Oxidation reduction reactions in biology and electron transfer cofactors

Oxidation reduction reactions

- "Group transfer" reactions where the "groups" being transferred are electrons
- Electrons are passed from an electron donor (reductant, reducing agent) to an electron acceptor (oxidant, oxidizing agent)
- Redox reactions can be broken into two "half reactions"

Oxidation reduction reactions

Complete reaction:

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

Half reactions:

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

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

Electrochemistry important terms

- Cathode
- Anode
- Salt bridge
- Electrolyte
- Half reaction
- Electromotive force

Electromotive Force (emf)

$Zn_{(s)} + Cu^{2+}_{(aq)} \rightarrow Zn^{2+}_{(aq)} + Cu_{(s)}$

- The difference in electrical potential between the anode and cathode is called the "electromotive force", "electron motion force", "cell potential", or "cell voltage"
- In a voltaic cell, the anode "pushes" electrons through a wire towards the cathode, while the cathode "pulls" the electrons creating the potential
- Symbol: "E"
- Units: "V"
- Numerical value of "E" depends on the nature of the reacting species, their concentrations, and the temperature
- Since no movement of electrons is necessary to have a potential, there is no Δ sign in front of E (note error in convention in biochemistry textbooks)

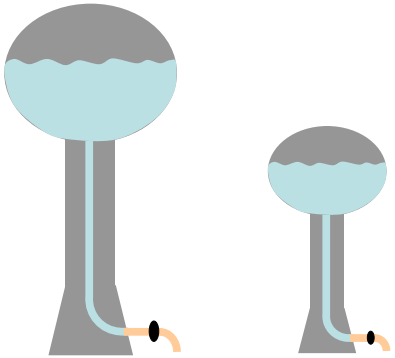
Voltage

$1\ V = 1\ \frac{J}{C}$

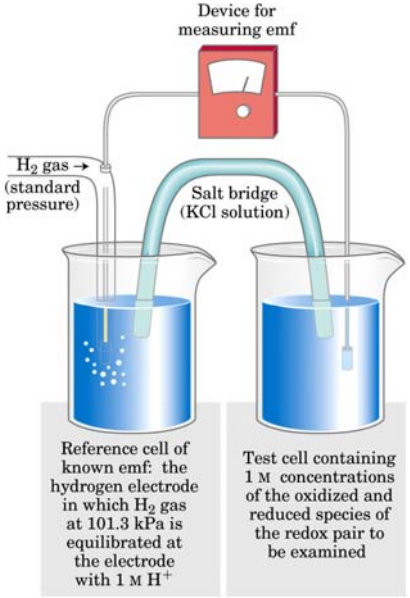
- The "potential" to do work; difference in potential between two points
- Analogy: water pressure in a pipe

No water has to be flowing to have pressure

Once water starts flowing, the pressure may drop. The lower the rate of flow, the lower the pressure drop



- Cathodic reaction
- Anodic reaction
- Pathway for electron movement between cathode and anode- "wire"
- Pathway for ion movement (maintain charge neutrality)
- ex.: Fe^{3+} reduction and H^+ oxidation



$$A^{n+}_{ox} + B_{red} \rightleftharpoons A_{red} + B^{n+}_{ox}$$

$$\Delta G' = \Delta G^{\circ\prime} + RT \ln \frac{[A_{red}][B^{n+}_{ox}]}{[A^{n+}_{ox}][B_{red}]}$$

$$E' = E^{\circ\prime} - \frac{RT}{nF} \ln \frac{[A_{red}][B^{n+}_{ox}]}{[A^{n+}_{ox}][B_{red}]}$$

$$\Delta G' = -nFE'$$

Assignment of redox potentials

- Reduction potential:

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

- Oxidation potential:

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

table 14–7

Standard Reduction Potentials of Some Biologically Important Half-Reactions, at 25 °C and pH 7

