Redox Cofactors

Bugg, Chapter 6

Nicotinamide (pyridine dinucleotide)
Bugg, Chapter 6 pp. 123 - 129

Vitamin B₃, nicotinic acid, niacin

\[ \text{E}^\ddagger \text{ NAD}^+ / \text{NADH couple} = -0.32 \text{ V vs NHE} \]
very strong reducing agent

\[ \text{NAD}(P)^+ \rightleftharpoons \text{NAD}(P)H \text{ mostly involved in } 2e^- \text{ chemistry} \]
\[ \text{H}^- \text{ (hydride) source} \]
Reaction types catalyzed by NAD(P)^+ / NAD(P)H

NAD(P)^+ / NAD(P)H is a carbon hydride source!? 

Electronegativities
Examples of carbon hydride sources:

**Eschweiler-Clark Reaction**

\[
\begin{align*}
R-NH_2 + H_2C=O + HCO_2H & \rightarrow [R-N=C\equiv CH_2]^{-} + CO_2 \\
& \rightarrow R-NH \_CH_3 \\
\end{align*}
\]

**Cannizzaro Reaction**

\[
2 \text{PhCHO} + 2\text{OH} \rightarrow \text{PhCOOH} + \text{PhCH_2OH}
\]

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**Ethanoll metabolism:**

**Alcohol Dehydrogenase:**

\[
\begin{align*}
\text{ethanol} & \rightarrow \text{acetaldehyde} & \rightarrow \text{acetic acid} \\
\text{CH}_3\text{CH}_2\text{OH} & \rightarrow \text{H}_2\text{C}^{-}N\_H & \rightarrow \text{H}_2\text{C}^{-}O\_H \\
\end{align*}
\]

- if run in T\(_2\)O or D\(_2\)O, no T or D incorporation in NADH
- if run with H\(_3\)CCD\(_2\)OH, complete D incorporation in NADH
- Results consistent with a hydride-transfer (H\(^+\)) mechanism and not a proton-transfer (H\(^+\))
Active site of horse liver alcohol dehydrogenase

Evidence for a hydride-transfer vs an electron-transfer mechanism
Cyclopropyl carbinyl radical ring opening as a probe for radical intermediates

Product consistent with a hydride-transfer mechanism
If an electron-transfer mechanism:

\[
\begin{align*}
\text{O} & \text{CO}_2 \text{H} & + e^- & \rightarrow & \text{O} \text{CO}_2 \text{H} \\
\text{O} & \text{CO}_2 \text{H} & & \rightarrow & \text{O} \text{CO}_2 \text{H} \\
\text{O} & \text{CO}_2 \text{H} & & \rightarrow & \text{O} \text{CO}_2 \text{H} \\
\end{align*}
\]

Chemical model for the electron-transfer mechanism

\[
\begin{align*}
\text{O} & \text{CO}_2 \text{H}_3 & \text{nBu}_3 \text{Sn} \text{H} & \rightarrow & \text{O} \text{SnBu}_3 \text{CO}_2 \text{H}_3 \\
\text{O} & \text{CO}_2 \text{H}_3 & \text{nBu}_3 \text{Sn} \text{H} & \rightarrow & \text{O} \text{SnBu}_3 \text{CO}_2 \text{H}_3 \\
\text{O} & \text{CO}_2 \text{H}_3 & \text{nBu}_3 \text{Sn} \text{H} & \rightarrow & \text{O} \text{SnBu}_3 \text{CO}_2 \text{H}_3 \\
\end{align*}
\]

Stereochemistry of alcohol dehydrogenase: pro-chirality

H's are enantiotropic, chemically equivalent
Enzymes are chiral and create a chiral environment around the substrate even though they are not covalently bound to each other.

Stereochemistry of alcohol dehydrogenase:
hydride transfer is stereospecific
Conformation of the nicotinamide cofactor determines if the pro-R or the pro-S hydrogen is transferred from the cofactor.

Axial H of NAD(P)H is preferentially transferred.

Conformation of NAD\(^+\) cofactors:

- NAD\(^+\) from Lactate Dehydrogenase (Pro-R specific)
- NAD\(^+\) from Glyceraldehyde-3-phosphate Dehydrogenase (Pro-S specific)
Mechanism of Aldehyde dehydrogenase

Covalent catalysis:

\[
\text{RCH(OH)\text{Cys} + NAD}^+ \rightarrow \text{RCOOH + Cys-NH}_2 + \text{H}_2\text{O + NADH}
\]

Non-covalent catalysis:

These are mechanistically equivalent to a Cannizarro Reaction

Regeneration of NADH from NAD\(^+\) (glycolysis):

Glyceraldehyde-3-phosphate Dehydrogenase (G3PDH)

\[
\text{Cys-SO}_3^- + \text{Cys-SO}_3^- + \text{glyceraldehyde-3-phosphate} \rightarrow \text{NAD}^+ + \text{NADH}
\]