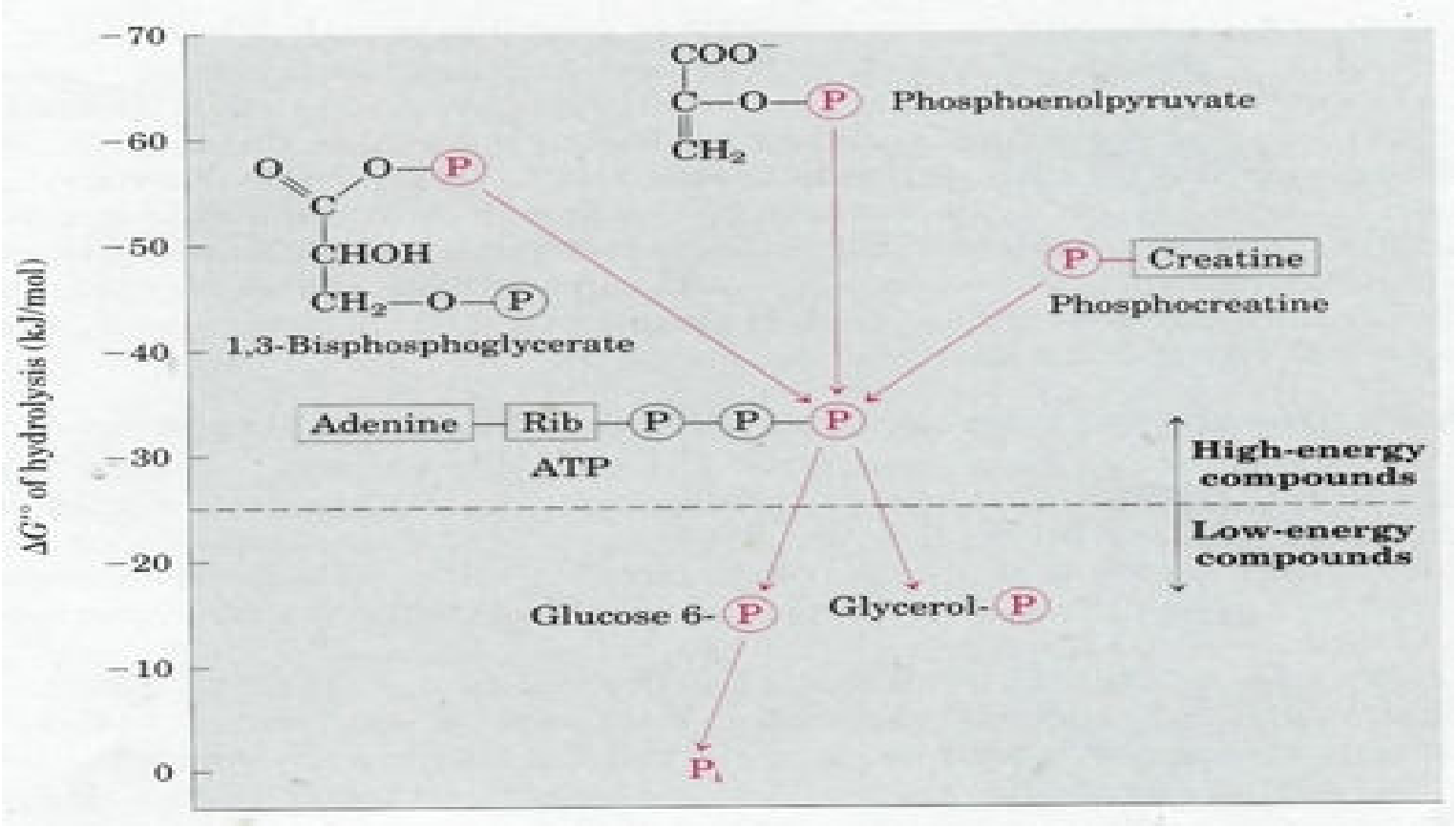


Carbons have various oxidation states, with hydrocarbon being the most reduced and CO_2 being the most oxidized.