Half-reaction	$E^{\circ\prime}$ (V)
$\frac{1}{2}O_2 + 2H^+ + 2e^- \longrightarrow H_2O$	0.816
$Fe^{3+} + e^- \longrightarrow Fe^{2+}$	0.771
$NO_3^- + 2H^+ + 2e^- \longrightarrow NO_2^- + H_2O$	0.421
Cytochrome f (Fe^{3+}) + e^- ⟶ cytochrome f (Fe^{2+})	0.365
$Fe(CN)_6^{3-}$ (ferricyanide) + e^- ⟶ $Fe(CN)_6^{4-}$	0.36
Cytochrome a_3 (Fe^{3+}) + e^- ⟶ cytochrome a_3(Fe^{2+})	0.35
$O_2 + 2H^+ + 2e^- \longrightarrow H_2O_2$	0.295
Cytochrome a (Fe^{3+}) + e^- ⟶ cytochrome a (Fe^{2+})	0.29
Cytochrome c (Fe^{3+}) + e^- ⟶ cytochrome c (Fe^{2+})	0.254
Cytochrome c_1 (Fe^{3+}) + e^- ⟶ cytochrome c_1 (Fe^{2+})	0.22
Cytochrome b (Fe^{3+}) + e^- ⟶ cytochrome b (Fe^{2+})	0.077
Ubiquinone + $2H^+ + 2e^-$ ⟶ ubiquinol + H_2	0.045
$Fumarate^{2-} + 2H^+ + 2e^- \longrightarrow succinate^{2-}$	0.031
$2H^+ + 2e^- \longrightarrow H_2$ (at standard conditions, pH 0)	0.000
Crotonyl-CoA + $2H^+ + 2e^-$ ⟶ butyryl-CoA	−0.015
$Oxaloacetate^{2-} + 2H^+ + 2e^- \longrightarrow malate^{2-}$	−0.166
$Pyruvate^- + 2H^+ + 2e^- \longrightarrow lactate^-$	−0.185
Acetaldehyde + $2H^+ + 2e^-$ ⟶ ethanol	−0.197
FAD + $2H^+ + 2e^- \longrightarrow FADH_2$	−0.219*
Glutathione + $2H^+ + 2e^-$ ⟶ 2 reduced glutathione	−0.23
$S + 2H^+ + 2e^- \longrightarrow H_2S$	−0.243
Lipoic acid + $2H^+ + 2e^-$ ⟶ dihydrolipoic acid	−0.29
$NAD^+ + H^+ + 2e^- \longrightarrow NADH$	−0.320
$NADP^+ + H^+ + 2e^- \longrightarrow NADPH$	−0.324
Acetoacetate + $2H^+ + 2e^-$ ⟶ β-hydroxybutyrate	−0.346
α-Ketoglutarate + $CO_2 + 2H^+ + 2e^-$ ⟶ isocitrate	−0.38
$2H^+ + 2e^- \longrightarrow H_2$ (at pH 7)	−0.414
Ferredoxin (Fe^{3+}) + e^- ⟶ ferredoxin (Fe^{2+})	−0.432

Data mostly from Loach, P.A. (1976) In *Handbook of Biochemistry and Molecular Biology*, 3rd edn (Fasman, G.D., ed.), *Physical and Chemical Data*, Vol. I, pp. 122–130, CRC Press, Boca Raton, FL.

*This is the value for free FAD; FAD bound to a specific flavoprotein (for example succinate dehydrogenase) has a different $E^{\circ\prime}$.

S. Ensign, Chem. 5700

O_2 is a strong oxidizing agent (is readily reduced)

NADH is a strong reducing agent (is readily oxidized)

table 14–7

Standard Reduction Potentials of Some Biologically Important Half-Reactions, at 25 °C and pH 7

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- For a redox reaction to be spontaneous, E°' for the overall reaction must have a positive value
- When writing a half reaction in the oxidative direction, the sign of E°' is switched
- The oxidized form of a given redox pair will react spontaneously with the reduced form of any redox pair that is below it in a table of standard reduction potentials
- E°' values for half cell reactions are additive

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Standard Reduction Potentials of Some Biologically Important Half-Reactions, at 25 °C and pH 7

O_2 will be spontaneously reduced by NADH

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Determine E°' for the oxidation of O_2 with NADH

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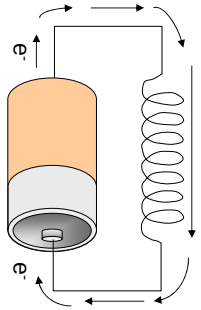
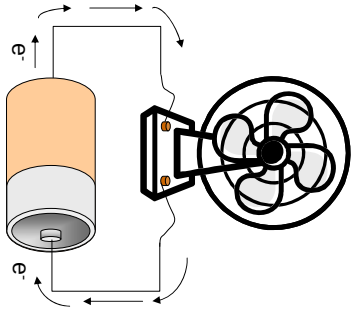
Calculate ΔG°' for the two electron oxidation of NADH using O_2 as electron acceptor

In theory, how many ATP can be synthesized using the free energy released from the two electron oxidation of NADH with O_2 as electron acceptor under biochemical standard state conditons?

