5.111 Principles of Chemical Science

Fall 2008

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

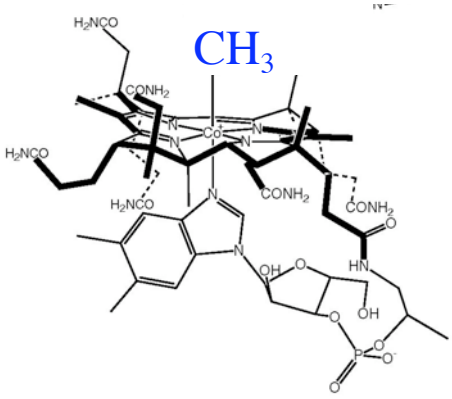
Methionine synthase (MetH) is an enzyme, "a catalyst of life".

It transfers a methyl group from methyltetrahydrofolate to homocysteine, generating methionine and tetrahydrofolate.

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

TRANSITION METALS

Methionine synthase requires vitamin B_{12} and zinc.



Zn^{+2} site

Methylcobalamin (methylB_{12})

The corrin ring is a _____dentate ligand

Chelate effect?

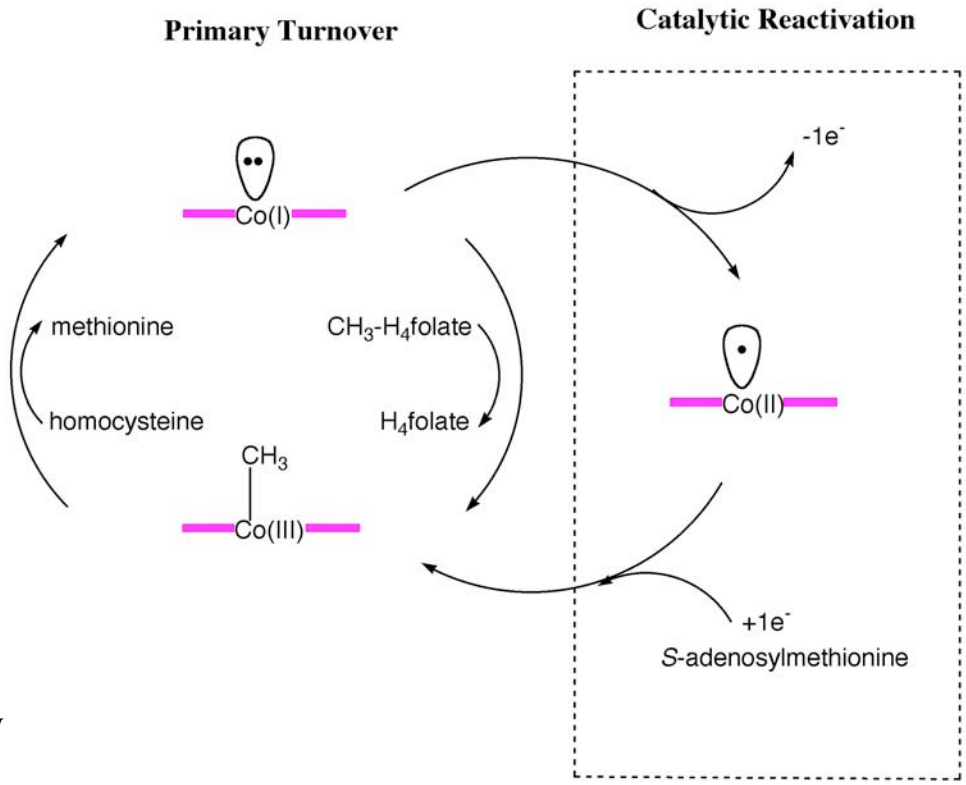
zinc site

d-count?

color?

OXIDATION/REDUCTION

Think about the reactions of methionine synthase:



REVIEW

Vitamin B_{12} is reduced by a protein called flavodoxin.

$E°$ for vitamin B_{12} is -0.526 V

$E°$ for flavodoxin is -0.230 V

Which is a better reducing agent?