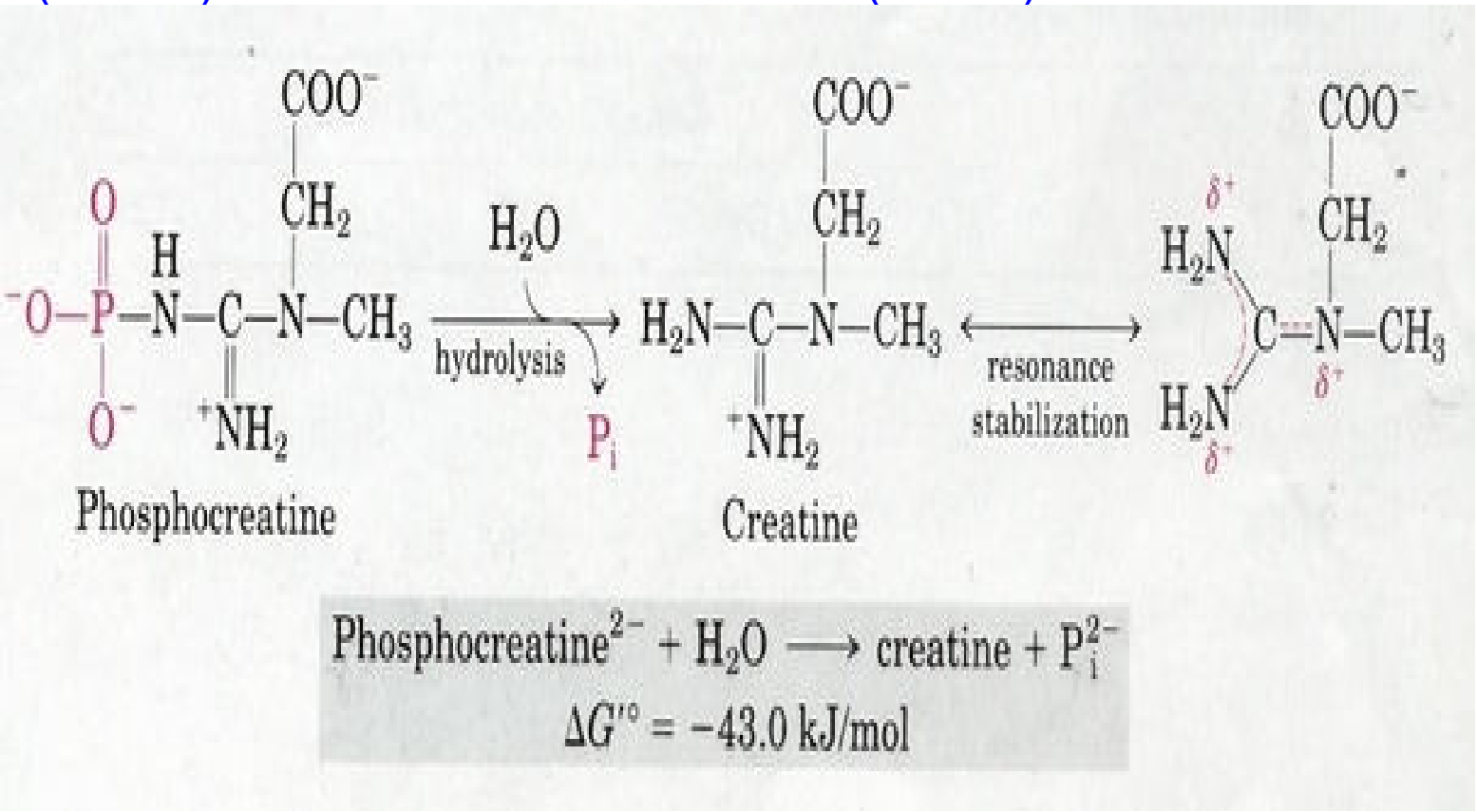
- NAD and NADP can easily diffuse out of the enzymes, but FMN and FAD are tightly bound to the enzymes (thus being called *prosthetic groups*, and the complex proteins being called *flavoproteins*).
- NADH and $FADH_2$ will be further oxidized via the respiratory chain for ATP production.
- ADP is commonly present in all these universal electron carriers (as well as in Coenzyme A and ATP).

ATP is the universal currency for biological energy

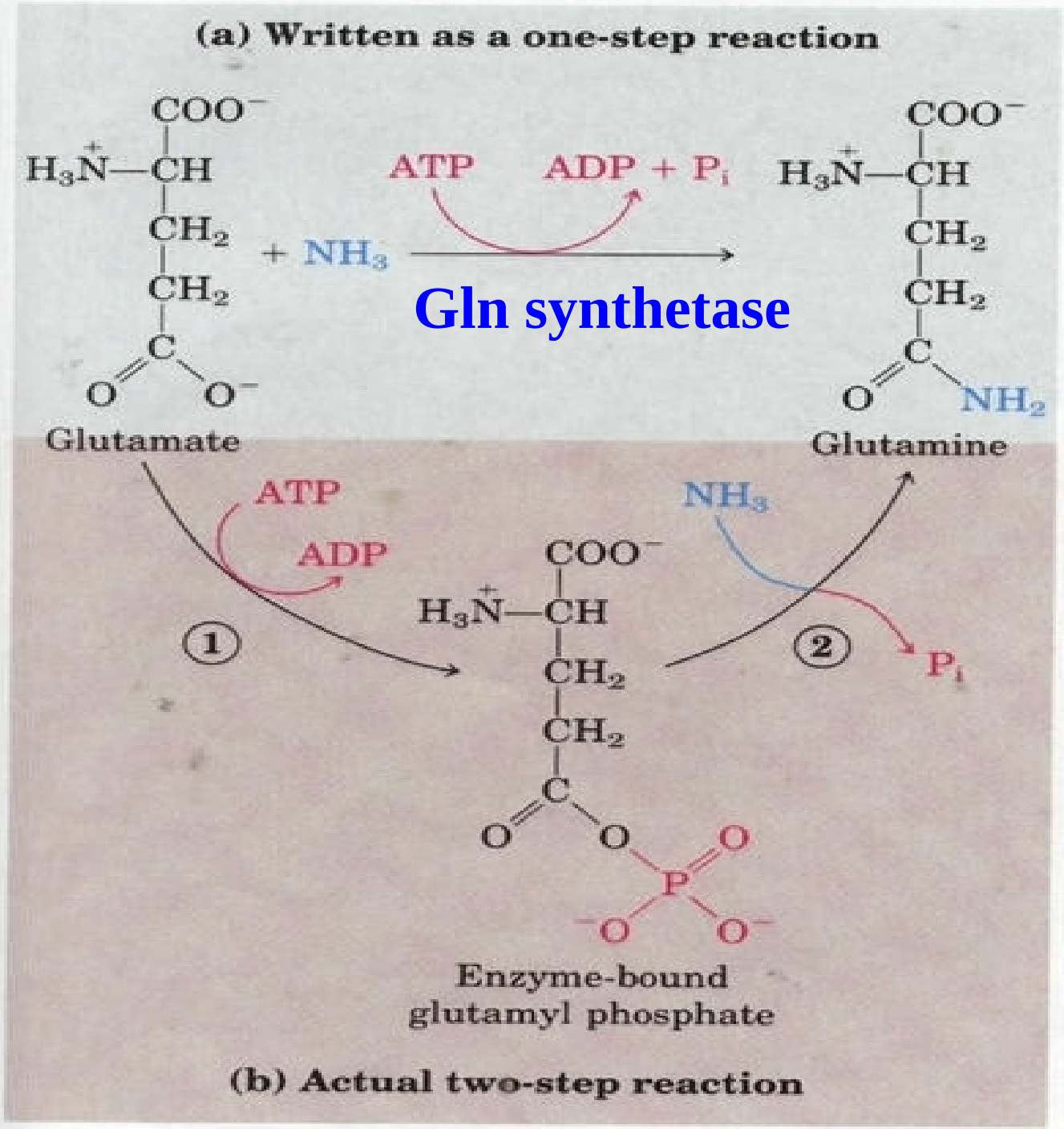
- This was first perceived by Fritz Lipmann and Herman Kalckar in 1941 when studying glycolysis.
- Hydrolysis of the two phosphoanhydride bonds in ATP generate *more stable products* releasing large amount of free energy ($\Delta G'^{0}$ is -30.5 kJ/mol; ΔG_p in cells is -50 to -65 kJ/mol).
- The ATP molecule is kinetically stable at pH 7 and enzyme catalysis is needed for its hydrolysis.
- ATP actually exists as a sum of various species in cells (e.g., ATP^{4-} $MgATP^{2-}$).