Electron flow with no conservation of energy



Electron flow with conservation of energy



Four categories of enzymes

1. Group transfer reactions
2. Oxidations/reductions
3. Eliminations/isomerizations/rearrangements
4. Reactions that make or break C-C bonds

How do enzymes mediate biological oxidation/reduction reactions?

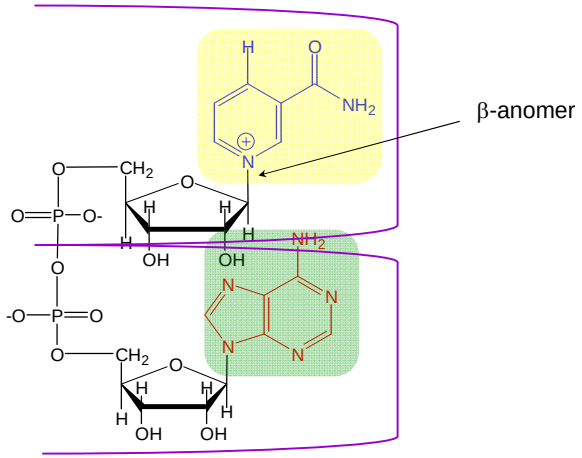
- e^- transfer through amino acid side chains?
- Use of redox cofactors
  - Organic (NAD+, FAD, lipoic acid, pterin, etc)
  - Metalloorganic (heme, chlorophyll, etc)
  - Inorganic (Fe, Cu, etc)

Two electron oxidations/reductions (transfer of e^- pairs) are the norm in enzyme-catalyzed reactions

- Two single electron steps (free radical int.)
  - Quinoid coenzyme mediation
  - Transition metal mediation
- A single two electron step
  - Hydride transfer $:H^- = 2e^- + H^+$

