Structure and Function of Dehydrogenases

How do you define dehydrogenase?

An enzyme that catalyzes the removal of hydrogen from a substrate and the transfer of the hydrogen to an acceptor in an oxidation-reduction reaction.

An enzyme that activates oxidation-reduction reactions by transferring hydrogen from substrate to acceptor.

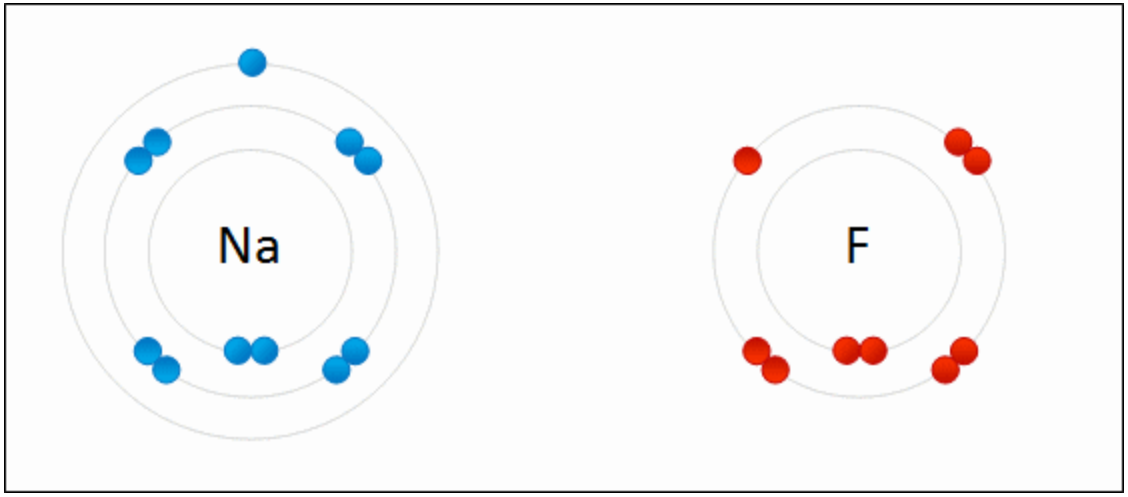
An oxidoreductase enzyme that catalyzes the removal of hydrogen.

Oxidoreductase

Oxidoreductases catalyze the transfer of electrons from one molecule (the oxidant) to another molecule (the reductant) i.e. they catalyze the following reactions:

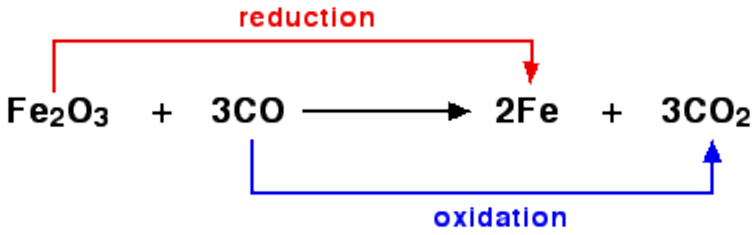
$$A^- + B \rightarrow A + B^-$$

where A is the oxidant and B is the reductant.



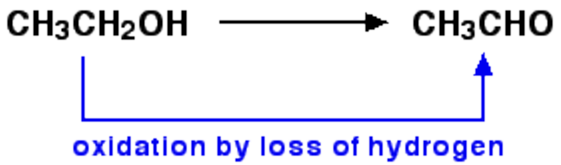
1. Oxidation and reduction in terms of oxygen transfer

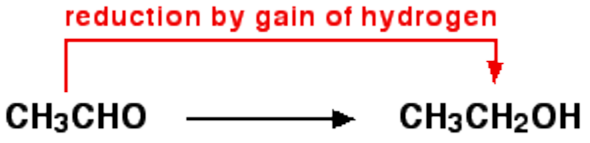
Oxidation is gain of oxygen
Reduction is loss of oxygen