−70
−60
−50
−40
−30
−20
−10
0
ΔG'° of hydrolysis (kJ/mol)
COO⁻
C—O—P
CH₂
Phosphoenolpyruvate
O
O—P
C
CHOH
CH₂—O—P
1,3-Bisphosphoglycerate
P
Creatine
Phosphocreatine
Adenine
Rib
P
P
P
ATP
High-energy compounds
Low-energy compounds
Glucose 6-
P
Glycerol-
P
Pi

(+ ADP) (+ ATP)



ATP is not a long-term storage form of free energy in living cells, but .



ATP provides energy usually through group transfer (protein could also be such acceptors)

There are five major pathways of glucose metabolism:

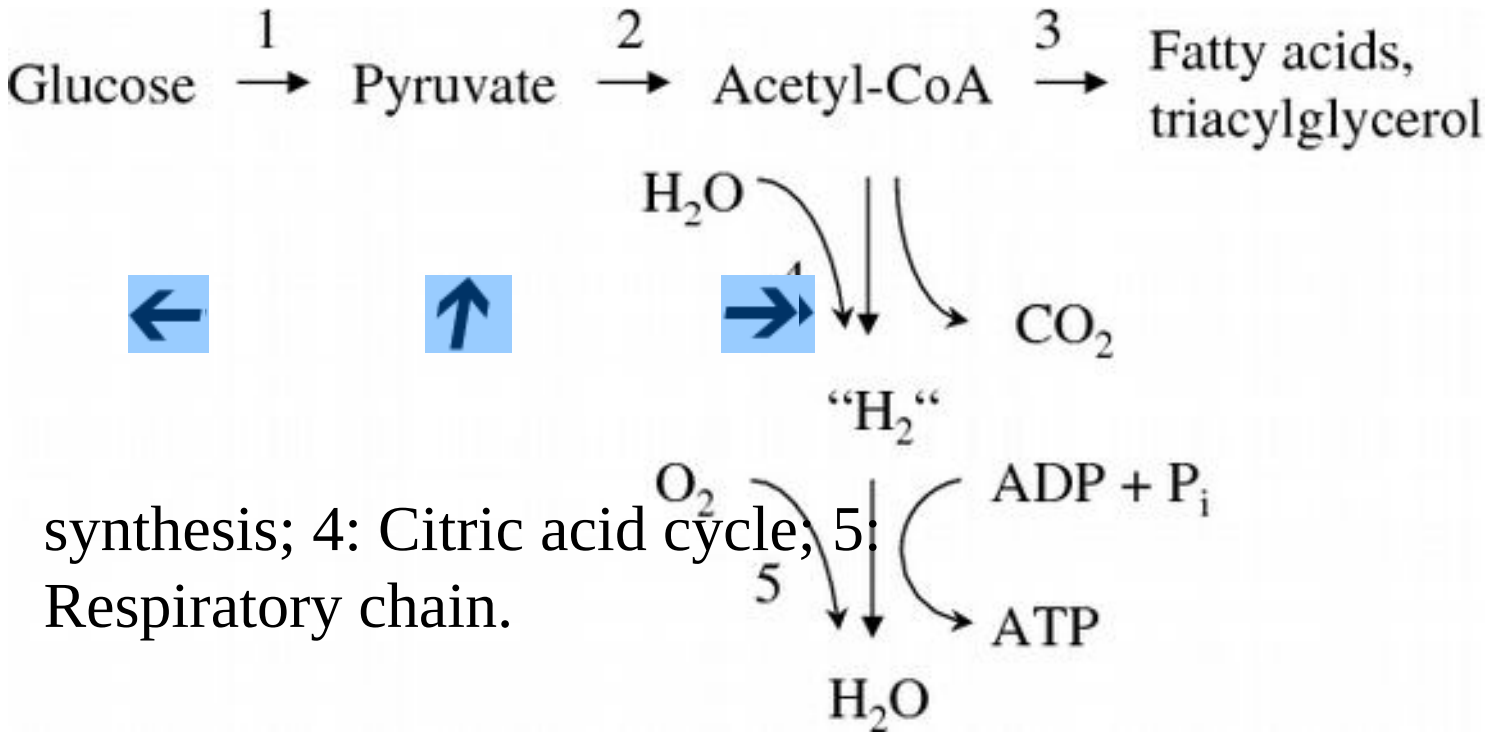
1.Glycolysis, which accomplishes the degradation of glucose to pyruvate. Its main purpose is the generation of energy (ATP). Glycolysis generates some ATP directly, and more indirectly by way of subsequent oxidation of pyruvate. The need for ATP is universal, so that the glycolytic pathway is found in every cell of our body.