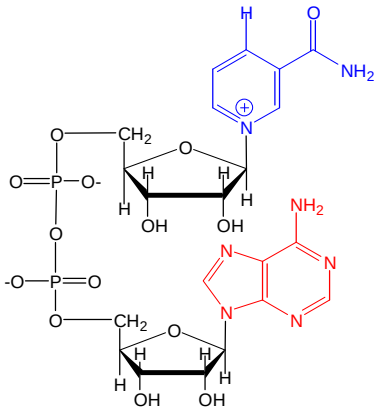
NAD+

Nicotinamide Adenine Dinucleotide



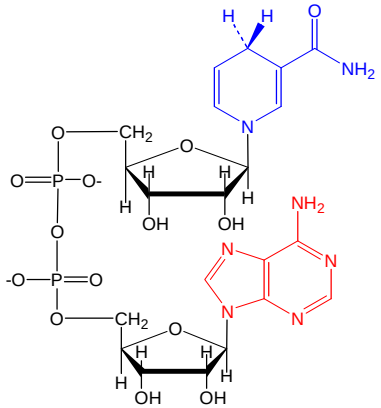
NAD+

Nicotinamide Adenine Dinucleotide



NADH

Reduced Nicotinamide Adenine Dinucleotide

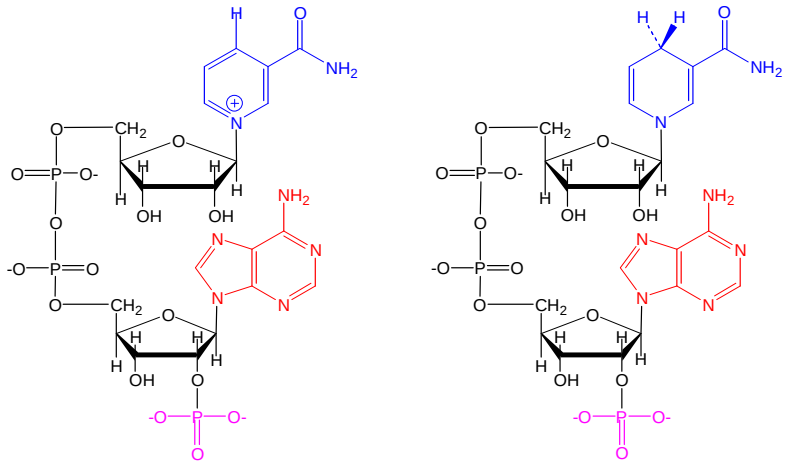


Chemical properties of NADH

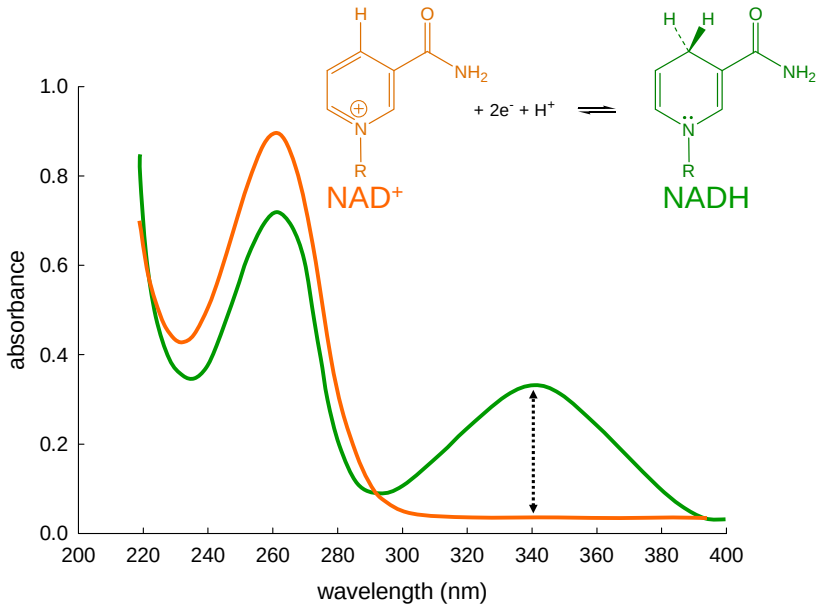
- Reduction potential = -320 mV
- Air stable in aq. Solutions (kinetic stability)
- An enzyme substrate, not an integral cofactor
- Follow oxidation/reduction at 340 nm
- NADP$^+$ and NADPH for biosynthesis
- Re vs. Si face hydride transfer
- Scope of reactions:
  - Redox
  - Masked redox
  - nonredox

NADP+ and NADPH

Nicotinamide Adenine Dinucleotide Phosphate

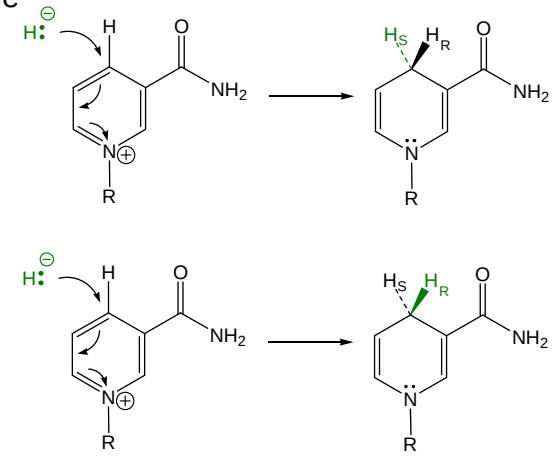


Spectral properties of NADH and NAD+



Stereospecificity of enzymes that reduce NAD+ and/or oxidize NADH

- Note there are two faces for attack on the sp^2-hybridized C4
- Transfer of a hydride occurs to a specific face, depending on the particular enzyme

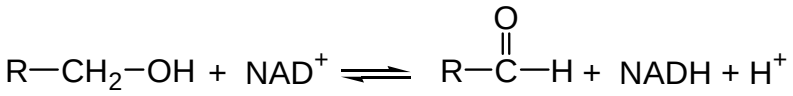


Scope of reactions of NAD(P)+-utilizing enzymes

- Redox
  - Alcohol dehydrogenation
  - Amine dehydrogenation
  - Aldehyde dehydrogenation
  - Alkyl group dehydrogenation
  - Dehydrogenation of other organic cofactors
  - Redox reactions involving NAD(P)+/NAD(P)H always involve transfer of *electron pairs* as *hydride ions*
- Masked redox
- nonredox