2. Oxidation and reduction in terms of hydrogen transfer

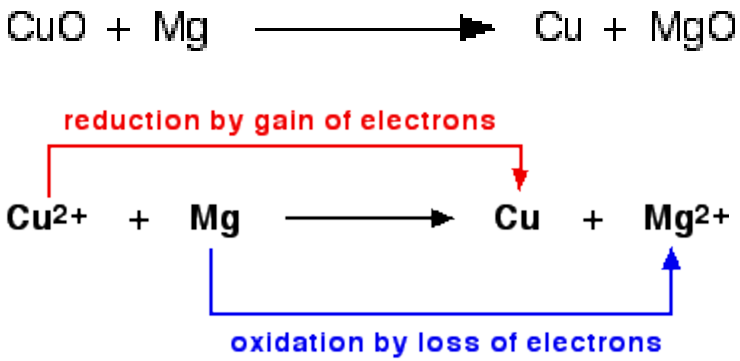
Oxidation is loss of hydrogen
Reduction is gain of hydrogen





3. Oxidation and reduction in terms of electron transfer

Oxidation is loss of electrons (OIL)
Reduction is gain of electrons (RIG)



Oxidation and reduction in one molecule

Reduction

Oxidant + e^- ⟶ Product

(Electrons **gained**; oxidation number **decreases**)

Oxidation

Reductant ⟶ Product + e^-

(Electrons **lost**; oxidation number **increases**)

Types of oxidoreductase

$$A^- + B \rightarrow A + B^-$$

In reality, free electrons do not exists as these reactions involve atoms transfer.

Most of the time, atoms transfer involved in these reactions are either hydrogen or oxygen.

Oxidorecuctases can be dehydrogenases or oxidases.

Dehydrogenases are enzymes that oxidize a substrate by transferring hydrogen to an acceptor that is either NAD^+/$NADP^+$ or a flavin enzyme.

Because most of metabolic oxidation reactions involve removing hydrogen from the electron donor, large fraction of oxidoreductases are **dehydrogenases**.

The term **oxidase** is used only for the enzymes in which the oxidation reaction with molecular oxygen (O_2) acting as an acceptor of hydrogen or electrons.

Other oxidoreductases:

Peroxidases are localized in peroxisomes and catalyzes the reduction of hydrogen peroxide.

ROOR' + electron donor (2 e^-) + 2H^+ → ROH + R'OH

Hydroxylases add hydroxyl groups to its substrates.

Oxygenases incorporate oxygen from molecular oxygen into organic substrates.

Reductases catalyze reductions. In most cases reductases can act like an oxidases.

Enzyme classification

Oxidoreductases - EC: 1.X.X.X

EC: 1.1.X.X - Acting on the CH-OH group of donors

EC: 1.2.X.X - Acting on the aldehyde or oxo group of donors

EC: 1.3.X.X - Acting on the CH-CH group of donors

EC: 1.4.X.X - Acting on the CH-NH(2) group of donors

EC: 1.5.X.X - Acting on the CH-NH group of donors

EC: 1.6.X.X - Acting on a sulfur group of donors

The common scheme for making names for oxidoreductases is adding donor name to the dehydrogenase, i.e. ***donor*** **dehydrogenase**.

EC: 1.1.1.X (With NAD+ or NADP+ as acceptor): 234 types of dehydrogenases

EC: 1.1.2.X (With a cytochrome as acceptor): 7 types of dehydrogenases

EC: 1.2.1.X (With NAD+ or NADP+ as acceptor): 69 types of dehydrogenases

EC: 1.3.1.X (With NAD+ or NADP+ as acceptor): 32 types of dehydrogenases

EC: 1.4.1.X (With NAD+ or NADP+ as acceptor): 19 types of dehydrogenases

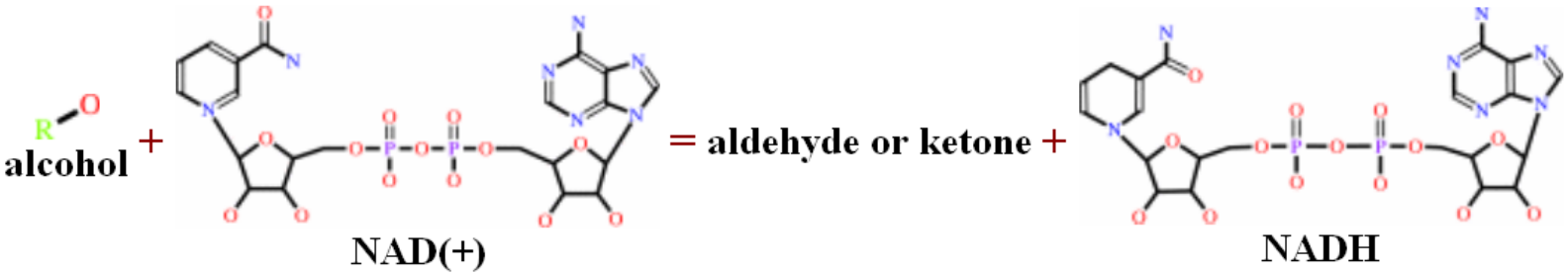
EC: 1.5.1.X (With NAD+ or NADP+ as acceptor): 19 types of dehydrogenases