2.The hexose monophosphate shunt. This pathway also breaks down glucose, but the main product is not ATP but NADPH. NADPH is universally needed as a reducing agent, so hat this pathway is ubiquitous, too.

3.Glycogen synthesis. Glycogen is a polymeric storage form of glucose, not unlike starch which is found in plants. This pathway is quantitatively most important in the liver and the striated muscle

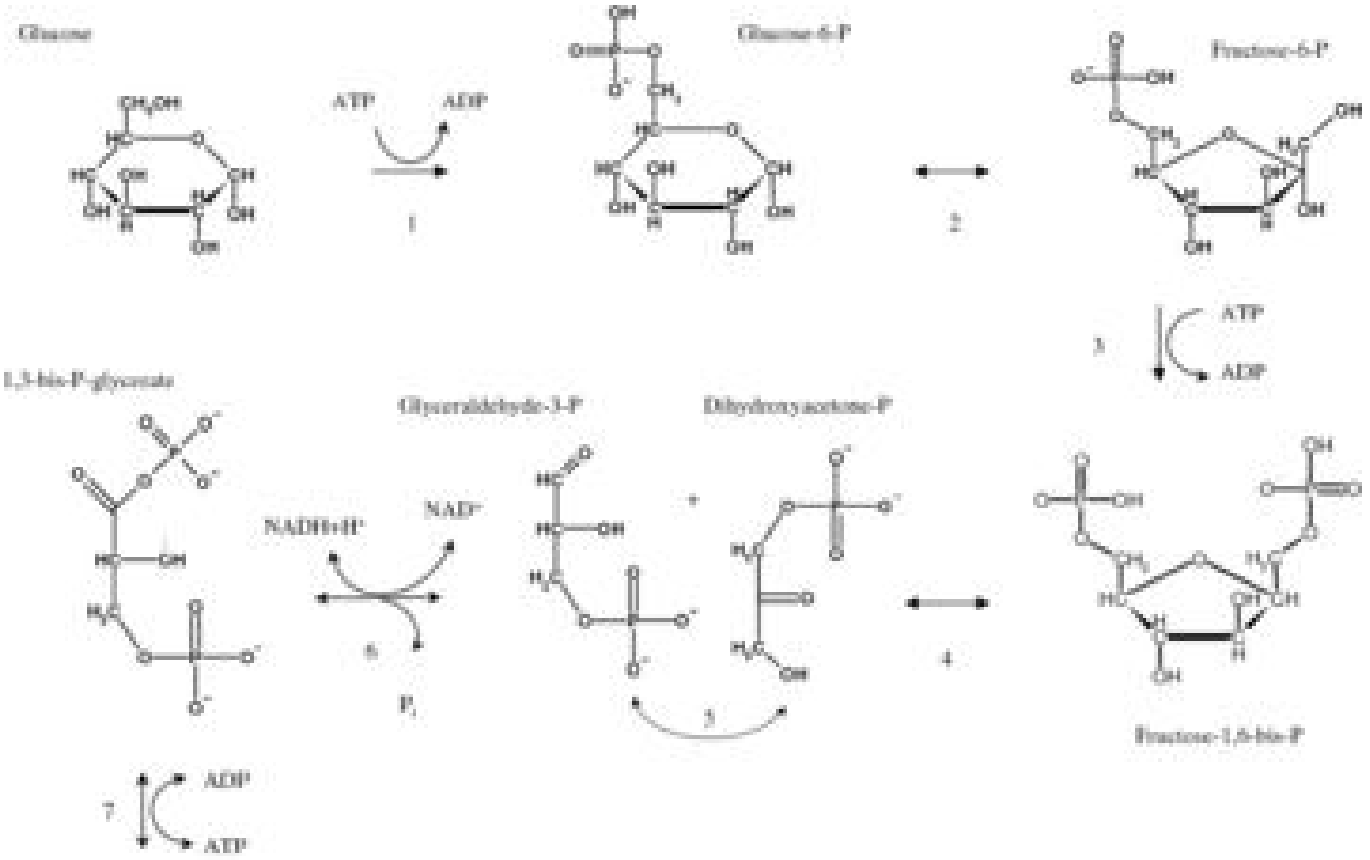
4 Glycogen breakdown to glucose, like glycogen synthesis most important in liver and muscle. This pathway is activated if the current external supply of glucose is low (as between meals). In the liver, the glucose generated from glycogen is released into the general circulation. Sceletal muscle cells utilize the glucose themselves, for the purpose of ATP synthesis and then muscle action.

