5.111 Lecture Summary #36
Review of Topics

Chemical Equilibrium, Acid Base, Oxidation Reduction, Transition Metals, and Kinetics

These topics represent the basic principles of how enzymes work, and one needs to understand how enzymes work to inhibit them.

Inhibition of enzymes is used to treat headaches, arthritis, cancer, HIV, etc
Big money for the Pharmaceutical industry

Let's review these topics using methionine synthase as a case study.

KINETICS
Methionine synthase (MetH) is an enzyme, "a catalyst of life".
It transfers a methyl group from methyltetrahydrofolate to homocysteine, generating methionine and tetrahydrofolate.

Inhibition of this enzyme has been associated with neural tube defects and heart disease. It is also a potential chemotherapeutic target.

TRANSITION METALS
Methionine synthase requires vitamin B₁₂ and zinc.

Methylcobalamin (methylB₁₂)  
The corrin ring is a ______dentate ligand  
Chelate effect?

Methyl site  
Zn⁺² site

d-count?  
color?
OXIDATION/REDUCTION

Think about the reactions of methionine synthase:

**Primary Turnover**

- Co(I)
- Methionine
- Homocysteine
- CH₃H₄folate

**Catalytic Reactivation**

- Co(II)
- -1e⁻
- +1e⁻
- S-adenosylmethionine

**REVIEW**

Vitamin B₁₂ is reduced by a protein called flavodoxin.

\[ E^\circ \text{ for vitamin B}_{12} = -0.526 \text{ V} \]
\[ E^\circ \text{ for flavodoxin} = -0.230 \text{ V} \]

Which is a better reducing agent?

\[ \Delta E^\circ(\text{cell}) = E^\circ(\text{reduction}) - E^\circ(\text{oxidation}) \]
\[ = E^\circ(\text{vitamin B}_{12}) - E^\circ(\text{flavodoxin}) \]
\[ = -0.526 \text{ V} - (-0.230 \text{ V}) = -0.296 \text{ V} \]

Is the reduction of vitamin B₁₂ by flavodoxin spontaneous?

\[ \Delta G^\circ = -n\Delta E^\circ = -(1)(96485 \text{ Cmol}^{-1})(-0.296 \text{ V}) = +28.6 \text{ kJ/mol} \]

S-adenosylmethionine provides the energy to drive the reaction. The \( \Delta G^\circ \) for the cleavage of S-adenosylmethionine is -37.6 kJ/mol

Cells that require energy to bring about non-spontaneous reactions are called?
ACID-BASE EQUILIBRIUM

protonated homocysteine   deprotonated homocysteine   methionine

At physiological pH (7.4), how much homocysteine is deprotonated? pKₐ for homocysteine is 10

Free homocysteine is _________________ and non-reactive at physiological pH

pHs above the pKₐ

pH = pKₐ

pHs below the pKₐ
Enzyme-bound homocysteine has a pKₐ of 6. The zinc acts as a lewis acid and binds homocysteine, lowering the pKₐ.

\[
pH = pK_a - \log \left( \frac{[HA]}{[A^-]} \right) \quad 7.4 = 6 - \log \left( \frac{[HA]}{[A^-]} \right) \quad \frac{[HA]}{[A^-]} = \frac{1}{25}
\]

Enzyme-bound homocysteine is ________________ and reactive at physiological pH!

CHEMICAL EQUILIBRIUM

Methionine synthase exists in multiple conformations. These conformations are in equilibrium with each other.

The enzyme needs to position three things above the B₁₂ and there is no room for any of them. Conformational changes need to occur.
"Methyl-cap" region must move

Methionine synthase is a modular protein

Enzymes are dynamic.
Chemistry is dynamic.
CHEMISTRY IN SOLUTION!!!!!