EC: 1.6.1.X (With NAD+ or NADP+ as acceptor): 3 types of dehydrogenases

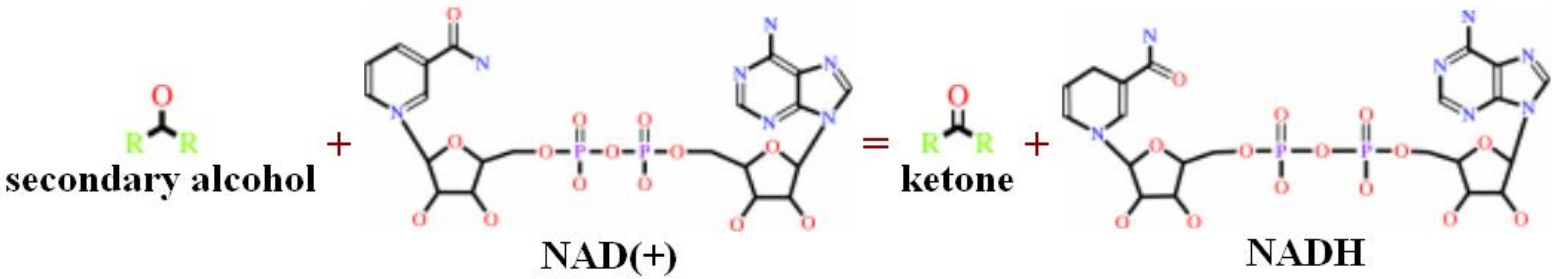
Alcohol dehydrogenase

EC: 1.1.1.1

(1) An alcohol + NAD(+) = an aldehyde or ketone + NADH



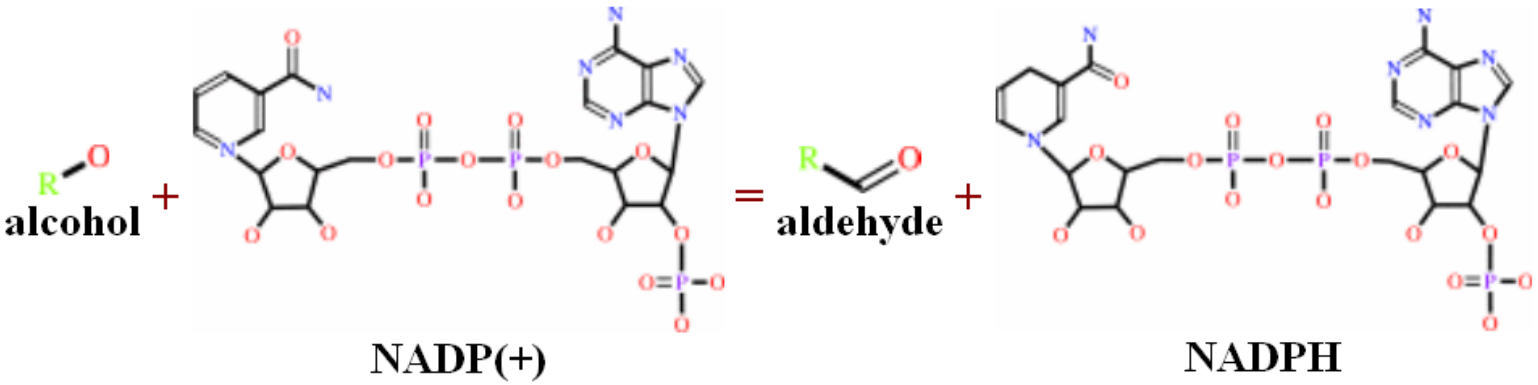
(2) A secondary alcohol + NAD(+) = a ketone + NADH