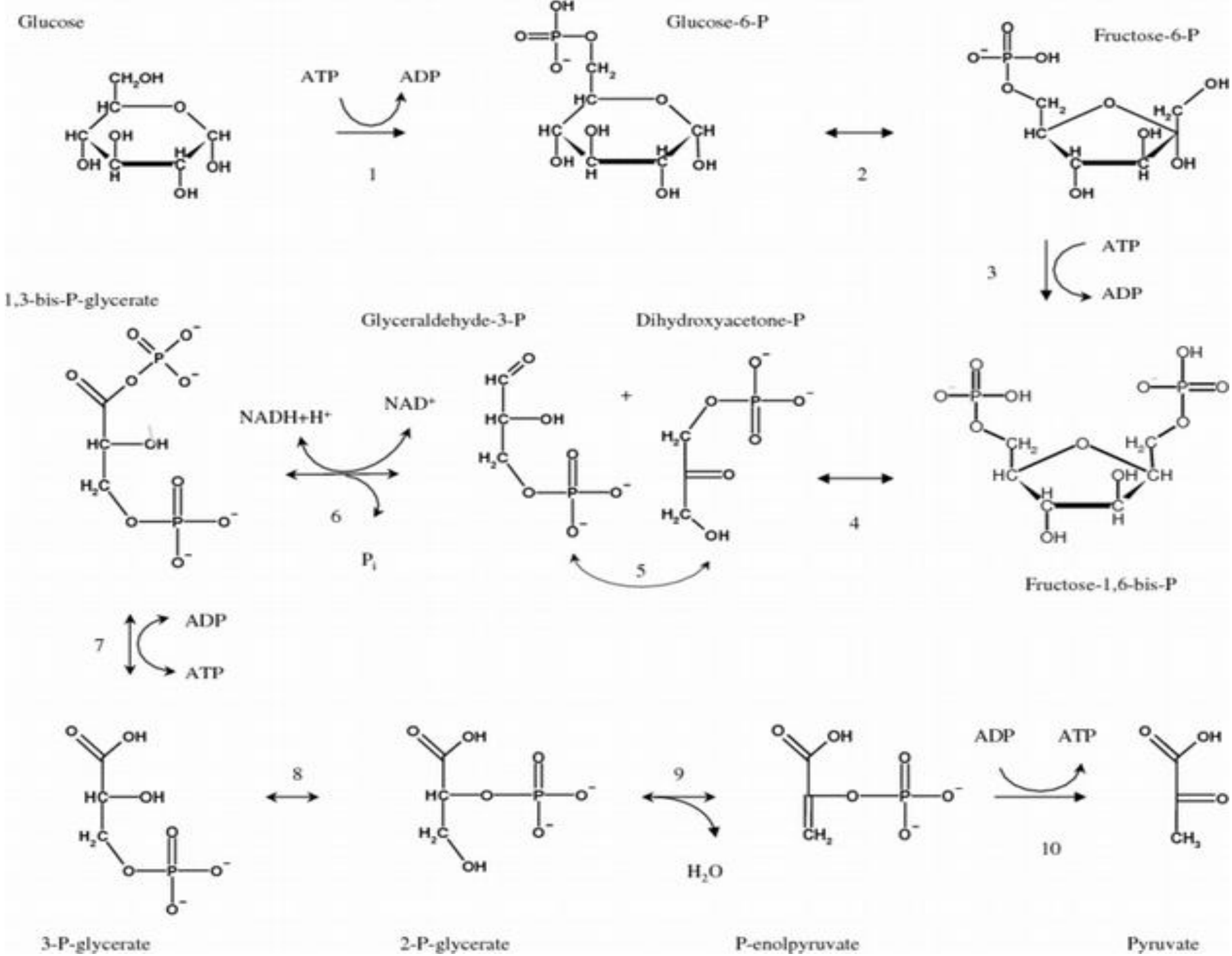
5 Gluconeogenesis. This pathway turns pyruvate derived from amino acids into glucose; it thus is essentially the reversal of glycolysis. It, too, is activated in times of low external glucose supply. The amino acid substrates may be obtained from a protein-rich diet (e.g. if we feast on meat exclusively) or by internal protein breakdown (mainly in the muscle). Gluconeogenesis occurs in the liver and in the kidneys.