$\Delta E°(\text{cell}) = E°(\text{reduction}) - E°(\text{oxidation})$

$= E°(\text{vitamin } B_{12}) - E°(\text{flavodoxin})$

$= -0.526 \text{ V} - (-0.230 \text{ V}) = -0.296 \text{ V}$

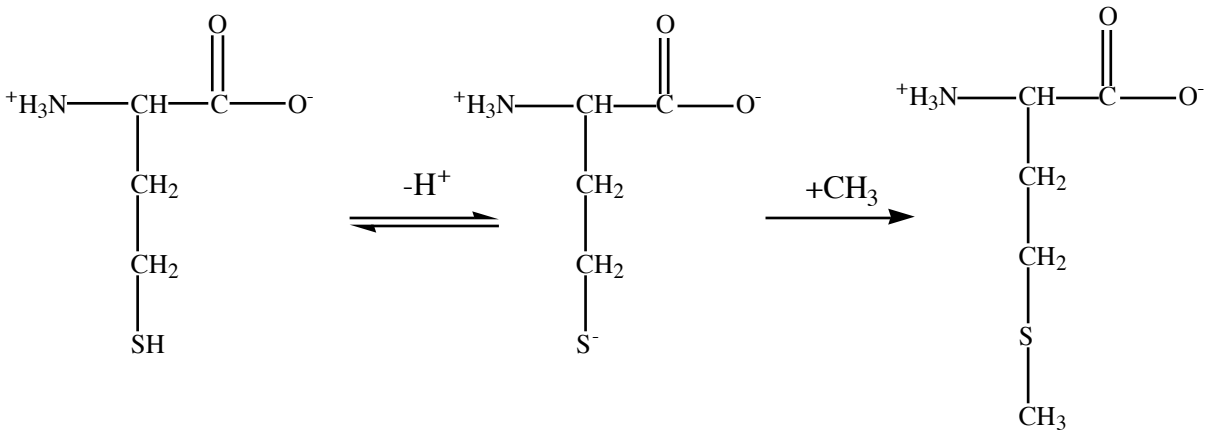
Is the reduction of vitamin B_{12} by flavodoxin spontaneous?

$\Delta G° = -n\mathfrak{F}\Delta E° = -(1)(96485 \text{ Cmol}^{-1})(-0.296 \text{ V}) = +28.6 \text{ kJ/mol}$

S-adenosylmethionine provides the energy to drive the reaction. The $\Delta G°$ for the cleavage of S-adenosylmethionine is -37.6 kJ/mol