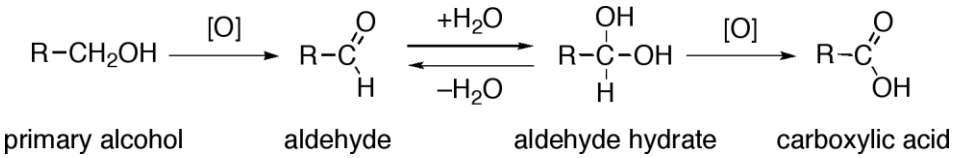
Aldehyde reductase

EC: 1.1.1.2

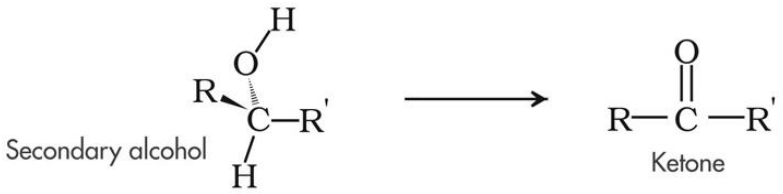
An alcohol + NADP(+) = an aldehyde + NADPH.



Primary alcohols (R-CH_2-OH) can be oxidized either to aldehydes (R-CHO) (e.g. acetaldehyde) or to carboxylic acids (R-CO_2H).



The oxidation of secondary alcohols (R^1R^2CH-OH) normally terminates at the ketone (R^1R^2C=O) stage.



Tertiary alcohols ($R^1R^2R^3C$-OH) are resistant to oxidation.

Why are tertiary alcohols resistant to oxidation?

Function of Alcohol dehydrogenases

In humans and many other animals, they serve to break down alcohols that otherwise are toxic.

They also participate in generation of useful aldehyde, ketone or alcohol groups during biosynthesis of various metabolites.

In yeast, plants and many bacteria, some alcohol dehydrogenases catalyze the opposite reaction as part of fermentation to ensure a constant supply of NAD^+.

Why is alcohol dehydrogenase evolved or selected over time?

Rotting fruit can contain more than 4% of ethanol. Animals eating the fruit needed a system to metabolize exogenous ethanol. This was thought to explain the conservation of ethanol active ADH in other species than yeast.

ADH-3 is now known to also have a major role in nitric oxide signaling

The metabolism of the endogenous alcohol vitamin A (retinol), which generates the hormone retinoic acid, although the function here may be primarily the elimination of toxic levels of retinol.

It oxidizes methanol to produce formaldehyde and ethylene glycol to ultimately yield glycolic and oxalic acids.

This allows the consumption of alcoholic beverages, but its evolutionary purpose is probably the breakdown of alcohols naturally contained in foods or produced by bacteria in the digestive tract.

Alcohol dehydrogenase activity varies between men vs women, between young and old and among populations from different areas of the world.

Unlike humans, yeast and some bacteria do not ferment glucose to lactate. Instead, they ferment it to ethanol and CO_2.

Glucose + 2 ADP + 2 Pi $\rightarrow$ 2 ethanol + 2 CO_2 + 2 ATP + 2 H_2O

If alcohols are toxic, why does yeast produce so much ethanol?

This feature is not adaptive from an energetic point of view, but by making alcohol in such high concentrations so that they were toxic to other organisms, yeast cells could effectively eliminate their competition.

Types of ADH

In humans, ADH is encoded by at least seven different genes.

There are five classes (I-V) of alcohol dehydrogenase.

In human liver and lining of stomach, primarily class I is used.

Class I consists of α, β, and γ subunits that are encoded by the genes ADH1A, ADH1B, and ADH1C.

The human genes that encode class II, III, IV, and V alcohol dehydrogenases are ADH4, ADH5, ADH7 and ADH6, respectively.

Reactions catalyzed by ADH

In humans, it catalyzes the oxidation of ethanol to acetaldehyde:

$$CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$$

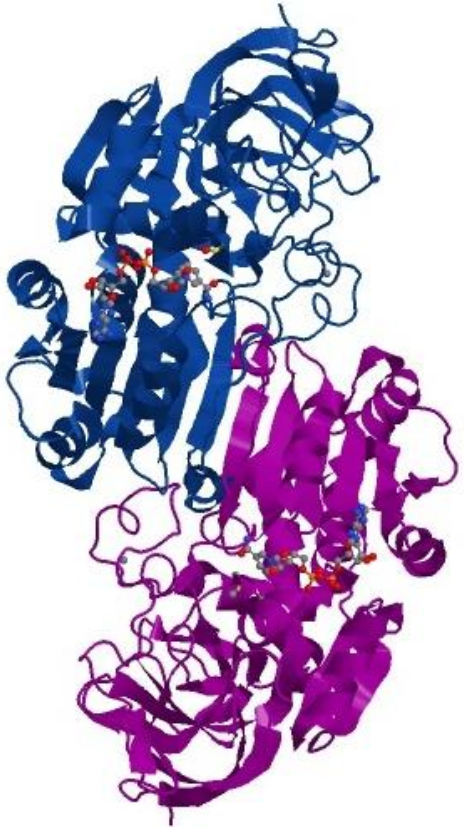
In plants, ADH catalyses the same reaction as in yeast and bacteria to ensure that there is a constant supply of NAD^+.

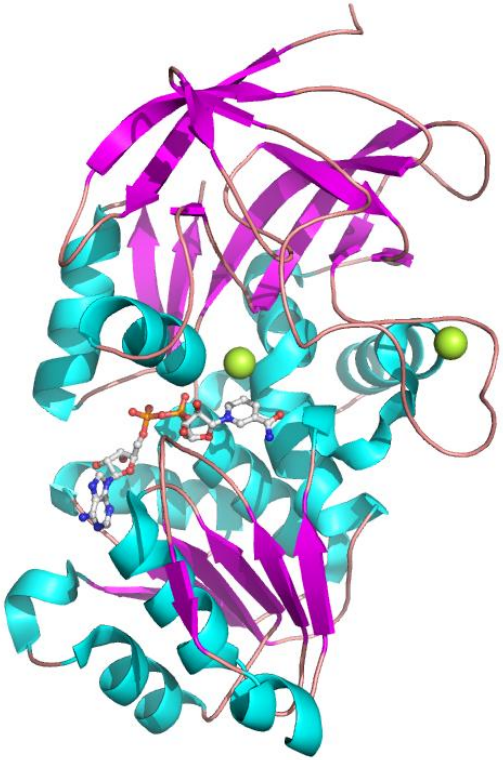
A third family of alcohol dehydrogenases, unrelated to the above two, are iron-containing ones. They occur in bacteria and fungi.

Properties

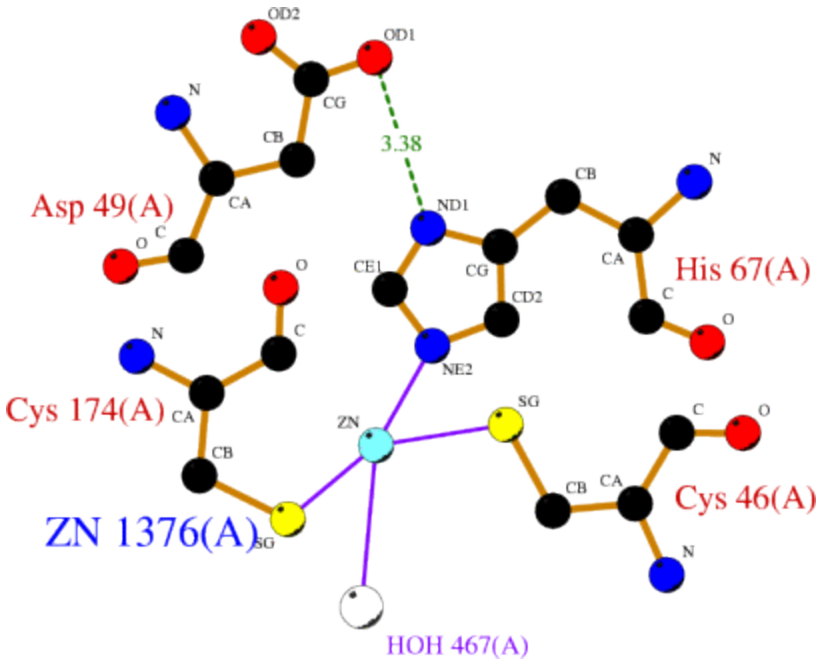
- ADH is activated by glutathione and EDTA and inhibited by heavy metals.
- Optimum is pH 8.6 though pH closer to 7 considered optimum for acetaldehyde reduction. ADH becomes increasingly unstable with higher pH values.
- The specific configuration of the active site makes it stereospecific and ADH will only remove the pro-R hydrogen from the alcohol group.