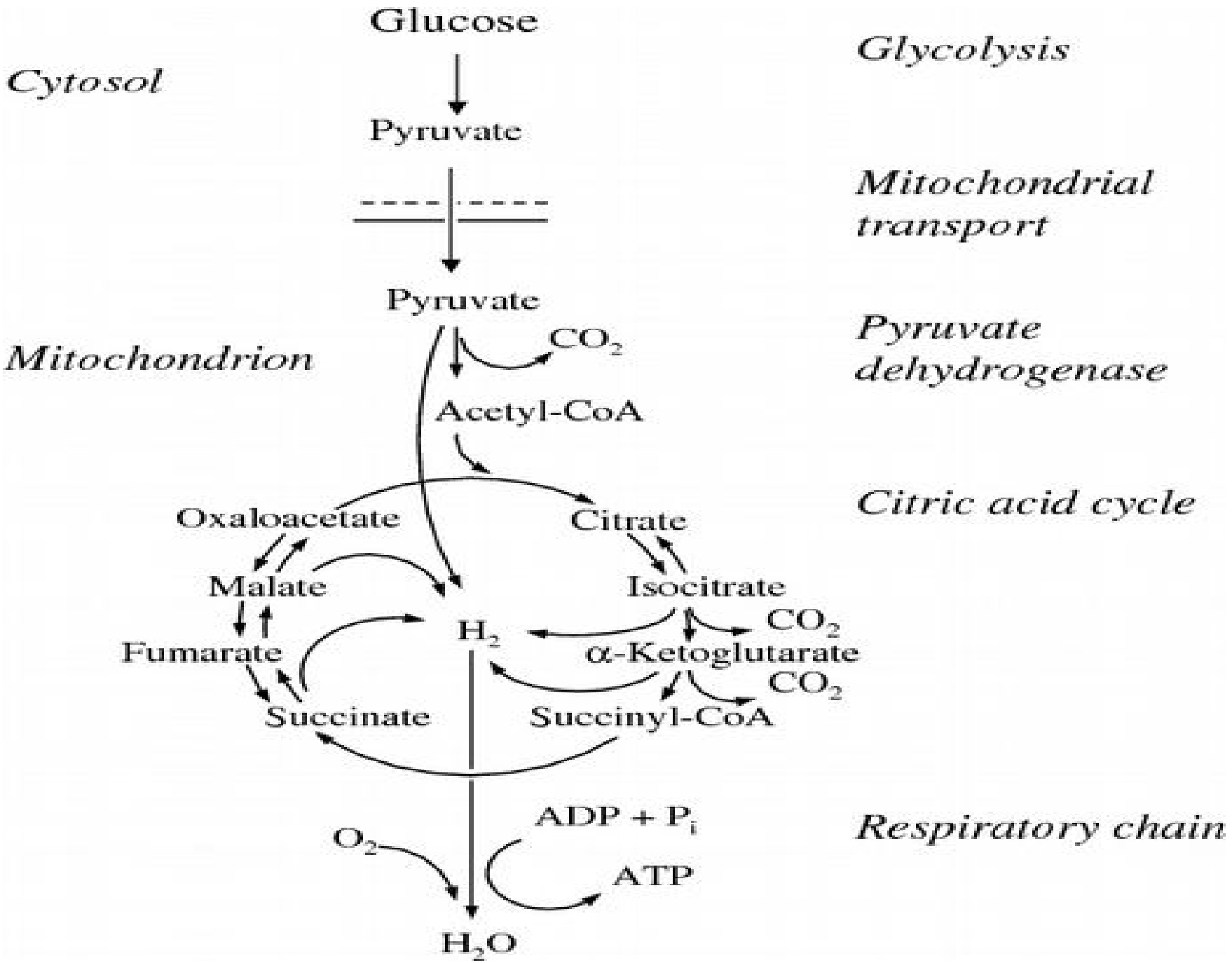


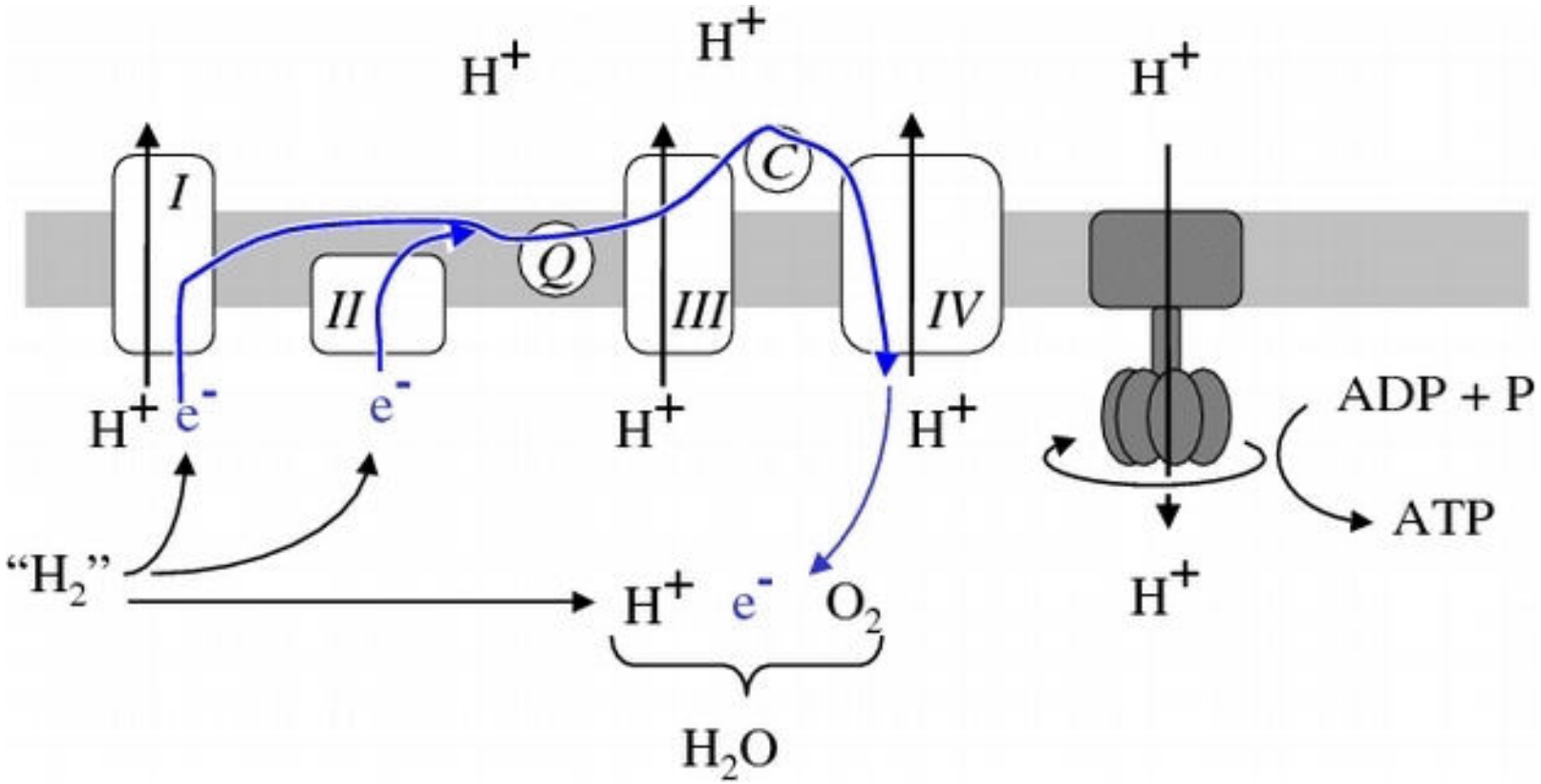
synthesis; 4: Citric acid cycle; 5: Respiratory chain.