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

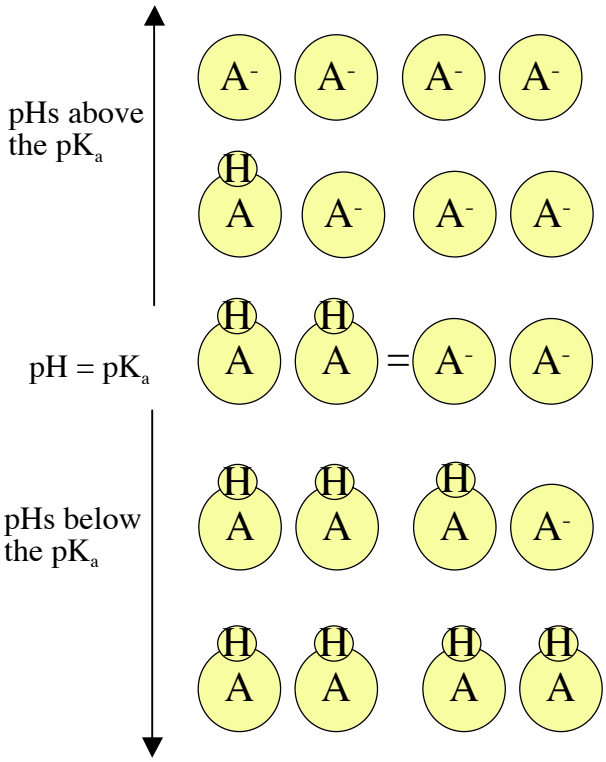
ACID-BASE EQUILBRIUM



protonated homocysteine deprotonated homocysteine methionine

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

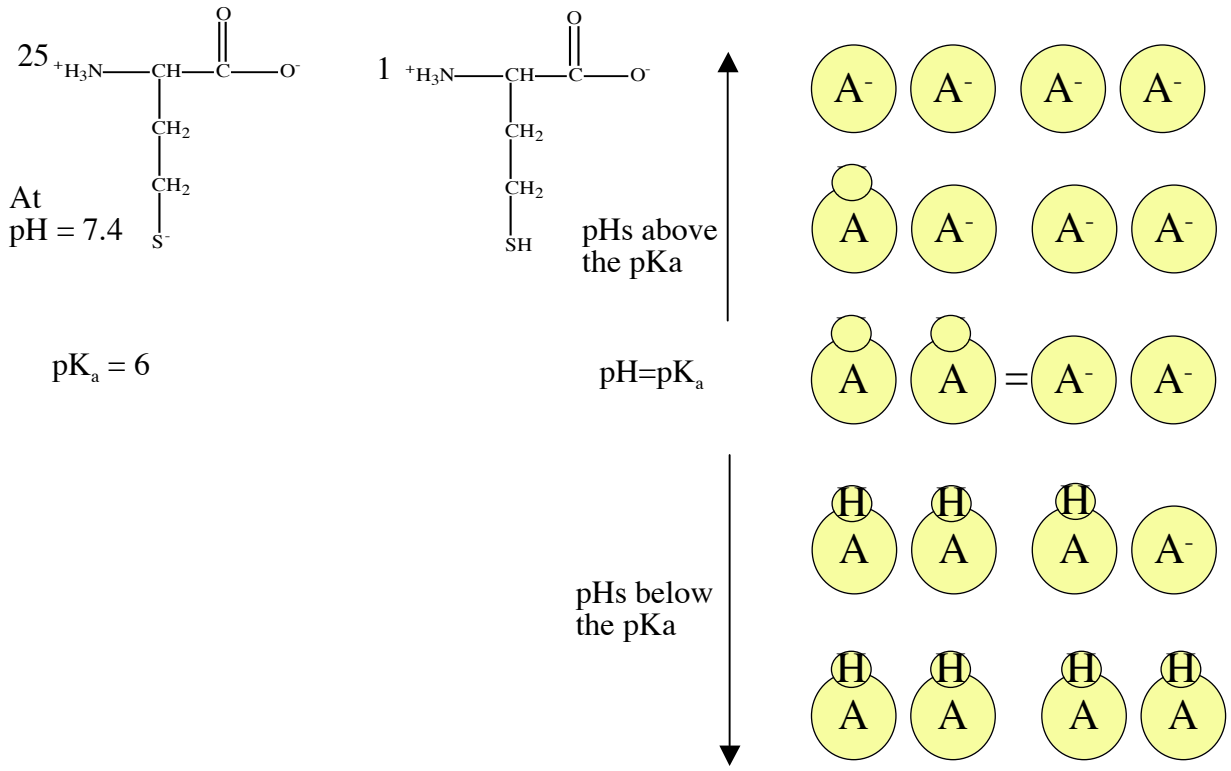
Free homocysteine is _____ and non-reactive at physiological pH



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

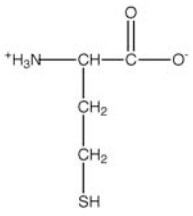
$$pH = pK_a - \log\left(\frac{[HA]}{[A^-]}\right) \qquad 7.4 = 6 - \log\left(\frac{[HA]}{[A^-]}\right) \qquad \frac{[HA]}{[A^-]} = \frac{1}{25}$$

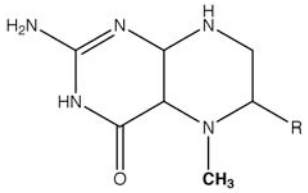
Enzyme-bound homocysteine is _____ and reactive at physiological pH!