Structure of ADH





The main alcohol dehydrogenase in yeast is larger than the human one, consisting of four rather than just two subunits.


OD2
OD1
3.38
N
CB
CG
Asp 49(A)
CA
C
O
ND1
CB
N
CE1
CG
CA
His 67(A)
CD2
C
O
O
C
N
NE2
Cys 174(A)
CA
ZN
SG
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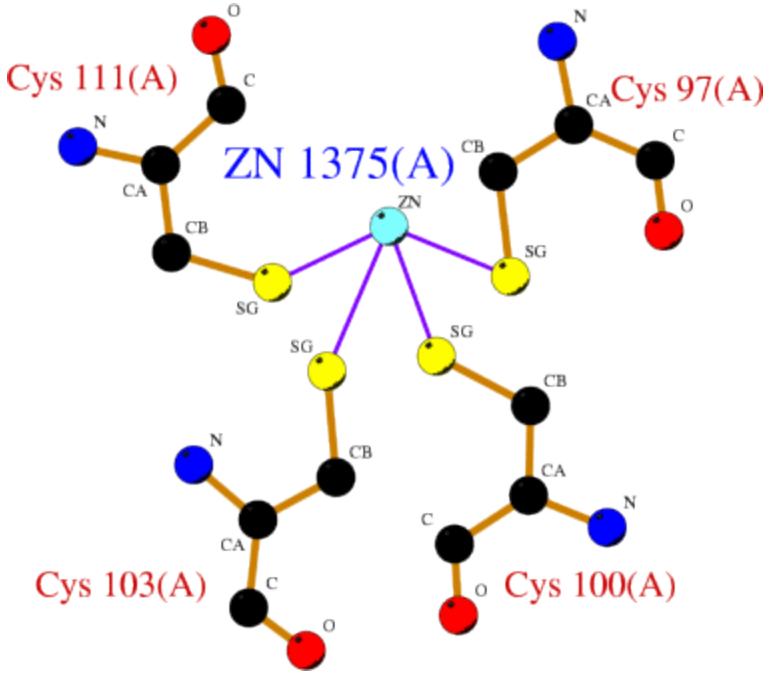
CB
CB
CA
Cys 46(A)
ZN 1376(A)
SG
N
HOH 467(A)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N
Cys 111(A)
C
CA
Cys 97(A)
N
ZN 1375(A)
CB
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CA
ZN
O
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SG
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Cys 103(A)
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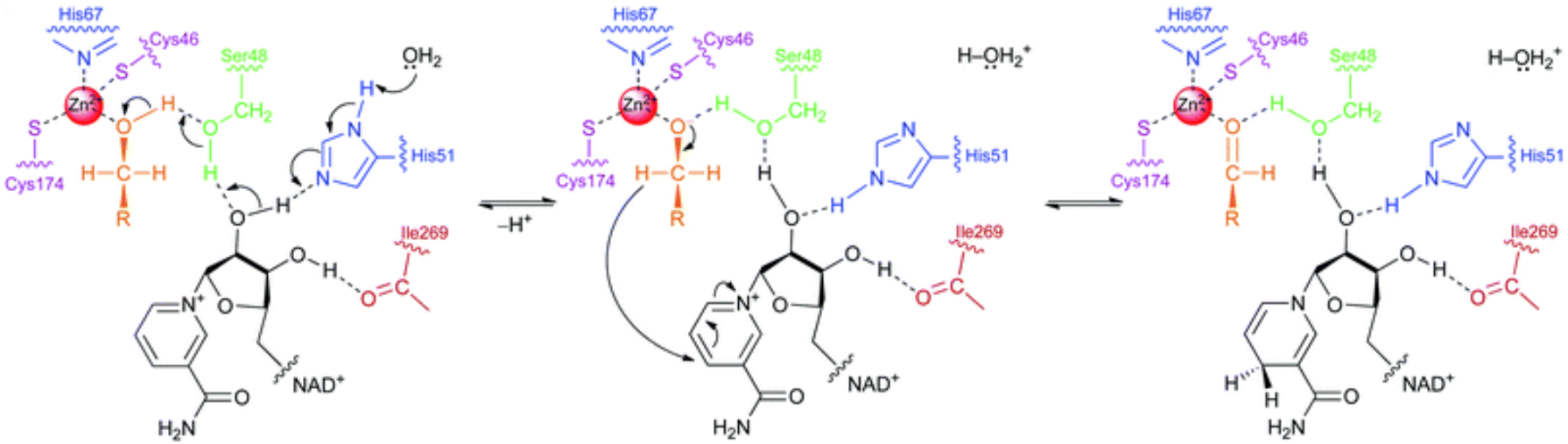
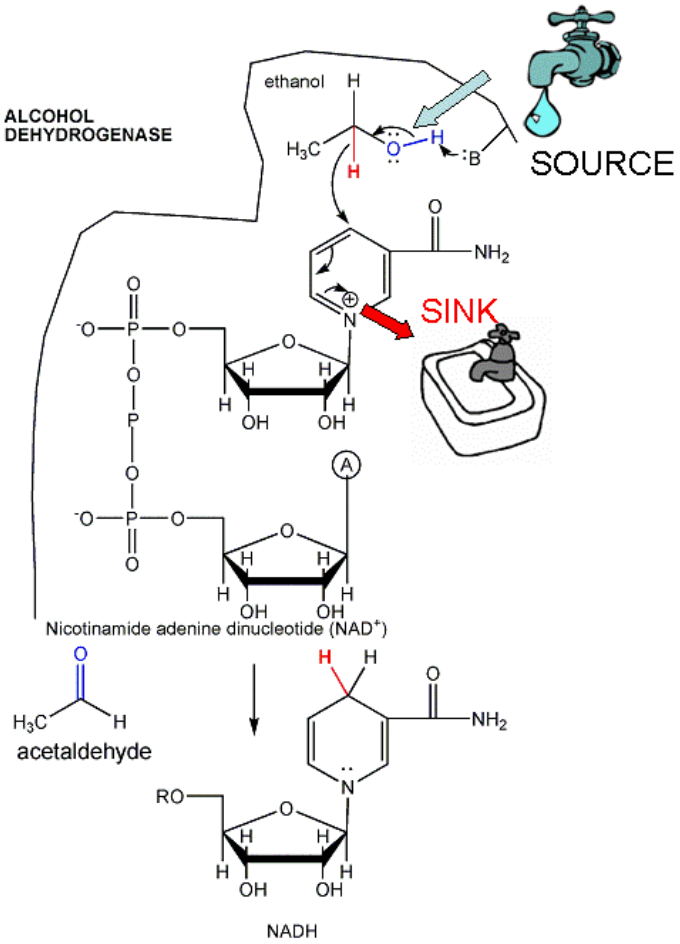
Mechanism of action