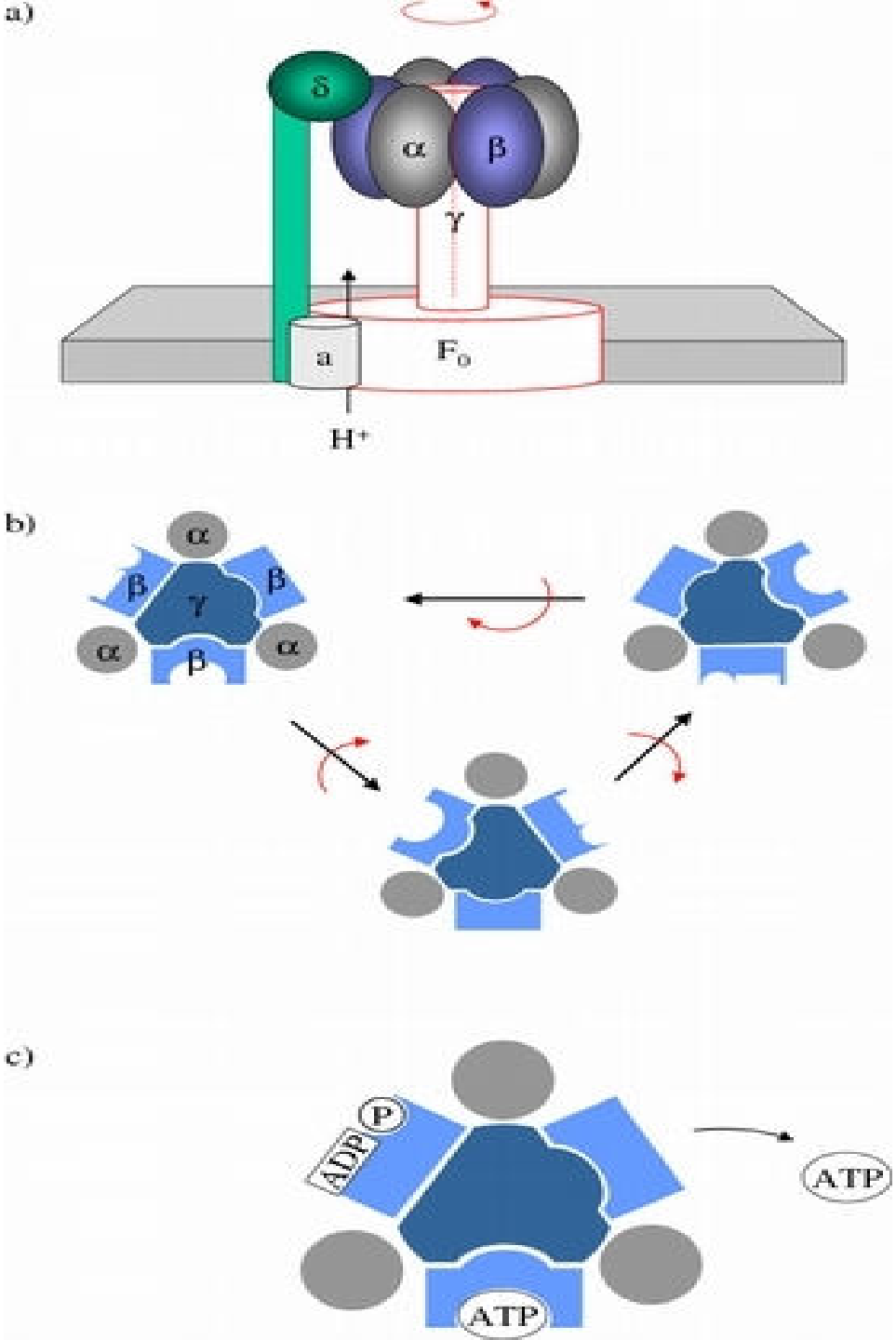
Overview of glucose degradation. 1: Glycolysis; 2: Pyruvate dehydrogenase; 3: Fatty acid synthesis; 4: Citric acid cycle; 5: Respiratory chain


Glucose
ATP
ADP
1
Glucose-6-P
2
Fructose-6-P
3
ATP
ADP
1,3-bis-P-glycerate
Glyceraldehyde-3-P
Dihydroxyacetone-P
NADH+H+
NAD+
6
Pi
4
5
Fructose-1,6-bis-P
7
ADP
ATP
8
9
H2O
ADP
ATP
10
3-P-glycerate
2-P-glycerate
P-enolpyruvate
Pyruvate