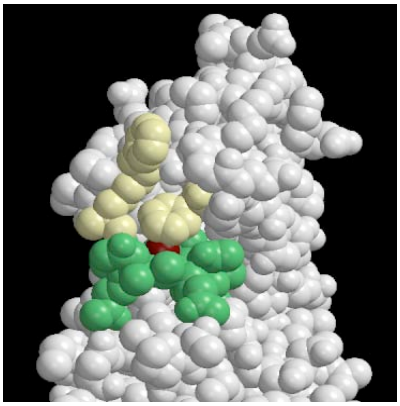


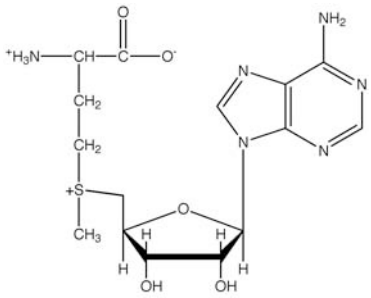
CHEMICAL EQUILIBRIUM

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





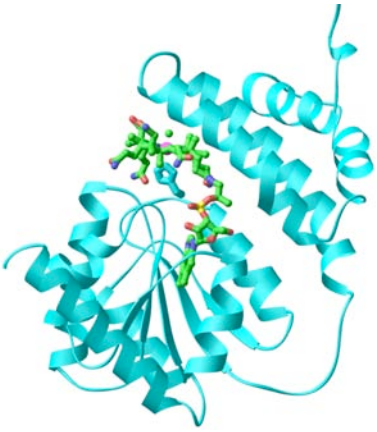




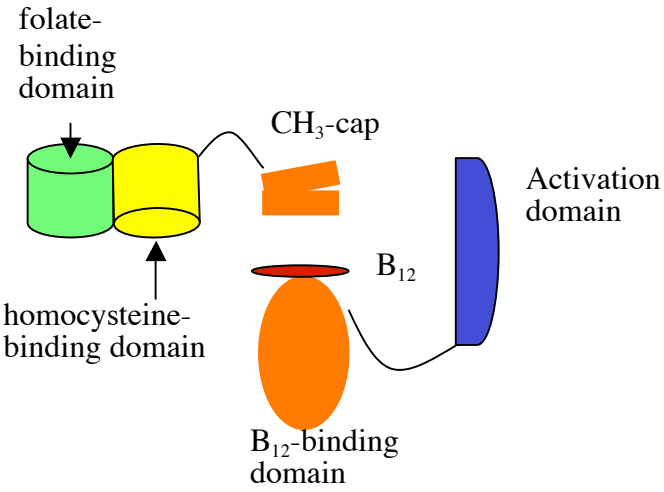
The enzyme needs to position three things above the B_{12} and there is no room for any of them.

Conformational changes need to occur.

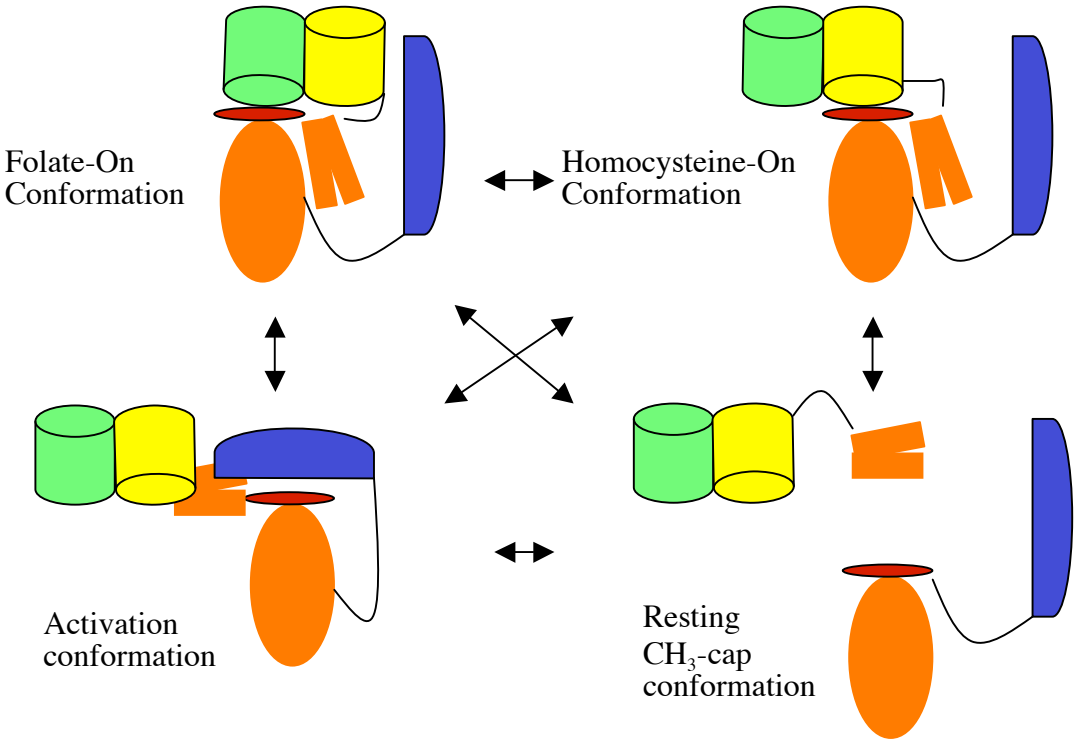
"Methyl-cap" region must move



Methionine synthase is a modular protein



Methionine synthase must exist in multiple conformations.



Enzymes are dynamic.

Chemistry is dynamic.

CHEMISTRY IN SOLUTION!!!!!