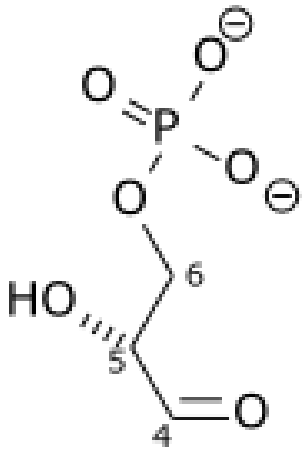


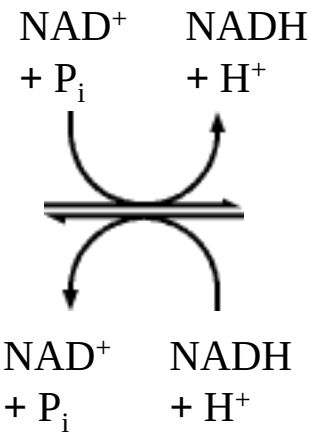
$NAD(P)^+$ as biological oxidizing agent

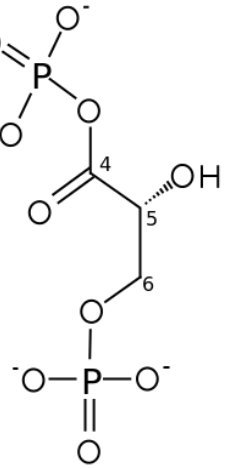


Regulation of NAD(P)$^+$ and NAD(P)H

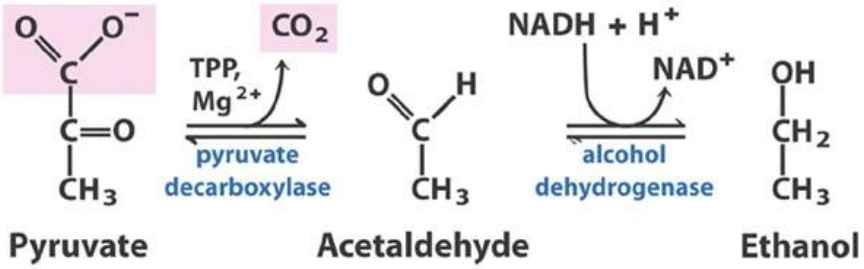
In glycolysis pathway, NADH generated by the oxidation of glyceraldehyde-3-phosphate (G-3-P).