Liver alcohol dehydrogenase

- α_2 dimer
- 2 Zn^{2+}/dimer
- Reversible oxidation of 1° and 2° alcohols



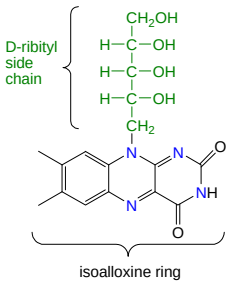
Alcohol dehydrogenase mechanism

Ways to transfer electrons

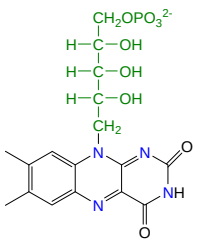
- Direct electron transfer (e.g. Cu^{+} + Fe^{3+})
- Hydride transfer ($H:^{-}$)
- Hydrogen atom transfer ($H\cdot = H^{+} + 1e^{-}$)

Quick introduction to flavins

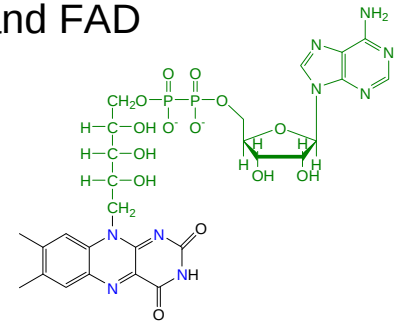
- Isoalloxazine ring is the “business end”
- vitamin precursor: riboflavin
- two active forms: FMN and FAD



riboflavin

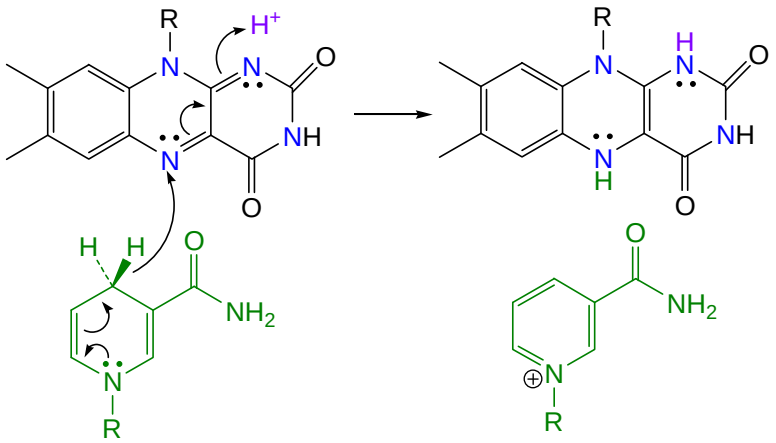


Flavin mononucleotide FMN

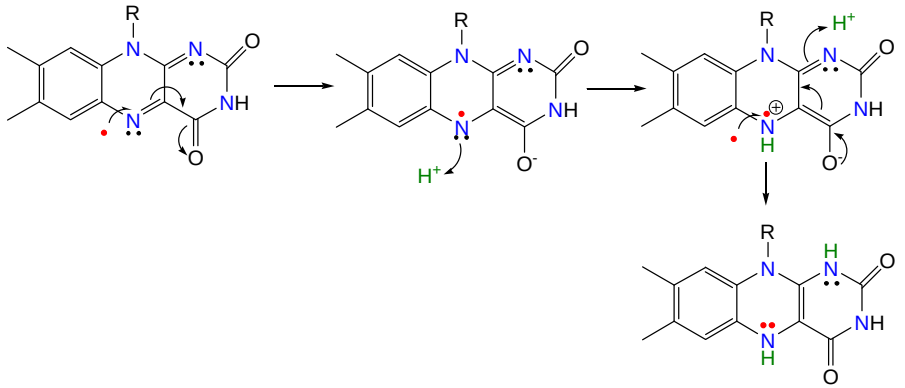


Flavin adenine dinucleotide FAD

Flavins can undergo direct two e- reduction via hydride transfer:



Flavins can undergo sequential one e- reduction reactions:



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