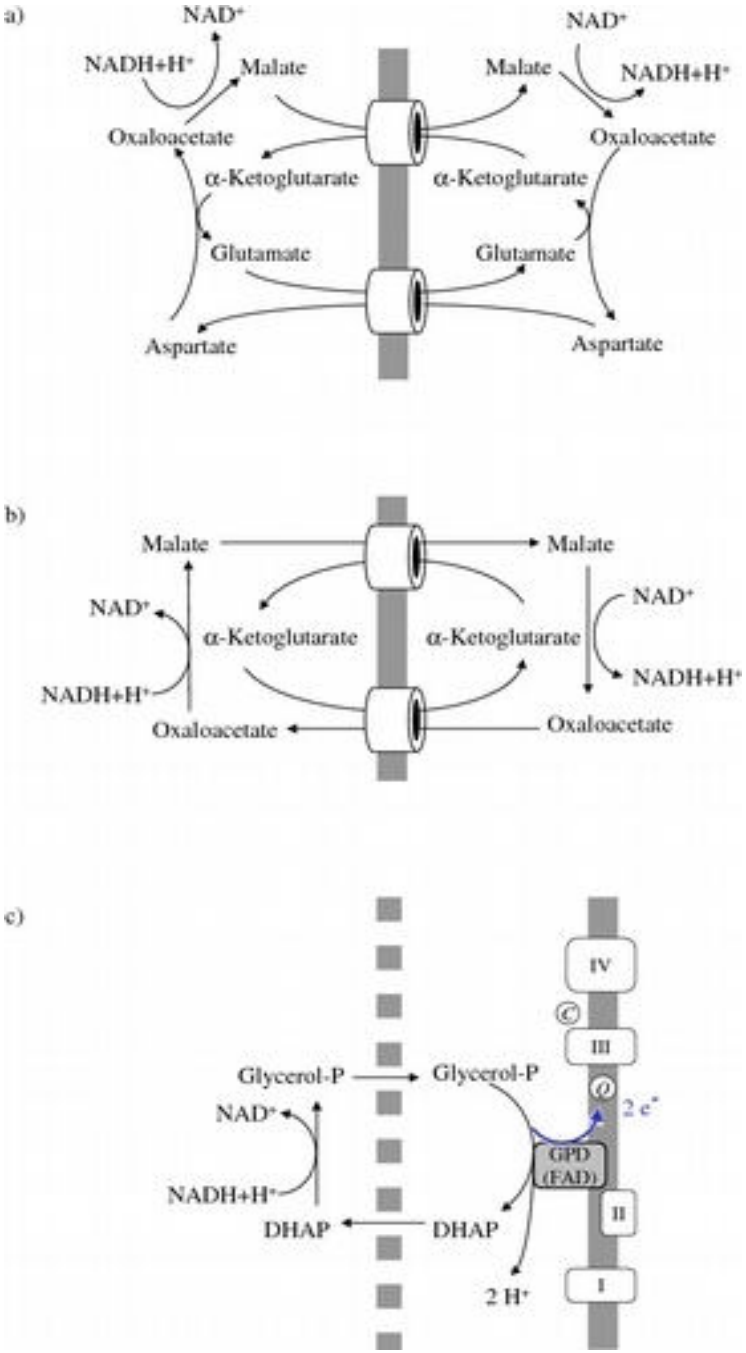

Glucose
ATP
ADP
1
Glucose-6-P
2
Fructose-6-P
3
ATP
ADP
1,3-bis-P-glycerate
Glyceraldehyde-3-P
Dihydroxyacetone-P
NADH+H+
NAD+
6
Pi
+
4
5
Fructose-1,6-bis-P
7
ADP
ATP
8
9
H2O
ADP
ATP
10
3-P-glycerate
2-P-glycerate
P-enolpyruvate
Pyruvate


Glucose
Cytosol
Glycolysis
Pyruvate
Mitochondrial transport
Pyruvate
Mitochondrion
CO_2
Pyruvate dehydrogenase
Acetyl-CoA
Citric acid cycle
Oxaloacetate
Citrate
Malate
Isocitrate
H_2
CO_2
Fumarate
α-Ketoglutarate
CO_2
Succinate
Succinyl-CoA
ADP + P_i
O_2
Respiratory chain
ATP
H_2O

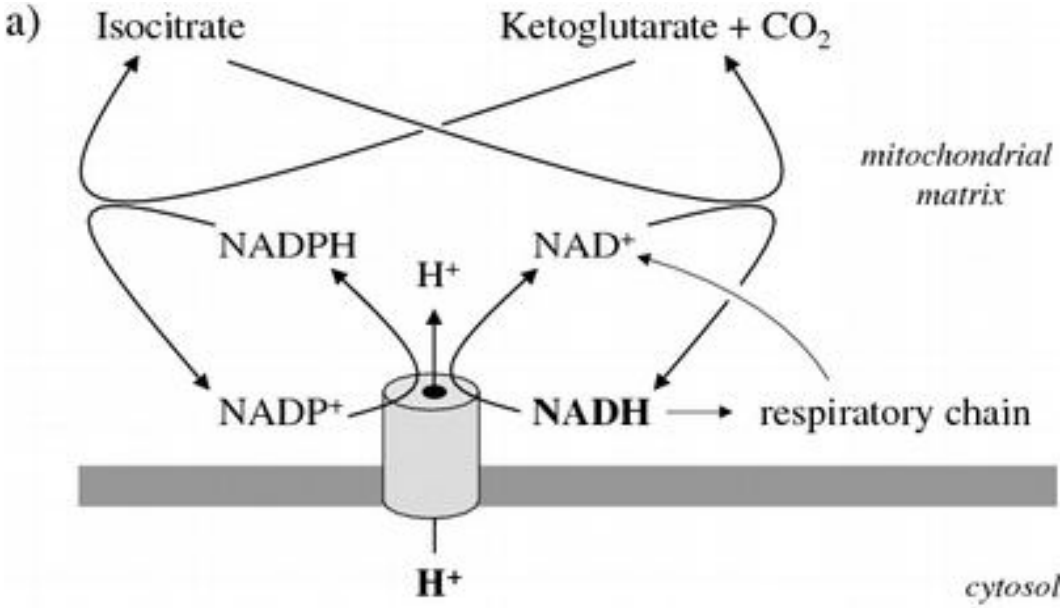

H+
H+
H+
I
II
Q
III
C
IV
H+
e-
e-
H+
H+
H+
ADP + P
ATP
"H2"
H+
e-
O2
H+
H2O


a)
δ
α
β
γ
a
F_o
H^+
b)
α
β
γ
β
α
β
α
c)
ADP
P
ATP
ATP

Shuttle systems for the oxidative regeneration of cytosolic NAD



a: The malate-aspartate shuttle. b: A hypothetical shuttle that is not in the textbooks. c: The glycerophoshate shuttle. DHAP: dihydroxyacetone phosphate; GPD: glycerolphosphate dehydrogenase. Continuous gray bars represent the inner mitochondrial membrane; the broken bar in c represents the outer mitochondrial membrane



Function of $NADP^+$/ NADH transhydrogenase, and its integration with the TCA and the respiratory chain. a: Function of transhydrogenase in 'idling mode', i.e. while the demand for ATP is low. b: Function of transhydrogenase during high demand for ATP.