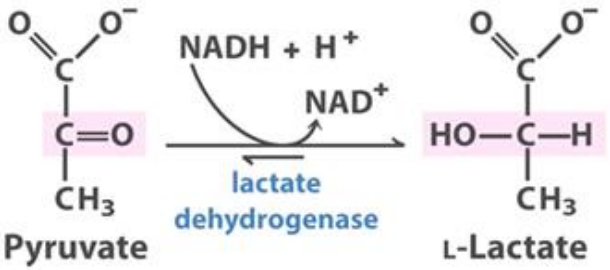


Pyruvate formed from gylcolysis undergoes decarboxylation by pyruvate decarboxylase, again using NAD as a cofactor.



Then NADH is converted to NAD^+ during the reduction of acetaldehyde to ethanol.

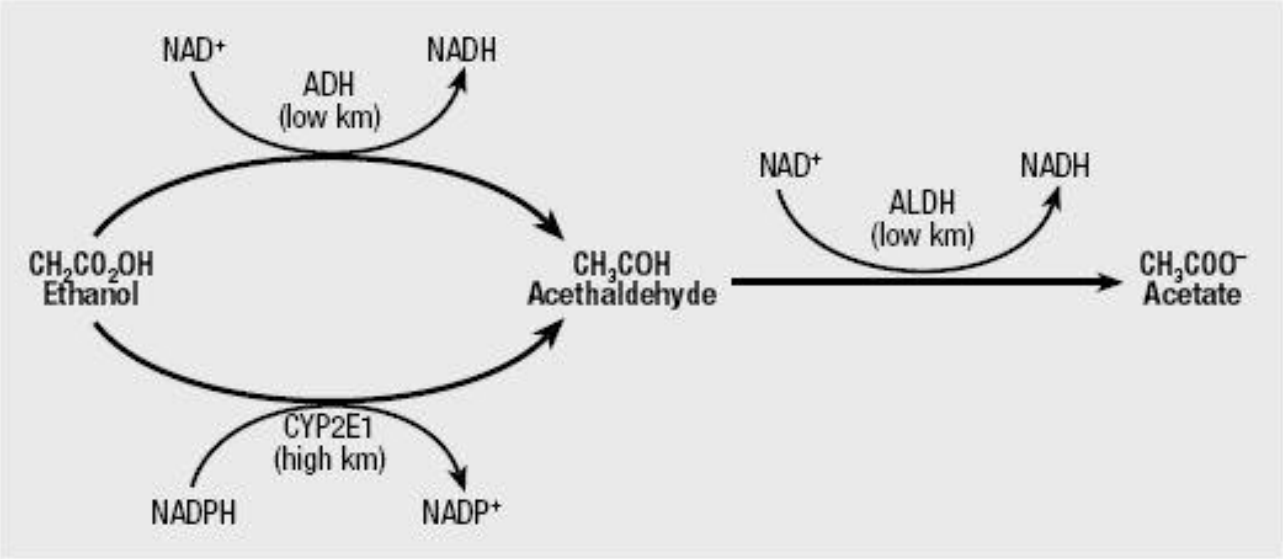
Lactate dehydrogenase also uses NADH to convert pyruvate to lactate.



Then how do organisms which undergo fermentation balance the redox?

The dangers of excessive ethanol consumption

What is the effect of excessive ethanol consumption on human body?



If ethanol is consumed in excess then resulting high NADH concentrations act to inhibit gluconeogenesis.

This, in turn, causes the reverse conversion of pyruvate to lactate which results in a build up of lactate.

Excess lactate can be especially dangerous as it can potentially result in hypoglycaemia or lactic acidosis which effectively changes the pH of the blood.

An excess of NADH will also inhibit fatty acid oxidation and, in fact, promotes the synthesis of fatty acids which can result in conditions such as alcoholic steatosis or fatty liver.